



Dieter Jaeger
Ranu Jung
Editors

Encyclopedia of Computational Neuroscience

Second Edition



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Second Edition

With 316 Figures and 18 Tables

 Springer

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Preface to the Second Edition

Computational neuroscience offers multi-scale models that span complexity from the gene to the whole living system levels, and can span different time and spatial scales. Such models offer hypotheses for testing in biological systems. Computational neuroscience also offers advanced statistical and data analysis techniques and approaches to interpret and analyze complex data. Collaborative effort among several disciplines and a convergence of diversity of approaches to knowledge inquiry and seeking of solutions are hallmarks of the field. Data sharing and model sharing based on modern markup language syntax and semantics shore up this effort.

In the 7 years since the print publication of the first edition of Springer's *Encyclopedia for Computational Neuroscience* in 2015, computational neuroscience has advanced significantly. In keeping with the rapid advancement of the field, as a live document, the online encyclopedia is continuously undergoing change, and over 120,000 downloads have occurred. This second print edition offers 46 new entries covering growing areas such as modeling of disease states, neural-glial interactions, and advances in applying information theory to computational neuroscience.

Several international conferences in this field of study, such as the annual meeting of the Organization of Computational Neuroscience <http://www.cnsorg.org/> and COSYNE <http://cosyne.org>, continue to bring the global community together, and standard-setting organizations, such as the International Neuroinformatics Coordinating Facility <http://incf.org/>, assure open and fair data exchange.

The growing allocation of research funding for computational neuroscience reflects the importance for understanding complex neurobiological systems in health and disease and translating that knowledge for clinical applications as well as design and development of neurobiology-inspired engineered systems. In the USA, the National Science Foundation, the National Institutes of Health, and the Department of Energy support collaborative research in computational neuroscience. Bilateral funding commitments to these agencies have been made by national research grant supporting agencies in France, Germany, Israel, Japan, and Spain. Support for multilateral projects and collaborations is also available. Thus, a global community of computational neuroscientists engage in “collaboratories.”

The encyclopedia highlights achievements and approaches to describe basic neural function and major brain systems as well as biomedical applications in 579 entries and 42 overviews over distinct research areas in

computational neuroscience. In-depth articles, written by subject-matter experts from around the globe, provide comprehensive coverage of important topics, whereas short articles summarize individual concepts and key terms. The interplay between computational and theoretical approaches and experimental data is highlighted at all levels from molecular to cognitive. Available shared database resources are also covered. While overall alphabetically sorted, an introduction of each section of topics covered is presented in entries denoted “Overview,” which also provide organized links to section entries.

The level of description in the encyclopedia is aimed to make the material accessible to graduate students in the many disciplines that contribute to computational neuroscience while also providing a valuable reference to advanced researchers. Cited website links allow the access to a more detailed level of information when needed. For those with institutional access to the online SpringerReference enterprise, a hot-linked version of this encyclopedia is available under [springerlink.com](https://www.springerlink.com).

The editors in chief are pleased to present this second edition of the *Encyclopedia of Computational Neuroscience* and are looking forward to readers’ comments that will be taken to further improve and complete future updates of this work.

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Fayetteville, USA
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Dr. Dieter Jaeger is a professor in the Department of Biology at Emory University in Atlanta, Georgia. His research examines how basal ganglia impact decision-making and motor control in thalamo-cortical networks through modeling and systems physiological approaches.

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Overview

Auditory Sensing Systems: Overview

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Detailed Description

This second edition of the Encyclopedia of Computational Neuroscience includes updates to the first edition's entries based on new findings in the field, and publishes several new reviews on recent topics of interest and modelling techniques for the study of auditory sensing systems. We thank the authors for their willingness to contribute to this section and thus provide a rich scientific resource on auditory neuroscience, for young and senior researchers alike.

Auditory sensing, or the sense of hearing, is concerned with detecting and extracting information from pressure waves in the surrounding medium, typically air or water. Since waves are generated by movements or collisions, this primarily tells the perceiver about things happening in the environment. In addition, since pressure

waves can be reflected, absorbed, and refracted by other objects, these pressure waves also contain a great deal of contextual information about the environment and the objects in it. A fundamental challenge for the auditory system is to segregate the contributions of individual sound sources to the sound pressure waves received by the sensors as these are made up of a combination of all concurrent sources and their various reflections. Sounds unfold in time, so modelers of auditory processing cannot ignore time and the need to process signals within time; this becomes especially challenging when considering the multiscale nature of the information contained within sounds.

Possibly due to the complexity of the problem, many aspects of auditory processing have not yet been modeled at a detailed neurocomputational level. In addition, a great deal of processing occurs even before the incoming signals reach cortex; with the result that there are more models related to subcortical processing, than to higher level, putatively cortical, functions. The articles commissioned for the auditory sensing systems section therefore span a range of topics from qualitatively different point of view, with a strong focus on the functionality of the auditory system. Together they provide an interesting and insightful view of current understanding of auditory processing, with a great deal of useful information for modelers regarding the neuroanatomy and

neurophysiology of the auditory system, methodological approaches to studying the auditory system, and functional requirements and perceptual constraints on auditory processing.

A well-illustrated overview of the anatomy and physiology of the auditory system, including the extensive but poorly understood efferent system is covered by ► [“Anatomy and Physiology of the Mammalian Auditory System.”](#) A detailed account of efferent control of the auditory sensor, the cochlea, is presented in the article on the ► [“Physiology and Function of Cochlear Efferents.”](#) It is in the cochlea that the biological system begins to analyze the pressure waves over multiple time scales and to do so within the time constraints of the ongoing multiscale information flow.

Another point of major transformation occurs at the gateway to the cortex, described in the article ► [“Auditory Thalamocortical Transformations.”](#) Three further overview articles dealing with electrophysiological correlates of auditory perception: ► [“Auditory Event-Related Potentials,”](#) ► [“Auditory Brainstem Responses,”](#) and ► [“Electrophysiological Indices of Speech Processing”](#) document methodological approaches to studying high-level perceptual functions. Specific aspects of the functional neurophysiology of the thalamocortical auditory system are addressed in a number of articles. The articles ► [“Associations and Rewards in the Auditory Cortex”](#) (revised) and ► [“Context-Dependent Processing in Auditory Cortex”](#) (revised) demonstrate that the auditory cortical code needs to be viewed in more complex terms than simple acoustic feature representations. For example, neural correlates of reward are found even within primary auditory cortex (► [“Associations and Rewards in the Auditory Cortex”](#)). In contrast, the articles ► [“Spectrotemporal Receptive Fields,”](#) ► [“Stimulus-Specific Information,”](#) and ► [“Stimulus Reconstruction from Cortical Responses”](#) show how auditory cortical activity can in some circumstances be usefully interpreted in terms of acoustic feature combinations.

An overview of theories and models of higher-level aspects of auditory perception are presented in ► [“Auditory Perceptual Organization,”](#)

► [“Music Processing in the Brain,”](#) ► [“Neural Coding of Speech Sounds,”](#) ► [“Pulse-Resonance Sounds,”](#) ► [“Auditory Memory”](#) (revised), ► [“Acoustic Timbre Recognition”](#) ► [“Pitch Perception, Models,”](#) ► [“Rhythm Perception: Pulse and Meter,”](#) and ► [“Sound Localization in Mammals and Models.”](#) These diverse topics emphasize the different ways in which sound is interpreted by the brain, while the article ► [“Tinnitus, Models”](#) shows how modelling may help advance understanding of a perceptual phenomenon that plagues 10–15% of the population.

The section also contains articles which present more detailed neurocomputational models and theories more closely related to the biology. These tend either to relate to very specific functions (► [“Sound Localization in Mammals and Models”](#) (revised), ► [“Stimulus-Specific Adaptation, Models,”](#) ► [“Auditory Precedence Effect,”](#) and ► [“Masking and Masking Release”](#) (revised)), or relate to processes at or near the sensor (► [“Auditory-Nerve Response, Afferent Signals”](#) (revised) and ► [“Cochlear Inner Hair Cell, Model”](#)).

Finally, new entries in the Auditory Sensing Systems section focus on neural features of sound perception such as neuronal phase-locking to the spectrotemporal components of the acoustic signal (► [“Auditory Frequency-Following Responses”](#)), enhancement of the cortical representation of auditory signals in the presence of noise at moderate signal-to-noise ratio (► [“Auditory Cortex: Separating Signal from Noise”](#)), and perceptual organization of environmental sounds (► [“Environmental Sound Perception: Effects of Aging and Hearing Loss”](#)). They also present recent advancements in mathematical and computational modeling of auditory processing in the auditory pathway and auditory perceptual representation. The articles review modeling of the interaural and internal time and level differences (► [“Internally Coupled Ears \(ICE\): Biophysical Consequences and Underlying Mechanisms”](#)), modeling of sound-evoked extracellular voltages in the auditory brainstem (► [“Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of”](#)), as well computational and statistical methods

used to study auditory stream segregation (► “Computational Models of Auditory Stream Segregation”).

Cross-References

- Acoustic Timbre Recognition
- Anatomy and Physiology of the Mammalian Auditory System
- Associations and Rewards in the Auditory Cortex
- Auditory Brainstem Responses
- Auditory Cortex: Separating Signal from Noise
- Auditory Event-Related Potentials
- Auditory Frequency-Following Responses
- Auditory Memory
- Auditory Perceptual Organization
- Auditory Precedence Effect
- Auditory Thalamocortical Transformations
- Auditory-Nerve Response, Afferent Signals
- Cochlear Inner Hair Cell, Model
- Computational Models of Auditory Stream Segregation
- Context-Dependent Processing in Auditory Cortex
- Electrophysiological Indices of Speech Processing
- Environmental Sound Perception: Effects of Aging and Hearing Loss
- Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of
- Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms
- Masking and Masking Release
- Music Processing in the Brain
- Neural Coding of Speech Sounds
- Physiology and Function of Cochlear Efferents
- Pitch Perception, Models
- Pulse-Resonance Sounds
- Rhythm Perception: Pulse and Meter
- Sound Localization in Mammals and Models
- Spectrotemporal Receptive Fields
- Stimulus Reconstruction from Cortical Responses
- Stimulus-Specific Adaptation, Models
- Stimulus-Specific Information
- Tinnitus, Models

Basal Ganglia: Overview

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Definition

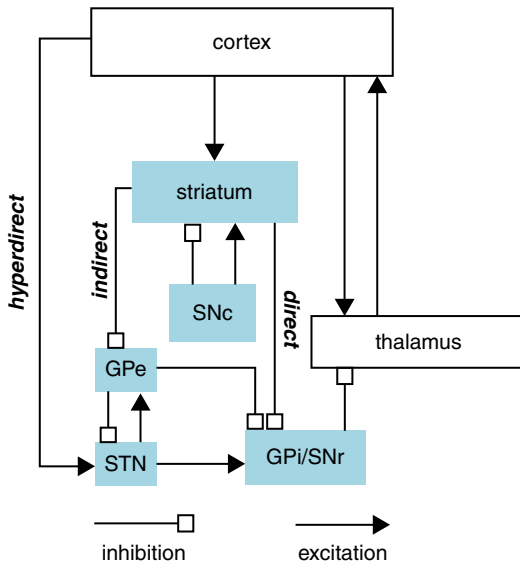
The basal ganglia are a collection of four subcortical nuclei, the striatum, substantia nigra, globus pallidus, and subthalamic nucleus. They are components of several apparently segregated circuits that can be classified according to function as motor, oculomotor, associative, and limbic. Certain neurons in the basal ganglia are major sources of the neurotransmitter dopamine, associated with reward, while others receive dopaminergic inputs; thus, the basal ganglia have received considerable attention in the context of learning. Imbalances in activity across the basal ganglia nuclei within the motor circuit are associated with various motor disorders.

Detailed Description

This section considers on the motor aspects of the basal ganglia, which have been the focus of most computational studies. The articles can be classified as those concentrating on activity within particular areas of basal ganglia, those concerning basal ganglia function, and those about the roles of basal ganglia in motor disorders, predominantly parkinsonism.

Basal Ganglia Structure

While the structures of the basal ganglia (Fig. 1) appear to be common across a wide range of vertebrate animals, from primates to lamprey (Stephenson-Jones et al. 2011), there are somewhat different naming systems used in different species, and there are some structural differences across species (e.g., mammals versus birds). Following the nomenclature used in primates, the striatum, encompassing the caudate nucleus and the putamen, is the predominant recipient of



Basal Ganglia: Overview, Fig. 1 Major structures and pathways of the basal ganglia. Basal ganglia areas are colored in blue. Connecting arrows and lines represent the existence of direct synaptic interactions between areas. A projection from GPe to the striatum recently discovered in rats is omitted here

cortical inputs. There are several types of neurons within the striatum, most of which release the neurotransmitter GABA, which has an inhibitory effect on its targets (see entry ► [“Basal Ganglia: Striatal Models Cellular Detail”](#)). Striatal neurons are also major recipients of dopamine. Different types of dopamine receptors arise in different striatal neurons, and this variability translates into diverse impacts of dopamine release. In coarse terms, dopamine promotes activity in some striatal neurons and inhibits it in others, but specific effects may be more complicated and may depend on ongoing activity levels.

The substantia nigra has two main parts, the substantia nigra pars reticulata (SNr) and the substantia nigra pars compacta (SNc). The former sends inhibitory output to areas outside of the basal ganglia that may be related to oculomotor activity (see entry ► [“Basal Ganglia: Control of Saccades”](#)) or other motor activity, particularly in rodents. The latter releases dopamine to the striatum and other basal ganglia areas (see entry ► [“Basal Ganglia: Dopaminergic Cell Models”](#)).

The globus pallidus is also a dichotomous structure, with segments that are referred to as external (GPe) and internal (GPi). Both parts predominantly contain GABAergic neurons that exhibit high firing rates, although with diverse firing patterns, under baseline conditions (see entry ► [“Basal Ganglia: Globus Pallidus Cellular Models”](#)). The GPe receives projections from a subset of striatal neurons as well as from the subthalamic nucleus (STN), and it innervates both the striatum and the STN in return, although it appears that the subpopulations of GPe neurons targeting these areas are distinct (Mallet et al. 2012). The GPi is subject to inputs from a different subset of striatal neurons, from the STN, and from the GPe and in turn projects to thalamic areas outside of the basal ganglia.

The STN stands out as the only basal ganglia area that releases the excitatory neurotransmitter glutamate. STN neurons exhibit intrinsic firing, albeit with heterogeneous properties (see entry ► [“Basal Ganglia: Subthalamic Nucleus Cellular Models”](#)). Besides participating in a reciprocal loop with GPe (see entry ► [“Subthalamopallidal Loop and Oscillations”](#)), the STN projects directly to GPi. The STN also receives direct glutamatergic input from the cortex and some dopaminergic input from the SNc.

The routes along which activity flows through the basal ganglia have been classified into the direct pathway, the indirect pathway, and the hyperdirect pathway (Fig. 1). This nomenclature refers to the number and types of steps between the cortex, which provides input to the basal ganglia, and the GPi, the primary source of motor outputs from the primate basal ganglia. The direct pathway is the stream from the cortex to the striatum to GPi. In net, the direct pathway inhibits basal ganglia output, since the cortex excites the striatum, which inhibits GPi. Since GPi inhibits downstream areas, reductions in its output can be pro-kinetic. The indirect pathway goes from the cortex through the striatum to GPe and continues on to STN and then GPi; the GPe-GPi connection may also be included in this pathway. Overall, the indirect pathway is believed to promote basal ganglia output and hence suppress movement. This view is based

on the idea that the cortex excites the striatum and thus inhibits GPe and disinhibits its target STN, which in turn excites GPi; the reduction in GPe activity also lowers its inhibition of GPi, yielding additional enhancement of GPi firing. This reasoning omits the complication of feedback pathways, such as the excitation that STN sends to GPe, however. The hyperdirect pathway, like the direct pathway, includes only one intermediary between the cortex and GPi: it refers to the cortical projection to STN together with the STN link to GPi. Presumably, this pathway is called “hyperdirect” because it features excitatory transmission via glutamatergic synapses from STN to GPi that is faster and has a more immediate effect than the direct pathway’s inhibitory signaling via GABAergic synapses from the striatum to GPi. Like the indirect pathway, the hyperdirect pathway promotes basal ganglia output.

Finally, note that in rodent, which is a useful experimental model, the output structure analogous to the GPi is called the entopeduncular nucleus, and the major motor output structure is thought to be the SNr.

Basal Ganglia Function

The basal ganglia have been postulated to have a wide range of functions related to motor learning and other steps contributing to goal-directed movements (Chakravarthy et al., 2010). Models have been developed to represent and make predictions about the mechanisms involved in several of these functions. In the Basal Ganglia section of this encyclopedia, articles discuss background information and computational work on the mechanisms for action selection, habit formation, decision-making, and control of saccades. Furthermore, additional articles treat the role of the basal ganglia as an exploration engine and the learning and production of songs by birds.

Several lines of evidence point to the basal ganglia as a major site of action selection (see entry ► [“Basal Ganglia: Mechanisms for Action Selection”](#)). In particular, the basal ganglia are well positioned anatomically to orchestrate action selection by integrating inputs from a broad range of cortical areas and providing outputs to

downstream motor-related sites. The basic idea of how action selection might work rests on the observations that under rest conditions, the output nuclei of the basal ganglia, GPi and SNr, exhibit high activity levels and that these areas release inhibitory neurotransmitters, which are well suited to block motor activity. To perform a movement, this inhibitory “gate” must be opened but only in a way that allows the desired action while maintaining a blockade on all other movements. Models of action selection position the direct pathway as the agent that removes inhibition and suggest that the indirect and hyperdirect pathways can act to suppress behavior and to participate in behavior switching (see entry ► [“Basal Ganglia: Mechanisms for Action Selection”](#); Nambu et al. 2002).

Gradually, particular actions can become habits, which are actions that are elicited by certain stimuli in a way that lacks flexibility. Although established habits are less dependent on external rewards than are other learned behaviors, rewarding feedback that leads to striatal activation and associated plasticity of corticostriatal synapses are central to their being formed, and the corresponding learning process has been considered in computational models (see entry ► [“Basal Ganglia: Habit Formation”](#)). Dopamine is central to this form of plasticity and learning, and impairments in habit formation and performance are noted in subjects with Parkinson’s disease.

A basal ganglia function that is distinct from pure action selection and habit learning arises in perceptual decision-making. In this process, in abstract terms, it is thought that evidence favoring each of a number of choices accumulates until one option becomes sufficiently supported to elicit a corresponding behavior. The evidence is presumably represented by firing of various sets of cortical neurons that can influence basal ganglia activity, and basal ganglia activity is involved in setting the selection threshold (see entry ► [“Basal Ganglia: Decision-Making”](#)). In this view, the dopamine-based reward induced by a behavior is involved in threshold adjustment and thereby influences future choices. Computational models consider how the activity in the pathways of the

basal ganglia interacts with dopaminergic reward signals to drive and adjust the decision-making process, positing various roles for particular brain areas in evidence accumulation, stimulus detection, threshold adjustment, and decision-making and cancellation. Some also treat impairments in parkinsonian conditions and alterations under deep brain stimulation (see entry ► [“Basal Ganglia: Decision-Making”](#)).

Unlike other actions to which the basal ganglia contribute, rapid eye movements known as saccades in primates are gated by outputs from SNr rather than GPi. Issues under investigation relating to saccade generation, which have been treated in computational models, include mechanisms of target selection, of learning of target priorities, and of interactions of these processes with working memory (see entry ► [“Basal Ganglia: Control of Saccades”](#)).

A less thoroughly investigated function of the basal ganglia is the generation of variability in motor responses. Such variability is certainly observed in the behaviors of many species and seems to be essential for optimizing behavior and attaining maximal rewards. There is significant experimental evidence implicating the basal ganglia as a source of such motor exploration, and some computational modeling work to instantiate these ideas and study their implications has been performed (see entry ► [“Basal Ganglia System as an Engine for Exploration”](#)). In relevant models, while the direct pathway takes on the traditional role of implementing action selection, the indirect pathway, and particularly the STN, injects variability into this process. Learning based on reward signals is critical to such models and helps control the relative dominance of direct and indirect pathway signals.

One example of the prominence of behavioral variability arises in song production by songbirds. Songs must be learned, which involves exposure to the song of another bird, trial-and-error behavior, and auditory feedback. This process appears to heavily involve a basal ganglia analogue that participates in learning, in the introduction of behavioral variability, and in the selection of rewarding behaviors. Certain songbird experimental preparations are advantageous

for studying this combination of processes, and corresponding models of associated reinforcement learning and song production have been informed by observations from these preparations (see entry ► [“Basal Ganglia: Songbird Models”](#)).

Basal Ganglia and the Motor Symptoms of Parkinsonism

The loss of dopaminergic neurons in the SNc appears to be the critical trigger for a slew of changes in neuronal activity within areas of the basal ganglia that result in the motor symptoms of parkinsonism. This loss is typically gradual, and the causes appear to involve a complex combination of environmental and genetic factors that are still under intensive investigation.

Classical models of parkinsonism attribute its motor signs to an imbalance in direct and indirect pathway outputs stemming from the loss of dopaminergic input to the striatum (Albin et al. 1989). The loss of dopamine removes a source of excitation to the striatal neurons with D1 receptors, which project to GPi. Less firing by these striatal neurons, viewed as a weakening of the direct pathway, results in disinhibition of GPi. Meanwhile, diminished dopamine translates to reduction in inhibition of the striatal neurons with D2 receptors, which in turn inhibit GPe. As a result, GPe output is suppressed, which relieves GPe inhibition of STN and allows enhanced STN firing. The increased STN activity provides more drive to GPi, viewed as a strengthening of the indirect pathway. Together, these changes tip the balance of direct and indirect pathway effects in a way that favors the indirect pathway and promotes GPi activity. GPi outputs inhibit the pallidal recipient areas of the thalamus and are believed to represent an inhibitory gate that shuts down movement. Thus, pathologically enhanced GPi firing could interfere with initiating and carrying out movements in a way that translates into some motor signs of parkinsonism.

The complete explanation for the emergence of parkinsonian motor signs likely involves phenomena that are omitted from this classical description. It has become clear that loss of dopamine leads to widespread modifications of neuronal

activity patterns, rather than just changes in firing rates, in the basal ganglia. These effects include an enhanced prevalence of bursting, altered oscillation structure, and increased correlation in outputs of neurons within, and across, basal ganglia areas (Rubin et al. 2012).

One potential source of oscillations within basal ganglia is the reciprocal excitatory-inhibitory loop between the GPe and the STN (see entry ► [“Subthalamopallidal Loop and Oscillations”](#)). Oscillations in the beta band (broadly taken as 10–30 Hz) appear to be particularly prevalent in parkinsonian conditions and may be particularly effective at hijacking activity in thalamic areas downstream from the basal ganglia, and several different sources for such oscillations have been posited (see entry ► [“Basal Ganglia: Beta Oscillations”](#)).

While oscillations observed in the activity of basal ganglia neurons seem like a natural candidate to contribute to parkinsonian tremor, the link between altered neuronal firing and other parkinsonian symptoms may be less explicit. In particular, the slowing of movement known as bradykinesia may emerge from the interactions of all of the motor signaling pathways through the basal ganglia, or it may be necessary to consider basal ganglia interactions with corticospinal-muscular pathways to explain its source (see entry ► [“Basal Ganglia: Bradykinesia Models”](#)).

The predominant treatments for Parkinson’s disease in its early stages are pharmacological, aimed at replacing lost dopamine. In cases where pharmacological treatments gradually lose efficacy or induce substantive side effects, deep brain stimulation therapy represents a treatment option that, while highly invasive, is at least partially adjustable (by tuning of stimulation parameters) and reversible (by cessation of stimulation). Deep brain stimulation for Parkinson’s disease typically is targeted at STN or GPi and proves effective for many patients; although the mechanisms underlying its efficacy are not known, theories have honed in on its potential impact on patterns of basal ganglia activity and outputs and their downstream effects (see entry ► [“Computational Models of Deep Brain Stimulation \(DBS\)”](#); Rubin et al. 2012).

Cross-References

- [Basal Ganglia System as an Engine for Exploration](#)
- [Basal Ganglia: Beta Oscillations](#)
- [Basal Ganglia: Bradykinesia Models](#)
- [Basal Ganglia: Control of Saccades](#)
- [Basal Ganglia: Decision-Making](#)
- [Basal Ganglia: Dopaminergic Cell Models](#)
- [Basal Ganglia: Globus Pallidus Cellular Models](#)
- [Basal Ganglia: Habit Formation](#)
- [Basal Ganglia: Mechanisms for Action Selection](#)
- [Basal Ganglia: Songbird Models](#)
- [Basal Ganglia: Striatal Models Cellular Detail](#)
- [Basal Ganglia: Subthalamic Nucleus Cellular Models](#)
- [Computational Models of Deep Brain Stimulation \(DBS\)](#)
- [Subthalamopallidal Loop and Oscillations](#)

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Bayesian Approaches in Computational Neuroscience: Overview

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Definition

Bayesian approaches in Computational Neuroscience rely on the properties of Bayesian statistics for performing inference over unknown variables given a data set generated through a stochastic process.

Detailed Description

Given a set of observed data $d_{1:n}$, generated from a stochastic process $P(d_{1:n}|X)$ where X is a set of unobserved variables, the posterior probability distribution of X is $P(X|d_{1:n}) = P(d_{1:n}|X)P(X)/P(d_{1:n})$ according to Bayes' theorem. X can be a set of fixed parameters as well as a series of variables of the same size as the data itself $X_{1:n}$.

Based on the posterior probability and a specified utility function, an estimate of X can be made that can be shown to be optimal, for example, by minimizing the expected variance.

One common use of this principle within computational neuroscience is for inferring unobserved properties (hidden variables X) based on observed data, d . These techniques can be used for inference on any data sets but has in neuroscience mostly been used for neurophysiological recordings, imaging, and behavioral data.

By their nature electrophysiological recordings are noisy and stochastic. Given the stochastic responses of neurons to stimuli, Bayesian methods can be used to infer the underlying stimuli or activation of the neurons, $X_{1:n}$ (Bayesian Electrophysiology Analysis).

For imaging data an underlying neural activity $X_{1:n}$, for example, firing rate at the level of individual columns of cortex, is assumed to give rise to measured responses $d_{1:n}$, for example, the blood flow measured by fMRI, through a stochastic process. Inverting the process through the Bayesian inference allows for estimating the unknown neural activity (Bayesian Imaging Analysis).

The ideas can also be useful for inferring properties about the behavior of individual human subjects, X , by the assumption of a stochastic process, $P(d_{1:n}|X)$, through which characteristics of each individual subject lead to individual choices in an experimental task, $d_{1:n}$ (Bayesian Behavioral Analysis).

The abovementioned techniques all use Bayesian inference to infer underlying properties of recorded data but are essentially used as very effective tools for data analysis. An alternative line of research takes as the working hypothesis that the human brain has evolved to the point of itself approximating an ideal Bayesian observer (sometimes referred to colloquially as the Bayesian Brain Hypothesis). Accordingly, this line of research compares human behavior to the output of such an ideal observer within, for example, perceptual (Bayesian Models of Perception) or cognitive tasks (Bayesian Models of Cognition).

A related effort has proposed that the computations necessary to perform the steps of Bayesian inference can be done through populations of biological neurons (Bayesian Inference with Spiking Neurons). Recent works on artificial neural networks have also reignited interest in combining ideas from the two areas of research including means of designing artificial networks able to perform Bayesian inference.

There is a continued effort to translate ideas on Bayesian inference from Machine Learning and Computer Science into Computational Neuroscience, including, for example, recent advances in sampling techniques for inference.

Cross-References

- [Bayesian Inference with Spiking Neurons](#)
- [Behavioural Analysis, Bayesian](#)
- [Cognition, Bayesian Models of](#)
- [Electrophysiology Analysis, Bayesian](#)
- [Imaging Analysis, Bayesian](#)
- [Perception, Bayesian Models of](#)

Biochemical Signaling Pathways and Diffusion: Overview

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Detailed Description

Signaling pathways modulate the function of neurons and neuronal networks through diverse processes. The most well-known function of signaling pathways is synaptic plasticity, which controls neuronal networks via modulation of the strength of synaptic connections. Signaling pathways also are critical for neuronal development, axon guidance, and regulation of transcription and translation. Signaling pathways are activated by the G protein-coupled transmembrane receptors, such as metabotropic glutamate receptors or noradrenergic receptors; by the receptor tyrosine kinases; and by calcium influx through NMDA receptors or voltage-dependent calcium channels.

Calcium

Due to the importance of calcium, its concentration is tightly regulated by buffers and pumps. One of these calcium buffers, known as calmodulin, is not inert; rather, it can activate diverse enzymes such as adenylyl cyclase, calcineurin, phosphodiesterase type 1B, and calcium-

calmodulin-dependent protein kinase II. In addition to calcium influx through plasma membrane channels, both the mitochondria and the smooth endoplasmic reticulum (SER) are sources of calcium. Two types of calcium permeable channels reside on the SER: the inositol trisphosphate receptor channel and the ryanodine receptor channel. Calcium-dependent calcium release through these channels can lead to oscillations or waves of calcium, depending on various factors.

Kinases

The second messengers activated through transmembrane receptors have multiple downstream targets, including ionic channels, kinases, and phosphatases. Of the thousands of kinases and phosphatases in the proteome, several have a demonstrated role in synaptic plasticity, though their relative importance depends on the brain region and cell type. Protein kinase type C is a calcium- and lipid-activated kinase which is critical for LTP in the cerebellum. Protein kinase type A is a cAMP-activated kinase, which is critical for LTP in the striatum, and for several long-lasting forms of LTP in the hippocampus. Gene transcription and protein translation are required for both memory and for long-lasting forms of synaptic plasticity. One kinase that appears to bridge these other kinases and transcription is the ERK1/2 forms of MAPK (mitogen-activated protein kinase).

Modeling Techniques

Calcium dynamics and signaling pathways are modeled as cascades of biochemical reactions, both bimolecular reactions and enzyme reactions, and diffusion. Many special purpose simulators are available to implement these signaling pathways, either using stochastic techniques or deterministic approaches. Modeling calcium influx requires the simulator to have capabilities for modeling membrane potential. Due to the diversity in temporal and spatial scale involved in modeling neuronal electrical activity coupled to reaction-diffusion pathways, very few models

incorporate signaling pathways in entire neurons, though the number of such models is increasing as computational power increases.

Cross-References

- [Bimolecular Reactions, Modeling of](#)
- [Biophysical Models of Calcium-Dependent Exocytosis](#)
- [Calcium Buffering: Models of](#)
- [Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis](#)
- [Calcium Pumps, Models of](#)
- [Calcium Release, Models of](#)
- [Calcium Waves, Models of](#)
- [Calmodulin, Models of](#)
- [Cerebellum: Overview](#)
- [Deterministic Reaction-Diffusion Simulators](#)
- [Diffusion Equation](#)
- [Enzyme Kinetics, Modeling of](#)
- [Extracellular Signal-Regulated Kinases, Models of](#)
- [Gillespie Algorithm for Biochemical Reaction Simulation](#)
- [High-Voltage-Activated Calcium Channels](#)
- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)
- [N-Methyl-D-Aspartate \(NMDA\) Receptors, Conductance Models](#)
- [Particle-Based Stochastic Simulators](#)
- [Protein Kinase A, Models of](#)
- [Protein Kinase C, Models of](#)
- [Signaling Pathways, Modeling of](#)
- [Stochastic Simulators](#)

Brain Imaging: Overview

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Synonyms

Functional neuroimaging

Definition

Brain imaging constitutes a set of techniques used to measure functional activity in networks of interacting brain cells as well as to reveal the major underlying structural properties of these networks. Functional data obtained with these techniques reflect local changes in brain perfusion, metabolism, and extracellular electric/magnetic potentials originated from the activity of these brain cell networks. Brain imaging has been traditionally used to explore both normal and pathological brains in a large variety of species ranging from rodents to primates. In principles, brain imaging could be applied for both in vitro and in vivo situations.

Detailed Description

Techniques for brain imaging have been developed for two major physical brain scales, i.e., the mesoscale and the macroscale. Theoretical models useful to interpret how these two physical scales interact have been developed in the past (see ► [“Multiscale Brain Connectivity”](#)). Brain imaging modalities have been combined with specific stimulation techniques to study brain activity in both mesoscopic (e.g., uncaging methods, optogenetics – see ► [“Optogenetics”](#)) and macroscopic (e.g., transcranial magnetic stimulation, TMS) levels. Brain imaging constitutes one of the most important building blocks in the development of brain-machine interfaces (see ► [“Brain-Machine Interface and Neuroimaging”](#)).

Neuroimaging at the Mesoscale

Functional refers to observations reflecting the activity of populations of cells (e.g., neurons, astrocytes) in a particular brain structure with the resolution of single cells. Examples of functional neuroimaging for this particular scale are confocal/multiphoton (MP) microscopy, current source density (CSD) analysis from intracranial recordings using MEA, intrinsic optical signal (IOS), optical coherence tomography (OCT), and

voltage-sensitive dye imaging (VSDI). These imaging techniques are based on either in vitro or very invasive in vivo experimental protocols. Some of the imaging techniques based on optical phenomena (confocal/MP microscopy, VSDI – see ► [“Voltage Sensitive Dye Imaging, Intrinsic Optical Signals”](#)) provide the ideal spatial resolution to explore the activity of single cells, but their temporal resolution is in the order of hundreds of milliseconds. In contrasts, images resulting from the CSD analysis could reflect electrical phenomena happening in the order of a few milliseconds, but they are associated with the activity of synchronized population of neurons in extended brain regions. IOS and OCT are employed mainly to record changes in blood flow/volume in the brain as well as alterations in blood oxygen concentration (see ► [“Voltage Sensitive Dye Imaging, Intrinsic Optical Signals”](#)).

Anatomical refers to static pictures of the cellular networks directly reflecting structural properties. These images are obtained using different modalities of sectioning microscopy (see ► [“Physical Sectioning Microscopy”](#)).

Neuroimaging at the Macroscale

Functional refers to observations reflecting the activity of large regions inside the brain. Examples of functional neuroimaging for this particular scale are functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission tomography (SPECT), functional near-infrared spectroscopy (fNIRS), and electro (EEG)/magneto (MEG) –encephalograms. The spatiotemporal profiles of these brain imaging techniques are quite different (Riera and Valdes-Sosa 2010). Deciphering the origin and nature of signatures in the functional neuroimaging imprinted by abnormal brain activity is important while using them for diagnosing, monitoring, and treating brain diseases and disorders (see ► [“Connectivity Analysis in Normal and Pathological Brains”](#)). To that end, it is crucial to understand the physiological mechanisms underlying these brain imaging techniques (see ► [“Biophysical Models: Neurovascular Coupling, Cortical Microcircuits,](#)

[and Metabolism,”](#) ► [“Kinetic Models for PET/SPECT Imaging,”](#) and ► [“Forward and Inverse Problems of MEG/EEG”](#)). These techniques classify either as slightly invasive (i.e., fMRI, fNIRS, EEG/MEG) or extremely invasive because of the use of radioisotopes (i.e., PET, SPECT, see ► [“Radiopharmaceuticals in Molecular Imaging”](#)). A variety of methods have been developed for the preprocessing and analysis of brain imaging data, with resulting software and platforms currently available (see ► [“Software for Neuroimaging Data Analysis,”](#) ► [“Statistical Analysis of Neuroimaging Data,”](#) and ► [“Meta-analysis in Neuroimaging”](#)).

Anatomical refers to static pictures of the entire brain, or part of it, directly reflecting structural properties. Example of imaging modalities used to study morphometric characteristics of brain tissues are the T1/T2 magnetic resonance imaging (MRI) and the computed tomography (CT). Diffusion tensor imaging (DTI) has been commonly employed to study the strengths of connections between different brain regions.

Cross-References

- [Applications of Information Theory to Analysis of Neural Data](#)
- [Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism](#)
- [Brain Atlases](#)
- [Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery](#)
- [Brain-Machine Interface and Neuroimaging](#)
- [Connectivity Analysis in Normal and Pathological Brains](#)
- [Current Source Density \(CSD\) Analysis](#)
- [Electrophysiology Analysis, Bayesian](#)
- [Forward and Inverse Problems of MEG/EEG](#)
- [Imaging Analysis, Bayesian](#)
- [Independent Component Analysis of Images](#)
- [Kinetic Models for PET/SPECT Imaging](#)
- [Local Field Potential, Relationship to BOLD Signal](#)
- [Local Field Potential, Relationship to Electroencephalogram \(EEG\) and Magnetoencephalogram \(MEG\)](#)

- [Meta-analysis in Neuroimaging](#)
- [Multiscale Brain Connectivity](#)
- [Neuroimaging, Neural Population Models for](#)
- [Noninvasive Brain-Computer Interfaces](#)
- [Optogenetics](#)
- [Physical Sectioning Microscopy](#)
- [Radiopharmaceuticals in Molecular Imaging](#)
- [Reconstruction, Electron Microscopy](#)
- [Software for Neuroimaging Data Analysis](#)
- [Statistical Analysis of Neuroimaging Data](#)
- [Voltage Sensitive Dye Imaging, Intrinsic Optical Signals](#)

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Brain-Machine Interface: Overview

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Abbreviations

AP	Action potentials
BCI	Brain-computer interfaces
BMI	Brain-machine interface
ECoG	Electrocorticogram
EEG	Electroencephalogram
EMG	Electromyogram
FES	Functional electrical stimulation
LTD	Long-term depression

LTP	Long-term potentiation
MIMO	Multi-input multi-output
NI	Neural interfaces
SCI	Spinal cord injury
SISO	Single-input single-output

Synonyms

Brain-computer interfaces; Neural interfaces

Definition

A brain-machine interface (BMI) is a direct communication pathway between the nervous system and a man-made computing device. This communication is *unidirectional* in BMIs that either record neural activity in the nervous system to affect the state of an external device or stimulate neural activity to affect the state of the nervous system. It can also be *bidirectional*, such as BMIs that record activity from certain parts of the nervous system and use this activity – or features extracted from it – *in real time* to stimulate activity in other parts of that system. This communication can occur at multiple levels, which may include muscles, peripheral nerves, spinal cord, or the brain.

Detailed Description

BMIs fundamentally rely on the concept of causation between electricity and movement or between electricity and cognition. The causal link between electrical current injection into the body and movement of parts of that body was first established in the late eighteenth century by Galvani (1791), Fowler and Galvani (1793), who could evoke muscle twitches in the frog legs by direct current injection into the muscle *ex vivo*. A similar discovery in the central nervous system was made in 1870 by Fritsch and Hitzig (1870), in which electrical stimulation of different areas of the cerebral cortex caused muscular contractions of specific parts of a dog's body *in vivo*. It was not until 1928 that recording of the all-or-none electrical discharge of single neurons in the optic nerve of the toad was made by Adrian (Adrian

and Bronk 1928) and was found to be strongly correlated with light stimuli. Ever since, countless studies have revealed numerous mechanisms of neural coding of sensory stimuli or movement parameters, such as orientation tuning by V1 neurons (Hubel and Wiesel 1962), spatial position by hippocampal place cells (Ranck 1973; O’Keefe 1979) and movement direction by primary motor cortex neurons (Georgopoulos et al. 1986).

The early 1990s nonetheless has witnessed a paradigm shift in the way recording and stimulation of neural activity is achieved. In particular, micro-wire bundles have been used to record the activity of a handful of neurons in awake behaving animals (McNaughton et al. 1983). Striking advances in the microfabrication technology of high-density micro-electrode arrays (HDMEAs) (Drake et al. 1988; Normann et al. 1999) have later permitted large-scale simultaneous recording of many neurons (tens to hundreds) in awake behaving subjects, which eventually paved the way for these arrays to become a key element in BMIs development in subsequent years (Nicolelis 1999).

Unidirectional BMIs

Afferent BMIs

Afferent BMIs (ABMIs) rely on transforming features of sensory stimuli (e.g., auditory, visual, etc.) to electrical pulse trains in order to stimulate neural activity in the central or the peripheral nervous systems to cause artificial sensation to compensate for some form of sensory loss (e.g., deafness or blindness) (Fig. 1). Auditory prosthesis, such as cochlear implants (CIs) – dating back to the first implant in 1957 by Djorno and Eyries – is the first example of an afferent BMI that was approved by the FDA in 1984 (House and Urban 1973). CIs transform sound features (e.g.,

intensity or pitch) recorded through a microphone to pulsatile currents in the spiral ganglia. This eventually elicits action potentials from residual hair cells in the auditory nerve of hearing-impaired subjects.

Likewise, visual prosthesis rely on transforming features of the visual scenes recorded through a video camera to stimulate different parts of the visual pathway in legally blind subjects. The site of stimulation along this pathway is a function of where neural degeneration occurs, but the most promising demonstration of visual prosthesis thus far has been through the stimulation of the retinal ganglion cell layer that provide input to the optic nerve in patients with retinitis pigmentosa and age-related macular degeneration (de Balthasar et al. 2008).

Efferent BMIs

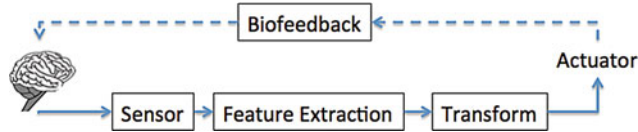
EBMIs rely on extracting features from recorded neural activity in real time that are subsequently transformed into control signals for actuating an external device (e.g. a paralyzed limb) (Fig. 2). They can be categorized based on the recorded signal modality, which is predominantly neural (but see (Sitaram et al. 2009) for an example of metabolic activity that utilizes blood-oxygen-level dependent (BOLD)).

In EBMIs, the neural readout may differ in the temporal and spatial scales of variations, as well as in information content, as shown in Fig. 3. While the 1–2 ms APs elicited by individual neurons are known to contain large information about behavioral covariates (typically measured in bits per second), they tend to be highly variable and can only be recorded thus far using penetrating microelectrodes (McNaughton et al. 1983; Drake et al. 1988; Normann et al. 1999; Nicolelis 1999), or using voltage-sensitive dye-based calcium imaging at shallow cortical depths (Koester and



Brain-Machine Interface: Overview, Fig. 1 Basic elements of an afferent BMI. Features are extracted from the sensory stimuli and then converted to electrical pulses that

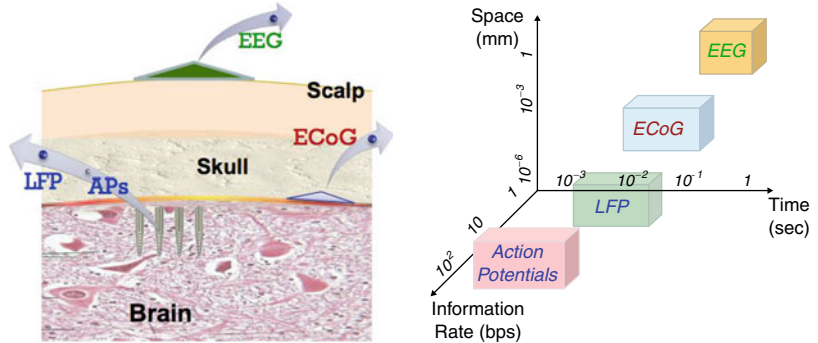
stimulate target areas in the afferent pathway of the corresponding sensory modality



Brain-Machine Interface: Overview, Fig. 2 Basic elements of an efferent BMI. The read out of neural activity can be a single signal source recorded from a target area within an efferent pathway – or multiple sources fused

together within the transform block, aka the “decoder” – to actuate an artificial device. The user is able to continuously monitor changes in the state of the actuator in real time, typically through visual feedback

Brain-Machine Interface: Overview, Fig. 3 Spatial, temporal, and information characteristics of neural signals recorded from the brain for efferent BMI operation. (Adapted from Oweiss 2010)



Sakmann 2000; Stosiek et al. 2003) – although the latter signals have not been used in BMIs. While local field potentials (LFPs) can also be recorded using penetrating electrodes, they contain less information than spike trains and are believed to provide a glimpse over the synchronized activity of large populations of neurons within a few 100 microns from the electrode tip (Mitzdorf 1985; Katzner et al. 2009). Macroelectrodes, either implanted subdurally to record ECoG or fixed extracranially to record surface EEG, offer another less risky alternative for EBMI since they are less- or noninvasive (Wolpaw et al. 2002; McFarland et al. 2005; Thongpang et al. 2011).

Historically, work in efferent BMIs (EBMIs) is more recent than ABMIs. The first EBMI dates back to the pioneering work of Fetz (1969) and was based on a single-neuron recording from a monkey’s precentral “motor” cortex. In this setting, the BMI was a single-input/single-output (SISO) system where the firing rate of a single neuron was integrated over small time intervals and used to control an illuminated meter whose pointer deflection was proportional to the activity integrator’s output. The animal had to volitionally modulate the firing rate of the selected neuron in order to bring the meter to a predetermined

threshold for reward. This operant conditioning paradigm constitutes the first proof of concept of an EBMI, though was not used to actuate any limbs. This approach has been extended in modern EBMIs to involve the simultaneous recording and use of hundreds of neurons that are subsequently transformed through a “decoding” filter to generate control signals that actuate multiple degrees of freedom (DOFs) (Hochberg et al. 2012). As such, these BMIs are considered multi-input/multi-output systems (MIMOs).

Cerebral BMIs

Another class of unidirectional BMIs – neither designed to directly cause sensation nor produce movements – is designed to stimulate neurons in the central nervous system to directly inhibit pathological behavior in subjects with neurological impairment. An example of such systems is deep brain stimulators (DBS), in which an electrode array is implanted in the subthalamic nucleus (STN) of a Parkinsonian patient, and macrostimulation of the STN through a few electrode leads ameliorates the disease symptoms by reducing bradykinesia and tremor (Coffey 2009). Similar designs are intended to regulate mood disorders (Mayberg et al. 2005; Hajcak et al.

2010) or abate epileptic seizures (Theodore and Fisher 2007; Halpern et al. 2008; Boon et al. 2009; Jones 2010).

Bidirectional BMIs

Bidirectional – or sometimes referred to as “recurrent” – BMIs differ from unidirectional BMIs in that neural measurements are used in the input to the transform to compute stimulation parameters *in real time*. As such, they are considered “closed loop” compared to unidirectional BMIs that are “open loop.” This specific feature allows stimulation to be dynamic and to follow the dynamics of the neural input to the transform, which may be volitionally modulated by the subject in certain applications (Fig. 4).

Sensorimotor BMIs

This class of bidirectional BMIs combines recording and stimulation to restore one or more functions. For example, motor signals can be recorded from cortical areas and used to directly control muscle contraction or hand grasp via FES (Moritz et al. 2008; Ethier et al. 2012). These signals can also be used to stimulate the spinal cord below the injury site using parameters extracted from cortical signals in real time (Harkema et al. 2011; Moritz et al. 2007; Shanechi et al. 2014) or via stimulation of peripheral nerves (Navarro et al. 2005; Micera and Navarro 2009). In that respect, this is a class of bidirectional BMIs that restores motor function through FES.

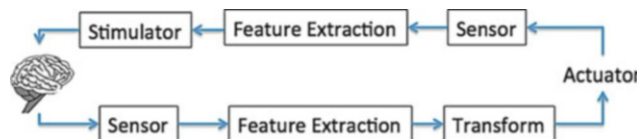
Another class of bidirectional BMIs combines efferent and afferent BMIs to restore movements as well as sensory feedback in the form of touch and proprioception. The importance of such

design is the indispensable role that somatosensation plays in the integration and coordination of limb movements, particularly for complex upper limb functions such as reaching and grasping. There is debate over which site(s) to stimulate to restore somatosensory feedback, but the majority of approaches have focused on stimulation of peripheral nerves (Raspovic et al. 2014). Peripheral stimulation, however, is not feasible in patients with spinal cord injury (SCI). Recent reports devised protocols for these patients based on subcortical (Daly et al. 2012; Liu et al. 2011) or cortical stimulation (Berg et al. 2013; Tabot et al. 2013).

A third class of bidirectional BMIs aims to induce plastic changes in neural circuits by using patterns of activity recorded from one brain site to stimulate activity in another distal brain site in real time (Jackson et al. 2006). Key to induce this plasticity is to ensure stimulation is delivered within a few milliseconds of recording spike events so as to promote LTP and LTD of synaptic connections, consistent with Hebbian plasticity (Hebb 1949). It is contended that this type of plasticity triggers functional as well as structural changes in the targeted neural circuits (Lucas and Fetz 2009); the longevity of this plasticity, however, is yet to be demonstrated, since neurons return to their original encoding properties shortly after stimulation is terminated.

Cognitive BMIs

Certain brain areas have specific cytoarchitectonic architecture with known role in cognitive functions, such as the hippocampus role in the formation and maintenance of long-term episodic memory (Bliss and Collingridge 1993). This knowledge is critical to the ability to restore



Brain-Machine Interface: Overview, Fig. 4 Basic elements of a bidirectional – or recurrent – BMI. Neural activity is read out to control an actuator. In turn, changes in the actuator state are measured and used to provide

information back to the nervous system through stimulation patterns of relevant areas in the peripheral nerve, the spinal cord, or the brain

inter-areal as well as intra-areal information exchange by means of artificial devices. In this setting, neural activity is recorded from one upstream region (e.g., hippocampus CA3) known to provide feedforward information to downstream regions (e.g., CA1) (Yeckel and Berger 1990). When the communication between the two regions is disrupted due to malfunctioning neural tissue, eventually causing memory loss, activity recorded from CA3 is “decoded” to predict the input to the CA1 region. The BMI then uses this prediction to derive the stimulation patterns needed to evoke biomimetic activity at the output of the CA1 region. Thus, the transform model in this BMI design lumps both a “decoder” of the input neural activity in CA3 and an “encoder” of the patterns to be evoked in CA1 through stimulation in one block (Song et al. 2007).

Bidirectional BMIs for Neurological Disorders

This class of BMIs extends cerebral BMIs to include a closed loop design that records neural activity and uses features extracted from this recordings to dynamically adjust stimulation patterns in real time (Rosin et al. 2011) (Carlson et al. 2013; Afshar et al. 2012). A similar approach is used to reduce or prevent seizures from occurring in drug-resistant epileptic patients (Nagel and Najm 2009) (Morrell and RNS System in Epilepsy Study Group 2011). This strategy is more advantageous compared to resection of the parts of the brain where hypothesized epileptic foci reside, which has been the standard clinical treatment for many years. Other examples use a similar concept to treat brain injury or psychiatric diseases, such as traumatic brain injury (Schiff et al. 2007), major depression (Malone et al. 2009), obsessive compulsive disorders (Goodman et al. 2010), among others (Mohr 2008).

The Computing Device

A key element in BMI design is the computational capability of the device and the corresponding number of inputs and outputs. For example, in SISO BMIs, computations can be as simple as

the detection of APs presence in a noisy electrode recording followed by a spike count within a fixed time interval (usually 50 ms). They can also consist of complex time varying (Kalman 1965) – and sometimes nonlinear (Hampson et al. 2013) – transformation of multiple electrode recordings in MIMO BMIs. EBMIs in particular are designed to have the decoder extract neural features (typically the firing rate of individual cells) to determine the “state” of the population. Because this state varies in time, it can be described by a “trajectory” in a neural state space (Oweiss 2010; Badreldin et al. 2013; Churchland et al. 2012). The transform then filters this state to reduce its dimension to a smaller number of variables that can be subsequently used to control the actuator (Gilja et al. 2012). As such, the subject is required to learn this transformation with extended practice.

Likewise, in ABMIs, the computing device extracts features from signals measured in the outside world to influence the “trajectory” of the stimulation parameter(s) in a stimulation parameter space. Because the mapping between the trajectory of natural stimuli in the task space and the evoked response in the neural state space – which is typically of much higher dimension – is unknown, methods for finding the “best” stimulation strategies in “open loop” BMIs are far from optimal. As such, the experimenter/clinician assumes the role of finding an optimal “tune-up” of stimulation parameters to restore a specific function by trial and error. For example, stimulation parameters (e.g., pulse frequency) in DBS systems are manually adjusted to fit each patient and reduce tremor (Kuncel et al. 2006). The lack of selectivity of electrical stimulation and the absence of knowledge of the dynamics of the neural circuits affected by stimulation, however, make this approach a real challenge. As such, characterizing the dynamics of stimulation-evoked neural activity in upstream or downstream circuits becomes important in order to optimize the stimulation “dose” for restoring a desired function and to minimize any side effects over the long term (Liu et al. 2010, 2011; Kuncel et al. 2008). Thus, studying the neural system being stimulated by an artificial device may offer advantages in clinical BMI applications.

Cross-References

- [Auditory Prosthesis](#)
- [Cortical Motor Prosthesis](#)
- [Decoding Field Potentials](#)
- [Deep Brain Stimulation \(Models, Theory, Techniques\): Overview](#)
- [Hippocampal Memory Prosthesis](#)
- [Memory Decoding Model](#)
- [Neural Decoding](#)
- [Noninvasive Brain-Computer Interfaces](#)
- [Recurrent Brain-Computer Interfaces](#)
- [Somatosensory Prosthesis](#)
- [Vestibular Prosthesis, Interface](#)
- [Vision Prosthesis](#)

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Brain-Scale Networks: Overview

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Definition

The brain is composed of many neurons, functional areas, and layers. Together these components work as a network to produce behavior. At minimum, the network behavior is determined by four things: (1) the network inputs, (2) the dynamics of the individual nodes, (3) the coupling functions between the nodes, and (4) the topology. This encyclopedia section will provide a brief overview on characterizing brain-scale networks. Often the coupled system will have emergent behaviors, behaviors that could not be predicted from analysis of the individual components alone. Understanding how the brain functions requires an understanding of how components work together in a network. In many diseases the cause cannot be pinpointed to dysfunction or

failure of a single component, such as an ion channel mutation. Instead, subtle changes in cellular behavior may lead homeostatic mechanisms to alter the coupling between the neurons and brain areas, resulting in pathological activity such as synchronous population oscillations or unchecked excitability. The ultimate goal in applying the network theory to understanding connections within the brain is to develop a measure that can explain the emergence of pathological behaviors and to perhaps develop approaches to treating diseases.

But first, we will introduce a few common terms. A **network** is a collection of coupled components. Generally, when the components coupled together are different elements, it is referred to as a **system**. If the components of the system are similar and interchangeable, it is instead called a **network**. The components in the network are referred to as **nodes**, which can be individual neurons or brain regions. The coupling between the nodes is referred to as **edges**, which can be synapses or fiber paths. Coupling in the nervous system is generally through chemical synapses which are **directional**, where the coupling of neuron or region A onto B will be different than B onto A. However, for networks of neurons coupled through electrical synapses, the coupling can be undirected. Networks are considered **weighted** if the strengths of coupling between nodes have a distribution and **unweighted** if they are all the same.

Generally, the dynamics of the nodes and coupling function are highly nonlinear. A **linear response** is defined as given twice the input, the output will be twice as strong. However, because neurons have thresholds and synapses are plastic, the responses are very nonlinear. Furthermore, neurons are a mixture of **deterministic** behavior, where its behavior can be determined from its past and its inputs, and **stochastic**, where the activity is also due to some noise in the system which cannot be accounted for.

The statistics of the coupling within a network is called the **topology**. A list of all the connections within a network is called the **graph**. If nodes have a physical location in space, such as brain regions, and coupling is dependent on the

distance, the network is considered to have a **geometry**.

In summary, neuronal networks are nonlinear, directional weighted graphs with a geometry. These networks are called complex networks, and few tools have been developed to analyze them. The development of these network analysis tools is at the cutting edge.

Detailed Description

The goal of these encyclopedia entries is to provide an introduction into the network theory. In the first entry (► [“Network Theory in Neuroscience”](#)), there is an overview of the network theory and its applications to diseases. In ► [“Functional Network Observations of Diseased Brain States,”](#) there is an introduction to functional networks in neuroscience. In ► [“Determining Network Structure from Data: Nonlinear Modeling Methods,”](#) we will introduce methods for reconstructing networks from the data using nonlinear measures. In ► [“Master Stability Function for Globally Synchronized Systems,”](#) we introduce a universal approach to determining if a network will synchronize given the dynamics of the individual components and the network topology, through the analysis of the master stability function. In ► [“Connectionist Models of CPG Networks,”](#) we will provide an introduction to non-synchronous network behaviors, such as seen in central pattern generators. In ► [“Neuropathologies and Networks,”](#) we will introduce pathological network function to characterize diseases.

Cross-References

- [Connectionist Models of CPG Networks](#)
- [Determining Network Structure from Data: Nonlinear Modeling Methods](#)
- [Functional Network Observations of Diseased Brain States](#)
- [Master Stability Function for Globally Synchronized Systems](#)
- [Network Theory in Neuroscience](#)
- [Neuropathologies and Networks](#)

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Brainstem Processing: Overview

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Detailed Description

The brainstem has received considerably less attention by computational neuroscientists than other regions of the mammalian brain. This section highlights key areas that have received attention: neural circuitry underlying the generation and control of the respiratory rhythm, the baroreflex underlying the regulation of blood pressure, and pathways for pain processing. Entries in this section cover all three of these areas.

The article titled ► [“Baroreflex Models”](#) reviews over two decades years of computational models focused on neural pathways where blood flows in response to pressure changes in the circulatory system mediated by the baroreflex pathway.

Much attention has been given to the modeling of respiratory rhythm generation. The generation

and control of breathing is covered by two entries in this section. The entry titled ► [“Pre-Botzinger Complex Rhythm Generation”](#) surveys computational models of rhythmic activity in the pre-Bötzinger complex, which underlies the inspiratory component of respiratory rhythm generation and is a central pattern-generating circuit itself when isolated. The article titled ► [“Control of Breathing, Integration of Adaptive Reflexes”](#) describes computational models of adaptation and plasticity of the respiratory rhythm in response to external perturbations. There are also relevant articles in other sections of this encyclopedia, including ► [“Computational Models of Mammalian Respiratory CPG”](#) and ► [“Brainstem Motoneurons, Models of”](#).

The area of pain processing has received much less attention by computational neuroscientists. The article titled ► [“Pain Processing Pathway Models”](#) summarizes computational efforts in this area.

Cross-References

- [Baroreflex Models](#)
- [Brainstem Motoneurons, Models of](#)
- [Computational Models of Mammalian Respiratory CPG](#)
- [Control of Breathing, Integration of Adaptive Reflexes](#)
- [Pain Processing Pathway Models](#)
- [Pre-Botzinger Complex Rhythm Generation](#)

Cable Theory: Overview

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Detailed Description

Cable theory has a prominent place in neuroscience as it forms the basis of models of single neurons, axons, and dendrites and has led to an

understanding of intraneuronal signaling. Starting with the conceptual model of a patch of membrane as an electric circuit, application of basic principles from physics leads to a mathematical equation, the cable equation. We start this section with an article on the cable equation, discussing the history of the cable equation in neuroscience, showing the derivation of the cable equation, providing solutions for the infinite cylinder, steady-state solutions for semi-infinite and finite cables and branched dendritic trees and transient solutions, concluding with a discussion of insights from cable theory. Several parameters play key roles in intraneuronal signaling including membrane capacitance, axial resistivity, the space (length) constant, and the time constant, and there are articles on each of these topics. From there we have two articles describing work done by Wilfrid Rall, widely regarded as the father of computational neuroscience. The first describes how Rall applied cable theory to dendritic trees and showed that given certain conditions a highly branched dendritic tree could be reduced mathematically to an equivalent cylinder. The simplicity and elegance of the equivalent cylinder model permitted mathematical analyses and insights regarding signaling in otherwise morphologically complex dendritic trees. The second describes various formulas Rall derived to estimate the electrotonic length of dendritic trees from simple voltage transients, formulas that have been applied in hundreds of studies. Finally, there are three articles that discuss extensions of cable theory in various ways. The first presents the morphoelectrotonic transform, a procedure that addresses the issue that attenuation of voltage from a synaptic input from the dendrite to the soma is not simply given by the electrotonic distance because of the effect of boundary conditions. The morphoelectrotonic transform provides a graphical means to visualize voltage attenuation both toward the soma and away from the soma, directly and intuitively. The second introduces the continuum theory for modeling dendritic spines. While there are various ways to incorporate the effect of dendritic spines in models, the continuum theory describes a novel way of doing this within the cable equation. Lastly, insights can be obtained from the

quasi-active approximation of a nonlinear cable. Here classic passive cable theory is extended by linearizing voltage-dependent conductances around a given membrane potential cable allowing the effect of voltage-dependent conductances on dendritic filtering to be studied mathematically. Almost all of these articles assume membrane is passive, but it is clear that both dendrites and axons contain voltage-dependent conductances. Nevertheless, cable theory is important for providing a basic understanding of intraneuronal signaling that forms the basis for understanding what happens with active conductances.

Cross-References

- ▶ [Cable Equation](#)
- ▶ [Capacitance, Membrane](#)
- ▶ [Dendritic Spines: Continuum Theory](#)
- ▶ [Electrotonic Length, Formulas and Estimates](#)
- ▶ [Equivalent Cylinder Model \(Rall\)](#)
- ▶ [Morphoelectrotonic Transform](#)
- ▶ [Quasi-active Approximation of Nonlinear Dendritic Cables](#)
- ▶ [Resistivity, Axial](#)
- ▶ [Space \(Length\) Constant, Lambda, in Neuronal Signaling](#)
- ▶ [Time Constant, Tau, in Neuronal Signaling](#)

Cerebellum: Overview

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Definition

The cerebellum processes sensory and motor information. Structurally is divided in the cerebellar cortex network and the deep cerebellar nuclei. Inputs to the cerebellar cortex arrive via the mossy fibers from multiple sources; mossy fibers contact granule cells, Golgi cells and unipolar brush cells. The second input to the cerebellar cortex comes

from the inferior olive in the form of climbing fibers that synapse Purkinje cells. The output of the cerebellar cortex is provided by Purkinje cells that integrate the synaptic activity of climbing fibers, granule cells, and inhibitory interneurons. Golgi cells provide an inhibitory feedback mechanism to the granule cell layer. The deep cerebellar nuclei are the final integrator of cerebellar information. Cells in the deep cerebellar nuclei receive input from Purkinje cells, mossy fibers and climbing fibers.

Detailed Description

Cerebellar Cortex

The widely studied cerebellar cortex is composed, mainly, of four types of neurons: Granule cells, Purkinje cells, inhibitory interneurons (stellate and basket), and Golgi cells. There are two inputs to the cerebellar cortex provided by mossy fibers and climbing fibers. Climbing fibers are axons from inferior olivary neurons. Mossy fibers are a collection of axons from multiple areas that can carry direct sensory or cerebro cortical information. The arrangement of the cerebellar cortical neurons is regular across the cortex. Mossy fibers contact granule cells and Golgi cells. Granule cells send an axon into the molecular layer that bifurcates. The bundle of bifurcated axons is known as the parallel fibers. Parallel fibers contact Golgi cells, inhibitory interneurons and Purkinje cells as they traverse the cerebellar cortex. Climbing fibers synapse onto Purkinje cells.

The particular arrangement of granule cell-to-Purkinje cell connectivity was very attractive to computational scientist early on. The ‘Beam Hypothesis’ stated that a focal stimulation of the granule cells would be transformed into a sequential activation of Purkinje cells along the path of the parallel fibers (Braitenberg and Atwood 1958). The evoked inhibitory activity from parallel fiber to inhibitory interneurons would reduce the activity of the Purkinje cells on either side of the beam of activated Purkinje cells. The feedback mechanism provided by Golgi cells on to granule cells would then reduce over-excitability. The central mechanism of information processing in

this model is the existence of a beam of activated Purkinje cells following the local stimulation of granule cells.

The lack of beams of Purkinje cell activity reported by multiple teams over the years has prompted a discussion on how the cerebellar cortex processes information. Several reports have shown that Purkinje cells are activated only when they are directly above the cluster of stimulated granule cells. The Purkinje cells along the parallel fiber path are either inhibited or show no change in firing rate. Experimental and computational evidence has shown that this is due to fast feed-forward inhibition from the inhibitory interneuron on Purkinje cells concomitantly stimulated by parallel fibers. In fact, blocking of inhibition reveals a beam of Purkinje cell activity as predicted by the Beam Hypothesis (Santamaria et al. 2007). Thus, the emergent understanding is not that different from a center surround receptive field model. Under this perspective, granule cell synapses are effective in driving Purkinje cells to fire only when the Purkinje cells are close to the site of stimulation. Parallel fibers provide excitatory and feed forward inhibitory input to Purkinje cells far from the site of stimulation without this stimulation being reflected in changes of the Purkinje cell firing rate. However, the dendritic stimulation results in activation of voltage sensitive calcium channels and calcium activated potassium channels, modifying the excitability of the dendrite. This dendritic activation can then modify the response of the Purkinje cell to direct granule cell stimulation. Therefore, the long range effect of parallel fibers is to provide contextual information.

The Purkinje cell was one of the first neurons to be studied using the compartmental modeling approach. The large amount of information on somatic and dendritic conductances permitted to develop detailed compartmental models. These models have been reused and enhanced over the years to study different aspects of cerebellar function (De Schutter and Bower 1994; Steuber et al. 2007). There are also several models of inhibitory interneurons, Golgi cells and granule cells. Recent work suggests that the Purkinje cell might be simplified to a perceptron (Clopath et al. 2012).

Synaptic Plasticity

Long term depression (LTD) in the parallel fiber-to-Purkinje cell synapses is a model of learning and memory (Ito 2006; Feil et al. 2003). LTD is induced by the concomitant activation of the climbing fiber input and stimulation of a small bundle of parallel fibers. It is widely assumed that the climbing fiber stimuli carries a training or error signal, while the encoding signals, e.g., motor command, is encoded in the parallel fiber activity. The biochemical transduction cascade is very well understood and has been modeled using mass action and Monte Carlo models (Doi et al. 2005). These models and their experimental tests have pointed out to positive feedback biochemical loop that triggers and sustains LTD. Briefly, LTD is induced by the influx of calcium ions through voltage sensitive channels and release from intracellular stores. Calcium ions activate protein kinase C (PKC) which eventually activates mitogen associated protein kinase (MAPK). MAPK interacts with other substrates to produce arachidonic acid which in return activates more PKC. PKC then continues working in the feedback loop or phosphorylate AMPA receptors. Phosphorylated AMPA receptors are then internalized and the synaptic strength is reduced. The activation of the feedback loop is not a linear integrator of calcium concentration, instead it acts as a leaky integrator, thus the total amount and the temporal release of calcium determines the expression of LTD (Tanaka et al. 2007; Xia et al. 2000).

Other Cells in the Cerebellar Cortex

There are other types of cells not traditionally included in cerebellar models. Lugaro cells are interneurons that are located in the granule cell layer (Lainé and Axelrad 1996). These neurons receive input from Purkinje cells and could be connected among themselves with gap junctions. These cells seem to be inhibitory and hypothesized to work in the burst frequency response of the granule cell layer. Another type of neuron,

primarily located in the vestibulo cerebellum, is the unipolar brush cell. These cells receive inhibitory inputs from Golgi cells and excitatory inputs from mossy fibers. Unipolar brush cells have multiple excitatory targets in the granule cell layer (Mugnaini and Floris 1994).

The Deep Cerebellar Nuclei

The deep cerebellar nuclei (DCN – dentate, interpositus, and fastigii) receive inhibitory inputs from Purkinje cells and excitatory activity from mossy fibers and climbing fibers. The cell from the cerebellar nuclei generates the bundles of axons that go to other areas of the brain. The cells of the DCN can be thought as the final and global integrator of the input and output signals to the cerebellum. DCN cells integrate inputs from the brain stem, inferior olive, and spinal cord with the Purkinje cell output from the cerebellar cortex. There are excitatory and inhibitory DCN neurons with their electrophysiological and computational contributions still being studied. The precise spike timing control of DCN spiking by Purkinje cell is believed to be the mechanism of the precise motor skills (Gauck and Jaeger 2000).

Summary

Although the function of the cerebellum is still being debated, how it processes information is becoming clearer due to vast amount of experimental information from ultra-structure to electrophysiology and behavior. Altogether, this large amount of data allows computational scientist to build realistic models at different levels of detail that can be experimentally tested.

Cross-References

- [Deep Cerebellar Nuclei](#)
- [Long Term Depression in the Granule Cell-Purkinje Cell Synapse](#)

- [Modeling Cerebellar Learning: Input Minimization](#)
- [Multiscale Modeling of Purkinje Cells](#)
- [Olivocerebellar Pathway](#)

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Computational Neuroanatomy: Overview

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Definition

Computational neuroanatomy is a subfield of neuroscience that aims to create functionally and structurally accurate models of the nervous system. These models are based on a wide range of input data, including microscopy and electrophysiology. These data acquisition methods encompass the broad scales across which neuroanatomy plays a role: (1) nanostructure describing individual connections between cells, (2) microstructure describing neuronal shape and cell type, and (3) gross structure describing cross-brain connectivity patterns. Computing in this field draws largely from the need to synthesize multiple modalities to statistically generate accurate models of morphology. For example, properties such as morphological structure, connection topology, wiring principles, and growth rules are statistically drawn from multiple sources and combined into motifs representing large-scale connectivity. High-performance computing can then be leveraged to simulate and verify the resulting models, with the end goal of studying neural behavior in silico.

Detailed Description

Computational neuroanatomy deals with the development of structural and functional models

of the nervous system. The structural data forming the basis for these models are collected across multiple scales using a variety of data-acquisition and imaging modalities. Electron microscopy is used to acquire ultrastructural information of synapses, axon terminals, and dendritic spines at the nanometer scale. Advances in serial sectioning electron microscopy have enabled the investigation of whole neurons at this scale, with large-scale efforts focused on three-dimensional reconstruction. Optical microscopy (bright field and fluorescence) is often leveraged at the micrometer scale to study neuronal morphology, local circuits, and long-range projections. Both physical and optical sectioning is routinely used to obtain 3D volume data. Magnetic resonance imaging (MRI) and other noninvasive techniques are frequently employed for mapping cortical areas, major nuclei and fiber tracts, as well as functional data across the entire brain network.

Topics of study in computational neuroanatomy focus largely on model reconstruction and generation. This includes data mining from multimodal images using segmentation algorithms, morphometry, and statistics. This raw reconstructed data must also be analyzed to establish fundamental rules for constructing viable large-scale models. This requires topological analysis (small world, scale-free, etc.), growth and development models, organizational and optimization principles (e.g., wiring length minimization, self-organization, etc.), representation and ontology, and neuroinformatics. In addition, tools must be designed to enable viable exploration of neuroanatomical structures across multiple scale, integrating visualization, and comparative analysis. One of the major goals of comparative tools is the study of diseased versus healthy neuroanatomy, as well as inferring function from structure. Early studies in computational neuroanatomy, especially at the cellular level, were strongly motivated by the need for morphologically detailed multicompartmental models for use in neuron simulators such as NEURON (Carnevale and

Hines 2006), GENESIS (Bower and Beeman 2012), and others (Ascoli 2002).

Overview of Chapters

The computational neuroanatomy section features chapters that touch upon the topics listed above. The chapters can be roughly grouped into four categories: (1) brain atlases and the connectome, (2) imaging, (3) geometric reconstruction, and (4) wiring principles and synthetic models.

The first group includes four chapters: (1) ► [“Brain Atlases,”](#) a collection of pointers to other chapters that describe in detail available brain atlases; (2) ► [“Connectome, *Drosophila*,”](#) a chapter with a detailed survey of the known partial connectomes of the *Drosophila*, with perspectives on the utility, progress, and future of *Drosophila* connectome research; (3) ► [“Connectome, Mouse,”](#) with a survey of publicly available mouse connectome data; and (4) ► [“Connectome, General,”](#) a general survey of connectomics, its potentials, and its challenges.

The second group includes imaging related chapters: (1) ► [“Imaging, Electron Microscopy”](#) discusses the use of electron microscopy for computational neuroanatomy, and (2) ► [“Imaging, Specimen Preparation”](#) presents methods for brain specimen preparation for subsequent sectioning and imaging. (There are other imaging modalities that are relevant to computational neuroanatomy such as ► [“Physical Sectioning Microscopy”](#) and others discussed in the Brain Imaging section.)

The third group of chapters includes reconstruction algorithms for the extraction of geometrical information from the raw image volumes: (1) ► [“Reconstruction, Electron Microscopy”](#) discusses reconstruction techniques for densely packed neurons in electron microscopy image stacks; and (2) ► [“Reconstruction, Techniques and Validation”](#) talks about general reconstruction methods and validation techniques.

Finally, the fourth group of chapters consists of theoretical insights and computational simulation methods that analyze and utilize the quantified neuroanatomical data: (1) [Networks/Networks](#) discusses various methods for automated

generation of realistic neurons and neuronal circuits for use in computer simulations (also see ► [“NeuroMorpho.org”](#)); and (2) ► [“Wiring Principles, Optimization”](#) presents optimization principles that could potentially be underlying neuronal morphology and connectivity patterns found in the brain.

Other Related Chapters and Resources

There are several chapters beyond this section (and sometimes whole sections) in this encyclopedia that are directly relevant to computational neuroanatomy: (1) Brain Imaging (► [“Connectivity Analysis in Normal and Pathological Brains,”](#) ► [“Multiscale Brain Connectivity”](#)), (2) Brain Scale Networks (► [“Network Theory in Neuroscience,”](#) ► [“Neuropathologies and Networks”](#)), (3) Databases in Computational Neuroscience (► [“NeuroMorpho.org”](#) and many other chapters in this section are relevant), and (4) Model Reproducibility (► [“NeuroML”](#)).

Also see the following edited books and monographs on computational neuroanatomy: (Ascoli 2002; Capowski 2012; Chung 2013).

Notable omissions at the moment include (1) dendritic spine morphology and statistics (Bourne and Harris 2008), (2) delay (axonal conduction delay and integration time) and delay statistics (Lamme and Roelfsema 2000; Nowak and Bullier 1997), and (3) how to utilize gene expression data combined with structural information to infer function (Toledo-Rodriguez et al. 2004).

Conclusion

Computational neuroanatomy provides the foundational framework for building, quantifying, and visualizing comprehensive models of large neurological tissues. These models form the foundation for understanding neural computation by providing the ability to validate hypotheses in silico as well as compare networks for the study of aging and neurodegenerative diseases. Computational neuroanatomy also forms the backbone of connectomics (Sporns et al. 2005), enabling the eventual understanding, replication, and repair of neurological tissues.

Cross-References

- ▶ [Brain Atlases](#)
- ▶ [Connectivity Analysis in Normal and Pathological Brains](#)
- ▶ [Connectome, *Drosophila*](#)
- ▶ [Connectome, Mouse](#)
- ▶ [GENESIS, the GENeral NEural SIMulation System](#)
- ▶ [Imaging, Electron Microscopy](#)
- ▶ [Imaging, Specimen Preparation](#)
- ▶ [Multiscale Brain Connectivity](#)
- ▶ [Network Theory in Neuroscience](#)
- ▶ [NeuroML](#)
- ▶ [NeuroMorpho.org](#)
- ▶ [NEURON Simulation Environment](#)
- ▶ [Neuropathologies and Networks](#)
- ▶ [Physical Sectioning Microscopy](#)
- ▶ [Reconstruction, Electron Microscopy](#)
- ▶ [Reconstruction, Techniques and Validation](#)
- ▶ [Wiring Principles, Optimization](#)

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Cortex: Overview

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Detailed Description

Anatomically, the cerebral cortex is the outermost neuronal tissue of the brain, and it is believed to play a key role in sensation, perception, higher cognitive functions, and motor control. It is a layered structure referred to as the gray matter, because it contains largely cell bodies as compared to the white matter containing largely myelinated axons. The evolutionary origin can be traced back to reptiles, but it first appeared as a uniform structure in early mammals. The increase in the size of this layered cortical sheet during evolution is believed to be crucial for the development of human cognition and ultimately human culture during human brain evolution. Even though many entries in this section on “Cortex: Models and Computation” are applicable to the **[hippocampus]** as well, the focus is on the phylogenetically younger six-layered neocortex.

Why is it so interesting and important to investigate the cortex using modeling? If the co-occurrence of the expansion of the neocortex during evolution of the emergence of human cognition and culture is more than a suspicious coincident, then understanding the cortex is essential to understand the human condition. Identifying brain and mind is certainly a too naïve approach, but it is now widely accepted that – whatever the relation between mind and brain is – an understanding of cortex will at least constrain theories of how the mind works. Testable theories and predictive models are needed to complement conceptual modeling and colloquial talk on that matter. Moreover, understanding how the cortex operates may help to diagnose neurological diseases earlier, to develop more efficient treatments,

and to construct **[brain-machine interfaces]**. Models in general, and patient-specific models in particular, will be useful to link measurements of macroscopic brain activity obtained with brain imaging techniques to the underlying causes. This rather practical justification for modeling cortex is becoming even more relevant today as a “deliverable” of computational neuroscience. However, accurate and faithful modeling has to deal with the complexity of the neural circuits and the cellular and synaptic heterogeneity. Multiple large-scale initiatives currently address this by collecting massive amounts of data to facilitate the development of faithful models of the cortex. Here, the role of cortical models is in organizing and summarizing the data, and they could even be integrated into (semi)automatic data-driven modeling pipelines with little intervention of a “modeler.” I argue that modeling cortex is interesting and exciting, because despite massive amounts of available data, the activity of modeling will remain in large parts an art: Finding the right level of abstraction to arrive at insights for the question at hand can hardly be automated.

On the one hand, the neocortex is an umbrella for a set of distinct structures that differ, for example, in terms of their function, connectivity, and cytoarchitecture. On the other hand, Mountcastle (1978) suggested that similarities of these neocortical regions point to a common computational machinery in the sense that each region has the same basic architecture and operates according to the same computational principles. This is also the guiding idea of this section, without accepting it as a truism or dogma. It is indeed conceivable that different regions of the neocortex operate according to fundamentally different principles, or that conventional notions of “computation” are not suited as a metaphor to understand the cortex. The philosophy of science is not conclusive regarding a clear distinction of theory vs. model. However, as a tentative distinction for modeling cortex, we may adopt the short-hand definition that theory provides meaning to models, while models explain data.

Computational principles come close to the notion of a theory. With that reading, the entries assembled in this section cover the whole spectrum between theories and models of cortex.

Robert Legenstein (► [“Recurrent Network Models, Reservoir Computing”](#)) summarizes the state of the art in how artificial recurrent neural networks (RNNs) address demanding learning tasks. RNN researchers can be thought of as being in the luxurious position to investigate computations in cortex-inspired architectures without the burden to comply with all the constraints set by experimental neuroscience. The performance of these architectures and learning algorithms can serve as a yardstick for existing biologically more faithful models and as a guideline for constructing new models. Jochen Triesch’s contribution on ► [“Cortical Function, Normative Models of”](#) gives a bird’s eye perspective on how to derive models from computational principles. Cortical modeling involves determining model structure and parameterization, and for data-driven approaches, computational neuroscience has developed a **[rich repertoire of methods]**. The normative approach endorsed by Triesch is a complementary addition for doing this, which applies in particular to explaining cortical networks in terms of their genesis via **[learning mechanisms]**. The contributions of Sophie Deneve (► [“Bayesian Inference with Spiking Neurons”](#)) and Walter Senn and Jean-Pascal Pfister (► [“Reinforcement Learning in Cortical Networks”](#)) are instances of this normative approach. Deneve shows how Bayesian inference can be carried out by spiking neurons. The Bayesian approach turned out to be very fruitful for understanding computations in the cortex as evident by a whole section in this encyclopedia being dedicated to the **[“Bayesian brain”]**. It should be noted that both Deneve’s and Senn’s and Pfister’s entries explicitly address computation with spiking neurons and thus represent an explicit formal link between computational principles and experimentally testable predictions at the level of individual neurons. Both of these

mutually compatible approaches make explicit a notion of optimality as required within the normative approach: The Bayesian approach is based on a principled way of conducting logical inference under uncertainty, whereas reinforcement learning is based on Bellman optimality, i.e., **[decision making]** in dynamic and often only partially observable environments.

In a similar way, Udo Ernst (► **“Center-Surround Processing, Computational Role of”**) addresses the phenomenon of center-surround processing (CSP) from a computational point of view. Even though CSP has been investigated mainly in the visual system, where it is exemplified, e.g., by the phenomenon of end stopping already described by Hubel and Wiesen (Hubel and Wiesel 1965), it is also a candidate for a canonical cortical computation to be found in various cortical regions. Ernst links CSP to the laws formulated by Gestalt psychologists in the early twentieth century but also to modern normative approaches that utilize the statistics of natural visual scenes in explaining physiological and perceptual phenomena. He points out that CSP has been successfully implemented in **[cortex-inspired artificial vision systems]**, where it improved object detection and recognition of natural scenes. Such real-world tests of cortical models are excellent yardsticks modelers may want to consider in addition to reproducing physiological or perceptual phenomena that are usually observed in rather artificial laboratory settings with less naturalistic stimuli. Michael Spratling (► **“Predictive Coding”**) reviews the concept of predictive coding. This is an instance of a theory (in the sense defined above), but models derived from this theory can predict CSP as a by-product. The distinctive feature of predictive coding is that downstream areas in the hierarchically organized cortex continuously predict activity in areas at a lower level of the hierarchy. Given that downstream areas in sensory cortices integrate signals from neuronal populations with adjacent receptive fields (RFs), the predictions carry not only information about anticipated future inputs but also from the

neighboring RFs as in CSP. Models derived from predictive coding are candidates for a canonical cortical computation. Applications to sensory cortices may be relatively straightforward, but the crucial test for a theory is its predictions when extrapolated beyond the *postdoc* explanations of already known phenomena. Let me point out three selected such extrapolations: First, it has been applied to explain mirror neuron activity as the natural consequence of predictive coding in the hierarchically organized “social brain” (Kilner et al. 2007). Second, it has been applied to interoception from which predictions about bodily self-consciousness could be derived (Seth et al. 2011). Third, it has been suggested that it may also be applicable to the **[motor system]** with the surprising consequence that the actual motor acts are carried out to fulfill predictions about sensory consequences of just these acts (Hawkins and Blakeslee 2004) as compared to being only the output stage of a sensory-to-motor transformation. Future experimental studies will need to further test these predictions. Interestingly, Spratling has shown that predictive coding and the concept of biased competition can be thought of as being just variants of the same mathematical model. Thus, while the interpretation of models derived from the predictive coding theory in terms of “prediction of inputs” may be unusual in some cases, as in the case of the motor system, the theory is still a rich framework to systematically derive mathematical models and testable predictions.

Computation cannot be considered in isolation. Communication engineers and designers of processors know this too well. Matthias Bethge (► **“Efficient Population Coding”**) considers how much information is communicated by cortical networks. Bethge introduces the psychometric and neurometric functions and highlights that the information contained in the spiking activity of populations of neurons is often enough to predict the behavioral responses of the whole organisms. This is an empirical finding, but computational neuroscience also needs to ask more fundamental questions such as “how

much information can be transmitted?” Only this allows for assessing how close to optimality the cortical circuits are actually operating. To address such questions, he reviews how the concepts of Fisher and Shannon’s mutual information can be applied to quantify the information content of population activity. Combining the approaches that focus on computation introduced so far with these studies of communication and information content could be a very fruitful direction for future studies, in particular when factoring in limitations due to fiber bottlenecks between cortical areas and energy expenditure.

RNNs are Turing-complete, which means that finite RNNs could, in principle, approximate any computation. However, to determine the computations actually performed by the cerebral networks, it is imperative to develop mechanistically plausible models that explicitly respect the anatomical and physiological constraints set by experimental neuroscience. Sean Hill (► [“Cortical Columns, Models of”](#)) presents models of the so-called cortical column, which itself is a theoretical concept motivated by early experimental studies that showed smooth variation of functional properties tangential to the cortical surface but an invariance across cortical layers at a given position. The notion of a cortical column remains controversial, but for computational neuroscience it is certainly a goal to deliver predictive mechanistic models of signal propagation across cortical layers within an area. Probably the most prominent example of mechanistic network modeling to explain a physiologically observed phenomenon is the models for orientation tuning in primary visual cortex (V1), which are reviewed by Nicholas Priebe and Benjamin Scholl (► [“Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling”](#)). Hubel and Wiesel discovered orientation tuning (Hubel and Wiesel 1959) and formulated a first model, namely, that the tuning derives from the pattern of afferent connections from the thalamus onto neurons in V1. The subsequently developed models emphasized the role of intracortical connections to account for experimentally observed properties of orientation tuning such as contrast

invariance. Interestingly, the original feedforward model by Hubel and Wiesel is still a guiding idea, even though it had to be refined. This highlights that such more informal and conceptual models remain valuable today, even though computational neuroscience has to show explicitly when and how models fail as reviewed by Priebe and Scholl.

In my first entrie (► [“Center-Surround Processing, Network Models of”](#)), I take a similar approach and address the question of how the CSP in V1, as introduced by Ernst, may be realized by cortical circuits. More specifically, I review network models of CSP that are distinct in terms of the assumed pathways. Early models emphasized the role of long-range connections within an area, but later models came to acknowledge the role of feedback from downstream areas. The cortical operating mode in vivo is characterized by strong recurrent excitation and balanced inhibition that affect how single neurons integrate and propagate signals (reviewed in my second short contribution ► [“Balanced State”](#)). Interestingly, more recent modeling studies investigated the role of short-range local connections in CSP and found that the properties of strongly connected recurrent networks in a balanced state need to be considered in models of CSP. Adaptation is another phenomenon that seems to be omnipresent in the cerebral cortex. Klaus Wimmer (► [“Adaptation in Sensory Cortices, Models of”](#)) reviews models of adaptation and considers both their role in perception and how plausible mechanisms such as short-term synaptic depression mediate them. Since strongly recurrent networks in a balanced state with static synaptic connections may already exhibit counterintuitive phenomena, Wimmer argues for systematic modeling studies of structured networks with adaptation mechanisms as an important approach to understand adaptation in sensory cortices.

Selected examples of higher cognitive functions are attention and working memory. Cortical models of these functions are reviewed by Philipp Schwedhelm and Stefan Treue (► [“Attentional Top-Down Modulation, Models of”](#)) and Gianluigi Mongillo (► [“Working Memory, Models of”](#)). Schwedhelm and Treue review

models of attentional top-down modulation. They highlight how phenomenological models have guided experiments and how those fed back into refining the models. Some of the models assume the mechanism of gain modulation but remain intentionally agnostic regarding the biophysical mechanisms. This exemplifies that cortical modeling with a properly chosen level of description could be integrated closely with experimental investigations. Working memory has also been studied experimentally in great detail, but most early network models of the persistent activity that is characteristic for the physiological correlate of working memory were variants of attractor networks, where a self-sustained “bump” of activity was identified with the content of working memory. Only more recent modeling studies suggested that self-sustained activity may not be restricted to the spiking activity of groups of neurons, because the state of synapses with short-term dynamics can also be considered as an activity variable that could be exploited to store self-sustained activity. The idea that synaptic variables, which are by multiple orders of magnitude more numerous than single cell state variables, may be crucial for cerebral information processing has been around in the computational neuroscience community for a long time. However, explicit formal models need to spell this out and show the potential benefit in, for example, systematic simulation studies even if the models are speculative and experimentally very hard to test as in the case of the synaptic theory of working memory. This also applies for models of attention: Given that after 50 years of the discovery of orientation tuning in V1, there is still no agreement on network models of even such a basal response property, it may not come as a surprise that the mechanisms of attention remain elusive. While, for example, mechanistic models of top-down gain modulation via synchronizing the discharges of inhibitory interneurons may be consistent with the available anatomical, physiological, and biophysical knowledge, recording multiple identified inhibitory interneurons in vivo in attentional demanding tasks remains to be achieved.

Another currently only poorly understood phenomenon is how the so-called resting state of the

brain is generated and maintained. Computational Neuroscience research has already identified the problem of explaining mechanistically the ongoing low-activity state in recurrently connected *local* networks (Brunel et al. 2013) and derived models to explain them as a stable attractor. Joana Cabral and Gustavo Deco (► “Spontaneous Activity, Models of”) review models of the *global* spontaneous activity that exhibits characteristic temporal properties and is found in the so-called default mode network. This activity (and the default mode network) has been studied intensively using functional magnetic resonance imaging (fMRI), but Cabral and Deco correctly point out that a deeper analysis of the network models is still needed to provide insights into the dynamical properties of the resting state.

The entries in this section cover computation and modeling of the cortex using different approaches and models at various levels of abstraction. Certainly, the cortex cannot be considered in isolation but needs to be modeled and understood in concert with other structures, such as the [thalamus] and [basal ganglia]. Will it be possible to understand cortex without modeling the whole brain or even closed sensory-motor loops within an “enactive” approach (Noe 2006) that states that to understand the brain – in our case, only the cortex – one needs to look at more than just the brain? This is indeed an open question that is of special interest for philosophers of science and mind. However, I argue that the cortex considered as a complex and self-assembled adaptive structure will remain a challenge for any kind of modeling conducted by Computational Neuroscientists who are open to empirical findings and brave enough to ignore irrelevant details without throwing out the baby with the bath water. The reward shall be motivating: to gain an insight into how the cortex works. Relevance and irrelevance of details needs to be decided on a case-by-case basis, which also depends on the taste of the modeler (or theoretician). Unfortunately, despite a multitude of models and some promising candidates for theories of cortical function, one needs to attest that we are not yet there: A unified theory of cortical computation with associated models still

needs to be derived *and* thoroughly tested. My own requirement for accepting such a theory is that it will cover at least the topics addressed by the entries in this section.

Cross-References

- [Adaptation in Sensory Cortices, Models of](#)
- [Attentional Top-Down Modulation, Models of](#)
- [Balanced State](#)
- [Bayesian Inference with Spiking Neurons](#)
- [Center-Surround Processing, Computational Role of](#)
- [Center-Surround Processing, Network Models of](#)
- [Cortical Columns, Models of](#)
- [Cortical Function, Normative Models of](#)
- [Efficient Population Coding](#)
- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [Predictive Coding](#)
- [Recurrent Network Models, Reservoir Computing](#)
- [Reinforcement Learning in Cortical Networks](#)
- [Spontaneous Activity, Models of](#)
- [Working Memory, Models of](#)

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Databases and Data Repositories in Computational Neuroscience: Overview

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Definition

Computational neuroscience research often produces models that help explain empirical data and provide predictions about the biological systems that produce the data. Empirical and theoretical researchers can benefit from resources that facilitate model publication and exchange and provide neuroscience data that informs and contains these existing and future models.

Detailed Description

Databases of Computational Models

One category of databases in computational neuroscience is those that focus on computational models. The BioModels Database (Li et al. 2010; Vijayalakshmi et al. 2013) is a general repository of computational models of biological processes that includes some models from neuroscience. The SenseLab database, ► [“ModelDB”](#) (Migliore et al. 2003), provides a resource for published neuroscience models in a variety of formats. Many of these were developed specifically for simulating the electrophysiological and neurochemical properties of single neurons and networks of neurons, for example, with multicompartment Hodgkin-Huxley type

conductance-based models (Hodgkin and Huxley 1952). The Physiome Model Repository (see ► [“Physiome Repository”](#)) (Yu et al. 2011) is a software suite that facilitates storage and management of models, focusing on those described in ► [“CellML,”](#) a standard markup language for biological models. Similarly, ► [“Open Source Brain”](#) (Gleeson et al. 2010b) is a community platform for collaborative development of computational neuron and network models that utilizes open standards such as ► [“NeuroML”](#) (Gleeson et al. 2010a) to facilitate interoperability and visualization of neuroscience models developed by different researchers. Thousands of models at multiple scales (ion channels, neurons, circuits) have been converted to the NeuroML standard, and these can be obtained at NeuroML-DB (Birgiolas et al. 2015), which also reports the results of many standard physiological, morphological, and computational measurements and experiments on these models to better understand how they behave.

Databases of Neuron Morphology and Physiology

A second category of databases that are important for the computational neuroscience community includes those that contain structured information specific to neurons and their properties. For example, information on the detailed shapes of neurons (morphology) is compiled by NeuroMorpho (see ► [“Neuromorpho.org”](#)) (Ascoli et al. 2007) which contains user-submitted neuron morphological reconstructions made, for example, using the NeuroLucida application (Glaser and Glaser 1990). Similarly, other SenseLab databases (see ► [“SenseLab: Integration of Multidisciplinary Neuroscience Data”](#)) including NeuronDB and CellPropDB (Crasto et al. 2007), contain information on the ionic currents and neurotransmitters expressed by each neuron and how these are distributed with respect to neuronal morphology.

Measured electrophysiological properties of neuron types, and the metadata associated with these measurements, are cataloged in the ► [“NeuroElectro Project”](#) (Tripathy et al. 2014). Detailed information on ion channel subtypes, including voltage and temporal dynamics, genetic homology, and corresponding literature

references, is available at Channelpedia (Ranjan et al. 2011, <http://channelpedia.net>), a subproject within the Blue Brain Project (Markram 2006).

Information about neurons in specific brain areas, including many representative examples, are also publicly available. For example, the Neocortical Microcircuit Collaboration Portal contains information about primary somatosensory cortex (citation), The Allen Institute for Brain Science Allen Brain Atlas includes a Cell Types Database that covers primary visual cortex (Sunkin 2013), and ► [“Hippocampome.org”](#) covers hippocampus (Wheeler et al. 2015).

Relevant to these databases that provide data that are helpful for constraining computational models, the performance of models on experimental-data-driven unit tests is reported at SciDash.org, enabling direct model comparison on properties or predictions of interest.

Resources for Brain Connectivity

Another category of databases focuses on the anatomical organization of the brain. Here we provide some widely used examples, focusing on those that could provide quantitative constraints for modeling efforts. ► [“BrainInfo”](#) provides general information about brain areas, including what they do, where they are located, and what they contain. The Allen Institute for Brain Science provides brain-wide gene expression atlases, where the expression of each of the genes in the mammalian genome has been systematically quantified throughout the brain for a number of animal species and across stages of neural development, as well as anatomical connectivity of different brain regions (Lein et al. 2007, <http://brain-map.org>).

Parallel to this effort is the ► [“Human Connectome Project”](#) (Marcus et al. 2013), a large-scale effort to map complete structural and functional neural connections in vivo in individual humans. ► [“BrainMap”](#) (Laird et al. 2004) consists of a database and related software to search published functional and structural human neuroimaging experiments. In contrast, CoCoMac (Stephan et al. 2001; Bakker et al. 2012) is focused on the primate brain, containing records of tracing studies in the macaque. Finally, the ► [“Cell Centered Database”](#) (Martone et al. 2003, 2009) focuses on images

from light and electron microscopy, ranging from whole brain areas to subcellular compartments.

Other Resources

In addition to these neuroscience domain-specific databases are federated databases that provide linking facilities for cross-resource data integration. For example, NeuroLex (Larson and Martone 2013) provides a platform for community annotation of neuron types on the basis of morphological, neurochemical, or electrophysiological properties. Given this wealth of neuroscience resources, the ► “Neuroscience Information Framework (NIF)” provides tools for semantic search across these diverse databases (Gardner et al. 2008) through the development and incorporation of neuroscience domain-specific ontologies (Bug et al. 2008; Larson and Martone 2009; Hamilton et al. 2012; Imam et al. 2012). For example, in NIF, the search query “mitral cell” returns a number of database records including relevant research literature from PubMed, computational models from ModelDB, and connectivity information from BAMS.

The number and size of these databases continue to grow with the collection and contribution of ever more models and data. These databases give computational neuroscientists a powerful tool for constraining data-driven models and serve as an alternative to conventional literature searches.

Cross-References

- [BrainInfo](#)
- [BrainMap](#)
- [Cell Centered Database](#)
- [CellML](#)
- [Hippocampome.org](#)
- [Human Connectome Project](#)
- [ModelDB](#)
- [NeuroElectro](#)
- [NeuroML](#)
- [NeuroMorpho.org](#)
- [Neuroscience Information Framework \(NIF\)](#)
- [Open Source Brain](#)
- [Physiome Repository](#)
- [SenseLab: Integration of Multidisciplinary Neuroscience Data](#)

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Decision-Making: Overview

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Detailed Description

Much of computational neuroscience begins and ends with the responses of individual neurons. The field itself sprang from work in the 1950s aimed at uncovering the biophysical mechanisms underlying spike generation (Hodgkin and Huxley 1952), and other classic studies focus on the computational capabilities of dendritic trees and on how neural activity encodes sensory stimuli or statistical information about the world, to mention a couple of well-known examples (Dayan and Abbott 2001). A different point of view, however, is one in which neurons are the intermediaries between a subject and its environment. As the engines of behavior, neurons need to be computationally powerful for the express purpose of giving the subject an advantage, and hence their efficiency or performance should be measured with respect to the subject's success. So the computational neuroscience of decision-making is computational neuroscience in this context; it is the quest to understand how single-neuron activity contributes to nonreflexive actions, actions that cannot be predicted from a subject's history alone.

The idea of quantitatively explaining a person's subjective experiences based on the responses of specific groups of neurons goes back to the 1960s, with the work of Vernon Mountcastle and colleagues in the somatosensory modality. They found, for instance, that when a small probe, similar to the tip of a ballpoint pen, vibrates at a frequency of 2–40 Hz, the intensity of the evoked sensation reported by a person is directly related to the neural responses of a particular type of mechanosensory receptor under the skin, now known as a Meissner corpuscle (Talbot et al. 1968). Many design elements and analytical

techniques used in contemporary experiments were already laid out in those pioneering studies: they applied information theory to determine the coding capacity of sensory neurons (Werner and Mountcastle 1965) very much as is done today, except for the rudimentary computers, and they recognized neuronal variability, as well as rate versus temporal coding, as fundamental issues for neural computation (Werner and Mountcastle 1963). This early work was limited, however, because it compared psychophysical performance in one system (behaving humans) with neural activity in a different system (e.g., anesthetized monkeys). It was later, with studies like those of William Newsome and colleagues (Salzman et al. 1992), that vision became the more popular modality and that both behavioral and neuronal responses were simultaneously recorded in the same subjects during the performance of perceptually based tasks. That became the standard and a cornerstone for investigating the neural basis of decision-making (Parker and Newsome 1998).

Thus, decision-making involves the study of neurons and neural circuits as a subject captures information about the sensory world; analyzes it; combines it with other stored information about current goals, priorities, and possible courses of action; and makes a response. In the laboratory, researchers attempt to simplify this as much as possible while still maintaining the essence of the process – an internal evaluation that is not fully predictable – and while measuring three quantities as accurately as possible: the sensory stimuli, the relevant neuronal activity, and the subject's behavior (Parker and Newsome 1998). So even the simplest possible decision-making task requires various types of neural computations, and indeed, one common strategy in the field has been to try to break down the problem into temporally discrete steps (e.g., fixation, stimulus presentation, response selection, reward delivery), to investigate how neurons in various areas participate in specific aspects of the decision-making process (Romo and Salinas 2003). The articles that comprise this section of the Springer Encyclopedia of Computational Neuroscience review key components of any such decision-making process.

Three of the entries (► [“Decision-Making Tasks”](#); ► [“Choice Behavior”](#); ► [“Categorical Decisions”](#)) emphasize the repertoire of tasks and associated mathematical models that have been successfully used to characterize and quantify behavior. This provides a foundation for understanding how primary factors, such as reward availability or the quality of sensory information, drive a subject's actions and how different tasks place demands on different cognitive functions, such as perceptual discrimination, conflict resolution, or working memory capacity, to name a few. Selection of a particular behavioral task thus determines both the specific cognitive function and the corresponding neural circuits under investigation. In this context, it has become clear that individual choices are often influenced by a variety of subtle factors that superficially may appear inconsequential (► [“Decision-Making, Bias”](#)). Such sources of bias are likely to attract increasingly more attention in the future, as our ability to correlate neuronal activity and behavior becomes more sophisticated.

Most decision-making tasks have at least two components: a perceptual step during which current sensory information is analyzed (e.g., is that spot red or green?) and a motor report whereby the result of the perceptual judgment is indicated (e.g., push a left or a right button). The rest of the articles in the section focus either on perception (► [“Accumulation of Evidence in Decision-Making”](#)), motor planning (► [“Decision-Making, Motor Planning”](#)), or their interface and interaction. Although some neurons clearly relate to either perceptual or motor processing, it is often the case that the cells that correlate most strongly with a subject's choices have elements of both (► [“Perceptual Decision-Making”](#)). In fact, determining the degree to which a neural response encodes perceptual information versus a motor plan turns out to be surprisingly difficult (► [“Target Selection vs. Response Selection”](#)); the ambiguity arises even at the psychophysical level (► [“Perceptual-Motor Dissociation”](#)). In spite of this, a number of principles describing how neurons participate in the generation of perceptual judgments and ultimately produce choices have been identified (► [“Perceptual Decision-](#)

Making”). Furthermore, relatively simple quantitative models have been highly successful at reproducing not only the traditional behavioral metrics of performance and reaction time but also key aspects of neuronal activity (► [“Accumulation of Evidence in Decision-Making”](#); ► [“Decision-Making, Models”](#)). Because of this, there is a relatively thorough understanding of at least some of the computations that are key to perceptual decision-making (► [“Accumulation of Evidence in Decision-Making”](#); ► [“Speed-Accuracy Tradeoff”](#); ► [“Decision-Making, Threshold”](#)). This trend is expected to continue.

Cross-References

- [Accumulation of Evidence in Decision-Making](#)
- [Categorical Decisions](#)
- [Choice Behavior](#)
- [Decision-Making Tasks](#)
- [Decision-Making, Bias](#)
- [Decision-Making, Models](#)
- [Decision-Making, Motor Planning](#)
- [Decision-Making, Threshold](#)
- [Perceptual Decision-Making](#)
- [Perceptual-Motor Dissociation](#)
- [Speed-Accuracy Tradeoff](#)
- [Target Selection vs. Response Selection](#)

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Deep Brain Stimulation (Models, Theory, Techniques): Overview

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Detailed Description

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for medically refractory patients with advanced Parkinson’s disease (PD) (Benabid et al. 1991; Blond et al. 1992; Benabid et al. 2002; Deuschl et al. 2006) as well as for patients with early motor complications (Deuschl et al. 2006; Schuepbach et al. 2013). Several neurological diseases, such as Parkinson’s disease (PD) or essential tremor, are characterized by pathological synchronization (Nini et al. 1995; Brown et al. 2001). Parkinsonian resting tremor, for example, seems to origin from a pacemaker-like population of neurons of the basal ganglia firing in a synchronized and oscillatory manner (Hutchison et al. 1997; Hurtado et al. 1999; Magill et al. 2001; Trottenberg et al. 2007). In contrast, under healthy conditions these neurons are active in an uncorrelated and desynchronized manner (Nini et al. 1995; Magill et al. 2001).

The standard DBS protocol employs permanent high-frequency (>100 Hz) pulse train stimulation (Benabid et al. 1991, 2002; Blond et al. 1992). Symptom suppression by DBS is strongly dependent on stimulation frequency – with only high frequencies (>100 Hz) being effective and effects being rapidly reversible (Birdno and Grill 2008). High-frequency DBS was developed empirically, mainly based on clinical observations and experimental results (Volkman et al. 2006), and the mechanism of high-frequency DBS is still a matter of debate (Benabid et al. 2005).

Experimental observations indicate that during high-frequency DBS, a regular bursting mode is induced (Beurrier et al. 2002), and after a reduction of stimulation artifacts, robust bursting activity in STN neurons was observed in slice experiments (Beurrier et al. 2001). In the same experiments, the offset of stimulation was followed by a blockade of activity, i.e., a depolarization blockade (Beurrier et al. 2001). These observations were made in anesthetized animals and are contradicted by measurements in awake behaving primates (Anderson et al. 2003; Hashimoto et al. 2003; Dorval et al. 2008) and rats (McConnell et al. 2012). Other groups argue that high-frequency DBS blocks neuronal activity in relevant target areas during stimulation and therefore mimics the effect of tissue lesioning (Benabid et al. 2002). In 2005, Benabid and coworkers summarized different hypothetical mechanisms: membrane inhibition, excitation of excitatory and inhibitory afferents, jamming, excitation of efferents, and plasticity (Benabid et al. 2005). Novel experimental techniques, such as optogenetics, enabled to further reveal the mechanism of DBS and, in particular, of the stimulation of afferent axons projecting to the target region (Gradinaru et al. 2009).

Spatially extended single- and multi-compartment neuron models were used to evaluate the contribution of these different mechanisms (Grill and McIntyre 2001; Terman et al. 2002; Rubin and Terman 2004). For example, Grill and McIntyre (2001) showed that depending on the stimulation amplitude and the shape of the stimulation pulses, cells were either activated directly or fibers mediating excitatory or strong inhibitory

action were activated. The activation of a larger number of structures takes place on the single-neuron level with different and possibly conflicting impacts on single-neuron dynamics (Grill and McIntyre 2001). For example, in the same neuron, the cell body (soma) is inhibited as a result of activation of presynaptic axons and GABA release, while the efferent axon is activated by the stimulation pulses on an approximately one for one basis (McIntyre et al. 2004). The various reactions of neurons toward stimulation on the network level further add complexity that is important for the creation of a sound model: cells responding differently to external inputs, such as somatosensory stimulation or stimulation owing to active movements, are present in the target tissue together with so-called no-response cells (Lenz et al. 1994). Therefore, high-frequency stimulation has a complex impact on these structures (Benabid et al. 2002; Shen et al. 2003). However, surprisingly, even single STN model neurons – lacking synaptic dynamics, neural circuitry, and contributions of glial cells – subjected to high-frequency stimulation reproduce clinically observed response characteristics (Pyragas et al. 2013).

To study another aspect of DBS, several groups use physical models based on Maxwell's equations to investigate the neuronal activation profile depending on electrode geometry and stimulation parameters (Butson and McIntyre 2005, 2006; Miocinovic et al. 2009; Yousif et al. 2008; Chaturvedi et al. 2010; Buhlmann et al. 2011).

While the standard DBS protocol was developed empirically (Volkman et al. 2006), novel stimulation approaches are based on electrophysiological as well as computational concepts. Personalizing and optimizing high-frequency stimulation in real time by demand-controlled, adaptive DBS might constitute a superior high-frequency stimulation mode, as shown in an acute study in externalized patients (Little et al. 2013). In addition, modeling studies are used to further develop the stimulation algorithm, beyond standard high-frequency DBS, in order to finally establish superior stimulation mechanisms. For example, coordinated reset (CR), a patterned

stimulation protocol specifically targeting the reduction of synchronized activity, was developed by means of mathematical models (Tass 2003) and essentially aims at an unlearning of both abnormal synaptic connectivity and synchrony (Tass and Majtanik 2006). CR was successfully tested in a preclinical study, where 5 days of low-dose CR stimulation induced long-lasting therapeutic effects for 30 days (Tass et al. 2012). Another example is a closed-loop approach, which was controlled by the extent of oscillatory beta-band activity. During stimulus delivery, this approach resulted in a better reduction of akinesia as well as pallidal firing rates as compared to classical DBS in parkinsonian nonhuman MPTP-treated primates (Rosin et al. 2011). Finally, modifications of the standard HF protocol might offer a novel approach to improve the efficacy of deep brain stimulation (Brocker et al. 2013; Hess et al. 2013).

The combination of all these modeling and experimental and technological approaches plays a vital role in shaping our understanding and helps to improve the promising therapeutic intervention DBS.

Cross-References

- [Computational Model-Based Development of Novel Stimulation Algorithms](#)
- [Computational Models of Deep Brain Stimulation \(DBS\)](#)
- [Computational Models Supporting Parameter Finding for Deep Brain Stimulation](#)
- [Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation](#)

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Dynamical Systems: Overview

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Definition

Many models of computational neuroscience are formulated in terms of nonlinear dynamical system (sometimes the dynamical system with noise) and include a large number of parameters. Therefore, it is difficult to analyze dynamics and find correspondence between parameter values and dynamical mode. Mathematical theory of dynamical systems and bifurcations provide a valuable tool for a qualitative study and finding regions in parameter space corresponding to different dynamical modes (e.g., oscillations or bistability). Thus, the dynamical systems (or nonlinear dynamics) approach to analysis of neural systems

has played a central role for computational neuroscience for many years (summarized, e.g., in recent textbooks, Izhikevich (2007) and Ermentrout and Terman (2010)).

Detailed Description

Theory of dynamical systems and bifurcations provides a list of universal scenarios of dynamics changes under parameter variation. For example, one scenario explaining the onset of oscillations is described by Andronov-Hopf bifurcation. In terms of neuroscience, this theory provides insight into the mechanisms underlying different neural response properties and firing patterns. Even more importantly, it allowed to elucidate the underlying mathematical structure that might be common to whole classes of firing behaviors. Thus, conclusions of such studies can be wide ranging, even if specific biophysical details of implementation may differ from case to case.

A common theme in all articles in this section is that they use concepts from nonlinear dynamics, especially geometrical methods like phase planes and bifurcation diagrams. Many exploit time scale differences to reduce dimensionality by dissecting the dynamics using fast-slow analysis, i.e., to separately understand the behaviors on the different time scales and then patch the behaviors together.

The articles in this section for the most part exploit the idealized model of neuron localized at one point (i.e., electrically compact neuron), focusing on the nonlinearities of spiking dynamics, and using biophysically minimal but biologically plausible description of neural dynamics. An article on ► [“Fitzhugh–Nagumo Model”](#) describes one of the first examples where dynamical systems approach has been applied to analysis of neural dynamics (Fitzhugh 1955). Although “Fitzhugh–Nagumo Model” is not biologically grounded and formulated in terms of the cubic nonlinearity, the model is still considered as one of the prototype models for excitable systems.

An article on ► [“Morris–Lecar Model”](#) describes the rich dynamic repertoire of the two-variable Morris–Lecar model, as its biophysical

parameters are varied. The original detailed analysis of this model (Rinzel and Ermentrout 1998) has laid ground for similar approaches in many different contexts and provided a theoretical justification for influential Hodgkin’s classification of “excitability types” (Hodgkin 1948, described in ► [“Excitability: Types I, II, and III”](#)).

The articles on ► [“Integrate and Fire Models, Deterministic”](#) and ► [“Theta Neuron Model”](#) models target the most idealized end of the modeling spectrum where the spiking activity is represented by simple mathematical models. This approach to modelling of spiking times is fruitful for implementation in the large neural network and when mathematical analysis (in addition to numerical simulations) is desired.

Somewhat more intricate features of single cell dynamics are described in articles on modelling of ► [“Postinhibitory Rebound and Facilitation”](#) and ► [“Spike-Frequency Adaptation”](#) phenomena. Finally, the fast-slow dissection and bifurcation analysis really shine in the description of bursting behavior. The bursting dynamics (of individual cells or of population activity) is dissected into active and silent phases when trajectories are restricted to lower dimensional manifolds, and transitions between these phases correspond to reaching the manifold’s boundary and jumping to a different manifold.

While most of these examples are for single-cell dynamics, the qualitative mathematical study is also applicable to the dynamics of neuronal networks and structures, especially in the mean-field approximations. One such example for network-generated rhythms is presented in the article on ► [“Spike-Frequency Adaptation.”](#)

Of course, the models presented in this section are rather idealized and simplified for mathematical study compared to many other neuronal models that are designed to investigate the biophysical details of action potential generation: interaction of many known ionic currents, or the spatial propagation of activity, etc. Such minimalistic models however are invaluable when the problem or question at hand require only qualitative or semiquantitative characterizations of spiking activity. This is especially important in studies of large networks of interacting cells.

Cross-References

- [Excitability: Types I, II, and III](#)
- [Fitzhugh–Nagumo Model](#)
- [Integrate and Fire Models, Deterministic](#)
- [Morris–Lecar Model](#)
- [Postinhibitory Rebound and Facilitation](#)
- [Spike-Frequency Adaptation](#)
- [Theta Neuron Model](#)

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Dynamics of Disease States: Overview

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Synonyms

Dynamical diseases; Periodic diseases

Definition

Computational neuroscience provides insights into the mechanisms that underlie dynamic diseases of the nervous system. Neuro-computationally inspired therapeutic devices that replace functions lost due to disease offer tangible hope to many for a better life.

Detailed Description

The evolution of an illness is one of the clues that a physician uses to arrive at a diagnosis and treatment strategy for diseases that affect the nervous system. Is the onset acute or subacute? the clinical course self-limited, relapsing-remitting, cyclic, chronic progressive? and so on. The impetus for studying disease dynamics comes from the mathematics and physics communities: their long experience has shown that insights into mechanism often derive from examining how dynamics change. Consequently, the time evolution of a disease is modeled using differential equations and disease processes are described in terms of the stability and nature of the model's dynamical behaviors. In 1977, Michael Mackey and Leon Glass associated changes in physiological dynamics from healthy to unhealthy with changes in underlying control parameters (Mackey and Glass 1977). Subsequently, this concept of a *dynamical disease* was extended to that of a *dynamic disease* to account for the possibility that mechanisms other than those associated with changes in parameters may be involved (see entry ► [“Dynamic Diseases of the Brain”](#)).

Computational neuroscience extends dynamical approaches to neurological disease in two ways (Erdi et al. 2017). First, by making it possible to include anatomical, physiological, and molecular details, computational models provide insights into how mechanisms acting at the level of molecules and individual neurons translate into phenomena manifested clinically at the bedside (see entry ► [“Modeling of Disease: Physical and Molecular Level, Overview”](#)). Historically, the two neurological diseases which provided the most insight into cortical function were temporal lobe epilepsy and classical migraine. Indeed the study of the geometry of migraine, drug, and flicker-induced visual fortification patterns (see entries ► [“Stochastic Neural Field Theory,”](#) ► [“Visual Hallucinations and Migraine Auras,”](#) and ► [“Flicker-Induced Phosphenes”](#)) and their propagation (see entry ► [“Migraines and Cortical Spreading Depression”](#)) has provided deep insights into the functional architecture of the visual cortex. Surgical approaches for the

treatment of patients with medically intractable epilepsy provided the impetus to directly record from cortex of awake humans. This, in turn, motivated studies into the ability of large populations of neurons to synchronize and generate seizures (see entry ► [“Neural Population Models and Cortical Field Theory: Overview”](#)). Moreover, computational models are now making it possible to gain insights into diseases ranging from blood pressure control (see entry ► [“Baroreflex Models”](#)) to the nature of cognitive, functional, and psychiatric diseases of the nervous system that up to now have largely remained mysterious (see entry ► [“Computational Psychiatry”](#)).

Second, by having “a disease in a computer model,” it is possible to efficiently evaluate and refine treatment strategies *in silico* before applying them to humans (Jirsa et al. 2017). Computational challenges remain because of the presence of multistability (see entries ► [“Multistability in Seizure Dynamics”](#) and ► [“Multistability: Stopping Events with Single Pulses”](#)) and time delays (see entry ► [“Time-Delayed Neural Networks: Stability and Oscillations”](#)). Indeed time-delayed, multistable dynamical systems have a tendency to generate transient oscillations that can be easily mistaken for limit cycle oscillations thus causing confusion (see entry ► [“Delay-Induced Transient Oscillation \(DITO\) and Metastable Behavior”](#)).

Although the ultimate goal of medicine is cure, one cannot overlook the need to improve the patient’s quality of life when cure cannot be achieved. The electrical properties of neurons make it possible to use electrical stimuli as a treatment modality. Applications range from aborting seizures with electrical stimuli (see entry ► [“Multistability: Stopping Events with Single Pulses”](#)) to improving the quality of movements of patients with Parkinson’s disease with deep brain stimulation (see entries ► [“Parkinson’s Disease: Deep Brain Stimulation”](#), ► [“Computational Models of Deep Brain Stimulation \(DBS\)”](#), and ► [“Deep Brain Stimulation \(Models, Theory, Techniques\): Overview”](#)). Even noisy stimuli can benefit the function of cochlear implants in the hearing impaired or balance control in those with peripheral neuropathies by making it easier for the sensory nervous system to detect weak signals

(see entry ► [“Stochastic Resonance: Balance Control and Cochlear Implants”](#)). In the last few years alone, these ideas have been translated into devices that can be used by patients, e.g., NeuroPace RNS[®] system for patients with epilepsy, Microsoft’s Emma Watch[®] for patients with essential tremor, shoes with vibrating insoles to improve gait and balance in the elderly (Lipsitz et al. 2015).

As insight increases in our understanding of neural encoding, it is becoming possible to replace broken parts with electronic ones that perform the same function. The large number of articles in this encyclopedia point to the current enthusiasm in this therapeutic approach. Applications include restoring vision to the visually impaired (see entry ► [“Retinal/Visual Interfaces \(Models, theory, Techniques\): Overview”](#)), hearing to those who cannot hear (see entry ► [“Peripheral Nerve Interface Applications, Cochlear Implants”](#)), continence to those incontinent (see entry ► [“Methodologies for the Restoration of Bladder and Bowel Functions”](#)), and relief from pain to those who suffer (see entries ► [“Pain Processing Pathway Models”](#) and ► [“Peripheral Nerve Interface Applications, Neuropathic Pain”](#)). Dramatically it has become possible to interface the brain directly with electronic devices and make it possible for a patient to move robotic limbs by thought alone (see entries ► [“Cortical Motor Prosthesis”](#) and ► [“Functional Neuroscience: Cortical Control of Limb Prostheses”](#)). Even direct brain-to-brain interfaces are possible (Rao et al. 2014).

The frontier for dynamic disease is to understand the collective behaviors of the nervous system that emerge over the time scale of years. Can the development of an epileptic focus (epileptogenesis) be halted early so that an individual at risk never experiences a seizure? Can the rate of learning of a complex voluntary skill, such as the golf swing, by a patient with a robotic or stem cell-derived limb prosthesis be sped up to the point that the individual could enjoy the use of these limbs throughout a lifetime? Large, complex physical systems tend to self-organize dissipative structures, namely dynamical entities whose existence is maintained far-from-equilibrium by a

supply of energy. Already dynamical signatures of this self-organization, including power laws, have been observed in the bursting propagating activities of living neural populations (see entry ► [“Neuronal Avalanches”](#)) and the dynamics of human balance control (see entry ► [“Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights”](#)).

Computational neuroscience provides the tools for understanding how the nervous system learns to exert control thereby bringing to many tangible hope of a better life.

Key Entries

- Computational Psychiatry
- Dynamic Diseases of the Brain
- Epilepsy: Computational Models
- Flicker-Induced Phosphenes
- Functional Neuroscience: Cortical Control of Limb Prostheses
- Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights
- Migraines and Cortical Spreading Depression
- Multistability: Stopping Events with Single Pulses
- Neuronal Avalanches
- Parkinson’s Disease: Deep Brain Stimulation
- Stochastic Resonance: Balance Control and Cochlear Implants
- Time-Delayed Neural Networks: Stability and Oscillations
- Visual Hallucinations and Migraine Auras

Cross-References

- [Baroreflex Models](#)
- [Computational Models of Deep Brain Stimulation \(DBS\)](#)
- [Cortical Motor Prosthesis](#)
- [Deep Brain Stimulation \(Models, Theory, Techniques\): Overview](#)
- [Delay-Induced Transient Oscillation \(DITO\) and Metastable Behavior](#)
- [Intermittent Control of Movement and Balance](#)
- [Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the](#)

- [Methods for Optimizing Stimulus Waveforms for Electroceutical Control](#)
- [Modeling of Disease: Physical and Molecular Level, Overview](#)
- [Multistability in Seizure Dynamics](#)
- [Pain Processing Pathway Models](#)
- [Peripheral Nerve Interface Applications, Cochlear Implants](#)
- [Role of Delayed Feedback in Human Balancing](#)
- [Stochastic Neural Field Theory](#)

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Gamma and Theta Oscillations, Hippocampus: Overview

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Detailed Description

The brain expresses several rhythms that are associated with normal and pathological states. The hippocampus is arguably the most heavily studied

structure in the brain for many reasons including its importance in learning and memory, and it generates several population activities that include theta and gamma rhythms. Many modeling studies have focused on these oscillatory activities, and the entries in this section detail much of this work. To develop and build models of any biological system, an in-depth appreciation of the biological and physiological basis of what is being modeled is required. This is provided in the ► [“Hippocampus, Theta, Gamma, and Cross-Frequency Coupling”](#) entry, where functional and experimental aspects are described, along with data analysis aspects in ► [“Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)”](#). In developing models, the cellular units and how they are connected need to be examined. Three entries on ► [“Hippocampus, Model Inhibitory Cells,”](#) ► [“Hippocampus, Model Excitatory Cells,”](#) and ► [“Hippocampus, Model Network Architecture”](#) provide these details, and the challenges and complexities in these aspects are laid bare. Three theoretical entries on ► [“Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models,”](#) ► [“Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities,”](#) and ► [“Mixed-Mode Oscillations in Single Neurons”](#) provide the reader with the types of theoretical approaches that can be used to help understand how these subthreshold and mixed-mode activities that are present in hippocampal cells may contribute to theta and gamma rhythms. Gamma rhythms have been extensively studied both theoretically and experimentally, and as such, there are well-developed mechanistic understandings for their generation. These mechanisms are described and illustrated in the entry ► [“Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)”](#). This is not the case for theta rhythms or nested theta/gamma rhythms. However, network models have been developed and these are described along with the many considerations that arise in developing such network models in ► [“Hippocampal Theta, Gamma, and Theta/Gamma Network Models.”](#)

In combination, the entries in this section provide the reader with a solid basis to learn about

theta and gamma oscillations in hippocampus considering mathematical modeling and experimental perspectives. An appreciation of the many aspects that are involved, both general and specific, can be gained from reading these entries.

Cross-References

- [Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)
- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Hippocampus, Model Excitatory Cells](#)
- [Hippocampus, Model Inhibitory Cells](#)
- [Hippocampus, Model Network Architecture](#)
- [Hippocampus, Theta, Gamma, and Cross-Frequency Coupling](#)
- [Mixed-Mode Oscillations in Single Neurons](#)
- [Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities](#)
- [Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models](#)
- [Subthreshold Resonance and Phasonance in Single Neurons: 2D Models](#)
- [Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)

General Overview of Spinal Anatomy and Physiology Organization

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Abbreviations

CNS	Central nervous system
CPG	Central pattern generator
CST	Corticospinal tract
DRG	Dorsal root ganglion

DSCT	Dorsal spinocerebellar tract
H-reflex (Hoffmann reflex)	Electrical analogue of the monosynaptic stretch reflex
PRV	Pseudorabies virus
RV	Rabies virus
SCI	Spinal cord injury
STT	Spinothalamic tract
VSCT	Ventral spinocerebellar tract

Definition

Organization of the mammalian spinal cord and activity-dependent and injury-induced plasticity of spinal pathways.

Detailed Description

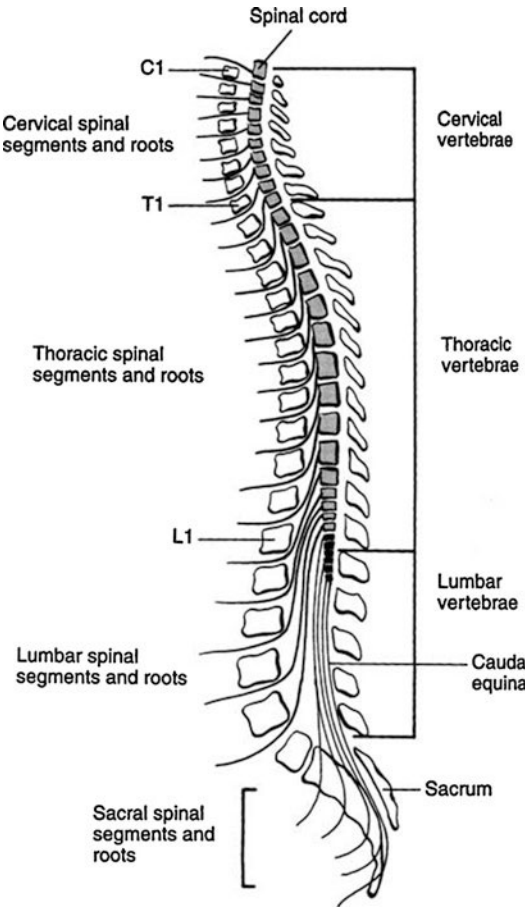
Somatic perceptions, coordinated movements, and autonomic functions depend on the integrity of the spinal cord and its projections. In Part I of this entry, we describe the classic organization of the human spinal cord which is similar in most respects, except size, to other vertebrate spinal cords (see Sengul et al. 2012; Watson et al. 2010). The organization of the cord determines the accessibility of the neural structures for delivery of stimulation aimed at reengaging or modulating spinal neuronal output. In Part II, consideration is given to how spinal pathways may be modified by activity, injury, and injury followed by activity/stimulation, which is increasingly important in the development and application of rehabilitation protocols. Both type of activity and severity of injury are important in determining the optimal protocols for rehabilitation of individuals with spinal cord injury.

The Spinal Cord Is Organized Segmentally

The human spinal cord is comprised of 31 continuous spinal segments (Fig. 1). These are divided into cervical (C1 through C8) segments that supply the neck and arms, thoracic (T1 through T12) segments innervating the trunk and sympathetic

ganglia, lumbar (L1 through L5) segments supplying the legs, and sacral (S1 through S5) and coccygeal (one segment) segments, supplying the saddle region, buttocks, pelvic organs, and parasympathetic ganglia. Dorsal and ventral roots enter and leave the vertebral column through intervertebral foramina at vertebral segments corresponding to the spinal segment. At its caudal end, the cord tapers to form the conus medullaris and the lumbar, sacral, and coccygeal roots extending to their appropriate vertebral levels to form a bundle, the cauda equina (“horse’s tail”).

The spinal cord is divided into cervical, thoracic, lumbar, and sacral segments. Note the exit of the lumbar and sacral roots through intervertebral foramina located caudal to the spinal segment with which the roots are associated.



General Overview of Spinal Anatomy and Physiology Organization, Fig. 1 Organization of the spinal cord

A segment is defined by dorsal roots that enter the cord carrying sensory information and ventral roots that exit the cord carrying motor commands (Fig. 2). The axons in the dorsal roots arise from dorsal root ganglion (DRG) cells located in paired ganglia lateral to the vertebral column. The axon from each DRG cell bifurcates to give rise to a centrally directed process (dorsal root axon or primary afferent) which projects into the spinal cord to terminate on neurons within the CNS. The peripherally directed axonal process enters a spinal nerve. Some of these peripheral sensory axons transmit information from sensory receptors in the skin; the strip of skin supplied by the peripheral process from cells in one dorsal root ganglion is known as a dermatome (Fig. 3). Other peripherally directed axons innervate the muscle spindles, sensory organs within muscles that mediate proprioception.

In this diagram of two segments of spinal cord, three dorsal roots enter the dorsal lateral surface of the cord, and three ventral roots exit. The dorsal root ganglion contains dorsal root ganglion cells whose axons bifurcate; one process enters the spinal cord through the dorsal root and the other extends peripherally to supply the skin and muscle of the body. The ventral root is formed by axons from motor neurons located in the spinal cord.

Axons from motor neurons in the spinal cord exit in the ventral roots and innervate skeletal muscles or autonomic ganglia. These ventral

root axons join with the peripheral processes of the DRG cells to form spinal nerves, which contain both sensory and motor axons. Several spinal nerves may join to form a peripheral nerve.

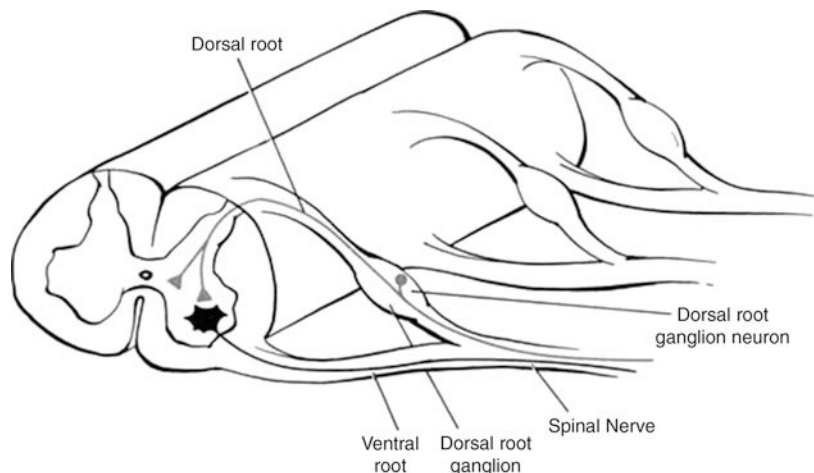
Spinal Neurons Are Organized into Nuclei and Laminae

In cross sections, the spinal cord is composed of a butterfly-shaped core of gray matter, containing neuronal and glial cell bodies and their processes that is surrounded by white matter, composed of axons and their associated glial cells. The gray matter is subdivided into a sensory portion, the dorsal (or posterior) horn, and a motor portion, the ventral (or anterior) horn, separated by the intermediate zone (Fig. 4, Table 1).

Comparison of the classification schemes for the neurons in the gray matter of the spinal cord. On the right, a section stained to show cell size, distribution, and location of neurons in the lumbar spinal cord and, on the left, the related laminar boundaries.

The neurons in the spinal gray matter are also classified according to their projections. These include sensory relay neurons, which receive dorsal root input and whose axons project into ascending pathways that terminate in the brain or spinal cord, motor neurons whose axons exit in the ventral roots to synapse on muscle fibers or on neurons in autonomic ganglia, and propriospinal neurons, spinal interneurons whose cell bodies

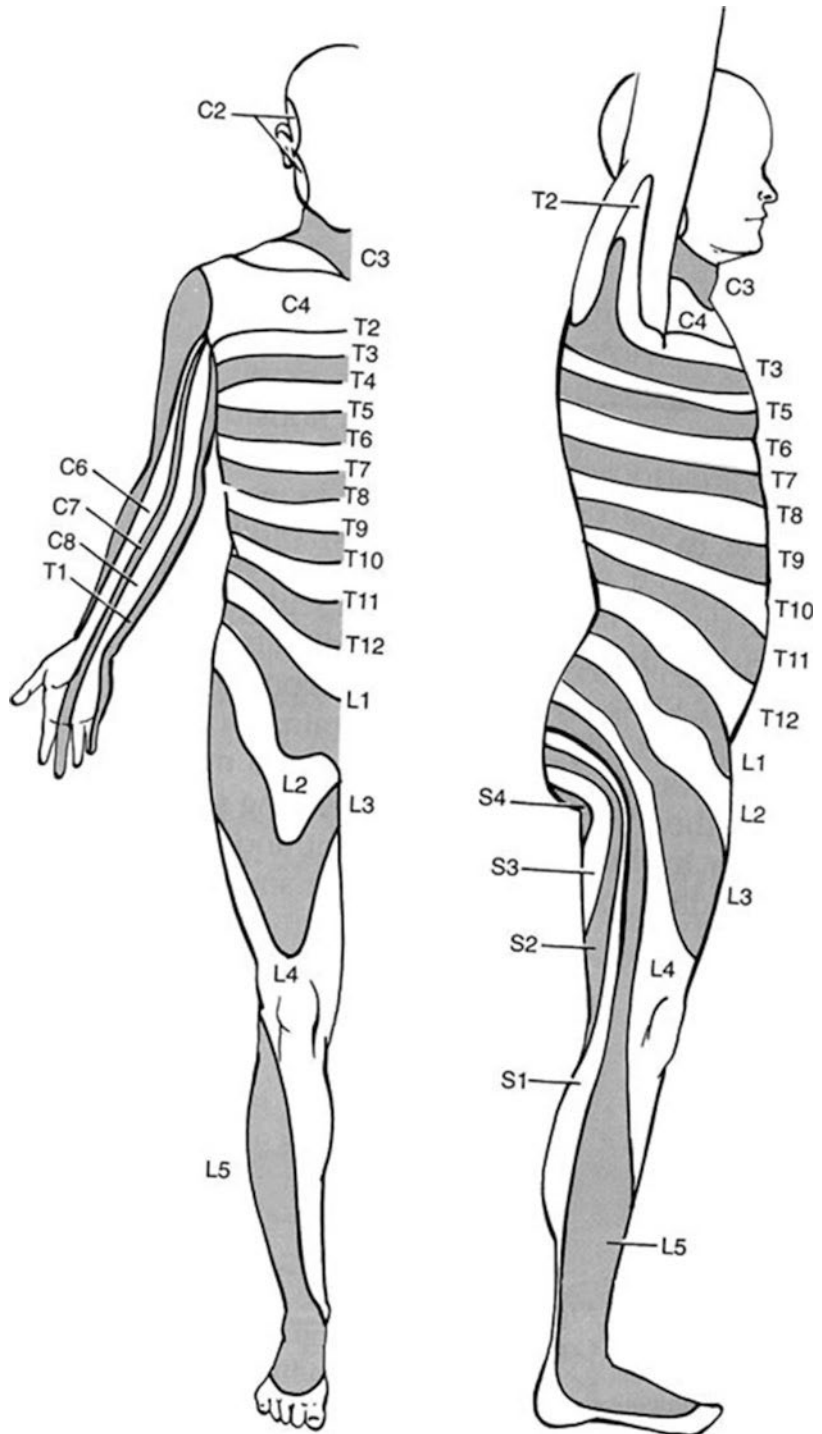
General Overview of Spinal Anatomy and Physiology Organization,
Fig. 2 Spinal segments



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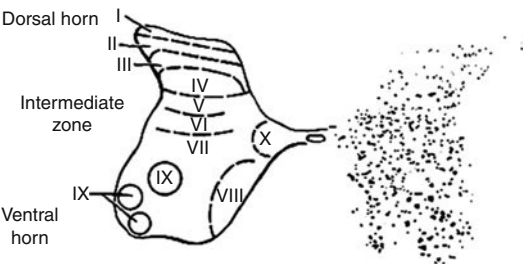
Fig. 3 Dermatome.

A dermatome is the area of skin supplied by axons from a single dorsal root ganglion



and axons are confined to the spinal cord. Proprioceptive neurons are by far the most numerous, accounting for about 90% of all spinal neurons, and the most poorly understood.

Many of the neurons in the gray matter are clustered in functionally related nuclei. These nuclei may extend much of the length of the spinal cord, forming columns of cells, e.g., Clarke's



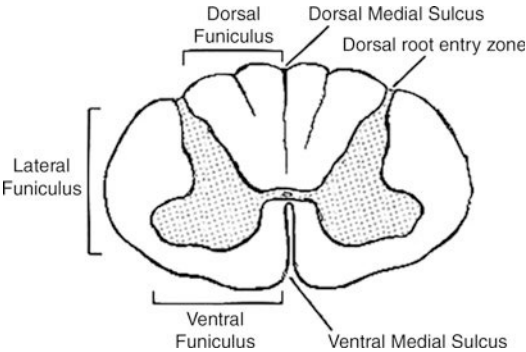
General Overview of Spinal Anatomy and Physiology Organization, Fig. 4 Organization of the spinal gray matter

General Overview of Spinal Anatomy and Physiology Organization, Table 1 Classification of spinal neurons

Gray matter subdivision	Lamina	Nuclei included in laminae
Dorsal horn	Lamina I	Marginal nucleus
	Lamina II	Substantia gelatinosa
	Lamina III, IV	Nucleus proprius
	Lamina V	Reticular nucleus
Intermediate zone	Lamina VI	Commissural nuclei
	Lamina VII	Clarke's, intermediolateral
		Nuclei
Ventral horn	Lamina VIII	Medial motor nuclei
	Lamina IX	Lateral motor nuclei
Commissure	Lamina X	Central gray

nucleus, the intermediolateral nucleus, and motor neurons. In cross sections, the neurons in the gray matter can also be seen to be distributed in a laminar arrangement, particularly in the dorsal horn. Because the histologic differences among laminae reflect functional differences, the spinal gray matter is sometimes also classified into laminae.

The dorsal horn and intermediate zones (laminae I through VII) contain sensory relay nuclei and include the marginal nucleus (lamina I), the substantia gelatinosa (lamina II), and the nucleus proprius (laminae III, IV). Motor neurons are subdivided functionally into somatic and visceral motor neurons. Somatic motor neurons are located in the ventral horn (laminae VIII and IX) at



General Overview of Spinal Anatomy and Physiology Organization, Fig. 5 External landmarks of the spinal cord

all spinal levels and innervate striated muscle. All visceral motor neurons are located in the intermediate zone (lamina VII) at C8 through L3 (sympathetic) or S2 through S4 (parasympathetic) and innervate neurons in autonomic ganglia. Commissural neurons whose axons cross to the contralateral side of the spinal cord are located primarily in lamina X. These schemes for classifying spinal neurons are compared in Fig. 4 and Table 1.

Ascending and Descending Tracts in the White Matter

The white matter is subdivided into three funiculi: dorsal (ascending pathways), lateral (ascending and descending pathways), and ventral (descending pathways), demarcated by the dorsal median sulcus, the dorsal root entry zone, the ventral roots, and the ventromedian sulcus (Fig. 5). Propriospinal axons ascend and descend in the fasciculus proprius bordering the gray matter. Short propriospinal axons are located medially, immediately adjacent to the gray matter, and longer propriospinal axons ascend and descend, adjacent to the shorter axons.

Cross section of cervical spinal cord shows major landmarks and divisions of white matter.

Cells in the dorsal root ganglia and spinal gray matter give rise to the axons that form the ascending pathways that transmit sensory information to the brain. Cell bodies whose axons course in descending tracts are located in many parts of the brain. Their axons descend in the lateral and ventral funiculi and terminate on motor neurons or, more often, on propriospinal neurons that

project to premotor or motor neurons within the spinal gray matter. Descending systems provide central control of movement and posture. Some descending axons terminate on sensory relay neurons in the dorsal horn and can therefore modify sensory input to the brain. Propriospinal axons may be very short, connecting one cell with its neighbor, others (commissural fibers) cross the midline dorsal or ventral to the central canal, and long propriospinal axons ascend or descend in the white matter to connect distant segments of the cord (e.g., segments supplying upper and lower limbs).

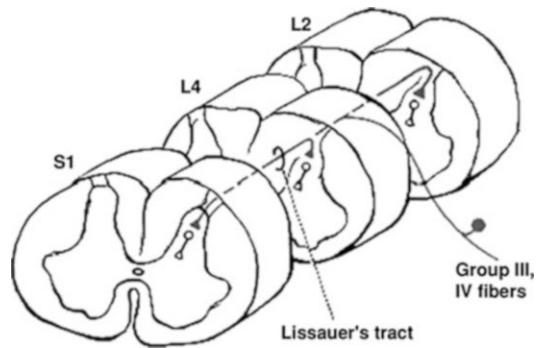
Sensory Pathways

The sensory input to the CNS from the body is organized according to information about the type of sensation (modality) and location of the stimulus. This information is used to produce appropriate spinal reflexes and is transmitted to appropriate parts of the brain for sensory processing. Information about a noxious stimulus to the skin is distributed in pathways that are different from those that transmit information about non-painful stimuli, such as light pressure or proprioception.

Upon entry into the spinal cord, the dorsal root fibers separate into a lateral and a medial division. The lateral division (Lissauer's tract) contains finer myelinated and unmyelinated fibers, originating from small dorsal root ganglion cells, and transmits responses to nociceptive (painful), non-discriminatory or crude touch and thermal stimulation of the skin and viscera. The medial division contains large-caliber fibers from large dorsal root ganglion cells, whose peripheral receptors lie in muscle, joints, and skin. These fibers relay information about muscle length and tension to motor neurons and to propriospinal neurons, at segmental levels and to Clarke's and the lateral cuneate nuclei more rostrally. These pathways provide respectively the basis for spinal reflexes and information about somesthesia and joint position relayed to the brain, providing the basis for stereognosis (i.e., identification of shape and size of an object).

The Lateral Division

Lissauer's tract (Fig. 6) contains small-diameter axons that convey the modalities of pain,

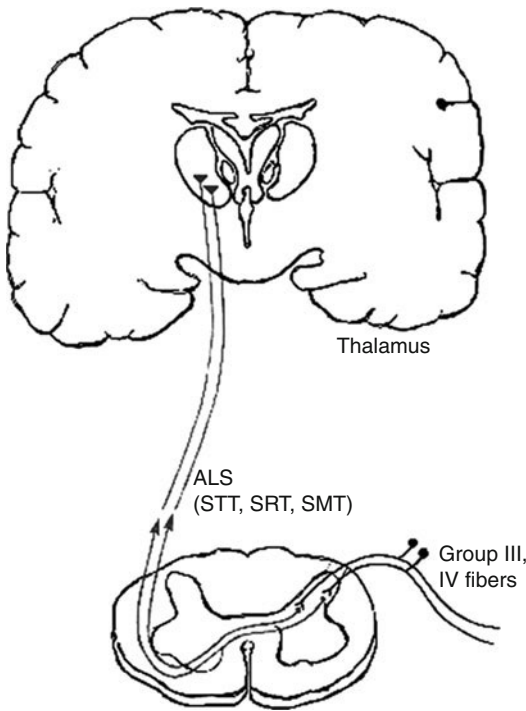


General Overview of Spinal Anatomy and Physiology Organization, Fig. 6 Lissauer's tract

temperature, and crude or nondiscriminatory touch. Some axons branch and the branches ascend or descend in Lissauer's tract for several segments before entering into the lateral portion of the dorsal horn to synapse on cells in the dorsal horn (marginal nucleus, substantia gelatinosa, nucleus proprius, laminae I to IV). This distribution of collaterals rostrally and caudally means that activation of axons in one segment of the lateral division may stimulate dorsal horn cells over several adjacent segments. Neurons in the dorsal horn relay sensory information received from dorsal root axons to nuclei in the brain. These second-order neurons transmit this information through axons that cross and ascend in the lateral funiculus. Sensory relay neurons also receive input from various descending tracts, either directly or via interneurons. In this way, the neuron's ability to respond to sensory input is modified by the brain.

Entry and central course of axons of the lateral division from one dorsal root ganglion. These unmyelinated and thinly myelinated axons may branch and ascend or descend several segments in the tract of Lissauer before entering the gray matter and synapsing on second-order neurons in the dorsal horn.

The formation of the spinothalamic tract (STT) is shown in Fig. 7. Most axons in the STT arise from the marginal cells in lamina I and from the nucleus proprius in laminae III and IV and transmit nociceptive and thermal information. The axons of these second-order neurons cross to the contralateral spinal cord through the ventral



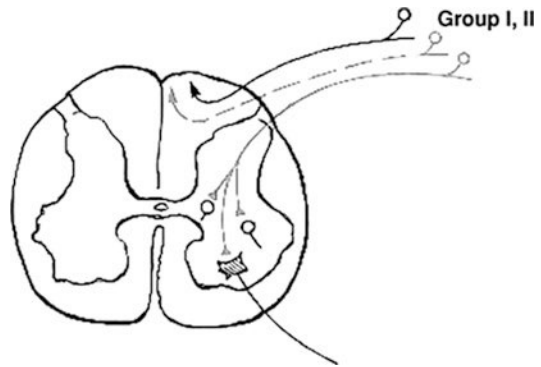
General Overview of Spinal Anatomy and Physiology Organization, Fig. 7 Formation of the spinothalamic tract (STT)

commissure and ascend in the white matter as the spinothalamic tract to terminate in the thalamus and other targets in the brain. They travel with other sensory spino-brainstem pathways in the anterolateral system (ALS).

Lateral division axons entering the dorsal root synapse on second-order neurons giving rise to axons that cross the spinal cord. Some axons form the spinothalamic tract (STT) and ascend to terminate in the thalamus. Some of these axons ascend to terminate in the reticular formation (spinoreticular tract, SRT) or mesencephalon (spinomesencephalic tract, SMT). These pathways travel together in the ventrolateral white matter to form the anterolateral system (ALS).

The Medial Division

Dorsal root axons in the medial division have local targets at their segments of entry. They may also give off collateral axonal branches that ascend to terminate in more distant targets in somatosensory relay and cerebellar relay nuclei.

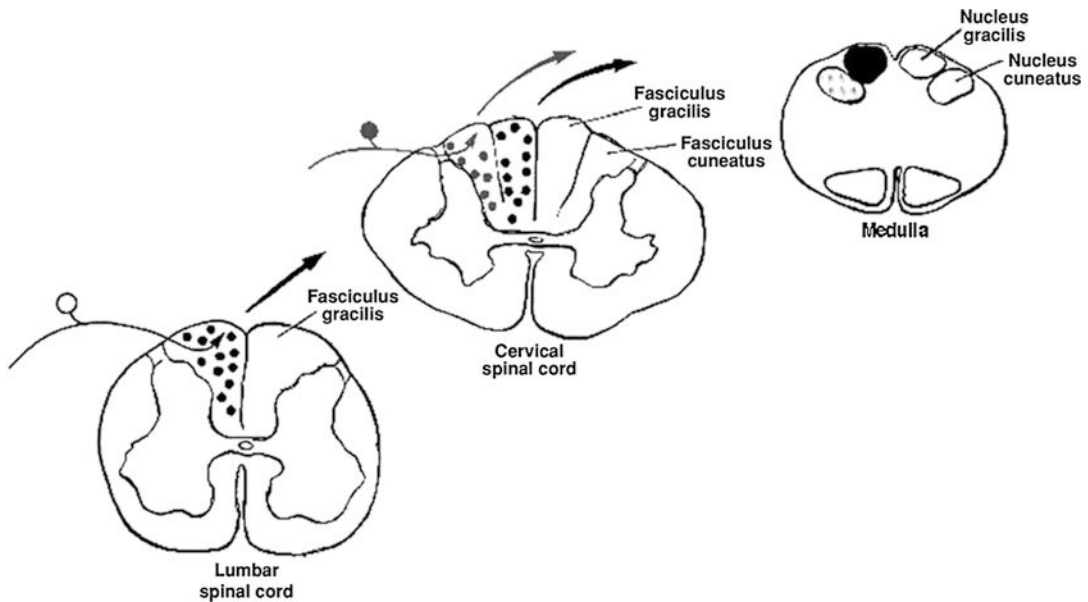


General Overview of Spinal Anatomy and Physiology Organization, Fig. 8 Medial division

Axons with local segmental targets enter the gray matter, synapse on propriospinal or motor neurons at that segmental level, and subserve reflex organization (Fig. 8). The Ia fibers of the medial division whose peripheral processes innervate stretch receptors in muscle spindles send central processes into the ventral horn, to synapse on the dendrites of motor neurons and propriospinal neurons. The monosynaptic connection between sensory axons and motor neurons is the anatomical basis for an important reflex, the stretch reflex. Other medial division axons, including collaterals of axons with segmental targets, enter the white matter in the dorsal funiculus, where they ascend to terminate in relay nuclei for somatosensory or cerebellar pathways. These relay nuclei receive sensory information from the skin, muscles, joints, fascia, and other tissues and then transmit the information to nuclei in the thalamus. The thalamus relays information to the cortex, where it is consciously appreciated or to the cerebellum, where it contributes to the control of posture and movement, without being consciously perceived.

Axons forming the medial division enter the spinal cord and ascend in the dorsal columns or make local reflex connections on motoneurons or propriospinal neurons or contact spinocerebellar nuclei.

Dorsal root fibers that project to somatosensory relay nuclei enter the dorsal funiculus at each segment, displacing medially the fibers originating from more caudal ganglia. As a result, these fibers become laminated, i.e., topographically

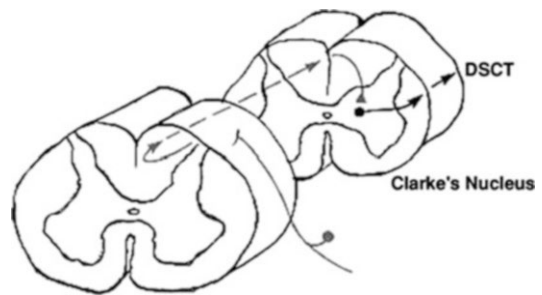


General Overview of Spinal Anatomy and Physiology Organization, Fig. 9 Dorsal column system

organized. In the cervical region, fibers from sacral dorsal roots are found nearest the midline and those from cervical roots nearest the dorsal root entry zone. Fibers representing the lower half of the body (sacral to T5) ascend in the gracile fasciculus; those from the upper half (T5 to C2) comprise the cuneate fasciculus. Axons in both bundles terminate ipsilaterally in nuclei of the medulla for which they are named, the nucleus gracilis and cuneatus. The gracilis and cuneate nuclei (dorsal column nuclei) then relay information to the thalamus (Fig. 9).

Axons mediating fine tactile sensibility contribute to the medial division. They ascend in the dorsal columns to the brainstem, where they terminate on second-order neurons in the dorsal column nuclei. The axons arising from lumbar and low thoracic dorsal root ganglia ascend in the fasciculus gracilis and terminate in the nucleus gracilis. Axons arising from upper thoracic and cervical ganglia ascend in the more laterally located fasciculus cuneatus and terminate in the nucleus cuneatus located lateral to the nucleus gracilis in the medulla.

Other dorsal root axons enter the dorsal funiculus to ascend for several segments before terminating in relay nuclei for cerebellar pathways.



General Overview of Spinal Anatomy and Physiology Organization, Fig. 10 Spinocerebellar systems

Axons arising from DRG cells in caudal thoracic, lumbar, and sacral regions ascend in the dorsal columns to terminate in Clarke's nucleus (Fig. 10), located in segments T1 to L2. Those arising from more rostral ganglia ascend in the dorsal columns to terminate in the lateral (also called the external or accessory) cuneate nucleus in the medulla. The dorsal spinocerebellar tract (DSCT) arises from neurons located in Clarke's nucleus; it ascends in the white matter ipsilaterally and is therefore uncrossed. The DSCT terminates in the cerebellum. Similarly, the cuneocerebellar tract carries information from the lateral cuneate nucleus to the cerebellum. Both nuclei therefore

relay sensory information from the periphery to the cerebellum. There is a third pathway to the cerebellum, the ventral spinocerebellar tract (VSCT). Cell bodies whose axons form the VSCT are distributed throughout the dorsal horn and intermediate zone; their axons cross in the ventral commissure to ascend in the contralateral VSCT, as part of the ALS, to the cerebellum, where they cross again before terminating. Although the course of the VSCT differs from that of the DSCT and cuneocerebellar pathways, their functions appear to be related.

Axons conveying proprioceptive and muscle information also form part of the medial division. Axons from lumbar and caudal thoracic dorsal root ganglia enter the spinal cord and ascend ipsilaterally in the dorsal columns to the thoracic level where they terminate on second-order neurons in Clarke's nucleus. The axons of Clarke's neurons ascend in the lateral funiculus as the dorsal spinocerebellar tract (DSCT) which terminates on third-order neurons in the cerebellum. Axons from more rostral segments ascend synapse in the lateral cuneate nucleus (not shown), which then projects to third-order neurons in the cerebellum.

Motor Pathways

Descending tracts are located in the lateral and ventral funiculi. Most of the axons in these tracts

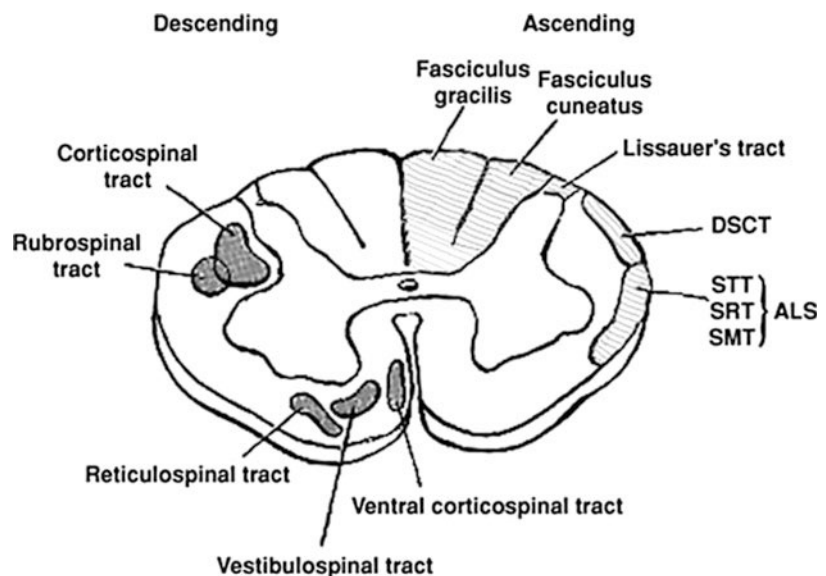
terminate on propriospinal neurons, which then project to premotor or motor neurons; very few terminate directly on motor neurons. The location of four important descending tracts, the corticospinal, rubrospinal, reticulospinal, and vestibulospinal tracts, is shown in Fig. 11.

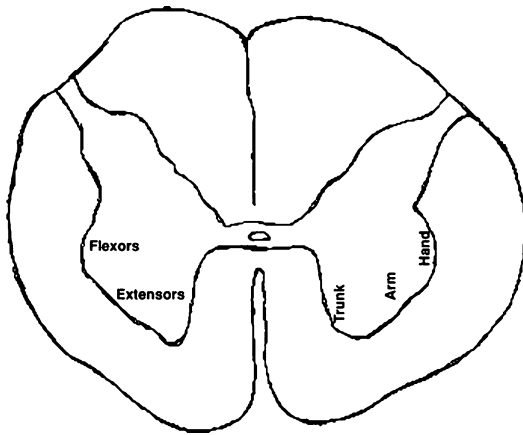
The corticospinal tract (CST) descends to the spino-medullary junction, where 90% of the axons cross, and then continues to descend as the lateral corticospinal tract in the lateral funiculus contralateral to the cell bodies of origin. Those axons that do not cross at the spino-medullary junction descend in the spinal cord as the ventral corticospinal tract but then cross in the spinal cord before their termination contralateral to their origin. In rodents, unlike primates and cats, the CST crosses at the spino-medullary but descends in the ventral portion of the dorsal columns within the spinal cord. The rubrospinal tract is also largely crossed and is located in the lateral funiculus. The reticulospinal tract, including the modulatory monoaminergic pathways (serotonergic and noradrenergic), contains axons that arise from reticular nuclei ipsilaterally and contralaterally. The vestibulospinal tract is almost entirely uncrossed.

Somatic motoneurons are somatotopically organized within the ventral horn (laminae VIII and IX). Their axons exit in the ventral roots and innervate striated muscle. A medial motor nucleus is present in the ventral horn throughout the length

General Overview of Spinal Anatomy and Physiology Organization,

Fig. 11 Location of ascending (*right*) and descending tracts (*left*)





General Overview of Spinal Anatomy and Physiology Organization, Fig. 12 Somatotopic organization of ventral motoneurons

of the cord. These motor neurons innervate axial (trunk) musculature. There are also prominent groups of nuclei located laterally in the ventral horn, which are particularly well developed in the lumbar and cervical segments that supply the limbs. The lateral group of nuclei is subdivided functionally into ventral nuclei, which innervate extensor muscles, and dorsal nuclei, which innervate flexors. Within these two subdivisions, the neurons innervating proximal muscles are located medially and those that supply the distal muscles more laterally (Fig. 12).

Axial musculature is supplied by motor neurons located medially and limb musculature by motor neurons located laterally in the ventral horn. Those innervating extensors are more ventral and flexors more dorsal; neurons innervating proximal muscles are more medial than those innervating distal muscles.

Visceral motoneurons (preganglionic neurons) are located in the intermediate zone. They innervate neurons in autonomic ganglia and the autonomic ganglion cells (postganglionic neurons) innervate visceral organs. Those preganglionic neurons in the intermediolateral nucleus in lamina VII at C8 to L3 send axons to the ganglia in the sympathetic chain, providing central regulation of the sympathetic nervous system. Neurons in the intermediate zone at levels S2 through S4 form the more poorly defined sacral parasympathetic

nucleus. Their axons innervate the sacral parasympathetic ganglia and thus provide central control of the sacral portion of the parasympathetic system that mediates bowel, bladder, and sexual reflexes. Central control of more rostral portions of the parasympathetic system is provided by groups of cranial nerve nuclei.

Propriospinal Systems

A great deal of detailed information is available about DRG cells, motor neurons, and their projections. The cell bodies of both motor neurons and DRG cells can be identified morphologically and by methods that label transmitters, receptors, or other cell-type specific molecules. Axonal projections can be visualized and traced by injecting dyes or viral vectors that are incorporated and transported retrogradely, anterogradely, or in both directions and can identify motor neurons that project to specific muscles and DRG cells, as reviewed in Lanciego and Wouterlood (2011).

Propriospinal neurons, however, make up the vast majority of spinal neurons. Because propriospinal neurons are engaged in complex spinal networks, e.g., the central pattern generator (CPG), and in pain transmission (see entry ► [“Sensory Input to Central Pattern Generators,”](#) this volume), a fuller understanding of their connectivity will be important in appreciating how these complex circuits form, how they function, and how they may be modified by activity or injury.

In the last few years, new technologies have accelerated progress in understanding the connectivity and functions of propriospinal neurons (reviewed in chapters in Ziskind-Conhaim et al. 2010, 2013; Conta and Stelzner 2008). The advent of transsynaptic tracing using pseudorabies virus (PRV) and monosynaptic tracing using a genetically modified replication-deficient rabies virus (RV) has provided more detail about interneuronal pathways (Arber 2012; Stepien et al. 2010; Coulton et al. 2011). RV or PRV labeling can be combined with immunocytochemical or other methods to identify the phenotype of the premotor propriospinal neurons.

Developmental neurobiology and molecular genetics have combined to provide additional

ways of differentiating subpopulations of propriospinal neurons, based on lineage (time of origin, birthdate), and the expression of transcriptional markers that control neuronal differentiation and migration to specific positions in the adult CNS. Genetic deletion or pharmacologic blockade can identify the consequences of loss of function in these propriospinal neurons and suggest their roles during development and as adults in the organization of spinal networks (reviewed in Arber 2012; Grossman et al. 2010; Kiehn 2011). These advances have been particularly fruitful in understanding the connectivity of the central pattern generator (CPG). While the network of propriospinal neurons that comprise the CPG is normally modulated by supraspinal projections and afferent input, it can function in the absence of information from the brain or periphery to produce rhythmic, patterned neural activity or fictive locomotion (Hägglund et al. 2010).

The complexity of the propriospinal neuronal connections is still only incompletely understood. The combination and further development of these and other methods that can detect activity in ensembles of functionally related neuronal network and provide 3-dimensional and live imaging, promises a rapid acceleration of progress in this area (Di Maio et al. 2011; Ertuk and Bradke 2013; Hinckley and Pfaff 2013; Laskowski and Bradke 2013).

Spinal Pathways Are Plastic

While the first part of this entry describes the organization of the spinal cord as if it were static, we know that the spinal cord retains the ability to adapt to changes in its environment (plasticity) even in adults. Significant changes in spinal cord neurons and their environment occur as a result of active or passive exercise or training (activity-dependent plasticity). Changes induced by injury occur in afferent, descending, and propriospinal systems and include sprouting, receptor regulation, and alterations in neuronal properties, in addition to the inflammatory and degenerative responses resulting from the injury. When spinal

cord injury is followed by a program of exercise, the functional and anatomical modifications in spinal organization may be further altered or even reversed sufficiently to support greater recovery of function. Understanding lesion-induced changes and promoting plasticity directed by activity can thus be exploited to improve function.

Activity-Dependent Plasticity

Activity-dependent plasticity refers to functional changes in response to activity related to movement. This may include exercise and specific training protocols (Harkema et al. 2012; Roy et al. 2012) or operant conditioning (Pillai et al. 2008; Wolpaw and Chen 2009; Chen et al. 2011) that modify motor output.

Plasticity Following Spinal Cord Injury (SCI)

An injury may be complete (transection spinalization), or it may spare some pathways and thus be incomplete (contusion, clip compression, hemisection, tractotomy). Contusion or clip-compression injuries are considered to be clinically more relevant, while hemisections or tractotomies are surgical injuries that allow evaluation of specific pathways. The consequences of an incomplete injury will depend on which pathways are spared. Spinal cord injury does not elicit substantial regeneration of axotomized neurons and will result in death of some short projecting propriospinal neurons in the vicinity of the injury (Conta Steencken and Stelzer 2010), structural changes in neurons located more distantly from the injury (Gazula et al. 2004), and apoptosis of oligodendroglia (Beattie et al. 2002). Axons that survive an incomplete injury may show long-lasting changes in transmission (Arvanian et al. 2009; Cote et al. 2012) and deficits (but perhaps not permanent) in conduction properties resulting from demyelination (James et al. 2011).

Incomplete SCI is often followed by some degree of spontaneous motor recovery, due in part to reorganization of spared spinal pathway mediated by sprouting and increased excitability of surviving neurons. While gain of function induced by injury may contribute to recovery, it

may also be maladaptive when it contributes to neuropathic pain (Ferguson et al. 2012; Tan et al. 2012), spasticity (Boulenguez and Vinay 2009; Edgerton and Roy 2010), and autonomic dysreflexia (Hou et al. 2008), disorders which often accompany SCI. Complete injury is likely to show little improvement of function in the absence of therapies and is more likely to be accompanied by maladaptive responses.

Activity-Dependent Plasticity After SCI

The functional benefits of treatment based on either exercise-/activity- or injury-induced changes may be modest by themselves, but they are noninvasive and can supplement traditional physical therapy. Consequently, locomotor training after spinal injury (Harkema et al. 2012) is now a widely used rehabilitative strategy to improve function after SCI in humans. Locomotor function on a treadmill can be recovered after spinal transection in experimental animals if training, combined with body weight support, is provided. The success of this therapy is based in part on the normalization of abnormal measures induced by injury when it is followed by training. This effect may relate to the relevance or predictability of the sensory stimulation (Ferguson et al. 2012). The mechanisms that contribute to training-mediated recovery include levels of neurotrophic factors or other molecules (Cote et al. 2011) or changes in gene expression in spinal neurons (Liu et al. 2012; Keeler et al. 2012) and also include changes in neuronal properties and sprouting where exercise/activity tend to ameliorate some of the effects of injury (Cote et al. 2011).

Summary

The spinal cord is contained within the vertebral canal and access to the cord limited by the vertebrae. The cord is somatotopically organized with sensory information being primarily processed in the dorsal horns and tracts, while motor information is mostly contained within the ventral horn and tracts. The intermediate region between the posterior and anterior halves of the cord contains

the largest number of interneurons and is likely the site of most computation processing although the circuitry is still poorly understood. Targeting the activation to certain portion of the circuitry is complicated by both the proximity of the elements forming the circuit and our lack of understanding of its organization. A greater understanding of the anatomical and computational modifications in the spinal circuitry in normal function will be essential for developing ways of improving rehabilitative strategies after injury.

Cross-References

► Sensory Input to Central Pattern Generators

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Information Theory: Overview

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Definition

Information Theory started with Shannon’s seminal paper “A Mathematical Theory of Communication” (Shannon 1948). Because its importance and flexibility were quickly recognized, there were numerous attempts to apply it to diverse field outside of its original scope. The entries in this section provide an overview of the current state of Information Theory in Neuroscience.

Detailed Description

When discussing a field, it is useful to review the basic concepts and their properties. That has been provided in multiple articles for Information Theory. To assist the reader, the entry ► “[Summary of Information-Theoretic Quantities](#)” provides a brief summary of the main information-theoretic quantities. For a more thorough investigation, we would direct interested readers to the most excellent introduction to Information Theory by Cover and Thomas (2006), now in its second edition.

Very soon after Shannon’s initial publication (1948), a small number of manuscripts provided the foundations for the current use of information theory in neuroscience. MacKay and McCulloch (1952) applied the concept of information to propose limits of the transmission capacity of a nerve cell. This work foreshadowed future work on

what can be termed “Neural Information Flow” – how much information moves through the nervous system, and the constraints that information theory imposes on the capabilities of neural systems for communication, computation and behavior. A second set of manuscripts, by Attneave (1954) and Barlow (1961) discussed information as a constraint on neural system structure and function, proposing that neural structure in sensory systems is matched to statistical structure of the sensory environment, in a way to optimize information transmission. This is the main idea behind the “Structure from Information” line of research that is still very active today. A third thread, “Information Estimates,” started with a forward-looking article (Miller 1955), which pointed out many potential pitfalls of extracting information quantities from observations. Its significance penetrated the mainstream neuroscience research later; once information-theoretic analysis became more widespread, the biases noted by Miller were rediscovered, and corrected.

Subsequent Developments

The theme that arguably has had the widest influence on the neuroscience community is that of “Neural Information Flow”. The initial works of MacKay and McCulloch (1952) showed that neurons are in principle able to relay large quantities of information. That research also started the first major controversy in the field, which still resonates today: the debate about timing versus frequency codes (Stein 1967). A steady stream of articles followed, both discussing these hypothesis and attempting to clarify the type of information relayed by nerve cells (Abeles and Lass 1975; Eagles and Purple 1974; Eckhorn and Pöpel 1974; Harvey 1978; Norwich 1977; Poussart 1971; Stark et al. 1969; Taylor 1975; Walloe 1970). After the initial rise in interest, the application of Information Theory to neuroscience was extended to a few more systems and questions but did not spread too broadly. This was presumably because, despite strong theoretical advances in Information Theory, its applicability was hampered by

difficulty in measuring and interpreting information-theoretic quantities.

The work of de Ruyter van Steveninck and Bialek (1988) started what could be called the modern era of information-theoretic analysis in neuroscience, in which Information Theory is seeing more and more refined applications. Their work advanced the conceptual aspects of the application of information theory to neuroscience and provided an impetus to removing biases in information estimates, discussed in detail in the entry ► [“Estimating Information-Theoretic Quantities.”](#)

Current State

Information Theory found applications in the study of neural processing as a theoretical and practical system for the analysis of communicated signals. A variety of information-theoretic quantities are in use in Neuroscience. The entry ► [“Applications of Information Theory to Analysis of Neural Data”](#) provides a general overview of current applications of Information Theory, as an analysis tool of neural information flow.

The structure of neural activity often introduces challenges that have been of marginal interest to the engineering community. The entry ► [“Metric Space Analysis of Neural Information Flow”](#) exemplifies one such case, metrization. In a metric-space approach to analyzing neural response, the data is reduced from a set of complicated objects, spike trains, to a much simpler object, the matrix of distances between the spike trains. When applied to neural information, this matrix is used to estimate information theory quantities for the corresponding spike train data. The tools developed in that direction combine metric properties of spike trains with their information transmission function.

Several entries discuss specific applications in neuroscience stemming from more recent developments in Information Theory. ► [“Directed Information Flow and Causality in Neural Systems”](#) discusses developments based on the natural ideas of information flow in a causal direction. Surprisingly, this idea has taken quite some time to develop in the communication literature due to

various technical difficulties. The works originate from the ideas of Granger (1969) on causal interactions. The information-theoretic perspective of (Massey 1990; Massey and Massey 2005) removed Granger’s linearity assumptions.

And lastly, applications in neuroscience are also pushing the development of new tools in Information Theory. One of the examples presented here, ► [“Information Measures of Redundancy and Synergy in Neural Activity,”](#) summarizes the progress made in that direction, for which the original definitions provided by Shannon proved inadequate.

In conclusion, Information Theory is thriving in the neuroscience community, and the long efforts are bearing fruit, as diverse research questions are being approached with more elaborate and refined tools. As demonstrated by several recent thematic journal issues (Dimitrov et al. 2011; Milenkovic et al. 2010), Information Theory is firmly integrated in the fabric of neuroscience research, and a progressively wider range of biological research in general, and will continue to play an important role in these disciplines. Conversely, neuroscience is starting to serve as a driver for further research in Information Theory, opening interesting new directions of inquiry.

Cross-References

- [Applications of Information Theory to Analysis of Neural Data](#)
- [Directed Information Flow and Causality in Neural Systems](#)
- [Estimating Information-Theoretic Quantities](#)
- [Information Measures of Redundancy and Synergy in Neural Activity](#)
- [Metric Space Analysis of Neural Information Flow](#)
- [Summary of Information-Theoretic Quantities](#)

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Invertebrate Pattern Generation: Overview

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Detailed Description

Central pattern generators (CPGs) are networks of neurons in the central nervous system (CNS) that produce patterned activity, usually as coherent oscillations, in the absence of external timing cues. CPGs provide timing input to motor neurons whose discharge dictates movements of muscles that control rhythmic behavior such as respiration or locomotion (Marder and Calabrese 1996). The long-held debate between scientists who believed half a century ago that rhythmic motor activity is generated by reflex chains and those who held the more radical view of centrally generated rhythms was resolved conclusively, in favor of the latter group, by demonstrating that neural networks generating rhythmic motor activity can do so in the isolated nervous system, in the absence of the body and therefore sensory feedback. In the early 1960s, these “fictive” motor patterns were first demonstrated to govern rhythmic activation in two invertebrate model systems: the movement of flight wings in locusts and the beating of swimmerets in crayfish (Wilson 1961; Ikeda and Wiersma 1964). The demonstration of fictive motor activity led to the development of *in vitro* preparations in search of the underlying CPG circuits. Although CPG networks have been

traditionally described in the context of controlling motor activity, a more contemporary viewpoint of CPGs includes networks that subserve brain oscillations connected to sensory, cognitive, and memory tasks (Yuste et al. 2005).

CPGs have historically led systems neuroscience in the understanding of neural circuit interactions, partly because of the ease of identification of neurons and networks whose activity correlates with a rhythmic motor activity. The identification of neural circuits has been more successful in invertebrates where the number of neurons involved in neural processing is lower, sometimes by orders of magnitude, and the ability of identifying synaptic connections among neurons is facilitated by dual recordings. Vertebrate and especially mammalian neural circuit analysis was, until recently, performed with cruder techniques such as lesions, but in the past decade or so, genetic tools and the identification of molecular markers have allowed for more precise circuit analysis in the large networks of vertebrate systems (Han 2012; Arrenberg and Driever 2013). However, neural circuits have been identified only in a few vertebrate model systems and simple behaviors (Issa et al. 2011; Cangiano and Grillner 2005). The knowledge of the neural circuits and the ability to record functionally identified neurons in invertebrates have allowed for the in-depth analysis of the mechanisms underlying circuit dynamics and plasticity (Marder et al. 2005) as well as a rigorous description of the computations performed by the neural circuits (Selverston 2010).

The computational description of pattern-generating circuits evolved in parallel with the in vitro experimental studies of cellular and synaptic mechanisms. The complexities of circuit analysis of invertebrate CPGs have led to numerous modeling studies, some of which have been influential in shaping our conceptual understanding of both single-neuron and network operations. For example, the computational description of bursting oscillations, led by models of invertebrate CPG neurons (Plant and Kim 1976), paved the way for the complete mathematical analysis of bursting mechanisms in neurons and other excitable cells (Rinzel 1987; Rinzel and Lee 1987). This section of the Encyclopedia of

Computational Neuroscience provides an overview of the contributions of invertebrate pattern generators in the context of computational models.

Cross-References

- ▶ [Automated Parameter Search in Small Network Central Pattern Generators](#)
- ▶ [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- ▶ [Bursting in Neurons and Small Networks](#)
- ▶ [Gap Junctions in Small Networks](#)
- ▶ [Neuromodulation in Small Networks](#)
- ▶ [Sensory Input to Central Pattern Generators](#)
- ▶ [Short-Term Synaptic Plasticity in Central Pattern Generators](#)
- ▶ [Stability and Homeostasis in Small Network Central Pattern Generators](#)

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Invertebrate Sensory Systems: Overview

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Definition

Invertebrate sensory systems specialize in gathering information from the surroundings allowing animals to locomote and behave appropriately given the current environmental conditions.

Detailed Description

Invertebrate neurobiology has long been at the forefront of computational neuroscience, starting with the mathematical model of the biophysical basis of the action potential by Hodgkin and Huxley in the squid giant axon almost 70 years ago (Hodgkin and Huxley 1952). Many invertebrate systems are highly suitable for detailed modeling because of their relatively compact size and the fact that their neurons can often be uniquely identified. This feature allows the formulation of precise descriptions of their behaviors and simplifies the interpretation of experimental results. Yet, as Hodgkin and Huxley's seminal analysis of action potential mechanisms has proved, invertebrate models possess characteristics similar to those of vertebrates, and the computational principles derived from either type of nervous systems have been found universally applicable, even if details of mechanistic implementations differ.

This section of the Encyclopedia focuses on the sensory systems of invertebrates, complementing the section on their motor systems. It presents an overview of computational modeling emphasizing salient topics in the field. While the coverage is far from exhaustive, it is our hope that these entries will provide the reader an overview and an entry point to the rich literature covering the modeling of invertebrate sensory systems and related topics.

Among the different sensory systems, vision has arguably been the most intensely investigated in invertebrates and vertebrates alike. The entry on ► [“Phototransduction Biophysics”](#) summarizes our understanding of the mechanisms by which invertebrate photoreceptors translate light signals into membrane potential changes. Most of the work on this topic has been carried out in flies and particularly the genetically tractable fruit fly, *Drosophila melanogaster*. The biochemical cascade mediating phototransduction has been studied in great detail and has recently led to a better understanding of the implications for neural coding. Another classical topic of insect vision has been the study of the mechanisms underlying directionally selective motion detection. This work originated in beetles and was later pursued in flies, leading to the correlation model of Hassenstein and Reichardt (1956). The neural circuits implementing this model, which is closely related to the motion-energy model of mammalian motion detection (van Santen and Sperling 1985), have long proven tricky to investigate due to difficulties in tracing the anatomical and physiological connections between the neurons that perform the computations of the correlation model.

Progress has been made by combining anatomical, electrophysiological, imaging, and genetic techniques in *Drosophila* that are summarized in the entry on ► [“Visual Motion Detection in *Drosophila*.”](#) Although *Drosophila* has recently helped better understand the circuitry underlying motion detection, a large body of work on the topic was carried out in bigger flies, leading to detailed biophysical models of a class of neurons involved in motion detection. These models are introduced in the entry on ► [“Fly Lobula Plate Tangential Cells \(LPTCs\), Models of.”](#) Local

motion detection is only the first step in processing visual information generated by an animal moving in its environment. Such information, often called “optic flow,” is particularly important for flying animals. The strategies and constraints on the processing of such information are summarized in the two entries on ► [“Optic Flow Processing”](#) and ► [“Visual Processing in Free Flight”](#).

Another function of the visual system of critical importance to animals is predator evasion and collision avoidance. Our understanding of the neural mechanisms of collision avoidance has rapidly progressed over the past decades in a variety of invertebrate model systems, including locusts, crabs, and fruit flies. Similar collision avoidance mechanisms have been documented in vertebrate systems such as goldfish, zebrafish, pigeons, and mice. The entry on ► [“Collision Avoidance Models, Visually Guided”](#) describes our understanding of those systems. Animal navigation and migration relies on an internal representation of the external world allowing orientation over long distances. In insects, particularly in monarch butterflies, ants, and locusts, the detection of polarized patterns of light in the sky provides an internal compass for navigation. The detection and processing of polarized light patterns leads to a sort of “cognitive map” in the central nervous system akin to those studied in the rodent hippocampus. The entry on ► [“Polarization Vision”](#) provides a summary of our understanding of this fascinating and exotic sensory modality.

Olfaction is a prominent and important sense in invertebrates, particularly in insects. The mechanisms of insect olfaction and their close relation to vertebrate olfaction have been investigated intensely, culminating in a detailed understanding in several organisms, including moths, locusts, and fruit flies. Examples of models of olfactory coding are presented in the entry entitled ► [“Insect Olfaction: A Model System for Neural Circuit Modeling”](#). Another primary sense, audition, is used by animals to locate preys or predators and for communication with conspecifics. Because of their small size, invertebrates and insects such as crickets and locusts, which are

among the best-studied auditory model systems, face physical constraints quite different from those applying to vertebrates. Their study has led to a wealth of information on how auditory information is processed, both at the level of the auditory periphery and in the brain. These results are summarized in the entry on ► [“Auditory Processing in Insects”](#).

Wind and air current sensing is carried out by a specialized sensory system called the cercal system in crickets and other orthopteran insects. This system provides a fascinating example of how information is processed by populations of sensory neurons, as summarized in the entry entitled ► [“Cercal System”](#). More broadly, the entry on ► [“Computation with Population Codes”](#) explains the role such neural codes play in a variety of other animals. The leech has proven to be one of the best models to study these topics because of the compact size of its nervous system, well-understood natural behaviors, and the applicability of large-scale imaging of neuronal activity using voltage-sensitive dyes and other electrophysiological techniques. Finally, invertebrate somatosensation is introduced in the entry on ► [“Tactile Sensing in Insects”](#).

Adaptation is a fundamental property of neuronal responses observed throughout sensory systems. The entry entitled ► [“Biophysics of Adaptation in a Computational Model of the Leech T Neuron”](#) details the ionic mechanisms of adaptation in one type of sensory neuron and its consequences for the processing of sensory stimuli.

In addition to the above-mentioned entries, the section includes one entry – entitled ► [“Nitric Oxide Neuromodulation”](#) – on a somewhat exotic and fascinating volume neuromodulator: nitric oxide. The computational properties of nitric oxide neuromodulation have been investigated in detail in several invertebrate systems, leading to models of its role in sensory processing and learning. Similar regulation of neuronal circuits by volume neurotransmission has been described in vertebrates as well (e.g., Oláh et al. 2009).

The last topic covered in this section is the efficient representation of neural information in the entry entitled ► [“Sensory Coding,](#)

Efficiency". The possibility that sensory neural codes may be efficient has been first raised in the 1960s (Barlow 1961). It has since then been investigated in several systems, including the visual system of invertebrates. The entry includes background information and a summary of results on efficient coding in these systems.

Cross-References

- ▶ Auditory Processing in Insects
- ▶ Biophysics of Adaptation in a Computational Model of the Leech T Neuron
- ▶ Cercal System
- ▶ Collision Avoidance Models, Visually Guided
- ▶ Computation with Population Codes
- ▶ Fly Lobula Plate Tangential Cells (LPTCs), Models of
- ▶ Hodgkin-Huxley Model
- ▶ Insect Olfaction: A Model System for Neural Circuit Modeling
- ▶ Nitric Oxide Neuromodulation
- ▶ Optic Flow Processing
- ▶ Phototransduction Biophysics
- ▶ Polarization Vision
- ▶ Spike-Frequency Adaptation
- ▶ Tactile Sensing in Insects
- ▶ Visual Motion Detection in *Drosophila*
- ▶ Visual Processing in Free Flight

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Learning Rules: Overview

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Definition

The title of this entry, namely, “Learning Rules,” refers to several type of methods and procedures that have been used in different neuroscience research areas to quantify how previous experiences, training, and stimulations protocols affect brain response and behavior in different animals and at different levels of description. The concept assumes the such previous experiences produce changes or plasticity in the brain (i.e., the learning rule) that affect its posterior behavior, e.g., under the action of related stimuli (the retrieval of what is learned). Such “Learning Rules” concept has been also extended to neural networks modeling and artificial intelligence research, providing precise mathematical definitions for different learning rules, a fact that has helped to gain a better understanding of their consequences.

Detailed Description

Learning is the most important procedure by which different stimuli in the environment alter the behavior in animals and humans, and today its neurobiological base is widely accepted (Thompson 1986). In fact, neurobiological and computational studies have stressed the significance of synaptic plasticity in the learning process (Black et al. 1990; Fusi 2017): Experience and training leads to modifications of synapses, which in turn lead to changes in neuronal firing patterns,

causing changes in behavior. A full understanding of the processes underlying learning, therefore, requires an understanding on the neural as well as on the systemic level.

In the behavioral literature, learning is studied by means of different experimental procedures in which animals or humans are exposed to sensory stimuli and interact with the environment (Mackintosh 1974). The paradigms which have been used gave rise to a categorization into associative and nonassociative learning. In non-associative learning an animal is repeatedly exposed to a single type of stimulus, and learning is described by the strength of its behavioral impact leading, for example, to the phenomena of habituation and sensitization (Thompson and Spencer 1966; Rankin et al. 2009). In associative learning animals learn predictive relationships in the presence of a reinforcement signal (Pearce and Bouton 2001). Historically, classical conditioning (where reinforcements are delivered independent of any action taken) is differentiated from operant conditioning (where reinforcements depend on the action and where behavior is associated with its outcome).

In the neural network literature (see, e.g., Haykin 2009), learning is often classified according to what kind of information is available in a particular learning scenario. In the so-called supervised learning, an agent (e.g., a neural network) forms associations between two sets of events with the goal to predict one by the other. Learning is based on a given set of correct pairings. Pairings between events are also formed in the so-called reinforcement learning; however, evaluative feedback about network performance is only provided in the form of reinforcements, for example, reward or punishment signals. Correct pairings imply high rewards; hence, learning is driven by maximizing returns. Reinforcement learning bears similarities with the abovementioned associative learning paradigms, and algorithms which were originally developed by the neural network community are now widely applied to quantify associative learning in animals and humans. In the so-called unsupervised learning, responses of an agent are modified when stimuli are presented but in a nonassociative way. In an artificial agent setting, supervised learning is often applied for solving pattern recognition problems,

and reinforcement learning is used to learn action sequences. Unsupervised learning, on the other hand, is applied to learn internal representations of the outside world. Statistical regularities are extracted and are used to build representations of stimuli and actions which are better suited for recognition, planning, memorization, decision-making, and other cognitive tasks.

In many areas of neuroscience where “real” neurons and networks are studied, learning is linked to changes of neuronal and synaptic properties. Activity-dependent synaptic plasticity is widely believed to be the most important feature underlying learning. It also plays an important role during neural development, where the interplay of neural activity with the so-called intrinsic processes shapes the circuitry and the neural response properties. Learning at the neuronal level is characterized by how the activation history of pre- and postsynaptic neurons relates to the efficacy of the synaptic connection between them. Different stimulation protocols of neurons in (mostly) *in vitro* preparations uncovered a wealth of phenomena associated to learning processes, the most prominent ones being long-term potentiation, long-term depression, or spike-timing-dependent plasticity.

“Learning Rules,” i.e., the title of this entry, refers to the quantification of the effects of experiences, training, and stimulation on the brain and behavior on all abovementioned levels of description. Learning Rules inserted into computational models then help to explore the consequences of the observed plasticity during different learning processes. Thus, one can explore, for example, how activity-dependent synaptic plasticity interacts with network responses which eventually induce behavior, how a network can adapt its parameters such that a desired function can be performed, or how interindividual differences in learning behavior can be related to interindividual differences in their objectives. Thus, learning rules serve as a computational tool to link experience-induced changes observed on a system level to the mechanisms operating on the level of neurons and networks and vice versa.

At the core of this entry are entries for activity-dependent learning rules, which quantify how pre- and postsynaptic activity changes the strength of a

synapse (see entries ► [“Hebbian Learning,”](#) ► [“Anti-Hebbian Learning,”](#) ► [“Spike-Timing Dependent Plasticity, Learning Rules,”](#) and ► [“Tempotron Learning”](#)). Here, the learning rules are formulated in a more abstract setting, and the biophysical foundations are addressed in entry ► [“Synaptic Dynamics: Overview”](#) (cf. ► [“Long-Term Plasticity, Biophysical Models,”](#) ► [“Short-Term Plasticity, Biophysical Models,”](#) and ► [“Spike-Timing Dependent Plasticity, Learning Rules”](#)). The effects of learning rules in terms of network dynamics and computation are then addressed in a neural network setting (see entries ► [“Boltzmann Machine,”](#) ► [“Hopfield Network,”](#) ► [“Perceptron Learning,”](#) and ► [“Slow Feature Analysis”](#)) covering supervised and unsupervised learning paradigms. They are also addressed in a neural modeling setting, where the computational models are used to understand some of the mechanisms underlying neural development (see entries ► [“Cortical Maps, Activity-Dependent Development”](#) and ► [“Cortical Maps, Intrinsic Processes”](#)). The entry is complemented by one entry on reinforcement learning (see ► [“Reward-Based Learning, Model-Based and Model-Free”](#)), which summarizes current computational approaches for quantifying behavior for reward-based, associative learning paradigms. Possible neural implementations of reinforcement learning are discussed in entry ► [“Cortex: Overview”](#) (cf. ► [“Reinforcement Learning in Cortical Networks”](#)).

Cross-References

- [Anti-Hebbian Learning](#)
- [Boltzmann Machine](#)
- [Cortex: Overview](#)
- [Cortical Maps, Activity-Dependent Development](#)
- [Cortical Maps, Intrinsic Processes](#)
- [Hebbian Learning](#)
- [Hopfield Network](#)
- [Long-Term Plasticity, Biophysical Models](#)
- [Perceptron Learning](#)
- [Reinforcement Learning in Cortical Networks](#)
- [Reward-Based Learning, Model-Based and Model-Free](#)
- [Short-Term Plasticity, Biophysical Models](#)

- [Slow Feature Analysis](#)
- [Spike-Timing Dependent Plasticity \(STDP\), Biophysical Models](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)
- [Synaptic Dynamics: Overview](#)
- [Tempotron Learning](#)

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LFP Analysis: Overview

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Detailed Description

Local field potentials (LFPs) are low-frequency electrical potentials recorded with micro- or

macro-electrodes throughout the brain. The upper frequency cutoff of the LFP is often considered to be around 100 Hz but may be as high as 500 Hz in some studies. The normal amplitude of the LFP can range from a few microvolts (e.g., in the basal ganglia) (Goldberg et al. 2004) to hundreds of microvolts in the cortex. Perhaps the earliest recording of an LFP may be attributed to Renshaw, Forbes, and Morison in 1940, who described these potentials in the cortex and the hippocampus of a cat under various anesthetics (Renshaw et al. 1940). Extensive electrophysiological studies have formed the current view that cortical LFPs result from synaptic activity (Eccles 1951; Creutzfeldt et al. 1966; Elul 1971; Klee and Rall 1977; Mitzdorf 1985; Bedard et al. 2004). Correspondingly, the LFP fluctuations tend to have a strict phase relationship to cortical discharge: negative deflections in the LFP coincide with increases in the instantaneous firing rates of cortical neurons in both superficial and deep layers (Lass 1968; Gray and Singer 1989; Murthy and Fetz 1996a; Donoghue et al. 1998; Destexhe et al. 1999). In addition, these fluctuations are highly correlated across distances of several millimeters in the cortex (Eckhorn and Obermueller 1993; Sanes and Donoghue 1993; Murthy and Fetz 1996b; Contreras et al. 1997; Bullock 1999; Destexhe et al. 1999), indicating that LFPs are not always strictly local.

Theoretical attempts to account for the LFPs and model their generation date back to Lorente de Nó (1947) and include the seminal works of Ulla Mitzdorf (1985), who implemented the technique of current source density (CSD), and Wilfrid Rall, who calculated the potentials generated by various spatial organization of electrical dipoles (Klee and Rall 1977; Goldberg et al. 2004). These theoretical accounts relied on the large-scale repetitive columnar structure of the cortical circuitry to generate large potentials due to the summed contribution of many aligned neuronal dipoles (Elul 1971; Klee and Rall 1977; Abeles 1982; Mitzdorf 1985; Eggermont and Smith 1995).

This “LFP analysis” section, which has contributions from several leading authorities, covers the following topics: (a) methods for measuring

the LFP; (b) modern accounts of how LFPs are generated; (c) the relationship between the LFP and other common measures of collective brain activity such as the EEG, the MEG, and the fMRI, as well as its relationship to and possible influence on single-cell membrane potentials; (d) the power spectral structure of the LFP, which often displays a $1/f$ structure, or marked oscillation peaks under various physiological and pathophysiological conditions (e) LFP in the context of particular brain functions such as vision and olfaction; and (f) current modeling methods of the LFP. These various topics are overviewed below.

Neurophysiological Basis of LFPs

A first important aspect of the LFP is the relation between this signal and other well-known signals of the brain. In the entry ► [“Local Field Potential, Relationship to BOLD Signal”](#), Nikos Logothetis and Stefano Panzeri review the relation between the LFP signals and the BOLD (blood oxygen level dependent) signal, as recorded by MRI techniques. The entry also discusses multiunit activity in relation with the BOLD signal.

A similar large-scale approach is followed by Stephanie Jones in ► [“Local Field Potential, Relationship to Electroencephalogram \(EEG\) and Magnetoencephalogram \(MEG\)”](#). This entry reviews the biophysical bases of the genesis of EEG and MEG signals and how such signals relate to the LFP. The “inverse problem” of estimating neuronal sources from EEG and MEG signals is also reviewed.

The relationship to unit activity is further described in detail in ► [“Local Field Potential, Relationship to Unit Activity”](#) by Bartosz Teleńczuk and Alain Destexhe. This entry reviews the relation between extracellularly recorded unit activity and LFP, as a function of the frequency of the different rhythmical activities found in LFPs. It is shown that unit activity correlates with the high-frequency (>200 Hz) components of the LFP and, to a lesser extent, with the low-frequency components (<10 Hz), whereas the intermediate-frequency bands have a rather weak correlation with unit activity.

In the entry ► [“Local Field Potential: Relationship to Membrane Synaptic Potentials”](#), Aryeh Taub, Ilan Lampl, and Michael Okun go a bit more deeper in the neuron and review the relation between the intracellularly recorded membrane potential and the LFP signal. The entry considers different types of brain activity, such as up-down states, and discusses the role of inhibition.

In the entry “Local Field Potentials and Ephaptic Coupling”, Costas Anastassiou discusses the hypothesis that the LFP is not merely an epiphenomenon of electrical brain activity but may actually serve as a global slow signal that can couple to other neural elements (e.g., axons, synapses). This ephaptic coupling results from the fact that the membrane voltages in these elements can be altered by fluctuations in the LFP simply because they are the difference between the intracellular potential and the extracellular (local field) potential.

Finally, in the entry ► [“Local Field Potentials: LFP”](#), Alain Destexhe and Claude Bedard review general properties of LFPs, such as their spatial coherence, namely, how LFPs recorded by neighboring electrodes relate to each other. They also review temporal (spectral) properties of LFPs, such as their typical $1/f$ structure. The entry also overviews different approaches for modeling LFPs.

Oscillatory Properties of LFPs

A fundamental property of LFP signals is their propensity to display oscillations. In the entry ► [“Local Field Potential and Deep Brain Stimulation \(DBS\)”](#), Manuela Rosa, Sara Marceglia, Sergio Barbieri, and Alberto Priori review the use of LFPs in the treatment of DBS in humans. It describes how DBS provides LFP recordings in humans, how they are related to oscillatory activity, and how DBS may interfere with these (sometimes pathological) oscillations.

Pathological oscillations are further investigated in the entry ► [“Local Field Potential and Movement Disorders”](#) by Annaelle Devergnas and Thomas Wichmann. They review the use of LFP recordings in movement disorders and show

that LFPs display various types of oscillations, at different frequencies, for different pathologies associated to movement disorders.

In the entry ► [“Local Field Potentials in Olfaction”](#), Leslie Kay review the LFP signals recorded in the olfactory system (olfactory bulb and pyriform cortex). Their review emphasizes the emergence of beta and gamma oscillations in olfactory structures.

The occurrence of LFP oscillations in the visual system is investigated in the entry ► [“Local Field Potential in the Visual System”](#) by Gregor Rainer. This entry reviews the occurrence of LFPs in visual cortex, with an emphasis on visually evoked potentials, and visually evoked oscillations in the gamma frequency band.

Finally, in the entry ► [“Local Field Potential, Synchrony of”](#), Ariana Frederick, Jonathan Bourget-Murray, and Richard Courtemanche review how LFPs can reveal the presence of network synchrony. Synchrony is here defined as the synchronization between different networks, which indicates a possible interaction between them, for example, using oscillations at different frequencies.

Modeling the Spectral Structure of LFPs

The modeling of LFP signals is first considered by Biyu Jade He in the entry ► [“Electrocorticogram \(ECoG\)”](#). This entry reviews models of the ECoG and how this surface signal relates to the LFP recorded in depth. The entry also discusses the spectral structure of these signals and their power-law frequency scaling.

The modeling of LFPs is further developed in the entry ► [“Local Field Potentials: Interaction with the Extracellular Medium”](#) by Claude Bedard and Alain Destexhe. This entry reviews models of LFPs by staying as general as possible and includes the electrical nature of an extracellular medium. Both microscopic and macroscopic (mean-field) models of the LFP are considered. It is shown that the frequency-filtering properties of the extracellular medium can fully explain the spectral properties of LFPs (such as power law or $1/f$ scaling).

Methodological Aspects of the LFP

Different methods to record LFPs are described in the entry ► [“Local Field Potential, Methods of Recording”](#) by Andrew Sharott. This entry describes important factors such as the type of electrode, the role of the reference, and the recording conditions. The entry discusses how such factors can be determined to correctly interpret the LFP signal.

In the entry ► [“Resistivity/Conductivity of Extracellular Medium”](#), Scott Lempka and Cameron McIntyre review another set of important biophysical properties that contribute to LFP genesis: the electrical properties of neural tissue, the associated measurements of conductivity, the frequency-filtering properties, as well as the influence of volume conduction.

Finally, in the entry ► [“Current Source Density \(CSD\) Analysis”](#), Daniel Wójcik reviews the physical bases of the CSD analysis, which consists of estimating neuronal current sources from LFP measurements performed by electrodes located at equidistant points in space. Different variants of the CSD analysis are presented and discussed.

Cross-References

- [Current Source Density \(CSD\) Analysis](#)
- [Electrocorticogram \(ECoG\)](#)
- [Local Field Potential and Deep Brain Stimulation \(DBS\)](#)
- [Local Field Potential and Movement Disorders](#)
- [Local Field Potential in the Visual System](#)
- [Local Field Potential, Ephaptic Interactions](#)
- [Local Field Potential, Methods of Recording](#)
- [Local Field Potential, Relationship to BOLD Signal](#)
- [Local Field Potential, Relationship to Electroencephalogram \(EEG\) and Magnetoencephalogram \(MEG\)](#)
- [Local Field Potential, Relationship to Unit Activity](#)
- [Local Field Potential, Synchrony of](#)
- [Local Field Potential: Relationship to Membrane Synaptic Potentials](#)

- [Local Field Potentials in Olfaction](#)
- [Local Field Potentials: Interaction with the Extracellular Medium](#)
- [Local Field Potentials: LFP](#)
- [Resistivity/Conductivity of Extracellular Medium](#)

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Low Frequency Oscillations (Anesthesia and Sleep): Overview

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Synonyms

Delta oscillations; Relay mode; Sleep; Sleep oscillations; Sleep spindles; Slow oscillations; Slow rhythms; Thalamic bursting

Definition

The transition from waking to sleep or to anesthesia is characterized by an increase in the amplitude and a decrease in the frequency of the electrical activity recorded in the electroencephalogram (EEG). The spectral composition of the EEG changes from one dominated by low-amplitude fast frequencies in the

beta gamma range to one dominated by the frequency ranges of slow (0.1–1 Hz), delta (1–4 Hz), and sigma (7–15 Hz, which corresponds with sleep spindles) oscillations (da Silva and Schomer 2011). The dramatic changes in the EEG during the transition from waking to sleep correlate with the deafferentation of the forebrain from the external world and the suppression of consciousness. This section describes cellular mechanisms and computer models of these oscillatory processes and their functional consequences. In this overview entry, some critical points are discussed about the organizations of these rhythms in slow wave sleep and anesthesia.

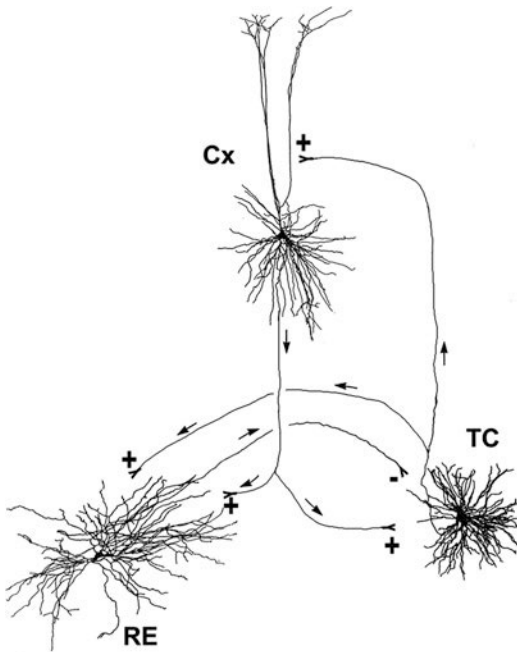
Detailed Description

Background

Slow sleep rhythms are generated within the vast networks connecting thalamus and cortex (Steriade et al. 1994; McCormick and Bal 1997). The main building blocks of thalamocortical circuits (Steriade 2003; Jones 2007), which are essential to understanding the basic principles of rhythm generation (Fig. 1), are (i) reciprocal excitatory glutamatergic connections between cortical pyramidal cells and thalamocortical neurons; (ii) collaterals of excitatory thalamocortical and corticothalamic axons onto reticular thalamic cells, which are established as these axons cross the reticular nucleus on their way in and out of the thalamus; and (iii) inhibitory connections from reticular thalamic cells onto thalamocortical neurons. Reticular thalamic neurons surround the thalamus in its dorsal and lateral surfaces and do not project to the cerebral cortex but project only back into all other thalamic nuclei (Ramon y Cajal 1911). The reciprocal excitation and feedback inhibition combined with various degrees of convergence and divergence are essential to the generation, distribution, and synchronization of the rhythms that characterize sleep and anesthesia (Jones 2001).

Cellular Mechanisms

The single most important cellular mechanism underlying the dramatic transformation in brain



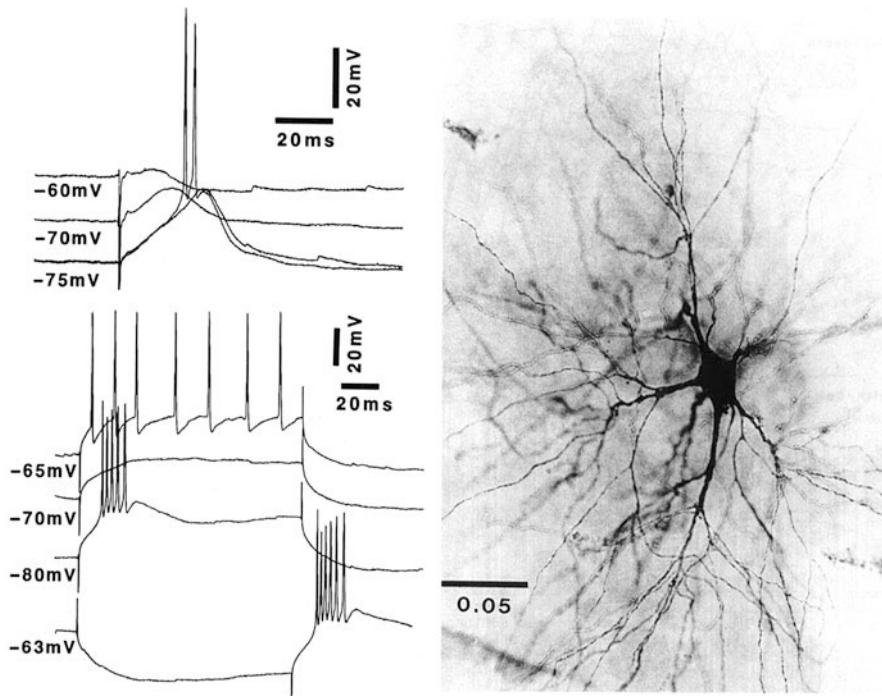
Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 1 A summary of the basic thalamocortico-thalamic circuit: 1. Reciprocal excitatory (glutamatergic) connections between thalamocortical (TC) and cortical (Cx) neurons. 2. Both ascending and descending axons leave collaterals in the reticular nucleus (RE). 3. RE neurons are exclusively GABAergic and project topographically only back into the dorsal thalamus (not to cortex). The three cells used for the schematic were recorded intracellularly in vivo and filled with biocytin

state during the transition from waking to sleep, or to anesthesia, is the change in firing mode of thalamocortical cells (Fig. 2) from tonic to bursting (Llinas and Jahnsen 1982; Jahnsen and Llinas 1984c; Steriade and Llinas 1988; Steriade et al. 1994; McCormick and Bal 1997). At depolarized membrane potentials (V_m) during activated brain states, such as waking, thalamocortical neurons respond to inputs with spike trains that reflect the amplitude and time of the inputs (Deschenes et al. 1984; McCormick and Feese 1990; McCormick and Huguenard 1992). The membrane hyperpolarization that results from the reduction in cholinergic and adrenergic input during the transition from waking to sleep (Oakson and Steriade 1982; Steriade et al. 1982, 1990; Lu et al. 1993; Steriade 1993) removes inactivation of T-type calcium channels (Jahnsen and Llinas

1984a; Nowycky et al. 1985; Coulter et al. 1989; McCormick and Huguenard 1992; Gutierrez et al. 2001). When fully de-inactivated, T-channels are capable of generating an all-or-none calcium spike, known as a low-threshold spike (LTS) because it is triggered at thresholds 10 mV lower than the sodium action potential (Deschenes et al. 1982; Llinas and Jahnsen 1982). The LTS in turn generates sufficient depolarization to trigger a high-frequency (100–300 Hz) burst of sodium action potentials (Llinas and Jahnsen 1982; Deschenes et al. 1984; Jahnsen and Llinas 1984b).

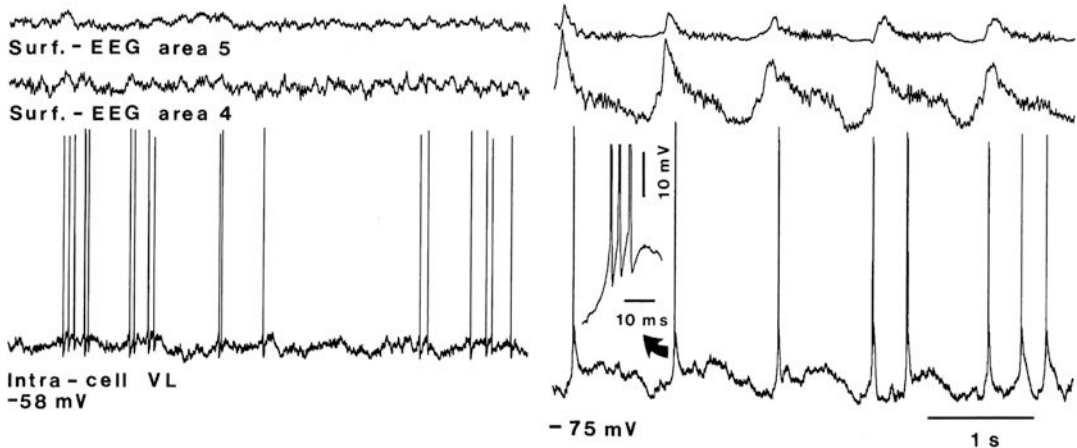
The amplitude of the LTS and, therefore, of the resulting burst of sodium action potentials depend on the proportion of T-channels that are de-inactivated (Deschenes et al. 1982, 1984; Coulter et al. 1989; McCormick and Huguenard 1992), which reaches 100% at the hyperpolarized V_m of late stages of sleep and deep anesthesia.

The mechanism by which LTS bursts are triggered changes throughout the progressive stages of sleep. This is due to the progressive hyperpolarization of thalamocortical cells as sleep (Hirsch et al. 1983) or anesthesia (Contreras and Steriade 1997a) deepens and EEG activity becomes larger and slower (Fig. 3). At early sleep stages, when sleep spindles are the most conspicuous feature of the EEG, thalamocortical cells are still relatively depolarized and T-channels are not fully de-inactivated. De-inactivation depends on the phasic strong chloride-dependent GABAA IPSPs generated by the inhibitory input from reticular thalamic cells during sleep spindles (von Krosigk et al. 1993; Bal et al. 1995; McCormick and Bal 1997). During spindles, LTS bursts are generated as rebound bursts at the offset of these large GABAA IPSPs. At later, deeper (defined by the higher threshold to wake up) stages of sleep, thalamocortical cells are further hyperpolarized and T-channels are fully de-inactivated. At this stage, T-channels are activated by the depolarization caused by the cationic inward rectifier current IH (McCormick and Pape 1990). IH is voltage dependent and activated at the hyperpolarized levels of deep sleep and deep anesthesia. This IH-dependent depolarization, which is a ubiquitous property of thalamocortical cells (Dossi et al. 1992), triggers an LTS and a spike burst, at the



Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 2 This figure shows a thalamocortical neuron, filled with biocytin (*right*) in vivo, responding to synaptic activation (*top three traces*) and direct current injection (*bottom four traces*) through the microelectrode.

Hyperpolarization switches firing mode from tonic to bursting in both cases. *Bottom trace* shows a rebound burst, a burst generated at the termination of a hyperpolarizing pulse (From Contreras and Steriade 1995)



Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 3 The transition from waking to sleep is characterized in the EEG by a transition from high-frequency (~40 Hz) low-amplitude activity to low-frequency (<15 Hz) high-amplitude oscillations. TC cells recorded simultaneously with the EEG show the transition from tonic, relay mode of firing during the waking state to the bursting, all-or-none mode of firing, incompatible with information transfer to the cerebral cortex. In addition, as

shown in the figure, the bursting mode of firing is associated with the presence of global slow oscillations that are synchronized and widespread over large cortical and thalamic territories (the figure shows how activity is synchronized only during sleep between areas 4 and 5, for example). The high-amplitude, synchronized oscillatory activity together with the thalamic bursting mode of firing disconnect the cortex from the outside world during sleep (From Contreras and Steriade 1997a)

end of which, the membrane returns to its hyperpolarized level and reactivates IH, thus restarting a rhythmic cycle at the delta frequency range (McCormick and Pape 1990; Dossi et al. 1992; Nunez et al. 1992a). At the deep stage of sleep where thalamocortical cells generate delta oscillations, the EEG is also dominated by large amplitude rhythmic waves at the delta frequency. However, it is not clear what the relationship is, if any, between the intrinsically generated delta oscillations of thalamocortical cells and the cortical generators of delta oscillations when this rhythm is the predominant feature of the EEG (Amzica and Steriade 1998; da Silva and Schomer 2011; Carracedo et al. 2013).

A fundamental consequence of the progressive hyperpolarization of the Vm of thalamocortical cells throughout sleep (Fig. 3) is that, at the deep sleep stages when delta oscillations dominate the EEG (Fig. 3), the Vm is at or below the reversal potential for chloride, and therefore sleep spindles cannot occur. This leads to an incompatibility of sleep and delta rhythms in thalamocortical cells, with sleep spindles characterizing early stages when the Vm is still relatively depolarized and delta oscillations characterizing late stages when the Vm is very hyperpolarized (Nunez et al. 1992b).

Functional Consequences of Slow Rhythms

Three main consequences result from the transition in firing mode from tonic to bursting during the transition from waking to sleep or anesthesia:

1. *Unreliability of Responses.* Rather than reliable and predictable responses to sensory, motor, or cortical input, thalamic cells respond to inputs with all-or-none bursts of spikes which bear little information about the incoming input. Furthermore, because voltage-dependent inactivation of T-channels lasts tens of milliseconds, bursting responses to depolarizing inputs can only occur at low frequencies and therefore represent a strong frequency filter to incoming inputs (McCormick and Feese 1990).
2. *Rhythmicity.* The transition to burst firing brings about slow rhythmic activity in thalamocortical networks. Three main slow rhythms characterize sleep and anesthesia: sleep spindles (7–15 Hz), delta oscillations (1–4 Hz), and slow oscillations (0.1–1 Hz). Such oscillatory activity requires participation of burst firing by thalamocortical cells and therefore extends the role of thalamic burst firing to the deafferentation of the forebrain. Indeed, in addition to the bursting properties described above, most thalamic spike bursts occur NOT in response to stimuli but, instead, as part of large oscillatory networks, further hindering thalamocortical relay of inputs (Steriade et al. 1994; Steriade 2000).
3. *Synchronization.* An inevitable consequence of thalamic burst firing and slow rhythm generation is the broad synchronization of thalamocortical networks (Contreras and Steriade 1997a, b). By virtue of the divergence and convergence of connections between reticular thalamic and thalamocortical cells, between thalamocortical and cortical neurons and within cortical networks, the strong bursting activity entrains large networks into the slow oscillations of sleep and anesthesia (Amzica and Steriade 1995).

As a result of the above three factors, the reliably responding, rapidly engaged thalamocortical networks that sustain information processing and consciousness in the awake state are transformed into networks that are slow and unreliable in responding and are engaged mostly in slow and synchronized oscillations. These oscillations are incompatible with information processing and ultimately determine the deafferentation of the forebrain during slow wave sleep and anesthesia (Steriade 2000).

Anesthesia and Slow Waves

In contrast with the organized and sequential arrangement of oscillations during sleep, anesthetics mimic and exaggerate one or more rhythmic patterns of sleep in different proportions. For example, during barbiturate anesthesia, the EEG shows spindles most prominently and virtually no delta or slow oscillations. Furthermore, under barbiturate anesthesia, spindle frequency is reduced and

duration increased with respect to naturally occurring sleep spindles. In contrast, ketamine-xylazine generates a strong and exaggerated slow oscillatory pattern on top of which rapid spindles may be triggered. In addition, the slow rhythm during ketamine-xylazine may reach frequencies above 1 Hz and may be confused with EEG delta waves. Urethane anesthesia generates a very stable pattern of slow oscillations with prolonged depolarizing and hyperpolarizing phases but very little spindle or delta oscillations. The combination of propofol and fentanyl produces a rich combination of rhythms including slow oscillations, occasional spindles, and delta waves. Detailed descriptions of oscillatory patterns under different anesthetics are far beyond this section.

Cross-References

- [Corticothalamic Feedback: Large-Scale Synchrony](#)
- [Delta Rhythms: Models and Physiology](#)
- [Slow Oscillations and Epilepsy: Network Models](#)
- [Slow Oscillations: Models](#)
- [Slow Oscillations: Physiology](#)
- [Spindle Oscillations: Models](#)

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Model Reproducibility: Overview

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Definition

The ability to reproduce an experimental result is the foundation of scientific inquiry. Similarly,

computational studies need to be reproducible to serve the advance of science. However, computational scientists often find it difficult to reproduce published computational results. Here we provide an overview of efforts to support model reproducibility in computational neuroscience.

Detailed Description

Reproducing the simulation results of computational models and establishing the provenance of results should be straightforward given that computational studies do not suffer from the measurement errors seen in the experimental sciences. However, computational science has its own challenges for reproducibility, which are described well by Crook et al. (2013). In particular, issues such as the sensitivity of a model to numerics or the publication of models that are computationally under-specified lead to the need for criteria for successful model reproduction in many cases. These authors also make distinctions among:

- *Replicability*, where the same code and tools are used to reproduce results
- *Cross-replicability*, where the same model is used but implemented using different software
- *Reproducibility*, where a new model is implemented and produces the same scientific result

As noted in Crook et al. (2013), the boundary between cross-replicability and reproducibility is not always clear, but all efforts along this continuum of reproducible research contribute to advances in the computational sciences.

Model Sharing

Model sharing provides a means for promoting replicability and transparency in the computational sciences. For many reasons, the best infrastructure for sharing models involves curated model repositories such as ModelDB (Migliore et al. 2003), the BioModels Database: a Public Repository for Sharing Models of Biological Processes (Li et al. 2010; Vijayalakshmi et al. 2013), the Physiome Repository (Yu et al. 2011), and Open Source Brain (Gleeson et al. 2019).

Simulator Independent Specification of Models and Simulations

There are a number of ongoing efforts in support of cross-replicability with the aim of providing declarative descriptions of models that are simulator independent. Many of these efforts focus on the use of Extensible Markup Language (XML) technology (Bray et al. 1998) as an ideal representation for complex models.

The Systems Biology Markup Language (SBML) (Hucka et al. 2003) and CellML (Lloyd et al. 2004) are two popular languages for describing systems of interacting biomolecules that comprise models that are often used in systems biology. Both languages also can be used for describing more generic dynamical models, including those in neuroscience. FieldML follows a similar approach but focuses on multivariate spatiotemporal models and models based on the finite element method. NeuroML (Goddard et al. 2001; Crook et al. 2007; Gleeson et al. 2010) differs from these languages in that it is domain specific, where neuroscience concepts like cells, ion channels, and synapses form the basis for objects described in the language. NineML is another domain-specific language that focuses on descriptions of spiking neural networks. Additionally, the Simulation Experiment Description Markup Language (SED-ML) (Köhn and Le Novère 2008) provides a language for describing the details of simulation experiments. These different markup languages are complementary, and together they cover the different spatial scales for the majority of models in neuroscience.

Other efforts focus on code-based approaches for simulator independent model descriptions. PyNN is a Python-based, simulator independent language for building neuronal network models then simulating the model on any simulation platform that PyNN supports such as NEURON, NEST, and Brian (Davison et al. 2009).

The International Neuroinformatics Coordinating Facility, or INCF, advocates for FAIR (Findable Accessible Interoperable Reproducible) principles across all of their projects and activities including neuroscience data and models. In support of this effort, the organization provides a process for the formal endorsement of community standards, including two for describing models, NeuroML and PyNN.

Improved Research Reporting

In the systems biology community, MIRIAM (Minimum Information Required in the Annotation of Models, <http://co.mbine.org/standards/miriam>) is a community-level effort to provide a set of guidelines for use with any structured format for sharing models. The idea of using best practices and some required metadata for sharing and publishing models is outlined by Novère et al. (2005). All of these requirements can be adapted readily to models in neuroscience. Nordlie et al. (2009) conducted a survey of neuronal network models in the literature and found that current approaches are diverse and inadequate. These authors propose the adoption of best practices for model descriptions in publications, recommending the inclusion of the hypothesis, model derivation, model description, implementation details, model analysis, and model justification. They also provide a concise tabular format for summarizing network models in publications. Publication standards such as those discussed by Le Novère et al. and Nordlie et al. ensure that all possible model details are provided; however, it is important to be aware of the limits of replicability and the impact on reproducibility.

Cross-References

- [CellML](#)
- [FieldML](#)
- [NeuroML](#)
- [NineML](#)
- [PyNN: A Python API for Neural Network Modelling](#)
- [Simulation Experiment Description Markup Language \(SED-ML\)](#)
- [Systems Biology Markup Language \(SBML\)](#)

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Modeling of Disease: Physical and Molecular Level, Overview

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Definition

Physical-, molecular-, and cellular-scale understanding is not only the first step in the long ladder of multiscale modeling for clinical translational application, it is also the critical scale: “Where the rubber meets the road.” The idiom from automotive engineering refers to the critical endpoint where all the ancillary engineering – fuel system, chassis, pistons, etc. – is finally tested. In the realm of translation, this point comes when we translate basic research results to the clinical setting. The physician intervenes at the molecular scale, using pharmacological agents to alter physiological activity only observed at far higher scales: the macroscopic realms of clinical tests and of signs and symptoms. The surgeon intervenes at a physical scale, for example, tying off or filling up a vascular aneurysm to prevent its bursting in the brain.

Given the vast scale gap between molecular or physical treatments and macroscopic outcome, there is enormous difficulty in understanding causal relations, so as to design better drugs and better drug combinations. Multiscale modeling can help make these connections in order to provide a basis for rational pharmacological or surgical treatment.

Detailed Description

This section includes entries of three types:

Techniques: These simulations are performed largely using techniques used elsewhere in computational neuroscience. However, some techniques have been introduced or expanded in the context of their use in translational studies.

Locations: Partitioning of the nervous system can be done at many scales, from organelle to major brain area.

Diseases: We make note of a few neurological and psychiatric illnesses that have been examined at this scale.

Techniques

The standard techniques of molecular and cellular computational neuroscience are utilized for clinical and translational modeling. The techniques that are applicable to simulation at the molecular and cellular level are listed here by their coverage in the entries of this encyclopedia (loosely grouped from micro to macro):

Stochastic Simulators

- [Gillespie Algorithm for Biochemical Reaction Simulation](#)
- [Deterministic Reaction-Diffusion Simulators](#)
- [Bimolecular Reactions, Modeling of](#)
- [Equivalent Cylinder Model \(Rall\)](#)

In this section, we add three additional methods that have been applied to clinical translational problems.

► [“Polypeptide and Protein Modeling for Drug Design”](#) takes us down to the lowest of the

multiple scales used in computational neuroscience. Polypeptide modeling largely utilizes ball-and-spring modeling, staying above the level of quantum mechanical representations. Individual atoms or atomic groups (e.g., amino acids) are represented as moving in a force field largely determined by the chemical bonds connecting them. This research has direct importance for clinical translation because the lock-and-key fit of a ligand (a drug) to a target is dependent on the physical relations of the interacting species.

“Application of Declarative Programming in Neurobiology to Decipher Normal and Pathological Processes” demonstrates the novel use of a declarative programming language to address problems in Alzheimer’s disease and in fear conditioning. Declarative programming is distinguished from the familiar imperative programming languages which we commonly utilize. Imperative programs implement an algorithm. Declarative programs describes relationships between elements, defining what computations are possible among these elements.

► [“Biomechanical Modeling of Traumatic Brain Injury”](#) provides physical-level models that consider the material properties of tissue, its geometry, and boundary conditions for stresses applied to the head, using finite element methods to predict injury from impact.

Locations

Disease strikes at many locations and at many scales. Parsimony and clinical efficacy depend on finding the proper scale and proper locus for clinical investigation and for clinical intervention – in some cases these are not the same location. A recent example from oncology is illustrative: a renal cancer and a leukemia were previously classified according to organ system and therefore treated by different subspecialists with different therapeutic approaches. These cancers have now been found to share the same tumor mutation and to benefit from similar treatments. As in this oncology example, protean neurological diseases will also express widely. For example, diseases of mitochondria such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers; the ragged fibers

being broken mitochondria) produce neurological disorders across many neural systems, beyond the already broad scope of their acronyms (DiMauro et al. 2013).

In addition to connoting locations in the brain and body (macroscale), disease localization also needs to consider the locus in the cell: particular organelles such as mitochondria, particular classes of molecules such as ion channels, and particular specialized subcellular spaces such as synapses and spines. Some of these locations are covered elsewhere in these volumes: see ► [“Synaptic Dynamics: Overview”](#) and ► [“Dendritic Spines”](#). It is to be expected that disorders of spine shape, and of proteins involved in synaptic plasticity, will produce neurological or psychiatric disorders. In this section, we consider the modeling of pharmacotherapeutic manipulation of ion channels in ► [“Neuropharmacological Modeling Alterations in Ionic Homeostasis”](#) and ► [“Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation”](#).

A literal route to clinical application is described here in ► [“Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery”](#). The blood-brain barrier and the extracellular space represent the major pathways for delivery of pharmacological agents. Due to therapeutic index (therapeutic concentration/toxic concentration ratio), it is important to consider how a particular drug can be delivered so as to arrive at adequate concentrations at the site of disease, without being present at excessive concentration at other locations (Brick and Erickson 2013).

At the cellular level, neurological disease has substantial overlap with disease in other excitable tissues. It is particularly valuable to consider the extensive work that has been done in cardiology, here represented by ► [“Cardiac Excitable Tissue Pathology \(Ion Channels\)”](#) and ► [“Cardiac Excitable Tissue Pathology \(Ischemia\)”](#). Cardiology models are generally more mature than those in neurology. They also have direct analogies to diseases of the brain, e.g., myocardial infarction and stroke, arrhythmias, and epilepsies. Similarly, excitable tissue is important in the islets of the pancreas and in other endocrine systems, where production and release of hormone are directly

analogous to production and release of neurotransmitters: see entry on ► [“Endocrine Cell Function and Dysfunction”](#). A broader physiological perspective, relevant to many of these cell types, is presented here in ► [“Neuropharmacological Modeling Alterations in Ionic Homeostasis”](#).

Many neurological diseases present outside of the brain or involve the brain in its association with the body. In particular, the enteric nervous system (ENS) and autonomic nervous system (ANS) are prone to disorders (Rao and Gershon 2016) and will be important areas for modeling in the future. In the present section, we feature an entry on ► [“Pathological Changes in Peripheral Nerve Excitability”](#), to consider disorders in the peripheral nervous system (PNS). It is important to note that myopathies (muscle diseases) also fall within the bailiwick of neurology and will benefit from modeling, some of which can be borrowed from the cardiology literature.

At the subcellular level, signaling occurs through second and third through nth messengers. There has been considerable modeling at this scale (Blackwell 2013), but not as much looking at dysfunction. These topics are covered in detail in the entry on ► [“Biochemical Signaling Pathways and Diffusion: Overview”](#). Particular note should be made of the major role of calcium as a second messenger, covered in eight entries in that section. Certainly, dysregulation of calcium control will play a major role in the production and expression of disease that has yet to be elucidated by modeling. A review of the key role of calcium in Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease and the current modeling efforts are presented in the entry on ► [“Calcium Dysregulation in Neurodegenerative Diseases”](#).

At the subcellular and intracellular level, neurons metabolic dependence on astrocytes is modeled in ► [“Brain Energy Metabolism”](#). The entry details how dysfunction, particularly glucose hypometabolism in neurodegenerative diseases, could lead to cognitive impairments. It includes a detailed example of a three-compartment metabolic network model of energy metabolism and the challenges of developing a spatial model.

A multiscale model of neuroinflammation is described in the entry ► [“Neuroinflammation,](#)

[Glia, and Cytokines: Networks of Networks](#)". It involves modeling networks of molecular interactions at the subcellular level, which influence a network of cell states that then feed into a network of inflammation states at the tissue level. Complex network interactions can lead to unexpected results. The entry describes several modeling approaches including machine learning, dynamic systems, and control theory that reveal underlying properties of the system.

All disease is to a greater or lesser extent multifactorial. Patient susceptibility is determined in substantial part by the genome and its control, as well as by the epigenome (and metagenome, representing additional genomes that are involved (mitochondrial, bacterial – commensal or pathological, viral). In a neuron, communication between genome and synapse is particularly complex, insofar as this is information flow between the organism's two primary loci of information storage. Synaptic changes depend on elaboration, transport, and insertion of membrane proteins, which start with signals at the synapse that trigger changes in transcription. In the present section, we cover the role of second messengers in providing communication with the cell nucleus: ► ["Transcriptional Control Dysfunction, Modeling"](#), evaluating potential pathology in the linkage between the cell and its nucleus at the molecular and organelle scales.

Diseases

Evaluation of individual diseases is the natural approach for clinical translation – as an end goal we want to know how to treat a particular disease or even a particular patient (personalized medicine) or subgroup of patients (precision medicine). We highlight here four diseases, although there are several others where some cellular/molecular modeling progress has been made and many more where such progress is greatly needed.

A model of molecular dependencies in Alzheimer's is presented in "Application of Declarative Programming in Neurobiology to Decipher Normal and Pathological Processes". Examples of modeling the role of calcium in this disease are given in ► ["Calcium Dysregulation in Neurodegenerative Diseases"](#).

As a lens through which to view computational neuroscience, disease modeling presents a number of difficulties. First, diseases are generally multi-organ, both in production and in expression. For example, we present here an entry on ► ["Brain Ischemia and Stroke"](#). Stroke is most often caused by atherosclerosis, a disease of blood vessels. A translational model would ideally include the cellular changes of the arterial wall and the changes in hemodynamics, along with factors that include the blood-brain barrier (which breaks) and the role of a broad dispersion of harmful neurohumoral agents. Stroke frequently co-occurs with myocardial infarction (MI). These coincident disorders, in the brain, heart, and local microvasculature, affect one another, e.g., MI reduces cardiac output and therefore increasing the extent of an incipient stroke (Gan and Ramani 2008). Another difficulty in providing a unified model of a disease is that the disease may involve many disparate variants: hemorrhagic vs. bland stroke, thrombotic vs. embolic stroke, and cortical stroke (gray matter) vs. internal capsule (white matter) stroke.

As mentioned in the ["Definition"](#) section above, modeling at physical, molecular, and cellular levels is only the lowest rung in the multi-scale ladder of both downward and upward causality. Disparate viewpoints at different scales represent a challenge but are a necessary stage in the development of future unified multiscale views, as can be illustrated by the case of epilepsy – contrast the entry in the section: ► ["Epilepsy: Abnormal Ion Channels"](#) with the perspective presented in entries on ► ["Epilepsy: Computational Models"](#), ► ["Slow Oscillations and Epilepsy: Network Models"](#), and ► ["Epilepsy, Neural Population Models of"](#).

How are we to build multiscale models out of these disparate pieces? Ideally it would be possible to embed one scale within the model for the higher scale, thereby creating a single unified multiscale model. In many cases this is not possible, so that the models remain separate, with each level informing the other via emergent properties discovered at the lower level. In the case of epilepsy research, emergences from the effect of a drug on a detailed model of an ion channel can be used to change the parameterizations of an ion

channel, which could then be directly embedded in a compartmental model. Emergences from the compartment model can then be used in a reduced model or to modify an integrate-and-fire model. Either of these models (or both as in a hybrid network) can be directly embedded to produce large network models. Emergences from the network can then be used to modify a mean-field model. While this upward sequence is difficult, the downward sequence is even more difficult: we want to follow the scales back down in order to apply lessons learned from the population model in order to eventually suggest changes to drug effect at the polypeptide level.

Conclusions

These initial efforts aimed at understanding the base scale of physical, molecular, and cellular interactions for understanding brain disease should be considered in the context of the wider field of computational systems biology, a field concerned with multiscale modeling across organ systems and medical specialties. Systems biology has been catapulted forward with the realization that the massive amounts of data being collected as genomes, proteomes, and other omes will not be interpretable without contexts, contexts that can only be provided by sophisticated computational models. Further future hope springs from the potential of computer simulation to provide personalized or precision medicine; physiological data from a particular patient would be used to adapt simulation parameters for simulation, just as anatomical data for a particular patient is currently used to provide specifics of beam targeting in radiation therapy.

Cross-References

- ▶ [Biochemical Signaling Pathways and Diffusion: Overview](#)
- ▶ [Biomechanical Modeling of Traumatic Brain Injury](#)
- ▶ [Bimolecular Reactions, Modeling of](#)
- ▶ [Brain Energy Metabolism](#)

- ▶ [Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery](#)
- ▶ [Brain Ischemia and Stroke](#)
- ▶ [Calcium Dysregulation in Neurodegenerative Diseases](#)
- ▶ [Cardiac Excitable Tissue Pathology \(Ion Channels\)](#)
- ▶ [Cardiac Excitable Tissue Pathology \(Ischemia\)](#)
- ▶ [Dendritic Spines](#)
- ▶ [Deterministic Reaction-Diffusion Simulators](#)
- ▶ [Endocrine Cell Function and Dysfunction](#)
- ▶ [Epilepsy, Neural Population Models of](#)
- ▶ [Epilepsy: Abnormal Ion Channels](#)
- ▶ [Epilepsy: Computational Models](#)
- ▶ [Equivalent Cylinder Model \(Rall\)](#)
- ▶ [Gillespie Algorithm for Biochemical Reaction Simulation](#)
- ▶ [Neuroinflammation, Glia, and Cytokines: Networks of Networks](#)
- ▶ [Neuropharmacological Modeling Alterations in Ionic Homeostasis](#)
- ▶ [Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation](#)
- ▶ [Pathological Changes in Peripheral Nerve Excitability](#)
- ▶ [Polypeptide and Protein Modeling for Drug Design](#)
- ▶ [Slow Oscillations and Epilepsy: Network Models](#)
- ▶ [Synaptic Dynamics: Overview](#)
- ▶ [Transcriptional Control Dysfunction, Modeling](#)

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Motoneurons and Neuromuscular Systems: Overview

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Definition

Motoneuron models are mathematical representations of motoneuron structure and function. Neuromuscular models represent computational models of neural components integrated with muscle models at various levels of detail and complexities. These models provide a computational framework for investigating neural control of movement. Together, motoneuron and neuromuscular models can guide the development of biomimetic neuromuscular control systems and neural prostheses.

Detailed Description

Motor neurons (or motoneurons) are the final common pathway for all neural drive to the skeletal musculature. Each motoneuron innervates one or more muscle fibers and the cell bodies of motoneurons are somatotopically organized in both vertebrates and invertebrates. Motoneurons were among the first neurons to be studied in great detail by experimentalists largely due to their unique position as output neurons of the nervous system. The rich tradition of the experimental work dates back to the early 1900s beginning with the historical work by Sir John Eccles (1903–1997) and Sir Charles Sherrington (1857–1952), followed by a host of physiologists to date whose work has laid the foundations for realistic models of motoneurons.

Like many neurons in the nervous system, motoneurons show repetitive firing behavior in response to excitation. However, like no other neurons in the nervous system, their frequency of spike discharge directly dictates the degree of muscle contraction. In this way, they mediate control of complex behaviors. At the cellular level, they possess complex morphologies that strongly influence their integrative function. They house a rich assortment of intrinsic membrane-bound ion channels that dynamically interact with a wide range of synaptic inputs to produce unique nonlinearities in their membrane properties. The heterogeneity of cellular properties within a motor pool further confers complex population dynamics. Taken together, motoneurons are an important class of neurons in the nervous system that are attractive candidates for modeling in order to gain a deeper understanding of the neural basis of motor control.

In this section, we discuss principles and methodologies used to develop models of motoneurons and motor effectors at various levels of complexities and scales. At the single cell level, articles presented describe two-compartment models ([► Algorithmic Reconstruction of Motoneuron Morphology](#)), more complex multi-compartment models ([► Brainstem Motoneurons, Models of](#)), and morphologically realistic models ([► Compartmental Models of Spinal Motoneurons](#)). Among vertebrate motoneurons, we explicitly address models of spinal ([► Brainstem Motoneurons, Models of](#)) and brainstem motoneurons ([► Computational Models of Motor Pools](#)). We further describe novel algorithms that can generate realistic motoneuron morphologies given a simple set of experimentally derived morphometric parameters ([► Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons](#)). At the population level, we describe motor pool models ([► Mammalian Motor Nerve Fibers, Models of](#)). We also describe the computational principles underlying models of the muscles ([► Morphologically Detailed Motoneuron Models](#)). Since motor fibers traverse long distances to provide electrochemical signals for these effectors, models of motor nerve fibers and propagation

of electrical signals along them are described (► [Neuromuscular Control Systems, Models of](#)). Lastly, systems-level models of the neural control systems that enable us to perform tasks by providing suitable input to motoneurons are described (► [Physiology and Computational Principles of Muscle Force Generation](#)).

neuronal system. In the absence of noise or perturbation, the neuronal system permanently exhibits one of the regimes. Multistability suggests that by an appropriate choice of perturbation or by resetting the initial state of the system, one could induce a switch from one regime into another.

Cross-References

- [Algorithmic Reconstruction of Motoneuron Morphology](#)
- [Brainstem Motoneurons, Models of](#)
- [Compartmental Models of Spinal Motoneurons](#)
- [Computational Models of Motor Pools](#)
- [Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons](#)
- [Mammalian Motor Nerve Fibers, Models of](#)
- [Morphologically Detailed Cellular and Pool Motoneuron Models](#)
- [Neuromuscular Control Systems, Models of](#)
- [Physiology and Computational Principles of Muscle Force Generation](#)

Detailed Description

Multistable neuronal system can exhibit two or more regimes of activity, depending on its initial state. Both isolated neurons and neuronal networks can exhibit coexistence of several activity regimes. The coexistence of silence, subthreshold oscillations, tonic spiking, and bursting regimes with each other has been observed in a number of theoretical and experimental studies. A multistable neuronal system can show long-lasting responses to short transient signals. Such systems also may respond to perturbations in a state-dependent fashion, demonstrating hysteresis, which is the hallmark of (Nadim et al. 2008). Multistability has clear implications for dynamical memory and information processing in neurons (Marder et al. 1996; Egorov et al. 2002; Durstewitz and Seamans 2006). In the area of motor control, multistability could be a major mechanism of operation of multifunctional central pattern generators (Getting 1989; Venugopal et al. 2007; Briggman and Kristan 2008). On the other hand, multistability can be a pathological feature; for example, seizure regimes can coexist with normal regimes (Ziburkus et al. 2006; Cressman et al. 2009; Frohlich et al. 2010). For the latter, the electrogenic pump has been implicated to play a crucial role (Cressman et al. 2009; Krishnan and Bazhenov 2011).

Multistability can be categorized in terms of the regimes of activity which coexist, e.g., coexistence of tonic spiking and silence (Rinzel 1978; Guttman et al. 1980; Forger and Paydarfar 2004; Hahn and Durand 2001), coexistence of bursting and silence (Malashchenko et al. 2011a, b), coexistence of different bursting regimes (Wang 1994; Butera 1998; Newman and Butera 2010), and

Multistability in Neurodynamics: Overview

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Synonyms

Bistability; Coexistence; Fold bifurcation; Hysteresis; Subcritical bifurcation

Definition

Multistability in neurodynamics is the coexistence of two or more observable regimes of activity, i.e., attractors, in the phase space of a

coexistence of bursting activity and tonic spiking (Canavier et al. 1994; Frohlich et al. 2010; Cymbalyuk et al. 2002; Shilnikov et al. 2005; Malashchenko et al. 2011a). These regimes can coexist in the phase space of a neuronal system if some unstable regime creates a barrier, i.e., a separatrix demarcating a border between the basins of attraction. The mechanism underlying multistability can also be described and classified in terms of the unstable regime that forms the barrier (Rinzel 1978; Guttman et al. 1980). One of the key ingredients of such descriptions is the identification of the transitions, i.e., bifurcations, at which the unstable regimes appear and disappear. Ubiquitously, a separating regime is either a saddle equilibrium or a saddle orbit (Rinzel 1978; Malashchenko et al. 2011a; Barnett et al. 2013; Marin et al. 2013). For example, the stable manifold of the saddle equilibrium separates tonic spiking and silence observed in the simplified model of the cerebellar Purkinje neurons (Loewenstein et al. 2005; Fernandez et al. 2007), and the stable manifold of the saddle periodic orbit is a cause of bistability of spiking and silence in the giant squid axon (Rinzel 1978; Hahn and Durand 2001).

The methods developed in the bifurcation theory allow one to investigate stability of, evolution of, and transitions between the silent and oscillatory regimes of neuronal models in response to variation of the system's parameters (Kuznetsov 2004; Terman and Ermentrout 2010; Izhikevich 2010). Application of these methods identifies and explains the mechanisms supporting multistability under normal and pathological conditions (Rinzel 1978; Guttman et al. 1980; Forger and Paydarfar 2004; Gutkin et al. 2009; Hahn and Durand 2001; Krishnan and Bazhenov 2011; Shilnikov et al. 2005; Fröhlich and Bazhenov 2006; Cressman et al. 2009; Cymbalyuk and Shilnikov 2005; Malashchenko et al. 2011a, b).

Cross-References

- [Coexistence of Bursting Regimes](#)
- [Multistability Arising from Synaptic Dynamics](#)

- [Multistability in Perception Dynamics](#)
- [Multistability in Seizure Dynamics](#)
- [Multistability of Coupled Neuronal Oscillators](#)

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Neural Population Models and Cortical Field Theory: Overview

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The term neural population models (NPMs) is used here as catchall for a wide range of approaches that have been variously called neural mass models, mean field models, neural field models, bulk models, and so forth. All NPMs attempt to describe the collective action of neural assemblies directly. Some NPMs treat the densely populated tissue of cortex as an excitable medium, leading to spatially continuous cortical field theories (CFTs). An indirect approach would start by modelling individual cells and then would explain the collective action of a group of cells by coupling *many* individual models together. In contrast, NPMs employ collective state variables, typically defined as averages over the group of cells, in order to describe the population activity directly in a *single* model. The strength and the weakness of his approach are hence one and the same: simplification by bulk. Is this justified and indeed useful, or does it lead to oversimplification which fails to capture the phenomena of interest?

In ► [“Mesoscopic Anatomy and Neural Population Models,”](#) Liley explains that the anatomy of the brain is organized into connected modules at the mesoscopic level, which can serve as a biological substrate for NPMs. In ► [“Neuropercolation and Neural Population Models”](#) and ► [“Neural Mass Action,”](#) Kozma describes how this undergirds coherent neural activity. Brunel and Hakim demonstrate in ► [“Population Density Model”](#) and ► [“Fokker-Planck Equation”](#) how NPMs can be derived mathematically from existing descriptions of individual cells, and in ► [“Stochastic Neural Field Theory,”](#) Bressloff shows this for the CFT variant as well. Liley then introduces the general NPM approach in ► [“Neural Population Model,”](#) and Hutt the CFT variant in ► [“Neural Field Model, Continuum.”](#)

Some historically important and/or particularly popular NPMs are showcased in ► [“Amari Model”](#) by Potthast, ► [“Down Under Neural Population Models”](#) by Liley, ► [“Jansen-Rit Model”](#) by Knösche, and ► [“Wilson-Cowan Model”](#) by Kilpatrick.

The modelling of connectivity in NPMs has been a topic of considerable development over the years and is covered in ► [“Propagator, Axonal”](#) and ► [“Synaptic Connectivity in Neural Population Models”](#) by Jirsa, as well as in ► [“Gap Junctions, Neural Population Models and”](#) by Sleight and the Steyn-Rosses. The dynamical properties of NPMs are key for their application to various brain phenomena. The quasi-linear and noise-driven mode is described in ► [“Transfer Function, Electrocortical”](#) by Molaei-Ardekani and Wendling. Transitions in dynamics, for example, to self-sustained oscillations, are discussed in ► [“Bifurcations, Neural Population Models and”](#) by Knösche and ► [“Phase Transitions, Neural Population Models and”](#) by Sleight and the Steyn-Rosses. Whereas the emergence of spatial structure is presented in ► [“Pattern Formation in Neural Population Models”](#) by Hutt and the chaotic regime in ► [“Chaos, Neural Population Models and”](#) by Knösche.

A fundamental strength of NPMs is their ability to predict the data generated by neuroimaging modalities like the electro- and magnetoencephalogram (EEG/MEG) and functional magnetic resonance imaging (fMRI), as described in ► [“Neuroimaging, Neural Population Models for”](#) by Bojak and Breakspear. This allows the comparison of model predictions with experimental data, be it for normal brain function as in ► [“Gamma Rhythm, Neural Population Models of the”](#) by Bojak and ► [“Sleep, Neural Population Models of”](#) by Phillips, under the influence of drugs as in ► [“Anesthesia, Neural Population Models of”](#) by Sleight and the Steyn-Rosses or in disease as in ► [“Epilepsy, Neural Population Models of”](#) by Wendling and Molaei-Ardekani. While many of the methods used to predict the recorded signals are sound and even sophisticated, some of the basics still require substantial improvements, as Einevoll reminds us in ► [“Extracellular Potentials, Forward Modeling of”](#) Much of the work so far has been in forward

prediction with NPMs; however, increasingly it is important to estimate the NPM state and parameters directly from the data. This is elucidated by Moran in ► [“Dynamic Causal Modelling with Neural Population Models”](#) and by Potthast in ► [“Inverse Problems in Neural Population Models.”](#) Finally, it is exciting that NPMs, and CFTs in particular, can be used to model perception and motor control, as Schöner describes in ► [“Embodied Cognition, Dynamic Field Theory of,”](#) with additional remarks by Schöner and Nowak given in ► [“Coordination Dynamics.”](#)

To answer the question that was posed in the beginning, not only is the NPM approach justifiable and has shown itself to be useful; we expect that within a decade or two, NPMs will take their rightful place as the primary means for describing mesoscopic brain activity. The central problem we face at this description level will not be to simulate millions of brain cells in a reasonable amount of time; the central problem is now, and will be then, that we cannot *specify* the properties and interactions of so many brain cells in a biologically meaningful manner and cannot generate actual *human insight* into principles of function from the plethora of individual cell activities. Once the computational power becomes readily available, this realization will be unavoidable. The way forward will be multi-scale descriptions wherein higher levels discard irrelevant detail of lower levels for an effective and efficient description that remains accessible to the human mind. And given their intimate connection to (noninvasive) neuroimaging, we expect that NPMs will play a privileged role in such a future scheme. This section provides a mere snapshot of a field that is currently growing rapidly and will continue to do so in the foreseeable future.

Cross-References

- [Amari Model](#)
- [Anesthesia, Neural Population Models of](#)
- [Bifurcations, Neural Population Models and](#)
- [Chaos, Neural Population Models and](#)
- [Coordination Dynamics](#)

- ▶ Down Under Neural Population Models
- ▶ Dynamic Causal Modelling with Neural Population Models
- ▶ Embodied Cognition, Dynamic Field Theory of
- ▶ Epilepsy, Neural Population Models of
- ▶ Extracellular Potentials, Forward Modeling of
- ▶ Fokker-Planck Equation
- ▶ Gamma Rhythm, Neural Population Models of the
- ▶ Gap Junctions, Neural Population Models and
- ▶ Inverse Problems in Neural Population Models
- ▶ Jansen-Rit Model
- ▶ Mesoscopic Anatomy and Neural Population Models
- ▶ Neural Field Model, Continuum
- ▶ Neural Mass Action
- ▶ Neural Population Model
- ▶ Neuroimaging, Neural Population Models for
- ▶ Neuroperturbation and Neural Population Models
- ▶ Pattern Formation in Neural Population Models
- ▶ Phase Transitions, Neural Population Models and
- ▶ Population Density Model
- ▶ Propagator, Axonal
- ▶ Sleep, Neural Population Models of
- ▶ Stochastic Neural Field Theory
- ▶ Synaptic Connectivity in Neural Population Models
- ▶ Transfer Function, Electrocardiac
- ▶ Wilson-Cowan Model

Neuromodulation: Overview

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Definition

Neuromodulation refers to the regulation of neural and synaptic function by regulatory extrinsic or intrinsic substances.

Detailed Description

Computational modeling of neural substrates provides an excellent theoretical framework for the understanding of the computational roles of neuromodulation. Neuromodulation can be defined as biophysical processes that serve to modify – or modulate – the computation performed by a neuron or network as a function of task demands and behavioral state of the animal. These modulatory effects often involve substances such as acetylcholine (ACh), norepinephrine (NE), histamine, serotonin (5-HT), dopamine (DA), and a variety of neuropeptides. Modulatory effects are difficult to define, because they often originate from different structures and have different spatial distributions and time courses of action. Because of the wider use of modeling techniques and growing interest in systems neuroscience, the computational role of neuromodulation in information processing has helped elucidate neuromodulatory function, and predictive theories have arisen from computational approaches.

Neuromodulation can be described by its spatial and temporal characteristics, as well as the specific computational function ascribed to it. Spatial characteristics include extrinsic, originating from an area extrinsic to the network under study, or intrinsic, originating from processes within the area under study. The computational functions of extrinsic neuromodulation, such as ACh, NE, 5HT, and DA, are usually considered somewhat global, because they modulate many areas of the brain simultaneously. Classically, ACh has been associated with attentional processes, NE with signal-to-noise modulation, DA with reward learning, and 5HT with sleep-wake transitions. In other cases, modulation is specific to the network under investigation and an integral part of the computations performed within. Second messenger systems, plasticity processes, and gene regulation are examples of such intrinsic modulation. From a functional point of view, neuromodulation is often regulatory, for example, in the cases of second messenger systems or activity-dependent regulation of conductances. In the sensory

systems, neuromodulation is often linked to tuning of receptive fields (ACh) and regulation of signal-to-noise ratio. A third highly important function of most neuromodulators is the regulation of plasticity, via excitability of neurons, synaptic plasticity, and broader modulation of network dynamics.

Exactly how neuromodulation is integrated in computational studies depends widely on the details of implementation of the computational model itself. Effects of neuromodulators can be implemented from the detailed biophysical level, to broader regulation of network parameters in case of more abstract large-scale models. For example, specific effects on voltage-gated channels may be implemented in a biophysical model by changing channel parameters, in a simplified integrate and fire model by changing a related parameter such as firing threshold. Each study chooses the level of detail appropriate to the question asked and data available. For a comprehensive review of levels of implementation of neuromodulation in computational models, we refer the reader to Fellous and Linster (1998). The chapters in this section cover overviews of neuromodulatory computation divided by substance, nature of task, as well as overviews of types of network implementations and specific examples.

Cross-References

- [Computation with Dopaminergic Modulation](#)
- [Computation with Serotonergic Modulation](#)
- [Computational Models of Modulation of Oscillatory Dynamics](#)
- [Computational Models of Neuromodulation](#)

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Neuromorphic Engineering: Overview

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Definition

Neuromorphic engineering is a recent interdisciplinary field involving biologists, physicists, mathematicians, computer scientists, and engineers to design hardware/physical models of neural systems. It aims at designing silicon-based neural systems for computational or biomedical purposes. The term “neuromorphic” relates to the computational architecture, shaped to model biological neural systems: neuromorphic engineering is by essence strongly linked to computational neuroscience.

Detailed Description

Neuromorphic engineering offers an interesting alternative to computer simulations of neural networks: while main components of computers are high-precision high-speed digital hardware with high-power dissipation, neural components are slow asynchronous computational elements which use a combination of analog and digital signal representations. Neuromorphic systems are hardware implementations that operate in physical time; they are inspired by the structure, function, and plasticity of biological nervous systems. Their design is facilitated by similarities between VLSI (very large-scale integrated circuits) hardware and neural bioware.

Since decades, researchers have been implementing electronic models of neural circuits, following the long history of artificial neural networks that started in the 1950s. Original neuromorphic circuits (Mead 1989) were VLSI systems that used the nonlinear and graded properties of transistors to emulate protein channels in neurons. More recently the term neuromorphic

has been used to describe analog, digital, and mixed analog-digital VLSI as models of neural computation.

Neuron model computation can be either analog, with a continuous-time and continuous-value representation, or digital using numerical algorithms. In both cases, neuromorphic devices classically use spiking (asynchronous binary signal analogs to neural spikes) representation for neuronal communication and learning mechanisms. At the neural network level, synaptic modification mechanisms are usually introduced to model learning and adaptation in neural systems. Furthermore, similar to robustness of neural networks to changes in the environment, dynamic synaptic modification in neuromorphic systems allows gaining a remarkable robustness against transistor-level variations. Whatever the technological support of the neuromorphic electronics, real-time computation is mandatory for systems interacting with a biological environment (sensory or motor).

To date, widely known neuromorphic systems are highly integrated VLSI that emulate sensory transduction (vision, olfaction, audition) or more sophisticated and multimodal neural systems like the head-direction system. Larger neuromorphic systems emerged in the last decade, emulating complex or cognitive biological functions and suggesting new research directions for robotics by the means of biomorphic engineering.

According to the VLSI technology road map, promising low-power and high-density nanoscale technologies, including organic electronics, memristors, or 3D technologies, are expected to fulfill the need for large-scale neuromorphic systems, currently implemented using standard CMOS VLSI technologies. Large neuromorphic systems have performance measures (high density, high speed, low power) that are good enough to enable the study of large-scale and biologically inspired neural networks. Such large networks represent a challenge for computational neuroscience. Researchers have recently started investigating cognitive neuromorphic systems that are able to perform adaptive behaviors and that merge neural fields and single-neuron representations courtesy of the increased computational power of microelectronic devices.

Entries in this section review state-of-the-art neuromorphic engineering computational principles, technologies, and applications. This transdisciplinary research field, at its heart, combines the physics of electronics and biology and algorithms and then engineers it for solving tasks. Despite the many challenges, neuromorphic engineering may hold great promises for a new generation of medicine or industry technologies.

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Dynamical Systems: Overview](#)
- [Neuromorphic Cognition](#)
- [Neuromorphic Hardware, Large-Scale](#)
- [Neuromorphic Sensors, Cochlea](#)
- [Neuromorphic Sensors, Head Direction](#)
- [Neuromorphic Sensors, Olfaction](#)
- [Neuromorphic Sensors, Vision](#)
- [Neuromorphic Technologies, Memristors](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)
- [Spiking Network Models and Theory: Overview](#)
- [Synaptic Dynamics: Overview](#)

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Neuronal Model Optimization: Overview

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Synonyms

Neuronal model hand-tuning

Definition

Neuronal Model Parameter Optimization is the process of adjusting the parameters of a computational model of a neuron or neuronal network in order to achieve model activity that mimics that of the living neuron or network being modeled.

Detailed Description

This section contains entries that explain the need for neuron and network model parameter optimization, discuss various optimization methods, describe existing software tools for optimization and visualization of the model databases that result from some of the optimization methods, and discuss related concepts that have emerged from model optimization and exploration efforts over the last few years.

Why Do Neuronal Model Parameters Need to Be Optimized?

Computational models of neurons and neuronal circuits are important investigative tools that allow the study of neuronal signaling and information processing mechanisms that would not be experimentally accessible. However, constructing a model neuron or network requires the specification of numerous parameters, such as maximal conductances, half-activation voltages, and time constants of ionic membrane currents, as well as the strength and dynamical properties of synapses. A complete set of parameters to describe a given neuron or network is virtually never available from experimental data, because some of the parameters cannot be directly measured. Combining parameters measured from different animals is also problematic because almost all parameters vary between animals, and the distributions in the space of parameter sets obtained from different animals are often non-convex, leading to ► [“Failure of Averaging,”](#) i.e., the problem that the set of parameter averages obtained from a distribution of parameter sets can fall outside that distribution in parameter space.

Neuronal models initially constructed from incomplete and averaged parameter sets therefore

usually generate activity that does not match that of the living system to be modeled. Such dysfunctional models then require parameter optimization, either through ► [“Neuronal Model Hand-Tuning”](#) by an expert employing educated guessing and trial-and-error parameter adjustments, or through one of the optimization methods described in this section.

Neuronal Model Optimization Methods

One approach that allows the identification of neuronal model parameter regimes that produce qualitatively different model behaviors (for example, spiking versus bursting versus silence) is ► [“Bifurcation Analysis,”](#) i.e., the use of dynamical systems analysis to determine critical parameters that cause transitions from one behavior to another. Bifurcation analysis is most powerful for models of low dimensionality. For models with many dynamic variables and parameters, the use of bifurcation analysis may therefore require prior model simplification through ► [“Neuronal Model Reduction,”](#) ideally without the loss of essential features of model activity.

A more agnostic approach to studying the dependence of neuronal model activity on the underlying model parameters is ► [“Neuronal Parameter Space Exploration,”](#) i.e., the brute-force computational exploration of many – often tens of millions – of parameter combinations that cover the model’s high-dimensional parameter space. Characteristics of the simulated model activity for each parameter combination are then stored in ► [“Neuronal Model Databases”](#) that can be mined for model versions with the desired activity, and to address general questions about the relationship between model parameters and output.

Less exploratory, more targeted model optimization methods are based on ► [“Evolutionary Algorithms.”](#) They require the definition of a ► [“Neuronal Model Output Fitness Function,”](#) which is a measure for how well a neuron or network model’s activity replicates that of the living system to be modeled. ► [“Multi-objective Evolutionary Algorithms”](#) constitute a class of evolutionary algorithms that simultaneously

optimize models to meet several different objectives, rather than maximizing a single fitness measure. An implementation of evolutionary neuronal model optimization is available in the software tool ► [“Neurofitter.”](#)

Finally, ► [“Hybrid Parameter Optimization Methods”](#) combine several of the above methods of neuronal model optimization to benefit from their respective advantages.

Visualization of Neuronal Model Parameter Spaces

Several of the model optimization methods described in this section produce long lists of parameter sets and their corresponding neuronal model activity that are often collected in ► [“Neuronal Model Databases.”](#) Because the underlying models and their parameter spaces are high-dimensional, it is difficult to analyze how the activity of a model varies across parameter space. This problem is addressed by recently developed methods of ► [“Neuronal Parameter Space Visualization,”](#) including the visualization tool ► [“NDVis-Neuro,”](#) which is designed for the visualization of model databases that cover parameter space with a regular grid of parameter sets.

Beyond Optimization

A number of recent neuronal model optimization efforts, as well as a growing body of experimental data, have revealed concepts that go beyond model optimization in the sense of identifying a single “optimal” model parameter set. Neuronal models and the living systems they mimic display ► [“Neuronal Parameter Non-uniqueness,”](#) meaning that different parameter sets can produce similar and functional neuron or network activity. The subset of parameter space that contains such functional parameter sets is called the “Neuronal Solution Space.” Analysis of the structure of neuronal solution spaces has revealed that parameters do not necessarily vary independently within the solution space, but often show ► [“Neuronal Parameter Co-regulation.”](#)

Apart from asking whether a given parameter set does or does not support functional model

activity, parameter space exploration also allows for the analysis of ► [“Neuronal Parameter Sensitivity,”](#) that is, in which direction and how strongly activity characteristics such as spike frequency depend on model parameters.

Together, the realization of ► [“Neuronal Parameter Non-uniqueness”](#) and the connected concept of “Neuronal Solution Space” have led to the strategy of “Ensemble Modeling,” i.e., the approach of analyzing an entire ensemble of parameter sets and model versions that produce functional activity, rather than focusing on a single “optimal” model version.

Cross-References

- [Bifurcation Analysis](#)
- [Evolutionary Algorithms](#)
- [Failure of Averaging](#)
- [Hybrid Parameter Optimization Methods](#)
- [Multi-objective Evolutionary Algorithms](#)
- [NDVis-Neuro](#)
- [Neurofitter](#)
- [Neuronal Model Databases](#)
- [Neuronal Model Hand-Tuning](#)
- [Neuronal Model Output Fitness Function](#)
- [Neuronal Model Reduction](#)
- [Neuronal Parameter Co-regulation](#)
- [Neuronal Parameter Non-uniqueness](#)
- [Neuronal Parameter Sensitivity](#)
- [Neuronal Parameter Space Exploration](#)
- [Neuronal Parameter Space Visualization](#)

Olfaction: Overview

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Definition

Olfaction refers to the sense of smell and the perception of odorants. This process involves

multiple peripheral and central structures of the nervous system, i.e., the olfactory pathway, and ultimately results in the creation of odor images in the brain as well as the generation of motor and behavioral responses. In several decades, olfaction has been investigated experimentally and theoretically, integrating physiological, behavioral, and computational studies. Here we focus on computational models of olfactory processing, showing how they can promote an understanding of olfaction that goes beyond the mere collection of experimental data.

Detailed Description

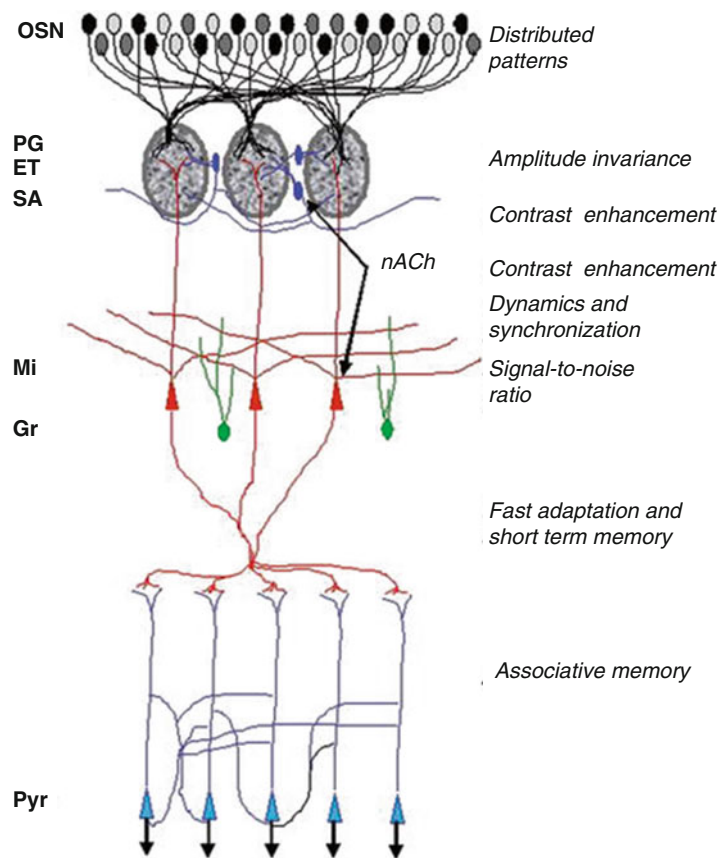
In natural environments, airborne chemicals stimulate continually the olfactory system,

with unpredictable occurrence in time and space. The olfactory system enables the detection of these odorants out of a chemically noisy environment, extracting relevant odor features, and making a comparison with previously memorized odors.

The multiple circuits forming the olfactory system are thought to contribute distinct computations to odor processing. Figure 1 shows a schematic representation of the most prominent olfactory circuits in mammals. The short-axon (SA), external tufted (ET), and periglomerular (PG) cells form a subnetwork in the juxtaglomerular area, which has been proposed to transform a disorganized odor representation into a concentration invariant and contrast-enhanced one (Cleland and Sethupathy 2006; Cleland 2010). In the next layer, mitral (Mi) and granule (Gr) cells form a reciprocal

Olfaction: Overview,

Fig. 1 Schematic description of olfactory structures. The olfactory sensory neurons (OSN) expressing a common receptor converge onto the common olfactory glomeruli, where they make excitatory synapses with the mitral (Mi), periglomerular (PG), and external tufted (ET) cells. ET, PG, and superficial short-axon (SA) cells are interconnected, forming a subnetwork in the glomerular layer. The high convergence between OSNs and glomerular cells can increase signal-to-noise ratio in the system (Linster and Cleland 2009). PG cells make inhibitory connections with Mi cell primary dendrites, allowing for contrast enhancement of the olfactory signals ahead of the Mi cell response (Cleland and Sethupathy 2006)



excitatory/inhibitory loop, which has been hypothesized to implement the neural substrate for fast oscillations and synchrony (Freeman 1974; Brea et al. 2009). Mi cell axons project to secondary olfactory structures, including the piriform cortex, in a non-topographically organized fashion. In the cortex, Mi axons make distal synapses with pyramidal (Pyr) cells, displaying short-term plasticity (Wilson and Linstner 2008). The extensive excitatory connections between cortical pyramidal (Pyr) cells, known to undergo synaptic plasticity, have long been proposed to implement an associative memory for odor storage (Hasselmo et al. 1990).

Computational models of olfactory processing have provided mechanistic and functional insights into odor perception and learning. Mechanistical models have long focused on generation and maintenance of fast oscillations in the olfactory system, and particularly in the gamma range (e.g., Freeman 1974; Lagier et al. 2004; Li and Cleland 2013). Functional models have focused on computations such as signal-to-noise ratio modulation (e.g., Hasselmo et al. 1997; Linstner et al. 2011), contrast enhancement (e.g., Linstner and Hasselmo 1997; Urban 2002; Cleland and Sethupathy 2006; Cavarretta et al. 2016), and odor learning (e.g., Hasselmo et al. 1990; Wilson and Linstner 2008; Cavarretta et al. 2016, 2018). A prominent subclass of functional models consists of biophysically detailed models, which accounts for diverse neuron types and mechanisms (e.g., Li and Cleland 2013; Gilra and Bhalla 2015; Cavarretta et al. 2018). Many models have focused on linking neural and perceptual processes (e.g., Mandaïron et al. 2006), while others have stayed abstract and predictive (e.g., Brea et al. 2009).

In this section, most entries are about computational modeling of the olfactory bulb. Here, different models address the biophysical mechanisms and network properties of the system (see entries ► [“Biophysical Models of Olfactory Mitral and Granule Cells”](#), ► [“Olfactory Computation in Mitral-Granule Cell Circuits”](#), ► [“Large-Scale Models of the Olfactory Bulb”](#), and ► [“Olfactory Computation in Glomerular](#)

[Microcircuits”](#)), and explain how glomerular and granule cell microcircuits organize odor response in specific patterns of spiking activity (see entries ► [“Olfactory Computation in Mitral-Granule Cell Circuits”](#), ► [“Large-Scale Models of the Olfactory Bulb”](#), and ► [“Olfactory Computation in Glomerular Microcircuits”](#)). Similarly, one entry is dedicated to a model of the insect olfactory system that gives insight into its basic functioning (see ► [“Olfactory Computation in Antennal Lobe and Mushroom Bodies”](#)). The olfactory sensory neurons are treated in one entry, where a mathematical model is proposed to predict the dose-response relationship for generic odor mixtures (see ► [“Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response”](#)). All these entries are then complemented by a short review on information processing in the olfactory bulb (see ► [“Information Processing in the Olfactory Bulb”](#)), and a more speculative entry on the functional implication of neurogenesis in these olfactory areas (see ► [“Olfactory Computation and Adult Neurogenesis”](#)). The olfactory cortex is discussed in the setting of associative networks (see ► [“Olfactory Cortical Associative Memory Models”](#)), providing a review of the existing literature. Furthermore, three examples show of how to cellular and neuromodulatory data can explain behavior (see ► [“Computational Modeling of Olfactory Behavior”](#)), integrating computational modeling of olfactory areas and behavioral data.

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Peripheral Nerve Interfaces: Overview

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Definition

The peripheral nervous system (PNS) comprises nerve fibers and ganglia located outside of the brain and spinal cord, including 11 pairs of cranial nerves and 31 pairs of spinal nerves. The spinal (or somatic) nerves originate as dorsal and ventral spinal nerve rootlets at their junction with the spinal cord. The dorsal spinal nerve roots contain afferent (sensory) nerve fibers and their cell bodies, which are located in the dorsal root ganglia (DRG). The ventral spinal nerve roots contain efferent (motor) fibers whose cell bodies are located in the ventral horn of the spinal cord. The dorsal and ventral roots merge to form the spinal nerve, which exits the spinal column through the intervertebral foramen. Upon exiting the spine, the nerve divides into dorsal and ventral rami, which may branch further and mix with other nerve fibers to form plexuses (e.g., brachial plexus) and eventually form distinct peripheral nerves and their branches.

Detailed Description

This section begins with background information on the anatomy and physiology of the peripheral nervous system (► [“Peripheral Nerves, Anatomy and Physiology of”](#)) and mathematical models for simulating the biophysical properties of peripheral nerves (► [“Peripheral Nerve Models”](#)). Subsequent entries describe devices and signal processing methods for acquiring and analyzing electrical signals from peripheral nerves.

Techniques for stimulating activity in peripheral nerve fibers are also described. This section also describes several research and clinical applications based on peripheral nerve recording and stimulation techniques.

Peripheral Nerve Interface Methods and Applications

Interfaces to the peripheral nervous system have long been considered of medical value, beginning in ancient Egypt where the pain-relieving properties of the electric catfish were discussed and continuing with the Mediterranean electric ray and torpedo fish. The nineteenth century saw renewed interest in electrical stimulation of the PNS due to dramatic advances in the understanding of electricity. Only relatively recently, however, through the pioneering modeling work of researchers like Hodgkin and Huxley, and those that have expanded and continued their work, have we begun to understand the PNS well enough to design safe and effective interfaces to it.

A wide variety of interface technologies has been developed to record or stimulate activity in peripheral nerves. Most interfaces rely on electrodes placed on the nerve surface (epineural) or penetrate the interior of the epineurium (intraneural) of the nerve (► [“Peripheral Nerve Interface, Intraneural Electrode”](#); ► [“Peripheral Nerve Interface, Epineural Electrode”](#); ► [“Peripheral Nerve Signal Processing, Multipole Cuff Methods”](#); ► [“Peripheral Nerve Interface, Regenerative”](#)).

Peripheral nerve interface technologies have been applied to the diagnosis or treatment of a wide range of medical conditions. Examples of diagnostic applications include electromyography and nerve conduction tests used to identify and localize nerve damage caused by carpal tunnel syndromes, diabetic neuropathies, and other injuries or diseases (► [“Peripheral Nerve Interface Applications, EMG/ENG”](#)).

Electrical stimulation of peripheral nerve fibers is used to evoke activity in sensory, motor, and autonomic fibers. The cochlear implant is a highly successful example of a sensory prosthesis that restores hearing to people with profound hearing

loss due to damage to the hair cells in the cochlea (► [“Peripheral Nerve Interface Applications, Cochlear Implants”](#)). Electrical stimulation of cutaneous nerve fibers with TENS/PENS devices is used to treat a variety of pain syndromes (► [“Peripheral Nerve Interface Applications, Neuropathic Pain”](#)). Other types of sensory prostheses are being developed (► [“Peripheral Nerve Interface Applications, Sensory Restoration”](#)), for example, to provide tactile and proprioceptive sensations to users of prosthetic limbs.

Summary

The highly structured nature of the peripheral nervous system makes it amenable to computational modeling. Advances in these interfaces have already made a profound impact on modern medical technology including cochlear implants (► [“Peripheral Nerve Interface Applications, Cochlear Implants”](#)); techniques to support bladder, bowel, and sexual function; and vagal nerve stimulation (► [“Peripheral Nerve Interface Applications, Vagal Nerve Stimulation”](#)). New techniques currently being investigated will address a variety of disorders throughout the body including obesity (► [“Peripheral Nerve Interface Applications, Obesity”](#)), neuropathic pain (► [“Peripheral Nerve Interface Applications, Neuropathic Pain”](#)), sleep apnea (► [“Peripheral Nerve Interface Applications, Sleep Apnea”](#)), and sensory restoration in amputees (► [“Peripheral Nerve Interface Applications, Sensory Restoration”](#)). The interfaces themselves come in a diverse array of forms from simple cuff electrodes (► [“Peripheral Nerve Interface, Epineural Electrode”](#)) which wrap around the nerve to more complex regenerative electrode arrays (► [“Peripheral Nerve Interface, Regenerative”](#)), and utilize many advanced stimulation and signal processing techniques (► [“Peripheral Nerve Signal Processing, Denoising”](#)).

Peripheral nerve interface technologies hold great promise in the diagnosis and treatment of a wide range of neurological disorders. Research in this area requires significant collaboration between researchers in computational modeling, neuroscience, biomedical engineering medicine, and physiology.

Cross-References

- ▶ [Peripheral Nerve Interface Applications, Cochlear Implants](#)
- ▶ [Peripheral Nerve Interface Applications, EMG/ENG](#)
- ▶ [Peripheral Nerve Interface Applications, Neuropathic Pain](#)
- ▶ [Peripheral Nerve Interface Applications, Obesity](#)
- ▶ [Peripheral Nerve Interface Applications, Respiratory Pacing](#)
- ▶ [Peripheral Nerve Interface Applications, Sensory Restoration](#)
- ▶ [Peripheral Nerve Interface Applications, Sleep Apnea](#)
- ▶ [Peripheral Nerve Interface Applications, Vagal Nerve Stimulation](#)
- ▶ [Peripheral Nerve Interface, Epineural Electrode](#)
- ▶ [Peripheral Nerve Interface, Intraneural Electrode](#)
- ▶ [Peripheral Nerve Interface, Regenerative](#)
- ▶ [Peripheral Nerve Models](#)
- ▶ [Peripheral Nerve Signal Processing, Denoising](#)
- ▶ [Peripheral Nerve Signal Processing, Multipole Cuff Methods](#)
- ▶ [Peripheral Nerve Signal Processing, Source Localization](#)
- ▶ [Peripheral Nerve Stimulation Technique, Nerve Block](#)
- ▶ [Peripheral Nerves, Anatomy and Physiology of](#)

Phase Response Curves: Overview

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Detailed Description

Phase response curves (PRCs, alternatively phase-resetting curves) are a powerful way of characterizing and explaining the behavior of

nonlinear oscillators without knowing anything about their specific internal dynamics. The phase response curve represents the shortening or lengthening of the cycle period caused by an input depending upon at what point (phase) within the cycle an input is received. In contrast, for a linear time invariant system, the effect of an input is independent of when it is applied. No matter whether the oscillations represent the flashing of fireflies, a pendulum-based clock, a cardiac cell, or a neural oscillator, the phase response curve predicts the phasic relationship of the oscillator to periodic forcing or to coupling within a network of other oscillators. Each oscillator can be reduced to a phase oscillator whose angular velocity on a circle is constant, except when it receives an input that resets (advances or delays) its phase on the circle. In a neural context, there is usually a threshold event, often the action potential or spike, which is used to demarcate the boundaries of a cycle. If an input shortens the cycle, the next spike occurs sooner than it otherwise would have, and so the next spike is advanced. Conversely, if the next spike occurs later than it otherwise would have, the spike is delayed.

The phase-resetting curve is sometimes presented as the response to a specific input. We have called this the general PRC. One example might be to perturb the oscillator underlying the circadian rhythm by exposing an animal to a period of light during its usual period of darkness; another example might be to stimulate a particular synaptic input or set of synaptic inputs to a neural oscillator. The ▶ [“Spike Time Response Curve”](#) is a way to plot the phase response to a specific input, that is, a spike in the presynaptic neuron, in a way that preserves information about time intervals. Phase-resetting theory is generally applied to neural circuits under a simplifying assumption; two common assumptions are that of pulsatile (brief) coupling or weak coupling. The entry on ▶ [“Pulse-Coupled Oscillators”](#) uses the information in the spike-time response curve (or the information in the general phase-resetting curve combined with the intrinsic period information) to predict the response of an oscillator to periodic forcing or mutual coupling, under the pulse-coupled

assumption that the effect of each input dissipates quickly compared to the cycle period.

A second use of the term phase-resetting curve is to represent the response of the oscillator to an infinitesimal input, in other words as a change in the period per unit of the input, called the infinitesimal PRC or iPRC. The entry on ► [“Phase Response Curve, Measurement of the Infinitesimal”](#) explains how to measure the infinitesimal phase response curve (iPRC). The iPRC is useful mostly in the context of the weak-coupling assumption, which assumes that the phase resetting due to two brief, sequential pulses summates linearly, and the phase resetting due to a single brief pulse rescales linearly with the height of the pulse. Thus, a complicated input like a postsynaptic current waveform can be conceptually broken up into a series of shifted and scaled pulses (Dirac delta functions). The entry on ► [“Weak Coupling Theory”](#) explains the connection between the iPRC and the general PRC. That is, if the coupling is sufficiently weak, the general phase resetting due to any arbitrary input waveform can be computed by summing the phase resetting due to each individual pulse: the timing of each pulse gives the phase, and the height of the pulse gives the scale factor for the resetting. This amounts to convolving the iPRC with the input waveform. Since the coupling is weak, the assumption is that the relative phases of the oscillators change very slowly. Weak coupling can be used to predict the synchronization tendencies of networks of oscillators. The entry on ► [“Phase Models, Noisy”](#) explains the effect of noise under the assumption of weak coupling.

Many factors, including the underlying bifurcation structure and the particular set of conductances expressed by the neuron, influence the PRC shape as described in the entry on ► [“Phase Response Curve, Measurement and Shape of General”](#). The influence of the underlying bifurcation structure described in that entry led to the classification of all PRCs with a single sign (all advances or all delays) as type 1 and those with both advances and delays as type 2. A completely separate, classification scheme into type 0 and type 1 PRCs is described in the entry on ► [“Phase Response Curve, Topology of”](#).

The two schemes are a potential source of confusion because of the similar terminology, but these schemes are unrelated. In the topology-based scheme, which was developed first, weak resetting leads to type 1 phase resetting, in which the phase immediately after an input can take on any value, but strong resetting leads to type 0 resetting in which only a limited set of phase values are allowed immediately after a strong input. This approach to classifying phase-resetting curves makes minimal assumptions, including pulse coupling, and is based on simple topological considerations.

In summary, phase response curves have been defined for both infinitesimal and general inputs. PRCs have been classified using separate, unrelated schemes based on bifurcation analysis or topology. Finally, PRCs have been used to analyze synchronization under assumptions of either weak or pulsatile coupling.

Cross-References

- [Phase Models, Noisy](#)
- [Phase Response Curve, Measurement and Shape of General](#)
- [Phase Response Curve, Measurement of the Infinitesimal](#)
- [Phase Response Curve, Topology of](#)
- [Pulse-Coupled Oscillators](#)
- [Spike Time Response Curve](#)
- [Weak Coupling Theory](#)

Retinal/Visual Interfaces (Models, Theory, Techniques): Overview

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Synonyms

Artificial vision; Prosthetic vision; Visual neuroprosthesis

Definition

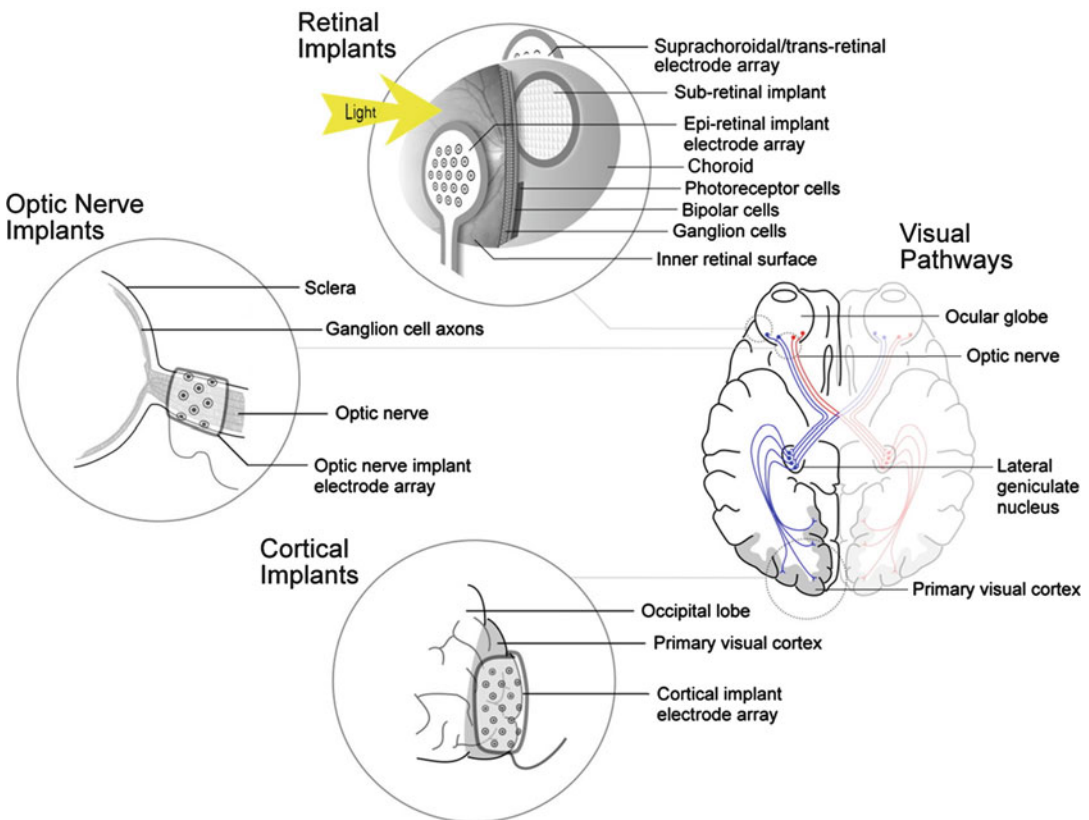
Retinal and visual interfaces encompass a range of approaches and technologies with the most common being that of a visual prosthesis, which is a subclass of sensory neuroprostheses. Such technologies can be used as a device therapeutic to restore some form of patterned vision to those suffering from profound vision impairment. Other approaches to vision restoration can also be included under the broad umbrella of a retinal/visual interface. These include optogenetic methods that use tissue engineering techniques to transfect remaining pathways in the visual system with photosensitive properties. Simulated prosthetic vision, methods to assess prosthetic vision, and computation models of the neural retina play important roles in increasing our

understanding of how such approaches function and can best be optimized.

Detailed Description

Vision is arguably the most feature rich and complex of the senses, with visual cues being critical to most activities of daily living. Vision impairment results in momentous personal and economic burdens to individuals and to society with global estimates of 285 million persons impacted (Pascolini and Mariotti 2012).

Figure 1 illustrates the human visual pathways. Pathology or trauma to various elements of the visual pathway results in vision impairment or profound vision loss. In retinal degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), the



Retinal/Visual Interfaces (Models, Theory, Techniques): Overview, Fig. 1 *Right panel:* an axial section of the human brain outlining a trace of the visual pathway from the retina to the primary visual cortex. *Other panels:*

possible intervention sites for artificial vision are categorized by retinal, optic nerve, and cortical placement locations. (Adapted from Lovell et al. 2010)

photoreceptors in the retina progressively die. In response to such diseases, there can be large-scale reorganization of the retina with substantial gliosis (Jones et al. 2003). Despite this, studies have shown that human retinal ganglion cells (RGCs) maintain their viability after the onset of these degenerative diseases, that the surviving retinal neurons are capable of being electrically stimulated (Humayun et al. 1996), and that rudimentary phosphene vision is achievable in humans with advanced retinal degeneration.

The etiology and/or site of insult to the visual pathway will dictate the range of possible target locations for a visual prosthesis (Guenther et al. 2012; Lovell et al. 2010). Possible sites for introducing a visual prosthesis include retinal (epiretinal (Humayun et al. 2012), subretinal (Zrenner et al. 2011; Palanker et al. 2005), suprachoroidal (Matteucci et al. 2013), trans-retinal (Fujikado et al. 2012)), optic nerve (Veraart et al. 2003), and cortical (Fernandez et al. 2005) locations (Fig. 1). In cases of trauma and diseases such as glaucoma, the RGCs can also be destroyed. As the RGC axonal processes form the optic nerve, in these cases electrical stimulation of visual pathways distal to the lateral geniculate nucleus (LGN) of the thalamus is ineffective.

In the case of retinal prostheses, to effectively replace vision with the same resolution as that of normally sighted humans would require an image capturing device to replace the function of the photoreceptor cells, of which there are approximately 125 million in each eye, converging to some one million RGCs. Current retinal devices, depending on placement and design, have electrode numbers from tens to several thousand at most.

The desired outcome is to have the electrode array placed in close proximity to the neural targets with the implanted components remaining securely fixed, even in the presence of rapid head and eye movements performed by the recipient. The device should maintain its position, integrity, and functionality for several decades of everyday usage, cause minimal injury, inflammation, or risk of infection to nearby tissue and cause minimal discomfort to the recipient. Also important in visual prosthesis design are aspects of size and battery life in the case of external componentry.

A typical vision prosthesis system comprises an external unit which using a camera and micro-processor performs the image capturing and processing and an implanted unit consisting of the microelectronic stimulator and the electrode array. Power and communication between the external and implanted units are normally facilitated by a transcutaneous radio-frequency (RF) link. The exceptions to this approach are typically sub-retinal devices that usually have photodiodes designed into the implantable component and thus have no need for an external camera.

Other more experimental approaches, in terms of readiness for human trials, are based around optogenetic techniques (Degenaar et al. 2009). This involves the use of viral transfection of rhodopsins to target various remaining cells in the visual pathway, making them photosensitive.

Common to all device therapies and target locations in the visual pathway are a list of challenges that must be overcome to improve efficacy and ensure device safety and longevity. These include maintaining a viable and stable neural interface over the long-term, device hermeticity and safe stimulation paradigms that allow concurrent stimulation at numerous electrode sites.

Cross-References

- ▶ [Computational Models of Neural Retina](#)
- ▶ [Prosthetic Vision, Assessment](#)
- ▶ [Prosthetic Vision, Perceptual Effects](#)
- ▶ [Retinal Disease and Remodeling](#)
- ▶ [Retinal Neurophysiology](#)
- ▶ [Retinal Prosthesis](#)
- ▶ [Visual Prosthesis, Cortical Devices](#)
- ▶ [Visual Prosthesis, Epiretinal Devices](#)
- ▶ [Visual Prosthesis, Optic Nerve Approaches](#)
- ▶ [Visual Prosthesis, Optogenetic Approaches](#)
- ▶ [Visual Prosthesis, Subretinal Devices](#)
- ▶ [Visual Prosthesis, Suprachoroidal and Trans-retinal Devices](#)

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Software Tools for Modeling in Computational Neuroscience: Overview

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Definition

A number of software tools have been made freely available to the neuroscience community to assist in building and analyzing biologically constrained

computational models of neuronal systems. This overview will present a number of the most widely used applications for model development in computational neuroscience.

Detailed Description

Modeling in computational neuroscience is becoming a crucial tool for understanding how experimentally observed properties of neural systems emerge from lower-level biophysical processes. In the same way that processing of information happens at multiple physical scales in the nervous system, software applications have been created which specialize in modeling different aspects of neurons and networks.

This overview deals primarily with simulators of spiking neural networks, but other applications for modeling at lower levels (e.g., for biochemical signaling networks or reaction–diffusion within spines or whole cells) or higher scale (e.g., models of cognitive processes) have also been developed. There is also a focus on freely available, open-source applications.

Simulators

Abstract Neuron Simulations

The emergent properties of networks are frequently studied using highly simplified neurons with complex network connectivity and synaptic dynamics. NEST (chapter ► [“NEST”](#)) is a widely used simulator for large neuronal models (e.g., 100,000 neurons and millions of synapses). It is highly optimized to run in a parallel computing environment. Another popular simulator of abstract neuronal networks is Brian (chapter ► [“Brian Spiking Neural Network Simulator”](#)), which is Python based and allows definition of new neuron and synapse models by writing the equations for their dynamics in a simple string-based format. Topographica (chapter ► [“Topographica”](#)) is a simulator which deals primarily with neural maps. It facilitates investigation of the transformation of information between layers of topographic maps as are found in sensory

and motor systems. XPP (<http://www.math.pitt.edu/~bard/xpp/xpp.html>) is a widely used tool for simulation and analysis of dynamical systems and has frequently been used to build and investigate neuronal systems. Nengo (<http://nengo.ca>) is a simulator for large-scale neuronal systems. It has been used for creating the Spaun (Semantic Pointer Architecture Unified Network) simulation (Eliasmith et al. 2012).

Conductance-Based, Multicompartmental Simulators

Single neurons possess a range of features enabling them to perform computational transformations on inputs, including complex morphological structures and a host of active membrane conductances. A number of simulators have been developed which allow researchers to construct neuron models at this level of detail and potentially link such cells together into networks inspired by anatomical circuits. NEURON (chapter ► “NEURON Simulation Environment”) is a general purpose neuronal simulation environment, which allows simulation of networks of neurons of varying levels of detail, from artificial/abstract cells to complex, morphologically detailed neurons. A key feature of NEURON is its extension language NMODL, which allows new ion channel and synapse models to be defined. An important recent addition to NEURON’s functionality has been the ability to run large scale network models across multiple processors. A number of other Python based applications have been created on top of NEURON, including NetPyNE (<http://netpyne.org>), which facilitates the creation of biophysically detailed network models, and LFPy (chapter ► “LFPy: Multimodal Modeling of Extracellular Neuronal Recordings in Python”), which allows the generation of higher level brain signals such as electroencephalography (EEG) and magnetoencephalography (MEG) from NEURON simulations.

GENESIS (► “GENESIS, The GENeral NEurol SIMulation System”) has also been widely used creating and analyzing detailed models of single cells and networks. MOOSE (► “MOOSE, the Multiscale Object-Oriented Simulation Environment”) was initially based on

GENESIS version 2 but has been further developed with a Python-based scripting interface, a new graphical user interface, and greater support for interacting with standardized modeling languages like SBML (► “Systems Biology Markup Language (SBML)”) and NeuroML (► “NeuroML”). PSICS (► “PSICS: The Parallel Stochastic Ion Channel Simulator”) can simulate multicompartmental, conductance-based cell models. Its particular strength is allowing efficient simulation of stochastic ion channels using a kinetic scheme-based approach.

Reaction–Diffusion Modeling

Modeling of the diffusion and reaction of biochemical substances in complex 3D structures can be useful for helping to understand the physical processes by which inputs are transformed in neurites and at synapses. Some of the applications available to create such models include MCell (MCell), STEPS (► “STEPS: STochastic Engine for Pathway Simulation”), and NeuroRD (► “Stochastic Simulators”). The NEURON simulator has also recently added support for reaction–diffusion simulations (McDougal et al. 2013).

Interoperability Frameworks

A diversity of simulation tools is beneficial from the point of view of offering greater choice to users and encouraging diverse approaches to neuronal simulation. There are a number of initiatives which aim to make it easier to use computational models across these simulators. PyNN (► “PyNN: A Python API for Neural Network Modelling”) is a Python library for building neuronal networks, which was inspired by an increasing number of neuronal simulators using the Python language as a scripting interface. A neuronal network can be created using PyNN and then can be simulated on (and the behavior compared across) multiple simulators. NeuroML (► “NeuroML”) is an XML-based language for describing models in computational neuroscience. This has been mainly used to encode 3D networks of multicompartmental, conductance-based neurons, but the recently developed version 2.0

increases its scope to more abstract neuron models. NineML (<http://incf.github.io/nineml-spec>) is another initiative to create an XML language for describing spiking neural networks. neuroConstruct (► [“neuroConstruct”](#)) is a graphical application which allows the construction of complex 3D networks of biophysically detailed neurons. Simulation scripts can then be automatically generated to execute the model in different simulation environments.

Neuronal Morphology Databasing and Generation

Many modeling studies use detailed neuronal morphologies to examine how information is processed and transformed by single neurons, through active membrane conductances and integration of synaptic input. Neuromorpho.Org (► [“NeuroMorpho.org”](#)) is the primary resource for obtaining neuronal morphologies which have been digitally reconstructed. It has contributions from many labs worldwide and covers a wide range of species and neuron types.

Detailed neuronal morphologies can also be automatically generated, based on data obtained from real neurons, for use in neuronal simulations. TREES Toolbox (► [“TREES Toolbox: Code for Neuronal Branching”](#)), CX3D (► [“Cx3D: Cortex Simulation in 3D”](#)) and NeuGen (<http://atlas.gcsc.uni-frankfurt.de/~neugen>) are just some of the applications which can be used for this purpose. More details on initiatives for generating artificial neurons which could be used in neuronal simulations can be found in the entry ► [“Synthetic Neuronal Circuits/Networks.”](#)

Useful Resources

Other useful resources where models, experimental data, and other software tools for computational neuroscience can be obtained include:

- ModelDB (► [“ModelDB”](#)): an archive of simulation scripts for published models in the format originally used by the model developers.

- Open Source Brain (► [“Open Source Brain”](#)): a resource for sharing and collaboratively developing neuronal models. Models reside in open-source repositories, and reusing, modifying, and converting the models to standardized formats such as NeuroML and PyNN are actively encouraged.
- Channelpedia (<http://channelpedia.epfl.ch>) is a resource developed by the Blue Brain Project which provides structured information on ion channels, and many of its entries have downloadable computational models of the channels.
- NeuroElectro (► [“NeuroElectro Project”](#)) provides structured information on electrophysiological properties of neurons obtained from the literature.
- NeuralEnsemble (<http://neuralensemble.org>) is a resource which aims to promote open, collaborative software development in computational neuroscience and hosts a number of related software packages (e.g., Brian and PyNN).

Other Software for Neuronal Simulation

Population-Based Modeling

While most of the simulation packages mentioned already use spiking neuron models, a significant amount of modeling work takes place in computational neuroscience using population-based models and mean-field approaches to model large-scale cognitive processes. Examples of software packages which allow this type of modeling are MIIND (► [“MIIND: A Population-Level Neural Simulator Incorporating Stochastic Point Neuron Models”](#)), a simulator for high-level population based modeling, and The Virtual Brain (► [“The Virtual Brain \(TVB\): Simulation Environment for Large-Scale Brain Networks”](#)), which provides a simulator and a web-based interface for constructing neural population models.

Hardware-Based Modeling Solutions

In addition to software-based neuronal simulators, many groups are investigating hardware-based

solutions to enable faster and larger-scale neuronal simulations. Many of these use off-the-shelf hardware like Graphics Processing Units (GPUs), for example, NeMo (<http://nemosim.sourceforge.net>) and GeNN (<http://genn-team.github.io/genn>), but other initiatives are developing new hardware, customized to simulate large-scale neuronal networks, for example, SpiNNaker (<http://apt.cs.man.ac.uk/projects/SpiNNaker>).

Systems Biology/Bioinformatics Tools

The Systems Biology community has been actively developing applications and model description languages in recent years to facilitate building and exchanging models of biochemical reactions, signaling pathways, and gene regulatory networks. SBML (► “[Systems Biology Markup Language \(SBML\)](#)”) and CellML (► “[CellML](#)”) are two widely used standards in this area, and many models in these formats, including neuronal models, can be obtained from the BioModels database (► “[BioModels Database: A Public Repository for Sharing Models of Biological Processes](#)”) and the CellML Model Repository (<http://models.cellml.org>).

Conclusions

The development of tools for modeling in computational neuroscience is a dynamic field. The overview here has no doubt left out a number of simulators and applications, which would be of use to the wider community. The author encourages developers to get in contact with details of their work for inclusion in future versions of this entry.

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Somatosensory System: Overview

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Detailed Description

Somatosensation includes multiple senses: pain (nociception), temperature (thermoreception), touch, and the sense of our limb position in space (proprioception). Each submodality of somatosensation relies on different types of receptors embedded in the skin, muscle, and joints and involves different structures in the spinal cord and in the brain.

Pain

Pain is arguably one of the most vital senses as it signals when our body is liable to being damaged. There are many different types of receptors in the skin that signal a potentially harmful stimulus. Some receptors respond to intense mechanical deformations of the skin, others to extreme temperatures, and still others to different kinds of chemicals. Pain comprises a sensory discriminative component, which provides information about the location, duration, intensity, and quality of the pain; an affective one, which signals its unpleasantness; and a cognitive-evaluative one, which is associated with cognitive variables such as attention, which can modulate the sensory experience.

Thermoreception

Our ability to sense whether an object is warm or cold relies on two types of thermoreceptive fibers – so-called “cold” and “warm” fibers – embedded in the skin. As their names suggest, “cold” fibers are activated when the skin is cooled

and “warm” fibers are activated when the skin is warmed. In contrast to thermosensitive nociceptive fibers, which respond at extreme temperatures, thermoreceptive fibers only respond at intermediate, non-noxious temperatures (with the exception of the paradoxical response of some cold fibers to high temperatures).

Touch

The sense of touch plays a critical role in our ability to grasp and manipulate objects. Indeed, cutaneous signals provide information about the forces we exert on objects and whether these are slipping from our grasp. Without these signals, we would routinely crush or drop objects. Touch also plays an important role in emotional communication: We touch the people we care about and wish to be touched by them. Finally, our sense of touch plays a key role in embodiment, making our body feel as a part of us.

The skin is innervated by several types of mechanoreceptive afferents, each of which conveys different information about skin deformations (link: sensory innervation of the skin) and conveys different types of information about events impinging upon the skin. Merkel cells convey information about the shape of objects grasped in the hand (link: cutaneous mechanoreceptive afferents: neural coding of shape), Meissner corpuscles about motion of objects across the skin, and Pacinian corpuscles about surface texture (link: cutaneous mechanoreceptive afferents: neural coding of texture). Afferents produce highly repeatable and temporally patterned responses to skin stimulation (link: somatosensory neurons: spike timing), and models have been developed that predict with high accuracy the responses of somatosensory neurons to spatiotemporal skin deformations (link: mechanotransduction: models).

When we palpate an object, we obtain information about its shape (link: somatosensory cortex: neural coding of shape), its texture (link: cutaneous mechanoreceptive afferents: neural

coding of texture), and its motion across the skin (link: somatosensory cortex: neural coding of motion).

Proprioception

Proprioception (link: proprioception) plays a critical role in guiding motor behavior. Individuals with intact motor systems but compromised proprioception have difficulty planning and executing movements, almost as if they had a motor impairment. Proprioception, like touch, is also important for our sense of embodiment.

There are several types of proprioceptive receptors, located in muscles, in the skin, and in joint capsules. Two types of muscle proprioceptors, muscle spindles and Golgi tendon organs, are thought to be the primary contributors to proprioception. One population of receptors in the skin is sensitive to skin stretch and can convey information about joint angle. Another type of proprioceptor, the joint capsule receptor, fires at the extreme ends of the joint’s range and may be involved in preventing overextension of the joint.

Proprioceptive and cutaneous signals are then processed in the dorsal column nuclei, then in the ventroposterior lateral nucleus in the thalamus, and then in primary and secondary somatosensory cortices (link: somatosensory cortex: organization).

Cross-References

- [Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture](#)
- [Mechanotransduction, Models](#)
- [Proprioception](#)
- [Somatosensory Cortex: Neural Coding of Motion](#)
- [Somatosensory Cortex: Neural Coding of Shape](#)
- [Somatosensory Cortex: Organization](#)
- [Somatosensory Neurons: Spike-Timing](#)

Spectral Methods in Neural Data Analysis: Overview

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Detailed Description

Spectral analysis is a powerful and widely used approach to the study of time series data (Warner 1998; Bloomfield 2000). It provides a useful complement to other types of analysis in computational neuroscience. Spectral analysis refers to a host of techniques relating to transformed time series in the frequency domain. A spectral representation of a time series is a function of frequency, where frequency is expressed in units of cycles per second, or hertz (Hz). Although spectral analysis is applicable to deterministic time functions, neural data is typically stochastic and thus requires statistical spectral analysis (Brillinger 2001; Bendat and Piersol 2010). Neural data types that are subjected to spectral analysis commonly include continuous time series such as the electroencephalogram (EEG), magnetoencephalogram (MEG), electrocorticogram (ECoG), and local field potential (LFP) but may also include point process time series such as single-unit and multiunit spiking activity (Glaser and Ruchkin 1976; Dumermuth and Molinari 1987; Hesselmann 1991).

Spectral methods in neural data analysis provide a frequency-based representation of neural time series data. They may be used to identify discrete, narrowband oscillations in time series or to decompose a broadband time series into frequency-specific components. Spectral methods are also employed in the frequency-based analysis of neural data arrayed in space rather than time (see ► “Spatial Spectral Analysis”). Spatial spectra are representations of spatial

data, and spatial frequency is expressed in units of cycles per unit distance.

The traditional approach to spectral analysis is based on the pioneering work of Joseph Fourier (1768–1830), the French mathematician who is credited with having first introduced the representation of a mathematical function as a sum of trigonometric functions. Nowadays, Fourier methods play a major role in a multitude of applications in mathematics, science, and engineering. Fourier analysis refers to the linear decomposition of a function into elemental trigonometric basis functions, whereas Fourier synthesis is the operation of rebuilding the original function from the component basis functions. Although functions subjected to Fourier analysis are often continuous and potentially infinite in length, they may also be discrete and finite in length. The wide availability of methods for Fourier analysis of digitized finite-length time series on digital computers has made spectral data analysis practical, rapid, and inexpensive (Marple 1987). As a result, spectral analysis of neural data has become increasingly popular in modern times, with a growing list of applications in theoretical, experimental, and clinical neuroscience.

Fourier analysis of a time series assigns values of amplitude and (absolute) phase to the trigonometric basis functions (sines and cosines) of the decomposition. For univariate time series, that is, from a single recording channel, Fourier analysis specifies a range of frequencies of the component basis functions, along with amplitude (or power, squared amplitude) and phase values for each frequency component. This (polar) representation in terms of amplitude and phase has an equivalent (Cartesian) representation in terms of the real and imaginary components of a complex quantity. The simplicity, symmetry, and facility of use of the complex Cartesian representation make complex algebra a useful mathematical tool in spectral analysis. However, complex algebra is not necessary. The polar and complex Cartesian representations are equivalent in providing a complete description of time series data, and Fourier synthesis can reconstruct the time series from either one.

Fourier analysis is often used to quantify interdependency relations between time series that are derived from different sources (see ► [“Spectral Interdependency Methods”](#)). Frequency-based interdependency measures may be derived from the complex-valued cross-spectrum. The cross-spectrum yields two important real-valued spectra. First is the relative phase (i.e., difference in phase) spectrum, given by the arctan of the ratio of imaginary to real components of the cross-spectrum. Second is the normalized modulus of the cross-spectrum, the coherence spectrum, which is the frequency domain equivalent of the time domain cross-correlation function. The relative phase spectrum reflects the mean, and the coherence spectrum reflects the variance, of the distribution of relative phase values of two time series. Coherence is roughly equivalent to the phase-locking value, defined as one minus the circular variance of relative phase, in that they both reflect relative phase variation. The difference is that coherence additionally reflects (to a lesser degree) amplitude covariation. Spectral methods are used to examine neural interdependency relations between continuous signals (e.g., between LFPs), or discrete signals (e.g., spiking activities), or between continuous and discrete signals (e.g., spike-field coherence).

Neural time series data are commonly multivariate, being derived from multiple sources, and their spectral analysis often involves the assessment of pairwise interdependency relations in the frequency domain. Some interdependency relations between time series are directional, meaning that the interdependency is directed from one time series to another. Directed spectral methods quantify directed interdependency in the frequency domain (see ► [“Directed Spectral Methods”](#)).

Because neural time series data commonly evolve over time, time-frequency, or spectrographic, representations are often useful (see ► [“Time-Frequency Analysis of Analog Neural Signals”](#)). This type of representation, which allows one to independently examine the temporal evolution of different frequency components, may be used to track the time-frequency evolution of a range of time-varying neural processes, including sleep, sensory, motor, and cognitive processing.

Spectrographic representations of the electroencephalogram (EEG) are heavily used in neuropharmacology to assess the actions of neuroactive drugs. A variety of different time-frequency methods, such as the short-time Fourier transform, Wigner-Ville distribution, Cohen’s class distribution, or wavelet transform (see ► [“Wavelet Analysis”](#)), have been applied in neural data analysis.

One important application of spectral methods in neural data analysis is filtering, the transformation of neural time series by the selection of certain frequency components and the exclusion of others (see ► [“Digital Filtering”](#)). Digital filtering, which refers to filtering operations performed on discretely sampled data in a digital computer, has the advantage of allowing data at both past and future time points to be used in determining the filtered value of a current time point, unlike analog filtering, where the filtering operation depends only on past time points. Although digital filtering may be performed in the time domain, it is more easily performed in the frequency domain by the selection of a range of frequencies (the passband) and exclusion of another range (the stopband). Data smoothing is an important operation in neural data analysis that is accomplished by digital (low-pass) filtering. Digital filtering is also used to separate spike and field signals recorded from a common microelectrode.

Neural time series are rarely deterministic, where each time series value is exactly determined by past values. For this reason, statistical spectral methods are usually required for neural time series analysis (Jenkins and Watts 1968; Percival and Walden 1993). Statistical spectral analysis considers time series data to be generated by stationary stochastic (random) processes, and the various spectral quantities are treated as data-derived statistical estimates of unknown population variables, rather than as deterministic quantities. Unlike non-parametric spectral analysis, which computes spectra directly from time series data by Fourier analysis, parametric spectral analysis is an approach that derives spectral quantities from a statistical model of the time series (see ► [“Parametric Spectral Analysis”](#)). In the model, the variable at a particular time is expressed by statistical relations with variables from past times. The

parametric model is typically autoregressive, meaning that each time series value is modeled as a weighted sum of past values (the weights being considered as the parameters of the model) (Kay 1988; Chatfield 2004). Although parametric models may be nonlinear, those used in neuroscience are typically linear because neural time series are commonly locally linear. Parametric modeling has some distinct advantages in neural data analysis: It allows a precise time-frequency representation of time-varying neural time series (Ding et al. 2000), and it serves as a theoretically sound basis for directed spectral analysis (Ding et al. 2006).

Spectral methods of neural data analysis utilize frequency-based representations. Since rhythmic activity, mostly in time but also in space, is ubiquitous in neuroscience, frequency-based techniques are very important tools in computational neuroscience. Given that many good software options exist for performing spectral data analysis, these techniques are readily available to neuroscience researchers working with many different types of neural data.

Cross-References

- Digital Filtering
- Directed Spectral Methods
- Parametric Spectral Analysis
- Phase-Locking Methods
- Spatial Spectral Analysis
- Spectral Interdependency Methods
- Time-Frequency Analysis of Analog Neural Signals
- Wavelet Analysis

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Further Reading

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Spike Train Analysis: Overview

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Definition

A sequence of action potentials (“spike train”) is the output of an individual neuron and is the input

to receiving neurons. It is assumed that neurons interact by sending and receiving spikes. Therefore, simultaneously observed spike trains are analyzed for correlations to identify neuronal interactions. This section presents analysis approaches for various statistical aspects of spike trains.

Detailed Description

The brain is composed of billions of neurons, the elementary units of neuronal information processing. The neocortex, which is critical to most higher brain functions, is a highly complex network of neurons, each of which receives signals from thousands of other neurons and projects its own output via sequences of spikes (► [“Spike Train”](#)) to thousands of other neurons (Braitenberg and Schüz 2009). In order to observe neuronal activity in the active brain, a large variety of recording techniques are being employed, ranging from recordings of individual neurons (intra- or extracellularly) to recordings of neuronal populations on mesoscopic or macroscopic scales. Any particular choice of the recording technique reflects the hypothesis the researcher has in mind about the mechanisms of neuronal processing. The focus on spike recordings from individual neurons implies that one strives to understand the elementary units of neuronal processing. However, approaching the relationship of different signal types may provide a means of relating processing on different spatial scales (► [“Spike Triggered Average”](#)).

Early electrophysiological experiments were bound to record from single neurons only. The resulting insights are now the basis for the “classical” view of sensory coding: firing rates are modulated in a feed-forward hierarchy of processing steps. Signals from sensory epithelia are assumed to eventually converge to cortical detectors for certain combinations of stimulus features (► [“Neural Coding”](#)) or finally transferred to motor output. Specific percepts or motor actions would be represented by the elevated firing of a single nerve cell (► [“Estimation of Neuronal Firing Rate”](#)) or by changes of firing rates of groups

of neurons which can be assessed by different conceptual approaches (► [“Neuronal Population Vector,”](#) ► [“Population Encoding/Decoding,”](#) and ► [“State-Space Models for the Analysis of Neural Spike Train and Behavioral Data”](#)).

An alternative concept of neuronal processing by groups of neurons was suggested by Donald Hebb (1949) who first demonstrated the conceptual power of a brain theory based on cell assemblies. Inspired by Hebb and driven by more recent physiological and anatomical evidence in favor of a distributed network hypothesis, brain theorists constructed models that rely on groups of neurons, rather than single nerve cells, as the *functional* building blocks for representation and processing of information. Despite conceptual similarities, such concepts of neuronal cooperativity differ in their detailed assumptions with respect to the spatiotemporal organization of the neuronal activity. To understand the principles of coordinated neuronal activity and its spatiotemporal scales, it is obligatory to observe the activity of multiple single neurons simultaneously. Due to recent technological developments in recording methodology, this can regularly be done. Coordinated activity of neurons is only visible in correlations of their respective spike trains, which typically admit no simple interpretation in terms of fixed synaptic wiring diagrams. Rather, it became evident that the correlation dynamics apparent in time-resolved multiple-channel measurements reflect variable and context-dependent coalitions among neurons and groups of neurons. Thus, the analysis of simultaneously recorded spike trains allows us to relate concerted activity of ensembles of neurons to behavior and cognition. Different analysis approaches are thereby relevant to distinguish different or even complementary spatio-temporal scales based on methods ranging from pairwise analysis (► [“Spike Train Distance,”](#) ► [“Correlation Analysis of Parallel Spike Trains,”](#) and ► [“Joint Peri Stimulus Time Histogram \(JPSTH\)”](#)) to concepts for the analysis of multiple parallel processes (► [“Gravity Analysis of Parallel Spike Trains,”](#) ► [“Unitary Event Analysis,”](#) ► [“Information Geometry as Applied to Neural Spike Data,”](#) ► [“Spatial Temporal Spike Pattern Analysis,”](#) ► [“Statistical Evaluation of](#)

Spatio-Temporal Spike Patterns,” and ► “Generalized Linear Models for Point Process Analyses of Neural Spiking Activity”). The evaluation of significance (► “Significance Evaluation”) is a basic element in these analyses, in some cases based on nonparametric methods (► “Surrogate Data for Evaluation of Spike Correlation”). Analysis of parallel spike trains (Grün and Rotter 2010; Kass et al. 2014) is the logical next step to improve our understanding of the neuronal mechanisms underlying information processing in the brain.

Cross-References

- Correlation Analysis of Parallel Spike Trains
- Estimation of Neuronal Firing Rate
- Generalized Linear Models for Point Process Analyses of Neural Spiking Activity
- Gravity Analysis of Parallel Spike Trains
- Information Geometry as Applied to Neural Spike Data
- Joint Peri Stimulus Time Histogram (JPSTH)
- Neural Coding
- Neuronal Population Vector
- Population Encoding/Decoding
- Significance Evaluation
- Spatial Temporal Spike Pattern Analysis
- Spike Train
- Spike Train Distance
- Spike Triggered Average
- State-Space Models for the Analysis of Neural Spike Train and Behavioral Data
- Statistical Evaluation of Spatio-Temporal Spike Patterns
- Surrogate Data for Evaluation of Spike Correlation
- Unitary Event Analysis

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Spiking Network Models and Theory: Overview

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Definition

Spiking neuronal networks are a type of neural network model where the neurons interact by sending and receiving the so-called spikes, short pulses that are only defined by their time of occurrence. Biologically, spikes correspond to the action potentials of neurons.

Neuron models that produce spikes are called *spiking neuron models*. Examples are the Integrate and Fire Models, Deterministic; the *Izhikevich model*; and the Hodgkin-Huxley Model.

The term spiking network was introduced to distinguish these models from formal neuron models which have graded activation functions.

Detailed Description

Historical Background

The first spiking neuron models were developed at the beginning of the twentieth century and focused on explaining the electrical behavior of isolated neurons. In 1907, Louis Lapicque proposed an electrical circuit model to describe the change in membrane potential after applying a current step. He assumed a fixed firing threshold to explain the occurrence of action potentials (Lapicque 1907; Tuckwell 1988). Lapicque’s model can therefore be seen as the first *integrate and fire model*. In 1936, Arthur Hill extended Lapicque’s model by adding an adaptive threshold (Hill 1936). These models are phenomenological

since they did not explain the biophysical mechanisms producing action potentials. In the 1950s Hodgkin and Huxley explained with a series of experiments that action potentials are caused by ionic currents which result from ion channels with voltage-dependent conductances (Hodgkin and Huxley 1952). But because of its simplicity, Lapicque's original threshold model is still used by experimental and theoretical neuroscientists.

Theoretical network models initially focused on explaining experimentally observed interspike interval distributions of individual neurons as well as the origin of the observed high variability of neuronal responses. Recent theoretical research mainly focuses on understanding low-rate spontaneous activity as well as multistability in the context of learning and memory.

Theoretical analysis of spiking neuronal networks is only possible if the network model is sufficiently simple. In recent years, computer simulations have become increasingly important to support and complement theoretical analysis, because they allow the inclusion of more biological detail and the analysis of heterogeneous network architectures.

Spiking Neuron Models

Theoretical network models typically resort to simplified neuron models, such as the leaky integrate and fire model (LIF), some variant of it, or more abstract models such as pulse-coupled oscillators.

All of these neuron models have in common that they interact by sending and receiving the so-called spikes which are abstractions of the action potentials produced by excitable cells such as neurons.

Spikes are temporal point events, characterized by their time of occurrence $\hat{t}$ and mathematically expressed by the Dirac delta function $\delta(t)$.

A sequence of spikes $S = \{\hat{t}^1, \hat{t}^2, \dots\}$ is called *spike train* and can then be written as

$$s(t) = \sum_k \delta(t - \hat{t}^k), \quad (1)$$

where the index k runs over all spikes in S .

Integrate and Fire Models

The leaky integrate and fire (LIF) model constitutes a whole class of models consisting of two parts. The first part consists of one or more differential equations, describing the subthreshold behavior of the neuron's membrane potential. The second part converts the continuous membrane potential into discrete spike events. Here we will present the LIF model in its most basic form and then discuss a number of common variations.

Subthreshold Dynamics

The subthreshold membrane potential V is described by the differential equation

$$\tau \frac{d}{dt} V(t) = V_0 - V(t) + RI(t) \quad (2)$$

where V_0 is the resting potential, τ the membrane time constant, and R the membrane resistance.

$I(t) = I_{\text{syn}}(t) + I_{\text{ext}}(t) + \dots$ is the total current across the cell membrane and comprises all external influences on the neuron, such as synaptic currents I_{syn} and externally applied currents I_{ext} .

Spike Generation

Spikes are generated, when the membrane potential V crosses a threshold value V_θ from below. The time of spike is then given by the relation

$$V(t') = V_\theta \text{ and } \frac{d}{dt} V(t') > 0 \quad (3)$$

In the following, we use t' to denote the times of endogenous spikes and $\hat{t}$ to denote input spikes from other neurons.

After a spike is generated, the membrane potential is reset to V_{reset} , a value which is often chosen to match the resting potential V_0 .

Immediately after a spike, neurons are unable to produce another spike for a short period of time t_r , called *refractory period*. Many models implement the refractory period by holding the membrane potential at its reset value, such that $V(t) = V_{\text{reset}}$ for $t \in (t', t' + t_r]$.

Threshold Adaptation

Many neurons adapt to sustained input by reducing their firing rate. In integrate and fire models,

this is often captured by a mechanism called *threshold adaptation*.

The spike threshold V_θ is then no longer constant, but increases with every spike by an amount a and decays back to its resting value θ with a time constant τ_θ :

$$\tau_\theta \frac{d}{dt} V_\theta = \theta - V_\theta + a \sum_k \delta(t - t'^k) \quad (4)$$

where the sum runs over all endogenous spikes t'^k of the neuron.

Synaptic Input

Synaptic input enters the membrane potential in the form of the synaptic current $I_{\text{syn}}(t)$. A presynaptic spike at time $\hat{t}$ causes a conductance change at the postsynaptic membrane, which in turn results in a postsynaptic current of the form

$$I_{\text{syn}}(t, V) = (E_{\text{syn}} - V) \cdot g_{\text{syn}}(t - \hat{t}) \quad (5)$$

where E_{syn} is the reversal potential of the synapse and $g_{\text{syn}}(t)$ the time course of the conductance change.

Many models implicitly assume that the synaptic conductance changes much faster than the membrane potential V . Then V in Eq. 5 can be treated as constant, and the synaptic current no longer depends on the membrane potential which greatly simplifies analytical and numerical analysis.

In recent years, the terms COBA and CUBA have become popular to distinguish the two cases. COBA refers to the original Eq. 5 and stands for *conductance based*, while CUBA stands for *current based* and refers to simplified synaptic currents of the form

$$I_{\text{syn}}(t) = \text{psc}(t - \hat{t}) \quad (6)$$

where the postsynaptic current $\text{psc}(t)$ is only a function of time (Vogels and Abbot 2005).

Since Eq. 2 is a linear differential equation with constant coefficients, its solution for arbitrary postsynaptic currents $\text{psc}(t)$ is given by

$$\text{psc}(t) = V_0 + \int_0^\infty H(t - s) \exp\left(\frac{-(t - s)}{\tau}\right) \cdot \text{psc}(s) ds \quad (7)$$

where $H(t)$ is the Heaviside step function and $\text{psc}(t)$ is the so-called postsynaptic potential.

In the case where the postsynaptic current is a delta function $\text{psc}(t) := \delta(t - \hat{t})$, Eq. 7 reduces to

$$\text{psc}(t) = V_0 + \exp\left(\frac{-(t - \hat{t})}{\tau}\right). \quad (8)$$

In response to a spike train $s(t)$, we obtain

$$\text{psc}(t) = V_0 + \sum_k H(t - \hat{t}^k) \exp\left(\frac{-(t - \hat{t}^k)}{\tau}\right). \quad (9)$$

Spike-Response Model

The spike-response model (SRM) is a generalization of the LIF model (Gerstner et al. 1996a; Gerstner and Kistler 2002). It exploits the linearity of Eq. 2 and expresses the membrane potential as convolution:

$$V(t) = \eta(t - \hat{t}) + \int_0^\infty k(t, t') I_{\text{syn}}(t - t') dt' \quad (10)$$

where $\eta(t - t')$ is a kernel that describes the action potential as well as the after hyperpolarization of the last spike of the neuron at $t = t'$. $k(t, \hat{t})$ is a kernel that describes the response of the membrane potential to a presynaptic spike at time $\hat{t}$. Like in the LIF model, a spike is generated when the membrane potential $V(t)$ crosses a threshold value V_θ from below.

For theoretical analysis of large spiking network, the spike-response model is more convenient than the original LIF model, since it captures the effects of incoming as well as self-generated action potentials in a closed mathematical form (Gerstner and Kistler 2002).

Stochastic Spike Generation and Escape Noise

For most neuron models with a deterministic spike threshold, it is also possible to use a stochastic spike generation mechanism by adding the so-called escape noise (Plesser and Gerstner 2000). This is done by relating the variable $V(t)$ to the probability density for observing an action potential in the

infinitesimal time interval $(t, t + \delta t]$ (Plesser and Gerstner 2000; Mensi et al. 2012). In this picture, the spike generation is a random point process with a conditional density function

$$\lambda(t|V, V_\theta) = \lambda_0 \exp\left(\frac{V(t) - V_\theta}{\Delta V}\right), \quad (11)$$

where λ_0 is a scaling factor with unit s^{-1} , V_θ is the firing threshold, and ΔV is a factor that determines the steepness of the exponential function and therefore also the sensitivity of the firing threshold to small fluctuations.

The spike-response model with escape noise belongs to the larger class of *generalized linear models* (GLM) which have recently been used successfully also in other areas of neuroscience (see, e.g., Pillow et al. (2008), Truccolo et al. (2011)).

Stochastic Models of Neural Activity

In many regions of the brain, neurons fire constantly at a low rate, even if they are not directly stimulated. In the cortex, this spontaneous activity is very irregular. Moreover, even if a cortical neuron in vitro or in vivo is stimulated repeatedly, its response will differ for each stimulus presentation.

One of the earliest approaches to explain this variability of neuronal firing is to consider the fluctuation of the membrane potential of a neuron, caused by randomly arriving spikes from the surrounding network. In the simplest case, each neuron in the surrounding network will fire at some constant rate v . The network, thus, generates a noisy *background activity* which then influences the firing probability of our neuron.

The number of excitatory and inhibitory spikes which arrive at neuron i during the interval $(0, t]$ can be written as

$$n_E(t) = \sum_{j \in E_i} \int_0^t s_j(t' - d) dt',$$

$$n_I(t) = \sum_{j \in I_i} \int_0^t s_j(t' - t) dt'$$

where E_i and I_i denote the sets of all excitatory and inhibitory neurons projecting to neuron i ,

respectively. The membrane potential of a neuron can then be written as (Stein 1965; Tuckwell 1988)

$$\frac{dV}{dt} = -\frac{1}{\tau}V + J_E \frac{dn_E}{dt} + J_I \frac{dn_I}{dt}. \quad (12)$$

For sufficiently large networks, we can assume that n_E and n_I are Poisson processes with rates v_E and v_I , respectively.

In the absence of a threshold, and for constant firing rates, the mean and variance of the membrane depolarization are (Tuckwell 1988; Stein 1965)

$$E[V] = \tau(J_E v_E + J_I v_I) \quad (13)$$

$$\text{Var}[V] = \frac{1}{2} \tau (J_E^2 v_E + J_I^2 v_I). \quad (14)$$

More generally, we can describe the randomly arriving spikes as a *shot noise* process (Papoulis and Pillai 2002). This allows us to compute the mean and variance of the resulting membrane potential as a function of the background firing rate $v(t)$ and the synaptic response kernel $\text{psp}(t)$. The mean membrane potential is then

$$E[V]_t = \int_0^{+\infty} v(t-s) \text{psp}(s) ds \quad (15)$$

with variance

$$\text{Var}[V]_t = \int_0^{+\infty} v(t-s) \text{psp}^2(s) ds \quad (16)$$

When an embedding into a cortical region is considered, random input comes from excitatory and inhibitory populations. Due to the linearity of the equations, the contributions from both populations superimpose, and the mean and variance of the combined membrane potential are given by

$$E[V]_t = E[V_E]_t + E[V_I]_t \quad (17)$$

and

$$\text{Var}[V]_t = \text{Var}[V_E]_t + \text{Var}[V_I]_t \quad (18)$$

respectively.

Connections

A network consists of a set of N neurons and their connections. In a connection between two neurons, the sending neuron is called *presynaptic* and the receiving neuron is called *postsynaptic*. We write the set of presynaptic neurons of neuron i as N_i .

Static Connections

In the simplest case, the synaptic current simply adds the spikes of all presynaptic cells:

$$I_{\text{syn},i}(t) = \sum_{j \in N_i} J_{ij} s_j(t - d_{ij}) \quad (19)$$

$$= \sum_{j \in N_i} J_{ij} \sum_{k=1} \delta(t - d_{ij} - \hat{t}_j^k) \quad (20)$$

where d_{ij} is the propagation delay between neuron j and neuron i and $\hat{t}_j^k$ the k th spike of neuron j . J_{ij} is the *weight* or *efficacy* of the connection between neurons j and i which is in many cases assumed to be constant.

Dale's Principle

Dale's principle states that the efferent synapses of a neuron are all of the same type. Thus, if one efferent synapse of a neuron is excitatory, we know that all other efferent synapses of this neuron will also be excitatory. The same applies to inhibition.

Dale's principle introduces correlations into the connectivity matrix of the network, which are visible in the eigenvalue distribution of the matrix in the complex plane (Rajan and Abbot 2006). Moreover, Dale's principle also affects the correlation structure of random spiking networks. In random networks without Dale's principle, correlations between neurons will vanish in the limit of infinitely large networks. In such networks, Dale's principle prevents the correlations from disappearing (Kriener et al. 2008).

Short-Term Plasticity

The weight of a connection can depend on the spike history of the presynaptic neuron such that the weight decreases or increases if several

presynaptic spikes arrive in short succession. These effects are called short-term depression (STD) and short-term facilitation (STF), respectively. Both can be described by a system of kinetic equations that model the depletion and replenishing of synaptic resources (Tsodyks et al. 1998, 2000).

Assume that there is a finite amount of resources available and that each spike uses a certain fraction of these resources which are then unavailable for a certain amount of time. Depleted resources are replenished at a constant rate D . The second factor in the model is the ability of a synapse to use its resources, expressed by a variable $u(t)$. In stochastic models of synaptic transmission, u corresponds to the release probability of a synaptic release site (Fuhrmann et al. 2002). If u is a constant, the synapse will be depressing. For facilitating synapses, u increases with each spike up to a maximum and decays at a constant rate F .

In the context of the STP literature, the maximal synaptic efficacy is usually denoted by A which corresponds to the synaptic weight J , used throughout the rest of this entry. The effective weight for the n th spike can then be expressed as

$$A_n = Au_n R_n \quad (21)$$

with initial values

$$u_i := U, \quad (22)$$

$$R_1 := 1. \quad (23)$$

u and R are then iteratively updated according to

$$u_{n+1} = U + u_n(1 - U) \exp\left(\frac{-\Delta t_n}{F}\right), \quad (24)$$

$$R_{n+1} = 1 + (R_n - R_n u_n - 1) \exp\left(\frac{-\Delta t_n}{D}\right), \quad (25)$$

where $\Delta t_n := \hat{t}^n - \hat{t}^{n-1}$.

The relation of the time constants D and F determines whether a synapse will be

depressing, facilitating, or a combination of the two. However, closer analysis of the equations as well as experimental results shows that the detailed behavior of dynamic synapses depends also on the spike frequency of the presynaptic neuron (Fuhrmann et al. 2002).

Dynamic synapses have a strong effect on the behavior of a network. Networks with facilitating synapses can show collective synchronization of all neurons, called population bursts (Tsodyks et al. 2000). By contrast, in networks where the facilitating and depressing synapses are distributed as indicated by experimental results, activity is more stable as the synapses exert some gain control on the network (Sussillo et al. 2007).

Short-term plasticity has also been linked to the persistence of network states with elevated firing rates. These are thought to play an important role in working memory (Mongillo et al. 2008).

Short-term plasticity is not related to Hebbian plasticity, since it depends only on the activity of the presynaptic neuron rather than on the activity of both the pre- and postsynaptic neurons.

Spike-Timing-Dependent Plasticity

Spike-timing-dependent plasticity (STDP) is a form of synaptic plasticity where the synaptic efficacy changes according to the relative timing of pre- and postsynaptic action potentials.

A typical experimental protocol for spike-timing-dependent plasticity involves two neurons with a synaptic connection. Action potentials are induced in both neurons in a defined temporal sequence by injecting current pulses. At the same time, the strength of the synaptic potential is measured in the postsynaptic neuron. This procedure is called *pairing*. After a number of pairings, each with the same timing relation between pre- and postsynaptic neurons, a change in the amplitude of the PSP can be observed. Systematic variation of the relative timing between pre- and postsynaptic action potentials then reveals that the change in PSP amplitude depends on the timing relation.

The classical results of Markram et al. (1997) and Bi and Poo (1998) show that potentiation is largest if the postsynaptic neuron spikes shortly after the presynaptic neuron, while the synapse became depressed if the postsynaptic neuron

fired shortly before the presynaptic neuron. This is captured by the following model (Gerstner et al. 1996b):

$$\Delta J_{ij} = \sum_{\hat{t}^i \in S_j} \sum_{\hat{t}^j \in S_i} W(\hat{t}^i - \hat{t}^j) \quad (26)$$

where the sums run over all pre- and postsynaptic spikes, respectively. $W(\Delta t)$ is the so-called learning window, with

$$W(\Delta t) = A_+ \exp\left(\frac{-\Delta t}{\tau_+}\right) \text{ for } \Delta t > 0, \quad (27)$$

$$W(\Delta t) = -A_- \exp\left(\frac{\Delta t}{\tau_-}\right) \text{ for } \Delta t < 0, \quad (28)$$

and

$$\Delta t := t_{\text{post}} - t_{\text{pre}}. \quad (29)$$

The learning window is modeled as an exponential function which scales the degree to which the weight changes, depending on the time interval Δt . If the spike of the presynaptic neuron precedes the spike of the postsynaptic neuron, Δt is positive and Eq. 27 will increase the weight W by a value that is largest for short and smallest for large intervals. If the postsynaptic neuron spikes first, Δt is negative and Eq. 28 will decrease W .

There are a number of variations to this model as well as a number of alternative models which incorporate hypothesized biophysical mechanisms, underlying STDP (Morrison et al. 2008; Sjöström and Gerstner 2010). But so far, the experimental evidence does not allow to identify one of the models as authoritative (Feldman 2012).

Spike-timing-dependent plasticity is a mechanism that acts in addition to the synaptic short-term plasticity, described in the previous section. To obtain the final synaptic efficacy which combines both short-term and spike-timing-dependent plasticity, we replace A in Eq. 21 with $J + \Delta J$:

$$A_n = u_n R_n (J + \Delta J) \quad (30)$$

where J is the equilibrium weight.

Network Topologies

In a spiking network, the weighted, directed graph of the connections defines the topology of the network. Common network topologies are feedforward networks, recurrent networks, and networks with spatial topologies.

Feedforward Networks

Feedforward networks can be broken down into disjunct groups or layers of neurons $G_1, G_2, \dots$ where each neuron in group G_i is only connected to neurons in group G_j with $j \geq i$.

The propagation of spiking activity in feedforward networks is directed and in the direction of ascending group numbers. As a result, the total number of spikes in feedforward networks is limited, and at any given time, only a fraction of the neurons are active (Griffith 1963).

Synfire Chains

Examples of feedforward networks are the complete *transmission line*, also known as *synfire chain* (Griffith 1963; Abeles 1991). It consists of l mutually exclusive groups G_i , with $1 \leq i, \leq G_l$, each containing w neurons. Each neuron in group i projects to a certain number of neurons in group $i + 1$, thus forming a chain of groups of neurons. If sufficiently many neurons in the first group fire near simultaneously, they will ignite the neurons in the second group and so on. The spikes of the first group will therefore travel along the chain until either the activity disperses or the chain comes to an end. Theoretically, this can be described by the so-called pulse packets, propagating from one group to the next (Diesmann et al. 1999). In the ideal case, that is, given a sufficient number of spikes with a sufficiently narrow temporal spread, the pulse packet will propagate unchanged from one group to the next. And due to the divergent-convergent connectivity, small deviations from this invariant shape are then automatically repaired. However, depending on the number of neurons in a group and the connections between the groups, the pulse packet may also win or lose spikes or change its temporal precision (Diesmann et al. 1999; Câteau and Fukai 2001).

Recurrent Networks

Networks with feedback connections are called *recurrent*. Recurrent networks are often random with mixed excitation and inhibition. In random networks with uniform connection probability, each neuron has an equal probability to be connected to another neuron. In other models, the connection probability between neurons i and j depends on their distance.

Neighborhood Preserving Topologies

Networks in which neurons have a well-defined position are called *topology networks*. In such networks, the connection probability of two neurons usually depends on their distance. For example, the closer two neurons are, the higher is their probability to be connected. The neuronal positions may correspond to the actual positions of the neurons within a brain region, but they may also correspond to positions in some abstract space, for example, the orientation angle of a visual stimulus or the direction of movement in a reaching task. Thus, neighboring locations in stimulus or response coordinates are mapped to neighboring neurons.

The simplest examples of topological networks are line or ring networks, where the neurons are aligned on a one-dimensional axis. If the two ends of the axis are connected back to each other, the line turns into a circle. This is useful for representing periodic coordinates such as orientation angle or simply to avoid boundary effects at the end of the line.

Models of visual processing often use two-dimensional sheets or layers of neurons. Here the coordinates can correspond to visual space, e.g., the center of the neuron's receptive field or cortical space, that is, the actual position of the neuron in the brain. To ameliorate processing at the boundaries of the sheet, the two pairs of opposing sides are often connected such that the rectangular sheet turns into a torus.

Typical models of visual processing will combine several sheets into a functional architecture (e.g., Masquelier and Thorpe 2007; Grossberg and Versace 2008). Topological networks can be feedforward, recurrent, or a combination of the two.

Network Dynamics

Spiking neural network models are an important tool to study the dynamics of cortical network activity and to understand physiologically observed phenomena such as spontaneous activity, neuronal synchronization, and network oscillations. These are macroscopic network phenomena which we call the *macro state* of the network. Each macro state usually comprises a large ensemble of *micro states*, defined by the individual states of all neurons and synapses.

Many macro states, observed in cortical networks, can be understood, using a simple network with randomly connected excitatory and inhibitory neurons (Brunel 2000). The model consists of three populations of neurons: one population of excitatory neurons, one population of inhibitory neurons, and a third population of excitatory neurons, representing the long-range input from other brain regions. The excitatory and inhibitory populations are mutually coupled, and both receive input from the background population. We can now study the activity patterns which emerge, depending on the ratio of inhibition to excitation and the strength of the background population.

If the amount of excitation and inhibition is roughly equal so that on average the respective synaptic currents cancel each other, we speak of a *balanced network*. In this regime, network activity is highly irregular, since spikes are generated by the difference in fluctuations of the excitatory and inhibitory currents (Tsodyks and Sejnowski 1995).

If all neurons fire independently of each other and their spike patterns are essentially random, we speak of *asynchronous-irregular* activity. This state is of particular interest, because it corresponds best to the state of low-rate spontaneous activity, observed in cortical networks.

Networks in the asynchronous-irregular state exhibit chaotic activity (van Vreeswijk and Sompolinsky 1996). Thus, even small perturbation such as adding or removing one spike will quickly result in a completely different micro state. Whether this critical dependence on the initial conditions is useful or detrimental for spike-based processing is still under debate (Izhikevich 2006; London et al. 2010).

If the neurons fire independently, but each at regular intervals, we speak of *asynchronous-regular activity*. In this state, each neuron oscillates at a different frequency, and occasionally, large parts of the network will fire synchronously. The intervals of these population events depend on the common multiples of the individual firing periods. It is also possible that all neurons fire at the same frequency, but out of phase. In this case, neurons will not be able to occasionally synchronize their spikes.

If all neurons fire synchronously with the same frequency, the network essentially oscillates and we speak of *synchronous-regular* activity. Oscillatory states are also of interest since they can serve as models for epileptic activity or for stimulus-evoked synchronization.

Theoretically, there is also a state of *synchronous-irregular* activity, a state where each neuron produces the same irregular spike train. Then the spikes of all neurons will occur in synchrony, but the intervals between the spikes will be irregular. However, this state is very unlikely to occur in random networks because it requires a well-chosen connectivity.

Cross-References

- [Bayesian Inference with Spiking Neurons](#)
- [Excitability: Types I, II, and III](#)
- [Fitzhugh–Nagumo Model](#)
- [Hodgkin–Huxley Model](#)
- [Integrate and Fire Models, Deterministic](#)
- [Morris–Lecar Model](#)
- [Multistability in Neurodynamics: Overview](#)
- [Neuronal Avalanches](#)
- [Pulse-Coupled Oscillators](#)
- [Recurrent Network Models, Reservoir Computing](#)
- [Spike-Frequency Adaptation](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)
- [Spontaneous Activity, Models of](#)
- [Theta Neuron Model](#)

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Further Reading

A thorough introduction to the theory of spiking networks can be found in the somewhat dated but still highly valuable textbooks *Introduction to theoretical neurobiology* by Tuckwell (1988). An equally thorough and more recent reference is the book *Spiking neuron models: Single neurons, populations, plasticity* by Gerstner and Kistler (2002) which also contains

- extensive treatment of learning and plasticity in spiking networks. A broader overview is given in the textbook *Theoretical Neuroscience* by Dayan and Abbot (2001)
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Spinal and Neuromechanical Integration: Overview

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Detailed Description

To interact with the environment or other organisms, the nervous system must move. Whether it is a fundamental protective reflex, a stabilizing postural adjustment, a rapid prey strike, or an expressive dance gesture, the motor repertoire of an organism defines the nature of its environmental interactions. Structures in the periphery of the motor system, the musculoskeletal system and spinal cord, most directly mediate these

environmental interactions. The actions of central brain regions such as cortex, cerebellum, or basal ganglia all ultimately have to pass through these peripheral structures. Understanding the properties of these peripheral systems is therefore critical for our understanding of the neural control of movement.

How should we consider these peripheral components of the motor system? In one common perspective, these systems are problems that the CNS must overcome. In this perspective, the complex properties of muscles, limb mechanics, motor neurons, and spinal circuits require that central motor systems develop strategies that invert, bypass, or suppress these complexities. Complexity could therefore lead to greater complexity: evolutionary changes to the periphery could require the co-evolution of more complex mechanisms to maintain performance.

In an alternate perspective, peripheral systems might simplify for motor control. The complexities of spinal systems or nonlinear properties of the musculoskeletal system might reflect adaptations that allow simplified control by descending systems. For example, passive mechanics can be used to assist movements (Collins et al. 2005), muscle properties can contribute to stability (Nichols and Houk 1973), basic reflexes allow for rapid control (Loeb et al. 1999), and defining adaptive muscle coordination patterns can potentially simplify movement (Tresch and Jarc 2009). In this perspective, energetic costs associated with inefficient, complex control might lead to evolutionary adaptations that simplify control and neural processing.

These two perspectives are not mutually exclusive, and both emphasize the importance of understanding the contribution of peripheral systems to motor control and brain function. Entries in other sections of this Encyclopedia and the *Encyclopedia of Neuroscience* describe the basic physiological properties of muscles (see Heckman et al. 2009), motor units (see Burke 2009), reflexes (see Grey and Nielsen 2009), and pattern generating spinal networks (see ► [Vertebrate Pattern Generation: Overview](#)). The entries in this section

expand on those descriptions, characterizing how these systems function and how they interact with descending systems. Spinal interneuronal systems have been studied extensively for more than a century, and although much remains unknown about their role in behavior, these studies have provided basic information that can be used to guide computational studies of motor control (► [Spinal Cord, Integrated \(Non CPG\) Models of](#)). Proprioceptors provide the nervous system with information about body state – the position of the limb, the forces produced by muscles, and the interactions with the environment. Understanding how these state variables are encoded in the activity of proprioceptor afferents is critical in understanding what information the nervous system has access to when interpreting and interacting with the environment (► [“Proprioceptor Models”](#)). Although spinal systems are capable of a great deal of motor coordination on their own, including central pattern generators for basic protective reflexes and for locomotion, voluntary behaviors are accomplished by descending pathways from the brain including the cortex. How these systems interact with one another to produce movement, however, remains poorly understood. One central computational issue in these interactions is how information about task goals (e.g., the location of food to be grasped) is translated into motor commands (e.g., the muscle activations that result in movement of the arm and hand to the food) ([Coordinate Transformations, Role of Spinal Circuitry in](#)).

Ultimately motor control is the result of a single dynamic system including both the nervous system and body, coupled together through intrinsic sensory feedback also through dynamic interactions with the environment. Neuromechanics is the field of study that seeks to understand how these two systems work together to produce behavior. Entries in this section examine the neuromechanics of postural control ([Neuromechanics of Postural Control](#)), characterizing how neural and musculoskeletal systems interact to stabilize the body to maintain upright stance, and the neuromechanics of joint

coordination during locomotion ([Neuromechanics of Joint Coordination](#)), characterizing how task goals are accomplished through dynamic coordination of low level execution variables.

Cross-References

- [Coordinate Transformations, Role of Spinal Circuitry in](#)
- [Decision-Making, Motor Planning](#)
- [General Overview of Spinal Anatomy and Physiology Organization](#)
- [Motoneurons and Neuromuscular Systems: Overview](#)
- [Neuromechanics of Joint Coordination](#)
- [Neuromechanics of Postural Control](#)
- [Neuromuscular Control Systems, Models of](#)
- [Proprioception](#)
- [Proprioceptor Models](#)
- [Spinal Cord, Integrated \(Non CPG\) Models of](#)
- [Vertebrate Pattern Generation: Overview](#)

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Spinal Interfaces: Overview

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Definition

Spinal interfaces have traditionally focused on electrical stimulation of spinal cord tissue (i.e., white matter axonal tracts and/or gray matter neurons) or associated spinal roots (see ► [“General Overview of Spinal Anatomy and Physiology Organization”](#) in this Encyclopedia). Spinal interface applications have primarily centered about restoration of function lost to neurological impairment and study of spinal neural circuitry (organization, basic functions). More recently, spinal interfaces are being developed to record neural activity from large populations of spinal neurons and to deliver pharmacological agents to specific regions of the spinal cord. These interfaces may also be capable of simultaneously stimulating spinal tissue. Emerging application areas of spinal interfaces include chronic monitoring of neural transmission to serve as a biomarker of pathology/recovery and so-called closed-loop stimulation protocols, in which delivery of spinal stimulation is contingent upon real-time detection of salient neural activity. This latter category is particularly useful for studying and promoting neural plasticity in spinal circuits.

Methodologies to record and/or modulate neural transmission in spinal tissue can be divided on the basis of applications (bladder, movement restoration, pain reduction, etc.), electrode technology employed (electrical, optical, etc.), electrode position (e.g., epidural, intradural, intraspinal), or a number of other characteristics. In this entry, spinal interface techniques are presented based on the degree of invasiveness, and the similar technological methods used to record from or stimulate the neural tissue are highlighted. In

increasing order of invasiveness, spinal interfaces can be divided into (1) transcutaneous (recording and stimulation), (3) epidural, (4) intradural or intrathecal, and (5) intraspinal.

Detailed Description

High-Density Surface Electromyography

Spinal alpha motoneurons have long been the only neuron in the human central nervous system from which it is possible to obtain direct recordings. This is because motoneuron action potentials occur in a one-to-one ratio with motor unit action potentials (MUAPs), which are discrete action potentials evident in muscle fibers that can be accessed via electromyography (i.e., recording muscle electrical activity, EMG). Because each MUAP waveform has unique spatiotemporal features and because each muscle fiber is innervated by only one motoneuron (together, a “motor unit”), neural firing patterns of individual motoneurons can be discriminated from one another based on the shape of a given MUAP. These firing patterns are referred to as spike trains. When EMG is used to discriminate individual motor units and/or spike trains, it can be considered a form of transcutaneous spinal interface.

Traditional approaches for recording MUAPs, and by extension for accessing spike trains of discrete motoneurons, have relied on percutaneous needle-style or fine-wire electrodes that penetrate the skin and anchor into the muscle fibers below (i.e., intramuscular EMG). In addition to its invasiveness, this technique results in an extremely low yield of detectable motor units (~2–5/muscle) and provides reliable information only during contractions of low force magnitude.

Over the last 5–10 years, however, a powerful new technology has emerged for accessing motoneuron spike trains: high-density surface EMG (HD-sEMG) decomposition (Del Vecchio et al. 2020). In this non-invasive technique, flexible skin-surface electrodes containing 10’s of electrically and spatially isolated recording channels (typically 64 or 128) are placed over a muscle of interest. Surface EMG activity is recorded

simultaneously from each channel. Subtle differences in the spatiotemporal and spectral characteristics of each channel are then exploited by advanced statistical signal processing techniques (e.g., blind-source separation algorithms, independent components analysis) to decompose the multichannel surface EMG activity into individual MUAP waveforms and spike trains. This approach enables access to entire populations of discrete motor units (to date, ranging from ~10 to 40/muscle), providing a remarkably detailed window into descending neural drive and spinal motor output and distinguishing HD-sEMG decomposition from the general overview of motor unit function afforded by traditional intramuscular EMG. HD-sEMG decomposition is also substantially more robust than intramuscular EMG during contractions of increasing force magnitude, enabling studies of human motor unit recruitment and rate modulation that were previously either inferential or, more often than not, infeasible.

While the potential applications of HD-sEMG decomposition are near limitless, early examples have included advanced myoelectric control of prostheses (Kapelner et al. 2019), pathological neural control of movement following neurologic injury (Miller et al. 2014), and spinal motor output in the decerebrate cat (Thompson et al. 2018).

Transcutaneous Stimulation

Transcutaneous spinal stimulation refers to the activation of spinal tissue through the skin. It is broadly categorized either as magnetic stimulation or electrical stimulation. In the case of magnetic transcutaneous spinal stimulation, a magnetic field induces ionic currents within the spinal tissue (see ► [“Paraspinal Magnetic and Transcutaneous Electrical Stimulation”](#) entry in this Encyclopedia). The basic methodology involves inducing depolarization via a time-varying magnetic field delivered transcutaneously by a coil applied to the skin surface. This approach is similar in concept to transcranial magnetic stimulation (TMS) used to probe cortical circuits. The principal applications of transcutaneous spinal magnetic stimulation have been for the initiation of locomotion following spinal cord injury or in Parkinsonian patients and for the treatment of pain

when stimulation is delivered over the dorsal columns (see ► [“Paraspinal Magnetic and Transcutaneous Electrical Stimulation”](#) entry in this Encyclopedia). Finite element model studies of the spinal cord indicate that the greatest site of activation is within the tracts due to the lower threshold of activation of myelinated fibers of the white matter versus the cells of the gray matter (see ► [“Finite Element Models of Transcutaneous Spinal Cord Stimulation”](#) entry in this Encyclopedia). Since activation is typically delivered dorsally, the largest site of depolarization typically involves posterior roots and dorsal columns, although the anterior motor roots are also hot spots of depolarization.

Transcutaneous *electrical* stimulation can be used to indirectly modulate neural transmission in spinal circuits. In this approach, skin-surface electrodes are placed dorsally over the relevant vertebrae and traditional, pulsatile electrical stimulation is delivered. Rather than passing current directly into the spinal cord, the electrical stimulation is used to modulate neural transmission in primary afferent nerve fibers providing sensory inputs to spinal circuits damaged or weakened by injury. Although rarely described as such, some variants of classical transcutaneous electrical nerve stimulation (TENS) for pain are examples of this approach. More recently, however, transcutaneous electrical spinal stimulation has been introduced as a possible means to aid locomotor and upper limb rehabilitation following spinal cord injury (Inanici et al. 2018). The efficacy of this approach has not been demonstrated in randomized controlled trials as yet, and efforts to characterize the neural mechanisms by which it exerts potential therapeutic effects are ongoing but remain incomplete (Benavides et al. 2020).

Transcutaneous electrical spinal stimulation can also be delivered as a form of direct current stimulation, referred to as spinal cord direct current stimulation or transcutaneous direct current spinal stimulation (sDCS, tDCSS). Its use for modulating neural transmission in spinal circuits has paralleled that of similar approaches for modulating neural transmission in the brain. In tDCSS, two adhesive skin surface electrodes are placed on either side of the abdomen, one ventrally and one

dorsally. These electrodes are connected to the anode and cathode of a constant current stimulator, which drives current between the two sites. Unlike traditional transcutaneous electrical stimulation approaches (above), in which current is delivered in discrete pulses or trains thereof, in tDCSS the current is continuous (i.e., non-pulsed). In this regard, it can be considered to polarize the neural tissue for a period of time. The potential applications of tDCSS and the mechanisms by which it modulates neural transmission remain a source of active research. However, tDCSS appears to modulate transmission in motor and sensory regions of the spinal cord, as well as primary motor and sensory cortices, in a polarity-dependent manner (Cogiamanian et al. 2008, Ahmed 2011, Song and Martin 2017). These effects are thought to be driven at least in part by facilitation of certain forms of *activity-independent* neural plasticity (Jankowska 2017). Given its modulatory capacity and relative lack of invasiveness, tDCSS may be useful for priming spinal circuits during rehabilitation interventions.

Epidural Stimulation

Epidural stimulation refers to electrical stimulation delivered via leads inserted within the vertebral canal but outside the dura. Surgery is involved, but no stimulating electrodes are actually placed within the central nervous system or in the cerebrospinal fluid (CSF). Epidural stimulation is currently employed in a number of applications. Sacral anterior root stimulation combined with posterior sacral rhizotomy has been used extensively to restore bladder and bowel continence and voiding following spinal cord injury (Brindley 1988). Although most electrodes are implanted intradurally around the sacral roots, epidural electrode leads are sometimes used to activate the anterior sacral roots (typically S2, S3, and S4) (Egon et al. 1998). The anterior root stimulator takes advantage of the different contraction and relaxation times of the sphincter and bladder muscles. While the muscle fibers that constitute the sphincter are mainly “fast-twitch” muscle fibers that fatigue easily and relax very quickly, the fibers that compose the detrusor muscles are “slow-twitch” fibers that contract

gradually and maintain force for a longer period of time. With intermittent short bursts of high-frequency electrical pulses to the sacral nerve roots, bladder and sphincter muscles contract, but while the sphincter relaxes rapidly at the end of each stimulus burst, the pressure in the bladder is still sufficiently high to produce urination. Activation of the S2–S4 roots with longer stimulus trains is used to obtain defecation in a number of patients. Variations of the basic principles are still employed today, although advances in our knowledge of urogenital anatomy and electrode design have led to more sophisticated stimulation schemes (see ► [“Methodologies for the Restoration of Bladder and Bowel Functions”](#) in this Encyclopedia).

Epidural stimulation has also been used extensively for the restoration of locomotion following spinal cord injury in various animal models and humans (see ► [“Epidural Stimulation”](#) entry in this Encyclopedia). In all species, stimulation is delivered over the dorsal columns with the most efficacious segments for initiating locomotion varying between species. The stimulus train is typically a low-frequency (40 Hz) train of pulses delivered continuously over the dorsal columns at lumbar levels to produce activation of the locomotor circuitry. The exact mechanisms of activation or even the neuronal composition of the locomotor centers remains unknown, but the technique has been used clinically to restore standing and some locomotor movements in individuals with complete motor paralysis below the level of injury when coupled with highly intensive physical therapy (Edgerton and Harkema 2011; Harkema et al. 2011, Wagner et al. 2018). In animal models, the technique has also been combined with intrathecal delivery of targeted therapeutics to further aid restoration of locomotion and for upper limb rehabilitation, although these areas have yet to be realized clinically (Musienko et al. 2011, Barra et al. 2018). Epidural stimulation has also been employed to facilitate the initiation of locomotion in Parkinsonian patients (Fuentes et al. (2010), also see ► [“Spinal Stimulation for Parkinson Treatment”](#) in this Encyclopedia).

Finally, epidural stimulation of the dorsal columns has been applied for the treatment of chronic

and intractable pain arising from conditions such as failed back surgery syndrome, phantom limb pain, spinal cord injury, diabetic neuropathy, and ischemic limb pain (Kumar et al. 1998; Ramasubbu et al. 2013, Chari et al. 2017). Stimulation is delivered through electrode leads placed over the dorsal columns in an attempt to provide analgesia for a number of various chronic pain conditions. Success rate in the long-term relief of pain is variable, ranging from about 20% to 80% (Kumar et al. 1998). Similar to epidural electrical stimulation for locomotor rehabilitation, the mechanisms of analgesia remain unclear. In more recent implementations, which use stimulation frequencies in the KHz range, it is thought that the stimulation blocks neural transmission in ascending pain pathways (Crosby et al. 2017, Linderroth and Foreman 2017).

For both locomotor and analgesic applications, epidural stimulation has faced two particular challenges in clinical translation: off-target effects and the duration of therapeutic benefits. Off-target effects frequently take the form of paresthesias, which range from mildly irritating to painful in their own right. In some individuals, these effects limit the time that stimulation can be tolerated. A benefit of newer KHz-range stimulation paradigms is that they may evoke fewer or less intense paresthesias, although the efficacy of these paradigms for locomotor rehabilitation has yet to be investigated (Crosby et al. 2017). Regarding the duration of effects, in studies to date the therapeutic benefits of epidural stimulation often diminish rapidly upon cessation of stimulation. This phenomenon is presumably related both to the relatively nonspecific delivery of current to the spinal cord and to the non-physiological and asynchronous stimulus waveforms used to modulate neural transmission. While more targeted stimulation approaches and closed-loop stimulation paradigms may address some of these drawbacks, they are not without their own barriers to clinical translation (see below and other entries in this section).

Intradural Stimulation

Next in order of increasing invasiveness is intradural or intrathecal stimulation. Here, leads

are placed within the dural sac itself. Surgical and infection risks increase with this approach, as the implant is now placed within the central nervous system space and CSF and the blood-brain barrier is breached. Dural closure remains a surgical difficulty. However, closer proximity to the spinal cord provides greater access to specific spinal structures, allowing stimulation to be delivered to particular roots. Thus, it is no surprise that the Brindley-Finetch (described in Epidural Stimulation above) sacral anterior root electrodes are mostly implanted intradurally over the divided (anterior separated from posterior) sacral roots to restore bladder and bowel functions.

Intraspinal Stimulation

Intraspinal microstimulation (ISMS) provides the greatest access to the spinal cord but is also the most invasive and thus riskiest stimulation technique in terms of the potential damage it may cause to the nervous system. Stimulation is delivered within the spinal cord, typically via microwires implanted within the white and gray matter, although new high-density microelectrode array and optogenetic techniques amenable to spinal cord applications are being developed (Alilain et al. 2008, Lu et al. 2017). A particular benefit of ISMS for rehabilitation purposes is that it preserves orderly, physiological recruitment of motor units based on Henneman's Size Principle and allows smooth grading of contraction magnitude. This is contrasted by the well-documented reversed recruitment order and ballistic contractions common to transcutaneous neuromuscular electrical stimulation (NMES) techniques. ISMS of motor pools also readily recruits groups of synergist muscles, which has fueled many advances in our basic science understanding of spinal physiology but also provides an opportunity to cohesively restore grouped movements via a single stimulation site (which is not possible with transcutaneous NMES).

Applications of ISMS have included direct activation of motor pools/motor units to cause muscle contractions that aid locomotion (Bamford and Mushahwar 2011), bladder and bowel functions (Pikov et al. 2007), and respiration (Sunshine et al. 2018) (see ► [“Intraspinal](#)

[Stimulation](#)” in this Encyclopedia). Emerging applications include the induction and study of neural plasticity – particularly spike-timing-dependent plasticity – for rehabilitation using closed-loop neural computer interface approaches (McPherson et al. 2015, and see ► [“Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits”](#) in this Encyclopedia). And while the invasiveness of ISMS has presented a conceptual barrier to widespread translation, multiple efforts are currently underway to achieve regulatory approval for ISMS electrodes in humans. One need look no farther than deep brain stimulation electrodes as an example of the potential clinical translational path for efficacious but invasive neuromodulatory therapies.

Electrode Technologies: Issues and Potential Solutions

The electrodes used to deliver stimulation to the spinal cord are for the most part similar to the ones used to deliver electrical stimulation to peripheral nerves and/or the brain. They include cuff electrodes that use metalized contacts (typically platinum) encapsulated within silicone or other materials. These electrodes are typically used to stimulate roots (Brindley-Finotech anterior root stimulator electrode, and see Xiao et al. 2012 for more advanced designs). Metal disk or lead wires are typically used to deliver stimulation epidurally, and microwires are used to deliver stimulation intraspinally. New electrodes being developed and tested in animal models aim to increase the number of contacts and stimulation sites which would allow for greater selectivity in the delivery of stimulation. These include electrode designs for intraspinal microstimulation (Snow et al. 2006) and multi-contact surface electrodes for epidural stimulation (Gad et al. 2013).

Intraspinal microstimulation remains one of the toughest applications as the stiff metal- or silicone-based electrode presents a mechanical impedance mismatch compared to the higher compliance of the spinal tissue, leading to tissue damage. In addition, the spinal cord glides substantially within the vertebral canal during

movements (Ranger et al. 2008), and the tension it produces in the cable attaching electrode to associated connector may cause further damage to the tissue unless the cable’s flexibility is sufficient to dissociate the motions of the vertebral canal and spinal cord. A promising approach to minimizing mismatches in tissue and electrode material impedances is the braided electrode design of the Giszter group (see ► [“Braided Electrodes”](#) entry in this Encyclopedia). By braiding extremely fine wires, a very high overall compliance electrode and cabling technology is produced that can be inserted within the spinal cord with the help of a removable cannula guide and produce minimal histological damage to the central nervous tissue after long-term implantation (Kim et al. 2013a). As part of recent translation efforts, Mushahwar and colleagues have also begun development of ISMS implants for humans, performing initial mechanical testing of the implants in porcine models (Toossi et al. 2017). Wireless stimulators may also offer freedom from the cable tethering problem and potentially dura resealing. Miniaturized stimulators can be implanted close to the neural target and controlled via wireless approaches (radio frequency, optical, or acoustic waves, etc.). The approach can have the benefits of a cable-free approach like the transcutaneous stimulators but will allow much more precise targeting of the stimulation delivery (see ► [“Wireless Microstimulators”](#) entry in this Encyclopedia).

Other stimulation techniques have been used experimentally to activate the spinal cord, but to date no clinical application of these techniques has been pursued. Bizzi and colleagues have used iontophoresis to deliver an excitatory neurotransmitter locally within the gray matter (Saltiel et al. 1998), but since electrodes are pulled glass micropipettes, applications are limited to cases where the spinal cord can be securely immobilized. More recently, cell soma-sized micropipes have been developed to deliver electrical stimulation while simultaneously recording neurotransmitter release (Schwerdt et al. 2018). Although their mechanical impedance is encouraging for spinal cord applications, they have yet to be rigorously tested for this application.

Optogenetic methods have also been used to activate spinal tissue in the rat animal model (see ► **“Intraspinal Stimulation”** entry in this Encyclopedia). Stimulation is usually achieved with delivery of light from the surface, but delivery of light deep into tissue is possible through pulled optic fibers inserted into neural tissue (Gradinaru et al. 2009, Lu et al. 2017) and the development of new miniaturized optoelectronics (Kim et al. 2013b, Montgomery et al. 2015, Samineni et al. 2017). While earlier generations of optical fibers suffered from the same mechanical impedance mismatch issues as their metal electrode counterparts, these newer optrodes represent a substantial improvement in flexibility and compliance.

Finally, infrared light from lasers has also been used to elicit action potentials in peripheral nerve and cochlea of small (rodents and guinea pig) animal models (Izzo et al. 2006; Wells et al. 2005a, b; Xia et al. 2014). The methodology is termed optical stimulation, and action potential initiation appears to be caused by the induction of thermal transient within the axons or neurons (Wells et al. 2007). Depth of penetration of the light is a limiting factor attempting to activate deep tissue, and to date the technology has not been used in the spinal cord. Optical stimulation methods offer the advantage of producing no electrical stimulation artifacts, which facilitates neural recordings and closed-loop configurations because the amplifiers and analog-to-digital converters used in recordings are no longer saturated by the large electrical signal generated by the stimulus pulses.

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changes in the amount and timing of transmitter released. In addition, surrounding cells such as glia can influence the local synaptic dynamics in tripartite synapse. Neurotransmitters bind to postsynaptic receptors that may induce current to flow that changes the postsynaptic neurons membrane potential or initiates signaling pathways that affect various properties of the postsynaptic neuron.

Synaptic Dynamics: Overview

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Definition

Synaptic dynamics describes the time-dependent changes in synaptic currents that alter the strength of coupling between neurons. Various mechanisms, both pre- and postsynaptic, contribute to ongoing changes of synaptic currents and modulate the overall network activity. These mechanisms operate on various time scales (milliseconds to years) and can lead to immediate changes in neuronal activity, ongoing adaptation of neuronal responses to changing inputs, and long-term learning and memory.

Detailed Description

Connections between neurons form network circuitry, and these connections are not static, but change in amplitude and timing. When a spike reaches a presynaptic terminal, processes are initiated that result in release of neurotransmitters that diffuse across the synaptic cleft to reach the postsynaptic receptors. Changes in these release dynamics can lead to short-term or lasting

Fast Dynamics

Changes of synaptic currents following a single synaptic transmitter release event are usually on the time scale of milliseconds to second and controlled by the dynamics of postsynaptic receptors. These fast dynamics follow a time course determined by transmitter diffusion, conformational changes in postsynaptic receptors that allows current to flow through the receptor pore, or changes that result in triggering second messengers that modify membrane currents. The resulting current flow is characterized by a sharp rise followed by a slower decay as the receptors inactivate and neurotransmitters unbind. The resulting currents can either excite or inhibit the activity of the postsynaptic neuron, depending on the selectivity of membrane channels for specific ions.

Ionotropic receptors. Receptors that allow direct current flow through a pore are called ionotropic receptors (Eccles and McGeer 1979) and provide the fastest synaptic dynamics. Mathematical representations of a synaptic current, $I_s(t)$, can be represented by a conductance $g_s(t)$ that regulates current flow across the membrane (Gerstner and Kistler 2002; Koch 2004),

$$I_s(t) = g_s(t) \cdot (V(t) - E_s), \quad (1)$$

where $V(t)$ is the membrane potential and E_s is the reversal potential of the current. If E_s is greater than the membrane potential, then the synaptic excites the neuronal activity, and if E_s is less than the membrane potential, then the synapse inhibits the neuronal activity.

The time-dependent synaptic conductance may be based on double exponential functions (or similarly shaped functions for $t \geq 0$).

$$g_s(t) = g_s \left(-e^{-t/\tau_1} + e^{-t/\tau_2} \right) \quad (2)$$

where τ_1 is the onset time constant and τ_2 is the decay time constant. More detailed representations of changes in synaptic conductances are developed in kinetic models of channels.

Two important types of excitatory currents are mediated by AMPA glutamate receptor and *N*-methyl-d-aspartate (NMDA) receptors that are excitatory in most neurons and have time constants for a risetime of a few milliseconds. They differ in two respects, time constants and dependence on postsynaptic voltage, but are often colocalized at the same synaptic zones. AMPA receptors usually have a larger peak conductance and decay with a few milliseconds (Trussell et al. 1993). NMDA receptors have a longer decay (Jahr and Stevens 1990), and the peak current is dependent on the postsynaptic membrane potential. NMDA receptors pass calcium ions that can initiate signaling cascades that may have a secondary effect on synaptic dynamics on a longer time scale such as long-term plasticity (Collingridge and Bliss 1987; Lisman 1989). Another important current is mediated by gamma-aminobutyric acid (GABA) receptors and is usually inhibitory in adult neurons.

Metabotropic receptors. Receptors that trigger second messengers to modify membrane currents are called metabotropic receptors (Eccles and McGeer 1979). These receptors are typically slower in their effect on the membrane potential than ionotropic receptors and can result in secondary long-lasting effects on the excitability of neurons. They can also help to initiate signaling cascades that lead to long-term synaptic plasticity. Their fast dynamics are mediated through changes in membrane currents, such as potassium currents, and the effects on membrane excitability can be either excitatory or inhibitory depending on the type of metabotropic receptor. In the simplest mathematical representations of these receptors, the conductance can be represented by a double

exponential function (Eq. 2) with a long onset time constant (τ_1) of several milliseconds.

Short-Term Dynamics

The synaptic dynamics caused by a spike may be affected by the history of previous spikes due to short-term plasticity (Zucker and Regehr 2002; Blitz et al. 2004). If the second of two spikes has a larger postsynaptic current than the first spikes, then the plasticity is called facilitation, and if the second spike has a smaller postsynaptic current, then it is called short-term depression. The amount of facilitation and depression on further spikes in a series changes over time and may saturate and last up to several seconds. The duration of facilitation and depression may occur on different time scales leading to complex sequences of postsynaptic currents that could be unique to the pattern of spikes.

Both pre- and postsynaptic mechanisms can be responsible for short-term plasticity. An important presynaptic mechanism is based on the presynaptic probability of neurotransmitter release for each spike combined with the rate of replenishment of presynaptic vesicles containing neurotransmitters. If the probability of release is high, then synaptic zones may not yet be prepared for the next spike leading to a reduced peak synaptic current observed in short-term depression. In contrast, if the release probability is low, then the first spike may have helped to prime the release so that the release probability is higher for the second spike. This increased release probability at each synaptic zone leads to an increase in peak synaptic current observed in facilitation.

Long-Term Dynamics

Changes in synaptic currents that last longer than several minutes are called long-term plasticity. Several mechanisms, both pre- and postsynaptic, may be responsible for these lasting changes that may increase or decrease the strength of synaptic currents. Increases in synaptic currents are called long-term potentiation (LTP) (Bliss and Lomo

1973), and decreases are called long-term depression (LTD) (Dudek and Bear 1993). Long-term plasticity may be dependent on the activity of pre- and postsynaptic neurons, and when the relative differences of timing of spikes between the neurons determine whether the change is potentiation or depression, then it is referred to as spike-timing-dependent plasticity (STDP) (Abbott and Nelson 2000). The processes of long-term depression and potentiation are balanced by synaptic scaling that adjusts the global input to neurons to maintain stable activity. Long-term plasticity is believed to form the basis of learning and memory as learned sensory cues, and behaviors are encoded in the strengths of synapse in neural circuitry (Hebb 1949).

Cross-References

- ▶ [AMPA Glutamate Receptor \(AMPA Receptor\), Conductance Models](#)
- ▶ [Anti-Hebbian Learning](#)
- ▶ [Biochemical Signaling Pathways and Diffusion: Overview](#)
- ▶ [Bimolecular Reactions, Modeling of](#)
- ▶ [Enzyme Kinetics, Modeling of](#)
- ▶ [Facilitation, Biophysical Models](#)
- ▶ [Gamma-Aminobutyric Acid Type-A \(GABA-A\) Receptors, Kinetic Models](#)
- ▶ [Gap Junctions in Small Networks](#)
- ▶ [Gap Junctions, Neural Population Models and](#)
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- ▶ [Tripartite Synapse \(Neuron–Astrocyte Interactions\), Conductance Models](#)
- ▶ [Working Memory, Models of](#)

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Further Reading

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Vertebrate Pattern Generation: Overview

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Synonyms

Central pattern generator; CPG; Neural oscillator;
Rhythm generators

Definition

Central pattern generators (CPGs) are neural networks that can produce organized rhythmic patterns in the absence of rhythmic sensory and descending inputs from other parts of the nervous system (Marder and Calabrese 1996).

Detailed Description

Vertebrate Central Pattern Generators

The central nervous systems of vertebrates contain many types of central pattern generators (CPGs) that generate and control various rhythmic movements. These CPGs control important functions, including different forms of locomotion, such as swimming, walking, running, and flying, and non-locomotor processes and behaviors, such as breathing, swallowing, chewing, mastication, scratching, whisking (in rodents), singing (in birds), etc. This overview focuses on computational models of locomotion and breathing in mammals, which are briefly discussed below. Other known models of vertebrate CPGs include CPGs controlling swimming in *Xenopus*

tadpoles (Wolf et al. 2009; ► [“Rhythm Generation in Young *Xenopus* Tadpoles”](#)), zebra fish (Hill et al. 2004; Knudsen et al. 2006), and lamprey (Grillner et al. 2007); CPGs controlling swimming and walking in salamander (Ijspeert 2001; ► [“Control of Aquatic and Terrestrial Gaits in Salamander”](#)); CPGs controlling locomotion and scratching in turtles (Hao et al. 2011; ► [“Control of Locomotion and Scratching in Turtles”](#)); CPGs responsible for rhythm generation in embryonic chick spinal cord (Tabak et al. 2001; ► [“Rhythm Generation in Embryonic Chick Spinal Cord”](#)); and others.

Locomotor CPG in Mammals

The *Half-Center* Concept of the Locomotor CPG
The ability of the spinal cord to generate coordinated locomotor-like rhythmic activity in the absence of rhythmic supraspinal and afferent inputs provides strong evidence for both the existence of locomotor CPGs in vertebrates including mammals and their location in the spinal cord (Grillner 1981; Rossignol 1986; Orlovsky et al. 1999; Stuart and Hultborn 2008; Guertin 2009). The first schematic of a locomotor CPG, called the “half-center” model, was proposed by Graham Brown (1914, see also Stuart and Hultborn 2008; Guertin 2009). This model consisted of two (flexor and extensor) half-centers that reciprocally inhibited each other. The mutual inhibitory interactions between the half-centers were mediated by corresponding inhibitory interneurons, which ensured that only one half-center could be active at a time. The activity of the currently active half-center reduced gradually because of some fatigue or adaptation mechanisms leading to the activation of the antagonistic half-center, inhibiting the currently active half-center, and switching the locomotor phase. It was suggested that the flexor and extensor half-centers project to and activate the flexor and extensor motoneurons, respectively. Studies on immobilized decerebrate cats demonstrated that continuous electrical stimulation of the midbrain locomotor region (MLR) can produce “fictive locomotion” – the rhythmic pattern of motoneuron activity characterized by alternating activation of flexor and extensor

motoneurons similar to that observed during normal locomotion in the intact animal (Rossignol 1986). Similar patterns of locomotor activity could be also produced by systemic administration of the noradrenergic precursor, L-DOPA (e.g., Jankowska et al. 1967a, b). The demonstrated possibility to produce either MLR-evoked or drug-evoked fictive locomotion in the cat spinal cord has provided strong evidence for the existence of locomotor CPGs in the mammalian spinal cord.

The Unit Burst Generators Concept

CPG half-center models can be theoretically analyzed and classified into categories such as intrinsic escape, intrinsic release, synaptic escape, and synaptic release depending on which half-center and which process associated with this half-center control the transitions between activity states (Wang and Rinzel 1992; Skinner et al. 1994; Ausborn et al. 2018b; ► [“Comparative Analysis of Half-Center Central Pattern Generators \(CPGs\)”](#)). At the same time, the classical half-center concept can only represent a simplified CPG organization and cannot reproduce and explain many features of the locomotor pattern observed in the mammalian spinal cord. Specifically, biological locomotor activity does not exhibit strictly alternating flexor and extensor activities (with all motoneurons clearly belonging to one of these two groups) as suggested by the classical half-center model. The real pattern is more complex and includes motoneuron pools (such as those controlling biarticular muscles) generating bursts during both the flexion and extension phases of the step cycle or during only a part of one phase. There are also noticeable differences in the timing of burst onset and/or offset between different flexor and/or between different extensor pools. To overcome these and other limitations of the classical half-center model, Grillner (1981) proposed a unit burst generator (UBG) concept suggesting the existence of several separate rhythmogenic modules (or unit burst generators) controlling each joint of the limb and interacting with each other as coupled neural oscillators. A simplified mathematical model of the mammalian locomotor CPG based on the

UBG concept was proposed and analyzed by Sherwood et al. (2011; ► [“Computational Analysis of Rodent Spinal CPG”](#)). Despite many obvious advantages, this model showed a very slow recovery after applied perturbations. The analysis of sub-networks of this CPG revealed that the endogenous bursting properties of coupled neurons dominated over the phasing and synchronization properties of the CPG network, leading to the slow phase resetting and rhythm stabilization in response to applied perturbations.

The Two-Level Model of the Locomotor CPG

An important extension of the classical half-center model was suggested based on the analysis of (a) spontaneous deletions (missing bursts) in the rhythmic motoneuron activities and (b) effects of afferent stimulations on the locomotor pattern during fictive locomotion in the cat (Rybak et al. 2006a, b; McCrea and Rybak 2007, 2008; ► [“Two-Level Model of Mammalian Locomotor CPG”](#)). This analysis led to the suggestion that the locomotor CPG has a two-level architecture with a separate top-level, half-center rhythm generator (RG) and a pattern formation network (PF). While the RG defines the locomotor frequency, the PF network is controlled by the RG and defines and coordinates the more complicated firing patterns of different motoneuron pools. The two-level model was able to reproduce a number of features of the locomotor pattern observed during cat locomotion, including phase maintenance of motoneuron activities following spontaneous deletions or brief stimulation of some afferents, which would be difficult or even impossible to explain in the framework of the classical half-center architecture (see ► [“Two-Level Model of Mammalian Locomotor CPG”](#)). Some aspects of supraspinal and afferent control of the two-level locomotor CPG were analyzed using computational modeling approaches (Rybak et al. 2006a; Markin et al. 2010; Spardy et al. 2011a, b).

One advantage of the two-level model is a possibility to perform independent control (by supraspinal and afferent inputs) of the step cycle duration (locomotor speed) at the RG level and the activity of motoneurons and motor synergies at the PF level. This CPG model was used in

several studies focused on the development of CPG-controlled legged robots (Chen et al. 2007; Maeda 2008; Amrollah and Henaff 2010).

Rhythmic Activity in Isolated Spinal Cord Preparations of Rodents

The mammalian locomotor CPG was also studied in vitro using isolated spinal cord preparations of rodents (Smith and Feldman 1987; ► “Locomotor Pattern Generation in the Rodent Spinal Cord”). The locomotor CPG in these preparations can be activated in several ways, including pharmacological manipulations [by using solutions with specific combinations of *N*-methyl-D-aspartate (NMDA) and serotonin], stimulations of sensory afferents or dorsal roots, and brainstem stimulation. The elicited motor output shows alternation of activity in the left and right ventral roots (e.g., left L2 and right L2) combined with alternation of ipsilateral flexor (L2) and extensor (L5) activities on each side of the cord. Significant progress in the understanding of functional and structural organization of spinal circuits has been achieved using special combinations of genetic, molecular, and developmental approaches. Several classes of spinal interneurons were defined in the embryonic and early postnatal spinal cord based on the dynamic expression pattern of transcription factors (Goulding 2009; Whelan 2010; Gosgnach 2011; Kiehn 2011; Dougherty and Ha 2019; ► “Locomotor Pattern Generation in the Rodent Spinal Cord”). The new genetic techniques allow visualization of identified neurons as well as manipulation of their activity and their selective elimination. Several classes of inhibitory (CINi) and excitatory (CINE) commissural interneurons (CINs) have been identified. The axons of these cells cross the midline, project to the opposite side of the cord, and mediate interactions between left and right circuits. The role of different CINs in locomotion has been identified by using transgenic mice with mutations in, or knockout (KO) of, specific genes resulting in various abnormal locomotor phenotypes (Kullander et al. 2003; Lanuza et al. 2004; Akay et al. 2006; Lundfald et al. 2007; Crone et al. 2008, 2009; Zhang et al. 2008; Zagoraïou et al. 2009; Rabe et al. 2009; Restrepo et al. 2011; Talpalar et al. 2013).

A two-level computational model of neural circuits in the spinal cord with left and right rhythm-generating populations interacting via inhibitory and excitatory CINs has been developed based on the analysis of spontaneous deletions in the isolated spinal cord preparation with rhythmic activity evoked by administration of NMDA and serotonin (Zhong et al. 2012; ► “Locomotor Pattern Generation in the Rodent Spinal Cord”) and further refined in subsequent studies (Rybak et al. 2013, 2015; Shevtsova et al. 2015; Shevtsova and Rybak 2016; Danner et al. 2016, 2017).

Modeling the Effects of Genetic Transformations on the Locomotor Pattern

A representative example of how genetic manipulations can change the phase relationships between ipsi- and contralateral neurons involved in control of locomotion in mice is based on the genetic ablation of special molecules involved in guidance of CIN axons, such as Netrin-1 and DCC. Also, the spinal cord contains glutamatergic interneurons with ipsilateral projections, whose axon guidance involves the EphA4 receptor. In *EphA4* knockout (KO) and *Netrin-1* KO mice, the normal left–right alternating pattern is replaced with a synchronized hopping gait, and the spinal cord of *DCC* KO mice exhibits uncoordinated left and right oscillations (Rabe et al. 2009; Restrepo et al. 2011; Rabe Bernhardt et al. 2012; Vallstedt and Kullander 2013). To investigate the effects of these genetic transformations, Rybak et al. (2013) developed a computational model of the spinal circuits containing the left and right rhythm-generating neuron populations (RGs), each with a subpopulation of EphA4-positive neurons, and the CINi and CINE populations mediating, respectively, mutual inhibition and mutual excitation between the left and right RGs. In the *EphA4* KO circuits, half of the axons of EphA4-positive cells crossed the midline and excited the contralateral RG neurons. In the *Netrin-1* KO model, the number of contralateral CINi projections was significantly reduced, while in the *DCC* KO model, the numbers of connections from both CINi and CINE were reduced. In the simulations performed, the models of *EphA4* and *Netrin-1* KO circuits showed switching from the left–right alternating

pattern to a synchronized hopping pattern, and the *DCC* KO network exhibited uncoordinated left–right activity. The model was able to reproduce multiple experimental data on the effects of above genetic transformations on the locomotor pattern, providing important insights into the organization of the spinal locomotor network and was later build upon by subsequent studies (Shevtsova et al. 2015; Danner et al. 2016, 2017; Ausborn et al. 2019).

Respiratory CPG in Mammals

Respiratory Pattern and Spatial Organization of the Respiratory CPG

The respiratory motor pattern observed during quiet breathing in mammals (“eupnea”) consists of three phases: inspiration (I), post-inspiration (post-I or E1), and late expiration (E2), which can be recognized in the integrated activity of the phrenic and cranial nerves. This pattern originates within a bilateral column of neurons, called the ventral respiratory column (VRC), located in the ventrolateral medulla and controlled by inputs from other medullary (retrotrapezoid nucleus, RTN, raphé, etc.) and pontine regions. The VRC includes several compartments arranged in the rostro-caudal direction: Bötzing Complex (BötC), pre-Bötzing Complex (pre-BötC), and rostral (rVRG) and caudal (cVRG) subregions of the ventral respiratory group (VRG). Respiratory neurons in these compartments are usually classified based on their firing pattern (e.g., decrementing, augmenting) and phase of activity relative to the breathing cycle, such as early inspiratory (early-I or I-DEC), i.e., inspiratory neurons with a decrementing discharge pattern; ramp-inspiratory (ramp-I or I-AUG), i.e., inspiratory neurons with an augmenting firing pattern; post-inspiratory neurons (post-I or E-DEC), i.e., neurons with a decrementing activity during expiration; augmenting or stage II expiratory (aug-E or E-AUG or E2), i.e., expiratory neurons with an augmenting pattern; and pre-inspiratory/inspiratory neurons (pre-I/I), i.e., the neurons whose activity starts before the onset of inspiration and continues throughout inspiration. The BötC, with predominately post-I and aug-E

neurons, is considered to be a major source of expiratory activity. The adjacent, more caudal pre-BötC contains neural circuits essential for generating inspiratory activity (Cohen 1979; Bianchi et al. 1995; Richter 1996; Smith et al. 2013).

Computational models of the respiratory network have been in development for several decades. Early computational models of the respiratory CPG focused on the network interactions between different types of respiratory neurons and did not consider intrinsic biophysical rhythmogenic properties of single respiratory neurons and their possible contribution to rhythmogenesis. Generation of the respiratory rhythm in these models was based on the half-center concept suggesting that the respiratory oscillations result from sequential phase switching resulting from the reciprocal inhibitory interactions between different types of respiratory neurons (Botros and Brace 1990; Duffin 1991; Ogilvie et al. 1992; Balis et al. 1994; Rybak et al. 1997; reviewed by Lindsey et al. 2012).

The Pre-Bötzing Complex and Rhythm Generation In Vitro

A fundamentally distinct concept of respiratory rhythm generation was derived from neonatal in vitro studies. An important discovery has been that a subregion of the VRC, called the pre-Bötzing Complex, contains a population of excitatory interneurons that can intrinsically generate an inspiratory-like rhythm (Smith et al. 1991). This rhythm was shown to persist after blockade of synaptic inhibition, indicating that the pre-BötC may contain cells with intrinsic bursting properties. Butera et al. (1999a, b) developed and analyzed a series of computational models of bursting pacemaker neurons and populations of these neurons with mutual excitatory connections. In these models, the intrinsic bursting was based on a slowly inactivating persistent sodium current (I_{NaP}) as the essential burst-generating, inward cationic current. The rhythmic bursting cycle in these models was controlled by the slow kinetics of inactivation and recovery from inactivation of I_{NaP} . Simulations performed have shown that the excitatory synaptic

interactions coupled with I_{NaP} activation can readily synchronize cellular bursts and produce population bursting. Importantly, generation of this rhythm does not require inhibitory interactions, which can explain the persistence of the *in vitro* oscillations after inhibitory synaptic transmission was blocked. It was also shown that even a small fraction of intrinsically bursting cells (5–10%) can produce a synchronized bursting activity of the entire population. Moreover, synchronized population activity may occur even if none of the cells operate in the intrinsic bursting state. Elevation of tonic drive to the population reduces burst duration, increases burst frequency, and, finally, switches population activity from population bursting to a regime of sustained asynchronous activity (Butera et al. 1999a).

Network-Based Versus Pacemaker-Driven Mechanisms for Respiratory Rhythmogenesis and Hybrid Pacemaker–Network Models

The early network models were able to generate a realistic respiratory motor pattern and simulate various alterations of this pattern under different conditions. However, these models failed to reproduce some characteristic behaviors observed in the reduced *in vitro* preparations and, specifically, the maintenance of the respiratory rhythm following inhibition blockade. Alternatively, the pacemaker-based models, developed to fit to *in vitro* data, could not explain many respiratory behaviors observed *in vivo*, such as the Hering–Breuer and other respiratory reflexes as well as the independent control of the duration of each respiratory phase. Neither could these models reproduce apneusis, a well-known abnormal breathing pattern characterized by a significantly prolonged inspiration (up to several seconds) alternating with short expiratory intervals. Moreover, the rhythmic activity generated in the reduced *in vitro* preparations and reproduced by the pacemaker-driven models is characterized by a decrementing shape of inspiratory discharges that clearly differs from the augmenting shape of phrenic discharges generated during eupneic breathing *in vivo*; these discharges rather resemble the decrementing bursts observed during gasping.

The above contradictions between the network-based and the pacemaker-based concepts and models can be resolved by postulating that (i) the pre-BötC, while capable of intrinsic bursting when isolated and under some special conditions, is normally embedded in the larger brainstem respiratory network which makes its behavior dependent on its interactions with other brainstem structures and (ii) the respiratory rhythmogenesis is state dependent, and therefore the respiratory oscillations may be generated by either a network-based or pacemaker-driven mechanisms or their specific combinations depending on the conditions (Smith et al. 2000, 2007; Rybak et al. 2002, 2004, 2007; Lindsey et al. 2012; Smith et al. 2013; Koizumi et al. 2016; Ausborn et al. 2018a; ► “Computational Models of Mammalian Respiratory CPG”).

The Respiratory CPG and Spatial and Functional Hierarchy of Multiple Rhythmogenic Mechanisms

Significant progress in understanding of spatial and functional organization of the respiratory CPG in the mammalian brainstem has been achieved by using an arterially perfused *in situ* rat brainstem–spinal cord preparation (Paton 1996) and applying sequential rostral-to-caudal microtransections through the brainstem while recording cranial and spinal motor outflow to observe transformations of network behavior (Rybak et al. 2007; Smith et al. 2007). This approach revealed the existence of a rostral-to-caudal stacking of network building blocks serving distinct circuit functions, which are fully integrated in the intact system, but can be revealed when particular compartments are removed or under special metabolic conditions (hypoxia, hypercapnia). These studies revealed that sequential reduction of the network progressively reorganizes network dynamics, such that new rhythmogenic mechanisms emerge. Specifically, starting from a transection at the pontine–medullary junction, the normal three-phase respiratory pattern is transformed to a two-phase rhythmic pattern lacking the post-I phase. With more caudal transections made close to or at the rostral boundary of the

pre-BötC, the respiratory activity transforms to “one-phase” inspiratory oscillations originating within the pre-BötC, without critical involvement of phasic expiratory inhibition (Rybak et al. 2007; Smith et al. 2007). These results led to the conclusion that (i) generation of the normal three-phase rhythmic pattern requires the presence of the pons (i.e., excitatory drive from pontine neurons to the VRC); (ii) generation of the two-phase pattern is intrinsic to reciprocal inhibitory synaptic interactions between the BötC and the pre-BötC and may also involve the RTN to provide excitatory drive to generate stable behavior; and (iii) the one-phase inspiratory oscillations are generated within the pre-BötC and rely on intrinsic cellular mechanisms operating in the context of the pre-BötC excitatory network. These data allowed the conclusion that there is a spatial and dynamical hierarchy of interacting pontine, BötC and pre-BötC circuits, each of which controls different aspects of respiratory rhythm generation and pattern formation, which can be revealed as the network is progressively reduced. The expression of each rhythmogenic mechanism is state dependent and produces specific motor patterns likely to underpin distinct motor behaviors (Smith et al. 2007, 2013; ► “Computational Models of Mammalian Respiratory CPG”).

A minimal network configuration proposed to represent the above multiple rhythmic states and their transformations included (i) a mutually inhibitory circuit with a ringlike architecture composed of post-I and aug-E neurons of the BötC compartment and early-I neurons within the pre-BötC and (ii) a pre-BötC kernel of excitatory pre-I/I neurons, with intrinsic I_{NaP} -dependent bursting properties. The latter participate dynamically in the expiratory–inspiratory phase transition and generation of the inspiratory phase. The detailed description and computational model of this core network and the circuit elements participating in each rhythmic state can be found in a series of related publications (Rybak et al. 2007; Smith et al. 2007; Rubin et al. 2009b; for review see also Lindsey et al. 2012; Smith et al. 2013; ► “Computational Models of Mammalian Respiratory CPG”).

Respiratory Rhythm Generation and Coupled Oscillators

As described above, the respiratory CPG is considered to comprise several interacting populations of respiratory neurons located in the pre-BötC and BötC circuits within the VRC. A distinct site of neural oscillations was identified in vitro in the isolated neonatal rat brain stem–spinal cord preparation (Onimaru and Homma 1987, 2003; Onimaru et al. 1988). This additional oscillator, called the parafacial respiratory group (pFRG), seems to reside within, or overlap with, the RTN. It was also found that RTN/pFRG oscillations in vivo drive abdominal motor activity, expressing late-expiratory (late-E, or pre-inspiratory) bursts or biphasic discharges (with pre-I and post-I components) in the abdominal motor output when the system operates in the active (forced) expiration regime (Janczewski et al. 2002; Janczewski and Feldman 2006; Feldman and Del Negro 2006; Abdala et al. 2009). Several competing concepts concerning the physiological role of RTN/pFRG oscillations have been suggested, including the dual oscillator concept that considers the RTN/pFRG as an independent expiratory rhythm generator coupled with a distinct inspiratory rhythm generator in the pre-BötC (Janczewski and Feldman 2006). However, the exact physiological role of pFRG oscillations, the specific conditions for their emergence, and the nature and mechanisms of the interactions between the BötC/pre-BötC and RTN/pFRG oscillators are not yet known.

Molkov et al. (2010; ► “Coupled Oscillations in Neural Control of Breathing”) extended the previous respiratory CPG model (Rybak et al. 2007; Smith et al. 2007) to include the RTN/pFRG oscillator and consider interactions between the BötC/pre-BötC and RTN/pFRG oscillators. The extended model incorporates an additional late-E population in the RTN/pFRG compartment, representing a source of late-E oscillatory activity. In the proposed model, under normal metabolic conditions, the RTN/pFRG oscillator is inhibited by the BötC/pre-BötC circuits, and the late-E oscillations can be only released by either hypercapnia-evoked activation of RTN/pFRG or by hypoxia-dependent

suppression of RTN/pFRG inhibition by BötC/pre-BötC. The proposed interactions between the BötC/pre-BötC and RTN/pFRG oscillators allow the model to reproduce several experimentally observed behaviors, including *quantal acceleration* of abdominal late-E oscillations with progressive hypercapnia and *quantal slowing* of phrenic activity with progressive suppression of pre-BötC excitability, as well as to predict a release of late-E oscillations by disinhibition of RTN/pFRG under normal conditions (Molkov et al. 2010; ► “Coupled Oscillations in Neural Control of Breathing”). Rubin et al. (2011) performed thorough analysis of the reduced model and explained the regimes of quantal acceleration and quantal slowing in terms of synchronization of the BötC/pre-BötC and RTN/pFRG oscillators. They have shown that the dynamics of each oscillator can be represented by a stable limit cycle in some phase space. The phase space of a system of two coupled oscillators is a Cartesian product of the phase spaces of each oscillator. The behavior of this system can be represented by a trajectory on 2D invariant torus. If the ratio of oscillation frequencies of the two oscillators is rational (i.e., equal to N/M , for some integers N and M), then this trajectory is closed, indicating N/M synchronization between oscillators, where N and M represent numbers of rotations around two orthogonal circles that together span the torus (Rubin et al. 2011). These modeling studies provide mechanistic explanations for the emergence of RTN/pFRG oscillations and their interaction with the BötC/pre-BötC circuits representing the core of the respiratory CPG.

Intrinsic Neuronal Properties Involved in Rhythmic Bursting in the Brainstem and Spinal Cord

The mechanisms generating neural oscillations in the mammalian brainstem, particularly in the pre-Bötzinger Complex involved in control of respiration, and in the spinal cord (locomotor CPG), that persist after blockade of synaptic inhibition, remain poorly understood. Experimental studies in medullary slices from neonatal rodents containing the pre-BötC identified two mechanisms that could potentially contribute to

generation of rhythmic bursting: one based on the persistent or slowly inactivating I_{NaP} (Butera et al. 1999a, b; Koizumi and Smith 2008) and the other involving the calcium-activated nonspecific cation current (I_{CAN}) activated by intracellular Ca^{2+} accumulated from extracellular (e.g., calcium currents, I_{Ca}) and/or intracellular sources (Pace et al. 2007). The involvement and relative roles of these mechanisms in rhythmic bursting are still under debate. Several related models combining the above two mechanism have been developed (Rubin et al. 2009a; Toporikova and Butera 2011; Dunmyre et al. 2011; Jasinski et al. 2013). Jasinski et al. (2013) investigated Na^+ - and Ca^{2+} -dependent bursting generated in single cells and in a heterogeneous population of synaptically interconnected excitatory neurons with I_{NaP} and I_{Ca} randomly distributed within the population. They analyzed the possible roles of network connections, ionotropic and metabotropic synaptic mechanisms, intracellular Ca^{2+} release, and the Na^+/K^+ pump in rhythmic bursting activity generated under different conditions. They showed that heterogeneous populations of excitatory neurons with these properties can operate in different oscillatory regimes with bursting dependent on I_{NaP} and/or on I_{CAN} , or independent of both. The exact oscillatory regime and the operating bursting mechanism may depend on neuronal excitability, synaptic interactions, and relative expression of particular ionic currents. The existence of multiple oscillatory regimes and their state-dependency may provide explanations for different rhythmic activities observed in the brainstem and spinal cord under different experimental conditions.

Interestingly, the Na^+ - and Ca^{2+} -dependent bursting mechanisms can be unexpectedly connected. Brocard et al. (2013) have shown that the evoked locomotor-like activity in the isolated neonatal rodent spinal cord reduces the extracellular calcium concentration ($[Ca^{2+}]_o$) to 0.9 mM and increases the extracellular potassium concentration ($[K^+]_o$) to 6 mM. Such changes in $[Ca^{2+}]_o$ and $[K^+]_o$ trigger a rhythmic bursting activity in spinal interneurons that may represent elements of the respiratory CPG. The performed experimental studies and modeling have shown that the

emergence of this rhythmic activity critically involves a $[Ca^{2+}]_o$ -dependent activation of the persistent sodium current (I_{NaP}). These results suggest that the locomotor oscillations in the spinal cord may relay on the I_{NaP} -dependent pacemaker properties in spinal interneurons, which can be turned on and off by activity-dependent changes in $[Ca^{2+}]_o$ and $[K^+]_o$ (Brocard et al. 2013).

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Vestibular System: Overview

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Detailed Description

The vestibular system is our sixth sense. Not only does it contribute to our sense of orientation and movement in space but, via the vestibulo-ocular reflex (VOR), it stabilizes our vision, especially during rapid unpredictable head movements. Without the VOR our visual world would appear to move every time we undertook an activity that involves head movement, such as during walking, running, climbing, or driving on a bumpy road.

The vestibular organ is located in the inner ear next to the cochlear. As our head movements consist of rotations (nodding in affirmation) and translations (jumping up and down when happy), the vestibular organ comprises two sensor systems. The semicircular canals sense angular head rotations while the otolith organs sense linear head translations (see ► [“Vestibular Otoliths, Response to Vibration and Sound”](#)). Both the semicircular canals and otolith organs rely on specialized hair cells and the inertia of fluid (canals) or a gelatinous mass (otoliths) to bend the sensory hairs. Because there are two types of hair cells and because individual vestibular afferents receive input from different combinations of these hair cells, the signals coming from the vestibular periphery contain a wealth of sensory information that includes head-rotation velocity and acceleration, head linear acceleration, or tilt angle (see ► [“Peripheral Vestibular Signal Processing”](#)). This information is encoded in the signals coming from the peripheral vestibular organs but further processing occurs centrally (see ► [“Central Vestibular Signal Processing”](#)) to generate the appropriate three-dimensional (horizontal, vertical, and torsional) eye

movements required to stabilize vision and the muscle responses that equilibrate balance. Some of this processing is very rapid. For example, the direct pathway of the VOR consists of a three-neuron arc that has a transmission delay of ~7 ms in primates. In fact, the VOR is our fastest neural reflex.

The central vestibular neural circuitry, located in the vestibular nuclei of the brainstem, receives input from the vestibulo-cerebellum to sustain, modify, and train the vestibular response (see ► [“Vestibular Adaptation and Compensation”](#)). Thus, the vestibular system is an exquisitely adaptable system during normal function. For example, the VOR response increases almost immediately when needed to view close objects or scenes, as if that context had been pre-programmed and can be trained to increase or decrease when wearing magnifying or minifying lenses. The vestibular system also has the ability to recalibrate to compensate for permanent injury to one (complete injury) or both (incomplete injury) of the vestibular organs and their associated nerves. There are many causes of damage to the vestibular end organ and associated nerves. The most common of these include age-related cell loss, tumors, head trauma, ototoxic injury (e.g., by aminoglycoside drugs), Meniere’s disease, infection (meningitis and vestibular neuritis), and cochlear implantation (see ► [“Vestibular Function After Cochlear Implantation”](#)). About 1% of adults under 65 and 25% over 65 will have an injury to the vestibular organs. Other patients will have normal functioning vestibular organs and nerves but suffer from abnormalities of the vestibular organs that result in conditions such as benign paroxysmal positional vertigo or superior canal dehiscence syndrome. Because the vestibular system operates over a large range of head-rotation frequencies (0 to ~15 Hz) and comprises the canals and otolith organs, a range of diagnostic tests have been developed to test for the different conditions above including the following: head impulse testing (see ► [“Vestibular, Canal Testing: The Head Impulse Test”](#)), video (see ► [“Vestibular, Eye Movement Testing”](#)), imaging, and

vestibular evoked myogenic potential testing. For example, the head impulse test is used to determine the function of each of the six semicircular canals and their associated nerves during physiologically relevant rapid head rotations. For patients with complete vestibular organ loss, vestibular function can be restored by a vestibular prosthesis that senses head movements and transmits an appropriately encoded electrical signal to drive the vestibular nerves (see ► [“Vestibular Prosthesis, Interface”](#)). For prosthesis recipients and also patients with incomplete vestibular loss, vestibular rehabilitation is essential for maximum recovery (see ► [“Vestibular, Rehabilitation”](#)). Ideally, vestibular rehabilitation exercises are tailored for each patient so that compensatory mechanisms are best enabled. The accepted techniques developed to diagnose, cure, and rehabilitate vestibular injury have helped many patients because they are

based on our fundamental understanding of vestibular signals and their processing. This is the focus of the articles in this section.

Cross-References

- [Central Vestibular Signal Processing](#)
- [Peripheral Vestibular Signal Processing](#)
- [Vestibular Adaptation and Compensation](#)
- [Vestibular Function After Cochlear Implantation](#)
- [Vestibular Otoliths, Response to Vibration and Sound](#)
- [Vestibular Prosthesis, Interface](#)
- [Vestibular, Canal Testing: The Head Impulse Test](#)
- [Vestibular, Eye Movement Testing](#)
- [Vestibular, Rehabilitation](#)

A

$\alpha 1G$

- [Low-Voltage-Activated Calcium Channels](#)

$\alpha 1H$

- [Low-Voltage-Activated Calcium Channels](#)

$\alpha 1I$

- [Low-Voltage-Activated Calcium Channels](#)

Absorbing Boundary

- [Decision-Making, Threshold](#)

Accumulation of Evidence in Decision-Making

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Definition

Accumulation of evidence in decision making is the process by which noisy sensory information is sequentially sampled until sufficient evidence has accrued to favor one decision over another or others.

Detailed Description

The accumulation of evidence over time is a central topic in computational neuroscience spanning behavior, brain, and theory (Huk and Meister 2012; Shadlen et al. 2006; Usher and McClelland 2001): (1) it is a fundamental aspect of tractable forms of cognition, such as simple forms of decision making; (2) mathematical models of how

evidence could (and should) be accumulated are available and have a rich history of accounting for performance in laboratory tasks; and (3) there is an apparent disconnect between the hundreds of milliseconds over which animals can integrate evidence and the individual computing elements of the brain, neurons, which integrate their inputs over a small number of milliseconds.

Although accumulating evidence over time is a central component of both cognitive function and many statistical models for decision making, the current emphasis on this topic is likely driven by the simple fact that remarkably direct neural correlates of such temporal accumulation appear to have been found in the spiking responses of neurons in brain areas such as the posterior parietal cortex, prefrontal cortex, and other areas with premotor functions (Gold and Shadlen 2007).

Mathematical Foundations

The computational neuroscience of evidence accumulation starts with Bloch's Law, a fundamental principle of sensory processing (Bloch 1985). Bloch's Law is a description of temporal summation, such that if more time results in more signal, simple behaviors such as detection will show increases in accuracy that depend on the product of stimulus intensity and time. At longer durations, a breakdown in Bloch's Law is interpreted as the limit of the temporal summation properties of the transducer. Despite its historical significance, Bloch's Law is rarely applied to modern decision-making tasks, as it focuses on "sufficiently short" durations and does not explicitly model noise, a critical tool for manipulating difficulty in many decision-making paradigms.

As opposed to the linear dependence of accuracy on time of Bloch's Law, statistical models within the "sequential sampling" framework assume that significant noise is present and that by accumulating many samples, accuracy can be improved. Under the simplest conditions of independent additive noise at each instant in time, accuracy based on ideal temporal accumulation will improve as a function of the square root of time. This root-time improvement in accuracy is

directly related to the square root (n) term that many students will recognize from basic statistics.

This statistical point is the basis of a large family of models in the "sequential sampling" framework, a set of models built and adapted within statistics, physics, mathematical psychology, and neuroscience (Stone 1960; Watson 1979; Luce 1986; Link 1992; Ditterich 2006). In essence, these models assume that noisy information about a stimulus is sampled sequentially, until sufficient evidence has been accrued to favor a decision. For binary choices, the accumulation follows a noisy trajectory, where information is represented as a single quantity in which input supporting one hypothesis is evidence against another (i.e., H_1 vs. H_2). Mathematically, sampled evidence is weighted to support one of the two hypotheses and may be expressed as the ratio of likelihoods, the probability of observing the evidence ("e") given the hypothesis ($p(e|H_1)/p(e|H_2)$). The logarithm of this quantity may be summed over time to represent the degree of evidence accumulated in favor of one of the hypotheses over the other, termed the "log likelihood ratio." This value can be used to determine the optimal stopping rule for an accumulation process as implemented in the sequential probability ratio test (Wald 1947).

Evidence Accumulation in Models of Decision Making

This family of models has been extensively used to account for behavioral data and linked to psychological mechanisms: the number of samples required to reach a bound reflects decision time, and the identity of the bound reached reflects the decision. The weight of sampled evidence is a function of stimulus strength such that a strong stimulus in favor of H_1 will require fewer samples to reach the H_1 bound, resulting in faster reaction times and higher accuracy. For choices where H_1 and H_2 are equally likely, the bounds are equidistant from the starting point, the magnitude of which primarily reflects the tight coupling between decision time and accuracy: fast decisions come at the cost of accuracy, and high accuracy comes at the cost of time (the speed-accuracy

trade-off). A shift in starting point position towards H1 may reflect an *a priori* bias, resulting in a higher proportion of H1 choices over H2, with faster decision times.

The first major distinction between model types is whether they posit a single accumulator or multiple, racing accumulators. If there is a single accumulation process, models posit a pair of decision bounds (for a two-alternative paradigm), and the accumulation process starts in between these upper and lower limits. Thus, incoming evidence is “signed” with positive evidence pushing the accumulator towards the upper bound and negative evidence pushing the accumulator towards the lower bound. In typical “race” models, a pair of parallel and competing mechanisms each accumulates evidence in favor of their particular outcome, and the decision is determined by the first accumulator to reach its respective bound (Usher and McClelland 2001). If the signal and noise available to both accumulators are identical, such perfectly correlated racing accumulators make the same predictions as a single accumulator, despite the difference in hypothesized architecture. On the other hand, racing mechanisms can exhibit increasingly complex behaviors as additional parameters between them become statistically uncorrelated. Independent noise changes the behavior of racing versus single-variable accumulators, and more baroque models can behave quite differently than a standard single accumulator (Ditterich 2006).

The second major distinction within sequential sampling models is whether they model time as discrete or continuous. Discrete models are more straightforward to implement in computer code, while continuous models avail themselves to closed-form mathematics. While it is of course true that in the limit (i.e., as discrete time steps go to infinitesimals) discrete models become continuous, this requires some care in practice. It is critical that discrete approximations of continuous models be implemented using appropriately fine time scale steps. Otherwise, small rounding artifacts can manifest themselves in peculiar behaviors of the model. It is therefore advisable that discrete models be implemented with checks relative to known properties of the continuous-math

model. Modern computers make the prospect of fine time steps less of a practical (speed) concern, but counterintuitive or quirky predictions of a discrete modeling exercise should be interpreted with caution.

The Drift-Diffusion Model

Perhaps the most common model of evidence accumulation is the (continuous time) diffusion model, increasingly referred to as the “drift-diffusion to bound” model (DDM) (Shadlen et al. 2006; Ratcliff 1978; Ratcliff and Rouder 1998; Palmer et al. 2005; Ratcliff and McKoon 2008). It stands as a hub because it is mathematically tractable (i.e., the psychometric and chronometric functions can be derived analytically) and can be flexibly extended to capture a wide range of behavioral data. The simplest diffusion models are composed of three parameters: a drift rate, bound height, and accumulator noise. The drift rate relates the stimulus units to a rate of drift of the diffusion process. The bound height is the stopping point (for two alternatives, e.g., H1 and H2, symmetrically above and below an unbiased start point). Accumulator noise is invariant across stimulus conditions and describes the noise in the accumulation process. This version of the model is overdetermined and can be rewritten as a two-parameter model with bound height or noise fixed. The diffusion model can be easily extended. For example, an additive nondecision time may be included to account for nondecisional sensory transduction and motor execution delays. Parameters added to model trial-to-trial variability in drift rate and residual time can capture phenomena like delayed reaction times for incorrect trials (Ratcliff 1978; Ratcliff and Rouder 1998; Ratcliff and McKoon 2008).

Evidence Accumulation in Neurons

The presence or implementation of diffusion-like algorithms in the brain is still a matter of significant interest and contention. The first direct evidence for a putative diffusion process in the brain

was observed in the spike rates of single neurons in the lateral intraparietal sulcus (LIP) of macaque monkeys during a stochastic motion discrimination task where the experimenter can control the amount of motion (the “evidence”) on a single trial (Shadlen and Newsome 2001; Roitman and Shadlen 2002). Neurons in the LIP have a mean spike rate that ramps up for choices that result in an eye movement into their response field (RF) and ramps down for choices out of their RF. Moreover, the slope of the ramp is steeper for trials with more evidence, mirroring the drift rate of a diffusion process. Time-varying motion stimuli have further supported the notion that LIP neurons reflect temporal accumulation (integration) of relevant sensory signals (Huk and Shadlen 2005; Kiani et al. 2008). Other work has shown that the spike rates of single neurons in a range of cortical and subcortical brain areas also exhibit correlates of a diffusion process (Ratcliff et al. 2007; Ding and Gold 2012a, b).

To date, these early investigations shed little light on exactly how neurons might implement time integration, yet understanding the biophysical mechanisms may provide significant insights into the cognitive constraints of evidence accumulation (Huk and Meister 2012; Wong and Wang 2006). Likewise, the current focus on responses as averaged over neurons, trials, and sessions paints a categorical and potentially inaccurate picture of what occurs on the time scale of individual trials and decisions (Churchland et al. 2011). The next generation of work on this topic will hopefully unpack how the theoretical mechanisms of evidence accumulation are implemented by real neural circuits (Bollimunta et al. 2012).

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Acoustic Memory

► Auditory Memory

Acoustic Timbre Recognition

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Synonyms

[Auditory recognition](#); [Sound source identification](#)

Definition

Timbre is what allows a listener to distinguish two sounds that have otherwise the same subjective pitch, loudness, location, and duration. For instance, when orchestral musicians tune at the beginning of a concert, they all play the same note, but one can still tell the difference between instruments. This is largely because of timbre.

Detailed Description

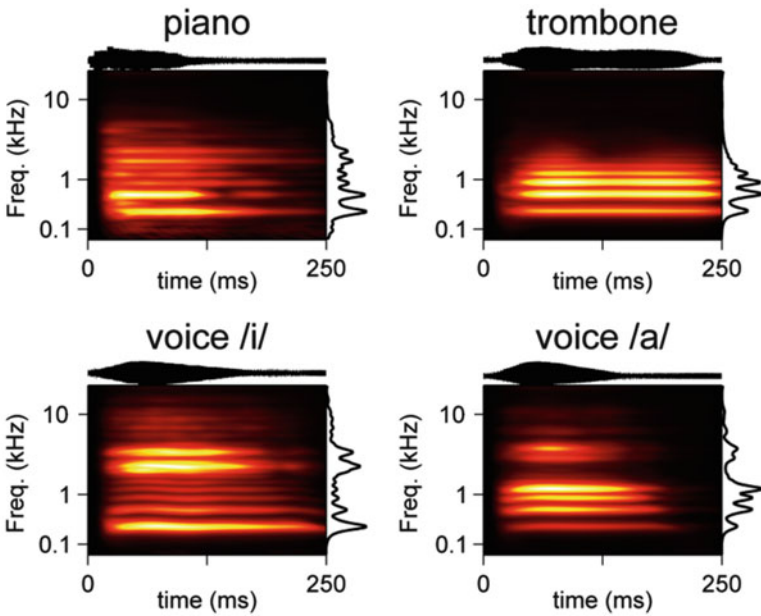
The standard definition of timbre has several shortcomings. First, it says what timbre is not, rather than what it is. Second, it relates to the comparison between two sound tokens, whereas

a more useful function for hearing is to associate a single timbre directly with a sound source (the timbre of the piano, the timbre of the voice of a friend). Perhaps as a consequence, there is still a lively debate about the acoustic features, mental representations, and neural mechanisms underlying timbre recognition. Here, we first outline the basic principles that make timbre such a powerful potential cue for sound source identification. Then we put forward two possible approaches to timbre, which we follow into the fields of acoustics, perception, neural mechanisms, and computational applications.

Why Do Different Sound Sources Produce Different Timbres?

Sound sources are physical objects that come in all shapes and sizes. Sound is produced when some energy makes the object vibrate. The vibrations spread around the source, which then propagate to the air and reach the ear of a listener in the form of pressure waves (Fig. 1). Simple physics shows that the wave pattern at the ear can contain a lot of information about what happened at the source (Helmholtz 1877). For instance, if the energy input was brief, such as a door knock, the chances are that the sound itself will be brief and have most of its energy concentrated around the time of the knock. After the knock, the way the door continues to vibrate is closely related to its geometry, because some wave patterns are consistent with some geometries and some are not. One such rule is that waves with low frequency and thus a long wavelength are not stable within small objects. Thus, the proportions of different frequency components that combine to make the sound of a door knock will be constrained by the size of the door. Other, more complex rules apply, depending on the shape of the object, the nature of the materials involved, and so on.

Being able to decode the intricate links between wave patterns and sound sources is extremely useful for humans and other animals. It allows the auditory system to serve as a warning sense, for instance, to identify sound-producing objects that are out of sight. For people, it is also



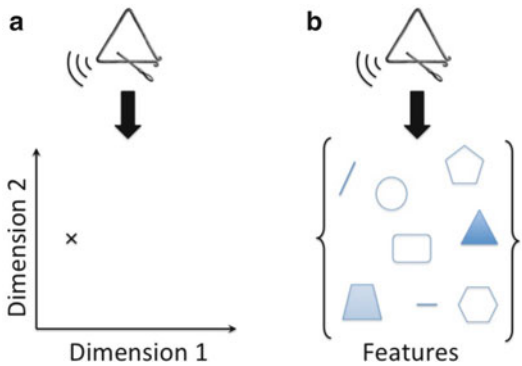
Acoustic Timbre Recognition, Fig. 1 Visual representations of four sounds with the same duration, loudness, and pitch, only differing by timbre. Each panel displays a time-frequency analysis derived from an auditory model (see Agus et al. 2012 for details). Briefly, color indicates the pattern of energy within frequency channels (y-axis) as it evolves over time (x-axis). The top trace is the corresponding pressure waveform. The right-hand trace is

the average energy over time. The two instruments illustrate classic dimensions of timbre: depending on the sound source and how it is excited, the attack time can be fast (piano) or slow (trombone); the spectral center of mass can be high (piano) or low (trombone). The two vowels illustrate that other possibly more complex features may also be used to distinguish, e.g., vowels from instruments or vowels from each other

the very basis of spoken language: vowels and consonants are produced by modulating the shape of the vocal apparatus, resulting in changes in timbre that are the building blocks of oral communication.

Dimensions Versus Features

There is no consensus on what makes timbre recognition possible for human listeners. To outline current controversies, it is useful to consider two opposite viewpoints (Fig. 2). A first view is that timbre is composed of a reasonably small number of perceptual dimensions, which are subjective descriptions of sound just as pitch or loudness. Such dimensions must be metameric, in that several different sounds may project to the same point on the dimension.



Acoustic Timbre Recognition, Fig. 2 Schematic representation of the dimensions approach versus the features approach for timbre. (a) For the dimensions approach, all different timbres can be projected in a low-dimensional space of continuous dimensions. (b) For the features approach, each timbre is defined by a set of distinctive features among a very large and unordered set of possible features

A second view is that timbre recognition relies on the distinctive features of a given sound source, learned through experience and selected among a very large space of potential features. The grain of a friend's voice may be unique, which is what allows us to recognize her instantly. Such features would be conceptually different from dimensions in that a feature does not necessarily apply to all possible sound sources; in fact, it is precisely because it is unique to only a few sources (or even a single source) that it could be efficient for recognition.

It is likely that a full account of timbre will lie somewhat in between these two simplified hypotheses. However, for clarity, we continue to contrast each approach for different aspects of timbre research.

Sound Representations

To investigate timbre, it is useful to represent sound visually. Classically, this has been done with tools such as the trace of the pressure waveform over time; the spectral analysis of component frequencies through, e.g., Fourier analysis; or spectro-temporal transformations such as the short-term Fourier transform or wavelet analyses. More recently, computational models that aim to mimic peripheral or central auditory processing have been suggested (e.g., Patil et al. 2012).

In the “dimensions” approach, summary statistics are computed on sound representations to define what are referred to as descriptors of timbre. For instance, the center of mass of all frequency components of a sound produces a single number that is correlated with the apparent “brightness” of a sound (McAdams et al. 1995). In the “features” approach, the tendency is rather to maximize the richness of the representation, by including complex spectro-temporal selectivities. Such a feature-based representation need not be orderly. It can be over-complete with thousands of partially overlapping features, or sparse, in the sense that a given sound would only activate a small number of features within that large possible space (Hromádka and Zador 2009).

Perceptual Data

The basic aim of the dimensions approach is to uncover the nature and number of the perceptual dimensions underlying timbre. To this effect, statistical techniques based on multidimensional scaling have been used: a pair of sounds is presented to the listener, who has to rate how similar to each other the two sounds seem. This is repeated for all possible pairs within a given sound set. Then, the similarity judgments are treated as perceptual distances and used to obtain the dimensionality and geometry of the corresponding mental representation. For musical instruments, classic studies point toward two to three main dimensions: one related to the attack time, one related to the spectral center of mass, and one additional dimension that is less consistently observed (Grey 1977; McAdams et al. 1995). More recent investigations, using both multidimensional scaling and verbal descriptions, suggest five main dimensions with more complex interpretations (Elliott et al. 2013).

In the features approach, the focus is not on similarity but rather on the recognition of the sound source. Again, using musical instruments, fast recognition times have been observed (Agus et al. 2012), and recognition was found to be preserved even for severely impoverished signals (Suied et al. 2013). Moreover, recognition was faster and more robust for highly familiar sources such as the human voice, an observation that could not be traced back to simple acoustic dimensions (Agus et al. 2012). These results strongly suggest the existence of diagnostic features that were learned by listeners, through experience, to recognize, e.g., voices in a robust and efficient manner.

Neural Bases

Neural correlates of generic timbre dimensions have been investigated with brain imaging. Using an EEG paradigm to probe sensory memory known as mismatch negativity, it has been found that timbre dimensions such as brightness

or onset time could each be represented separately within auditory cortex (Caclin et al. 2006).

From the features perspective, single-unit recordings have uncovered a rich variety of selectivities, at many levels of the auditory system, often without any obvious ordering principle (other than by frequency). Using linear analysis techniques such as reverse correlation, spectro-temporal receptive fields have been derived. Various spectral and temporal modulation preferences have been observed, e.g., in the primary auditory cortex (Depireux et al. 2001). Adding a nonlinear component to the analysis adds another layer of complexity (Machens et al. 2004). Furthermore, the neural encoding of timbre may interact with supposedly independent sound characteristics, such as pitch or location (Bizley et al. 2009).

A further question is whether the identity of a source will be encoded by the activity of a wide network shared by many sound sources or by the activity of only a small network specifically tuned to that source category. Evidence has been put forward for both models. Using fMRI, the identity of a sound source can be inferred from distributed activity (Staeren et al. 2009). At the same time, there are clear indications of localized brain areas specialized for familiar sound sources such as the human voice (Belin 2006).

Timbre Recognition by Machines

There are several applications for acoustic timbre recognition, such as speaker identification or music information retrieval. Even though the techniques used are fast evolving and a detailed description is beyond the scope of this section, it is interesting to note that the dimensions versus features contrast can also be seen in the architectures of the computational systems.

Automatic speech recognition, which can to some extent be viewed as a timbre-decoding exercise, has a long tradition of performing classification on a small number of generic coefficients (e.g., mel-frequency cepstrum coefficients

and their variants (Hermansky 1990)). For musical instruments, a descriptor-based approach has been directly inspired by the perceptual dimensions of multidimensional studies, with a reasonably small number of explicit descriptors (Peeters et al. 2011). However, other systems exist that are based on feature generation from a huge potential feature space, followed by ad hoc selection for a given classification task (Coath and Denham 2005; Pachet and Roy 2009). For musical instrument classification, machine-learning algorithms applied on a high-dimensional auditory model representation have also been successfully demonstrated (Patil et al. 2012).

Perspectives

The outstanding issues for timbre research will probably benefit from considering the various strategies available to a listener. For instance, when asked for subjective distance judgments, the most reasonable thing to do may be to abstract common dimensions to a sound set, and then use those for the comparisons. However, when asked to recognize a source as fast as possible, the mere presence of a diagnostic feature may be sufficient. The set of useful timbre dimensions or features can also depend on the task: for a same set of spoken words, different strategies are used if listeners are asked to identify the speaker or report the word content (Formisano et al. 2008). Finally, the very neural representation of timbre may be dynamically tuned to the immediate acoustic context, through rapid plasticity (Fritz et al. 2003). A fundamental reason that makes timbre so elusive may therefore be that timbre recognition is a profoundly adaptive mechanism, able to create and use opportunistic strategies that depend on the sounds and task at hand.

Cross-References

- [Auditory Event-Related Potentials](#)
- [Pulse-Resonance Sounds](#)

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Action Planning

► Decision-Making, Motor Planning

Action Potential Back-Propagation

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Synonyms

Back-propagating action potentials (bAPs);
Back-propagating spikes

Definition

Action potential (AP) back-propagation, as opposed to forward-propagation along the axon, consists of the conduction of the axonally initiated AP along neuronal dendrites, in the form of a depolarization sustained by both active and passive mechanisms. The amplitude of the depolarization generally decreases along the dendrites with increasing distance from the soma; the degree of attenuation is highly variable and depends on the neuronal type.

Detailed Description

Simultaneous recordings from dendrites, soma, and axon have shown that action potentials are generally initiated in the axon initial segment, the region with the lowest threshold for AP initiation (Stuart et al. 1997; Spruston et al. 2016). In addition to canonical forward-propagation along the axon to the presynaptic terminals, APs rapidly invade the soma and propagate back into the dendrites, where voltage-dependent channels actively support the depolarization (Spruston et al. 2016). As opposed to all-or-none axonal APs, the amplitude of back-propagating action potentials (bAPs) can be modulated and generally decreases along the dendrites with the distance from the soma. The extent of back-propagation varies widely in the different neuronal types investigated, ranging from non-decremental to almost passive (Fig. 1).

Determinants of Action Potential Back-Propagation

The main factors that determine the extent of action potential back-propagation are (a) density and properties of dendritic voltage-dependent channels, (b) neuronal morphology, and (c) neuronal activity (firing history and concurrent inputs).

Dendritic voltage-dependent channels: Different neuronal types have distinct distributions of dendritic voltage-dependent ion channels (Migliore and Shepherd 2002, 2005; Magee 2016). AP back-propagation is sustained by dendritic voltage-dependent Na^+ channels and activates Ca^{2+} channels (Johnston et al. 1996). Dendritic K^+ channels can modulate the

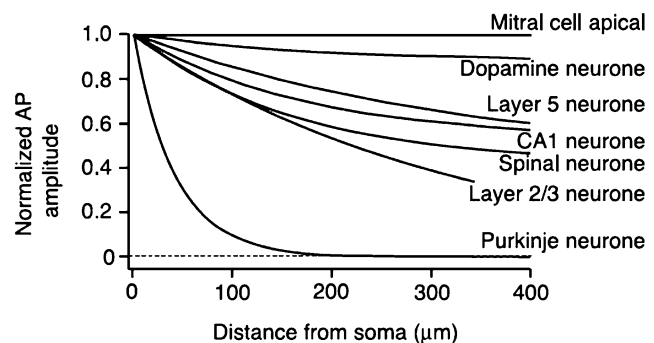
amplitude and extent of back-propagation; their role has been most extensively studied in hippocampal CA1 pyramidal neurons, where the density of A-type ($\text{Kv}4.2$) K^+ currents increases along the apical dendrites with the distance from the soma (Johnston et al. 2000). Therefore, the extent of back-propagation along the dendrites depends on the relative density of dendritic Na^+ and K^+ channels (see the interactive example in Fig. 2) and is affected by channel modulation by neurotransmitters or plasticity (Johnston et al. 1999; Magee and Johnston 2005).

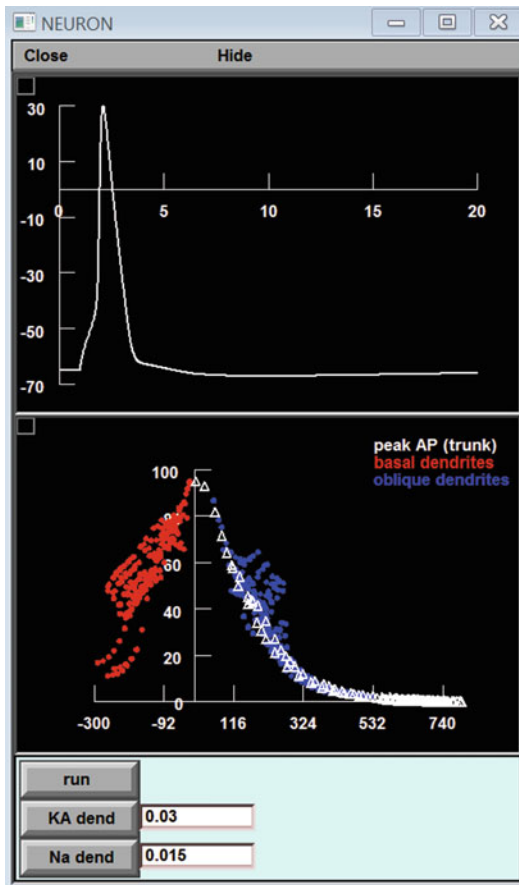
Morphology: It is difficult, if not impossible, to experimentally assess the exclusive contribution of dendritic morphology, and the relation to ion channel properties, to action potential back-propagation. However, computational simulations have shown that significant differences in propagation can be attributed exclusively to dendritic geometry. When the same active and passive parameters were inserted in compartmental models with reconstructed morphologies of various neuronal types, there was a strong correlation between back-propagation and dendritic geometry (branch points and relative impedance; see Fig. 3; Vetter et al. 2001; Spruston et al. 2016). These results indicate that dendritic morphology and branching patterns have a fundamental role in shaping back-propagation.

Neuronal Activity: Dendritic excitability and AP back-propagation are highly dependent on the membrane potential and therefore on concurrent neuronal activity, as well as the firing history of neurons. Hippocampal CA1, entorhinal layer V, and neocortical layer V (but not layer II/III) pyramidal neurons show a significant

Action Potential Back-Propagation,

Fig. 1 Amplitude of bAPs, normalized to the amplitude of the somatic AP, along the apical dendrite, plotted as a function of the distance from the soma, in neurons from different brain areas. (Reproduced with permission from Waters et al. 2005)





Action Potential Back-Propagation, Fig. 2 Effect of different densities of dendritic Na^+ and A-type K^+ currents on AP back-propagation in CA1 pyramidal neurons. An interactive example, where channel densities can be modified, is available at <http://senselab.med.yale.edu/ModelDB/ShowModel.asp?model=148646>

activity-dependent decrease in the amplitude of bAPs along the apical dendrites during high-frequency trains (Johnston et al. 1999; Gasparini 2011). In CA1 and entorhinal layer V pyramidal neurons, this behavior is mostly due to a slow, cumulative inactivation of dendritic Na^+ channels and can be reduced by neurotransmitters activating protein kinase C (Johnston et al. 1999; Magee 2016). In addition, the amplitude of bAPs at distal locations can be boosted by appropriately timed synaptic inputs (see the interactive example in Fig. 4), which promote back-propagation by inactivating A-type K^+ channels or by facilitating Na^+ channel activation (Migliore et al. 1999;

Spruston 2008). On the other hand, the bAP-induced depolarization and Ca^{2+} influx can be significantly reduced by inhibition, achieved experimentally through either GABA uncaging or stimulation of individual of inhibitory interneurons (Boivin and Nedivi 2018).

Functional Role

The depolarization and Ca^{2+} influx associated with bAPs provide feedback to the region that received the synaptic input, signaling that the neuron has generated an output. This feedback signal has important consequences on neuronal firing and synaptic plasticity. In neocortical layer V neurons, pairing bAPs with a distal synaptic input initiates a dendritic Ca^{2+} spike (back-propagation-activated Ca^{2+} or BAC spike), which results in a burst of somatic APs, possibly a marker for cortical associations (Spruston 2008; Palmer et al. 2016). In many neurons, the appropriate timing of bAPs and EPSP can cause long-term changes in synaptic efficacy (spike-timing-dependent plasticity or STDP). The depolarization associated with the bAP provides the coincidence detection needed for the removal of Mg^{2+} from NMDA glutamatergic receptors, triggering plasticity phenomena (Maheux et al. 2016). The Ca^{2+} influx caused by bAP has also been suggested to mediate dendritic release of neurotransmitters (Ludwig and Pittman 2003). The functional role of bAPs in relation to animal behaviors is more difficult to establish, since dual dendritic and somatic recordings in vivo are extremely more challenging than in vitro (but see Roome and Kuhn 2018 for recent developments); therefore dendritic signals cannot be unequivocally interpreted (Palmer et al. 2016).

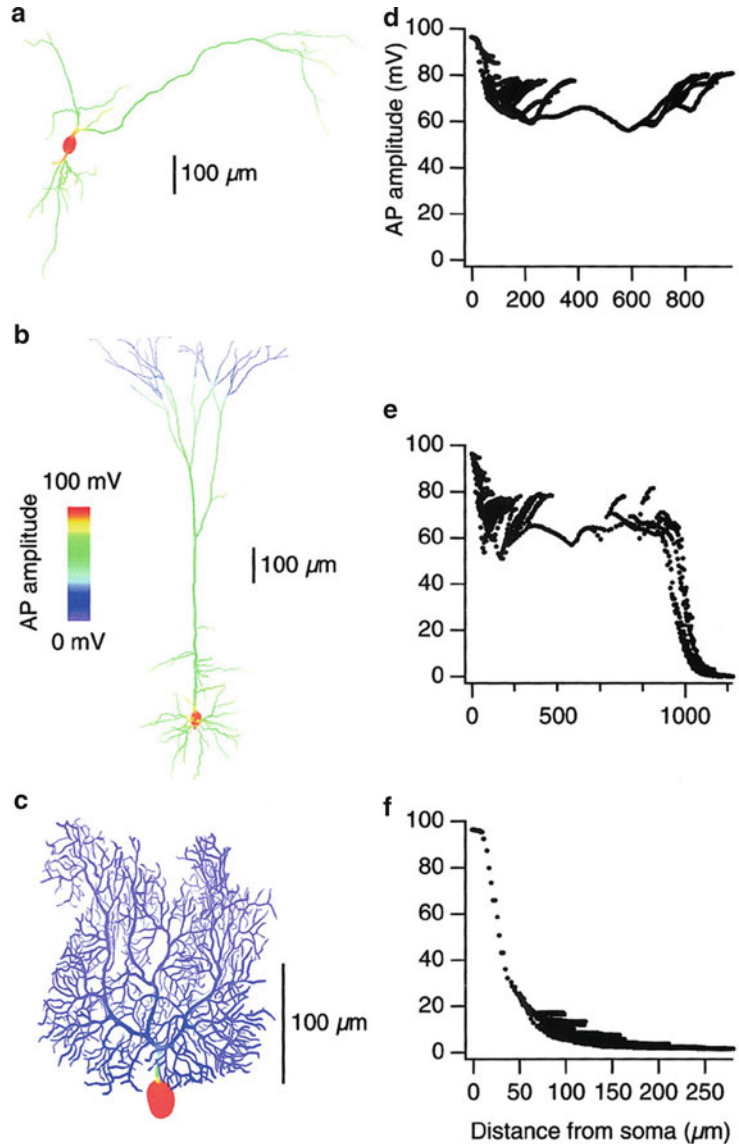
Techniques to Study Back-Propagation

The interaction of experimental and computational methods has been essential to understanding the mechanisms underlying AP back-propagation, allowing intrinsic limitations of the individual approaches to be overcome.

Direct **electrophysiological recordings** with the patch-clamp technique in different configurations have been performed at various distances from the soma mostly on larger diameter dendrites

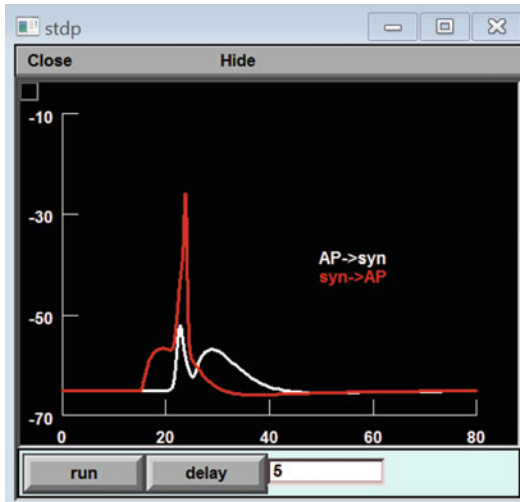
Action Potential Back-Propagation,

Fig. 3 Effect of dendritic morphology on AP back-propagation in computational simulations with identical dendritic passive properties and channel types and densities. (a–c) color-coded representation of dendritic AP amplitude in reconstructed morphologies from a substantia nigra dopaminergic neuron (a), neocortical layer V neuron (b), and cerebellar Purkinje neuron. (d–f) bAP amplitude as a function of the distance from the soma for the cells in a–c. Reproduced with permission from Vetter et al. 2001



(Gurkiewicz and Korngreen 2006), providing information on channel distributions (Magee 2016) and back-propagation (Waters et al. 2005). **Fluorescence imaging techniques** (using Ca^{2+} - or voltage-sensitive dyes) have been used to assess smaller dendrites and compartments and/or to obtain data from many dendritic locations in a single neuron. More recently, **genetically encoded calcium and voltage indicators** have been developed and expressed in neurons,

pushing the boundaries of large-scale, high-resolution monitoring of neuronal activity (Deo and Lavis 2018). These experimental techniques have advantages and limitations (Waters et al. 2005; Scanziani and Häusser 2009). For this reason, the investigation of AP back-propagation and its functional roles have greatly benefitted from **computational models** that use biophysically and morphologically accurate implementations. These models have supported, explained, and predicted



Action Potential Back-Propagation, Fig. 4 Effect of pairing a synaptic input with AP back-propagation in CA1 pyramidal neurons. If the timing is appropriate, bAP is boosted by the synaptic input (red trace). An interactive example, where the timing between AP and synaptic input can be modified, is available at <http://senselab.med.yale.edu/ModelDB/ShowModel.asp?model=148646>

several experimental findings on AP back-propagation (Schaefer et al. 2003; Watanabe et al. 2002). An optimal approach to studying and understanding AP back-propagation is therefore a synergistic loop, with experiments suggested by computational simulations, and experimental outcomes used to constrain the models.

Cross-References

- ▶ Action Potential Initiation
- ▶ Delayed Rectifier and A-Type Potassium Channels
- ▶ Basal Ganglia: Dopaminergic Cell Models
- ▶ High-Voltage-Activated Calcium Channels
- ▶ Long-Term Plasticity, Biophysical Models
- ▶ Low-Voltage-Activated Calcium Channels
- ▶ Multiscale Modeling of Purkinje Cells
- ▶ N-Methyl-D-Aspartate (NMDA) Receptors, Conductance Models
- ▶ Neuromodulation: Overview
- ▶ NEURON Simulation Environment

- ▶ Patch Clamp Technique
- ▶ Reduced Morphology Models
- ▶ Short-Term Plasticity, Biophysical Models
- ▶ Sodium Channels
- ▶ Spike-Timing Dependent Plasticity (STDP), Biophysical Models
- ▶ Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

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Action Potential Initiation

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Synonyms

[Spike initiation](#)

Definition

Electrical impulses (action potentials (APs) or spikes) which encode and transmit information in the nervous system are initiated in the proximal anatomical region of the axon termed axon initial segment (AIS). The voltage threshold for spike initiation and the exact location and length of the spike trigger zone (TZ) within AIS, as well as the amplitude and waveform of the action potential in different neuronal classes, depend on the geometry and passive electrical properties of a neuron as well as on the type, spatial distribution, and density of a variety of voltage-sensitive ionic channels.

Detailed Description

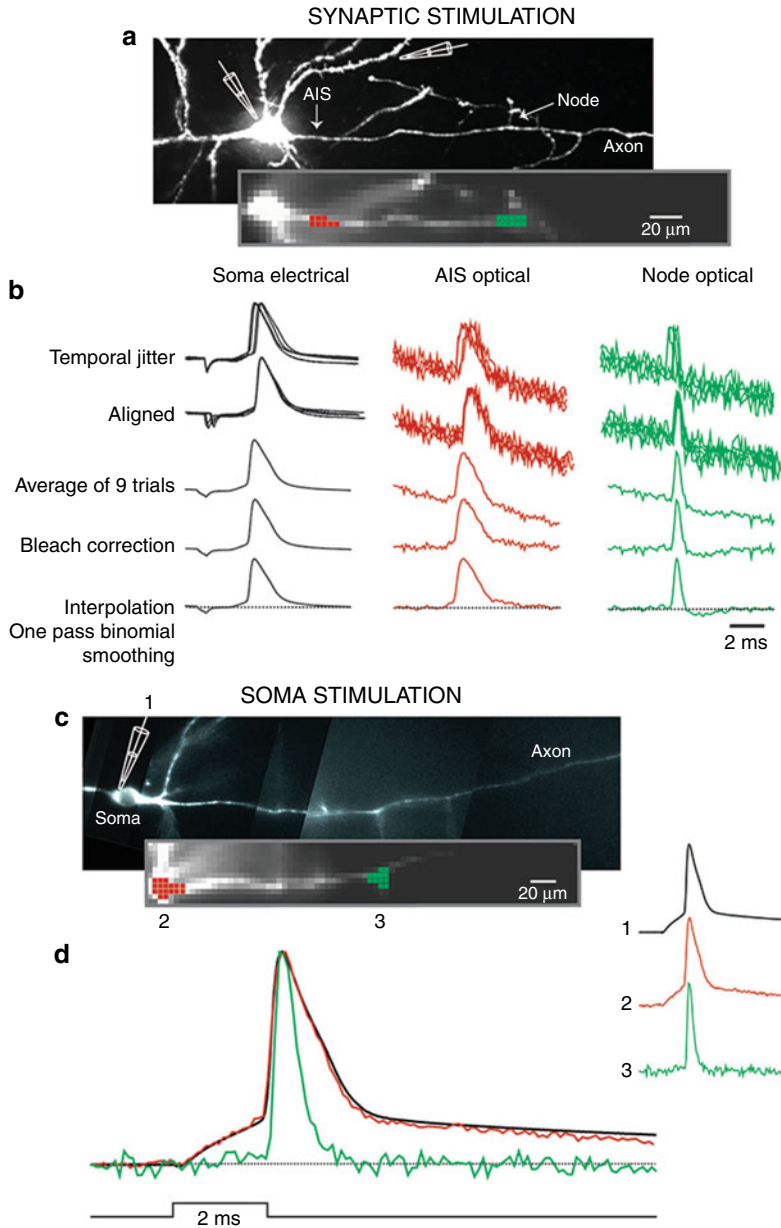
There is little disagreement over attributing action potential initiation to a site in the axon initial segment (AIS) under most circumstances. The question of the exact location and length, however, of the spike trigger zone (TZ) in the axon, as defined in functional terms, is less clear. In most studies, the spike TZ was characterized by a single parameter, the distance from the soma, implying a point of initiation. The length of the initiation site, however, is fundamentally important because successful initiation and propagation of the action potential wave requires that a certain length of an axon is brought to the threshold for excitation (Rushton 1937). Besides the fundamental importance of characterizing the action potential (AP) initiation site, the spike TZ location and

length have a recently discovered specific role in tuning neuronal computation underlying a well-defined function in auditory neurons which mediate sound source localization (Carr and Boudreau 1993; Kuba et al. 2006; Kuba and Ohmori 2009). Moreover, subsequent studies of Kuba et al. (2010) and Grubb and Burrone (2010) reported a novel finding that the structure of the spike TZ mediates an intrinsic plasticity of the axon and regulates the final stage of integration of synaptic inputs. This places a great significance on our ability to directly probe the location and length of the spike TZ under different conditions. The available information regarding TZ plasticity is based on structural data (Grubb and Burrone 2010; Kuba et al. 2010). Molecular structure of the spike TZ, however, is indirectly correlated with function in a way that is not fully understood (Fleiderovich et al. 2010; Johnston 2010). Thus, the anatomical data require functional confirmation. The location and length of the spike TZ have been difficult to measure directly using electrodes because extracellular recordings cannot be interpreted with sufficient accuracy and intracellular recordings lack the necessary spatial resolution (e.g., Meeks and Mennerick 2007). Membrane potential imaging (Vm imaging) offers a unique advantage of high spatial resolution compared with electrical recordings and has been used to directly measure the location of action potential initiation in invertebrate neurons (Zecevic 1996; Antic et al. 2000) and mammalian axonal arbors (Palmer and Stuart 2006; Palmer et al. 2010). This technique was recently improved and utilized to characterize functionally relevant parameters of the spike TZ in layer 5 pyramidal neurons of the cerebral cortex (Popovic et al. 2011). The measuring technique and the analysis of data used to determine the location and length of the spike trigger zone are shown in Fig. 1.

A typical experimental measurement used to determine the location and length of the spike TZ is illustrated in Fig. 2. These two parameters are obtained directly from multisite optical recording of the membrane potential transients (Fig. 2a–c) either by investigating spike latencies at the soma/axon hillock and more distal axonal recording locations or by the inspection of the spatial

distribution of membrane potential as a function of time. The soma–axon latency is plotted against recording distance from the edge of the soma in Fig. 2d. An alternative way to derive the same information from the data is to analyze a time sequence of color-coded frames showing the spatial maps of AP amplitude (Fig. 2e). The result of this analysis is a temporal series of individual frames separated by 10 μ s; each showing the spatial map of membrane potential at one point in time. In Fig. 2e, four frames from this series were selected to illustrate characteristic regions along the axon that can be clearly identified during AP initiation. The red region closest to the soma was the first to cross the threshold value and reach 50% amplitude (time point 0 μ s) and was identified as the AP TZ. The more distal red region appearing with a delay (45 μ s time point) is likely to be the first node of Ranvier, corresponding to the issuance of an axon collateral, as indicated in the high-resolution image (Fig. 2a). The same data are shown in Fig. 2f as AP signals scaled to the same height and compared on an expanded time scale. The two red traces show AP signals from the two red areas in Fig. 2e corresponding to the spike TZ and the first node. The green dashed trace is the AP signal from the axon hillock. The green trace is the AP signal from the first internodal region. The mean length of the TZ determined from the type of data shown in Fig. 2 was $16.5 \pm 1.1 \mu$ m with the mean center located at $28.9 \pm 1.0 \mu$ m from the edge of the soma.

Vm imaging can be used to analyze the spatial pattern of AP propagation as revealed by monitoring transmembrane potential over longer sections of individual myelinated axons. Previously, this information was not available for any neuron. A representative experiment (well-stained neuron characterized by long axons in one plane of focus close to the surface of the slice) is illustrated in Fig. 3. The spatial plot of the soma–axon latency along an axonal section of approximately 300 μ m clearly identified the position of the spike TZ and putative nodes of Ranvier; all characterized by localized reduction in soma–axon latency typical for saltatory conduction (Fig. 3a). The spatial plot of AP latency provides a functional readout for the position of the nodes of Ranvier. Figure 3c shows

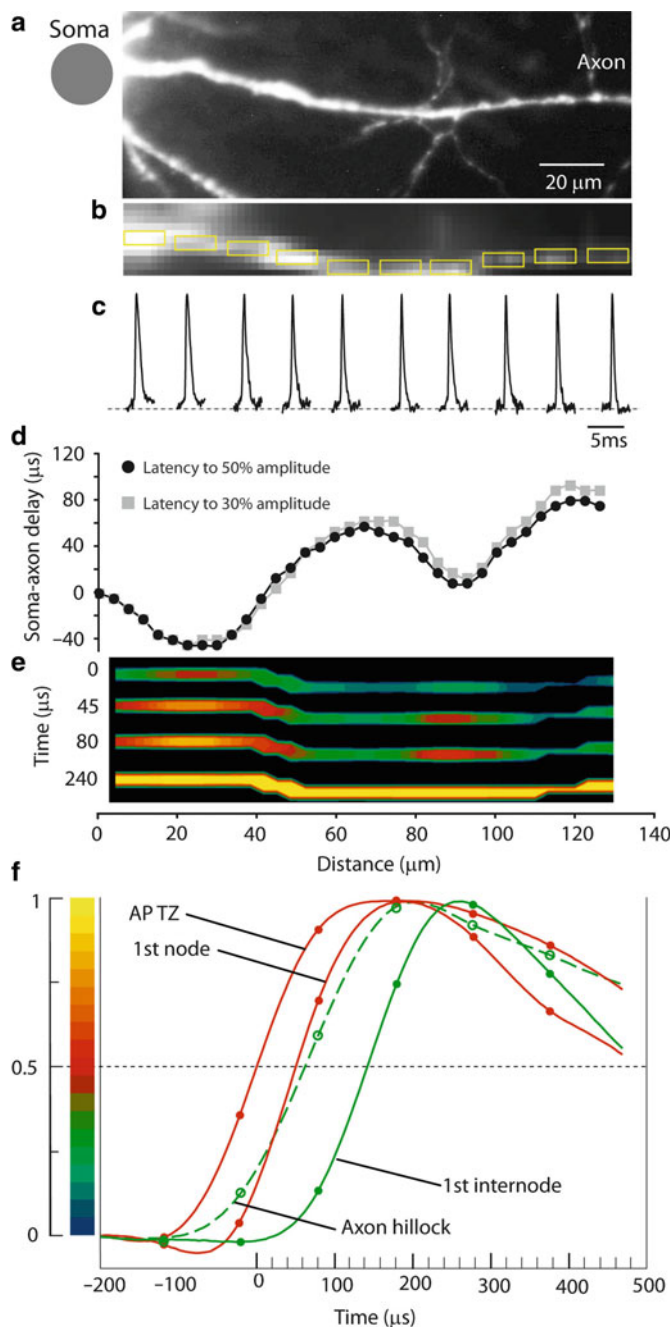


Action Potential Initiation, Fig. 1 Signal processing. (a) Synaptic stimulation: *Upper image* – high-resolution confocal image of a stained neuron with axon in recording position. Recording electrode attached to soma and stimulating electrode next to basal dendrite shown schematically. *Lower image* – low spatial resolution fluorescence image of the axon obtained by CCD used for V_m imaging. (b) Electrode recordings from soma and optical recordings from spike TZ (red) and from node of Ranvier (green). *Top traces*: raw data from nine trials showing temporal jitter in AP initiation following synaptic activation. Second row of traces: temporally aligned signals. Third row of traces:

averaged signal. Fourth row of traces: bleach correction. *Bottom traces*: cubic spline interpolation with one pass of temporal smoothing. (c) Somatic stimulation: *Upper image* – high-resolution confocal image of another neuron with axon in recording position. *Lower image* – low spatial resolution fluorescence image of the axon obtained by CCD used for V_m imaging. *Traces on left*: AP transients from three locations: 1, electrode recording from soma; 2, optical recording from axon hillock; and 3, optical recording from the first node of Ranvier. *Bottom traces*: Super-imposed signal from the same three locations

Action Potential Initiation,

Fig. 2 Measurement of the spatial distribution of membrane potential as a function of time along the proximal axon during AP initiation. **(a)** High resolution confocal image of the axon in recording position. **(b)** Low spatial resolution fluorescence image of the axon obtained by CCD used for V_m imaging. **(c)** AP signals from 10 locations indicated by yellow rectangles, each 10 μm in length. **(d)** Soma-axon latency to 30% (grey) and 50% (black) AP amplitude as a function of distance from the cell body. The first minimum identifies the location and length of the spike TZ. **(e)** Time sequence of frames showing spatial profile of colour coded relative V_m amplitude in the axon at four characteristic time points: 0 μs – AP initiation at TZ; 45 μs and 80 μs – invasion of the first node; 240 μs – peak depolarization. **(f)** Comparison of AP signals from four characteristic locations on an expanded time scale. The measured data points and cubic spline interpolation curves are shown. Red traces – TZ and first node; green dashed trace – axon hillock; green trace – first internodal region. Membrane potential colour scale shown on left



a color-coded spatial map of the depolarizing AP wave at one characteristic point in time which indicates the position of the spike TZ as well as nodes of Ranvier.

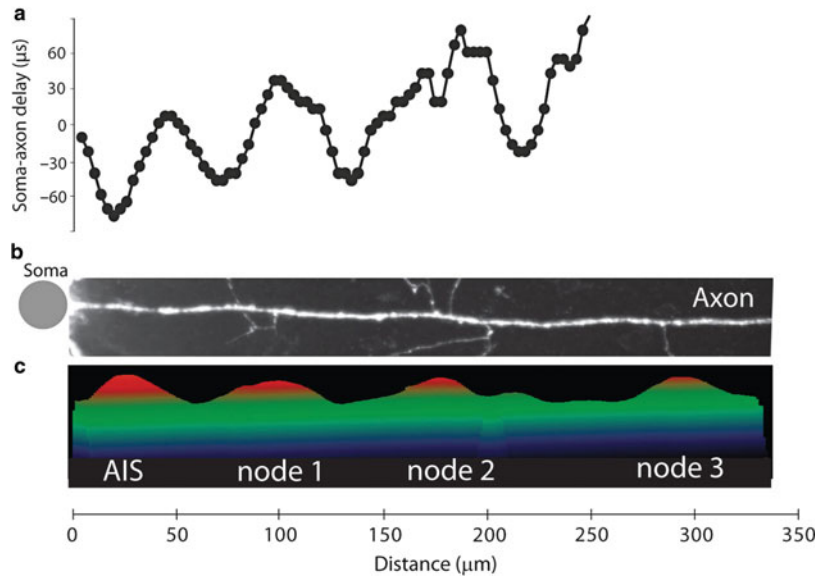
The voltage-sensitive dye imaging approach allows determination of the location and length of

the spike TZ in the AIS of pyramidal neurons, as defined in functional terms. In addition, it is possible to characterize the AP propagation pattern in the main axon and collaterals. It is plausible to predict that this approach will facilitate the analysis of signal interactions underlying input-output

Action Potential

Initiation, Fig. 3

Spatial pattern of AP initiation and propagation in an individual axon. (a) Soma–axon latency to 50% AP amplitude as a function of distance from the soma. (b) High-resolution image of an axon in recording position. (c) A color-coded spatial distribution of relative V_m amplitude in the axon at one characteristic point in time showing correlation between the positions of functionally determined nodes of Ranvier and axonal branch points in panel B



transformations carried out in neuronal processes of different classes of nerve cells. The question of TZ dimensions is of fundamental importance because the size of the initiation site is a critical functional parameter. Successful initiation and propagation of the action potential wave requires that a certain length of an axon is brought to threshold for excitation to generate an action current large enough to propagate. This follows from intuitive considerations, from the classical theory (Rushton 1937), as well as from more recent experimental studies (Colbert and Pan 2002; Meeks and Mennerick 2007). Additionally, Na⁺ channel clustering in the axon, which is critical in determining the spike TZ location and length, serves an important specific function in tuning neuronal computation underlying a well-defined function (sound localization) in auditory neurons (Carr and Boudreau 1993; Kuba et al. 2006; Kuba and Ohmori 2009). These findings advocate that the size and position of the spike TZ might be cell specific in other central neurons, depending on their function. Additionally, new data (Kuba et al. 2010; Grubb and Burrone 2010) show that the structure (and, by extrapolation, the function) of the spike TZ participates in neuronal plasticity and might, in fact, be one of the key factors controlling neuronal excitability and computation (Grubb and Burrone 2010; Kuba et al. 2010; Rasband 2010).

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Action Potential Model

- [Hodgkin-Huxley Model](#)

Action Selection

- [Decision-Making, Motor Planning](#)

Activation of the Olfactory Sensory Neurons as a Function of Odor Concentration

- [Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response](#)

Adaptation

- [Visual Aftereffects, Models of](#)

Adaptation in Sensory Cortices, Models of

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Synonyms

[Models of pattern adaptation](#); [Models of sensory adaptation](#)

Definition

Models of adaptation in sensory cortices provide a functional and/or mechanistic description of the changes in neural responses and perception caused by sensory stimuli observed in the recent past. Sensory systems compute dynamic representations of the environment: cortical neurons typically adapt their “code” according to the recently received sensory input. This continuous recalibration is reflected in changes in neuronal response properties and has been interpreted as an adjustment of the limited dynamical range to compensate changes in the environment or changes in the observer. Functional models of sensory adaptation have linked these findings to optimal coding. Moreover, adaptation has also been studied in biophysical and network models, with the goal of understanding the mechanisms that give rise to adaptation in biological cortical circuits.

Detailed Description

Sensory adaptation refers to the changes in neuronal responses and perception caused by a prolonged exposure to sensory stimuli. Adaptation

is a rapid form of plasticity that has a reversible effect on neuronal selectivity: responses adapt (on short time scales) and recover to their pre-adapted state when the source of adaptation is removed. It is found ubiquitously across different sensory modalities (visual system (Kohn 2007; Clifford et al. 2007); auditory system (King et al. 2011); whisker system (Petersen et al. 2009)).

In psychophysical experiments, it can be shown that adaptation alters perception: prolonged exposure to a stimulus typically leads to “repulsive” aftereffects, which means stimuli similar to the adapting stimulus appear to be more different from the adapting stimulus than they actually are. An example is the tilt aftereffect, in which – after prolonged viewing of oblique lines – vertical lines appear briefly as if they were tilted in the opposite direction (see ► “Visual Aftereffects, Models of”).

Here, we focus on (1) functional models of the computational principles that may underlie the adaptive encoding of sensory information and (2) models of the neuronal and synaptic mechanisms giving rise to adaptation in cortical circuits.

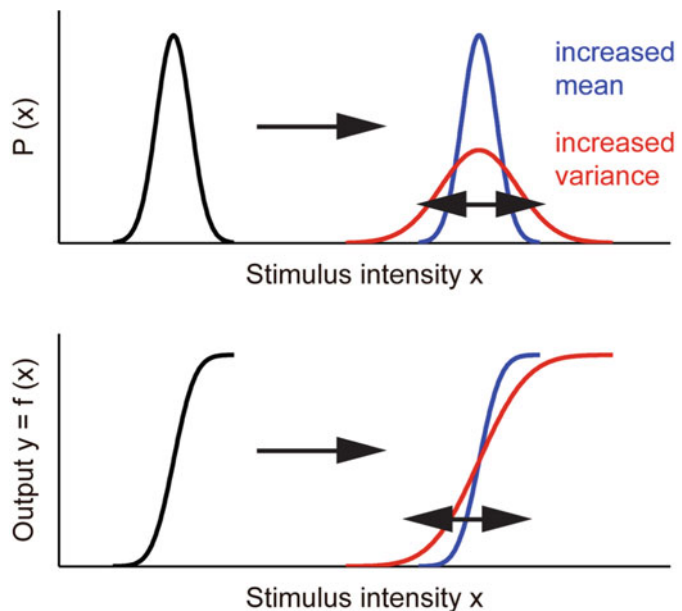
Adaptation as Optimal Coding

Sensory systems must encode natural stimuli which change over many orders of magnitude with the limited dynamical range of neuronal firing rates. Adaptation has been proposed to serve for adjusting the sensory representation to the current statistics of the ever changing environment (Fig. 1). This was formalized in the *efficient coding hypothesis* (grounded in information theory), which states that sensory systems seek to provide an efficient representation of the natural environment by maximizing their information transmission capacity (Barlow 1961; Laughlin 1981; Wark et al. 2007). Given the statistics of the environment, this hypothesis predicts the optimal input–output behavior of a single neuron (Fig. 1) and how it should adapt to the mean and variance of the current stimulus intensity distribution.

Experimental evidence for efficient coding has been found across a wide range of sensory modalities and species: contrast adaptation in the visual system (Kohn 2007; Clifford et al. 2007), fly visual system (Laughlin 1981; Fairhall et al. 2001), mid-brain of guinea pigs (Dean et al. 2005), inferior colliculus of cats (Kvale and Schreiner 2004),

Adaptation in Sensory Cortices, Models of,

Fig. 1 Adaptation to the mean and the variance of incoming sensory stimuli. According to the efficient coding hypothesis, a change in the stimulus distribution (top) should yield an adaptive change of a neuron’s transfer function (bottom)



songbird auditory forebrain (Nagel and Doupe 2006), and rat barrel cortex (Maravall et al. 2007).

In a similar spirit, adaptation has also been linked to Bayesian inference, tackling questions such as how to optimally combine sensory observations with prior knowledge about the stimulus distribution (Doya et al. 2007). Adaptation could be interpreted as changing the prior distribution within the Bayesian theory of perception, or even the likelihood model could be affected by adapting stimuli (Stocker and Simoncelli 2006). How cortical circuits might implement Bayesian inference is an active research topic.

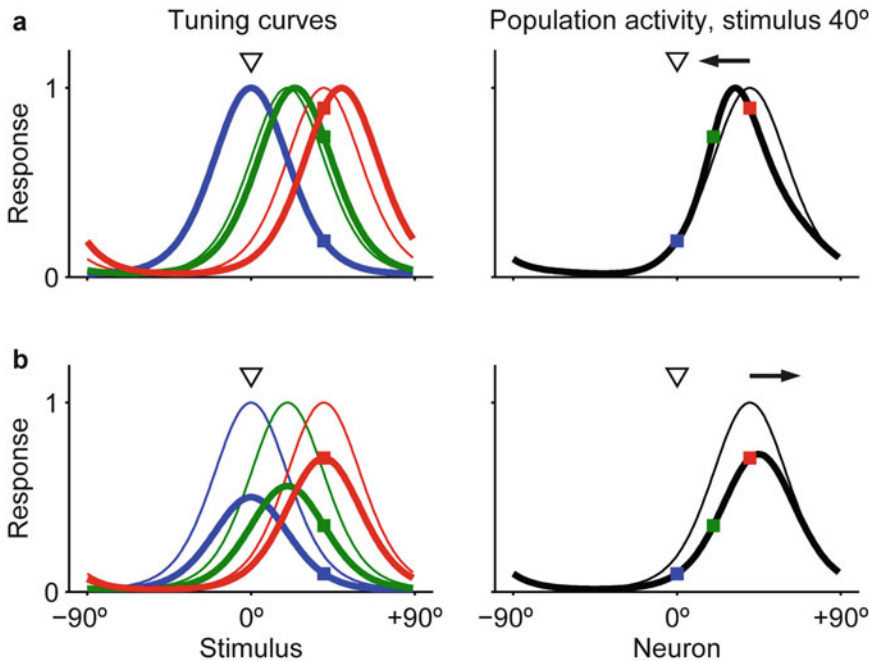
Modeling Underlying Neural Mechanisms

A different class of models aims at understanding the neuronal mechanisms that underlie adaptation. In some cases the mechanisms have been studied in detail experimentally, an example is contrast adaptation in the visual system. Adaptation shifts the contrast response curve of individual neurons toward higher contrast levels, and this can be well explained by the hyperpolarization of individual neurons caused by the activation of intrinsic channels (Sanchez-Vives et al. 2000). This mechanism accounts for a decrease in a neuron's firing rate due to sustained stimulation and is usually called spike-frequency adaptation; for a phenomenological model, see Benda and Herz (2003).

Often, however, the mechanisms underlying adaptation are not well characterized experimentally. Models can serve to integrate existing data and to create testable predictions in order to discern different potential mechanisms. An example is orientation adaptation, in which the prolonged exposure to a visual stimulus of a particular orientation yields changes of individual neuronal tuning curves in the early visual system (Dragoi et al. 2000) (see Fig. 2). A potential mechanism underlying this adaptation phenomenon, in addition to spike-frequency adaptation, is short-term synaptic depression. This form of rapid and reversible plasticity leads to a decrease of synaptic efficacy lasting from milliseconds to several seconds, due to prolonged presynaptic activity. This

timescale is comparable to the timescale of orientation adaptation, but synaptic depression has mostly been studied in vitro, and direct experimental evidence demonstrating that it is involved in orientation adaptation is lacking. Synaptic depression can be described by a change in transmitter release probability in a phenomenological model (Abbott et al. 1997; Tsodyks and Markram 1997). Computational studies have investigated how synaptic depression, spike-frequency adaptation, and other mechanisms contribute to adaptive changes of visual cortical neurons. The different studies do however reach different conclusions about which particular intrinsic or circuit mechanism is the most likely origin of orientation adaptation (Bednar and Miikkulainen 2000; Chelaru and Dragoi 2008; Cortes et al. 2011). We argue that for a full understanding of adaptation mechanisms in early visual areas, it is necessary to study how adaptation interplays with the dynamics of local circuits, which are dominated by strong, approximately balanced, excitation and inhibition (Stimberg et al. 2009).

On the other hand, computational network models have elucidated the link between orientation adaptation and the psychophysically observed tilt aftereffect, which has long been a challenge (Teich and Qian 2003). Computational models showed how adaptive changes in the location, the width, and the magnitude of single neuron tuning curves give rise to characteristic changes in population responses (Clifford et al. 2000; Compte and Wang 2006). In fact, the relationship between changes in experimentally measured single neuron tuning curves and the response of a population of neurons to a single stimulus (which is thought to underlie perception) can be counterintuitive (Fig. 2). For example, when neuronal tuning curves shift *away* from the adapting orientation (as typically observed experimentally), the corresponding population activity shifts *toward* the adapting orientation (Fig. 2a). If, on the other hand, adaptation only causes a suppression of neuronal responses close to the adapting stimulus (Fig. 2b), the result is a shift of the population activity *away* from the adapting stimulus (as observed in the tilt aftereffect). Considered together, the combination of adaptive changes



Adaptation in Sensory Cortices, Models of, Fig. 2 Example of the relationship between adaptive changes in single neuron tuning curves and changes in the population activity, which is thought to underlie perception. **(a)** Adaptation shifts response curves of individual neurons away from the adapting stimulus. Shown are the tuning curves (responses of a neuron to visual stimuli of different orientation) of three neurons with preferred orientation 0°, 20°, and 40° (*thin lines* before adaptation, *thick lines* after adaptation; *triangle* indicates the adapting

stimulus). **Right:** The *repulsive* tuning curve shifts correspond to a shift of the population activity (response of a population of neurons to a particular stimulus) *toward* the adapting stimulus. The neuron label is determined by each neuron's preferred orientation. **(b)** Same as **(a)**, but now adaptation suppresses responses of individual neurons with preferred direction close to the adapting stimulus. **Right:** This corresponds to a shift of the population activity *away* from the adapting stimulus

observed at single neuron level in visual cortex is indeed consistent with the observed changes in perception (Jin et al. 2005). Note that in this framework it is commonly assumed that adaptation alters encoding in sensory cortical neurons, whereas downstream areas “reading out” the stimulus-related information are unaware of adaptation (Seriès et al. 2009). The predicted perceptual effect also depends on the hypothetical link between population activity and perception, that is, on the “read-out” strategy (such as peak activity, population vector, or maximum likelihood decoding).

More recently, there has been increasing interest in studying high-level adaptation effects, including face adaptation (Webster 2011) and adaptation to the perception of causal interactions

(Rolfs et al. 2013). Computational modeling will be helpful in answering interesting questions related to these phenomena, such as to what degree high-level effects can be explained by adaptation to low-level features or how they arise across the processing hierarchy due to recurrent interactions between cortical areas.

Cross-References

- ▶ [Perception, Bayesian Models of](#)
- ▶ [Perceptual Decision-Making](#)
- ▶ [Short-Term Plasticity, Biophysical Models](#)
- ▶ [Spike-Frequency Adaptation](#)
- ▶ [Visual Aftereffects, Models of](#)

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Adaptive Control

- [Spinal Cord, Integrated \(Non CPG\) Models of](#)
-

Adaptive Design Optimization

- [Adaptive Stimulus Optimization](#)
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Adaptive Sampling

- [Adaptive Stimulus Optimization](#)
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Adaptive Stimulus Optimization

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Synonyms

[Adaptive design optimization](#); [Adaptive sampling](#); [Closed-loop experiments](#); [Optimal experimental design](#); [Optimal stimulus design](#)

Definition

Adaptive stimulus optimization refers to an experimental approach in neuroscience where neuronal or behavioral responses to stimuli presented on previous trials are utilized to adaptively generate new stimuli in an iterative, closed-loop manner, usually by optimizing an objective function. There are different choices for the objective function. For example, if the objective function is the neural response itself, the optimization procedure finds an optimal stimulus that drives maximum

response or is at least a local optimum in the stimulus space. When the objective function is the mutual information between the responses and the unknown parameters of a stimulus-response model, the optimization finds the stimulus set that yields the most accurate parameter estimation.

Detailed Description

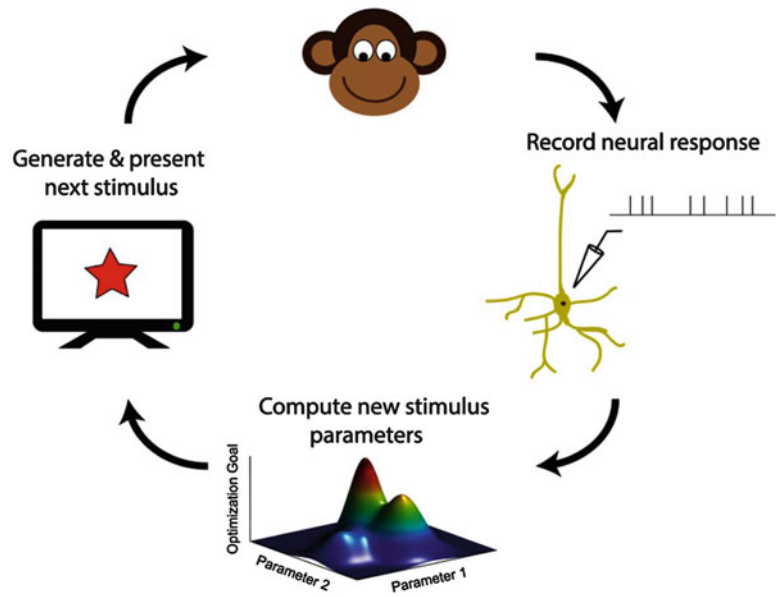
Overview

Traditional experiments in the neurosciences have typically a fixed set of stimuli chosen *a priori* to elicit responses from neurons in an open-loop paradigm, with data analysis and model fitting taking place post hoc. In recent years, with increases in computer power and improvements of algorithms, there has been a growing interest in adaptively generating stimuli online during the course of experimentation in an iterative, closed-loop manner, where neuronal responses from previous trials are used to generate new stimuli (Benda et al. 2007; DiMattina and Zhang 2013; Potter et al. 2013; Park and Pillow 2016). This general paradigm is illustrated schematically in Fig. 1.

Adaptive stimulus optimization has long been used in psychophysics for estimating sensory thresholds (Watson and Pelli 1983; Kontsevich and Tyler 1999) and enjoys a large body of theoretical results from the statistics and machine learning literature (Paninski 2005; Chaloner and Verdinelli 1995). In sensory neuroscience studies, stimuli have been adaptively optimized for a wide variety of experimental goals, including maximizing neural firing rates (O'Connor et al. 2005; Chambers et al. 2014), finding maximally informative stimulus ensembles, (Machens et al. 2005), and estimating and comparing models of sensory processing (Lewi et al. 2009; DiMattina and Zhang 2011; Tam 2012; Park and Pillow 2012, 2016). In addition to applications in systems-level sensory neuroscience, closed-loop approaches have also been applied in many diverse areas including cognitive science, cellular neurophysiology, and brain-computer interfaces (Myung et al. 2013; Potter et al. 2013).

Adaptive Stimulus Optimization,

Fig. 1 Schematic illustration of adaptive stimulus optimization, where responses to preceding stimuli are used to generate subsequent stimuli in a closed-loop manner (Reproduced from DiMattina and Zhang 2013)



Optimizing Firing Rate

Methods for adaptive optimization of neuronal firing rate fall broadly into two categories: (1) hill-climbing methods and (2) genetic algorithms. Hill-climbing methods utilize local perturbations of a reference stimulus to estimate the local response surface from noisy neural responses, iteratively moving the reference stimulus in a direction (e.g., the gradient) which increases neural firing rate (Harth and Tzanakou 1974; O'Connor et al. 2005; Nelken et al. 1994; Koelling and Nykamp 2012). Genetic algorithms mimic biological evolution by broadly populating the stimulus space with numerous stimuli and using their elicited neural responses as a measure of fitness. The fittest stimuli in each generation are then used to define the next generation of stimuli by recombination of their features in a manner analogous to sexual reproduction (Yamane et al. 2008; Chambers et al. 2014). Genetic algorithms have the advantage of being more robust to local maxima than hill-climbing methods and more extensively sampling the stimulus space.

Iso-response Surfaces

Instead of finding the single stimulus that optimizes the firing rate, it is also useful to find the set of all stimuli which elicit the same firing rate response.

The shape of these firing rate level sets can tell us about how a sensory neuron combines stimulus dimensions. This method has been applied in diverse contexts, including studies of spectral integration in grasshopper auditory neurons and integration of photoreceptor inputs by V1 neurons (Gollisch et al. 2002; Horwitz and Hass 2012).

Optimizing Information

Instead of characterizing a neuron by its preferred or “optimal” stimulus, an alternative approach is to characterize the neuron in terms of the stimulus ensemble which its responses most reliably distinguish. This may be quantified by maximizing the mutual information between the stimuli and neural responses, and this technique was applied by Machens et al. (2005) in a study of grasshopper auditory receptor neurons.

Estimating and Comparing Models

Given an accurate model of the input-output relationship for a sensory neuron, it is possible in principle to predict the neuron's response to an arbitrary stimulus. However, estimating high-dimensional models from limited experimental data often poses a serious technical challenge. A study by Lewi et al. (2009) demonstrated that adaptively selecting stimuli to optimize expected

mutual information between neural responses and model parameters allowed fast and robust estimation of generalized linear models. Subsequent work by DiMattina and Zhang (2011) extended this idea to arbitrary stimulus-response models and also considered the problem of adaptively optimizing stimuli for comparing multiple, competing neural models. These methods were verified experimentally in a study of spectral integration in the primate inferior colliculus (Tam 2012). More recent work has considered the use of well-chosen priors to further speed convergence of receptive field estimates (Park and Pillow 2012, 2016). Optimization of sensory stimuli for model estimation and comparison have also been recently applied in vision psychophysics and cognitive science (Wang and Simoncelli 2008; Myung et al. 2013; Kim et al. 2014).

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Estimation of Neuronal Firing Rate](#)
- [Information Theory: Overview](#)
- [Neural Coding](#)
- [Spectrotemporal Receptive Fields](#)

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Afferent Feedback to Neural Oscillators

- [Sensory Input to Central Pattern Generators](#)

Afferent Input to Rhythm Generating Networks

- [Sensory Input to Central Pattern Generators](#)

Algorithmic Generation of Motoneuron Morphology

- [Algorithmic Reconstruction of Motoneuron Morphology](#)

Algorithmic Reconstruction of Motoneuron Morphology

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Synonyms

[Algorithmic generation of motoneuron morphology](#); [Computational synthesis of motoneuron morphology](#); [Computer generation of motoneuron morphology](#)

Definition

Algorithmic reconstruction of neuronal morphology is the process of parameterizing neurite branching patterns, quantifying the parameters for a given population of experimentally reconstructed neurons, and then feeding the data into an algorithm which computationally generates populations of “virtual” neurons.

Detailed Description

Background

Digitization of neuronal morphology is important for computational neuroscience because neuronal morphology affects synaptic integration and firing behavior within individual neurons as well as determining potential connectivity with other neurons (Ascoli 2002). However, experimental reconstruction techniques are still largely manual or, at best, semiautomated, requiring time and skill to accurately capture neuronal morphology. As computational models of the nervous system grow in scale with computational power, there is an increasing need for large numbers of digitized (“virtual”) morphologies. Algorithmic generation of virtual morphologies has the potential to fulfill this need.

Motoneurons, as the nervous system’s “final common pathway” of motor control (Sherrington 1906), have long been studied. These neurons exhibit extensive dendritic arborizations that may stretch over several millimeters in the spinal cord (Cullheim et al. 1987a, b) which makes their reconstruction particularly challenging. As such, the earliest forays into algorithmic generation of neuronal morphology occurred in motoneurons. In particular, one set of reconstructed motoneurons from Cullheim et al. (1987a, b) has been the basis of algorithmic generation research by multiple groups (these morphologies are available for download at neuromorpho.org).

The general process of algorithmic generation begins by parameterizing the neurite branching patterns. These parameters are statistical distributions which are then quantified from experimental reconstructions. Generation then proceeds from the soma outwards, first generating primary neurites which go on to branch or terminate according to the chosen algorithm. This process continues until all branches have terminated. The algorithmic reconstructions are then compared to the experimental reconstructions, whereupon persistent differences are explored to improve the parameterization and algorithm. As this process is repeated, the algorithmic reconstructions become more and more similar to the experimental. The ultimate goal of this line of research is the

capability of generating populations of unique morphologies which are statistically indistinguishable from the experimental population upon which they are based and which capture the natural variability of such a population.

Parameterization

Hillman (1979) was the first to propose that a set of “fundamental” parameters could be used to completely and parsimoniously describe neuronal morphology. He recognized that there are two separable aspects of neuronal morphology that must be parameterized: the branching patterns and the space-filling behavior. It is important to remember that these parameters are not scalar values, but rather statistical distributions, and also that these parameters may be intercorrelated or correlated with other local properties of the arborization.

To capture the branching patterns, Hillman proposed that every neurite tree begins with a “stem diameter” and grows for a certain “segment length” while changing diameter by “segment taper.” If the final diameter of a branch is larger than the “terminal diameter,” the branch bifurcates into two daughter branches, whose diameters are related to that of their parent by the “branch power” and whose relative diameters are determined by the “daughter ratio.” Hillman proposed that quantifying these parameters was sufficient to completely describe neurite branching patterns.

To capture the space-filling patterns, Hillman proposed that one must measure the initial direction of neurite trees and the branching angles (the angles that daughter branches make with regard to the parent branch). Since that time, it has been recognized that to capture space filling, more parameters need to be measured. Proposed additions include some measure of “meander” (how much a neurite’s direction changes as a branch extends outwards) and some measure of “tropism” (a force inducing a directionality in neurite behavior, such as an apical dendrite extending towards the pia).

Slightly different parameter sets have since been proposed and explored based on Hillman’s original fundamental parameters.

Algorithms

Burke et al. (1992) were the first to realize that parameterization of neuronal morphology could be used to algorithmically generate virtual neurite trees. Using experimentally reconstructed motoneurons (Cullheim et al. 1987a, b), their strategy was to “(1) devise a model system that can simulate dendritic trees, (2) derive the required model parameters directly from measurements of real dendrites, and (3) refine the parameter derivations or basic model assumptions, based on the degree of congruence between real and simulated dendrites” (Burke et al. 1992). Using this methodology, Burke et al. found correlations between their parameters and local diameter and path length from the soma. Marks and Burke later extended this work (2007a, b) to include space-filling parameters and the generation of entire neurons.

Ascoli and Krichmar (2000) were the first to apply the methodology in order to create entire neurons, by adding somatic and neurite trunk parameters to a software package called L-Neuron. This software package could replicate Burke et al.’s (1992) algorithm, as well as several algorithms derived more closely from Hillman’s (1979) parameterization. Ascoli et al. (2001) then went on to explore these algorithms using experimental reconstructions of several different types of neurons, including the motoneurons from Cullheim et al. (1987a, b). Donohue and Ascoli (2008) later extended this work to allow parameters to be correlated with local neurite properties (branch order, diameter, and path length from the soma). In an extensive analysis, they explored which local properties are most important for generating realistic morphologies.

Many groups have been exploring algorithmic generation of neuronal morphology, but relatively few have explicitly explored motoneurons. Torben-Nielsen et al. (2008) developed a very different sort of algorithm which they used to explore motoneuron morphology. In this algorithm, parameters are not quantified in advance, but rather the entire parameter space is explored in an evolutionary algorithm which can converge on parameter values which produce realistic morphologies.

Summary

Algorithmic generation of motoneuron morphology is a subset of general algorithmic generation of neuronal morphology. The methodology offers the promise of a deeper understanding of neuronal morphology and may eventually fulfill the need of computational neuroscientists for large numbers of realistic morphologies for use in simulations. While no algorithm has yet been capable of producing morphologies which are statistically indistinguishable from experimental reconstructions across all morphometrics, much progress has been made. The study of motoneurons is especially useful for algorithm development because several different groups have explored the same data set (Cullheim et al. 1987a, b), thus providing a basis for further improvement.

Cross-References

- [Compartmental Models of Spinal Motoneurons](#)
- [Morphologically Detailed Cellular and Pool Motoneuron Models](#)
- [Reconstruction, Techniques and Validation](#)
- [Synthetic Neuronal Circuits/Networks](#)
- [Synthetic Neuronal Morphology](#)

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Algorithms for Generating Neuronal Morphologies

- [Synthetic Neuronal Morphology](#)

Amari Model

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Definition

The Amari neural field model (cf. (Amari 1975, 1977)) provides a simple field-theoretic approach to the dynamics of neural activity in the brain. The model uses excitations and inhibitions over some distance as an effective model of mixed inhibitory and excitatory neurons with typical cortical connectivities. The model is a scalar dynamical equation for the voltage or activity $u(x, t)$ of the form.

$$\begin{aligned} \frac{\partial u}{\partial t}(x, t) &= -u(x, t) \\ &\quad + \int_B w(x, y) f(u(y, t)) dy, x \in B, t \\ &\geq 0, \end{aligned} \tag{1}$$

where initial conditions $u(x, 0) = u_0(x)$, $x \in B$ are given. Here, B is our *brain*, i.e., some domain where the neural activity takes place; f is the local *activation function* or *firing rate function*; and w is the *connectivity function* which models the strength of the connectivity or signal propagation from $y \in B$ to the point x .

A common choice for the activation function has *sigmoidal shape*.

$$f(s) := \frac{1}{1 + e^{-\beta(s-h)}}, s \in \mathbb{R}, \quad (2)$$

which is monotonously growing from $f(-\infty) = 0$ to saturation $f(\infty) = 1$ for large s , where h is the *threshold* and β is a *steepness parameter*. Often, the kernel w is chosen to be homogeneous, i.e., $w(x, y) = w(x - y)$. In this case, the integral becomes a convolution integral, such that the Amari equation can be written in the form.

$$\frac{\partial u}{\partial t} = -u + w \otimes f(u). \quad (3)$$

The Amari equation provides a continuous analogue or continuous description of *neural networks*, which has become widely used in the engineering community.

Historic Background and Applications

The earliest *field models* for describing and studying neural activity dynamics go back to Beurlle (1956), investigating the proportion of active neurons in randomly connected networks, followed by work of Griffith (1963, 1965). The basis of modern field dynamical models has been the work of Cowan, Nunez, and Amari in the 1970s (see Wilson and Cowan 1972, 1973; Nunez 1974; Amari 1977). Cowan proposed an activity-based model with two distinct populations of excitatory and inhibitory subpopulations. Amari suggested a more condensed scalar model with a Mexican hat-type connectivity function, where excitation and inhibition are reflected by the changing sign of the connectivity kernel $w(x - y)$.

The Amari neural field model has been applied, e.g., to autonomous robotic behavior (Erlhagen and Bicho 2006), embodied cognition (Schöner and Dineva 2007), dynamic causal modeling (Daunizeau et al. 2009), and language processing (beim Graben et al. 2008; beim Graben and Potthast 2012); for further details, we refer to the recent tutorial by Coombes et al. (2013).

Theory

The problem (4) is an integrodifferential equation, establishing an *evolutionary dynamical system* with initial condition $u(x, 0) = u_0(x)$, $x \in B$, at time $t = 0$. For a Lipschitz continuous activation function f , *existence* and *uniqueness* of a solution u of Eq. 4 for all times and in one or several dimensions are obtained under quite general conditions based on elementary arguments and the fixed-point theorem (compare Potthast and beim Graben 2010). Over time, there has been significant activity to study the existence and uniqueness of *bumps* and *waves* in one spatial dimension when a particular homogeneous kernel $w(x - y)$ is given (see Kishimoto and Amari 1979; Ermentrout and McLeod 1993) where smooth sigmoidal firing rates are used (see also Coombes and Schmidt 2010; Oleynik et al. 2013; Coombes and Owen 2004 for more general but still rather restricted classes of functions f).

Delay Neural Field Equation and Homogeneous Kernels

Geometric singular perturbation analysis investigates the stability of static or transient solutions, and *numerical bifurcation techniques* investigate the existence and properties of bifurcation points in state or parameter spaces (compare Pinto and Ermentrout 2001a, b; Laing and Troy 2003b). For studies in two or more dimensions, we refer to Taylor (1999), Laing and Troy (2003a), Folias and Bressloff (2004), Laing (2005), Owen et al. (2007), Kilpatrick and Bressloff (2010a), and

Coombes et al. (2012). Often, the Eq. 4 is complemented by a *delay term*.

$$\frac{\partial u}{\partial t}(x, t) = -u(x, t) + \int_B w(x, y) f\left(u\left(y, y - \frac{D(x, y)}{v}\right)\right) dy, \quad (4)$$

$x \in B$, $t \geq 0$, where $D(x, y)$ is the length of the fiber between x and y and v is the finite propagation speed of signals. The above analysis for neural field equations has been extended to delay equations (see Nunez 1974; Jirsa and Haken 1997; Coombes et al. 2003; Hutt 2004; Venkov et al. 2007; Grindrod and Pinotsis 2010), including dendritic processing (Bressloff and Coombes 1997) and synaptic depression (Kilpatrick and Bressloff 2010b).

Most of the above work uses homogeneous kernels $w(x - y)$. More recent work that tackles heterogeneity (primarily using simulations) can be found in Brackley and Turner (2007), Bressloff (2012), Schmidt et al. (2009), and Coombes et al. (2012) and functional analytic results in Faugeras et al. (2008), and Potthast and beim Graben (2010). The *inverse problems* perspective for either homogeneous or nonhomogeneous kernels has been investigated by Potthast and beim Graben (2009) and beim Graben and Potthast (2009). More recently, *stochastic neural field equations* have become very popular; compare the review by Bressloff (2012).

Advantages of the Approach

The Amari neural field model provides a very concise scalar equation to model neural activity and dynamics. In contrast to microscopic models, it summarizes the activity of neurons into the activity function $u(x, t)$, which can be used to reduce the computational complexity significantly. The field-theoretic approach opens the dynamic system to mathematical analysis and beyond the range of discrete network models.

Limitations

The strength of the Amari model is its simplicity, which is at the same time its strongest limitation. It does not take into account the complex chemical and physiological processes which take place in addition to electrical dynamics in neural tissue, nor is it capable to include the different temporal scales on which these processes work and propagate.

Cross-References

- [Bifurcations, Neural Population Models and](#)
- [Chaos, Neural Population Models and](#)
- [Inverse Problems in Neural Population Models](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Model](#)
- [Pattern Formation in Neural Population Models](#)
- [Phase Transitions, Neural Population Models and](#)
- [Stochastic Neural Field Theory](#)
- [Wilson-Cowan Model](#)

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synaptic current by processes of synaptic plasticity and they co-localize with NMDA receptors.

Detailed Description

AMPA receptors are named for the selective agonist (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) that does not bind well to other glutamate receptors. The receptor is permeable to cations and can allow Na^+ , K^+ , and Ca^{2+} to cross the membrane and has an equilibrium potential $E_{\text{AMPA}} = 0 \text{ mV}$. The permeability to Ca^{2+} is small and is not considered important for initiating signaling cascades. AMPA receptors are composed of four types of subunits, and the combination of subunits determines the kinetics and permeability to cations.

Kinetics of AMPA Receptors

Mathematical representations of AMPA currents include the time-dependent synaptic conductance, $g_{\text{AMPA}}(t)$, in the current–voltage equation:

$$I_{\text{AMPA}}(t) = g_{\text{AMPA}}(t)(V(t) - E_{\text{AMPA}}) \quad (1)$$

The time-dependent synaptic conductance represents the opening and closing kinetics of the receptor channels and may be based on a double exponential function (or a similarly shaped function).

$$g_s(t) = \bar{g}_s \left(e^{-t/\tau_1} - e^{-t/\tau_2} \right) \quad (2)$$

where τ_1 is the onset time constant ($\tau_2 < 0.1 \text{ ms}$) and τ_2 is the decay time constant ($\tau_2 < 3 \text{ ms}$) (Hestrin et al. 1990; Trussell et al. 1993; Jonas et al. 1993). AMPA currents have a faster decay than NMDA currents (Jonas and Spruston 1994) and typically have a substantially larger peak current.

Because AMPA currents are usually the dominant excitatory synaptic currents, simple representations of these currents may be the only synaptic currents included in the practice of

Ambiguous Stimuli

► Multistability in Perception Dynamics

AMPA Glutamate Receptor (AMPA Receptor), Conductance Models

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Definition

A glutamate receptor that is permeable to sodium ions and carries an excitatory synaptic current following the binding of glutamate. AMPA receptors are regulated to control the maximum

modeling neural circuits. In models with low time resolution, AMPA currents may be represented as increased currents in a single time bin without short-term temporal details. However, these simple models may contain long-term plasticity that changes the circuit dynamics over time by changing the strength of connections between neurons.

Computational Functions of AMPA Receptors

The excitatory characteristics of AMPA currents can be the main driver of activity in a network of neurons and for communication across long distances such as from the periphery to the central nervous system. Due to the short time constants of AMPA kinetics, signal transmission can carry high temporal precision. An example of this precision is found in the auditory pathway where the interaural time difference can be discerned to extreme precision (Konishi 1990).

Another consequence of the short duration of AMPA currents is that they require a large population of independent asynchronous inputs to deliver a constant depolarization to a neuron. A single AMPA synapse can deliver a fast synaptic current that is filtered by cable properties of the dendrite where the postsynaptic terminal is located (Rall 1967). But there are temporal limitations to how much filtering is possible to deliver the excitatory effect to the spike-generating zone of the postsynaptic neuron. Multiple AMPA currents located on the postsynaptic neurons can overcome this constraint if the rate of incoming spikes is high enough and well distributed in time to overlap. Thus, the synaptic dynamics of a single synaptic terminal may not have a great influence on the postsynaptic activity.

The strength of the synaptic current is not the only determinant of the efficacy of the synaptic input to generate a spike in the postsynaptic neuron. Spikes are triggered by changes in membrane potential, and the filtering properties of the neuron are critical in how the dynamics of the individual synapses are transformed into changes in postsynaptic activity.

AMPA Synaptic Dynamics

In addition to the channel kinetics, AMPA currents exhibit short-term plasticity that can result from both pre- and postsynaptic mechanisms (Zucker and Regehr 2002; Blitz et al. 2004). Presynaptic mechanisms affect the release of glutamate and can influence the peak of the current on subsequent presynaptic spikes. Postsynaptic mechanisms affect the response of AMPA receptors to the concentration of glutamate in the synaptic cleft.

AMPA currents are also involved in long-term plasticity and can be the main component of changes in synaptic strength. AMPA currents do not play a direct role in inducing long-term plasticity but reflect the changes in presynaptic release and their own response to glutamate caused by other mechanisms.

Cross-References

- [Kinetic Models of Postsynaptic Currents](#)
- [N-Methyl-D-Aspartate \(NMDA\) Receptors, Conductance Models](#)

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Amplitude-Amplitude Coupling

► [Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)

Anatomy and Physiology of the Mammalian Auditory System

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List of Abbreviations

A1	Primary auditory cortex
AC	Auditory cortex
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AN	Auditory nerve
AVCN	Anteroventral cochlear nucleus
CNC	Cochlear nucleus complex
CNIC	Central nucleus of the inferior colliculus
DAS	Dorsal acoustic stria
DCIC	Dorsal nucleus of the inferior colliculus

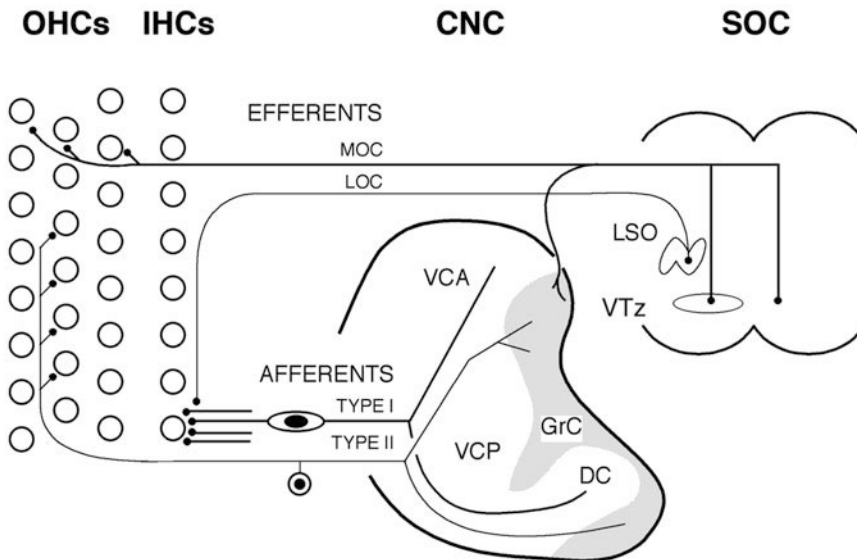
DCN	Dorsal cochlear nucleus
DLL	Lateral lemniscus dorsal nucleus
GABA	γ -Aminobutyric acid
IAS	Intermediate acoustic stria
IC	Inferior colliculus
IHC	Inner hair cell
LCIC	Lateral cortex of the inferior colliculus
LOC	Lateral olivocochlear neurons/system
LSO	Lateral superior olive
MGB	Medial geniculate body
MGD	Dorsal division of the medial geniculate body
MGM	Medial division of the medial geniculate body
MGV	Ventral division of the medial geniculate body
MNTB	Medial nucleus of the trapezoid body
MOC	Medial olivocochlear neurons/system
MSO	Medial superior olive
NLL	Nuclei of the lateral lemniscus
NMDA	<i>N</i> -Methyl-d-aspartate
OHC	Outer hair cell
PO	Periolivary nuclei
SOC	Superior olivary complex
SPO	Superior paraolivary nucleus
VAS	Ventral acoustic stria
VCN	Ventral cochlear nucleus
VLL	Ventral nucleus of the lateral lemniscus
VNTB	Ventral nucleus of the trapezoid body

An auditory system is found in all classes of vertebrates, including fish, amphibians, reptiles and birds, and mammals. Although there are important similarities across classes, the system has evolved differently in the different groups. Even within the class of mammals, there are notable specializations, especially in echolocating mammals such as cetaceans and bats. Because one major objective in hearing research is to understand the structure and physiology of the human auditory system, this entry is restricted to an overview of the general plan of organization of the mammalian system. Insights gained from research in animals should aid in identifying the causes of hearing impairments in humans and represent an important step toward developing effective treatments.

The specific auditory stimulus consists of pressure waves arriving at the ear within a certain frequency range. This audible frequency range varies among species (e.g., humans, 0.02–20 kHz; rat, 0.25–70 kHz; mouse, 2–70 kHz; guinea pig, 0.2–45 kHz; and cat, 0.125–60 kHz) (reviewed in Malmierca 2003; Fay 1988). Within their audible range, some species, such as echolocating bats, are tuned to particular frequencies of special importance for their behavior (reviewed in Fay and Popper 1994) and are considered to be “auditory specialists” (Echteler et al. 1994).

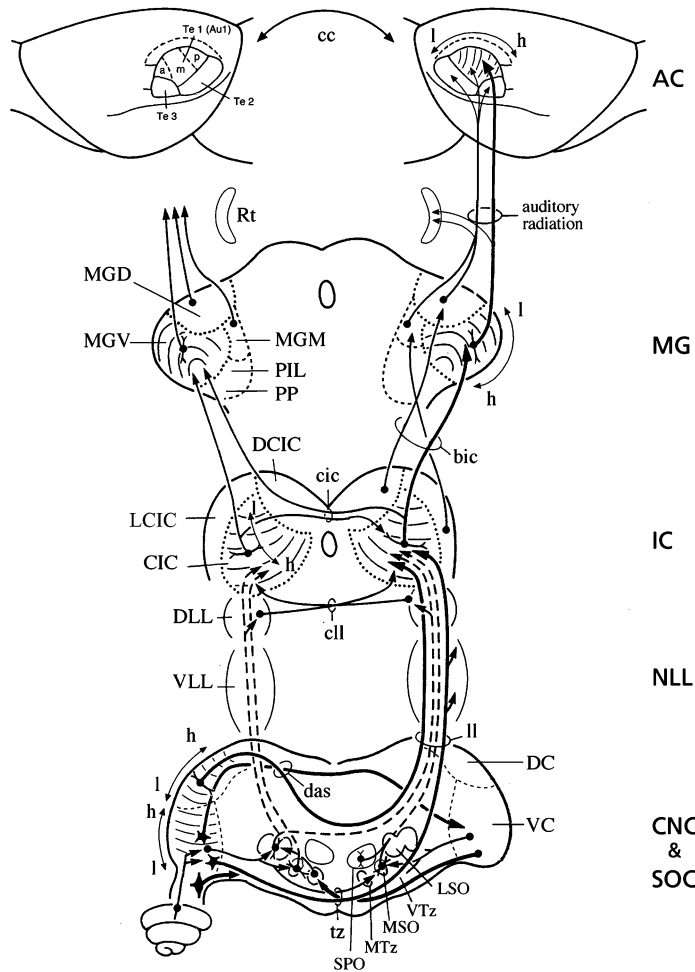
Sound waves are transmitted mechanically through the outer and middle ear to the sensory hair cells of the organ of Corti, in the cochlear partition of the inner ear. Auditory nerve fibers transmit information about receptor potentials generated by the sensory hair cells to the brainstem (Fig. 1). In contrast to the minimum of two relay stations between the periphery and cerebral cortex in the visual and somatosensory

systems, there is a minimum of three relays in the auditory system (Fig. 2), with several stages of convergence and divergence, and at least seven levels of crossing fibers (Figs. 2 and 3), making the auditory system uniquely complicated. In the first relay center, the cochlear nuclear complex (CNC), signals carried by the cochlear nerve are channeled into a number of parallel ascending tracts (Figs. 1 and 2), each with a particular course and destination and each presumably serving a different function (Fig. 3). Some of these terminate in a collection of nuclei in the pons known as the superior olivary complex (SOC). Ascending auditory tracts from both the CNC and the SOC converge on the inferior colliculus in the midbrain (Figs. 2, 3, and 8). From the midbrain upward, the auditory pathway is often divided into core or “lemniscal” projections with a clear tonotopic organization and belt or “nonlemniscal” projections where tonotopy is less sharp or absent (for review, see Malmierca 2003; Malmierca and Hackett 2010).



Anatomy and Physiology of the Mammalian Auditory System, Fig. 1 Afferent and efferent innervation of the cochlear epithelium. Several type I afferent fibers converge onto single IHCs, while a single type II afferent fibers innervate several OHCs. Type I fibers terminate in the AVCN, and type II fibers terminate on the granule cell regions (*GrC*) and marginal shell areas of the VCN and

DCN. The efferent MOC innervate the OHCs, and the efferent LOC innervate IHCs (cf. Figure 19) (Modified after Brown et al. 1988). Abbreviations in the figure: *DC* Dorsal cochlear nucleus, *LTz* Lateral nucleus of the trapezoid body, *VCA* Anteroventral cochlear nucleus, *VCP* Posteroventral cochlear nucleus



Anatomy and Physiology of the Mammalian Auditory System, Fig. 2 Schematic wiring diagram of the ascending auditory pathway (Modified after Brodal 1981, AC is from Herbert et al. 1991). Abbreviations in the figure: *bic* Brachium of the inferior colliculus, *cc* Corpus callosum, *CIC* Central nucleus of the inferior colliculus, *cic* Commissure of the inferior colliculus, *cil* Commissure of the lateral lemniscus (Probst), *das* Dorsal acoustic stria, *h* High-frequency region, *DC* Dorsal cochlear nucleus,

l Low-frequency region, *ll* lateral lemniscus, *LTz* Lateral nucleus of the trapezoid body, *MG* Medial geniculate body, *MTz* Medial nucleus of the trapezoid body, *PIL* Posterior intralaminar nucleus, *PP* Peripeduncular nucleus, *Rt* Auditory sector of the reticular thalamic nucleus, *SPO* Superior paraolivary nucleus, *Te1* Temporal area 1, *Te2* Temporal area 2, *Te3* Temporal area 3, *tz* Trapezoid body (or ventral acoustic stria), *VC* Ventral cochlear nucleus

The Auditory Nerve

The auditory nerve (AN) is made of both *afferent* and *efferent* fibers (for review, see Slepecky 1996). The afferent fibers transmit impulses from the organ of Corti to the cochlear nuclear complex, while the efferent fibers convey impulses from the superior olivary complex to the organ of Corti (Fig. 1). There are two subtypes of

afferent fibers: myelinated and unmyelinated fibers (Fig. 1). The myelinated (type I) fibers are relatively thick and originate from bipolar spiral ganglion cells that innervate the inner hair cells (IHCs). The unmyelinated (type II) fibers are thinner and arise from small, pseudounipolar spiral ganglion cells that innervate the outer hair cells (OHCs). About 90–95% of auditory nerve fibers are type I (Fig. 1); each type I fiber terminates on a

single IHC. The type II fibers constitute only about 5% of all auditory nerve fibers (Fig. 1). As opposed to type I, type II fibers are highly branched, and a single fiber forms synapses with many (6–100) OHCs.

Three types of type I fiber have been characterized based on morphological features that correlate with their spontaneous activity and threshold sensitivity (Liberman et al. 1990). Fibers with a low threshold and a high spontaneous firing rate have the larger diameter and terminate on the pillar side of the IHC, whereas fibers with a high threshold and a low spontaneous firing rate are thinner and terminate on the modiolar side.

The efferent fibers of the olivocochlear system belong to the descending auditory pathways (Fig. 1). They can be divided into two groups: the lateral efferent system (lateral olivocochlear system) that innervates auditory nerve fibers near their synapses with IHCs and the medial efferent system (medial olivocochlear system) that innervates the OHCs (Warr 1992).

The Cochlear Nuclear Complex

The cochlear nucleus complex is situated laterally and superficially in the brainstem (CNC, Figs. 1–5) and is the first relay center for ascending auditory information. It is the site of termination of all auditory nerve (AN) fibers (Ryugo and Parks 2003). The CNC consists of a ventral cochlear nucleus (VCN) and a dorsal cochlear nucleus (DCN). The VCN is subdivided by the cochlear nerve root into anteroventral (AVCN) and posteroventral (PVCN) parts. The DCN curves around the inferior cerebellar peduncle in the floor of the lateral recess of the fourth ventricle. The axons of CNC projection neurons leave the complex via the three primary pathways to reach higher auditory structures: the dorsal, intermediate, and ventral acoustic striae (DAS, IAS, and VAS, respectively). The VAS is usually referred to as the trapezoid body (Figs. 2 and 3). The projections are largely tonotopically organized, and neurons within an isofrequency lamina of the CNC project to a corresponding

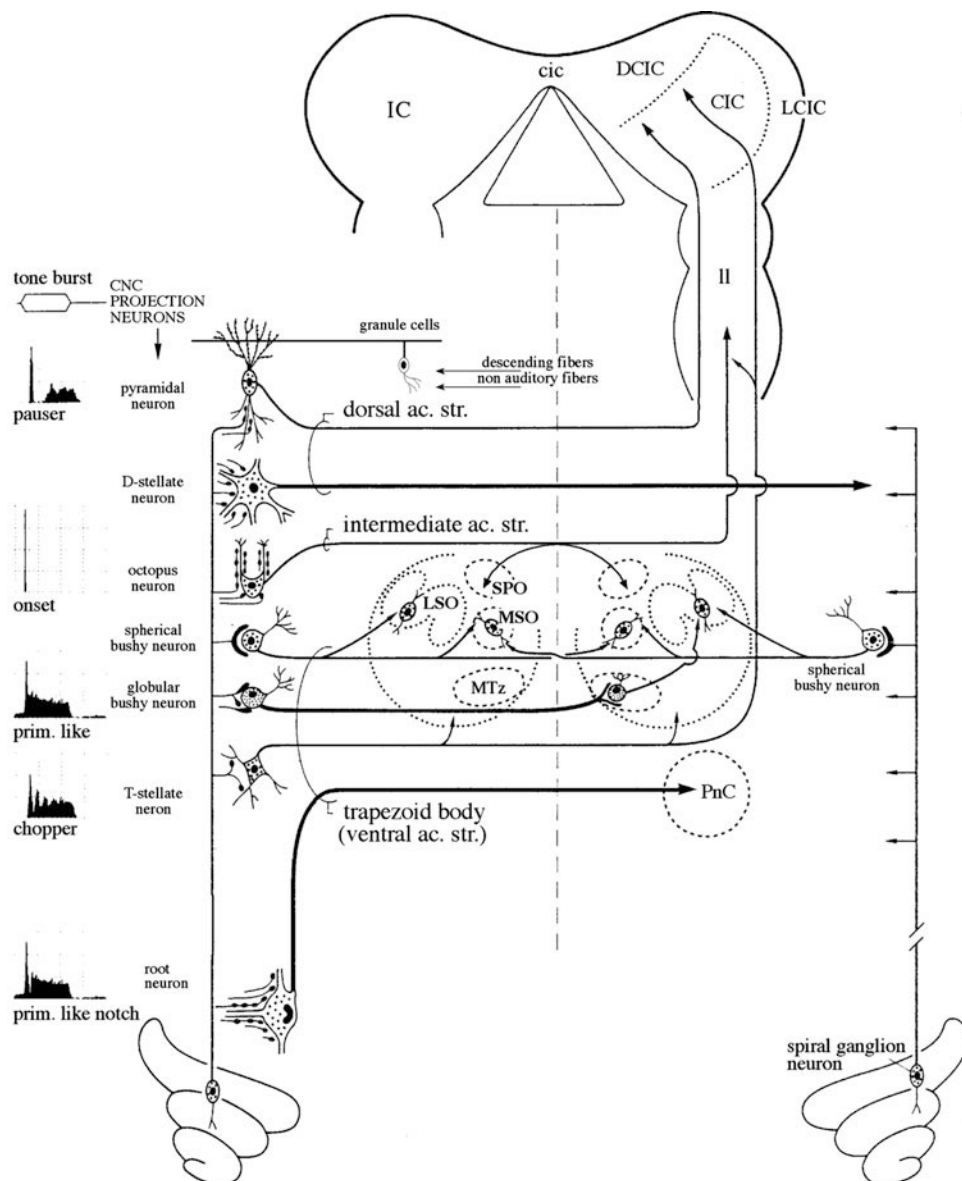
isofrequency lamina in higher-order centers. The right and left CNC are also interconnected by fibers of glycinergic commissural neurons as described below (for review, see Cant and Benson 2003). In addition to its ascending inputs from the AN, the CNC receives descending projections from the auditory cortex, the inferior colliculus; the ventral complex of the lateral lemniscus; and the superior olivary complex (see Malmierca 2003). A large proportion of the latter fibers may be inhibitory, glycine and/or GABA being the transmitters, but there are also excitatory descending fibers, e.g., collaterals of the cholinergic olivocochlear bundle (Osen et al. 1984). The CNC also receives some projections from non-auditory brain structures.

Primary Afferents

Each AN fiber bifurcates into an ascending branch, which supplies the AVCN, and a descending branch, which supplies the PVCN and DCN (Fig. 1). The anatomical distribution of the primary fibers forms the basis for the laminar tonotopic organization of the three subnuclei observed electrophysiologically (for review, see Ryugo and Parks 2003). Type I fibers supply all parts of the CNC except the superficial granule cell areas and the molecular layer of the DCN (Fig. 1). Two basic types of terminals are found: large, axosomatic endings called “endbulbs of Held” and small boutons. The endbulbs of Held arise from the ascending branches, while small boutons arise from loosely ramifying collaterals of both ascending and descending branches. The type II fibers innervate areas rich in granule cells and appear to supply the marginal shell of the VCN (Fig. 1) (for review, see Ryugo and Parks 2003).

Ventral Cochlear Nucleus

Five main neuronal types are recognized in the VCN based on patterns of Nissl staining, dendritic arborization, and main axonal projections: spherical bushy, globular bushy, octopus, multipolar



Anatomy and Physiology of the Mammalian Auditory System, Fig. 3 Projecting cell types of the CNC and their corresponding physiological responses (Modified after Moore and Osen 1979). For abbreviations, see list. Abbreviations in the figure: *CIC* Central nucleus of the

inferior colliculus, *cic* Commissure of the inferior colliculus, *ll* lateral lemniscus, *MTz* Medial nucleus of the trapezoid body, *PnC* Pontine reticular nucleus, caudalis, *SPO* Superior paraolivary nucleus

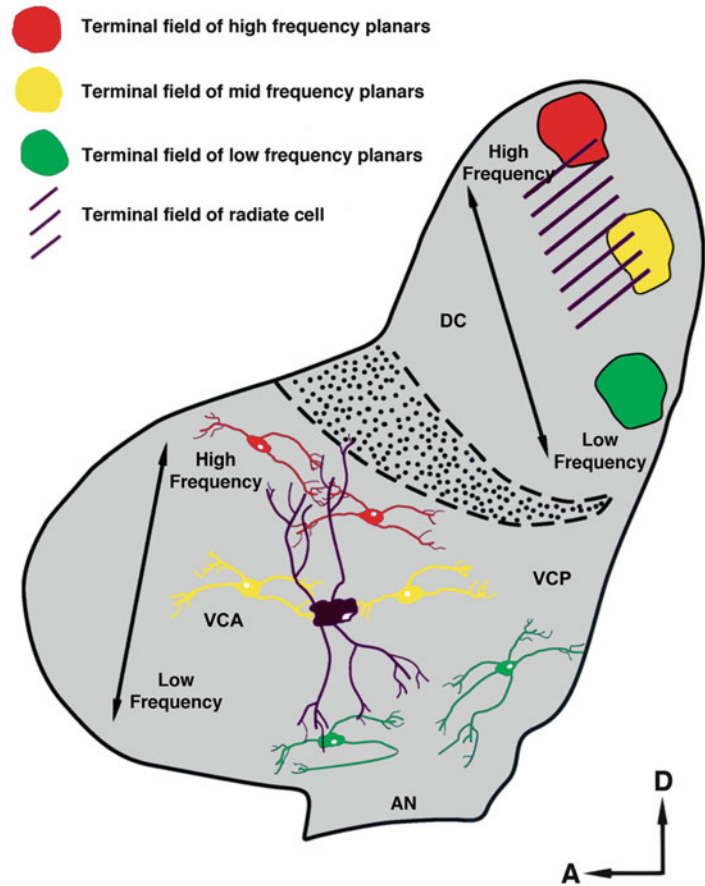
(or stellate), and small cells (Figs. 3–5; Osen 1969; Brawer et al. 1974).

The spherical bushy cells are found rostrally in the AVCN, the globular bushy cells lie centrally on both sides of the nerve root in the caudal AVCN and the rostral PVCN, and the octopus

cells are found caudally in the PVCN. The spherical bushy, globular bushy, and octopus neurons (Fig. 3) have non-tapering dendrites that end in bushy-like formations, but they differ with regard to the appearance of the terminal bush, the number of root segments, and the relative length of the

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Fig. 4 Diagram of the planar (T-stellate) and radiate (d-stellate) cells in the VCN and their projections to the DCN. Planar cells have frequency-specific projections, while radiate cells have across frequency projections (Figure kindly provided by Dr. D. K. Ryugo. Reproduced from Doucet and Ryugo 1997). For abbreviations, see list. Abbreviations in the figure: AN auditory nerve, DC Dorsal cochlear nucleus, LTz Lateral nucleus of the trapezoid body, VCA Anteroventral cochlear nucleus, VCP Posteroventral cochlear nucleus

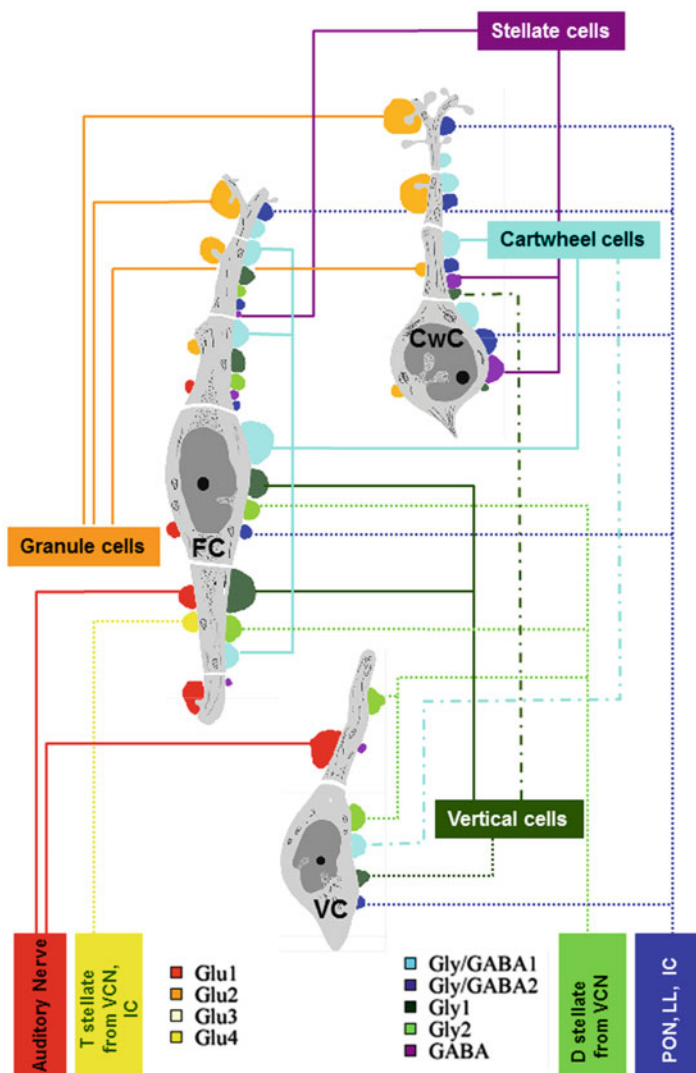


stem dendrites. The spherical bushy cells receive a small number of large axosomatic terminals, the endbulbs of Held (for review, see Ryugo and Parks 2003), and have the so-called primary-like responses to pure tone stimulation, similar to those of the auditory nerve fibers (Young et al. 1988; Young and Davis 2002). The spherical bushy cells (Fig. 3) project bilaterally to the medial superior olive and to the ipsilateral lateral superior olive (Cant and Benson 2003). Globular bushy cells receive a larger number of distinct inputs than do the spherical bushy cells, including small (or “modified”) endbulbs. In response to pure tone stimulation, they exhibit a firing pattern known as “primary-like with notch.” The globular bushy cells (Fig. 3) project to the ipsilateral lateral nucleus of the trapezoid body and the contralateral medial nucleus of the trapezoid body. Axons from both globular and spherical bushy cells

course ventrally in the trapezoid body. The patterns of their AN input, along with unique cell membrane properties, make these cells capable of transmitting precise temporal information necessary for both high- and low-frequency sound localization (Young et al. 1988; Young and Davis 2002). The octopus cells (Fig. 6) receive small boutons from collaterals arising from the descending branch of the AN. They respond to a tone burst with a single spike and so have been called onset units (Young et al. 1988; Young and Davis 2002). Their main projection is to the superior paraolivary nucleus on both sides and to the contralateral ventral complex of the lateral lemniscus, and their axons course dorsally, looping over the restiform body in the intermediate acoustic stria (Wickesberg and Oertel 1988; for review, see Cant and Benson 2003). Their function is still unclear, but it has been suggested that they encode

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Fig. 5 Synaptic endings containing glutamate, glycine, and GABA in the rat dorsal cochlear nucleus. Synaptic endings and of the known (*solid lines*) and putative (*dashed and dotted lines*) neuronal sources of excitatory and inhibitory endings onto pyramidal (FC), vertical (VC), and cartwheel (CWC) cells (Figure kindly provided by Dr. M. E. Rubio. Reproduced from Rubio and Juiz 2004)



the pitch period in their temporal firing patterns (Oertel 1999).

The *multipolar* and *small* cells are present throughout the VCN (Figs. 3 and 4). The small cells are most abundant around the peripheral margins of the nucleus deep to the superficial granule cell layer. A large collection of small cells located dorsolaterally in a superficial location forms the *small cell cap* of the VCN (Osen 1969). This is particularly conspicuous in cat. The *multipolar cells* (Figs. 3 and 6) possess moderately branched, tapering dendrites which are contacted by small boutons from many primary afferent fibers. Two types of multipolar cell have

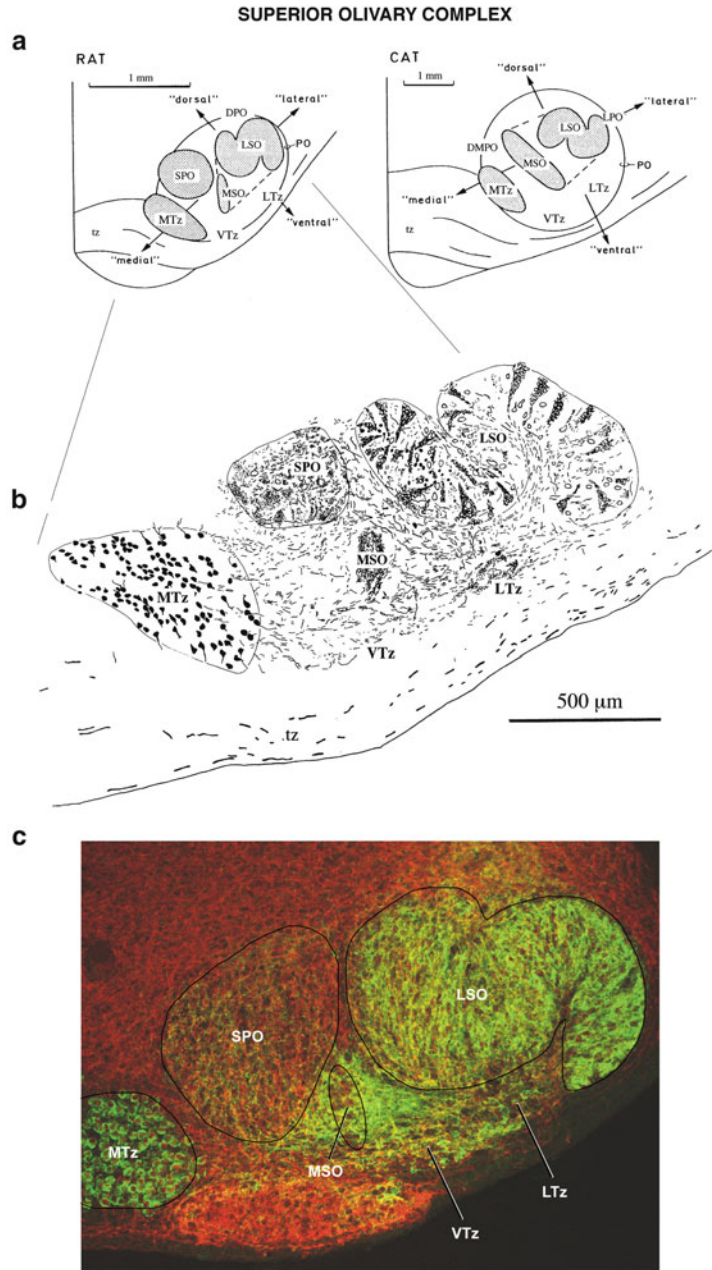
been described (Fig. 3): type I, also referred to as T-stellate (mouse) and planar (rat), and type II, also referred to as d-stellate (mouse) or radiate (rat).

Multipolar type I cells (Figs. 3 and 4) have oriented dendritic arbors and project to the periolivary region of the superior olivary complex via the trapezoid body, the nuclei of the lateral lemniscus, and the central nucleus of the inferior colliculus through the lateral lemniscus (Adams 1979; Cant and Benson 2003; Malmierca et al. 2005). They also give rise to frequency-specific collaterals within the VCN and DCN (Lorente de Nó 1981). These multipolar neurons exhibit a

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Fig. 6 (a) Comparison of the superior olivary complex in the rat and cat (Redrawn after Osen et al. 1984). Note the relative size of the LSO–MSO in the two species and the existence of a distinct SPO in the rat. (b), Camera lucida drawing of a section showing calbindin-positive neurons in the MTz and processes in the rat SOC (Redrawn after Friauf 1993). (c) Confocal image illustrating VGLUT1-ir in the SOC of adult rats. VGLUT1-ir is green, and MAP 2-ir is red. For abbreviations, see list (Data from Blaesse et al. 2005. Figure kindly provided by Dr. E. Friauf).

Abbreviations in the figure: DMPO Dorsomedial periolivary region, LPO Lateral periolivary zone, LTz Lateral nucleus of the trapezoid body, MTz Medial nucleus of the trapezoid body, PO Periolivary regions, SPO Superior paraolivary nucleus, tz Trapezoid body (or ventral acoustic stria); VTz Ventral nucleus of the trapezoid body



“chopper” response to tone bursts with regularly repeated firing. They may be specialized for conveying frequency-specific excitatory information about complex acoustic stimuli such as speech.

Multipolar type II cells (Figs. 3 and 4), also known as commissural neurons, have non-oriented dendritic arbors. They project

to the contralateral CNC via the dorsal acoustic stria (Smith and Rhode 1989; Oertel et al. 1990; Doucet and Ryugo 1997). They also emit extensive (probably broadly tuned) collaterals within the ipsilateral VCN and DCN. They are the only known inhibitory (glycinergic) projection neurons of the CNC (Osen et al. 1990; Doucet et al. 1999)

and respond to pure tone stimulation with an “on-chop” pattern (Smith and Rhode 1989).

The *small cells* are abundant in the marginal shell of the VCN, which is composed of the “granule cell layer” and the subjacent “cap area”. The granule cell layer is continuous over the free surface of the CNC and forms a lamina partly separating the VCN and DCN (Mugnaini et al. 1980a, b; for review, see Cant and Benson 2003). In the DCN, the granule cell layer is covered superficially by a molecular layer. The granule cell axons project as parallel fibers (Fig. 5) to the molecular DCN layer (Mugnaini et al. 1980a, b). The cap area is small but still distinguishable due to its contingent of small cells, many of which show glycine- and/or GABA-like immunoreactivity (for review, see Cant and Benson 2003). The cap is supplied by both type I and type II fibers (Fig. 1), and at least in cat, nearly all type I auditory nerve fibers that innervate the cap have low spontaneous rates (for review, see Ryugo and Parks 2003). The marginal shell also receives descending input. Its cells show a wide dynamic range (Ye et al. 2000) and have a large diversity of projections (Adams 1979; Malmierca et al. 2002, 2005; Ye et al. 2000). The available electrophysiological studies suggest that they form part of a feedback gain control system made up of the cochlea, cochlear nuclear complex, medial olivocochlear system, and outer hair cells (Ye et al. 2000).

Cochlear Root Neurons (Fig. 3). The CNC of rodents contains a population of large cells scattered in the cochlear nerve root, between the main body of the VCN and the glial Schwann-cell border of the AN. It has been suggested that these root neurons participate in the acoustic startle reflex (Sinex et al. 2001).

Dorsal Cochlear Nucleus

The DCN varies from being markedly laminated in rodents and carnivores, where it resembles the cerebellar cortex, to appearing nonlaminated in humans (but see Rubio et al. 2008) and some bat species; it is virtually absent in some cetaceans. The three superficial layers of the DCN are related

to the morphology of the principal pyramidal (fusiform) cells (Figs. 3 and 5). The spiny apical dendritic arbor of pyramidal cells occupies layer 1 together with granule cell axons and several other types of interneurons (Fig. 5, see below). Pyramidal cell bodies define layer 2, and their aspiny basal dendritic arbors comprise layer 3. Pyramidal cell dendritic arbors are flattened across the long, frequency gradient axis of the DCN (see, e.g., Cant and Benson 2003; Malmierca 2003). The highest degree of flatness and mutually parallel orientation is found in the basal arbor, which is supplied by primary afferent fibers in a strictly tonotopic manner.

The pyramidal cells are the main projection neurons of the DCN, supplying fibers to the contralateral IC via the DAS (Fig. 3). In addition, some have a direct projection to the medial division of the medial geniculate body (Malmierca et al. 2002). The deepest layer of the DCN contains two categories of cells based on their size, the giant cells which project to the contralateral IC through the DAS and smaller glycinergic tuberculoventral interneurons (Fig. 5). Pyramidal and giant cell excitatory responses are more strongly influenced by their inhibitory inputs than are those of other projection neurons in the CNC and have been classified as types III and IV (Oertel and Young 2004). The type IV units have been found to be sensitive to spectral notches created by the pinna, which may be important cues for localizing sounds. DCN projection neurons receive and respond not only to auditory information but also to somatosensory inputs from muscle proprioceptors in and around the pinna. This innervation has led to speculation that the DCN may be involved in coordinating pinna orientation with localization cues found in the different spectra of sounds located at different points in space. In fact, bilateral lesions of the DAS in cats result in reduced accuracy in head orientation responses to broadband sounds, particularly in elevation (reviewed in Young and Davis 2002).

DCN possesses a large number of interneurons that may be divided into two systems: the tuberculoventral system and the granule cell system (Fig. 5). The *tuberculoventral system*

reciprocally interconnects the DCN and VCN. It contains both frequency-specific and diffuse projections (Malmierca 2003). The frequency-specific projection from the DCN to the VCN originates from small interneurons, a subset of the glycinergic “vertical cells” (Fig. 5). A separate set of vertical cells with only local collaterals contain both GABA and glycine, the relative amounts of which vary among species. They are located between the basal pyramidal cell dendrites in layer 3, have flattened dendritic arbors, and provide the DCN and VCN with a tonotopically organized inhibition. One projection from the VCN to the DCN is made up of the collaterals of type I multipolar cells described above and probably is excitatory and tonotopic. An inhibitory projection arises from axonal collaterals of the glycinergic commissural (type II) cells. The vertical cells of the DCN provide inhibition over a narrow frequency range, whereas the on-chop, type II stellate cells generate inhibition over a wide frequency range.

The granule cell system includes two types of excitatory cells: granule cells and unipolar brush cells and three types of inhibitory cells: the GABAergic Golgi and stellate cells and the glycinergic cartwheel cells (Fig. 5; Oertel and Young 2004; Rubio and Juiz 2004). The granule cells receive direct excitatory input from many sources including the somatosensory system and inhibitory inputs via the Golgi cells. The granule cell axons contribute parallel fibers to the molecular layer. The unipolar brush cells seem to represent a device for feedforward excitation to the mossy fiber pathways, while the stellate cells and cartwheel cells provide feedforward inhibition to the pyramidal cells (Rubio and Juiz 2004; Fig. 5).

The Superior Olivary Complex

The superior olivary complex (SOC) comprises a group of nuclei in the caudal pons (Figs. 2 and 6). Three main nuclei are consistently identified: the lateral superior olive (LSO), the medial superior olive (MSO), and the medial nucleus of the trapezoid body (MNTB). These three nuclei are

surrounded by more diffusely organized cellular areas, collectively referred to as the periolivary region (PO) (Adams 1983; Osen et al. 1984; Schofield and Cant 1991). The LSO and MNTB are well developed in both the rat and cat, while they are relatively small in human. In contrast, the MSO is small in the rat but is prominent in both the cat and human (Fig. 6). These differences appear to be related to the ability to use specific frequency cues for directional hearing. The MSO extracts the information about interaural timing differences that is available in low-frequency sounds. Together, the LSO and MNTB detect interaural intensity differences generated by high-frequency sounds.

Lateral Superior Olive

The LSO consists of layers of flattened multipolar neurons (principal cells) with their dendrites oriented perpendicular to its long axis, which is curved into an S-shape. The LSO is tonotopically organized with low frequencies represented laterally and high frequencies, medially. In addition to the principal cells, other, less abundant, neuronal types are also present (Rietzel and Friauf 1998). In some species, neurons of the lateral olivocochlear system lie within the LSO.

The LSO receives direct input from the AVCN on the ipsilateral side and indirect input from the AVCN on the contralateral side (Fig. 6). The ipsilateral input derives from spherical bushy cells and is excitatory. Globular bushy cells in the contralateral AVCN project to the MNTB ipsilateral to the LSO. The MNTB, in turn, sends an inhibitory (glycinergic) input to the LSO (Fig. 6). Multipolar type I neurons from the AVCN also innervate the LSO (reviewed in Helfert and Aschoff 1997; Thompson and Schofield 2000).

The LSO projects to the central nucleus of the inferior colliculus bilaterally (Figs. 2 and 6). Most of the ipsilaterally projecting cells are inhibitory (glycinergic), while the contralaterally projecting cells are glycine-negative and presumably excitatory. The LSO also innervates the dorsal nucleus of the lateral lemniscus bilaterally (Fig. 2).

Medial Nucleus of the Trapezoid Body

Cells of the MNTB are situated among fascicles of fibers in the trapezoid body (Figs. 2 and 6). The principal cells resemble the globular bushy cells of the AVCN, whereas non-principal (marginal) cells have a multipolar appearance (Fig. 6; Morest 1968; Banks and Smith 1992; Sommer et al. 1993).

The MNTB receives input from the globular bushy cells in the contralateral VCN (Fig. 2). These cells give rise to thick axons that terminate on the principal cells in the MNTB as large axosomatic calyces of Held (1893) in a one-to-one relationship. These calyces provide a fast and secure relay of information from the CNC to the MNTB and from there to the LSO. They constitute the largest synaptic terminals in the mammalian brain. The responses of cells in the MNTB to acoustic stimuli show a sharp onset spike that is also characteristic of the globular bushy cells.

In addition to its projection to the LSO, the MNTB projects to the ipsilateral MSO as well as other parts of the ipsilateral SOC and the dorsal portion of the ventral complex of the lateral lemniscus, providing a source of widespread glycinergic inhibition.

The microcircuitry and neurochemistry of the LSO and MNTB suggest that a major function of the MNTB is to transform excitatory contralateral input into ipsilateral inhibition, allowing the LSO to faithfully encode interaural intensity differences in the high-frequency range of audition (for review, see Kopp-Scheinflug et al. 2008).

Medial Superior Olive

The MSO lies between the LSO and the MNTB (Fig. 6) and is populated by two types of cells: principal and non-principal or marginal cells. The bipolar principal cells are organized into a transversely oriented row, with their dendrites extending in the medial and lateral directions. The multipolar non-principal cells are scattered

among these dendrites and are much less numerous (Smith 1995). The MSO is tonotopically organized with low-frequency tones represented dorsally and high-frequency tones ventrally, although most of the nucleus appears to be devoted to low frequencies (Guinan et al. 1972).

The MSO receives direct, excitatory input from spherical bushy cells in the AVCN bilaterally (Fig. 6; for review, see Malmierca 2003), but these inputs remain segregated on the cell surface, such that the lateral dendrites receive input from the ipsilateral side, while the medial dendrites receive input from the contralateral side (Smith 1995). A rostrocaudal organization of the axons is reminiscent of the required input configuration in the Jeffress model for sound localization. The direct bilateral input suggests that the MSO neurons are ideally suited to measure interaural phase or time differences (Joris et al. 1998).

The MSO also receives inhibitory inputs, mostly glycinergic, from the medial and lateral nuclei of the trapezoid body on the same side. The latter may also provide GABAergic inhibitory input (Smith 1995). The principal cells project to the inferior colliculus and to the ipsilateral dorsal nucleus of the lateral lemniscus (Fig. 8).

Superior Paraolivary Nucleus

A fourth distinct nucleus in the SOC of rodents, the so-called superior paraolivary nucleus (SPO), is found in the dorsomedial part of the complex (Fig. 6; Osen et al. 1984; Schofield and Cant 1991; Schofield 1995). It consists of GABAergic multipolar cells, which are the largest in the SOC, and receives inputs from octopus and multipolar cells in the contralateral VCN, from multipolar cells in the ipsilateral VCN, and a substantial glycinergic input from the MNTB on the same side. SPO projects to the ipsilateral IC (Schofield 1995) and may represent a hyperdevelopment of periolivary cells with a similar projection, present in smaller numbers in other mammals (Adams 1983). It appears that the SPO neurons are well suited for the analysis of temporal features of

complex sounds and stimulus features across broad frequency ranges (Dehmel et al. 2002; Kulesza et al. 2003).

Periolivary Nuclei

The PO contains several distinct types of neurons with different projection patterns (Adams 1983; Osen et al. 1984). Neurons in the PO areas receive input from VCN bilaterally, the lateral areas, from the ipsilateral side, and the medial areas, from both sides (Fig. 6). Certain parts of the PO also receive input from the ipsilateral MNTB (probably inhibitory), from the ipsilateral inferior colliculus (probably excitatory), and from the dorsal nucleus of the lateral lemniscus (probably inhibitory).

PO cells project either to the cochlea, the CNC, or the IC, but individual cells do not appear to project to all three structures (Adams 1983). The ventral nucleus of the trapezoid body (VNTB) is a PO region situated ventral to the MNTB and is of particular interest because it may be involved in the activation of the olivocochlear neurons (Rajan 1990). It is strategically situated at the intersection of ascending projections from the CNC and descending projections from the IC. The VNTB receives major afferent projections from the contralateral VCN, the ipsilateral PVCN (Smith et al. 1991; Thompson and Schofield 2000), and the marginal shell in the AVCN from both sides (Ye et al. 2000). It is the major target in the SOC for the descending projections from the IC.

The Nuclei of the Lateral Lemniscus

The nuclei of the lateral lemniscus (NLL) is made of two distinct functional systems (Fig. 2), a monaural *ventral* (VLL) and a binaural *dorsal* (DLL) system (Covey and Casseday 1991). There are connectional, neurochemical, and physiological properties which are unique to each system (Covey and Casseday 1991; Malmierca et al. 1998).

The Ventral Nucleus of the Lateral Lemniscus: The Monaural System

The VLL consists of groups of neurons embedded within the part of the lateral lemniscus, located between the SOC and DLL (Fig. 2). It receives its inputs mainly from the contralateral ear via the contralateral VCN and ipsilateral MNTB (Fig. 2). VLL neurons exhibit a variety of shapes and sizes in Nissl-stained sections, and most of them project to the ipsilateral IC. The majority of cells in the ventral part of the complex are glycine and/or GABA (Riquelme et al. 2001).

In vitro, some VLL neurons show an onset firing pattern and a nonlinear current-voltage relationship, while others exhibit a linear current-voltage relationship and other firing patterns (Wu 1999; Zhao and Wu (2001)). Similar differences have also been found in in vivo studies (Zhang and Kelly 2006a, b). The VLL neurons are suitable for encoding temporal events (Covey and Casseday 1991).

The Dorsal Nucleus of the Lateral Lemniscus: The Binaural System

The DLL receives input from both ears, and it projects both to ICs and to its counterpart on the opposite side through the commissure of Probst (Fig. 2). The DLL plays an important role in functions dependent on binaural processing such as sound localization.

Several neuronal types have been described, depending on the species and the criteria used for cell classification. Regardless of the morphological type, all cells have similar membrane properties with a sustained series of regular action potentials produced by the injection of positive current.

Generally speaking, the DLL receives collaterals from afferent fibers that also innervate the IC (Fig. 8). Thus, DLL receives contralateral inputs from the ventral cochlear nucleus and DLL, ipsilateral input from the medial superior olive, superior paraolivary nucleus and VLL, and bilateral inputs from the lateral superior olive. The DLL projection to the IC is laminar and bilateral, with a

predominant projection to the contralateral IC. Most DLL cells are GABAergic and therefore have an inhibitory influence on the IC.

The Inferior Colliculus

The inferior colliculus (IC) is the principal auditory nucleus in the midbrain and is characterized by a massive convergence of inputs from lower and higher auditory centers as well as from non-auditory structures (Figs. 2 and 7; Irvine 1992; Malmierca 2003; Casseday et al. 2002; Loftus et al. 2008). The IC is divided into a central nucleus (CNIC) surrounded by cortical regions

(Fig. 7). These collicular cortices include a dorsal cortex (DCIC) that covers the CNIC dorsally and caudally, a lateral cortex (LCIC) that covers it laterally, and a rostral cortex (RCIC) that covers it rostrally (Loftus et al. 2008; Fig. 8).

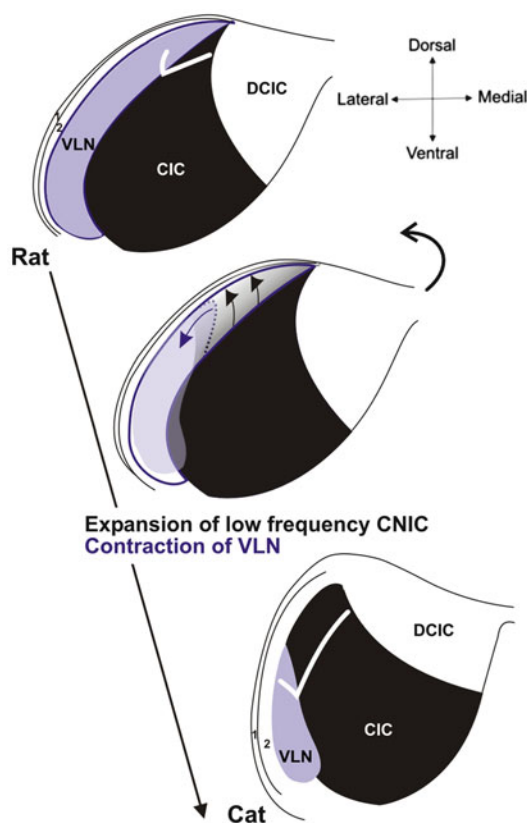
Neurons in the CNIC tend to be most strongly influenced by lower auditory centers, while neurons in the DCIC and RCIC tend to be most strongly influenced by the descending pathways and commissural inputs. The LCIC (and probably the RCIC) receives both auditory and nonauditory (e.g., somatosensory) inputs.

In addition, to its intrinsic and commissural fiber systems (Malmierca et al. 1995; Saldaña and Merchán 1992), the IC provides the major ascending projections to the MGB as well as descending projections to the SOC and the CNC (Oliver et al. 1999; Malmierca et al. 1996; Peruzzi et al. 1997; Ito and Oliver 2012; Cant and Benson 2007).

The Central Nucleus of the Inferior Colliculus

The CNIC is distinguished by layers of cells and fibers organized into “fibrodendritic laminae” (Oliver and Morest 1984; Faye-lund and Osen 1985; Malmierca et al. 1993). These consist of a parallel organization of afferent lemniscal fibers and neurons with flattened dendritic arbors and constitute the structural basis for the tonotopic organization of the IC (Schreiner and Langner 1997; Malmierca et al. 2008; Fig. 9).

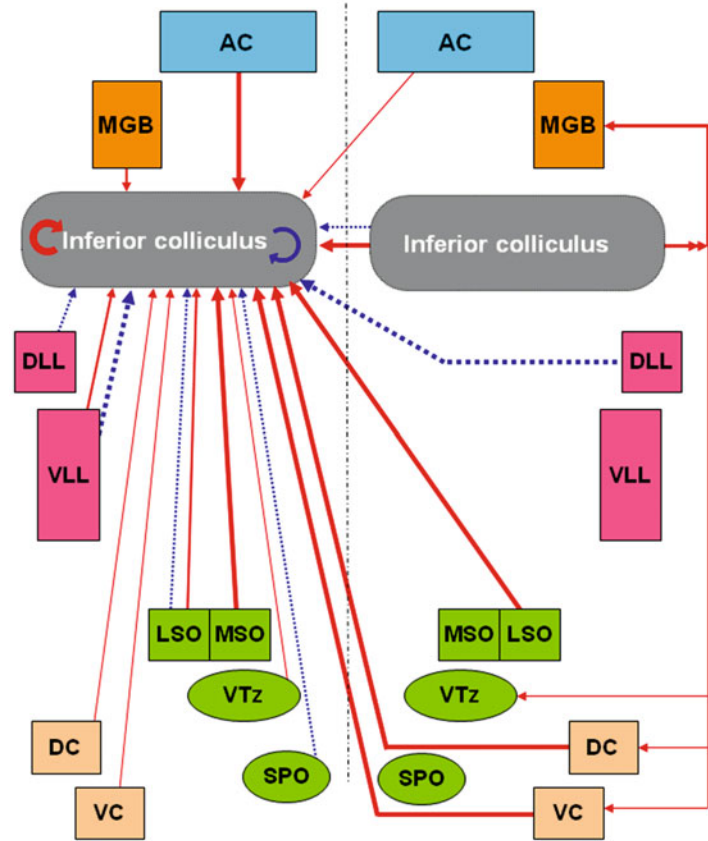
The CNIC is composed of two main neuronal types: disk-shaped or flat neurons and stellate or less flat neurons (Oliver and Morest 1984; Malmierca et al. 1993). These neurons differ in several respects, including the thickness, branching pattern and orientation of their dendritic arbor, and their location with regard to the laminae (Fig. 10). The flat neurons lie parallel to the ascending fibers and form laminae that are mostly one cell thick, about 40–70 μm (Faye-Lund and Osen 1985; Malmierca et al. 1993). These laminae are separated by interlaminar compartments that are populated by the stellate neurons. IC neurons show complex functional



Anatomy and Physiology of the Mammalian Auditory System, Fig. 7 Subdivisions of the inferior colliculus in the rat and cat. The low-frequency representation in the central nucleus (CIC) is expanded in cat and contracted in rats, while the size of the ventrolateral nucleus (VLN) (layer 3 of LCIC) is expanded in rat and contracted in cats. (Redrawn from Loftus et al. 2008)

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Fig. 8 Summary of major sources of inputs to the inferior colliculus on one side of the brain (*left*) from auditory brainstem (*ascending inputs*) and auditory cortex (*descending inputs*). Connection strength is denoted by the thickness of the *arrows*. *Red lines* represent excitatory connections, and *blue/dashed lines* represent inhibitory connections. Abbreviations in the figure: *DC* Dorsal cochlear nucleus, *LSO* Lateral superior olive, *MSO* Medial superior olive, *SPO* Superior paraolivary nucleus, *VC* Ventral cochlear nucleus, *VTz* Ventral nucleus of the trapezoid body

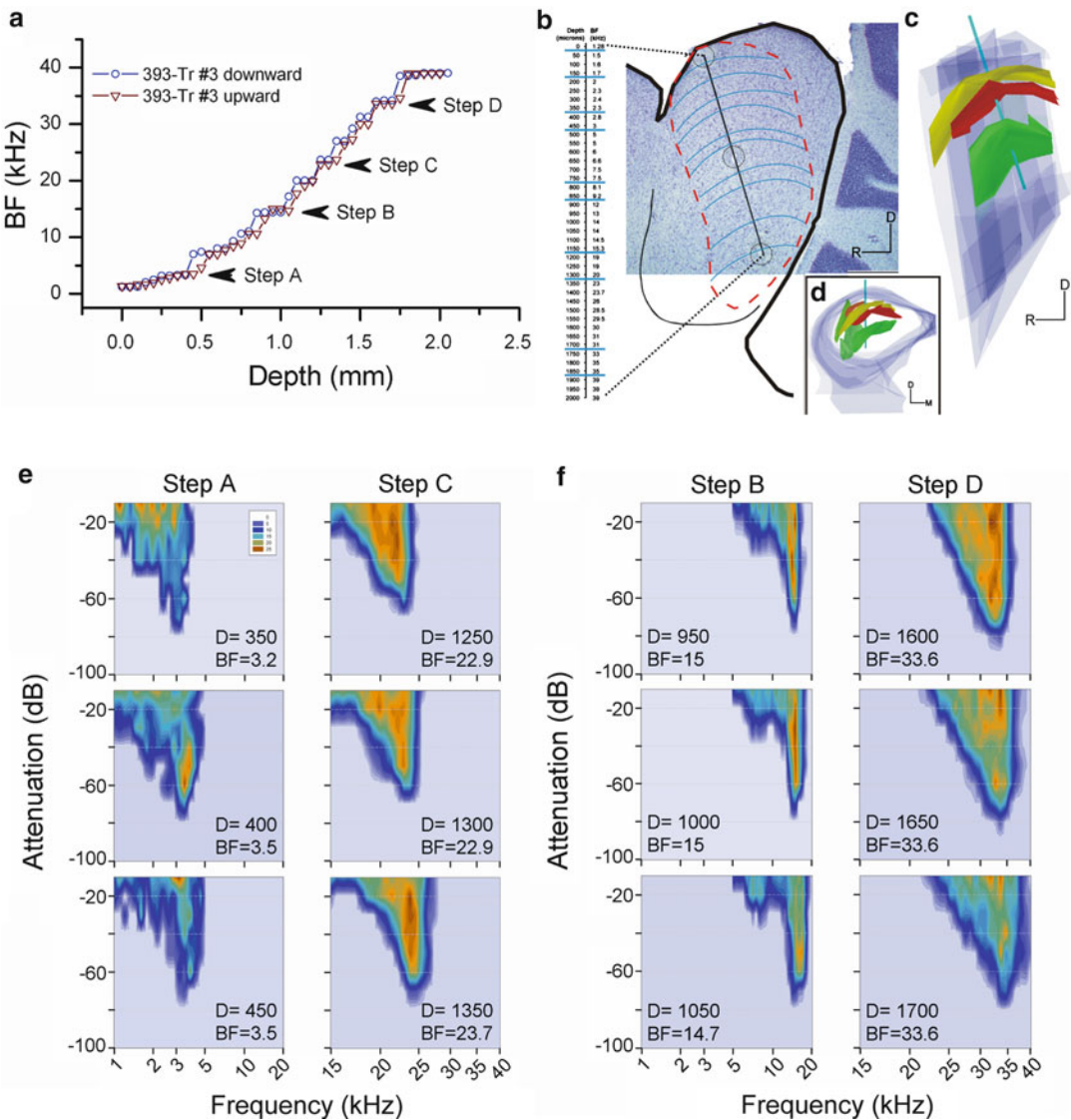


properties, and there is no simple correlation between physiological response properties and morphological classifications (Sivaramakrishnan and Oliver 2001).

The CNIC receives *ascending afferent projections* (Fig. 8) that originate in the AVCN, PVCN, and DCN bilaterally (although mainly contralaterally); the VLL and MSO ipsilaterally; and the DLL and LSO bilaterally (Malmierca 2003; Cant and Benson 2006). These inputs are tonotopically organized and tend to show a “banded” pattern of projections with dense bands (about 200 μm thick) parallel to the iso-frequency fibrodendritic laminae. The terminal fields of the various ascending projections may also vary in their distribution along the main axis of the IC. For example, in the dorsomedial parts of the laminae, the axons from the DCN do not overlap with afferents from the LSO. The CNIC projects to the ventral division of the MGB in a

tonotopic manner (Fig. 10), largely to the ipsilateral side but also with a crossed component. A majority of neurons use glutamate as the neurotransmitter, but about a quarter of the cells in the CNIC are GABAergic (Merchán et al. 2005), and some of these project to the MGB, making short-latency, monosynaptic inputs (Peruzzi et al. 1997).

IC neurons possess NMDA and AMPA receptors as well as GABA_A, GABA_B, and glycine receptors (reviewed in Kelly and Caspary 2005). Studies using microiontophoresis *in vivo* have demonstrated that the AMPA receptors regulate the onset response. Both AMPA and NMDA are involved in the maintenance of the response for the duration of the stimulus, and both GABA and glycine inhibit IC neurons and shape different temporal, spectral, and binaural properties (e.g., LeBeau et al. 2001; reviewed in Kelly and Caspary 2005). Neurons in the IC show a variety



Anatomy and Physiology of the Mammalian Auditory System, Fig. 9 Summary of the tonotopic organization of the inferior colliculus. **(a)** A single electrode penetration *downward* (blue trace) and *upward* (red trace) along the same electrode track (*Tr*) along the CIC in which FRA obtained from multiunit clusters were recorded at every 50 μ m. **(b)** Frequency representation in the CIC obtained in a sagittal section after Nissl staining showing an electrode track (black line), three electrolytic lesions (circles), and best frequency recorded at 50 μ m

intervals. Frequency increases as a function of depth in a stepwise manner. **(c)** 3-D reconstruction of three axonal laminae (yellow, 1.7 kHz lamina; red, 1.8 kHz; green, 4.5 kHz) (Data from Malmierca et al. 2008). **(d)** A frontal view of the same 3-D reconstruction seen in **(c)** after 90° rotation. **(e and f)** FRAs recorded at every 50 μ m in the electrode penetration illustrated in **(a)** at four different steps (*step A–step D*). *D* Depth. (Redrawn from Malmierca et al. 2008)

of frequency response areas that include both V-shaped and non-V shaped types (LeBeau et al. 2001; Palombi and Caspary 1996). Binaural responses are generally classified as suppression,

summation, or mixed. The laminae of the CNIC contain a highly organized representation of both spectral and temporal parameters (for review, see Schreiner and Langner 1988).

The Dorsal Cortex of the Inferior Colliculus

The DCIC covers the dorsomedial and caudal aspects of the CNIC (Figs. 7 and 9b) and is made of three layers (Faye-Lund and Osen 1985). Layer 1 (the most superficial layer) is a thin fibrocellular capsule that wraps the entire surface of the IC including the LCIC. It contains scattered, small, flattened neurons. Layer 2 is slightly thicker and contains mostly small- and medium-sized multipolar neurons. Layer 3 includes a heterogeneous group of multipolar neurons that vary in soma size and shape and in their dendritic orientation. A distinct feature of neurons in DCIC (and also LCIC) is that they contain the neuromodulator nitric oxide, a fact that may explain some of the long-term potentiation and neuronal plasticity observed in some IC neurons (Zhang and Wu 2000).

The ascending input from lower auditory centers to the CNIC encroaches upon the DCIC, as do the intrinsic projections (Saldaña and Merchán 1992; Malmierca et al. 1995). In addition, the DCIC receives descending input bilaterally that originates largely from the primary AC. This projection may generate long-lasting changes in the neuronal responses of the IC. The DCIC projects to the dorsal division of the MGB (Winer 1985).

The Lateral Cortex of the Inferior Colliculus

The LCIC covers the CNIC laterally (Fig. 7) and ventrally (Loftus et al. 2008) and is made up of three layers (Faye-Lund and Osen 1985; Loftus et al. 2008). Layer 1 is a continuation of the fibrodendritic capsule of the DCIC. Layer 2 is composed of small- and medium-sized neurons that are partly aggregated into dense clusters rich in acetylcholinesterase and GABA. Layer 3 of the ECIC constitutes its largest part and appears to continue also into the non-stratified rostral cortex. In addition to auditory inputs, the LCIC receives somatosensory input from spinal cord, dorsal column nuclei, and spinal trigeminal nuclei in the cat (Zhou and Shore 2006). Neurons in the LCIC

appear to have relatively broad somatosensory receptive fields in addition to auditory responses, which are also broadly tuned (Aitkin et al. 1978). The multisensory integration in the LCIC mirrors similar types of function at higher levels of the “extralemniscal” auditory pathway. Although the functions of the LCIC are not known, it may be a major source of binaural cues for gaze control in the superior colliculus (King et al. 1998), and it is very likely that LCIC plays an important role in providing auditory input to visual-motor areas that direct the head and eye movements involved in gaze initiation. A second role of the LCIC may be in multisensory integration, distinct from the “classical” auditory role of the central nucleus. Finally, the CNIC and LCIC differentially activate the medial and lateral olivocochlear system (Ota et al. 2004).

The Rostral Cortex of the Inferior Colliculus

The rostral cortex (RCIC) is adjacent to the anterior CNIC (Fig. 9b) and includes the largest multipolar cells in the IC. There are also small- and medium-sized multipolar neurons (Faye-Lund and Osen 1985; Malmierca et al. 1993). Like the LCIC and DCIC, the RCIC receives input from the cerebral cortex as well as from nonauditory structures (for review, see Malmierca 2003). The RCIC projects to the dorsal and medial divisions of the MG (Fig. 2). The functional role of RCIC neurons is still unknown, although recent studies have demonstrated that many neurons in this region (and in other cortical regions) may be specialized for detecting novel sounds (Malmierca et al. 2009).

The Medial Geniculate Body

The principal auditory nucleus in the thalamus is the medial geniculate body (MGB), which is also the last opportunity for subcortical processing in the ascending auditory pathways (Fig. 2). The MGB is divided into three major divisions named relative to their locations within the

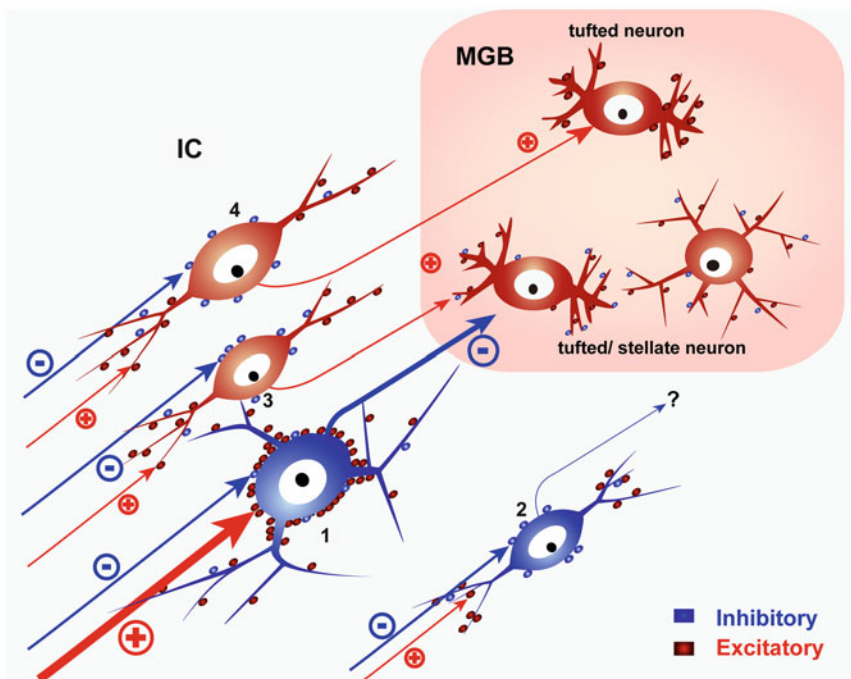
complex: the ventral (MGV), dorsal (MGD), and medial (or magnocellular) (MGM) divisions (Figs. 11 and 12). Additional subdivisions are also recognized in some species, usually representing smaller domains within each of the major subdivisions. Physiological studies have shown that the caudal part of the reticular thalamic nucleus (Fig. 2) is also a part of the auditory pathway (Cotillon et al. 1999; Yu et al. 2009). It provides the MGB with an inhibitory GABAergic input (Bartlett and Smith 1999; Yu et al. 2009).

The main source of ascending projections to the MGB is the IC (Figs. 2 and 10), but other inputs include the thalamic reticular nucleus and auditory subcollicular nuclei, including the SOC, NLL, and CNC, challenging the idea that the IC is an obligatory relay station (Malmierca et al. 2002). Ascending fibers enter the structure medially through the brachium of the IC and terminate among neurons in each subdivision. Connections

with auditory cortex pass through the posterior limb of the internal capsule, and, for the most part, these connections are reciprocal.

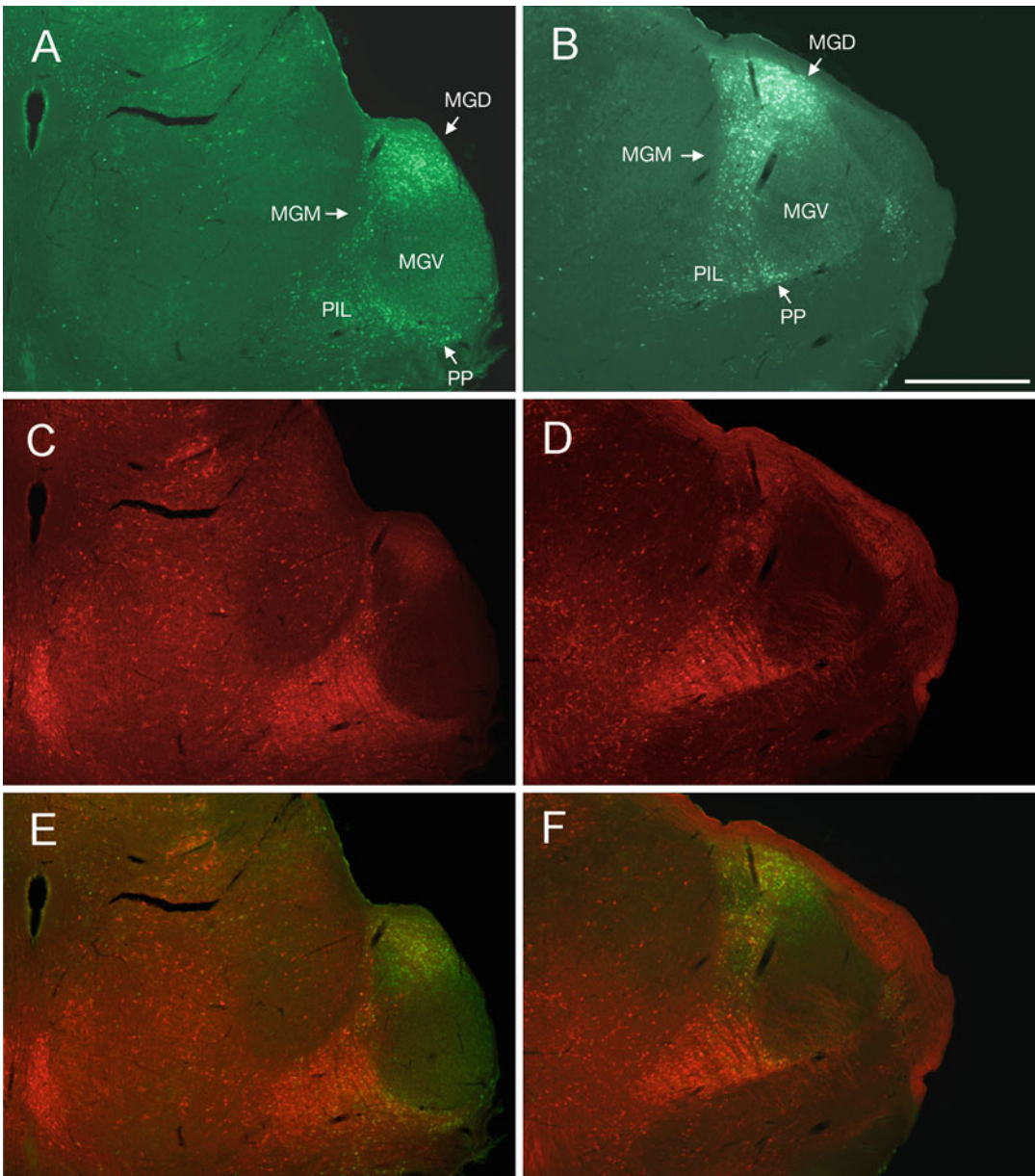
The Ventral Division of the Medial Geniculate Complex

The MGV contains bi-tufted principal neurons that tend to be arranged in rows with oriented dendritic fields (Fig. 12a–c; Winer et al. 1999). These neurons are glutamatergic, and most of them are immunoreactive for parvalbumin (Jones 2007). In the cat, a quarter of the neurons in the MGV are GABAergic interneurons, but these are absent in rodents and bats (Winer and Larue 1988). The MGV neurons are well tuned to frequency, exhibiting low-threshold short-latency responses to tones and complex sounds. They



Anatomy and Physiology of the Mammalian Auditory System, Fig. 10 Schematic diagram of the basic circuitry in the IC. Large GABAergic neurons (1) receive excitatory inputs on their somata, send their axons to the MGB, and inhibit tufted or stellate neurons in the MGB. Small GABAergic neurons (2) do not project to MGB.

Glutamatergic neurons (3, 4) project to the MGB and lack the dense VGLUT2 axosomatic inputs. Red puncta indicate excitatory glutamatergic terminals. Blue puncta indicate inhibitory (GABAergic and glycinergic) terminals (Figure kindly provided by Dr. D. L. Oliver. Reproduced from Ito and Oliver 2012)



Anatomy and Physiology of the Mammalian Auditory System, Fig. 11 Distribution of calbindin and calretinin areas at two different rostrocaudal levels of the MGB in mouse. (a and b) Two sections from same mouse immunostained for calretinin, visualized with Alexa Fluor 594. (c and d) Identical sections from (a and b),

immunostained for calbindin, visualized with Cy-2. (e) Overlay images from (a and c). (f) Overlay images from (b and d). Scale bar = 500 μ m (Figure kindly provided by Dr. Daniel Llano. Adapted from Lu et al. 2009). Abbreviations in the figure: *PIL* Posterior intralaminar nucleus, *PP* Peripeduncular nucleus

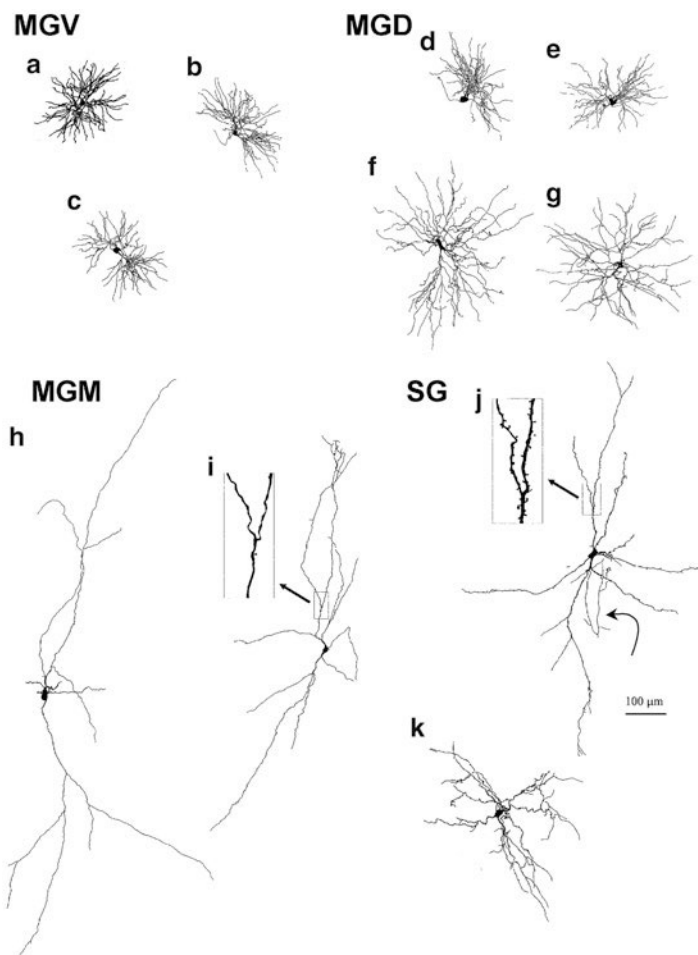
are sensitive to both interaural time and intensity differences.

The MGCV receives its ascending inputs primarily from the ipsilateral CNIC (Fig. 10),

(Malmierca 2003; Jones 2007). These projections arise from both glutamatergic and GABAergic neurons (Bartlett and Smith 1999; Ito and Oliver 2012). MGCV neurons project mainly to layers III

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Fig. 12 Camera lucida drawings of neurobiotin-labeled cells of the rat MG. Tufted cells populate the MG. Cells with two distinct morphologies, tufted and stellate, populate MGD. Cells (d and e) and cells (f and g) are typical examples of MGD tufted and stellate cells, respectively. The dendritic trees of these cells appear similar regardless of the plane of section. Magnocellular neurons populate the MGM (Figure kindly provided by Dr. Philip Smith (some parts reproduced from Bartlett and Smith 1999)). Abbreviations in the figure: SC supragenulate nucleus



and IV of the primary (core) areas of the auditory cortex.

The Dorsal Division of the Medial Geniculate Complex

The MGD is generally characterized by a lower cell-packing density than the MG, and it lacks a laminar organization. At least two subdivisions are clearly recognized on the basis of architectonic variations and connections in most species (Burton and Jones 1976; Winer 1985). The most common neuronal type is the radiate cell (Fig. 12f–g). These have radially symmetric dendritic fields with a simple branching pattern. Tufted cells (Fig. 12a–c) are also present and

tend to form thin sheets. Finally, there is a small population of small stellate cells. Compared to the MG, parvalbumin immunoreactivity is reduced in the MGD, but there is a relative increase in the numbers of calbindin-positive cells (Jones 2007). GABAergic interneurons are also abundant in the MGD. Most MGD neurons respond over a wide range of latencies, typically longer than MG neurons, and exhibit broader frequency tuning, so a clear tonotopic organization is not obvious, if it is present at all.

The main ascending inputs to the MGD arise from the DCIC and LCIC (Malmierca 2003; Jones 2007) and may be either glutamatergic or GABAergic in nature (Bartlett and Smith 1999). The MGD projects to the nonprimary (belt) areas of auditory cortex.

The Medial Division of the Medial Geniculate Complex

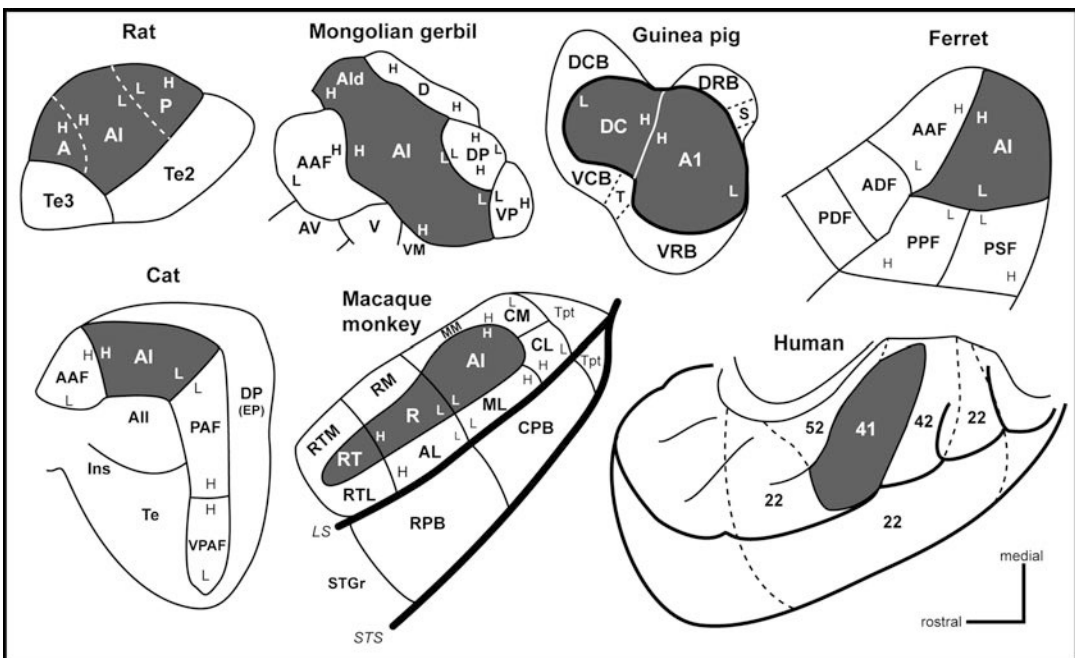
The MGM is located medial to the MGv and MGD and stretches from the rostral to caudal poles of the MGB (Fig. 11). The MGM is rather heterogeneous with respect to cell types and connections. Several different types of cells have been identified including the magnocellular type, the largest neurons in the entire MGB (Fig. 12h–i; Winer and Morest 1983). Some of the neurons are calbindin reactive and project mainly to layers I and II of cortex. Projections to the middle layers of cortex arise from both calbindin- and parvalbumin-positive neurons (Jones 2007). Some neurons are narrowly tuned to frequency and respond robustly at short latencies, similar to MGv neurons, while others are broadly tuned and have longer latencies. Some authors define a separate division referred to as suprageniculate nucleus (Fig. 12j–k).

MGM receives inputs from both auditory and nonauditory sources. The main auditory inputs

arise from the cortical regions of the IC, as well as the CNC, SOC, and VLL (Anderson et al. 2006; Malmierca et al. 2002). Nonauditory inputs include the deep layers of the superior colliculus and other nuclei that appear to drive responses to somatic, vestibular, visual, and nociceptive stimuli in some species (see Jones 2007). In addition to auditory cortex, the MGM also projects to the striatum and amygdala (Doron and Ledoux 1999).

The Auditory Cortex

The auditory cortex (AC) is located in the temporal lobe of the cerebral hemisphere and represents the site of termination for fibers ascending from the auditory thalamus (Fig. 2). The most obvious species differences observed in the auditory brain are those seen in the AC (Fig. 13). For example, the number of areas identified in the AC ranges from 5 to 6 in mice and rats, 6–9 in cats and ferrets, 10–12 in primates, and over



Anatomy and Physiology of the Mammalian Auditory System, Fig. 13 Schematics of auditory cortex models in several mammals. Primary (core) auditory

areas are shaded. Tonotopic gradients are indicated by H (high) and L (low) frequency. (Reproduced from Malmierca and Hackett 2010)

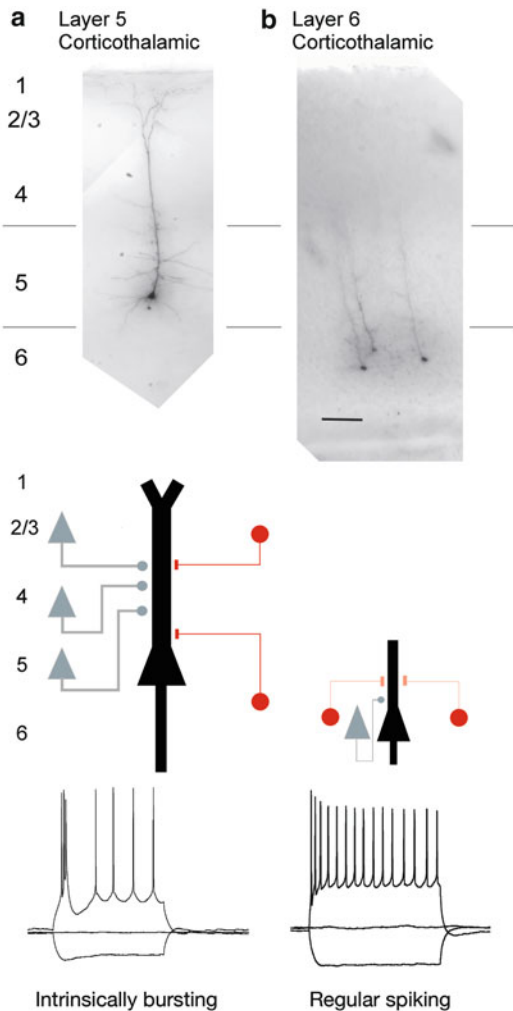
30 in some studies of humans (Fig. 13). Species differences include the number of areas present, their relative position and arrangement, cell density, connections, and tonotopic organization, and it is likely that species differences will also be reflected in the organization of auditory cortex in other ways. However, a common theme is that a central primary region, or *core*, is surrounded by a variable number of secondary, or *belt*, areas in all mammals studied (Fig. 13). In nonhuman primates, the core–belt scheme has been extended to include a third region, known as the *parabelt* (Kaas and Hackett 1998; Winer and Schreiner 2011).

The Core Region of Auditory Cortex

The core region is made of the primary field (A1) and two other tonotopically organized areas (Fig. 13). Areas in the core are characterized by high cell density in a thick layer IV, dense myelination across laminae, and relatively high expression of several markers in the horizontal band involving layers III and IV, compared to secondary areas in the belt (Jones 2003; Kaas and Hackett 1998). Several different classes of pyramidal and nonpyramidal cells are found across the six layers of auditory cortex (Winer 1992). Pyramidal cells tend to be glutamatergic and are concentrated in layers III and V, while many nonpyramidal cells are GABAergic and account for about one-fourth of the neurons in most layers, except layer I, where they constitute more than 90%. Layer II contains both pyramidal and nonpyramidal neurons. The smaller cells are located superficially in layer II, while the larger pyramidal cells predominate near the border with layer III. Layer III is populated by several types of pyramidal and nonpyramidal cells. Layer IV is mainly populated by small tufted cells, which have radially oriented dendritic fields and are involved mainly in local columnar projections. Layer V contains both pyramidal and nonpyramidal neurons. The somata of the conspicuous large pyramidal neurons located in layer Vb have apical dendrites that extend to layer I, with several branches along the way. Other pyramidal

cells in layer V are smaller and more evenly distributed. Layer V is of particular interest because its cells form part of the projection to the thalamus and other subcortical areas (Fig. 14; Games and Winer 1988; Hefti and Smith 2000; Malmierca and Ryugo 2011). As in other cortical regions, two distinct types of pyramidal cells, “intrinsically bursting” and “regular spiking” can be distinguished on the basis of their correlated morphology and physiology (Fig. 14; Kawaguchi 1993; Kasper et al. 1994). The *intrinsically bursting* pyramidal cells (Fig. 14) have large cell bodies and long, thick apical dendrites that branch extensively in layer I. Their axons arborize locally in the infragranular cortical layers and project into subcortical white matter. In contrast, the *regular-spiking* pyramidal cells (Fig. 14) have smaller cell bodies and a thinner apical dendrite that seldom extend to layer I. Their axons also project to the white matter and arborize locally in the supragranular cortex. In slice preparations, the intrinsically bursting neurons exhibit a characteristic firing pattern with a burst of action potentials followed by either additional bursts or single spikes, whereas the regular spiking neurons tend to fire single spikes with a variable degree of adaptation (Hefti and Smith 2000, 2003). Intrinsically bursting cells make up the majority of layer V’s input to subcortical targets (Fig. 15; Games and Winer 1988; Winer 1992; Weedman and Ryugo 1996a, b; Saldaña et al. 1996) and are capable of providing a robust input to postsynaptic neurons (Hefti and Smith 2000). In contrast, most regular spiking neurons are strongly inhibited and may provide less robust but perhaps more specific, information to their inputs. Finally, layer VI has the widest variety of cell types, including several classes of pyramidal cells and multipolar, bipolar, and horizontal cells.

The main source of ascending inputs to A1 and other core areas is the MGv (Fig. 2; Jones 2007; Winer 1985; Winer and Lee 2007). The thalamocortical termination is concentrated in layers III and IV. The organization of these connections is topographic, reflecting tonotopic organization within the MGv, as well as the areas to which it projects. Additional inputs to the core



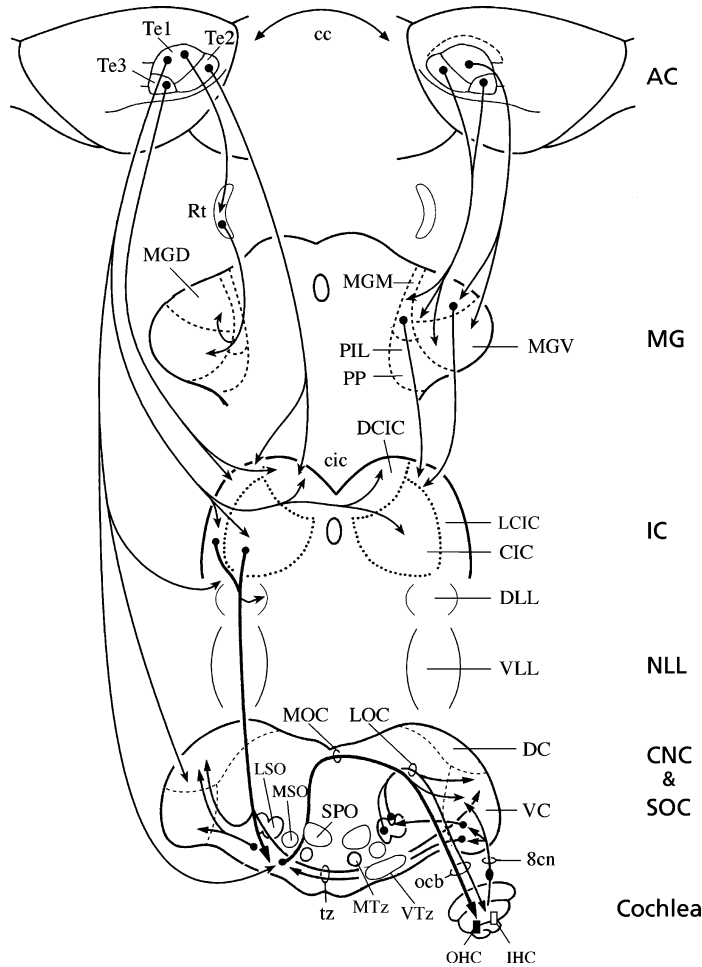
Anatomy and Physiology of the Mammalian Auditory System, Fig. 14 *Top panel*, examples of morphology of layer V and layer VI corticothalamic neurons biocytin-filled corticothalamic neurons. Scale bar 100 μ m; *Bottom panels*, Llano and Sherman model of differences of synaptic input and response properties between auditory layer V and layer VI corticothalamic neurons. In response to excitatory input, layer V corticothalamic neurons fire a burst of action potentials at low threshold, and these neurons receive excitatory input from neurons in layers II/III, IV, and V (gray) and GABA-mediated inhibitory input mostly from lower layer V with a smaller contribution from layer II/III (red). In contrast, in response to excitatory input, these neurons fire a regular train of individual action potentials, and these neurons receive excitatory input primarily from layer VI and inhibitory input from adjacent areas in layer VI (Figure kindly provided by Dr. Daniel Llano. Adapted from Llano and Sherman 2009)

include MGM, which projects broadly to all areas of auditory cortex. The intracortical connections of the core mainly include other areas of auditory cortex ipsilaterally and sparse connections with areas beyond auditory cortex. Tonotopically matched sites are more densely interconnected than non-matched sites (Lee and Winer 2005). Connections with auditory cortex in the opposite hemisphere are concentrated in the homotopic (matching) area, (Wallace and Harper 1997) and heterotopic connections are relatively weak. The main callosal projections arise from both pyramidal and nonpyramidal cells in layers III and V. Layers V and VI represent the main source of descending projections to the MGB and IC and brainstem (Fig. 15).

The Belt Region of Auditory Cortex

Areas that lie outside of the core region are often referred to as the nonlemniscal or belt areas (Fig. 13). These areas are anatomically and physiologically distinct from the core fields and from one another. Architectonically, each of the belt areas is distinct, but compared to the core region, cell density and myelination are generally reduced, as is the expression of cytochrome oxidase, acetylcholinesterase, and parvalbumin (Jones 2003).

In addition to the inputs from the core, the main source of projections to most of the belt areas is the MGD (Jones 2007; Winer 1985; Winer and Lee 2007). Additional connections include the MGM and thalamic nuclei that surround the MGB. Belt areas tend to differ with respect to the balance of inputs from different thalamic nuclei. In nonhuman primates, an additional group of areas has been identified that surround the belt areas adjacent to the core. This region is known as the *parabelt* (Kaas and Hackett 1998). The parabelt region receives inputs from the belt region and MGD, but not the core. Thus, some ascending information appears to pass serially through the core and belt regions before reaching the parabelt (Kaas and Hackett 1998).



Anatomy and Physiology of the Mammalian Auditory System, Fig. 15 Schematic wiring diagram of the descending auditory pathway of the rat (Modified after Brodal 1981, AC is from Herbert et al. 1991). Abbreviations in the figure: *bic* Brachium of the inferior colliculus, *cc* Corpus callosum, *CIC* Central nucleus of the inferior colliculus, *cic* Commissure of the inferior colliculus, *cil* Commissure of the lateral lemniscus (Prosbt), *das* Dorsal acoustic stria, *DC* Dorsal cochlear nucleus, *h* High-frequency region, *IC* Inferior colliculus, *l* Low-frequency

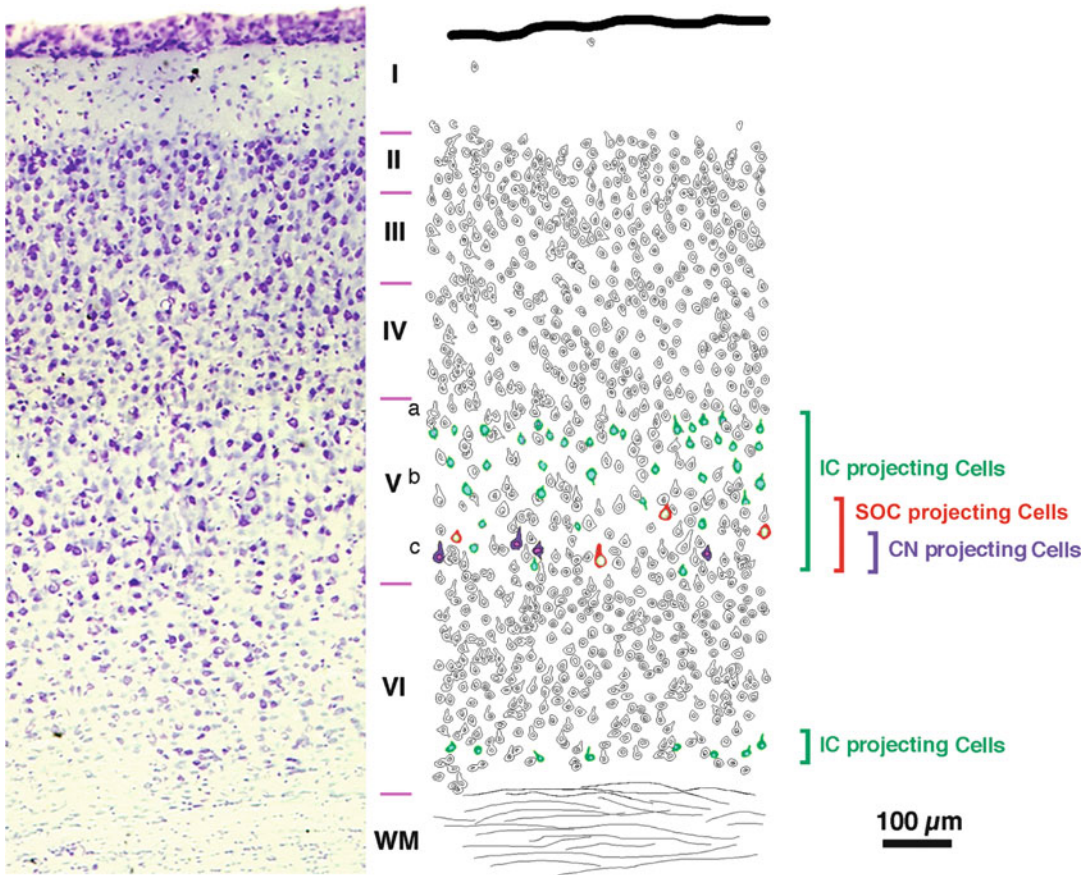
region, *ll* Lateral lemniscus, *LTz* Lateral nucleus of the trapezoid body, *MG* Medial geniculate body, *MTz* Medial nucleus of the trapezoid body, *ocb* Olivocochlear bundle, *PIL* Posterior intralaminar nucleus, *PP* Peripeduncular nucleus, *Rt* Auditory sector of the reticular thalamic nucleus, *SOC* superior olivary nucleus, *SPO* Superior para-olivary nucleus, *Te1* Temporal area 1, *Te2* Temporal area 2, *Te3* Temporal area 3, *tz* Trapezoid body (or ventral acoustic stria), *VC* Ventral cochlear nucleus, *8cn* Cochlear root of the vestibulocochlear nerve

The Descending Auditory Pathways

In parallel to the ascending auditory pathways, there are stepwise, descending projections from the auditory cortex to the organ of Corti (Fig. 15). The descending auditory pathway could be considered to consist of both (1) a descending chain

of connections and (2) a series of regional feedback loops (Warr 1992).

The descending chain comprises three main levels. The first level originates in the AC and includes corticothalamic, corticotectal, and corticopontine projections (Fig. 16). The corticothalamic projection forms reciprocal and



Anatomy and Physiology of the Mammalian Auditory System, Fig. 16 Diagrammatic summary of the laminar organization of cortical cells projecting to the inferior colliculus (IC), superior olivary complex (SOC), and cochlear nucleus (CN). All three distributions overlap;

however, the cortical neurons projecting to more distant targets are more narrowly distributed and centered in deeper regions of layer V (Figure kindly provided by Dr. D. K. Ryugo. Reproduced from Doucet et al. 2003)

nonreciprocal connections between the AC and MGB. The corticotectal projection terminates in the IC and subcollicular nuclei (Feliciano and Potashner 1995; Meltzer and Ryugo 2006). The second level of the chain originates in the IC, whose descending fibers form colliculo-olivary and colliculo-cochleoneuronal projections (Fig. 15). The colliculo-olivary fibers terminate on the periolivary medial olivocochlear cells which supply the OHCs (Caicedo and Herbert 1993; Faye-Lund 1985; Vetter et al. 1993). They may also terminate on lateral olivocochlear cells, which supply the IHCs (Feliciano and Potashner 1995). The last and third level of the chain consists of the olivocochlear system that provides

efferent innervation to the cochlea (Figs. 15 and 19).

The regional feedback loops consist of a series of cortical projections to subcortical nuclei that project back to cortex, directly or indirectly, allowing AC to control its inputs from lower centers.

The Corticofugal Pathways

The major AC projections target the MGB and IC (Figs. 15–18), but there are also AC projections to subcollicular nuclei, including the nucleus sagulum, paralemniscal regions, superior olivary complex, cochlear nuclear complex, and pontine

nuclei. The AC also supplies the amygdala, basal ganglia, striatum, superior colliculus, and central gray (reviewed in Malmierca and Ryugo 2011, 2012), suggesting that the AC has important roles in addition to auditory sensory processing (Winer 2006).

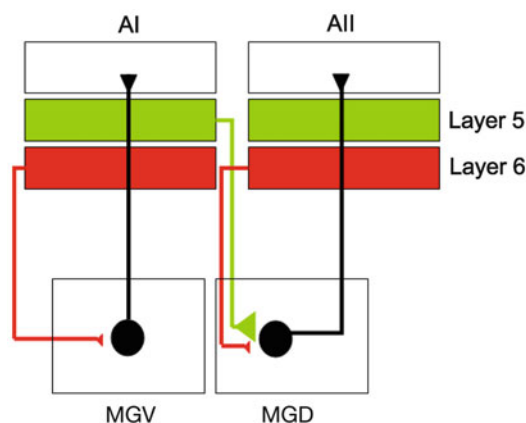
In the auditory thalamus, the MGV receives its heaviest source of input from the primary AC, while the MGM the least and the MGD receives an intermediate amount. A prominent feature of the corticothalamic projection is reciprocity, in which a cortical region projects to the part of the thalamus from which it receives input. However, there are also nonoverlapping regions (Llano and Sherman 2008). In the MGB, there are two main types of terminal synaptic boutons (I and II) arising from the core of the AC (Fig. 17; Bartlett et al. 2000; Llano and Sherman 2009). Type I terminals are small ($<1\ \mu\text{m}$ in long-axis diameter), synapse on small caliber dendrites of the MGV and MGD, and arise from the pyramidal cells of layer VI. Type II terminals are large ($>2\ \mu\text{m}$ in long-

axis diameter), mostly synapse in the MGD and occasionally in the MGM (Bartlett et al. 2000; Llano and Sherman 2009) and arise from pyramidal neurons from layer V.

Sherman and Guillery (1996) first proposed the notion of “drivers” and “modulators” of thalamic neurons in the visual and somatosensory thalamus, but this hypothesis has been applied to the auditory system as well (Llano and Sherman 2008). According to this theory, type I terminals play a modulatory role in the first-order thalamic nuclei, such as the MGV (Fig. 17). Thus, the corticothalamic inputs converge with ascending inputs on thalamic neurons such that the ascending inputs drive the thalamic neurons and the cortical inputs modulate them. In contrast, in the “higher-order” thalamic nuclei, such as the MGD, the “driver” inputs arise from the large type II axons and terminals that originate from the cortex and interact with other ascending input from the IC.

The corticofugal projection is glutamatergic and modulates the MGB responses to sound through a direct excitatory pathway, but the AC can also provide the MGB with an inhibitory influence (Bartlett et al. 2000) via its projections to the auditory sector of the thalamic reticular nucleus which, in turn, projects to the MGB.

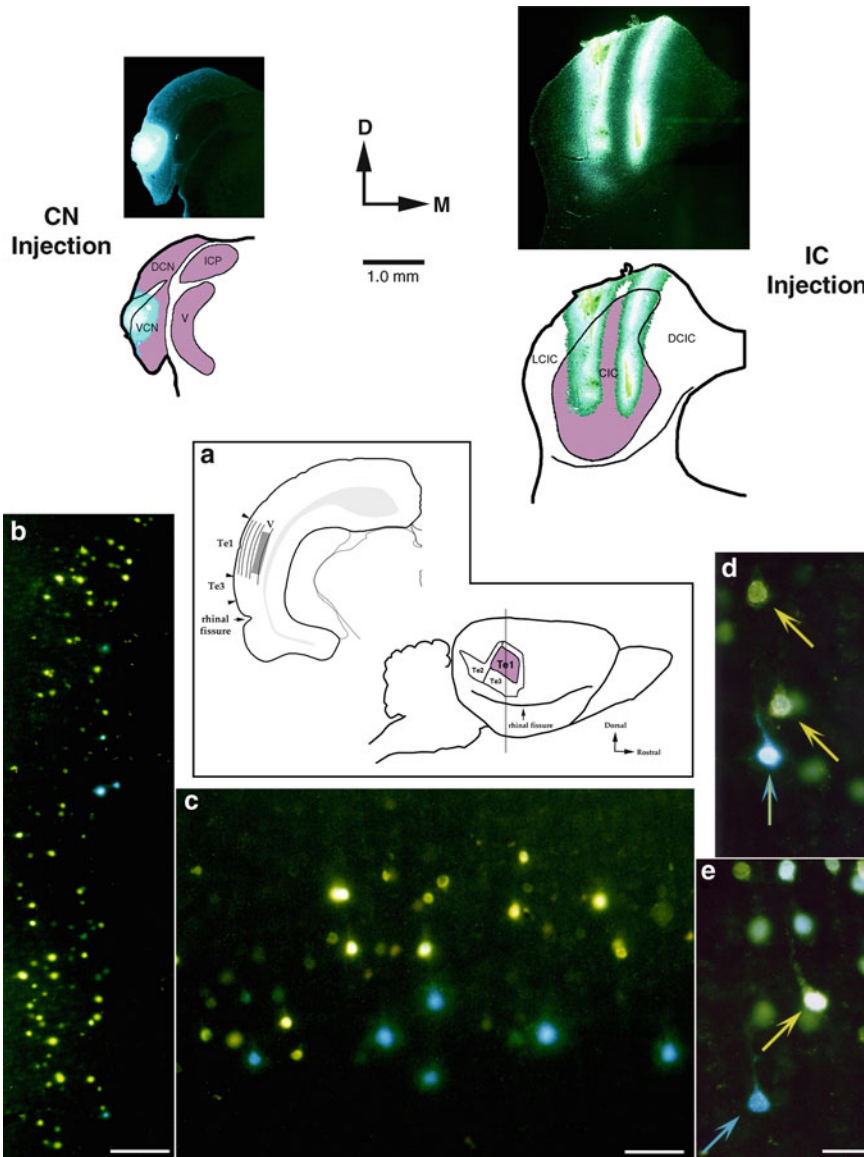
As in the MGB, AC may modulate the processing of sounds in the IC through the activation of local inhibitory connections within the IC. Several studies have shown direct neocortical projections to regions surrounding the lateral lemniscus, including the nucleus sagulum ipsilaterally and the SOC and CNC bilaterally (Feliciano and Potashner 1995; Weedman et al. 1996; Weedman and Ryugo 1996a, b).



Anatomy and Physiology of the Mammalian Auditory System, Fig. 17 Diagram of a cortico-thalamocortical model of cortical processing. Information reaches the *lemniscal* AC via a projection from the MGV to layer IV of either the AAF or the AI. From here, a layer 5 pyramidal projects to the MGD, where a thalamocortical relay cell projects to layer IV of the *nonlemniscal* AC (DP or AII). From the nonlemniscal AC, a layer VI projection is sent to the MGB, adhering to the principle that all thalamocortical projections, whether coming from the first- or higher-order thalamus, receive a modulator, reciprocal projection from layer VI (Figure kindly provided by Dr. Daniel Llano. Adapted from Llano and Sherman 2008)

The Colliculofugal Pathways

Studies in several species have shown that the IC has descending projections to the LL, SOC, and CNC (Fig. 15; reviewed in Malmierca and Ryugo 2011, 2012). Perhaps, the most interesting projections are the *colliculo-olivary* projections that originate in the CNIC and LCIC because they terminate on the VNTB, the site of origin of the



Anatomy and Physiology of the Mammalian Auditory System, Fig. 18 Retrograde labeling in area Te1 for a rat that received an injection of Fast *blue* (FB) into the CNC and Diamidino *yellow* (DiY) into the IC (*top*). (a) Sagittal view of the brain, the *gray line* through AC indicates the position of the cells along the rostral/caudal axis display of the location of labeled cortical cells shown in panels (b–e). (b) Photomontage of layer V with few FB-labeled cells located in deep layer V whereas the DiY-labeled neurons are distributed more broadly. (c) Higher magnification photomontage illustrating the

laminar organization of cortical cells (cortical surface is towards the *top*) projecting to the CNC (*blue*) vs those targeting the IC (*yellow*) within layer V. (d and e) Examples of labeled cortical cells. Cortical cells that contained both dyes (*blue and yellow arrow* in d) were observed much less frequently (Figure kindly provided by Dr. D. K. Ryugo). Reproduced from Doucet et al. 2003). Abbreviations in the figure: CN Cochlear nucleus, CIC Central nucleus of the inferior colliculus, D Dorsal, M Medial, Te1 Temporal area 1, Te2 Temporal area 2, Te3 Temporal area 3

MOC (White and Warr 1983), suggesting that the IC influences MOC neurons (Vetter et al. 1993). The IC also projects to nonauditory nuclei including the pontine nuclei, lateral paragigantocellular nucleus, gigantocellular reticular nucleus, ventrolateral tegmental nucleus, and caudal pontine reticular nucleus (Caicedo and Herbert 1993).

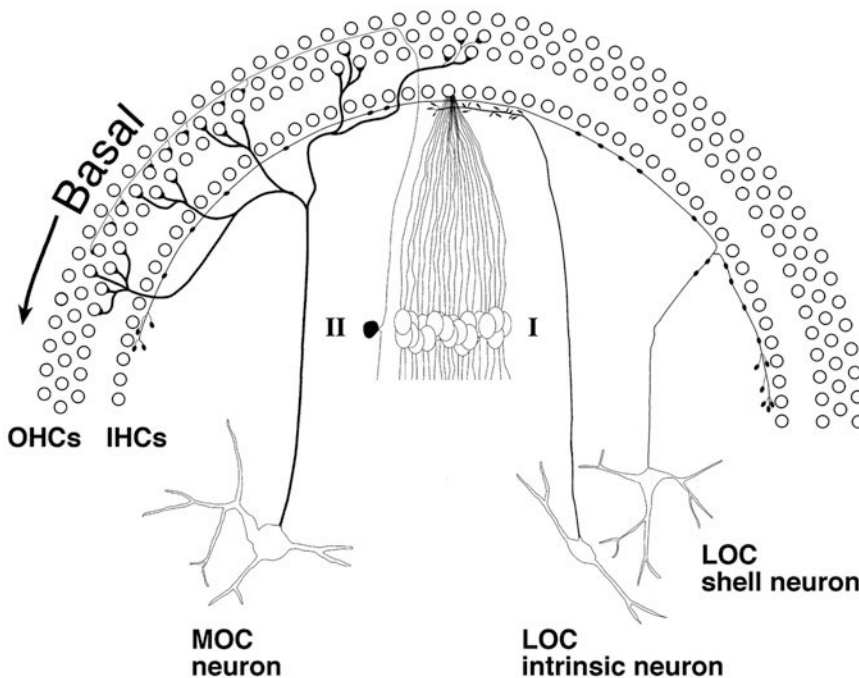
The Olivocochlear System

The olivocochlear bundle provides the organ of Corti with efferent innervation (Figs. 15 and 19; Rasmussen 1946) and plays a critical role in maintaining the normal operation of the cochlea (Figs. 15 and 19). It may introduce nonlinear dynamics into the auditory system (Eggermont 2001). There are two systems of olivocochlear neurons, medial (MOC) and lateral (LOC). The MOC neurons are located medial and ventral to the main nuclei of the SOC in the PO nucleus known as the VNTB and project mainly to the

contralateral cochlea, whereas the LOC neurons are located within or near the LSO and project to the ipsilateral cochlea (Warr 1992; White and Warr 1983).

The MOC neurons constitute a homogeneous population of cholinergic cells and innervate the OHCs (Figs. 15 and 19). About 75% of them originate on the contralateral side with the remainder originating ipsilaterally (Warr 1992; Brown and Levine 2008). They probably receive descending input from the ipsilateral IC and ascending input bilaterally from the VCN.

In rodents, the LOC neurons (Figs. 15 and 19) consist of two distinct types of neurons: *intrinsic* and *shell* neurons (Vetter and Mugnaini 1992; Warr et al. 1997). *Intrinsic neurons* are confined to the ipsilateral LSO and constitute about 85% of all LOC neurons (Brown and Levine 2008; Vetter and Mugnaini 1992; Warr et al. 1997). Most *shell neurons* surround the ipsilateral LSO and constitute the remaining 15% (Vetter and Mugnaini 1992; Brown and Levine 2008; Warr et al.



Anatomy and Physiology of the Mammalian Auditory System, Fig. 19 Scheme of the LOC and MOC neurons, their projections to the IHCs and OHCs, respectively, and afferent fiber types I and II projecting to the

CNC. In rodents, two types of LOC cells occur: intrinsic located inside the LSO and shell located in the margins of the LSO (Figure kindly provided by Dr. Bruce Warr. Adapted from Warr 1992)

1997). (In contrast, in the cat the LOC neurons surround the LSO, and two populations have not been distinguished.) The LOC neurons innervate the type I primary afferent fibers near the region where they contact the IHCs. Virtually all of them originate on the ipsilateral side (Brown and Levine 2008).

The functional role of the MOC neurons may be to enhance transduction or signal detection through an unmasking effect, thus regulating the slow motility of the OHCs and thereby the stiffness of the basilar membrane (Eggermont 2001). Another function may be to protect the inner ear from acoustic injury (Taranda et al. 2009). Although the functional role of the LOC is uncertain, several studies (Safieddine et al. 1997; Safieddine and Eybalin 1992) have shown that these neurons may provide a modulatory effect to the afferent fibers that contact the IHCs.

Cross-References

- Acoustic Timbre Recognition
- Associations and Rewards in the Auditory Cortex
- Attentional Top-Down Modulation, Models of
- Auditory Event-Related Potentials
- Auditory Evoked Brainstem Responses
- Auditory Memory
- Auditory Perceptual Organization
- Auditory Precedence Effect
- Auditory Processing in Insects
- Auditory Prosthesis
- Auditory Sensing Systems: Overview
- Auditory Thalamocortical Transformations
- Auditory-Nerve Response, Afferent Signals
- Brainstem Processing: Overview
- Cochlear Inner Hair Cell, Model
- Context-Dependent Processing in Auditory Cortex
- Cortical Maps, Activity-Dependent Development
- Local Field Potentials: LFP
- Music Processing in the Brain
- Neural Coding of Speech Sounds
- Neuromorphic Sensors, Cochlea

- Peripheral Nerve Interface Applications, Cochlear Implants
- Pitch Perception, Models
- Receptive Field Modeling
- Sensory Coding, Efficiency
- Sound Localization and Experience-Dependent Plasticity
- Sound Localization in Mammals and Models
- Spectrotemporal Receptive Fields
- Spike-Frequency Adaptation
- Stimulus-Specific Adaptation, Models
- Stimulus-Specific Information
- Tinnitus, Models

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Anesthesia, Neural Population Models of

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Definition

General anesthesia is a reversible, drug-induced state of unconsciousness characterized by lack of awareness of surroundings, lack of responsiveness to painful stimuli (nociception), and inability to form memories (amnesia). The change in brain state from wakeful to unconscious produces alterations in cortical electrical activity that can be monitored with electrodes placed on the scalp (electroencephalogram (EEG)) or on the surface of the cortex (electrocorticogram (ECoG)). The goal of neural modelers is to develop equations that describe the gross behavior of spatially averaged populations of neurons during both induction of and recovery from general anesthesia.

Detailed Description

Classes of General Anesthesia

There are two broad classes of anesthetic drugs: inductive agents (such as propofol, etomidate, isoflurane) that produce a slowed sleeplike EEG and dissociative agents (e.g., ketamine, nitrous oxide) that induce a dissociated state with an activated EEG similar to that of REM sleep.

Most commonly used intravenous and volatile agents – such as propofol or sevoflurane – boost inhibition by increasing the influx of chloride ions at gamma-aminobutyric acid (GABA) receptors on postsynaptic membranes (Weir 2006), causing the postsynaptic neuron to become hyperpolarized. In contrast, dissociative drugs are believed to disrupt excitatory synaptic transmission. In both cases, the excitatory – inhibitory balance required for normal brain function has been shifted to favor inhibition.

The Induction: Recovery Trajectory

At low concentrations, most GABAergic agents (e.g., propofol, sevoflurane, etomidate) cause a paradoxical boost in cortical activity (called the “biphasic effect”) across most EEG frequency bands (Kuizenga et al. 2001), with the biphasic peak appearing first in the high beta frequencies (24–28 Hz), then sliding smoothly towards lower frequencies in time (e.g., see Fig. 3 of Koskinen et al. (2005)). With further increase in concentration, the EEG slows as large-amplitude delta-band oscillations (1–4 Hz) become dominant, then changes to an intermittent burst-suppression pattern (bursting activity alternating with relative silence), and finally collapses into a flat-line trace at the deepest levels of comatose anesthesia.

This sequence is reversed as the anesthetic drug is eliminated naturally from the body, allowing the patient to return to consciousness. However, the fact that the recovery of responsiveness generally occurs at a *lower* drug concentration (as measured in the blood) than that required to induce unresponsiveness suggests a hysteresis separation between induction and recovery trajectories. Part of this hysteresis can be explained in terms of the time required for the drug to diffuse

across the blood–brain barrier (Voss et al. 2007) and so can be compensated using pharmacokinetics models (Roberts 2007), but such compensations are typically only partially successful (Ludbrook et al. 1999; Coppens et al. 2010). The remaining hysteresis may be a consequence of a recently proposed “neural inertia” that resists transitions between conscious and unconscious states (Friedman et al. 2010); such distinct induction/recovery paths arise naturally if the brain has access to multiple steady states as suggested by the modeling of Steyn-Ross et al. (1999, 2004).

Cellular Effects of General Anesthetic Drugs

Studies of propofol, halothane, and isoflurane have shown that, at drug concentrations rendering human subjects unresponsive, cerebral blood flow and metabolism are reduced by about 50% (Antkowiak 2002) as a result of global reductions in cortical activity. This is consistent both with in vivo investigations in rat cortex – where sedative-level concentrations were found to suppress neural firing rates by 50–70% (Gaese and Ostwald 2001) – and with cultured brain-slice studies in which low concentrations of general anesthetics (GABAergic agonists propofol, halothane, isoflurane, enflurane, sevoflurane, etomidate, ethanol, and pentobarbital and the non-GABAergic agent ketamine) significantly decreased mean firing rates (Antkowiak 2002).

All anesthetic drugs influence cellular function in a number of different ways, but the major mechanism for GABAergic suppression of firing rates is believed to be the prolongation of the opening of chloride channels on the postsynaptic neuron, thus causing a substantial increase in negative charge transfer (by a factor of 2–4 times control at clinically relevant concentrations (Kitamura et al. 2003; Banks and Pearce 1999)) during the inhibitory postsynaptic current (IPSC) pulse.

Dissociative drugs reduce excitatory transmission by blocking *N*-methyl-d-aspartate (NMDA) glutamate channels, which probably has a significant role in producing the characteristic dissociated anesthetic state (Petrenko et al. 2013); however, these drugs also have other effects such as inhibition of hyperpolarization-activated

cyclic nucleotide-gated (HCN1) channels (Chen et al. 2009) or increased potassium channel opening (Gruss et al. 2004).

Modeling Anesthetic Effects

The challenge for anesthesia modelers is to bridge the scales from the microscopic cellular drug effects to the consequent *macroscopic* population behaviors detected with scalp or cortical electrodes. By considering spatially averaged (“mean-field”) properties of cortical tissue, we can avoid the need (and computational expense) of attempting to explicitly represent myriads of individual neurons (as is done in neural networks). There is a steadily growing interest in applying mean-field methods to the challenge of understanding anesthesia; see Foster et al. (2008) and Steyn-Ross et al. (2011) for reviews.

The notion of *neural fields* dates from foundation work by Wilson and Cowan (1972) that modeled the brain as homogenous populations of excitatory and inhibitory neurons. The first attempt at modeling propofol anesthesia by Steyn-Ross et al. (1999) incorporated prolongation of inhibitory response into the mean-field neural model of Liley et al. (1999); it predicted the possibility of multiple steady states with distinct first-order phase transitions between activated (“conscious”) and inactivated (“unconscious”) states and provided a possible explanation for the hysteretically separated biphasic power surges observed at loss and recovery of consciousness (Kuizenga et al. 2001).

Subsequent work by Bojak and Liley (2005) on isoflurane anesthesia showed that, for suitable choices of cortical parameters, a smooth descent into unconsciousness can also generate a biphasic drug response. Using an alternative mean-field model, Hutt and colleagues (Hutt and Schimansky-Geier 2008; Hutt and Longtin 2010) predicted that biphasic power surges can be expected for both the bistable (jump transition) and monostable (smooth) inductions of anesthesia.

General anesthetic agents are widely used to treat seizures, but paradoxically, some anesthetics (e.g., enflurane) can also provoke cortical seizures when the patient is deeply anesthetized. Liley and

Bojak (2005) and Wilson et al. (2006) used mean-field modeling to show that subtle changes in the shape and duration of the drug-induced inhibitory postsynaptic response can explain why enflurane, but not isoflurane, is seizurogenic.

An important part of general anesthesia is the suppression of noxious stimuli. A practical index of antinociception has been developed from a mean-field model (Liley et al. 2010) that informed construction of an autoregressive – moving-average (ARMA) noise-driven filter whose output approximates the scalp-recorded EEG. The mean filter frequency tracks the level of propofol-induced hypnosis (“cortical state”), while the decrease in required noise intensity (“cortical input”) tracks the concentration of a coadministered analgesic agent (remifentanyl). This computed “cortical input” signal is presumed to be a measure of cortical stimulus, both noxious and normal, entering from the thalamus, and potentially allows differentiation between hypnotic and analgesic drug effects.

The unconscious state of anesthesia and of deepest natural sleep are both characterized by large-amplitude, slow (0.5–4 Hz) delta waves of EEG activity. The source of these slow waves is unknown but is generally supposed to originate from gradual alternations in depolarizing and hyperpolarizing ionic currents. By introducing a slow ionic gating variable into a mean-field model for desflurane anesthesia, Molaee-Ardekani et al. (2007) demonstrated emergence of realistic slow waves. A quite different slow-wave mechanism has been proposed by Steyn-Ross et al. (2013): if inhibitory gap junctions are included in the two-dimensional cortical sheet, then a Turing (pattern-forming) instability can interact with a weakly damped low-frequency Hopf instability to produce turbulent slow-wave activity across the cortex. Anesthetic-induced closure of inhibitory gap junctions (Wentlandt et al. 2006) is predicted to weaken the Turing instability in favor of the Hopf oscillation.

There has been interest in modeling some of the specific details of EEG spectral changes caused by various general anesthetic drugs, for example, the displacement in alpha peak frequency induced by ketamine (Bojak et al. 2013)

or propofol (Hindriks and van Putten 2012; Hutt 2013) and the burst-suppression pattern of deep anesthesia (Liley and Walsh 2013).

Increasingly there has been a realization that general anesthesia may disrupt neuronal networks in an anatomically specific fashion (Kuhlmann et al. 2013; Lee et al. 2013) and that the current homogenous and isotropic neuronal population models might need to include aspects of network topology. This has led to attempts to link EEG patterns probabilistically with underlying anesthetic effects on inhibitory and excitatory neuronal groups – this should provide a quantitative basis for the estimation of model parameters. At an abstract level, dynamic causal-modeling methods have been employed (Moran et al. 2011; Boly et al. 2012), but a more direct Bayesian approach – which has been used for natural sleep (Dadok et al. 2013) – could be applied to anesthesia EEG.

Cross-References

- Bifurcations, Neural Population Models and
- Epilepsy, Neural Population Models of
- Gap Junctions in Small Networks
- Gap Junctions, Neural Population Models and
- Neural Population Model
- Pattern Formation in Neural Population Models
- Phase Transitions, Neural Population Models and
- Sleep, Neural Population Models of

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Animal Calls

► Pulse-Resonance Sounds

Animal Models of Pain

► Biomechanical Model of Low Back Pain

Anomalous Rectifier Potassium Channels

► Inward Rectifier Potassium Channels

Anti-Hebbian Learning

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Definition

Anti-Hebbian learning is a form of activity-dependent synaptic plasticity that is defined as the opposite of Hebbian learning. Hebbian learning is commonly defined as follows: correlated activation in the pre- and postsynaptic neurons leading to the strengthening of the connection between the two neurons. However, the original definition offered in Hebb (1949) talks about the increase in the presynaptic neuron's efficiency of eliciting activity in the postsynaptic neuron, under the same correlated firing condition. These two definitions (strengthening of connection vs. increased efficiency) are compatible only when the presynaptic neuron is excitatory. They are contradictory when the presynaptic neuron is inhibitory: increased connection strength (weight, efficacy) corresponds to decreased efficiency in

eliciting response. Assuming the original definition of Hebbian learning, we can define anti-Hebbian learning as a form of synaptic plasticity where correlated activation in the pre- and post-synaptic neurons leads to the reduction in the efficiency of the presynaptic neuron's ability to elicit activation of the postsynaptic neuron.

Detailed Description

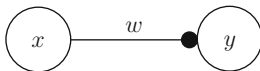
In this entry, we will review computational formulations of anti-Hebbian learning and their theoretical implications. We will also briefly touch upon neurobiological correlates of the learning mechanism. The literature on anti-Hebbian learning is not as rich as that on Hebbian learning. A review of Hebbian learning by Frégnac (2003) includes a brief discussion on the neurobiological bases of anti-Hebbian learning. See Földiák (1990) for a computational treatment of the subject and Palmieri et al. (1993) for a review.

Basic Formulation

Consider a simple configuration with a single presynaptic neuron x connecting to a single post-synaptic neuron y with synaptic weight w as shown above (Fig. 1). Anti-Hebbian learning is the same as Hebbian learning, except for the flip of the sign.

$$\frac{dw}{dt} = -\eta xy, \quad (1)$$

where the learning rate η is a small, fixed, positive value. The neuronal activities x and y are normally assumed to be positive (or zero), but for purely computational purposes, they can be negative values as well. In Hebbian learning, adaptive threshold or normalization approaches are used



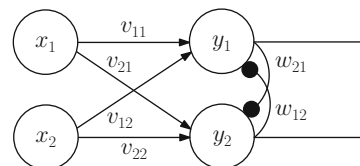
Anti-Hebbian Learning, Fig. 1 A pair of neurons forming an anti-Hebbian connection

to check unbounded growth in the synaptic weight. However, in anti-Hebbian learning, such a check is unnecessary since the mechanism is inherently stable (Földiák 1990). At first glance, it appears that the weight w can tend toward $-\infty$, but this will never happen because high levels of inhibition will shut off y after a certain point and thus w will not change any further thereafter. When x and y are allowed to be negative, w can increase under the same learning rule. Some formulations prevent this from causing infinite growth by imposing a limit (w is assumed to be negative and it is reset to 0 as soon as it becomes positive; Földiák 1990), but others do not include such a limit (e.g., Girolami and Fyfe 1996).

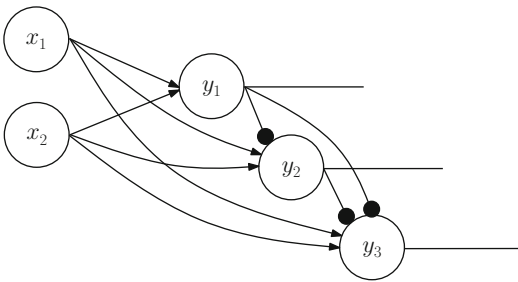
Theoretical Perspectives

Anti-Hebbian learning is usually combined with Hebbian learning to produce interesting theoretical and practical results. Figure 2 below shows such an example (adapted from Földiák 1990). In this figure, two downstream neurons y_1 and y_2 receive afferent input from x_1 and x_2 through Hebbian synapses (with weights v_{ij}) and exchange activations via anti-Hebbian lateral connections (with weights w_{ij}). (The subscripts ij on the weights indicate the target $[i]$ and source neuron index $[j]$, respectively.)

Földiák showed that the above network can learn to decorrelate the output neurons' activity (sparse coding in neurons y_i), which results in the learning of afferent representations (v_{ij}) that are components that make up the input mixtures. The model included an anti-Hebbian rule similar to Eq. 1 with an added threshold (w_{ij}), a Hebbian



Anti-Hebbian Learning, Fig. 2 Neurons connected with Hebbian (arrows) and anti-Hebbian synapses (discs). (Simplified from Földiák 1990)



Anti-Hebbian Learning, Fig. 3 A hierarchy of neurons y_i with Hebbian afferent connections (arrows) and anti-Hebbian connections in a cascade (discs). (Adapted from Carlson 1990)

rule with weight decay (v_{ij}), and a dynamic neural activation equation ($\frac{dy_i}{dt}$) with adaptive threshold and sigmoid nonlinearity (for details, see Földiák 1990).

Now consider a hierarchical network shown above (Fig. 3). Hebbian learning is known to extract the first principal component of the inputs (Oja 1982), so neuron y_1 would serve this role. Using a hierarchical network like Fig. 3 with anti-Hebbian connections arranged in a cascade, second, third, and subsequent principal components of the input can be found (see Carlson 1990 for a review and details). The main idea is that once y_i learned the i -th principal component, and y_{i+1} is decorrelated with $y_1, y_2, \dots, y_i$ through anti-Hebbian connections (note that y_3 receives anti-Hebbian connections from both y_1 and y_2), y_{i+1} will find the $i + 1$ -th principal component.

For a review of more complicated network topologies that involve anti-Hebbian learning, see Palmieri et al. (1993).

Neurobiological Underpinnings

As Hebbian learning is usually associated with long-term potentiation (LTP), anti-Hebbian learning is typically explained by long-term depression (LTD). LTP is a phenomenon where high frequency stimulation of the presynaptic neuron leads to a prolonged increase in synaptic efficacy (Bliss and Collingridge 1993). LTD is the

opposite, where low-frequency stimulation causes a prolonged decrease in synaptic efficacy (Dudek and Bear 1992); thus, it fits the anti-Hebbian profile.

Examples of LTD associated with anti-Hebbian mechanisms have been found in the mammalian cerebellum (e.g., mouse and rat) and also in the electrosensory lobe (ELL) in the teleost electric fishes, and these LTD mechanisms are thought to be playing an anti-Hebbian role (see Frégnac 2003 for a brief review).

In some cases, LTP can also be associated with a form of anti-Hebbian learning, when LTP is induced not by correlated activation but by pre-synaptic firing not being met by or negated by the postsynaptic activity. Such a phenomenon has been observed in the hippocampus and has been dubbed anti-Hebbian LTP. Kullmann and Lamsa (2007) provide an extensive review on this topic and provide a comparison of anti-Hebbian LTD and anti-Hebbian LTP.

Finally, spike timing-dependent plasticity (STDP; see Caporale and Dan 2008 for a review) has also been linked to anti-Hebbian learning. STDP is a short-term synaptic plasticity mechanism where depending on the ordering of pre- and postsynaptic events, either LTP or LTD can entail. LTP is induced when the presynaptic activity precedes postsynaptic activity and LTD when the ordering is reversed. Some views the LTD part of STDP as implementing an anti-Hebbian rule (see Nelson 2004 for a discussion).

Applications of Anti-Hebbian Learning

Anti-Hebbian learning has been applied to several signal and data processing tasks including vision and speech processing. Girolami and Fyfe (1996) used anti-Hebbian rule to learn finite impulse response (FIR) filter coefficients and applied the technique to blind source separation in the speech recognition domain. Schraudolph and Sejnowski (1992) used anti-Hebbian rule to learn invariances in disparity tuning for stereo vision. Földiák (1990) combined Hebbian and anti-Hebbian rule to learn sparse representations from overlapping visual inputs.

Cross-References

- [Hebbian Learning](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)

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Aperture Problem

- [Somatosensory Cortex: Neural Coding of Motion](#)

Application of Declarative Programming in Neurobiology

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Definition

The main technique in computational neuroscience is imperative programming, which is often used to implement simulations of dynamics, and describes *how* a computation is performed. A complement to this approach is declarative programming. Declarations provide descriptions of relationships between elements, effectively describing *what* the computation should accomplish. The use of declarative programming for modeling biological processes is still in its infancy (Fisher and Henzinger 2007) yet has shown itself to be a valuable first step for analysis of the seemingly impenetrable complexity of molecular interactomics: the interplay of the myriad proteins and signaling species in the cell. Declarative programming can also be used at the connectomic level of understanding connections among neurons or among brain areas.

Detailed Description

Declarative Programming

The *declarations* of a declarative program describe the relationships between system elements. Because of this descriptive nature, a model implemented in a declarative program may be considered as a system *specification*. Many declarative programming languages utilize term-rewriting logic: the declarations are rewrite laws that specify how one term should be replaced by another. Abstract rewriting systems are written with arrows, specifying that the left-hand side (LHS) is to be replaced by the term

on the right-hand side (RHS). Other notations, such as Backus-Naur Form, utilize some variant of an equal sign to specify that RHS is replaced by LHS.

Crucially, because the declarations are descriptions of system properties, the specification can be used not only for simulation but also for analyses such as state-space search and temporal-logic model checking (explained below; for a general reference see Huth and Ryan 2004). Term-rewriting declarative languages are readily used for expressing data-driven models constructed directly from experimental observations. These models do not require an overarching conceptual framework or preconceived hypothesis, allowing the enormous amounts of data generated by neurobiological experiments to be directly entered. This allows the data to “speak for itself” and provides a model that can be used as a tool to help develop subsequent hypotheses.

The first term-rewriting language was the λ -calculus, developed in the 1930s by Alonzo Church (Cardone and Hindley 2006). Since then several other term-rewriting, declarative programming languages have been developed. Some well-known examples are Scheme (<http://www.r6rs.org/>), Alloy (<http://alloy.mit.edu/alloy/index.html>), Simile (<http://www.simulistics.com/tour/declarative.htm>), and ECLiPSe (<http://eclipseclp.org/index.html>). One declarative programming language that has been used effectively for modeling molecular interactions and neurobiological processes is Maude (<http://maude.cs.uiuc.edu/>; Clavel et al. 2007).

A specification in Maude is based on an underlying algebra, which is defined by *sorts* (data types) and by *operations* that are allowed for each sort (e.g., natural numbers – sort, can be added together – operation). Preset algebras such as the natural numbers are available, but new algebras can be defined by the user. Declarations in Maude are written in terms of the underlying algebra and can be expressed either as equations or as rules. Equations in Maude specify functional relationships that simplify the state of the system being modeled, while rules specify transitional relationships that change the state of the model

system. For example, an equation could specify that 2 apples plus 4 apples plus 3 apples equals 9 apples, while a rule could specify that 9 apples can transition to an apple pie. Equations and rules can be unconditional (`eq` and `rl`, respectively) or conditional (`ceq` and `cr1`). For example, a conditional rule could specify that 9 apples can transition to an apple pie, but only if mom is available to bake it. While an unconditional equation or rule applies whenever its LHS is present, a conditional rule requires both the LHS and the required conditions.

All rewrite systems have rules (a.k.a. syntax) that transition the system state and evaluations (a.k.a. semantics) that can reduce the state, in whole or in part, to its underlying value at arbitrary times (Kain 1972). Another characteristic of Maude is that equations (i.e., evaluations) *must* execute whenever they apply while applicable rules may execute or not. Rules, by executing, can transition the system to a state in which equations become applicable that were not so in the previous state. In using Maude for simulation, all applicable rules would ultimately execute according to a *fairness criterion*: every applicable rule must execute once before any other rule can execute twice. In using Maude for analyses, such as state-space search or logical model checking, the rules execute in all possible combinations and orders. Because rules cause state transitions, Maude thereby elaborates the state transition tree implied by the specification and later searches this tree for specific states or to verify certain temporal-logic propositions.

Maude has been used to specify and analyze a broad range of complex engineered systems used for computer network security, encryption, and avionics, among others (Meseguer 2012). Maude is also used to model other programming languages, and analysis of a Maude model can verify that a language behaves as intended. This type of analytical capability suggests how Maude can be used to assess interactomic “programs,” so as to determine where they have vulnerabilities, predicting sites for potential failure which would produce disease, as well as sites where intervention could compensate for these failures,

predicting sites where pharmacological intervention would be of value.

Declarative Models of Neurobiological and Neurodegenerative Processes

Maude has been used to model several biological processes (Eker et al. 2002; Talcott 2008). An initial neurobiological application explores the synaptic plasticity thought to underlie fear conditioning and its extinction (Anastasio 2013b). In that microconnectomic model, rules specified synaptic weight changes while equations specified changes in neural responses caused by weight changes. Thus, each state of the model system had a different one of the many possible configurations of synaptic weights. This particular model had only nine synapses, which were allowed only a limited number of discrete weights, so the state space was large but still small enough to permit exhaustive search. Analysis via state-space search provided testable hypotheses by revealing which of these very many synaptic weight configurations were compatible with fear conditioning followed by extinction.

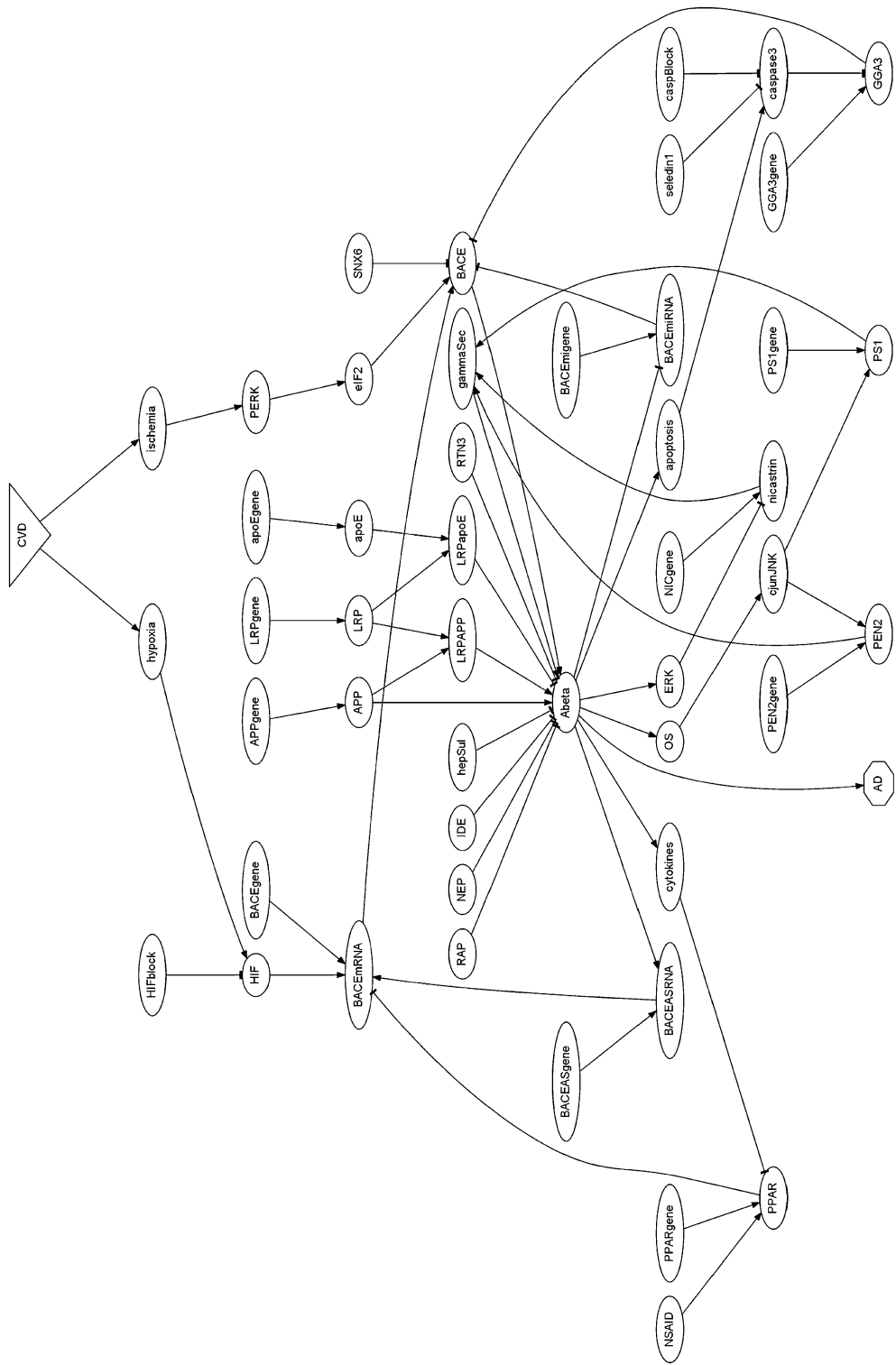
More recent neurobiological applications involve the food-intake control system (Tabebordbar and Anastasio 2016) and the monoaminergic neurotransmitter system (Camacho and Anastasio 2017). The system of hypothalamic neurons, distinguishable both in terms of sub-nucleus and neurotransmitter/neurohormone profile, was specified in Maude. State-space analysis revealed activation configurations consistent with new experimental findings that contradicted current understandings. For example, high food-intake had been associated only with high levels of activity of arcuate nucleus neurons secreting Agouti-related peptide (AgRP neurons). Search of the model state-space found many configurations consistent with that relationship but also found some configurations consistent with new findings that *low* AgRP neuron activity also can be associated with high food intake. The model showed how overall activity patterns, comprising all of the neurons modeled, which were consistent with high food-intake differed between those having low versus high AgRP neuron activity. The differences stand as

model predictions. A similar approach based on a model of the monoaminergic neurotransmitter system was used to study neuroadaptation to chronic antidepressant administration due to changes that are known to occur in various neurotransmitter/neurohormone receptor types. State-space analysis found many configurations adapted to chronic selective serotonin reuptake inhibitors (SSRIs) that nevertheless did not have serotonin levels that had been elevated to therapeutic levels. These findings provide an explanation for the low clinical efficacy of SSRIs, since elevated serotonin is thought to be the therapeutic mechanism of SSRIs. The analysis also uncovered chronic antidepressant combinations that should be more effective than single SSRIs in treating depression.

Maude models of some of the molecular interactions that underlie Alzheimer Disease (AD) have also appeared (Anastasio 2011, 2013a, 2014a, b, 2015). These studies were based on the amyloid hypothesis, which posits that AD results from buildup of the amyloid-beta peptide (Hardy and Selkoe 2002). A subset of the molecular and cellular interactions believed to underlie the regulation of amyloid-beta is diagrammed in Fig. 1.

Space constraints prohibit description of all of these interactions. They are based directly on findings from the primary literature and described in detail in Anastasio (2011). Each of 36 declarations specified how the level of biological activity of one model element, representing a molecular species, was determined through interaction among the others. Many model elements could assume multiple levels, so the entire state space was too large to be managed on a desktop computer. As an alternative to high-performance computing, the declarations, first specified as equations, were then divided into subsets that could be converted to rules. In this way, the space of configurations involving a subset of interactions could be analyzed using state-space search and temporal logical, while the rest of the interactions took place in the background.

An example of an equation in the Maude model of amyloid-beta regulation is



Application of Declarative Programming in Neurobiology, Fig. 1 Schematic diagram of many of the cellular and molecular interactions that regulate the level of the peptide amyloid-beta

```
ceq [PPARexpress] : PPARgene(G) NSAID
(X) cytokine(Y) PPAR(Z) =
PPARgene(G) NSAID(X) cytokine(Y) PPAR
(max(0, G + (X - Y)) * G)
if Z /= max(0, G + (X - Y)) * G.
```

This equation, labeled `PPARexpress`, describes the interaction that determines the level of the peroxisome proliferator-activated receptor (PPAR). The operator `PPAR(Z)` assigns integer level `Z` to PPAR, and the equation describes how that level is determined by the presence of its gene `PPARgene` and the levels of cytokines and nonsteroidal anti-inflammatory drugs (NSAIDs). This equation is conditional (`ceq`) and executes only if doing so changes the level assigned by PPAR. To convert this conditional equation to a conditional rule, it would be relabeled `cr1` and `=` would be replaced with `=>`.

The model depicted in Fig. 1 incorporates the hypothesis that mild cerebrovascular disease (CVD) can trigger amyloid-beta accumulation (Scheibel et al. 1989; de la Torre 2009). Simulations and analysis were focused on compounds known to modulate the activities of model elements. Specifically, cilnidipine blocks hypoxia-inducible factor (HIF) (Oda et al. 2009) while ifenprodil blocks caspase 3 (`casp3`) (Dave et al. 2003). It was of interest to see whether a HIF-blocker or a `casp3`-blocker would be more effective in reducing the rise of amyloid-beta in the presence of CVD in the model.

In the model, amyloid-beta rose from its normative level of 4 to the pathological level of 8 in the presence of CVD (Table 1). NSAIDs, known to increase PPAR levels in vitro (Sastre et al. 2006), and HIF-blocker each separately held the rise of amyloid-beta to 5 while `casp3`-blocker only held it to 7. NSAID and HIF-blocker together held amyloid-beta to its normative level of 4 but `casp3`-blocker provided no further benefit in combination with NSAID or HIF-blocker or both.

These simulations showed that an HIF-blocker was more effective than a `casp3`-blocker in reducing the rise of amyloid-beta in the face of CVD. We then used temporal-logic analysis to show why this effect occurs. Temporal-logic analysis

Application of Declarative Programming in Neurobiology, Table 1 Modeling the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and blockers of hypoxia-inducible factor and caspase 3 (HIF-blocker and `casp`-blocker) on the level of amyloid-beta in the presence of incipient cerebrovascular disease (CVD)

CVD	NSAID	HIF-blocker	Casp-blocker	Amyloid-beta
0	0	0	0	4
1	0	0	0	8
1	1	0	0	5
1	0	1	0	5
1	0	0	1	7
1	1	1	0	4
1	1	0	1	5
1	0	1	1	5
1	1	1	1	4

provides answers to questions such as whether a particular property is always true, never true, or only true after some other property becomes true. For the AD model, temporal-logic analysis was used to determine the value of propositions of the form $\sim \text{hasAPO} \text{ U } \text{cytACT}$, where `hasAPO` is the property that apoptosis has occurred, `cytACT` is the property that cytokines have been activated, and $\sim$ and `U` are the temporal-logic operators “not” and “until,” respectively. Maude demonstrated that this proposition is true, meaning that apoptosis will not occur until cytokines are activated in the model. That is important because apoptosis activated caspase 3 in the model. Similar analyses revealed that cytokines were not activated if HIF-blocker was present. Taken together, the temporal-logic analyses show that `casp3`-blocker was not effective in combination with HIF-blocker because HIF-blocker already prevented caspase 3 activation.

These analyses made several testable predictions:

1. An HIF-blocker will be effective in reducing amyloid-beta levels in the presence of incipient CVD.
2. A `casp`-blocker will be less effective than an HIF-blocker.

3. A casp-blocker will provide no further benefit if administered in conjunction with an HIF-blocker.
4. NSAIDs will be more effective in combination with an HIF-blocker than alone.

Conclusion

Declarative programming can be applied in the simulation and temporal-logic analysis of complex neurobiological processes, whether normal or pathological. The phenomenon at issue in the above example, the regulation of amyloid-beta, occurs predominantly on the molecular level. However, term-rewriting and declarative programming can also be used to create and analyze models of neurobiological phenomena at all scales, from molecular to cellular to network to whole brain, or to create multiscale models in order to understand phenomena arising from interactions across multiple scales.

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Applications of Information Theory to Analysis of Neural Data

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Definition

Information theory is a practical and theoretical framework developed for the study of communication over noisy channels. Its probabilistic basis and capacity to relate statistical structure to function make it ideally suited for studying information flow in the nervous system. It has a number of useful properties: it is a general measure sensitive to any relationship, not only linear effects; it has meaningful units which in many cases allow direct comparison between different experiments; and it can be used to study how much information can be gained by observing neural responses in single trials, rather than in averages over multiple trials. A variety of information-theoretic quantities are commonly used in neuroscience – (see entry ► [“Summary of Information-Theoretic Quantities”](#)). In this entry we review some applications of information theory in neuroscience to study encoding of information in both single neurons and neuronal populations.

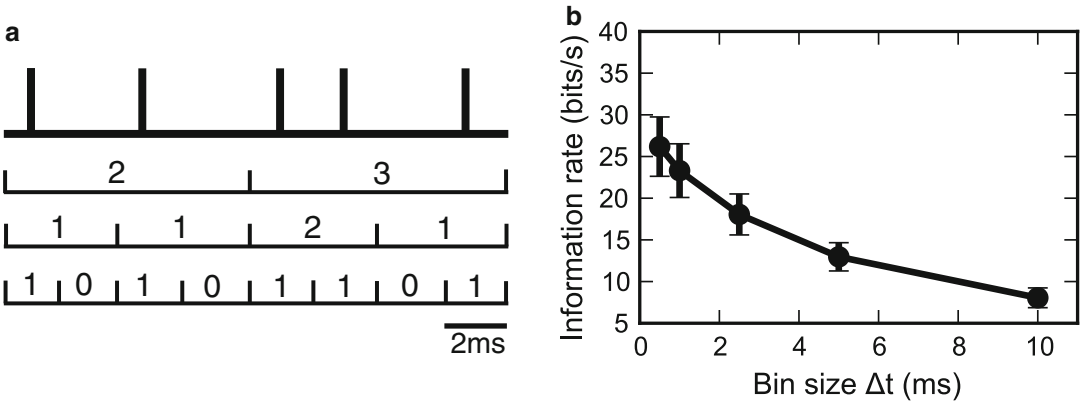
Detailed Description

Information Analysis of Spike Trains to Investigate the Role of Spike Times in Sensory Coding

Mutual information is a widely used tool to study how spike trains encode sensory variables.

A typical application of mutual information to spike train analysis is to use it to compare the information content of different representations of neural responses that can be extracted from spike trains. The neural code used by a neuron is often defined operationally as the smallest set of response variables that carries all (or almost all) the information contained in the spike train of the neuron. Mutual information is used to quantify the information content of increasingly complex representations of the neural response, and the simplest representation that carries the most information is chosen as the putative neural code.

An example of this general approach is the investigation of the role of spike times in encoding information. The most established hypothesis on how sensory information is represented in the brain is the spike count-coding hypothesis (Adrian 1928) which suggests that neurons represent information by the number of spikes discharged over some relevant time window. Another hypothesis is the spike timing encoding hypothesis, which suggests that the timing of spikes may add important information to that already carried by spike counts (Rieke et al. 1997; Panzeri et al. 2001). Information theory can be used to understand the role of spike times in carrying sensory information, by using it to characterize the temporal resolution needed to read out the information carried by spike trains. This can be performed by sampling the spike train at different temporal precisions, Δt , (Fig. 1a) and computing the information parametrically as a function of Δt (Ruyter et al. 1997). The temporal precision required to read the temporal code then can be defined as the largest Δt that still provides the full information obtained at higher resolutions. If this precision is equal to the overall length of the window over which neurons carry information, then information is carried only by the number of spikes. As an example, we carried out this type of analysis on the responses of neurons from the VPM thalamic nucleus of rats whose whiskers were stimulated by fast white noise deflections (Montemurro et al. 2007). We found that the temporal precision Δt at which neurons transmitted information about whisker deflections was finer than 1 ms (Fig. 1b), suggesting that these neurons



Applications of Information Theory to Analysis of Neural Data, Fig. 1 *Effect of temporal resolution of spike times on information. (a)* The response of a neuron is initially recorded as a series of spike times. To investigate the temporal resolution at which spike times carry information, the spike train is binned at a variety of different time resolutions, by labeling the response at each time with the number of spikes occurring within that bin, thereby transforming the response into a discrete integer

sequence. **(b)** The information rate (information per unit time) about whisker deflections carried by VPM thalamic neurons as a function of bin width, Δt , used to bin neural responses. Information rate increased with bin resolution up to 0.5 ms, the limit of the experimental setup. This shows that a very fine temporal resolution is needed to read out the sensory messages carried by these thalamic spike trains. (Figure reprinted with permission from Ince et al. 2010)

use high-precision spike timing to carry information.

Information Analysis of Local Field Potentials to Examine the Information Content of Network Oscillations

Information analysis in neuroscience is not limited only to spike train analysis, but it has been used also to study the measure of massed population activity, such as local field potentials (LFPs) (Buzsáki et al. 2012). LFPs are operationally defined as the low-pass filtered extracellular potential measured by an extracellular intracranial electrode. There are at least three reasons why LFPs are widely used in neuroscience. The first is that they are more easily and stably recorded in chronic settings than is the spiking activity of individual neurons. The second is that the LFP captures key integrative synaptic processes and aspects of subthreshold neural activity that cannot be measured by observing the spiking activity of a few neurons alone (Einevoll et al. 2013). The third is that LFPs are more sensitive to network oscillations than measures of spiking activity from small populations. LFPs from a sensory area typically show a power spectrum containing

fluctuations over a wide range of frequencies, from <1 to 100 Hz or so. Given that the power of oscillatory activity typically increases during the presentation of a sensory stimulus, many authors have speculated that this oscillatory activity plays a role in brain communication and in particular in sensory-related computations. However, understanding the function of these oscillations has remained elusive and controversial. To gain insights into the function of oscillations in sensory encoding, it is important to understand how they contribute to the representation of the natural sensory environment.

This problem can be addressed by quantifying the oscillation power in any given trial in response to different stimuli and then computing the information gained by the power at each frequency. Since the power is a continuous variable, the computation of its information is potentially more difficult than the one based on discrete variables like the spike train ones described above. There are at least two ways to solve this problem. The first is to discretize the power in a number of equi-populated bins and to use bias corrections to eliminate the bias. The second is to fit the data to a parametric distribution. In this case, it is worth

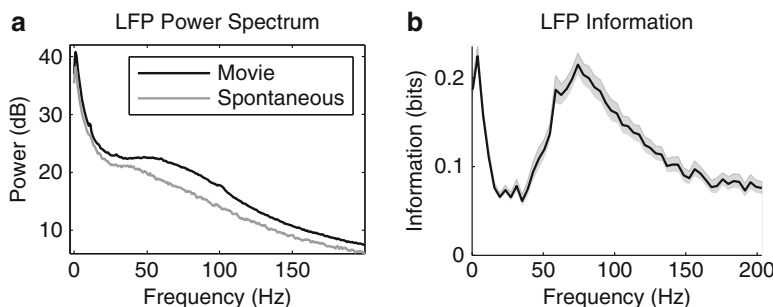
reminding that the power computed with most spectral methods follows a chi-square distribution, and thus, its square or third can reasonably be well approximated by a Gaussian distribution (Magri et al. 2009). This makes the computation of information relatively straightforward. The third potential approach is to use binless methods such as Nearest Neighbors approaches (Kraskov et al. 2004). We tried out these methods extensively on computation of information in power of LFPs, obtaining very similar results with all approaches (see, e.g., Magri et al. 2009).

We applied this method to recordings from primary visual cortex of anesthetized macaques during stimulation with naturalistic color movies (Belitski et al. 2008; Magri et al. 2012a). This revealed, for the first time, how information about the naturalistic sensory environment is spread over the wide range of frequencies expressed by cortical activity. Although the broadband nature of the spectrum suggests a contribution to coding from many frequency regions, we found that only two separate frequency regions contribute to coding: the low-frequency range and the gamma range (Belitski et al. 2008; see Fig. 2 below). Interestingly, low- and high-frequency ranges act as perfectly complementary or “orthogonal” information channels: they share neither signal (i.e., stimulus information) nor “noise” (i.e., trial to trial variability for a fixed stimulus). This finding has several implications. First, it shows that, despite the broadband spectrum,

only a small number of privileged frequency scales are involved in stimulus coding. Second, it suggests that high-frequency and low-frequency oscillations are generated by different stimulus-processing neural pathways. Third, the finding that different frequency bands code different sensory features in separate, truly independent information channels reinforces the concept of “cortical multiplexing” that we proposed above.

Information Analysis of Imaging Data to Study Neural Population Coding or Coupling Between Different Neural Signals

The analysis tools that we have described above have, to date, largely been applied to spike train and time series data recorded using electrophysiological techniques. However, in recent years, imaging technologies have been developed which are capable of resolving neural signaling at systems’ cellular and subcellular resolutions on a single trial basis (Denk et al. 1990, 1994; Stosiek et al. 2003; Chen et al. 2013). One way to apply information-theoretic tools to the analysis of such imaging data is to convert the data to a “spike train,” for instance, by applying an algorithm for the detection of action potential-evoked calcium transients to calcium imaging data (Oñativia et al. 2013). Such an approach has been used to perform information-theoretic analysis of simultaneously recorded populations of cerebellar Purkinje cell complex spikes extracted from in vivo calcium imaging movies (Schultz et al. 2009). However,



Applications of Information Theory to Analysis of Neural Data, Fig. 2 The visual information carried by LFP power at different frequencies. (a) LFP power spectrum of V1 recordings anesthetized macaques either during spontaneous activity in the dark (dashed line) or during the

presentation of a color movie stimulus (solid line). (b) Information about the movie stimulus carried by LFP power at different frequencies. The area indicates the SEM. (Reproduced from Magri et al. 2012a)

the use of imaging data may also allow a wider set of questions to be approached than can be examined electrophysiologically, by directly examining patterns of pixel intensities.

Another interesting application of information theory to neuroimaging data regards its use for understanding the nature of the coupling between neural activity and fMRI responses. In fact, although there is evidence that fMRI BOLD responses reflect neural activity, it is not clear whether the BOLD signal reflects only the total power of massed neural activity, or only the power in a given band, or rather the relationships between powers of neural activity in different frequency bands. This problem can be cast theoretically into quantifying whether more information about BOLD can be gained from simultaneously observing the power of neural activity in two or more bands of neural activity than the information gained by observing either band alone. Because mutual information captures all the ways a signal may statistically relate to another, finding that another signal carries extra information demonstrates that this signal truly provides some information that cannot be possibly obtained from the first one. This does not necessarily hold when using methods that capture only specific relationships between signals. For example, an increase in predictability based on linear models may reflect both additional information from the second regressor as well as information that was already present in the first regressor but was not captured by the linear assumption. Application of this idea to simultaneous recording of LFPs and fMRI BOLD in primary visual cortex showed that the beta and alpha bands carry information about BOLD that complements that carried by the gamma band, the band that most correlates to the BOLD signal (Magri et al. 2012b).

Since imaging signals such as fMRI have an analogue rather than discrete nature, the practicality of application of information theory to analogue brain signals is crucially dependent upon the development of appropriate regularization and dimensionality reduction algorithms. These might stem from simple yet efficient discretization algorithms (Belitski et al. 2008; Magri et al. 2009),

Nearest Neighbors regularization algorithms (Kraskov et al. 2004), the use of manifold learning techniques for nonlinear dimensionality reduction (Roweis and Saul 2000; Seung and Lee 2000; Gan 2006), and/or the evaluation of information through a decoding step (Quiñero Quiroga and Panzeri 2009).

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Artificial Retina

- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)
- [Visual Prosthesis, Subretinal Devices](#)

Artificial Silicon Retina (ASR)

- [Visual Prosthesis, Subretinal Devices](#)

Artificial Vision

- [Prosthetic Vision, Perceptual Effects](#)
- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)

Associations and Rewards in the Auditory Cortex

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Definition

In psychology, the term *association* refers to a connection between different elementary mental entities (sensations, thoughts, feelings; Dudai 2002). Aside from innate, reflex-like associations, novel associations are typically acquired during learning. In Pavlovian/classical conditioning, a stimulus-stimulus association is formed by repetitively pairing an initially neutral stimulus with a biologically significant unconditioned stimulus that automatically triggers an unconditioned behavioral response. In instrumental/operant conditioning, a stimulus-response association is formed in the presence of reinforcers. Reinforcers can be either positive, such as water, food, money, and brain stimulation reward, and result in an increase in the probability of a response to the stimulus. Negative reinforcers (e.g., footshocks, airpuffs, money loss) decrease the probability of a response to the stimulus. If the reinforcer is removed, the learned associations risk extinction.

Detailed Description

Classical View of Brain Structures Reflecting Associations and Reinforcement

Traditionally associative functions are assigned to the so-called association cortex (Creutzfeldt 1983). Inspired by “associationism” (the philosophical doctrine that the mind learns and constructs the world bottom up by associating mental entities) and based on anatomical considerations, Flechsig originally defined the association cortex as that part of the cerebral cortex that appeared to lack direct afferences from the senses and efferences to peripheral motor structures. He proposed that the association cortex provides the substrate for the fusion of primary sensations to obtain ideas of objects as a whole. This idea is challenged, *inter alia*, by studies demonstrating associative functions already in primary sensory cortices, which have direct afferences from the senses. In addition, the sensory cortex is affected by reinforcement (Shuler and Bear 2006; Brosch et al. 2011a; Arsenault et al. 2013; Weis et al. 2013), which generally is thought to involve the limbic system, including the hypothalamus, amygdala, hippocampus, septal nuclei, ventral tegmental area, and anterior cingulate gyrus. These findings put into question the existence of unisensory cortical areas at all (Ghazanfar and Schroeder 2006).

Learning

Learning associations between stimuli, between stimuli and behavioral responses, or between stimuli and reinforcers change the auditory cortex, such as the feature sensitivity (spectrotemporal receptive field) of neurons in the auditory cortex, their response strength and response latency, as well as interneuronal synchrony (Scheich and Brosch 2013; Shepard et al. 2013). In detection tasks, the direction of the receptive field change at the frequency of the conditioned tone depends on the valence of the tone (Scheich et al. 2011); if it is negative (associated with punishment), the response to the tone is increased (receptive field is sensitized at the conditioned tone frequency); if it is positive (associated with reward), the response is decreased (receptive field is

suppressed at the conditioned tone frequency). In frequency discrimination tasks, slopes of spectral tuning curves become sharper around the conditioned frequencies. In categorization tasks, stimuli of the same category evoke (spatiotemporal) neuronal activity patterns that are more similar to each other than those evoked by stimuli of other categories.

These changes coincide with or may even form the basis of changes in representation maps (e.g., tonotopic frequency map) in the auditory cortex that occur, at least transiently, after learning (Shepard et al. 2013; Grosse et al. 2015). They may also underlie plasticity of neuronal mass activity, as revealed by electro- and magnetoencephalography (EEG, MEG) or functional magnetic resonance imaging (fMRI) (Rüsseler et al. 2005).

Neuromodulators

The formation of novel associations in the auditory cortex requires the involvement of neuromodulators (Shepard et al. 2013). Some of the described changes can also be mimicked by repetitively pairing auditory stimuli with electrical stimulation of neuromodulatory systems, such as the ventral tegmental area (dopamine; Huang et al. 2016a), the nucleus basalis of Meynert (acetylcholine; Bakin and Weinberger 1996), the locus coeruleus (norepinephrine; Martins and Froemke 2015), or the vagus nerve (triggering widespread release of neuromodulators; Engineer et al. 2011). Formation of associations in the auditory cortex also involves cognitive factors: changes in the auditory cortex and learning do not occur when an animal is passively exposed to the stimulus-reward pairings of another animal while it was instrumentally conditioned (Blake et al. 2006).

Neuronal Correlates of Association

Sustained firing and slow firing changes may provide neuronal correlates of associations between mental entities (Brosch et al. 2011a). The main condition necessary for the emergence of slow firing changes is that subjects have learnt that conditioned associations are contingent on reinforcers. When the reinforcer is removed, the slow

firing changes disappear within a few trials, concomitantly with behavioral changes (Huang et al. 2016b). These firings may be related to the contingent negative variation (Walter et al. 1964), an event-related potential that can be obtained in electroencephalography in humans. It is considered to reflect the contingency and the contiguity of two events that have a motivational “value.”

Different types of events may be associated through event-related slow firing changes (Brosch et al. 2011a). Events that trigger such changes can be auditory (and possibly visual) stimuli, reinforcers, and behavioral responses, like grasping. An event with which slow firing changes end is the reinforcer. Slow firing changes have been observed between (1) an auditory stimulus and a reinforcer, (2) a behavioral response and an auditory stimulus, and (3) a behavioral response and another behavioral response.

The association between behaviorally significant events provided by slow firing changes might even be directed in some cases, that is, this type of firing might provide some sort of either prospective coding of an upcoming event or retrospective coding about a preceding event.

Neuronal Correlates of Rewards

In animals actively engaged in listening to auditory stimuli, direct reflections of rewards have been demonstrated in the auditory cortex. Neuronal activity in the auditory cortex varied with the size of the delivered reward and the size of the reward that was expected to be earned in a future auditory task, as well as the magnitude of the mismatch between the expected and delivered reward (the reward prediction error) (Brosch et al. 2011b). Reflections of rewards are also present in other sensory cortices (Shuler and Bear 2006; Arsenault et al. 2013).

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Associative Learning

► Eye-Blink Conditioning

Attentional Top-Down Modulation, Models of

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Definition

Attention – the ability of a sensory system to facilitate the processing of specific information at the expense of disregarding the remainder.

Bottom-up processes – information processing in the nervous system that operates in a feedforward way, advancing from sensory organs or areas at a low level of the cortical processing hierarchy.

Top-down influence – modulatory signals in the nervous system that originate from areas at a high level of the cortical processing hierarchy, influencing information processing in lower areas.

Saliency – a measure of the magnitude of the difference of a stimulus from its neighbors in space and time.

Detailed Description

The Case for Attention

Evolution has provided humans and other highly evolved species with powerful sensory systems. While our cortical processing capacity has also evolved and grown impressively, the torrent of information provided by our sensors far outstrips our ability to process it all. In addition, most of the sensory information picked up at any moment has little importance for our survival. Complex nervous systems faced with this challenge have developed sophisticated selection mechanism to identify the most relevant incoming information and to focus processing resources (and ultimately perception) onto this small fraction. This process is called attention and for the purpose of this entry can be defined as the selective modulation of sensory information based on its assumed behavioral relevance.

Bottom-Up Versus Top-Down

The selection processes underlying attention need to fulfill two requirements: on the one hand their ubiquitous (central and incessant) role in the continuous stream of perceptual decisions requires that they operate efficiently and as fast as possible. At the same time, the selection processes' purpose of dynamically identifying the most relevant components of the sensory input demands harnessing as much of the cognitive power of the species' central nervous system as possible.

These seemingly incompatible demands, efficient and fast vs. computationally demanding and thus slow, have created two flavors of selection:

1. A bottom-up (automatic, exogenous) attentional selection that exploits the realization that the most informative aspects of our sensory environments are those where one stimulus differs from their neighbors in space and time. This local saliency can be identified and enhanced by simple feedforward filter mechanisms embedded throughout the processing of sensory signals in the nervous system.

2. A top-down (voluntary, endogenous) attentional selection that integrates any information available to the organism about the current situation to make the most informed decision about which sensory input component represents the most relevant information in the given situation.

In the visual domain, this distinction is well illustrated with visual search tasks: If we are confronted with a fairly homogenous visual scene, any outlier will be identified, enhanced, and selected by the continuous parallel computation of local saliency, creating the perceptual “pop-out” characteristic of simple search tasks where the features of the target stimulus differ substantially from the distribution of features of the distractors. Conversely, a target stimulus, which is less distinct, either because it is defined as a conjunction of more than one feature or because it does not differ substantially from the distribution of distractor features, does not pop out, but rather requires a more demanding and correspondingly slower selection process.

Taking a Computational Approach to Attention

Here we illustrate how the attentional modulation of sensory information processing is implemented in computational models. Due to the brevity of the entry, we focus on a few examples of models of top-down attentional modulation in the visual system of man and other primates.

One of the most influential computational models of visual attention is the **feature integration theory** (FIT; Treisman and Gelade 1980). In the FIT, information about different features of stimulus, such as its shape, color, orientation, and movement, is extracted in parallel, automatically and effortlessly through a system of feature maps, which topographically represent the spatial distribution of specific features in the visual scene. This process detects and locates a target stimulus defined by a single unique feature value (such as the color red) because it is represented by a unique hotspot in a single feature map (with each

distractor represented by a hotspot in its corresponding feature map, such as the one for the color blue). This target detection is very quick and is unaffected by the numerosity of distractor stimuli, matching the experimental observation that human reaction times in such simple search tasks are independent of the number of distractor items. If the target stimulus is not defined by a single feature alone, but by a conjunction of multiple features, information from different feature maps needs to be integrated to detect and localize a target. This requires a serial process that actively integrates information from different maps to detect the target’s unique feature conjunction at one topographical location, matching the linear increase in reaction time observed with an increase in the number of distractors in a conjunctive search task. The FIT proposes that this serial integration process is accomplished by means of a top-down, spatial “spotlight” of attention.

An alternative account for the pattern of reaction times in search experiments is offered by the **guided search theory** (GST, Wolfe 1994), which does not assume an attentional spotlight. Instead, the top-down attentional signal changes the weight of activation maps before they are combined to create a ranking of all present stimuli based on their likelihood to represent a target. The selection of stimuli is then again performed serially, from high to low probability, until the target stimulus is detected.

While the FIT and the GST emphasize the role of feature maps in attentional selection, the **theory of visual attention** (TVA; Bundesen 1990) takes a different approach. Here the selection of stimuli is dependent on their processing speed. Before a stimulus can be encoded in visual short-term memory and thus enter awareness, it needs to compete in a computational race with other stimuli. In the TVA top-down attention speeds up the processing of certain items, making them likely to win the race.

While the FIT, GST, and TVA have been developed to account for the perceptual data available at the time, more recent models of attention have been developed to capture data from single-cell recordings from monkey visual cortex. Two early conceptual models attempted to account for the enhanced neuronal response to attended stimuli

and the reduced response to unattended stimuli. The **biased competition model** of attention (Desimone and Duncan 1995) envisages a competition between the stimulus representation of attended and unattended stimuli that can be biased by a top-down attentional signal in favor of the attended stimulus' representation. The **feature similarity gain model** of attention (Treue and Martinez-Trujillo 1999) alternatively proposes that the enhancement of neural responses by attention reflects a process where top-down attentional signals enhance the gain of those neurons whose preferred features match the current attentional state of the organism, independent of the stimulus that currently activates a neuron.

These two conceptual models have inspired a large number of computational models. The most prominent of those are models that emphasize an interaction of top-down attention with the normalization process that creates the sigmoidal contrast response functions typical for neurons throughout sensory cortex. Multiple varieties of such **normalization models** of attention have been proposed (Ghose and Maunsell 2008; Boynton 2009; Ghose 2009; Lee and Maunsell 2009, 2010; Reynolds and Heeger 2009). They all emphasize the similarity, in perception, as well as in the neural encoding and also in the central role of the response normalization process between two influences on the strength a neural stimulus representation. One is the physical (bottom-up) strength of the stimulus (most directly represented by its contrast) and the other is the attentional weight (implemented as a kind of sensory prior) assigned to them through a top-down attentional signal.

Beyond models that emphasize response normalization, there have been numerous other approaches to model the attentional modulation of sensory information processing. They include the **selective tuning model** (Tsotsos et al. 2005) that proposes a layered network architecture (representing the hierarchy of cortical areas) to implement a spatial "spotlight of attention" that endows certain regions of the visual scene with enhanced processing. The **spiking network model** (Deco and Rolls 2005; Deco and Thiele 2011) places much more emphasis than any of the models discussed above on building its approach

on biological components, such as spiking neurons and specific neurotransmitters.

The Integrated Saliency Map

It should be noted that almost all models of attention incorporate the concept of an **integrated saliency map** (Treue 2003), that is, a topographic representation of the stimuli in the current visual scene that combines their relative physical strength and their assumed behavioral relevance. This combination implements a weighing of bottom-up and top-down aspects of a stimulus, providing processing resources to strong unattended stimuli as well as to weak attended ones. While such an integrated saliency map. Is consistent with a number of perceptual phenomena and is ideally suited to guide eye movements across a visual scene, it is a matter of some debate which of the many topographically organized areas in the visual cortex represents this map or whether multiple such maps exist.

Similarly, while functional imaging and single-cell recording studies have implicated a network of frontoparietal areas in the guidance process that is necessary to appropriately allocate processing resources (Kastner and Ungerleider 2001; Corbetta and Shulman 2002), such anatomic specificity is rarely included in current computational models of attention.

Conclusion

In conclusion, in the last decade, a large number of computational models of top-down attention have been developed that can account for a large variety of perceptual and physiological aspects of the attentional modulation of sensory information processing. These models emphasize several core issues, such as the response normalization in cortical networks, the multistage nature of cortical information processing, and the concept of an integrated saliency map. Despite this progress much more work is needed to achieve a complete computational description of top-down attentional modulation.

Cross-References

- [Hierarchical Models of the Visual System](#)
- [Working Memory, Models of](#)

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Attractor Neural Network

- [Hopfield Network](#)

Auditory Brainstem Responses

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Synonyms

[Auditory evoked brainstem responses](#); [Brainstem auditory evoked potentials \(BAEP\)](#)

Definition

Auditory brainstem responses (ABRs) are the earliest auditory event-related potentials (cf. ► [“Auditory Event-Related Potentials”](#)) elicited during the first 10 ms after stimulus onset in the anatomical relays of the auditory pathway. ABRs are typically recorded with scalp electrodes attached to the vertex and referenced to the earlobe or the mastoid. Two types of ABRs have been described: the transient-evoked responses and the sustained frequency-following response (FFR). While the transient-evoked ABRs are elicited to high-intensity clicks or tone bursts, FFRs can only be recorded to periodic auditory stimuli, and their duration extends to the length of the eliciting sound. In the ABRs elicited to periodic and complex auditory stimuli,

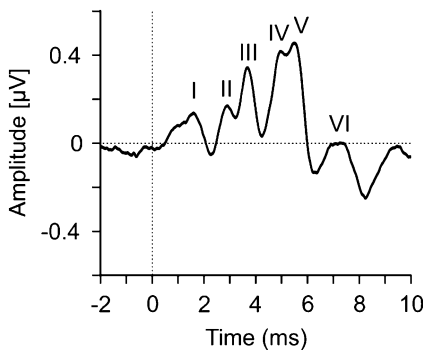
such as speech sounds or music, the two types of ABRs can be observed.

Detailed Description

Transient-Evoked ABRs

The first systematic observation of the human transient ABRs was by Jewett, Romano, and Williston in 1970 (Jewett et al. 1970; Jewett and Williston 1971) who described a series of six or seven fully visible waveforms spanning the first 10 ms after sound onset. ABRs are characterized for being fast, vertex-positive response peaks spaced at intervals of about 1 ms and are evoked by brief stimulus features, such as broadband clicks, tone bursts, or the abrupt onset of a sound (Pratt 2012).

The different ABR waveforms define a very characteristic morphology and are labelled in sequence by Roman numerals from I to VI (Fig. 1). Their amplitude is in the order of tenths of a microvolt, smaller than 0.5 mV (Pratt 2012), with the most positive component being wave V (Picton 2011; Pratt 2012). The first component of the sequence, wave I, is the most positive peak occurring at approximately 1 ms after stimulus onset and corresponds to the N1 wave of the



Auditory Brainstem Responses, Fig. 1 Morphology of the human transient ABR. The figure depicts the typical morphology of a healthy human adult ABR. It was obtained by averaging the responses to 6000 presentations of a click delivered bilaterally at 85 dB SPL at a rate of 19.3/second. The recording is between electrodes placed at FPz and the right mastoid. The EEG was acquired at 20 kHz sampling rate using a band-pass filter from 100 to 3000 Hz. Waves I to VI are identified at their typical latencies

electrocochleogram. Between waves I and V, the most prominent deflection is wave III, which occurs at a latency of about 3.5 ms. Wave II is a small peak halfway between wave I and III, and waves IV and VI can be observed in both sides of wave V. Wave IV is not always identified in humans, and when present it is often merged partially with wave V, yielding a wave IV-V complex (Picton 2011; Pratt 2012).

The different ABR components are generated by distinct anatomic structures of the auditory pathway. The first components of the sequence, waves I and II, are generated exclusively by the auditory nerve (Gelfand 2010). More precisely, wave I originates in the ipsilateral distal portion of the auditory nerve in the region of the ganglion cells and wave II from the ipsilateral proximal portion of the auditory nerve in the vicinity of its entry into the brainstem (Stone et al. 2009; Pratt 2012). The later components, waves III, IV, and V, have contributions from more than one anatomical structure. Wave III has been attributed to the region of the ipsilateral cochlear nucleus and the superior olivary complex (Stone et al. 2009; Picton 2011). The generators of wave IV are still under debate, but all evidence points to bilateral multiple brainstem sources (Stone et al. 2009), between the superior olivary complex through the lateral lemniscus, with a possible contribution from the inferior colliculus (Pratt 2012). Wave V is originated in the contralateral distal lateral lemniscus and the inferior colliculus (Stone et al. 2009), so overall, the wave IV-V complex is attributed to bilateral generators in the region of the midbrain tegmentum (Starr et al. 2008). Wave VI has been attributed to the medial geniculate body (Gelfand 2010). Although these sources are the most accepted ones across the literature, there are still divergent opinions regarding the exact origins of the components from wave II onwards, as it is known that multiple generators in the auditory brainstem may be contributing to them (Gelfand 2010; Picton 2011).

The transient ABRs are typically elicited by broadband clicks or chirps (Fobel and Dau 2004; Maloff and Hood 2014) presented at a rate ranging from 10 to 20 stimuli per second. They are optimally recorded from the scalp with an electrode at

the vertex of the head (Cz or Fz) referenced to an electrode in the vicinity of the stimulated ear (mastoid or earlobe). To extract the ABR from the auditory evoked potential, a frequency band-pass filter from 30 to 3000 Hz is necessary, and, due to the small amplitude of the components, an average of at least 2000 stimulus presentations is required. The sampling rate of the electroencephalographic signal should not be lower than 20 kHz to avoid waveform distortions (Picton 2011; Pratt 2012). When measuring ABRs, the stimulus polarity must also be taken into account, as although the full set of components can be obtained with stimuli presented in any polarity (i.e., condensation and rarefaction), the latency of the different components is modulated depending on it (Ballachanda et al. 1992; Hall 2007).

A range of non-pathological factors affect the transient ABR, such as subject's age, gender, and body temperature. Also, stimulus factors like intensity or presentation rate do affect the recorded ABR (Picton 2011; Pratt 2012); a typical example is the shortening of the ABR peak latencies by increasing stimulus intensity. On the other hand, the ABR has high sensitivity, specificity, and reliability, and it is not susceptible to the evoking stimulus being attended or ignored nor to changes during sleep or under anesthetics (Picton 2011). Fields of clinical application of ABR recordings are, among others, newborn and infant auditory screening (i.e., the estimation of auditory sensitivity in infants and difficult-to-test children) and neurodiagnosis of eighth nerve or auditory brainstem dysfunction (i.e., monitoring eighth nerve and auditory brainstem status intraoperatively during surgery potentially affecting the auditory system and the diagnosis of auditory neuropathy) (Hall 2007).

Frequency-Following ABRs

The frequency-following response (FFR) is a component of the auditory brainstem response that reflects sustained and synchronous neural phase-locking to the individual cycles of the eliciting stimulus waveform and/or to the periodicity in the envelope of an acoustic stimulus (Skoe and Kraus 2010; Kraus et al. 2017). The scalp-recorded FFR can be evoked by frequencies

in the range of 100–1500 Hz approximately. By reflecting the phase-locked activity to sounds, the FFR physically “mimics” the eliciting stimulus and is as complex as it, thus providing a stable window into the neural transcription of sounds in neuronal aggregates along the auditory hierarchy (Galbraith et al. 2000; Bidelman 2018).

The FFR was first recorded in humans by Moushegian, Rupert, and Stillman in 1973 (Moushegian et al. 1973), and it is suggested to represent phase-locked neural activity from multiple generators within the auditory system. Currently, the neural origins of FFR are still debated, yet it is treated as a putative window into subcortical sound encoding. The FFR can be obtained under passive and active listening paradigms, and it is highly sensitive to context-dependent contingencies and to real-time statistical properties of the stimulation sequence. It is also modulated by short-term auditory training and by the individual's lifelong auditory experience, such as that with language and music. Consequently, the FFR has become a relevant tool in assessing the neural encoding of speech sounds in both healthy and clinical populations (Escera 2017; Kraus et al. 2017).

By means of the appropriate analytical tools, the FFR provides an objective indicator of fundamental acoustic features intrinsic to speech and other complex sounds, including timing (onsets), pitch (fundamental frequency, f_0) and timbre (the harmonics information), as well as their timing (see Kraus et al. 2017).

For more detailed information, cf. ► [“Auditory Frequency-Following Responses.”](#)

Cross-References

- [Auditory Event-Related Potentials](#)
- [Auditory Frequency-Following Responses](#)

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Auditory Cortex: Separating Signal from Noise

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Synonyms

[Auditory scene analysis](#); [Auditory scene segmentation](#)

Definition

The process of separating signal from noise is an aspect of the process of auditory scene segmentation in which the pressure waves from multiple, concurrent sound sources that mix in the air must be de-mixed by perceptual processes to generate an auditory object-based model of sound sources in the environment. Sounds that interfere with the detection or discrimination of an informative sound of interest, the signal, are often described as noise. The use of the term “noise” is informed by a long history of psychophysical experiments that measure the adverse effects of adding sounds, usually based on stochastic processes, to more behaviorally relevant signals, such as speech. Neurophysiological experiments have demonstrated that brain regions that process sound act to filter out noise while retaining information about behaviorally important sounds, such that the neural representations of sound mixtures in central structures like auditory cortex are significantly de-noised relative to representations of those sounds in more peripheral brain regions, such as the cochlear nucleus. The effects of background noise on neural responses to a signal depend on the relative amplitudes of the signal and noise, which is typically quantified in terms of the signal to noise ratio (SNR), in decibels. The similarity between signal and noise in terms of frequency content, temporal pattern, and spatial location have important implications for how

much noise at a particular SNR will disrupt processing of the signal. Neurophysiological recordings from auditory cortex have demonstrated significant diversity in how background noise affects cortical responses to certain classes of signals, including cases where noise at moderate SNRs can enhance the cortical representation of some signals.

Detailed Description

Perceptual segmentation of complex scenes relies on assigning the most likely distribution of sound sources based on the mixtures of sounds arriving at the ears (Bregman 1990; Yost 1992). Most naturally occurring sounds are complex and time-varying, so the auditory system must not only correctly attribute acoustic energy at different frequencies to a single sound source, but, in the presence of multiple concurrent sounds, must often parse acoustic energy at a single frequency among multiple sources. When thinking about this process, it is often useful to categorize sounds as “signal” or “noise” with respect to the listener’s specific goals. For example, on a busy street, the sound of passing cars is noise that interferes with the conversation between two pedestrians. However, the pedestrians’ conversation can also be noise that interferes with the ability a nearby bystander listening for the sound of passing cars to determine whether it is safe to cross the street. The term “background noise” is often contrasted with “foreground sound” to indicate the attentional focus of the listener.

Although the neurophysiological literature sometimes makes reference to intrinsic noise that results in variable neural responses across repeated presentations of identical stimuli, for the purposes of this entry, “noise” should be understood to refer to external, physical sounds that disrupt the processing of another sound. Traditionally, the sounds used as background noises in studies of cortical responses tend to be stochastic in nature, and as such, are defined by their time-averaged statistics, rather than a specific time-frequency pattern. For example, broadband or “white” noise has a flat spectrum over the audible range when measured over a sufficiently

long interval, but the spectra of short segments of white noise vary considerably, and the output of a filter with a narrow bandwidth will show considerable modulation over time. These considerations are important when considering the expected responses of cortical neurons. In primary auditory cortex, for example, sharply tuned neurons with short temporal integration windows can exhibit highly reproducible, time-locked responses to repeated presentations of an identical (“frozen”) instance of broadband noise (Scott et al. 2011). In fact, humans in laboratory settings distinguish among distinct instances of broadband noise (Agus et al. 2010). In natural listening conditions, however, the exact time-frequency patterns of environmental noise sources such as wind or ocean waves do not repeat and are not perceptually meaningful beyond their adverse effects on the processing of more behaviorally relevant signals (McDermott et al. 2013).

We define the neural representation of a stimulus as the pattern of activity that occurs in response to the stimulus and conveys information about that stimulus to auditory structures further along in the processing pathway. Background noise can corrupt the signal representation by eliciting responses that would otherwise not occur, or by reducing or eliminating responses that are typically elicited by the signal. Effectively, signals and noises compete for neural representation by influencing the patterns of neural activity in a given auditory area. It is possible that changes in signal representations might not necessarily interfere with perceptual discrimination if those changes are small relative to the differences in the responses to a set of distinct signals. Central auditory representations of complex sounds have been described as “noise invariant” (Moore et al. 2013; Rabinowitz et al. 2013) when response features associated with the signals are preserved while those associated with the noise are attenuated at successive stages of the auditory pathway.

Early studies that measured auditory cortical responses to simple stimuli such as pure tones containing a single frequency tended to focus on how tuning curves that relate neural firing rates to signal amplitude shift in the presence of additional background noise (Ehret and Schreiner 2000;

Phillips 1990; Phillips and Cynader 1985; Phillips et al. 1985) and have typically reported increases in response thresholds and latencies. Studies that have employed complex, time-varying signals have considered how the pattern of cortical responses changes in the presence of noise. For example, background noise reduces synchronization to the phrases of primate vocalizations (Nagarajan et al. 2002) and birdsong (Narayan et al. 2007).

Despite increasing research focus on cortical signal in noise processing (Bar-Yosef and Nelken 2007; Schneider and Woolley 2013), important questions remain about the underlying neural mechanisms. Proposed mechanisms include spectrotemporal filtering (Lee and Theunissen 2015), adaptation (Rabinowitz et al. 2013), synaptic depression (Mesgarani et al. 2014), and feedback gain normalization (Mesgarani et al. 2014). Recent studies have demonstrated additional complexities in how cortical neurons encode signals in noise. Similar to perceptual studies, the adverse effects of background noise at a given SNR depend on the absolute levels of both the signal and noise, such that loud noise is more disruptive than moderate noise at equivalent SNRs (Teschner et al. 2016). Among distinct clusters of cortical neurons, background noise can disrupt, fail to affect, or even enhance the representation of frequency-modulated sweeps, even in animals that are not required to attend to the stimulus (Malone et al. 2017).

Importantly, auditory cortex spans multiple levels of processing in the auditory pathway. In humans and many other vertebrate animals, the auditory cortex is comprised by a number of areas in the temporal lobe of the brain. In primates, including humans, auditory cortex is organized into core areas which receive direct projections from the ventral division of the medial geniculate body and then project to belt areas that project, in turn, to parabelt areas. Because cortical responses are believed to be more modulated by attentional mechanisms and more plastic in response to sensory exposure and perceptual learning than more peripheral structures, the question of how auditory cortical regions represent signals of interest in the presence of competing sounds is of special relevance. The balance of “bottom-up” mechanisms

acting on sensory input and “top-down” mechanisms engaged by attentional focus likely shifts at different levels of the cortical processing hierarchy (Niwa et al. 2013, 2015).

Separation of signal from noise is of great clinical relevance, since the inability to follow ones stimulus among many, the “cocktail party problem” (Cherry and Bowles 1960; Cherry and Wiley 1967; Plomp 1977) is a hallmark of hearing loss, and among the most common hearing complaints in the elderly. Neurophysiological experiments in older animals suggest that reductions in the strength of inhibition may prevent the appropriate suppression of background noise (Presacco et al. 2016; Recanzone 2018).

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Further Reading

The Auditory System at the Cocktail Party, Springer Handbook of Auditory Research. <https://www.springer.com/gp/book/9783319516608>

Auditory Event-Related Potential (AERP)

► Auditory Event-Related Potentials

Auditory Event-Related Potentials

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Synonyms

Auditory event-related potential (AERP); Auditory evoked field (AEF); Auditory evoked potential (AEP)

Definition

Auditory event-related potentials are electric potentials (AERP, AEP) and magnetic fields (AEF) generated by the synchronous activity of large neural populations in the brain, which are time-locked to some actual or expected sound event.

Detailed Description

Measurement and Derivation of AERPs/AEFs

AERPs are derived from the continuous electro-/magnetoencephalogram (EEG/MEG) by extracting segments of the signal (epochs) time-locked to some actual or expected acoustic event. AERPs were first recorded by Hallowell and Pauline

A. Davis in 1935–1936 (Davis 1939; Davis et al. 1939). Because EEG/MEG is typically recorded non-invasively (outside the brain, e.g., from/around the scalp), these measures only reflect synchronous activity of large neural populations (for measuring methods and instrumentation). Consequently, the acoustic events eliciting detectable AERPs consist of relatively large changes of spectral energy occurring within a relatively short time period, such as abrupt sound onsets, offsets, and changes within a continuous sound, because large acoustic changes affect many neurons within the auditory system and the short transition period synchronizes the responses of individual neurons (Nunez and Srinivasan 2006; cf. ► “Anatomy and Physiology of the Mammalian Auditory System”). Furthermore, the expectation of such changes in the auditory input can elicit AERP responses even in the absence of actual stimulation (cf. the *Omitted Stimulus Response* in “Long-Latency AERP Responses,” below).

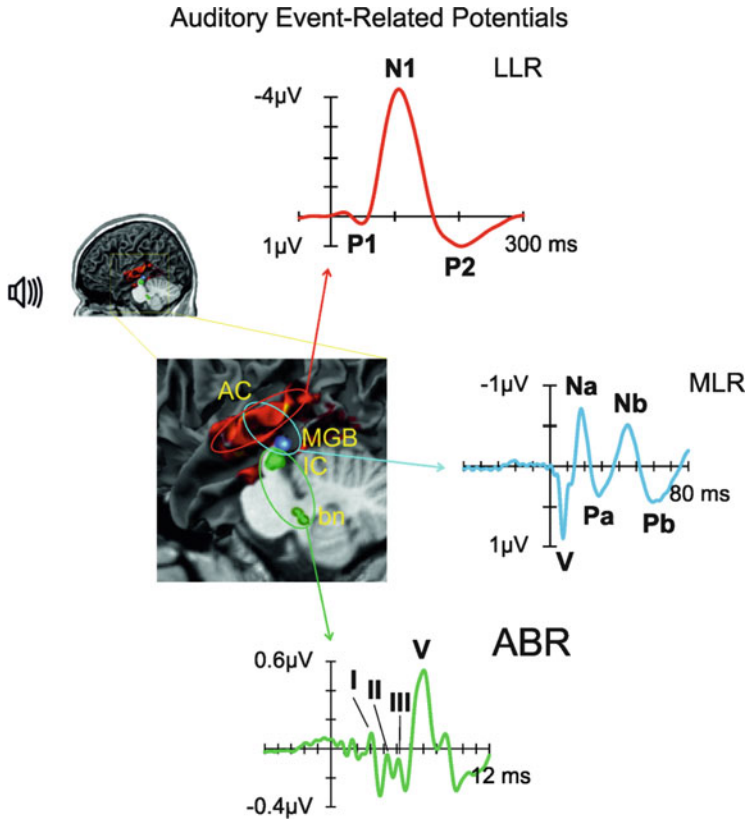
The EEG/MEG signal mixes together on-going (spontaneous) neuroelectric activity with that elicited by the event. In order to better estimate the brain activity evoked by the event, it is usually repeated several times (typically 50–200 trials/sweeps, but up to 2000 times for ► “Auditory Evoked Brainstem Responses”) and the EEG/MEG segments are entered into some mathematical algorithm extracting the common part of the single-trial epochs. The most commonly used method for extracting AERPs aligns the single-trial epochs by their common onset and averages them point by point (the averaging method; Alain and Winkler 2012). There are many other algorithms for extracting ERPs from EEG/MEG, each based on different assumptions regarding the properties of the event-related response and the spontaneous EEG/MEG activity (for a general primer, see Luck 2005; for detailed discussion of ERPs, see Handy 2005; Fabiani et al. 2007; for special considerations of MEG/AEFs, see Hansen et al. 2010; Nagarajan et al. 2012; for AERPs, see Picton 2010; Alain and Winkler 2012).

EEG/MEG signals can contain components up to a few kHz with the faster components mainly originating from lower levels of the auditory

system (cf. ► “Anatomy and Physiology of the Mammalian Auditory System” and ► “Auditory Evoked Brainstem Responses”). Cortical contributions are much slower, up to a few tens of Hz. Unless one is specifically looking for very slow (Vanhatalo et al. 2005) or fast responses (Curio 2005), AERP recordings are usually made with bandpass filter settings of 0.01–50 Hz (or 250 Hz for extracting the Middle-Latency Response, see below). AERP amplitudes are typically below 10 μ V with the reference (zero) level set to a baseline voltage (unless direct current is recorded), which is usually the average signal amplitude in a time interval preceding the AERP-eliciting event. Although in general, there is no unique solution to the inverse problem of finding the origins (the neural generators) of electromagnetic potentials measured outside the brain, by utilizing anatomy/physiology based constraints, the generators of AERPs can be located with reasonable accuracy in the brain (Nunez and Srinivasan 2006; see also ► “Brain Imaging: Overview”). Due to the underlying physics, magnetic AEFs provide more accurate source localization compared with electric AERPs (Nunez and Srinivasan 2006; Nagarajan et al. 2012). On the other hand, MEG only allows one to measure the tangential components of the electromagnetic activity in the brain, whereas EEG represents the full activity (Hansen et al. 2010). For AEFs, however, this limitation of the MEG signal is less severe than for other sensory/cognitive systems (Picton 2010; Nagarajan et al. 2012). This is because a large part of the human auditory system in the cortex is located in the Sylvian fissure (see ► “Anatomy and Physiology of the Mammalian Auditory System”), thus mostly producing magnetic signals which can be picked up by the MEG device.

AERP Waves, Components, Naming Conventions

Figure 1 illustrates the progression of stimulus-related neuronal activity through the auditory system and the corresponding series of positive and negative waveforms observable in the AERP response. The earliest detectable responses (< ca. 10 ms after the acoustic event) originate



Auditory Event-Related Potentials, Fig. 1 The human Auditory Event-Related Potential (AERP), its main waveforms and its generators in the brain. The human AERP is composed of three groups of waveforms in three different latency ranges: the Auditory Brainstem Response (ABR) elicited within the first 8–10 ms from sound onset (*green, bottom panel*); the Middle-Latency Response (MLR), elicited within the 12–50 ms interval from sound onset (*blue, central panel*), and the Long-Latency Responses (LLR) emerging after 50 ms (*red, top panel*). The anatomical inset (*left panel*) highlights the main stages of the

auditory pathway: “bn”, brainstem nuclei (including the cochlear nucleus, the superior olivary nucleus, the nucleus of the lateral lemniscus); “IC”, inferior colliculus; “MGB”, the medial geniculate body in the thalamus; “AC”, auditory cortex. The main assumed brain sources of the different AERPs are marked by colored circles: the ascending auditory pathway of the brainstem for ABRs (*green*); the thalamo-cortical loops and parts of auditory cortex for MLRs (*blue*); the auditory cortex for LLRs (*red*). AERPs can be broken down into a series of waves (see the naming convention in the main text)

from subcortical brain structures and are termed the *Auditory Brainstem Response* (ABR; cf. ► “*Auditory Evoked Brainstem Responses*”). These are followed by AERP responses of thalamo-cortical origin (mainly from the primary auditory cortex), termed the *Middle-Latency Response* (MLR), elicited during the ca. 10–50 ms post-event latency range. The waveforms following are called *Long-Latency Responses* (LLR) and they originate largely from auditory cortex, but may also include contributions from parietal and frontal areas.

ABRs are referred to by Roman numerals set in the order of their elicitation. MLR waveforms are usually denoted by their polarity at the vertex (approximately the top of the head); P for positive and N for negative polarity waves, and a letter or a number (see Fig. 1). There are two conventions for the numbers in referring to LLRs: They either denote the serial order of the response starting with the first detected response (Davis 1939; Davis et al. 1939), termed N1, or they denote the typical peak latency of the waveform, such as P50 (the same as Pb or P1). However, as more and

more responses elicited with the same polarity and in overlapping latency ranges have been discovered, both notations have become equivocal. Therefore, some recently discovered AERP responses are denoted by acronyms referring to their functional aspects, such as ORN (Object Related Negativity) or MMN (Mismatch Negativity) (for a detailed description of the variety of ERP responses, see Luck and Kappenman 2012; for AERPs, Picton 2010; Alain and Winkler 2012). Magnetic response fields are usually marked by the letter ‘m’ appended to the name of the corresponding (A)ERP (e.g., N1m or N100m).

Beyond the categorization based on the ERP peak latency there are two other typical distinctions in use. ERPs are termed obligatory or exogenous if they are elicited by each event irrespective of its relation to preceding or concurrent events or the person’s task, motivations, knowledge, etc. ERP components elicited only when there is a certain relation between the event and other events or some aspect of the person’s mental state are termed endogenous. Another distinction refers to the person’s voluntary activity with respect to the given stimulus event. ERP responses only elicited when the person has some explicit task involving the event (task-relevant even) are termed “active” ERP responses, while those elicited irrespective of the person’s task (task-irrelevant) are termed “passive” ERP responses.

However, waveforms (peaks and dips) are not the true building blocks of ERP responses. The brain is a massively parallel processing instrument. Therefore, at any given moment of time, multiple processes may contribute to the observable waveform. For a neurophysiologically and functionally more meaningful decomposition of the complex neuroelectric response, one should be able to delineate how each of the concurrent processes contributed to the observed neuroelectric activity. This objective is reflected by Näätänen and Picton’s (1987) definition of an ERP component: ‘... we define an EP “component” as the contribution to the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by

a specific pattern of input’ (p. 376). Thus a component is defined by two criteria: (1) it should have a specific generator structure (e.g., secondary auditory and frontal cortices) and (2) it should be specific to some experimentally definable stimulus configuration (such as stimulus change after several stimulus repetitions). One could amend this definition with the person’s task/goals/knowledge regarding the given stimulus configuration (e.g., instructed to respond to the given stimulus event). However, the criteria set up by the above definition are seldom met in ERP research. This is partly due to limitations in separating generators (i.e., they are usually distributed over an area in the brain and concurrently active processes often occupy areas very close, possibly even overlapping each other) as well as not knowing what stimulus configurations are handled by the same processes in the brain (are all expectation violations processed in the same way? – probably not). Thus in practice, the majority of ERP research reports use the terms “waveform” and “component” interchangeably, sometimes linking the effects of multiple manipulations to the same waveform, while at other times, attempting to separate the specific generator process affected by a given stimulus or state variable.

There are many different processes, which can be reflected in AERPs. Early, obligatory responses typically reflect processes extracting auditory features, such as pitch, intensity, location, etc. Most AERP responses are sensitive to the amount of sound energy change and also to some aspects of the sound presentation rate or the ratio between sound and silence in time. These attributes of auditory stimuli belong to the primary descriptors of sound events as studied in psychoacoustics (Zwicker and Fastl 1990). There are also AERP responses indicating the presence of automatic memory for sounds (Cowan 1984; Demany and Semal 2007) and predictive processing of the auditory input (Friston and Kiebel 2009; Winkler et al. 2009). Further, some AERP responses reflect processes involved in auditory scene analysis (Bregman 1990), the separation of concurrently active sound sources in the environment and the formation of auditory perceptual objects (Griffiths and Warren 2004; Winkler

et al. 2009). Many AERP responses are also sensitive to attentional manipulations, including the active storage of sounds, selective attention, and target identification (Cowan 1988; Näätänen 1990). AERP responses specific to music and speech perception are described in the corresponding entries (► “Music Processing in the Brain” and ► “Electrophysiological Indices of Speech Processing”). Therefore, AERPs have been extensively used to test theories of perception (e.g., Bregman 1990; Friston 2005), memory (e.g., Broadbent 1958; Baddeley and Hitch 1974; Cowan 2001), and attention (e.g., Broadbent 1958; Lavie 1995) and in recent years they have received increased interest from computational modelling (e.g., Garrido et al. 2009; May and Tiitinen 2010; Wacongne et al. 2011) as well as from clinical applications (e.g., Picton 2010; Näätänen et al. 2012).

In the following, we shall describe the most important middle- and long-latency AERP responses (for the auditory brainstem responses, see ► “Auditory Evoked Brainstem Responses”).

Middle-Latency AERP Responses

Discrete auditory stimuli elicit a sequence of very small (<1 μ V) negative and positive waveforms in the 10–50 ms post-stimulus latency range, termed the Middle Latency Response (MLR). These responses can usually be best seen on signals recorded from the vertex with a mastoid or neck electrode as reference. The names and typical latencies of MLRs when elicited by click stimuli are: *N0* (10 ms), *P0* (15 ms), *Na* (20 ms), *Pa* (30 ms), and *Nb* (~40 ms) (see Picton 2010). An additional later waveform, the *Pb*, which peaks at about 50 ms from sound onset, is not always included amongst the MLR components, because it can also be obtained as the P50 or P1 with the filter bandwidth optimised for measuring LLRs (Regan 1989; see below). Because of their small amplitude and specific spectro-temporal characteristics, recording the MLR requires (a) averaging across close to 1000 responses, (b) appropriate filter settings (15–200 Hz, Bell et al. 2004), and (c) careful removal of

electromagnetic interference from power supplies and lines, as a large part of the power of the MLR responses falls into the 50–60 Hz range. It is also important to avoid artefacts stemming from the myoelectric activity of the postauricular muscle (PAM), which lies behind the ear and is activated by loud sounds. This is usually achieved by placing the reference electrode on the neck or the sternum (Bell et al. 2004). Optimal sounds for eliciting clear MLRs are chirps and clicks, which have sharp onsets and a broad spectrum. Pure tones elicit MLRs of somewhat different morphology and smaller amplitude (Borgmann et al. 2001). However, MLRs can be obtained even with low-intensity tone bursts and relatively independently of the arousal level (Jones and Baxter 1988).

No hemispheric asymmetry was found for MLRs as a function of the stimulated ear (Starr and Don 1988). Based on precise structural maps of individual brains, the spatiotemporal pattern of neural activation giving rise to MLRs has been identified in supratemporal auditory areas using either current estimates derived from intracerebral recordings (Yvert et al. 2005) or equivalent dipole source modelling of scalp-recorded electric brain potentials (Yvert et al. 2001). These studies localized the earliest cortical activity (P0) at 16–19 ms from sound onset in the medial portions of Heschl’s sulcus (HS) and Heschl’s gyrus (HG), which likely correspond to primary auditory cortex (PAC). Na generation resulted from activity in more posterior regions of the same HS and HG areas. During the Pa/Pb complex, which includes also the Nb, the electric brain activity propagates in postero-anterior and medio-lateral directions in HG to the Planum Temporale (PT) and then to more anterior parts of the Superior Temporal Gyrus (STG), which correspond to secondary auditory areas. Also, frontal and parietal brain regions contribute as early as 30 ms from sound onset (the P30 m AEF response) to MLR (Itoh et al. 2000). Animal studies have suggested that MLRs involve parallel thalamocortical activation of areas 41 (PAC), and 36 (parahippocampal gyrus), while human lesion studies have implicated contributions from thalamic projections to Pa (Kraus et al. 1982) and Na (Kaseda et al. 1991),

supporting a thalamo-cortical interaction in MLR generation.

With increasing sound intensity, MLR component latencies decrease while the amplitudes increase, although these effects may not uniformly apply to each component (e.g., Na, but not Pa; Seki et al. 1993; Althen et al. 2011). Galambos et al. (1981) found a systematic reversed U-shaped relationship between the MLR amplitudes and stimulus presentation rate. At slow rates (≤ 10 Hz), peak-to-trough amplitudes are rather small (0.4 μ V) and they reach the maximum of 1 μ V by about 40 Hz presentation rate. This twofold increase in amplitude is due to superimposition of MLRs elicited by successive sounds. In contrast, at stimulation rates below and above 40 Hz out-of-phase responses to successive MLR responses cancel out each other. Some authors interpret this finding in terms of the “steady state” potentials (oscillatory activity generated in sensory cortical areas that is time-locked to the periodicity of stimulus presentation; typically measured from visual and somatosensory cortical areas; Rees et al. 1986). Other authors assume that this phenomenon reflects the contribution of transient early evoked gamma-band oscillations to the auditory MLR (Basar et al. 1987; Pantev et al. 1991; Müller et al. 2001). Based on the stimulus-driven properties outlined above, MLRs have been considered exogenous AERP components. However, this view has been challenged by studies showing that MLRs are enhanced by strongly focused attention as early as 20 ms from sound onset (Woldorff and Hillyard 1991; Woldorff et al. 1993; cf. “Attention-Related AERP Responses” below), and that MLR amplitudes are modulated as early as 50 ms from sound onset by task difficulty and whether or not a motor response is required (Ninomiya et al. 1997). Further, a recent series of studies has shown that MLRs are sensitive to stimulus probability in a feature-specific manner (Grimm and Escera 2012) with infrequent frequency changes enhancing the Pa (Slabu et al. 2010) and Nb (Grimm et al. 2012; Alho et al. 2012), whereas location changes enhance the Na (Sonnadara et al. 2006; Grimm et al. 2012; Cornella et al. 2012). These results suggest that the MLR components reflect processes

subserving higher-order sensory/cognitive functions.

Long-Latency AERP Responses

The auditory *P1* (*P50*, *Pb*; Fig. 1) component is at the border between MLR and LLR. In fact, when recorded and analysed with the filter setting most useful for deriving MLRs it is termed the *Pb* (see “Middle-Latency AERP Responses,” above). Using the parameters better suited for assessing LLRs, it typically peaks at about 50 ms from stimulus onset, appearing with positive polarity at the vertex and with reversed (negative) polarity at electrodes placed on the other side of the Sylvian fissure (e.g., electrodes placed over the mastoid apophysis). *P1* is the first wave of the *P1-N1-P2* obligatory exogenous AERP complex. It is thought to be generated bilaterally in primary auditory cortex, somewhat larger contra- than ipsilaterally for pure tones (Godey et al. 2001) and for other types of pitch-evoking sounds (Butler and Trainor 2012), with some spreading of the neuroelectric activity over its time course (Yvert et al. 2005). *P1* is often used as a landmark for primary auditory cortex in AERP and AEF studies aimed at localizing the AERP components. Similarly to other obligatory AERP responses, *P1* is highly sensitive to stimulus features and presentation rate (fully recovering within a few hundred milliseconds) as well as to attentional manipulations (Picton 2010). The *P1* was initially assumed to reflect neural activity involved in extracting auditory features (e.g. Näätänen and Winkler 1999). Recent evidence also links this response with the automatic separation of auditory streams (Gutschalk et al. 2005; Snyder et al. 2006; Szalárdy et al. 2013; cf. ► “Auditory Perceptual Organization”): The amplitude of the *P1* component has been found to be modulated by whether a sequence with two interleaved sounds (e.g., ABABAB... , where ‘A’ and ‘B’ denote two different sounds) was perceived as a single coherent stream or in terms of two concurrent streams of sound (one made up of the ‘A’ and the other by the ‘B’ sounds).

The auditory *N1* (*N100*; Fig. 1) wave was the first AERP response discovered historically (Davis et al. 1939) as it is the most prominent

deflection at the vertex. It is elicited by abrupt changes in sound energy, such as sound onsets and offsets (Näätänen and Picton 1987). N1 typically peaks with negative polarity over the vertex ca. 100 ms after the eliciting event. It is also the most widely studied AERP response, having been linked with virtually any and all assumed auditory processing steps. The N1 wave has a complex generator (and thus subcomponent) structure (Näätänen and Picton 1987). The subcomponent most tightly related to auditory processes (the supratemporal N1) is mostly located in secondary auditory areas (Godey et al. 2001), but it also overlaps the areas active during the P1 component (Yvert et al. 2005). Similarly to the P1, N1 is larger contralaterally to the ear of stimulation and it is highly sensitive to stimulus features, presentation rate, and attentional manipulations. However, unlike the P1, the N1 recovery is much slower, extending beyond 10 s (Cowan et al. 1993). Further, N1 is sensitive to perceived sound features (e.g., pitch), as opposed to raw spectral parameters (such as the harmonic frequencies of a complex tone; Pantev et al. 1989b), although feature extraction is not yet complete at the time the N1 wave is elicited (Winkler et al. 1997). The supratemporal N1 also shows both tonotopic (Pantev et al. 1988) and amplitopic organization (Pantev et al. 1989a); that is, the location of its generator varies with the frequency and amplitude of pure tones. However, the N1 generators are not sensitive to combinations of sound features (i.e., feature conjunctions).

The processes reflected by N1 have been linked with onset and acoustic change detection (Näätänen 1992), feature extraction, sensory memory (Lü et al. 1992; at least for sound features, Näätänen and Winkler 1999) and, recently, with auditory stream segregation (Gutschalk et al. 2005; Snyder et al. 2006; Szalárdy et al. 2013). For example, the length of the silent period after which an N1 with maximal amplitude is elicited by a sound is in good correspondence with the behaviourally measurable duration of auditory sensory memory traces (Cowan 1984). When sounds are presented in a train with <10 s silent intervals between them, the N1 amplitude

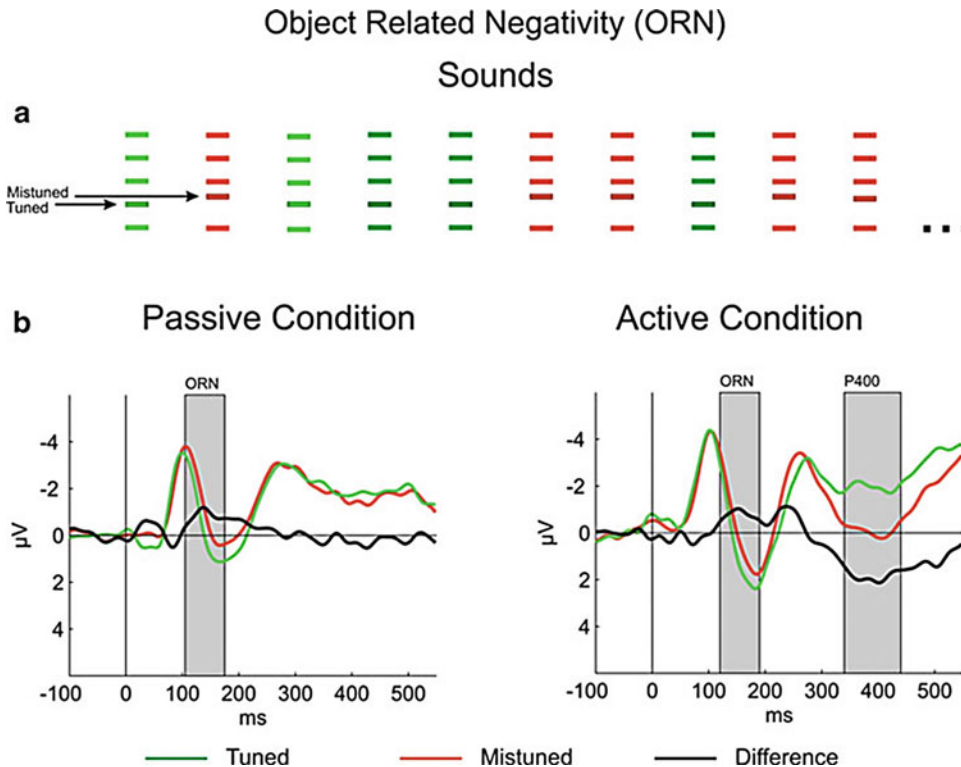
decreases sharply within the first few presentations, reaching an asymptote within 5–10 presentations (e.g., Cowan et al. 1993). Based on this finding, some authors argue that through adaptation (see ► [“Adaptation in Sensory Cortices, Models of”](#)), the neurons underlying the N1 response may retain all sound information and thus provide the basis for detecting violations of auditory regularities (May and Tiitinen 2010). However, this hypothesis is debated in the literature (e.g., Näätänen et al. 2011). The sensitivity of the auditory N1 wave to selective attention initially suggested that the difference between the N1 responses elicited by task-relevant (attended) and task-irrelevant (unattended) sounds (the Nd; Hillyard et al. 1973) may reflect an orientation to the attended auditory features and/or maintenance of the memory trace of the target sound. However, others argued that the differential response is separate from the N1, with the early part overlapping the N1 (termed Nd_e) assumed to reflect feature processing, and the later part (Nd_i, also termed the Processing Negativity, PN; Näätänen 1982; see PN in [“Attention-Related AERP Responses”](#)) the maintenance of the attentional trace (Koch et al. 2005; Näätänen et al. 2011).

Little is known about the auditory P2 (P175, P200; Fig. 1) AERP response. It has been mostly studied within the P1-N1-P2 or N1-P2 complex. P2 typically peaks between 175 and 200 ms from the event onset with positive polarity over the vertex, inverting polarity over the Sylvian fissure. The generators of P2 lie anterior to those of the N1 in secondary auditory areas (Mäkelä et al. 1988; Bosnyak et al. 2004). Lesion (Woods et al. 1993) and maturation studies (Ponton et al. 2000) suggest that P2 may reflect the output of the mesencephalic reticular activating system (see ► [“Anatomy and Physiology of the Mammalian Auditory System”](#)). Only a few studies have attempted to distinguish P2 from the N1 wave. The P2 amplitude was found to be more sensitive to perturbing the feedback of one’s voice than the N1 (Behroozmand et al. 2009) as well as to training with specific types of sounds (e.g., speech: Tremblay et al. 2001; music: Bosnyak et al. 2004; or frequency discrimination: Tong et al. 2009). There are several speculations regarding

the functions of the processes reflected by P2. Based on its assumed neural origin, P2 has been suggested to be generated by a pre-attentive alerting mechanism (Tremblay and Kraus 2002). Other suggestions include P2 reflecting stimulus classification (Crowley and Colrain 2004), modulating the threshold for conscious perception (Melara et al. 2002), protecting against interference from irrelevant stimuli (Garcia-Larrea et al. 1992), and the accuracy of memory traces in short-term memory (Atienza et al. 2002).

The *Object Related Negativity* (ORN) is elicited when more than one sound are simultaneously heard (Alain et al. 2001). Thus ORN reflects the outcome of the analysis of simultaneous (concurrent or vertical) auditory grouping

cues (cf. ► “Auditory Perceptual Organization”). Components of sounds emitted by a single source usually commence at the same time, they originate from the same spatial location and, if composed of discrete frequencies, they consist of harmonics derived from the same base (i.e., integer multiples of the same frequency). When the acoustic input does not meet these criteria, one usually experiences it as two or more concurrent sounds and ORN is elicited. ORN is typically recorded by presenting complex tones with one harmonic mistuned by 4% or more (Fig. 2, panel A) and derived by subtracting the response to the one-sound stimulus (e.g., tuned tone) from that to the multiple-sound stimulus (e.g., mistuned tone). ORN peaks between 140 and 180 ms from sound onset, with



Auditory Event-Related Potentials, Fig. 2 Object Related Negativity (ORN) (a) Complex tones with the second of five harmonics tuned (green) or mistuned upwards by 8% (red) were presented equiprobably in a sequence. (b) Group-averaged ($N = 20$, left; $N = 23$, right) AERP responses elicited by tuned and mistuned complex tones recorded at the vertex, separately in the passive (participants disregarded the sounds) and the active

condition (participants judged whether they heard one or two concurrent tones). Mistuned-minus-tuned difference waveforms (black) show a negative waveform appearing between 100 and 200 ms from sound onset in both task conditions. This is the ORN response (the range is marked by grey shading). The positive difference waveform observed in the 300–500 ms latency range in the Active Condition is termed the P400

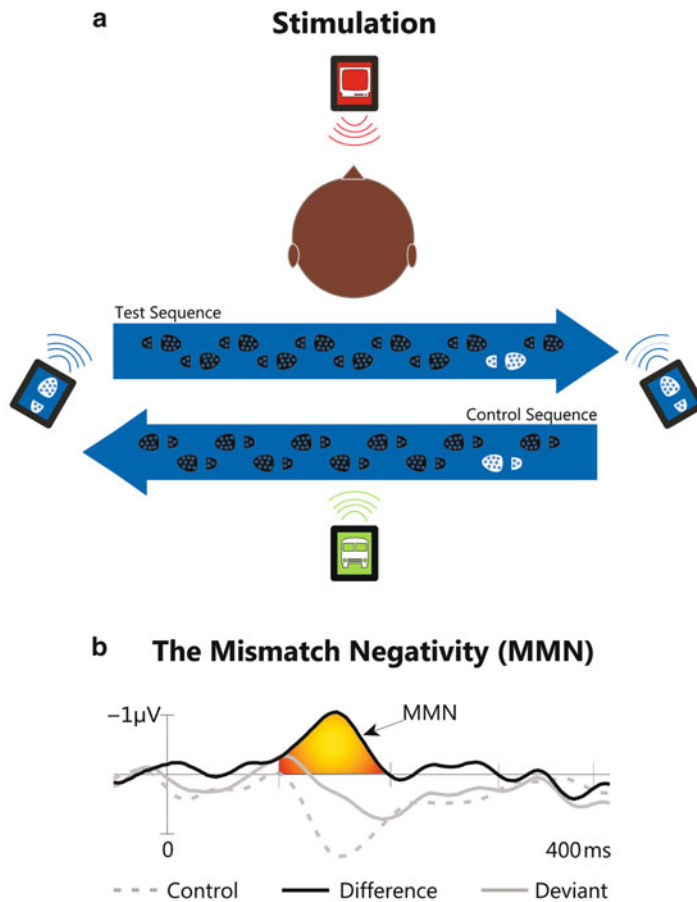
the largest amplitude over the fronto-central region of the scalp (Fig. 2, panel B *left*). ORN has bilateral neural generators in auditory cortex, which are separate from those of the previously described obligatory AERP responses (Arnott et al. 2001). Some studies have indicated the existence of two independent lateralized generator processes, since although ORN is elicited even when most tones in the sequence have been mistuned, the probability of mistuned sounds within the sequence differentially affected the ORN generators in the two hemispheres (Bendixen et al. 2010). If the listener is instructed to respond when he/she hears two concurrent sounds, a late positive response (P400) is elicited in addition to the ORN (Fig. 2, panel B *right*; Alain et al. 2001).

The auditory N2 (N200; Fig. 1) wave covers at least three (N2a or MMN, N2b, N2c; see Pritchard et al. 1991), possibly more AERP components (Folstein and Van Petten 2008) appearing partly overlapping in time between 150 and 300 ms from the eliciting event. The somewhat earlier N2a or MMN does not require attention to be focused on the event (cf. MMN), whereas the later components are related to attentive monitoring of the acoustic input and they are not specific to sounds.

The *Mismatch Negativity* (MMN, N2a) is an AERP component elicited by violations of auditory regularities (Winkler 2007; Näätänen et al. 2011; Fig. 3). MMN typically emerges between 100 and 200 ms from the onset of deviation with frontocentrally dominant negative polarity that is inverted over the Sylvian fissure. MMN generators are located bilaterally in secondary-auditory and frontal areas (Alho 1995). Although traditionally regarded as a component reflecting auditory change detection, technically, MMN does not reflect acoustic change, as for example, an alternating sequence of sounds does not elicit the MMN, whereas repeating a sound within such a sequence does (Horváth et al. 2001). MMN is derived by subtracting from the response elicited by the regularity-violating sound (termed “deviant”) the response elicited by a control sound. Optimally, the control sound is either identical or very similar to the deviant sound but does not violate any auditory regularity (for a detailed discussion of selecting the correct control, see Kujala

et al. 2007). MMN is elicited even when the sounds are task-irrelevant, although it can be suppressed by strongly focusing attention on a parallel auditory channel and/or by contextual information (Sussman 2007). Initially discovered within the oddball paradigm (Näätänen et al. 1978), MMN has since been observed for violations of a large variety of abstract and complex regularities (Näätänen et al. 2001). In parallel, its interpretation shifted from MMN being an AERP correlate of auditory sensory memory (Näätänen and Winkler 1999; Cowan 1984) tasked with detecting potentially relevant events in the auditory environment (Näätänen 1992) towards the compatible but more general notion of representing a process that updates the detected auditory regularities when their predictions are not met by the incoming sound (Winkler 2007). The latter interpretation links MMN with predictive coding theories (Friston 2005; Winkler and Czigler 2012) and posits that it plays a role in auditory stream segregation (cf. ► “Auditory Perceptual Organization”) by maintaining the predictive models underlying auditory perceptual objects (Winkler et al. 2009).

The *Repetition Positivity* (RP) appears as a fronto-central amplitude modulation of the P50, N1 and P2 AERP responses (Fig. 4); all three of them overlap the slow positive RP waveform so that the P50 and P2 become more positive and the N1 less negative with increasing number of repetitions of the eliciting sound (Haenschel et al. 2005; Costa-Faidella et al. 2011a, b). Similar stimulus repetition effects have been observed even at shorter latencies, during the MLR latency range (Dyson et al. 2005). The RP was first observed by Baldeweg et al. (2004) and characterized by Haenschel et al. (2005) in a study that aimed at investigating the neural correlates of the sensory memory trace implicated in the generation of the MMN. It was argued that the MMN amplitude dependence on the number of standard-stimulus repetitions preceding the deviant (e.g., Sams et al. 1983; Javitt et al. 1998) provides only an indirect measure of the strength of the underlying memory trace. The AERP elicited by the standard sound was expected to show effects of repetition suppression (Desimone 1996), as was

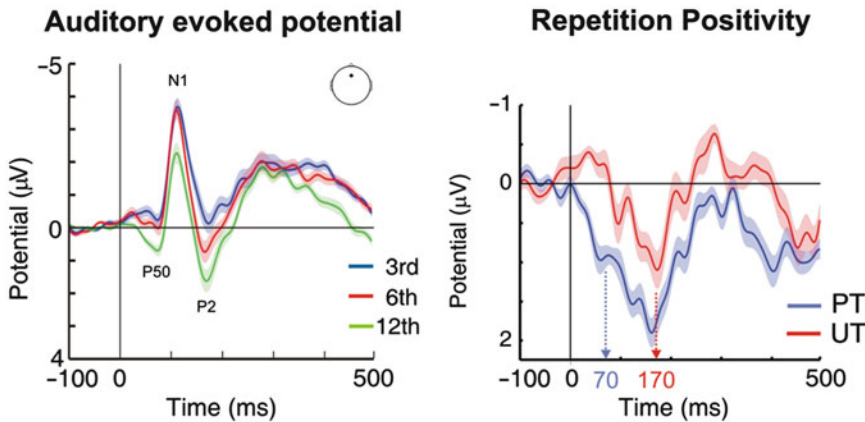


Auditory Event-Related Potentials, Fig. 3 The Mismatch Negativity (*MMN*). (a) The experimental setup. Participants watched and listened to a movie presented on a TV screen directly in front of them. A series of footsteps perceived as moving from left to right (Test Sequence; *upper arrow*) or right to left (Control Sequence; *lower arrow*) were delivered by a pair of loudspeakers placed symmetrically on two sides, slightly behind the participant's head. Ten out of the 11 different digitized natural footstep sounds (marked as *black footprints* on the *blue arrows*) could be perceived as a coherent sequence produced by someone walking across a room. The tenth footstep of the Test Sequence ("deviant") and the second footstep of the Control Sequence ("control") however sounded as if the person stepped on a different surface (marked by the *white footprint* on the *blue arrows*). Street noise was delivered through a loudspeaker placed directly behind the participant. (b) Group-averaged ($N = 8$) AERP responses elicited by the deviant (*continuous grey line*) and the identical control sound (*dashed grey line*) measured

from the frontal midline electrode. The MMN component, derived by subtracting the control response from that to the deviant (difference: *black line*) is marked with *yellow-orange* fill in the MMN latency range. The results illustrate that (1) *MMN* is only elicited when a sound violates a detected regularity, as the regular progression of footsteps needed to be detected and represented by the brain before it could be violated (which could not happen if only one "regular" footstep sound preceded the different one); (2) regularities can be extracted from acoustic variance as all regular footstep sounds were acoustically different; (3) regularities are separately maintained for concurrent auditory streams, as *MMN* was elicited for deviation in the footstep stream despite the presence of two other active sound sources; and (4) *MMN* elicitation does not require one to attend the stream in which a regularity has been violated, as participants in this experiment attended the movie, not the footsteps. (Adapted from Winkler et al. 2003)

observed for individual neurons in the primary auditory cortex of the cat (Ulanovsky et al. 2003), and this could provide a more direct

measure of the strength of standard-stimulus memory trace. The typical paradigm use for obtaining the RP is called the "roving-standard"



Auditory Event-Related Potentials, Fig. 4 The Repetition Positivity (RP). *Left:* Group-averaged ($N = 14$) frontal midline (marked on the schematic head drawing at the top right corner) AERPs elicited by pure tones in a roving-standard stimulus paradigm (see in the text). The panel shows AERPs (averaged across different frequencies) elicited for the 3rd (blue), 6th (red) and 12th (green) repetition of the same tone. Note that the positivity covering the latency range of the P50-N1-P2 waveform complex emerges at the sixth repetition and becomes more

pronounced by the 12th repetition. *Right:* Difference waveforms resulting from subtracting the response to the third repetition from that to the 12th repetition under two conditions: Predictable Timing (PT: isochronous presentation, blue) and Unpredictable Timing (UT: the within-train inter-onset interval was varied, red). Note that the onset of RP is earlier (ca. 70 ms post-stimulus) for the predictable than for the unpredictable timing condition (ca. 170 ms). (Adapted from Costa-Faidella et al. 2011a)

paradigm (introduced by Cowan et al. 1993), as the classical oddball paradigm yields less clear results (Cooper et al. 2013). In the roving-standard paradigm, short trains of a repeating sound are delivered without a break with each train delivering a different sound (e.g., pure tones with different frequencies). The number of sound repetitions can also vary from train to train. To separate the RP from other concurrent AERP components, the average response elicited by the second or the third of the train is subtracted from that elicited by the last tone of the train. The response to the first sound of the train is not used in the subtraction, because, due to the sound change between the trains, it should elicit the MMN (Haenschel et al. 2005; Costa-Faidella et al. 2011a, b). The generator structure of the RP has not yet been fully characterized, but its early onset latency (commencing during the P50) and its long duration (ending during the P2) suggest that it may involve a distributed cortical network spanning from PAC up to auditory association areas (Baldeweg 2007). The RP has been shown to simultaneously encode repetitions

over multiple time scales (Costa-Faidella et al. 2011b; Cooper et al. 2013) similarly to single neurons observed in the cat's PAC (Ulanovsky et al. 2004). In addition to stimulus repetition, the RP is also sensitive to temporal regularities, such as whether the sounds are presented isochronously or with random timing: Costa-Faidella et al. (2011a) found earlier and larger RP's for isochronous as compared with randomly timed tones in the trains. The latter result supports the predictive coding view of auditory deviance detection (Winkler 2007; Winkler and Czigler 2012), according to which detection of a regularity helps to encode the sensory memory trace of upcoming stimuli. Thus higher levels in the auditory processing hierarchy feed back to lower processing levels (Baldeweg 2006).

Auditory brain responses can also be elicited without hearing sounds. By omitting sounds from an isochronous sequence, one can record potentials time-locked to the moment when the sequence would have continued in a regular manner. The responses are termed the *Omitted Stimulus Response (OSR)*. Some of them are elicited

even when listeners don't focus on the sounds, thus demonstrating a basic tendency of the auditory system to generate predictions for incoming sounds (Friston 2005; Winkler et al. 2009). It has been shown that when all features of the upcoming sound can be predicted from the preceding sound sequence, the OSR elicited by sound omission during the first 50 ms does not differ from the AERP elicited by the sound itself; however, when only the timing of the sound can be predicted, but not its features, the OSR starts to differ from the corresponding AERP at an earlier time (Bendixen et al. 2009). When sounds are predictably caused by some action of the listener, occasionally omitting one elicits an AERP that is initially (up to ca. 100 ms) morphologically similar to that elicited by the corresponding self-initiated sound; although the brain generators underlying the two responses partly differ from each other (SanMiguel et al. 2013). There is also an MMN-like OSR (Yabe et al. 1999). Elicitation of these responses is limited to inter-onset-intervals (IOI) shorter than ca. 200 ms (Horváth et al. 2007), except when the omitted sound is part of a pattern (Salisbury 2012). With longer IOIs, an early posterior negative (180–280 ms) response and a later anterior positive wave have been obtained (Busse and Woldorff 2003). Further, ERP responses can also be elicited by mental imagery of sounds, although the results vary somewhat with the procedure employed (Meyer et al. 2007; Cebrian and Janata 2010; Wu et al. 2011).

Attention-Related AERP Responses

Attention-related AERPs include two distinct groups of responses: those related to involuntary (passive or exogenous) attention, and those related to voluntary, mainly selective attention. Regarding involuntary attention, at least three components have to be considered. The MMN (described above), or at least its frontal component (Giard et al. 1990; Deouell et al. 1998; Escera et al. 2000a; Deouell 2007), has been associated with involuntary attention (Näätänen and Michie 1979; Näätänen 1990, 1992). Some studies have also related the activation of the supratemporal MMN generator with behavioural correlates of

involuntary attention, i.e., delayed response times to target stimuli on a primary task (Yago et al. 2001). Näätänen and Michie (1979) proposed that the process generating MMN may issue a call for focal attention (Öhman 1979) upon the detection of an unexpected change in the acoustic environment. Initial supportive evidence was provided by Schröger (1996; Schröger and Wolff 1998a) and Escera et al. (1998), who introduced new auditory-auditory and auditory-visual distraction paradigms (for a more recent design, see Horváth and Winkler 2010). In these paradigms, participants are instructed to perform a primary auditory or visual task while ignoring rare task-irrelevant violations of an auditory regularity. Several studies have shown that these rare deviations prolong the reaction time and reduce the hit rate to target stimuli in the primary task (Escera and Corral 2007), thus demonstrating involuntary attention switching to the task-irrelevant deviations.

Following the MMN, AERPs recorded in the distraction paradigm display a fronto-central positive deflection ca. 250–350 ms from stimulus onset, termed the *P3a* or *novelty-P3*. *P3a* was first described by Squires et al. (1975) as an earlier and more frontal positive deflection compared to the later and more posterior *P3b* component (for a review on *P3b*, see Donchin and Coles 1988). Whereas *P3a* is elicited by rare task-irrelevant sounds, *P3b* is elicited by target sounds (for a detailed comparison between the *P3a* and *P3b*, see Polich 2007). *P3a* is also elicited by widely different and “novel” (unique, categorically different from the context) sounds (Knight 1984), hence it is sometimes referred to as the *novelty-P3* (for a discussion of whether the *P3a* and the *novelty-P3* can be considered as the same ERP component, see Simons et al. 2001). Compelling evidence linking the *novelty-P3* to the orienting reflex (OR; Sokolov 1963) was obtained by Knight (1996), who found strong correlation between the *novelty-P3* and one of the well-known autonomic components of OR, the galvanic skin response (GSR). The *P3a* is composed of two subcomponents distinctly differing in latency (early and late), scalp distribution, and

sensitivity to attentional manipulations (Escera et al. 2000a; Yago et al. 2003). Source modelling of the magnetic counterpart of P3a (P3am) elicited by auditory deviants and novel sounds has revealed a genuine auditory cortical contribution to the early part of P3a (Alho et al. 1998). Whereas the early part of the novelty-P3 appears to be insensitive to attentional manipulations (Escera et al. 1998), the later part is modulated by working memory (SanMiguel et al. 2008) and emotional load (Domínguez-Borràs et al. 2008). The early P3a is sensitive to stimulus-specific information predicting task-irrelevant auditory deviance, whereas the late P3a appears to be more closely correlated with distraction (Horváth et al. 2011). P3a is widely regarded as a correlate of attention switching (Escera et al. 2000a; Friedman et al. 2001). However, some recent studies suggested that although P3a is probably an antecedent of attention switching it can be elicited without a corresponding shift in the focus of attention (Rinne et al. 2006; Horváth et al. 2008b; Horváth and Winkler 2010; Hölig and Berti 2010).

The third involuntary attention related AERP component is the so-called *Reorienting Negativity* (RON), first described by Schröger and Wolff (1998b). RON is observed as a negative deflection following the P3a (Escera and Corral 2007). RON has been suggested to reflect processes of reorientation (restoring the task set of the primary task) after a distracting stimulus. RON is composed of two subcomponents (Escera et al. 2001; Munka and Berti 2006; Berti 2008) the functional characterization of which are still debated (Escera et al. 2001; Berti 2008). The cortical generators of RON are not well known. Horváth et al. (2008a) found contributions from primary motor areas to RON, suggesting that action-selection related activity plays a role in the reorientation process. Both P3a and RON as well as behavioural correlates of distraction (but not MMN) are eliminated or at least strongly diminished when the task-irrelevant deviant is predicted by a visual cue (Sussman et al. 2003; Horváth and Bendixen 2012). Cues that provide more specific information about the distracting stimulus are more effective in preventing

distraction and the elicitation of P3a and RON (Horváth et al. 2011).

Selective attention related AERPs have been traditionally studied in the context of the classical “cocktail-party” situation described by Cherry (1953). In the simplified dichotic listening model of this situation, participants are exposed to two concurrent messages (one to each ear). Using this paradigm, many studies attempted to decide between the “early” (Treisman 1964; Treisman 1998; Broadbent 1970) versus “late” selection theories of attention (Deutsch and Deutsch 1963; Norman 1968). These theories of attention primarily differ from each other in the placement of a selective filter within the chain of information processing (Broadbent 1958): whereas early selection theories suggest that stimuli are selected for elaborate processing based on simple sensory features (such as pitch) and unattended stimuli do not receive processing beyond extracting these sensory features, late selection theories propose that all stimuli receive elaborate processing and stimuli can therefore be selected on the basis of higher-order properties. (Note that more recent theories of attention do not posit a single selective filter; see e.g., Lavie 1995.) The seminal observation by Hillyard et al. (1973) that selective attention enhances the N1 amplitude for stimuli presented in the to-be-attended channel favoured the early filtering view. However, the findings of Näätänen et al. (1978) of a long-lasting negativity elicited by all attended stimuli, the *Processing Negativity* (PN; Näätänen 1982) challenged this interpretation providing support to late-selection theories. Subsequent studies confirmed both of these effects (Okita 1979; Hansen and Hillyard 1980; Näätänen et al. 1980) and proposed subtraction of the AERP elicited by the non-attended stimuli from that elicited by the attended stimuli as the method to reveal the *Negative Difference* (N_d) potential to isolate the AERP correlates of selective attention (N_d ; Hansen and Hillyard 1980). The N_d is composed of two parts: the early one, termed N_{de} , associated with a gating mechanism preferentially processing the task-relevant stimulus features, and a later part (N_{dl}) related to the maintenance of the attentional trace (correspond to the PN). The functional distinction

between the Nd and PN has been debated in detail (Alho et al. 1986a; Alho et al. 1986b; Alho et al. 1994; Teder et al. 1993). Studies showing very early selective attention effects, e.g., at the latency range of the MLR (Woldorff et al. 1987; Woldorff and Hillyard 1991) and possibly even earlier, at the level of the cochlea (Giard et al. 1994) support the interpretation of the Nd_e as a correlate of gating by simple stimulus features. On the other hand, the fact, that the more similar the stimulus to the target the longer the corresponding PN, supports the notion of a comparison with the attentional trace. The frontal scalp distribution of Nd_i (Woods and Clayworth 1987) and the cerebral sources of PN (Giard et al. 1988) are also compatible with the memory-based interpretation of Nd_i. There are several further ERP components related to various facets of attention. However, these are not specific to the auditory modality and thus fall outside the scope of this entry.

AERPs Reflecting Speech and Music processing

The sounds of speech and music may elicit any and all the AERP responses described above. There are, however, also some ERP responses, which arise from events that can be defined in syntactic or semantic terms. It should be noted that most speech-related ERPs can also be elicited through reading. Most AERP responses specific to speech and music have been obtained in paradigms, in which the expectation for the most likely (or simplest) continuation of a sequence of words has been violated. For example, violating the expectation for the first phoneme of the upcoming word elicits a negative shift in the 150–350 ms latency range, termed the *Phonological Mismatch Negativity* (PMN; Connolly and Phillips 1994). It is, however, debated, whether this response can be separated from that elicited by words, which are semantically incongruent with respect to the preceding context (D'Arcy et al. 2004; Van den Brink and Hagoort 2004). Violating speech syntax can lead to the elicitation of the *Early Left Anterior Negativity* (ELAN) in the 150–200 or the *Left Anterior Negativity* (LAN) in the 300–500 ms latency range, depending on the type of violation, whereas potentially correct

but syntactically complex sentences elicit the *Syntactic Positive Shift* (SPS or P600) (for reviews, see Friederici 2002; Hagoort 2008). Violating semantic expectations in speech elicits the N400 component (Kutas and Federmeier 2011). Musical syntax violations elicit an ELAN-like but predominantly right-hemispheric response, the *Early Right Anterior Negativity* (ERAN) in the 180–200 ms or the *Right Anterior-Temporal Negativity* (RATN) in the 200–400 ms latency range and N400 has been also observed in musical models of semantic incongruence (Koelsch and Siebel 2005). For a more detailed discussion of speech- and music-related ERPs, see ► “Electrophysiological Indices of Speech Processing” and ► “Music Processing in the Brain”.

Development of AERPs

Previous sections described the AERP responses elicited in adults. Although AERPs can be recorded immediately after birth and even in fetuses within the womb (Draganova et al. 2005), their morphology and functional characteristics widely differ from the adult responses. Further, different AERP components become mature at different times and they often undergo several intermediate phases before reaching adult-like characteristics. As this topic would require a full entry of its own, here we point the reader to some of the existing literature. The most complete reviews of the maturation of AERPs from infancy to adolescence were provided by Wunderlich et al. (2006) and Coch and Gullick (2012). The early infantile development of the AERP components has been summarized by Kushnerenko (2003); for the maturation of the AERPs reflecting auditory change detection, see Jing and Benasich (2006), for large deviations, see Kushnerenko et al. (2013). The maturation of obligatory AERP components from 5 to 20 years of age is covered in Ponton et al. (2000, 2002). AERP maturation during adolescence is described in Bishop et al. (2007). Summarizing these works, one can conclude that the adult AERP morphology characterizes humans from 17/18 years onward and remains more or less unchanged through ageing. There are, however several findings of differences between elderly

and young adults in specific tasks (for a review, see Friedman 2012).

Modelling AERP's: Some General Principles

Theories that seek to explain some of the LLRs have also been explored using more tightly constrained mathematical and computational models. Here we focus on models of the mismatch negativity (MMN) component, as it has arguably received the most widespread attention. Theoretically, MMN has been variously associated with change detection, adaptation, prediction error, novelty detection, and model adjustment, although for some years, there has been controversy as to whether anything more than adaptation is required to explain the experimental data (e.g., see May and Tiitinen 2010 vs. Näätänen et al. 2011).

Using a modelling framework in which exemplars of each of the competing explanations, listed above, were expressed as mathematical functions of stimulation-induced changes in an *unobservable* 'internal state' and resulting *observable* (EEG) responses, Lieder et al. (2013) investigated the ability of each model to explain empirical MMN responses on a trial-by-trial basis. The models were expressed in a rather abstract way, as summarized below, with simple expressions for internal state and response functions (intended to predict stimulus-evoked MMN amplitudes), that captured a range of possibilities for each of the categories. Change detection was modelled with the internal state simply a record of the log frequency of the previous tone in the sequence, and response functions as: a) a flag, set if a difference was detected, b) the signed and c) absolute difference between the frequency of the incoming and previous tone; giving three change detection models. Adaptation was modelled by the exponential decay and recovery of the internal state variable associated with each stimulus frequency, and the response function as a read out of the internal state corresponding to the incoming stimulus. The internal state for the prediction error, novelty detection, and model adjustment accounts was modelled as a Bayesian observer's belief in the tone category of the stimulus, with the evolution of tone category modelled

according to a transition matrix derived incrementally from the data according to the 'free-energy-minimisation principle' (Friston 2005). Two prediction error response functions were modelled: prediction errors with respect to sensory input and internal state, respectively. Novelty response functions were modelled as surprise about sensory input and temporal structure (tone category), respectively. Model adjustment response functions were modelled in terms of adjustments to the parameters of the internal model, e.g. mean frequency of a category, expected sequence length, transition probabilities between categories. Simulations showed that, at least at this level of detail, prediction error (with respect to tone category) and model adjustment models (change in expected sequence length, change in transition probabilities between categories), accounted best for the data (Lieder et al. 2013).

On the other hand, May and Tiitinen (2010) have argued strongly that their neural model which includes adaptation on the inputs can explain all MMN data to date; the key mechanism being the activation of fresh afferents by stimuli that deviate in some way from the standards. In this account, MMN is seen as a modulation of the N1 component rather than as a separate component in its own right. The model, consisting of a bank of neural oscillators driven via adapting input synapses, can account for the latency as well as the amplitude of the MMN (May et al. 1999). In addition, extending the model to include local inhibitory feedback circuits, results in a set of non-homogeneous band-pass temporal filters that can also support the topographic representation of stimulus presentation rate (May and Tiitinen 2001). Ringing in these filters is argued to account for the MMN elicited by a missing expected sound. Diverse receptive fields, e.g. to frequency modulations, also allow the model to simulate MMN responses elicited by violations of some abstract rules, such as a repeated tone in a random pattern of ascending tone pairs. However, although adaptation is claimed to be the key to MMN, the model responses also depend upon the amplification of recurrent excitation, lateral inhibition, and the connectivity of the network. The

model thus essentially contains within its changing pattern of adaptation and inhibition, a memory trace of recent activation, and in this sense, contains a memory component embedded within it.

Building on their previous work on a brain-inspired architecture for learning long-term representations of action-perception associations, Garagnani and Pulvermüller (2011) proposed a similar model in which, in addition to adaptation and inhibition, spreading activation through circuits strengthened by learning (long term memory) caused MMN responses to familiar deviants to be larger than that to unfamiliar deviants. They pointed out that only through some form of long term memory mechanism could this differential sensitivity of MMN to familiarity/unfamiliarity be explained. By modelling multiple auditory areas they also provided a novel explanation for differences between the N1 and MMN generators, with N1 being generated in primary auditory areas subject to strong adaptation, and MMN in addition to adaptation also being influenced by reverberating excitation within distributed memory circuits. However, the model processes sequences of static patterns, and as presented, it is not able to account for the sensitivity of MMN to unexpected changes in the timing of sequences, such as the omission MMN (Yabe et al. 1997).

A model that explicitly includes a separate memory module to keep track of the short term history of activation and simulates MMN at a finer level of granularity, i.e. at the level of spiking neurons, was proposed by Wacongne et al. (2012). Memory in the model is implemented using a set of neurons organised into a delay line, i.e. their connectivity ensures that activity passes in one direction across the population, and the progress of activity through this population explicitly represents the timing of the previous event, up to 400 ms. Separate delay lines are used for each tone frequency modelled, thereby also recording their identity. The model simulates MMN by means of prediction errors. Through exposure to tone sequences it learns to generate a prediction of the next tone (both its timing and identity) in a repeating pattern. These predictions are compared with the incoming stimuli in the prediction error units, where mismatches result

in a larger signal than matches. The model learns transition probabilities between successive events, as long as they fit within its fixed memory span. In contrast to the adaptation account of MMN, the model relies exclusively on prediction errors. An experiment designed to distinguish between these two explanations for MMN found evidence in favour of a predictive error model of MMN (Wacongne et al. 2012), a result compatible with the findings of Lieder et al. (2013).

A predictive coding account of MMN has also been modelled at a more abstract level using a Kalman filtering (Kalman 1960) approach (Kaya and Elhilali 2013). In this case the timing of events is modelled using a separate filter from the one used to model feature distributions. The advantage of the Kalman filter is that it provides a well-understood way to recursively estimate the system state, refined through analysis of prediction errors, and has been shown to be implementable in the form of a neural network (Szirtes et al. 2005). The model adapts to the variance in observations and, with time, as its predictions improve so its tolerance decreases, making it more sensitive to outliers. Deviants are detected as events not predicted by any existing filter, and trigger the creation of a new set of Kalman filters intended to model a potentially new sound source, making this an interesting framework for more general auditory scene analysis problems, e.g. (Chakrabarty and Elhilali 2013).

In summary, computational models of the theoretical accounts of MMN have begun to be explored. However, so far they have either only been implemented at a rather abstract level; e.g. (Garrido et al. 2009; Lieder et al. 2013; Kaya and Elhilali 2013), focus exclusively on a single mechanism for explaining MMN; e.g. (May and Tiitinen 2001; Wacongne et al. 2012) or account only for MMN responses to unexpected within-event properties (Garagnani and Pulvermüller 2011; Garagnani et al. 2008). The finding, using dynamic causal modelling, that modifications to both feed forward and feedback connections are required (Garrido et al. 2009), and evidence in auditory cortex for adaptation, short term and long term plasticity, recurrent excitation

and inhibition suggests that MMN in the brain may actually depend on the combination of all these factors. Furthermore, while the learning of transition probabilities may be sufficient for some scenarios, in the short term at least, people become sensitive to specific tone patterns; it is unclear whether any of the models discussed here could respond differentially to violations of more extended pattern sequences or more abstract rules.

Utility of AERP for Clinical Practice

Clinical applications of AERPs range from routine practice in audiology, neurotology, neurology, and neurosurgery by ABRs and MLRs (Picton 2010) to highly promising tools for cognitive assessment by some long-latency endogenous components, of which MMN is a prime example. In audiology, ABRs are used universally for hearing screening in neonates failing the Otoacoustic Emission test (OAEs; Robinette and Glatcke 2007). Currently, about 97% of infants are screened for hearing impairment in the USA (Gaffney et al. 2010). ABRs, elicited by click stimuli, are used as a tool for objective audiometry, and ABRs elicited by pure tones can also be used for assessing frequency-specific thresholds in infants (Stapells and Oates 1997; Stapells et al. 1993). In neurotology and neurology, AERPs are combined with the patient's medical history and with an extensive battery of tests for evaluating the anatomy and functional properties of the ear-brain relationship (Picton 2010) in search for an extensive range of disorders of the ear and the auditory pathway, such as Ménière's disease and demyelinating lesions such as Multiple Sclerosis. In these applications, AERPs are used to determine conduction times along the auditory pathway and to localize the anatomical locus of the brain damage with the help of the known origin of the different ABR waveforms (see reviews in Baloh 1997; Chiappa 1997; Lustig et al. 2003). In addition, ABRs are used in combination with evoked potentials from other modalities to monitor coma prognosis (Guérit 2005; Fischer et al. 2006; see below), or in isolation to corroborate brain death (Machado et al. 1991). In the surgical theatre, MLR is used to monitor the depth of

anaesthesia in adults (Bell et al. 2004) and children (Kuhnle et al. 2013). It has been recently shown that, compared with the traditional clinical assessment of depth of anaesthesia, MLR monitoring led to a reduction in (a) the amount anaesthetic drug requirement, (b) the use of vasopressors to manage hypotension, and (c) consequential cognitive impairment (Jildenstål et al. 2011).

Regarding cognitive AEPRs, MMN (see above) has shown great promise for potential clinical applications (Näätänen and Escera 2000). Part of this expectation stems from the fact that MMN indexes auditory discrimination accuracy without the requirement to perform some task (i.e., it can be recorded without the patient's collaboration and even in newborn infants; see Alho et al. 1990) and that it can be elicited very reliably, compared with other cognitive event-related potentials (Escera and Grau 1996; Escera et al. 2000b). Yet, after two decades of clinical research (see Näätänen et al. 2012), except for coma monitoring and prognosis no routine clinical application has emerged for the MMN. As for coma monitoring, it has been demonstrated that the presence of MMN in a comatose patient is associated with the return of consciousness (Kane et al. 1993; Fischer et al. 1999), and that as part of a battery of physiological indicators of brain activity, MMN can be used in the decision tree for estimating awakening from coma (Fischer et al. 2006). Given the large variety of disorders and clinical conditions in which impaired MMNs have been observed, it has been suggested that, rather than providing a specific diagnostic measure for any particular disease, the MMN provides an objective index of dysfunction of *N*-methyl-D-aspartate (NMDA) receptor-mediated cognitive functions (Näätänen et al. 2011). In general, due to their high variability and complex functional and anatomical origin, endogenous AERPs can only be employed within large test batteries for diagnostic and monitoring purposes. However, some of these responses provided new insights into the cognitive and emotional aspects of various neurological and psychiatric disorders (e.g., for schizophrenia research using MMN, see Mondragón-Maya et al. 2011).

AERPs: Advantages and Limitations

(A)ERPs provide information about sound-elicited neural activity with millisecond accuracy. Thus they are ideally suited for breaking down the steps of auditory information processing in the brain in the empiricist tradition. It is thus understandable that some of the most recent theoretical developments in the field (e.g., predictive coding theories; Friston 2005) trace back their roots to Helmholtz' (1860/1962) theories of perception. High temporal resolution coupled with the possibility of finding the neural generators of the various ERP responses is also appealing to neurologists and medical doctors, in general. By finding correlations between AERPs and conscious perception on the one hand (such as the link between ORN and the perception of two concurrent sounds; Alain et al. 2001), and discovering the neural mechanisms underlying the observed AERP waveforms on the other hand (e.g., linking SSA and the deviance-detection responses observed in the MLR latency range; Slabu et al. 2010; Grimm et al. 2011; for a review, see Ayala and Malmierca 2013), AERPs can provide a crucial link in understanding the neural mechanisms of perception.

However, there are a number of limitations to the utility of (A)ERPs for research and applications. Firstly, they only reflect a part of the information processing in the brain. When the number of neurons involved in some process is relatively small, or the neurons are distributed over a large area in the brain, or the neural activation is not fully time-locked to the given auditory event, no ERP can be measured. Other methods, such as time-frequency analysis of the EEG, provide better information about these types of processes. AERPs are usually smaller than their visual counterparts. Consequently the signal to noise ratio, where activity not time-locked to the sound onset is regarded as noise, is quite low. This forces one to present many trials to the participant and rely on assumptions which are not fully met by the EEG signal (such as the independence of the signal from the noise, ergodicity, etc.). Further, the accuracy of localizing the sources of neuroelectric activity is limited by the quality of constraints (e.g., anatomical knowledge) required to solve

the inverse problem, and the dispersion of the electrical fields. Although magnetoencephalography provides a better spatial resolution, as was already mentioned, AEFs only reflect tangential sources, but not radial ones, thus restricting their general usefulness. In terms of spatial accuracy, other neuroimaging methods, such as fMRI, provide a superior alternative (at the cost of much lower temporal resolution). Further, the correspondence between perception and AERP responses is often not straightforward, as can be gleaned from the often controversial psychological interpretations mentioned in the main text of this entry. Few AERP components can be consistently observed across different stimulus paradigms, thus limiting the validity of most process-based interpretations. Efforts to discover the neural bases of ERP responses must overcome many obstacles. One of the most difficult problems is that whereas individual neurons can mainly be studied in animal models due to the invasive nature of such investigations, it is often difficult to assess how well findings in various species can be extended to characterizing the human brain. Finally, the biggest issue for clinical applications is, as was already mentioned, the large inter- and even intra-individual variability of AERPs.

In summary, AERPs can potentially provide much information about sound processing in the brain, but for extracting this information, better theories and more tightly constrained models, which can integrate information from the diverse fields of anatomy, neuroscience, and psychology, are required.

Cross-References

- [Adaptation in Sensory Cortices, Models of](#)
- [Anatomy and Physiology of the Mammalian Auditory System](#)
- [Auditory Evoked Brainstem Responses](#)
- [Auditory Perceptual Organization](#)
- [Brain Imaging: Overview](#)
- [Electrophysiological Indices of Speech Processing](#)
- [Music Processing in the Brain](#)

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Auditory Evoked Brainstem Responses

► Auditory Brainstem Responses

Auditory Evoked Field (AEF)

► Auditory Event-Related Potentials

Auditory Evoked Potential (AEP)

► Auditory Event-Related Potentials

Auditory Frequency-Following Responses

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Synonyms

Complex auditory brainstem response (cABR); Envelope-following response (EFR); Speech auditory brainstem response (sABR)

Definition

The frequency-following response (FFR) is a sustained auditory evoked potential that reflects synchronous neural phase-locking to the spectrotemporal components of the acoustic signal. FFRs are recorded noninvasively from the scalp with electroencephalography (EEG) and with magnetoencephalography (MEG) and emerge at circa 7–15 ms from sound onset to auditory frequencies in the range 100–1500 Hz. By reflecting phase-locked activity to the incoming sounds, FFRs faithfully mimic and are as complex as the eliciting stimulus as it unfolds in time, so that they can be recognized as such when played through a speaker. The FFR has gained recent interest in auditory cognitive neuroscience as it captures with great fidelity the tracking accuracy of the periodic sound features in the ascending auditory system. By decomposing the FFR in the temporal and spectral domains, it is possible to read neural traces from the scalp as sounds are transcribed in neuronal aggregates and

how these neural sound traces are shaped by experience, context, and challenging conditions, such as listening in noise, with age and in speech and language disorders.

Detailed Description

Introduction to the FFR

The auditory system is essential for us humans, as it allows to make sense of the sounds around us and to decipher the complex spectrotemporal signals hidden in the ongoing acoustic flow, hence supporting human communication, building our cognitive system through the use of language, and promoting social interaction through the joy of music. Acoustic signals are transduced into a neural code in the inner ear and then released through the auditory nerve to the central nervous system. Understanding how the central auditory system encodes for the different spectrotemporal attributes of sounds and isolates different auditory objects is thus capital to understand the way we use sounds to communicate and interact with others, and the frequency-following response provides a valuable neurophysiological tool to unravel these mysteries. The FFR was originally recorded in animal preparations of the auditory nerve and ascending fibers of the auditory pathway as synchronous phase-locked activity in neuronal aggregates elicited to pure tone stimuli. In humans, it was first recorded by Moushegian, Rupert, and Stillman in 1973 (Moushegian et al. 1973) to pure tone stimuli of frequencies of 0.25, 0.5, 1.0, 1.5, and 2.0 kHz, as they could show compelling evidence of the neuroelectric recordings to follow the cycles of the eliciting stimuli at these different frequencies, and of these neuroelectric signals being of central nervous origin.

The FFR is currently conceived to reflect an aggregation of phase-locked neural activity from multiple generators along the auditory system, although it has been considered for long as a putative measure of subcortical sound encoding. The FFR can be obtained under passive and active listening paradigms, and it is highly sensitive to context-dependent contingencies and to real-time

statistical properties of the incoming stimulation (Escera 2017). It is also modulated by short-term auditory training and lifelong auditory experience, including musical training and linguistic competence. Consequently, the FFR has become a major tool in the assessment of the neural encoding of speech sounds in both healthy and clinical populations (Kraus et al. 2017). By means of a range of analytical tools in the temporal and spectral domains, the FFR provides an objective indicator of the fundamental acoustic features intrinsic to speech sounds, including timing (onsets), pitch (fundamental frequency, F0), and timbre (the harmonics information). Specifically, it informs about the latency and amplitude of the auditory input in the time domain and the magnitude of the fundamental frequency and its harmonics in the frequency domain (Kraus et al. 2017) (Fig. 1).

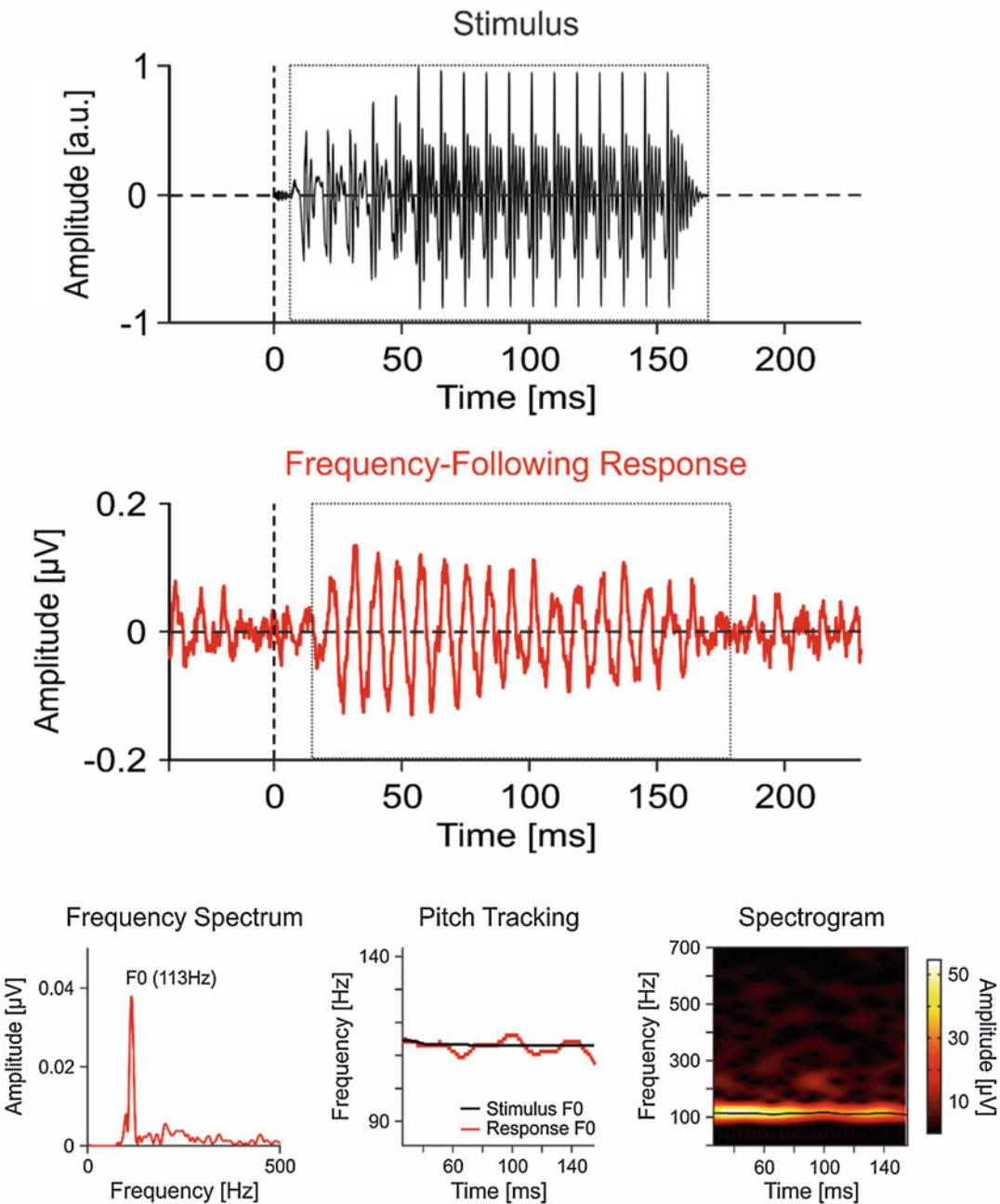
While the term frequency-following response is the most broadly used and probably the most comprehensive one, there are other terms that have been used interchangeably or which highlight a specific aspect or variant in the response. These include *complex auditory brainstem response* (cABR), *speech auditory brainstem response* (sABR), *envelope-following response* (EFR), and *amplitude-modulation following response* (AMFR). As seen, some of these variants refer to the auditory brainstem response (ABR) for good technical reasons: FFRs are recorded with the same equipment and settings as the ABR. In fact, the ABRs can be decomposed into two distinct components, the transient-evoked responses and the FFR (see entry ► “Auditory Brainstem Responses”). In addition, as introduced above and explained in further detail below in this entry, the use of the term “brainstem” in naming this auditory evoked potential conveys an anatomical implication that has been overcome by the available evidence. Indeed, FFR was considered since seminal studies to have a primary origin in the inferior colliculus of the auditory midbrain, yet recent studies have indicated that the FFR represents an integrated response of the entire auditory system, with contributions from both subcortical but also cortical centers. Therefore, including anatomical indications on the terminology can lead to

misconception. Overall, the scientific community has agreed to the term FFR being the most appropriate one, as it only refers to what the component is: a response that follows the frequency of the incoming stimulus (Kraus et al. 2017).

Importantly, the FFR has a great potential to inform basic and applied questions in learning and communication. Throughout this entry we will review the technical considerations for recording the FFR and computing a large range of FFR-derived measures. We will also discuss its neural origins and how it develops throughout the individual’s life-span. Finally, we will characterize the FFR by showing its sensitivity to different auditory contexts and experiences and its role in the study of clinical conditions.

Recording the FFR: Technical Considerations

Selecting appropriate stimuli to elicit reliable FFRs depends on several factors, including specific research purposes as well as taking into account the properties of the electrophysiological response per se. Some of the most commonly used stimuli include *pure tones* (i.e., simple sinusoids), which allow the assessment of responses phase-locked to the sound waveform (response peaks appear with the same periodicity than in the eliciting stimulus); *amplitude-modulated tones*, enabling the study of responses to the amplitude envelope; *complex tones*, used to study both the encoding of different spectral components and the periodic aspects of the sound; *synthetic vowels* and *natural vowels*, used to study the encoding of vowel formant structure with linguistic material; *consonant-vowel syllables*, possibly the best studied, allowing to reveal the encoding of fast formant transitions and sustained responses to vowels (e.g., /da/ vs. /ga/) as well as meaningful pitch contours in tonal languages (slower changes in sound periodicity, e.g., in Mandarin lexical tones); *musical sounds* from different musical instruments, used to study the encoding of harmonic structure and other timbre characteristics; and even *iterated rippled noises*, which are noise stimuli with periodic structure that can be used to study the emergence of perceptual pitch and its neural encoding (Chandrasekaran and Kraus 2010; Skoe and Kraus 2010a).



Auditory Frequency-Following Responses, Fig. 1 Morphology and characteristics of the human scalp-recorded FFR. The frequency-following response (FFR) can be recorded to complex auditory stimuli, such as a consonant-vowel /da/ utterance (upper panel). The middle panel shows the FFR recorded from the Fpz electrode in one single individual (human neonate) to such a stimulus. As can be appreciated, the FFR faithfully mimics the incoming stimulus by phase-locking to its temporal features; notice

the same number of cycles within the framed portion in both the stimulus and the neural response. The central origin of the FFR, as opposing to a cochlear origin, is reflected by the short delay in the emergence of phase-locked neuroelectric signal, which corresponds to the neural delay the signal needs to reach the central generating structures within the auditory pathway. In addition to phase-locking to the stimulus temporal components, the FFR also encodes for the spectral features of the incoming stimulus, as can be seen

All these stimulus types are fully periodic or contain periodic sections, and, in order to elicit robust FFRs, their fundamental frequencies (F0) usually range between 80 and 300 Hz, falling within the natural speech range. Their frequency content may span up to 10 kHz, but the FFR signal becomes weaker with increasing frequency (Greenberg 1980), and its phase-locking limits are around 1500 Hz. However, most of the spectral information needed to distinguish vowels is well below 3000 Hz. Stimuli are commonly delivered binaurally at conversational suprathreshold intensities (60–85 dB SPL) to approach naturalistic settings, although monaural stimulation can as well be used. Stimulus duration ranges from several tens of milliseconds to seconds (e.g., 40 ms to 2 s), and interstimulus intervals also vary widely, only limited by experimental time constraints, which may depend on the studied population (recording sessions are shorter in babies or patients suffering from different conditions than in young healthy adults). A common practice is to deliver half of the stimuli with opposite polarity (180° phase shift) to allow averaging and subtracting responses across polarities in order to emphasize responses to the sound envelope (useful to extract pitch tracking measures) or to the spectral content (and study vowel formant structure encoding), respectively (Aiken and Picton 2008; Skoe and Kraus 2010a). Given the small amplitude of the FFR signal (i.e., in the range of a tenth of a μV), a typical recording needs roughly 1000–2000 stimulus presentations to be averaged further per polarity (if applicable).

FFRs are typically recorded with scalp electrodes using essentially the same montage and settings than those used to record ABRs (see entry ► “Auditory Brainstem Responses”). In a characteristic montage, an active electrode is placed over the vertex of the scalp or on top of the forehead; a reference electrode is placed on an earlobe (or the mastoid or a high vertebra, at the expense of muscle noise and bone vibration), and a ground electrode is located either on the other earlobe or on the middle of the forehead (Skoe and Kraus 2010a). Impedances are usually kept below 5000 Ω . Recording sampling rate should be at least as high as the double of the highest sound frequency to be studied, although researchers usually oversample (10 or 20 kHz) in order to obtain fine temporal variations in the signal that could be informative (Skoe and Kraus 2010a).

Regarding the most common analysis methods, the FFR is generally computed as an auditory event-related potential (see entry ► “Auditory Event-Related Potentials”) by averaging or sub-averaging per polarity the total number of available trials, in windows lasting typically from –40 ms to 20 ms poststimulus ending. Importantly, the FFR can be distinguished from the cochlear microphonic, a receptor potential generated in the outer hair cells that mimics the incoming stimulus, as the FFR has a 6–10 ms delay poststimulus onset/peaks, while the cochlear microphonic is nearly coincident with the stimulus waveform, or by cancelling the latter via averaging responses to opposite stimulus polarities (Skoe and Kraus 2010a).

Due to the shared characteristics between the FFR and the sound used to elicit it, most of the

Auditory Frequency-Following Responses, Fig. 1 (continued) in the *frequency spectrum*, *pitch tracking* accuracy, and *spectrograms* computed from FFR of this very same individual (bottom panel). The *frequency spectrum* illustrates the amplitude spectral decomposition of the whole FFR, which reveals a clear peak corresponding to the stimulus fundamental frequency. *Pitch tracking* accuracy provides a measure of the ability to track changes in the fundamental frequency along the stimulus entire duration (stimulus frequency depicted in black; response tracking in red). The *spectrogram* provides combined information regarding the frequency and the amplitude at

which the FFR is phase-locked to the different spectral components of the incoming stimulus along its entire duration. The color scale from black to white indicates the spectral amplitude in μV , with lighter colors depicting highest amplitude values. Overall, this figure illustrates how the FFR faithfully tracks the eliciting stimulus and its complexity even in a single individual, thus providing a valuable tool to address issues in auditory cognitive neuroscience as well as the assessment of hearing abilities at individual level. Figure adapted and reproduced with permission from Ribas-Prats et al. (2019)

analyses and interpretation on FFRs are based on the acoustic properties of the stimulus, assessing timing and neural synchrony magnitude, as well as phase-locking strength and precision (Skoe and Kraus 2010a). The following are common parameters that are extracted from time and frequency domains, in fixed or sliding windows (to capture changes as a function of time), attempting to disentangle several auditory neural processing features that the FFR may reveal: *stimulus-to-response cross-correlation*, showing the accuracy with which the FFR replicates the stimulus waveform; *neural lag*, an estimation of the temporal delay between stimulus and response; *consistency*, a measure of neural response stability; *root mean square (RMS) amplitude*, indicating the overall magnitude of neural activity over a determined period of time; *pitch strength*, a measure of periodicity based on autocorrelation that reflects the robustness of the response's phase-locking to the stimulus F0 contour; *pitch error*, a measure of how faithfully the FFR encodes the pitch along the stimulus duration, measured as a difference in Hz from the stimulus F0 contour; *spectral amplitude*, usually computed with fast Fourier transform, indicating the magnitude of neural phase-locking at a certain frequency (F0 and harmonics); and *points below noise floor*, describing how the signal can be differentiated from baseline (i.e., pre-stimulus) noise (see Ribas-Prats et al. 2019, for an empirical implementation of all these measures).

Neural Generators

Despite the accumulation of studies on the neural origins of the FFR, no clear picture has emerged so far regarding its anatomical generators, and certain controversy is still being debated. Early seminal studies were addressed to demonstrate that the FFR had a central rather than a cochlear origin, and its sources were attributed to neuronal aggregates in caudal brainstem and midbrain structures, with the inferior colliculus (IC) being the major neuronal source. These seminal studies supported somehow the use of “brainstem” in variants of the nomenclature and its treatment as a putative correlate of subcortical sound encoding. The midbrain origin is supported by the fact that the short latency of the FFR aligns with the latency of the first spikes

in IC (Langner and Schreiner 1988) and since FFRs contain phase-locked activity up to 1500 Hz, which spans beyond the upper limit of phase-locking capabilities of cortical neurons (~100 Hz; Aiken and Picton 2008). Additionally, focal lesions (Sohmer et al. 1977) as well as the cryogenic cooling of the IC result in the abolishment of FFRs, with subsequent heating in this later case yielding recovering of FFRs both in the IC and at the scalp (Marsh et al. 1970; Smith et al. 1975). Nevertheless, a mixture of brainstem sources was indeed recognized in the generation of the FFR (Chandrasekaran and Kraus 2010; Tichko and Skoe 2017) and was further supported by other studies that reported weaker contributions of the IC to the FFR, with the major source located in the CN (Gardi et al. 1979a) or in the MGB (Weinberger et al. 1970).

Recently, the controversy around the neural origins of the FFR was renewed with MEG evidence demonstrating that the responses to a complex auditory stimulus of a fundamental frequency close to 100 Hz receive contributions not only from the subcortical nuclei (i.e., the cochlear nucleus and the IC) but also from the medial geniculate body of the thalamus and to a major extent from the auditory cortex (Coffey et al. 2016, 2017). The implications of these findings need, however, a re-examination in the light of the phase-locking capabilities of neuronal aggregates along the auditory hierarchy. Indeed, the upper limit of temporal precision in phase-locked firing reduces with each ascending step in the auditory pathway, so that the ability of neurons to follow fast modulations reduces upstream the auditory hierarchy (Batra et al. 1989; Langner 1992; Joris et al. 2004), and therefore the specific frequency of the eliciting stimulus used to obtain the FFR may play a critical role in engaging multiple sources and a specific configuration of subcortical and cortical generators. Hence, capitalizing on the frequency-specific phase-locking capabilities along the auditory hierarchy, it has been observed that the relative contribution of subcortical and cortical sources to the scalp-recorded FFR varies systematically with stimulus frequency. In fact, the cortical contributions to the scalp-recorded FFR observed were restricted to the lowest

(fundamental) frequencies of the speech spectrum (100 Hz), and recent evidence demonstrated that this cortical contribution to the FFR disappears at frequencies higher than 150 Hz (Bidelman 2018). These findings challenge the assumption of the FFR as a correlate of subcortical sound encoding and support an emerging viewpoint in the literature that the FFR represents an integrated response of the entire auditory system (Kraus and White-Schwoch 2015; Kraus and Slater 2016), with its specific neural origins depending on the frequency of the eliciting sounds.

Developmental Issues: The FFR from Birth to Adulthood

The refinement and modulation of the encoding and representation of complex sounds in the cortico-subcortical auditory system, as reflected by the FFR, remain active and undergo stages of progression along the human life-span. The first FFR recording in human neonates was carried out by Gardi and colleagues in 1979 using low-frequency tone bursts (Gardi et al. 1979b), but it was not until three decades later when the neonates' adultlike capabilities to phase-lock to the incoming stimulus fundamental frequency were fully characterized (Jeng et al. 2010; Ribas-Prats et al. 2019). FFRs recorded in neonates have a similar response morphology to those from adults, in both the phase-locking to the periodicity of the stimulus waveform and its latency, thus confirming that the integrity of the subcortical auditory pathway can be assessed using FFRs from the first day of life at the maternity hospital room.

To understand the encoding and processing of complex sounds in infants, it is important to consider first the development of the auditory pathway during the gestational age. The inner ear and the cochlea become fully mature and functional by 5 months of gestation, which makes the fetus sensory and neurally capable to receive acoustic inputs from both its mother's body and from the external world. However, the only acoustic vibrations that reach the fetus are through the mother's womb, which filters out the input of higher frequencies and allows only the transmission of low-frequency sounds to the fetus. This influence of prenatal

listening experience on the neural development of auditory subcortical structures has been supported by studies showing that the FFR amplitude to the fundamental frequency of the eliciting stimuli was clearly observed in neonates (Ribas-Prats et al. 2019) and did not increase significantly in older infants (Anderson et al. 2015). On the other hand, the amplitudes of the FFR to higher frequencies (corresponding to the first formant and higher harmonics) are significantly smaller than the ones of the fundamental frequency (Ribas-Prats et al. 2019) and increase significantly with increasing age (Anderson et al. 2015). The mandatory delay of exposure to high frequencies until birth and the continued myelination of neural structures at the subcortical level during the first year of life may explain the different sensitivity to the input frequency content during the first years of life.

The encoding of spectral and temporal speech components becomes adultlike by the age of 6 months or around, period at which, according to electrophysiological and behavioral studies, the preference for the native language becomes evident. The auditory system suffers rapid maturational changes during the first months of age, followed by an overshoot during childhood (5–11 year old), and remained stable throughout adulthood until aging-related modulations come into effect (Skoe et al. 2015a).

Contrasting with the abundance of literature describing cortical responses in infants, very few studies have focused on the sound processing at subcortical stages of the auditory pathway in neonates. One remarkable attempt to characterize subcortical auditory processing of complex sounds during the first 3 months of age was by Jeng et al. (2016), who conducted a longitudinal study in which the FFR was recorded in a group of infants in two periods of time: during their first days of life (1–3 days after birth) and at the age of 3 months (Jeng et al. 2016). Although only 13 of the initial group of 44 were recorded at 3 months, the results suggested an improvement in pitch processing with increasing age. These findings are in line with a preliminary work by the same group in which the FFR was collected in one of their participants at 1, 3, 5, 7, and 10 months of age (Jeng et al. 2010). However, further

longitudinal follow-up studies are necessary to fully characterize the developmental stages the FFR may follow.

Effects of Experience-Dependent Plasticity on the FFR

As mentioned above, the FFR has gained recent interest in cognitive auditory neuroscience, as it allows investigation of the biological mechanisms and environmental conditions that modulate the encoding of complex sounds in the auditory hierarchy in service of human communication.

One of the most remarkable features of the FFR is its sensitivity to context-dependent contingencies and to real-time statistical properties of the stimulus. A number of studies have demonstrated that the FFR is able to capture the rapid statistical features of the incoming stimulation, disclosing the encoding of auditory regularities along the auditory hierarchy. In particular, it has been shown that the second harmonic of the FFR is enhanced for both local and global repetitions of a five-tone melody, thus indicating encoding of both global and local statistical regularities within the ongoing stimulation, and that regularity encoding mechanisms might be involved when an auditory object must be separated from background noise (Skoe and Kraus 2010b). In a similar vein, the use of an oddball stimulus sequence with consonant-vowel stimuli revealed that the FFR is not only enhanced for local regularities but also attenuated on its second harmonic in response to a deviant event (e.g., one with low local probability; Slabu et al. 2012). These findings were replicated and extended by subsequent studies, thus supporting the role of the entire auditory hierarchy in extracting statistical information from the acoustic background and demonstrating that context-dependent contingencies and learning-dependent plasticity interact in subcortical stages of the auditory hierarchy (Skoe et al. 2014). In a related account, it was further shown that not only stimulus predictability but also temporal predictability of the incoming stimulation enhances regularity encoding of the acoustic environment, thus indicating that context-dependent contingencies of the ongoing auditory input modulate the encoding of stimulus statistics

in the ascending auditory pathway (Gorina-Careta et al. 2016).

The neural sensitivity to stimulus statistics generalizes to more ecological conditions, in which sound patterns were embedded within a single uninterrupted sequence, as was demonstrated in a number of studies in which a series of musical notes were presented in random or patterned sequences. In the patterned sequences, the occurrence of a tone predicted with high accuracy the following one. By using this design, attenuated responses were obtained for the patterned condition compared to the random one, and the more enhanced were the subcortical responses to the patterned condition to the random one, the greater was the individual capability to learn the sequence (Skoe et al. 2013). This sensitivity to stimulus statistics is biased by prior experience and the expectations arising from this experience (Skoe et al. 2015b). Interestingly, the sensitivity to the contingencies of the incoming stimulation is not exclusive of adults but is already seen in children with good reading skills (Chandrasekaran et al. 2009). These results indicate that the whole auditory hierarchy is sensitive to the ongoing stimulus context and that prior experience modulates the responses to the incoming sounds.

Evidence for experience-dependent plasticity has also been provided by the results of short-term training studies, in which FFRs were recorded before and after a period of training (for a review, see Carcagno and Plack 2017). For example, as mentioned above, context-dependent contingencies interact with the effects of short-term training on the accuracy of the encoding of the fundamental frequency (F0) of sounds (Skoe et al. 2014), and, as a result of short-term F0 discrimination training, it has also been observed an improvement of the bilingual robustness of the subcortical temporal encoding (Carcagno and Plack 2011). FFR plasticity has also been investigated after the training on the identification of lexical tones (Song et al. 2008; Chandrasekaran et al. 2012) as well as using general speech-in-noise training protocols (Song et al. 2012). By using this latter one, it has been shown that the subcortical encoding of temporal information

is improved after training. The finding that subcortical auditory processing is not static but can be manipulated by training led to the hypothesis that sensory deficits caused by degraded sound processing could be improved by training. Indeed, it was shown that auditory training can alter the preconscious neural encoding of complex sounds by improving the neural synchrony in the auditory brainstem in children with learning disabilities (Russo et al. 2005).

Furthermore, the FFR is not only modulated by short-term auditory training but also by different auditory experiences, such as musical training or language exposure. The first study on the influence of musical training on the FFR was conducted by Musacchia and colleagues (Musacchia et al. 2007), where they demonstrated that musicians have earlier and larger FFRs than nonmusicians to both speech and musical stimuli presented in auditory and audiovisual conditions. Their work was extended by the observation that musicianship enhances the FFR tracking of pitch contours (Wong et al. 2007) and that this experience-dependent plasticity is shaped along the dimensions that are the most behaviorally salient for the listener (Bidelman et al. 2011). Musicians also have a more robust subcortical representation of acoustic stimuli in the presence of noise (Parbery-Clark et al. 2009) and enhanced encoding of speech syllables presented in a predictable condition relative to a variable condition than nonmusicians (Parbery-Clark et al. 2011), thus leading to the hypothesis that subcortical regularity encoding is shaped by musical training and may contribute to the musicians enhanced speech-in-noise perception. Interestingly, the neural changes produced by musical training during childhood are retained in adulthood, as the magnitude of the FFR correlates with how recently the training ceased (Skoe and Kraus 2012).

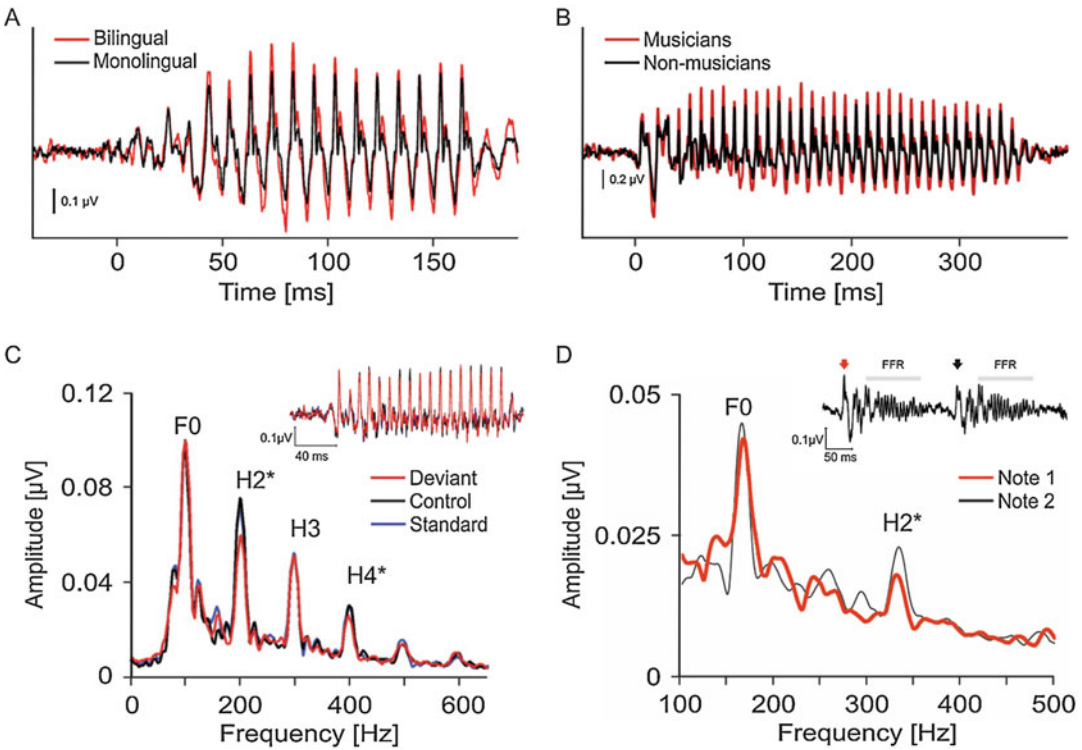
Language experience is another factor that strongly influences the encoding of speech sounds along the auditory pathway. Bilingual experience enhances the neural responses to the fundamental frequency of sounds (Krizman et al. 2015; Skoe et al. 2017) as well as the subcortical representation of pitch-relevant information (Krizman et al.

2012) and neural consistency, which correlates with both a better attentional control and language proficiency (Krizman et al. 2014). In addition, long-term experience with a tone language (such as Mandarin) sharpens the tuning characteristics of neurons along the pitch axis with enhanced sensitivity to linguistically relevant, rapidly changing sections of pitch contours (Krishnan et al. 2008). In summary, neural encoding of sounds in the subcortical auditory pathway, as revealed by means of the FFR, is shaped by long-term experience with language or music, thus supporting that early sensory processing can undergo experience-dependent plasticity (Fig. 2).

FFR in Challenging Conditions

Human auditory function in challenging conditions can be understood from different perspectives. First, the challenge can be imposed by external situations in which the acoustic signal is degraded by concurrent competing sound streams (i.e., listening in noise) or by room acoustics introducing echoes and reverberation, which necessarily hamper the intelligibility of speech signals. A serious challenge in listening, of an internal nature, is also imposed by hearing loss and even normal aging. A further challenge to central auditory processing is conveyed by clinical conditions, mostly neurodevelopmental, that have been shown to affect auditory, speech, and language perception. In all these domains, the FFR has played a significant role in characterizing the effects of the challenges in the neural encoding of complex, typically speech sounds and its consequences in listening, linguistic, and even cognitive competence.

Both noise- and reverberation-related changes in the FFR are shown in both the time and frequency domains. In particular, noise masks the spectral details of speech, reducing the contrast between the salient frequency features of the sound and the baseline noise (Russo et al. 2004; Li and Jeng 2011). In contrast, reverberation causes a smearing of the spectrotemporal details of the acoustic signal, thus producing a temporal overlap of time-frequency information which results in a systematic degradation in neural periodicity as it degrades the normal phase-locking ability of the FFR (Bidelman and Krishnan 2010). Interestingly,



Auditory Frequency-Following Responses, Fig. 2 Modulation of the FFR by auditory experience and context-dependent contingencies. The FFR to different acoustic stimuli is sensitive and can be modulated by a range of different auditory experiences, such as language exposure and musical training. In particular, this influence is so strong that it can be appreciated in the temporal representation of the FFR when comparing groups with different levels of exposure, for example, to two (bilinguals) instead to only one (monolinguals) language (a), or in participants with musical experience as compared to nonmusicians (b). The FFR is also highly sensitive to context-dependent contingencies (c) and to real-time statistical properties of the stimulus (d). In some cases, as the ones illustrated here, differences in the FFRs are not evident in the time domain but can be appreciated in the

spectral decomposition of the neural signal. The bottom left panel (c) depicts the spectral representation of the FFRs elicited to the same stimulus having three different contextual roles as a function of its probability of occurrence (i.e., as a low-probable [Deviant], red; high-probable [Standard], blue; control, black). Differences became clearly (and statistically) visible in the amplitude of the second harmonic. The bottom right panel (d) shows a similar approach to illustrate the effects of short-term statistics (stimulus repetition) on the FFR (first presentation in red; tone repetition in black). Differences between tone statistics (e.g., repetition) are clearly observed in the second harmonic. Figures adapted and reproduced with permission from (a) Krizman et al. (2012), (b) Skoe and Chandrasekaran (2014), (c) Slabu et al. (2012), and (d) Skoe and Kraus (2010b).

the two types of acoustic interference do not result in uniform impairment in the speech signal. Indeed, pitch (measured in the encoding of the fundamental frequency) and timbre (assessed by the spectral energy in higher harmonics and spectral envelope) are differentially affected and hence encoded in the FFRs. Little degradation in the FFR fundamental frequency is observed neither with noise nor reverberation, whereas higher harmonics degrade quickly with acoustic interference.

The encoding of speech sounds along the auditory hierarchy with acoustic interference is not stable across the life-span. Rather it naturally declines with age and is impaired in certain auditory disorders. The evoked responses for the three fundamental acoustic features intrinsic to speech sounds are shown to be inefficiently encoded, reduced, or delayed in different ways for distinct clinical populations compared to typically developing controls, but, overall, they all

lead to a weakness in the neural processes that are important for the appropriate auditory processing of the auditory signal. In particular, reduced representation of the fundamental frequency and the harmonics or delayed onset of the FFRs have been observed for children with learning problems (Cunningham et al. 2001) and/or with language deficits and reading disorders such as dyslexia (Banai et al. 2005, 2009; Banai and Ahissar 2006; Chandrasekaran et al. 2009; Anderson et al. 2010; Hornickel et al. 2012; Hornickel and Kraus 2013). Additionally, neural synchrony (timing) and phase-locking (frequency encoding) are also decreased in children with autistic spectrum disorders (Russo et al. 2008, 2009).

Conclusions

In this entry we have attempted to characterize the frequency-following response (FFR) as an auditory evoked potential which is called to play a relevant role in modern auditory cognitive neuroscience. By virtue of its “neurophonic” nature, its ability to reproduce the eliciting sound when played through a speaker, the FFR faithfully reveals how the fine-grained spectrotemporal features of complex auditory stimuli are analyzed and represented along the entire auditory system. Furthermore, by its multi-dimensional sensitivity to the individual’s experience with acoustic surroundings along the life-span, including long-term exposure to language, music, and noise but also short-term, dynamic processing of auditory streams, the FFR has demonstrated the profound plasticity of the auditory system in the service of auditory perception, the use of language, and communication. By characterizing the complex generating pattern of anatomical structures contributing to the FFR, from the cochlear nucleus to the inferior colliculus, the medial geniculate body of the thalamus, and the auditory cortex, studies with the FFR have revealed the auditory system to be the core of a neural network that interacts with the motor and reward systems to guide and refine our life in sound (Kraus and White-Schwoch

2015). Also, the FFR may have a major translational role in audiologic, neurodevelopmental, and educational domains. In the first place, the FFR recorded at a preschool age has been shown to predict performance across multiple domains of emergent literacy as measured 1 year later (White-Schwoch et al. 2015). Second, given these predictive capabilities of the FFR, one is tempted to speculate that a simple FFR recording at birth (Ribas-Prats et al. 2019) may give a snapshot into the speech-learning abilities on the neonate. Such a test could be routinely applied at the maternity unit, together with the universal newborn hearing screening, right after birth and could lead to early preventive intervention in babies at risk of speech acquisition or developmental delays (Kraus and White-Schwoch 2016). Finally, the FFR may provide a complementary tool in the practice of audiology to objectivize auditory perceptual deficits in patients with complaints about hearing loss in the presence of a normal audiogram and negative testing.

Cross-References

- [Auditory Brainstem Responses](#)
- [Auditory Event-Related Potentials](#)

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Auditory Memory

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Synonyms

[Acoustic memory](#); [Echoic memory](#)

Definition

Auditory memory is the storage of information about sounds, including both acoustic features (sensory memory) and categorical information about sound categories and multi-sound structure.

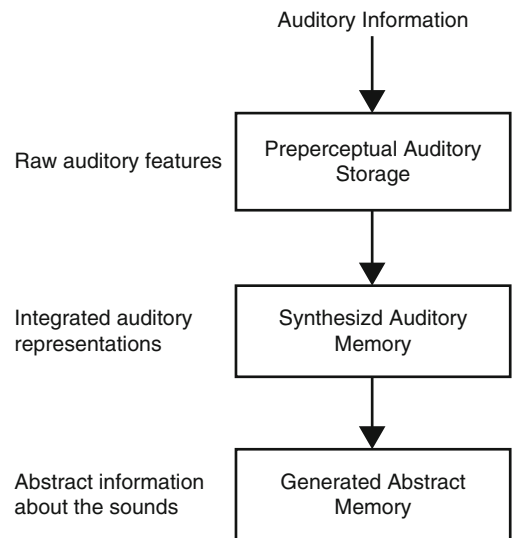
Detailed Description

Auditory memory plays a critical role in various aspects of human activities, such as music, verbal learning, and communication. For example, when a person says, “I said ‘rice,’ not ‘lice,’” the listener must keep the word “rice” in auditory memory to compare it with the word “lice” afterward.

It is widely accepted that auditory memory can be partitioned into three components (Cowan 1984; Crowder 1976; Massaro 1975; Neisser 1967), which Massaro terms preperceptual auditory storage (known also as echoic memory), synthesized auditory memory, and generated abstract memory. Figure 1 illustrates these components and their relationships.

Preperceptual Auditory Storage

Preperceptual auditory storage retains the uncategorized representations of auditory inputs



Auditory Memory, Fig. 1 Three phases of auditory memory according to Massaro (1975)

that have not yet been fully processed (Massaro 1975) and is also referred to as short auditory storage (Cowan 1984). It is the auditory counterpart of what is thought of as iconic memory in the visual domain. Preperceptual auditory storage is the first step in auditory processing and starts right after an auditory stimulus enters perception. The duration of preperceptual auditory storage is very short. Most researchers agree that it lasts less than 300 ms. One compelling source of evidence for the duration of preperceptual auditory storage comes from the finding that when a sound is very short (e.g., less than 100 ms), it is still perceived as lasting for about a quarter of a second, which is considered to be the duration of preperceptual auditory storage (for a review see Cowan 1984).

Synthesized Auditory Memory

The auditory features stored in preperceptual auditory storage can be further analyzed to form integrated representations of sound. These integrated representations are considered to be stored in synthesized auditory memory (Massaro 1975). The term “synthesized” refers to the process in which auditory features such as pitch, loudness, and aspects of timbre are analyzed and combined into integrated auditory representations. The duration of the synthesized auditory memory appears to vary from less than 1 s up to 30 s, depending on how it is measured, but it is most often found to be several seconds (Cowan 1984).

The distinction between preperceptual auditory storage and synthesized auditory memory is supported by several lines of research, including backward masking, dichotic listening, and the suffix effect (Cowan 1984). One of the most convincing sources of evidence comes from a backward masking study by Kallman and Massaro (1979). Backward masking refers to the phenomenon that when two sounds are presented sequentially with a very short interval between them, the processing of the first sound (target) sustains interference from the second one (mask). Kallman and Massaro (1979) used two types of sound sequence: (1) standard tone, target tone, and mask (referred to as mask third or “M3”) and (2) standard tone, mask, and target tone (referred

to as mask second or “M2”). The participants needed to judge whether the target tone had a higher or lower frequency than the standard tone. In each type of sequence, the interval between the mask and its preceding tone (stimulus onset asynchrony or SOA) was varied, and the mask was either similar to the preceding tone or quite different from it (it was then a white noise). A prediction can be made on the basis of two forms of memory, preperceptual auditory storage and synthesized auditory memory. These two forms can be separately interfered with. In both types of trials, the comparison between the target and standard tones should be impaired by target-mask similarity at a very short SOA because at short SOAs, the similar mask interferes with preperceptual auditory storage of the preceding target tone. Additionally, in the M2 trials only, it is expected that the comparison is always impaired by a similar mask, regardless of the SOA. The reason is that the mask in this procedure comes between the standard and target tones and therefore can interfere with synthesized auditory memory of the standard tone. These expectations exactly match what was found; the target-mask similarity mattered only at short SOAs in the M3 condition, but it mattered at all SOAs in the M2 condition. This finding supports the distinction between preperceptual auditory storage and synthesized auditory memory.

Generated Abstract Memory

The integrated representations in synthesized auditory memory can be further processed to form abstract representations in generated abstract memory (Massaro 1975). The abstract representations are considered to be domain general, meaning that they do not carry information about specific sensory details. Thus, abstract representations generated from each sensory domain (hearing, vision, touch, and so on) are all stored together in the generated abstract memory.

In more recent literature, generated abstract memory is often referred to as “the focus of attention” and is reported to have a core capacity of three to five items when various memory strategies are controlled (Cowan 2001). It is thought that information must be saved in generated

abstract memory before high-level thinking about it can occur.

How Auditory Memory Is Used

Although auditory memory is usually partitioned into three phases, all three phases can be used in parallel to process auditory information. Suppose that you are sitting in a noisy airport reading and a stranger asks you what time it is. Even though you did not catch the words immediately, you can still extract the raw auditory information from the preperceptual auditory storage, except for the very last sounds that were masked by someone else nearby talking immediately afterward. The extracted information is then integrated into synthesized auditory memory, which can save the auditory information long enough for you to turn your attention away from the reading and toward the sounds. When your attention is focused on the sounds, you can analyze the sounds based on their memory, using your existing language knowledge. You form a generated abstract memory of what the stranger meant, and you can then respond with the correct time if you have it. This is a typical scenario in which all three phases of auditory memory work together to serve the auditory processing involved in social interactions.

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Auditory Pathway

► [Auditory Processing in Insects](#)

Auditory Perceptual Grouping

► Auditory Perceptual Organization

Auditory Perceptual Organization

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Synonyms

[Auditory perceptual grouping](#); [Auditory scene analysis](#); [Cocktail party problem](#); [Sound source separation](#)

Definition

The process of extracting acoustic features from sound waves and partitioning them into meaningful groups.

Detailed Description

Introduction

Traveling pressure waves (i.e., sounds) are produced by the movements or actions of objects. So sounds primarily convey information about *what is happening* in the environment. In addition, some information about the structure of the environment and the surface features of objects can be extracted by determining how the original (self-generated or exogenous) sounds are filtered or distorted by the environment (e.g., the notion of “acoustic daylight,” Fay 2009). In this entry we consider how the auditory systems process sound signals to extract information about the environment and the objects within it.

The auditory system faces a number of specific challenges which need to be considered in any account of perceptual organization: (1) sounds unfold in time; we can’t (normally) go back to reexamine them. Therefore, information must be extracted and perceptual decisions made in a timely manner. (2) The information contained within sounds generally requires processing over many timescales in order to extract their meaning (Nelken 2008). For example, a brief impulsive sound may tell the listener that two objects have been in collision, but a series of such sounds is needed in order for the listener to know that someone is clapping rather than walking. (3) Many objects of interest generate sounds intermittently. Therefore, some means for associating temporally discontinuous events are required. (4) Sound pressure waves are additive; what the ear receives is a combination of all concurrently active sound sources and their reflections off any hard surfaces. Many animals and birds communicate acoustically in large social groups, making the problem of source separation particularly tricky (Bee 2012). Despite these challenges, if the auditory system is to provide meaningful information about individual objects in the environment (e.g., potential mates or aggressors), it needs to partition the acoustic features into meaningful groups, a process known as *auditory perceptual organization* or *auditory scene analysis* (Bregman 1990).

Grouping Principles

Auditory Events

Natural environments typically contain many concurrent sound sources, and even isolated sounds can be rather complex, e.g., animal vocalizations contain many different frequency components, and both the frequencies of the components and their amplitudes can vary within a single sound. The problem for the auditory system is to find some way of correctly associating the features which originate from the same sound source. The classical view of this process is that the cochlea decomposes the incoming composite sound waveform into its spectral components, generating a topographically organized array of

signals which sets up the *cochleotopic* (or *tonotopic*) organization found throughout most of the auditory system, up to and including the primary auditory cortex (Zwicker and Fastl 1999). Other low-level features such as onsets, amplitude and frequency modulations, and binaural differences are extracted subcortically and largely independently within each frequency channel (Oertel et al. 2002). These acoustic features are bound together to form auditory *events* (Bertrand and Tallon-Baudry 2000; Zhuo and Yu 2011) or *tokens* (Shamma et al. 2011), i.e., discrete sounds that are localized in time and perceived as originating from a single sound source (Ciocca 2008). Events are subsequently grouped sequentially into patterns, streams, or perceptual objects.

Gestalt Grouping Principles

Perceptual decisions regarding the *causes* of the signals received by the sensors must in general be made with incomplete information (Brunswick 1955). Therefore, potential solutions need to be constrained in some way, e.g., by knowledge about likely sound sources (Bar 2007) or by expectations arising from the recent context (Winkler et al. 2012). In his seminal book, Bregman (1990) pointed out that many such constraints had already been identified by the Gestalt school of psychology (Köhler 1947) early in the twentieth century. The core observation of Gestalt psychology was that individual features form larger perceptual units, which have properties not present in the separate components (von Ehrenfels 1890), and, conversely, that the perception of the components is influenced by the overall perceptual structure (Wertheimer 1912). Focusing primarily on visual stimuli, the Gestalt psychologists described the following grouping principles (laws of perception), here discussed in terms of auditory grouping.

(a) **Good continuation:** Smooth continuous changes in perceptual attributes favor grouping, while abrupt discontinuities are perceived as the start of something new. This principle can operate both within and between individual events.

- (b) **Similarity:** Similarity between the perceptual attributes of successive events (e.g., pitch, timbre, location) promotes grouping (Bregman 1990; Moore and Gockel 2002, 2012). Similar to the perception of visual motion (Weiss et al. 2002), it appears that it is not so much the raw difference that is important, but rather the *rate of change*; the slower the rate of change between successive sounds, the more similar they are judged (Winkler et al. 2012). In other words, in the auditory modality, *similarity* and *good continuation* may be equivalent.
- (c) **Common fate:** Correlated changes in features promote grouping, recently formalized as *temporal coherence*, i.e., feature correlations within time windows that span periods longer than individual events (Elhilali et al. 2009; Shamma et al. 2011).
- (d) **Disjoint allocation (or belongingness):** Refers to the principle that each element of the sensory input is only assigned to one perceptual object, e.g., exclusive border assignment in Rubin's face-vase illusion. However, although generally true, this principle is sometimes violated in auditory perception, e.g., in *duplex perception*, the same sound component can contribute to the perception of a complex sound as well as being heard separately (Rand 1974; Fowler and Rosenblum 1990).
- (e) **Closure:** Objects tend to be perceived as whole even if they are not complete, e.g., a glide continuing through a masking noise if the glide offset is masked (Miller and Licklider 1950; Riecke et al. 2008). This applies more generally to the perception of global patterns (or "Gestalts"), e.g., individual notes are subsumed into a melodic pattern (McDermott and Oxenham 2008) and predictable individual speech sounds are perceived as present even if they are masked or missing (Warren et al. 1988). The auditory system is extraordinarily sensitive to repeating patterns and appears to readily use this cue to parse complex scenes (Winkler 2007; McDermott et al. 2011).

An important concept that emerges from the idea of a “Gestalt” as a pattern is that of predictability. In the case of auditory perception, this refers to expectancies about sound events that have not yet occurred. By detecting patterns (or feature regularities) in the acoustic input, the brain can construct representations that allow it to anticipate or “explain away” (Pearl 1988) future events. In this way Gestalt theory connects to the ideas of unconscious inference (Helmholtz 1885) and perception as hypothesis formation (Gregory 1980).

Auditory Objects

While visual objects are widely accepted as fundamental representational units, the notion of an auditory object is less well established, and there is as yet no universal agreement on how they should be defined, e.g., see Kubovy and Van Valkenburg (2001), Griffiths and Warren (2004), Winkler et al. (2006), Shinn-Cunningham (2008). Based on the Gestalt principles and ideas of perceptual inference, outlined above, Winkler et al. (2009) proposed a definition of an auditory perceptual object as a predictive representation, constructed from feature regularities extracted from the incoming sounds. These object representations are temporally persistent and encode distributions over featural and temporal patterns, determined by the current context. The consolidated object representation therefore refers to *patterns of sound events*; individual sound events are processed within the context of the whole to which they belong. This definition of an auditory perceptual object is compatible with the definition of an auditory stream, as a coherent sequence of sounds separable from other concurrent or intermittent sounds (Bregman 1990). However, whereas the term “auditory stream” refers to a phenomenological unit of sound organization, with separability as its primary property, the definition proposed by Winkler et al. (2009) emphasizes the extraction and representation of the unit as a pattern with predictable components (Winkler et al. 2012). While the usage of the term object is not universally accepted within the auditory domain, we will use it in this entry as defined by Winkler et al. (2009).

Auditory Scene Analysis

In order to determine the perceptual qualities of individual sound events, the brain must first bind their component features even though the number of concurrent auditory objects and which features belong to each is unknown a priori; this must be inferred incrementally from the ongoing sensory input. Therefore, it is clear that the auditory system needs to use (top-down) contextual information to guide its grouping decisions and some means for evaluating these decisions and revising them in the event that they prove to be incorrect. In the currently most widely accepted framework describing perceptual sound organization, auditory scene analysis, Bregman (1990) proposes two separable processing stages. The first stage is suggested to be concerned with partitioning sound events into potential groups based primarily on featural similarities and differences. The second stage, within which prior knowledge and task demands exert their influence, is a competitive process between candidate organizations that determines which one is perceived. Within this framework there are two types of grouping: *simultaneous* grouping based on concurrent cues and *sequential* grouping based on contextual temporal cues. For the reasons outlined above, these two are not really distinct (simultaneous cues are influenced by prior sequential grouping, e.g., Darwin et al. (1995) and Bendixen et al. (2010b), just as sequential grouping is influenced by the perceptual qualities of individual events (simultaneous grouping) (Bregman 1990); nevertheless, they provide a useful starting point for models of auditory scene analysis.

Simultaneous Grouping

In the absence of sequential grouping cues, there are some features which automatically trigger the formation of individual sound events; for reviews see Darwin and Carlyon (1995) and Ciocca (2008). Common onsets and offsets form clear temporal boundaries, and the strategy adopted by the auditory system is to match onsets to offsets (including similarities between features and temporal proximity) in order to segregate perceptual events (Nakajima et al. 2000). Harmonicity

(i.e., the presence of frequency components which are integer multiples of a common fundamental frequency) is another important grouping cue (Darwin and Carlyon 1995). For example, when one component of a complex harmonic tone is mistuned, listeners perceive two concurrent sounds, a complex tone consisting of the harmonically related components and a pure tone, corresponding to the mistuned component (Moore et al. 1986). However, not all acoustic features trigger concurrent grouping, e.g., a location cue (common interaural time differences) between a subset of frequency components within a single sound event does not generate a similar segregation of component subsets within individual sound events (Culling and Summerfield 1995).

Another important strategy for segregating sound events is template matching. If people have prior knowledge of events, then it is possible to hear them out. This effect was exploited in the many double-vowel experiments used to test the influence of different acoustic features, e.g., Assmann and Summerfield (1990) and Summerfield and Assmann (1991), and even in the absence of featural differences, it was shown that known vowel sounds can be identified well above chance (Assmann and Summerfield 1989). This template-matching phenomenon appears to be rather general and applies to any sound that is repeated. The auditory system is very sensitive to repetition (Teki et al. 2011). If a previously unheard sound is repeated against a different background, then it can be segregated and identified significantly above chance, even with only a single repetition, and even if many of usual grouping cues are absent (McDermott et al. 2011). Similarly, arbitrary repeated noise segments can be rapidly learnt within a few trials (Agus et al. 2010).

Models of Event Formation

Many models have been developed to investigate simultaneous grouping and the segregation of perceptual events, e.g., see models described in Wang and Brown (2006). A model of auditory saliency which used low-level cues of spectral and temporal contrast to highlight salient events

in continuous noisy soundscapes predicted human event detection very well (Kayser et al. 2005). Temporal contrasts effectively highlight onsets and offsets, while spectral peaks carry information about the resonances of sound sources and to some extent their identity (von Kriegstein et al. 2007). The segregation of overlapping events using pitch cues has been widely explored (c.f. Pitch Perception, Models), e.g., for explaining enhanced double-vowel segregation (de Cheveigne et al. 1995). The segregation of events using repetition was shown to be possible in principle by using a combination of cross-correlation and averaging to incrementally build a representation of the repeated target (McDermott et al. 2011). Because of the importance of longer-term context on grouping, none of these models provide general solutions to the problem of auditory scene analysis; nevertheless, they provide important building blocks in this process.

Sequential Grouping

Sequential grouping generally conforms to the Gestalt principles of *similarity/good continuation* and *common fate*. In contrast to concurrent grouping, sequential grouping is necessarily based on some representation of the preceding sounds; for reviews, see (Moore and Gockel 2002; Carlyon 2004; Haykin and Chen 2005; Snyder and Alain 2007; Ciocca 2008; Shamma and Micheyl 2010; Shamma et al. 2011; Moore and Gockel 2012). Most studies of this class of grouping have used sequences of discrete sound events to investigate the influences of acoustic features and temporal structure. In the most widely used experimental approach (termed the auditory streaming paradigm), sequences of alternating sound events differing in some feature(s) are presented to listeners (van Noorden 1975). When the feature separation is small and/or they are delivered at a slow pace, listeners predominantly hear a single *integrated* stream containing all the sounds. With large feature separation and/or fast presentation rates, listeners report hearing the sequence separate out into two *segregated* streams. In this there is a cue trade-off: smaller feature differences can be compensated with higher presentation rates and

vice versa (van Noorden 1975). Differences in various auditory features, including frequency, pitch, loudness, location, timbre, and amplitude modulation, have been shown to support auditory stream segregation (Vliegen and Oxenham 1999; Grimault et al. 2002; Roberts et al. 2002). Thus it appears that sequential grouping is based on perceptual similarity, rather than on specific low-level auditory features (Moore and Gockel 2002, 2012). Temporal structure has also been suggested as a key factor in segregating streams either by guiding attentive grouping processes (Jones 1976; Jones et al. 1981; Large and Jones 1999) or through temporal coherence that binds correlated component features in the auditory input (Elhilali et al. 2009; Shamma and Micheyl 2010; Shamma et al. 2011, 2013).

Models of Auditory Streaming

Early models of auditory streaming, e.g., Beauvois and Meddis (1991), focused on the relationship between frequency differences and event rate and the proposal that streaming could be explained almost exclusively by peripheral channeling mechanisms (Hartmann and Johnson 1991) or the degree of overlap between neural responses to each of the alternating tones, e.g., McCabe and Denham (1997). In these models the perceptual decision was represented by levels of activation across a spatial array of neurons; see also Micheyl et al. (2005) for a similar interpretation of neural activity in primary auditory cortex. A different approach in which grouping is signaled by temporal correlations within network responses was proposed by Wang, Brown, and colleagues (Brown and Wang 2006; Wang and Chang 2008). For example, the model proposed by Wang and Chang (2008) consists of a 2-dimensional array of oscillators with one dimension representing frequency and the other external time. Units are connected by local excitatory connections and by global inhibition. Characteristic results of classical auditory streaming experiments (van Noorden 1975) are simulated by including strong local excitatory connections (encouraging synchronization) and weaker long-range connections (which are easily overcome by inhibition and therefore encourage

desynchronization). Sensitivity to event rate is modeled by dynamic weight adjustments. However, while the representation of grouping is different from the models previously outlined, this model also depends on peripheral channeling and the degree of overlap in the incoming activity patterns to determine its grouping decision.

A similar focus on temporal coherence (in this case the average correlation within a sliding window 50–500 ms in duration) is seen in the model of streaming proposed by Elhilali and colleagues, e.g., Elhilali and Shamma (2008) and Shamma et al. (2011) (Note, Figs. 6 and 9 in this entry have incorrect colour scale labels (0% and 100%, interchanged; Shamma and Elhilali (2013)). The computational model developed by Elhilali and Shamma (2008) extracts multiple features from the incoming acoustic input including frequency, pitch, direction, and spectral shape and assigns the resulting activity patterns to one of two clusters which come to represent the properties of the events in each stream. The temporal coherence measure is used to determine which components should be grouped. The clusters compete to incorporate each event, and the winning cluster uses the event features (as determined by the grouping process) to refine its representation. These correlation-based models overcome a problem faced by the population separation account of streaming (Micheyl et al. 2005) that predicted widely separated components would be segregated even if they overlapped in time, which is not the case (Elhilali et al. 2009). They also provide a means for binding the component features of an event, not considered in the earlier models. Later refinements to the temporal coherence account of streaming (Shamma et al. 2011, 2013), included the strong claims that (a) feature binding occurs only with attention, i.e., attention is responsible for grouping features that belong to the foreground object, c.f. (Treisman 1998), and (b) all other features remain ungrouped in an undifferentiated background. However, the proposed role of attention in feature binding has long been debated in the visual domain, e.g., Duncan and Humphreys (1989), and it is not consistent with the results of experiments testing feature binding in the absence of attention by

recording auditory event-related potentials (AERP) in response to rare feature combinations (Takegata et al. 2005; Winkler et al. 2005a).

Competition and Selection

The models described above all conform to the assumptions that in response to alternating two-tone sequences, (a) auditory perception always starts from the integrated organization and (b) that eventually a stable final perceptual decision is reached (Bregman 1990). However, it has been found, when listeners report their percepts continuously while listening to such sequences for long periods, that perception fluctuates between different perceptual organizations (Winkler et al. 2005b; Pressnitzer and Hupe 2006). Perceptual switching occurs in all listeners and for all combinations of stimulus parameters tested (Anstis and Saida 1985; Roberts et al. 2002; Denham and Winkler 2006; Pressnitzer and Hupe 2006; Schadwinkel and Gutschalk 2011; Denham et al. 2012), even combinations very far from the ambiguous region identified by van Noorden (1975). Furthermore, for stimuli with parameters that strongly promote segregation, participants often report hearing segregation first (Deike et al. 2012; Denham et al. 2012). It has also been found that perceptual organizations other than the classic integrated and segregated categories may be reported (Bendixen et al. 2010a, 2012; Böhm et al. 2012; Denham et al. 2012; Szalárdy et al. 2012), showing that auditory perceptual organization in response to alternating two-tone sequences is multistable (Schwartz et al. 2012).

The notion of perceptual multistability is challenged by everyday subjective experience of a world perceived as stable and continuous and by experimental results obtained by averaging over the reports of different listeners, which generally show that within the initial 5–15 s of two-tone sequence, the probability of reporting segregation monotonically increases (termed the buildup of auditory streaming) (but see Deike et al. (2012)). For these reasons it has been suggested that perceptual multistability observed in the auditory streaming paradigm may be simply a consequence of the artificial stimulation protocol used. However, there is a growing body of experimental data

supporting the existence of multistability and just as visual multistability has provided new insights into visual processing, e.g., Kovacs et al. (1996); it seems likely that understanding spontaneous changes in the perception of unchanging sound sequences will help throw new light on auditory perception.

Modeling Multistability in Auditory Streaming

Multistability of auditory perceptual organization cannot be explained by any of the theories or models outlined above, which all have essentially one fixed attractor. Models of visual multistability have a longer history, e.g., Laing and Chow (2002); Shpiro et al. (2009); van Ee (2009). These models typically contain three essential components (Leopold and Logothetis 1999): (a) mutual inhibition between competing stimuli to ensure *exclusivity* (i.e., perceptual awareness generally switches between the different alternatives rather than fusing them), (b) adaptation to ensure the observed *inevitability* of perceptual switching (the dominant percept cannot remain dominant forever), and (c) noise to account for the observed *stochasticity* of perceptual switching (successive phase durations are largely uncorrelated, and the distribution of phase durations resembles a gamma or log-normal distribution) (Levelt 1968). The questions for auditory multistability are what are the competing entities, and what form does this competition take in order to explain dynamic nature of perceptual awareness reported by listeners.

The computational model of auditory multistability proposed by Mill et al. (2013) is based on the idea that auditory perceptual organization rests on the discovery of recurring patterns embedded within the stimulus, constructed by forming associations (links) between incoming sound events and recognizing when a previously discovered sequence recurs and can thus be used to predict future events. These predictive representations, or *proto-objects* (Rensink 2000; Winkler et al. 2012), compete for dominance with any other proto-objects which predict the same event (a form of local competition) and are the candidate set of representations that have the potential to become the perceptual objects of

conscious awareness. This model accounts for the emergence of, and switching between, alternative organizations; the influence of stimulus parameters on perceptual dominance, switching rate, and perceptual phase durations; and the buildup of auditory streaming. In a new sound scene, the proto-object that is the easiest to discover determines the initial percept. Since the time needed for discovering a proto-object depends largely on the stimulus parameters (i.e., to what extent successive sound events satisfy/violate the *similarity/good continuation* principle), the first percept strongly depends on stimulus parameters. However, the duration of the first perceptual phase is independent of the percept (Hupe and Pressnitzer 2012), since it depends on how long it takes for *other* proto-objects to be discovered (Winkler et al. 2012). The model also accounts for the different influences of similarity and closure on perception; the rate of perceptual change (similarity/good continuation) determines how easy it is to form the links between the events that make up a proto-object, while predictability (closure) does not affect the discovery of proto-objects, but can increase the competitiveness (salience) of a proto-object once it has been discovered (Bendixen et al. 2010a).

Neural Correlates of Perceptual Organization

Neural responses to individual sounds are profoundly influenced by the context in which they appear (Bar-Yosef et al. 2002). The question is to what extent the contextual influences on neural responses reflect the current state of perceptual organization. This question has been addressed by a number of studies ranging in focus from the single neuron level (c.f. stimulus-specific adaptation) to large-scale brain responses (c.f. auditory evoked potentials), and the results provide important clues about the processing strategies adopted by the auditory system.

Studies investigating single neuron responses to alternating tone sequences, e.g., Fishman et al. (2004), Bee and Klump (2005), Micheyl et al. (2005), and Micheyl et al. (2007), have shown

an effect called *differential suppression*, i.e., at the start of the sequence, the neuron responds to both tones, but with time the response to one of the tones (typically corresponding to the best frequency of the cell) remains relatively strong, while the response to the other tone diminishes. Since neuronal sensitivity to frequency difference and presentation rate was found to be consistent with the classical van Noorden (1975) parameter space, it was claimed that differential suppression was a neural correlate of perceptual segregation (Fishman et al. 2004). This was supported by the finding that spike counts from neurons in primary auditory cortex predict an initial integration/segregation decision closely matching human perception (Micheyl et al. 2005; Bee et al. 2010). However, differential suppression does not account for perceptual multistability or for the perception of overlapping tone sequences (Elhilali et al. 2009); therefore, while differential suppression may be a necessary component of the auditory streaming process, it does not provide a complete explanation.

Auditory event-related brain potentials (AERPs) represent the synchronized activity of large neuronal populations, time locked to some auditory event. Because they can be recorded noninvasively from the human scalp, they have been widely used to study the brain responses accompanying auditory stream segregation; c.f. auditory event-related potentials, especially long-latency AERP responses. Three AERP components are of particular relevance in this regard: (a) the “object-related negativity” (ORN) which signals the automatic segregation of concurrent auditory objects (Alain et al. 2002), (b) the amplitude of the auditory P1 and N1 which varies depending on whether the same sounds are perceived as part of an integrated or segregated organization (Gutschalk et al. 2005; Szalárdy et al. 2013), and c) the mismatch negativity (MMN; Näätänen et al. 1978) which has been used as an indirect index of auditory stream segregation, e.g., Sussman et al. (1999); Nager et al. (2003); Winkler et al. (2003a); Gutschalk et al. (2005).

The detection and representation of regularities by the brain, as indexed by the MMN, provided the basis for the definition of an auditory object

proposed by Winkler et al. (2009). Using evidence from a series of MMN studies, they defined an auditory object as a perceptual representation of a possible sound source, derived from regularities in the sensory input (Winkler 2007, 2010) that has temporal persistence (Winkler and Cowan 2005) and can link events separated in time (Näätänen and Winkler 1999). This representation forms a separable unit (Winkler et al. 2006) that generalizes across natural variations in the sounds (Winkler et al. 2003b) and generates expectations of parts of the object not yet available (Bendixen et al. 2009).

It should be pointed out that while traditional psychological accounts of auditory perceptual organization implicitly or explicitly refer to representations of objects, there are models of auditory perception which are not concerned with positing a representation directly corresponding to auditory objects. The hierarchical predictive coding model of perception, e.g., Friston and Kiebel (2009), includes predictive memory representations, which are in many ways compatible with the notion of auditory object representations (Winkler and Czigler 2012), but no explicit connection with object representations is made. Shamma and colleagues' temporal coherence model of auditory stream segregation (Elhilali and Shamma 2008; Elhilali et al. 2009; Shamma et al. 2011, 2013) provides another way to avoid the assumption that object representations are necessary for determining sound organization; instead it is proposed that objects are essentially whatever occupies the perceptual foreground and exist only insofar as they *do* occupy the foreground. In summary, there is currently little consensus on the role of auditory object representations in perceptual organization, and the importance placed on object representations by the various models and theories differs markedly.

fMRI studies of auditory streaming have found neural correlates in a number of brain regions. In one of the earliest studies, Cusack (2005) failed to find differential activity in auditory cortex corresponding to perceptual organization into one or two streams, but he did find such activity in the intraparietal sulcus, an area associated with

cross-modal processing and object numerosity. Shortly afterwards Wilson et al. (2007) showed that auditory cortical activity increased with increasing frequency difference and that as the frequency difference increased, the cortical response changed from being rather phasic (i.e., far stronger at the onset of the sequence) towards a more sustained response throughout the stimulus sequence. Taking a closer look at the dynamics of cortical activity associated with perceptual switching, Kondo and Kashino (2009) showed that both auditory cortex and thalamus are involved, with an increase in thalamic activity preceding that in cortex associated with a switch from the nondominant to the dominant percept and, conversely, an increase in cortical activity preceding that in thalamus associated with a switch from the dominant to the nondominant percept. They also found differential activation in posterior insular cortex and in the cerebellum. Interestingly, activations in the cerebellum and thalamus are negatively correlated in auditory streaming, with the left cerebellar activation level increasing with the rate of perceptual switching and thalamus (medial geniculate) decreasing (Kashino and Kondo 2012). Consistent with these findings, Schadwinkel and Gutschalk (2011), using a different stimulus paradigm which allowed them to influence the timing of perceptual switching, found transient auditory cortical activation associated with perceptual switching and a further transient activation in inferior colliculus, although whether the inferior colliculus is responsible for triggering switching or simply reflects the transient switching activation in cortex is not clear. In summary, neural correlates of auditory streaming have been found in many areas within the auditory system and beyond, suggesting that creating and switching between alternative perceptual organizations involve a broadly distributed network within the brain.

Conclusions and Open Questions

The Gestalt principles and their application to auditory perception instantiated in Bregman's

(1990) two-stage auditory scene analysis framework provided the initial basis for understanding auditory perceptual organization, and recent proposals have extended this framework in interesting ways. Nevertheless, there remain many unanswered questions and there have been few, if any, attempts to build neuro-computational models capable of dealing with the complexity of real auditory scenes in which grouping and categorization cues are not immediately available; however, see (Yildiz and Kiebel 2011). Feedback connections are pervasive within the auditory system, including all stages of the subcortical system, yet to our knowledge no models include such connections. Although fMRI results are useful for identifying regional involvement, detailed understanding of the neural circuitry involved in auditory perceptual organization is sketchy, and the neural representations of auditory objects and perceptual organization are unknown. Even the role of primary auditory cortex remains something of a mystery, e.g., see Nelken et al. (2003) and Griffiths et al. (2004); perhaps studying the switching of perceptual awareness between different representations in awake behaving animals will help to elucidate the representations and processing strategies adopted by cortex.

Cross-References

- [Auditory Event-Related Potentials](#)
- [Stimulus-Specific Adaptation, Models](#)

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Auditory Precedence Effect

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Synonyms

[Law of the first wavefront](#)

Definition

The precedence effect is a well-studied phenomenon in spatial hearing that is related to how we localize sounds accurately in everyday settings. Specifically, when two sound sources reach a listener close together in time, listeners often hear a single “fused” image whose perceived direction is near the location of the first-arriving sound.

Detailed Description

The Effects of Room Acoustics on Auditory Spatial Cues

The signals reaching the listener’s ears directly from a sound source convey information about the source’s location (Blauert 1997; Schnupp et al. 2010). However, in ordinary

settings, soon after the direct sound reaches the listener, reflected sound arrives from random directions, coming off of walls, floors, and other reflective surfaces. This reflected sound energy adds acoustically to the direct sound before entering each ear, changing the total signal reaching the ear (e.g., see Allen and Berkley 1979). The content of this reflected sound energy depends on the geometry of the listening space, the positions of objects in the space, and the location and orientation of the listener. Moreover, the reflected sound energy differs at the left and right ears. As a result, this late-arriving sound distorts the spatial information conveyed by the direct sound, degrading the spatial cues in the total signal. As a result, the acoustic location information in the signals a listener hears in everyday settings is less reliable after an initial “clean glimpse” of the direct sound that happens at sound onset, before the reflected energy arrives.

The Precedence Effect

Perceptually, judgments of the direction of a sound source depend strongly on spatial information in the onset of sound and relatively weakly on spatial information in later-arriving portions of sound (e.g., see Brown and Stecker 2010). This phenomenon is known as the precedence effect (Wallach et al. 1949; Zurek 1987; Litovsky et al. 1999). Given that in ordinary listening spaces the onset of the sound has the most reliable information about source direction, the precedence effect is thought to be one of the reasons why listeners are relatively good at judging source location even when listening in rooms.

The precedence effect has been studied extensively with pairs of clicks (one leading and one lagging); for such brief stimuli, the precedence effect is strongest when the leading click precedes the lagging click by 1–5 ms and then rapidly becomes weaker (so that listeners start to hear the second click as a separate event and then begin to localize it with increasing accuracy; see Blauert 1997). For more “natural” sounds, like speech or music, the precedence effect persists for tens of ms. Many researchers argue that the precedence effect has a longer time course for ongoing signals because they can be thought of

as containing multiple “onsets” due to local energy fluctuations, each of which can add to the precedence effect (e.g., see Zurek 1980).

Mechanisms of the Precedence Effect

Although the precedence effect is often discussed as a single psychophysical phenomenon, many different mechanisms likely contribute to the dominance of early spatial information on later-arriving information. For instance, the most peripheral portion of the auditory system, the auditory nerve, responds more vigorously at the onset of a sound than to later-arriving portions of a sound. This peripheral adaptation helps explain why a lagging sound that arrives within a few milliseconds of a leading sound does not convey strong spatial cues (Hartung and Trahiotis 2001). However, there are numerous studies that show that the perceptual dominance of the leading sound extends beyond very brief lead-lag delays that can be fully explained by peripheral adaptation. It is likely that microcircuitry in the brainstem contributes to the precedence effect at longer lead-lag delays through some type of inhibition triggered by the leading sound (Xia and Shinn-Cunningham 2011).

Cross-References

- [Sound Localization and Experience-Dependent Plasticity](#)
- [Sound Localization in Mammals and Models](#)

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Auditory Processing in Insects

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Synonyms

[Auditory pathway](#); [Hearing](#)

Definition

Auditory processing in insects serves to extract relevant information from acoustic signals about identity and location of acoustic objects, usually in the context of mate attraction and predator avoidance. For this goal, insects process spectral information from the carrier frequency of a signal and obtain temporal information from the sound's amplitude modulation pattern (the envelope). Auditory processing in insects is constrained by size in several aspects: first, the signal often contains ultrasonic frequencies due to small sender size; second, for localization, insects have only poor directional cues because of the small distance between their ears; and third, due to their small brains, the auditory processing capacity is limited to a small number of neurons.

Detailed Description

Overview and Background

Large Diversity of Hearing Insects and their Ears

The sense of hearing has evolved in vertebrates and arthropods, and hearing organs are known from several orders of insects. Ears have evolved in rather different locations of their body, not only on the head but also on the thorax, abdomen, and even wings and legs (Fig. 1a, Fullard and Yack 1993). Consequently, numerous neuronal substrates for the processing of acoustic information are known that evolved from a mechanosensory modality employed in a different context (proprioception by chordotonal organs; Meier and Reichert 1990; van Staaden and Römer 1998). In insects, two types of ears are known that are sensitive to two different physical attributes of sound, that is, the movement of particles in an elastic medium: tympanal ears that are specialized to sense changes in sound pressure and antennae or filiform hairs that are sensitive to particle velocity (Fig. 1b–d, Michelsen 1979).

Goals of Hearing and Auditory Processing

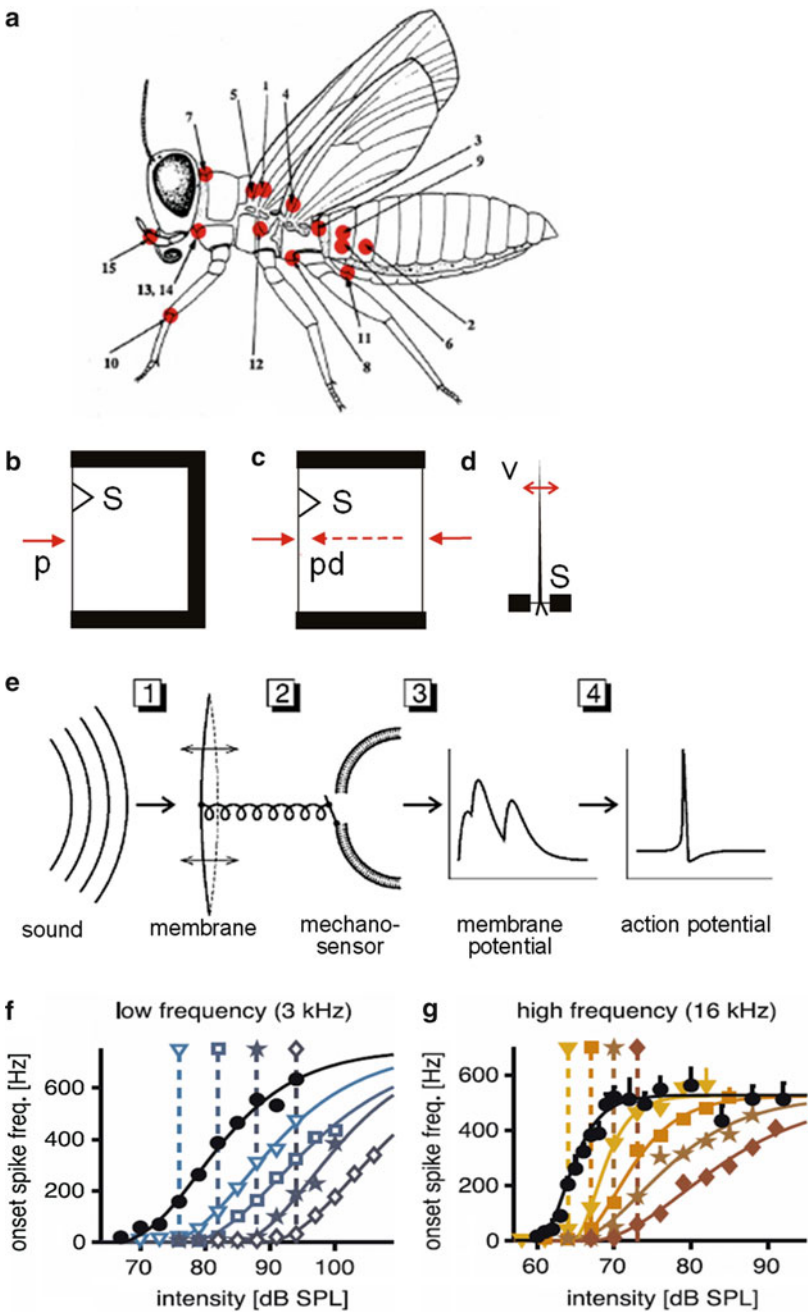
The ability to hear sound and to extract relevant information from an acoustic signal has evolved in three functional contexts. Notably, the production of sound alone is not a sufficient indicator of hearing ability as many insects produce defensive sounds when threatened (e.g., Bura et al. 2011). Conversely, numerous insects can hear sound but are themselves mute (Riede 1987; Riede et al. 1990).

Acoustic Communication

In many species the perception of acoustic signals occurs in the context of acoustic communication for mate recognition and mate localization. The most prominent examples stem from grasshoppers, crickets, and bushcrickets (orthoptera), but cicadas and moths have also evolved elaborate acoustic signals. A major goal of intersexual acoustic communication is to discriminate conspecific from heterospecific signals which helps to avoid fitness losses (Fig. 2). Sexual selection by

Auditory Processing in Insects, Fig. 1

Insect ears and sound transduction. (a) Evolution of insect ears in different body locations (b–d). Types of ears: (b) sound pressure receiver (mammals and humans); (c) pressure difference receiver (insects); (d) sound velocity receiver (filiform hair of insects); *S* sensory cells, *p* sound pressure, *pd* sound pressure difference, and *v* particle velocity. (e) Sensory transduction at a tympanic ear: 1, sound wave; 2, vibration of membrane and movement of mechanosensitive ion channels due to sound pressure; and 3–4, membrane potential and elicited action potential in sensory cell. (f, g) Intensity-response curves of an auditory neuron in crickets for different background intensities and different carrier frequencies (f, 3 kHz; g, 16 kHz). At increasing background intensities as indicated by the *top symbols* in (f, g), the response curves shift to higher intensities. ((a) Modified from Fullard and Yack 1993, with permission; see also there for explanation of numbers. (b–d) From Penzlin 2005, with permission. (e) From Gollisch and Herz 2005, with permission. (f, g) From Hildebrandt et al. 2011, with permission)



female choice for song signals of particularly attractive mating partners is also well known (von Helversen and von Helversen 1994; Andersson and Simmons 2006). Insects employ very stereotyped signals for acoustic communication, the production and recognition of which has a strict innate basis (Bentley and Hoy 1972, von

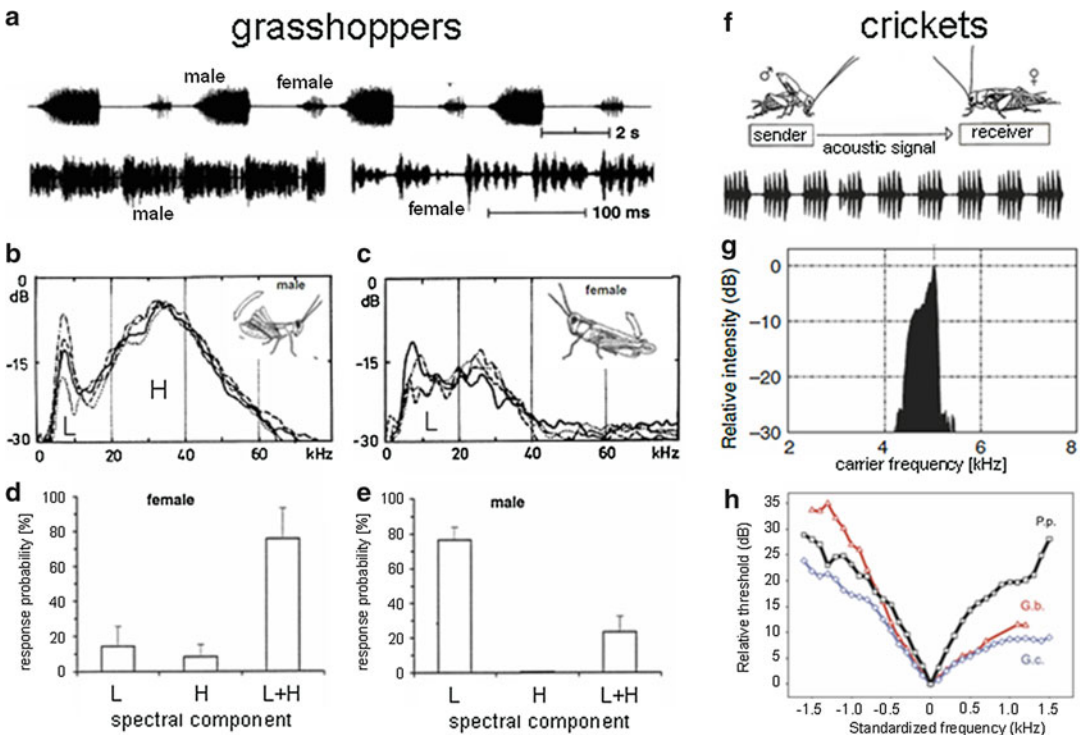
Helversen and von Helversen 1975a, b, 1987). For this reason, the acoustic communication of grasshoppers, crickets, and bushcrickets has served as a model system to study the mechanisms of neuronal processing within the auditory pathway by carefully designed behavioral experiments and recordings of neuronal activity of

single cells (Schildberger and Elsner 1994; Huber et al. 1989; Gerhardt and Huber 2002).

Since the nervous system of insects is small, all computations must be performed by relatively few neurons. This likely imposes a strong pressure for an efficient and sparse representation of the external world. A big advantage of investigating nervous system processes via the study of communication signals is that an animal's "external world" can be reduced to a manageable set of relevant stimuli, the stimulus space. This rather small set of highly relevant stimuli allows one to characterize how the stimuli are represented

within the nervous system and how these representations are transformed at different stages of processing.

To allow for successful communication, signal properties must be matched to the sensory characteristics of receivers. A straightforward example is the frequency tuning of a cricket female's ears to the narrowband signals of the males (see Fig. 2g, h). However, since in many species the temporal pattern of communication signals conveys the species-specific information, sender and receiver should be matched not only for carrier frequency but also for temporal characteristics.



Auditory Processing in Insects, Fig. 2 Acoustic communication in grasshoppers and crickets. (a, f) A sender, the male, produces a specific sound signal that is transmitted and perceived by a receiver, the female. (a) In some grasshoppers, the female responds to the male with her own song (upper trace). Songs of males and females have different pulse shapes (lower traces). (b, c) The power spectra differ between males (b) and females (c) in relative content of low (L)- and high (H)- frequency components. (d, e) Females and males respond selectively to the relative content of low- and high-frequency components in a signal. (d) Females prefer the combination of low and high components as they occur in the male song (as in

b). (e) Males prefer signals with only low-frequency components as they are typical for a female song (as in c). (g) The spectral content of a song of a cricket as in (f) is narrowly tuned to a peak frequency (5.0 kHz). (h) Auditory tuning for the specific carrier frequency of a conspecific song for different species of crickets (frequency axis was normalized to the respective best frequency; P.p. *Paroecanthus podagrosus*, G.b. *Gryllus bimaculatus*, G.c. *G. campestris*). Note the differences in the sharpness of tuning ((a–e) From von Helversen and von Helversen 1997; (f) modified from Huber 1992; (g) modified from Montealegre-Z et al. 2011; and (h) from Schmidt et al. 2011, with permission)

Here, a new problem arises: temperature. Since the function of neurons and muscles is strongly temperature-dependent (Janssen 1992; Robertson and Money 2012) and in general insects' body temperatures vary directly with ambient temperature, a signal's temporal pattern will vary with ambient temperature. This creates a recognition problem for the receiver's auditory system, in particular, if sender and receiver differ in their body temperatures (von Helversen and von Helversen 1987; Gerhardt and Huber 2002; Ronacher et al. 2004).

Detection and Avoidance of Predators

Although hearing in insects evolved more than 200 million years ago (MYA), the appearance of bats about 60 MYA sparked an explosion of insect species with ears (Fig. 1a, Fullard and Yack 1993; Hoy et al. 1998; Stumpner and von Helversen 2001). While some species modified already-existing ears for the detection of ultrasound, numerous other insects that had previously lacked hearing evolved ultrasonic ears at this time (Miller and Surlykke 2001). For moths this acquired sensory ability may even have served as a starting point for the evolution of intraspecific acoustic communication. Within their auditory pathways, insects employ different neuronal substrates for the processing of intraspecific signals and sounds from predators (see below: categorical perception in crickets and parallel processing of information). Some species perform stream segregation within individual neurons by spectral and temporal cues (Schul and Sheridan 2006). Numerous species of grasshoppers have ears and hearing abilities, but produce no sound during mate attraction. For these species, hearing likely serves for predator detection only, and predation was the selection pressure under which ears evolved or were conserved (Riede 1987; Riede et al. 1990; Lehmann et al. 2007).

Host Finding

Hearing has evolved independently at least twice in parasitic flies in the context of finding hosts for their eggs. The performance of flies in localizing their host by its sound signal is most impressive, in view of their tiny ears located underneath the

head (Robert et al. 1996; Lakes-Harlan et al. 1999). With these tympanal ears flies can detect and localize not only the broadband sounds of bushcrickets and cicadas but also the pure tone signals emitted by crickets. For that goal flies possess sharply tuned hearing, as is evident from the sensitivity of their sensory receptors and auditory interneurons (Stumpner and Lakes-Harlan 1996; Robert and Hoy 1998; Robert and Göpfert 2002). Another example of host finding via auditory cues is a bloodsucking corethrellid fly that is attracted by frog calls (Bernal et al. 2006).

Two Types of Ears in Insects and their Constraints by Size and Signals

Generally, two principal types of ears are known: particle velocity receivers and sound pressure receivers (Fig. 1b–d, Michelsen 1979; Faure et al. 2009). (1) Particle velocity receivers exploit the vector component of sound particles close to the sound source. The antennae (arista) of flies, especially of *Drosophila* and mosquitoes, are a well-investigated model system for sound perception, auditory transduction, and active sensing (Robert and Göpfert 2002). Many insects, as well as arthropods in general, employ filiform hairs (located on the abdomen, cerci, legs, or other parts of the body, Fig. 1d) of different length to detect sounds of predators and prey (Barth 2002). A general property of particle velocity receivers is their limitation to lower frequency ranges (<500 Hz). Low frequency signals from small senders commonly have low amplitude and thus small range (e.g., wing movements by *Drosophila*), and the perception of particle velocity is then usually limited to the near field of the sender (a distance of a few wavelengths). Since the vector component of sound is perceived, these ears also provide directional information (Michelsen 1979; Faure et al. 2009). Their sensitivity matches or even surpasses that of tympanal ears (Robert and Göpfert 2002). (2) The perception of sound pressure is mediated by tympanal ears and follows the same principles as in vertebrates including humans (Fig. 1b, c, Montealegre et al. 2012). Tympanal ears in insects arose from the cuticular surface of their exoskeleton under which large air sacs derived from tracheal tubes, the respiratory

system of insects, were located. Since insects possess an abundance of mechanosensory proprioceptors for monitoring the strain and movement of their cuticle, auditory organs were prone to evolve from chordotonal organs in almost any part of the body (e.g., the legs, thorax, abdomen, and wings, Fig. 1a, Fullard and Yack 1993; van Staaden and Römer 1998). Tympana are usually small, and the sensitivity of the ears often extends into the ultrasonic frequency range. Sound localization via tympanal ears in larger vertebrates (Fig. 1b) requires the computation of interaural intensity and time differences as pressure receivers do not respond to the vector component of sound (Brown 1994; Yost 2000). Due to the small size of insects, intensity differences and in particular interaural time differences are too small to be exploited directly. Insects circumvent this problem by using tympanic *pressure difference* receivers, in which an internal connection by tracheal tubes exists between both ears (Fig. 1c). Small frogs, lizards, and birds face similar problems and also have developed pressure difference receivers. In these ears, the vibration amplitude of the tympanum is determined not only by the sound pressure at the outer side but also by the sound traveling through the body to the inside of the tympanum (Autrum 1942). The resulting pressure difference between the inside and outside will then determine the tympanal vibration. The amplitude of these vibrations depends on sound direction, because the phase angle of a given sound frequency at both sides of the tympanum is also dependent on the direction of the incident sound wave (Michelsen et al. 1994).

Themes of Auditory Processing in Insects

A major challenge in summarizing the capacities for auditory processing of insects results from the overwhelming diversity of hearing species, of functional ears, and of the different designs of auditory pathways. The subchapters below therefore give only a brief overview of the computational capabilities of insects for different tasks and under different constraints.

For auditory processing, insects exploit numerous general principles of sensory processing that are well known from other modalities and from

vertebrates, including mammals. Among these are the capacity for sound frequency analysis by a traveling wave, tonotopic representations and formation of internal neuronal maps, parallel processing of information, the timing and balance of excitation and inhibition for feature extraction, lateral and contralateral inhibition for contrast enhancement, transformation of coding from a temporal code to a place code, burst coding, resonant properties of neurons, selective attention, and even stream segregation.

However, insects face constraints on the computational power provided by their small brains. The concept of identified neurons, in which individual neurons could be identified by their morphology and physiology, arose from neurobiological research in insects and other arthropods (Huber and Markl 1983). Computations performed by thousands of neurons in mammals may find their counterpart in a single identifiable neuron of an insect, which illustrates an impressive compression of function (e.g., contralateral inhibition for directional hearing is mediated by the lateral superior olive in mammals and by a single local interneuron, ON1, in crickets and bushcrickets (Grothe 2000; Selverston et al. 1985; Römer and Krusch 2000).

Notably, the processing and coding capacity of insect nervous systems is restricted to relevant tasks. Peripheral filters and computations for instance aid in reducing the required processing power. Therefore, the ears of insects and their auditory pathways are by no means all-purpose devices, and processing is rather specific to function. Examples include crickets that distinguish only 2 categories of sound (mate signals and predators, Hoy 1989) and the tympanic ear of a moth that is equipped with only 2 sensory cells for bat detection (Boyan and Fullard 1988). Generally, insects also employ simple algorithms for processing at the cost of acuity, for example, by computing acoustic hemispheres rather than localizing the angle of a sound source (von Helversen 1997; Römer and Krusch 2000). Nevertheless, insects are by no means imprecise. At least in some species their performance for temporal resolution in a gap detection task has a precision in the millisecond range, rivaling that

of humans (von Helversen 1972; Prinz and Ronacher 2002).

Basic Steps of Auditory Processing: Transduction and Information Coding by Sensory Neurons

In both tympanal ears and particle velocity receivers, sound induces the vibration of a structure (a thin membrane or a lever on a flexible pivot, Michelsen 1979; Robert and Göpfert 2002). The mechanical oscillation distorts the dendrite of a scolopidial cell, which is attached to the lever, the tympanum, or a tracheal tube (Fig. 1e1, e2). This distortion opens mechanosensitive ion channels, which are not yet fully characterized, and the resulting current transduces the movement into a change of the cell's membrane potential (Fig. 1e3; Gollisch and Herz 2005). Evidently, the membrane potential of sensory neurons cannot follow the fast vibrations of the tympanal membrane in the kilohertz range; rather, the membrane potential depends on the instantaneous sound pressure level. Similar to vertebrates, frequency discrimination occurs according to a frequency-place transformation (Montealegre et al. 2012). Either in the sensory neuron itself or in a downstream neuron, the membrane depolarization is then translated into a series of action potentials, a spike train, which encodes the sound envelope by modulations of the spike rate (Fig. 1e4). Spike rates of auditory afferents can be high, up to 400 Hz or more (Römer 1976).

Although insect and vertebrate ears obviously evolved independently, and the insect mechanoreceptors (scolopidia) differ from auditory hair cells of vertebrates, in the last decade many unexpected commonalities were detected. Recently, active processes were found in insect ears that serve to attain and adjust their formidable sensitivity, similar to the function of outer hair cells in the mammalian cochlea (Robert and Göpfert 2002; Nadrowski et al. 2011). In both locusts and bushcrickets, traveling waves were observed to play an essential role in frequency discrimination. As in the mammalian cochlea, traveling

waves exhibit peaks at different locations, depending on sound frequency (Windmill et al. 2005; Hummel et al. 2011; Montealegre et al. 2012). In addition, in central projections of auditory afferents, there is a tonotopic representation of frequencies (Römer 1983; Römer et al. 1988; Stumpner 1996; Stölting and Stumpner 1998). Finally, the development of the auditory organ of *Drosophila* depends on similar genes, e.g., of the atonal family, as the vertebrate ear (Senthilan et al. 2012).

Although the *temporal* resolution of insect ears can match that of vertebrates in some respects (see below), the *frequency resolution* of insects is generally inferior to that of vertebrates. In crickets we find a kind of “categorical response,” by which the frequency scale is segmented into two parts: sound pulses with carrier frequencies above 15–20 kHz (up to 100 kHz) evoke an avoidance response, whereas sound pulses with frequencies between 3 and 10 kHz are attractive and evoke a positive steering response when flying (Moiseff et al. 1978; Hoy 1989). Remarkably, however, in an interneuron of a bushcricket, a sharpening of the broader frequency tuning of auditory receptors by frequency-dependent “lateral” inhibition similar to vertebrates has been observed (Stumpner 1997). The sharpness of frequency tuning of auditory neurons is commonly described by the $Q_{10\text{dB}}$ score. This gives the ratio between the characteristic frequency (i.e., the frequency of the neuron's lowest threshold) and the width of the tuning curve 10 dB above the lowest threshold. Typical values for insects are between 0.5 and 2.5 and only rarely extend to 3.5 (Hennig et al. 2004), whereas in vertebrates, we find much higher values, between 1 and 25 (and up to 400 in the acoustic foveae of bats, Suga et al. 1997).

The dependency of spike rate on sound intensity is commonly depicted by the f-I curve (firing rate vs. intensity, also rate-intensity curve; Fig. 1f, g). The dynamic range between threshold and saturation indicates the region of discriminable sound intensities. The steepness of the f-I curve determines how well small sound pressure differences can be discriminated – which is important for directional hearing and when fine modulation details of a signal have to be assessed (compare

Fig. 1f, g). A steep f-I curve, however, has the disadvantage that it covers only a small part of the relevant sound intensity range which may extend to 100–120 dB SPL (Fig. 1f). (Note that the dB SPL scale is a logarithmic scale that expresses sound pressure relative to 20 μ Pa; a 100 dB sound has a 10^5 larger sound pressure compared to the human hearing threshold at 1 kHz.) As in other sensory systems, the intensity range problem may be solved by adaptation, by which the f-I curve can be adjusted to the average ambient sound pressure levels (Benda and Herz 2003; Benda and Hennig 2008). Spike frequency adaptation as early as the level of sensory neurons helps to attain a certain degree of intensity invariance that is important for object identification and behavioral decisions (Benda and Hennig 2008). However, in different neuron types we may find different biophysical realizations, ranging from cell-intrinsic spike-triggered adaptation currents to inhibitory inputs and presynaptic adaptation mechanisms (Gollisch and Herz 2004; Hildebrandt et al. 2009). A complementary way to cope with the large range of encountered sound intensities may be a kind of “range fractionation.” In locusts and bushcrickets, for example, we find auditory receptors with a rather limited dynamic range of 20–30 dB. Since different receptors exhibit a similarly broad frequency tuning but very different thresholds, intensity discrimination is possible over a broad range (Römer 1976; Römer et al. 1998).

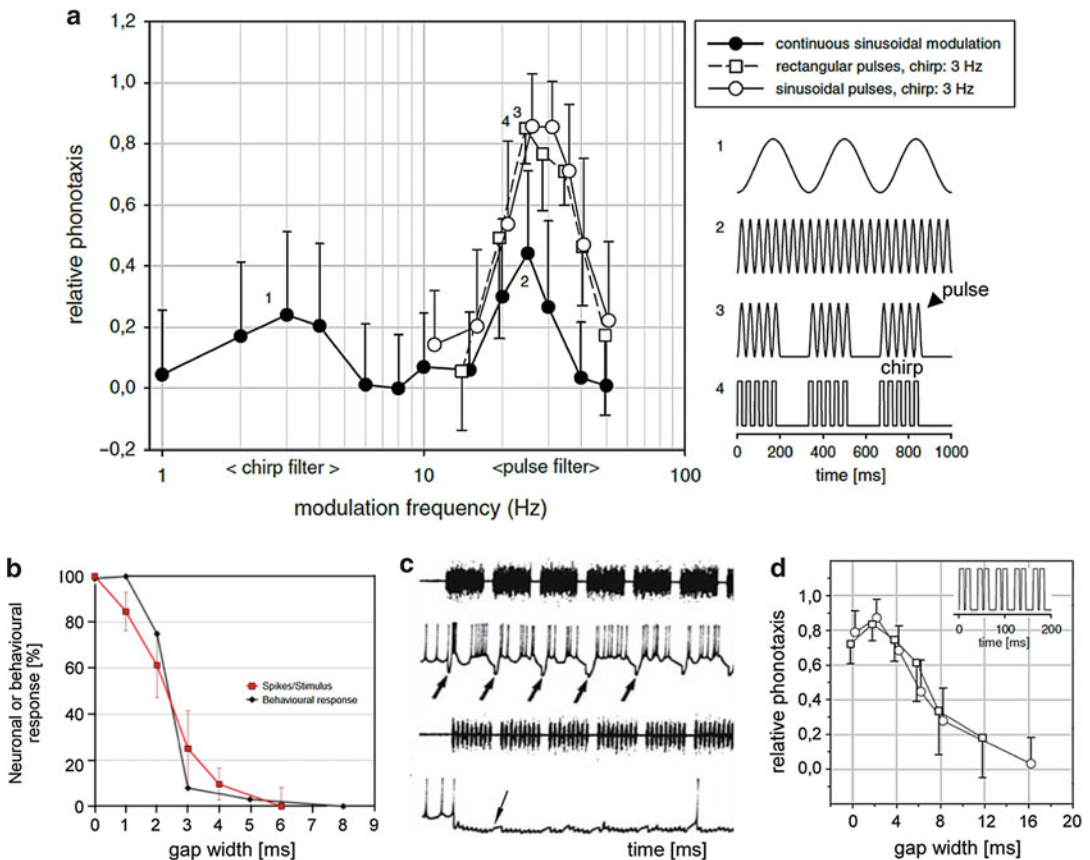
Obviously, the spike trains of sensory neurons are the only information any central nervous system has about events in the external world. In other words, the brain has to infer the structure of the outer world from the spike trains arriving from various sense organs. The very successful stimulus reconstruction methods seek to understand signal processing from the viewpoint of the central nervous system and to infer information about an external stimulus from the spike trains of sensory neurons (Rieke et al. 1997). The basic idea is to reconstruct the stimulus envelope from spike trains that have been recorded in response to that stimulus. By this procedure we can estimate how much information the CNS can obtain about a sensory stimulus and what aspects

of the stimulus are lost. For example, from the spike trains of the locusts’ auditory afferents, stimuli with large modulation amplitudes can be reconstructed more accurately than stimuli with small modulation depths (Machens et al. 2001). Remarkably, grasshopper songs seem to be matched to this feature of the receiver’s auditory periphery. This investigation has further shown that in the very periphery of the auditory pathway, a single sensory neuron transmits a high amount of information, up to 180 bits/s (Machens et al. 2001).

Processing of Signal Envelopes within the Auditory Pathway

Temporal Resolution and Temporal Integration

The communication signals of many species contain fast amplitude modulations that are evaluated by females to assess the attractiveness of potential mates. Hence, we must ask whether there are neuronal constraints that determine the behavioral *limits of temporal resolution*. Two widely used paradigms to investigate these limits are modulation transfer functions (MTF) and gap detection (for reviews see Green 1985; de Boer 1985; Michelsen 1985; Viemeister and Plack 1993; Joris et al. 2004). In the MTF paradigm either random modulations in a certain frequency band or sine wave modulations are used. The latter paradigm can be applied in neurophysiological as well as in behavioral experiments. Stimuli with appropriate carrier frequencies are presented that exhibit sinusoidal amplitude modulations of different frequencies and reveal what range of modulation frequencies the system is able to represent, and if there are specific modulation frequencies to which a system responds particularly well, see Fig. 3a for an example. The black dots in this diagram show the attraction of cricket females to a 4.5 kHz tone that was amplitude modulated at frequencies between 1 and 50 Hz; two regions of enhanced attractiveness around 3 and 30 Hz are obvious (Wendler 1989; Hennig 2009). In spike train recordings one can determine the average spike count



Auditory Processing in Insects, Fig. 3 Temporal resolution of amplitude modulations in grasshoppers and crickets. **(a)** Behavioral modulation transfer function of crickets (filled symbols, stimuli as in 1 and 2 at right). Best responses are obtained if lower and higher modulation frequencies for pulse and chirp (i.e., groups of pulses) are combined in one stimulus as in patterns 3 and 4 at right (open symbols). **(b)** Gap detection in a grasshopper measured in behavioral experiments (black curve) and neuronal response (red curve, AN4). **(c)** Response of the AN4 neuron to uninterrupted and gap containing sound

syllables. This neuron responds to sound onset first with a deep inhibition, an IPSP (arrows), followed by excitation and spikes (upper traces). In the interrupted stimuli, each onset after a gap triggers the IPSP anew which leads to an effective suppression of spiking (lower traces, adapted from Ronacher & Stumpner 1988). **(d)** Gap detection in crickets (behavioral data) ((a) From Hennig 2009; (b) modified from von Helversen 1972 and Franz and Ronacher 2002; (c) modified from Ronacher and Stumpner 1988; and (d) from Schneider and Hennig 2012, with permission)

(rate, r-MTF) or evaluate how well the spikes are locked to a period of the stimulus envelope (temporal, t-MTF). r-MTF reveals a neuron's filter properties, e.g., high-pass, low-pass, band-pass, or band-reject features for sound pulse rates. The t-MTF, in contrast, indicates how well fast modulations can be resolved by a neuron. One should be aware, though, that the construction principle of MTFs is based on a large amount of averaging, and therefore, the information provided by single spike trains may be lower

than that suggested by a MTF (Wohlgemuth et al. 2011).

The second paradigm, gap detection, has been applied in behavioral experiments to grasshoppers and crickets (von Helversen 1972; von Helversen and von Helversen 1997; Schneider and Hennig 2012). Grasshoppers detect gaps of 2–3 ms duration and in this respect are not inferior to vertebrates (Fig. 3b, Prinz and Ronacher 2002). This high resolution of gaps seems to be mediated by the specific interactions between inhibition and

excitation in one identified interneuron (Fig. 3c; Ronacher and Stumpner 1988). The temporal resolution of cricket ears is lower compared to grasshoppers; minimal detectable gap widths are between 6 and 8 ms (Fig. 3d, Schneider and Hennig 2012). One reason for this may stem from the males' sound production system: cricket songs are produced by a resonant mechanism which precludes very fast amplitude changes (Bennet-Clark 1998). Hence, on the receiver's side there is no need to push the temporal resolution to extremes. In addition, compared to broadband signals, which are typical in many grasshoppers and bushcrickets, pure tone signals, such as those produced by many crickets, tend to be more strongly affected by random amplitude fluctuations when traveling through the habitat, which also sets limits for temporal resolution (Römer and Lewald 1992).

Temporal integration refers to the *time-intensity trading* paradigm. In these experiments the minimal audible threshold was found to depend on the duration of the stimuli used. To detect very short stimuli, e.g., of 5 ms duration, higher sound intensities are necessary than for longer, e.g., 100 ms, stimuli. The product of sound intensity and stimulus duration determines the threshold up to durations around 200–300 ms, whereas for longer stimuli, the threshold stays constant (Green 1985). Hence, we are confronted with an apparent discrepancy, the temporal integration-resolution paradox (de Boer 1985): gap detection and MTF paradigms yield time constants in the order of 1–6 ms, whereas from the time-intensity trading paradigm, we are left with time constants in the range of 150–300 ms (for a discussion of this paradox and possible solutions, see de Boer 1985; Viemeister and Wakefield 1991; Tougaard 1998; Pohl et al. 2013).

Transformation of Coding Along the Auditory Pathway

In insects and other arthropods, many neurons can be uniquely identified on the basis of their characteristic morphology. The peripheral stage of a grasshopper's auditory pathway comprises sensory neurons (afferents), local neurons whose processes are confined to the thoracic ganglia, and

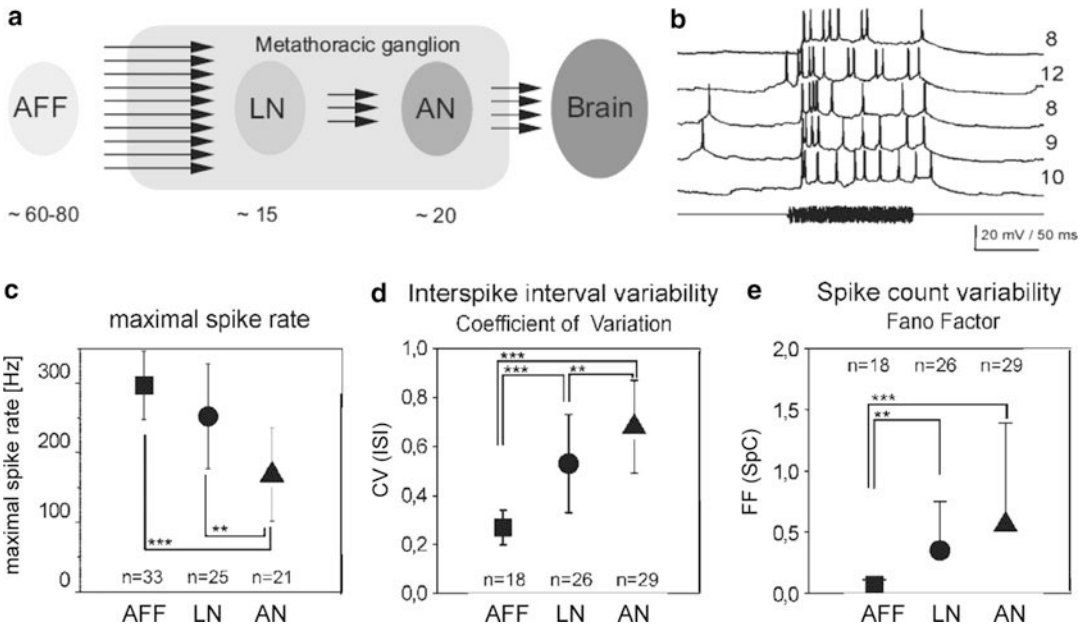
ascending neurons, whose axons reach the brain. Present knowledge indicates that this corresponds to a feedforward network (Fig. 4a, Vogel et al. 2005; Vogel and Ronacher 2007).

Auditory afferents exhibit high firing rates, up to several hundred Hertz (Fig. 4c). Their tonic spike responses represent the amplitude modulation patterns of auditory stimuli by a modulation of the firing rate. The variability of their responses is rather low (see Fig. 4d, e). The precise responses of sensory neurons allow for a good discrimination and classification of auditory stimulus ensembles (Machens et al. 2003; Wohlgemuth and Ronacher 2007).

Along the auditory pathway the maximal spike rates decrease, whereas the spike train variability increases (both spike count and inter-spike-interval variability, Fig. 4c–e). In accordance with the larger variability of higher-order neurons, the temporal resolution and the classification success for similar stimuli decrease markedly among the ascending neurons. At the level of afferents and among primary-like local neurons, we find a high classification success that depends almost exclusively on the timing of spikes. In contrast, among ascending neurons the classification success based on a single neuron's responses decreases, and spike count differences between stimuli become more important (Wohlgemuth and Ronacher 2007). Among ascending neurons, the information appears to be distributed among several neurons and to be represented as a labeled-line population code (Clemens et al. 2011, 2012). A similar reduction in spike rates from ascending to brain neurons is observed within the auditory pathways of crickets (Schildberger 1984; Kostarakos and Hedwig 2012).

Central Processing in the Frequency or Time Domain?

With Fourier analysis, a signal's temporal structure can be broken down into sine waves, each having a particular amplitude and phase (see, e.g., Yost 2000). If both the resulting spectra for amplitude and phase are known, the original signal can be fully reconstructed. Therefore, there are two principal means of processing a periodic signal: an analysis in the frequency domain, i.e., of the



Auditory Processing in Insects, Fig. 4 Transformation of coding along the auditory pathway. (a) Scheme of a grasshopper's auditory pathway (AFF auditory afferents, LN local neurons, AN neurons whose axons ascend to the brain). Numbers indicate approximate numbers of neurons at the respective levels. (b) Response (numbers of action potentials at right) of an ascending neuron (AN1) to five presentations of an identical stimulus. (c) Maximal spike

rates at different processing levels. (d) Variability of interspike intervals (CV variation coefficient). (e) Variability of spike count (expressed as Fano factor FF). Axis in (c–e) *AFF* afferents, *LN* local neurons, and *AN* ascending neurons; numbers indicate sample size ((a) From Ronacher 2013; (b–e) modified from Vogel et al. 2005, with permission)

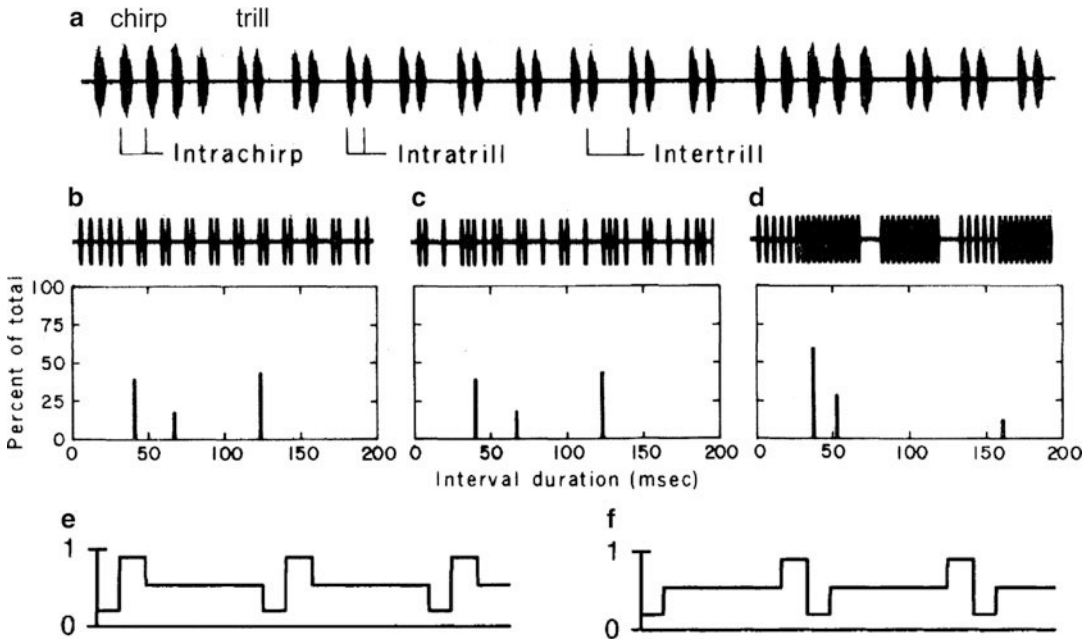
amplitude spectrum without phase and thus without temporal information, and an analysis in the time domain by the computation of temporal parameters such as durations and periods of events. For instance, the processing of the sound carrier by a traveling wave is equivalent to the computation of an amplitude spectrum for a frequency analysis.

The envelopes of the communication signals of many insect species have a highly regular and repetitive structure and consist of a series of stereotyped subunits. Remarkably, several experiments have shown that crickets and grasshoppers accept song signals with randomized or shuffled patterns as conspecific (Fig. 5, Pollack and Hoy 1979; von Helversen and von Helversen 1998; Schmidt et al. 2008). This suggested that central processing may be restricted to the frequency domain and serve to compute an amplitude spectrum of the song envelope. A crucial experiment

to determine whether a signal is processed in the frequency or time domain is to present reversed or inverted versions of an attractive signal (see Fig. 5e, f). Inverted variants exhibit the same amplitude spectrum as the original but differ in their phase components and thus temporal qualities. If such modified song models show the same attractiveness as the original, a spectral analysis of the signal envelope is very likely as opposed to temporal processing. However, evidence from experiments as shown in Fig. 5e, f and others revealed large differences in attractiveness which suggests that insects process the amplitude modulations of sound stimuli in the time domain (von Helversen and von Helversen 1998; Schmidt et al. 2008; Hennig 2009).

Global Algorithms of Coding

Which global algorithms of coding are implemented in the auditory pathways of insects

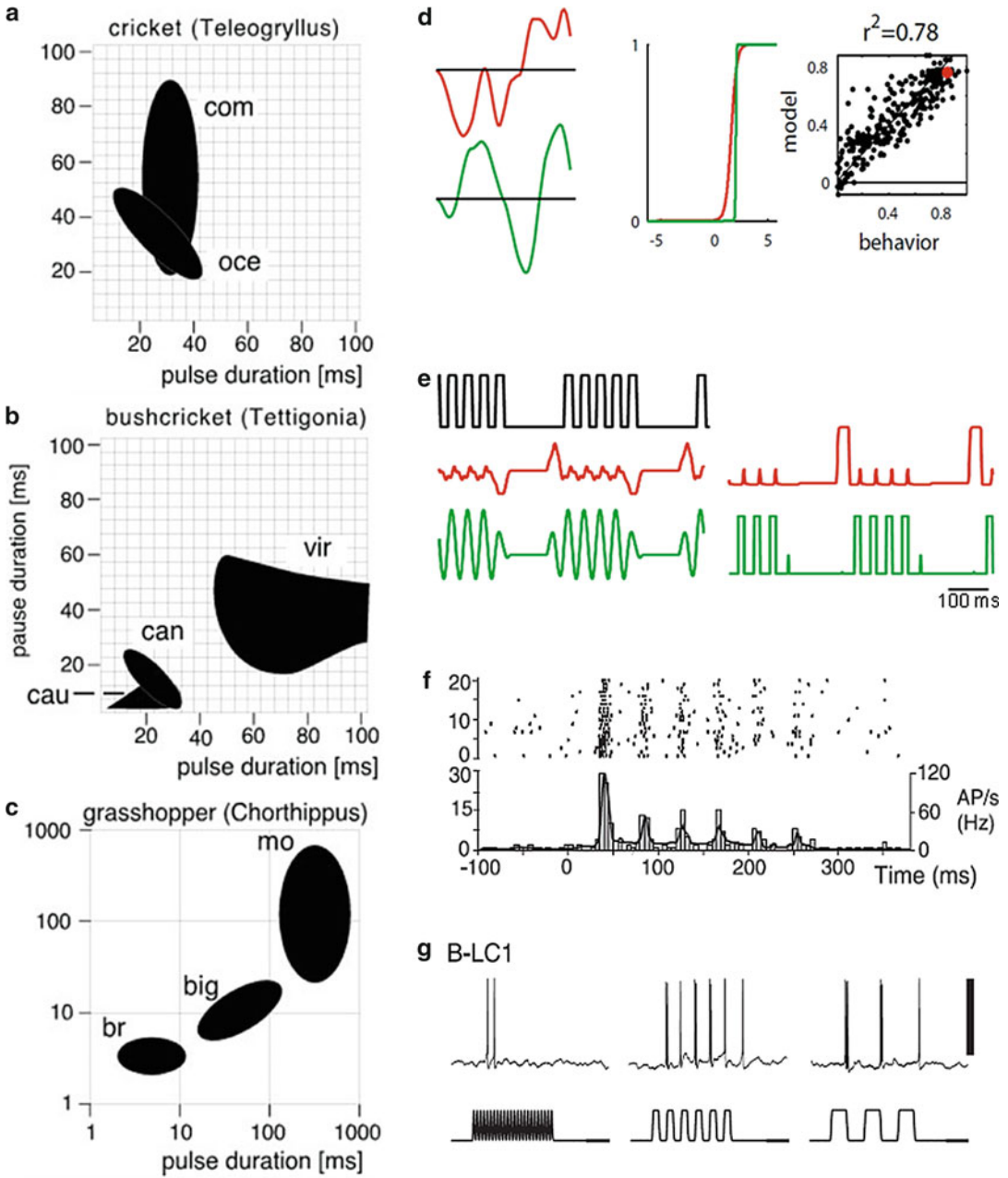


Auditory Processing in Insects, Fig. 5 Regular song patterns and the importance of temporal order for recognition. (a) Regular calling song of the cricket *Teleogryllus oceanicus*. (b–d) Song models (top) for tests of preference of females and relative frequency of different pulse intervals (bottom). Note the differences in the interval distributions between (b, c, and d). (b) Song model of *T. oceanicus*. (c) Shuffled song model with the same relative frequency of pulse intervals as in (a). (d) Song model of *T. commodus*. Song models of (b) and (c) are attractive for females of *T. oceanicus*, although the temporal order in

c is randomized. The song pattern in (d) from the sibling species is not attractive. Although this experiment suggested central processing of the signal envelope in the frequency domain, the bulk of experimental evidence demonstrates processing in the time domain by crickets and other Insects. (e, f) Envelopes of reversed song models for behavioral tests with grasshoppers. The pattern in (e) is very attractive, but the reversed version in (f) is rejected (von Helversen and von Helversen 1998) ((a–d) From Pollack and Hoy 1979 with permission; (e, f) from von Helversen and von Helversen 1998, with permission)

to achieve the goals of hearing (see Overview and Background)? In the context of acoustic communication as well as predator avoidance, insects have to recognize specific sound signals for which they possess an innate, internal representation. Presently there is no evidence for a maplike neural representation of specific features in the auditory pathways of insects, except for the tonotopic frequency maps in the periphery (Hildebrandt 2014). For predator avoidance ultrasonic cues and the detection of strong onsets as a typical effect of intense bat calls appear to be most important. Burst coding in the auditory pathways of crickets and grasshoppers shows how onsets are detected (see below, Marsat and Pollack 2006; Creutzig et al. 2009; see also Krahe and Gabbiani 2004). For the recognition of conspecific signals, several global schemes were proposed:

autocorrelation, cross-correlation with a template, or combinations of high-, low-, and band-pass filters. All these schemes are derived from Fourier transformation and represent mathematical and technical solutions, for which evidence from several investigations exists (Schildberger 1994; Weber and Thorson 1989; Hennig 2003). However, only a few studies have been able to reproduce the preferences exhibited by female insects over a wider range of signals (see Fig. 6a–c for response profiles from several species of crickets, bushcrickets, and grasshoppers upon presentation of stereotyped sound patterns composed of subunits built by regular pulses and pauses (von Helversen and von Helversen 1994)). In a recent alternative approach, the recognition of sound signals was examined using linear-nonlinear (LN) models adapted from computational



Auditory Processing in Insects, Fig. 6 Preference profiles of female insects for song signals and LN models. (**a–c**) Preference profiles for song signals in the time domain by crickets, bush crickets, and grasshoppers (A: oce oceanicus, com commodus; B: cau caudata, can cantans, vir viridissima; C: br brunneus, big biguttulus, mo mollis). (**d–e**) LN models account for preference functions of the cricket *Gryllus bimaculatus*. (**d**) Two LN models (red, green) that predict the preferences for pulse patterns by female crickets (*G. bimaculatus*): linear filters (left panels)

and the respective nonlinearities (central panel) that predict behavioral responses of female crickets (right panel). Note that the duration of the linear filters is only 64 ms. The red dot in the right panel of (**d**) refers to the pattern in (**e**). (**e**) Output of the LN models (**d**) in response to a song model (upper trace). Response of the linear filters to the song model before (left panels) and after passing through the nonlinearity (right panels). The upper filter (red in **d** and **e**) responds like an onset detector; the lower filter resembles a Gabor-function and selectively responds to

neuroscience (Clemens and Hennig 2013; Clemens and Ronacher 2013). For crickets as well as grasshoppers, Gabor functions emerged as filters that responded best to particular subunit shapes common to the conspecific song signal (combinations of pulse and pause or pairs of pulses, Fig. 6d, e). Gabor functions (a sine wave multiplied with a Gaussian function) are well known from sensory pathways in vertebrates (visual, Daugman 1984; Simoncelli and Olshausen 2001; Priebe and Ferster 2012; auditory, Smith and Lewicki 2006). However, the most notable property of the proposed LN model was the independence of the computation from the exact timing of occurrence of the template within a larger time window. Therefore, this LN-model approach offers an elegant solution to the attractiveness of shuffled and irregular song signals (see Fig. 5 and subchapter: processing in the frequency or time domain). Small modifications of Gabor functions are capable of reproducing response profiles known from several species of insects (Fig. 6a–c, Clemens and Hennig 2013). Although these filters by default describe the output of the whole recognition system, present evidence suggests that certain identified neurons in crickets may represent a neuronal correlate of specific LN features (compare Fig. 6e–g, Zorović and Hedwig 2011; Kostarakos and Hedwig 2012; Clemens and Hennig 2013).

Local Mechanisms of Coding

For insects there exist several prominent examples of how global algorithms of coding are at least in part implemented by identified neurons. For instance, the detection of bat predators by crickets is mediated by a specific auditory neuron (AN2), whose bursting is crucial for a behavioral response (Fig. 7, Nolen and Hoy 1984; Marsat and Pollack 2006). Similarly, the AN12 in

grasshoppers codes for a specific song feature by bursts (Creutzig et al. 2009). Specific combinations of excitation and inhibition account for feature extraction in grasshoppers (gap detection by AN4; Ronacher and Stumpner 1988 – see temporal resolution) and serve as a basis for pulse rate detection by the identified neuron B-LI4 in crickets (Kostarakos and Hedwig 2012). Similarly, resonant properties within the auditory pathway of bushcrickets mediate the detection of specific pulse rates and can be modeled as a property of single neurons (Bush and Schul 2006; Webb et al. 2007). Short time constants of single identified neurons allow them to act as feature detectors for ultrasonic pulses in the auditory pathway of moths (Boyan and Fullard 1988).

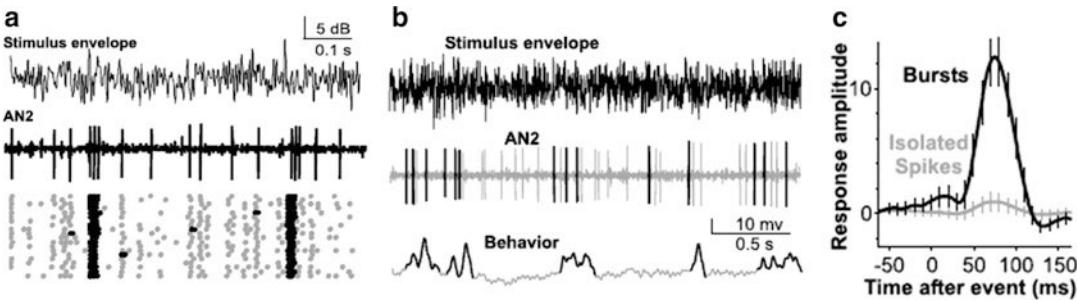
Processing under the Constraints of Noise: A Twofold Problem

Noise poses unavoidable problems for all sensory systems. There are two classes of noise, external and internal. Various types of external noise influence sound waves on their way from sender to receiver. Hence, as a rule, receivers have to cope with signals that are masked and degraded in their temporal structure (e.g., Michelsen and Larsen 1983; Römer et al. 1989; Römer 2001; Schmidt et al. 2011; see also Brumm and Slabbekoorn 2005; Wiley 2006).

Crickets with their pure tone songs have found a solution to reduce the impact of external noise. The females' hearing system is tuned to the carrier frequency of male songs and becomes increasingly less sensitive to frequencies farther from the carrier frequency (Fig. 2g, h). The sharpness of the tuning curve may depend on ecological conditions (Schmidt et al. 2011). A cricket species (*Paroecanthus podagrosus*) living in very noisy tropical rainforests exhibits an exceptionally narrow tuning ($Q_{10dB} \sim 4$) that allows for an efficient

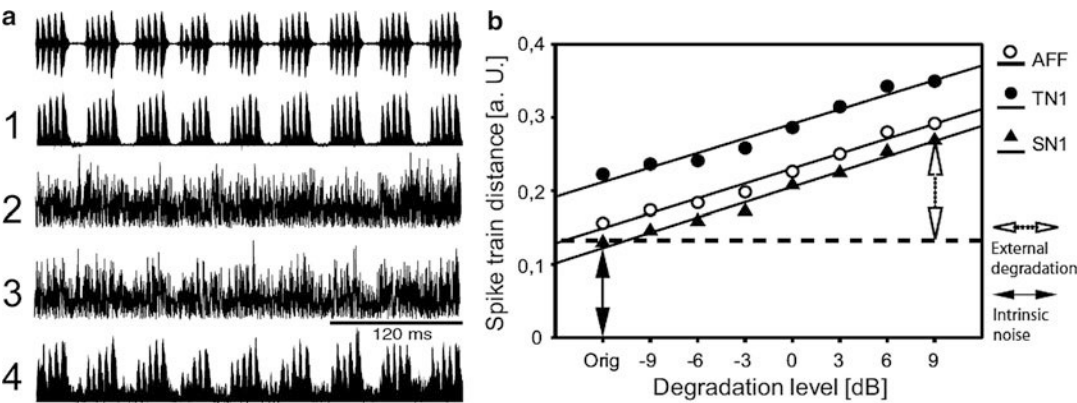
Auditory Processing in Insects, Fig. 6 (continued) pairs of pulses (green in d and e). (f–g) The response pattern of an auditory interneuron in the cricket brain resembles the output of the onset detector (red in d, e). The neuronal discharges in (g) illustrate onset responses to

sound patterns with different pulse rates ((a–c) From Hennig et al. 2004; (d, e) modified from Clemens and Hennig 2013; and (f, g) from Zorović and Hedwig 2011, with permission)



Auditory Processing in Insects, Fig. 7 Burst coding by an identified interneuron (AN2) and avoidance behavior in crickets to bat like stimuli. (a) Bursts in AN2 in response to amplitude-modulated stimuli (carrier frequency: 30 kHz); burst spikes are marked as *black* dots in raster plot. (b) Response of AN2 to a sound stimulus (as in a) and

behavioral response (*bottom trace*: abdominal movements away from the sound source). (c) Amplitude of abdominal movements after isolated action potentials (*gray*) or bursts (*black*). Positive values indicate abdomen flexion away from the sound source (From Marsat and Pollack 2006, with permission)



Auditory Processing in Insects, Fig. 8 Processing under the constraints of noise: a twofold problem. (a) Song of a tropical cricket *Paroecanthus podagrosus* (*upper trace*). Lower traces. 1: Song envelope. 2: Song envelope under ambient noise levels as recorded in the habitat. 3: Song plus noise less efficiently filtered with the broader tuning curve of a European cricket (*Gryllus bimaculatus*). 4: Song plus noise filtered with the narrow tuning curve of *P. podagrosus*, compare Fig. 2h (Adapted from Schmidt et al. 2011). (b) Effects of intrinsic noise and external signal degradation on spike train dissimilarities of

three representative neurons, assessed with the van Rossum metric and corrected for spike rate differences. The *black* arrow at “orig” indicates the average spike train distance found for repeated presentation of the original song pattern, i.e., the result of trial-to-trial variability. The *open* arrow indicates the additional distance caused by the most strongly degraded signal. AFF sensory neuron, TN1, and SN1 two primary-like local neurons. ((a) Modified from Schmidt et al. 2011. (b) Modified from Neuhofer et al. 2011 and Ronacher 2013, with permission)

suppression of ambient noise (Figs. 2h, 8a). Thus, in this species we find a narrow peripheral filter that is perfectly matched to the carrier frequency of conspecific signals and dismisses signals from other species, at the expense of reducing the range of perceivable sounds (Fig. 8a). Many bushcrickets use broadband communication signals which yield a twofold advantage. First,

broadband signals are less likely to be degraded in the biotope compared to narrowband signals (Michelsen and Larsen 1983; Römer and Lewald 1992). In addition, the receiver’s nervous system can compare the neuronal signals from differently tuned auditory receptors and thereby reduce intrinsic neuronal noise (see below). Note that the hearing systems of vertebrates (mammals,

owls) also use broadband signals to reduce noise or to resolve localization ambiguities (Konishi 1990).

In addition to external noise, auditory systems face a second noise problem. Neuronal signals are inherently noisy due to the stochastic opening and closing of ion channels. This *intrinsic noise* becomes evident as trial-to-trial variability of spike trains in response to repeated presentations of an identical stimulus (see Fig. 4b). Animals with a large nervous system may alleviate this problem by averaging responses from many neurons with similar properties. However, due to size constraints insects probably cannot afford this solution. Under some conditions noise may play a beneficial role and improve neural computations, for example, by stochastic resonance (for review see McDonnell and Ward 2011).

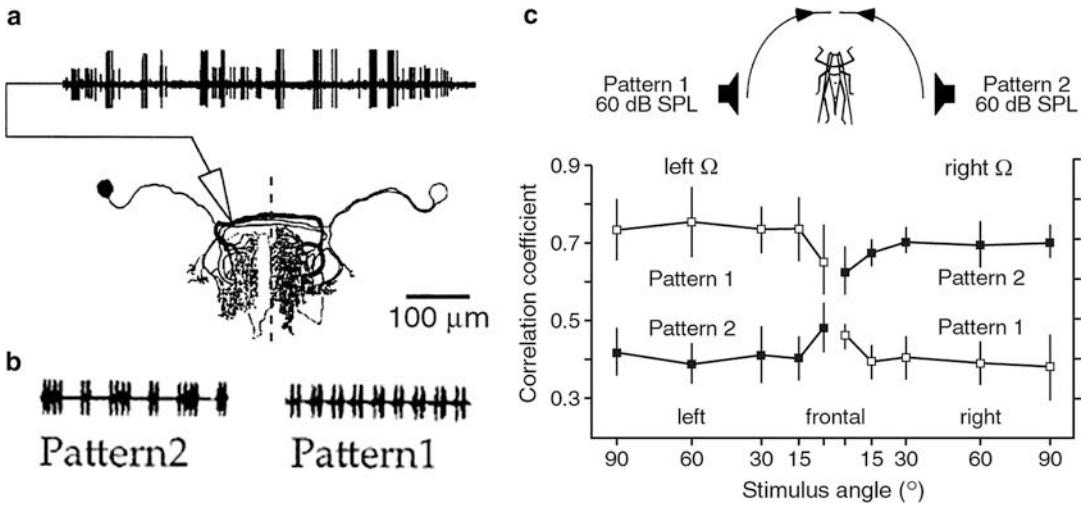
To quantify the trial-to-trial variability or to compare neuronal responses to different stimuli, one can apply a *spike train metric* (see, e.g., van Rossum 2001). This metric describes the similarity of two spike trains by a single number, which is in line with our intuition of distance: small values indicate high similarity. The metric uses an adjustable parameter to take into account both differences in the spike count as well as in the timing of spikes. This metric approach was used to determine the relative impacts of external and intrinsic noise on the encoding of envelope-degraded stimuli by auditory neurons of grasshoppers (Neuhofer et al. 2011). Unexpectedly, the contribution of external signal degradation to the overall spike train distances was low: even for the highest degradation level, its amount did not exceed that of intrinsic noise (Fig. 8b).

As long as rather different signals have to be analyzed, neuronal noise may not be a very serious problem. However, with communication signals that serve to attract mates, it will be necessary to discriminate between similar signals and to detect small deviations from a species-specific pattern. This is especially the case if quality cues from the sound signals of potential partners are to be extracted. Remarkably enough, the spike trains of even a single

auditory afferent allow for an almost perfect discrimination of songs of different males of one species (Machens et al. 2003). At higher stages in the auditory pathway, however, the discrimination deteriorates and intrinsic noise cannot be neglected as a limiting factor. Grasshoppers appear to have circumvented this intrinsic noise problem by changing the coding scheme at a rather peripheral stage of processing (see Fig. 4a): among the ascending neurons information is distributed according to a labeled-line code (Clemens et al. 2011, 2012; see also Clemens and Ronacher 2013).

Directional Hearing

The biophysical qualities of the pressure difference receivers equip the ears of insects with a directional dependence of the vibrational amplitudes of their tympana (Michelsen 1998). Sensory neurons reflect this dependence in spike numbers, and for some species, this difference in response strength is also translated into timing differences (enhanced by ramps Krahe and Ronacher 1993; Ronacher and Krahe 2000). The contrast in response magnitude of sensory neurons for left and right differences is enlarged by contralateral inhibition from local interneurons (ON neurons in crickets, Selverston et al. 1985; bushcrickets, Römer and Krusch 2000; LN in grasshoppers, Marquart 1985). The representation of sound from one side is therefore enhanced, because the responses to sound from the opposite side are suppressed, and this takes place already at early levels of auditory processing of sound direction, usually at the first synapse after sensory receptors. This mechanism of contralateral inhibition in auditory pathways transforms the acoustic environment of insects into acoustic hemispheres. These hemispheres enable a rather accurate distinction of left and right sound signals at the cost of accuracy in determining the angle of the sound source (lateralization in grasshoppers, von Helversen and Rheinlaender 1988). A corollary of the computation of acoustic hemispheres is that sound signals are selectively represented on one side of the insect or the other. This computation resembles the phenomenon of selective attention



Auditory Processing in Insects, Fig. 9 Acoustic hemispheres and selective representation of sound patterns in bush crickets. (a, b) Left and right specimens of the local interneuron ON1 were recorded simultaneously, while different sound signals (pattern 1 and 2) were presented from

either side. (c) Both interneurons selectively represent only the sound pattern from one side (inset: experimental arrangement, correlation coefficient of the spike train with the sound pattern as a measure for copying fidelity) (From Römer and Krusch 2000, with permission)

(Pollack 1988) and allows insects to discriminate sound sources in much the same way as the cocktail party effect well known from humans (Fig. 9, Römer and Krusch 2000). Notably, contralateral inhibition and acoustic hemispheres can exert a considerable influence on mate choice as females of bushcrickets prefer males that take a leader role among singing males, since the representation of the song signal of a follower is suppressed in their auditory pathway (Hartbauer et al. 2005; Siegert et al. 2011). These local computations for enhanced directional responses can also affect the singing behavior of males and promote synchronization and thus chorusing among males (Greenfield and Roizen 1993; Greenfield 1994; Hartbauer et al. 2005). Due to the computational conflict between representation of sound pattern and sound source, grasshoppers split the sensory pathways for processing of cues for pattern and direction by parallel processing (von Helversen 1984; Ronacher et al. 1986). However, in the evolutionarily older communication systems of crickets and bushcrickets, serial processing of pattern and direction appears to prevail (Wendler 1989; Stabel et al. 1989; von Helversen and von Helversen 1995; Schul et al. 1998).

Conclusions

Auditory processing in insects is constrained by small body size and a relatively small number of neurons. Thus, the hearing capacities are focused on highly relevant tasks, such as predator detection, mate attraction, and, in some cases, eavesdropping on prey or host signals. Insect ears evolved from cuticular mechanosensory proprioceptors and may respond to different aspects of sound waves – particle velocity or sound pressure; ears can be found in almost any part of the body, and as a consequence, different neural structures are involved in auditory processing. In the auditory pathways, we find similar computational principles and transformations of sensory representations as in vertebrates, however, with an important difference: complex computations are often performed by single neurons or very small populations of identifiable neurons. This size constraint and the focus on a few relevant tasks facilitate experimental approaches.

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Auditory Prosthesis

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Synonyms

Bionic ear; Cochlear implant; Inner ear prosthesis

Definition

An auditory prosthesis is an implantable device used to (partially) restore the auditory function in people with a severe to profound hearing loss by electrically stimulating the auditory neural pathway. The cochlear implant, stimulating the auditory nerve from within the cochlea, is widely accepted as the standard rehabilitation device for this population. An auditory brain stem implant uses the same technology to stimulate the neurons of the cochlear nucleus in the brain stem and is used when the cochlea is not accessible (e.g., due to ossification after meningitis or severe hypoplasia) or the cause of deafness is found in the internal auditory canal (bilateral acoustic neuroma, aplasia of the auditory nerve).

Detailed Description

Background

Due to their reduced oral communication skills, severe to profoundly deaf people are restricted in their social functioning. Since the pioneering work of Djourno and Eyries (1957) and House

in the 1970s of the last century (House and Urban 1973), it has become possible to restore some of the hearing functions through direct electrical stimulation of the auditory nerve. Currently used cochlear implants utilize electrode arrays with 12–22 contacts on a Silastic carrier that are most commonly inserted into the scala tympani through either the round window membrane or a drilled cochleostomy in its vicinity. This allows taking advantage of the tonotopic organization of the cochlea and the auditory nerve, where the high frequencies are encoded at the basal end, while the low frequencies are encoded more to the apical end (Ruggero 2009). In this way, each electrode contact of a multichannel implant aims to stimulate a different neural population, which physiologically encodes a certain pitch as determined by its intracochlear position. With current devices, however, the wish to encode all spectral information relevant for speech understanding leads to a mismatch between their tonotopic map and the physiological one.

In 1984, the first cochlear implant obtained FDA approval for implantation in adults. This was followed by an NIH consensus in 1995 stating that cochlear implantation is a proven and effective rehabilitation method for deaf children and deaf adults. Today, over 188,000 people have received a cochlear implant (<http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=83>). Initially, the implants provided a signal function and an aid in lipreading. Nowadays, driven by improved electronics and speech coding strategies, better electrodes and changes in inclusion criteria, the majority of the recipients achieves open set speech understanding and is able to use the telephone, although this still requires an intensive rehabilitation process (see Fig. 1).

Components and Signal Processing of Multichannel Implants

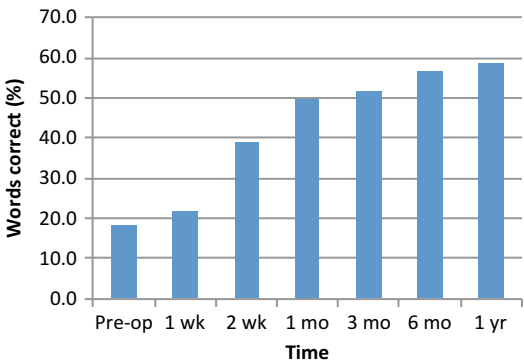
A cochlear implant consists of an external part and an internal part, as shown in Fig. 2.

An otolaryngologist surgically implants the internal part (the so-called receiver-stimulator package with the electrode array) under general

anesthesia; the externally worn speech processor (body worn or behind the ear) is connected after several weeks of wound healing. The speech

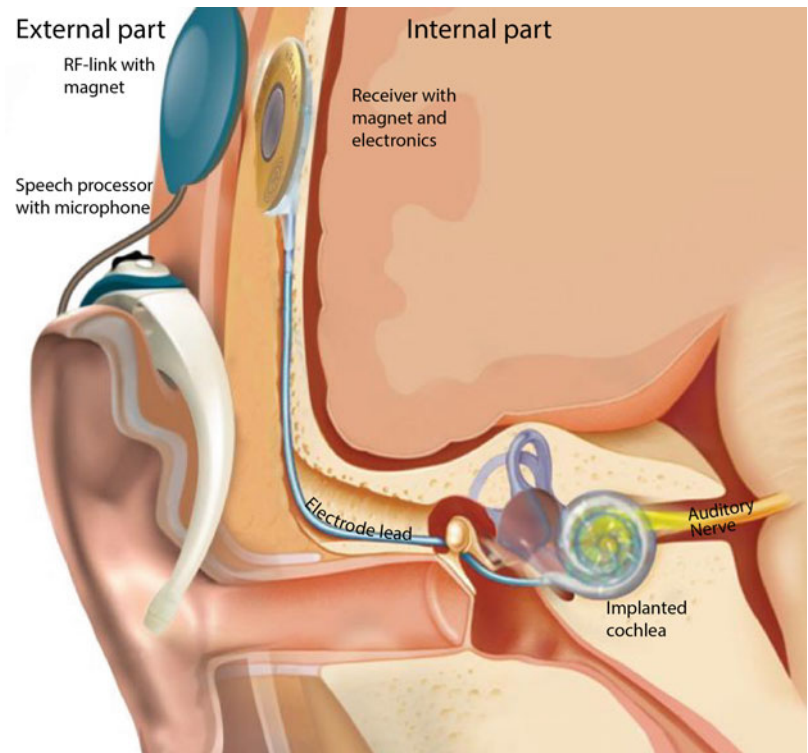
processor captures the incoming sound and, after preprocessing (typically noise cancellation and amplitude compression), encodes it into frequency-specific electrical information to be sent to the individual electrode contacts in the cochlea.

The speech coding strategies used in all current implants are extensions of the continuous interleaved sampling (CIS) strategy (Wilson et al. 1991). This strategy tries to avoid electrical interaction between neighboring electrode contacts by stimulating all contacts in a sequential mode rather than simultaneously. A digital filter bank is used to process the signal into separate frequency bands. Next, the envelope of each band, determined by rectification and low-pass filtering of the signal, is used to set the amplitude of a sequence of nonsimultaneous pulses on the implanted electrode contacts. The rate of stimulation is determined by the device brand and by the patient's performance, but typically ranges between 400 pulses/s and 4000 pulses/s per channel.



Auditory Prosthesis, Fig. 1 Performance over the first year of cochlear implant use of 70 consecutive patients implanted with a HiRes90K implant with a HiFocus 1 J electrode array (Advanced Bionics, Valencia, CA). The bars represent the percentage of correctly understood Dutch monosyllabic (CVC) words, presented from CD (65 dB SPL, free-field in quiet). The preoperative data were obtained with the best-fitted hearing aid

Auditory Prosthesis, Fig. 2 The components of a cochlear implant with a behind-the-ear speech processor. (Courtesy of Advanced Bionics)



Both the encoded stimulation pattern and the energy are transmitted to the implanted receiver-stimulator package through an RF-link. The external and internal coils for this RF-link are kept aligned with magnets in the center of both coils. The signal is picked up by the electronics in the receiver-stimulator package, which in turn delivers electrical pulses to the auditory nerve fibers via electrode contacts in the electrode array.

Modern cochlear implants also have back telemetry, allowing to record electrically evoked compound action potentials (eCAPs) of the auditory nerve via the implanted electrode array.

Computational Modeling

To provide more insight in the fundamentals of functional electrical stimulation of the auditory nerve, computational models have been developed. This involves stimulating not only the response of a nerve fiber to an externally applied potential field but also the calculation of this potential distribution from the currents on the stimulating electrodes. This is especially intricate in the case of cochlear implants due to the complex geometry of the inner ear.

Electrical Volume Conduction in the Cochlea

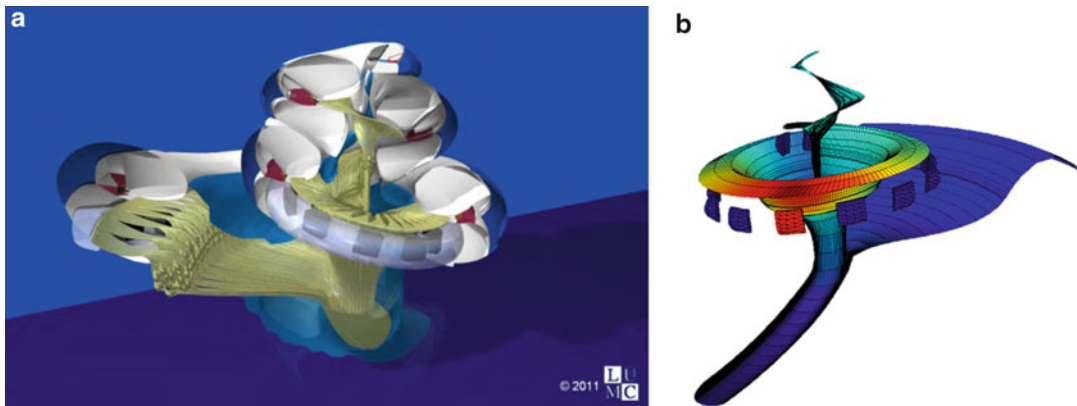
An analytic solution of such a 3D volume conduction problem is restricted to geometries that are much simpler than the cochlea, and many theoretical models on the (actually three-dimensional) potential pattern set up in the cochlea by the stimulating current sources assumed an exponential decay of current from its source to the nerve fibers along the cochlea, modeled in one dimension (O’Leary et al. 1985), while other analytical approaches assume a simplified unrolled anatomy (Goldwyn et al. 2010). Suessermann and Spelman (1993) used an electrical network as a practical representation of the electro-anatomy of the cochlea.

Numerical methods nowadays, however, allow to incorporate much more detailed (electro-) anatomical information (including the shape and

position of the electrode array) and sometimes even allow for patient-specific modeling on the basis of CT-scans (Carlyon et al. 2010). The numerical methods that have been used include the finite difference method (Whiten 2007), the finite element method (Rattay et al. 2001; Hanekom 2001), and the boundary element method, also known as the integral equation method (Frijns et al. 2001).

Simulating the Auditory Nerve Fiber Responses

Colombo and Parkins (1987) were the first to develop a cable model of the mammalian auditory nerve neuron based on the classical work on amphibian nerve fibers of Frankenhäuser and Huxley (1964). In order to fine tune the model to represent physiological data obtained from single auditory nerve fiber experiments in squirrel monkeys, they had to adapt the modeled nerve fiber’s anatomy significantly. Motz and Rattay (1986) used a single-node model with the Hodgkin and Huxley model of unmyelinated squid giant axon membrane (► “Hodgkin-Huxley Model”) to investigate the time structure of the response of the (myelinated!) auditory nerve to electrical stimuli. The gSEF model (Frijns et al. 1995) is a nonlinear cable model, which represents essential mammalian nerve fiber properties, including spike duration and conduction velocity, refractory behavior, and repetitive firing, better than previous models and can deal with arbitrary stimulus wave forms. It is based upon voltage clamp measurements in rat and cat motor nerve fibers at mammalian body temperature performed by Schwarz and Eikhof (1987). The gSEF model and its variants have, in conjunction with electrical volume conduction models, been used not only to predict which (intact or degenerated) fibers are excited by specific patterns of electrical stimulation (Smit et al. 2010; Frijns et al. 2009a, 2011) or to explain the results obtained with psychophysical experiments (Carlyon et al. 2010; Snel-Bongers et al. 2013) but also to calculate the eCAP produced on the basis of predicted single fiber action potentials (Briaire and Frijns 2005; Westen et al. 2011).



Auditory Prosthesis, Fig. 3 (a) The structure of a 3D volume conduction model of the implanted human cochlea (as developed at the Leiden University Medical Center), including the auditory nerve (in yellow) and a realistic

representation of the electrode array in the scala tympani. (b) The potential distribution in the neural compartment due to monopolar stimulation

The abovementioned neural models have in common that they are deterministic in the way they treat the neural membrane responses. If the focus of research is more on the effect of high stimulation rates or on repetitive near-threshold stimulation, stochastic models come into play. Most models of this type are single-node threshold models (Bruce et al. 1999), while cable models (Rubinstein et al. 1999; Imennov and Rubinstein 2009), although computationally very intensive and requiring supercomputers, can give insight in more complex stimulation patterns.

Integrated Use of Volume Conduction and Neural Models: State of the Art

While in the early days of cochlear implantation all insights in the mechanisms underlying their function had to come either from clinical practice and associated psychophysics or from animal experiments, nowadays sophisticated computational models exist, which integrate a model of electrical volume conduction in the cochlea with active neural models. Such models can not only be used to explain effects of current and future electrode designs and stimulation schemes but are also able to predict the of anatomical variations (Frijns et al. 2009b), species differences (Frijns et al. 2001), and

the effects of neural degeneration (Briaire and Frijns 2006; Snel-Bongers et al. 2013) (Fig. 3).

Cross-References

► [Hodgkin-Huxley Model](#)

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Further Reading

NIH factsheet cochlear implants: <http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=83>

Auditory Recognition

► Acoustic Timbre Recognition

Auditory Scene Analysis

- Auditory Cortex: Separating Signal from Noise
- Auditory Perceptual Organization

Auditory Scene Segmentation

- Auditory Cortex: Separating Signal from Noise

Auditory Sensory Receptor Cell, Model

► Cochlear Inner Hair Cell, Model

Auditory Thalamocortical Transformations

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Definition

Auditory thalamocortical transformations arise from the ascending neural processing of spontaneous activity as well as external sound-evoked activity from the auditory thalamus, the medial geniculate body, to the thalamorecipient layers of the auditory cortex in mammals.

Detailed Description

Thalamic and Cortical Organization

The Thalamus

The thalamus is the obligate neural station conveying ascending sensory information to the cortex (Sherman and Guillery 2006; Jones 2007). Each sensory modality, except for olfaction, is represented in defined nuclei of the thalamus through which sensory information must first be processed before eventually being transmitted to the respective sensory areas of the neocortex (Sherman and Guillery 2006; Jones 2007). In the auditory system, the medial geniculate body is the main auditory thalamic nucleus (Winer 1984; Jones 2007). Classically, the medial geniculate body has been divided into three main subdivisions, i.e., the ventral division, the dorsal division,

and the medial division (Winer 1984; Imig and Morel 1985). Each of these thalamic nuclei can be identified on the basis of their cytoarchitecture, physiological properties, and connections (Huang and Winer 2000; de la Mothe et al. 2006; Lee and Winer 2008a). The thalamocortical transformation is constrained by the neuroanatomical organization of projections from each of these thalamic nuclei to each of the several areas of the auditory cortex (Winer et al. 2005; Winer and Lee 2007; Lee and Winer 2011b).

The Ventral Division of the Medial Geniculate Body
The ventral division of the medial geniculate body is the principal thalamic nucleus conveying ascending auditory information to the primary auditory cortex (Huang and Winer 2000; Smith et al. 2012). A subregion within the ventral division, the pars ovoidalis, is located in the medial part of the nucleus, bordering the dorsal division and medial division (Winer 1984; Jones 2007). Neurons in the ventral division are sharply tuned to sound frequencies (Imig and Morel 1985). These neurons are arranged in laminar rostrocaudal sheets, with their dendritic fields aligned in parallel along the sheet. The neurons in each sheet respond to similarly tuned frequencies (Imig and Morel 1985). These sheets are organized lateromedially in most species studied, with neurons in the lateral regions responding to lower frequencies of sound, while neurons in the medial regions respond to higher frequencies of sound (Imig and Morel 1985). Other physiological properties, such as bandwidth tuning and aurality, are found interdigitated among neurons across these isofrequency laminae (Ehret 1997). The main ascending projection to the ventral division originates from the central nucleus of the inferior colliculus (Calford 1983; Wenstrup 2005). These projections preserve the topographic organization connecting similarly tuned regions in the inferior colliculus to matched regions in the ventral division of the medial geniculate body (Wenstrup 2005). The main output of the ventral division is to the primary auditory cortex. These projections terminate primarily in layer 4 of the

primary auditory cortex but also have branched projections to layer 6 (Huang and Winer 2000; Smith et al. 2012). Similar to the projection from the inferior colliculus, these projections are also topographically organized, such that the low-frequency regions of the ventral division project to the lower-frequency regions of the primary auditory cortex (Morel and Imig 1987; Morel et al. 1993). The ventral division also connects with other tonotopically organized auditory cortical areas, which vary in number in different species, e.g., five in the cat (Reale and Imig 1980) and three in the monkey (Kaas and Hackett 2000). These areas also receive topographically organized projections from the ventral division but mainly from nonoverlapping sectors (Morel and Imig 1987). Very few neurons in the ventral division send branched projections to multiple auditory areas, i.e., low-frequency neurons in the ventral division do not connect with multiple low-frequency regions in different tonotopically organized areas (Lee et al. 2004, 2011).

The Dorsal Division of the Medial Geniculate Body
The dorsal division of the medial geniculate body is the part of the auditory thalamus that connects to non-tonotopically organized areas of the auditory cortex (de la Mothe et al. 2006; Lee and Winer 2008a). This nucleus is composed of various subnuclei, including the dorsal superficial, deep dorsal, dorsocaudal, and ventrolateral nuclei (Winer et al. 2005; Lee and Winer 2008a). Neurons in the dorsal division are broadly tuned to frequencies, many with multi-peaked and complex receptive fields (Morel and Imig 1987; Winer et al. 2005). In contrast to the organization of the ventral division of the medial geniculate body, neurons in the dorsal division do not exhibit an oriented laminar pattern of organization (Winer 1984). The dendritic arborizations of neurons in the dorsal division are more isotropically organized. The subdivision of this nucleus is based primarily on cytoarchitectonic densities and connections with several non-tonotopic auditory areas (Lee 2013). Projections to the dorsal division originate primarily from the non-tonotopic area of the inferior colliculus, i.e., the dorsal cortex (Wenstrup 2005). The dorsal division nuclei

project broadly to the non-tonotopic areas of the auditory cortex, which also include multimodal and limbic-related areas, whose relation to auditory processing in part is derived from the direct inputs received from thalamocortical sources (Lee and Winer 2008a, 2011a). Although a functional metric, such as tonotopy, appears to be absent in the nuclei of the dorsal division, their projections to the non-tonotopic areas of the auditory cortex are highly topographic, similar in extent to the topography of projections from the ventral division to the tonotopic regions of the auditory cortex (Lee and Winer 2005; Schreiner and Winer 2007). The termination pattern of the dorsal division projections to the non-tonotopic cortical areas, in particular, the secondary auditory cortical region, is similar to that of the ventral division projection to the primary auditory cortex, i.e., terminations primarily in layers 4 and 6 (Huang and Winer 2000). However, the synaptic terminals of the dorsal division projection to the secondary auditory cortex are slightly larger on average than the projections from the ventral division to the primary auditory cortex (Smith et al. 2012). Again, although the dorsal division projects broadly to several non-tonotopic auditory areas, very few neurons within the dorsal division send branched projections to multiple areas (Kishan et al. 2008; Lee and Winer 2008a; Lee et al. 2011).

The Medial Division of the Medial Geniculate Body
The medial division of the medial geniculate body projects widely across all auditory cortical areas, with a pattern of axonal termination that contrasts with the projections from the ventral division and the dorsal division of the medial geniculate body (Huang and Winer 2000; Jones 2007). Neurons in the medial division exhibit highly complex receptive fields, which often extend beyond purely auditory responses, with many neurons responding to stimuli from several modalities, i.e., visual and somatosensory (Bordi and LeDoux 1994). Neurons in the medial division differ from those in the ventral division and dorsal division, in that they display a wide range of sizes and dendritic arborization patterns (Bartlett and Smith 1999; Smith et al. 2007). The medial division contains the magnocellular neurons, which are

the largest neurons in the medial geniculate body (Winer 1984). Like the dorsal division, the neurons in the medial division do not appear to be organized isotropically along any particular anatomical domain and are loosely packed compared with the other divisions (Winer 1984). The medial division receives its primary input from both the dorsal cortex and external cortex regions of the inferior colliculus, which also contain non-tonotopic and multimodal responsive neurons (Wenstrup 2005). Every area of the auditory cortex receives a projection from the medial division (Lee and Winer 2008a), but unlike the ventral division and the dorsal division, the laminar terminations of axons in these areas are primarily concentrated in layer 1 (Huang and Winer 2000). While axonal divergence from the medial geniculate body is low in general, the highest proportion of neurons projecting to multiple auditory cortical areas is found in the medial division; however, these comprise on average less than 2% of neurons in the medial division of the medial geniculate body (Kishan et al. 2008, 2011; Lee et al. 2011).

Inhibitory Circuits in the Thalamus

The thalamic reticular nucleus, although not a specific constituent of the medial geniculate body, is intimately intertwined with the operations of both the thalamus and cortex and thus is an essential structural component of the thalamocortical transformation (Winer and Larue 1996; Crabtree et al. 1998; Pinault 2004; Sherman and Guillery 2006). The thalamic reticular nucleus is composed of inhibitory GABAergic neurons that form a shell surrounding the thalamus, roughly located along the lateral border of the thalamus and extending rostrocaudally along nearly its entire length (Pinault 2004; Lam and Sherman 2005, 2007, 2010). In general, each nucleus of the thalamus innervates a specific sector of the thalamic reticular nucleus and receives reciprocal topographic inhibitory feedback projections from that region of the thalamic reticular nucleus (Lam and Sherman 2005). In addition, feedback projections from layer 6 of the neocortex en route to the thalamus branch to innervate the thalamic reticular nucleus (Lam and Sherman

2010), which establishes an extended thalamocorticothalamic inhibitory feedback loop (Pinault 2004). The thalamic reticular nucleus and the inferior colliculus are the main sources of inhibition in the medial geniculate body of rodents, which contain very few local inhibitory neurons (Winer and Larue 1996). In humans, local inhibitory neurons in the medial geniculate body comprise ~20% of the total number of neurons, which is accompanied by a proportional reduction in inhibitory projections from the thalamic reticular nucleus, compared with rodents and other species, which have fewer than 1% of local inhibitory neurons in the medial geniculate body (Winer and Larue 1996).

The Cerebral Cortex

The cerebral cortex is phylogenetically the newest structure in the mammalian brain, responsible for the higher-order processing of sensory, motor, and limbic information (Kaas 2008). Broadly, the cerebral cortex is composed of regions of “gray” matter and “white” matter, the former residing near the outer cortical surface and containing all of the neuronal cell bodies and the latter residing beneath the gray matter and composed of the axonal fiber tracts of afferent and efferent projections (Nieuwenhuys 2013). Although regional variations exist, the gray matter of the cerebral cortex has a laminar organization divided into cytoarchitectonically distinguishable layers, such that neuronal cell bodies are situated in structural and functional groups relative to their location along the pial to white matter axis (Mountcastle 1997). These layers of neuronal cell bodies have specific afferent and efferent connections with other cortical regions and with subcortical structures, in particular the thalamus (Sherman and Guillery 2006). In total, there are six classically defined layers of the cortex (Mountcastle 1997). Of these, layer 4 of the cerebral cortex is the main recipient layer for sensory information ascending from the primary sensory thalamic nuclei (Sherman and Guillery 2006). In addition, layer 6 receives branched projection from these primary sensory thalamic nuclei (Huang and Winer 2000; Smith et al. 2012; Lee and Imaizumi 2013), and layer 1 is the recipient of thalamocortical inputs

from nonspecific thalamic nuclei, e.g., the medial division of the medial geniculate body (Huang and Winer 2000; Jones 2007). In addition, layer 6 is the source of neurons that send feedback projections to the thalamic nucleus that provides its main thalamocortical input in layers 4 and 6, which establishes a thalamocorticothalamic feedback loop (Sherman and Guillery 2006). Cortical layer 5 is the source of feedforward nonreciprocal thalamocortical projections, which serve as a conduit for communication between cortical areas via a corticothalamocortical route (Sherman and Guillery 2006).

The surface of the cerebral cortex is regionally specified into distinct functional areas that are involved in processing sensory and motor information (Kaas 2008). The boundaries of these cortical areas, including those involved with audition, are broadly defined based on their cytoarchitectural organization, connections with other structures, and physiological responses of constituent neurons, although precise borders and definitions for many cortical areas in different organisms still remain elusive (Kaas and Hackett 2000; Hackett 2011). Although all mammals have cortical regions devoted to the processing of auditory information, the number of auditory cortical areas varies widely among different species (Lee and Winer 2008b, 2011b). Despite this heterogeneity, all mammals studied thus far have an identifiable auditory cortical region that receives direct input from the ventral division of the medial geniculate body (Lee and Winer 2011b). This primary auditory cortical area is also defined on the basis of a clearly identifiable tonotopic map, which reflects the frequency segregation established in the cochlea and propagated along the auditory pathway (Ehret 1997).

Although the primary auditory cortical area is the most conserved across species, constellations of other cortical regions devoted to the processing of sound exist among the cortices of different mammalian species (Kaas 2008). However, their physiological and anatomical organization is generally less well understood relative to that of the primary auditory cortex. Nevertheless, these other areas can be broadly grouped into distinct categories: tonotopic, non-tonotopic, multimodal, and

limbic related (Lee and Winer 2011a). The tonotopic regions, like the primary auditory cortex, contain identifiable maps of frequency across their surface, generally with frequency reversals at their borders, and receive strong projections from the ventral division of the medial geniculate body (Reale and Imig 1980; Hackett et al. 1998; Hackett et al. 2011). The non-tonotopic areas contain disordered representation of frequency and generally receive more prominent inputs from the dorsal division of the medial geniculate body (Schreiner and Cynader 1984; Smith et al. 2012). Multimodal and limbic areas reside at the limits of the classical auditory areas and receive inputs from multimodal and limbic thalamic nuclei and areas and have complex responses reflective of these convergent inputs (Bowman and Olson 1988; Clarey and Irvine 1990; Clascá et al. 1997; de la Mothe et al. 2006). As discussed above, features of the thalamocortical inputs to these other areas resemble those to the primary auditory cortex (Huang and Winer 2000; Smith et al. 2012), which could serve as an anatomical basis for common thalamocortical transformations across the expanse of auditory cortical areas (Lee and Sherman 2008, 2011).

Receptive Fields and the Thalamocortical Transformation

Spectral Receptive Field

An important physiological parameter in the auditory thalamocortical transformation is the spectral receptive field. The spectral receptive field is, in general, measured based on a frequency-threshold tuning curve (response to sound level as a function of sound frequency). A common measure is the Q factor by which characteristic frequency is divided by a linear measure of bandwidth at a given sound level above threshold (e.g., Q_{10} ; Q value at 10 dB above threshold) (Imaizumi et al. 2004). Because the Q value is a normalized measure, the larger the Q value, the more sharply tuned are the neurons. Another measure is the square root transformation:

$$\sqrt{F_2} - \sqrt{F_1}$$

where $F2$ and $F1$ are the highest and lowest edges of bandwidth at a given sound level (Rouiller et al. 1981; Calford 1983). Unlike the Q value, the smaller the square root transformation value, the more sharply tuned are the neurons.

The auditory thalamocortical transformation is mediated by the excitatory neurotransmitter, glutamate, from the medial geniculate body to the auditory cortex. Therefore, only the excitatory receptive field is transformed in thalamocortical projections. A problem describing spectral receptive fields in the thalamocortical transformation is the availability of data utilizing the same recording method (e.g., local field potentials, single- or multiunit extracellular recording, whole-cell recording, etc.) under similar recording conditions (e.g., anesthesia: isoflurane, ketamine, or pentobarbital; depth of anesthesia; awake states; restricted or freely moving) in the same animal species. This creates some controversy and readers should use caution for the following section.

Functional organization of the spectral receptive field has been well appreciated in the auditory cortices of several species. The most well-known example is the primary auditory cortex of the mustached bat. A large area, called the DSCF (Doppler-shifted constant frequency) area, of the primary auditory cortex is devoted to a particular frequency range (60.6–62.3 kHz) for their prey-hunting behavior (Suga 1994). Neurons in the DSCF area are extremely sharply tuned to characteristic frequency ($Q50$ values range from ~10 to 500 or higher) (Suga and Manabe 1982; Suga et al. 1997). Neurons in the anterior and posterior parts of the DSCF area are more broadly tuned. Similarly organized clusters of sharply or broadly tuned neurons are also found in the auditory cortex of carnivores and primates (Recanzone et al. 1999; Cheung et al. 2001; Read et al. 2001; Imaizumi et al. 2004; Philibert et al. 2005; Imaizumi and Schreiner 2007). In particular, the cat primary auditory cortex has an interesting functional organization of spectral receptive fields. Sharply or broadly tuned neurons are clustered alternatively along the dorsoventral axis only in the mid-frequency range (5–20 kHz) (Imaizumi and Schreiner 2007). Unlike those animal species, functional organization of spectral

receptive fields in the rodent auditory cortex is not clear (Polley et al. 2007). Whereas rich information of functional organization of spectral receptive fields is available in the auditory cortex, only limited information is available in the medial geniculate body. Neurons in the ventral division are, in general, more sharply tuned than in the dorsal division (Rouiller et al. 1981; Calford 1983; Edeline et al. 1999). However, no clear spatial organization is available due to the deep location in the brain.

In general, it is believed that spectral receptive fields become broader through the thalamocortical transformation (Kaur et al. 2004, 2005). However, more recent studies using in vivo whole-cell recordings combined with pharmacological manipulation (blocking cortical input by muscimol and SCH50911) have revealed that thalamocortical input is not as sharp as was thought (Liu et al. 2007). These examples above are based on studies in rodents. Spectral receptive fields, however, vary widely across species. In the human auditory cortex, neurons are extremely sharply tuned (Bitterman et al. 2008), which suggests that spectral receptive fields may become sharper through the thalamocortical transformation. How does this opposite trend occur in thalamocortical transformation? Clear evidence is available in the awake mustached bat. Based on $Q10$, $Q30$, and $Q50$ values, DSCF neurons in the primary auditory cortex are more sharply tuned than those in the medial geniculate body (Suga et al. 1997). Similar evidence is also available in the awake marmoset (Bartlett et al. 2011). Thus, the sharpening of spectral receptive fields through the thalamocortical transformation may relate to behavioral and/or ethological functions.

For thalamocortical transformation of spectral receptive fields, limited experimental cases are available using in vivo single-unit recordings in awake guinea pigs (Creutzfeldt et al. 1980) and anesthetized cats (Miller et al. 2001, 2002). For secure functional transformation, medial geniculate body and auditory cortex neurons require an alignment of less than 1/3 octave difference in best frequency (sound frequency evoked the best response in a neuron at a given sound level)

(Miller et al. 2001). To fully activate a neuron in the auditory cortex, synaptic convergence from 20 to 25 neurons in the medial geniculate body is required (Miller et al. 2001). Using a ripple noise stimulus and computational analytical approach of reverse correlation technique, Miller et al. (2002) estimated spectral *modulation* rates through thalamocortical transformation. Both thalamic and cortical neurons show lower spectral *modulation* rates. Whereas cortical neurons have significantly lower spectral *modulation* rates than thalamic neurons based on the best spectral *modulation* rates, the overall spectral filter properties between thalamic and cortical neurons are similar.

Overall, spectral receptive (*modulation*) fields in the thalamocortical transformation are not simple. Depending on animals and the behavioral significance of sound frequency, spectral receptive fields become broader or sharper through the thalamocortical transformation.

Temporal Receptive Field

An important function of the central auditory system is to decode species-specific communications and human speech sounds. Periodic modulations are ubiquitous temporal features of species-specific communications and human speech sounds (Rosen 1992; Joris et al. 2004). Measuring repetition-rate transfer functions or modulation transfer functions captures response characterization to assess information for a temporal range that corresponds to periodicities in communication sounds (Eggermont 2001; Joris et al. 2004). Two commonly used measures to characterize repetition-rate transfer functions are firing rate and vector strength (VS). Firing rate estimates overall response magnitude in a particular time window. Vector strength estimates spike-timing precision to a particular phase of repetition or modulation stimulus:

$$VS = \frac{\sqrt{(\sum \cos \theta)^2 + (\sum \sin \theta)^2}}{n}$$

$$\theta = 2\pi \frac{t}{T}$$

where n is the total number of spikes, t is time of spike occurrence, and T is the interstimulus interval (Goldberg and Brown 1969). Significance of synchronization to the stimulus is examined by a Rayleigh test, >13.8 ($p < 0.001$) (Mardia 1972). Because vector strength does not incorporate response strength, it may give rise to high vector strength values when the response strength is low. To overcome a shortcoming of the VS measure, phase-projected vector strength (VS_{pp}) is used (Yin et al. 2011; Niwa et al. 2012). VS_{pp} compares the mean phase angle for each trial with the mean phase angle of all trials and penalizes single-trial vector strength values if they are not in phase with the global response. VS_{pp} is computed on a trial-by-trial basis as follows:

$$VS_{pp} = VS_t \cos(\phi_t - \phi_c)$$

where VS_{pp} is the phase-projected vector strength per trial, VS_t is the vector strength per trial, and ϕ_t and ϕ_c are the trial-by-trial and mean phase angle in radians, calculated for each stimulus condition, and,

$$\phi = \arctan 2 \frac{\sum_{i=1}^n \sin \theta_i}{\sum_{i=1}^n \cos \theta_i}$$

where n is the number of spikes per trial (for ϕ_t) or across all trials (for ϕ_c) and $\arctan 2$ is a modified version of the arctangent that determines the correct quadrant of the output based on the signs of the sine and cosine inputs. Whereas vector strength value ranges from 1 (all spikes occur at the same stimulus phase) to 0 (spikes occur randomly), phase-projected vector strength value ranges from 1 (all spikes in phase with population mean phase) to -1 (all spikes 180° out of phase with population mean phase) with 0 corresponding to randomly occurring spikes (Yin et al. 2011; Niwa et al. 2012). Another way to overcome a shortcoming of vector strength is the product of two measures (vector strength and firing rate), i.e., phase-locked rate or synchronized rate (Eggermont 1998b; Joris et al. 2004; Imaizumi et al. 2011). The synchronized rate measure incorporates both timing and response strength measures.

Two coding schemes for temporal receptive fields have been proposed: precise spike timing estimated by vector strength codes slow repetition rates (or modulation frequencies), while firing rate codes faster repetition rates (De Ribaupierre et al. 1972; Bieser and Muller-Preuss 1996; Schulze and Langner 1997; Lu and Wang 2000; Lu et al. 2001; Joris et al. 2004). However, more recent studies have proposed different coding schemes, as will be described later.

A problem describing temporal receptive fields in the thalamocortical transformation is also the availability of data utilizing the same stimulus (e.g., nature of stimulus: click or white noise; modulation carrier: pure tone or noise; modulation depth; and modulation shape: rectangular or sinusoidal), stimulus presentation method (free field or sealed earphones), and recording method (single- or multiunit extracellular recording) under similar recording conditions (e.g., anesthesia: isoflurane, ketamine, or pentobarbital; depth of anesthesia; awake states: restricted, freely moving, or engaged behavior) in the same animal species. In many cases, the analytical criteria are also different. These create difficulty for direct comparisons and some discrepancy. Thus, the readers should treat the following section with caution.

The vast majority of studies regarding temporal receptive fields have focused on the primary auditory cortex. However, functional magnetic resonance imaging or positron emission tomography in humans and macaques suggested that the superior temporal plane is specific to human speech or macaque species-specific calls over nonspecific calls or other sounds (Belin et al. 2000; Poremba et al. 2004; Petkov et al. 2008). These fields are located anterior to the primary core fields and may correspond to the rostral field in primates. Reversible lesion experiments in cats also show that the anterior auditory field is specific to temporal pattern discrimination (Lomber and Malhotra 2008). Thus, the rostral field in primates and the anterior auditory field in carnivores (and rodents) may be more important for temporal pattern processing.

Rodent Auditory Cortex and Thalamus

Under anesthesia of pentobarbital, neurons in the rat primary auditory cortex, in general, show a low-pass filter property of repetition-rate transfer functions by rate coding (firing rate) or band-pass filter property by temporal coding (vector strength) (Kilgard and Merzenich 1999; Chang et al. 2005). Ter-Mikaelian et al. (2007) examined the effects of anesthesia (a combination of pentobarbital and ketamine) and awake (head-fixed) states in the gerbil primary auditory cortex. While anesthesia certainly affects modulation transfer functions in individual neurons, overall, the population response seems to be similar between anesthesia and awake states (Ter-Mikaelian et al. 2007). Clear evidence of an effect of anesthesia is available in the rat primary auditory cortex (Rennaker et al. 2007). Ketamine anesthesia significantly decreased cutoff repetition rates (higher border of repetition-rate transfer function) to <20 Hz from 80 to 90 Hz in the awake state. A more recent study using awake state (head-fixed) rats examined repetition-rate transfer function using click trains in the primary auditory cortex and the anterior auditory field (Ma et al. 2013). Both core fields show high best repetition rates (up to 32–64 Hz) and cutoff repetition rates (up to 256 Hz), although neurons in the anterior auditory field prefer significantly higher repetition rates than those in the primary auditory cortex. These best and cutoff repetition rates in the awake rat auditory cortex are, in general, higher than those in the anesthetized rat (Kilgard and Merzenich 1999; Chang et al. 2005). Attention or engaged behaviors also alter temporal receptive fields. By presenting at 15 Hz repetition rate (with various carrier frequencies) paired with electrical stimulation of the nucleus basalis for 20–25 days, neurons in the rat primary auditory cortex are capable of following higher repetition rates by rate coding than those in control (Kilgard and Merzenich 1998). Training in a sound maze in which rats use sound source location for food rewards based on auditory cues (noise repetition rates increased with decreasing distance between the rat and target location) also enhanced temporal receptive fields (Bao et al. 2004). Compared to

studies in the rodent auditory cortex, a small number of studies are available in rodent thalamus. In awake guinea pigs, thalamic neurons show more robust responses to higher modulation frequencies than cortical neurons (Creutzfeldt et al. 1980).

Cat Auditory Cortex and Thalamus

The cat auditory cortex has been a focus of studies of temporal pattern processing. In particular, the primary auditory cortex and the anterior auditory field are readily identifiable based on their location relative to sulcal patterns (Knight 1977; Imaizumi et al. 2004; Lee et al. 2004) and are often compared in temporal pattern processing (Schreiner and Urbas 1988; Eggermont 2000; Joris et al. 2004). Under anesthesia, neurons in the anterior auditory field prefer higher modulation frequencies (and repetition rates) than those in the primary auditory cortex (Schreiner and Urbas 1988; Eggermont 1998b). Anesthesia also reduces temporal receptive fields by half in neurons of the cat primary auditory cortex (Goldstein et al. 1959). In the cat anterior auditory field under ketamine anesthesia, Imaizumi et al. (2010) proposed different coding schemes using a combination of an *in vivo* high-resolution cortical mapping technique with information theory. Because this study was made using multiunit recordings, they computed discriminability of six different low repetition rates (1–30 Hz) (Imaizumi et al. 2010). Unlike the traditional coding scheme (precise spike timing codes low repetition rates), inter-spike intervals can carry much more information than timing and rate codes: some multiunits carried an information value >2 bits that is close to a maximum of ~ 2.58 bits ($=\log_2(6)$). Furthermore, spatial distribution of normalized firing rate to six different repetition rates differs across the stimuli, which provides a potential coding scheme in the view of an ideal observer. These results suggest concurrent coding schemes of temporal pattern processing by inter-spike intervals, firing rate, and a map (Imaizumi et al. 2010). Using behaviorally trained cats, Dong et al. (2011) compared neurometric (neural responses to six repetition rates from 12.5 to 200 Hz by *in vivo* single-unit recordings) with psychometric (Go/No-Go behavioral responses to the same six

repetition rates) functions. Their recordings were focused on the relatively low-frequency locations <16 kHz of the primary auditory cortex. Prevalence is found of more synchronized units in the behaviorally engaged primary auditory cortex than in an anesthetized one (Lu and Wang 2000; Dong et al. 2011). However, rate coding by non-synchronized units correlates well with psychometric functions.

Compared to the studies in the cat auditory cortex, a small number of studies are available in the cat thalamus. In nitrous oxide-anesthetized cats, approximately half of the thalamic units showed precisely time-locked responses to click trains (Rouiller et al. 1981). Half of these units had cutoff repetition rates (higher border of repetition-rate transfer function) up to 100 Hz. Local field potentials in the auditory cortex record subthreshold responses potentially from thalamocortical fibers (and corticocortical fibers), thus indicating thalamic responses. Both best modulation frequencies and cutoff modulation frequencies are generally higher in local field potentials than unit recordings in the primary auditory cortex and anterior auditory field (Eggermont 1998b). Under ketamine anesthesia in the primary auditory cortex and the ventral division of the medial geniculate body of cats, Miller et al. (2002) conducted *in vivo* simultaneous single-unit recordings from thalamus and cortical neurons. They found that temporal modulation transfer functions are significantly deteriorated through thalamocortical projections.

Primate Auditory Cortex and Thalamus

A majority of studies of temporal receptive fields in primates are conducted in the awake state. In the awake squirrel monkey, neurons in the primary auditory cortex and the rostral field show both temporal and rate codes to amplitude modulation frequencies up to 64 or 128 Hz (Bieser and Muller-Preuss 1996). Neurons in the primary auditory cortex showed higher best modulation frequencies than those in the rostral field. In the awake macaque, neurons in the primary auditory cortex have higher best modulation frequencies by both temporal (means are 13 and 4.8 Hz) and rate (means are 45 and 19 Hz) codes and higher

vector strength than those in the rostral field (Malone et al. 2010; Scott et al. 2011). These examples from the awake squirrel monkey and macaque have suggested the opposite trend of temporal receptive fields in the core auditory fields to rodents and cats (Schreiner and Urbas 1988; Eggermont 1998b; Joris et al. 2004) despite the similar cortical locations (relative to the primary auditory cortex) of the anterior auditory field in rodents and cats and the rostral field in the primates. In the awake primate auditory cortex, neurons may carry both temporal and rate codes for lower and higher repetition rates (or modulation frequencies) (Bieser and Muller-Preuss 1996; Lu et al. 2001; Liang et al. 2002; Malone et al. 2007; Yin et al. 2011). However, a proportion of synchronized (using vector strength or similar measures) and non-synchronized (using firing rate) neurons are different among the studies. These discrepancies may be caused by the stimulus, the range of repetition rates, and/or analytical criterion (Yin et al. 2011). There is an interesting proposal of low to mid range of repetition rates (10–45 Hz) corresponding to flutter perception by two different populations of neurons in the awake marmoset auditory cortex. One population of neurons increases firing rate with increasing repetition rates, while the other population decreases firing rate with increasing repetition rates (Bendor and Wang 2007). All examples reviewed above are based on studies of primates passively listening to stimuli in awake state. However, active engagement of behaviors (discriminating modulated sounds, 2.5–500 Hz, from unmodulated sounds) improves both temporal and rate codes in single neurons of the macaque primary auditory cortex (Niwa et al. 2012).

Compared to the studies in primate auditory cortex, a small number of studies are available in primate thalamus. In the awake squirrel monkey, neurons in the thalamus show a similar tendency of temporal and rate coding to best modulation frequencies up to 128 Hz (Preuss and Muller-Preuss 1990). In the awake marmoset, neurons in the ventral and the anterodorsal divisions of the medial geniculate body show a mixture of temporal and rate coding, while neurons in the

posterodorsal division show a dominant tendency of rate coding (Bartlett and Wang 2011). These examples suggest that separation of temporal and rate coding for low and high repetition rates may be created within the auditory cortex (Bartlett and Wang 2007). However, other data suggest that separation from temporal to rate coding for low to high repetition rates may be completed through thalamocortical transformation (Malone et al. 2007; Yin et al. 2011). Thalamic neurons are capable of following higher repetition rates by both temporal and rate coding than cortical neurons in the awake marmoset (Bartlett and Wang 2007).

Overall, temporal receptive fields change through the thalamocortical transformation. In general, thalamic neurons are more capable of following higher repetition rates (modulation frequencies) than cortical neurons. However, neurons in the auditory cortex may employ different coding schemes to follow different ranges of repetition rates (this is not restricted only to high repetition rates but also low to mid repetition rates) either through the thalamocortical transformation or at the cortical level.

Latency

First-spike latency (hereafter latency) is another important physiological parameter (Eggermont 2001). However, because only the experimenter knows the stimulus onset (the brain and neurons do not know it), relative latencies might be a good candidate for neural coding of temporal patterns (Eggermont 1998b; Schreiner and Raggio 1996; Lu and Wang 2000; Liang et al. 2002; Ter-Mikaelian et al. 2007; Imaizumi et al. 2011), vocalizations (Wang et al. 1995; Nagarajan et al. 2002), sound localization (Eggermont 1998a; Furukawa et al. 2000), and auditory scene (Dear et al. 1993). Latency, in general, decreases with increasing sound level (Heil 1997). However, neurons in the primary auditory cortex of the little brown bat show shorter latencies to lower sound level than higher sound level (Sullivan 1982b). Furthermore, when the two sounds (higher and lower sound levels) are presented by a behaviorally relevant delay between pulse and echo, latencies are facilitated and become shorter for the

echolocating behavior (Sullivan 1982a). In general, neurons in the anterior auditory field have shorter latencies than those in the primary auditory cortex across many different species (Schreiner and Urbas 1986, 1988; Linden et al. 2003; Rutkowski et al. 2003; Imaizumi et al. 2004; Bizley et al. 2005). However, neurons in the primate primary auditory cortex show shorter latencies than those in the rostral field (Scott et al. 2011), which is related to the fact that neurons in the primate primary auditory cortex follow higher repetition rates than those in the rostral field (Bieser and Muller-Preuss 1996; Malone et al. 2010).

Neurons in the ventral division of the medial geniculate body show shorter latencies than those in other divisions (Rouiller et al. 1981; Calford 1983; Edeline et al. 1999). However, more recent studies in the mouse and guinea pig thalamus show that neurons in the medial division have shorter latencies than those in the ventral division of the medial geniculate body (Anderson et al. 2006; Anderson and Linden 2011). This evidence strongly supports the shorter latencies in neurons of the anterior auditory field than those in the primary auditory cortex (Schreiner and Urbas 1986, 1988; Linden et al. 2003; Rutkowski et al. 2003; Imaizumi et al. 2004; Bizley et al. 2005) because the anterior auditory field receives input not only from the ventral division but also from the medial division. Latency through thalamocortical transformation can be estimated by in vivo simultaneous single-unit recordings and cross-correlation analysis. A maximum peak in the correlogram is shifted to the expected travel and synaptic delay (e.g., a few milliseconds) (Miller et al. 2001). Thus, it is generally believed that latency in thalamocortical transformation is inherited from the thalamus to cortex. However, a recent study using in vivo whole-cell recordings combined with a pharmacological application (to silence cortical activity by a mixture of muscimol and SCH50911) in the rat primary auditory cortex unfolds a different story: difference in latency between the thalamus and cortex is generated by synaptic integration time by excitation and inhibition through corticocortical interactions (Zhou et al. 2012).

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Auditory Transducer, Model

► Cochlear Inner Hair Cell, Model

Auditory-Nerve Response, Afferent Signals

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Definition

Sequences of action potentials (spikes) of individual auditory-nerve fibers (ANFs), the primary auditory afferents, in response to sounds impinging upon the ears.

Detailed Description

Anatomical Foundations

Acoustic information relayed from the inner ear to the central nervous system is encoded in the sequences of spikes produced by (type I) ANFs. In mammals, each ANF contacts only one receptor cell (an inner hair cell, IHC) and is excited by transmitter release events from a single ribbon synapse (Ashmore 2010; Matthews and Fuchs 2010; Chapochnikov et al. 2014). Each IHC has 5–30 ribbons, depending upon species and cochlear location (e.g., Meyer et al. 2009; Zhang

et al. 2018). The ANFs innervating a given IHC therefore share some, although not all, functional response properties.

Spontaneous Activity

ANFs produce spikes in the absence of external sound (spontaneous activity). The mean spontaneous rate varies between ANFs, in mammals from near zero up to more than 100 spikes per second (e.g., Liberman 1978; Temchin et al. 2008), even between ANFs innervating the same IHC (Wu et al. 2016). The timing of the spikes of a given ANF during spontaneous activity is highly variable. The spike-count statistics and the distribution and serial correlation of inter-spike intervals in an ANF spontaneous spike train can be understood as the result of excitatory transmitter release events produced by the random depletion and random replenishment of a small number of identical but independent presynaptic release sites at each ribbon, in combination with the ANF's refractory properties (Peterson and Heil 2018).

Driven Activity

Sounds impinging on the ipsilateral ear, when of appropriate spectral composition and amplitude, affect the spiking behavior of ANFs, most often increasing the spike rate. A threshold sound level may be defined at which the driven rate of a given ANF exceeds its spontaneous rate by some criterion. The compound action potential (CAP), a gross stimulus-evoked potential which reflects a weighted sum of ANF responses (Bourien et al. 2014), can be recorded in or near the cochlea, such as at the round window.

Frequency Tuning

Each ANF is tuned to sound frequency and is most sensitive, i.e., threshold is lowest, at a particular frequency (the characteristic frequency, CF) which is determined by the position along the cochlear partition of the IHC which it contacts (cochleotopy). Threshold versus frequency curves (tuning curves) are approximately V-shaped but have a plateau region above CF with very high thresholds (Huang and Olson 2011), and curves for high-CF ANFs exhibit low-frequency tails. The sharpness of tuning is often quantified by

the Q-value, defined as the CF divided by the bandwidth of the tuning curve at some level (e.g., 10 dB) above threshold at CF. Q_{10} -values increase with increasing CF (in cats from about 1 to 10 for CFs from 0.2 to 10 kHz; Pickles 2012) but can reach exceptionally high values (>200) in behaviorally relevant frequency ranges in species such as echo-locating bats.

Sound Level Dependence

With increasing sound level, the mean spike rate of a given ANF increases before saturating at several hundred spikes per second at higher sound levels. The range of sound levels over which the spike rate increases (the dynamic range, DR) varies between ANFs. DR is inversely related to the spontaneous rate of an ANF which in turn covaries with the ANF's sensitivity (e.g., Winter et al. 1990). For a given ANF, DR varies with sound frequency and is largest at CF due to compressive growth of mechanical responses in the inner ear with sound level. For frequencies below CF, where the mechanical responses are linear, the increase of the spike rate can be described by a Hill equation with a Hill coefficient of 3 and with the independent parameter being the sum of the sound amplitude and a baseline (Heil et al. 2011). DR and maximum spike rate also adapt to stimulus statistics (Wen et al. 2009).

Adaptation

Adaptation is also manifest as a decrease in spike rate over time in response to sounds of constant amplitude. Within a few milliseconds, the spike rate drops rapidly and then more gradually. The decrease can be modeled as the sum of multiple exponential decays with different time constants and a fractional power law (Zilany et al. 2009; Bruce et al. 2018). Upon cessation of the sound, the spike rate temporarily decreases below the spontaneous rate before recovering over tens to hundreds of milliseconds.

Phase Locking

In response to low-frequency sounds or broadband sounds containing low frequencies, ANFs exhibit phase locking, i.e., spikes are

nonrandomly distributed across the period of a low-frequency component (van der Heijden and Joris 2006; Heil and Peterson 2017). Phase locking is often quantified by the measures of vector strength and of the phase angle of the mean vector. For a given ANF, vector strength (a measure of the degree of phase locking) and phase angle of the mean vector vary with frequency and sound level. Across ANFs, maximum vector strength decreases with increasing frequency in a low-pass fashion, with cutoffs of a few kilohertz, depending on species. Phase locking is also seen in the responses of low-CF ANFs to acoustic clicks, elicited by multiple mechanical responses caused by these brief broadband sounds (Guinan 2012). ANFs also phase lock to the modulation envelope of sinusoidal amplitude-modulated tones and noise (e.g., Michelet et al. 2012).

For more detailed reviews of auditory-nerve responses, see Pickles (2012) and Heil and Peterson (2015, 2017). Several of these properties can be altered by sensorineural hearing loss (for reviews, see Young 2012, Henry and Heinz 2013). Loss of ANFs or of their synapses with IHCs can lead to overt and hidden hearing losses (e.g., Kujawa and Liberman 2009). Cochlear implants function by evoking spiking activity in ANFs.

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Augmentation

- [Short-Term Synaptic Plasticity in Central Pattern Generators](#)

Autoassociative Networks

- [Olfactory Cortical Associative Memory Models](#)

Automated Parameter Search in Small Network Central Pattern Generators

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Definition

Automated parameter search in small network central pattern generators (CPGs) involves the use of any methods other than manual (i.e., hand-tuning) to generate or tune sets of

parameters that result in physiologically realistic neuronal models of the CPGs. Such methods include “brute-force” explorations of predefined parameter spaces, as well as various heuristics (e.g., multi-objective evolutionary algorithms) used to arrive at a single or more of viable model parameter combinations.

Detailed Description

Central pattern generators (CPGs) are neural networks that produce rhythmically patterned outputs, without relying on any sensory feedback (Hooper 2001). CPGs drive such critical rhythmic activity as breathing, chewing, swimming, walking, heartbeat control, etc. CPGs have been shown to produce rhythmic outputs akin to normal rhythmic activity patterns, even in isolation from other parts of the nervous system, which makes them popular physiological models. Furthermore, due to their relative simplicity, especially in such model organisms as lobsters, crabs, or leeches, CPGs have also become quite widespread in computational modeling studies of cellular and synaptic properties of individual neurons and small neural networks.

While hand-tuning has been traditionally used in the process of creating CPG neuronal models (e.g., Soto-Treviño et al. 2005), in light of recent advances in the computational capabilities of modern computing systems, which now facilitate the use of more complex neuronal models (i.e., in terms of the number of compartments or free parameters), and allow for the exploration of unprecedentedly large parameter search spaces, this approach has become virtually obsolete. Therefore, automated methods for model parameter search have been lately gaining much attention.

There are basically two approaches to the problem of searching for optimal (i.e., physiologically realistic) sets of parameter values for models of small network central pattern generators: (1) “brute-force” explorations of predefined parameter spaces and (2) explorations utilizing heuristic optimization approaches, such as multi-objective evolutionary algorithms (MOEAs).

“Brute-Force” Explorations of Predefined Parameter Spaces

In the case of “brute-force” explorations of predefined parameter spaces, the study usually starts with a hand-tuned model of the CPG, which serves as the “center” for the parameter search space that is created around it. Then, physiologically realistic ranges for the model parameters (e.g., maximal conductances of membrane and synaptic currents) are chosen, along with the granularity for each of the parameters. The granularity determines how many possible values each of the parameters can assume and does not have to be the same for all the parameters, as some of them will exhibit different sensitivities to changes in their values. In some cases, the first step may be omitted and only the parameters, along with their ranges and granularities, are determined.

After such a grid-based parameter search space has been constructed, all of the possible combinations of the parameter values are simulated and tested for their physiological adequacy (possibly under multiple simulation scenarios, such as spontaneous activity, response to current injections, removal of neuromodulation, etc.). Only those models that match the behavior of the biological CPG, which is determined by means of one or more quantitative or qualitative measures of the CPG’s characteristics (e.g., spike height, interspike interval, burst duration, period, preservation of the phase of the rhythm, etc.), are retained for further analyses. However, the rejected models are also sometimes subjected to examination in order to determine what makes “bad” models unacceptable.

Explorations Utilizing Heuristic Optimization Approaches

In the case of explorations utilizing various heuristic approaches, such as multi-objective evolutionary algorithms, the study usually starts with the determination of the model parameters, along with their ranges and granularities, similarly to the “brute-force” approach, but often on a much larger scale. In other words, while the range in

the “brute-force” approach may reflect a 3- to four-fold variation in the parameter values, and the granularity may allow for five to ten possible values, incorporating up to 20-fold variation with hundreds of possible values for each parameter is not unheard of in a heuristic approach. Since this approach is not tasked with simulation and analysis of all of the possible combinations of values in such created parameter search space, it remains computationally feasible.

Another critical step in this approach is the definition of one or more measures of the given CPG’s characteristics that will be used to determine physiological adequacy of the models. While such measures can be virtually identical to the ones used in the “brute-force” approach, the difference lies in the fact that they are being used during the process of model generation itself, rather than at the end to filter out the unwanted models. These measures, in essence, become the fitness functions utilized in the process of optimizing model parameter values to drive it toward generating as many as possible “good” models which match the biological system, while limiting the number of “bad” solutions.

After the model parameters and the corresponding ranges and granularities have been determined, and the appropriate fitness functions (possibly multiple, even conflicting) have been defined, the iterative process of optimization of the model parameter values begins and ultimately yields a collection of physiologically realistic CPG models.

Applications

Most of the hitherto applications of the automated parameter searches in small network central pattern generators have been performed in relatively simple invertebrate CPGs. For example, Doloc-Mihu and Calabrese (2011) utilized the “brute-force” approach to construct a large (on the order of terabytes) database of conductance-based models of the half-center oscillator from the leech heartbeat central pattern generator to determine how neuronal parameters influence the network activity. Using the same approach, Günay and Prinz (2010) utilized a

large (20,250,000) database of models of the lobster pyloric network to study calcium sensors for network homeostasis. Smolinski, Prinz et al., used both the “brute-force” approach and multi-objective evolutionary algorithms to study the cellular and synaptic properties of the AB/PD (anterior burster/pyloric dilator) pacemaker kernel in the lobster pyloric network (2006, 2009), as well as the conductance correlations involved in the recovery of bursting after neuromodulator deprivation (Shim et al. 2012; Malik et al. 2013).

Cross-References

- [Neuronal Model Databases](#)
- [Neuronal Parameter Space Exploration](#)

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Axon Model

► Peripheral Nerve Models

Axon, Modeling

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Definition

Computational modeling of axons is used to determine the action potential initiation and propagation properties along these long and highly branched structures. Issues under investigation include the site and threshold of action potential initiation, propagation speed in unmyelinated and myelinated axons, and safety factors of propagation through branch points and other geometrical inhomogeneities, such as presynaptic boutons. Modeling allows exploration of the interaction between axonal morphology (diameters and branching structure) and passive and active membrane properties in determining the speed and reliability of action potential propagation. This can include the effects of ion channel noise. Modeling is also used to explore axonal development, including growth cone guidance and branching.

Detailed Description

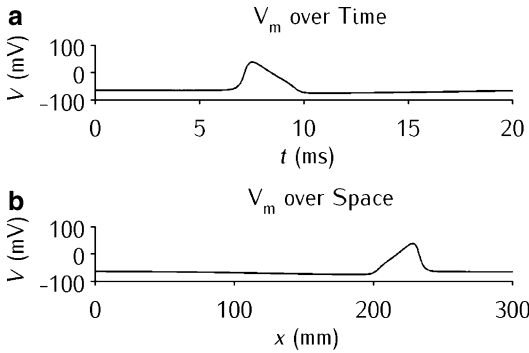
The axon is the principle communication pathway from one neuron to another. Brief voltage pulses called action potentials (AP) are initiated near the cell body and travel along the axon to reach the many presynaptic boutons. The AP causes neurotransmitter release in a bouton in a stochastic manner, resulting in an electrical response in a target neuron. The reality is more complex than this: AP propagation is not always reliable due to geometrical and electrical constraints in the axon; timing of AP arrival at boutons may vary, having

implications for information processing in target nuclei; and AP shape in boutons will influence transmitter release. The experimental data showing these effects is nicely summarized in Debanne (2004). How theoretical results and computational models have been used to aid our understanding of these processes is described in Segev and Schneidman (1999), a paper that is still highly relevant to the field.

Computational modeling is also making a significant contribution to our understanding of how axons develop, from their differentiation from dendrites at initiation to their guidance to target structures and formation of functional connections. This work is documented by van Ooyen in a recent review (van Ooyen 2011) and in an edited volume (van Ooyen 2003).

Hodgkin-Huxley Model of the Action Potential

Computational modeling of the action potential in axons begins with the work of Hodgkin and Huxley in determining a model based on experimental data of the action potential in the squid giant axon (Hodgkin and Huxley 1952). Their model forms the basis of most subsequent models of action potentials and also of models of current flow through membrane-bound ion channels in general in the nervous system. Based on their experimental data, they formulated models of the electrical currents generated by the flow of sodium (Na) and potassium (K) ions across the membrane. Importantly, these currents are voltage sensitive, so that a membrane depolarization results in an increase in the sodium current, which in turn leads to further depolarization and an increase in the sodium current through a positive feedback mechanism. This activation of the sodium conductance is curtailed by a rapid inactivation. The potassium current also increases with depolarization, but more slowly than the sodium current. Eventually, the potassium current grows large enough that it, along with the inactivation of the sodium current, leads to a repolarization of the membrane. This entire process takes place within a few milliseconds, forming a sharp voltage wave of around



Axon, Modeling, Fig. 1 Action potential (AP) in a long, uniform axon. (a) AP over time at 25% along the axon. (b) AP over space after 20 ms. Simulation performed using the NEURON simulator

100 mV, which is the action potential (Fig. 1a). The basic model describes changes in the transmembrane voltage (V_m) in an isopotential patch of neuronal membrane as a function of membrane capacitance (C_m), sodium (I_{Na}) and potassium (I_K) ionic currents, a nonspecific “leak” current (I_L), and experimentally injected electrode current (I_e ; to initiate the action potential). The equations of this model are as follows:

Membrane Voltage

$$C_m \frac{dV_m}{dt} = -g_L(V_m - E_L) - g_{Na}m^3h(V_m - E_{Na}) - g_Kn^4(V_m - E_K) + I_e$$

Sodium Current

$$I_{Na} = g_{Na}m^3h(V - E_{Na}) \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$$

$$\alpha_m = 0.1 \frac{V + 40}{1 - \exp(-(V + 40)/10)} \beta_m = 4 \exp(-(V + 65)/18)$$

$$\alpha_h = 0.07 \exp(-(V + 65)/20) \beta_h = \frac{1}{\exp(-(V + 35)/10) + 1}$$

Potassium Current

$$I_K = g_Kn^4(V - E_K) \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$$

$$\alpha_n = 0.01 \frac{V + 55}{1 - \exp(-(V + 55)/10)} \beta_n = 0.125 \exp(-(V + 65)/80)$$

Action Potential Propagation

This model can be extended to include action potential propagation along the axon using these membrane active properties (sodium and potassium currents) in a compartmental model of an elongated axon (Fig. 1b). The compartmental model arises as a spatial discretization of the partial differential equation describing spatially extensive current flow along an axon:

$$C_m \frac{\partial V_m}{\partial t} = \frac{d}{4R_a} \frac{\partial^2 V}{\partial x^2} - g_L(V_m - E_L) - g_{Na}m^3h(V_m - E_{Na}) - g_Kn^4(V_m - E_K)$$

For the simulation shown in Fig. 1, the axon is a cylinder 300 mm long, with a uniform diameter of 476 μm . It is divided into 500 equal-length computational compartments to obtain the numerical solution. The simulation was performed using the NEURON simulator (Carnevale and Hines 2006) with code derived from that used in Chap. 3 of *Principles of Computational Modeling in Neuroscience* (Sterratt et al. 2011).

Speed and Reliability of Propagation

Axons are rarely simply long, uniform cylinders. Many axons become highly branched as they near their target structures. Diameters can change along

the length of the axon, with a general tapering to thinner diameters toward terminals but with large increases in diameter at presynaptic boutons. Branch points may impose a change in electrical load, depending on the diameters of the daughter branches. The work of Rall and colleagues (see collected papers in Segev et al. 1995) established the important concept of the geometrical ratio (GR) between the diameters of two daughter branches (d_1 and d_2) to that of the parent branch (d_p ; section of axon or dendrite closer to the cell body), defined as.

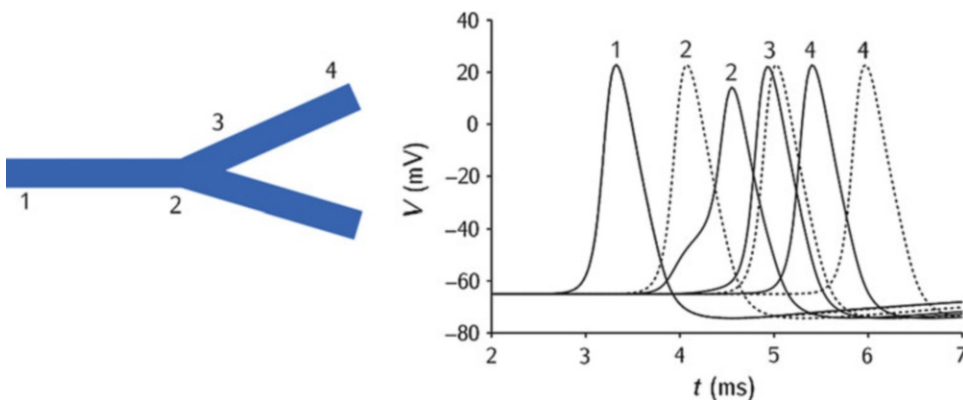
$$GR = \frac{d_1^{3/2} + d_2^{3/2}}{d_p^{3/2}}$$

Given uniform membrane properties, if $GR = 1$, the branch point imposes no change in electrical impedance, and the branching can be collapsed to an equivalent uniform cylinder. However, if $GR > 1$, the branch point imposes an extra electrical load that slows the AP, reduces its height, and can potentially lead to a failure of AP propagation. In contrast, if $GR < 1$, AP velocity and its height both increase as the branch point is approached, and propagation is reliable. Goldstein and Rall (1974) provided the first comprehensive computational investigation of AP propagation through specified geometrical inhomogeneities. An example is shown in Fig. 2. Here there is a single bifurcation in a long axon. The parent axon (at the left) has a diameter of

1 μm . The two daughter branches have an equal diameter of 2.52 μm , giving $GR = 8$. The action potential (AP) traces are from the parent axon, branch point, and one daughter branch, as illustrated in the figure. In this configuration (solid lines in time plots), the AP is significantly slowed and reduced in amplitude at the branch point (second trace from left), before quickly recovering and increasing in velocity. If the daughter diameters are reduced to 0.63 μm , then $GR = 1$, and the configuration is equivalent to a single, uniform axon of 1 μm diameter. In this case, the AP propagates with uniform amplitude and velocity (dashed lines). Note that though the AP at the branch point is significantly delayed when $GR = 8$, compared to $GR = 1$, the larger daughter branch diameter results in a higher velocity for the AP once it is through the branch point, and it quickly overtakes the AP traveling in the uniform axon (right-hand solid and dash plots, respectively). Goldstein and Rall (1974) showed that for axons with the same membrane (R_m) and axial (R_a) resistivity, AP speed is constant in units of length constant per unit time, irrespective of diameter (d). The passive length constant (λ) is.

$$\lambda = \sqrt{\frac{dR_m}{4R_a}}$$

This equates to an increase in speed in units of physical length per unit time with an increase in diameter.



Axon, Modeling, Fig. 2 Action potential (AP) in a branched axon. Recording sites illustrated at *left*. Traces of APs over time shown at *right*. *Solid lines*: $GR = 8$. *Dashed lines*: $GR = 1$. Simulations performed using the NEURON simulator

Manor et al. (1991) considered AP propagation in realistic axonal branching structures, with a particular emphasis on the delays imposed by geometrical irregularities. This study shows that though delays in AP propagation at individual branch points are at most small (a few tenths of a millisecond), accumulated delays in a complex, branching axon can result in arrival times at boutons differing by a few milliseconds. Delays or speedups from successive, nearby branch points do not sum linearly. In particular, successive summed delays may be supralinear compared to the delays at the individual, isolated branch points.

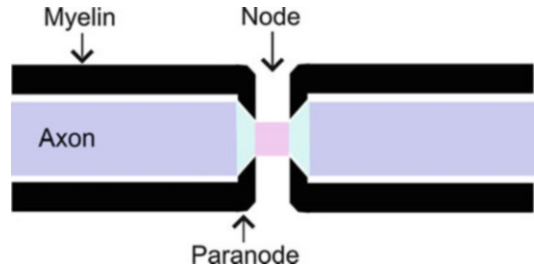
Differential branch point failure, in which the AP fails to propagate along one daughter branch, while successfully propagating along the other, which has been seen experimentally (Debanne 2004), cannot arise due to the branch point geometry alone (Segev and Schneidman 1999). Changes in the active membrane properties are also required and may arise due to differences in ion channel distributions between branches or differential extracellular ion accumulation during successive AP propagations leading to alterations in ion current reversal potentials (particularly E_K ; see the Hodgkin-Huxley model current equations) and hence current magnitudes.

In summary, computational modeling has been fundamental to improving our understanding of the characteristics of and constraints to AP propagation along branched and irregular axons.

Myelinated Axon

Propagation speeds along axons containing a continuous distribution of ion channels along their length (so-called unmyelinated axons) are rather modest, on the order of <1 m/s. Most long axons in the nervous system are myelinated, with glial cells providing a high-resistance membrane sheath around the axons for much of their length. Ion channels are largely restricted to the sites of regular breaks in this sheath, known as *nodes of Ranvier*. Action potential propagation speeds are much greater along these axons than along unmyelinated fibers, on the order of 10–100 m/s.

Computational modeling contributes to our understanding of AP propagation along



Axon, Modeling, Fig. 3 Myelinated axon. Structural details around a node of Ranvier

myelinated axons, particularly the implications of the very specific locality of sodium and potassium ion channels at and around the nodes of Ranvier (Fig. 3). Sodium channels are located at the node, with potassium channels largely restricted to the paranodal region.

In a simplistic approach, myelination may be modeled as an increased passive resistance and a decreased capacitance of the internodal (myelinated) axonal membrane, along with non-uniform distribution of active sodium and potassium channels. However, the narrow extracellular (periaxonal) space afforded by the myelination, plus the spatial separation of sodium and potassium channels, may require the modeling of ion concentrations and the electro-diffusion of ions intra- and extracellularly, to fully capture the action potential propagation properties of the myelinated axon (Nygren and Halter 1999).

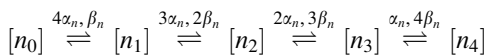
Models show that excessive accumulation of potassium in the periaxonal space following high-frequency repetitive activity can lead to action potential failure (Parnas and Segev 1979). Models are also used to explore the impact of loss of myelin, as occurs in diseases such as multiple sclerosis (Coggan et al. 2010). Loss of myelin leads to a slowing of action potential propagation or even action potential failure altogether.

Ion Channel Noise

Noise in the nervous system comes in many different forms (Faisal et al. 2008), with a major source being the stochastic opening and closing of ion channels in neuronal membrane. The thinness of axons makes them vulnerable to this form

of noise. Computational models in which the deterministic ion channel models of Hodgkin and Huxley are replaced by equivalent stochastic models are used to investigate the impact of ion channel “noise” on action potentials (Goldwyn and Shea-Brown 2011).

The standard approach to turning a deterministic model of the action potential, such as the Hodgkin-Huxley model, into an equivalent stochastic model is to treat the ionic conductance in a patch of membrane of a particular ionic species as being a function of the number of open ion channels for that species. Firstly, the dynamics of conductance change in the deterministic model can be rewritten in the form of a kinetic scheme, which is interpreted as the concentration of ion channels in different states, one of which is an “open” state and provides the conductance. An example of such a scheme for the potassium conductance in the Hodgkin-Huxley model is.



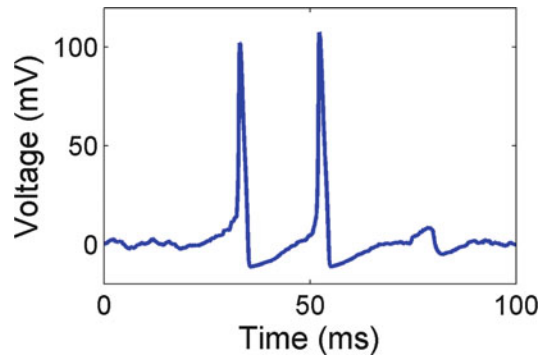
Now the total conductance for potassium in a patch of membrane is.

$$g_K(v, t) = \gamma_K[n_4]$$

where γ_K is the conductance of a single open potassium channel.

This becomes a stochastic model if the patch of membrane is assumed to contain N ion channels and the rates of the kinetic schemes become transition probabilities between states for individual channels, resulting in continuous-time Markov chain. The stochastic model approaches the deterministic model as N goes to infinity. However, for finite numbers of all ion channels, N , the stochastic model can exhibit significantly different behavior from the deterministic model.

Ion channel numbers in a patch of axon may be such that the variation in membrane potential from the opening and closing of individual ion channels may be apparent, particularly near the threshold of action potential initiation where the number of open ion channels is small (Schneidman et al. 1998). This can lead to stochasticity in the generation of action potentials, as illustrated in Fig. 4.



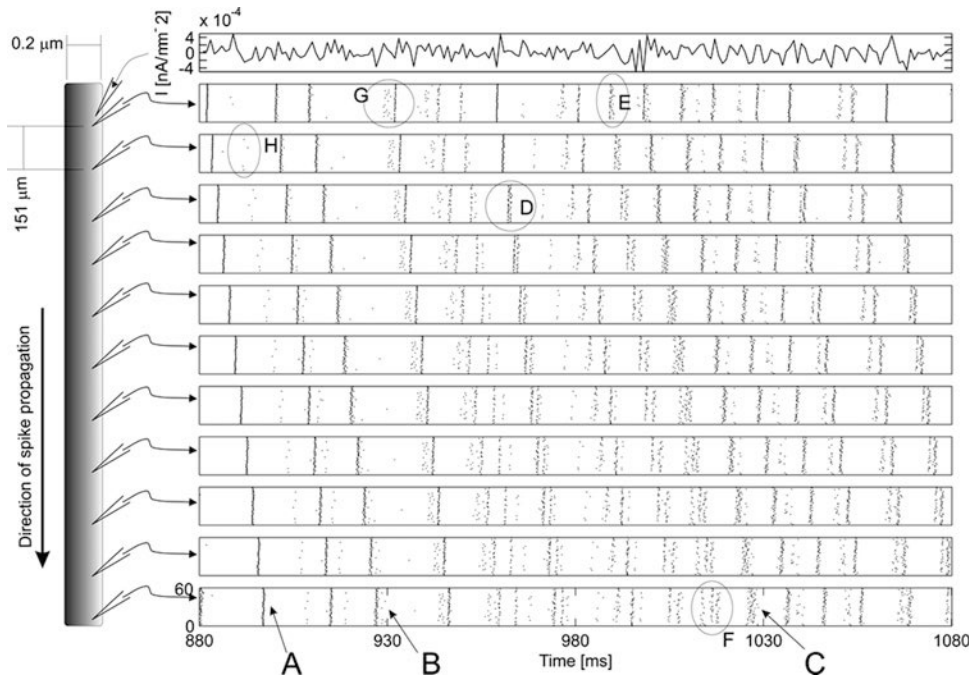
Axon, Modeling, Fig. 4 Spontaneous generation of action potentials in a stochastic Markov model of a $100 \mu\text{m}^2$ patch of membrane containing 6000 sodium and 1800 potassium channels. Simulation performed using the MATLAB code of Goldwyn and Shea-Brown (2011) as available in ModelDB (accession number 138950)

Fluctuations in ion channel opening can advance or retard action potential initiation and even lead to failures in propagation, though propagation is more reliable than initiation (Faisal and Laughlin 2007). Multiple trials of a stochastic model of axon stimulation by a fluctuating current are shown in Fig. 5.

Simulating the Markov model for all ionic species is computationally demanding. Other ways of incorporating membrane noise, which involve some stochastic description of the noise contribution of channel fluctuations, have been tried and can provide a good approximation to the full Markov description (Goldwyn and Shea-Brown 2011).

Axon Development

A completely different class of model is used to explore the development of axons. A major issue here is how an axon reaches its target nucleus and forms synapses therein. Models of axon guidance make explicit the interaction between extracellular attractive and repulsive cues and intracellular growth mechanisms in the growth cone and trailing axon. This requires modeling some form of extracellular environment that contains physical barriers to axon growth and diffusible or membrane-bound molecules acting as attractive and repulsive cues (Fig. 6). Krottje and van

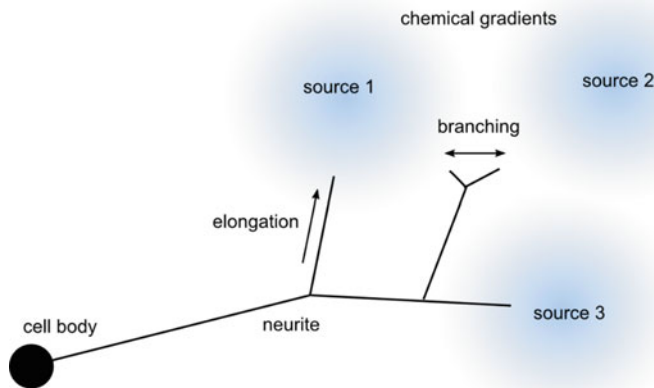


Axon, Modeling, Fig. 5 Action potential initiation and propagation due to fluctuating current stimulation in a stochastic membrane model of a squid-type axon with 0.2 μm diameter. The topmost row shows the stimulus current. Below, each row contains spike raster plots of

60 repeated trials recorded at equally spaced axonal positions. Data is extracted from 10-s trials (Fig. 1 from Faisal and Laughlin (2007), reproduced with permission according to the Creative Commons Attribution License)

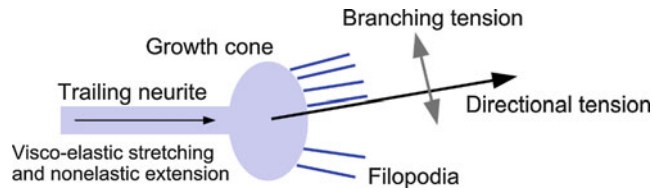
Axon, Modeling,

Fig. 6 Neurite outgrowth in an external environment containing three sources of a diffusible attractive chemical. (Reproduction of Fig. 10.10 from Sterratt et al. (2011), with permission of the authors)



Ooyen (2007) provide a suitable mathematical description of such an environment in the form of partial differential equations (PDEs) and quasi-steady-state approximations solved across a spatial grid. Axons themselves may not play a space-filling role in the environment.

Models concerned with the details of axon growth and branching, on the other hand, need to include the mechanisms of intracellular signaling, the viscoelastic properties of the axon, and the spatial extent of growth cones (Fig. 7).



A

Axon, Modeling, Fig. 7 Axonal pathfinding. Detection of chemoattractants in the external environment by filopodia produces tension on the growth cone in particular directions. The growth cone will turn toward and grow along the dominant direction. If similar forces are exerted

on opposite sides of the cone, the tension may be enough to split the cone into two, leading to the formation of daughter branches (Reproduction of Fig. 3 from Graham and van Ooyen (2006), with permission according to the Creative Commons Attribution License)

Computational simulation environments, including CX3D (Zubler and Douglas 2009) and NETMORPH (Koene et al. 2009), provide facilities for modeling aspects of axonal and dendritic development and the subsequent formation of neural networks. A review of modeling and computer simulation techniques for neuronal development is provided by Graham and van Ooyen (2006).

Cross-References

► [Hodgkin-Huxley Model](#)

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Axon-Glial Signaling

► [Neuron-Glial Interactions](#)

B

Back-Propagating Action Potentials (bAPs)

- [Action Potential Back-Propagation](#)

Back-Propagating Spikes

- [Action Potential Back-Propagation](#)

Baer-Rinzel (BR) Continuum Model

- [Dendritic Spines: Continuum Theory](#)

Balance Control Dynamics

- [Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)

Balance Following Cochlear Implantation

- [Vestibular Function After Cochlear Implantation](#)

Balanced Propagation

- [Neuronal Avalanches](#)

Balanced State

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Synonyms

[High-conductance state](#)

Definition

The balanced state of neurons is characterized by a high value of the total membrane conductance caused by synaptic inputs. It is the state of cortical neurons in vivo in awake animals, and it is due to massive excitatory and inhibitory inputs that almost cancel out. In this state, the responses are driven by fluctuations (possible also due to coincident events) in the input, and due to a greatly reduced effective membrane time constant, the neuron responds rapidly.

Detailed Description

The notion of high-conductance states, and the fact that neurons could integrate differently in such states, was first proposed by modeling studies. A meanwhile classical dichotomy distinguished between two operating modes of neurons: the integrator mode and the coincidence detection mode. In the integrator mode, the postsynaptic neuron is emitting spikes, because it integrates over time the excitatory presynaptic inputs. In the coincidence detection mode, it fires spikes, because many presynaptic excitatory neurons synchronize their excitatory inputs. By changing the time constant of the postsynaptic neuron, one could switch between these two modes: Coincidence detection calls for a short time constant, where the neuron quickly “forgets” previous inputs and needs coincident spikes so that the membrane potential is elevated enough to emit a postsynaptic spike; in the integration mode, the time constant should be longer to allow for summing inputs over time. Cortical neurons *in vivo* are likely to operate in the latter mode, because due to massive excitatory and balanced inhibitory inputs, the effective time constant is very small. This has various consequences for cortical computations at both the single-neuron and network levels, which are now addressed in greater detail, over the observation of a “high-conductance state” in recapitulated.

Empirical Evidence for a “High-Conductance State”

It is well known to physiologists that neurons in anesthetized animals often appear during intracellular recordings as if they operate in two distinct states, namely a so-called “up” state and a “down” state. In the “up” state, the neurons are depolarized and can fire action potentials, which are irregular as observed in extracellular recordings in awake animals. In the “down” state the neurons are hyperpolarized and emit no spikes. How do these two states emerge? The detailed mechanisms are still under investigation, but experiments revealed that the “down” state can

be much more easily manipulated via current injections than the “up” state. The lack of strong effects in the “up” state is consistent with a very high membrane conductance. A plausible explanation of this approximately 2–3 times increase of conductance relative to the resting leak conductance is to assume it as due to synaptic inputs.

Consequences for Single-Neuron Computations

In 1994 Shadlen and Newsome explored the idea that excitatory and inhibitory synaptic inputs might be balanced and keep the membrane potential close to, but below, the firing threshold (Shadlen and Newsome 1994). In this scenario the neuron can still respond, because fluctuations can push the membrane potential above a threshold. Simulation studies showed that in this regime, the neural responses are much more irregular compared to a non-balanced scenario with little or no inhibition, i.e., when strong excitation drives the responses. For neuronal models this means that neurons in a balanced state are best described with stochastic formalisms (Tuckwell 1988).

Given that neurons in the balanced state are sensitive to fluctuations in the inputs, they could also detect *changes* in such fluctuations. Of particular interest have been those brought about by changing correlations between presynaptic excitatory, inhibitory, or between excitatory and inhibitory spikes (Salinas and Sejnowski 2000). Interestingly, such correlations could change without affecting the average of the inputs. For neuronal modeling this is important, because it calls for stochastic models beyond simplistic rate-based descriptions. The fluctuations of balanced inputs have been implicated in changing the gain of neurons. Such gain modulations have been described as a physiological signature of attentional top-down modulations. Chance et al. (2002) have shown the feasibility of this mechanism using modeling and dynamic-clamp (Sharp et al. 1992), but *in vivo* tests of this hypothesis remain technically too challenging.

Another consequence of the balanced state is that responses to inputs can be very rapid as

pointed out already in 1975 by Barrett (1975). This can be demonstrated using the simple RC circuit model of the subthreshold membrane potential dynamics: Let us consider a leaky integrator, modeled as an RC circuit, with a time constant $\tau = RC = C/g$, where R is the membrane resistance (and $g = 1/R$ the conductance) and C is the membrane capacitance. The dynamics of membrane potential V are given by.

$$C \frac{dV}{dt} = -gV + g_{\text{AMPA}}(t)(E_{\text{AMPA}} - V) + g_{\text{GABA}}(t)(E_{\text{GABA}} - V)$$

where $g_{\text{AMPA}}(t)$ and $g_{\text{GABA}}(t)$ are the excitatory and inhibitory synaptic conductances (with reversal potentials E_{AMPA} and E_{GABA}) due to approximately balanced presynaptic inputs, i.e., the resulting currents cancel each other at a certain subthreshold voltage. These synaptic conductances are time dependent due to the different arrivals of spikes at the synapses and the kinetics of synaptic transmission. Averaging these conductances over time yields g_{AMPA} and g_{GABA} . Setting $\frac{dV}{dt} = 0$ and solving for the effective time constant τ_{eff} shows that.

$$\tau_{\text{eff}} = \frac{C}{g + g_{\text{AMPA}} + g_{\text{GABA}}} < \frac{C}{g}.$$

Thus, with increasing synaptic conductance, the neuron responds faster. This may be of particular relevance in sensory systems with high-frequency inputs, because in a non-balanced state, the neuron could not lock to such inputs.

Such a high-conductance state also affects the integration of dendritic signals. In line with Rall's classical works (Rall 1964), Barrett also suggests a location-dependence of the impact of dendritic inputs onto the somatic membrane potential. He emphasized the role of synaptic background activity, which would decrease the resistance and further reduce the impact of distal dendritic inputs. Experiments showed, however, that the dendritic inputs are approximately location-independent (Magee 2000). This observation could be a natural consequence of the massive synaptic inputs onto

active excitable dendrites in the balanced state, i.e., dendrites that support the local initiation of spikes (London and Häusser 2005). Rudolph and Destexhe have shown in simulation studies (Rudolph and Destexhe 2003) that the decreased impact with increasing distance from the soma predicted by Rall and Barrett could be balanced by an increased likelihood of evoking a dendritic spike as the input resistance increases with distance from the soma.

Consequences for Network-Based Computations

While single-neuron modeling studies usually assume background inputs with certain properties such as balanced inputs, network models need to explicitly account for them. In 1996 van Vreeswijk and Sompolinsky (1996) showed that sparsely connected recurrent networks with strong but balanced excitation and inhibition naturally lead to the temporally irregular spiking patterns observed in awake animals. One may wonder how such a tight balance between excitation and inhibition required by network models could be realized in cortical networks, given that local inhibitory interneurons are far less numerous than the excitatory neurons. Despite their lower absolute number, inhibitory neurons are often reported to have higher firing rates. Moreover, their synapses onto postsynaptic targets show much less short-term depression than excitatory synapses. In combination, this could make the recurrent inhibition much stronger than evident by their lower absolute number.

It is known that blocking inhibition causes the cortex to become epileptic (Dichter and Ayala 1987), and already in 1975 Sillito showed that reducing inhibition lets sensory neurons (in primary visual cortex, V1) lose their orientation selectivity (Sillito 1975). This further supports the notion that the balanced state is the natural cortical state of awake animals. Experimental studies later investigated in greater detail the potential network mechanisms underlying the spike responses in vivo using paired recordings. For example, Okun and Lampl showed in 2008 via simultaneous intracellular recordings of pairs

of nearby neurons in rat somatosensory cortex (Okun and Lampl 2008) that the excitatory and inhibitory inputs covary in strength and time. They found this covariation during both the spontaneous “resting-state” activity and during sensory stimulation. Mariño et al. (2005) performed intracellular recordings in vivo in V1 and showed that such a covariation in space could explain the experimentally observed invariance of the orientation tuning with location in the orientation map of V1. The balanced state as observed in single neurons may also have large-scale macroscopic correlates, namely, the spontaneously occurring states reported during resting-state activity in V1 (Kenet et al. 2003). From a modeling perspective, it is worth mentioning that such macroscopic phenomena can be simulated and analyzed using rate model (Blumenfeld et al. 2006).

Discussion and Future Directions

Meanwhile, the balanced state is accepted in the community as the state that characterizes cortical neurons in vivo. Many studies have investigated how it affects single-neuron computations. Other studies have developed self-consistent network models that reproduce the balanced state. Experimental tests of model predictions appeared in the literature with quite some delay relative to the modeling studies. This is not a surprise, because direct empirical evidence for the balanced state is technically very hard to obtain, as it calls for intracellular multiunit recordings of connected neurons in vivo. Future modeling studies should respect this and aim at specific predictions for easier to access macroscopic observables. Future modeling studies could also investigate how adaptation at various timescales affects the balance between excitation and inhibition. Given that cortical networks seem to be exquisitely balanced, even small perturbations could have major impacts. The role of inhibitory plasticity in maintaining the balanced state has been addressed in first modeling studies (Vogels et al. 2012). Exploring how a certain adaptation or learning mechanism behaves in the balanced state in vivo is now becoming a necessity for all modeling

studies of adaptation, learning, and cortical computation. Finally, one may need to address explicitly the energetic costs of the balanced state. Are the potential benefits, from a normative point of view, really worth all the energy the brain is investing into maintaining this mode of operation? It could be that the most fascinating properties of the balanced state that warrant this investment are still to be discovered.

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Baroreceptor Reflex

► Baroreflex Models

Baroreflex Models

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Synonyms

[Baroreceptor reflex](#)

Definition

Blood pressure is controlled by several feedback mechanisms. The fastest one baroreceptor reflex (baroreflex) can be defined as the biological neural control system responsible for the **short-term** blood pressure regulation.

From modeling perspective the baroreflex feedback control system consists of three parts (Fig. 1):

- The afferent part where the arterial pressure is being read out, transduced, and supplied
- The central nervous system (CNS) where this input is processed and converted to the sympathetic and parasympathetic nerve activities
- The effector organs that respond to sympathetic and parasympathetic tones by adjusting

heart rate, contractility, vascular resistance, and a number of other physiological parameters

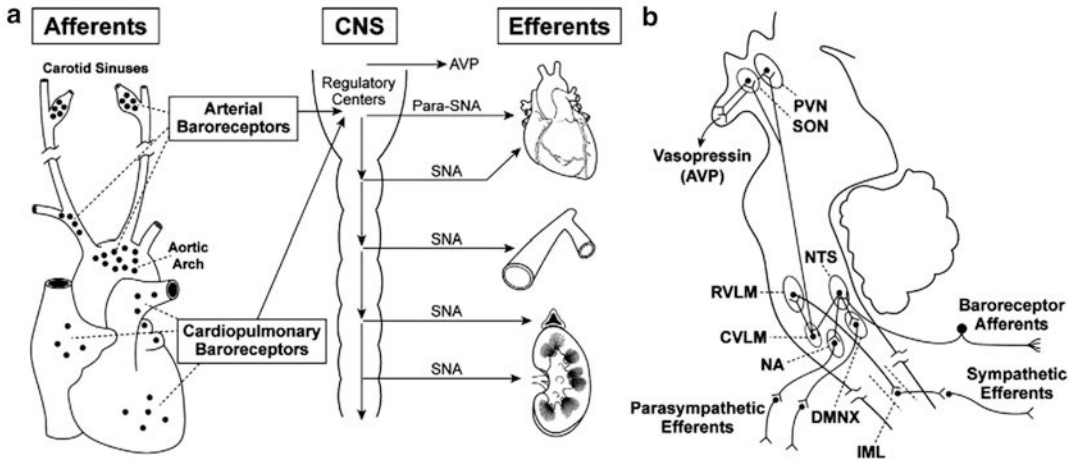
The afferent part is represented by baroreceptors, mechanoreceptors located in the great arteries, heart, and pulmonary vasculature, that transduce arterial pressure into action potential trains. Baroreceptors provide input to second-order neurons in nucleus tractus solitarius (NTS) located in the lower brainstem. Via a network of interneurons, the second-order barosensitive neurons provide an excitatory input to cardiac vagal motoneurons (CVM) in nucleus ambiguus (NA) and dorsal motor nucleus of vagus (DMNX) and inhibit the pre-sympathetic neurons in rostral ventrolateral medulla (RVLM). CVMs and pre-sympathetic RVLM neurons define parasympathetic (para-SNA) and sympathetic (SNA) nerve activities, respectively. **Baroreflex models** are aimed to quantify para-SNA and SNA reflex responses to sharp changes in arterial BP and, thus, attempt to describe the neural part of the system.

Closed-loop models of cardiovascular system usually include a baroreflex compartment, and a number of effector organs controlled by sympathetic and parasympathetic activities (Fig. 2).

Detailed Description

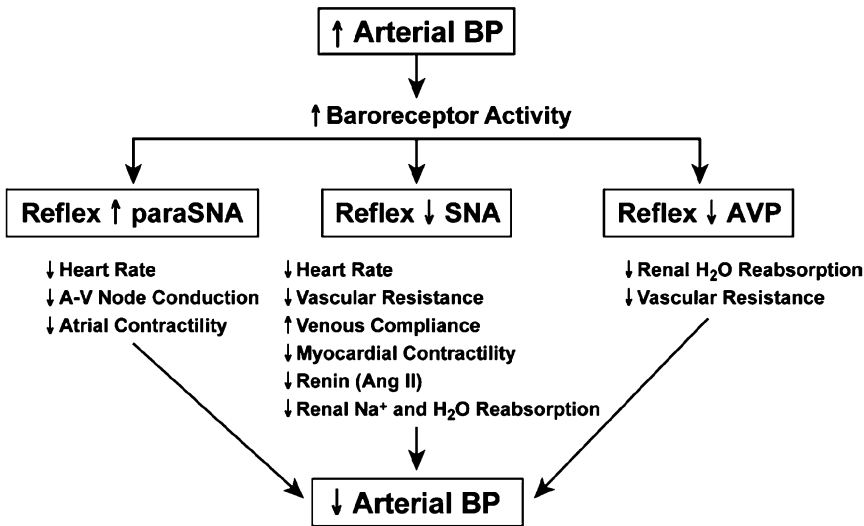
Deviations in blood pressure (BP) and blood volume are sensed in cardiovascular system by **baroreceptors**, mechanosensitive nerve endings activated by vascular or cardiac distension (Fig. 2). **Arterial baroreceptors** (located in the aortic arch and the carotid sinuses, see Fig. 1) increase their activity when BP rises, and reduce it if BP lowers. **Cardiopulmonary baroreceptors** in the heart, vena cava and pulmonary vasculature are aimed to sense central blood volume, and are sometimes called *volume receptors* or *low-pressure receptors*.

The afferent activity from arterial baroreceptors is sent to the medullary brainstem area called nucleus tractus solitarius (NTS) through glossopharyngeal nerve (from carotid sinus baroreceptors) and vagus nerve (from aortic arch) that



Baroreflex Models, Fig. 1 Location of baroreceptors and neural pathways of baroreflex responses. Abbreviations: *CNS* central nervous system, *para-SNA* parasympathetic nerve activity, *SNA* sympathetic nerve activity, *NTS* nucleus tractus solitarius, *NA* nucleus ambiguus, *DMNX*

dorsal motor nucleus of vagus, *CVLM* caudal ventrolateral medulla, *RVLM* rostral ventrolateral medulla, *IML* intermediolateral column, *PVN* paraventricular nucleus, *SON* supraoptic nucleus of hypothalamus (From Chapleau 2011 with permission)



Baroreflex Models, Fig. 2 Baroreflex negative feedback control of arterial blood pressure (*BP*) (From Chapleau 2011 with permission)

together are known as the **buffer nerves**. In the NTS this information is processed by an intricate network of interneurons that control efferent para-sympathetic (para-SNA) and sympathetic (SNA) nerve activities and release of antidiuretic peptide vasopressin (AVP) (see Fig. 1). All these

mechanisms in response to changes in the arterial BP cause reflexes (Fig. 2) that ultimately push BP in the opposite direction providing a negative feedback control of arterial BP called **arterial baroreflex**. The CNS pathways of cardiopulmonary baroreceptors are similar to that of arterial

ones except their activation has little effect on heart rate (HR) which is the fastest mechanism of BP control.

Due to complexity of the system, modeling studies usually focus on a particular aspect depending on phenomena considered while using simplified description of other compartments. Several integrative mathematical models were used to elucidate the role of baroreflex in cardiovascular instabilities, such as heart rate variability and spontaneous fluctuations of the arterial pressure (e.g., Mayer waves).

Pressure-Electrical Transduction

As a result of a change in arterial pressure, the cross-sectional area of the arteries changes leading to mechanical deformation of artery walls. Changes in the membrane strain resulting from the artery wall deformation lead to changes in the conductance of a variety of mechanosensitive ion channels in the sensory terminals of arterial baroreceptors. The cumulative effect of the opening of those channels in response to rise in pressure is an increased inward (depolarizing) current. If the resulting depolarization exceeds certain threshold, baroreceptors start firing action potentials with a rate defined by the magnitude of this current.

In mechanoreceptors variations in membrane strain affect protein conformations and, hence, cause changes in the probabilities for mechanosensitive membrane channels to be in open and close states (Morris 1990). Accordingly, a net inward current flow through mechanosensitive ion channels is often modeled as a nonspecific current with zero reversal potential and Boltzmann-like dependence of the conductance on arterial pressure P :

$$I_{\text{baro}} = \frac{g_{\text{max}}}{1 + \exp(-K(P - P_{1/2}))} (V - E_m)$$

where g_{max} is a maximal conductance of this current, $P_{1/2}$ is half-activation pressure, K defines the sensitivity and E_m is a reversal potential usually accepted 0.

Rose et al. (1995) used a little different approach. Their baroreceptors had a pressure-dependent depolarizing current which was linear above a threshold pressure: $I_{\text{baro}} = K(P - P_{\text{thr}})$ if $P > P_{\text{thr}}$ and $I_{\text{baro}} = 0$ otherwise.

Baroreceptors

Baroreceptor response to changes in arterial BP is very complex, nonlinear, and has multiple time-scales. Rapid jumps in BP lead to much stronger changes of baroreceptor activity than gradual excursions of the same magnitude. Acute hypertension results in a sharp rise in the baroreceptor activity which, however, declines in time if hypertension is maintained. After acute withdrawal from the increased BP, baroreceptors first exhibit reduced activity (post-excitatory depression) which then adapts back to baseline.

In short, the properties of the firing rate of the baroreceptors in response to changing arterial pressure modeling-wise important can be formulated as follows (Ottesen et al. 2004):

- Firing rate increases with BP.
- The response exhibits threshold and saturation.
- Sufficiently fast decreases in pressure cause firing rate to fall below the threshold.
- A step change in pressure causes a step change in firing rate followed by a decay in firing rate (called adaptation or resetting depending on the timescale).
- Response curves are sigmoidal and show asymmetric hysteresis-like behavior.

Conductance-Based Baroreceptor Model

Baroreceptor fibers are divided into two different types, A-type and C-type, depending on whether they are myelinated or not. Schild et al. (1994) performed a thorough study of their electrophysiological properties and developed a conductance-based model of A- and C-type cells based on voltage-clamp recordings in rat nodose sensory neurons (carotid sinus baroreceptors). Their model included two Na^+ currents exhibiting fast and slow tetrodotoxin (TTX)-insensitive kinetics; low- and high-threshold Ca^{2+} currents exhibiting

transient and long-lasting dynamics, respectively; and outward K^+ currents consisting of a delayed-rectifier K^+ current and Ca^{2+} -activated K^+ current. The model also includes extra- and intracellular Ca^{2+} dynamics.

Firing Rate-Based Baroreceptor Model

In Ottesen et al. (2004) a very elegant model is suggested that accounts for major properties of baroreceptor response. His model describes nonlinear responses of a baroreceptor to changes in carotid pressure in terms of a single nonlinear ordinary differential equation:

$$\frac{dn}{dt} = k \cdot \frac{dP_c}{dt} \cdot \frac{n(M-n)}{(M/2)^2} - \frac{n-N}{\tau}$$

where n is the firing rate of the baroreceptor, P_c is the carotid pressure, M is the maximal firing rate, τ is the adaptation time constant, k is a weighting constant, and N denotes the threshold. Instantaneous rate of change of the firing rate is proportional to the time derivative of carotid pressure and to the firing rate itself. Accordingly, the change in firing rate is most sensitive to change in carotid pressure when the value of the firing rate is in the middle of its physiological range $[0, M]$ and almost insensitive near the boundary. This defines the sigmoidal form of the response curve.

Experimental data shows that the adaptation has many different timescales from seconds to hours or even days. As mentioned, baroreceptor fibers are divided into different types, fast A and slow C fibers, in accordance to whether they are myelinated or not. The fast A fibers are further divided into subtypes. It was suggested that different types of baroreceptors can be characterized by significantly different adaptation time constants (Ottesen and Olufsen 2011). In this case their integrated activity n is calculated as

$$n = N + \sum_{i=1}^K \Delta n_i$$

where Δn_i is a deviation of the firing rate of the type i baroreceptor from the threshold value N , driven by a nonlinear differential equation similar to the above:

$$\frac{d}{dt} \Delta n_i = k_i \cdot \frac{dP_c}{dt} \cdot \frac{n(M-n)}{(M/2)^2} - \frac{1}{\tau_i} \Delta n_i$$

and K is a number of different baroreceptor types. Ottesen and Olufsen (2011) show the example where a satisfactory fit of the experimentally observed responses of the firing rate to a step input pressure requires $K = 3$ types of baroreceptors with time constants $\tau_1 \approx 0.5$, $\tau_2 \approx 10$, and $\tau_3 \approx 3000$ s.

Nucleus Tractus Solitarius (NTS)

Baroreceptors map the spatial pressure distribution onto the inputs to the second-order neurons in the NTS. One of the puzzles of the identified baroreflex-related neurons in NTS is that in spite of receiving direct inputs from the first-order neurons, their activity does not have any frequency component corresponding to cardiac frequency. Somehow they do not respond to each heartbeat by performing a “low-pass filtration” of their inputs.

Rogers et al. (2000) suggested that this property can be concerned either with specific biophysical properties of NTS baroreceptors (Fig. 3) or with specific interactions in the NTS network of second-order interneurons (Fig. 4). By analyzing the responses of the second-order NTS neurons to induced blood pressure pulses, they have noticed that barosensitive second-order NTS neurons respond to blood pressure changes with a burst of activity whose frequency is much lower than the frequency of cardiac cycle, and the activity of these neurons is inhibited just before and after the bursts. Using these observations they developed a series of mathematical models of early stages of baroreflex based on the intrinsic cell properties and network mechanisms.

Intrinsic Properties-Based Model

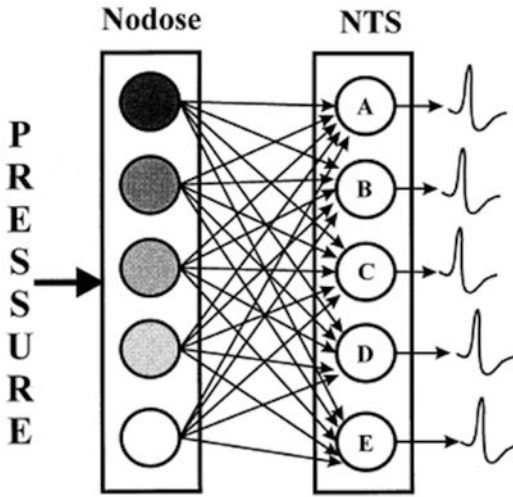
Individual NTS neurons were modeled using a single-compartment description in the Hodgkin–Huxley formalism. The most important feature of

their individual neuron model was that in addition to ionic channels responsible for spiking behavior (like fast sodium and potassium delayed rectifier channels), they incorporated

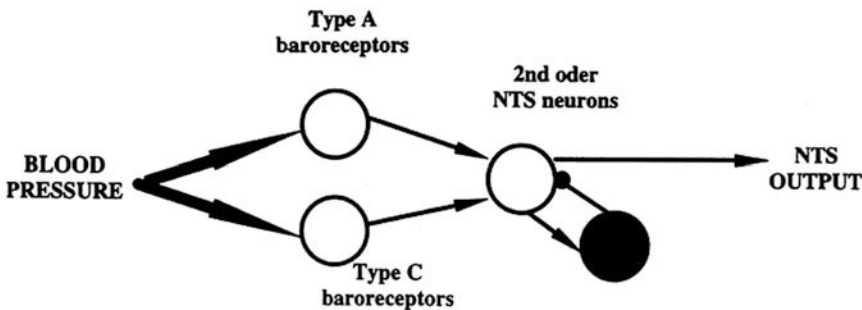
mechanisms for the response adaptation (A-type potassium, calcium-dependent potassium, and low threshold calcium currents). This mechanism together with intracellular calcium dynamics allowed them to reproduce several important properties of the second-order baroreceptors previously identified experimentally: (1) frequency adaptation in the cell's response to a step stimulus; (2) sensitivity to the rate of change of input; and (3) the lack of response to each pulse of a pulsatile stimulus; however, if these pulses were imposed on a ramp stimulus, the cell could respond to each pulse.

Inhibition-Based Model

Barosensitive NTS neurons show a variety of responses to both buffer nerve shock and arterial pressure increases. These neurons may respond to buffer nerve shock with excitation (EPSPs), inhibition (IPSP), or an EPSP/IPSP combination. Accordingly, they may be excited, inhibited, or responded with an extinction response to increases in arterial pressure. To account for a variety of responses, Rogers et al. (2000) proposed a populational model of barosensitive NTS neurons based on specific neural circuitry. In this case they also used Hodgkin-Huxley-based description but without Ca^{2+} and $\text{K}(\text{Ca}^{2+})$ conductances. So this model solely relies on the network architecture, rather than on the neurons' biophysical properties.



Baroreflex Models, Fig. 3 Schematic used by Rogers et al. (2000) for NTS model based on specific electrophysiological properties. Arterial pressure is transduced by baroreceptors (nodose) according to their pressure thresholds, indicated by shading (*top cell*: highest pressure threshold). All NTS neurons receive input from all baroreceptors. Each input to any given NTS cell is equally weighted. The only difference between the NTS neurons is the total synaptic weight provided by the baroreceptors, which is varied systematically with the top neuron (A) receiving the highest total drive and the bottom neuron (E) receiving the lowest total drive



Baroreflex Models, Fig. 4 Architecture of the model proposed to explain variability of NTS neuronal responses to buffer nerve shock and arterial pressure increases. This model consists of two populations of baroreceptors, type A and type C, that have different pressure thresholds and sensitivities. The two baroreceptor populations provide

input to the excitatory population of second-order NTS neurons. This population sends excitatory inputs to the population of inhibitory neurons (represented by the *shaded circle*), which in turn inhibits the former (Adapted from Rogers et al. 2000 with permission)

Barotopic Hypothesis

Because of the different pressure thresholds, baroreceptors have a distributed sensitivity to BP and its rate of change. “Barotopic” organization hypothesis suggests that individual baroreceptors’ pressure thresholds (below which they are silent) are topically distributed in an interval of the pressures and that each second-order barosensitive neuron receives inputs from the first-order ones, whose thresholds lie in a definite small interval of pressure values.

Rose et al. (1995) used this architecture in their model of baroreflex control of heart rate. The neural portion of their model included baroreceptors, neurons of the nucleus tractus solitarius (NTS), and cardiac vagal motoneurons (CVM) (Fig. 5) all described in Hodgkin–Huxley style.

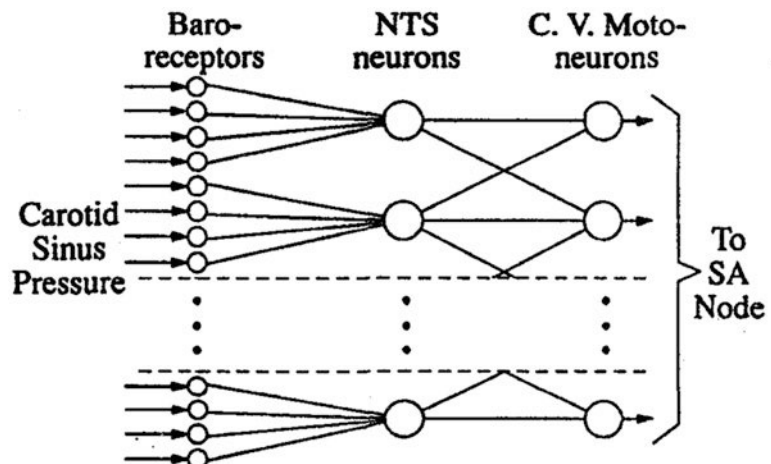
In addition to basic spiking currents baroreceptors in their model included A-type potassium current responsible for rapid adaptation and a pressure-dependent depolarizing current which was linear above a threshold pressure (see section “Pressure-Electrical Transduction”). Each baroreceptor had its own threshold pressure P_{thr} , and the thresholds had a sigmoidal distribution. Each NTS neuron received excitatory inputs from several baroreceptors with close thresholds and projected to several CVMs. The NTS neurons and CVMs had six conductances: sodium, delayed-rectifier potassium, A-type potassium, AHP-type potassium, I-type calcium, leakage conductances,

and intracellular calcium dynamics including pumping and buffering. The CVMs projected to the sinoatrial (SA) node where their action potentials activated an acetylcholine (ACh)-activated inward rectifier K^+ hyperpolarizing current which slowed the depolarization of the node and hence decreased the heart rate. The effect of vagal impulses on the hyperpolarizing current was greater for those arriving later in the cardiac cycle.

Sympathetic and Parasympathetic Activities

Second-order baroreceptors in the NTS through a network of interneurons modulate parasympathetic and sympathetic efferent outputs by exciting cardiac vagal motoneurons (CVM) in NA and DMNX and inhibiting pre-sympathetic neurons of RVLM, respectively. The details of this network are unknown. For the sake of simplicity, NTS is often considered as a source of single excitatory drive that directly activates CVMs. The effect on SNA is mediated by GABAergic interneurons in CVLM that in turn inhibit pre-sympathetic neurons in RVLM. In firing rate-based approach, the parasympathetic and sympathetic activities are usually calculated as ascending and descending sigmoid functions of aggregate NTS output, respectively. Ottesen et al. (2004), for example, suggest the following sigmoids:

Baroreflex Models,
Fig. 5 Architecture of a neural portion of the model by Rose et al. (1995). (Reproduced with permission)



$$n_{\text{sym}}(n) = \frac{1}{1 + (n/n_0)^v}, n_{\text{par}}(n) = 1 - n_{\text{sym}}(n)$$

$$= \frac{1}{1 + (n/n_0)^{-v}}$$

where $n_{\text{sym}}(n)$ and $n_{\text{par}}(n)$ are SNA and para-SNA, respectively, n is NTS output, n_0 is the baseline NTS output with fully adapted baroreceptor activity, and v defines the steepness of the curves.

The parasympathetic output is provided directly by vagal motoneurons, while sympathetic activity is formed by a longer chain of neural structures and involves several neurotransmitter systems. This difference is often taken into account by introducing a time delay in sympathetic response which can constitute up to several seconds. Ottesen and Olufsen (2011), for example, model parasympathetic activity as proportional to the baroreceptor firing rate $n(t)$ and SNA is defined by the delayed version of $n(t)$:

$$n_{\text{par}}(t) = \frac{n(t)}{M}, n_{\text{sym}}(t) = 1 - \frac{n(t - t_d)}{M}$$

where M is the maximal baroreceptor firing rate, and t_d is the time delay.

Respiratory Baroreflex

As mentioned, the classical baroreflex control of sympathetic nerve activity (SNA) operates via the second-order baroreceptor neurons that project to the caudal ventrolateral medulla region (CVLM). Through this path, the baroreceptor activation provides activation of CVLM neurons which in turn inhibit the pre-sympathetic rostral ventrolateral medulla (RVLM) neurons hence lowering both the RVLM activity and SNA. This pathway provides a direct negative SNA reflex response.

Sympathetic activity contains the respiratory modulation, which suggests that sympathetic and respiratory networks interact. Respiratory activity is also known to be modulated by the baroreceptor input. Together these facts imply that there may be another baroreflex pathway mediated by the respiratory neurons.

Baekey et al. (2010) have demonstrated that transient pressure pulses perturb the respiratory

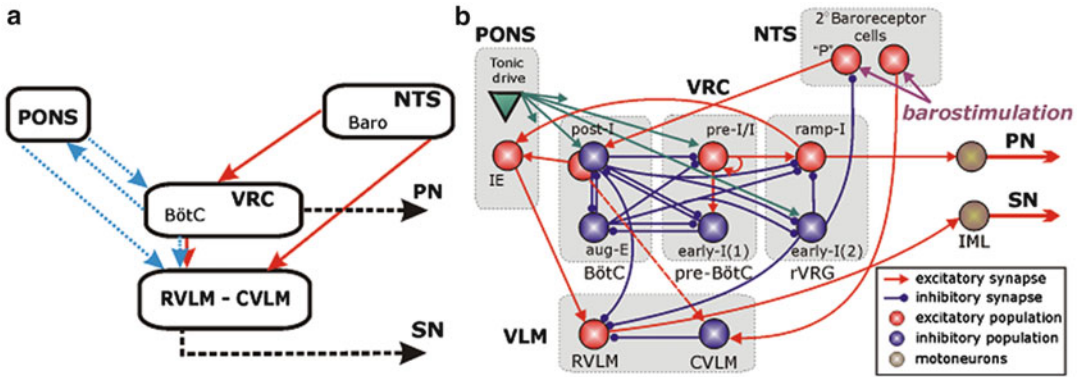
pattern in a phase-dependent manner, and those perturbations strongly depend on the integrity of the pons. The stimuli were delivered during inspiration, post-inspiration, or late expiration. With pons intact, the applied barostimulation had almost no effect on the amplitude and duration (i.e., inspiratory period) of the phrenic bursts even when stimuli were delivered during inspiration. At the same time, these stimuli suppressed or abolished inspiratory modulation of SNA. In contrast, the same stimuli delivered during post-inspiration or late expiration produced an increase in the expiration period and decreased SNA. The barostimulation-evoked prolongation of expiration was greater if stimulation was applied later during the expiratory phase. After pontine transection the barostimulation shortened the apneustic inspiratory burst. In all cases the sympathetic baroreflex-induced lowering of SNA persisted confirming the presence of a direct baroreflex pathway which bypasses the respiratory network.

Based on their experimental findings, Baekey et al. (2010) developed a mathematical model of baroreceptor-respiratory-sympathetic interactions that explained phase-dependent respiratory response to transient barostimulation. One of the implications of their model was that there is indeed a second pathway from baroreceptors to pre-sympathetic neurons in RVLM. This second pathway is mediated by respiratory circuits, specifically by the post-I neurons of BötC. This baroreflex pathway is strongly dependent on the respiratory-sympathetic interactions and needs pons to be intact.

Another interesting implication of their model is that the sympathetic baroreflex gain depends on the respiratory phase, because a subpopulation of NTS second-order baroreceptors is inhibited during inspiration (Fig. 6).

The Role of Cardiopulmonary Baroreceptors

A majority of modeling studies only take into account arterial baroreceptors. However, under certain conditions blood volume regulation provided by cardiopulmonary baroreceptors plays a



Baroreflex Models, Fig. 6 (a) Conceptual model of interaction between respiratory-related activity of the ventral respiratory column (VRC), pontine circuits (PONS), sensory network in the nucleus tractus solitarius (NTS), and rostral and caudal ventrolateral medulla (RVLM/CVLM). The sympathetic baroreceptor reflex operates via two pathways (red solid arrows): one direct pathway includes baroreceptors, 2nd-order barosensitive cells (Baro) in the NTS and CVLM, which inhibits RVLM and SNA; the other pathway routes via the Böttinger complex (BötC) in the VRC, whose post-inspiratory neurons inhibit RVLM and

SNA. Blue dotted arrows represent the effects of VRC and PONS on RVLM providing respiratory modulation of SN activity. (b) The schematic of the computational model by Baekey et al. (2010) showing interactions between different populations of respiratory neurons within major brainstem compartments involved in the control of breathing and sympathetic motor activity (pons, BötC, pre-BötC, rVRG, VLM, and NTS). Each population (shown as a sphere) consists of 20–50 single-compartment neurons described in the Hodgkin–Huxley style (Adapted from Baekey et al. 2010 with permission)

major role in blood pressure control. To understand the interplay between different mechanisms, Ursino (2000) developed a closed-loop mathematical model which included both arterial and cardiopulmonary baroreceptors and four effector components: heart period, systemic peripheral resistance, systemic venous unstressed volume, and heart contractility. He simulated the model to mimic the baroreflex response to mild and severe acute hemorrhages and found that the cardiopulmonary baroreceptors play a significant role in the control of systemic arterial pressure during mild hemorrhages (lower than 3–4 % of the overall blood volume). Under these conditions arterial pressure could be maintained at its normal level solely by cardiopulmonary feedback loop without the intervention of the arterial baroreceptors. During more severe hemorrhages the latter take over the responsibility for pressure control, and the contribution of cardiopulmonary baroreceptors becomes negligible.

Ursino (2000) noticed that according to their model the stability region in the parameter space of the closed-loop system is quite narrow. For

example, an increase in the static gain of the baroreceptors or a decrease in the rate-dependent component may lead to self-sustained oscillations similar to Mayer waves.

Baroreflex and Mayer Waves

Mayer waves are synchronous oscillations in SNA and arterial BP slower than respiratory rhythm. The origin and physiological mechanisms of these oscillations are currently unknown. The fact that Mayer waves are abolished by sinoaortic baroreceptor denervation strongly suggests the involvement of arterial baroreflex in this phenomenon. The baroreflex theory of Mayer waves explains the emergence of self-sustained oscillations in arterial pressure by the instability caused by fixed time delays in the baroreflex (presumably sympathetic) feedback loop (see the review by Julien (2006) and the literature therein cited). Since virtually any system with the delayed feedback is unstable for sufficiently large time delay values, many different models of dynamic

arterial pressure control have succeeded in predicting Mayer waves (Julien 2006). The magnitude of the time delay is the determinant factor of the emerging oscillation frequency. Mayer wave frequency varies significantly between species which suggests that different species should have significantly different time delays in baroreflex feedback loop. In spite of numerous hypotheses suggested, no consistent explanation of this species-to-species variability was yet provided. Another challenge for the baroreceptor theory is the dependence of Mayer wave amplitude on the mean SNA level which the existing models fail to explain.

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Basal Ganglia System as an Engine for Exploration

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Definition

The basal ganglia (BG) system is a deep brain circuit with wide-ranging brain functions. Exploration refers to the sampling of a variety of behaviors not firmly established within a learned repertoire. While the neural source of variability driving exploration within the subcortex has not been identified, the hypothesis that the indirect pathway of the BG is the subcortical substrate for exploration leads to explanations for how a range of putative BG functions might be performed.

Detailed Description

Reinforcement Learning and the Basal Ganglia

For nearly a century, a certain “mysteriousness” has been attributed to the function of the basal ganglia (BG) system – a deep brain circuit of multiple interconnected nuclei, with rich connections to large parts of the cortex (Kinnier Wilson in his Croonian lectures in 1925, Marsden 1982). The mystique surrounding BG has its roots perhaps in the multifarious functions of this circuit. Action selection, action gating, sequence generation, motor preparation, reinforcement learning, timing, working memory, goal-directed behavior, and exploratory behavior – the list of putative BG functions is long and perhaps, by the current state of knowledge, is also incomplete. Lesions of this circuit can show manifestations in many forms – from simple reaching movements to handwriting, balancing and gait, speech and language function, eye movements, and force generation, in addition to cognitive and affective manifestations. A long

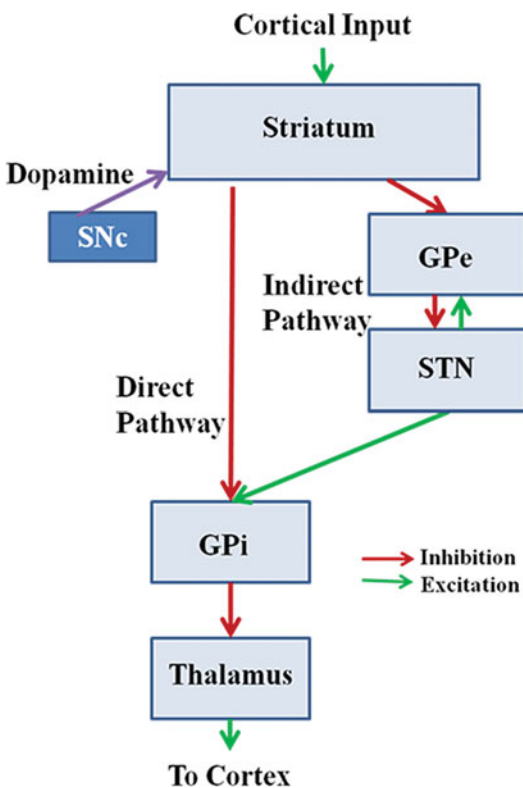
line of neurological (Parkinson's disease, Huntington's disease, athetosis, chronic fatigue syndrome) (DeLong 1990) and neuropsychiatric disorders (schizophrenia, obsessive-compulsive disorder, ADHD, apathy, abulia, insomnia) (Ring and Serra-Mestres 2002) are associated with BG impairment.

In one of the earliest forays into the mystery of the BG, Albin et al. (1989) interpreted BG anatomy to consist of two pathways (Albin et al. 1989) with complementary roles in motor manifestations (Fig. 1). BG consist of several nuclei – striatum (caudate and putamen), globus pallidus externa/interna, subthalamic nucleus, and substantia nigra pars compacta (SNc)/reticulata. The BG circuit as a whole receives extensive inputs from the cortex and projects back to cortex via thalamus. Cortical signals to BG flow along two pathways: the direct pathway (DP) and the indirect pathway (IP). The projections from the

striatum, the input port to BG, to globus pallidus interna (GPi), one of the output ports, constitute the DP. The indirect route which connects the striatum to GPi via globus pallidus externa (GPe) and subthalamic nucleus (STN) is the IP (Alexander and Crutcher 1990). Lesions of DP affecting particularly the projections from the striatum to GPi are associated with hypokinetic disorders (distinguished by a paucity of movement), and lesions of IP produce hyperkinetic disorders like chorea and tremor. These findings led to the thinking that activation of the DP facilitates movement, and hence it became known as the “Go” pathway. Contrarily, IP was dubbed the “NoGo” pathway since its activation typically inhibits movement (Contreras-Vidal and Stelmach 1995).

A need to go beyond the simple Go/NoGo picture of BG function had its seeds in experiments (Houk et al. 1995; Schultz et al. 1997) on the firing properties of mesencephalic dopamine cells. Although activities of dopaminergic cells have been linked to reward sensing for a long time, experiments by Schultz et al. (1997) specifically showed that dopamine neurons of ventral tegmental area (VTA) respond to unconditional rewards (food or juice). When a sensory stimulus (like a sound or a light flash) consistently precedes the appearance of reward such that the stimulus is predictive of the reward, then dopamine cells fire in response to the stimulus and also the reward. Such findings led to the insight that dopamine cell activity is analogous to a quantity known as temporal difference error (TD error) that appears in reinforcement learning (RL) theory – a branch of machine learning (Sutton and Barto 1998). Recognition of the analogy between mesencephalic dopamine signals and TD error signals of RL has inspired a much larger effort to draw parallels between other elements of RL theory and anatomical components of BG. Although the effort to explain various functions of BG using RL concepts is a story in the making, it is believed that RL holds the promise to create a comprehensive theory of BG in the long term (Chakravarthy et al. 2010).

RL theory describes how an agent can learn correct stimulus–response (SR) relationships using reward feedback from the environment.



Basal Ganglia System as an Engine for Exploration, Fig. 1 The schematic showing the direct and indirect pathways of basal ganglia

For a given stimulus, responses that yield rewards are reinforced, while those that result in punishment are attenuated. The problem is often complicated by the fact that rewards come after a delay following the response or even after a whole series of responses. The agent then needs a surrogate to reward, which guides its responses in the intervening period. RL theory proposes the *value* function as such a surrogate; a computational module called the *critic* computes value. (The module that performs actions is known as the *actor*.) Value is defined as the total discounted future reward that an agent expects to receive from a given state. Thus, once the value is known, at any instant, the agent chooses the response or action that brings about the greatest increase in value, a process known as *exploitation*. Sometimes it is desirable for the agent to try out actions that are not optimal, by way of adapting to the changing reward patterns of the real world. This selection of suboptimal actions, typically stochastically, is known as *exploration*. Thus, exploitation and exploration are two key complementary processes, the yin and yang, of RL theory (Sutton and Barto 1998).

The Indirect Pathway and Exploration

In actor/critic (AC) models of BG, the emphasis is often on the respective substrates for the actor and critic components in the striatum (Joel et al. 2002), and the dopamine signal for its role in training the AC components. Thus, though exploitation and exploration are complementary processes, exploitation receives most of the attention. Such omission is perhaps not surprising as even in the AC framework, the actor and critic are recognized explicitly as *modules*, while exploration is a mere *mechanism* obtained by a “noise term” in RL equations. Since variability is ubiquitous in the brain – either arising due to thermal noise or chaotic neural dynamics – the search for a specific substrate for exploration in BG was felt unnecessary.

Experimental evidence particularly from functional neuroimaging seems to support this partial view, with a bias towards cortical substrates over

subcortical ones. In fMRI studies, gamblers were asked to choose between slots that are expected to give highest rewards (“exploit”) and less familiar slots that might turn out to be more profitable (“explore”). The areas in the brain that are preferentially activated during exploitation or exploration are noted (Daw et al. 2006). While substrates for value computations were found in orbitofrontal cortex (Knutson et al. 2001), substrates for exploration were found in anterior frontopolar cortex and intraparietal sulcus (Daw et al. 2006). The anterior cingulate cortex (ACC) is suggested to be involved in balancing between exploitation and exploration (Rushworth and Behrens 2008). Studies by Yoshida and Ishii (2006) found activation in prefrontal cortex and ACC when subjects were exploring a maze (Yoshida and Ishii 2006). In the subcortex, it was suggested that the ventral and dorsal striata correspond to critic and actor, respectively (O’Doherty et al. 2004). Thus, though both cortical and subcortical substrates of exploitation have been discovered, no corresponding subcortical substrates for exploration have been found.

Can there be subcortical substrates for exploration? Stein et al. (1997) showed that decorticated kittens can exhibit exploratory and goal-oriented behavior (Stein et al. 1997). Rats with damaged STN were shown to exhibit perseverative behavior or reduced exploration of new options, with persistent selection of older unrewarding ones (Baunez et al. 2001). When bicuculline, a GABA antagonist, was injected into the anterior GPe of primates, the animals exhibited stereotypic movements, and when it was injected into dorsolateral GPe, the animal produced hyperactivity that included exploratory or searching movements for food (Grabli et al. 2004). Drawing inspiration from the studies of Usher et al. (1999), Doya (2002) suggested a link between norepinephrine levels and the “inverse temperature” parameter which controls exploration in RL literature. It is noteworthy that globus pallidus is reported to have high norepinephrine levels (Russell et al. 1992).

Thus, it appears compelling that the STN–GPe system constituting the IP of BG might be the subcortical substrate for exploratory behavior.

The STN–GPe system and its intriguing oscillatory activity do not seem to occupy a prominent place in AC modeling literature. On the other hand, there is an entire line of modeling work that presents the STN–GPe system as a pacemaker in the brain, in reference to its oscillatory activity (Ring and Serra-Mestres 2002; Willshaw and Li 2002). These oscillations have also been linked to Parkinsonian tremor (Hurtado et al. 1999; Terman et al. 2002). Though the aforementioned STN–GPe models explain the behavioral effects of pathological oscillations, they attribute no role to the oscillations in the RL framework that is thought to govern the processes of BG. Under dopamine-deficient or Parkinsonian conditions, the firing patterns of STN and GPe neurons show dramatically increased correlation without significant increase in firing rate (Bergman et al. 1994; Brown et al. 2001). Since exploration is driven by noise in RL models, a brain region that drives exploration is expected to be a source of noise generated perhaps by complex neural dynamics. Considering the low correlation in STN–GPe under normal conditions, with increased correlation or loss of complexity in pathology, it is plausible that the STN–GPe is a subcortical substrate for exploration.

By an extended application of RL concepts, a comprehensive model of BG can be built in which the exploitative dynamics of the DP can be combined with STN–GPe oscillations that drive exploratory behavior (Chakravarthy et al. 2010). Thus emerges a view that while DP supports exploitation, IP subserves exploration, differing from the classical Go/NoGo view of BG. In a recent modeling study, it was shown that the exploitation (DP) versus exploration (IP) can be reconciled with Go (DP) versus NoGo (IP) view, by inserting a third regime dubbed the *Explore* regime. This regime would correspond to exploration and resides between the classic Go and NoGo regimes (Kalva et al. 2012). A series of BG models based on this view have been developed to account for a wide variety of BG-related motor and cognitive behaviors such as spatial navigation, saccades, reaching, and reward–punishment learning (Sridharan et al. 2006; Chakravarthy et al. 2010; Krishnan

et al. 2011; Kalva et al. 2012; Priyadharsini et al. 2012; Gupta et al. 2013; Muralidharan et al. 2013).

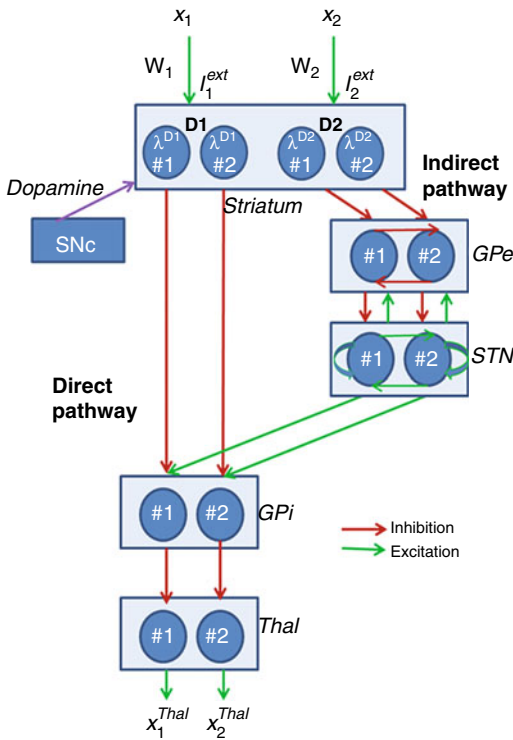
The Basic Model

The intuitive ideas outlined before can be embodied in a simple mathematical model of BG. The framework explicitly represents striatum, STN, GPe and GPi, and DP and IP, to capture the structural aspects of BG, and also models:

- The nigrostriatal dopamine signal as TD error, using it to train corticostriatal connections
- The action of dopamine in switching between DP and IP, via its differential action on the D1 and D2 receptors of striatal medium spiny neurons
- Oscillations in the STN–GPe system
- Value computations in the striatum
- The classical Go (DP) and NoGo (IP) with the added “Explore” behavior.

Striatum

The binary action selection problem consists of choosing between two inputs based on their “salience.” Thus, the input, a 2D vector, I^{ext} , representing the corticostriatal afferents, is presented to the striatum that consists of two 1D layers of sigmoidal neurons representing medium spiny neurons (MSNs) (Fig. 2). The first layer represents neurons that express D1-type dopamine receptors (R), whereas the second layer represents D2R-expressing MSNs. The D1R- and D2R-MSN layers project to GPi and GPe, respectively, and they also receive dopaminergic projections from SNc. Each component of I^{ext} is uniquely connected to one neuron each in D1 and D2 layers. The dopamine signal (δ) controls the sigmoidal gain of neurons in D1 and D2 layers. Whereas the gain of D1 neurons increases with δ , that of D2 neurons decreases with δ . With such an arrangement, it can be noticed that the DP is selected at higher dopamine levels and the IP at lower levels (Humphries and Gurney 2002; Humphries and Prescott 2010).



Basal Ganglia System as an Engine for Exploration, Fig. 2 The schematic of signal flow in the BG network model

The STN–GPe System

STN and GPe form a loop with excitatory projections from STN to GPe and inhibitory projections in the reverse direction. Excitatory/inhibitory pairs of neuronal pools are known to exhibit limit cycle oscillations (Gillies et al. 2002). The STN and GPe system receives two inputs: the inhibitory (GABAergic) projection from D2R MSNs of striatum to GPe and the excitatory (glutamatergic) cortical input via the hyperdirect pathway to STN. Several factors elicit oscillations in a STN–GPe neuron pair.

1. Increased striatal input to GPe: This property is corroborated by electrophysiological data from Bergman et al. (1994). Kravitz et al. (2010) observed that increased firing of D2R-MSNs in the striatum induce a state similar to Parkinson’s, with motor symptoms like freezing, bradykinesia, and difficulty in movement initiation (Kravitz et al. 2010).

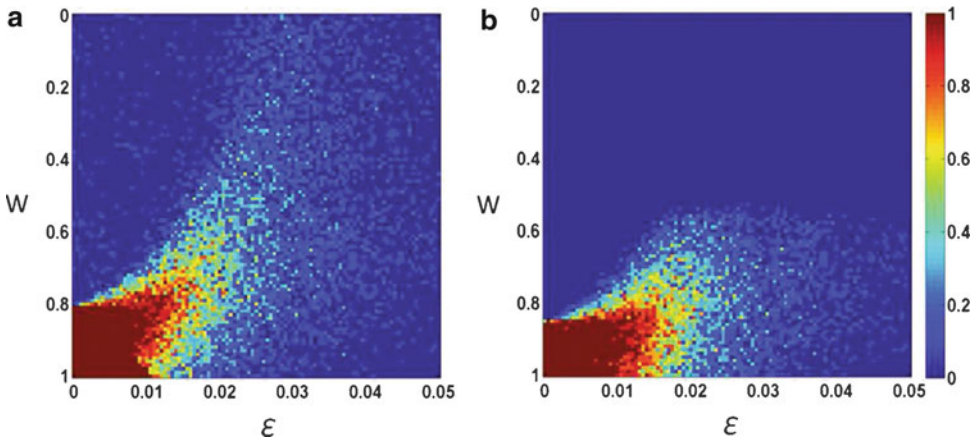
2. Increasing cortical input to STN: Electrophysiological studies show that ablation of cortical areas that project to STN largely abolished low-frequency oscillations in STN–GPe (Magill et al. 2001).
3. Reducing dopamine levels in STN–GPe: Organotypic culture studies show that the STN–GPe system exhibits low-frequency oscillations under dopamine-deficient conditions as in that of Parkinson’s disease (Plenz and Kital 1999). STN and GPe oscillations seem to be triggered by the effect of dopamine loss on D2R which strengthens the STN–GPe coupling (Steiner and Tseng 2010).

Now consider a network model of the STN–GPe system in which STN and GPe layers have equal number of neurons with each STN neuron uniquely connected bidirectionally to a GPe neuron. Assume that both STN and GPe have complete internal connectivity with all connections within a nucleus having the same strength: ϵ_s for STN, ϵ_g for GPe; the one-to-one common connection strength for STN $\rightarrow$ GPe is w_{sg} and that of GPe $\rightarrow$ STN is w_{gs} . With $(\epsilon = \epsilon_s = -\epsilon_g)$ and $(w = w_{sg} = -w_{gs})$ and searching the (ϵ, w) space for finding the oscillatory behavior of the STN–GPe system, simulations show that for strong connections between STN and GPe (w) and weak lateral connections (ϵ), the network exhibits oscillations (Fig. 3) with poor correlation between the STN–GPe neuronal activity (Fig. 4).

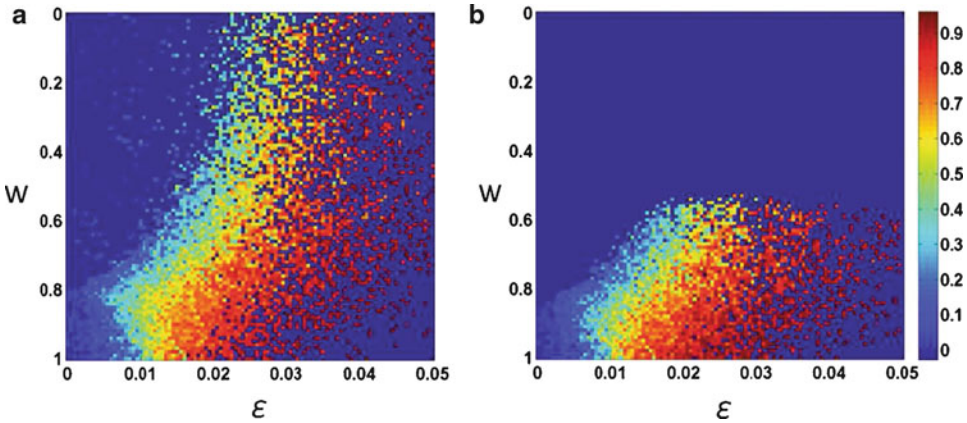
If the STN–GPe system is to serve as a source of exploration, a high spatiotemporal complexity in STN activity manifested in the form of low pair-wise correlations among neurons is expected. The Figures 3 and 4 also illustrate the ability of ϵ_s to control correlation within STN and show that ϵ_s can be used to control the exploration in the BG model.

GPe

GPe combines the GABAergic striatal output via DP with glutamatergic STN output from IP. There is evidence that this combination of DP and IP outflows in GPi is modulated by dopamine projections to GPi. When D1R in GPi, primarily located on the GABAergic striato-pallidal axonal



Basal Ganglia System as an Engine for Exploration, Fig. 3 The regions of parameter space (ϵ , w) over which probability of oscillations in (a) STN and (b) GPe is depicted (averaged over 50 trials)



Basal Ganglia System as an Engine for Exploration, Fig. 4 Correlations within (a) STN and (b) GPe over the parameter space (ϵ , w) averaged for 50 instances. For given

values of parameter pair (ϵ , w), correlation is calculated only when there is at least 1 oscillating neuron in the case of STN for (a) and GPe for (b)

projections, is activated, firing levels of GPi neurons are reduced (Kliem et al. 2007). Since DIRs are activated at increased dopamine levels, the facilitation of the DP outflow over IP at higher dopamine levels is consistent with the nature of switching facilitated by dopamine in the striatum.

Action Selection in Thalamus

If the primary function of the BG circuit is action selection, where in the circuit is the precise site of such selection? If action salience is computed in the striatum and STN–GPe provides exploration, action selection could be happening downstream in GPi or

in the thalamic nuclei receiving afferents from GPi. The competitive dynamics of neurons of thalamic reticular complex makes them ideally suited for implementing action selection (Humphries and Gurney 2002). During binary action selection in the model, the GPi outputs to thalamus converge on two neurons that represent the two action alternatives. These two thalamic neurons integrate the GPi inputs through time: the one that crosses a preset threshold first wins the competition, while the second neuron is reset immediately. Accordingly, if $x_i^{Thal}(t) > x_{th}$ for $i (= 1, 2)$ at time t , then the states of all the other thalamic neurons

immediately reset when “ i ”th action being selected is expressed by $x_j^{Thal}(t) = 0; j \neq i$. If all $x_i^{Thal}(t)$ fail to reach x_{th} , no action is selected.

Simulation Experiments

Binary Action Selection

Salience-based action selection is considered to be one of the primary functions of BG (Redgrave et al. 1999; Gurney et al. 2001). Consider a *binary action selection* problem. The corticostriatal input, I_i^{ext} with $i = 1, 2$, represents two possible actions, and the components of I_i^{ext} represent action salencies. The selected action is denoted by the winning neuron in the thalamus. Due to the complex dynamics of the STN–GPe system, it is not necessary that the winning action is always the one with greater salience. There could be three possible outcomes:

“Go” – winning neuron has greater salience.

“Explore” – winning neuron has lesser salience.

“NoGo” – no winner and therefore no action selection.

Now consider the effect of δ (dopamine) in determining the type of action selection: When the network depicted in Fig. 2 is simulated with the STN–GPe system exhibiting uncorrelated oscillations, a new Explore regime in addition to the classical Go and NoGo regimes (Fig. 5b) can be observed. This is consistent with the classical picture of selecting the Go regime with high probability for large δ and the NoGo for small δ . In addition, the Explore regime is also selected with the probability maximized for moderate δ (Fig. 5a). This Go/Explore/NoGo profile is called the GEN profile.

The notion that higher correlations (caused by higher ϵ_s) among STN neurons result in weaker exploration is depicted by the GEN profiles of Fig. 6a, b, c. Note the progressive reduction in the Explore regime with increasing ϵ_s (Fig. 6).

Modeling the N-Armed Bandit Problem

In the n -armed bandit problem, a generalization of the binary action selection problem, the setup consists of n slot machines each delivering a

fixed reward (deterministically or probabilistically) on selection. The objective is to maximize the total reward received by the agent. Additional features that need to be added to the binary action selection for simulating the n -armed bandit problem are (1) value computation in the striatum, (2) feedback of previous action to the striatum, and (3) resolving the nigrostriatal signal into two dopamine signals – δ_{TD} and δ_V .

If x denotes the action selected ($x_i = 1$, if the i th arm is selected; $x_j = 0$ for $j \sim i$), the action value is computed as

$$V = \sum_{i=1}^n w_i x_i \quad (1)$$

where w_i denote the corticostriatal weights. Instantaneous output error, δ_{TD} , is defined as

$$\delta_{TD} = r - V \quad (2)$$

where r is the reward. Note that δ_{TD} in Eq. 2 above is a special case of the more general temporal difference (TD) error (Eq. 3) in RL,

$$\delta_{TD} = r(t) + \gamma V(t+1) - V(t) \quad (3)$$

that arises when $\gamma = 0$.

This δ_{TD} is used to update the corticostriatal connections as

$$\Delta w_i = \eta \delta_{TD} x_i \quad (4)$$

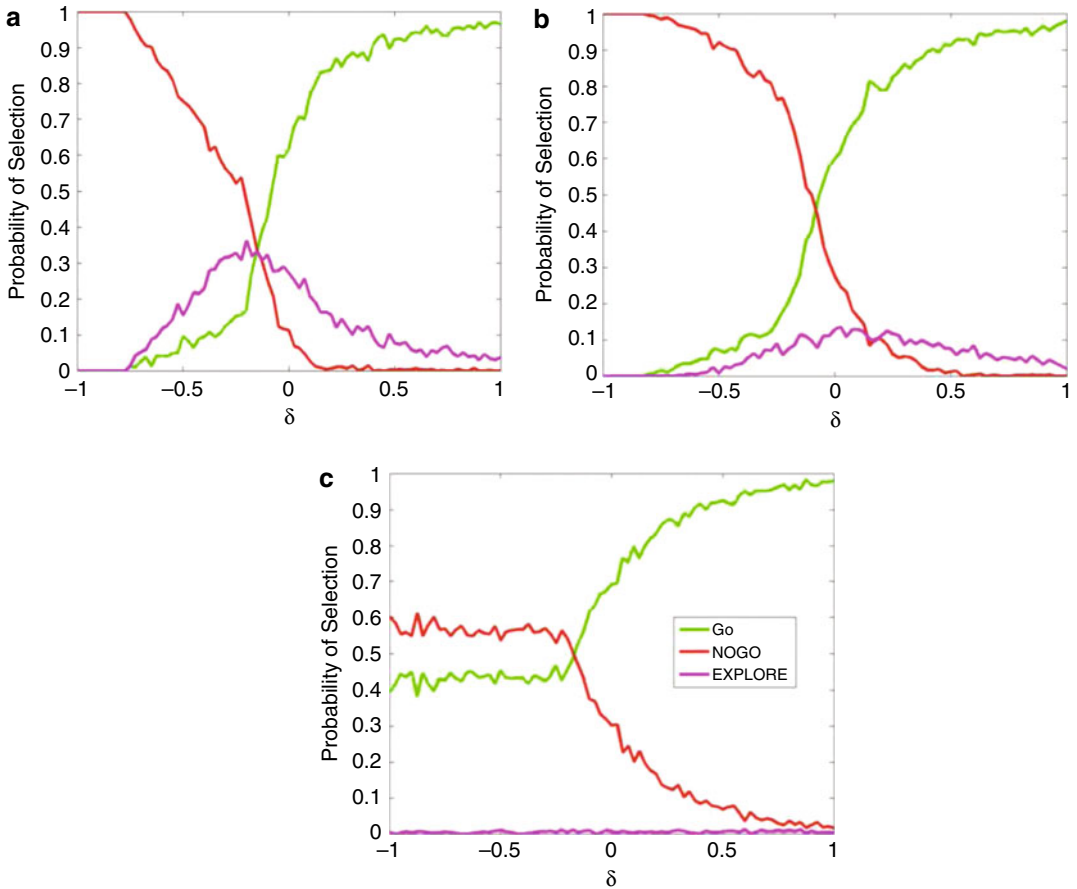
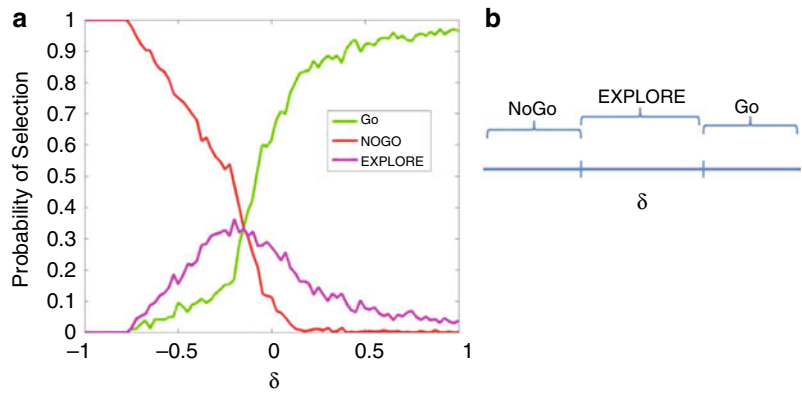
In addition to δ_{TD} , δ_V is introduced as a similar yet novel quantity representing the temporal gradient of value function and is expressed as

$$\delta_V(t) = V(t) - V(t-1) \quad (5)$$

The difference between *TD error* (Eqs. 2 and 3) and *value gradient* (Eq. 5) is as follows. While TD error controls learning of corticostriatal weights (Eq. 4), value gradient controls the gain of D1R- and D2R-MSNs. D1R-MSNs are modeled to be activated at higher δ_V and D2R-MSNs at lower levels. Thus, δ_V controls exploration by determining the relative contributions of DP or IP.

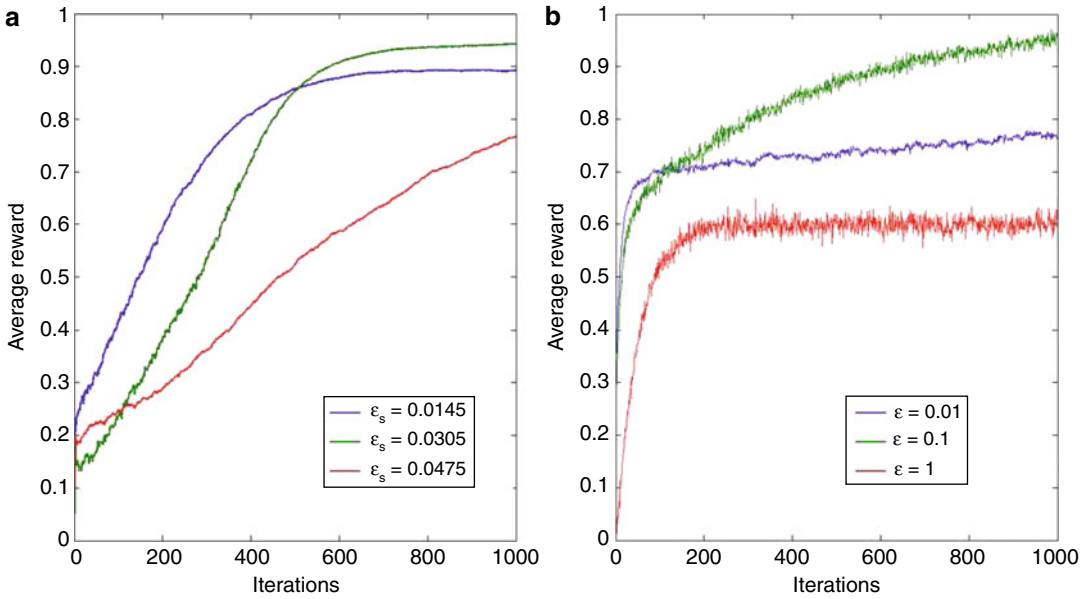
Basal Ganglia System as an Engine for Exploration, Fig. 5

(a) Probability of selection of Go/Explore/NoGo; (b) schematic: Go–Explore–NoGo (*GEN*) regime selection for higher–intermediate–lower values of δ , respectively



Basal Ganglia System as an Engine for Exploration, Fig. 6 Probability of selection of Go/Explore/NoGo regimes as a function of δ : (a) for $\epsilon_s = 0.001$, (b) for $\epsilon_s = 0.05$, (c) for $\epsilon_s = 0.95$

A large positive δ_v implies a large increase in value, which therefore recommends selection of the same action next time (Go), since the contribution of DP to GPi dominates that of STN. A large negative δ_v implies a large reduction in value, suggesting exploration for new actions.



Basal Ganglia System as an Engine for Exploration, Fig. 7 The mean reward versus iterations obtained with (a) different ϵ_s using the BG network model and (b)

different ϵ values using ϵ -greedy policy, for a five-armed bandit task averaged for 500 trials

Since the IP is selected for strong negative δ_v , IP contribution dominates that of DP at GPi, thereby suppressing action (NoGo). For small magnitudes of δ_v , DP is still reduced, and driven by the complex dynamics of STN, a random action is selected next time (Explore).

Figure 7a shows the change in value function with time for the above model applied to a five-armed bandit problem. The rewards are generated by the following distribution: $r_i = i/n + A \cdot v$, where r_i is the reward of the i th arm, v is a random variable uniformly distributed over $[0, 1]$, and $A = 0.3$. Note the effect of the strength of STN lateral connection, ϵ_s , on the growth of value function. For small ϵ_s ($= 0.0145$), value increases rapidly but settles at a lower value. For large ϵ_s ($= 0.0475$), value rises slowly, but for moderate ϵ_s ($= 0.0305$), it rises slower than the previous case but settles at a level higher than two previous cases. In this respect, the effect of ϵ_s on action selection seems to be analogous to that of the ϵ parameter in ϵ -greedy methods used in RL (Fig. 7b). The parameter ϵ , usually a small positive number, refers to the probability with which a nonoptimal action is selected (Sutton and Barto 1998).

Climbing Value Gradient Using δV

It can be observed from the network model used for the n -armed bandit problem that the value function increases gradually when the action selected is iterated through the loop (thalamo-striatal) in Fig. 2. Thus, the network dynamics implements hill-climbing over the value function, which is a form of stochastic hill-climbing, thanks to the complex dynamics of STN-GPe system. In fact, the aforementioned effect of δ_v on value change (by selecting the previous/random/no action for large positive/moderate/large negative values of δ_v , respectively) is strongly reminiscent of simulated annealing – a form of stochastic optimization (Kirkpatrick et al. 1983). It is noted that the BG model exhibits three behaviors depending on dopamine: (1) Go regime (“repeat the previous action”) for large positive δ_v , (2) Explore regime (“try random actions”) for intermediate values of δ_v , and (3) NoGo regime (“no action”) for large negative values of δ_v . These regimes inspire a simple mechanism of hill-climbing in continuous action spaces as follows.

Let $V(x)$ be value function, x be n -dimensional state vector ($x \in S$, where $S \subset \mathbb{R}^n$), $\delta_v = V(t) - V$

($t - 1$), and $\Delta x = x(t) - x(t - 1)$. Δx is then updated by the following equations:

$$\begin{aligned} &\text{if } (\delta_v > D_{hi}) \\ &\Delta x(t+1) = \Delta x(t) - \text{"Go"} \text{ (a)} \\ &\text{elseif } (\delta_v > D_{lo} \wedge \delta_v(t) \leq D_{hi}) \\ &\Delta x(t+1) = \phi - \text{"Explore"} \text{ (b)} \\ &\text{else } (\delta_v \leq D_{lo}) \\ &\Delta x(t+1) = 0 = \text{"NoGo"} \text{ (c)} \end{aligned} \quad (6)$$

where $D_{hi} > 0$, $D_{lo} < 0$, and Φ is a random vector whose each component, Φ_i , is given by Eq. 7:

$$\phi_i = G(0, 1) \exp(-\delta_v^2 / \sigma^2) \quad (7)$$

where $G(0,1)$ is a Gaussian random variable with mean 0 and standard deviation 1. The last Eq. 6c seems redundant as there is no state update in that case. It can be altered by substituting 0 in Eq. 6c with $-\Delta x(t)$. Now in NoGo regime, the state x is updated in an opposite direction compared to the previous update. The Eq. 6a, b, c may be expressed in modified form as follows:

$$\begin{aligned} &\text{if } (\delta_v > D_{hi}) \\ &\Delta x(t+1) = \Delta x(t) - \text{"Go"} \text{ (a)} \\ &\text{elseif } (\delta_v > D_{lo} \wedge \delta_v(t) \leq D_{hi}) \\ &\Delta x(t+1) = \phi - \text{"Explore"} \text{ (b)} \\ &\text{else } (\delta_v \leq D_{lo}) \\ &\Delta x(t+1) = -\Delta x(t) = \text{"NoGo"} \text{ (c)} \end{aligned} \quad (8)$$

In Eq. 8 above, the Go, Explore, and NoGo regimes are depicted as discrete, disjoint regimes demarcated by thresholds $-D_{hi}$ and D_{lo} . But the regimes observed in the GEN profile obtained from binary action selection problem are not disjoint; their probability distributions as a function of δ_v overlap (Fig. 5). This inspires a combination of Eq. 8a, b, c into a single update equation where the three regimes smoothly overlap as follows:

$$\begin{aligned} \Delta x(t+1) &= \log \text{sig}(k_3(\delta_v(t) - D_{hi})) \Delta x(t) \\ &+ \psi \exp(-\delta_v^2(t) / \sigma_E^2) \\ &- \log \text{sig}(k_4(\delta_v(t) - D_{lo})) \Delta x(t) \end{aligned} \quad (9)$$

where $\text{logsig}(x) = 1/(1 + \exp(-x))$. Thus, Eq. 9 describes a map between the current state update

($\Delta x(t)$) to the next state update ($\Delta x(t+1)$). $\Delta x(t+1)$ is nearly in the same direction as $\Delta x(t)$ for large positive δ_v and is nearly in the same direction as $-\Delta x(t)$ for large negative δ_v ; $\Delta x(t+1)$ is random for the intermediate values of δ_v . Note that the map of Eq. 9 is stochastic due to the middle term on the right-hand side.

Equation 9, known as the GEN rule, represents an abstract, summarized representation of how BG selects actions based on DA signals. The GEN rule or the approach that it is based on has been applied successfully to model a range of BG functions.

Discussion

Application of RL concepts to BG function (Houk et al. 1995; Schultz et al. 1997; Hollerman and Schultz 1998) sought a revision of the Go/NoGo picture as the models may not have given sufficient attention to exploration – the complementary process to exploitation. The Go/NoGo picture of BG can explain how the BG circuit can learn simple binary action selection using RL, but it is inadequate to know how the BG circuit can solve more challenging RL problems in continuous state and action spaces.

The binary Go/NoGo thinking about BG function is supported by a simplistic interpretation of the functional neurochemistry of the two BG pathways (Albin et al. 1989; Contreras-Vidal and Stelmach 1995). But presence of the feedback from STN to GPe allows the possibility of complex dynamics in the STN–GPe loop, thereby introducing an added complication in our functional understanding of BG pathways. The STN–GPe loop has also been dubbed as the “pacemaker” of BG considering its role in generating pathological oscillations associated with Parkinsonian tremor (Hurtado et al. 1999; Terman et al. 2002). This STN–GPe system is an excitatory–inhibitory pair that is capable of exhibiting oscillations and other forms of complex dynamics (Brunel 2000). The fact that neurons in this system exhibit uncorrelated firing patterns in normal conditions, and highly correlated and synchronized firing under dopamine-deficient pathological conditions, seems to offer

an important clue to the possible role of this circuit in exploration. From the above studies, it can be concluded that the STN–GPe system is in the best position to serve as an explorer, thereby supplying the missing piece in the RL-machinery of BG. Behavioral strategies of reaching, saccades, spatial navigation, gait, and willed action are shown to be better modeled using the above theory as follows.

A model of reaching movements highlighting the role of BG was described in Magdoo et al. (2011), where a neural network representing motor cortex is trained to drive a two-joint arm to a target. The output of the BG that is predominant in early stages of learning is combined with that of motor cortex whose relative contribution grows with learning. The BG dynamics governed by the earlier described GEN rule discovers desired activations which are used by the motor cortex for learning. When the dopamine signal is clamped to reflect dopamine deficiency in Parkinsonian conditions, the model exhibited Parkinsonian features in reaching like bradykinesia, undershoot, and tremor.

The idea that the DP and IP subserve exploitation and exploration respectively was used in a model of BG on saccade generation (Krishnan et al. 2011) when applied to standard visual search tasks like feature and conjunction search, directional saccades, and sequential saccades. On simulating Parkinsonian conditions by diminished BG output, the model exhibited impaired visual search with longer reaction times – a characteristic symptom in Parkinson’s disease (PD) patients.

The GEN approach (Eqs. 6, 8, and 9) was used to model the relative contributions of BG and hippocampus to spatial navigation (Sukumar et al. 2012). The model combines two navigational system: the cue-based system subserved by BG and the place-based system by hippocampus. The two navigational systems are associated with their respective value functions that are combined by the softmax policy (Sutton and Barto 1998) to select the next move. This model describes the results of an experimental study that investigates competition between cue-based and place-based navigation (Devan and White 1999). Under dopamine-deficient conditions, the

model exhibited longer escape latencies similar to PD-model rats (Miyoshi et al. 2002).

The GEN approach to BG was also applied to model impaired gait patterns in PD (Muralidharan et al. 2013). Studies by Cowie et al. (2010) investigated gait changes, as PD patients walked through a narrow doorway and observed a strong dip in velocity a short distance from the doorway. In the model of Muralidharan et al. (2013), the simulated agent passed through the doorway without any significant velocity dip under control conditions and exhibited a significant reduction in velocity close to the doorway under PD conditions.

Clinical literature shows that BG has a role in willed action, and its impairment is seen in conditions of BG lesions or diseases like Parkinson’s disease that affect BG (Mink 2003). Recently it was suggested that the BG circuit amplifies will signals, presumably weak, by a stochastic resonance process (Chakravarthy 2013). This study shows that the GEN policy, which is a combination of deterministic hill-climbing process and a stochastic process, may be reinterpreted as a form of stochastic resonance. Applying the model to a simple reaching task, it was shown that the arm reaches the target with probability close to unity at optimal noise levels. The arm dynamics for subthreshold noise is reminiscent of Parkinsonian akinesia, whereas for superthreshold noise the arm shows uncontrolled movements resembling Parkinsonian dyskinesias.

A perspective that the BG circuit is an exploration engine, carved out of the popular RL approach to BG modeling, can thus be substantiated.

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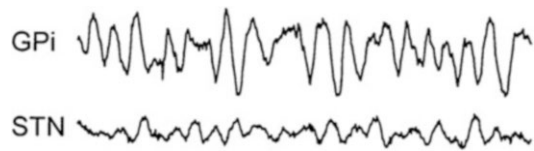
Basal Ganglia: Beta Oscillations

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Definition

Beta oscillations are defined as the oscillations in neural activity with frequencies between 13 and 30 Hz (Fig. 1). In the basal ganglia, the power of



Basal Ganglia: Beta Oscillations, Fig. 1 One second of local field potentials recorded from internal segment of globus pallidus (*top panel*) and subthalamic nucleus (*bottom panel*) from a patient with Parkinson's disease who was off medications. (Reproduced from Brown et al. (2001) with permission)

beta oscillations is significantly increased in Parkinson's disease (Hammond et al. 2007).

Detailed Description

Relationship to Behavior

The power of beta oscillations is reduced prior to and during movements in both the cortex and basal ganglia (see Engel and Fries 2010 for review) and increased during tonic contractions (Baker et al. 1997). Consequently, it has been suggested that beta oscillations are related to maintaining the current body posture (Engel and Fries 2010). The causal influence of beta oscillations on inhibition of movement is suggested by observations that stimulation at beta frequency with transcranial magnetic stimulation (Pogosyan et al. 2009) and with deep-brain stimulation (Chen et al. 2007) results in slower movements.

Relationship with Symptoms

The relationship between beta oscillations and inhibition of movements discussed above suggests that the increased beta power in Parkinson's disease may directly relate to the impaired movements observed in the disease (Brown 2007). This hypothesis is supported by the observation that the power of beta oscillations is reduced by the treatments that alleviate symptoms, namely, dopaminergic medications and high-frequency (>100 Hz) deep-brain stimulation of subthalamic nucleus (STN)

(Hammond et al. 2007). Furthermore, the patients with the best improvement in motor skills due to medications also have the largest reduction in beta power in STN after taking the medications (Kuhn et al. 2006).

Models of the Effects of Beta Oscillations

Simulations demonstrated that the exaggerated oscillatory activity leads to movement difficulties possibly because the thalamic neurons (see Fig. 2) become entrained to the excessively oscillatory input from basal ganglia and are no longer able to transmit sensorimotor signals from the cortex (Rubin and Terman 2004). Additionally, an analysis of neural activity in the external segment of globus pallidus (GPe) using information

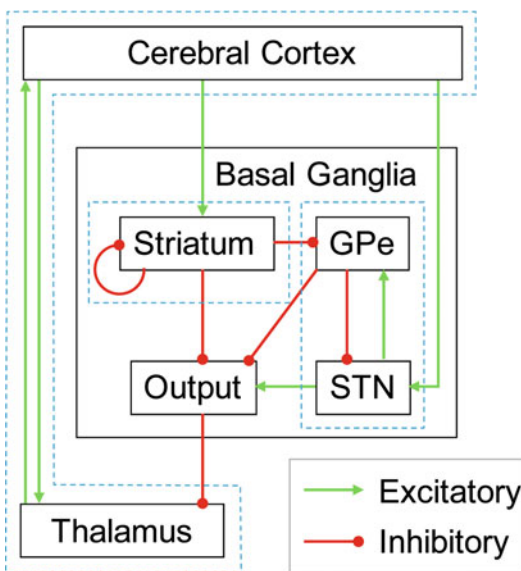
theory showed reduced entropy during beta oscillations in rats, suggesting that the beta oscillations limit the amount of information transmitted by the neurons in the basal ganglia (Cruz et al. 2009).

Origin of Beta Oscillations

Parkinson's disease is caused by the death of dopaminergic neurons which project throughout the basal ganglia and modulate synaptic transmission and plasticity. However, the exaggerated beta oscillations do not appear immediately after the death of these neurons, but only several days later (Mallet et al. 2008a). This suggests that the beta oscillations result from the adaptations in the network following the reduced dopamine level.

It is still uncertain which of the changes in the connectivity and the levels of neuronal activity, occurring in Parkinson's disease, trigger beta oscillations. Furthermore, due to the complex connectivity in the cortico-basal-ganglia-thalamic circuit (Fig. 2), it is still unclear in which part of the circuit the beta oscillations are generated. The circuit contains many feedback loops, and it is known that neuronal populations connected in loops can generate oscillations (Tiesinga and Sejnowski 2009).

One of the parts of the circuit which is thought to be critical for generation of Parkinsonian beta oscillations is a sub-circuit composed of STN and GPe (Bevan et al. 2002). Its role is suggested by observations that the beta oscillations are prominent in this network (Mallet et al. 2008b), this sub-circuit was shown to be able to produce slower (delta) oscillations in vitro (Plenz and Kital 1999), and blocking connections between STN and GPe abolishes excessive beta oscillations (Tachibana et al. 2011). Additionally, interactions between the STN-GPe network and cortex are likely to play important role in generating Parkinsonian beta, because the cortex and STN become coherent in the disease (Mallet et al. 2008b) and blocking connections between the cortex and STN abolishes excessive beta oscillations (Tachibana et al. 2011).



Basal Ganglia: Beta Oscillations, Fig. 2 Subset of connectivity in the cortico-basal-ganglia-thalamic circuit. Black rectangles denote brain structures, and the rectangle labeled “Output” denotes the output nuclei of the basal ganglia comprised of the internal segment of globus pallidus and substantia nigra pars reticulata. Green arrows and red lines with circles denote excitatory and inhibitory connections, respectively. Blue dashed contours indicate sub-circuits that have been shown to generate beta oscillations in simulations

Computational Models of Beta Generation

Three sub-circuits containing feedback loops (indicated by blue contours in Fig. 2) have been shown to generate beta oscillation in simulations. First, models of the STN-GPe network were shown to generate beta oscillations (a population-level model: Nevado-Holgado et al. 2010; and a model using integrate-and-fire neurons: Kumar et al. 2011). Mathematical analyses of the population-level model revealed conditions the parameters of the STN-GPe model need to satisfy to generate oscillations (Nevado-Holgado et al. 2010; Pavlides et al. 2012; Passillas-Lepine 2013). Second, a computational model of striatum (using Hodgkin-Huxley neurons: McCarty et al. 2011) has been shown to generate beta oscillations. Third, the beta oscillations have been also observed in simulations of the entire cortico-basal-ganglia circuit (a population-level model: van Albada et al. 2009), and the analysis of the model suggested that the beta oscillations originate in the corticothalamic loop in this model.

Additionally, beta oscillations have been also observed in simulations of the entire cortico-basal-ganglia circuit (using integrate-and-fire neurons: Humphries et al. 2006). Furthermore, oscillations close to the beta range (~ 12 Hz) were generated in a model of a subset of cortico-basal-ganglia circuit (in which firing rates of individual neurons were described: Leblois et al. 2006). The analysis of the model suggested the oscillations were generated in a loop composed of cortex, STN, output nuclei, and thalamus in this model.

Model-Based Data Analysis

Computational models have been used to infer the changes in network structure occurring in Parkinson's disease. Eusebio et al. (2009) fitted a simple damped oscillator to event-related potentials recorded from the cortex of Parkinson's patients after stimulation of STN. They observed that the fitted oscillator had a natural frequency in

the beta range, and the data from patients on medications were described by a model with higher damping parameter than data from patients off medications. Also, the dynamic causal modeling was used to infer from local field potentials the differences in effective connectivity in cortico-basal-ganglia-thalamic circuit between healthy and Parkinsonian rats (Moran et al. 2011), and between patients on and off medications (Marreiros et al. 2013). Both of these studies reported increased effective connectivity between the cortex and STN in the states associated with higher beta power.

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Basal Ganglia: Bradykinesia Models

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Synonyms

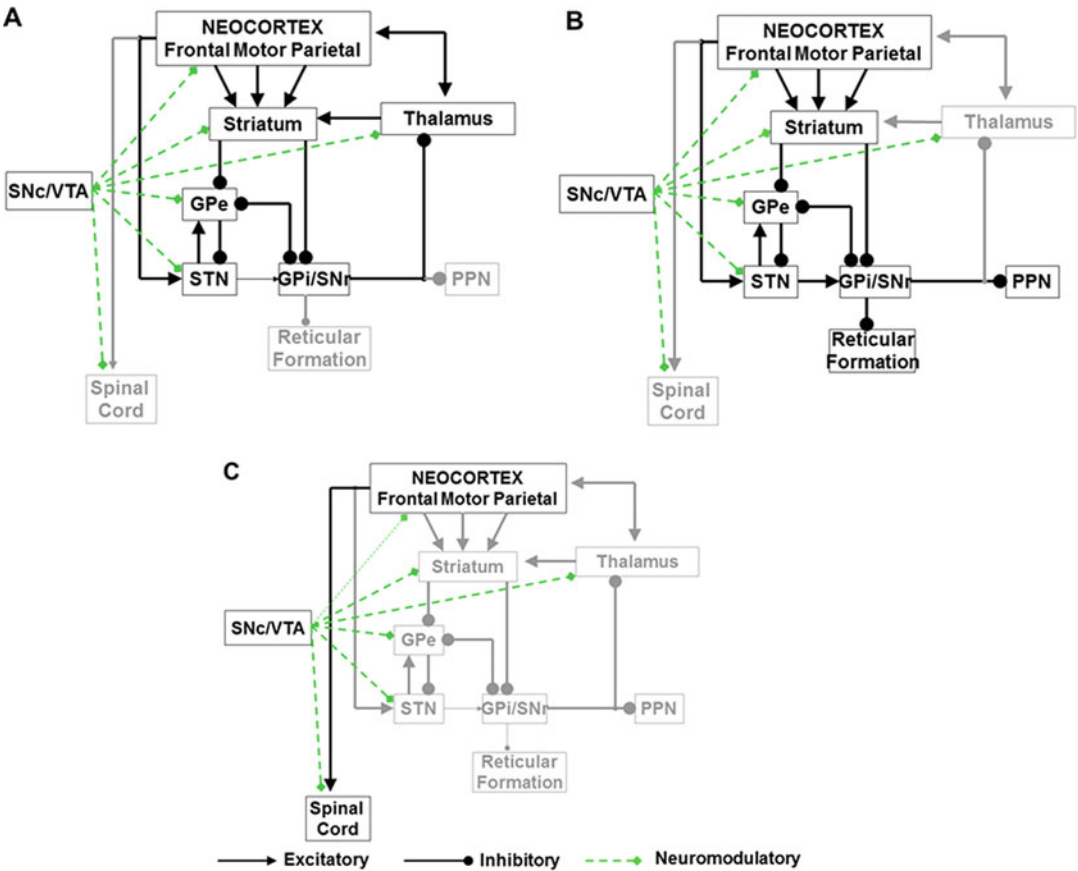
[Hypokinesia model](#); [Slowness of movement model](#)

Definition

Bradykinesia is the cardinal symptom of Parkinson's disease (PD). It is related to an abnormal slowness of movement. The causes of PD bradykinesia are not known largely, because there are multiple brain areas and pathways involved from the neuronal degeneration site (dopamine (DA) neurons in substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)) to the muscles (see Fig. 1). Bradykinesia models are mathematical and computational constructs attempting to uncover how information is processed in the affected brain areas and what are the biophysical mechanisms giving rise to the observed slowness of movement in PD bradykinesia.

Detailed Description

Bradykinesia, the hallmark and most disabling symptom of PD, refers to an extreme slowness of movement. In early stages of the disease, PD



Basal Ganglia: Bradykinesia Models, Fig. 1 Brain circuits implicated in PD bradykinesia. (a) Pathways from the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) to the striatum and from there to the thalamic nuclei and the frontal cortex through the substantia nigra pars reticulata (SNr) and the globus pallidus

internal segment (GPi). (b) Pathway from the SNc and the VTA to the striatum and from there to the brainstem through the SNr and GPi. (c) Pathway from the SNc/VTA to cortical areas such as the supplementary motor area (SMA), the parietal cortex, and the primary motor cortex (M1) and from there to the spinal cord

patients have difficulties with daily activities such as walking, speaking, or getting in and out of chairs (Gibberd 1986). In the later phases of the disease, the entire movement process becomes increasingly slow and occasionally results in a complete inability to move. Patients must concentrate intensely to overcome the inertia of their limbs even when they are executing the simplest motor tasks. Movement is particularly impaired when novel movements are attempted (Connor and Abbs 1991) or when several movements are combined (Benecke et al. 1986; Lazarus and Stelmach 1992).

Anatomical Overview

Initiation and execution of voluntary movements involve brain areas and pathways. The “motor circuit” originates in the motor areas of the frontal cortex, which activate motor portions of the basal ganglia subcortical structures (striatum (STR), globus pallidus external (GPe) and internal (GPi) segments, the subthalamic nucleus (STN), the substantia nigra pars reticulata (SNr)), and the thalamus and which in turn project back to the frontal motor areas of the cortex. The basal ganglia (BG) structures are implicated in the selection of the most appropriate motor command given the current context. Motor commands from

the frontal motor areas of the cortex (premotor, supplementary, and primary motor areas) activate the corresponding motor spinal centers, which then activate the muscles.

Dopaminergic Pathways

A widespread DAergic innervation from SNc and VTA to BG, thalamus, cortex, and spinal cord exists (Williams and Goldman-Rakic 1998; Bjorklund and Lindvall 1984; Sanchez-Gonzalez et al. 2005; Anaya-Martinez et al. 2006). DA heavily innervates STR and modulates its activity (Gerfen et al. 1990). In addition, DA modulates other BG structures including GPe and GPi segments, STN, and SNr (Rommelfanger and Wichmann 2010).

DAergic neurons also innervate and modulate various thalamic nuclei including the ventrolateral nuclei (motor region) (Sanchez-Gonzalez et al. 2005). In rats a common DA projection exists to GP and the reticularis nucleus of the thalamus (Anaya-Martinez et al. 2006).

DA also innervates the cerebral cortex (Berger et al. 1988; Elsworth et al. 1990; Gaspar et al. 1991, 1992; Scatton et al. 1983; Lewis et al. 1988; Lidow et al. 1989; Williams and Goldman-Rakic 1998). DA afferents are densest in cortical areas 24, 4, 6, and SMA, where they display a trilaminar pattern of distribution, predominating in layers I, IIIa, and V–VI (Berger et al. 1988; Williams and Goldman-Rakic 1998; Elsworth et al. 1990; Gaspar et al. 1991, 1992). In the granular prefrontal (areas 46, 9, 10, 11, 12), parietal (areas 1, 2, 3, 5, 7), temporal (areas 21, 22), and posterior cingulate (area 23) cortices, DA afferents are less dense and show a bilaminar pattern of distribution in the depth of layers I and V–VI (Berger et al. 1988; Gaspar et al. 1991, 1992; Scatton et al. 1983; Lewis et al. 1988; Lidow et al. 1989).

Finally, DA innervates the dorsal (sensory input) and ventral (motor output) horns of the spinal cord (Blessing and Chalmers 1979; Shirouzou et al. 1990; Weil-Fugazza and Godefroy 1993; Takada et al. 1988; Commissiong et al. 1979).

Physiological and Behavioral Phenomena

PD bradykinesia has been linked with the degeneration of dopamine neurons in SNc and VTA.

Bradykinesia manifests only when 80–90% of dopamine neurons die. The degeneration of dopamine neurons leads to a number of changes relevant to bradykinesia in the neuronal, electromyographic (EMG), and movement parameters reported in parkinsonian human and animal brains:

- Increases in background activity (spontaneous firing) of STR and STN cells (Kita and Kita 2011).
- An oscillatory response to motor cortical stimulation of STR cells consisting of an excitation, a long inhibition and a slow excitation (Kita and Kita 2011).
- The latencies of the STR excitations are significantly shorter than in the controls (Kita and Kita 2011).
- An oscillatory response to STR oscillatory stimulation of GPe cells consisting of an early excitation, a short inhibition and a late excitation (Kita and Kita 2011).
- An oscillatory response to motor cortical and GPe oscillatory stimulation of STN cells consisting of either an early and late excitation or a single excitation followed by a very long inhibition (Kita and Kita 2011).
- The latency of the GPe inhibition is decreased in the DA depleted case (6-OHDA), whereas the duration and strength of the late excitation are increased (Kita and Kita 2011).
- An oscillatory pattern of GPi cells consisting of an early excitation and a long inhibition or a pattern consisting of a solo long inhibition (Kita and Kita 2011).
- The duration of the GPi excitation and long inhibition is significantly increased in the DA depleted case (Kita and Kita 2011).
- The peak GPi excitatory activity is reduced in the DA depleted case (Kita and Kita 2011).
- Reduction of peak neuronal activity and rate of development of neuronal discharge in the primary motor cortex and premotor area (Gross et al. 1983; Watts and Mandir 1992).
- Disinhibition of reciprocally tuned cells (Doudet et al. 1990). Reciprocal tuned cells are cells that discharge maximally in one

movement direction but pause their activities in the opposite direction.

- Significant increase in mean duration of neuronal discharge in motor cortex preceding and following onset of movement (Gross et al. 1983; Doudet et al. 1990; Benazzouz et al. 1992).
- Multiple triphasic patterns of muscle activation (Hallett and Khoshbin 1980; Doudet et al. 1990). Triphasic pattern of muscle activation is a characteristic electromyographic (EMG) pattern characterized by alternating bursts of agonist and antagonist muscles. The first agonist burst provides the impulsive force for the movement, whereas the antagonist activity provides the braking force to halt the limb. Sometimes a second agonist burst is needed to bring the limb to the final position. In PD patients multiple such patterns are observed in order for the subjects to complete the movement.
- Reduction in the rate of development and peak amplitude of the first agonist burst of EMG activity (Godaux et al. 1992; Corcos et al. 1996; Hallett and Khoshbin 1980; Doudet et al. 1990; Watts and Mandir 1992; Berardelli et al. 1986).
- Co-contraction of muscle activation (Benazzouz et al. 1992). In PD patients the alternating agonist-antagonist-agonist muscle activation is disrupted resulting in the co-activation of opponent muscle groups.
- Increases in electromechanical delay time (time between the onset of modification of agonist EMG activity and the onset of movement) (Benazzouz et al. 1992; Doudet et al. 1985, 1990).
- Asymmetric increase in acceleration (time from movement onset to peak velocity) and deceleration (time from peak velocity till end of movement) times of a movement.
- Decrease in the peak value of the velocity trace (Godaux et al. 1992; Camarata et al. 1992; Weiss et al. 1996; Benazzouz et al. 1992; Doudet et al. 1985, 1990; Rand et al. 2000).
- Significant increases in movement time (Rand et al. 2000; Weiss et al. 1996; Doudet et al.

1985, 1990; Watts and Mandir 1992; Benazzouz et al. 1992).

Types of Theoretical Models of Bradykinesia

Theoretical models of bradykinesia fall under two major categories:

- Verbal-conceptual models: using informal and natural language, describe the brain areas, pathways, and interactions leading to parkinsonian bradykinesia.
- Mathematical and computational models: using mathematical equations as a language, describe the interactions between the various brain areas involved in movement control and execution in parkinsonian bradykinesia.

Verbal-Conceptual Models

An influential model of basal ganglia intrinsic organization was proposed by Albin and colleagues (1989). In their model, motor cortical areas drive two populations of striatal medium spiny output neurones. Neurones containing substance P and D1-type dopamine receptors comprise the “direct” pathway and make contact with the basal ganglia output nuclei. At the same time, striatal neurones containing enkephalin and D2-type dopamine receptors comprise the “indirect” pathway and contact the output nuclei via relays in the GPe and STN. Connections between the various BG components are topographically ordered (Mink 1996). Some projections such as the striatonigral projection (direct pathway) are more focused, whereas others such as the subthalamo-nigral projection (indirect pathway) are more diffuse (Mink 1996). Basal ganglia output is thought to reflect a balance between these two projections, which is disrupted when dopamine neurons die, resulting in a reduction in transmission through the direct pathway and an increase in transmission through the indirect pathway. Dominance of the indirect pathway leads to an excessive inhibition of the thalamus by the GPi, thus leading to an abnormal slowness of movement (i.e., bradykinesia).

Additional anatomical observations have suggested a more complex intrinsic organization of BG structures:

- Cortical layer V pyramidal neurons excite the striatal medium spiny neurons (MSN) giving rise to the striatopallidal projections (indirect circuit) (Lei et al. 2004).
- Cortical layer III and upper layer IV pyramidal neurons excite striatal MSN in the direct striatonigral circuit (Lei et al. 2004).
- Both populations of striatal output neurones project to the GPe, one exclusively (enkephalin/D2 neurones), the other via collaterals from the fibers innervating the output nuclei (substance P/D1 neurones) (Parent et al. 2000).
- GPe neurones make direct contact with the output nuclei as well as with the STN (Smith et al. 1998).
- GPe projects back to the striatum (Bevan et al. 1998).
- STN is driven by cortical layer V inputs (Monakow et al. 1978; Nambu et al. 1997) and subcortical ones external to the basal ganglia, now known as the “hyperdirect” pathway (Nambu et al. 2002).
- GPe is excited by the cortex-STN projection (Obeso et al. 2008; Kita 2007).

The hyperdirect pathway provides a widespread excitation of the GPi via the STN (Mink 1996) and is considered to suppress thalamic and cortical areas related to both the selection of the most appropriate motor program given the current context and competing programs before movement begins.

These experimental observations extend the original Albin and colleague model (1989) of BG information processing. Some of the mathematical and computational models of the next section attempt to explain how dysfunction of these various interconnected BG structures may lead to bradykinesia.

Mathematical and Computational Models

Cortico-Basal Ganglia-Thalamic Interactions

In line with the Albin and colleagues (1989) and Nambu et al. (2002) models, Contreras-Vidal and Stelmach (1995) introduced a detailed population-based model of basal ganglia-

thalamocortical relations in normal and parkinsonian movements. The model's architecture was based on the direct, indirect, and hyperdirect pathways schema of the basal ganglia. Activation of the direct pathway resulted in activation of thalamocortical motor circuits leading to initiation and modulation of movement, whereas activation of the indirect pathway led to breaking of ongoing movement. Activation of the hyperdirect pathway facilitated rapid movement switching or the prevention of movement release. The model showed that loss of striatal DA as it occurs in PD leads to an imbalance in the neurotransmitter dynamics in the direct and indirect pathways, producing smaller than normal BG output signals. In turn these output signals activate insufficiently otherwise normally functioning motor cortical and spinal sites and produce weak and slow movements.

Moroney and colleagues (2008) extended the previous model to investigate the factors that contribute to the slowness of movements of PD patients when they perform simple and complex voluntary movements. Excessive dopamine depletion in the striatum and loss of spatial segregation of neuronal populations operating as functionally independent modules somatotopically mapping particular body parts contribute to a slowness of movement and to a reduced ability to suppress unwanted movements. They further showed that the therapeutic effects of deep brain stimulation (DBS) in STN result from stimulation-induced inhibition of STN, partial synaptic failure of efferent projections, or excitation of inhibitory afferent axons.

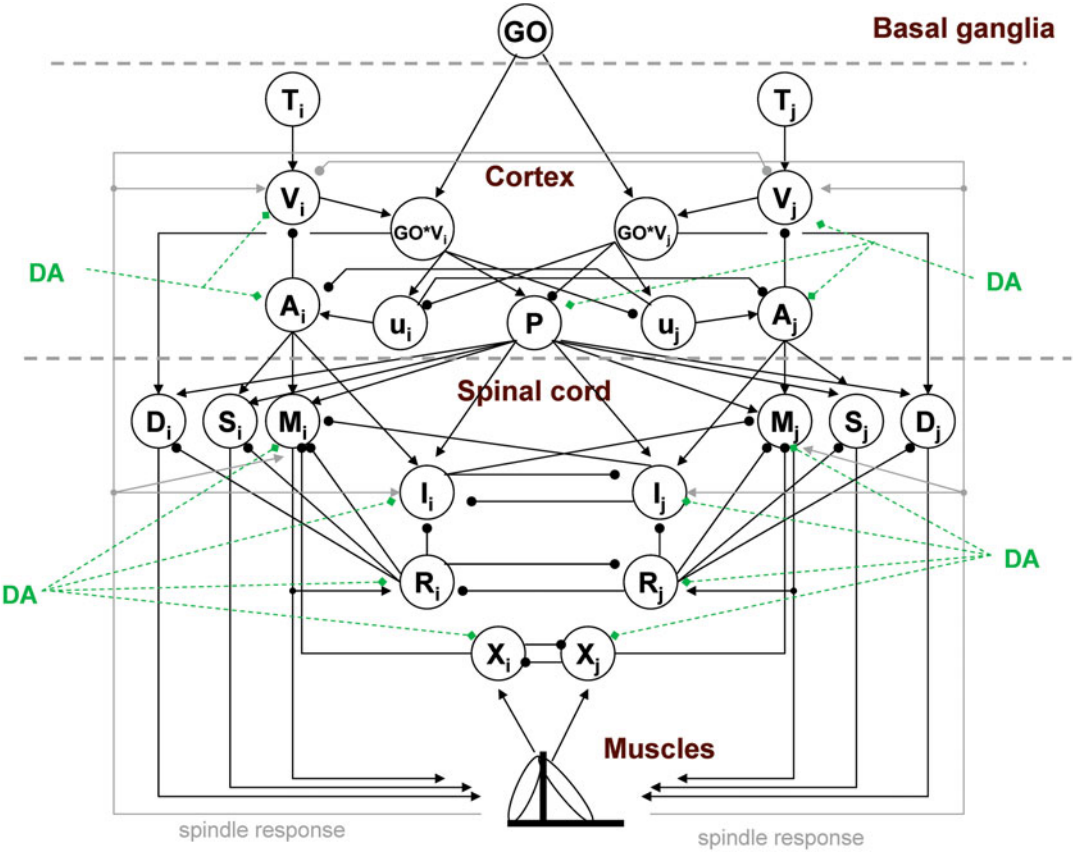
DBS is an effective treatment of PD. Chronic high frequency DBS in STN or GPi reduces motor PD symptoms including bradykinesia, although the therapeutic mechanisms of DBS are not fully understood. Recent computational studies have focused on deciphering these mechanisms on BG nuclei. Johnson et al. (2012) investigated which BG neuronal pathways when modulated with high frequency stimulation best correlated with improvement in motor symptoms (bradykinesia and rigidity). Their model predicted that stimulation of a combination of sensorimotor axons within and near the globus pallidus (specifically at the medial medullary lamina) can

have the most beneficial effects on PD bradykinesia. In contrast, improvements in PD rigidity correlated more strongly with the activation of less than 10% of neuronal fibers in internal capsule (IC). Recently, Kumaravelu and colleagues (2016) computationally investigated the effectiveness of different frequencies of STN-DBS in suppressing pathological low-frequency oscillatory neural activity correlated with PD bradykinesia. The model showed that low-

frequency stimulation (<40 Hz) was ineffective in suppressing the PD-related low-frequency oscillatory activity in GPi. PD low-frequency oscillatory power decreased gradually for frequencies between 50 and 130 Hz and saturated at frequencies higher than 150 Hz.

Cortico-Spino-Muscular Interactions

An alternative view to the observed abnormal slowness of movement in PD bradykinesia was



Basal Ganglia: Bradykinesia Models, Fig. 2 Neural architecture of the dopamine modulated cortico-spinal model with muscle spindle feedback to cortex. Top: basal ganglia module (GO signal representing the opening of the thalamocortical gate via inhibition of GPi response). Middle: cortical module for trajectory formation. Bottom: opponent-processing spino-muscular module for agonist-antagonist-agonist muscle activation. Arrow black lines, excitatory projections; solid dot black lines, inhibitory projections; diamond-dotted green lines, dopamine modulation; solid arrow gray lines, excitatory feedback pathways

from muscle spindles. Solid dot gray lines: inhibitory feedback pathways from muscle spindles. GO, globus pallidus internal segment (GPi) output signal; P, bidirectional co-contractive signal; T, target position command; V, difference vector (DV) activity; u, desired velocity vector (DVV) activity; A, current perceived position vector (PPV) activity; M, alpha motoneuronal activity; R, Renshaw cell activity; X, spinal type-b inhibitory interneuronal activity; I, spinal type-a inhibitory interneuronal activity; S, static γ MN activity; D, dynamic γ MN activity; i and j, antagonist cell pair

proposed by Cutsuridis (Cutsuridis 2006a, b, 2007, 2010, 2013; Cutsuridis and Perantonis 2006). He suggested that the observed abnormal slowness of movement in PD bradykinesia is due to inadequately activated motor cortical and spinal cord centers because of not only dopamine reduction in basal ganglia but also in cortical and spinal sites. His models, which were population-based models, were composed of two modules coupled together: (1) the cortical module and (2) the spino-muscular module (see Fig. 2). Both modules and their corresponding neuronal components were modulated by dopamine. The cortical module computed the motor commands sent to the spino-muscular module. The spino-muscular module was an opponent-processing control model of how spinal circuits afford independent voluntary control of joint stiffness and position. Both modules consisted of all major neuronal populations as they have been reported in the experimental literature. The model accounted for all physiological and behavioral phenomena as they have been described in a previous section. Model simulations showed that reduction of DA in cortical and subcortical motor areas disrupts, via several pathways, the rate of development and peak neuronal activity of primary motor cortical cells. These changes lead in delays in recruiting the appropriate level of muscle force sufficiently fast and in a reduction of the peak muscle force required to complete the movement. Repetitive and sometimes co-contractive patterns of muscle activation are needed to complete the movement. These disruptions result in an abnormal slowness of movement.

In a subsequent study, Cutsuridis (2011) investigated the origins of the co-contractive and repetitive pattern of muscle activation as observed in PD bradykinesia. Computer simulations showed that an oscillatory disrupted GPi response signal comprising at least two excitation-inhibition sequences as an input to a normally functioning cortico-spinal model of movement generation resulted in a repetitive but not co-contractive agonist-antagonist pattern of muscle activation. A repetitive and co-contractive pattern of muscle activation resulted when also dopamine was depleted in the cortex. Additional dopamine depletion in the spinal cord sites resulted in a

reduction of the size, duration, and rate of change of the repetitive and co-contractive EMG bursts. These results had important consequences in the development of dopamine replacement therapies in cortex and spinal cord, which could alleviate some of the impairments of PD such as slowness of movement (bradykinesia).

Cross-References

- [Basal Ganglia: Mechanisms for Action Selection](#)
- [Basal Ganglia: Subthalamic Nucleus Cellular Models](#)
- [Basal Ganglia: Overview](#)
- [Subthalamopallidal Loop and Oscillations](#)

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Further Reading

Scholarpedia

Basal Ganglia
Dopamine Anatomy
Models of Basal Ganglia

Models of Parkinson’s Disease
Bradykinesia
Models of Spinal Cord
Models of Thalamocortical System

Wikipedia

Hypokinesia
Motor Control
Motor System
Parkinson’s Disease

Basal Ganglia: Control of Saccades

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Definition

The basal ganglia are a set of subcortical interconnected nuclei, subdivided in parallel circuits. They form loops with specific cortical and subcortical regions and play a central role in the selection of actions as well as in learning to bias these selections towards the most profitable options. One of these loops appears to be specialized in saccadic eye movements. Most of the existing computational models consider that it is responsible for the choice, among all possible targets, of the target of the next saccade.

Detailed Description

Basal Ganglia Saccadic Circuitry

The basal ganglia are a set of subcortical nuclei common to all vertebrates (see ► [“Basal Ganglia: Overview”](#)). The basal ganglia are components of two main types of loops: cortico-baso-thalamo-cortical loops (Alexander et al. 1986) as well as subcortical ones (McHaffie et al. 2005). Within these two categories, sub-loops can be characterized, dedicated to various functions; one cortical loop dedicated to eye movements has been identified, as well as a few subcortical ones, all projecting to the superior colliculus, where

information converges to allow the generation of eye movements (see ► [“Oculomotor Control, Models of”](#)). The cortical loop receives contributions from the frontal eye fields, the supplementary eye fields, the dorsolateral prefrontal cortex, and the parietal cortex and goes through the ventral anterior, ventrolateral, and medial dorsal thalamic nuclei. The subcortical ones all receive inputs from the superior colliculus via the lateral posterior, the intralaminar, and the pulvinar nuclei of the thalamus.

The outputs of the basal ganglia are inhibitory and tonically active, so that at rest, they maintain their targets under constant inhibition, preventing their activation. The generic role of the basal ganglia is understood as an action selection system, used to solve resource allocation problems (Mink 1996; Redgrave et al. 1999): competing channels within the basal ganglia represent the different potential actions, and when simultaneous inputs activate different channels, the basal ganglia resolve the competition and disinhibit only one of the outputs and thus allow the activation of a single action. In the context of saccadic eye movements, at a given moment, the activities caused by multiple points of interest present in the visual field are susceptible of eliciting multiple saccades, which would allow for the refined analysis by the fovea of these points of interest. The role of the basal ganglia is thus understood as filtering these multiple solicitations in order to keep only the one with the highest priority.

The basal ganglia also interact with dopaminergic nuclei (the ventral tegmental area and the substantia nigra pars compacta): the basal ganglia project to these nuclei and receive modulatory projections at the striatal, pallidal, and subthalamic levels. The current theory proposes that these interactions are the neural substrate of reinforcement learning. They would allow learning, by trial and error, of which actions are the most profitable and would bias the selection process accordingly. The dopaminergic signal is thought to correspond to a measurement of the reward prediction error, which is used to modify the strength of the cortico-striatal synapses according to temporal-difference learning algorithms (see

► [“Reward-Based Learning, Model-Based and Model-Free”](#)). In the saccadic eye movement context, this would be the substrate of the evaluation of the priority of the competing targets, allowing the brain to make the best decision according to experience.

Electrophysiological recording in monkeys showed that saccade-related activity in the basal ganglia of monkey is quite rich (Hikosaka et al. 2000). Input neurons in the striatum exhibit visual and motor saccade-related activity, which is also reflected in the output activity of the substantia nigra. But more interestingly, one third of the neurons have a working memory-specific activity: some of them have visual or motor burst activity only for memory-driven saccades, while the rest have sustained activity while the position of a target is kept in working memory.

Computational Models of the Basal Ganglia Saccadic Circuitry

Relatively few computational models of the basal ganglia have specifically targeted the saccadic circuitry (Dominey and Arbib 1992; Dominey et al. 1995; Brown et al. 2004; Chambers et al. 2005; N’Guyen et al. 2010, 2014; Guthrie et al. 2013; Thurat et al. 2015; Cope et al. 2017; James et al. 2018); thus no final consensus about the role and the specific mechanisms of the basal ganglia saccadic circuit has been reached. All of them have been built at the same level of description, using variations of rate-coding models of neuron populations.

A specificity of models of the saccadic basal ganglia, compared to other basal ganglia models (see ► [“Basal Ganglia: Overview”](#)), is that the targeted motor systems (namely, superior colliculus and brainstem saccade generators) are relatively well known and have already been extensively modeled. Consequently, most of the aforementioned models include motor components allowing to simulate actual behavior.

All of these models consider that the neurons that are involved in saccades towards visible targets belong to a circuit in charge of selecting the target of the next saccadic movement in a winner-

takes-all manner, in line with the current understanding of the general basal ganglia function (see ► [“Basal Ganglia: Mechanisms for Action Selection”](#)). Those models are based on traditional basal ganglia computational models, adapted to saccade selection: each channel in competition codes for a given saccade metric, and the selected channel disinhibits the area of the superior colliculus specifically encoding that metric. The common selection mechanism among those models is based on the focused inhibition of the striatum, by which each channel tries to inhibit its output, and the diffuse excitation of the subthalamic nucleus, used to excite the competitors.

The models which also incorporate reinforcement learning (Dominey et al. 1995; Brown et al. 2004; N’Guyen et al. 2010, 2014; Guthrie et al. 2013) rely on variations of classical temporal-difference reinforcement learning algorithms (see ► [“Reinforcement Learning in Cortical Networks”](#)). In these models, derived from machine learning theories, the dopamine released in the striatum is supposed to correspond to the reward prediction error signal used by these algorithms; it drives the modifications of the strength of the cortico-striatal synapses.

Notably, in the Dominey and Arbib (1992) model, a second loop parallel to the “visual” one is dedicated to working memory. It is supposed to select which of the current potential targets have to be stored, in order to allow for saccades towards targets that may disappear from the visual field. Such a functionality requires a remapping capability: as the frontal eye field, parietal cortex, or superior colliculus maps, which are supposed to store these memories, are retinotopic, the positions of the next saccades have to be updated after each eye movement. This mechanism can be extended to store the order of the targets, allowing for a more elaborated sequence generation capability (Dominey et al. 1995). Note that models of the role of the basal ganglia in working memory have been proposed in other contexts and could easily be adapted to the saccadic function (see ► [“Working Memory, Models of”](#)).

Concerning the subcortical basal ganglia loops through the superior colliculus, no model has ever considered the cohabitation and the possible interactions of the three anatomically described circuits

(McHaffie et al. 2005). Those which considered the basal ganglia-superior colliculus loops included only one of them. Earlier models used it in a slave mode (Brown et al. 2004), where it executes the motor decisions taken by a master cortical loop; more recently it has been considered as an additional player operating in parallel to the cortical loops (Chambers et al. 2005; N’Guyen et al. 2010, 2014; Cope et al. 2017; James et al. 2018), and its possible ability to autonomously make decisions hasn’t been much explored yet (Thurat et al. 2015).

Cross-References

- [Basal Ganglia: Dopaminergic Cell Models](#)
- [Basal Ganglia: Mechanisms for Action Selection](#)
- [Basal Ganglia: Overview](#)
- [Oculomotor Control, Models of](#)
- [Reinforcement Learning in Cortical Networks](#)
- [Reward-Based Learning, Model-Based and Model-Free](#)
- [Working Memory, Models of](#)

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Basal Ganglia: Decision-Making

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Definition

The basal ganglia (BG) participate not only in the selection of motor plans but also in perceptual

decision-making. The functional structure of the BG and their close interconnections with the cortex and dopamine system allow the BG to be actively involved in the perceptual decision-making processes.

Detailed Description

The role of the BG in perceptual decision-making processes has recently attracted much attention (Ding and Gold 2013). Although the BG were much earlier proposed to be the central substrate for action selection and habit learning (Graybiel 1995; Mink 1996; Redgrave et al. 2010), their active participation in perceptual decision-making has been investigated only more recently (Ding and Gold 2010). The BG have close interaction with the frontal cortex and the lateral intraparietal area (LIP), where are believed to be the sites of evidence accumulation in decision processes (Gold and Shadlen 2007; Huk and Shadlen 2005; Kim and Shadlen 1999). The BG also have prominent interaction with the downstream subcortical motor-related areas, such as the thalamus and the superior colliculus (SC), and the midbrain dopamine system (Hikosaka et al. 2000). As diagrammed in Fig. 1, information from the cortex can be transmitted to the thalamus and SC through three BG pathways: (1) the direct pathway, from the striatum directly to the output nuclei GPi/SNr; (2) the indirect pathway, from the striatum through the GPe and STN to the output nuclei; and (3) the hyper-direct pathway, from the cortex directly to the STN then to the output nuclei. The opposing effect of dopamine signals on striatum medium spiny neurons that project through the direct and indirect pathways differentially makes the BG suitable for implementing reward dependence learning during the training process in decision-making tasks (Gerfen and Surmeier 2011). In addition, the hyper-direct pathway provides a natural substrate for inhibitory control when an evidence accumulation process needs to be cancelled. Parkinson’s disease (PD), originating from depleted dopamine levels within the BG, shows significant disruption of BG activity (DeLong and Wichmann 2009; Obeso et al. 2008). Impairment in perceptual decision-

alternatives, i.e., the multi-hypothesis sequential probability ratio test (MSPRT) (Baum and Veeravalli 1994). A model used to explore this concept (Bogacz and Gurney 2007) was based on the same BG functional structure as employed in a previous work (Gurney et al. 2001). In this model, each BG nucleus was represented by its average firing rate. The formula for detection probability in MSPRT was first log-transformed, and then each term in the expression for the log-transformed probability was connected with the firing activity of the STN and GP (GPe of primates). This mapping posed requirements for the input–output relation in these two nuclei. Specifically, the STN firing rate was required to be an exponential function of the inputs from the cortex and from the GP, while the GP firing rate was related to the summation of STN output for different channels corresponding to each alternative action. These requirements for the STN and GP input–output relationship were supported by experimental data from *in vitro* measurements of rat BG. The implementation of MSPRT could also be extended to include the indirect pathway. In this model, the interaction between the direct and hyper-direct pathways and the diffusive innervation from the STN to the GP and entopeduncular nucleus (EP), which is the homologue of GPi of primates, are essential for the BG in implementing the MSPRT.

Basal Ganglia Mechanism for Optimal Threshold Modulation

A biophysically based spiking network model involving the BG, the cortex, and the SC has been proposed to provide a mechanism for setting and adjusting the threshold in perceptual decision-making (Lo and Wang 2006). In this model, integrate-and-fire neuron model was used to describe individual neurons and tuned to specific properties in each area. The SC neurons fired a burst when the input was higher than a threshold value. The cortical circuit was modeled as an attractor network in which evidence accumulation occurred (Wang 2002). The cortical circuit projected to the SC through two routes: one was

direct projection from the cortex to the SC and the other route through the BG to the SC. In the BG, only the direct pathway was included. The neurons in the striatum were designed to be silent and fire spikes only when the input was higher than a threshold level. When one of the competing populations in the cortex reached a value that drove the CD neurons to spike, the output nucleus SNr was inhibited, which in turn led to a disinhibition of the SC. When the SC was disinhibited, it could fire a burst in response to the excitatory input arriving directly from the cortex. This burst sent feedback to the cortex, terminated the evidence accumulation there, and set a threshold for perceptual decision-making. The SC burst was turned off by local recurrent connections within the SC. It was found that adjusting the strength of the corticostriatal connection could modulate the threshold within a wide range. On the contrary, adjusting the cortex to SC connection strength could only modestly modulate the threshold. A large range of threshold variability is beneficial when a subject needs to make a transition between response speed and accuracy (Gold and Shadlen 2002). In this model, modulation of the corticostriatal connection led to an inverted u shape of reward rate, reflecting a trade-off between speed and accuracy. The peak reward rate could be shifted according to the task difficulty. Physiologically, the modulation in the corticostriatal connection efficacy could be realized by a reward-dependent reinforcement learning process through dopaminergic synapses observed extensively in the striatum projection neurons (Gerfen and Surmeier 2011). Further experiments are needed to test this hypothesis.

Future Directions

Computational modeling represents an important approach in investigating possible roles of the BG in perceptual decision-making. Such work usually invokes some assumptions that require further experimental testing and also suggests new research directions. For example, in some circuit models, the STN and striatum received the same copy of input from the cortex, which usually

represents evidence accumulated over time (e.g., Bogacz and Gurney 2007). But further experiments are needed to clarify the origin of cortical inputs to the direct and hyper-direct pathways of the BG (Mathai and Smith 2011). Ramping of striatal neuronal activity during evidence accumulation has been observed in primates (Ding and Gold 2013) and will curtail the efficiency of a corticostriatal mechanism for threshold modulation that includes only the direct pathway of the BG (as introduced in Lo and Wang 2006). Therefore, an extension of such a mechanism to incorporate the new experimental observation is called for, and experiments are needed to test the idea that the corticostriatal connection strength is modulated during tasks requiring a speed-accuracy trade-off.

Cross-References

- Basal Ganglia: Habit Formation
- Basal Ganglia: Mechanisms for Action Selection
- Decision-Making: Overview

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Basal Ganglia: Dopaminergic Cell Models

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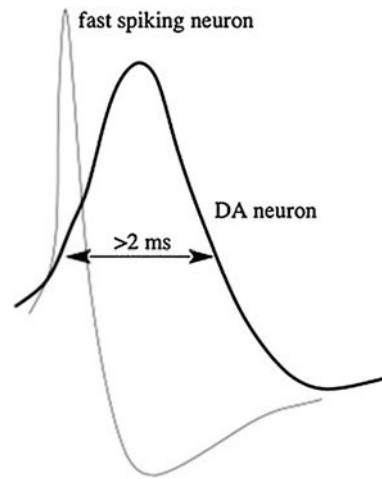
Definition

- Dopaminergic (DA) neurons are defined as neurons synthesizing and containing the neurotransmitter and neurohormone dopamine. Such neurons release dopamine synaptically as well as dendritically (Bustos et al. 2004).
- The electrophysiological signatures of this neuron are broad action potentials (Fig. 1) and a low-frequency, regular spontaneous activity (Fig. 2a).
- A distinctive property of the DA neuron is that it differentially responds to different types of excitatory synaptic inputs (Fig. 2a, b).
- Models have explained these properties and connected them with one another and with particular current compositions (Figs. 3 and 4).

Detailed Description

Importance

The central dopamine system is involved with many behavioral and cognitive tasks (Carlson

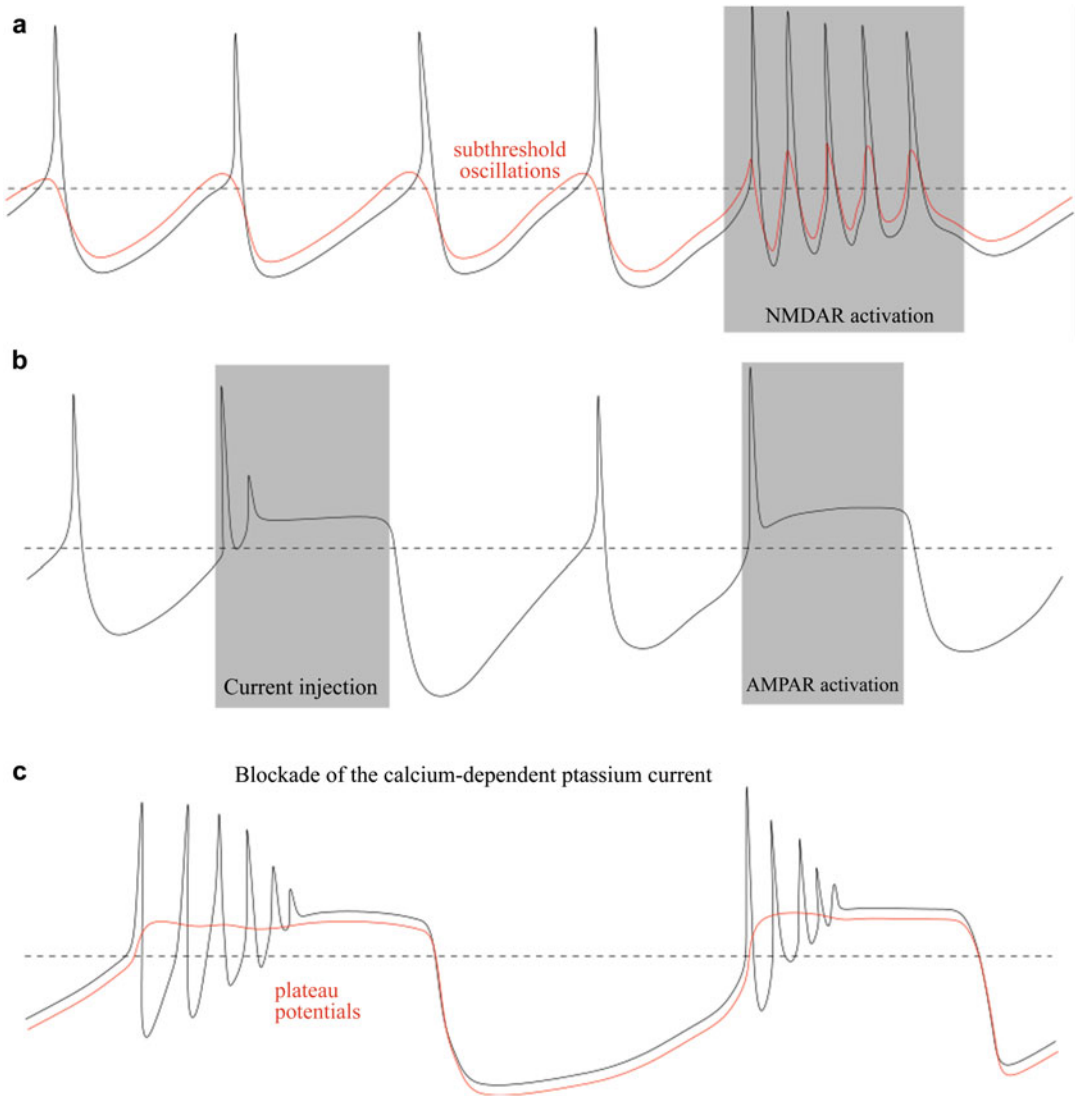


Basal Ganglia: Dopaminergic Cell Models, Fig. 1 A single spike of a DA neuron

1999). Dopamine neurotransmission is found to play a role in addictive behavior (Wise 2004) and is altered in psychiatric disorders (Strange 2001). DA neurons fire a burst of action potentials whenever a subject or an animal receives an unpredicted reward or a reward-predicting stimulus (Schultz 2002, but see Redgrave and Gurney 2006). Do the DA neurons synthesize the reward-related signal by some type of neuronal computation, or do they simply relay a signal generated elsewhere? This question motivates the research on the DA neuron and leads to the more specific questions addressed in experiments and modeling.

Anatomy

Midbrain DA neurons are positioned within three cell groups in different brain areas: the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc), and the retrorubral area. There is no clear anatomical distinction between the groups, but heterogeneities in biophysical properties of the DA cells both within and between these groups are documented (see, e.g., Wolfart et al. 2001; Neuhoff et al. 2002; Kotter and Feizelmeier 1998). Nevertheless, the characteristics listed below are common for all three groups of midbrain DA neurons.



Basal Ganglia: Dopaminergic Cell Models, Fig. 2 Firing patterns of DA neurons. **(a)** Low-frequency background firing is replaced by a burst during NMDA receptor activation (e.g., by glutamate iontophoresis). The blockade of the spike-producing fast sodium current (with TTX) reveals subthreshold oscillations. **(b)** Neither applied

depolarization nor activation of the AMPA receptor evokes a burst. **(c)** The blockade of the calcium-dependent potassium current (by apamin) reveals subthreshold plateau potentials. The dashed line shows the spike threshold of -40 mV

Firing Patterns

DA neurons show multiple activity patterns: low-frequency regular (tonic) spiking and different types of bursting. Mechanisms of the firing patterns of the DA neuron are currently debated in the literature. Here, we present most established results and the different views.

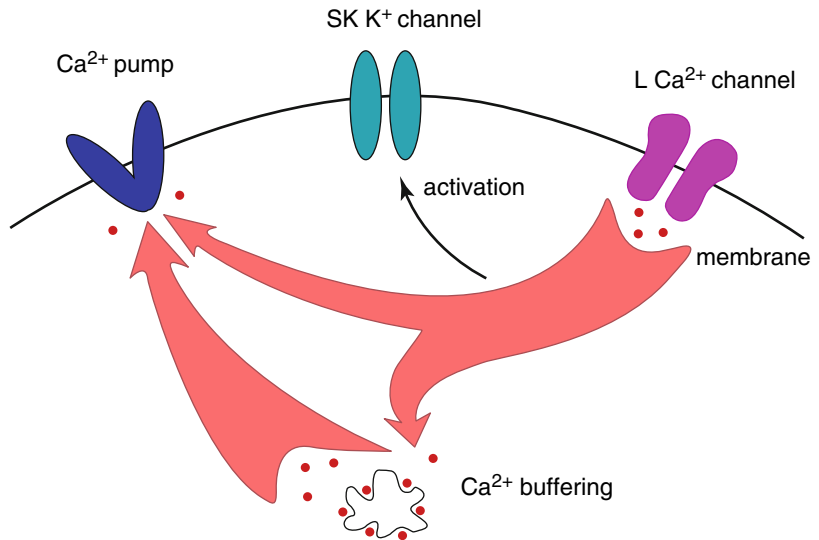
Background Firing

In isolation, DA neurons spontaneously display low-frequency (1–5 Hz) tonic spiking. A less regular pattern of a similar average frequency is most commonly seen *in vivo*. Together, these two low-frequency patterns are called background firing.

The major properties of background firing are:

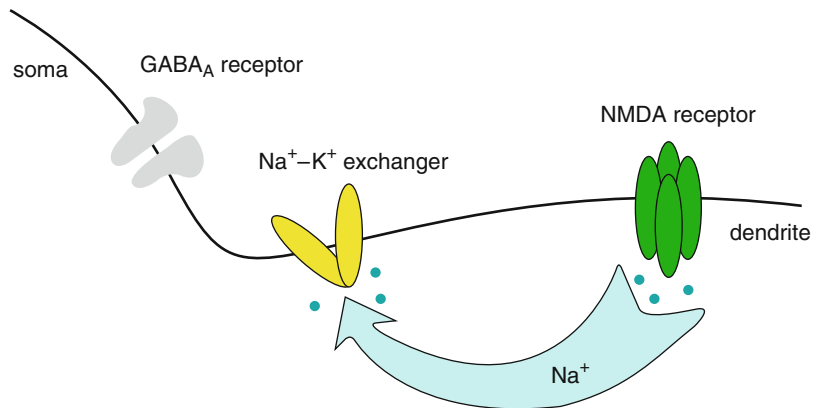
Basal Ganglia: Dopaminergic Cell

Models, Fig. 3 Calcium processes generating the subthreshold oscillations: the persistent L-type calcium current is responsible for depolarization and simultaneous accumulation of intracellular calcium, whereas the SK-type calcium-activated potassium current produces the repolarization phase of the oscillation. These two currents constitute a calcium-potassium mechanism for pacemaking in DA neurons



Basal Ganglia: Dopaminergic Cell

Models, Fig. 4 Generation of the oscillatory plateau potentials that underlie bursting induced by bath application of NMDA relies on the NMDAR current and Na^+ - K^+ exchanger



- Injection of a depolarizing current can increase the frequency of repetitive firing only up to 10 Hz (Fig. 2b; Richards et al. 1997).
- **Modeling** and experiments have shown that, during its background firing, DA neuron is class 1 excitable, which means that its frequency grows continuously from zero as an injected current grows (Lobb et al. 2010; Morozova et al. 2016a).
- Higher firing rates are possible during a transient at the onset of the depolarization.
- **Modeling** suggests that the frequencies remain low due to very weak spike-producing currents:
 - The current initiating the spike is weak: the maximal conductance of the fast sodium current is drastically lower than

in fast-spiking neurons (Kuznetsova et al. 2010).

- The spike-initiating current remains inactivated: the potassium currents causing hyperpolarization after a spike (after hyperpolarizing or AHP currents) are weak and cannot fully remove inactivation (Kuznetsov et al. 2006; Drion et al. 2011), or the inactivation is slow (Qian et al. 2014).

This has two consequences, which contrast the DA neuron with other neuron types:

1. The action potentials generated by these currents are broad (Fig. 1).
2. Background firing must rely on a subthreshold oscillation to be robust.

- Two types of the subthreshold oscillations were found:
 - Calcium-based (Fig. 3; see, e.g., Harris et al. 1989); the corresponding minimal model includes only two currents, L-type calcium and SK-type calcium-activated potassium (Amini et al. 1999; Wilson and Callaway 2000).
 - Sodium-based (calcium-independent; Yung et al. 1991; Nedergaard and Greenfield 1992; Chan et al. 2007; Guzman et al. 2009; Blythe et al. 2009; Khaliq and Bean 2010).
- **Modeling** has shown that the sodium and calcium currents contribute to the same oscillatory mechanism responsible for both spiking and subthreshold oscillations (Puopolo et al. 2007; Drion et al. 2011).
- The calcium-based oscillatory mechanism is distributed along dendrites (Wilson and Callaway 2000), and a special type of synchrony among dendrites and the soma sets in due to electrotonic coupling (Medvedev and Kopell 2001; Medvedev et al. 2003). The frequency of background firing results from a compromise between the oscillations arising in the soma, dendrites, and axon initial segment (AIS; Meza et al. 2018).
- The background frequency in DA neuron subpopulations correlates with the presence of a calcium-binding protein calbindin and the strength of the hyperpolarization-activated cationic current I_h (Neuhoff et al. 2002), and this relation is reproduced in modeling (Evans and Khaliq 2015).
- Both in vivo and in vitro, bursting is dependent on the activation of NMDA receptors (Fig. 2a).
- Activation of AMPA receptors alone does not elicit bursting (Fig. 2b; Chergui et al. 1993; Overton and Clark 1997; Tong et al. 1996; Morikawa et al. 2003; Deister et al. 2009).
- **Modeling** has shown that the failure to burst in response to AMPAR stimulation follows immediately from the limited frequency of the response to applied depolarization (see above and Kuznetsov et al. 2006).

Bursts In Vivo

Firing rates of ≥ 20 Hz can be achieved for irregularly distributed short time intervals in the DA neuron in vivo (Hyland et al. 2002). The main properties of these bursts are:

- The bursts are singular events as opposed to repetitive bursting (but see Freeman et al. 1985).
- Bursts are not superimposed on a depolarizing plateau, and may not be followed by a pause in activity.
- Within the burst, the spike amplitude progressively decreases, and the spike duration and interspike interval progressively increase (but see Hyland et al. 2002).
- Burst evocation relies on excitatory synaptic inputs.
- NMDA but not AMPA receptor activation is critical for the burst (Chergui et al. 1993; Overton and Clark 1997; Tong et al. 1996; Meltzer et al. 1997).
- The frequency of burst occurrence can be regulated differentially from the average firing rate in vivo (Grace and Bunney 1984; Tepper et al. 1995), which was explained in **modeling** (Canavier and Landry 2006).
- The burst is critically dependent on calcium (Grace and Bunney 1984).
- SK channel blockers induce burst firing in vivo (Ji and Shepard 2006; Waroux et al. 2005).
- Blockade of GABA_A receptor currents has been shown to induce bursting in DA neurons, suggesting a disinhibition hypothesis of DA burst firing in vivo (Tepper et al. 1995).
- **Modeling** has shown that synchronizing GABA input to DA neurons may also induce

Burst Firing

The stereotypic response of the DA neuron to an unpredicted reward is a burst of activity with firing frequencies above 20 Hz. Different experiments result in bursts that are significantly different from one another (see, e.g., Johnson and Wu 2004; Overton and Clark 1997). A central question is how similar is in vitro bursting to that observed in vivo. The main features of each type of bursting in the DA cell are described below with the following common properties to be emphasized:

bursting by short pulsatile disinhibitions (Morozova et al. 2016b). The mechanism is different from above because it requires the average GABA-mediated inhibition to stay high and dynamically replace the long-lasting SK-mediated inhibition.

Modeling proposed two distinctly different mechanisms for in vivo bursting:

- In Kuznetsov et al. (2006) and Ha and Kuznetsov (2011, 2013), the NMDAR current directly interacts with the subthreshold oscillatory mechanism and increases the frequency of oscillations (Fig. 2a). This provides the distinction between responses to AMPA and NMDA receptor activation.
- In Komendantov and Canavier (2002) and Canavier and Landry (2006), the role of the NMDAR current is identified as opposing the SK current and therefore reducing the amplitude and duration of the AHP.

In Vitro Bursting Induced by Stimulation of NMDA Receptors

Repetitive bursting can be elicited in DA neurons in vitro via bath application of NMDA (Johnson and Wu 2004). The properties of this bursting are:

- This is a repetitive bursting pattern.
- The high-frequency firing is superimposed on a depolarizing phase of a subthreshold oscillation called a plateau potential.
- This bursting is Ca^{2+} -independent: bursting persists in Ca^{2+} -free solution, or upon chelation of intracellular Ca^{2+} .
- This bursting is critically dependent on extracellular sodium (Johnson et al. 1992).

These properties contrast with those for bursting in vivo (see above).

Other in vitro stimulation techniques evoked bursts more similar to those found in vivo. A burst has been observed after extracellular electrical stimulation (a train of short pulses) or iontophoresis of a glutamate receptor agonist onto the DA cell (Morikawa et al. 2003; Blythe et al. 2009; Deister et al. 2009).

Glutamate influences the firing through NMDA receptors:

- Subsequent bath application of an NMDA receptor antagonist inhibited the burst.
- In dynamic clamp experiments, injection of a virtual NMDA current elicited a burst (Deister et al. 2009; Putzier et al. 2009).
- Removing the voltage dependence of the virtual NMDAR current, which converts it into AMPAR-like current, abolished the burst.

The properties contrasting these bursts from bursts elicited by other methods in vitro, and resembling bursts in vivo, are:

- Spikes within a burst are not superimposed on a depolarizing plateau.
- The hyperpolarization after the burst originates from a separate pathway, which can be blocked or desensitized without affecting the burst.
- Switches between the low-frequency background firing and the high-frequency bursts follow the on-off pattern of the stimulation.

Thus, the high-frequency firing cannot be a consequence of the depolarizing phase of the underlying plateau potentials.

Modeling has shown that the high-frequency firing can be elicited independently of the plateau potentials (Kuznetsov et al. 2006). However, the plateau potentials and the high-frequency firing share certain properties:

- The nonlinear voltage dependence of the NMDAR current is critical for evoking plateau potentials (Li et al. 1996; Canavier 1999; Komendantov et al. 2004), as well as for the high-frequency oscillations (Kuznetsov et al. 2006; Ha and Kuznetsov 2013).
- By contrast, activation of linear currents, such as AMPAR or GABAR, suppresses plateau potentials as well as the high-frequency firing.

In Vitro Bursting Induced by Apamin

Repetitive bursting of the DA neuron was observed during the bath application of an SK current blocker apamin (Fig. 2c; Shepard and

Basal Ganglia: Dopaminergic Cell Models, Table 1 Comparison of different ways to induce a burst in the DA neuron

Property/burst type	In vivo	In vitro			
		NMDA iontophoresis	Bath NMDA	SK block	Bath NMDA + SK block
Repetitive pattern	No	No	Yes	Yes	Yes
Plateau potentials	No	No	Yes	Yes	Yes
Ca ²⁺ dependence	Yes	Yes	No	Yes	No
Na ⁺ dependence	No	No	Yes	No	Yes

Bunney 1991). The main properties of this bursting pattern are:

- This is also a repetitive bursting pattern.
- The high-frequency firing is superimposed on depolarizing plateau potentials.
- Blockade of spike generation preserves the oscillatory plateau potentials underlying bursts (Fig. 2c; Ping and Shepard 1996).
- **Modeling** reproduces the transition from the low-frequency subthreshold oscillation to the plateau potential oscillation upon simulated blockade of the SK current (Amini et al. 1999; Canavier et al. 2007; Oster and Gutkin 2011).
- Without the SK current, DA cells become prone to depolarization block, and each burst collapses to a plateau (Fig. 2c).
- Apamin-induced bursting is critically dependent on calcium: L-type Ca²⁺ channel blocker abolishes the plateau potential oscillations, and this bursting is abolished in Ca²⁺-free medium.
- **Modeling** and modeling-driven experiments show that the ether-a-go-go-related gene (ERG) current contributes to the repolarization phase of the plateau potential wave (Canavier et al. 2007; Ji et al. 2012).
- **Modeling** suggests that the ERG current also provides repolarization after each spike and, therefore, is involved in generation of low- and high-frequency firing (Ha and Kuznetsov 2013).

Together, these characteristics suggest that this bursting pattern is different from in vivo bursting (see above).

Bursting has been shown to be most robust in simultaneous bath application of NMDA and

apamin. Properties of bursting in this case are similar to those for whole bath NMDA-induced burst firing (see above) (Johnson and Wu 2004). This suggests that apamin, by blocking the SK current, can facilitate two different bursting mechanisms, one of which is intrinsic and the other based on the NMDA receptor activation. **Modeling** reproduced the facilitation of high-frequency firing during simulated NMDAR activation combined with partial blockade of the SK current (Oster and Gutkin 2011) (Table 1).

Summary of Models

All models of DA neurons have a conductance-based form

$$c_m \frac{dv}{dt} = \sum_j I_j$$

where v is voltage and I_j are various transmembrane currents. The following firing patterns were reproduced by the inclusion of different currents in various models:

- *Subthreshold calcium-driven oscillations*

A calcium and a calcium-dependent potassium current constitute a mechanism for subthreshold oscillations (Figs. 2a and 3). The calcium current has the form $I_{Ca} = \bar{g}_{Ca} c_{inf}^4(v)(E_{Ca} - v)$, which assumes instantaneous gating. The calibration of the gating function $c_{inf}(v)$ reflects an activation threshold of an L-type current, which is significantly lower in DA cells than in other neurons (~ -50 mV). The calcium-dependent potassium current (SK type) has the form $I_{KCa} =$

$\bar{g}_{KCa} \frac{[Ca^{2+}]^4}{[Ca^{2+}]^4 + k^4} (E_K - v)$, which also assumes instantaneous gating.

- *Spike generation*

The delayed rectifier potassium current is taken in a standard form $I_{DR} = \bar{g}_{DR} n^4 (E_K - v)$. Here, n is a gating variable, which obeys a standard equation $dn/dt = (n_{inf}(v) - n)/\tau_n(v)$. The gating function $n_{inf}(v)$ and time constant $\tau_n(v)$ in this equation are calibrated to reflect high half-activation and slower activation kinetics of the current. This calibration and the current's low maximal conductance weaken the hyperpolarization produced by the delayed rectifier and lead to a low safety factor or robustness of spike generation.

The fast sodium current also takes a standard form with instantaneous activation $I_{Na} = \bar{g}_{Na} m_{inf}^3(v) h (E_{Na} - v)$, where the function $m_{inf}(v)$ reflects the spike threshold of -40 mV. The maximum conductance of this current is quite low, around 550 uS/cm², which gives a moderate slope of the spike upstroke and broad action potentials (Fig. 1).

- *Subthreshold plateau potentials*

Slow subthreshold oscillations called plateau potentials are observed after the blockade of the spike-producing sodium current in two conditions:

- The blockade of the calcium-dependent potassium current (Fig. 2c)
- The activation of a synaptic NMDA receptor current by bath application of an NMDAR agonist

In the latter case (Fig. 4), voltage rises due to the NMDAR current, and the subsequent voltage decline is due to a sodium pump current (Na^+K^+ exchanger): $I_{NP} = \bar{I}_{NP} / (1 + (K_{mNa}/[Na]_i)^{1.5})$, where $[Na]_i$ is the intracellular sodium concentration.

During the blockade of the calcium-dependent potassium current, the subthreshold depolarization is produced by the calcium current. Two mechanisms were proposed for the repolarization phase: the calcium pump current $I_{CP} = \bar{I}_{CP} / (1 + K_{mCa}/[Ca]_i)$ and the ether-a-

go-go-related gene (ERG) current $I_{ERG} = \bar{g}_{ERG} e (E_K - v)$, where e is its activation variable.

- *Responses to synaptic inputs*

An NMDA receptor current elicits high-frequency firing in the DA neuron. The non-linear voltage dependence of the current is assumed to be instantaneous: $I_{NMDA} = \frac{\bar{g}_{NMDA}}{1 + 0.1[Mg]e^{-m_e v}} (E_{NMDA} - v)$, where $[Mg]$ is the magnesium concentration. The low slope of the voltage dependence ($m_e = 0.062$) is critical for the increase of the frequency of spikes or subthreshold oscillations during NMDA application.

An AMPA receptor current differs by its linearity: $I_{AMPA} = \bar{g}_{AMPA} (E_{AMPA} - v)$. Constant (tonic) AMPAR current does not elicit high-frequency firing.

Complete description of these models can be found in the literature cited above.

Conclusions and Future Directions

Our understanding of the electrophysiological properties of the DA neuron and the underlying mechanisms is not complete. However, modeling studies have clarified some relations between its characteristics.

Weak Spike-Producing Currents Determine Low-Frequency and Broad Action Potentials

First, the high-frequency firing within bursts must be considered in the context of limited firing frequencies in response to applied depolarization (but see Blythe et al. 2009). The high frequency is not a simple consequence of a depolarizing plateau potential. The spike-producing currents cannot reliably support repetitive firing, and both high- and low-frequency firing must rely on the subthreshold oscillations to be robust. The main reason is that the fast AHP currents are weak, as suggested by modeling studies. Additionally, the fast sodium current has a drastically lower maximal conductance compared to that in fast-spiking neurons. This results in even weaker activation of

the fast AHP currents and simultaneously ensures the broad action potentials, which are characteristic for DA neurons.

Calcium-Dependent and Calcium-Independent Oscillations

Modeling suggests that a single oscillatory mechanism combines multiple currents that support subthreshold oscillations in different experimental conditions. Both calcium and subthreshold sodium currents contribute to the depolarizing phase of the oscillation. Similarly, both calcium-dependent and voltage-dependent currents must contribute to the repolarization phase of the oscillation. The SK current is known to provide the calcium-dependent component. The ERG current is suggested by modeling studies as the voltage-dependent component.

Distinct Responses to AMPA and NMDA Receptor Stimulation

The delicate oscillatory mechanism of the DA neuron results in its distinct responses to different stimuli. In general, a passive (linear) or injected (constant) current can only impair oscillations. To complement the oscillatory mechanism, the current must be active (nonlinear). This is the difference between AMPAR and NMDAR currents: the NMDAR current contributes to the regenerative depolarization phase of the oscillation. In various other types of neurons, the spike-producing oscillatory mechanism is so powerful that the type of stimulation does not make much difference. Taken together, because the oscillations in the DA neuron are much less robust than in fast-spiking neurons, the ability of an input to contribute to the oscillation becomes critical, and the difference between NMDA and AMPA receptor currents is revealed.

Major Future Directions for Modeling Firing Patterns of the DA Neuron

- Combine mechanisms for all types of oscillations in a single model to examine their interaction and establish the connections among different experiments.
- Model burst evocation in realistic in vivo-like conditions, which includes accurate calibration

of the glutamate and GABA synaptic inputs and dynamic gating of receptors.

- Study the influence of dopamine autoreceptors on firing of the DA neuron.
- Investigate the functional consequences of the distinctive morphology of the DA neuron, such as the separation of each spike into somatodendritic (SD) and initial segment (IS) components due to the distant location of the axon hillock from the soma.

Cross-References

- [Computation with Dopaminergic Modulation](#)
- [Parkinson's Disease: Deep Brain Stimulation](#)
- [Reward-Based Learning, Model-Based and Model-Free](#)

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Basal Ganglia: Globus Pallidus Cellular Models

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Definition

The globus pallidus is a part of the basal ganglia in the vertebrate brain. Cellular models of the globus pallidus are computer representations of the specific dynamics of globus pallidus neurons.

Detailed Description

Goals of Globus Pallidus Cellular Models

Detailed cellular models of globus pallidus (GP) neurons are typically constructed to better understand how they integrate synaptic input and how their intrinsic properties contribute to the input-output function of the GP. The exploration of GP function in larger network models is typically carried out using less detailed cell models. The level of complexity and biological realism best used for a GP neuron model depends on the questions one wants to address (Herz et al. 2006) and ranges from simple integrate-and-fire models to complex full morphological reconstructions with a full complement of ion channel types found in these neurons.

Models that Capture the Detailed Dynamic Properties of Globus Pallidus Neurons

The GP is divided into an external (GPe) and internal (GPi) segment. All detailed models to date have focused on GPe properties. The GPe is primarily made of large GABAergic inhibitory projection neurons with very few interneurons. Anatomically GPe neurons can be subdivided into arky pallidal neurons projecting almost exclusively to the striatum and prototypic neurons, which project to multiple downstream targets like the GPi and STN (Mallet et al. 2012). The electrical properties of GPe neurons are overlapping (Deister et al. 2013) and can be simulated by a variable density of the different ion channel types in the membrane (Gunay et al. 2008). Biophysically detailed GPe neuron modeling has revealed a complex dependency of cellular dynamics on the interactions between multiple voltage-gated channel types. The hallmark of these neurons is a fast spontaneous regular spiking activity that depends on steady depolarization through a persistent sodium channel (Mercer et al. 2007), though arky pallidal neurons have less persistent sodium current and slower spontaneous spike rates (Abdi et al. 2015). Each spike causes a calcium inflow through voltage-gated calcium channels and subsequent activation of calcium-dependent small conductance (SK) potassium channels that results in a spike – afterhyperpolarization that regularizes spiking (Deister et al. 2009). A biophysically detailed modeling study showed that dendritic integration of synaptic input in GPe neurons may depend on dendritic fast sodium channels that can lead to synaptically evoked dendritic spike initiation (Edgerton et al. 2010). Further, the phase response curve (i.e., the spike time delay or advance resulting from synaptic input) was shown to be principally different for distal dendritic input (Schultheiss et al. 2010), where excitatory input at the beginning of a spike cycle can lead to a delay in subsequent spiking (type II phase response curve). Overall, it is the detailed examination of local dendritic processing that provides the most compelling rationale for detailed morphological neuron models, and the GPe neuron models are no exception in revealing potentially significant aspects of such dendritic processing. Biophysically detailed

GPe models are available for download in the Yale ModelDB archive at <http://senselab.med.yale.edu/modeldb/ModelList.asp?id=88217>.

Models that Capture the Interaction Between GP and Subthalamic Nucleus (STN)

A special GPe neuron modeling interest in the first decade of the twenty-first century has been concerned with the interactions between STN and GPe in the generation of pathological rhythmic bursting activity that is observed in Parkinson's disease. The feedback pathway consisting of STN excitation of GPe and GPe inhibition of STN has been suspected to be the cause of such pathological oscillations based on earlier experimental results in slice cultures (Plenz and Kitai 1999) and was first modeled with a set of connected STN and GPe single-compartment neurons by the group of David Terman at Ohio State University (Terman et al. 2002). This model set off a host of subsequent modeling studies confirming the possibility of triggering oscillations in this network, notably in the beta band, with synaptic changes and disrupted striatal input patterns to GPe expected in parkinsonism (Holgado et al. 2010; Park and Rubchinsky 2012). These models typically employ dynamical systems analysis to examine the parameter range and stability required to exhibit different activity patterns. Nevertheless, to date the question of where beta activity originates in Parkinson's disease is not solved, and cortical and striatal mechanisms are also thought to be important contributors (McCarthy et al. 2011; Kerr et al. 2013) and may interact with GP-STN oscillations (Nevado-Holgado et al. 2013; Ahn et al. 2016). Several models of GP-STN interactions are available for download in the Yale ModelDB archive.

Integration of GP Neuron Models in Large-Scale Network Simulations of Action Selection

The ultimate question of GP neuron modeling of course concerns the computational function of GP in basal ganglia information processing. Notably, GP neurons are included in basal ganglia network models that perform an action selection function (Gurney et al. 2001a, b; Humphries et al. 2006; Bogacz and Gurney 2007; Bogacz et al. 2016). This network simulation paradigm gives GPi a

function as the key output of the selection pathway where selected actions are represented by decreased activity. In contrast GPe is part of a control pathway that allows setting selection thresholds via global modulation of GPi output rates. Networks are typically modeled with populations of leaky integrate-and-fire neurons with synaptic time constants matched to experimental data. In this type of model, simulated GP spike trains can replicate key features of rodent recordings (Magill et al. 2001). The Humphries et al. (2006) spiking network model is available on the Yale ModelDB archive.

Modeling the Effects of Deep Brain Stimulation in Parkinson's Disease

Deep brain stimulation (DBS) in STN or GP has proven to be an effective treatment for Parkinson's disease in many patients (Dostrovsky et al. 2002; Vitek et al. 2012). The mechanisms underlying these beneficial effects have been examined with simulations including GP neuron models at all levels of abstraction ranging from detailed biophysical dendritic models to network function. Detailed dendritic GP neuron models have been used to establish how pallidal deep brain stimulation results in changes of local neuron depolarization and firing (Johnson and McIntyre 2008). The effect of DBS to suppress pathological rhythmic synchronization has been the subject of numerous simulation studies and is typically carried out in networks of single-compartment neurons including GP as one structure (Rubin and Terman 2004; Cleary et al. 2013; Kang and Lowery 2013). Network modeling has also addressed the question of how stimulation of fibers and neurons in DBS differentially contributes to information flow in cortico-thalamic loops of information processing (So et al).

Cross-References

- [Basal Ganglia: Beta Oscillations](#)
- [Basal Ganglia: Overview](#)
- [Basal Ganglia: Subthalamic Nucleus Cellular Models](#)
- [Deep Brain Stimulation \(Models, Theory, Techniques\): Overview](#)

- [Integrate and Fire Models, Deterministic](#)
- [Parkinson's Disease: Deep Brain Stimulation](#)
- [Phase Response Curves: Overview](#)

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Further Reading

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Basal Ganglia: Habit Formation

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Definition

In large part, learning is characterized by the formation of new associations. Habit learning appears to be a form of associative learning that can occur in the absence of awareness of what has been learned. Behaviors that lead to a reward can become habitual with sufficient training. When behaviors are habitual, they can be automatically elicited by antecedent stimuli even when the outcome of the behavior is no longer attractive.

Detailed Description

The Representation of Habits

Fundamentally, habits are associations between stimuli and responses, or S-R associations (Graybiel 2008; Mishkin and Petrie 1984; Packard and Knowlton 2002). For example,

when you are confronted with an intersection on your drive to work, this visual stimulus may automatically elicit a left-turn response after years of driving the same route. S-R associations contrast with arbitrary associations between stimuli that we typically think of as declarative learning, such as learning associations between word pairs. However, the distinction between stimulus-stimulus (S-S) associations and S-R associations does not fall neatly in the distinction between declarative and nondeclarative memory. For example, Pavlovian conditioning is the S-S association of a conditional stimulus with an unconditional stimulus, and at least simple Pavlovian conditioning can occur in the absence of awareness of what has been learned and independently of medial temporal lobe structures, including the hippocampus, that support declarative memory. Thus, both S-S and S-R associations can be formed implicitly.

Properties of Habits

Independence of Awareness

In order to make the case that habit learning is distinct from other types of learning, it is necessary to develop a list of its properties. As stated above, learning of S-R habits does not appear to require awareness of what has been learned. That is, people may be acquiring a habit, and not recognize it until they recognize themselves performing it. A powerful means to examine whether learning depends on awareness is to test amnesic patients. These patients have a selective deficit in declarative memory due to damage in the medial temporal lobe or associated diencephalic structures (Squire and Zola-Morgan 1991). Thus, if these patients are able to learn habits, it would suggest that habit learning can proceed independently of awareness. Several studies have demonstrated that patients with severe memory problems can acquire associations between stimuli and responses normally. For example, in a “weather prediction” task in which different cues were associated with the outcome either “rain” or “sun,” amnesic patients were able to learn to select the correct choice at the same rate as healthy control

subjects. Over about 100 trials, both groups were able to achieve a level of performance significantly above chance. However, amnesic patients were unable to remember much about the testing event, such as the layout of the screen or the order of events on each trial (Knowlton et al. 1996). Amnesic patients’ knowledge of the association between the cues and the outcomes also seems to differ from that of the control subjects. Control subjects were able to answer questions about the cue-outcome associations when posed in a different way than what was present during learning. For example, subjects may be asked to imagine that the outcome is sunny and that two cues had been presented, and they should decide which cues would they most likely be. While control subjects seem to have flexible knowledge of these associations, amnesic patients do not (Reber et al. 1996). It seems that their knowledge of the association between the cues and outcomes is encapsulated as a set of stimulus–response habits, while control subjects have gained declarative knowledge of these associations. While the control subjects may have an S-R representation of the cues and the correct responses that are associated with them, they also appear to have declarative knowledge of which cues are associated with each outcome that allows them flexible access to this knowledge. It appears that the amnesic patients are only able to solve the task using S-R habits, such that the cues come to elicit the correct response (pressing either the sun or rain key). These habits may exist independently of awareness and are only observable when the subject is confronted with the eliciting stimulus.

Lack of Flexibility

Another characteristic of habits is that the knowledge gained is not readily applied in other contexts, for example, in a forced-choice task, in which subjects were presented with a series of pairs of items and were required to make a choice between the items of the pair. One item of the pair was consistently rewarded. Patients with dense amnesia were able to gradually learn to select the correct item across many trials. However, they did not have any explicit knowledge of why they were

selecting one item over the other, and they attributed their choices to preference rather than their experience on previous trials (Bayley et al. 2005). In contrast, control subjects learned to pick the correct item in each pair more quickly, and they were well aware that their choices were based on which item had been rewarded on previous trials. Their conscious memory for the rewarded items of each pair enabled them to pick these items out from among all the items – that is, their memory was flexible in that they could readily demonstrate their memory in a context that was different than the one that was present during training. Although the amnesic patients eventually reached the same level as the control subjects in the original forced-choice task, they were making their responses based on S-R habit. They did not have awareness of which items were rewarded and they were unable to use their knowledge flexibly. This lack of awareness and flexibility of knowledge can be considered hallmarks of habit learning.

Insensitivity to Devaluation

One difficulty in determining whether performance on a task is based on habit or declarative memory is that just about every circumstance in which performance could be supported by a habit, performance also could be supported by declarative memory. If a rat learns to press a lever resulting in a food reward, it may be that it has developed an S-R habit, with the lever automatically eliciting a response. However, it may be that the rat remembers that food appears as an outcome of the lever pressing action, an A-O association. Similarly, a person may open their refrigerator door in order to get food that is known to be inside (and A-O association), or they may be simply opening the door out of “force of habit,” in an S-R fashion.

In order to determine the nature of the memory supporting behavior, we need to use probe tasks. For example, we can test subjects’ awareness and flexibility of knowledge to demonstrate that what was learned differed for control subjects and amnesic patients. However, these tasks did not probe the structure of the underlying association – whether performance was supported by S-R or

A-O connections. In studies of animal learning, this has been accomplished by assessing the effect of devaluing the outcome on subsequent performance. The logic here is that in an S-R association, unlike in an A-O association, the outcome is not represented. Thus, performance of the habit should not change if the outcome is no longer desired (Dickinson 1985). For example, if you are in the habit of turning left at a certain intersection on your route to work, you may unintentionally make this turn one Saturday when you meant to go somewhere else. Although the outcome (getting to work) was not desired at that time, the habitual response persisted when the intersection was encountered. Another example may be entering a room and reaching to turn on a light switch through force of habit. Even when you have learned that the light has burned out or perhaps it is daytime and you do not need any light, the habit persists.

In several studies of instrumental learning, the training schedule was shown to be an important factor as to whether learning is based on an A-O or S-R association (Dickinson et al. 1983; Yin et al. 2004). When rats were trained to press a bar for food under a ratio schedule, devaluing the food reinforcer resulted in a decrease in response rate, suggesting that the rats were pressing the bar in order to get food. In a ratio schedule, reinforcement is given each time the animal makes a certain number of responses – in other words, food is given after every third bar press. In contrast, training rats under an interval schedule leads to performance that is insensitive to reinforcer devaluation. In an interval schedule, reinforcement is given if a response is made at any time during an interval (e.g., 30 s). No more reinforcement is given if 1 or 100 responses are made during the interval. A real-world example may be like checking your mail. After training rats in an interval schedule, one can then make the food that was used during training unattractive to the rats. One way to accomplish this is to give the rats an unlimited amount of the food while they are in their home cage. When they become sated on the food, they are immediately tested to see whether they will continue to respond as vigorously as a hungry rat.

When rats are trained on an interval schedule, devaluation of the reinforcer has no effect. This is some of the strongest evidence that performance can be supported by S-R associations and that such habit learning is distinct from learning the association between responses and their outcomes.

One reason why training with ratio and interval schedules leads to such different underlying associative representations is that the contingency between the response and the outcome differs. Under a ratio schedule, each sequence of responses is reinforced – if responding decreases, the number of reinforcers decreases. However, with an interval schedule, the number of reinforcers received is not nearly so tied to the response rate – under a 30-s schedule – and responding once per second and once per 30 s would yield the same amount of reward. The level of contingency between an action and its outcome appears to be a key factor in whether learning results in a habit (Balleine and Dickinson 1998).

Historically, the idea that learning is based on the formation of stimulus–response habits has been influential. Hull promoted the idea that all learning could be reduced to a series of S-R habits (Hull 1943). The role of reinforcement was to strengthen these S-R bonds. However, this view was challenged by the fact that some types of learning did not seem to be consistent with the acquisition of an S-R habit. The most striking example is latent learning described by Tolman and Honzik (1930), who showed that animals learn the spatial layout of an environment even when not given reinforcement. Although it seems clear in hindsight that not all learning is habit learning, the later acknowledgment that there are multiple learning and memory systems made it clear that habit learning can coexist with other forms of learning. Mishkin and colleagues made this point in drawing the distinction between habit and cognitive learning, with these two different types of learning depending on different brain systems (Mishkin et al. 1984). Differences in the neural architecture supporting these different types of learning give rise to differences in their psychological properties.

Automaticity

Another feature of habit learning that seems to distinguish it from declarative or “cognitive” learning is that it occurs relatively automatically. Declarative learning and the retrieval of information from declarative memory are fairly attention demanding. Memory encoding is poorer when performing a concurrent task, and while retrieval from memory may be accurate under dual task conditions, it is significantly slower (Craik et al. 1996). We certainly understand that being distracted while studying will hamper learning of new facts and that it is more difficult to remember information on a test when a distraction is present. In contrast, habit learning does not seem to benefit as much from focused attention. In fact, it is often when we are distracted that we produce a habitual response when we intended otherwise, such as when we make the turn to go to work when we in fact had set out for a different destination.

The presence of distraction during learning may result in a reliance on the habit learning system under circumstances in which one is likely to form declarative memory representations when attention is not divided. In a study using the probabilistic classification task, subjects learned two different sets of associations (Foerde et al. 2006). They were told that they would be learning to predict the weather in two different cities (Budapest and Prague) using two different sets of cues. The two different sets of cues were in different colors to make it clear which task they were performing on each trial. The subjects predicted the weather for one city under single task conditions – the weather prediction task was the focus of their attention. In other blocks, subjects predicted the weather for the other city while they concurrently performed another task in which they had to keep a running count of the number of tones that were presented. Although subjects performed numerically worse at predicting the weather when they were learning under dual task conditions, performance was similar for the two cities when subjects were later tested under single task conditions for both tasks. This suggests that while the performance on a concurrent task may slightly impair performance of a habit (perhaps by occasionally causing the subject to misperceive

the cues or make the wrong response), it does not seem to impair the acquisition of the habit.

One of the most interesting behavioral findings of this study was the fact that the representations underlying single and dual task learning in these two tasks appeared to be different. For the city in which the task learned under single task conditions, subjects had flexible knowledge of the cue-outcome associations. They were able to accurately assess which cues were most likely to be present if it was rainy or sunny, so they were able to access their knowledge of the cue-outcome associations in a way that was different than that posed in the original task. For the city in which the weather prediction learning occurred under dual task conditions, this flexible knowledge was much less apparent, even though performance on the task itself was fairly normal. These results are consistent with the idea that habit learning can proceed under conditions in which attentional resources are limited. In addition, these data suggest that learning while distracted can result in the learned knowledge restricted to S-R habits rather than flexible declarative representations.

Incremental Learning

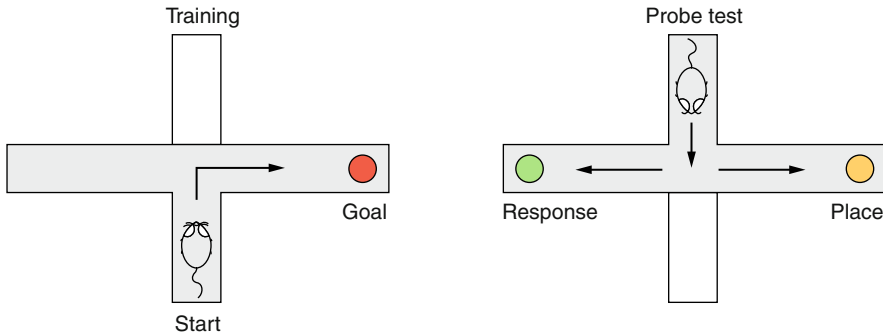
An important characteristic of declarative learning is that it can occur in a single trial. We have conscious memories for specific moments in time that we will keep in our entire lives. The unique structure of the hippocampus is thought to be able to support the rapid learning necessary for the encoding of episodes (Rolls 2007). Our experience of habit learning is different in that we think of habits as behaviors that develop over time. Habits are acquired gradually, with feedback incrementally strengthening the bond between stimulus and response (Packard and Knowlton 2002). The neural structures that support habit learning may not be capable of single-trial learning. It may be that the slow incremental learning of habits and the rapid learning of episodes are complementary, ensuring that behaviors that have a long history of reward are automatic and stable while still maintaining the flexibility to alter behavior when there is a conditional change (Squire 1992).

The gradual nature of habit learning is exemplified by the fact that overtraining typically results in goal-directed actions becoming habits. As discussed above, when rats are trained to make an instrumental response under a ratio schedule, performance is goal directed, in that responding will decrease when the reinforcer used is devalued. However, when training is continued, performance will eventually become insensitive to reinforcer devaluation, indicating that the response has become “habitized” (Dickinson 1985). Overtraining may serve to break down the contingency between responding and the outcome, because very few responses are withheld at this point. The animal no longer experiences the consequences of not making a response, so the link between the response and the outcome is less apparent (Dickinson et al. 1983).

The effect of overtraining on the development of habit learning can also be seen using the cross-maze task (Tolman et al. 1946). In this task, a rat is trained to go to a baited arm that is either to the left or to the right of the start arm (e.g., for a rat that starts in the “south” arm, the food reward will always be at the end of the “east” arm). If rats are given a moderate amount of training and are then tested using the opposite start arm (in the example, the “north” arm), they go to the location where they received the reward. However, with overtraining, rats persist in making the same motor response as during training – they turn in the same direction, and thus when they are started from the “north” arm, they turn right and end up in the “west” arm (Hicks 1964; Packard and McGaugh 1996; Fig. 1). Overtraining results in this shift to a reliance on a response strategy, in which the maze elicits a motor response in an S-R fashion.

Dependence on Feedback

Finally, an important characteristic of habit learning is that rewarding feedback is necessary to strengthen the habit. Declarative learning is thought to occur continually and incidentally (Stark and Okado 2003). As in the case of the latent learning procedure described above, information is stored in memory even without



Basal Ganglia: Habit Formation, Fig. 1 The cross maze used to probe whether a rat is responding based on memory for the location of a reward or based on a habitual motor response. If the rat chooses based on its memory for the location of the reward, during the probe test, it will go

to the “place” the reward had been presented (the right arm). If the rat is responding based on habit (making the right-turn “response” when in the maze), it will go to the left arm in the probe trial

reinforcement. For habit learning, reinforcement is thought to be critical for strengthening S-R bonds, even though the reinforcer is not part of the learned representation. One study that specifically examined the role of feedback in habit learning used the probabilistic classification task (Shohamy et al. 2004). In the version of the task used by these investigators, subjects learned to guess which flavor of ice cream (chocolate or vanilla) was preferred by a Mr. Potatohead figure that was presented on each trial. Unbeknownst to the subject, the features that could be present or absent on the Mr. Potatohead were probabilistically associated with either a chocolate or a vanilla preference. The procedure was similar to that used in the weather prediction version of the task for some of the subjects. These subjects made a response (pressing either the “chocolate” or “vanilla” key) and received feedback that they were correct or incorrect on every trial. The other subjects received an “observational” version of the task in which the figures were presented followed by the correct answer (chocolate or vanilla). In the observational task, the same information about the association between cues and outcomes was present, but the subjects did not make a response that was rewarded. It appeared that these two learning situations differ, in that only feedback learning was impaired in patients with Parkinson’s disease. This finding suggests that feedback-based learning is supported by

different neural substrates than observational learning.

The idea that feedback-based and observational learning differ in terms of neural mechanisms is also supported by findings from neuroimaging. Results from a study using the weather prediction version of the probabilistic classification task have shown that when the task is learned with feedback, learning is associated with activation in the striatum, while learning through observation results in activation of medial temporal lobe (Poldrack et al. 2001).

Brain Mechanisms of Habit

Mishkin and Petrie (1984) argue that “Hullian” habit learning and cognitive learning described by Tolman coexist based on the idea that distinct brain systems support different forms of learning. Mishkin and Petrie identify the basal ganglia and medial temporal lobe structures as supporting habit versus cognitive learning. A great deal of support for this idea has come from lesion studies that illustrate double dissociations between the effects of damage to the striatum of the basal ganglia on habits and lesions of the medial temporal lobe on cognitive learning. In nonhuman primates, damage to medial temporal lobe structures including the hippocampus and surrounding temporal lobe cortices results in significant impairment in cognitive memory tasks such as the delayed non-match to sample task (Murray

2000). In this task, the subjects are presented with a sample item and after a delay (from seconds to hours) are presented with the sample item and a different item. The subject's task is to pick the new item. This task requires the monkey to remember an event – the presentation of the sample stimulus – in order to make the correct choice. Learning in this task is unaffected by lesions of the tail of the caudate nucleus – the region which receives visual information from cortex. In contrast these lesions severely impair performance on a concurrent discrimination task (Fernandez-Ruiz et al. 2001). As described above, in this task the subject is given pairs of objects, with one element of the pair consistently rewarded. As discussed previously, this task can also be learned either declaratively or as a set of S-R habits. It appears that when monkeys are given a single trial per day for each discrimination, learning becomes habitual, perhaps because they are unable to readily recall previous trials with such a long delay between them. Under these conditions, lesions of the tail of the caudate nucleus disrupt learning, while medial temporal lobe lesions have no effect (Fernandez-Ruiz et al. 2001; Malamut et al. 1984). These results indicate that habit learning and declarative learning rely on different neural systems.

Double Dissociations Between Memory Systems

Several studies using rats have demonstrated clear double dissociations between medial temporal lobe and striatal learning systems. In a seminal study by Packard et al., rats were trained on two different versions of the radial arm maze task (Packard et al. 1989). In the radial arm maze, eight arms radiate out from a central platform, and a food reward is placed at the end of each arm. In the win-shift version of this task, arms are not rebaited as the rat eats the food, so the rat should not return to these arms during the session. The win-shift version of this task taps into foraging strategies that rats have presumably evolved to efficiently recover food over an area. Packard et al. (1989) replicated the findings from a number of studies that lesions of the hippocampus severely disrupt performance in this task (Becker et al. 1980). In order to avoid revisiting arms, the

rat must remember the locations it has just visited on that session. This would seem to require episodic memory, or memory for specific events.

In contrast to the win-shift version of the task, rats can also learn a win-stay discrimination on the radial arm maze, in which a cue consistently signals when an arm is baited, for example, the cue may be a light, which when illuminated indicates that food is present at the end of the arm. Unlike in the win-shift version of the task, the rat does not need to remember any specific event. Rather, the rat simply must learn to run down lit arms. Perhaps because it does not tap into a natural foraging strategy, rats learn this task gradually over many sessions – keep in mind that the important information learned in the win-shift task is acquired in single trial on each testing day. Packard et al. (1989) found that lesions of the striatum (the lateral caudate nucleus, which roughly corresponds to the primate putamen) impair learning of the win-stay version of the radial arm maze task. Like other habit learning tasks, this task is not affected by damage to the hippocampal system. Because the win-shift version of the task was not impaired by lesions of the striatum, there is a double dissociation between the effects of lesions on the hippocampus and striatum. This finding provides strong evidence that these two tasks depend on independent brain systems.

A similar dissociation was shown using the cross maze described above (Packard and McGaugh 1996). Rats in which the hippocampus was inactivated by an intracranial injection of lidocaine did not exhibit a preference for the location strategy after a moderate amount of training, unlike rats in the control group which received saline injections. Hippocampal inactivation appeared to prevent the expression of the location response. In contrast, rats in which the dorsolateral striatum was inactivated after moderate training showed normal expression of the location response, but when the dorsolateral striatum was inactivated after overtraining, the rats maintained the location response and did not switch to the habit response. Thus, the dorsolateral striatum must be active for expression of the gradually developing habit response.

There is also evidence in human subjects that there is a dissociation between striatal-dependent habit learning and learning that depends on the medial temporal lobe. The probabilistic classification task has been extensively studied in patient groups. For example, patients with Alzheimer's disease, which is accompanied by damage to the medial temporal lobe memory system, are able to learn the S-R associations in the probabilistic classification task (Eldridge et al. 2002). However, patients with Parkinson's disease, which affects dopaminergic input to the striatum, appear to be impaired on this task (Knowlton et al. 1996). In patients with mild Parkinson's disease, performance is not different than that of healthy control subjects. However, fMRI showed that the patients and control subjects used different neural systems during performance of this task (Moody et al. 2004). Performing the weather prediction task was associated with greater activation in the putamen in control subjects than in the patients. The control subjects also showed a decrease in activation in the hippocampus during the weather task, a finding that has been seen before. It appears that in the controls, the hippocampus is more active in the baseline condition, in which the subject is performing a very simple task (it is likely that under such conditions, the mind can wander and the subject spontaneously engages in mnemonic activity). In contrast, in the patients with Parkinson's disease, hippocampal activation was greater than the level seen in the baseline condition, consistent with the idea that these subjects were relying on declarative memory to support performance in this task. Because the habit learning system was compromised in these patients, they appear to have relied on declarative memory to perform this task.

A similar distinction between habit and declarative learning was found in the fMRI data of the study described above comparing performance of the weather prediction task under single task conditions and during distraction (Foerde et al. 2006). For the associations learned under single task conditions, performance was actually correlated with hippocampal activity in these healthy young subjects. For the associations learned under distraction, performance correlated with activity in

the striatum and not the hippocampus, suggesting that the different neural systems were responsible for learning under the two conditions. These findings also suggest that when declarative memory is functioning well, as in undistracted young subjects, it can support learning in the probabilistic classification task. However, habit learning appears to support performance when declarative memory is not strong (older subjects, distracted young subjects).

Although these dissociations based on lesions strongly suggest that different memory systems exist, these findings do not directly demonstrate that the striatal-dependent form of learning has the defining features of habit learning. While win-stay learning in rats has some of the properties of habit learning in that it is gradual and does not depend on brain regions important for declarative learning, more recent work demonstrated that learning in this task does indeed depend on S-R associations (Sage and Knowlton 2000). After training rats on a win-stay task in which they ran down lit arms to receive food, the food reward used was devalued by pairing it in the home cage with an injection of lithium chloride, which results in a learned taste aversion to the reward food. The key question was when the rats were placed on the radial arm maze after devaluation, would their behavior be modified in any way in light of their acquired aversion to the food reward. In fact, rats continued to run down the correct arms just as rapidly as they had when the food was attractive to them. This suggests that the rats had learned an association between the light and the response to run down the arm, with the reward not represented in the association. In contrast, rats trained in the hippocampal-dependent win-shift task slow down significantly when the food reward is devalued. They still employ their typical foraging strategy of efficiently traversing the maze, but their slow responding indicates that their behavior is influenced by the reward value.

Lesions of the dorsolateral striatum have been shown to prevent habit learning in instrumental procedures as well. In one study, rats with dorsolateral striatal lesions and control rats were trained under an interval schedule to press a bar for a food reward (Yin et al. 2004). Both the lesioned group

and the control group learned to make the response at roughly the same rate. However, when the reward food was devalued by pairing it with illness, the two groups behaved very differently. The performance of the control group was as expected for animals trained using an interval schedule; they continued to make the instrumental response even though the food reward was no longer attractive to them. In contrast, rats with dorsolateral striatal lesions showed a significant decrease in responding. In a sense, the lesioned rats are behaving with greater “insight” in that they are avoiding a response that is associated with undesired outcome. These data strongly make the case that the dorsolateral striatum is necessary for the development of habits. In the absence of the structure, habitual responding does not appear to develop and responding is guided by the outcome.

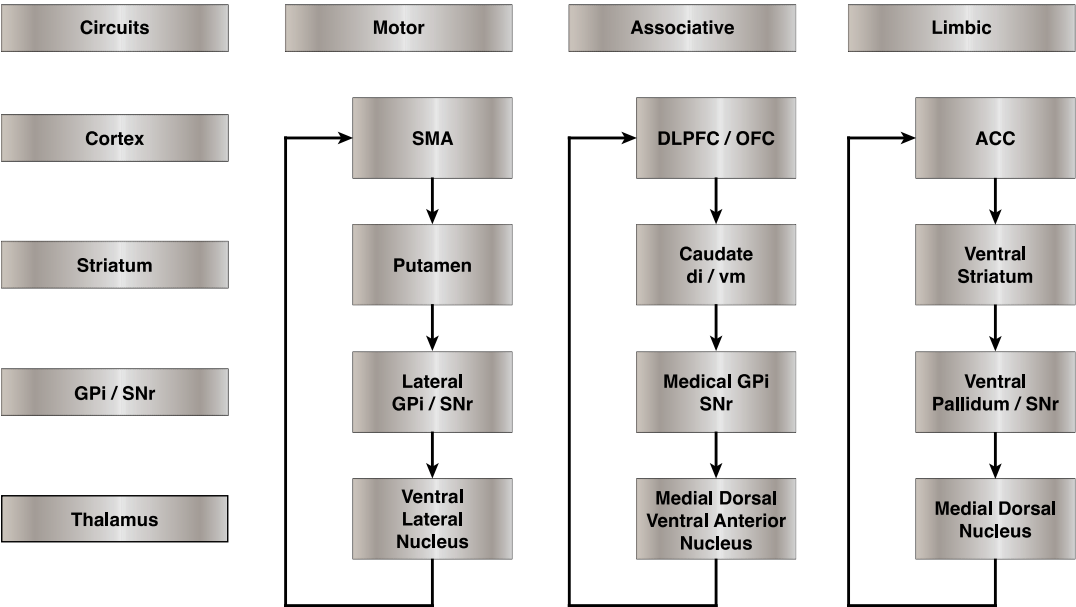
Basal Ganglia Loops

While the distinction between medial-temporal-lobe-dependent memory and striatal-dependent

memory is an appealing idea, it is also too simple. The striatum is organized into fairly discrete loops that include the pallidum and thalamus and different cortical regions. A seminal paper by Alexander et al. (1986) describes the architecture of these loops based on neuroanatomical findings (Fig. 2). Just as different regions of cortex have very different functions, these loops support rather different cognitive operations. Thus, it does not make sense to think of the striatum as the substrate of a particular type of memory, but rather that the different loops may serve to support different memory processes (Yin and Knowlton 2006). Lesions that affect habit learning appear to involve the dorsolateral striatum in the rat or the putamen in the primate, suggesting that the motor loop is critical for habit learning. The fact that this loop includes cortical regions that are important for motor output is consistent with the idea that habit learning involves an association with a response.

Other corticostriatal loops also appear to be important for behavior dependent on declarative

Parallel cortical-basal ganglia-cortical circuits



Basal Ganglia: Habit Formation, Fig. 2 Abbreviations: SMA supplemental motor area, DLPFC/OFC dorsolateral prefrontal cortex/orbitofrontal cortex, ACC anterior

cingulate cortex, dl/vm dorsolateral/ventromedial, GPi/SNR globus pallidus internal/substantia nigra reticulata

learning. Damage to the dorsomedial caudate nucleus in the rat results in behavior that appears habitual under conditions in which intact rats perform based on declarative memory. In the Morris water maze, rats with dorsomedial caudate lesions have difficulty learning the location of a hidden platform and behave similarly to rats that have hippocampal lesions (Devan et al. 1999). This contrasts with the performance of rats with lesions of the dorsolateral caudate nucleus – this group is able to learn the location of the hidden platform, but has difficulty learning to swim to a cue that signals the location of the platform.

In another study using the cross maze, a dissociation was found between lesions of the dorsolateral and dorsomedial striatum (Yin and Knowlton 2004). Rats with dorsolateral striatal lesions did not show the typical tendency to run down an arm based on a stimulus–response habit after extensive overtraining. They retained the tendency to go to the rewarded location even when starting from a new arm. However, lesions placed more medially produced an effect more similar to that of hippocampal system lesions. These rats did not go to the location where they had been rewarded on previous trials, but rather, they responded based on the motor habit. The mediodorsal striatum in the rat is similar to the head of the caudate in the primate. This region is interconnected with prefrontal regions that may be more involved in goal-directed action than in habit learning (Yeterian and Pandya 1991). This loop may in fact be important for implementing actions based on the contents of declarative memory.

Electrophysiological studies have also supported the idea that goal-directed actions and habits depend on different corticostriatal loops. In nonhuman primates, performance early in training is accompanied by increased firing in the caudate nucleus. When the slope of the learning curve is steep, firing in the caudate nucleus was correlated with the slope of the learning curve. In contrast, firing in the putamen was correlated with the level of learning, with firing highest after extensive training when the monkeys were adept at the task (Williams and Eskandar 2006).

Communication Between Loops

Corticostriatal loops are often characterized as functioning independently, based to a great extent on anatomy. The thalamic targets of these loops are the same cortical regions that originated the loop. For example, in the motor loop, cortical projections from the motor cortex are directed to the putamen, which projects to relatively discrete regions of the globus pallidus that project to the ventrolateral nucleus of the thalamus. This thalamic nucleus sends its cortical projections back to motor cortex, thus completing the loop. However, it is also the case that these loops have the potential to interact based on other features of the anatomy. The thalamocortical projections terminate in multiple cortical layers, including layer III, the site of neurons that gives rise to cortico-cortical projections. Thus, the output of one loop is able to influence another through these cortico-cortical projections (McFarland and Haber 2002). In addition, there are extensive projections from the cortex back to the thalamus. For example, cortical regions involved in planning actions (pre-supplementary motor area and premotor cortex) send projections to VL, which is part of the motor loop that projects to primary motor cortex and supplementary motor cortex. By these “open loop” projections, different cortical regions can influence corticostriatal loops at the level of the thalamus.

A third mechanism by which loops can communicate is through the projections from the striatum to dopaminergic neurons in the midbrain (Joel and Weiner 2000). These dopaminergic neurons in the ventral tegmental area and the substantia nigra are the source of a major projection to the striatum. There is reciprocity in these projections, in that the different striatal regions project back to the midbrain region that supplied dopaminergic input to that region. For example, the ventral tegmental area is a major source of dopaminergic input to the ventral striatum, and the ventral striatum projects back to the ventral tegmental area. In addition, however, the ventral tegmental region also projects to other striatal regions, thereby allowing communication between the limbic loop and the other striatal loops. The dopaminergic neurons targeted by

striatal regions of the association loop (i.e., the caudate nucleus) also give rise to both reciprocal projections and projections that target the striatal regions of the motor loop (i.e., the putamen). Thus, the midbrain dopaminergic system is another means by which corticostriatal loops may interact.

An interesting feature of the striatal projections to both the thalamus and the dopaminergic system is that there seems to be a hierarchical organization in the potential interactions between loops (Joel and Weiner 2000). Cortical regions in the limbic loop project to thalamic regions in loops involved in executive function, and cortical executive regions project to thalamic regions involved in the motor loop. A similar hierarchy exists for the dopaminergic projections. The ventral striatum (limbic loop) projects to midbrain dopaminergic regions supplying all other loops, striatal regions in the executive loop send projections to dopaminergic regions supplying the executive and motor loops, and the motor striatum primarily sends only reciprocal connections back to the dopaminergic neurons that project to it. Thus, it seems that in both mechanisms of interaction, the limbic loop has the potential for greater influence over the other loops, loops involved in executive function can influence those involved in motor function, while the motor loops have limited ability to influence the other loops.

The reciprocity of connections in the motor loop has been incorporated into computational models of learning in the striatum. Dopaminergic input plays an important role in providing a reinforcement signal in these models. The actor-critic architecture (Barto et al. 1983) captures this role of reinforcement, by postulating a “critic,” in the form of dopaminergic input, that provides the “actor,” in the form of striatal neurons, with a reinforcement signal based on whether success has been obtained. One challenge to these models is the problem of credit assignment – the consequences of an action are often delayed. These models are able to address this challenge based on the fact that the dopaminergic input to each region of the striatum arises from cells in that same zone that receives input from that striatal region. This reciprocity means that dopaminergic

activity will strengthen the response just preceding it. On subsequent trials, dopaminergic activity will then occur during this response, thus strengthening the response just before it. Through this recursive mechanism, activity in the dopaminergic neurons becomes a predictive signal for reinforcement (Houk et al. 1995).

Plasticity in the Striatum

One question that arises in discussing the role of the neostriatum in learning is where the plastic changes that support learning occur, and whether the physiological mechanisms of this plasticity are similar to or different than those that have been described in the medial temporal lobe system. As in the hippocampus, long-term potentiation (LTP) occurs in the striatum, and this phenomenon has been considered a model system for the formation of habit memories (Reynolds et al. 2001). In addition, long-term depression (LTD) can also be induced in the striatum. High-frequency stimulation of the cerebral cortex induces LTP or LTD at the corticostriatal glutamatergic synapses. Dopamine is important for the induction of plasticity in the striatum. LTP or LTD cannot be readily induced in slices from animals in which dopamine is depleted (Calabresi et al. 1992; Kerr and Wickens 2001).

Unlike in the hippocampus, where LTP has been studied more extensively than LTD, striatal LTD has received more attention in the past than LTP. High-frequency stimulation trains that produce LTP in the hippocampus produce LTD in the striatum. In fact, LTP was not initially obtained in the striatum unless magnesium was absent. It appears that the facilitative effects of the lack of magnesium were mediated by dopamine-NMDA receptors, which are normally blocked by magnesium, and can be activated on presynaptic dopamine terminals, leading to an increase in dopamine levels (Wickens and Arbuthnott 2005).

More recently, the role of dopamine in striatal plasticity has been shown to be complex. The different types of dopamine receptor (D1 and D2) are on different populations of medium spiny neurons in the striatum. Both receive dopaminergic input from the substantia nigra, but these two classes of neurons participate in two different

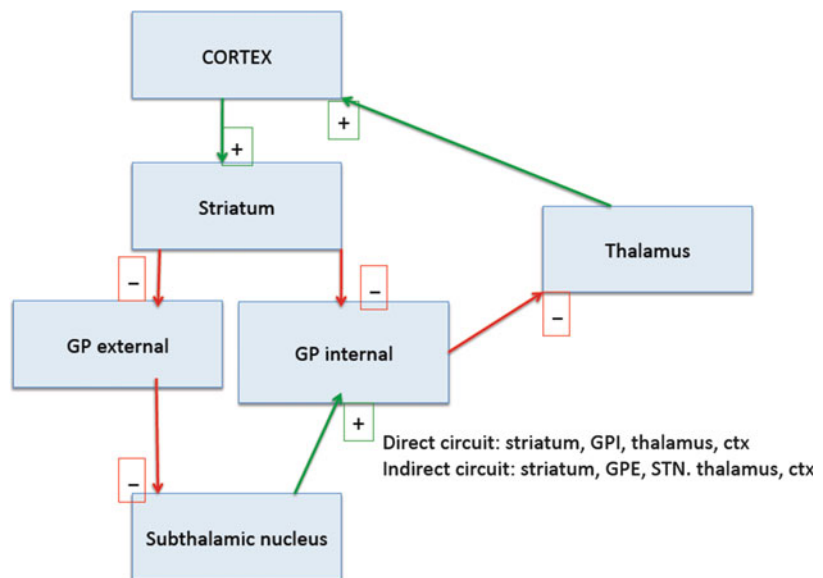
striatal output pathways: D1 receptors are on neurons in the direct pathway, and D2 receptors are on neurons in the indirect pathway that includes the globus pallidus external and the subthalamic nucleus (Gerfen et al. 1990; Fig. 3). On both of these pathways, glutamate input from the cortex is excitatory, but the net effect of the two pathways is different. Exciting the direct pathway serves to remove tonic inhibition in the thalamus, which thus is excitatory to the cortex. Exciting the indirect pathway has the net effect of strengthening this tonic inhibition. Thus, striatal plasticity can lead to either increased or decreased cortical activity.

In a study examining the role of dopamine in striatal plasticity, Shen et al. (2008) assessed LTP and LTD in both the direct and indirect pathways. On striatal medium spiny neurons that have D1 receptors (the direct pathway), LTP can be generated from pairing presynaptic activity with postsynaptic depolarization. When D1 receptors are blocked, this pairing leads to LTD. In medium spiny neurons with D2 receptors (the indirect pathway), LTP and LTD can be induced, depending on the timing of the pre- and postsynaptic stimulation. Blocking D2 receptors disrupts LTD, while increasing D2 receptor activation results in LTD under conditions in which LTP is normally induced. Thus, under low dopamine

levels, when only higher-affinity D2 receptors are activated, plasticity is bidirectional in neurons containing D2 receptors, while only LTD is enabled in neurons containing D1 receptors. However, when dopamine levels rise, as when a reinforcing stimulus is present, LTP can be induced in neurons containing D1 receptors, while those containing D2 receptors will be biased toward LTD.

These findings point to an important role for dopamine in the control of plasticity in corticostriatal synapses and suggest that medium spiny neurons with D1 and D2 receptors play different roles in learning. When D1 receptors are activated, as in the case of a large, unexpected reward, efficiency will increase in corticostriatal synapses on neurons containing D1 receptors, thus strengthening the direct pathway, leading to greater excitation of the cortex. However, when dopamine is at a tonic level, experience would result in enhancement only in corticostriatal synapses on neurons containing D2 receptors, thus strengthening the indirect pathway, leading to increased tonic inhibition of cortex (Shen et al. 2008). In addition to differences in the role of different corticostriatal loops in behavior, conditions within each loop (e.g., dopamine levels) control the net effect of that loop on its target cortical region.

Basal Ganglia: Habit Formation, Fig. 3 Direct and indirect pathways in the basal ganglia.
Abbreviations: *GPI* globus pallidus internal, *ctx* cortex, *GPE* globus pallidus external, *STN* subthalamic nucleus



It is tempting to think of these two mechanisms of plasticity of supporting learning of actions and habits; early in learning, new associations are formed in the direct pathway when dopamine signals the presence of reinforcement. As practice increases and reinforcement becomes expected, dopamine levels decrease and performance becomes increasingly controlled by the indirect pathway, characterized by a lack of flexibility and insensitivity to devaluation.

The interplay between the direct and indirect pathways is incorporated into models of dynamic gating by the basal ganglia (Frank et al. 2001). When the direct pathway is activated, there is a disinhibition of cortex, enabling the updating of working memory and flexibility. Activity in the indirect pathway has the opposite effect – it increases inhibition in the cortex, thus favoring maintenance. In this way, the architecture of the cortico-basal ganglia system balances between the conflicting demands of updating vs. maintaining behavior. Furthermore, the existence of parallel loops with relative independent neuronal circuits allows the updating of some information, but not others according to these gating models (O'Reilly and Frank 2006).

Interactions Between Learning Systems

What does the anatomy and neurophysiology of the striatum suggest about how different systems for learning interact? The loop architecture suggests parallel modes of learning; loops involving the caudate and prefrontal cortex may be more involved in voluntary action than loops involving the putamen and motor cortex. Learning may proceed in these loops in parallel, with behavior controlled by whichever loop is the most effective at influencing the structures supporting behavioral output. While the limbic and associative loops are able to influence the effectiveness of the motor loop, there is substantial independence – one could be learning a goal-directed action while also strengthening a habit based in the motor loop. By this view, learning a goal-directed action does not impede the learning of a habit or vice versa. On the other hand, the antagonistic relationship between plasticity in the direct and indirect pathways suggests that at some level there is

competition between types of learning. Linking plasticity in the direct and indirect pathways with behavior is essential for understanding the significance of striatal architecture.

If different memory systems acquire memories in parallel, competition is likely to occur at the level of control for behavioral output. It may be that the selection is based on the strength of the learned representation. Declarative memories may be formed faster and thus control behavior early in training, while habits accumulate associative strength more slowly, but eventually become dominant. For example, in the cross-maze task described above, the correct response according to a declarative memory for the location of reward is incompatible with the stimulus–response-based habit to turn in one direction in that these two responses lead to different places when a new starting location is used at the opposite end of the maze. Thus, the control of behavioral output may be determined by relative memory strength, which would likely change with practice level. If behavioral output is determined by memory strength, the critical question is how the “strongest” memory is determined that will control behavioral output. Of course, in most situations, declarative memory and habit would presumably lead to the same outcome. However, situations such as the cross maze can bring these two systems into conflict. This could be seen in the “real-life” example of making a turn along a well-learned route when in fact you had intended to turn the other way at the intersection to go to a different destination on this day. Responding based on habit and on declarative memory will lead to opposing responses.

Given that responses based on declarative memory and habit learning can differ, it is important to determine the conditions that favor the use of one representation over another. Our awareness is based on declarative knowledge. Thus, when we are consciously aware of responding based on memory, we are using declarative memory. However, when awareness is otherwise occupied, behavior is more likely to depend on habits due to their relative insensitivity to working memory load (Foerde et al. 2007). Conditions that occupy or reduce working memory resources, such as

anxiety, depression, and fatigue, may bias behavior toward the learning and retrieval of habits. Individuals suffering from depression and anxiety exhibit impaired working memory (Rose and Ebmeier 2006; Samuelson et al. 2006). In addition, even mild forms of depression are accompanied by a tendency to ruminate and have intrusive thoughts, thus squandering working memory resources (Joormann and Gotlib 2008). Emotional factors may thus play a role in the type of representations that are learned and that control behavior. The implications of this idea are that people under stress or preoccupied may be more likely to fall back on old habits even when an updated approach is warranted.

Habit learning is a form of instrumental learning, in that making the response is necessary to obtain the outcome during training. In Pavlovian conditioning, pairing of the conditional stimulus (e.g., a buzzer) and an unconditional stimulus (e.g., food) leads to the conditional stimulus eliciting a conditional response (e.g., salivation). The response has no bearing on whether the unconditional stimulus is received. Interestingly, these two different forms of learning interact. Presenting cues that have been conditional stimuli in Pavlovian conditioning can act to facilitate the transfer of actions to habits. This phenomenon has been discussed most extensively in the context of addiction, where behaviors such as drug taking become compulsive and persist despite the desire to cease. The transition from voluntary action to habitual responding is thought to characterize, at least in part, the transition from drug user to drug addict (Everitt et al. 2001). During drug use, Pavlovian conditioning occurs that associates drug-related cues and contexts (conditional stimuli) with the physiological effects of the drugs (unconditional stimuli). In animal models of addiction, the presence of these conditional stimuli leads to faster learning of an instrumental response (Pavlovian-instrumental transfer) but also a faster transition from voluntary responding to habitual stimulus–response responding. This effect of Pavlovian conditioning may result from the influence of limbic loops of the striatum on other loops (Everitt and Robbins 2005).

Conclusion

Although we are often not aware of our habits, they arguably have a greater influence on our ongoing behavior than declarative memories do. Our habits provide a backdrop to our conscious behavior. Psychiatric disorders such as addiction and compulsive behaviors are fundamentally problems with habits that are intrusive in daily life. Thus, how habits are formed and how they interact with declarative memories are key questions in understanding both normal and abnormal behaviors.

Cross-References

- [Basal Ganglia: Overview](#)
- [Hippocampus, Model Network Architecture](#)

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Basal Ganglia: Mechanisms for Action Selection

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Definition

The basal ganglia are an interconnected circuit of fore- and midbrain nuclei common to all extant vertebrates, including the lamprey, which

diverged from the main vertebrate line approximately 560 MYA. Moreover, there are analogous structures in birds and bony fish. The preservation of this circuit implies a crucial operation that solves a problem common to all vertebrates. While many functions for the basal ganglia have been proposed, our current best theory to unify these ideas is that this circuit solves the common problem of action selection. Informally put, this is the problem of how to decide what to do next.

Detailed Description

Why Action Selection?

The necessity of a mechanism for action selection is imposed by the strong constraint that complex animals have a final common motor pathway: the connections of the spinal cord and the number of muscle groups limit the set of actions that can be expressed simultaneously. Some mechanism is required to reduce the repertoire of currently available actions to just those actions capable of simultaneous expression. Given the constraints of biological tissue, a central rather than distributed selection mechanism is likely the preferred solution implemented by a neural substrate (Prescott et al. 1999). Briefly, the argument runs as follows. Typically, distributed selection mechanisms, formed by reciprocal, inhibitory links between n behavior-representing nodes, contain $n(n - 1)$ links and grow as $2n$ for every additional node. By contrast, a central selection device which is reciprocally connected with all n nodes (thus allowing control over the expression of each node's represented behavior) requires just $2n$ links and grows by 2 for each additional node. Thus, a central selection device is more economical in both the number of connections required and the cost of adding nodes. Such economy of wiring appears to be a priority for the central nervous system (Cherniak 1994).

The basal ganglia appear to fulfill the criteria for such a central mechanism (Redgrave et al. 1999). The main input nucleus, the striatum, receives input from every region of cortex, from primary visual, auditory, and somatosensory cortex, through motor cortices, to the subregions of

prefrontal cortex. It is thus in a position to integrate sensory information, current motor commands, planning, and goals into representations of the relative importance, or *salience*, of each action. The output of the basal ganglia targets regions in the thalamus and brain stem that underpin the execution of different actions. The basal ganglia are thus also in a position to directly control the activity in neural systems responsible for executing actions.

The idea that the basal ganglia perform action selection is also a potential solution to the long-standing paradox of their role in controlling movement (Marsden and Obeso 1994). Activity in the basal ganglia is strongly correlated with movement onset and parameters of that movement, and stimulation of regions of the striatum can evoke discrete, smooth limb movements (Alexander and DeLong 1985). Yet lesions of basal ganglia nuclei in animal studies or in Parkinson's disease patients to alleviate their symptoms do not clearly impair the initiation of movement (Marsden and Obeso 1994). The theory that the basal ganglia are necessary to control the choice of actions explains how movement-related activity can arise yet not be needed to directly generate movement.

How Can the Basal Ganglia Circuit “Select”?

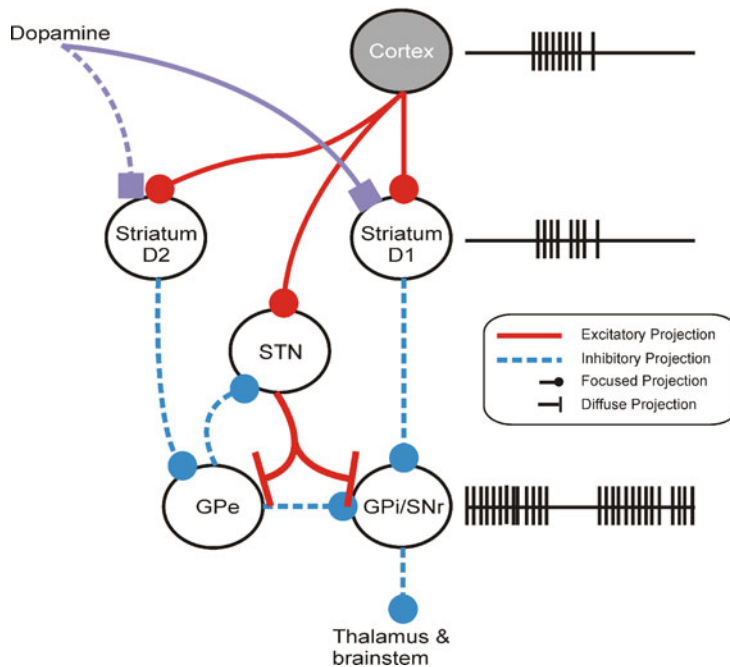
While the basal ganglia's inputs and outputs position these nuclei to potentially act as a central selection mechanism, the key evidence in favor of this idea is that their internal circuitry is seemingly designed to implement a selection process. Figure 1 illustrates the basic circuitry of the basal ganglia as currently understood. The original proposals for how the internal circuitry of the basal ganglia may implement a selection process envisioned a division of labor between the “direct” and “indirect” pathways (Albin et al. 1989; DeLong 1990; Alexander and Crutcher 1990). The direct pathway was proposed to be responsible for selection through a process of *disinhibition* (Chevalier and Deniau 1990), illustrated in Fig. 1. The output nuclei of the basal

ganglia are continuously active, providing a source of constant (or “tonic”) inhibition to their targets. A sufficiently strong input signal from cortex can elicit activity in a population of projection neurons in the striatum, which in turn converge on and temporarily inhibit the firing of neurons in the output nuclei. This pause in tonic firing is then interpreted as the signal for selection.

This disinhibition process has been worked out in detail for the control of voluntary eye movements, or *saccades*, in primates (see Hikosaka et al. 2000). Phasic activity in the caudate region of the striatum precedes saccade initiation and is time-locked to a decrease in activity in a subset of SNr neurons. The SNr projects to the intermediate layers of the superior colliculus, which contains a retinotopic map – neurons are laid out in a sheet that represents coordinates of gaze direction. A buildup of neural activity on this map drives the brain stem circuitry that controls the eye muscles and moves gaze to the location signaled by the map. The pause in SNr activity precedes and appears to be required for the buildup of activity in the retinotopic map of the superior colliculus. Conversely, continuously inhibiting SNr activity results in the inability to suppress saccades, as though every eye movement motor command was being executed (Hikosaka and Wurtz 1985). Thus, the direct striatum-SNr pathway likely controls the selection of saccade direction through a process of disinhibition.

Multiple Mechanisms Contributing to Action Selection

Computational models have provided quantitative tests of these ideas, revealed the further necessary mechanisms for successful selection, and shown how these mechanisms are implemented by components of the basal ganglia circuit. The box-and-arrow model accounts of “direct” pathway control of selection focussed on the flow of signals necessary to select one input and so omitted two crucial aspects of a selection process: how to resolve the *competition* between multiple action-representing inputs and how to *switch* from a



Basal Ganglia: Mechanisms for Action Selection, Fig. 1 Basal ganglia circuit and selection. The striatum receives input from most of cortex and many thalamic nuclei; a subset of the same regions project to the subthalamic nucleus (STN). The striatum is split into two populations of projection neurons according to whether they predominantly express the D1 or D2 receptor for dopamine: the populations and their targets respectively form the “direct” and “indirect” pathways. The globus

pallidus external segment (GPe) projects within the basal ganglia; the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr) project to targets in the brain stem and thalamus. The cartoon spike-trains illustrate the basic process of disinhibition in the “direct” pathway: continuous firing from the GPi/SNr tonically inhibits their targets; brief phasic activity in striatum, driven by coordinated cortical activity, can pause that tonic inhibition, allowing the targets to fire

currently selected action to another, more salient, action.

Competition

To be able to resolve a competition between actions first requires a substrate for separately representing each of those actions. A long-standing concept in basal ganglia research is the existence of parallel loops running through the basal ganglia (Alexander et al. 1986; Middleton and Strick 2000). At the macroscopic level, independent *domains* of the basal ganglia have been identified by the closed send-and-return loops originating in broad cortical regions (Alexander et al. 1986). Each macroscopic domain is thought to subdivide into a further large set of discrete parallel loops, termed *channels* here to distinguish them from the macroscopic-scale loops. For

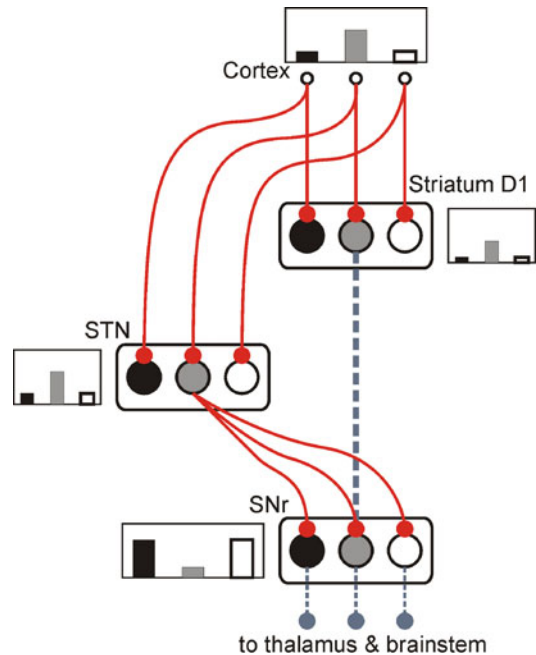
example, the somatotopic map found within the striatal motor domain is maintained throughout the basal ganglia’s intrinsic circuitry, such that there are separate channels for arm, leg, and face representations (Alexander and Crutcher 1990; Romanelli et al. 2005). Similar topographic maps have been proposed for the other macroscopic loops (Alexander and Crutcher 1990). Moreover, within these limb representations, there may be additional discrete channels corresponding to particular movements, demonstrated in striatum by microstimulation (Alexander and DeLong 1985) and markers for metabolic activity during behavior (Brown and Sharp 1995), and to repeated representations of body map locations (Brown et al. 1998). Computational models of the basal ganglia have proposed that it is these channels which form the basis for

action representation, and so the resolution of competition is expressed by the selection of a particular channel in the output of the basal ganglia (Gurney et al. 2001a).

The basal ganglia circuit contains a number of mechanisms potentially suited to resolving competition between competing channels. One candidate mechanism is the inhibitory network formed by the local axon collaterals of the projection neurons in striatum, which could underpin a winner-takes-all competition between input signals (Alexander and Wickens 1993). A problem with this idea is that these feedback connections are weak and asymmetric so that a classical winner-takes-all competition is unlikely to be supported (Plenz 2003). Even if it is, because of the range of the local axon collaterals, this interaction can only extend over a short distance in the striatum, on the order of 200–300 μm (Wickens 1997; Humphries et al. 2010). Consequently, any dynamics within striatum are likely only to resolve very local competitions between cortical inputs (Gurney et al. 2001b).

The competition between a set of channels most likely takes place at the inputs to the basal ganglia output nuclei, the SNr and GPi. As shown in Fig. 2, each population of striatal neurons projects to a corresponding population of SNr or GPi neurons, but the output of each population of STN neurons also contacts neighboring channels in SNr and GPi. This creates an off-center, on-surround network ideal for resolving competition between action signals (Mink 1996; Gurney et al. 2001a; Humphries et al. 2006; Leblois et al. 2006) as illustrated in Fig. 2.

A key insight from computational models is that the on-surround effect of the combined STN output can lead to SNr/GPi activity in many channels increasing above their tonic rate at the time of action selection – a phenomenon termed *contrast enhancement*. This makes functional sense: an enhanced tonic inhibitory signal being output from most channels indicates a definite non-selection of that action. However, when observed in experimental data, such increases in activity, time-locked to movement, have been interpreted as encoding that movement. By contrast, the models show how an increase in SNr/GPi neuron



Basal Ganglia: Mechanisms for Action Selection, Fig. 2

Competition resolution and switching by the basal ganglia. Actions are thought to be represented in parallel loops or channels running throughout the basal ganglia, with each action's relative salience computed by inputs from cortex. The bars in each box are cartoons of activity of each population in each structure. Each striatal population projects to a corresponding SNr/GPi population, providing focussed inhibitory input; STN output is comparatively diffuse, projecting across neighboring channels and providing diffuse excitatory input. The result is an off-center, on-surround network in SNr/GPi, where the strongest signal from among the striatal populations is able to inhibit the firing of its target SNr/GPi population, while at the same time the combined excitatory output of the STN counteracts the effect of the other inhibitory signals from striatum

output time-locked to an action does not encode that action, but rather encodes the simultaneous nonselection of another potential action. Moreover, the models show that the number of neurons with such increased activity, time-locked to an action, will be in the majority and hence will appear more frequently during neural recordings (Humphries et al. 2006).

Switching

Once action selection has been achieved, then action switching is required: the sudden

availability of a more salient action through changes in the environment or the animal's needs should terminate the ongoing action and then switch to selecting the new, more salient alternative. Computational models have again shown how the same off-center, on-surround design naturally handles this: the new input further increases the STN output, canceling selection of the current action, while the corresponding new, strong inhibitory signal from striatum inhibits its target population in GPi/SNr (Gurney et al. 2001b; Humphries and Gurney 2002). Embedding these models in mobile robots has shown how smooth behavioral sequences naturally emerge from the changing saliences of each action, without the need for explicit storage of sequences (Khamassi et al. 2005; Prescott et al. 2006).

The “Indirect” Pathway: Prevention of Selection and Scaling of Selection

The contribution of the “indirect” pathway to selection has been more difficult to unravel. The original box-and-arrow models proposed that this pathway acts to counteract the selection of an action: increased inhibition of the GPe by its striatal inputs would lead to enhanced STN output to SNr/GPi, thereby counteracting inhibition they were receiving in the direct pathway (Alexander and Crutcher 1990). Consequently, it was proposed that any imbalance between the relative strengths of the direct and indirect pathways could lead to movement disorders (Albin et al. 1989). Recent experimental studies have shown how selectively activating the striatal D1 or D2 projection neuron populations does indeed lead to opposite effects on behavior: stimulation of D1 projection neurons facilitates behavior, whereas stimulation of D2 neurons suppresses ongoing behavior (Kravitz et al. 2010).

The computational models of Frank and colleagues (Frank et al. 2004; Frank 2005) have extended these ideas by proposing that recruitment of these “go” and “no-go” pathways by cortical input during learning would depend on

the level of available dopamine. They showed these models could account for a range of learning biases exhibited by Parkinson's disease patients, providing support for the go versus no-go competition between the direct and indirect pathways.

A further mystery was the role of STN feedback to the GPe (Fig. 1). An analysis by Gurney et al. (2001b) showed that this negative feedback loop provided *capacity scaling* for action selection. Without a loop between STN and GPe, the diffuse STN output means that the total excitatory input to the SNr/GPi would grow in proportion to the number of active inputs to the basal ganglia; with a sufficient number of inputs, the excitatory input would grow large enough to overwrite all focussed inhibition from the striatum and prevent any selection. However, the negative feedback loop ensures that the STN output is scaled to the number of active inputs: the more the inputs, the more the STN output tries to grow, but is held in check by the GPe output which is itself a function of the STN output. In this way, the basal ganglia's capacity can scale and so can operate as a selection mechanism independently of the number of currently competing channels.

Cross-References

- [Basal Ganglia: Overview](#)
- [Decision-Making: Overview](#)
- [Reinforcement Learning in Cortical Networks](#)

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- ## Basal Ganglia: Songbird Models
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- ## Definition
- Songbirds use learned vocalization to communicate. During initial song acquisition, juvenile birds reproduce adult vocalizations through a

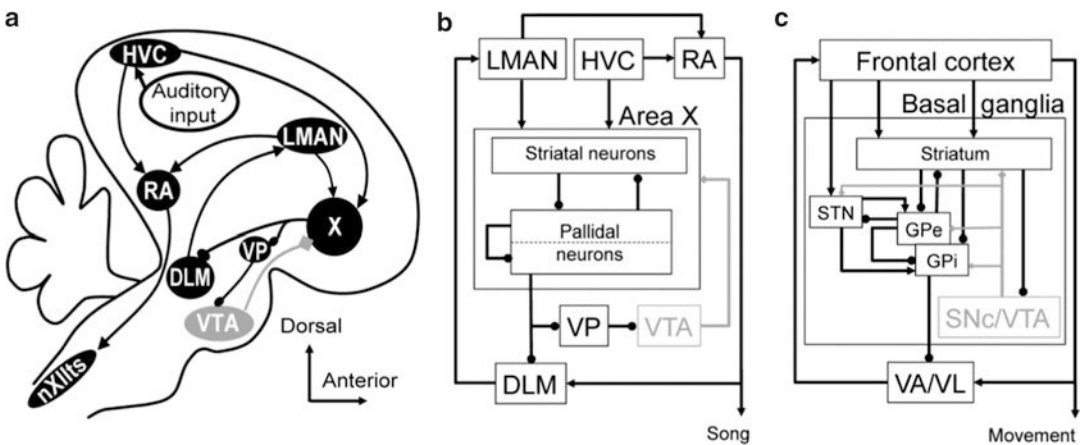
process very similar to speech learning in babies. Initial “babbling” vocalizations are turned into a faithful copy of the tutor song through a trial-and-error process that relies on a basal ganglia-thalamo-cortical circuit (► [Basal Ganglia: Overview](#)).

Detailed Description

Songbirds use learned vocalizations to communicate during courtship or aggressive behaviors. These vocalizations, called song, require fast coordination of laryngeal and respiratory muscles. Songbirds learn their song as juveniles through a long process comprising two sequential phases: the juvenile first listens to and memorizes one or more tutor songs, and then uses auditory feedback to match its song to the memorized model through trial-and-error.

While song production is under the control of two cortical nuclei, HVC (used as a proper

name) and the robust nucleus of the arcopallium (RA, Fig. 1a), song learning and plasticity strongly rely on the basal ganglia (BG, Scharff and Nottebohm 1991). Interestingly, songbirds display a specialized portion of their BG-thalamo-cortical circuitry, called the anterior forebrain pathway (AFP), devoted to song learning and plasticity (Fig. 1b; Brainard and Doupe 2002), and homologous to the mammalian motor BG-thalamo-cortical loop (Fig. 1c; Reiner et al. 1998). In particular, the song-related BG nucleus Area X receives dense dopaminergic innervation and contains neuron types homologue to both the mammalian striatal and pallidal neurons, forming similar circuits (Farries and Perkel 2002; Leblois et al. 2009). Songbirds and their specialized BG-thalamo-cortical loop devoted to a naturally learned complex sensorimotor task offer a unique opportunity to study the function of the BG in skill learning and execution (Doupe et al. 2005).



Basal Ganglia: Songbird Models, Fig. 1 The song-related BG-thalamo-cortical network in songbirds, and its homologue circuit in mammals. In panels **a**, **b**, and **c**, the nature of synaptic transmission is indicated by the end of the arrow: Black arrows for excitatory (glutamatergic) connections, black discs for inhibitory (GABAergic) connections, and gray diamonds for dopaminergic connections. **(a)** Schematic parasagittal representation of the song system. *DLM* Dorso-lateral nucleus of the anterior thalamus. *LMAN* Lateral magnocellular nucleus of the anterior nidopallium, *RA* Robust nucleus of the

arcopallium, *VP* Ventral pallidum, *VTA* Ventral tegmental area, *nXIIIs* Supraspinal nucleus. **(b)** Diagram of the synaptic connectivity in the song-related BG-thalamo-cortical network of songbirds. **(c)** Diagram of the synaptic connectivity in the motor loop of the mammalian BG-thalamo-cortical network. *GPe* Globus pallidus pars externa, *GPI* Globus pallidus pars interna, *SNc* Substantia nigra pars compacta, *STN* Subthalamic nucleus, *VA* Ventral anterior nucleus of the thalamus, *VL* Ventral lateral nucleus of the thalamus

BG Functions in Songbirds: Experimental Background

The BG loop in songbirds is necessary for song learning but not for song production per se. BG neurons respond selectively to playbacks of the bird's own song (Doupe and Solis 1997), and were initially thought to convey auditory feedback signals to be compared with a stored template of the tutor song. However, no neuronal correlate of such comparison can be found in the BG-thalamo-cortical loop (Leonardo 2004). Auditory feedback-related activity has however been reported in upstream cortical nuclei (HVC), where similar neuronal responses can be observed in response to syllable production or playback ("mirror neurons," Prather et al. 2008). During song production, the BG-thalamo-cortical loop introduces motor variability allowing vocal exploration (Kao et al. 2005; Ölveczky et al. 2005, for comparison to its role in mammals, see ► ["Basal Ganglia System as an Engine for Exploration"](#)), as needed in a reinforcement learning (RL) framework (see also ► ["Reinforcement Learning in Cortical Networks"](#)), and can guide adaptive changes in song to minimize errors (Andalman and Fee 2009). Moreover, dopaminergic neurons projecting to the song-related BG nucleus (Area X) provide an online evaluation of current singing behavior (Gadagkar et al. 2016) and the dopaminergic input to Area X is necessary for song plasticity (Hoffmann et al. 2016). These data are consistent with the implementation of a reinforcement learning mechanism in the BG-thalamo-cortical loop in birds (Fee and Goldberg 2011), just as it has been proposed also in mammals (Doya 2000; ► ["Basal Ganglia: Mechanisms for Action Selection"](#)).

Reinforcement Learning in Songbirds

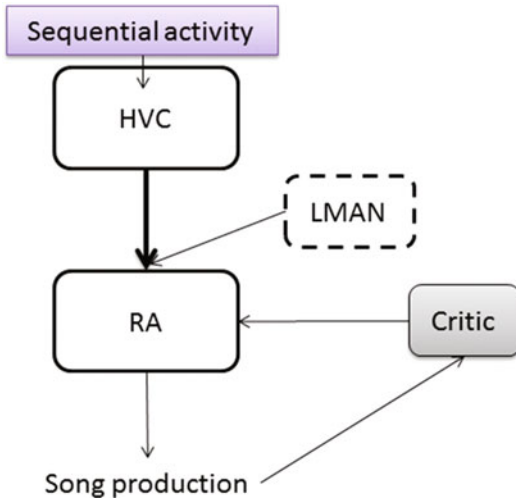
Most models of BG-dependent learning in songbirds are in an RL framework (but see Ganguli and Hahnloser 2013). In these models, a timing signal is assumed to be produced in HVC, where output is sent to the BG to serve as a clock input during learning. Based on this clock input, the RL

circuit learns to produce the correct motor gestures at each time step. In the RL framework, the agent learns to correlate random motor explorations with fluctuations in a reward signal in order to select motor patterns that lead to the highest reward. For example, changes in the song (the motor output) that increase the amount of expected reward should be implemented, whereas song changes leading to lower expected reward should be discarded. Implementation of such RL framework in the song-related neuronal circuitry must include four components: (1) an "actor" that produces the song, (2) a mechanism for exploration, implemented in a variability circuit (Fee and Goldberg 2011), a searcher (Doya and Sejnowski 1998), or an experimenter (Fiete et al. 2007), which may be based on a recently proposed mechanism for generating correlated variability (Darshan et al. 2017), (3) a comparator circuit, or "critic" (Doya and Sejnowski 1998) that computes the reward signal by evaluating the produced song with respect to the memorized template, and (4) a learning mechanism to modifies motor output with time.

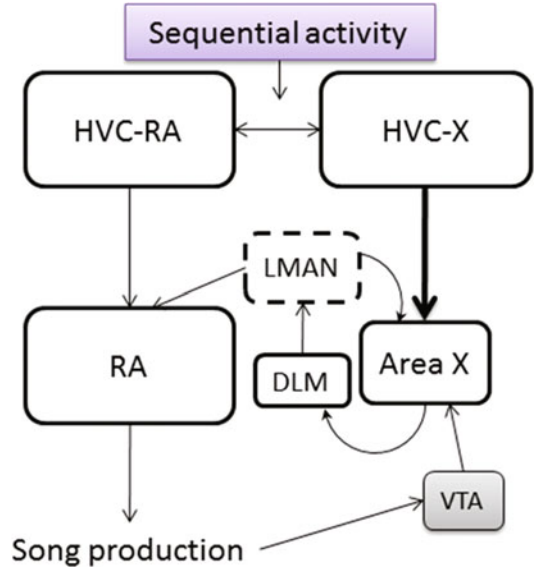
Different Models of Song Production and the Involvement of the AFP

In a first RL model for song learning, Doya and Sejnowski (1998) proposed that nucleus LMAN could act as the "searcher," perturbing each synaptic connection between HVC and RA independently, while the BG would evaluate each produced song using tutor-selective neurons (Fig. 2). This weight perturbation algorithm results in a plasticity in HVC-RA synapses after each epoch, that is, at the end of song rendition.

Fiete et al. (2007) elaborated on Doya and Sejnowski model in a biologically realistic network of spiking neurons. While the location of the critic in their model was only speculative, the other elements of the model were similar to Doya and Sejnowski (1998): plasticity took place in HVC-to-RA synapses and LMAN was again the search element, called "experimenter." Besides its realistic nature, their model differs from previous models by utilizing a new learning



Basal Ganglia: Songbird Models, Fig. 2 Architecture of the basic song RL models (Doya and Sejnowski 1998; Fiete et al. 2007). Dashed box represents the search/experimenter element. Gray box represents the critic. Plastic synapses are displayed in wide black arrows



Basal Ganglia: Songbird Models, Fig. 3 Architecture of the more complete song RL model including BG circuits (Goldberg and Fee 2011). Arrows and color code as in Fig. 2

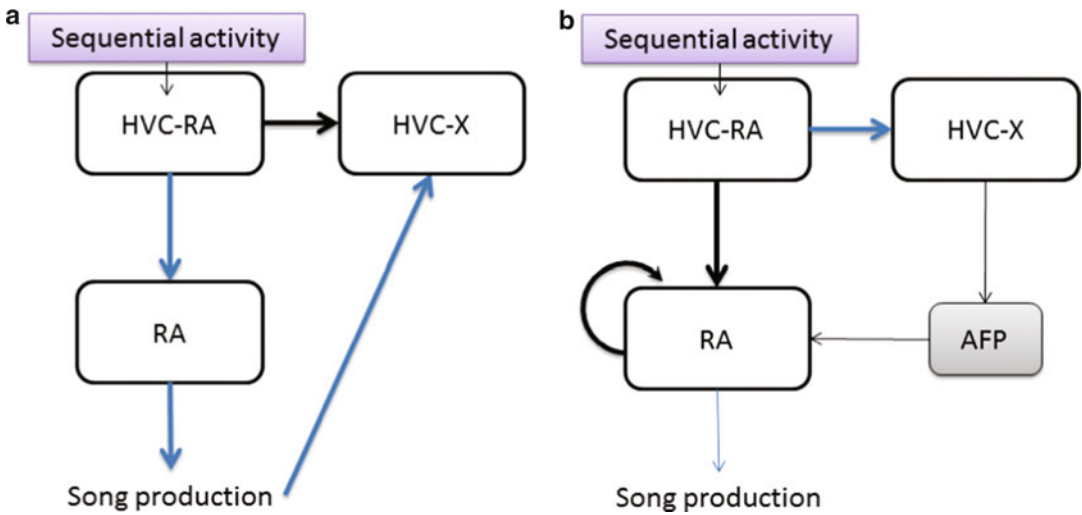
algorithm relying on node perturbations, where LMAN neurons perturb the activity of RA neurons instead of their synaptic efferences from HVC (Fig. 2), and an online reward signal during song. Using such a realistic learning algorithm, the circuit learns a simple song in a biologically plausible number of song renditions.

Recently, Fee and Goldberg (2011) have published a conceptual model that argues that the AFP is not a comparator but is rather biasing the motor system (Fig. 3). Based on ideas taken from the classical implementation of RL in the mammalian motor BG loop (Wickens et al. 2003), they hypothesize that the song-related BG receives an evaluation signal from neuromodulators such as dopamine, and uses this signal to select the relevant motor gestures at the right time. As in mammals, the avian BG-thalamo-cortical circuit and the descending connections to motoneurons form a topographically organized circuit displaying segregated “motor channels.” In this model, LMAN again drives variability in song production, and sends a copy of this variability signal to striatal neurons. Receiving a convergent timing signal (or “context”) from HVC, and a global

dopaminergic reward signal, the striatal neurons are considered as coincidence detectors and select the right motor variation in the right context in each motor channel. Synaptic plasticity at HVC-to-X synapses then allows the acquisition of correct motor biases. Although this model has not been computationally implemented yet, it is algorithmically similar to Fiete et al. (2007), with the learning occurring at HVC-to-X synapses instead of HVC-to-RA synapses.

Template Comparison, Efference Copy, or Inverse Model?

In the RL models discussed above, a global reward signal evaluating auditory feedback quality is delivered by the critic. Because of delays that are inherent in the transformation of neural activity into vocal gestures and in the auditory processing of produced sounds, the reward signal is necessarily delayed with respect to the neuronal activity underlying the rewarded gesture. In other words, the reward is likely temporally imprecise.



Basal Ganglia: Songbird Models, Fig. 4 Schematic description of the efference copy learning (a) and song learning (b) in the Troyer and Doupe model (2000). Blue

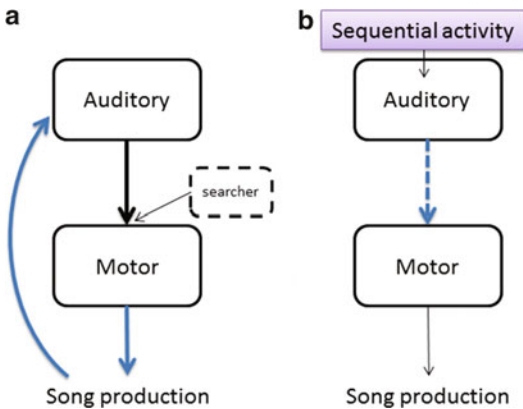
arrows represent the motor-auditory transformation in (a) and the “efference copy” of this transformation in (b). Other color code as in Fig. 2

To overcome this delay problem, an eligibility trace can be used (Doya and Sejnowski 1998; Fiete et al. 2007).

A different solution for the delay problem was given by Troyer and Doupe (2000; Fig. 4). While they still assume that the AFP evaluates the song, they propose that evaluation is based on an efference copy of the song’s motor program. In a first stage, a motor-to-sensory mapping is built by implementing Hebbian learning at synapses between HVC neurons projecting to RA (HVC_{RA}), assumed to be motor, and HVC neurons projecting to Area X (HVC_X), assumed to be auditory. The bird thereby learns to predict auditory consequences of its motor gestures. Such a mapping is usually termed a “forward model,” or “efference copy.” During this initial learning stage, the plastic connection (thick black arrow in 4a) is modified to implement such efference copy. After implementing the motor-to-sensory transformation (blue arrow in Fig. 4b), the auditory feedback to HVC_X is switched off by adaptation mechanisms and the AFP neurons displaying tuned responses to tutor song evaluate the vocal production through the comparison between the efference copy and a representation of the tutor song. In this stage the AFP acts like a

critic. As in Doya and Sejnowski, synapses within RA and from HVC_{RA} to RA are modified to optimize song.

The last model, proposed by Ganguli and Hahnloser (2013), consists of two brain areas, an auditory area and a motor area, represented in a very simplified framework. Their model relies on three already mentioned assumptions: production of highly variable vocalization during learning, gating mechanisms for specific synaptic inputs, and a synaptic mechanism for Hebbian learning (see ► “Hebbian Learning”). It is not based on an RL framework and no evaluation of the song, or comparison with the tutor’s song is needed. Instead, the bird learns an inverse model through the mapping of sensory (auditory) commands to the appropriate motor commands, relying solely on Hebbian learning. First, random vocalizations induce Hebbian learning between auditory and motor representation of the produced sounds (Fig. 5a), creating an inverse model. Secondly, the song is produced by gating auditory feedback inputs to the auditory area and playing the template, stored in the recurrent synapses inside the auditory area (Fig. 5b). Interestingly, sensory neural responses to song playback mirror motor-related activity recorded during singing in nucleus



Basal Ganglia: Songbird Models, Fig. 5 Architecture of the inverse model for song learning (Ganguli and Hahnloser 2013). Wide blue arrows represent the motor-auditory transformation. (a) Learning the inverse model (in wide black). (b) Song production. After learning the inverse model (dashed blue arrow), auditory feedback and the searcher element are gated

LMAN (Giret et al. 2014). Such matching of mirroring offsets and loop delays is consistent with the implementation of an inverse model in or upstream from the cortico-basal ganglia loop.

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Basal Ganglia: Striatal Models Cellular Detail

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Definition

Models of neuron types of the striatum, which include details of ion channels and neuron morphology.

Detailed Description

Striatal Function in Disease and Health

The striatum is the main input structure of the basal ganglia and is implicated in habit learning, addiction, and neuropathologies such as Parkinson's disease and Huntington's disease. Parkinson's disease is a motor dysfunction caused by degeneration of dopaminergic neurons that project strongly to the striatum. Huntington's disease is another motor dysfunction caused by degeneration of a subset of the neurons in the striatum. Experiments in both humans and animals have demonstrated that normal habit learning involves the striatum, and changes in striatal neural activity are observed consequent to cortical glutamatergic activity (in response to environmental stimuli or motor activity) and dopamine release in response to reward.

Cell Classes in the Striatum

The projection neurons of the striatum are the spiny projection neurons (SPNs) which make up the majority (90–95%) of the neurons and are subdivided into two classes: those with dopamine D1 receptors which co-release substance P and dynorphin and those with dopamine D2 receptors which co-release mu-opioids. Three other classes of interneurons have been extensively studied: the GABAergic fast-spiking interneurons (FSIs) which are connected by gap junctions, the GABAergic neuropeptide Y-positive (NPY) interneurons which also produce nitrous oxide and are characterized electrophysiologically as low-threshold-spiking interneurons (LTSIs), and the acetylcholinergic (ACh) interneuron, also called the tonically active neuron because of its spontaneous and regular firing pattern. An additional NPY-expressing interneuron type has been recently characterized as a neurogliaform (NGF) interneuron which exhibits distinctly slow inhibitory kinetics in its synapses to SPNs. More recently it has been possible to characterize a set of tyrosine hydroxylase neurons using transgenic expression systems. These neurons exhibit four different firing patterns, but their role in striatal circuits remains to be elucidated. The GABAergic interneurons are positioned to modulate the timing and pattern of firing of the projection neurons of the striatum. In addition, their interconnections via both chemical and electrical synapses may play a role in synchronization. The acetylcholinergic neurons modulate dopamine release from the substantia nigra and modulate striatal neuron properties through pre- and post-synaptic metabotropic receptors.

One of the compelling questions about striatal function is the role of the D1 versus D2 SPNs. The prevalent theory regarding Parkinson's disease is that dopamine increases excitability of D1 SPNs and decreases excitability of D2 SPNs. The absence of dopamine leads to overactivity of the D2 SPNs which tend to inhibit voluntary movement. Thus, some striatal models have been developed to evaluate which characteristics of SPNs can explain the difference between D1 and D2 neurons and the effect of dopamine. Both neuron

classes exhibit a characteristic bimodal membrane potential distribution during anesthesia and sleep, known as upstates and downstates. Though the significance of this activity is still unclear, several models have investigated which neuron mechanisms underlie this activity. Both normal habit learning and the overly strong habit learning of drug addiction likely involve synaptic plasticity of the SPNs; thus several models have investigated the control of calcium concentration during synaptic and neuronal activity, which are essential for synaptic plasticity.

Simple SPN Models

Some models contain only a small subset of cellular components and attempt to reproduce a specific cellular phenomenon. The purpose of these types of models is to explain cellular behavior using the smallest possible subset of mechanisms. This has the dual advantage of minimizing the number of free parameters while demonstrating that specific channels/interactions are required. It has the disadvantage of being unable to demonstrate possible alternative mechanisms which might explain the data. Examples of this approach are Gruber et al. (2003) which use two potassium channels and one calcium channel to test whether the known effects of dopamine on these channels affect membrane bistability and Mahon et al. (2000) which implement detailed channels but a single compartment to show that the slow A-type potassium channels in SPNs confer short-term facilitation of excitability. Another model (Koos et al. 2004) represents the complete morphology but contains no voltage-dependent channels. This model shows that morphological characteristics, such as electrotonic distance, can account for the difference in amplitude of inhibitory postsynaptic potentials (IPSPs) produced by FSIs compared to SPNs. Simple modeling approaches have also been extended to model striatal network activity. For instance, McCarthy et al. (2011) demonstrated that inhibitory GABAergic currents and M-type potassium currents can interact to produce beta oscillations symptomatic of Parkinson's disease in the striatal network, using single compartment models with detailed channels.

Complex SPN Models

The more complex models contain many cellular features (Table 1) and attempt to reproduce many characteristics of voltage and/or calcium waveforms. The advantage of this approach is being able to isolate specific channels or morphological characteristics within the context of many cellular characteristics to demonstrate the necessity or sufficiency of a mechanism in replicating an experimental finding. In addition, these complex models can be used to evaluate interactions between mechanisms and whether the proposed mechanism exhibits the same function or characteristics in a different context, e.g., in vivo versus in vitro. Ideally, these models can be reused to explain new data with minimal change. The disadvantage of this approach is having numerous free parameters, and the complexity can sometimes hinder the ability to illuminate concepts.

The first complete SPN model (Wolf et al. 2005) used the NEURON simulation software to model a neuron from the ventral striatum (nucleus accumbens). This model replicates many of the characteristics of SPNs, such as the long delay to action potential at rheobase and the low frequency of spiking. The model was used to test the effects of the NMDA/AMPA ratio on entrainment to oscillation (Wolf et al. 2005) and later to test the effects of dopamine modulation on synaptic integration (Moyer et al. 2007). The inwardly rectifying potassium current (Kir) was retuned (Stephen and Manchanda 2009) and implemented in this model to investigate the role of inactivating Kir in SPN excitability. This model also was adapted by Spiga et al. (2010), who added morphology based on a digital reconstruction of an SPN and tested the effects of dendritic spine loss and AMPA current reduction on AP frequency during simulated upstates.

Several other complex models of dorsal striatal SPNs have been developed. A NEURON model SPN by (Gertler et al. 2008) was used to test the contribution of morphological differences between D1 and D2 SPNs in accounting for their different electrophysiological characteristics. This model was adapted (Plotkin et al. 2011) to test the ability of distal dendrites to evoke sustained somatic depolarizations. A similar model, by the

Basal Ganglia: Striatal Models Cellular Detail, Table 1 Computational models of striatal neurons

Citation	Cell type	Morphology	Channels	Software	Available modelDB
Mahon et al. 2000	SPN	Single compartment	Na^+ (3); K^+ (5);	MATLAB	Yes
Gruber et al. 2003	SPN	Single compartment	K^+ (2); Ca^{2+} (1)	NEURON	Yes
McCarthy et al. 2011	SPN, network	Single compartment	Na^+ (1); K^+ (2);	C++	No
Koos et al. 2004	SPN	Multi-compartment	None	NEURON	No
Moyer et al. 2007; Wolf et al. 2005; Steephen and Manchanda 2009	SPN, N. Acc.	Multi-compartment	Na^+ (2); K^+ (6); Ca^{2+} (6); NMDA, AMPA, GABA	NEURON	Yes
Flores-Barrera et al. 2009	SPN	Multi-compartment	Na^+ (1); K^+ (5); Ca^{2+} (2); NMDA, AMPA, GABA	NEURON	No
Spiga et al. 2010	SPN, N. Acc.	Multi-compartment; reconstruction	Na^+ (2); K^+ (6); Ca^{2+} (6); NMDA, AMPA, GABA	NEURON	Yes
Gertler et al. 2008; Day et al. 2008; Plotkin et al. 2011	SPN	Multi-compartment	Na^+ (1); K^+ (5); Ca^{2+} (4); NMDA, AMPA, GABA	NEURON	No
Nakano et al. 2013	SPN	Multi-compartment; reconstructed; spines	Na^+ (2); K^+ (6); Ca^{2+} (6); NMDA, AMPA	NEURON	Yes
Mattioni and Le Novère 2013	SPN	Multi-compartment; spines; multiscale	Na^+ (2); K^+ (6); Ca^{2+} (6); NMDA, AMPA	NEURON; Python	Yes
Damodaran et al. 2014, 2015.	SPN, FSI	Multi-compartment; network model	Na^+ (1); K^+ (6); Ca^{2+} (5); NMDA, AMPA, GABA	Genesis	Yes
Evans et al. 2012, 2013; Jędrzejewska-Szmek et al. 2017; Dorman et al. 2018	SPN	Multi-compartment; spines	Na^+ (1); K^+ (6); Ca^{2+} (5); NMDA, AMPA, GABA	Genesis	Yes
Du et al. 2017; Lindroos et al. 2018	SPN	Multi-compartment; reconstructed; spines	Na^+ (1); K^+ (6); Ca^{2+} (5); NMDA, AMPA, GABA	Genesis	Yes
Song et al. 2016	LTSI	Single compartment	K^+ (1); Ca^{2+} (2); Cl^- (1)	N/A	No
Kotaleski et al. 2006	FSI	Multi-compartment	Na^+ (1); K^+ (3); AMPA, GABA	Genesis	Yes
Wilson 2005	ACh	Single compartment	Kir, HCN	XPPAUT	No
Wilson and Goldberg 2006	ACh	Single compartment	K^+ (2); Ca^{2+} (1);	XPPAUT	No
Goldberg et al. 2009	ACh	Single compartment	Calcium dynamics	XPPAUT	No

same group (Day et al. 2008), was used to investigate attenuation of the action potential as it back-propagated into SPN dendrites. Another NEURON model SPN by (Flores-Barrera et al. 2009) was used to test whether GABAergic input, which is depolarizing below its reversal potential (roughly -60 mV), plays a role in maintaining

the depolarization of an SPN during a cortico-striatal upstate. Additionally, a NEURON model with calcium dynamics including calcium release from internal stores was used to investigate the effects of synaptic inputs and back-propagating action potentials on spine calcium (Nakano et al. 2013). Most electrical models do not incorporate

significant intracellular biochemical signaling; however one SPN modeled in NEURON was coupled to a biochemical signaling model in dendritic spines to create a multiscale model (Mattioni and Le Novère 2013).

Several iterations of a dorsal striatal SPN model (Evans et al. 2012) using the GENESIS simulation software have been developed. Evans et al. (2012) investigated whether the NMDA receptor subtypes, based on the four GluN2 subunits, differentially affect the calcium influx into spines during closely timed pairings of pre- and postsynaptic activity (spike-timing-dependent plasticity protocols). Evans et al. (2013) incorporated more sophisticated calcium dynamics in dendrites to investigate the effect of action potential timing during an upstate, finding that earlier action potentials induce higher calcium influx due to calcium-dependent inactivation of calcium channels. A network implementation of this model, together with an FSI model, has been developed to investigate the effects of dopamine depletion on striatal network synchrony (Damodaran et al. 2014; Damodaran et al. 2015). The most recent iterations of this model incorporated sophisticated spine calcium dynamics and a calcium plasticity rule to successfully predict spike-timing-dependent plasticity outcomes from several experimental studies (Jędrzejewska-Szmek et al. 2017) and show that spine calcium encodes patterns of synaptic inputs with spatial specificity (Dorman et al. 2018).

An SPN model with realistic morphology was recently used to investigate the effects of clustered synaptic inputs on input/output firing properties, showing that clustered inputs which could evoke a dendritic plateau potential facilitated spiking in response to additional dispersed inputs and that distal dendritic inhibition could attenuate the plateau potential and its effect on firing (Du et al. 2017). This model was adapted (Lindroos et al. 2018) to investigate dopaminergic modulation of D1 SPNs.

Interneuron Models

Most striatal models focus on the spiny projection neurons, but there are several models of striatal interneurons.

The first complete model of a fast-spiking interneuron (FSI) (Kotaleski et al. 2006) replicated the observed spike latency and high firing frequency of striatal FSIs. This model was used to investigate how upstate firing of FSIs is controlled by transient potassium currents and the contribution of these channels to enhancing signal-to-noise ratio. This model was further used to construct a network model (Hjorth et al. 2009) that investigated the contribution of gap junctions in FSI sensitivity to coincident input from the cortex.

Several simple models of acetylcholinergic neurons (Ach) have been developed. The goal of most of these models is to explain mechanisms underlying the rhythmic firing and burst firing observed in these neurons. Two models demonstrate that two alternative mechanisms can explain membrane potential. The first model (Wilson 2005) demonstrates that Kir, HCN (hyperpolarization-activated and cyclic nucleotide-gated channel), and leak conductance in a single compartment could explain membrane potential oscillations in the voltage range of -80 to -60 mV. A second model shows that a calcium current plus calcium-dependent potassium current produces oscillations, though with a slower time course (Wilson and Goldberg 2006). Simulations further demonstrated how the slow afterhyperpolarization (sAHP) is activated by long depolarizations (even of small amplitude) but not activated by brief ones. Another model of ACh neurons (Goldberg et al. 2009) was used to investigate the role of calcium channel colocalization in mediating slow and fast afterhyperpolarizations. This model had a single electrical compartment that was subdivided into multiple concentric calcium compartments coupled by diffusion. Several calcium-binding proteins enabled the model to demonstrate that the transient calcium influx produced by an action potential preferentially binds to SK channels, whereas the lower but more prolonged calcium influx produced by subthreshold depolarization preferentially binds to the slower, higher-affinity binding proteins.

To date, there is a lack of models of other striatal interneuron types. However, a recent simple LTSI model has been published that utilizes a single compartment and reduced channels to

analyze the source of subthreshold membrane oscillations (Song et al. 2016). This model suggests that calcium-activated chloride channels may be important to regulating membrane potential oscillations in LTSIs.

Conclusion

There are several models of striatal neurons that contain cellular detail. These models vary in complexity, morphology, and active channels. Each model is configured to test a specific aspect of striatal physiology as efficiently and accurately as possible, and therefore both the simple and the complex models are valuable. With the increasing power of computers and tools for parameter optimization, the accuracy and complexity of models is likely to increase.

Cross-References

- [Genesis, the GEneral NEural Simulation System](#)
- [Neuron Simulation Environment.](#)

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Basal Ganglia: Subthalamic Nucleus Cellular Models

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Definition

The subthalamic nucleus is a key basal ganglia structure providing an excitatory innervation to the globus pallidus and substantia nigra. The

spontaneous activity of these neurons is sustained by an autonomous oscillation and interacts with ongoing activity in the external segment of the globus pallidus, with which it has reciprocal connections.

Detailed Description

Why Build a Model of Neurons in the Subthalamic Nucleus?

Interest in models of subthalamic nucleus (STN) neurons is driven by the need to understand pathological oscillations in the basal ganglia seen in Parkinson's disease and in animal models of the disease (e.g., Bergman et al. 1994) and in the therapeutic mechanism of subthalamic deep brain stimulation. The low-frequency oscillations characteristic of subthalamic cell firing in the disease are not expressed in isolated neurons and so are thought to arise from a network mechanism (e.g., Wilson 2014). A likely mechanism is offered by the reciprocal connections between the subthalamic nucleus and the globus pallidus. The STN consists of glutamatergic neurons that excite GABAergic neurons in the GPe. These in turn inhibit the STN.

The Gillies et al. (2002) mean field model indicated that oscillations in the STN- > GPe circuit could arise if the STN were powerfully self-excitatory, but experimental evidence for this was lacking (Kita et al. 1983; Sato et al. 2000). The recognition that STN neurons are intrinsic oscillators (Bevan and Wilson 1999) revived the possibility of STN-GPe oscillations without excitatory coupling between STN cells. An STN of independent oscillators would be self-exciting, but without lateral interactions the cells would not synchronize, and oscillations in the correct frequency range might not occur. Synchronization of STN cells might occur disynaptically through interactions with the GPe. A simulation of the mechanism by which the sparse connections between STN and GPe could produce synchronization requires models at the neuron level rather than mean field models.

Many models of this kind have employed generic neuron models not designed to

specifically represent the cell type-specific dynamics of the subthalamic neurons. Such models are based on the hypothesis that network activity depends only on the connectivity of the network, not the functional properties of the neurons. Some networks have been built using more faithful representations of the cells involved, using one small group of subthalamic cell models.

The Terman et al. Model

Terman et al. (2002) developed conductance-based point models of the STN cell and the GPe cell as components of a model of the pallido-subthalamic network. These included features that duplicated the cells' firing patterns as they were known at that time. The relevant components of the subthalamic cell model were autonomous single-spiking and a powerful post-hyperpolarization rebound, both of which had been emphasized in recent studies of cells in slices (Bevan and Wilson 1999; Beurrier et al. 1999). The model subthalamic neuron was validated by showing qualitative similarity to the slice data, specifically autonomous firing in the appropriate range of rates and a powerful brief depolarization and burst after termination of a hyperpolarizing current injection.

Firing Pattern

Autonomous firing was generated by a persistent sodium current. This was implemented using a strong window current at subthreshold membrane potentials as suggested by Bevan and Wilson (1999). Later work is inconsistent with this mechanism (Do and Bean 2003), but this difference makes little difference for firing properties. The simplifications of action potential repolarization and after-hyperpolarization (AHP) currents were more sweeping, employing a single non-inactivating K^+ channel adjusted to activate and deactivate very slowly in the subthreshold range. A Ca-dependent K^+ current was present but contributed little to the single-spike AHP. It was de-emphasized because STN cells show little spike-frequency adaptation during brief

episodes of high-frequency firing, rather increasing their firing over the first 100–200 ms (Hallworth et al. 2003; Wilson et al. 2004). Calcium removal was slow so that Ca-dependent K^+ current was strongly accumulating and produced a long-lasting AHP after periods of high-frequency firing. Subsequent studies of the AHP currents of STN cells suggest substantially different mechanisms governing firing rate. The fast repolarizing K^+ current deactivates rapidly, and its AHP component is brief. It also depresses during high-frequency firing (Teagarden et al. 2008). Most of the AHP is caused by SK-type Ca-dependent K^+ current. This current does not accumulate during high-frequency firing but produces a 10–30 ms AHP current following every action potential. Slow spike-frequency adaptation in STN neurons results from inactivation of persistent Na^+ current (with time constant ~ 5 s) and the accumulation of a very slow voltage-sensitive K^+ current (with time constant ~ 20 s) (Barraza et al. 2009), and the latter creates the slow AHP current seen after firing at high rates. Spike frequency adaptation is not included in any of the commonly used models.

Rebound

Two rebound currents contribute to the low threshold spike (LTS) that follows strong hyperpolarizations. The faster one is carried by calcium and caused by t-type calcium channels (Hallworth et al. 2003). Longer hyperpolarizations engage HCN currents and induce a more prolonged depolarization. In the STN cell model, these two currents were combined into a single mechanism. Post-inhibitory rebound was thought to be critical to the oscillations in STN-GPe co-cultures (Plenz and Kitai 1999). Experimental attempts to verify the presence of rebounds after synaptic inhibition have been unimpressive. Rebounds in STN neurons require hyperpolarizations lasting much longer than typical for GABA_A IPSPs (Bevan et al. 2002). On the other hand, rebound excitation in STN cells often lasts longer than in the model cell because L- and N-type calcium channels are activated by the LTS. High voltage-activated calcium

channels were included in the model but did not act to prolong rebound firing.

Effective Time Constant

In the model STN cell, slope conductance is high throughout the interspike interval. When the membrane potential is not changing rapidly, it is because strong currents are balanced. Large synaptic currents are required to change the membrane potential, and it then changes rapidly. The charge deposited by synaptic currents dissipates rapidly. This enhances the response to rapid fluctuations in synaptic current and precise timing of inhibition from the GPe. In contrast, the STN cell's I–V curve is nearly flat over most of the voltages visited during the interspike interval (Farries et al. 2010). The rise time of synaptic potentials is slow, and the charge placed on the cell by subthreshold synaptic inputs is retained and alters the membrane potential trajectory and timing of action potentials tens of milliseconds later (Fig. 1).

It is unknown whether any of these differences between the Terman et al. model and the real STN neuron are important in generating oscillatory activity in the STN–GPe network or, if they are, what kind of difference they would make. The list of ionic mechanisms that could be included in a neuron model increases with every new experimental study, and no cellular model simple enough to be used in a network model can be expected to incorporate every known cellular feature. Nobody knows which features are essential, and as always that complicates model design.

The Terman et al. model has been widely used in a variety of influential network models of Parkinson's disease and its treatments, including deep brain stimulation (e.g., Guo et al. 2008).

Otsuka Model and Plateau Potentials

Studies of STN neurons have described plateau potentials following applied current pulses or post-inhibitory rebound (Nakanishi et al. 1987; Beurrier et al. 1999), which depend on voltage-activated Ca^{2+} currents. A one-compartment conductance-

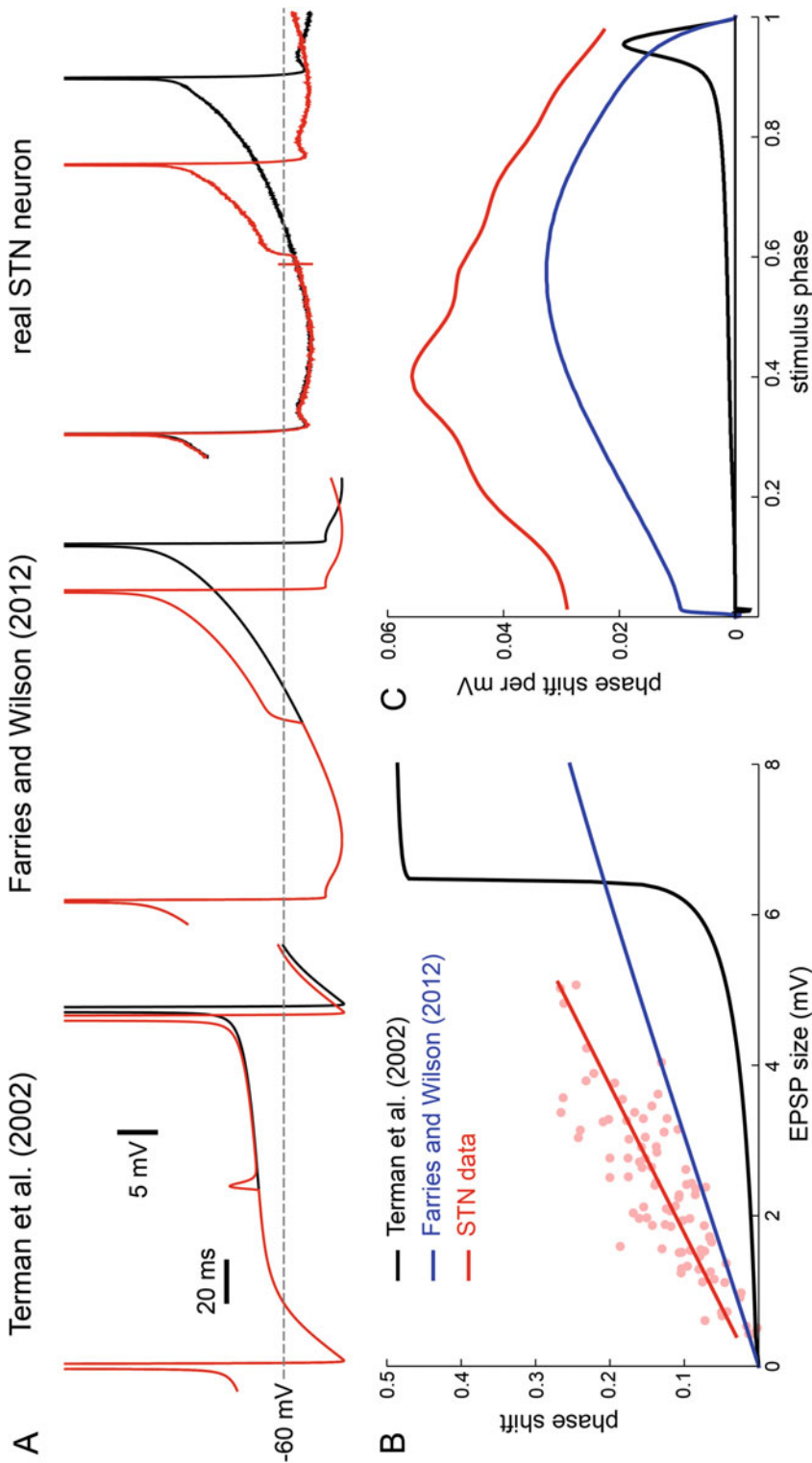
based model STN cell incorporating these Ca^{2+} currents and capable of plateau potentials was presented by Otsuka et al. (2004). This was not a comprehensive model but demonstrated that Ca^{2+} currents measured in voltage clamp possessed properties necessary for plateau potentials as in intracellular recordings. The features of the Otsuka model should be incorporated into any comprehensive model of the STN neuron. However, not all STN cells show plateau potentials, so their inclusion in STN models must be accompanied by some treatment of heterogeneity. The Otsuka et al. model has been used as is or with slight modifications in several basal ganglia network models (e.g., Shouno et al. 2017).

Gillies and Willshaw Model

Models of STN neurons have rarely included dendrites or an axon. One exception is the model by Gillies and Willshaw (2006). This model contains a simplified but still complex dendritic tree, separate fast and persistent Na^{+} currents, fast repolarization current, and realistic Ca^{2+} and Ca -dependent K^{+} currents. Many of its channel properties are based on measurements from other neurons, and the distribution of channels on the dendrites is largely speculative, but it reproduces several of the neurophysiological properties of STN neurons, including long rebounds, plateau potentials, and rhythmic bursting during hyperpolarization. Execution of this model is more computationally intensive than the others, and it has not been extensively used in models of STN- > GPe interactions.

Farries and Wilson Model

Neuron models for networks are not expected to be quantitatively accurate. It is usually considered enough for the neuron representation to share some single property with its real-life counterpart—for example, steady-state gain or time constant of adaptation. The cellular property chosen for validation of the model reflects the network designer's interpretation of what constitutes the essential computational features of the cell in its network. Farries



Basal Ganglia: Subthalamic Nucleus Cellular Models, Fig. 1 (continued)

and Wilson (2012) constructed a simple model of the STN cell intended to reproduce its spontaneous activity and phase resetting curve. The phase resetting curve describes the changes in interspike intervals produced by one or more small synaptic currents occurring in the interspike interval during repetitive firing. This model was motivated by the observations that subthalamic neurons are autonomous pacemakers and receive many small synaptic inputs from cells that also have ongoing background firing. This model did not include the response to deep hyperpolarizations, as it omitted rebound currents, which are not engaged by the kind of stimuli used to generate phase resetting curve. This may not be a critical omission, as rebounds are probably rarely engaged during ongoing synaptic activity (Bevan et al. 2002). The model implemented more accurate repolarizing and AHP currents, and its I–V curve was adjusted to match that of the STN cell. Slope conductance was low during most of the interspike interval, and synaptic inputs arriving during most of the interspike interval produced changes in the timing of the next spike, like those observed in STN neurons. The model was used to derive the phase resetting curve from the shape of the I–V curve and the AHP conductance (Fig. 1).

Phase Model

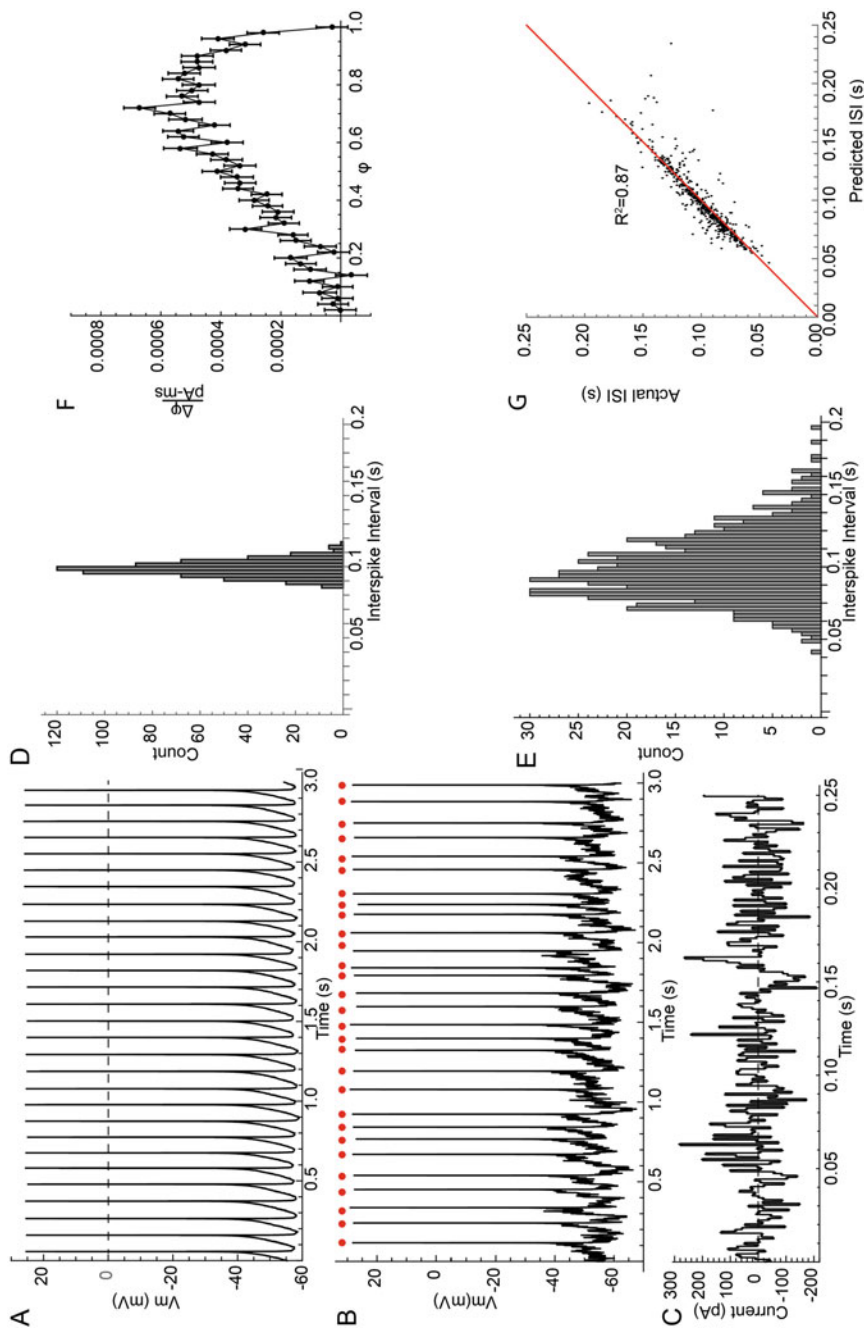
Phase-resetting curves are readily measured in experiments and can be used to predict the responses of the same neuron to arbitrary patterns of synaptic input. The neuron's response is calculated using a phase model, characterized by only a baseline firing rate, an input current, and a phase resetting curve. The validity of the model's prediction is not guaranteed, because the model assumes that the cell's state does not stray far from its unperturbed closed path in parameter space. For this reason, the use of phase models has usually been restricted to models of weakly connected networks, in which cells continue to fire rhythmically. Wilson et al. (2014) tested the accuracy of the phase model for STN neurons subjected to dense noise stimuli, which strongly disrupted rhythmic firing (Fig. 2). The model provided an accurate quantitative prediction of the statistics of firing (e.g., coefficient of variation). A phase model based on the experimentally measured phase resetting curve of each cell accurately predicted the individual interspike intervals from the same cell during application of arbitrary patterns of current noise.



Basal Ganglia: Subthalamic Nucleus Cellular Models,

Fig. 1 (a) Response of two STN models and an example STN neuron to an EPSP. The reversal potential of the models' leak conductance was adjusted to produce autonomous ISIs of 160 ms, matching the unstimulated ISI of the recorded STN neuron (*black traces*). The EPSC was simulated as a product of exponentials ($\tau_{\text{rise}} = 0.8$ ms, $\tau_{\text{decay}} = 1.5$ ms), and EPSC amplitude was adjusted for each model to produce a peak depolarization of 4 mV, matching the recorded neuron's EPSP (*red traces*). The real STN neuron was recorded in a rat brain slice in the presence of GABA receptor antagonists. (b) Phase shift (advance in spike time caused by an EPSP divided by the duration of the autonomous ISI) as a function of EPSP size for EPSPs delivered halfway through the autonomous ISI (i.e., same time as in *A*, at a phase of 0.5). Because the EPSPs arrived at a phase of 0.5, the maximum possible phase shift (corresponding to a spike triggered immediately by the EPSP) was 0.5. The *red circles* plot average phase shift in recorded STN neurons for EPSPs arriving at phases of 0.45–0.55 against average EPSP size; each circle

is from a different neuron. The *red line* is a linear regression on these data ($r^2 = 0.71$, fit slope = 0.05 of phase shift per mV EPSP, $p < 0.0001$, $n = 89$). For the Terman et al. (2002) model, "EPSP size" is EPSC amplitude multiplied by 0.6 mV per unit current density, allowing the graph to include synaptic strengths that trigger spikes at short latency. This conversion factor is derived from the measured 4 mV EPSP shown in *A*. (c) Infinitesimal phase response curves (iPRCs) for two STN models and an example STN neuron (same cell as in *A*). The iPRC gives the phase shift (normalized change in spike time) caused by a stimulus per unit stimulus strength (EPSP size, in this case) in the limit of very weak stimuli. This measure of sensitivity to input (phase shift per mV EPSP) varies as a function of when during the autonomous ISI (stimulus phase) the input is delivered. For real STN neurons and the Farries and Wilson (2012) model, this sensitivity to very small inputs is a good predictor of the response to much larger inputs, as illustrated in *B* by the near-linear relationship between stimulus size and response magnitude



Basal Ganglia: Subthalamic Nucleus Cellular Models, Fig. 2 Example activity from an STN cell in the absence (a) and presence (b) of dense current noise (c). In the presence of the noise stimulus, repetitive firing is greatly disrupted, as indicated by the change in interspike interval distribution, as shown by comparison of d (without noise) and

e (with noise). (f) Measured phase resetting curve for the same cell. A phase model using the interpolated phase resetting curve was integrated starting at each spike time to predict the interspike intervals. The predicted intervals are indicated using red dots in b. (g) Comparison of predicted and actual interspike intervals. The red line in g indicates identity

Summary

The diversity of STN neuron models reflects the diversity of goals set by model designers. STN neurons have complex dynamics that deviate greatly from models of the integrate-and-fire family. Many more accurate models focused on reproducing plateau potentials or post-hyperpolarization rebound, but these features may not be prominent during normal firing. For models to be used in networks, it is most desirable for the model to accurately reproduce the STN neurons' autonomous firing and dynamic response to changing synaptic input.

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Bayesian Estimation

► Estimation of Neuronal Firing Rate

Bayesian Inference with Spiking Neurons

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Definition

Neurons respond reliably to external stimuli despite the fact that their input is noisy and the state of the environment changes constantly (e.g., stimuli appear or disappear unpredictably). The Bayesian spiking neuron (BSN) framework interprets neural dynamics as a form of probabilistic inference and describes how neurons and neural circuits should be optimally tuned to the temporal statistics of their inputs and the level of noise. Output spike trains communicate probability distributions over stimulus states to downstream neurons using a predictive coding strategy.

Detailed Description

General Framework

In BSN formalism, prior assumptions about the input tuning curves, noise, and temporal dynamics of the stimulus are treated as the parameters of an internal predictive model (Lochmann and Deneve 2011). Such an internal model represents how the “hidden” stimulus state causes the “observed” noisy inputs. These assumptions are in turn reflected in the structure and dynamics of a corresponding neural network. For example, the presence or absence of an external sensory stimulus can be represented as a binary “hidden” variable modulating the input rates. Such internal model can be implemented in a single spiking neuron (Fig. 1a, Deneve 2008a).

In turn, the parameters of the internal model fully predict the biophysical properties of the spiking neurons, e.g., synaptic time constants, adaptation, synaptic weights, and ring dynamics.

Since these parameters also reflect the “natural” (i.e., expected) statistics of the synaptic inputs, these optimal biophysical parameters can be learned in an unsupervised way (through spike-time-dependent plasticity rules) (Deneve 2008b; Mongillo and Deneve 2008).

Dynamics of Bayesian Spiking Neurons

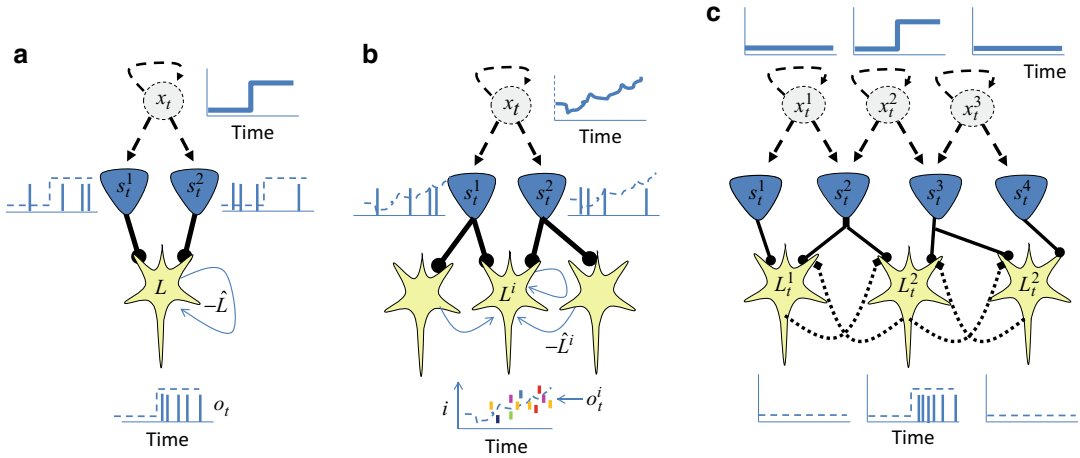
BSNs are similar to adaptive “integrate-and-re” neurons and are described by two dynamic equations, one corresponding to synaptic integration of inputs (inference) and the other to a dynamic neural threshold dependent on recent spike history (encoding).

Inference consists of computing the probability distribution over the stimulus state x_t , given the feed-forward synaptic inputs received so far, $s_{0 \rightarrow t}$. This can be expressed in terms of the log posterior probability, $L(x, t) = \log(p(x_t | s_{0 \rightarrow t}))$. Using simplifying assumptions such as (1) Poisson distributed input spike trains and (2) Markovian dynamics for stimulus x_t (i.e., x_t only depends on x_{t-dt}), this equation takes the general form:

$$\frac{\partial L(x, t)}{\partial t} = -\phi(L(x, t)) + \sum_i w_i(x) s_i(t) \quad (1)$$

where $s_i(t)$ is an input spike train while the “synaptic weights” $w_i(x)$ depend on the input tuning curves. ϕ is a (typically nonlinear) “leak” term dependent on the dynamics of the hidden variable (e.g., how quickly the stimulus changes). This equation can correspond to synaptic integration in single neuron (for binary x_t) or in a recurrent neural network (for multinomial or continuous x_t , as in Fig. 1b).

Encoding consists of representing an estimate $\hat{L}(x, t)$ of the log posterior in the output spike trains. In order to do this, the BSN uses a “greedy” predictive coding scheme, i.e., neurons reset whenever their membrane potential, defined as the prediction error $V_j(t) = k_j * (L - \hat{L})$ (where k_j is a kernel specific to each neuron), exceeds a particular threshold. As a result, each new spike decreases the coding (prediction) error $L(x, t) - \hat{L}(x, t)$. With respect to self-consistency, $\hat{L}(x, t)$ is



Bayesian Inference with Spiking Neurons, Fig. 1 Examples of internal predictive models and their BSN implementations. (a) Case of single binary stimulus (dashed circle), modulating two input ring rates (dashed arrows and line), generates two input spike trains (vertical lines). A single spiking neuron (yellow star) receiving these convergent synaptic inputs (plain connections) can represent the log probability of stimulus present in its output spikes, using predictive coding (thin plain arrow).

(b) Case of a single continuous variable evolving with Markovian “Brownian motion.” In this case, the log posterior is represented by a population of neurons whose spike trains (colored vertical lines) track the stimulus. Predictive coding requires lateral inhibitory connections (thin arrows). (c) Case of 3 different binary stimuli co-modulating the synaptic inputs. Explaining away requires divisive presynaptic inhibition between neurons (dashed connections)

assumed to be the result of postsynaptic integration of the output spike trains in downstream neurons, e.g.,

$$\tau \frac{\partial \hat{L}(x, t)}{\partial t} = -\hat{L}(x, t) + \sum_i k_j(x) o_j(t) \quad (2)$$

The result can be interpreted as a recurrent network of adaptive leaky integrate-and-re neurons with lateral connections $k_i * k_j$ (Fig. 2b). By always maintaining a small prediction error, BSNs represent the posterior probability efficiently (Fig. 2a).

Extension to Multiple Stimuli

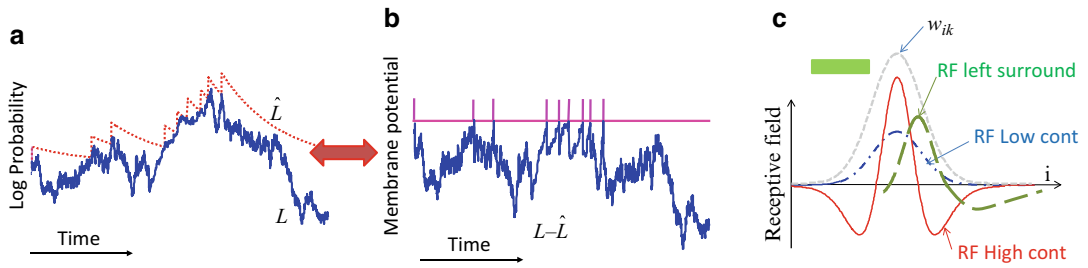
The framework can be extended to the tracking of more than one stimulus at a time (Fig. 1c). This is particularly relevant for the processing of sensory scenes, since the same sensory inputs can usually be explained by different combinations of overlapping features. For example, different speech sounds activate highly overlapping sets of auditory receptors. The auditory input is explained by

either one or the other phoneme, but not both. Thus, neurons selective to similar phonemes (e.g., “ba” and “da”) will need to compete: if they did not, neurons would have highly correlated, nonselective responses. This phenomenon is called “explaining away.”

Let us assume that the sensory input is caused by K different stimuli $x_k(t)$ combining linearly to cause the sensory scene, i.e., each input $s_i(t)$ is a Poisson process with instantaneous firing rate $f_i(t) = \sum_k w_{ik} x_k(t)$. In a BSN implementation of this internal model, the *encoding* is identical, but the *inference* needs to implement explaining away. The network equations are as same before, except that the synaptic weights are no longer fixed (as in Eq. 1), but divisively gain modulated by the context. More precisely, the effective weights $\tilde{w}_{ij}(t)$ between input i and feature detector k are given by

$$\tilde{w}_{ik}(t) = \frac{w_{ik}}{1 + \sum_{j \neq k} w_{ij} \hat{x}_j(t)} \quad (3)$$

where $\hat{x}_j(t)$ is the prediction (i.e., the expected value) of feature j at time t . This can be



Bayesian Inference with Spiking Neurons, Fig. 2 Predictive coding and implication for contextual modulation of receptive fields. **(a)** The log probability of stimulus, $L_t = L(x, t)$, is tracked over time by an output estimate $\hat{L}_t$ corresponding to a leaky integration of the output spike train. **(b)** This can be implemented by an adaptive integrate-and-re neuron whose membrane potential is a function of the prediction error $L_t - \hat{L}_t$. **(c)** When

multiple overlapping “blob-shaped” stimuli are represented (*dashed grey line*), the receptive field of the corresponding neuron is highly dependent on context. For example, it is narrow and center surround for high-contrast stimuli (*plain red*), wide and without surround for low-contrast stimuli (*dot-dashed blue*), and repulsed in the presence of a stimulus in the left surround (*dashed green*)

implemented by lateral divisive inhibition in a recurrent neural network (Fig. 1c). Each input to each neuron is presynaptically shunted according to how well this input is predicted by other neurons.

Some Applications of the BSN Framework

One of the most important implications of the BSN framework is that the “Poisson-like” variability observed in cortical spike trains is a natural consequence of predictive coding. It reflects sensory noise and redundancy between neurons (e.g., many neurons have similar coding kernels), but *not* neural noise. The variability persists even when the inputs are not Poisson distributed and even when the input is completely deterministic (Bourdoukan et al. 2012).

Moreover, this framework assumes highly dynamical and adaptive response properties. BSNs provide “ideal observer” models of single neurons or microcircuit and thus are useful tools to relate neural spike trains with their hypothetical functions. While those models are highly testable (and disprovable), they largely remain to be tested experimentally.

More specifically, BSNs have been shown to achieve quasi-optimal information transmission in single neurons (Lochmann and Deneve 2008).

Populations of BSN neurons can represent slowly varying variables (such as position or direction of motion) and implement optimal working memories (Boerlin and Deneve 2011). Finally, BSNs representing overlapping stimuli can account for a large number of contextual modulation of sensory responses, such as divisive normalization, adaptation, surround suppression, and repulsion, as illustrated in Fig. 2c (Lochmann and Deneve 2011).

Relation to Other Approaches

In addition to the BSN, several other frameworks have proposed different encoding of uncertainty with spikes. For example, sampling models interpret spikes as samples from the posterior probability distribution (rather than a deterministic representation of the log posterior) (Berkès et al. 2011; Buesing et al. 2011). The “probabilistic population coding” (PPC) approach represents log-posteriors in the output firing rates. This can be implemented in a spiking network using random spike generators or large balanced spiking networks (Beck et al. 2008), the underlying assumption being that the added noise is neglectable compared to the uncertainty already present in the input.

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Bayesian Modeling of Neural Recordings

- [Electrophysiology Analysis, Bayesian](#)

Bayesian Neural Data Analysis

- [Electrophysiology Analysis, Bayesian](#)

Beat

- [Rhythm Perception: Pulse and Meter](#)

Behavior of Just-Hatched Frog Tadpoles and the Neuronal Networks Underlying It

- [Rhythm Generation in Young *Xenopus* Tadpoles](#)

Behavioural Analysis, Bayesian

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Definition

Bayesian analysis is a method for reasoning probabilistically about parameters of a model given some observed data. Applied to behavioral data, Bayesian analysis can be used to fit and compare models of cognition. This approach to behavioral data analysis offers a number of advantages over classical (frequentist) analysis, including a coherent representation of uncertainty, flexibility to handle complex models and missing data, and an avoidance of pathologies inherent to significance testing based on p -values.

Detailed Description

Bayesian analysis starts with the specification of a joint distribution on the data D and parameters (or hidden variables) H . This joint distribution can be broken down into two components: $P(D, H) = P(D|H) P(H)$. The first component, $P(D|H)$, is known as the *likelihood*, and the second component, $P(H)$, is known as the *prior*. Given some data, we are interested in

the conditional distribution, $P(H|D)$, commonly known as the *posterior*; this distribution specifies everything we know about H given the observed data and our prior beliefs. Bayes' rule stipulates how to form the posterior from the prior and likelihood:

$$P(H|D) = \frac{P(D|H)P(H)}{\sum_R P(D|H)P(H)}$$

The denominator is sometimes known as the *marginal likelihood*. When H is continuous, the summation is replaced by integration. A practical overview of Bayesian analysis can be found in Kruschke (2010). Below we discuss some of the relevant issues that arise in applying Bayesian analysis to behavioral data.

Posterior Probabilities Versus P -values

The classical approach to behavioral data analysis is based on the null hypothesis significance testing (NHST) framework, in which the significance of a summary statistic is evaluated by calculating the probability of obtaining an equally or more extreme value if the statistic was drawn from a null distribution. If the resulting p -value is below some conventional threshold (e.g., 0.05), the null hypothesis is rejected and the result is considered significant. This framework is related to Bayesian analysis: the p -value is the tail probability of the likelihood when H corresponds to the null hypothesis.

In contrast to p -values, posterior probabilities quantify the evidential support for all possible values of H . Often different values of H can plausibly have generated the data, and the posterior captures this uncertainty. In contrast, the confidence intervals of NHST express the range of H that would not be rejected by a significance test.

Under NHST, when multiple tests are applied to a data set, the probability of erroneously declaring a null effect significant increases. This necessitates some kind of correction for multiple comparisons. Bayesian analysis does not require such corrections, since there is a single posterior

distribution that does not depend on how many ways you examine it.

Hierarchical Models

A powerful use of Bayesian analysis is the construction of hierarchical models in which uncertainty about the parameters of the prior is captured by placing a “hyper-prior” on these parameters (Lee 2011). An important example of this is modeling individual differences: each subject in a study has a separate set of parameters, but these parameters are coupled by virtue of being drawn from a common group-level distribution. One advantage of hierarchical models is that they allow sharing of “statistical strength” between subjects, such that the parameter estimates of one subject are informative about the parameter estimates of another subject. At the same time, subjects are allowed to express idiosyncratic parameters. Hierarchical models can thus strike a balance between forcing all subjects to have the same parameters and modeling each subject separately.

Model Comparison

An important problem in cognitive modeling is model comparison. The Bayesian approach to this problem centers on calculating the *Bayes factor* (Kass and Raftery 1995), which is the ratio of marginal likelihoods for two models. The Bayes factor rewards models that fit the data better but penalizes model complexity. Intuitively, complex models are able to fit a given data set better than simple models, but complex models also spread their probability mass over many data sets, and consequently the probability of any given data set will tend to be smaller.

Whereas the posterior will often be relatively insensitive to the prior when the amount of data is large, Bayes factors can be exquisitely sensitive to the choice of prior (Kass and Raftery 1995). This has sometimes been considered a drawback of Bayesian model comparison. However, others

(e.g., Vanpaemel 2010) have argued that prior sensitivity is reasonable, since the prior should be considered part of a fully specified cognitive model.

Computation

For all but a small class of models, employing Bayes' rule exactly is computationally intractable. This happens because the marginal likelihood computation involves summing over all possible hypotheses, which is infeasible for large hypothesis spaces. Consequently, most algorithms for Bayesian analysis use approximations. Most commonly, these algorithms approximate the posterior with a set of stochastic samples – the so-called *Monte Carlo* approximations (Robert and Casella 2004). As the number of samples increases, the approximation becomes increasingly accurate. There are several software packages that compute Monte Carlo approximations automatically given a probabilistic model (see Kruschke 2010 for an introduction), making Bayesian methods widely accessible for behavioral data analysis.

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Bidirectional Brain-Machine Interface

► Recurrent Brain-Computer Interfaces

Bifurcation Analysis

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Definition

Bifurcation analysis provides theoretical guidelines and a powerful analytical framework to tune the activity of neuronal models. A bifurcation is a qualitative change in the activity of a dynamical system, such as a transition from silence to spiking. Bifurcation analysis identifies general dynamical laws governing transitions between activity regimes in response to changes in controlling parameters. By using these quantitative laws, the temporal characteristics of a neuronal model can be tuned to reproduce the characteristics of experimentally recorded activity by navigating the parameter space in the vicinity of bifurcations. In most of the bifurcations described here, the general shape of the waveform – for example, the shape of action potentials in a time series – is preserved, while a specific temporal characteristic changes.

Detailed Description

The knowledge of the bifurcations of a model neuron provides quantitative laws governing the temporal characteristics of spiking activities. Neurons can be envisaged as nonlinear dynamical systems. Bifurcation analysis has been applied to the study of spiking, bursting, and chaotic neuronal systems (Rinzel 1987; Guckenheimer et al. 1993, 1997; Rinzel and Ermentrout 1998; Ermentrout and Terman 2010; Ghigliazza and Holmes 2004; Rabinovich et al. 2008). Biophysical parameters are used as controlling parameters, and changes in regimes of activity can be identified concomitantly with bifurcations (Rinzel 1978; Guckenheimer et al. 1993, 1997; Shilnikov and Cymbalyuk 2005; Shilnikov et al. 2005; Medvedev 2006; Barnett

Bifurcation Analysis, Table 1 Dynamical laws arising from specific bifurcations. The bifurcation parameter α takes its critical value for bifurcation at α^*

Bifurcation	Dependence
Homoclinic	Period $\propto -\ln(\alpha - \alpha^*)$
SNIC	Period $\propto 1/\sqrt{ \alpha - \alpha^* }$
Blue Sky catastrophe	Period $\propto 1/\sqrt{ \alpha - \alpha^* }$
Andronov-Hopf	Amplitude $\propto \sqrt{ \alpha - \alpha^* }$

and Cymbalyuk 2014). The association of transitions between regimes of neuronal activity with specific bifurcations gives predictions about the properties of stationary and oscillatory solutions (Booth et al. 1997; Doiron et al. 2003; Shilnikov and Cymbalyuk 2005; Shilnikov et al. 2005; Barnett and Cymbalyuk 2014). This approach is applicable for tuning the dynamics of neuronal activity – such as bursting, spiking, and rest states – with biophysical parameters. We provide examples of four bifurcations that determine quantitative characteristics of activity: the homoclinic bifurcation, the saddle-node bifurcation on an invariant circle (for bursting and for tonic spiking), the blue sky catastrophe, and the Andronov-Hopf bifurcation (Table 1). We present the dynamical laws generated by these bifurcations in the context of spiking, bursting, and transient activity.

Spiking

Three bifurcations of closed periodic orbits are ubiquitously implicated in the control of spiking activity. A saddle-node bifurcation on invariant circle (SNIC) and a homoclinic bifurcation describe how the frequency of spiking depends on a controlling parameter α , e.g., the injected current. A supercritical Andronov-Hopf bifurcation describes the dependence of the amplitude of oscillations on the bifurcation parameter.

A SNIC occurs when an equilibrium possessing the properties of both a saddle and a node – a saddle-node equilibrium – is born on a closed periodic orbit and the eigenvectors

associated with the half-stable direction of the saddle-node equilibrium are tangent to the periodic orbit. This bifurcation describes the transition of spiking into silence (Gutkin and Ermentrout 1998). At the critical value for bifurcation, α^* , the saddle-node equilibrium obstructs the spiking orbit. For values of α that support spiking and are close to α^* , the frequency of spiking activity is proportional to $\sqrt{|\alpha - \alpha^*|}$. This bifurcation does not constrain the amplitude of spiking. This scenario is an example of the type I spiking scenario (Gutkin and Ermentrout 1998; Izhikevich 2007).

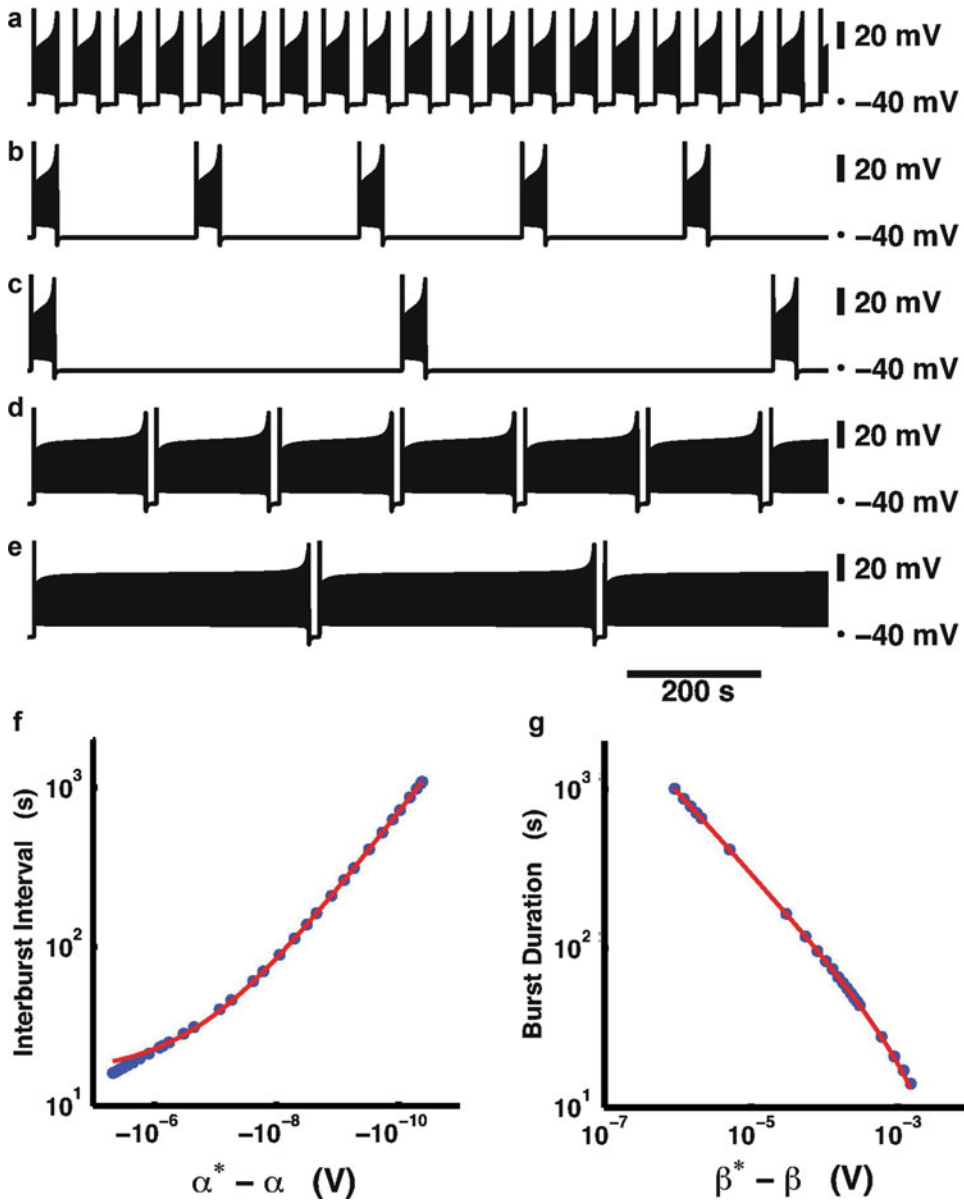
A homoclinic bifurcation of a saddle equilibrium can terminate a spiking regime (Izhikevich 2007). It occurs when an orbit is interrupted by the saddle; as α changes and approaches the critical value for bifurcation, α^* , the spiking frequency decays according to $-1/\ln(|\alpha - \alpha^*|)$.

In a supercritical Andronov-Hopf bifurcation, a stable focus loses stability, and a stable periodic orbit with zero amplitude and nonzero frequency is born. The frequency is inherited from the resonant frequency of the focus. In subthreshold oscillations or spiking activity associated with this bifurcation, the amplitude of the orbit grows proportionally to $\sqrt{|\alpha - \alpha^*|}$. This scenario is an example of the type II spiking scenario (Gutkin and Ermentrout 1998; Izhikevich 2007; Rinzel and Ermentrout 1998).

Bursting

Four types of bifurcations are crucial for the control of temporal characteristics in bursting activity: the SNIC for bursting, the blue sky catastrophe, the cornerstone bifurcation, and the Lukyanov-Shilnikov bifurcation.

In bursting activity, the SNIC describes the transition from bursting to silence (Booth et al. 1997; Doiron et al. 2003; Barnett and Cymbalyuk 2014). According to this bifurcation, the interburst interval grows smoothly and is proportional to $1/\sqrt{|\alpha - \alpha^*|}$ as the bifurcation parameter, α , approaches the critical value α^* (Fig. 1). At the bifurcation, a saddle-node equilibrium is born on the bursting orbit.

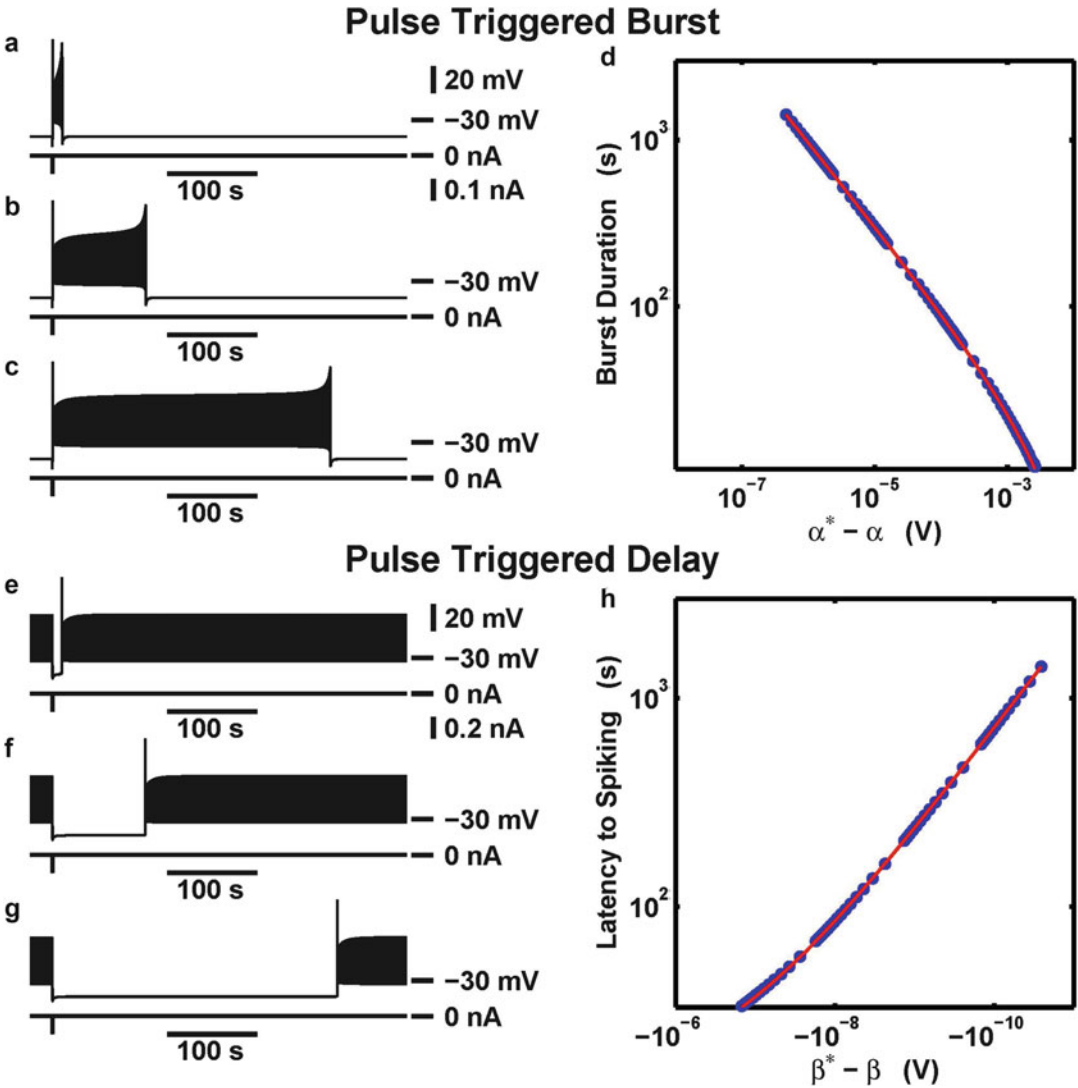


Bifurcation Analysis, Fig. 1 The transition from bursting to silence and the transition from bursting to tonic spiking. (a) Initial values for α and β produce periodic bursting activity. (b, c) The parameter α is varied to approach its critical value for bifurcation, α^* , and the interburst interval increases. (f) Curve fits for the interburst interval took the form $b/\sqrt{|\alpha - \alpha^*|} + c$. (d, e)

The parameter β is varied to approach its critical value for bifurcation, β^* , and the burst duration increases. (g) Curve fits for the burst duration took the form $b/\sqrt{|\beta - \beta^*|} + c$. (f, g) Graphs are plotted in the log-log scale. The interburst interval and burst duration are depicted as blue dots. The curves fitted to these data are depicted as red curves

The blue sky catastrophe occurs when a saddle-node periodic orbit is born on the manifold that governs spiking in a bursting neuron

(Shilnikov and Cymbalyuk 2005; Barnett and Cymbalyuk 2014). This bifurcation describes the transition from bursting to tonic spiking. The



Bifurcation Analysis, Fig. 2 The inverse-square-root laws in transient responses triggered by a pulse of current for parameter values that support silent and tonic spiking regimes. (a–d) An individual burst was triggered by a hyperpolarizing pulse of injected current. Burst duration was controlled by the voltage of half activation of a potassium current (α). The duration of individual bursts were (a) 10.3 s, (b) 103.5 s, and (c) 309.3 s for different values of α . (d) The log-log graph of burst duration of individual bursts plotted against the difference between the voltage of half activation of a potassium current and its critical value for bifurcation (α^*). The blue dots correspond to the burst duration measured

at the respective values of α . The red curve is the graph of the curve fitted in the form $b/\sqrt{\alpha^* - \alpha} + c$. (e–h) Latency to spiking was shown by administering an individual pulse of injected current. Interburst interval was controlled by the half activation of a hyperpolarization-activated current (β). The delays shown here are (e) 10.3 s, (f) 103.4 s, and (g) 317.7 s for different values of β . (h) Latency to spiking for sampled parameter values (blue dots) and the graph of the curve fitted to $b/\sqrt{|\beta^* - \beta|} + c$ (red curve) were plotted in log-log scale against the sampled values of β where β^* is the critical value for bifurcation

burst duration grows smoothly and is proportional to $1/\sqrt{|\beta - \beta^*|}$ as the bifurcation parameter, β , approaches the critical value β^* (Fig. 1).

The cornerstone bifurcation satisfies the conditions of both the SNIC and the blue sky catastrophe; it is a global codimension-2 bifurcation

(Shilnikov and Turaev 2000; Barnett and Cymbalyuk 2014). This bifurcation describes the independent control of interburst interval and burst duration: one parameter, α , controls the transition from bursting to silence as in the SNIC, and another parameter, β , controls the transition from bursting to spiking as in the blue sky catastrophe. At the critical value for both parameters, (α^*, β^*) , there occurs both the saddle-node equilibrium and the saddle-node periodic orbit. In this way, the duration of the interburst interval is controlled as in the SNIC, and the burst duration is controlled as in the blue sky catastrophe (Fig. 1) (Barnett and Cymbalyuk 2014).

The Lukyanov-Shilnikov bifurcation is a homoclinic bifurcation of a periodic orbit (Lukyanov and Shilnikov 1978). In bursting, this bifurcation occurs when the unstable manifold of the saddle-orbit leads into the stable manifold of the orbit (Shilnikov et al. 2005). The unstable manifold near the saddle-orbit determines the duration of each burst. Near this bifurcation, bursting is commonly chaotic, and on average, the burst duration grows proportionally to $-\ln(|\alpha - \alpha^*|)$ as the bifurcation parameter, α , approaches the critical value α^* .

Transient Activity

Transient dynamics are critical for information processing (Rabinovich et al. 2008). The temporal characteristics of transient activity can similarly be governed by bifurcations. Typically, temporal laws are associated with global bifurcations. However, a local bifurcation can determine the timescale of transient neuronal responses to external perturbations, such as a pulse of synaptic current (Fig. 2).

The saddle-node bifurcation for periodic orbits can impose temporal laws on transient spiking activity in an endogenously silent neuron (Roa et al. 2007). For values of the bifurcation parameter α which support silence and are close to the birth of the spiking regime at α^* , the dynamics of perturbation-induced transient spiking activity are controlled by the proximity ($|\alpha - \alpha^*|$) to the bifurcation. Far from the bifurcation, a

perturbation may trigger a single action potential, but as the quantity $|\alpha - \alpha^*|$ becomes small, the same perturbation induces an increasing number of spikes. The duration of this transient activity – under the condition of an invariant external stimulus – is proportional to $1/\sqrt{|\alpha^* - \alpha|}$. A similar scenario is generated by the cornerstone bifurcation (Fig. 2) (Barnett and Cymbalyuk 2014).

In the context of the endogenously tonically spiking neurons, the cornerstone bifurcation describes a transient silent interval after inhibition according to the properties imposed by a saddle-node bifurcation for equilibria (Barnett and Cymbalyuk 2014). The return to the spiking state after inhibition is delayed if α is close in value to α^* , and this delay is proportional to $1/\sqrt{|\alpha - \alpha^*|}$ (Fig. 2).

Conclusions

We have described how the applications of bifurcation analysis to neuronal dynamics governs characteristics of oscillatory activity. In spiking activity, the homoclinic and saddle-node bifurcation on invariant circle each control spike frequency, and the Andronov-Hopf bifurcation controls spike amplitude. In bursting activity, the SNIC, the blue sky catastrophe, the cornerstone bifurcation, and the Lukyanov-Shilnikov bifurcation each impose temporal laws on the period of bursting activity. In transient dynamics, the saddle-node bifurcation for periodic orbit determines the duration of individual perturbation-evoked bursts in endogenously silent neurons, and the saddle-node bifurcation for equilibria determines the delay before spiking after inhibition in an endogenously spiking neuron. Knowledge of these laws describes mechanisms underlying modulation and adjustment of stationary and oscillatory regimes and transient responses of neurons.

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Bifurcations Dynamics of Single Neurons and Small Networks

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Definition

A bifurcation occurs when a system undergoes a qualitative change in its output as a result of a change in parameter. Under certain conditions, the voltage of a cell membrane can change from being at rest to becoming oscillatory as a result of a bifurcation. Oscillatory properties of small networks are often understood using bifurcation analysis.

Detailed Description

What Is a Bifurcation?

The word bifurcate is commonly used to denote a split, as in “up ahead, the road bifurcates into two parts.” The use of the term in this context implies that a driver traveling on this road can make a real-time choice of being able to take one or the other branch of the road when the bifurcation point is reached. In mathematics, and in its application to neuroscience, the term bifurcation has an entirely different contextual meaning. While a mathematical bifurcation is similar in that it involves different branches, the decision on which branch is chosen is largely made a priori and depends on the choice of parameters.

It is instructive to first gain some insight into situations that are not bifurcations. Different initial conditions converging to different solutions of the same differential equation while all parameters are held constant are not examples of bifurcations. Instead it may be that one initial condition lies in the basin of attraction of a particular solution, while the other one does not. Think, for example, of a double well potential where each well can trap particles starting with different initial conditions.

A solution to a differential equation that is perturbed and then suddenly veers off toward another attracting solution is also not an example of a bifurcation. In these examples, just because a change in behavior has occurred or a difference in convergence is observed, a bifurcation has not occurred. To qualify as a bifurcation, the change in behavior must be associated with a change in a parameter value.

Bifurcations arise in mathematical equations called dynamical systems. A dynamical system can generically be defined by the equation.

$$\frac{dx}{dt} = F(x, \mu). \quad (1)$$

where x is an n -dimensional vector of unknowns, μ is an m -dimensional vector of parameters, and F is a function that depends on the two. For the time being, assume that $m = 1$ and there is only one parameter of interest. Eq. 1 describes how the dependent variable x evolves in time under the flow dictated by $F(x, \mu)$. A bifurcation occurs when a system undergoes a qualitative change in its output as a result of a change in the parameter μ . A bifurcation analysis of Eq. 1 would involve systematically characterizing the different types of solution $x(t)$ that arise for different values of the parameter μ .

In general, a dynamical system can exhibit local and/or global bifurcations. Local ones are more prevalent in neuroscience and also easier to recognize and understand. The simplest local bifurcation involves assessing the existence and stability of fixed points of Eq. 1. A fixed point x^* is a value such that $F(x^*, \mu) = 0$ for either a specific value of μ or a set of values of μ . A fixed point can be asymptotically stable (all nearby initial conditions converge to it), stable (initial conditions that start nearby stay nearby it), or unstable (at least one nearby initial condition leaves a neighborhood of it). Often, and somewhat confusingly, the term stable is used in place of asymptotically stable. Both the existence and stability of a fixed point x^* can depend on the parameter μ in which case the possibility of a local bifurcation exists. To determine if one occurs, Eq. 1 is linearized about x^* and the eigenvalues

of the ensuing Jacobian matrix are analyzed. The eigenvalues also depend on the parameter μ . Different bifurcations correspond to the eigenvalues satisfying specific mathematical conditions for different values of μ . Similarly, a periodic solution of Eq. 1 can undergo a local bifurcation as a parameter is varied. As discussed later, such bifurcations can often be studied using a discrete map rather than a continuous flow. See Guckenheimer and Holmes (1983) for a detailed analysis of both local and global bifurcations.

Bifurcation analysis is a useful tool in mathematics because it simplifies the identification of different kinds of stable and unstable solutions. Each bifurcation type has a concomitant set of stable or unstable solutions that are produced (or destroyed) as a result of it. The conditions for identifying the existence of a bifurcation are often easier to satisfy than proving the existence of an actual solution. In neuroscience, bifurcations are of importance not just at the single-cell level but also in understanding the dynamics of networks. As described below, often a bifurcation mechanism that has been identified at the single-cell level suggests how dynamical changes (not necessarily bifurcations) occur at the network level.

Typical Bifurcations in the Dynamics of Single Neurons

Perhaps the most widely studied bifurcations involving single neurons are those that give rise to oscillations. Take a neuron whose voltage is at rest. The resting membrane potential represents a stable state. If after the injection of a constant amplitude current, the membrane voltage exhibits rhythmic behavior, then a bifurcation has occurred. Mathematically, there are two typical bifurcations that characterize this change in behavior. The first is called an SNIC (saddle node on an invariant circle) bifurcation and the second is a Hopf bifurcation. Both bifurcations arise in common neuronal models such as the two-dimensional Hodgkin-Huxley (Ermentrout and Kopell 1998) or Morris-Lecar (Morris and Lecar 1981) equations.

Consider a set of two equations that depend the parameter I_{ext} .

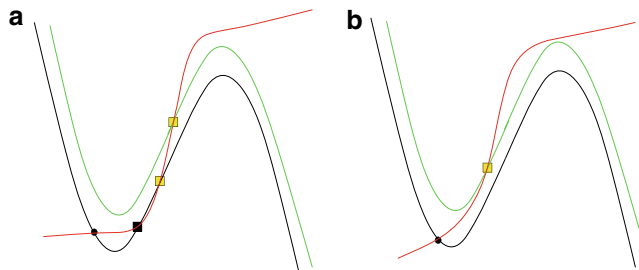
$$\begin{aligned}\frac{dv}{dt} &= f(v, w) + I_{ext} \\ \frac{dw}{dt} &= \epsilon g(v, w).\end{aligned}\quad (2)$$

In Eq. 2, the variable v represents voltage, w a recovery variable, and ϵ a positive number used to demarcate the time scales of the two variables. When ϵ is small, then Eq. 2 effectively has a fast and a slow time scale; v is called the fast variable and w the slow. The parameter I_{ext} can be thought of as an external current that only affects the membrane voltage. The v -nullcline is defined as the set of points (v, w) that satisfy the equation $f(v, w) = 0$. For the two models mentioned above, the v -nullcline is a cubic-shaped curve. The w -nullcline, the points (v, w) such that $g(v, w) = 0$, is sigmoidal-shaped like a typical activation or inactivation curve.

To understand the SNIC bifurcation, suppose that at $I_{ext} = 0$, there are two intersections of the v - and w -nullclines near the local minimum of the cubic (Fig. 1a). These intersections correspond to fixed points of Eq. 2. Linearizing at them would show that under generic assumptions, the intersection on the left branch is a stable node (attracting nearby trajectories) and the one on the middle branch is a saddle point (unstable with only one attracting direction and other directions being repelled). As I_{ext} is increased, the v -nullcline moves up in the $v - w$ phase plane and the two fixed points come closer to one another. At the SNIC bifurcation value I_{SNIC} , the fixed points coincide and become one. For $I_{ext} > I_{SNIC}$ there

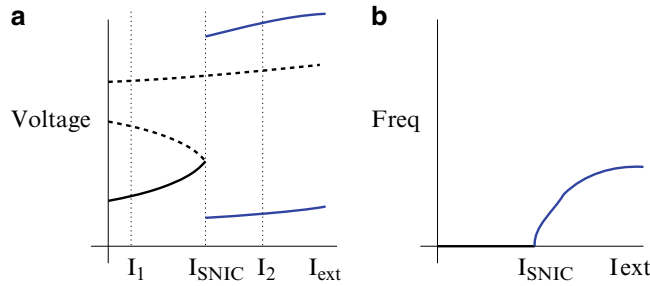
are no longer any fixed points in a neighborhood of the local minimum and a periodic orbit arises. Figure 2a shows a bifurcation diagram associated with this situation. The diagram can be interpreted as follows. For each fixed value I_{ext} , the vertical slice at that value shows the steady-state solutions that exist. Solid curves denote stable solutions and dashed curves are unstable ones. For instance, when $I_{ext} = I_1$, there are three fixed points. The one with smallest voltage is stable, while the other two are unstable. At $I_{ext} = I_2$, there is an unstable fixed point and a stable periodic solution. The solid blue curves are the upper and lower boundaries of the voltage amplitude of the periodic solution. In this and subsequent figures, blue curves are associated with periodic solutions and black curves with fixed points. Oscillations that arise through an SNIC bifurcation can have arbitrarily low frequencies and typically are of large amplitude. The $f - I$ curve associated with an SNIC bifurcation is continuous at I_{SNIC} (Fig. 2b). Ermentrout (1996) has shown that neurons that oscillate through an SNIC bifurcation have type I phase response curves that are strictly of one sign.

A Hopf bifurcation can arise when the v - and w -nullclines only intersect once in a neighborhood of the local minimum (Fig. 1b). Suppose when $I_{ext} = 0$, this single intersection (fixed point) is on the left branch. This fixed point is asymptotically stable. Linearization at it would show that the eigenvalues of the Jacobian matrix are complex with negative real part. As I_{ext}



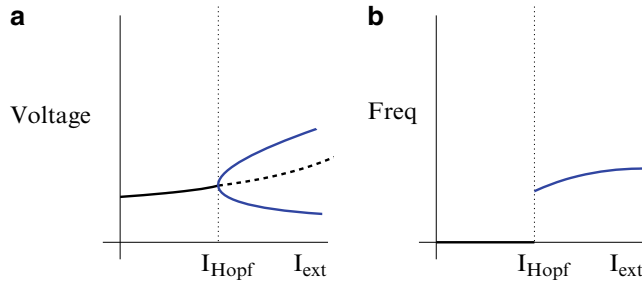
Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 1 Nullclines of (1). (a) Typical structure for an SNIC bifurcation. The lower black v -nullcline for $I_{ext} < I_{SNIC}$ has a stable (black circle) and an unstable (black square) fixed points near the local minima and an

unstable (yellow square) fixed point along the middle branch. The upper v -nullcline for $I_{ext} > I_{SNIC}$ has only the unstable (yellow square) fixed point. (b) Typical structure for an Hopf bifurcation. Here there is only one fixed point associated with each cubic



Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 2 SNIC bifurcation diagrams. (a) Stable (solid curves) and unstable (dashed curves) solutions as a function of I_{ext} . Black curves denote fixed points and blue curves periodic solutions. As I_{ext} increases, the two fixed

points that meet at I_{SNIC} are destroyed. At this point a branch of stable periodic solutions arises. See text for explanations for I_1 and I_2 . (b) The $f-I$ curve shows that oscillations begin with arbitrarily low frequency



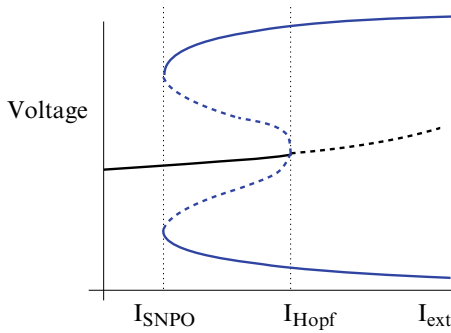
Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 3 Hopf bifurcation diagrams. (a) A single stable fixed point (black curve) loses stability at a supercritical Hopf bifurcation point spawning the branch

of stable periodic solutions. (b) The $f-I$ curve shows that oscillations begin with a frequency that is bounded from below away from zero

increases, the v -nullcline moves up and the fixed point moves toward the local minimum and eventually occurs on the middle branch. The eigenvalues depend continuously on I_{ext} and their real parts become smaller in absolute value. At some point, $I_{ext} = I_{Hopf}$, after the fixed point has moved to the middle branch, the eigenvalues at the linearization are pure imaginary. For $I_{ext} > I_{Hopf}$, the eigenvalues have positive real part. A Hopf bifurcation occurs at I_{Hopf} resulting in the creation of a periodic orbit. There are two distinct types of Hopf bifurcations: supercritical which produce stable periodic solutions and subcritical which produce unstable ones. Figure 3a shows the bifurcation diagram associated with a supercritical Hopf bifurcation. The amplitude of oscillations just after bifurcation is small. The frequency of oscillations just above the Hopf bifurcation points is bounded from below resulting in a

discontinuous $f-I$ curve (Fig. 3b). Neurons that oscillate through a Hopf bifurcation mechanism typically have a type II phase response curve that is of both signs.

In some neuron models, the subcritical Hopf bifurcation is often found in conjunction with another bifurcation called the saddle node of periodic orbits (SNPO) bifurcation. Figure 4 shows such a case where the branch of unstable orbits extends from I_{Hopf} for decreasing values of I_{ext} . Surrounding the branch of unstable periodic orbits is a branch of stable periodic orbits of larger amplitude. The stable and unstable periodic branches come together at $I_{ext} = I_{SNPO}$ which destroys the two orbits. As the bifurcation diagram shows, for $I_{SNPO} < I_{ext} < I_{Hopf}$ bistability exists between the stable fixed point on the middle branch and the larger amplitude periodic orbit. Starting at the stable rest state, as I_{ext} is increased



Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 4 Subcritical Hopf bifurcation diagram. A single stable fixed point (black curve) loses stability at a subcritical Hopf bifurcation point spawning the branch of unstable periodic solutions. That unstable branch merges at I_{SNPO} with a branch of stable periodic orbits. The interval $I_{SNPO} < I_{ext} < I_{Hopf}$ is a region of bistability in that both a stable fixed point and a stable periodic solution exist

past the Hopf bifurcation point, the solution suddenly changes to a large amplitude periodic orbit. Once on this branch of large amplitude solutions, decreasing I_{ext} shows an example of hysteresis whereby the stable branch of periodic solutions exists over a range where the stable fixed points also do.

Variations in different parameters besides I_{ext} can lead to bifurcations. For example, in a model associated with the circadian rhythm, *per1* neurons in the suprachiasmatic nuclei undergo a subcritical Hopf bifurcation as the maximal conductance of their calcium channel, g_{Ca} , is increased (Belle et al. 2009). Belle et al. show that as g_{Ca} is increased, an asymptotically stable rest state undergoes a subcritical Hopf bifurcation leading to oscillations during only a certain phase of the circadian rhythm. They also show that a second Hopf bifurcation can arise during a phase corresponding to daytime in which a highly depolarized resting state becomes stable. Mathematically, the mechanism for the creation and control of oscillations is exactly the same whether the bifurcation results from changes in g_{Ca} as in this case or from I_{ext} as shown in Fig. 4.

Bifurcation analysis is also a primary tool in understanding bursting oscillations where a neuron exhibits a sequence of (relatively) high-frequency spikes, followed by a (relatively) long

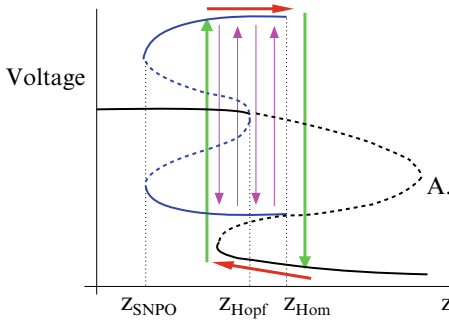
interburst interval. The main idea here is to exploit the difference in time scales between the high-frequency spikes and the long interburst interval to define fast and slow variables. Consider the following set of three first-order equations:

$$\begin{aligned} x' &= f_1(x, y, z) \\ y' &= f_2(x, y, z) \\ z' &= \epsilon g(x, y, z). \end{aligned} \quad (3)$$

The small positive parameter ϵ implies that x and y are fast variables and z is the slow variable. To use bifurcation analysis, set $\epsilon = 0$ in Eq. 3 and note that now $z' = 0$, implying that z will not change. This means that z will act as a parameter in the fast equations for x' and y' . The fast subsystem can now be studied with z acting as a bifurcation parameter to see what, if any, bifurcations exist. For each z , the equations $f_1(x, y, z) = 0$ and $f_2(x, y, z) = 0$ are the nullclines of the fast subsystem. They form null surfaces in the full three-dimensional phase space. Intersections of any two null surfaces form curves of fixed points of the fast subsystem and their bifurcations can readily be studied. The mathematical technique of singular perturbation theory then shows that solutions to the actual $\epsilon > 0$, but small, problem lie close to the null surfaces except for times when they make very fast transitions between different null surfaces. The location where these fast transitions occur is computable through bifurcation and singular perturbation analysis. Rinzel (1985, 1987) first used these ideas to mathematically classify different types of bursting in single-cell models. Figure 5 shows an example of square wave bursting bifurcation diagram which illustrates this type of analysis. See (Izhikevich 2000) for a rigorous mathematical exploration of bursting in single neurons or (Ermentrout and Terman 2010) for an overview of several important types of bursting arising in neuroscience.

Bifurcations in Small Neuronal Networks

Just as certain parameters intrinsic to a neuron can determine whether an individual neuron can oscillate, these parameters can also do the same for a



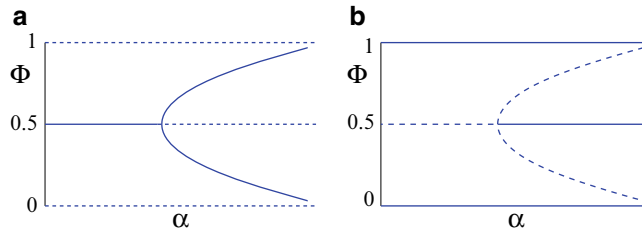
Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 5 Bifurcation diagram associated with square wave bursting. The variable z acts as a parameter for the $\epsilon = 0$ fast subsystem of (3). As z is increased along the upper branch of fixed points (upper solid black curve of the Z-shaped curve), the fixed point undergoes a subcritical Hopf bifurcation. The unstable periodic branch merges with a stable branch of periodic solutions at z_{SNPO} . The stable branch of periodic solutions terminates at a homoclinic bifurcation point at z_{Hom} . The actual flow of (3) for ϵ small is graphically depicted. The red lines pointing left (right) indicate that the solution closely follows the lower (upper) branch of the Z-shaped curve as z slowly decreases (increases). The green lines indicate the fast transitions between the upper and lower branches of the Z-shaped curve. Magenta arrows between the stable periodic branches indicate the fast spiking portion of the burst

coupled network of neurons. A small network of cells may not be able to oscillate unless some or all of the individual cells can. Thus, whatever bifurcation causes the individual cell to oscillate may, in turn, cause the network to be rhythmic. Changes in intrinsic parameters having nothing to do with the existence of oscillations can also lead to bifurcations in network output. For example, Zhang et al. (2009) show that increases in the maximal conductance of an A-current in a postsynaptic cell can cause the cell to go through a sequence of border collision bifurcations (Nusse et al. 1994), resulting in a cascade of different phase-locked solutions.

In networks, many interesting bifurcations occur with changes in synaptic parameters. Consider a network of two mutually coupled spiking neurons governed by the integrate and fire model and connected by alpha synapses $g_{syn}\alpha^2te^{-\alpha t}$. Here g_{syn} governs the strength and α the speed of the synapse. The phase ϕ at which one cell fires with respect to the other can be used to define a

function whose roots correspond to phase-locked periodic solutions. For this model of two identical cells, both the synchronous ($\phi = 0$ or 1) and antiphase ($\phi = 0.5$) solutions exist for both excitatory ($g_{syn} > 0$) and inhibitory ($g_{syn} < 0$) coupling. Van Vreeswijk et al. (1994) showed that these solutions change stability through a pitchfork bifurcation as the parameter α changes; at the pitchfork bifurcation point, three branches emerge from one. In particular, for excitatory synapses, increases in α make the antiphase solution bifurcate from being stable to unstable (Fig. 6a). At the bifurcation point, a new stable out-of-phase solution arises; by symmetry there are two such solutions. Further increasing α causes these new curves of out-of-phase solutions to come closer to the curve corresponding to the synchronous solution. Note in this case, that while the synchronous solution is always unstable, as α increases and the synapse becomes faster, the phase of locking ϕ tends to synchrony. The opposite happens for inhibitory synapses (Fig. 6b). As α increases and the synapse is made faster in its rise and decay, the antiphase solution undergoes a pitchfork bifurcation taking it from unstable to stable. The curves of out-of-phase solutions that are born are unstable. The synchronous solution is stable for all values of α , but its basin of attraction shrinks as α increases.

A common way to find bifurcations in a neuronal network is to define a Poincaré return map or a time T map. The Poincaré map records the values of relevant variables along a defined hyperplane in the mathematical phase space. The time T map records the values of appropriate variables at every time nT , for $n = 1, 2, 3, \dots$. In either case, a fixed point of the map corresponds to a periodic solution of the network. In this way, mathematical tools to study bifurcations of fixed points of maps (discrete dynamical systems) can be used to study bifurcations of periodic solutions of networks. For example, in a model consisting of an excitatory cell reciprocally coupled to an inhibitory cell whose synapse exhibits short-term synaptic depression, Bose et al. (2001) showed how changes in the maximal synaptic conductance of the inhibitory synapse give rise to saddle-node bifurcations of fixed points of a one-dimensional



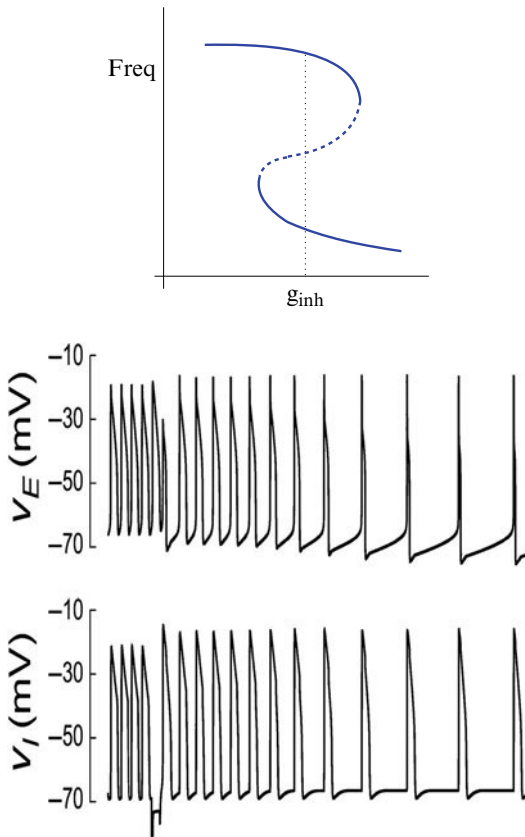
Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 6 Bifurcation diagram as a function of synaptic speed, (Adapted from Van Vreeswijk et al. (1994)). (a) For excitatory synapses, as the synaptic speed increases, the stable antiphase solution at $\phi = 0.5$ undergoes a pitchfork bifurcation. The new curve of stable

out-of-phase solutions shows that solutions approach synchrony as the synapse gets faster. (b) For inhibitory synapses, the synchronous solution is always stable. The antiphase solution stabilizes by increasing α though the pitchfork bifurcation point

return map (Fig. 7). The fixed points of the map correspond to different oscillatory solutions of different frequency. Solutions on the upper branch are controlled by parameters that are intrinsic to the excitatory cell and are of high frequency. The high frequency causes the inhibitory synapse to remain in a depressed state and never recover. Solutions on the lower branch correspond to low-frequency solutions with a long interspike interval. Because of this long interval, the depressing synapse has a chance to recover between spikes and the synaptic current to the excitatory cell at each spike is large. Here the frequency is controlled by a parameter governing the decay of inhibition. Note that this network also exhibits bistability and hysteresis similar to what was seen to occur in certain single-neuron models. Perturbations can cause the solution to switch between different oscillatory solutions as seen in Fig. 7. The switch is a consequence of the bifurcation structure, but is not in and of itself a bifurcation.

As is suggested by the prior example, bifurcations in networks of neurons are also closely related to the issue of what sets of parameters control the oscillatory state. This is especially true in central pattern generating (CPG) networks where the existence of oscillations is a given. What is more relevant is what controls the existence of oscillations and their frequency. For example, in a network of two cells mutually coupled by fast inhibitory synapses, Skinner et al. (1994) describe circumstances under which the synaptic threshold is of importance in

controlling the frequency of antiphase, half-center oscillations. They define the terms intrinsic escape, intrinsic release, synaptic escape, and synaptic release to indicate different ways in which the oscillators can switch orientations from being active to silent and vice versa. The synaptic threshold turns out to be irrelevant in the intrinsic escape or release mode but is highly relevant in the synaptic escape or release mode. Understanding how the synaptic threshold can play this role relies, in part, on bifurcation dynamics associated with single cells. For single cells it was earlier shown that increasing I_{ext} causes the stable solution to bifurcate from being a rest point to an oscillatory one by shifting the v -nullcline up in the phase space and removing a fixed point on its left branch. In this two-cell network, the removal of an inhibitory synaptic current to the postsynaptic cell acts similarly to increasing I_{ext} in a single cell by shifting the v -nullcline up in phase space and removing an intersection of the v - and w -nullclines. Thus, although there is not a bifurcation in the network as the result of the application or removal of a synaptic current, the mechanism by which the postsynaptic cell fires is readily understood as a result of single-neuron bifurcation analysis. The possible application or removal of inhibition occurs only when the synaptic threshold is crossed. When the individual cells are modeled as relaxation oscillators (with cubic-shaped v -nullclines), then the fast transition between the silent and firing states effectively occurs at the local minima and maxima of the cubic nullcline. Thus, when the synaptic threshold



Bifurcations Dynamics of Single Neurons and Small Networks, Fig. 7 Dynamics of an excitatory-inhibitory network. *Upper panel* shows bifurcation diagram as a function of maximal inhibitory conductance g_{inh} . The two branches of stable periodic solutions are connected by an unstable branch. *Lower panel* shows voltage trajectories (E excitatory, I inhibitory) with g_{inh} chosen at the value of the dotted line in *upper panel*. The solution starts off at high frequency along the upper branch. A brief perturbation given to the inhibitory cell temporarily suppresses its activity allowing its synapse to recover from depression and strengthen. In turn, this causes the solution to switch to a lower frequency periodic orbit along the lower branch

lies between these two extrema, the threshold is not relevant for controlling frequency as small changes in its value have little effect on the time spent above or below it. On the other hand, if the synaptic threshold intersects either the left or right branch of the cubic, then small changes in its value can have an effect since the cell's trajectory evolves slowly there; that the evolution is slow is a consequence of the assumption of relaxation oscillations. It is through the scaffold of single-

cell bifurcation analysis and fast/slow time scale decomposition that Skinner et al. are able to define intervals for the synaptic thresholds that demarcate intrinsic versus synaptic escape/release mechanisms and thereby control the frequency of oscillations.

A more complicated example of using bifurcation analysis is found in a model of a respiratory CPG due to Rubin et al. (2009). The authors consider a four-cell network of excitatory and inhibitory cells and are interested in understanding transitions between oscillatory patterns that correspond to different phasic states of the respiratory rhythm. By using fast/slow time scale analysis, they show how to identify certain transitional curves associated with the fast subsystem. These curves lie on equilibrium surfaces (null surfaces) of the fast subsystem. In the problem considered, there are relevant equilibrium surfaces corresponding to cells being either in the active or inactive state. When the trajectory of the system reaches one of these transitional curves, there is a switch from inspiration to expiration or vice versa. The transitional curves are themselves defined because they satisfy certain bifurcation conditions for fixed points of the fast subsystem. Through their analysis, the authors show how changes in the maximal conductance of a persistent sodium current in one of the cells play a major role in controlling the frequency and duty cycle of oscillations within the network. They also show how changing the total synaptic drive to individual cells modulates the bifurcation diagram again resulting in an understanding of how frequency and duty cycle change. The interested reader is referred to (Rubin et al. 2009) to see further details.

Concluding Remarks

Bifurcations at the single-neuron level often focus on understanding how a single fixed point is created or destroyed or how it gains or loses stability. Different kinds of bifurcations imply the existence of different kinds of oscillatory solutions, each possessing different properties. As a single-neuron model becomes more complicated, say

for describing a bursting neuron, bifurcations occurring in a fast subsystem help to build the skeleton on which the dynamics of the full system can be understood. In networks, the bifurcation parameter can be either intrinsic to a cell or related to one of the synapses. Bifurcations within them are often understood by knowing the bifurcation possibilities of single neurons. But networks have the potential to be much richer and complicated in their bifurcation structure. An important concept highlighted above is that bifurcation analysis can reveal how certain parameters determine which network elements control the behavior in the network. Interestingly, a bifurcation occurring as a result of a change in an intrinsic parameter may imply that a synaptic mechanism becomes relevant for controlling the network output, or vice versa.

Bifurcations of the type described here are associated with steady-state solutions (fixed points or periodic orbits) of differential equations. They are local in the sense that the information obtained from the bifurcation only provides information in a neighborhood of the bifurcation point. While this neighborhood may in fact be mathematically large, it is important to keep in mind that the entire set of possible solutions in the global phase space are not determined through local bifurcations. Nonetheless, bifurcation analysis is a powerful tool for understanding the dynamics of neurons and the networks in which they participate.

Acknowledgments This work was supported in part by NSF DMS 1122291.

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Bifurcations, Neural Population Models and

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Definition

In neural population models (NPMs), as in dynamical systems in general, smooth changes in system parameters, for example, coupling strength, input levels, and time constants, may result in sudden qualitative changes in system

dynamics, such as the occurrence or disappearance of oscillatory or chaotic behavior. Such phenomena are referred to as bifurcations and are interesting because they may account for switching phenomena, which are common in both brain signals and organisms' behavior.

Detailed Description

Depending on their particular parameter set, NPMs experience different asymptotic dynamic behaviors characterized by constant output, harmonic (i.e., sinusoidal) or nonharmonic oscillations, which can be periodic or quasiperiodic (i.e., the signal repeats itself approximately, but not exactly), and even chaotic behavior (Frascoli et al. 2011; Spiegler et al. 2010, 2011). The transitions in parameter space between these qualitatively different states are called bifurcations (see Breakspear and Jirsa 2007). They partition the parameter space into regions with different dynamics. Their analysis is of fundamental importance for the description of the behavior of neural systems, which often features the transition of gradual changes in some variables into sudden qualitative changes in system behavior. Bifurcation diagrams are an important utility for the investigation of bifurcations. They show the stable and unstable fixed points (i.e., points, where the time derivatives of the state variables are zero; also referred to as equilibrium points) and limit cycles (i.e., closed trajectories in state space) as a function of one or more system parameters (see Fig. 1). In the following, we will give a brief overview on types of bifurcations that are relevant for neural population models. Then we will demonstrate, using the example of the Jansen-Rit model (Jansen and Rit 1995), how bifurcation analysis characterizes the dynamic fingerprint of a neural population model.

Types of Bifurcations

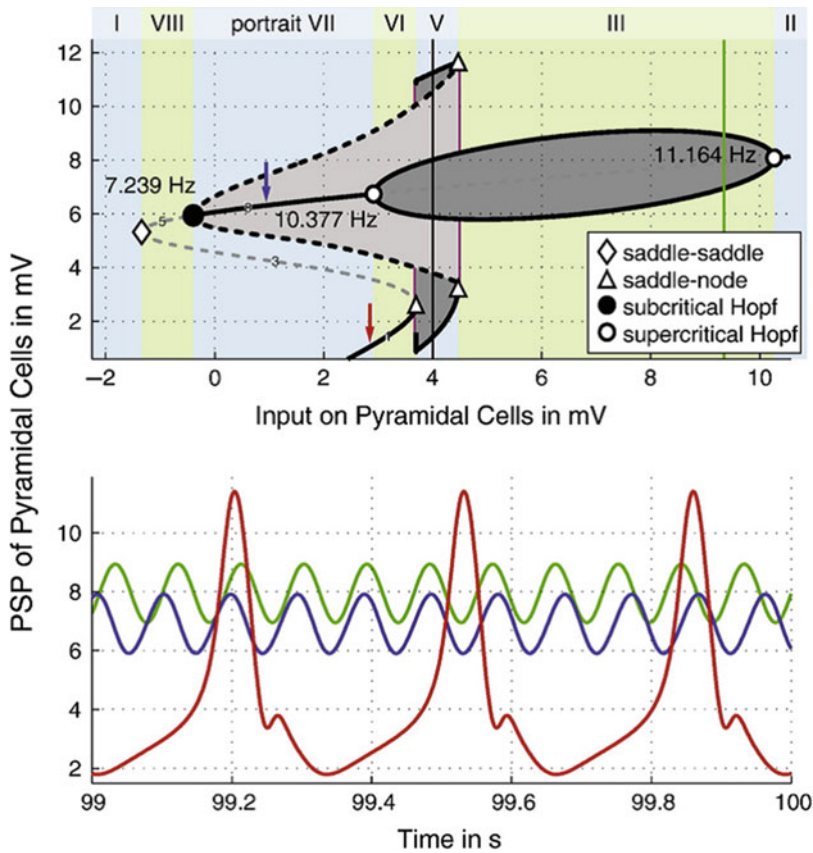
There is a great variety of different types of bifurcations (see also Guckenheimer 2007; Breakspear and Jirsa 2007). Depending on whether or not it

can be identified just by stability analysis in a small vicinity of a fixed point, a bifurcation is termed local or global. In addition, bifurcations are characterized by their codimension, which is the number of independent parameters that need to be varied for the bifurcation to occur. Consider the bifurcation diagram in Fig. 1, where the asymptotic behavior of the pyramidal cells' membrane potential is plotted versus a single system parameter, namely, the mean input to the pyramidal cells. It shows a number of codimension 1 bifurcations (see figure legend).

Local (or subtle) bifurcations are characterized by a change of asymptotic stability, that is, fixed points and limit cycles suddenly change stability upon smooth change of a system parameter. They can be analyzed by looking at the, generally complex, eigenvalues of the system's local linearization (Jacobian matrix). If the real parts of one or several of the eigenvalues change sign, the local stability of the system is altered and a bifurcation occurs. Types of local bifurcation that are most often identified in neural population models include Andronov-Hopf (AH) as well as saddle-node (SN), saddle-focus (SF), and saddle-saddle (SS) bifurcations (Grimbert and Faugeras 2006; Spiegler et al. 2010; Touboul et al. 2011). Further important local bifurcations are the pitchfork, transcritical, and period-doubling bifurcations (see Breakspear and Jirsa 2007).

AH bifurcations occur if two conjugate complex eigenvalues cross the imaginary axis. They mark the transition between a fixed point (real part is negative) and a limit cycle (real part is positive). Depending on the largest Lyapunov exponent, the bifurcation can be supercritical (i.e., both limit cycle and fixed point are stable) or subcritical (i.e., limit cycle and fixed point are unstable). AH bifurcations give rise to oscillations, which are more or less harmonic, depending on their amplitude and the system's degree of nonlinearity.

SN/SF bifurcations (also called tangential or fold bifurcations) occur if, upon change of a parameter, two fixed points, one unstable (the saddle) and one stable (the node or focus), collide and annihilate each other. When approaching the bifurcation from the other side, this means that two fixed points are suddenly created. At the



B

Bifurcations, Neural Population Models and, Fig. 1 Bifurcation diagram and exemplary solutions of the original configuration of the Jansen and Rit (1995) with no input to the interneurons and time constants 10 and 20 ms for excitatory and inhibitory interneurons, respectively. Solid lines represent stable and dashed lines unstable states. Branches of limit cycles correspond to gray regions bounded by solid lines for stable and dashed

black lines for unstable limit cycles. Bifurcations are indicated by diamonds, triangles, and circles (see legend in inset). For all Andronov-Hopf bifurcations, the eigenfrequencies of the limit cycles are indicated. Different extrinsic input levels on pyramidal cells (black and green vertical lines) result in different behaviors depending on the past of a system's trajectory (blue and red arrows) (Modified from Spiegler et al. (2010))

critical point itself, the fixed points lose asymptotic stability, as they become non-hyperbolic (i.e., the second derivative becomes zero). If both colliding fixed points are saddles, the bifurcation is an SS bifurcation.

Global (or catastrophic) bifurcations have to be studied by considering the vector field outside the local neighborhood of fixed points. They are characterized by a loss of structural stability, that is, fixed points and limit cycles suddenly occur or vanish upon smooth change of a system parameter. Accordingly, the saddle family of bifurcations (see above) can also be considered global, as the two colliding fixed points vanish. One typical

example of a global bifurcation is given by the infinite period bifurcation, where a stable fixed point (node or focus) is connected to a saddle via a particular trajectory, called the heteroclinic orbit. Upon change of the parameter toward the critical point, these two fixed points get closer and closer, until they collide and vanish. Now, the trajectory connecting the former fixed points turns into a periodic orbit, giving rise to sustained oscillations of the system. If approached from the other side, this bifurcation is characterized by a slowing of the oscillation, until at the critical point the period becomes infinite and the periodic orbit is turned into a heteroclinic orbit connecting two fixed

points. Global bifurcations also include homoclinic and heteroclinic bifurcations, in which periodic orbits collide with one or several saddle points, or collisions between more than one periodic orbit.

Examples for higher codimension bifurcations include the following: (1) the Bautin (generalized Hopf, GH) bifurcation, which occurs if an AH bifurcation, upon change of a second parameter of the system, turns from supercritical to subcritical; (2) the Bogdanov-Takens (BT) bifurcation, where AH, SN, and homoclinic curves intersect; and (3) the cusp (C) bifurcation, where two branches of saddle-node bifurcation curve meet tangentially, giving rise to hysteresis phenomena. For more information, refer to Guckenheimer (2007) and Kuznetsov (2004).

Bifurcations of the Jansen-Rit Model

The Jansen-Rit model has been investigated by Touboul and Faugeras (2007) as well as Spiegler et al. (2010, 2011) by generating codimension one bifurcation diagrams, where the membrane potential of the pyramidal cells is plotted as the relevant state variable against the constant input level to the same cell population (Fig. 1).

For the original parameter configuration of Jansen and Rit, the following dynamics occur, while gradually increasing the pyramidal cell input: At very low input levels, only one stable fixed point (node) exists (Sect. I in Fig. 1). At about -1.2 mV, two unstable fixed points (saddles) appear in an SS bifurcation (Sect. VIII). The system still remains monostable with one stable fixed point. With further increase of the input level to about -0.5 mV, one of the saddles undergoes a subcritical AH bifurcation, resulting in an unstable limit cycle and stable focus (sect. VII). The system is now bistable. At about 3 mV the stable focus undergoes a supercritical AH bifurcation, giving rise to stable harmonic oscillations (sect. VI). Further increase to about 3.5 mV lets the stable node and the unstable saddle collide, and a periodic homoclinic orbit is born in an infinite period bifurcation (sect. V). In another global bifurcation, this orbit collides at about 4.5 mV with unstable limit cycle originating

from the subcritical AH bifurcation. The cycles vanish and the system's only remaining stable state is the stable limit cycle (sect. III), which turns into a stable node by another supercritical AH bifurcation at about 10.5 mV.

This exemplary bifurcation scheme is subject to drastic change, if the other system parameters are varied, which has been shown by systematic sampling of the parameter space (Spiegler et al. 2010) and by characterization of higher codimension bifurcations (Touboul and Faugeras 2007). In addition to the SN and AH bifurcation manifolds, Touboul and Faugeras (2007) found some codimension two and three bifurcations for the Jansen-Rit model, namely, C, BT, and GH bifurcations.

Cross-References

- [Anesthesia, Neural Population Models of](#)
- [Bifurcation Analysis](#)
- [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- [Chaos, Neural Population Models and](#)
- [Epilepsy, Neural Population Models of](#)
- [Gamma Rhythm, Neural Population Models of the](#)
- [Jansen-Rit Model](#)
- [Deep Cerebellar Nuclei](#)
- [Pattern Formation in Neural Population Models](#)
- [Phase Transitions, Neural Population Models and](#)
- [Sleep, Neural Population Models of](#)

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Bimolecular Reactions, Modeling of

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Definition

A bimolecular reaction refers to the chemical combination of two molecular entities in a reaction that can be considered either reversible or irreversible. The reaction can involve two chemically distinct molecules, e.g., $A + B$, or two identical molecules, e.g., $A + A$. The reaction can be characterized with respect to association and dissociation rate constants, which also define the equilibrium constant. However, it is also possible to establish the equilibrium constant without direct knowledge of the rate constants. For many applications to biological systems, one or both of the components possess multiple reaction sites and/or distinct conformational states, adding levels of complexity that must be considered for a complete description of the system.

Detailed Description

For computational neuroscience encompassing the molecular level, bimolecular reactions are

encountered for virtually all topics considered. Neurons and their accompanying cells of other classes are living entities with a complete array of biochemical reactions, most of which are not specific to the nervous system, such as the full complement of metabolic enzymes. Enzyme-substrate reactions are one form of bimolecular reactions, but will not be considered here, since another chapter that included this topic was recently completed (Endler et al. 2012). For reactions in individual neurons, only small numbers of molecules are involved in many cases and stochastic principles must be applied to consider the reactions appropriately. This subject will not be treated, but general principles are well described elsewhere (Steinfeld et al. 1989), along with a detailed description for ligand-gated channels based on terminologies that are presented here (Edelstein et al. 1996). The focus for this entry is on ligands binding to multisite proteins that can exist in more than one functionally distinct conformational state, as commonly occur for allosteric membrane proteins (Edelstein and Changeux 2010) and other allosteric regulatory proteins, such as calmodulin (Stefan et al. 2008). These phenomena are most efficiently represented by the formalism of the Monod-Wyman-Changeux (MWC) model (Monod et al. 1965; Edelstein et al. 1996; Changeux and Edelstein 2005).

Formalism for Two Conformational States

The MWC model defines a multisite (oligomeric) protein with two conformational states, T and R related by the allosteric constant, L_i , where $L_i = [T_i]/[R_i]$. Here “i” refers to the number of ligand molecules bound up to the limit of “n” molecules, usually equivalent to the number of subunits in an oligomeric protein. Ligand is represented by “X,” with distinct dissociation equilibrium constants for the T and R states: K_T and K_R . The model is formulated such that the T state is favored in the absence of ligand ($L_0 \gg 1$), but the R state binds the ligand more tightly ($K_R \ll K_T$). Hence, typically for a dimer with two ligands bound, $L_2 \ll 1$. Each reaction equilibrium constant is the ratio of the appropriate kinetic constants, $k_{\text{off}}/k_{\text{on}}$. Because

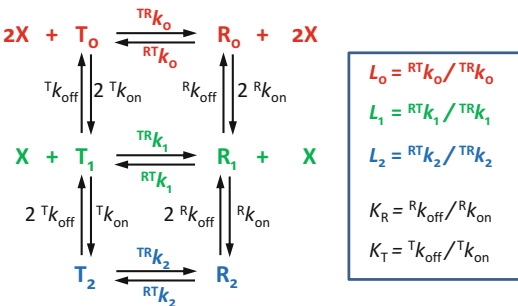
more than one binding site is involved, statistical factors come into play. For example, for a ligand binding to an unliganded dimer ($n = 2$), the on rate must be increased by a factor of two, since two sites are available on the dimer. Similar reasoning applies to the dissociation of ligand from a fully or partially saturated oligomer. Generally, for a protein with n sites and i ligands bound, the binding of an additional ligand is modified by the statistical factor $(n - i + 1)/i$. The binding reactions are illustrated in Fig. 1, along with the equations for occupancy and fraction of molecules in the R state. Finally an energy diagram is presented

Equations for occupancy ($\bar{Y}$) and fraction in R state ($\bar{R}$):

$$\bar{Y} = \frac{\alpha(1 + \alpha)^{n-1} + Lc\alpha(1 + c\alpha)^{n-1}}{(1 + \alpha)^n + L(1 + c\alpha)^n}$$

$$\bar{R} = \frac{(1 + \alpha)^n}{(1 + \alpha)^n + L(1 + c\alpha)^n}$$

Reaction cycle for dimer with two-states:



Energy diagram for dimer with two-states:

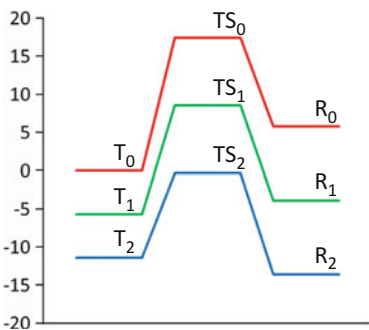


Fig. 1

in the figure to reveal how the kinetic constants are related to the thermodynamic parameters in terms of activation barriers fixed by linear free energy relations (Edelstein et al. 1996).

Limitations

The concepts presented here do not distinguish between the free and the total concentrations for the ligand in question. Commonly the total concentration is assumed to be effectively indistinguishable from the free concentration, but under conditions that approximate the physiological state, this assumption is often inapplicable. In that case, the binding of ligand can cause a significant change in the free concentration (a phenomenon known as “ligand depletion”) and the appropriate corrections must be introduced, since the effects may be substantial (Edelstein et al. 2010).

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Binary Neural Network

► [Hopfield Network](#)

Binocular/Monocular Rivalry

► [Multistability in Perception Dynamics](#)

Biomechanical Model of Low Back Pain

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Synonyms

[Animal models of pain](#); [Computational models of painful loading](#); [Finite element models of the spine](#); [Lumbar spine pain](#); [Model systems for spine pain](#); [Spinal biomechanics](#); [Tissue loading and pathology](#)

Definition

Low back pain can arise from a wide range of inciting conditions and pathologies in the lumbar and sacral spines. Symptoms can remain localized to the axial spine but also can extend to the torso and upper back, buttocks, legs, and feet, depending on which tissues in the spine are affected and the extent of the related pathology. The most common spinal tissues involved in producing low back pain are the intervertebral disc, facet joints, nerve roots, and musculature. Many different biomechanical models have been developed in order to study low back pain. In particular, such models mimic the mechanical loading to the spine and/or its isolated tissues that serve as sources of pain, and define the local tissue biomechanics for various normal and abnormal spinal

loading conditions. Biomechanical models focus on describing and informing different aspects of the cascades related to tissue loading, mechanical responses, physiological cascades that are initiated and maintained, and the symptom response.

Detailed Description

Biomechanical models can be categorized into several different types: animal and human cadaveric models, in vivo animal models, and computational and mathematical models. Over the years, each of these modeling approaches has incorporated biomechanical techniques and together provides a complementary and increasingly more detailed insight about the causes, consequences, and complications associated with low back pain.

Cadaveric Models

Cadaveric models of both humans and other species have formed the basis of the early efforts in biomechanical modeling. They most often describe the spine's kinematic and kinetic response to loading, as well as the mechanical response that individual tissues undergo during spinal loading. In addition to defining the anatomical, material, and structural relationships between the various tissues in the spine, these models have defined how such relationships vary with various loading configurations in the context of normal motions, injury, degeneration states, and following surgical treatments (White and Panjabi 1990; Winkelstein 2012). The main findings have defined injury tolerance for failure of different tissues and the physical consequences of repetitive loading to certain tissues, such as the production of ligament laxity, loss of disc height, and increased motion (Shapiro and Risbud 2013).

In Vivo Animal Models

Despite the potential differences in anatomy, scaling, and physiology between animals and humans, in vivo models have tremendous utility

for biomechanical modeling of LBP (DeLeo and Winkelstein 2002; Winkelstein 2011), especially given the ethical and financial advantages they offer while also providing meaningful insight on the mechanics of spinal tissues and the related physiological and symptom responses. Animal models of nociception help in understanding neural mechanisms of pain from the spine, such as arthritis, discogenic pain, and radicular nerve root injury, all of which can lead to the development of acute and chronic LBP (Deleo and Winkelstein 2002; McMahon and Koltzenburg 2005; Jaumard et al. 2011).

The earliest studies using animal models of chronic back pain involve direct surgical manipulation of the sciatic nerve including sciatic cryoneurolysis (DeLeo et al. 1994); sciatic nerve transection, ligation, or crush (Przewłocka et al. 1999; Obara et al. 2003); partial nerve injury (Seltzer et al. 1990); chronic constriction injury (Bennett et al. 2003); and L5/L6 spinal nerve ligation (Colburn et al. 1999). Although those models have been important for defining the cascades that lead to pain following neural injury in the spine, they have not standardized the role of biomechanics. More recent work in the rodent has defined the role of tissue loading for nerve root and disc injuries (Iatridis et al. 1999; DeLeo and Winkelstein 2002; Winkelstein et al. 2002; Jaumard et al. 2011; Showalter et al. 2012). Only recently, with the advances in measurement technologies, have local tissue mechanics been able to be incorporated in such models to relate specific injury and loading environments to tissue responses, neuroimmune cascades regulating pain, and resulting symptoms of pain.

Computational/Mathematical Models

Due to the complexity of modeling injury and pain from tissue loading, cadaveric and in vivo modeling have only limited utility for modeling LBP. As such, computational models have been developed based on anthropomorphic measurements that permit many loading configurations to be tested. Such models extrapolate the

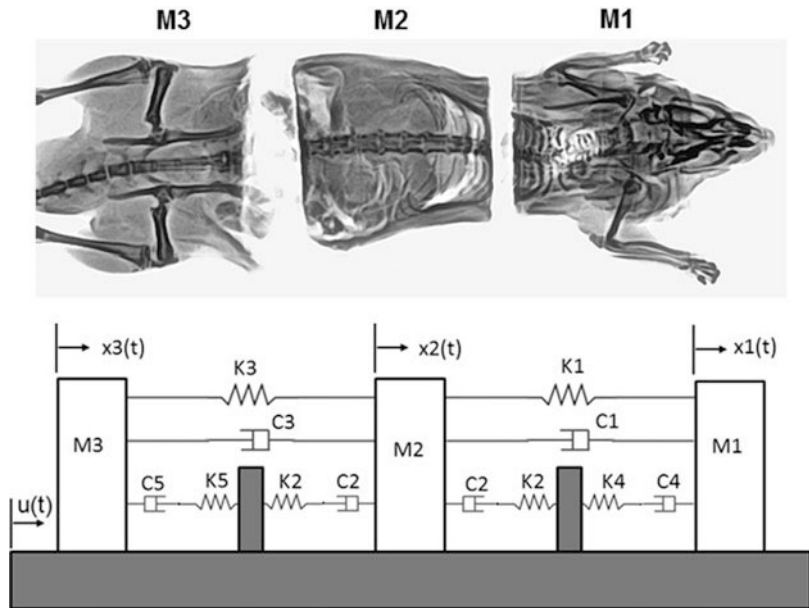
biomechanics of the lumbar spine for loading conditions that cannot be tested using live subjects, such as injury scenarios from vehicle impacts, sports injury, and exposure to high-frequency vibrations. This is particularly relevant when modeling LBP in which ethical considerations limit the exposures that are allowed.

Biomechanical computational models can be grouped as lumped-parameter, multibody, or finite element models (Liang and Chiang 2006). Lumped-parameter models (Fig. 1) are generally limited to only one-dimensional analysis, simulating the human body as an assembly of concentrated masses, representing different parts of the body, connected by springs and dampers that simulate the viscoelastic properties of the biologic tissues. The lumbar spine can be represented as masses for the vertebrae connected by a spring and damper in parallel to simulate the intervertebral disc (Keller et al. 2002). Multibody models consist of rigid bodies connected by hinges and/or ball-and-socket joints and can be used to study the kinematics and kinetic response of the body to a direct or indirect mechanical excitation (Ma et al. 1995).

Finite element (FE) models are the most complex since they mimic the anatomical and material properties of the spinal tissues and their relationships based on different loading scenarios and motions. Several FE models have been developed to evaluate spine biomechanics and simulate clinical procedures. Such models were designed to understand how changes in the spine, such as disc degeneration, osteophytes, disc arthroplasty, facetectomy, or laminoplasty, affect the local mechanical response of its tissues (bone, ligament, cartilage), as well as the overall spinal biomechanics (Rohlmann et al. 2007; Rundell et al. 2008; Zhang and Teo 2008; Kuo et al. 2010). Other FE models provide utility for evaluating tissue loading from spinal biomechanics during nonphysiological injurious loading (Sairyo et al. 2005; Kitagawa et al. 2006; El-Rich et al. 2009). While these approaches have become tremendously intricate, with detailed physiological and mechanical processes captured in the models, there are currently no such models that can

Biomechanical Model of Low Back Pain,

Fig. 1 Example of a lumped-parameter model of the rodent used to evaluate spinal kinematics and kinetics in whole body vibration along the spine's axis. The three masses ($M1$, $M2$, $M3$) simulate the mass of the three body segments. Springs (K) and dampers (C) simulate the viscoelastic interactions between the masses and the masses and the vibrating platform



simulate the nociceptive processes that are initiated or modulated by spinal loading as it relates to pain.

Overall, computational models help to understand how the biomechanics of the lumbar spine and its associated spinal tissues can be altered and enable inferences about the development of low back pain. The outcome of these models also provides means to design interventions, devices, and therapeutic interventions to protect, repair, and treat the lumbar spine in order to avoid and/or reduce the symptoms intrinsic to low back pain.

Cross-References

- [Pain Processing Pathway Models](#)
- [Spinal and Neuromechanical Integration: Overview](#)

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Biomechanical Modeling of Traumatic Brain Injury

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Abbreviations

FE	finite element
GM	grey matter
TBI	traumatic brain injury
WM	white matter

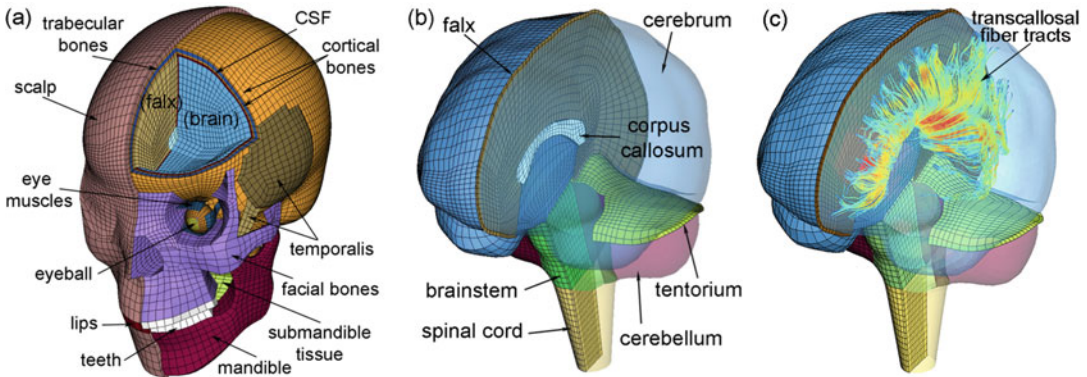
Definition

Biomechanical modeling of traumatic brain injury (TBI) refers to the use of a computer model of the human head to simulate brain mechanical responses when the head is subjected to external blunt impact or blast exposure. The resulting tissue responses such as strain, strain rate, and pressure in specific regions of the brain can then be used to predict the occurrence of TBI.

Detailed Description

A computational head injury model is composed of three basic constituents: model geometry, boundary conditions, and tissue material properties. With properly measured impact loading conditions as input for simulation, whole-brain biomechanical responses can then be estimated.

The most widely used method to model the biomechanical responses of TBI is through a finite element (FE) model of the human head (Yang et al. 2006) (illustrated in Fig. 1). This technique discretizes the spatial domain of the head, including the brain, skull, cerebrospinal fluid, falx, tentorium, and other intracranial components, into small interconnected “elements” via a process called meshing. The continuum deformation field



Biomechanical Modeling of Traumatic Brain Injury, Fig. 1 The Worcester Head Injury Model (WHIM) showing the head exterior features (a), intracranial

components (b), and transcallosal white matter (WM) fiber tracts (c) (Zhao et al. 2016)

of the brain is then represented by the displacements of the discretized element nodes. These nodal displacements are interrelated to each other in a large linear system of equations. The structure of the linear system of equations depends on how the nodes are interconnected, or, the connectivity of the FE mesh. The stress-strain relationship of every component of the model, including the brain and skull, that governs the biomechanical behavior of the underlying material is embedded into the coefficients of the linear system of equations. For moderate and severe blunt head/brain injury as well as blast-induced brain injury where skull deformation is anticipated, the skull is treated as nonrigid to allow for deformation. In contrast, for mild TBI (mTBI) in which skull deformation is often assumed to be negligible, the skull is idealized as a rigid body to simplify the linear system of equations.

Applying loading conditions obtained from external head impact such as recorded linear and rotational acceleration time history profile in the case of blunt-induced TBI, solutions to the linear system of equations are then calculated for the duration of the head impact. The nodal displacement solutions are subsequently used to calculate stress, strain, and pressure for each element. The resulting brain biomechanical responses are further used to predict the occurrence of injury. It is generally believed that the magnitude of strain

and its rate (i.e., how fast brain tissue deforms) are both important factors behind the mechanisms of TBI (King et al. 2003).

Model Validation

The accuracy of the FE model depends on a number of factors, including the material properties of the brain, falx, tentorium, etc., the brain-skull interfacial condition (such as whether to allow relative movement along the brain surface), and the quality and density of the brain mesh. To gain confidence in model-estimated brain responses, it is important to first validate the head injury model. This is performed by comparing the estimated brain tissue deformation with measurements from cadaveric head impact tests, often conducted at very high impact magnitudes (Hardy et al. 2007). More recently, biomechanical data from live humans measured from magnetic resonance imaging (MRI) are also becoming available (Bayly et al. 2012). They provide additional data for validation at the other, low end of the impact severity spectrum far away from the injury level (Zhao et al. 2018). Using the recorded impact acceleration profiles as input, the relative brain-skull displacement or strain response history (for the cadaveric and live human data, respectively) are generated from the given model under scrutiny. The degree of model-experiment response

agreement indicates the quality of model validation. When a model is successfully validated at both ends of the impact severity spectrum, the confidence in model simulation for the majority of real-world head impacts such as seen in contact sports can then be improved.

The brain material properties are the most frequent target for adjustment in order to satisfy and maximize model validation performance. In part, this is because there is no consensus at present on the most appropriate material model or property constants to use for impact simulation (de Rooij and Kuhl 2016; Yang et al. 2006). Despite decades of active research, a large variation exists in the literature resulting from differences in testing methods and conditions (Cheng et al. 2008), in vitro test conditions (Hrapko et al. 2008), in vitro vs. in vivo tests (Chatelin et al. 2010). Reviews on imaging methods (Bayly et al. 2012; Di Ieva et al. 2010), constitutive models (de Rooij and Kuhl 2016; van Dommelen et al. 2009), and the diverse material properties used in head injury models (Yang et al. 2006) also exist. This provides room for model parameter adjustments.

The brain mesh resolution is also a significant factor affecting the accuracy in brain response simulation. The dependency on mesh resolution is investigated through a “mesh convergence” study, in which multiple mesh resolutions of the brain or head are generated to simulate an identical impact. Mesh convergence is achieved when the solution no longer changes significantly with further mesh refinement.

Incorporation of Neuroimaging

Head injury models have been continually developed and improved over the last several decades. Among many efforts, recent advancements include the incorporation of neuroimaging for brain biomechanical modeling. For example, subject-specific FE models of the heads are generated based on high-resolution neuroimages of individual MRI volumes (Ji et al. 2015). In addition, whole-brain white matter (WM) tractography is incorporated to estimate stretches along WM fibers for injury analysis, and advanced anisotropic material properties of the

WM are also integrated to improve model biofidelity (Giordano and Kleiven 2014; Zhao et al. 2016). A multiscale modeling approach can be used to mitigate the mesh-image resolution mismatch (Lytton et al. 2017; Zhao and Ji 2018).

While a sophisticated head injury model is able to provide detailed brain strain maps for a given head impact, not all information is utilized for injury analysis at present. Most existing studies only employ the peak strain magnitude of the whole brain or a volume fraction of the brain above a certain threshold to predict injury. Conceptually, this is analogous to down-sampling the detailed strain map into a single scalar variable. Inevitably, loss of information ensues.

This limitation is now recognized, and efforts to utilize advanced neuroimaging to facilitate the sampling of the simulated brain responses are emerging. A potential remedy is to use responses in specific brain regions (e.g., corpus callosum or brainstem, vs. the whole brain) or a collection of brain regions (e.g., the 50 deep WM regions based on a well-developed neuroimage atlas (Zhao et al. 2017)) and their interconnections or neural pathways obtained from whole-brain tractography. The latter approach enables characterizing the distribution of peak brain responses. Potentially, this could allow modern feature-based machine learning classification for improved TBI detection (Cai et al. 2018) (vs. mostly univariate logistic regression in current TBI biomechanical studies).

Cross-References

- [Brain Atlases](#)
- [Brain-Scale Networks: Overview](#)
- [Connectome, General](#)
- [Human Connectome Project](#)
- [Modeling of Disease: Physical and Molecular Level, Overview](#)

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BioModels

► [BioModels Database: A Public Repository for Sharing Models of Biological Processes](#)

BioModels Database: A Public Repository for Sharing Models of Biological Processes

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Synonyms

[BioModels](#); [Mathematical models of biological processes](#); [Model repository](#)

Definition

BioModels Database is a public repository for mathematical models of biological processes. It provides access to models described in peer-

reviewed scientific literature, as well as those generated automatically from pathway resources. Model components, structure, and behavior of a large proportion of models in the database are thoroughly checked. This manual procedure ensures model correspondence with the original publication. Furthermore, model components are semantically enriched with cross-references to external ontologies and other relevant data resources. Models are exported in various formats, including SBML. Graphical representations of reaction networks are also provided. Simple and advanced search options are available to facilitate model retrieval. BioModels Database can be accessed through a web interface and programmatically using web services.

All models are distributed under the terms of the Creative Commons CCO Public Domain Dedication License, ensuring that models are available free for use, modification, and distribution for any user.

Detailed Description

BioModels Database (Li et al. 2010) hosts mathematical models of varying complexity, from simple biochemical reaction systems to larger and complex dynamic models, metabolic network models, and flux balance analysis (FBA) models. It is a part of the [BioModels.net](http://biomodels.net) initiative (<http://biomodels.net>; Le Novère 2006), which aims to help modelers to exchange and integrate existing models, through the use of established and shared standards.

Model Categories

BioModels Database holds two major sets of models: (A) models described in scientific literature and (B) models automatically generated from pathway resources.

A. Models published in peer-reviewed scientific literature.

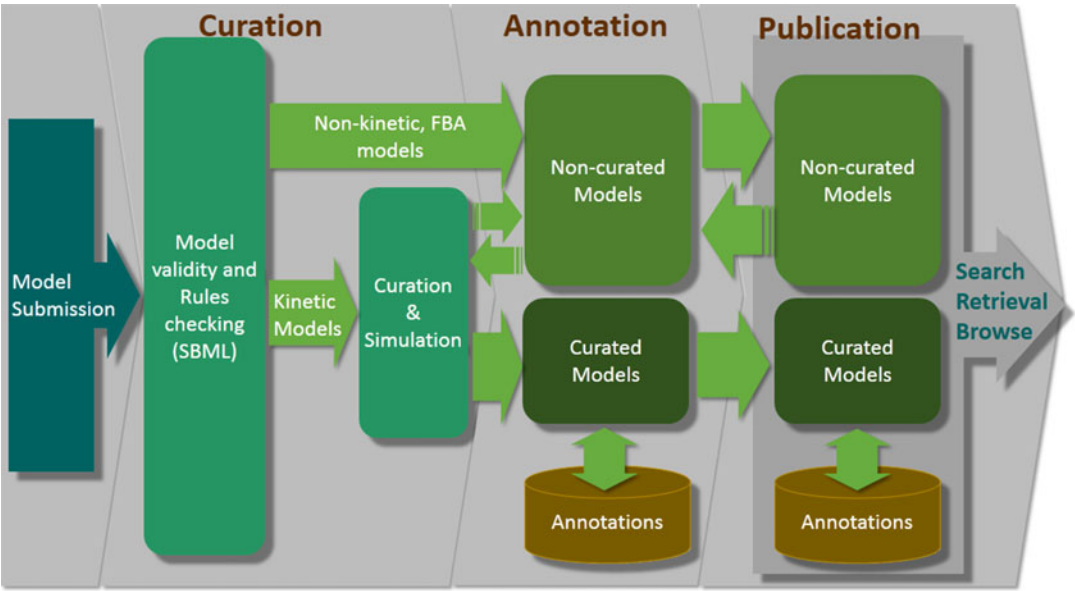
These models are included in the resource either directly by a team of curators or after direct submission by modelers or authors. Models have

also been contributed through established collaborations with other model repositories, such as the former SBML model repository (Caltech, USA), JWS Online (<http://jjj.biochem.sun.ac.za>), the Database Of Quantitative Cellular Signaling (DOQCS) (<http://doqcs.ncbs.res.in>), and the CellML Repository. More importantly, several publishers of scientific journals recommend deposition of models to BioModels Database in their author's instruction guidelines. These include *Biophysical Journal*, *FEBS*, *PNAS*, *Nature Publishing Group (NPG)*, *Public Library of Science (PLOS)*, *Royal Society of Chemistry (RSC)*, and *BioMed Central (BMC)*.

Model submission to BioModels Database is free and open to everyone. Models are accepted in two formats, SBML (Systems Biology Markup Language) (Hucka et al. 2003) and CellML (Lloyd et al. 2004). Once submitted, each model is assigned a unique and perennial identifier, which allows users to access and retrieve it. It then passes through a series of checking steps before it is published in BioModels Database (Fig. 1). Models are divided in two subbranches. Models in both subbranches are fully SBML compliant but differ in their curation status:

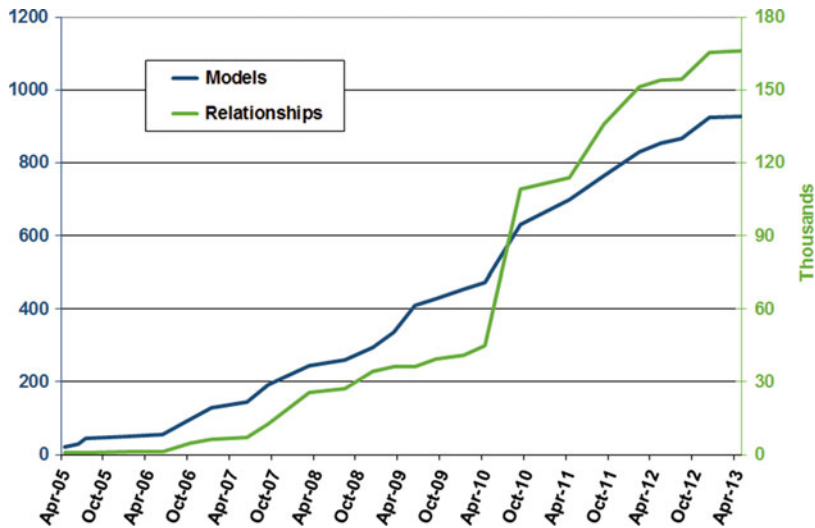
- (i) Curated models: Models that satisfy the MIRIAM (Minimum Information Required in the Annotation of Models) guidelines (Le Novère et al. 2005) progress to the curated branch. These models are thoroughly checked for standard compliance, correspondence with the reference publication and reproducibility of results.
- (ii) Non-curated models: Models can be in the non-curated branch for several reasons: non-MIRIAM-compliant models (e.g., they do not reproduce results published in the reference publication), pathway maps or models of networks, and models that provide insufficient quantitative results required for validation. This branch also temporarily includes models that have not yet been curated due to time or resource constraints.

Following curation and annotation (see section “Model Annotation” below), models are tagged as



BioModels Database: A Public Repository for Sharing Models of Biological Processes, Fig. 1 Production pipeline of the literature-based

models. This figure illustrates the sequence of steps that each model undergoes, from submission to publication

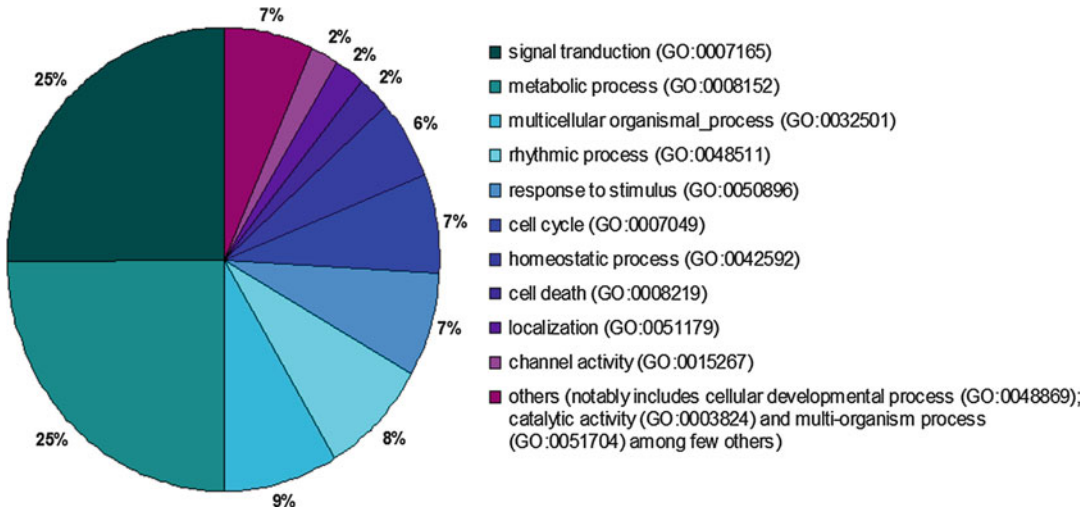


BioModels Database: A Public Repository for Sharing Models of Biological Processes, Fig. 2 Growth of BioModels Database. Number of models (blue) and number of variable relationships (green). The number of relationships includes SBML’s “reactions,” “rate rules,”

“assignment rules,” and “events.” There has been approximately a 20-fold increase in the number of models since the launch of the resource in 2005, with the average complexity of the models being increased five times during the same period

ready for publication and become available online with the following release of BioModels Database. Releases are scheduled two to four times a year.

Figure 2 shows the growth in number and size (complexity) of models, since its origin in 2005. Figure 3 shows the classification of curated models based on Gene Ontology



BioModels Database: A Public Repository for Sharing Models of Biological Processes, Fig. 3 Classification of models based on GO annotation of curated models

(GO) (Ashburner et al. 2000) terms present in the model annotation.

Certain simulation tools support only specific Levels or Versions of SBML. For this reason, BioModels Database provides models in alternative SBML versions, in addition to the version that was used by the curators to check the model. It also provides models in a variety of other formats such as BioPAX (<http://www.biopax.org/>), the Virtual Cell Markup Language (VCML) (<http://vcml.org/>), XPPAUT (<http://www.math.pitt.edu/~bard/xpp/xpp.html>), Scilab (<http://www.scilab.org/>), Octave (m-file) (<http://www.gnu.org/software/octave/>), and PDF (<http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX>). Furthermore, the reaction network of the model encoded in the Systems Biology Graphical Notation (SBGN) (Le Novère et al. 2009) is available in PNG and SVG formats.

BioModels Database provides a basic online simulation using SOSlib (Machne et al. 2006). The simulation results are returned both in graphical and textual forms. An additional and more flexible simulation tool is available for many models using JWS Online. Some models are described in greater detail in the “Model of the Month.” This takes the form of a brief article discussing the biological background, significance, structure, and results of a particular

model. Another important feature provided for curated models is the ability to generate sub-models from a user-selected set of model elements. These sub-models can be downloaded in SBML and used, for instance, in the modular design of new models or to expand existing models.

B. Models Generated from Pathway Resources (Path2Models).

Driven by the growing number of biochemical pathways and reconstructions, the Path2Models project (Büchel 2013) targeted the conversion of pathway information initially from KEGG (Kanehisa and Goto 2000), BioCarta (Schaefer et al. 2009), MetaCyc (Karp et al. 2000), and SABIO-RK (Wittig et al. 2012) into standard-compliant computational models.

There are currently three major types of models in this branch:

- (i) Genome-scale metabolic reconstructions: These models are generated by extracting pathway data from the KEGG and MetaCyc databases and subjected to FBA.
- (ii) Quantitative, kinetic models of metabolic pathways: These models are generated based on the metabolic pathways distributed by KEGG described as processes, in combination with experimentally determined rate

laws and parameter values from the SABIO-RK database.

- (iii) Qualitative, logical models of non-metabolic (primarily signaling) pathways: These models are generated based on the non-metabolic pathways distributed by KEGG, with additional information from BioCarta pathways.

Model Annotation

In order to facilitate efficient search and enhance interpretability both by users and software tools, models are cross-linked with other database entries and terms from controlled vocabularies. Annotations are included in the models directly using [Identifiers.org](http://identifiers.org) URIs (Juty et al. 2012). Such annotations provide a consistent and perennial way to identify model components, and an anchor which may be used to merge, or expand the scope of models.

Model Search, Browse, and Retrieval

BioModels Database provides a complete list of models available for browsing. Curated models can also be browsed based on taxonomy or Gene Ontology (GO) terms used in their annotation. Users can also search and retrieve models of interest using the annotations and related information.

Web Services

BioModels Database provides web services (<http://www.ebi.ac.uk/biomodels-main/web-services>), allowing, for example, direct search and retrieval, and the creation of sub-models. A Web Services Description Language (WSDL) file enables software to understand available functions and their usage. The complete list of available methods, as well as a Java library and the associated documentation is provided on the BioModels Database website.

BioModels Database is developed under the GNU General Public License and the software is freely available from its SourceForge repository

(<http://www.ebi.ac.uk/biomodels-main/webservices>).

Cross-References

- [Systems Biology Markup Language \(SBML\)](#)

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Bionic Ear

- [Auditory Prosthesis](#)

Bionic Eye

- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)
- [Visual Prosthesis, Optogenetic Approaches](#)

Bionic Vision

- [Prosthetic Vision, Perceptual Effects](#)
- [Visual Prosthesis, Optogenetic Approaches](#)

Biophysical Mechanisms that Photoreceptors Use to Sample Light Information

- [Phototransduction Biophysics](#)

Biophysical Models

- [Computational Models of Neural Retina](#)

Biophysical Models of Calcium-Dependent Exocytosis

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Synonyms

[Non-constitutive exocytosis](#) [exocytosis](#); [Regulated exocytosis](#)

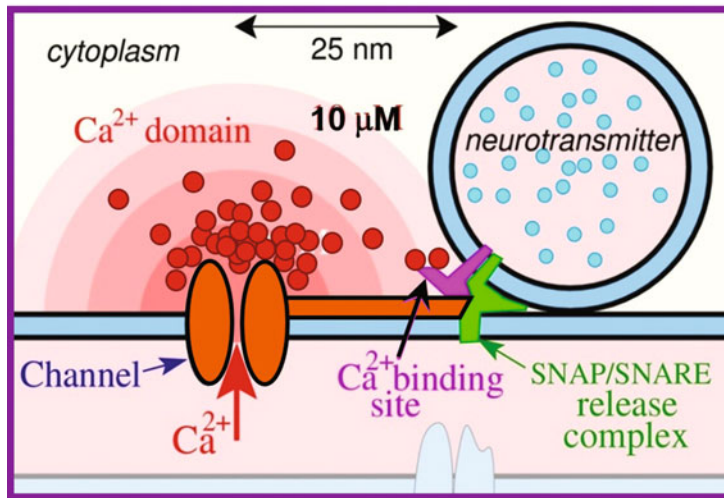
Definition

Calcium-dependent exocytosis is the biochemically controlled fusion of the bilipid secretory

vesicle membrane with the bilipid cell membrane, triggered by the binding of several calcium ions (Ca^{2+}) to control proteins such as synaptotagmins anchored at the interface between these two membranes. Exocytosis results in the release of vesicle contents into the extracellular space, namely the release of neurotransmitter into the synaptic cleft in the case of neuronal synapses and neuromuscular junctions, or the secretion of hormone into the blood stream in the case of endocrine cells. Exocytosis also allows the transmembrane proteins contained in the vesicle membrane to be incorporated into the cell membrane, although such membrane protein trafficking is more characteristic of Ca^{2+} -independent, constitutive exocytosis.

Detailed Description

In synapses, neuromuscular junctions, and endocrine cells, exocytosis of a neurotransmitter or hormone-containing vesicle occurs through the interaction of the fast-binding isoforms of the Ca^{2+} -sensing protein synaptotagmin (namely Syt1, Syt2, and Syt9) with the molecules of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex spanning the cell and vesicle membranes (Jahn and Fasshauer 2012; Moghadam and Jackson 2013). The main elements of the secretory channel-vesicle complex are schematically illustrated in Fig. 1. Despite their highly specialized morphology, a similar exocytosis triggering mechanism is found at most high-throughput ribbon sensory synapses (Cho and von Gersdorff 2012; Sterling and Matthews 2005), except for the cochlear hair cells. Those auditory synapses may differ in both the molecular exocytosis machinery and their Ca^{2+} sensitivity (Nouvian et al. 2011), and may involve nonneuronal isoforms of synaptotagmin (Johnson et al. 2010) or a distinct Ca^{2+} sensor, otoferlin (Michalski et al. 2017; Pangrsic et al. 2012; Roux et al. 2006). The mechanism of exocytosis of hormone-containing large dense-core vesicles in endocrine cells is very similar to the mechanisms of neurotransmitter vesicle release (Chow et al. 1992; Heinemann et al. 1994; Voets 2000), but typically proceeds at



B

Biophysical Models of Calcium-Dependent Exocytosis, Fig. 1 Secretory channel-vesicle release complex. The vesicle is shown in a fully docked state preceding fusion. The opening of a voltage-gated Ca^{2+} channel leads to the entry of Ca^{2+} ions (red circles) into the cell, resulting in a “domain” of elevated Ca^{2+} concentration, which can reach tens of μM close to the vesicle, some 20–30 nm away from the channel. The SNARE protein

complex (green polygon) interacts with synaptotagmin (magenta polygon) that serves as the fast Ca^{2+} -sensitive trigger of the vesicle-membrane fusion. Multiple SNARE complexes around the base of the vesicle are involved in exocytosis, only one of which is shown. At many synapses, the tight co-localization of Ca^{2+} channels and SNARE proteins is promoted by direct interactions between the relevant proteins (orange bar)

slower rates due to a somewhat different morphology of the release site, slower Ca^{2+} binding kinetics of the relevant synaptotagmin isoforms, and looser coupling between voltage-dependent Ca^{2+} channels and release-ready vesicles (Kasai 1999; Martin 2003; Moghadam and Jackson 2013; Verhage and Toonen 2007; Wu et al. 2009). It should be noted however that certain classes of endocrine cells such as pancreatic beta cells exhibit a close channel-vesicle coupling similar to that of neuronal synapses (Barg et al. 2001).

The dependence of the neurotransmitter or hormone release rate on Ca^{2+} concentration is known to be steeply nonlinear, as was first observed (Dodge and Rahamimoff 1967) when examining neuromuscular junction potentials at different extracellular Ca^{2+} concentrations, and later confirmed in studies that directly varied intracellular Ca^{2+} concentration using caged- Ca^{2+} release in endocrine cells, the giant calyx of Held synapse, and other synaptic terminals (Gentile and Stanley 2005; Neher and Sakaba 2008; Stanley 2016). For low, sub-saturating concentrations of Ca^{2+} , this nonlinear relationship can be summarized as:

$$R([Ca]) \propto [Ca]^n \quad (1)$$

Here $[Ca]$ denotes Ca^{2+} concentration at the vesicle fusion site, R denotes instantaneous neurotransmitter release rate, and n is the intrinsic (biochemical) Ca^{2+} cooperativity of exocytosis, which varies from 3–5 in most preparations. Note however that a significantly less cooperative, near-linear Ca^{2+} dependence has been reported in mature auditory hair cells, possibly because of differences in molecular exocytosis sensors mentioned above (Cho and von Gersdorff 2012; Johnson et al. 2010; Nouvian et al. 2011), although it has been suggested that the linear dependence could potentially arise from the averaging across synaptic contacts (Heil and Neubauer 2010).

The release (exocytosis) rate R is usually given in units of vesicles per second and measured as a membrane capacitance increase or by electrochemical detection of released molecules, using a carbon fiber electrode, but often assessed only indirectly by measuring postsynaptic currents or potentials. The steep nonlinear dependence given by Eq. (1) indicates that simultaneous binding of

several Ca^{2+} ions to synaptotagmin Ca^{2+} sensors is needed for release. In fact, the biochemical cooperativity provides a lower bound on the number of Ca^{2+} binding events required for exocytosis. Although the C2A and C2B domains of a given synaptotagmin molecule do possess a total of five Ca^{2+} ion-binding sites (Chapman 2002), not all of these sites are necessarily involved in fast (phasic) Ca^{2+} -triggered exocytosis. Therefore, it is likely that the relevant Ca^{2+} -binding sites are distributed among several synaptotagmin molecules, which dimerize and bind Ca^{2+} simultaneously to trigger vesicle fusion (Mutch et al. 2011). In fact, studies suggest that more than 10 synaptotagmin molecules typically associate with a single neurotransmitter vesicle (Takamori et al. 2006). However, in accordance with the above-mentioned Ca^{2+} cooperativity measurements, most models reviewed below assume about five Ca^{2+} -binding sites, all of which have to be occupied for vesicle fusion to occur. An alternative detailed model that assumes an excess of Ca^{2+} -binding sites and includes Monte-Carlo simulation of Ca^{2+} ion diffusion and binding have been examined (Dittrich et al. 2013; Luo et al. 2015b).

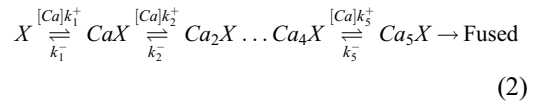
While the main characteristics of exocytosis outlined above are in general understood, and the molecular components of exocytosis have been identified, the precise sequence of molecular steps leading to exocytosis is still being debated, which explains the high degree of interest in biophysical models of this phenomenon. We also note that this process involves spatial scales of tens of nanometers, and sub-millisecond temporal resolution, well beyond the resolution of optical imaging methods, which underscores the important role of biophysical modeling in understanding exocytosis and in interpreting indirect measurements of its properties.

A complete biophysical model of secretory vesicle exocytosis requires specifying the following model components: (1) the morphology of the synaptic vesicle docking site, namely the spatial channel-vesicle arrangement; (2) the properties of endogenous Ca^{2+} buffers and other Ca^{2+} homeostasis mechanisms; (3) a method for simulating Ca^{2+} diffusion and buffering to endogenous Ca^{2+} buffers; and (4) a model of Ca^{2+} binding by the

synaptotagmin release sensors. Here we focus on the latter component of the model. Examples of comprehensive models of this process are given at the end of this entry.

Sequential Ca^{2+} -Binding Model

Assuming for concreteness five distinct Ca^{2+} -binding sites comprising the putative exocytosis gate (sensor) X , the most general Ca^{2+} -sensitive exocytosis process can be described by the following reaction (Heidelberger et al. 1994; Kasai 1999):



where $[Ca]$ is the Ca^{2+} concentration at the vesicle site, $k_j^\pm$ are the binding and unbinding rates of each binding site, and the final irreversible reaction represents the actual vesicle fusion event. In Eq. (2) and below, Ca^{2+} binding is indicated by a product between the relevant binding rate and the Ca^{2+} concentration variable, $[Ca]$. In a deterministic simulation, this reaction is converted to a system of ordinary differential equations, using the principle of mass action:

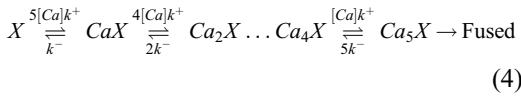
$$\begin{cases} \frac{d[X]}{dt} = -k_1^+[Ca][X] + k_1^-[CaX] \\ \dots \\ \frac{d[Ca_5X]}{dt} = k_5^+[Ca][Ca_4X] - (\gamma + k_5^-)[Ca_5X] \end{cases} \quad (3)$$

where $[Ca_nX]$ represents the fraction of exocytosis gates with n binding sites occupied by a Ca^{2+} ion. The fusion rate is given by the product $\gamma [Ca_5X]$. Note that the Ca^{2+} concentration, $[Ca]$, should be modeled independently; in the simplest case of global Ca^{2+} elevation produced by caged Ca^{2+} release, it is approximately constant. When modeling exocytosis triggered by action potentials, $[Ca]$ can be represented as a brief pulse of a certain width and amplitude; more detailed models of Ca^{2+} dynamics are reviewed below.

In Eqs. (2 and 3), the binding and unbinding rates $k_j^\pm$ are in general distinct, and if the earlier unbinding rates are slow, a significant accumulation of partially bound states $[Ca_nX]$ can result during a train of stimuli; such accumulation due to slow unbinding is the basis for the so-called bound- Ca^{2+} model of synaptic facilitation (Bertram et al. 1996; Matveev et al. 2006).

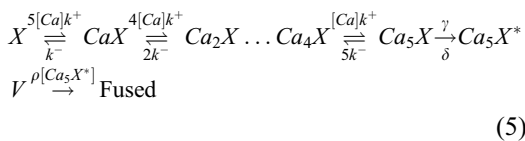
Parallel Ca^{2+} -Binding Model

It is instructive to first consider the simplest scenario where all five release sites comprising exocytosis gate X are identical and can bind Ca^{2+} independently, leading to the following simplified version of the reaction given by Eq. (2) (Kasai 1999; Voets 2000):



Here the final reaction representing vesicle fusion is irreversible and is triggered when all five binding sites are occupied; exocytosis proceeds at rate $r = \gamma [Ca_5X]$. Even though Eq. (4) appears to describe a series of five consecutive binding reactions, it is equivalent to five identical reactions occurring in parallel, with fusion taking place when all five sites are bound.

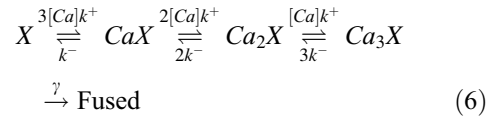
The following alternative version of the exocytosis model by Bollmann and Sakmann (2005) and Bollmann et al. (2000) partially decouples the vesicle pool variable undergoing release and the Ca^{2+} sensor state variables, and also postulates the existence of an independent final release-promoting conformational transition reaction occurring after the release sensor is fully Ca^{2+} bound:



Here V represents the vesicle pool undergoing fusion, with vesicle fusion rate given by the

product $\rho V[Ca_5X^*]$, where ρ is the maximal vesicle fusion rate. The inclusion of an additional post-binding step helps to achieve more constant shape of the release time course at different amplitudes of Ca^{2+} influx seen in experiments (Bollmann et al. 2000; Yamada and Zucker 1992). In (Bollmann et al. 2000) the parameter values that were found to fit well the data from the calyx of Held synaptic terminal are given by $\rho = 40 \text{ ms}^{-1}$, $k^+ = 0.3 \mu\text{M}^{-1} \text{ ms}^{-1}$, $k^- = 3 \text{ ms}^{-1}$, $\gamma = 30 \text{ ms}^{-1}$, $\delta = 8 \text{ ms}^{-1}$.

We note that most of the Ca^{2+} binding rates quoted in the literature are inferred from the studies on the calyx of Held synapse and other synapses that primarily involve the faster Syt2 isoform of synaptotagmin in its natural physiological environment. Other isoforms of synaptotagmin may have significantly different values of the Ca^{2+} binding and unbinding rates (Bornschein and Schmidt 2018; Moghdam and Jackson 2013). For example, the following model by Voets (2000) accurately predict exocytosis of the readily releasable pool of vesicles in chromaffin cells caused by the Ca^{2+} binding to synaptotagmin isoform Syt1:

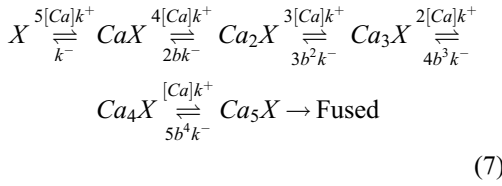


where $k^+ = 4.4 \cdot 10^{-3} \mu\text{M}^{-1} \text{ ms}^{-1}$, $k^- = 0.056 \text{ ms}^{-1}$, and $\gamma = 1.45 \text{ ms}^{-1}$.

Cooperative Ca^{2+} -Binding Model

Some studies suggest that the Ca^{2+} -sensitive exocytosis triggers exhibit strong cooperativity, whereby the target protein undergoes a conformational change with each successive Ca^{2+} ion binding, which in turn leads to an increase in the Ca^{2+} affinity of the remaining (yet unoccupied) Ca^{2+} -binding sites. The following widely used modification of reaction given by Eq. (2) has been proposed to implement this possibility (Beutner et al. 2001; Felmy et al. 2003; Heidelberger et al. 1994; Kochubey et al. 2009;

Sakaba 2008; Schneggenburger and Neher 2000):



Note that cooperative binding can be represented as either a progressive increase in forward binding rates or decrease of backward rates; Eq. (7) corresponds to the latter possibility. The cooperativity parameter should satisfy $b < 1$, with a typical value used in the literature of 0.25, indicating that the final Ca^{2+} -binding reactions are only slowly reversible. In (Schneggenburger and Neher 2000; Wolfel and Schneggenburger 2003) quantifying the Ca^{2+} -dependence of vesicle release at the calyx of Held synaptic terminal, the following parameter values were obtained: $k^+ = 0.09 \mu M^{-1} ms^{-1}$, $k^- = 9.5 ms^{-1}$, $\gamma = 6 ms^{-1}$, and the cooperativity parameter $b = 0.25$.

We note that the use of the term “cooperativity” is ambiguous in the context of exocytosis mechanisms. Cooperativity may refer to the high number of Ca^{2+} -binding sites (as inferred from the log-log slope of the Ca^{2+} concentration-response curve given by Eq. (1)) or may indicate that the Ca^{2+} binding affinities of these sites are not equal but increase as the first sites become Ca^{2+} bound.

Models with Independent Sets of Ca^{2+} -Binding Sites

Several recent biophysically detailed models of exocytosis take into account the possibility that Ca^{2+} may bind to several different proteins or to different domains of the same protein, such as the C2A and C2B domains of synaptotagmin, each characterized by a distinct set of rates and cooperativity values. Examples of such models are given further below in the context of more comprehensive models of exocytosis – see model schemes (16 and 20).

Exocytosis Rate at a Steady Ca^{2+} Concentration

To understand the exocytosis rate during prolonged Ca^{2+} elevation, for instance, to reproduce caged- Ca^{2+} release experiments, it is of interest to consider the equilibrium point of the Ca^{2+} -binding reactions summarized above. Since all release models contain an irreversible transition to the fusion state, in the absence of endocytosis or vesicle refill from a reserve pool, the true equilibrium is achieved only when all vesicles are fused and release rate equals zero. Therefore, below we will assume a model with decoupled sensor binding state and vesicle pool state variables, as in Eq. (5), or consider a quasi-equilibrium in the case where resource depletion is small on the time scale of Ca^{2+} binding.

The equilibrium occupancy of a single first-order Ca^{2+} -binding reaction $Ca + X \rightleftharpoons CaX$ with forward rate k^+ and backward rate k^- is found by setting the rate of the first reaction in Eq. (3) to zero, which yields:

$$[CaX] = \frac{k^+[Ca]}{k^+[Ca] + k^-} = \frac{[Ca]}{[Ca] + K} \quad (8)$$

where the ratio of the backward and forward rates $K = k^-/k^+$ is referred to as the Ca^{2+} affinity or dissociation constant and is an important Ca^{2+} -sensitivity parameter: the lower the K , the higher is the affinity (sensitivity) of the release sensor. It follows from Eq. (8) that K represents the Ca^{2+} concentration at which half the sensors become bound. If the final fusion reaction requires the binding of all five sensors, in the absence of vesicle depletion, the release rate at equilibrium will be proportional to the fifth power of the steady-state binding occupancy given by Eq. (8):

$$R([Ca]) = \gamma \left(\frac{[Ca]}{[Ca] + K} \right)^5 \quad (9)$$

At low Ca^{2+} concentration, this agrees with the cooperativity condition given by Eq. (1). Note that the release rate equals $1/2^5$ of its maximal value when $[Ca^{2+}] = K$.

For the case of cooperative binding, Eq. (7), the steady-state fusion rate R in the absence of resource depletion ($\gamma \ll 1$) is

$$R([Ca]) = \frac{\gamma [Ca]^5}{[Ca]^5 + 5[Ca]^4 b^4 K + 10[Ca]^3 b^7 K^2 + 10[Ca]^2 b^9 K^3 + 5[Ca] b^{10} K^4 + b^{10} K^5} \quad (10)$$

where $[Ca]$ is the Ca^{2+} concentration at the release site. In the limit of very small values of b (strong cooperativity limit), the above expression approaches the well-known and widely used Hill function:

$$R([Ca]) \approx \gamma \frac{[Ca]^n}{[Ca]^n + K_D^n} \quad (11)$$

where $n = 5$ and $K_D \approx b^2 K$ ($b \ll 1$). The dissociation constant K_D quantifies the Ca^{2+} sensitivity of the entire five-step process, as opposed to the sensitivity of any individual Ca^{2+} -binding site: when $[Ca] = K_D = b^2 K$, the exocytosis rate reaches its half-maximal value. Note that this is the most constrained and most important model parameter, since extensive experimental data on Ca^{2+} sensitivity has been collected at various types of synaptic terminals. In general, physiological rates of release are found when $[Ca^{2+}]$ at the vesicle location reaches the range of 10–50 μM (Neher and Sakaba 2008), although there are reports that highly sensitive vesicle pools exist at some endocrine cells, possibly controlled by distinct isoforms of the synaptotagmin sensor with Ca^{2+} affinity of several μM (Pedersen and Sherman 2009).

Note that the Hill functional form given by Eq. (11) should only be viewed as a crude qualitative approximation of the true Ca^{2+} -dependence of exocytosis rate, even at equilibrium, and tends to be somewhat overused (Weiss 1997). This is because the agreement between Eqs. (10 and 11) becomes sufficiently accurate only for values of cooperativity parameter satisfying $b < 0.1$; in the absence of firm experimental evidence for such a strong cooperativity, the Hill function should be avoided. Assuming a more moderate but still strong cooperativity corresponding to the typically used value $b = 0.25$, fitting the data to a Hill function would lead to a gross underestimate

proportional to the equilibrium value of fully bound state Ca_5X , which yields (Weiss 1997):

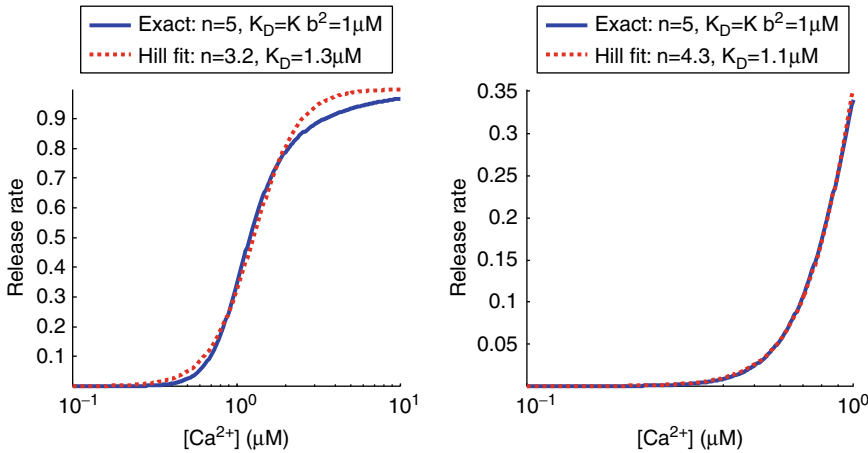
of the true number of Ca^{2+} -binding sites, as illustrated in Fig. 2. This underestimate is mostly due to the poor match of the saturating part of the Hill curve and can be greatly improved by omitting the data from saturating levels of $[Ca^{2+}]$. Therefore, the most model-independent way of estimating the cooperativity factor n is to fit only the log-log slope of the experimentally obtained Ca^{2+} sensitivity curve below the saturation inflection, which is often done in practice.

Cumulative Release During Prolonged Ca^{2+} Elevation

The Ca^{2+} -dependence of release rate can be used to quantify the total cumulative release with prolonged Ca^{2+} elevation, as measured by the total membrane capacitance increase or the total amount of released neurotransmitter. In the case of prolonged and approximately steady Ca^{2+} elevation of duration Δt , the amount of fused vesicles is given by (Kasai 1999; Quastel et al. 1992):

$$F([Ca]) = F_{\max} [1 - \exp(-R_{eq}([Ca]) \Delta t)] \quad (12)$$

where $F_{\max}$ represents the total amount of available exocytosis resources (say, vesicles) and $R_{eq}([Ca])$ represents the equilibrium reaction rate at Ca^{2+} concentration $[Ca]$ attained at the vesicle location. We note once again that this analysis assumes that the vesicle depletion is decoupled from the sensor binding state, as in the model given by Eq. (5). The exponential term can be interpreted as the probability of release failure. For pulses raising $[Ca^{2+}]$ to sub-saturating levels, given Eq. (1), we have $R \approx k[Ca]^n$, therefore (Quastel et al. 1992):



Biophysical Models of Calcium-Dependent Exocytosis, Fig. 2 Hill-function fit underestimates true biochemical cooperativity and affinity of a fifth-order Ca^{2+} -binding reaction (Eqs. (7 and 10)), even in the case of moderately strong cooperativity parameter ($b = 0.25$). Note that the

low quality of the fit is mostly a result of poor matching of the saturating part of the curve by the Hill function: the cooperativity is more accurately predicted if only the non-saturating part of the data is considered (right panel)

$$F([Ca]) = F_{\max}[1 - \exp(-k[Ca]^n \Delta t)] \quad (13)$$

However, if $[\text{Ca}^{2+}]$ is high enough to saturate the release sensor during the long depolarizing pulse, the total amount of released neurotransmitter will become limited by the duration of stimulation only:

$$F = F_{\max}[1 - \exp(-R_{\max} \Delta t)] \quad (14)$$

As was explained above, Eqs. (12 and 13) only apply to the situation where $[\text{Ca}^{2+}]$ is elevated for a long time relative to the kinetics of the Ca^{2+} -binding sites, as for instance, during whole-cell $[\text{Ca}^{2+}]$ elevation produced by Ca^{2+} uncaging experiments. If on the other hand $[\text{Ca}^{2+}]$ is understood as the *peak* concentration achieved in the vicinity of the vesicle during a brief action potential, the above steady-state results would overestimate the true release and could only serve as an upper bound on release rate (Shahrezaei and Delaney 2005). The “true” neurotransmitter release rate would be given by a solution to the differential Eq. (5), with $[\text{Ca}^{2+}]$ representing the time-dependent Ca^{2+} concentration at the vesicle release site, which has to be modeled independently, using simulations of Ca^{2+} entry through Ca^{2+} channels, diffusion and binding to intracellular Ca^{2+} buffers.

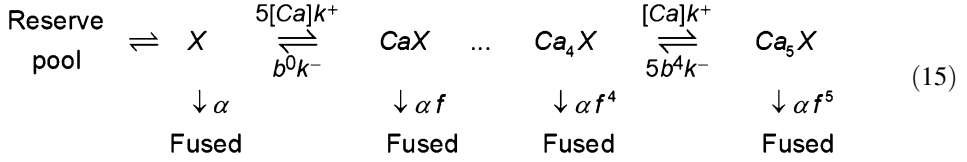
Asynchronous Synaptic Transmission

Many synapses display a delayed phase of neurotransmitter release that persists after the stimulating presynaptic depolarization has ceased. This delayed component of exocytosis is termed asynchronous or delayed exocytosis, and at some synapses, it makes a significant contribution to the overall neurotransmitter release under physiological conditions (Rozov et al. 2019). There is continued debate whether the asynchronous component of synaptic transmission is a result of synaptic Ca^{2+} accumulation or whether it is caused by a distinct vesicle pool released via special mechanisms independent of the synchronous release component (Chung and Raingo 2013; Smith et al. 2012). The connection between delayed release and the so-called spontaneous release seen in the absence of stimulation is also not fully understood. Biophysical modeling is used extensively in testing different hypotheses about the mechanisms of asynchronous and spontaneous neurotransmitter release.

An intriguing feature of asynchronous release is that it seems to exhibit a lower, almost linear Ca^{2+} dependence (Kochubey and Schneggenburger 2011; Lou et al. 2005; Sun et al. 2007). The so-called allosteric model proposed by Lou et al.

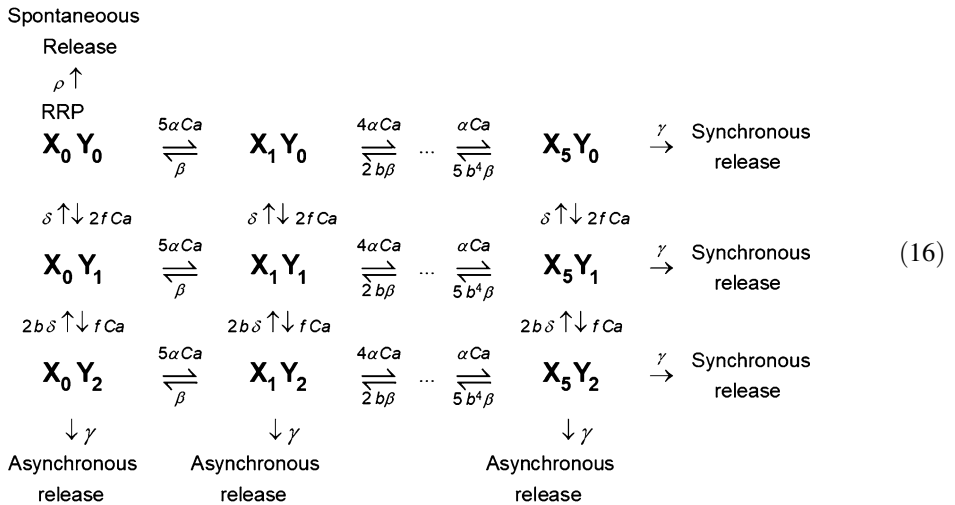
(2005) explains the observed decrease in apparent cooperativity of Ca^{2+} action at low Ca^{2+} concentration by the presence of a slow conformational change of the release proteins, leading to a second

route of vesicle fusion, which becomes progressively less likely at higher Ca^{2+} concentration. This is implemented by the following scheme with a reverse-cooperativity parameter $f < 1$:



A more detailed model proposed by Sun et al. (2007) and referred to as the *dual sensor* model provides an improved quantitative description of release at low Ca^{2+} concentrations, since it reproduced more accurately the

latency of synaptic response at very low levels of Ca^{2+} . This model assumes two independent Ca^{2+} sensors acting in parallel and each triggering a distinct mode of neurotransmitter release:



Here the synchronous release involves a sensor “X” with Ca^{2+} -cooperativity of five, while a different and independent sensor “Y” is responsible for asynchronous release and possesses a cooperativity of two. Note that in this model implementation both sensors bind Ca^{2+} cooperatively, with equal cooperativity parameter b . The existence of two distinct sensors is supported by recent evidence that in some synapses asynchronous release is controlled by distinct Ca^{2+} -binding proteins. Among the candidates for such a specialized asynchronous release regulator are the

non-synaptotagmin sensor Doc2 (Yao et al. 2011), a distinct isoform of vesicle SNARE protein VAMP4 (Raingo et al. 2012), and the Syt7 isoform of synaptotagmin characterized by slow but high-affinity Ca^{2+} binding (Luo et al. 2015a; Turecek and Regehr 2018; Weber et al. 2014). An alternative possibility is that asynchronous release becomes prominent when the faster synaptotagmin isoforms like Syt1 are depleted, which removes their release-clamping influence (Turecek and Regehr 2019). However, as mentioned above, the mechanisms of asynchronous

as well as spontaneous release are still under debate and may well vary across synaptic types (Chung and Raingo 2013; Kaeser and Regehr 2014; Smith et al. 2012).

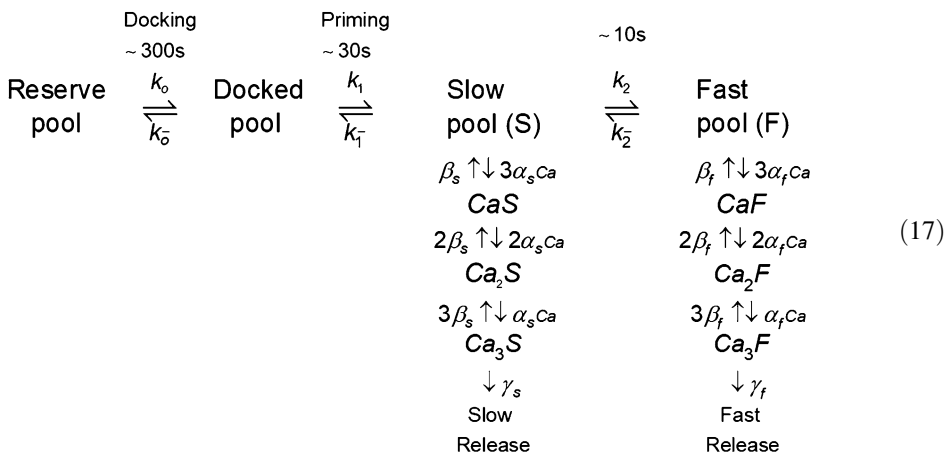
Multiple Vesicle Pool Models

Apart from the intrinsic heterogeneity in Ca^{2+} affinity and speed of exocytosis due to the existence of distinct release pathways guiding exocytosis of each vesicle, an additional explanation for the observed heterogeneous components of vesicle release is the existence of independent pools of vesicles with variable degree of “preparedness” for exocytosis. This heterogeneity is especially pronounced in endocrine cells, which exhibit a fast-decaying initial phase of release followed by a second, more slowly decaying component, but such behavior is also found in other high-throughput neuronal synapses such as the calyx of Held synaptic terminal and in ribbon synapses (Neher 2012; Neher and Sakaba 2008; Pedersen and Sherman 2009; Verhage and Toonen 2007; Voets 2000). The identity of such distinct vesicle pools is currently under debate: they could be distinguished either by the variations in the distance between vesicles and corresponding voltage-gated Ca^{2+} channels (“positional

priming”: (Wadel et al. 2007)) and/or by differences in the arrangement of the molecular machinery needed for exocytosis (“molecular priming” and “super-priming”: (Chung and Raingo 2013; Lee et al. 2013; Neher 2017; Sorensen 2004; Taschenberger et al. 2016; Verhage and Toonen 2007)).

Exocytosis models comprising multiple vesicle pools allow reproducing the observed heterogeneous release components. However, simple two-pool models comprising a readily releasable pool and a reserve pool of vesicles were already proposed in the earliest modeling studies of vesicle release, in order to account for the short-term depression of synaptic response arising from vesicle depletion (Elmqvist and Quastel 1965; Liley and North 1953; Neher 1998; Zucker and Regehr 2002).

Most quantitative models of exocytosis that include multiple releasable vesicle pools are based on the two-pool model of (Heinemann et al. (1993), Voets (2000), and Voets et al. (1999)) that was put forward to quantify two temporal components of secretory vesicle release in adrenal chromaffin cells. One implementation of such a two-pool model was explored by Sorensen (2004):



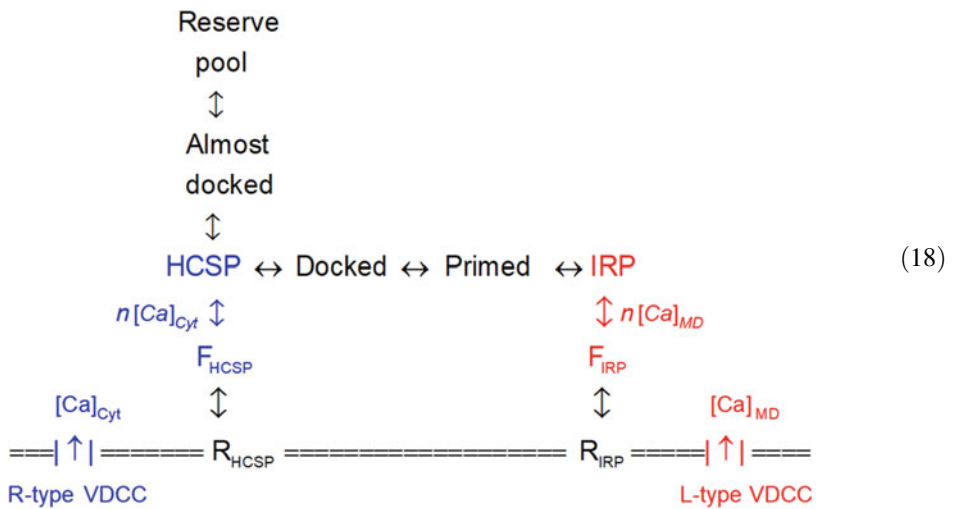
In this model, exocytosis proceeds with cooperativity value of three from both the slow (“sustained”) and fast synchronous pools, which are replenished via two

preparatory steps, docking and priming, from the reserve pool.

There are indications that in some cells, the slowly releasing pool may in fact have a much

higher sensitivity to Ca^{2+} , in the range of several μM rather than 10s of μM , which allows it to participate in exocytosis despite a much longer separation from the Ca^{2+} channels compared to the immediately releasable fast pool (reviewed in Pedersen and Sherman (2009)). The delay in the release of the highly sensitive vesicles is explained by the longer diffusional distance and therefore longer time required for Ca^{2+} concentration to reach μM range far from the Ca^{2+} channels. Such so-called highly Ca^{2+} sensitive pool (HCSP) has been described in adrenal chromaffin cells (Yang et al. 2002), rod photoreceptor ribbon synapses (Thoreson et al. 2004), and in insulin secreting beta cells (Yang and Gillis 2004). A recent multiple-pool model that includes the HCSP pool along with the lower-

affinity immediately releasable pool (IRP), and implements a deterministic bi-domain model of $[\text{Ca}^{2+}]$ dynamics, can be found in Pedersen and Sherman (2009). This model is based on an earlier model of Chen et al. (2008), and it accurately predicts the characteristic biphasic release of insulin from pancreatic beta cells. The first phase of secretion is mostly due to the docked vesicles that are rapidly recruited to the immediately releasable pool (IRP) and exocytosed in response to local “microdomain” $[\text{Ca}^{2+}]$ ($[\text{Ca}]_{\text{MD}}$) entering through L-type Ca^{2+} channels. In contrast, the second, delayed phase of insulin release builds up more slowly due to the recruitment of the reserve vesicles into the HCSP and gradual accumulation of cytosolic Ca^{2+} ($[\text{Ca}]_{\text{Cyt}}$) entering through R-type Ca^{2+} channels:



Here Ca^{2+} -dependent transitions are indicated in color, according to the primary source of Ca^{2+} for the corresponding transition. The R-type and L-type voltage-dependent Ca^{2+} channels (VDCCs) contribute respectively to the cytosolic and the microdomain pools of Ca^{2+} , $[\text{Ca}]_{\text{Cyt}}$ and $[\text{Ca}]_{\text{MD}}$ (the diffusional exchange between these two Ca^{2+} pools is not shown). The Ca^{2+} -dependent exocytosis steps lead to the two “fused” states, F_{HCSP} and F_{IRP} , which in turn feed into the final released insulin states R_{HCSP} and R_{IRP} through a final Ca^{2+} -independent pore-expansion transition.

Note that the existence of multiple vesicle pools can also serve as a potential explanation for asynchronous release reviewed above (Chung and Raingo 2013; Neher 2017). Another possibility is that the intrinsic sources of heterogeneity in release properties captured by the allosteric and the dual-sensor models (Eqs. (15 and 16)) are present in each vesicle (Kaesler and Regehr 2014; Sun et al. 2007). In particular, as reviewed above, in some synapses, asynchronous release may be mediated by specialized Ca^{2+} sensors. Further, both the synchronous and the delayed components are observed with global

(whole-terminal) Ca^{2+} elevations that activate vesicles in all pools. Therefore, both sources of heterogeneity, the ones intrinsic to each vesicle and the extrinsic ones (existence of distinct pools), may be relevant in many synapses (Kaesler and Regehr 2014). In order to take into account all factors of vesicle release heterogeneity and predict more accurately the exocytosis rate under low Ca^{2+} conditions, one can combine the dual-pool model with the allosteric model of Lou et al. (2005) or the dual-sensor model of Sun et al. (2007). This was done, for instance, by Wolfel and Schneggenburger (2003), who considered allosteric Ca^{2+} binding for both pools, as in Eq. (15) (neglecting however the exchange between the two pools due to the short time scales considered in that work). Finally, it should be noted that the separation of releasable vesicles into only two pools instead of a larger set of pools or a continuum of states is most probably a simplification, but this level of detail is sufficient to accurately quantify release under most physiological conditions (Neher 2017). Including more than two pools should be done with great care to avoid an underdetermined model and data over-fitting.

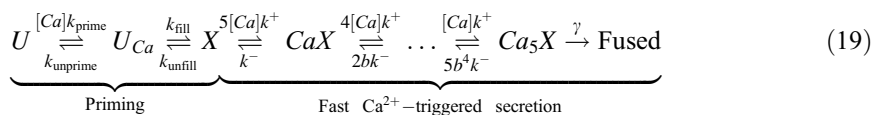
Models with Ca^{2+} -Dependent Vesicle Priming

Vesicle docking and priming steps in reactions 17 and 18 most likely include multiple molecular processes (involving Munc18 and other proteins) and morphological steps (e.g., positional priming), the identity and sequence of which are still under investigation (Lee et al. 2013; Verhage and Toonen 2007). Experimental evidence suggests that at least some of these

vesicle-priming steps are Ca^{2+} dependent in many synapses, albeit with a lower Ca^{2+} cooperativity compared to exocytosis itself, with a near-linear dependence on intracellular Ca^{2+} concentration (Neher and Sakaba 2008). Depending on the balance between the different vesicle pools at resting Ca^{2+} , the Ca^{2+} -dependent priming can manifest itself in two different properties of short-term synaptic plasticity (Zucker and Regehr 2002):

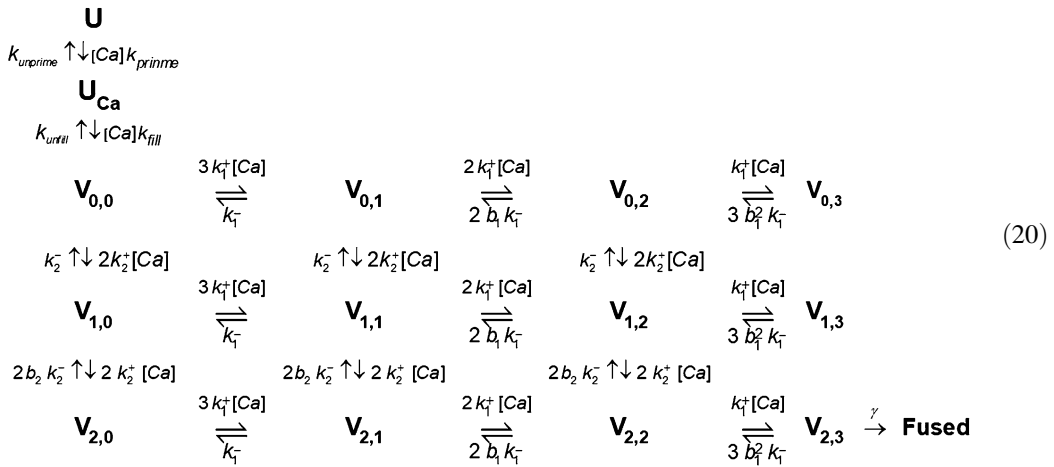
1. Under conditions of low initial release-ready vesicle pool size, Ca^{2+} -dependent priming would cause the secretion rate to increase during stimulation as a result of an increase in vesicle “mobilization” to the release-ready primed pool, which can serve as a mechanism of short-term synaptic facilitation (Dittman et al. 2000; Millar et al. 2005; Pan and Zucker 2009; Worden et al. 1997) (see also encyclopedia entry on ► “Facilitation, Biophysical Models”).
2. Under conditions of high vesicle release probability, Ca^{2+} -dependent priming would manifest itself through activity-dependent acceleration of recovery from short-term synaptic depression (Dittman and Regehr 1998; Hosoi et al. 2007; Stevens and Wesseling 1998; von Ruden and Neher 1993; Wang and Kaczmarek 1998).

The simplest model of release that includes a Ca^{2+} -dependent priming step can be obtained by modifying reaction 7: for instance, Millar et al. (2005) considered the following scheme (see also (Bornschein et al. 2013, Brachtendorf et al. 2015, Sakaba 2008) for a slightly modified version of this scheme):



The study of Millar et al. (2005) also considered a more detailed version of this model that takes into account the independence of Ca^{2+}

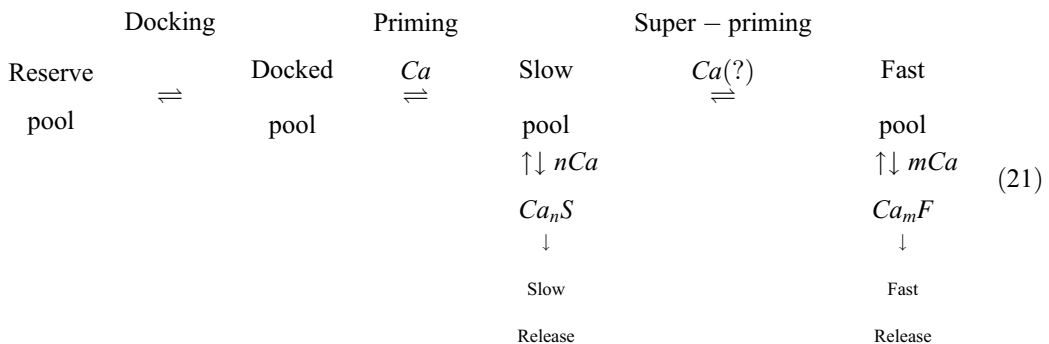
binding to C2A and C2B domains of synaptotagmin, leading to the following modification of above (see also (Pan and Zucker 2009)):



Here the horizontal state transitions represent the binding of the three C2A sites of synaptotagmin, while the vertical transitions correspond to the binding of the C2B sites, which is assumed to be independent of the Ca^{2+} binding of the C2A domain. Both domains are assumed to bind Ca^{2+} cooperatively (with cooperativity parameter $b_1 = b_2 = 0.5$). These models were successful in explaining the difference between release properties of the facilitating “tonic” and depressing “phasic” crustacean neuromuscular

junctions (Millar et al. 2005; Pan and Zucker 2009).

Vesicle priming has also been considered in the context of more detailed models that include multiple releasable vesicle pools. In such models, the priming step is usually assumed to occur upstream of the process of exchange between the slow-releasing and the fast-releasing vesicle pools. Adding the priming step to the scheme (17) leads to the following class of models (Verhage and Toonen 2007):



In this scheme, “super-priming” refers to the conversion of the slowly releasable pool to the fast releasable pool, the nature and the Ca^{2+} -dependence of which is currently unknown. Note that the use of the term “super-priming” is model-dependent; recently, it has been used to describe a newly identified additional kinetic

step in the priming of the fast pool at the calyx of Held synaptic terminal (Lee et al. 2013). The possible Ca^{2+} dependence of the conversion of the slow pool to the fast pool is unknown; it is possible that this conversion may even be retarded by Ca^{2+} at some synapses (Neher and Sakaba 2008). At the calyx of Held, the contribution of the fast

component of release is observed to increase with increasing Ca^{2+} levels, at the expense of the slow component (Wolfel et al. 2007). An explanation of this observation was suggested that the slow pool may be small at rest but increases due to activity-dependent conversion of vesicles from the fast pool, and that this conversion is less pronounced at high Ca^{2+} levels, so it is not able to reduce the fast pool at more intense stimulation levels (Neher and Sakaba 2008).

Spatially Resolved Exocytosis Models and the Vesicle-Channel Coupling

Models of Ca^{2+} binding by synaptotagmin sensors controlling the release of one or more vesicle pools are often combined with simplified models of intracellular Ca^{2+} dynamics that involve only one or two well-mixed spatial Ca^{2+} compartments. This level of detail is sufficient to simulate exocytosis in response to global elevations of Ca^{2+} produced by caged- Ca^{2+} compounds. However, deep understanding of physiological synaptic or endocrine transmission requires full three-dimensional simulation of intracellular Ca^{2+} diffusion and buffering. This in turn requires taking into account the latest data on the spatial arrangement of voltage-dependent Ca^{2+} channels and membrane-docked vesicles, which varies considerably across distinct cell types and stages of development (Bornschein and Schmidt 2018; Eggermann et al. 2012; Gentile and Stanley 2005; Matveev et al. 2011; Moser et al. 2006; Oheim et al. 2006; Stanley 2015, 2016; Walter et al. 2018). In fact, the heterogeneous release probability of secretory vesicles captured by the multiple vesicle pools models reviewed above can be a result of heterogeneous distance between vesicles and the presynaptic Ca^{2+} channels.

Since the geometric arrangement of vesicles and functional Ca^{2+} channels at the release sites is hard to probe using existing experimental techniques, testing the hypotheses on channel-vesicle distance has been one of the primary aims of the more comprehensive biophysical models of exocytosis. To simulate three-dimensional Ca^{2+}

dynamics, such detailed models use either stochastic simulation (Bennett et al. 2004; Ditttrich et al. 2013; Glavinovic and Rabie 2001; Ma et al. 2015; Nadkarni et al. 2012; Scimemi and Diamond 2012; Shahrezaei et al. 2006; Shahrezaei and Delaney 2005), deterministic solution of reaction-diffusion equations (Bohme et al. 2018; Bucurenciu et al. 2008; Gandasi et al. 2017; Matveev et al. 2009, 2011; Meinrenken et al. 2002, 2003; Schmidt et al. 2013; Weber et al. 2010; Zucker and Fogelson 1986), or steady-state approximations of Ca^{2+} distribution near an array of open Ca^{2+} channels (Bertram et al. 1999; Coggins and Zenisek 2009; Matveev 2016; Montefusco and Pedersen 2018).

Several particularly detailed modeling studies combine together many of the mechanisms reviewed above to build a comprehensive model of secretory vesicle exocytosis:

1. The model implemented in Ditttrich et al. (2013), Luo et al. (2015b), and Ma et al. (2015) is one of the most complete recent models of exocytosis that includes stochastic simulations of Ca^{2+} ions diffusion, buffering and binding to synaptotagmin sensors, taking into account the copy number of synaptotagmin molecules and SNARE complexes per vesicle (Chapman 2002; Han et al. 2004; Mutch et al. 2011). This is the first modeling study that considered the possibility that only a subset of synaptotagmin sites have to be Ca^{2+} -bound to trigger exocytosis, and Ditttrich et al. (2013) examines the effective Ca^{2+} cooperativity of exocytosis as an emergent characteristic of such partial binding of a subset of Ca^{2+} sensors.
2. The study of Pan and Zucker (2009) builds a comprehensive model of release and short-term plasticity at tonic and phasic crustacean neuromuscular junctions, based on Eq. (20) above, but adds positional priming, leading to a transition scheme describing vesicle exchange between the following distinct vesicle pools: reserve, docked, primed channel-detached, and primed channel-attached. One of the main aims of this study was to build a model that most fully accounts for the properties of short-term synaptic facilitation

observed at crustacean tonic neuromuscular junctions, as well as the properties of short-term depression and asynchronous release at phasic neuromuscular junctions.

These models are just two representatives of a class of comprehensive models of Ca^{2+} -dependent exocytosis that go beyond the simulation of vesicle release in response to a single presynaptic depolarization, aiming to reproduce short-term changes in synaptic transmission strength in response to prolonged or repeated stimulation. Such modeling work is reviewed in more detail in the entry ► [“Facilitation, Biophysical Models”](#).

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Biophysical Models of Olfactory Mitral and Granule Cells

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Definition

Biophysical models of olfactory mitral and granule cells are conductance-based compartmental models based on the morphological and electrophysiological properties of mitral and granule cells. Each cellular model incorporates a number of interconnected sections that represent physical cellular elements such as the soma, axon, dendrites, and/or specialized compartments such as spines. Each section, in turn, consists of one or more isopotential compartments, each of which contains passive and active ionic channels along with other mechanisms such as calcium buffering, typically modeled using the Hodgkin-Huxley formalism (Hodgkin and Huxley 1952). The parameters of these coupled equations are then adjusted to reproduce the salient membrane properties of mitral and granule cells. These biophysical models serve as an important tool to understand

information processing within the olfactory bulb (OB) quantitatively.

Detailed Description

Morphological and Electrophysiological Properties of Mitral Cells

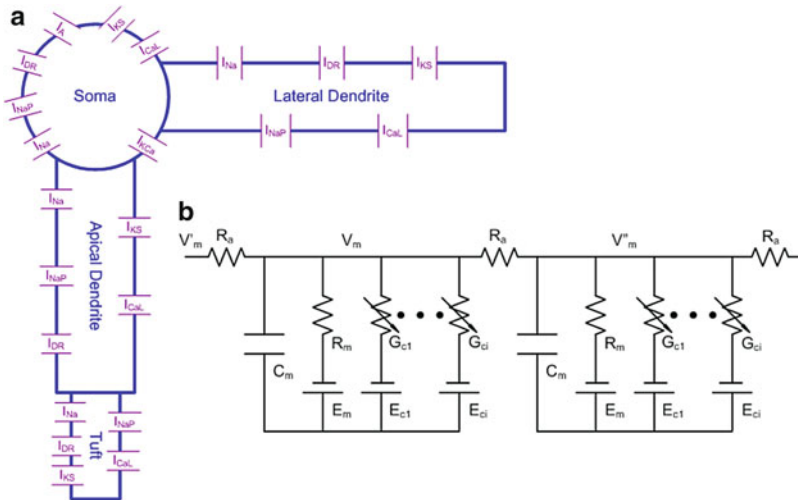
Mitral cells (MCs) in OB have several salient morphological characteristics (Shepherd and Greer 1998). The cell body sends out a single primary (apical) dendrite and several secondary (lateral) dendrites. The primary dendrite extends several hundred micrometers and arborizes in a complex tuft within a glomerulus, while lateral dendrites are widely distributed in the external plexiform layer (EPL). The input resistance ranges from 88 to 280 M Ω , and the mean resting potential is about -63 mV (Desmaisons et al. 1999; Cang and Isaacson 2003). In response to depolarizing current pulses, MCs generate clusters of action potentials interspersed with long period of subthreshold oscillations (STOs) (Chen and Shepherd 1997; Desmaisons et al. 1999; Balu et al. 2004). Inhibitory postsynaptic potentials (IPSPs) reset the phase

of the STOs and also can generate rebound action potentials (Desmaisons et al. 1999).

Development of a Biophysical MC Model: An Example

Based on the morphology of mitral cells, a reduced, oligocompartmental MC model could consist of four sections: a soma, an apical dendrite, a lateral dendrite, and a glomerular tuft at the distal end of the apical dendrite (Fig. 1a). Each section is modeled as a cylinder whose dimensions are based on morphological measurements from mitral cells; reasonable examples are shown in Table 1 (Li and Cleland 2013). The long apical and lateral dendrite sections can be further divided into multiple compartments to more accurately model cable properties (individual compartments are by definition isopotential). For example, in the Li and Cleland model (Li and Cleland 2013), the apical dendrite comprises five compartments, and the lateral dendrite comprises seven compartments, whereas the electrotonically compact soma comprises a single compartment.

Generally, each compartment contains a passive leakage current and a number of active ionic



Biophysical Models of Olfactory Mitral and Granule Cells, Fig. 1 Compartmental model of a mitral cell (MC, Li and Cleland 2013). (a), Schematic representation of the MC model with distribution of active ionic conductances in each of its four sections. (b), Equivalent electrical circuit

of two identical interconnected neural compartments used to simulate MC cell excitability. Subscripts c1..ci denote i different active (variable) conductances and their associated reversal potentials (G_{Na}, G_K, etc., with reversal potentials E_{Na}, E_K, etc.).

Biophysical Models of Olfactory Mitral and Granule Cells, Table 1 Morphological parameter values and passive electrical properties of an MC model (Li and Cleland 2013)

	Diameter (μm)	Length (μm)	C_m ($\mu\text{F}/\text{cm}^2$)	R_m ($\Omega \cdot \text{cm}^2$)	R_a ($\Omega \cdot \text{cm}$)	E_m (mV)
Soma	20	25	1.2	30,000	70	-60
Apical dend	3.5	370				
Tuft	0.5	20				
Lateral dend	3.4	500				

currents (Fig. 1a, compartments within a section have identical currents). The Li and Cleland model contains seven active currents: fast, spike-generating (I_{Na}), and persistent (I_{NaP}) sodium currents; a potassium delayed rectifier I_{DR} ; two transient potassium currents (fast-inactivating I_{A} and slow-inactivating I_{KS}); an L-type high-voltage-activated calcium current (I_{CaL}); and a Ca^{2+} -dependent potassium current I_{KCa} , based on previous experimental and modeling studies (Bhalla and Bower 1993; Wang et al. 1996; Desmaisons et al. 1999; Davison et al. 2000; Balu et al. 2004; Rubin and Cleland 2006; Balu and Strowbridge 2007). Figure 1b shows the equivalent electrical circuit of two basic neural compartments connected with an axial resistance R_a . Each compartment has a membrane capacitance C_m , a fixed membrane resistance R_m , and an equilibrium potential E_m associated with the ohmic leakage current that flows across R_m (values shown in Table 1 for the Li and Cleland model).

All ionic conductance kinetics in this model are modeled using the Hodgkin-Huxley formalism (Hodgkin and Huxley 1952). Specifically, the conductance for channel i , G_{ci} , is modeled as:

$$G_{ci} = g_{ci} m^p h^q \quad (1)$$

where g_{ci} is its maximal conductance density, m its activation variable (with exponent p), and h its inactivation variable (with exponent q). The kinetic equation for the gating variable x (m or h) satisfies a first-order kinetic model,

$$\frac{dx}{dt} = \phi_x \frac{x_{\infty}(V) - x}{\tau_x(V)} \quad (2)$$

where ϕ_x is a temperature-dependent factor, $x_{\infty}(V)$ is the voltage-dependent steady state, and

$\tau_x(V)$ is the voltage-dependent time constant. Equivalently, Eq. 2 can be written as:

$$\frac{dx}{dt} = \phi_x (\alpha_x(V)(1 - x) - \beta_x(V)x) \quad (3)$$

where $\alpha_x(V)$ and $\beta_x(V)$ are the voltage-dependent rate constants. The parameter values for the rate constants α_x and β_x , steady state x_{∞} , and time constant τ_x of the gating variables determine the model's dynamical properties and are typically based on electrophysiological measurements of mitral cells (e.g., voltage clamp or current clamp). The excitability of a segment of MC cell membrane modeled by a compartment of the type depicted in Fig. 1b can then be described by the following equation:

$$C_m \frac{dV_m}{dt} = \frac{(E_m - V_m)}{R_m} + \sum_i G_{ci}(E_{ci} - V_m) + \frac{(V'_m - V_m)}{R_a} + \frac{(V''_m - V_m)}{R_a} \quad (4)$$

where V'_m and V''_m are the voltages of the two adjacent compartments. Solving many coupled equations of the form in Eq. 4, with appropriate parameters, will generate the dynamical behavior of a mitral cell. Fortunately, specialized neuronal simulators such as NEURON (Carnevale and Hines 2006) and GENESIS (Bower and Beeman 2003) have made the implementation and numerical simulation of biophysical models easy and straightforward.

After implementation of the model, the next step is to select suitable parameters, so the model reasonably reproduces the experimental data from a particular cell type of interest. This usually involves adapting parameter values from previous literature, estimating or inferring them from

experimental data, and finally performing a parameterization and fitting procedure. Parameterization can be performed via exhaustive searching (brute force), supervised trial and error, and/or any of a number of more advanced, automated parameterization techniques. The Li and Cleland model, after parameterization, reproduces the experimentally observed activation patterns of mitral cells such as delayed first spike, clusters of action potentials interspersed with subthreshold oscillations (STOs), STO phase reset, and rebound spikes generated by IPSPs (Li and Cleland 2013).

Other Biophysical MC Models

A number of biophysical MC models incorporating different levels of detail and complexity have been developed (Bhalla and Bower 1993; Shen et al. 1999; Davison et al. 2000; Migliore et al. 2005; Bathellier et al. 2006; Rubin and Cleland 2006; Inoue and Strowbridge 2008). The model developed by Bhalla and Bower is a detailed, 286-compartment model based on intracellular recordings and morphological measurements. It aimed to study the details of single-cell morphology and channel distribution in cellular information processing. This complex model was reduced to two-, three- and four-compartment models by Davison et al. (2000) for computational efficiency in larger networks (Davison et al. 2003). Neither model implemented STOs or intermittent cluster firing patterns, however, which are important membrane characteristics of MCs (Desmaisons et al. 1999; Balu et al. 2004); consequently, Rubin and Cleland (2006) adapted the four-compartment Davison model to replicate these dynamical properties by adding additional current mechanisms as described by Desmaisons et al. (1999). The Shen et al. (1999) and Migliore et al. (2005) models are detailed, multi-compartmental biophysical models, but, as they sought only to study action potential generation and inter-glomerular synaptic transmission, they included only the fast sodium and delayed potassium channels. Bathellier et al. (2006) developed a single-

compartment model with five core currents capable of reproducing the essential firing properties of MCs for implementation of an oscillatory network. This single-compartment model was very efficient in network simulation, although at the price of neglecting the signal interactions between the soma and the dendrites (e.g., forward and back propagation). The model by Inoue and Strowbridge (2008) comprised two compartments (a soma and a dendrite) and utilized reduced current mechanisms in order to study persistent activity in OB. Thus, biophysical models of MCs can vary substantially in implementational details depending on the investigators' particular goals.

Morphological and Electrophysiological Properties of Granule Cell

Granule cells (GCs) differ from mitral cells – e.g., very different morphologies, channel components, and kinetics – and consequently are modeled differently. GCs have a soma (~8 μm diameter), which connects to a number of basal dendrites in the vicinity of the cell body, and several thin (approximately 1–2 μm), long (up to about 600 μm) radial dendrites projecting to the EPL, where they contact mitral/tufted cell secondary dendrites via large dendritic spines (Egger et al. 2003; Pinato and Midtgaard 2003). Two prominent features of GCs are their extremely high input resistances and Na^+ spike thresholds. Depending on the species, the input resistance ranges from 0.5 to 2 $\text{G}\Omega$, and the spike threshold is about –28 mV (Egger et al. 2003; Pinato and Midtgaard 2003; Pressler and Strowbridge 2006). The resting potential is about –65 mV for rats (Cang and Isaacson 2003; Pressler and Strowbridge 2006), and the membrane time constant is about 50 ms (Pinato and Midtgaard 2003). In response to positive current injection, GCs fire a short burst of Na spikes with a gradual attenuation of spike amplitude and slowly activating “ramping” depolarization often terminating in a sustained plateau near –20 mV (Wellis and Kauer 1994; Hall and Delaney 2002; Egger et al. 2003; Pinato and Midtgaard 2003). Biophysical models

of granule cells should replicate these basic properties.

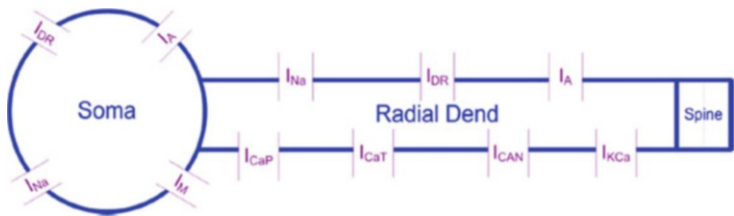
Development of a Biophysical GC Model: An Example

A simple yet functional oligocompartmental GC model can consist of a soma and a radial dendrite connected to a spine shaft and body (Fig. 2; Li and Cleland 2013). Omitting detailed simulations of multiple spines, for example, this model was built for efficient integration of synaptic inputs from MCs in a network model. Its morphological parameter values and passive electrical properties are shown in Table 2. The GC model cell contains the following eight active ionic currents: a fast, spike-generating sodium current I_{Na} ; a potassium delayed rectifier I_{DR} ; a transient A-type potassium current I_A ; a noninactivating muscarinic potassium current I_M ; a low-threshold inactivating (I_{CaT}) and a high-threshold ($I_{CaP/N}$) calcium currents; a Ca^{2+} -activated nonspecific cation current I_{CAN} , and a Ca^{2+} -dependent potassium current I_{KCa} (Li and Cleland 2013). The GC is modeled as an equivalent electrical circuit of connected compartments as described above for the MC.

After parameterization, the Li and Cleland model reproduced the experimentally observed salient properties of GCs, including delayed first spike generation, ramping depolarization, and muscarinic neuromodulatory effects including the conversion of afterhyperpolarizations (AHPs) into afterdepolarizations (ADPs) and conditional persistent firing (Li and Cleland 2013). This type of model enables the direct association of channel properties with cellular responses. For example, the initial spike delay is caused by an “A”-type potassium current I_A , whereas blocking the I_M and I_{KCa} currents abolishes AHPs, thereby revealing latent ADPs mediated by the nonspecific cation current I_{CAN} (Pressler et al. 2007).

Other Biophysical GC Models

Several other biophysical GC models have been developed, exhibiting different levels of details and complexity (Bhalla and Bower 1993; Davison 2001; Inoue and Strowbridge 2008; Migliore and Shepherd 2008). The model developed by Bhalla and Bower is a detailed, 944-compartment model based on intracellular recordings and



Biophysical Models of Olfactory Mitral and Granule Cells, Fig. 2 Schematic representation of the Li and Cleland GC model with distribution of active ionic

currents. The spine compartments have the same ionic currents as the radial dendrite

Biophysical Models of Olfactory Mitral and Granule Cells, Table 2 Morphological parameter values and passive electrical properties of a GC model (Li and Cleland 2013)

	Diameter (μm)	Length (μm)	C_m (μF/cm ²)	R_m (Ω · cm ²)	R_a (Ω · cm)	E_m (mV)
Soma	8	8	2	30,000	70	−60
Dend	1	150				
Spine shaft	1	1				
Spine body	1	1				

morphological measurements. That complex model was reduced by Davison (2001) to a three-compartment model that exhibited most of the original model's physiological properties and was later implemented in a network simulation (Davison et al. 2003). A separate GC model developed by Migliore and Shepherd (2008) contained a soma, a main radial dendrite, and three second-order dendrites representing the medial and distal dendritic tree. This model only included three conductances (Na , K_{DR} , K_{A}), omitting all Ca^{2+} and Ca^{2+} -dependent currents. To investigate persistent firing properties in GCs, Inoue and Strowbridge (2008) developed a two-compartment GC model containing low- and high-threshold Ca^{2+} currents, a Ca^{2+} -dependent nonselective cation current, a sodium current, and two potassium currents. The model was able to reproduce Ca^{2+} spikes and Ca^{2+} - and voltage-dependent ADP responses as observed experimentally. It also suggested that persistent spiking in granule cells results from the interaction between a voltage-dependent after depolarization and a low-threshold Ca^{2+} spike.

Summary

Biophysical models of olfactory mitral and granule cells are conductance-based compartmental models constrained by the specific morphological and electrophysiological properties of mitral and granule cells. The general procedures for building such models include three steps: (1) represent the cell morphology with interconnected isopotential compartments, (2) decide upon appropriate ionic channels in each compartment based on their physiological properties, and (3) select suitable parameters so the model exhibits patterns of activity that correspond to experimental data. Depending on the particular goals of interest, different biophysical mitral and granule cell models incorporating different levels of detail and complexity have been developed. These biophysical models serve as important tools to integrate and interpret experimental data and to formulate quantitative working hypotheses concerning olfactory bulb function.

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Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism

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Synonyms

Forward-generative models of functional neuroimaging data

Definition

Forward-generative models are considered crucial to interpret and integrate data obtained with different functional neuroimaging modalities (Riera 2014). Typically, these models are formulated to represent biological principles at the mesoscopic scale, which basically stand for an average voxel (1 mm^3) in any brain imaging technique. To this end, biophysical models for neuronal activity, which are mostly available from the *neuronal computation* community, have been modified to incorporate general physiological mechanisms governing glial cell activity, vascular dynamics, and metabolism. For the cerebral cortex, the most relevant brain structure in functional neuroimaging, a variety of such extended biophysical models has been consolidating around three main research topics over the last decade: (a) the principles for neurovascular coupling, (b) the organization of cortical microcircuits, and (c) the cellular metabolism with emphasis on the nerve-ending particles. After modeling from mesoscopic variables to neuroimaging data, inversion of generative models provides insight into these underlying mechanisms of brain function and cognition.

Detailed Description

Neuroimaging data constitute different reflections, governed by basic principles in physics, of a common cause originated from the activity of connected cellular networks. Therefore, formulating biophysical models that embrace both the underlying causal phenomena and the observational principles is essential for (Stephan et al. 2006):

- (a) Performing statistical inference about the cellular states, exogenous inputs, and network topology.
- (b) Combining different modalities of functional neuroimaging data.

The state-space formalism constitutes one of the most general forms for representing these models. In this formalism, a state-space equation

is used to describe the evolution of the cellular activity, and an observation equation specifies how these hidden (cellular) states $x(\vec{r}, t)$ produce discrete neuroimaging data y_{t_k} .

The state equation:

$$x(\vec{r}, t) = f(x(\vec{r}, \tau \in [t - \tau, t]), i(\vec{r}, t), \Theta(\vec{r})) \quad (1)$$

$$\text{The states } x(\vec{r}, t) = (x_1(\vec{r}, t), x_2(\vec{r}, t), \dots, x_N(\vec{r}, t))$$

are represented by an N-dimensional vector field that dynamically evolves on time as described by Eq. 1. An exogenous multivariate input $i(\vec{r}, t)$ is assumed to perturb the system at each time instant. In principle, this input could include both deterministic $u(\vec{r}, t)$ and stochastic $\xi(\vec{r}, t)$ components. A vector field $\Theta(\vec{r})$ is included to represent important physiological parameters of the neuronal network (e.g., synaptic strength, metabolic rate, vascular reactivity). In general, the state vector $x(\vec{r}, t)$ depends through the function f in Eq. 1 on its present/ τ -past values. Note that since neuronal networks are intrinsically autonomous systems, the dependency with time is exclusively by way of the exogenous input.

The observation equation:

$$y_{t_k} = g(x(\vec{r}, t_k)) + \varepsilon_{t_k} \quad (2)$$

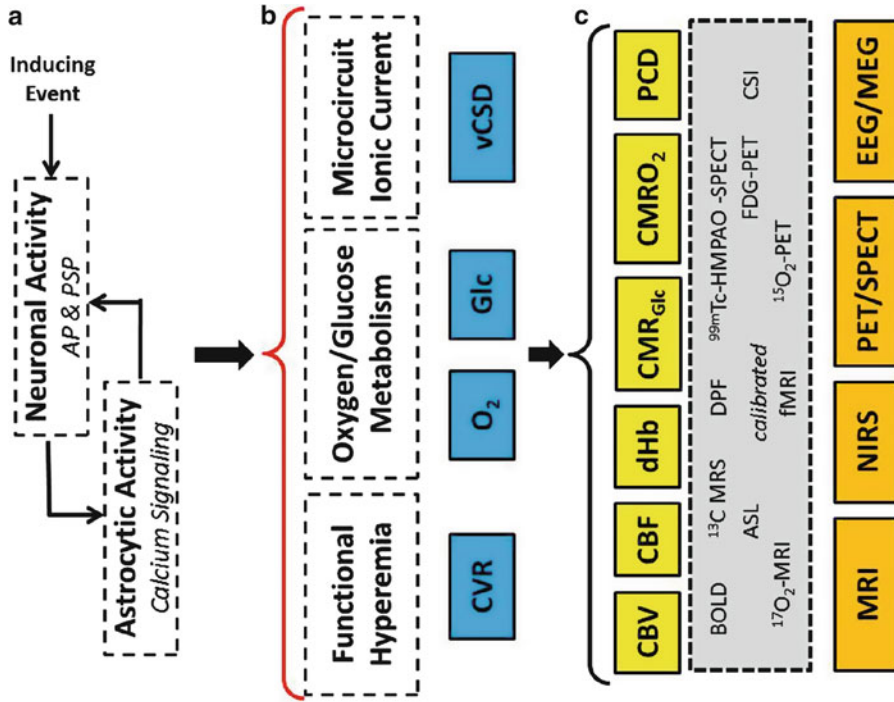
The data vector y_{t_k} comprises neuroimaging observations $\{y_{t_k}^{l,m}\}$ from different locations (subscript l) and modalities (superscript m). Function g in Eq. 2 does not depend explicitly on time. The detailed form of this function for each particular modality could be found in Toga and Mazziotta (2002). They may depend on instrument characteristics, sensor specificities, and experimental conditions. An independent multivariate white noise ε_{t_k} is typically added to the observations. Figure 1 summarizes cause-effect mechanisms and mesoscopic states underlying biophysical models in neuroimaging as well as typical observation modalities and techniques.

The state Eq. 1 is written in a general form. There are two relevant cases that are of interest.

Discrete Nonparametric Models

$$X_{t_k}^l = f_l\left(\left\{X_{t_k-k}^l, k' = 0, \dots, N_l\right\}, u_{t_k}^l, \Theta_l\right) + \xi_{t_k}^l \quad (3a)$$

This constitutes a type of multivariable autoregressive (MAR) model, which is useful to characterize discrete cellular state dynamics. For each voxel, the system comprises a deterministic and time-varying external input $u_{t_k}^l$ as well as a vector of parameter Θ_l . In this particular case, the system noise is represented by a multivariate white noise $\xi_{t_k}^l(0, \sum_{t_k}^l)$. When $\sum_{t_k}^l$ varies with time, it represents a heteroscedastic state-space model for non-stationary time series. Compartmental GARCH models are very useful for dynamic nonstationary signal decomposition. For neuroimaging, time series can be assumed in general stationary ($\sum_{t_k}^l = \sum^l$). Function f_l can be represented by the Hammerstein, ExpAR, and RBF-AR models for nonlinear dynamics. An innovation-based approach is typically used for the characterization of nonlinear and/or non-Gaussian time series. This approach is combined with maximum likelihood criteria to define proper statistical identification methods. Hidden cellular states can be estimated using Kalman and extended Kalman filtering techniques. There exist useful empirical (e.g., bootstrap, cross-validation, Jackknife) and theoretical (Akaike information criteria “AIC,” Bayesian information criteria “BIC”) criteria for model selection. We can use some version of Granger causal modeling (i.e., *Wiener-Akaike-Granger-Schweder influence*, *WAGS causality*) to study the topology of the cellular networks. Although discrete nonparametric models are not formulated on pure biological assumptions, they are very useful to explore specific hypotheses about working principles of cellular networks and accordingly narrow the family of plausible biophysical models. The following literature is recommended for details about this particular type of state-space models (Ozaki 2012, 2014; Valdes-Sosa et al. 2011; Stephan and Roebroeck 2012). This type of model has been extendedly used to describe EEG/MEG and fMRI data.



Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism, Fig. 1 Cause-effect relationship between the cellular states and actual observations. A particular inducing event will trigger neuronal (i.e., action potential “AP,” postsynaptic potential “PSP”) and astrocytic (i.e., calcium signaling) activities. These activities will cause three major responses: (a) a flow of ionic currents across the cortical microcircuits, (b) the metabolizing of oxygen and glucose to build the required energy substrates, and (c) the functional hyperemic response necessary for new supplies and residual cleaning. The ionic currents will create volumetric current source densities (vCSD) within a voxel of interest. Changes in the d-glucose concentration (*Gluc*) and the oxygen partial pressure (*pO₂*) will result from the metabolism of these two molecules. A reduction in the cerebral vascular resistance (CVR) constitutes the primary effect of the functional

hyperemic response. The final mesoscopic variables are as follows: the primary current density (*PCD*), the cerebral metabolic rate of oxygen (*CMRO₂*), the deoxyhemoglobin (*dHb*), the cerebral blood flow (*CBF*), and the cerebral blood volume (*CBV*). There are constitutive relationships between some of these mesoscopic variables. They are either directly or indirectly reconstructed from functional neuroimaging (e.g., EEG/MEG, PET/SPECT, NIRS, and MRI) by a variety of techniques, e.g., current source imaging (*CSI*); 99 mTc hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) by SPECT; fluorodeoxyglucose (*FDG*) and ¹⁵O₂ by PET; the differential path-length factor (*DPF*) method by NIRS; calibrated fMRI, blood-oxygen-level dependent (*BOLD*) signal, arterial spin labeling (*ASL*), ¹³C MRS, and ¹⁷O₂ by MRI

A model by Riera et al. (2005) constitutes one of the most representative examples of using a discrete nonparametric model for the combination of both multimodal neuroimaging and the statistical inference about network dynamics/topology.

Continuous Parametric Models

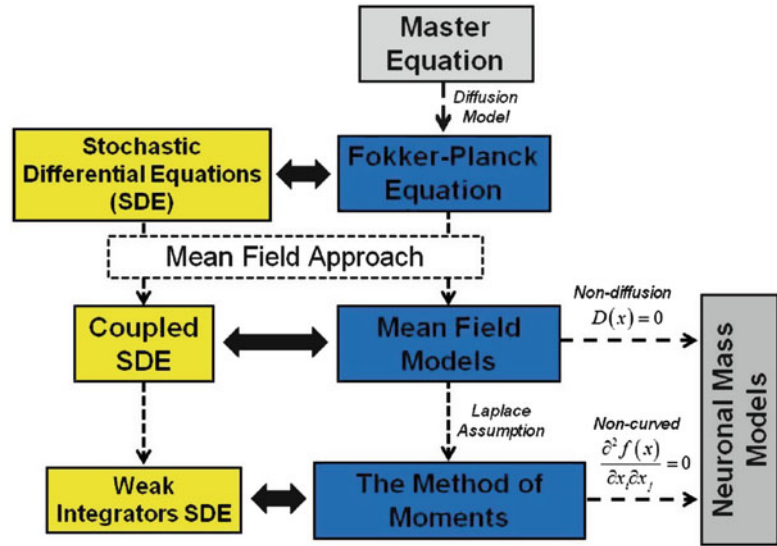
$$dX^l(t) = f_l(X^l(t), u^l(t), \Theta_l)dt + G^l dw^l(t) \quad (3b)$$

This constitutes a stochastic differential equation (SDE), which is useful to represent cellular

states with a continuous dynamics. Eq. 3b can be used to represent the states of single cells in a population, which are affected by a deterministic external input $u^l(t)$ and a stochastic thermal noise $w^l(t)$ (i.e., Wiener process, $E[w^l(t + \tau), w^l(t)] = 2D\delta(\tau)\delta_{ll}$ for each voxel. A vector Θ_l is also included to represent biologically meaningful parameters. While dealing with large amount of interacting cells, theoretical frameworks for assemblies are very useful (summary in Fig. 2). Among them, the Fokker–Planck equation for populations of cells having a diffusion model

**Biophysical Models:
Neurovascular Coupling,
Cortical Microcircuits,
and Metabolism,**

Fig. 2 Theoretical frameworks for assemblies of interacting cells



of interactions constitutes one of the most attractive. The Fokker–Planck equation describes the time evolution of the probability density function $p_I(x^I, t)$ of the cellular states $x^I(t)$ that follow the SDEs Eq. 3b.

$$\begin{aligned} \frac{dp_I(x^I, t)}{dt} = & -\nabla \cdot (f_I(x^I(t), u^I(t), \Theta_I)p_I(x^I, t))dt \\ & + \frac{1}{2} \sum_{ij} \frac{\partial^2}{\partial x_i \partial x_j} (H_{ij}^I p_I(x^I, t)) \end{aligned} \quad (4)$$

with $H^I = 2G^I D G^{I^T}$.

Equation 4 is also known as the Kolmogorov forward equation. It is assumed that the sample trajectories of the particle are continuous functions of time. However, they are nowhere differentiable with respect to time. The high dimensionality of the Fokker–Planck equation can be reduced by using the mean-field approximation, $p_I(x^I, t) = \prod_k p_k^I(x_k^I, t)$. The resulting low-dimensional Fokker–Planck equations describe the evolution of separable ensembles that are coupled by mean-field effects. These ensembles could represent different neuronal populations of a cortical minicolumn, e.g., layer II/III (or V) pyramidal cells (PCs), spiny stellate cells, and GABAergic interneurons. For example, the mean firing rate of large basket GABAergic

interneurons could be used as a postsynaptic-driven force to each individual layer II/III PC. However, these ensembles could also represent different types of cells (e.g., neurons and astrocytes). For example, the mean firing rate of a particular population of nitrgergic GABAergic interneurons could be the driven vasodilative force acting on individual smooth muscle cells at the same cortical area. In other words, by coupling the ensembles through the mean-field approach the flow in the phase space of one ensemble is $\Gamma_I^k(x_k^I(t), \{\mu_k^I(t), \forall_{k' \neq k}\}, u^I(t), \Theta_I)$, with the means $\mu_k^I(t) = E[x_k^I(t)]$. In the SDE representation, the mean-field approach is equivalent to a system of coupled SDEs. Still, the main problem with both approaches is to create efficient methods to integrate respective differential equation systems, which have in principle a high dimensionality. Circumnavigating the problem of integrating high-dimensional Fokker–Planck equation systems for the density in state-space models defined by coupled SDEs is not a new topic. There are two main methods for solving this problem. One of them is based on the assumption of Gaussianity for densities $p_I(x^I, t)$ (i.e., the Laplace assumption). Therefore, it focuses on obtaining ordinary differential equations for the first two moments (i.e., means and variances) of the state variables (Marreiros et al. 2008). However, the most popular method is based on the so-called weak integrators for SDEs. The weak

methods allow the computation of any smooth functional on the state variables, where the moments are particular cases. Several methods have been proposed for weak integration of stochastic differential equations (Kloeden and Platen 1999). Continuous parametric models with delays have been solved in the past for neuroimaging data by transforming them into systems of SDEs and algebraic equations. The following literature is recommended for details about this particular type of state-space models (Deco et al. 2008; Deco 2014; Valdes-Sosa et al. 2011). The dynamic causal modeling (DCM, Friston et al. 2003; Stephan et al. 2007; Daunizeau et al. 2011) constitutes the most established type of continuous parametric models with variants in almost of blue-highlighted levels in Fig. 2. The DCM formalism has been extensively used to obtain connectionist diagrams (i.e., effective connectivity) between neuronal populations in different brain locations from neuroimaging data. Different variants of the local linearization (LL, Ozaki 2012) method have been applied to EEG and fMRI data covering all yellow-highlighted levels in Fig. 2.

Neuronal Mass Models

The so-called neuronal mass models result from particular approximations either from the mean-field models (no diffusion) or from the coupled mean-field models through the method of moments (non-curved). In general, for the neuronal mass models, the full ensemble density is replaced by a center of mass at a particular point. Then, a dynamic equation is used to describe the evolution of this center of mass with time. The neural-field models are an important generalization of the neural-mass models by allowing for states to be functionals of position on the cortical sheet. This type of model cannot be defined as particular case of general Eq. 1. A general discussion about these two types of models can be found in Deco et al. (2008).

General mesoscopic states: PCD, $\vec{J}_P$; CMR_{O_2} , cMR_{O_2} ; CMR_{Glc} , cMR_{glc} ; dHb, q ; CBF, f ; CBV, v .

Examples of Relationships between Mesoscopic Variables

In general, these mesoscopic states can be represented by some of the abovementioned coarse-grained versions of Eq. 1. Biophysical generative models with balanced excitatory and inhibitory neuronal populations with specific oxygen-to-glucose indexes (OGI) have been systematically introduced to establish relationships between $\vec{J}_P$ and metabolic/hemodynamic variables. Some of these models link $\vec{J}_P$ with instantaneous (ensemble average) postsynaptic membrane depolarizations and/or presynaptic firing rates of neurons. The nonlinear balloon model was introduced to relate states q , f , and v , which was inspired by the **Windkessel theory** for the *flow–volume relationship* and the **oxygen limitation assumption**. Oxygen transport models are combined with **mass-balance equations** to establish relationships between cMR_{O_2} , f , and q , through some internal states such as the intra-/extravascular oxygen contents and the blood oxygen saturation fraction. In some models, neuronal demand of oxygen is defined by complex dependencies in the oxygen extraction fraction (OEF). Compartmental models for plasma and tissue (with both phosphorylated and dephosphorylated Glc) have been employed to describe the relative changes in cMR_{glc} and v .

In order to understand the origin of the relationships between mesoscopic variables in the neocortex, three main biological mechanisms must be studied in detail: (a) the neurovascular coupling, (b) the cortical microcircuits, and (c) the cellular metabolism.

Neurovascular Coupling

Functional Hyperemia

The cerebral circulatory system is endowed with assorted vascular controlling mechanisms to facilitate the desirable cerebral perfusion in any particular brain area at a given time. Surface vessels in the brain are richly innervated at strategic positions by both sympathetic and parasympathetic nerves, known as the extrinsic innervations of

the brain circulation. Specific perivascular structures of an intrinsic origin come into view after arterioles leave the Virchow–Robin space to penetrate the cerebral cortex, the latter including subcortical innervations. Spontaneous vasomotions originate from active mechanisms existing in cortical vessels, which to some extent are influenced by these innervations. However, the perfusion of the brain rapidly increases in areas where the activity of neuronal networks is prolonged or enhanced. In such a case, the CBF is locally intensified, a phenomenon denominated functional hyperemia. It is hypothesized that such a blood flow increase is accomplished by increased capillary blood velocity rather than capillary recruitment. From many years now, researchers have been trying to elucidate the basic principles for this phenomenon (Riera and Sumiyoshi 2010). We summarize below six major pathways by means of which neurons could communicate with the surrounded vasculature. They can be classified into two major groups: (1) a **phasic signaling** (e.g., gases, neurotransmitters, and lipids) issued directly from the neurons may reach the microvasculature through either fuzzy diffusion or local axonal release and b) a **tonic signaling** (i.e., Ca^{2+} waves underlying long-term brain requirements such as metabolites/oxygen) originated from gap-junction-connected astrocytes, which is evoked by the release of various neurotransmitters from nearby neurons during activation.

1. The release of large vasoactive molecules [e.g., neuropeptide Y (NPY), vasointestinal polypeptide (VIP), somatostatin (SOM), cholecystokinin (CCK), and acetylcholine (ACh)] by GABAergic interneurons through direct innervations of neighboring (even distances $>100\ \mu\text{m}$ away from the cells) microvessels. Some nitrergic GABAergic interneurons with specific laminar profiles in the neocortex transmit also neuronal signals from subcortical regions to the vasculature of a given cortical area. (**phasic signaling**).
2. The release of nitric oxide into the extracellular space from the axon terminals of some GABAergic interneurons via activation of the nNOS. These interneurons could release these large vasoactive molecules perivascularly through vessel innervations. This particular population of interneurons is very small and is not homogeneously distributed along the cortical layers. As nitrergic glutamatergic neurons are very rare in the neocortex, this mechanism might be very specific for inhibitory neuronal networks. The impact of such neuronal nitric oxide signaling on the vasculature via a cyclic GMP (cGMP)-dependent mechanism has been proposed to be modulatory rather than mediatory. (**phasic signaling**).
3. The release of prostaglandin E2 (PGE2) from certain pyramidal cells, which have dendritic and axonal profiles containing inducible prostanoid-synthesizing enzyme cyclooxygenase-2 (COX-2). These specific glutamatergic neurons are frequently in close proximity to the penetrating microvessels. Released PGE2 might reach a variety of receptors on either nearby glial processes or vascular smooth muscle cells (SMCs). COX-2 is peculiarly restricted to presynaptic and postsynaptic regions in these pyramidal cells, showing robust synaptic antilocalization with the nitric oxide-synthesizing enzyme. Nitric oxide diffusion into the synaptic sites of these glutamatergic neurons may result in COX-2 activation. Cortical microvessels are also targets of axonal varicosities of such pyramidal cells. (**phasic signaling**).
4. Enhancements of astrocytic Ca^{2+} signaling cause the production of arachidonic acid through the action of phospholipase A2 enzymes on membrane phospholipids. Arachidonic acid is able to diffuse towards adjacent cells, where it serves as a substrate for two cytochrome P450 enzymes (i.e., CYP4A subtype in SMCs and CYP2C subtype in astrocytes) to produce 20-hydroxyecosatetraenoic (20-HETE) and epoxyecosatrienoic (EET) acids. 20-HETE has a contractive effect on the SMCs through the activation of the l-type calcium channels and deactivation of the calcium-activated potassium (BK) channels. EET diffuses into the tissue, producing vasodilations by

hyperpolarizing nearby SMCs through the activation of BK channels. The negative and positive effects on the activation of BK channels in the SMCs caused by 20-HETE and EET acids, respectively, may be in equilibrium with low levels of nitric oxide, which constitutes an inhibitory agent for CYP4A. This equilibrium gives way whenever nitric oxide dissemination in the tissue increases. Nitric oxide signaling from neurons and endothelial cells activates the soluble guanylate cyclase in the SMCs, resulting in cGMP-related muscle relaxations. **(tonic signaling).**

5. Arachidonic acid increase causes PGE2 production from the astrocytic constitutive COX-1 enzyme. This lipid diffuses in the tissue and via PGE2 receptors could stimulate cyclic AMP formation in SMCs. The intracellular lactate is used by the astrocytic prostaglandin transporter to take up extracellular PGE2. However, when extracellular lactate levels are increased, this PGE2 clearance mechanism is lost, causing augmented vasodilations. The extracellular lactate rises by enhancing the activity of the lactate dehydrogenase enzyme, for example, increasing the substrate levels (pyruvate and NADH) of this redox reaction. Indeed, the levels of these substrates increase under either hyperglycolytic activity or suppression of the tricarboxylic acid (TCA) cycle. Astrocytic lactate transported to the extracellular space by monocarboxylate transporters MCT-1 provides a signaling that bring together metabolism and functional hyperemia through the lactate–PGE2 coupling mechanism. **(tonic signaling).**
6. External K^+ promotes dilation of vessels through Kir2.1 channels in SMCs. Large-conductance BK channels have been found in astrocytic end feet, which might open in response to significant Ca^{2+} increases. A variant of this hypothesis, named the K^+ siphoning, was initially proposed as a mechanism for controlling the vascular tone through astrocytic Kir4.1, but recently criticized. **(tonic signaling).**

The spatiotemporal profiles of these mechanisms show strong laminar variations (Herman

et al. 2013; Hirano et al. 2011) as a function of the brain state (Maandag et al. 2007; Smith et al. 2002).

Cortical Microcircuits

Cortical neurons display a wide variation in their morphological, electrophysiological, synaptic, and molecular properties. The clearest distinction is between pyramidal cells (e.g., “principal cells,” DeFelipe and Fariñas 1992) and interneurons. Interneurons are divided into excitatory (spiny stellate cells) and inhibitory types (Markram et al. 2004).

Pyramidal neurons (PCs) comprise more than 70% of all cortical neurons. They are the main output source of the neocortical microcircuit, projecting to subcortical brain areas such as the thalamus, basal ganglia, and brainstem but also connecting cortical regions, e.g., the contra- and ipsilateral sections of a sensory area. Although they appear in a variety of forms, the following common features are typically reported: (a) an apical dendrite branch which extends from the soma vertically towards the cortical surface with a gradually tapering form and (b) basal dendrites which originate from the soma towards random transversal directions. PC dendrites have highest spine density in the middle portions of the apical dendrite. Their axons project vertically downwards into the white matter after sending local collaterals within the cortical layers. The apical dendrites of layer VI PC project also to non-vertical angles before climbing up towards the superficial layers. Some PCs generally form a dendritic tuft in layer I. Local axon collaterals of PCs innervate neighboring cortical neurons. Layer V thick-tufted PC constitutes one of the best known types of cortical neurons. Their apical dendrite always reaches layer I where it bifurcates extensively forming a wide tuft. These neurons have broad basal dendrites that span radially up to 300 μm around the soma. The local axonal collaterals of this neuron project vertically to all layers and horizontally within layers V and VI. They project to deeper brain areas (e.g., superior colliculus and brainstem nuclei). These neurons are considered the microcircuit integrators of inputs from neurons in all cortical layers, which

eventually result in the main cortical outputs. These typical cytoarchitectonic structures for principal cells in occipital and parietal – and, to a lesser extent, temporal – lobes are not conserved in prefrontal cortices.

Interneurons consist of ~20% of neocortical neurons. Interneurons lack of apical dendrites. Their axons are mostly confined to the same functional column. Usually, interneurons do not project to other cortical areas via the white matter, i.e., they are “local circuit neurons.” In terms of their dendritic spine density, interneurons are divided into smooth, sparsely spiny, and spiny cells. These neurons have a very diverse axonal ramification, with characterization established according to the postsynaptic domain (axon, soma, or dendrite) innervated by them. Spiny stellate cells are the only excitatory interneurons and they are mostly located in layer IV of primary sensory cortices. They constitute the major input to the cortex from subthalamic nuclei. They display radially projecting spiny dendrites originated from small somata, some of them spreading to neighboring layers. Inhibitory interneurons have a large diversity of morphological and electrophysiological properties, which help interneuron classification. According to their arborizations, inhibitory interneurons are subclassified into bipolar, bitufted, and multipolar neurons.

- *Basket cells (BC)* are the most common inhibitory interneurons in the neocortex. They are found in cortical layers II–VI. There are three main subclasses of BC (i.e., large, small, and net). Their dendrites extend to different directions, with the morphology being multipolar and dendrites either smooth or sparsely spined.
- *Chandelier (axo-axonic) cells* are found throughout layer II to V in different cortical areas of mammals. They have an ovoid-like soma, from which smooth (or sparsely spined) dendrites develop in opposite directions. Their dendrites can be found in cortical layers I–VI, and their axons form a candle-like arrangement of vertical bouton strings that target PC axon initial segments, primarily in the supragranular layer. This type of neurons plays a crucial role in controlling PC activity.
- *Double bouquet cells (DBC)* are interneurons present in superficial layers with vertically oriented ovoid-like somata. Therefore, they have two dendritic bundles that extend from two opposite directions. Their axons form tight axonal bundles that descend vertically to infragranular layers. They display a regular spacing into microcolumns.
- *Martinotti cells* are interneurons with bitufted dendritic morphology and an ovoid soma. They are primarily found in cortical layers II–VI. Their axons ascend to and spread in layer I up to a few millimeters laterally from the somatic location. They inhibit the tuft and distal dendrites of PCs.
- *Neurogliaform cells* are small interneurons existing in all cortical layers. They have fine and multipolar-spanning dendrites. Their axons are thin and extensively branched. They innervate PCs with GABA type B synapses.

Main Microcircuit Principles

Cortical neurons display a large variety of geometrical and intrinsic electrophysiological properties (DeFelipe et al. 2002). These properties determine the input–output relationships for each particular neuron. They depend on the expression of ionic channels along the dendrites as well as on the geometry of dendritic trees. Cortical neurons are engaged in different time scales. The single-cell mRT-PCR method allows the establishment of relationships between ion-channel expression patterns and electrophysiological profiles of cortical neurons. A widely used classification scheme considers neurons as (a) regular spiking (RS), (b) fast spiking (FS), and (c) intrinsic bursting (IB), which rely only on the response to long suprathreshold stimuli. With the addition of the “chattering cell” type, this classification scheme has been used to quantitatively evaluate electrophysiological behaviors in vivo. Two other electrophysiological types of neurons have been later added to the original scheme: (a) low-threshold spiking (LTS) and (b) late spiking (LS). The majority of synaptic connections in the neocortex are between PCs, most of them in layer V (formed on basal, apical, oblique, and tuft dendrites).

Short-term connections between spiny stellate neurons in layer IV are formed on dendrites. Interlaminar connections between excitatory neurons target also dendrites. The spatial properties of excitatory and inhibitory synaptic inputs determine the efficacy at which individual neurons are excited. Synapses are distributed at specific distances from the soma (i.e., Euclidean and electrotonic distances) and with targeted locations relative to dendritic bifurcations and branches. Ionic channel densities along dendritic trees, soma, and axon, as well as their reversal potential distributions, play an important role in the genesis/propagation of action potentials. For example, as a consequence of the higher values of chloride reversal potential at the postsynaptic location (axon initial segment), chandelier cells have excitatory effects on PCs. Due to the physical proximity, axon- and soma-targeting synapses can immediately affect the action-potential initiation; hence, they act as action-potential “editors.” Distal dendritic synapses have low temporal precision because signals produced by them are filtered at the soma and initiation zone. Dendritic spines are the preferable postsynaptic targets of most excitatory synaptic connections. They play a crucial role in dendritic integration and synaptic plasticity. Although dendritic arbors are physically stable, dendritic spines and filopodia are variable elements (i.e., elimination and growth). These spines are the means by which dynamically postsynaptic target cells connect selectively to specific presynaptic boutons. The selectivity of synaptic contacts between cortical neurons can be divided into two separate questions: (i) selectivity in the postsynaptic element being connected to and (ii) selectivity in the unique identity of the innervated neuron.

(i) *Domain selectivity*

- (a). Axon-targeting cells (e.g., chandelier cells).
- (b). Somatic and perisomatic targeting interneurons (e.g., basket cells).
- (c). Dendritic targeting cells (e.g., double bouquet, neurogliaform, and Martinotti cells).

(ii) *Target cell selectivity*

How does a neuron choose its postsynaptic partners? The selection of a target pyramidal neuron by chandelier cells may occur because of a random axodendritic proximity with a further proliferation as the result of local interactions. While both basket and chandelier cells develop connections to neighboring cells, they selectively decided which PCs are going to be their final target, for which multiple boutons will be created around the axon initial segment. This selection process cannot be explained by random processes and geometrical considerations, which is far from the characteristic connectivity patterns between pyramidal neurons.

Metabolism

Vital functions in neurons and astrocytes requiring cellular work are as follows: (a) the glutamate/GABA–glutamine cycle; (b) vesicularization, docking, and exocytosis of neurotransmitters from vesicles; (c) the transmembrane ATPases in both types of cells; (d) actin-filament growth in dendrites; (e) phospholipid and glycolipid metabolism; and (f) axoplasmic transport. The isolated nerve-ending particle (i.e., synaptosome) preparation has been used successfully to study many principles of the metabolic pathways in the brain (Riera et al. 2008). It has been recently demonstrated that in spite of the complexity, metabolism shows certain level of homogeneities across cortical networks of the human brain (Hyder et al. 2013a).

Abbreviations: *Glc*, glucose; *GLUT*, glucose transporter; *HK*, hexokinase; *PGI*, phosphoglucose isomerase; *F6P*, β -D-fructose 6-phosphate; *G6P*, α -D-glucose 6-phosphate; *PFK-1*, phosphofructokinase-1; *FI,6BP*, β -D-fructose 1,6-bisphosphate; *GADP*, D-glyceraldehyde 3-phosphate; *PGK*, phosphoglycerate kinase; *PEP*, phosphoenolpyruvate; *PK*, pyruvate kinase; *MCT*, monocarboxylate transporter; *LDH*, lactate dehydrogenase; *PDH*, pyruvate dehydrogenase; *CS*, citrate synthase;

α -KG, α -Ketoglutarate; *SDH*, succinate dehydrogenase; *OAA*, oxaloacetate; *GDH*, glutamate dehydrogenase; *GLT*, glutamate transporter; *AAT*, aspartate aminotransferase; *PAG*, phosphate-activated glutaminase; *GAD*, glutamate decarboxylase.

Postsynaptic and Action Potentials

Neurotransmitters (e.g., Glu, GABA) released into the synaptic cleft in the course of presynaptic neuronal activity will freely diffuse towards neuronal postsynaptic buttons and nearby astrocytic processes. They will cause either excitatory (EPSP) or inhibitory (IPSP) postsynaptic potentials by receptor-specific flows of ions in the postsynaptic neurons. After the genesis of EPSP/IPSP, ionic gradients are reestablished by way of transmembrane ATPases, which consume large amounts of ATP. Action potentials are generated as a consequence of the spatiotemporal integration of these postsynaptic potentials, and they propagate along nerves. The genesis and propagation of these action potentials cause also the breakdown of the ionic balances across cellular membranes and, therefore, require the use of ATP. In the postsynaptic buttons and axons, the required ATP is produced from Pyr through the TCA cycle and electron-transport/oxidative-phosphorylation pathways.

The Glycolytic Pathway

The glycolytic pathway involves breakdown of Glc into Pyr. Glc is continuously delivered from capillaries to the extracellular milieu through GLUT-1. Cells take up extracellular Glc through GLUT-1 (astrocytes) and GLUT-3 (neurons). In different proportions, Pyr and ATP are produced from glycolysis in both cell types. Breakdown steps at different levels can be either impeded or hastened through the activity of many enzymes in this pathway, which constitute checkpoints located in different cellular compartments. The preparatory phase comprises four steps: the first phosphorylation of Glc by enzyme HK (control point G-1), an isomerase reaction of G6P by enzyme PGI, a phosphorylation of F6P by enzyme PFK-1 (control point G-2), and an aldol reaction

on F1,6BP by enzyme ALDO that finally produces DHAP and GADP. DHAP and GADP are rapidly and reversibly interconverted by TPI, a step essential to produce energy efficiently. The payoff phase comprises five steps: a redox reaction on GADP by enzyme GAPDH to form 1,3BPG, a product with high phosphoryl-transfer potential; a substrate-level phosphorylation of 1,3BPG by enzyme PGK (it is the break-even point in glycolysis); a mutase reaction on 3PG by enzyme PGAM, a hydration of 2PG by enzyme ENO; and a substrate-level phosphorylation of PEP by enzyme PK (control point G-3) to produce Pyr and ATP. There are no transmembrane transporters for G6P; thus, Glc cannot leak out of the cells after it is phosphorylated by HK.

The Glycogen-Shunt Proposition

G6P could have two fates, either being converted into F6P by PGI, and thus continuing along the glycolytic pathway, or otherwise being stored as glycogen polymer. Glycogen polymers are considered as one of the largest energy reservoirs in the brain and could be used as an emergency fuel supply during severe energetic stress resulting not only from a pathological condition (e.g., hypoglycemia, cerebral ischemia) but also from high neuronal activity in a healthy brain. Glycogen polymer breakdown preferentially occurs in the astrocytic compartment, but its activation would plausibly seem to be linked to the neuronal compartment. The OGI may be an important link mediating the balance between the glycolytic pathway and glycogen shunt.

The Astrocyte–Neuron Lactate Shuttle

A fraction of around 15% of the Glc oxidized in neurons is not coupled to the total glutamate–glutamine cycle (Hyder et al. 2006). This fraction might represent ATP needed for non-cycling activities. Based on these observations, it has been suggested that the glutamate–glutamine cycle, a two ATP-consuming dual task (i.e., one ATP is used to convert glutamate into glutamine by glutamine synthetase and the other to reestablish the Na⁺ gradient by the activation of the Na⁺/K⁺ -ATPase), might trigger lactate

production by glycolysis in the astrocytes during the course of neuronal activity, so stimulating them to take up extracellular Glc (Pellerin and Magistretti 2004). Lactate so produced may be released for oxidation in adjacent neurons. It is not at all clear where the oxidation of lactate derived from Glc and/or glycogen metabolism may occur (Hertz et al. 2007). Moreover, during activation, glutamatergic activity in neurons seems better preserved by Glc metabolism than by lactate metabolism. The observed increase of lactate under steady-state sensory stimulation has been explained on the basis of stimulation evoked glycolysis and glycogen-shunt pathways (Shulman et al. 2001a, b). Lactate may be taken up into neurons through the monocarboxylate transporter MCT-2, which has the highest affinity for its substrate. An extensive overproduction of lactate must efflux into the circulating blood. In summary, the astrocyte–neuron lactate shuttle may be facilitated by the differential presence of LDH-1 and LDH-1&5 in neurons and astrocytes, respectively. This shuttle may be favored by the existence of monocarboxylate transporters MCT-2 and MCT-1&4 in neurons and astrocytes, respectively.

TCA Cycle and Oxidative Phosphorylation

The majority of ATPs yielded from Glc oxidation are generated by breakdown of carbon skeletons in the TCA cycle and electron donors located inside the mitochondria. The biochemical mechanisms underlying these energy substrates as well as major enzymatic checkpoints inside the TCA cycle and electron-transport/oxidative-phosphorylation pathway are detailed below. The PDH complex performs the decarboxylation of Pyr by enzymes pyruvate dehydrogenase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3). In order to sense the cellular energy charge, two enzymes (i.e., the PDH kinase and the PDH phosphatase) are endowed with a variety of allosteric modulators and covalent modifiers. The TCA cycle comprises eight steps: a condensation of acetyl-CoA by enzyme CS, an isomerization of citrate by enzyme (aconitase), an oxidative decarboxylation of isocitrate by enzyme IDH, an oxidative

decarboxylation of α -KG by the multienzyme complex α -KGDH, a substrate-level phosphorylation of succinyl-CoA by enzyme SCS, a dehydrogenation of succinate by enzyme SDHA (SDHA is tightly bound to the mitochondrion inner membrane through the protein subunits SDHB, SDHC, and SDHD, which all constitute the complex II of the electron-transport chain), a hydration of fumarate by enzyme FH, and a dehydrogenation of malate by enzyme MDH to produce OAA. Energy in the form of ATP and NADH is produced at several points along the entire TCA cycle. Glu can enter the TCA cycle by either oxidative deamination catalyzed by GDH or transamination via the aspartate aminotransferase (AAT), an enzymatic reaction producing aspartate from OAA.

The Glutamate/GABA–Glutamine Cycle

The glutamate (Glu) released by a glutamatergic presynaptic terminal is mainly taken up into astrocytes, although a small portion could flood back into the terminal through the transporter GLT-1b. In the GABAergic synapse, the released GABA is taken up into both the presynaptic terminal and the astrocytes, with the former having higher affinity for the neurotransmitter. Inside the astrocyte, GABA is catabolized to succinate before entering the TCA cycle. The carbon skeleton of this amino acid exits the TCA cycle as α -KG, which is then transformed to glutamate. The Glu is amidated to glutamine (Gln) by glutamine synthetase, an enzymatic reaction that benefits adjacent tissues by consuming and detoxifying free ammonia. The synthesized glutamine returns to the presynaptic terminals of both glutamatergic and GABAergic neurons, with a preference for the former. In both terminals, glutamine is used to regenerate Glu and ammonia via phosphate-activated glutaminase (PAG). The regenerated Glu in the GABAergic presynaptic terminal is converted back into GABA via Glu decarboxylase (GAD).

Oxygen Transport

Since oxygen, unlike Glc, does not have specific transporters to enter the extravascular space, oxygen transport from blood to tissue is mainly driven

by diffusion. Diffusion-limited models suggest that blood flow is the only way by which tissue oxygen capacity can be increased (Buxton and Frank 1997; Gjedde 1997). The prediction of such diffusion-limited oxygen transport models is nonlinear coupling between blood flow and oxygen metabolism. Based on observed linear relationships between blood flow and oxygen metabolism (across regions, conditions, and/or species), other empirically derived models suggest facilitated diffusion through processes like altering number of perfused capillaries and/or intracapillary stacking of erythrocytes (Hyder et al. 1998, 2000). The general assumption in all of these models that all of the oxygen leaving the capillary is metabolized and that there is no oxygen back flux into the blood has been experimentally confirmed (Grieb et al. 1985; Kassissia et al. 1995; Herman et al. 2006).

Major Controversies

- What does underlie the brain functional hyperemia: subthreshold synaptic activity or spiking (Logothetis et al. 2001; Mukamel et al. 2005).
- Are the EEG brain sources purely dipolar in nature (Riera et al. 2012; Gratiy et al. 2013).
- Does oxidatively derived ATP contribute equally to postsynaptic and action potentials (Attwell and Laughlin 2001) across a range of activity levels and/or species (Hyder et al. 2013b)?

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Biophysics of Adaptation in a Computational Model of the Leech T Neuron

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Definition

Adaptation is a change over time in the responsiveness to stimuli. In adaptation to stimulus statistics, this change is relative to statistical properties of the stimulus like the standard deviation. Biophysical models of this phenomenon are computational models of the components of a neuron or a circuit to show the mechanistic basis of adaptation.

Detailed Description

Computational models are instrumental to investigate and understand the mechanisms that shape the spike pattern of a neuron’s response given its synaptic inputs. They can complement experimental approaches by providing insights

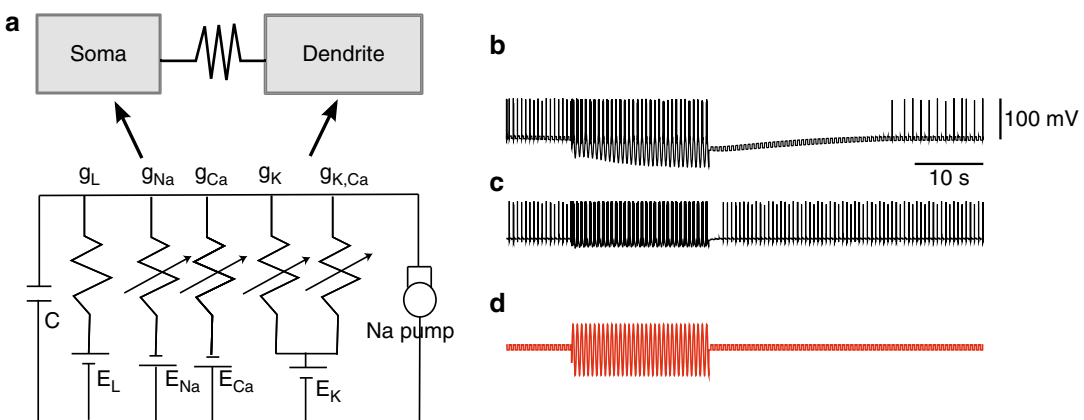
into possible mechanisms. One important feature of many sensory systems is that they can adapt their response to the levels and context of the stimuli. Adaptation of the neuronal response is a process by which the responsiveness of the neuron changes as a result of previous stimulation. In the present case, we had experimentally studied adaptation mechanisms using a mechanosensory neuron of the leech *Hirudo medicinalis* known as the T neuron and built a computational model to further test some of the proposed mechanisms of adaptation to stimulus statistics (Arganda et al. 2007). Here we review how to use a simple two-compartment model to get insight into realistic mechanisms of bursting and adaptation.

An important function of adaptation in the T neuron is to mediate adaptive scaling of neuronal responses to stimulus statistics. Sensory systems have to deal with stimuli that fluctuate in time and even change their scale. A sensory neuron has a limited range of outputs, insufficient to represent all the stimulus values present in a natural context, which can span several orders of magnitude. To efficiently encode naturalistic stimuli, a neuron then needs to adapt its response to the stimulus variance, adjusting its output range to the range of inputs (Wark et al. 2007). This adaptive scaling to the variance of the stimulus distribution

enhances information transmission (Brenner et al. 2000; Sharpee et al. 2006).

Very simplified models, such as “integrate and fire,” are useful for neurons whose spiking output directly reflects the amplitude of the input. More complex responses as the ones discussed here (bursting and adaptation) require the explicit consideration of specific voltage-gated conductances and different biophysical mechanisms. While detailed multi-compartment models including all known conductances of the cell and the neuron’s geometry are more realistic (at least when we know all parameters in some detail), the large number of variables involved makes it difficult to isolate and understand the basic mechanisms responsible for a given response feature. An intermediate approach is to consider a biophysical model including the known experimental conductances of the neuron and look for the minimal ingredients necessary to reproduce a given behavior.

Following this idea, we simplified a detailed multi-compartment model of the mechanosensitive T neuron (Cataldo et al. 2005) and considered only two compartments (soma/axon and dendrite) represented as equivalent electrical circuits and including all known conductances of the T cell (Fig. 1a). Each compartment consists of a membrane capacitance $C = 1 \mu\text{F}/\text{cm}^2$



Biophysics of Adaptation in a Computational Model of the Leech T Neuron, Fig. 1 (a) Two-compartment model of the T neuron including known conductances and the Na⁺ pump. (b) Model response during a stimulation protocol consisting of a low-amplitude periodic train of

pulses followed by an epoch of high-amplitude pulses before returning to the initial, low-amplitude pulses (panel d, in red). (c) Model response after removing the Na⁺ pump

in parallel with the conductances associated to two inward currents (a fast Na^+ current, I_{Na} , and a high-threshold Ca^{2+} current, I_{Ca}); an outward persistent K^+ current, I_K ; a leak current, I_L ; and two outward currents solely regulated by intracellular Na^+ and Ca^{2+} pools, a Ca^{2+} -activated K^+ current, $I_{K,Ca}$, and the Na^+ pump, I_{pump} .

The voltage-dependent currents I_{Na} , I_K , and I_{Ca} are described by Hodgkin-Huxley-type equations. The properties of the Na^+ and K^+ currents were adjusted to reproduce the amplitude, duration, and shape of the action potential of the T cell, as well as the resting membrane potential and membrane time constant of the neuron. The conductance of the leakage channel, I_L , was chosen to obtain values of input resistance in the range of the experimental values. These currents are given by

$$I_{Na}^i = g_{Na} m_{Na}^3 h(V_i - V_{Na})$$

$$I_K^i = g_K n^2 (V_i - V_K)$$

$$I_{Ca}^i = g_{Ca} m_{Ca} (V_i - V_{Ca})$$

$$I_L^i = g_L (V_i - V_L),$$

where the index $i = s, d$ stands for soma or dendrite. Conductances (in mS/cm^2) and Nernst potentials (in mV) are the same for both compartments and are given in Table 1. The activating and inactivating gating variables m , n , and h evolve according to first-order kinetics, $\frac{dm(V_i)}{dt} = [m_\infty(V_i) - m(V_i)]/\tau_m(V_i)$, where the asymptotic values and time constants (in milliseconds) are taken from (Cataldo et al. 2005).

$$m_\infty Na(V_i) = \frac{1}{1 + e^{-(\gamma_i + 35)5}} \tau_{mNa} = 0.1$$

$$h_\infty(V_i) = \frac{1}{[1 + e^{(\gamma_i + 50)9}]^2}$$

$$\tau_h(V_i) = \frac{13.8}{1 + e^{(\gamma_i + 36)35}} + 0.2$$

$$n_\infty(V_i) = \frac{1}{1 + e^{-(\gamma_i + 22)9}}$$

$$\tau_n(V_i) = \frac{5}{1 + e^{(\gamma_i + 10)10}} + 1$$

$$m_{\infty, Ca}(V_i) = \frac{1}{1 + e^{-(\gamma_i + 10)2.8}} \tau_{m, Ca} = 0.6$$

The two outward currents $I_{K,Ca}$ and I_{pump} are modulated by activity and are therefore responsible for different adaptation processes. On the one hand, the Ca^{2+} -dependent K^+ current $I_{K,Ca}$ is fast (Wang 1998; Cataldo et al. 2005) and, in combination with the high-threshold, non-inactivating Ca^{2+} current I_{Ca} , is responsible for the bursting mechanism (Wang 1998; Kepecs et al. 2002). The role of the persistent inward current I_{Ca} is to produce a positive feedback on membrane potential, thus driving a high firing rate, whereas the activity-dependent current $I_{K,Ca}$ generates a slower negative feedback that terminates firing, thus producing a burst of action potentials. Therefore, the $I_{K,Ca}$ current mainly determines burst duration, and its parameters can be tuned to produce the burst duration distribution observed experimentally.

On the other hand, the Na^+ pump acts on a much slower time scale and is responsible for the long refractory times observed after sustained activity (Cataldo et al. 2005). As spiking activity is maintained, the concentration of Na^+ ions inside the cell increases, elevating the activity of the slow Na^+ outward current, I_{pump} . This generates a delayed negative feedback on the membrane

Biophysics of Adaptation in a Computational Model of the Leech T Neuron, Table 1 Nernst potentials and maximum conductances of the ionic currents used in the model

Currents	I_{Na}	I_K	I_{Ca}	I_L	$I_{K,Ca}$	I_{pump}
$V_{\text{Nernst}}(\text{mV})$	45	-62	60	-48	-62	-200
g (mS/cm^2)	350	90	0.5	0.1	3	0.5

potential, hyperpolarizing the membrane in an activity-dependent manner. When firing activity stops, the action of the pump decreases, allowing a slow recovery of the membrane potential.

The two currents modulated by the intracellular Ca^{2+} and Na^+ pools are given by

$$I_{K,Ca}^i = g_{K,Ca} k_{Ca} (V_i - V_k)$$

$$I_{\text{pump}}^i = g_{\text{pump}} k_{Na} (V_i - V_{\text{pump}})$$

where the dynamics of the ion-dependent conductances k_{Ca} and k_{Na} and of the ion concentrations is given by first-order kinetics (Yamada et al. 1998).

$$\frac{dk_{Ca}}{dt} = \frac{[Ca^{2+}] - k_{Ca}}{\tau_{k,Ca}}$$

$$\frac{d[Ca^{2+}]}{dt} = \frac{-[Ca^{2+}] - \alpha_{Ca} I_{Ca}}{\tau_{i,Ca}}$$

$$\frac{dk_{Na}}{dt} = \frac{[Na^+] - k_{Na}}{\tau_{k,Na}}$$

$$\frac{d[Na^+]}{dt} = \frac{-[Ca^{2+}] - \alpha_{Na} I_{Na}}{\tau_{i,Na}}$$

Note that the terms $\alpha_{Ca} I_{Ca}$, $\alpha_{Na} I_{Na}$ represent the increase in intracellular ionic concentrations due to influx of ions through specific channels (I_{Ca} and I_{Na} are negative) and that ion removal is exponential with decay constants $\tau_{i,Ca}$, $\tau_{i,Na}$. Strictly, removal of Na^+ ions should depend on the pump activity, I_{pump} . However, this contribution is very small compared to the influx of sodium due to the fast current, I_{Na} (because I_{pump} is on the order of few pA, while I_{Na} spans tenths of nA), and sodium removal can be modeled using an exponential decay. In the model, we do not consider diffusion of ions between compartments.

Time constants for removal of Ca^{2+} are $\tau_{i,Ca} = 1,250$ ms for soma and 1,000 ms for dendrite. The time constants for Na^+ removal are adjusted to reproduce the delay in response after prolonged periods of activity observed in real T neurons and are set to $\tau_{i,Na} = 16,000$ ms for soma and 20,000 ms for dendrite. Note that these time

constants are one order of magnitude larger than those for calcium to take into account the empirical observation that the decrease in excitability and recovery due to the Na^+ pump is much slower than that due to the $I_{K,Ca}$ (Jansen and Nicholls 1973; Cataldo et al. 2005).

The parameters α_{Na} and α_{Ca} give the proportion of the ionic currents contributing to the sodium and calcium pools, respectively, and are set to $\alpha_{Na} = 0.016$, $\alpha_{Ca} = 0.1$ for the somatic compartment and $\alpha_{Na} = 0.16$, $\alpha_{Ca} = 0.2$ for the dendritic one. Time constants for concentration-dependent conductances take the values $\tau_{k,Ca} = 10$ ms, $\tau_{k,Na} = 100$ ms for both compartments.

With these currents, the membrane potential of both compartments changes in time according to the equations:

$$-C \frac{dV_s}{dt} = I_L + I_{Na} + I_K + I_{Ca} + I_{K,Ca}^s + I_{\text{pump}}^s + g_c (V_s - V_d) / p$$

$$-C \frac{dV_d}{dt} = I_L + I_{Na} + I_K + I_{Ca} + I_{K,Ca}^d + I_{\text{pump}}^d + \frac{g_c (V_d - V_s)}{1 - p} - I_{\text{stim}}$$

where the indices s and d stand for soma and dendrite, respectively. The electrotonic coupling between compartments, given by the parameter g_c , and the ratio of soma to total membrane area, p , also modulate bursting dynamics (Kepecs et al. 2002; Izhikevich 2007). Within our simplified two-compartment model, we choose these parameters to mimic experimental burst sizes when stimulated by a random stimulus with Gaussian distribution and set $g_c = 1.5 \text{ mS cm}^{-2}$ and $p = 0.7$.

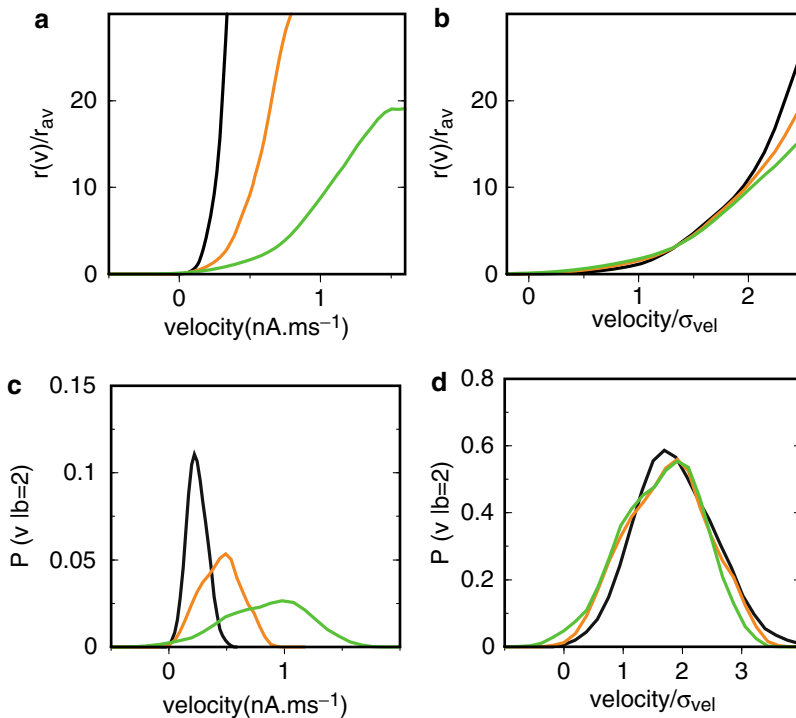
We inject in the dendritic compartment an electrical current I_{stim} with the same features than the mechanical stimulation delivered to real T cells: a slowly varying Gaussian white noise with a frequency cutoff and different standard deviations (Arganda et al. 2007). Note, however, that the mechano-electrical transduction processes are unknown and the amplitude and cutoff frequencies of the stimulus current are not directly comparable to those of the mechanical stimulation. Moreover, the T cell model responds with bursts

only to upstrokes of the stimulus (detects only positive slopes) contrary to the real T cell.

First, we tested if our model neuron was able to reproduce the behavior observed in experiments in response to simple stimulation protocols that hyperpolarize the membrane. We thus injected a current I_{stim} consisting of a train of low-amplitude pulses followed by a long period of high-amplitude periodic stimulation (Fig. 1d), before returning to the low-amplitude train. With the full model, the somatic membrane potential hyperpolarizes in a way similar to the real T cell neuron (Fig. 1b), inducing a latency period of no spiking until the basal resting potential is recovered. To see the role of the sodium pump on this behavior, we repeated the protocol in a model with the current I_{pump} absent from the equations (Fig. 1c).

This rendered a response similar to the T neuron treated with the drug strophanthidin, a sodium pump blocker (Arganda et al. 2007). The small gap that we observe in Fig. 1c is a consequence of the recovery time of the after-hyperpolarization current $I_{K, Ca}$, with a faster time scale than that of the sodium pump.

Once that we had properly modeled the hyperpolarization effect of the sodium pump, we could check its role on coding and adaptive scaling. First, we probed the dynamic range of the bursting neuron model stimulating the dendrite with random stimuli of different amplitudes. The full neuron model is able to respond with a large burst rate (in bursts per second) to moderate stimulus velocities (Fig. 2a) and only saturates at large velocities of the high-amplitude stimulus (green line).



Biophysics of Adaptation in a Computational Model of the Leech T Neuron, Fig. 2 Adaptive scaling of the two-compartment model. (a) Burst rate, $r(v)$, as a function of the stimulus velocity, v , in the two-compartment model, normalized by mean burst rate, r_{av} . Three random stimuli with different amplitudes (standard deviations σ) were used: $\sigma = 4.5$ nA (black line), $\sigma = 9$ nA (orange), and

$\sigma = 18$ nA (green). (b) Normalized burst rate as in (a) versus input velocity rescaled by the standard deviation of the stimulus velocity ensemble. (c) Probability distribution of velocities before bursts of two spikes, for the same stimulus ensembles. (d) Probability distributions prior to bursts of two spikes versus rescaled input velocity

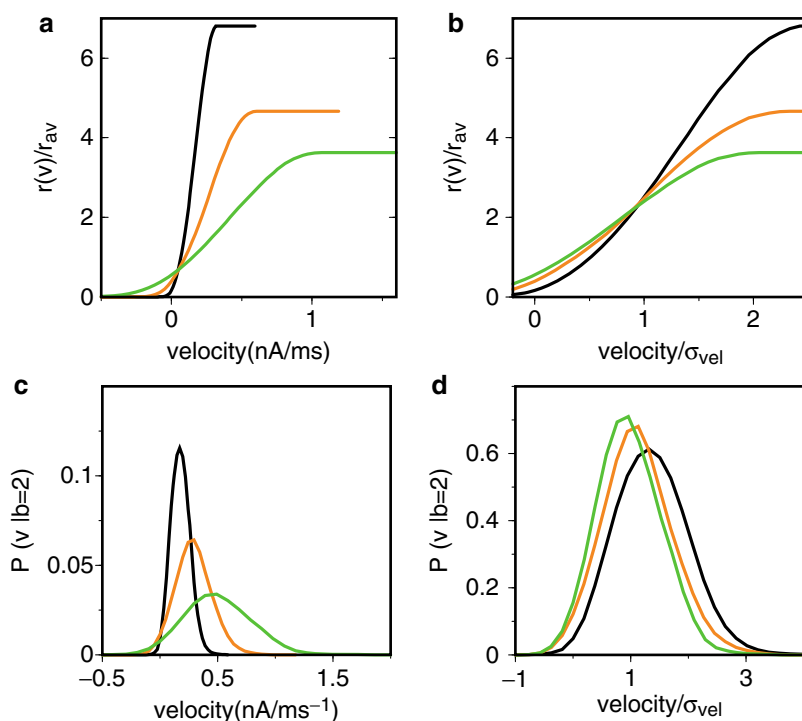
When the input velocity is scaled by the width of the distribution of velocities, we see that burst rates code for a very similar range of scaled velocities independently of the stimulus statistics (Fig. 2b). This adaptive scaling holds for velocities as large as twice the standard deviation of the stimulus, demonstrating that our simple model is able to reproduce the experimentally observed statistical adaptation for burst rates.

Since the neuron also codes information about the stimulus velocity in the duration of bursts, we checked whether the burst code can also adapt to the stimulus statistics. We built the probability distribution of velocities prior to bursts of two spikes, for different stimulus ensembles (Fig. 2c). The probability range increases with

stimulus width (orange and green lines in Fig. 2c), but when velocities are normalized by the standard deviation, the velocity code spans the same range independently of the stimulus ensemble (Fig. 2d).

Next, we investigated the role of the sodium pump in the neuron coding properties. We repeated the stimulation protocols with three different ensembles, but in a model without the I_{pump} current (Fig. 3).

We see that the sodium pump affects both the dynamic range of the neuron response and the adaptive scaling to the stimulus distribution. First, we see that burst rates saturate much earlier (compare Figs. 3a and 2a) and the probability distribution of velocities before bursts span a narrower range (compare Figs. 3c and 2c). This



Biophysics of Adaptation in a Computational Model of the Leech T Neuron, Fig. 3 The sodium pump is responsible for adaptive scaling. (a) Burst rate as a function of the stimulus velocity in the two-compartment model without the sodium pump current, I_{pump} , for three Gaussian stimulus ensembles of different amplitude: $\sigma = 4.5$ nA (black line), $\sigma = 9$ nA (orange), and $\sigma = 18$ nA (green).

Compare to Fig. 2a. (b) Normalized burst rate versus input velocity rescaled by the standard deviation of the stimulus velocity ensemble. (c) Probability distribution of velocities before bursts of two spikes in the model without sodium pump. (d) Probability distributions prior to two spike bursts versus rescaled input velocity

suggests that the response dynamics without the sodium pump is restricted and probably not able to adapt the response to wide stimulus ensembles. This is indeed what we observe when we plot burst rates and probabilities versus the rescaled input velocities (Fig. 3b, d). The rescaled plots show a marked difference between the low- and high-amplitude ensembles especially at large velocities.

We thus conclude that slow activity-dependent hyperpolarization, as that induced by the sodium pump, is a general mechanism to enlarge the dynamic range of a neuron's response and achieve adaptation to the statistical context of the stimulus, providing the flexibility needed for changing real-world stimuli.

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Bistability

► [Multistability: Stopping Events with Single Pulses](#)

BK Channels (KCa1.1)

► [Calcium-Dependent Potassium Channels](#)

Boltzmann Machine

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Synonyms

[Noisy neural network](#); [Stochastic Hopfield network](#)

Definition

Boltzmann machines are usually defined as neural networks in which the input-output relationship is stochastic instead of deterministic (as it is in the original Hopfield network). Then, Boltzmann machines are normally defined as stochastic versions of the Hopfield model or other attractors neural networks. A main difference between Hopfield networks and Boltzmann machines lies in the fact that while in Hopfield networks the deterministic dynamics brings the state of the system downhill, toward the stable minima of some energy function related with some information content, in a Boltzmann machine such *prescribed* states of the system cannot be reached accurately due to stochastic fluctuations. For a

Boltzmann machine, then, the steady-state of the system is characterized by an equilibrium probability distribution to be in such states, which is given, as a function of the energy of such states, by the Boltzmann distribution. The inherent stochastic dynamics of Boltzmann machines allows the system sometimes to go uphill and, therefore, to have some probability to escape from undesirable local minima and reach a global minimum. In practice, this can be done using a *simulating annealing* procedure, that is, start the network dynamics at high temperature and decrease it until an equilibrium state is reached with energy fluctuating around the global minimum. Boltzmann machines are used, for instance, to retrieve or complete patterns distributed according to some predefined equilibrium distribution, and make use of *visible* units which are clamped to the patterns in the training set and *hidden* units which are free-running variables of the system. Boltzmann machines were invented by G. Hinton and T. Sejnowski (1983a, b).

Detailed Description

As in the Hopfield model, the simplest form of a Boltzmann machine is constituted by a network of N binary units or “neurons” whose state is represented by state variables $s_i = 1$ or 0 , $i = 1, \dots, N$. The main difference with Hopfield network arises in the fact that Boltzmann machine units are stochastic. Also, the Boltzmann machine is characterized by an “energy function” characterizing a particular configurational state of the network $\mathbf{s} = (s_1, \dots, s_N)$, and which is defined as in the Hopfield model, that is:

$$E(\mathbf{s}) = -\frac{1}{2} \sum_{\substack{i,j \\ i \neq j}} w_{ij} s_i s_j + \sum_i \theta_i s_i \quad (1)$$

where w_{ij} represents the weight or strength of the link or “synapse” connecting neuron i and j . w_{ij} is assumed to be symmetric, that is $w_{ij} = w_{ji}$ with $w_{ii} = 0$, and θ_i is a “bias” of unit i that represents an activation neuron threshold.

In a Boltzmann machine, the state of a given neuron i is determined by its total input current, or *local field*, defined as

$$h_i(t) = \sum_j w_{ij} s_j(t) - \theta_i,$$

where the bias term is assumed to be fixed. Then, the dynamics of the Boltzmann machine is implemented as follow: given the state of the network at time t , a neuron is chosen at random at time $t + 1$ from the population and its state is updated according with the probabilistic rule

$$\text{Prob}(s_i(t+1) = \sigma) = \frac{1}{1 + \exp[-(2\sigma - 1)\beta h_i(t)]}, \quad (2)$$

with $\sigma = 1, 0$, and $\beta = \frac{1}{k_B T}$ where k_B is the Boltzmann constant and T is a *temperature* parameter that drives the stochastic changes in the neurons. Expression (2) implements the so-called *Glauber dynamics* and can be obtained from the *Hamiltonian* or energy function (1) if one assumes that at each time t the configurational energy of the network is given by $E(\mathbf{s}(t))$. Then, a stochastic change at time t in the state of neuron i from $s_i = \sigma$ to $s_i = 1 - \sigma$ implies a change in this configurational energy given by

$$\begin{aligned} \Delta E_i(t) &= E(\mathbf{s}^i(t)) - E(\mathbf{s}(t)) \\ &= (2\sigma - 1) \left[\sum_j w_{ij} s_j(t) - \theta_i \right] \\ &= (2\sigma - 1) h_i(t). \end{aligned}$$

Here $\mathbf{s}^i(t)$ represents a network state in which the state of neuron i is $s_i(t) = 1 - \sigma$, assuming that the network state $\mathbf{s}(t)$ has $s_i(t) = \sigma$. Equation (2) finally is obtained when $\text{Prob}(s_i(t+1) = \sigma)$ is supposed to be given by the Boltzmann factor, that is

$$\text{Prob}(s_i(t+1) = \sigma) = \frac{e^{-\beta E(\mathbf{s}(t))}}{Z}, \quad (3)$$

where Z is obtained from normalization of Eq. (3), that is:

$$\text{Prob}(s_i(t+1) = \sigma) + \text{Prob}(s_i(t+1) = 1 - \sigma) = 1.$$

The last, then, implies

$$Z = e^{-\beta E(\mathbf{s}(t))} + e^{-\beta E(\mathbf{s}'(t))},$$

and therefore

$$\begin{aligned} \text{Prob}(s_i(t+1) = \sigma) &= \frac{e^{-\beta E(\mathbf{s}(t))}}{e^{-\beta E(\mathbf{s}(t))} + e^{-\beta E(\mathbf{s}'(t))}} \\ &= \frac{1}{1 + e^{-\beta[E(\mathbf{s}'(t)) - E(\mathbf{s}(t))]}} \end{aligned}$$

which has the form given by Eq. (2) using the definition of $\Delta E_i(t)$ above.

The use of Glauber dynamics (2) to describe stochastic changes in neurons in a Boltzmann machine allows to study its equilibrium properties using statistical physics techniques. One can assume, for instance, that this stochastic dynamics drives the Boltzmann machine state into a steady state which is described by a probability distribution $P(\mathbf{s})$. Let's consider as above two configurations or states of the network $\mathbf{s}$ and $\mathbf{s}'$ that differ only in the value that the neuron state s_i takes. Since stochastic changes in each neuron occur independently from the others and using Eq. (3), one has

$$\frac{P(\mathbf{s})}{P(\mathbf{s}')} = \frac{\text{Prob}(s_i = \sigma)}{\text{Prob}(s_i = 1 - \sigma)} = e^{-\beta[E(\mathbf{s}) - E(\mathbf{s}')]}, \quad (4)$$

which implies a steady state distribution

$$P(\mathbf{s}) = \frac{e^{-\beta E(\mathbf{s})}}{Z}. \quad (5)$$

The last has the form of the Boltzmann distribution with the normalization factor $Z = \sum_{\mathbf{s}} e^{-\beta E(\mathbf{s})}$ being the so-called *partition function*. Therefore, $P(\mathbf{s})$ as in Eq. (5) characterizes an equilibrium state of the Boltzmann machine described by the Hamiltonian $E(\mathbf{s})$.

Master Equation Description

Under the probabilistic rule (2), stochastic changes in neurons in a Boltzmann machine occur as in a Markov chain (van Kampen 1990). That is, the dynamics of the state of the network can be view as a Markovian stochastic process whose dynamics is governed by the *master equation*

$$\begin{aligned} \partial_t P_t(\mathbf{s}) &= \sum_i c(\mathbf{s}^i \rightarrow \mathbf{s}) P_t(\mathbf{s}^i) \\ &\quad - c(\mathbf{s} \rightarrow \mathbf{s}^i) P_t(\mathbf{s}), \end{aligned} \quad (6)$$

where $\mathbf{s} = (s_1, \dots, s_i, \dots, s_N)$ and $\mathbf{s}^i = (s_1, \dots, 1-s_i, \dots, s_N)$ are network states which differ in the value of one neuron state, and $c(\mathbf{s}^i \rightarrow \mathbf{s})$ is the transition probability from state $\mathbf{s}^i$ to $\mathbf{s}$. In fact, one has for a Boltzmann machine

$$c(\mathbf{s}^i \rightarrow \mathbf{s}) = \text{Prob}(s_i(t+1) = \sigma) \quad (7)$$

when $\mathbf{s} = (s_1, \dots, \sigma, \dots, s_N)$ and $\mathbf{s}^i = (s_1, \dots, 1-\sigma, \dots, s_N)$. Moreover, a sufficient condition to reach a steady state in Eq. (6) is

$$c(\mathbf{s}^i \rightarrow \mathbf{s}) P(\mathbf{s}^i) = c(\mathbf{s} \rightarrow \mathbf{s}^i) P(\mathbf{s})$$

which is equivalent to Eq. (4) and it is known as *detailed balance condition*. With the choice (7), this condition guarantees that the stationary distribution is $P(\mathbf{s}) = \frac{e^{-\beta E(\mathbf{s})}}{Z}$.

Mean-Field Boltzmann Machines

One can define the mean firing rate of neuron i as

$$m_i(t) \equiv \langle s_i \rangle_t = \sum_{\mathbf{s}} s_i P_t(\mathbf{s}),$$

and the derivative in time of this expression leads to

$$\partial_t m_i = \sum_{\mathbf{s}} s_i \partial_t P_t(\mathbf{s}).$$

Introducing the master equation (6) in the rhs of the last equation gives

$$\partial_t m_i = -2 \langle s_i c(\mathbf{s} \rightarrow \mathbf{s}^i) \rangle_t + \langle c(\mathbf{s} \rightarrow \mathbf{s}^i) \rangle_t,$$

where $\langle \cdot \rangle_t$ means an average over $P(\mathbf{s})$. Using Eq. (7) one gets after some algebra

$$\partial_t m_i = -m_i + \frac{1}{2} + \frac{1}{2} \left\langle \tanh \left(\frac{\beta h_i}{2} \right) \right\rangle_t.$$

The steady state of this dynamics leads to

$$m_i = \frac{1}{2} + \frac{1}{2} \left\langle \tanh \left(\frac{\beta h_i}{2} \right) \right\rangle$$

where now the average is performed over the stationary distribution $P(\mathbf{s})$. Finally using the mean field assumption $s_i \rightarrow m_i$ one obtains

$$m_i = \frac{1}{2} + \frac{1}{2} \tanh \left(\frac{\beta \left(\sum_j w_{ij} m_j - \theta_i m_i \right)}{2} \right),$$

which defines the steady-state mean-field equation for a Boltzmann machine.

Learning in Boltzmann Machines

Boltzmann machines are used to retrieve some particular global states (the training set) distributed according to some external given probability distribution over these states. For this purpose, it is necessary to train the network such that the final weights induce global minima in $E(\mathbf{s})$, associated with the training set and with the highest probabilities according with the external probability distribution. This task cannot be done in standard stochastic Hopfield networks with Hebbian weights since the obtained equilibrium distribution describes minima of the $E(\mathbf{s})$ related with global states, for instance, $\mathbf{s} = \xi$, only with second order correlations among units as maximum. In fact, in this case the minimization of Eq. (5) through gradient descent gives

$$\frac{\partial \ln P(\xi)}{\partial w_{ij}} = \beta \left[\xi_i \xi_j - \sum_{\mathbf{s}} P(\mathbf{s}) s_i s_j \right]. \quad (8)$$

This, in practice, prevents the network from learning global states with correlations that involve more than two units. Such higher order correlated states occur, for instance, in the well know XOR problem, where the global states to be retrieved involve correlations among 3 units. For a Hopfield network with $N = 3$, for instance, there are $2^3 = 8$ possible global states, each one with a probability $\frac{1}{8}$ to occur without previous learning. However, only the patterns (110), (101), (011) and (000) solve the XOR problem, which implies some particular three units structure to be learned by the network, which cannot be implemented by Eq. (8).

To consider higher order correlations to be learned by Boltzmann machines, it is necessary to separate units in the network in two sets, the so-called “visible” units, $v_i, i = 1, \dots, n$ with $n < N$ that are *clamped* during learning to the training set of vectors (which now have only n units) and the “hidden” units, $u_i = n + 1, \dots, N$ which are *free-running* variables of the system. The network state then is $\mathbf{s} = (v_1, \dots, v_n, u_{n+1}, \dots, u_N)$ and the equilibrium steady state distribution (5) can be written now as $P(\mathbf{s}) = P(\mathbf{v}, \mathbf{u})$. We can compute the marginal equilibrium probability distribution for visible units as follow

$$P(\mathbf{v}) = \sum_{\mathbf{u}} P(\mathbf{v}, \mathbf{u}) = \sum_{\mathbf{u}} \frac{e^{-\beta E(\mathbf{v}, \mathbf{u})}}{Z}$$

with

$$Z = \sum_{\mathbf{v}, \mathbf{u}} e^{-\beta E(\mathbf{v}, \mathbf{u})}.$$

$P(\mathbf{v})$ gives, then, the probability of visible units in the free-running system. However, we want these units to be distributed according to some desired probabilities $\bar{P}(\mathbf{v})$ which are the real probabilities of the training set or *environment*. An useful quantity to measure the difference between distributions $P(\mathbf{v})$ and $\bar{P}(\mathbf{v})$ is the Kullback–Leibler divergence or relative entropy (Kullback and Leibler 1951) defined as

$$G = \sum_{\mathbf{v}} \bar{P}(\mathbf{v}) \ln \frac{\bar{P}(\mathbf{v})}{P(\mathbf{v})},$$

which ever is positive or zero. Precisely, G has the minimum zero value when the equilibrium probability $P(\mathbf{v})$ coincides with the desired probability $\bar{P}(\mathbf{v})$. One can use this fact to find an algorithm which learns the training set or environment patterns using a gradient descent of G as follows

$$\Delta w_{ij} = -\eta \frac{\partial G}{\partial w_{ij}} = \eta \sum_{\mathbf{v}} \frac{\bar{P}(\mathbf{v})}{P(\mathbf{v})} \frac{\partial P(\mathbf{v})}{\partial w_{ij}} \quad (9)$$

with $\eta > 0$ being the learning rate and where it is used that the clamped probability $\bar{P}(\mathbf{v})$ is independent of w_{ij} . After some algebra (see for instance Ackley et al. (1985)) one finally obtains

$$\Delta w_{ij} = \eta \beta \left[\langle s_i s_j \rangle_c - \langle s_i s_j \rangle_f \right] \quad (10)$$

where $\langle s_i s_j \rangle_f \equiv \langle s_i s_j \rangle = \sum_{\mathbf{s}} P(\mathbf{s}) s_i s_j$ is the standard average over the equilibrium joint probability $P(\mathbf{s}) = P(\mathbf{v}, \mathbf{u})$ of the free-running system (without being clamped to any external environment state) and $\langle s_i s_j \rangle_c = \sum_{\mathbf{s}} \bar{P}(\mathbf{s}) s_i s_j$ is the average over the equilibrium joint probability $\bar{P}(\mathbf{s}) = \bar{P}(\mathbf{v}, \mathbf{u})$ when the visible units are clamped to the vectors of the external training set (i.e., the standard Hebbian learning term). It is worth noting that in Eq. (10) s_i can be either a visible or a hidden unit in the network.

Learning in Boltzmann machines, as it is given in Eq. (10), can be very slow in practice when many hidden layers are considered, a fact that increases the size of the network. In this case, the system needs a long time to reach its equilibrium distribution, particularly when the system is free-running due to the existence of many local minima. Then, many different approaches have been developed to decrease learning time. One of the most successful of these techniques is to consider some restrictions in the network topology, as in the so-called *restricted Boltzmann machines* where the *visible-visible* or the *hidden-hidden* connections are not permitted, being the

connections between the visible and hidden neurons the only ones allowed.

Cross-References

- [Boltzmann Machine](#)
- [Hopfield Network](#)

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Bottom-Up Attention, Models of

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Definition

- | | |
|-----------|---|
| Attention | A general concept covering all factors that influence selection mechanisms, whether they are scene-driven and bottom-up or expectation-driven and top-down. |
| Salience | Parts of a stimulus (e.g., image, video, audio) that appear to an |

	observer to stand out, relative to their neighboring parts. It is a subjective perceptual quality.
Gaze	A coordinated motion of the eyes and the head that is long enough to concentrate on something. It is a key property of attention in natural behavior.
Scene free-viewing	A task in which participants are asked to look at an image, without any specific instruction. As a default scene analysis task, the free viewing paradigm offers a wealth of insights regarding the cues that attract attention.

Detailed Description

History, Scope, and Organization

Deciphering the computational mechanisms by which the brain deals with the computational complexity of an overwhelmingly high volume of incoming data (at a rate of 10^8 bits/s (Koch et al. 2006)) and how the brain programs eye movements continue to be important problems in neuroscience. Where humans look in images and videos provides important clues regarding how they perceive static (still images) and dynamic scenes (videos), locate the main focus of the image, recognize actions or events, and identify the main participants.

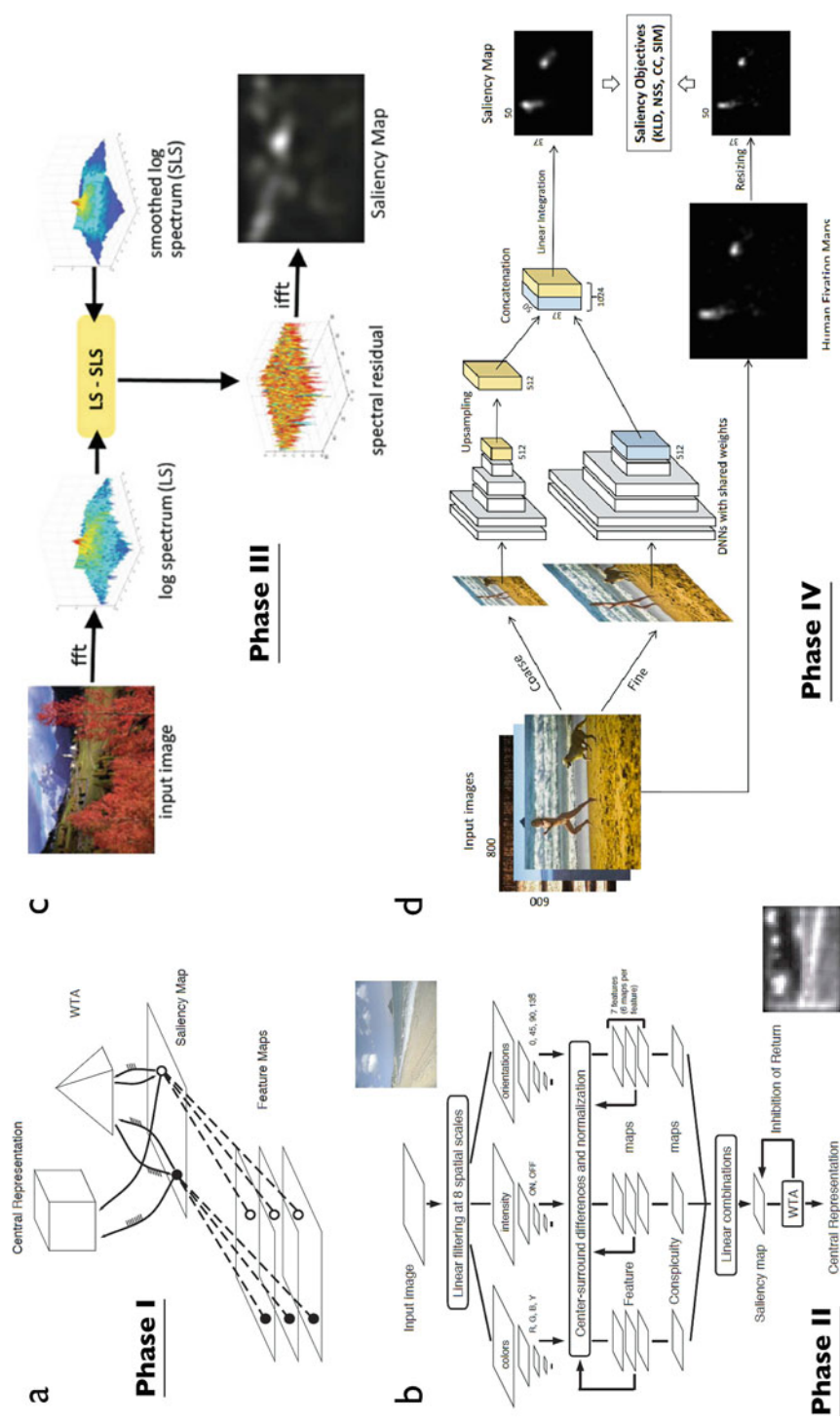
A significant amount of behavioral and computational research on attention has revealed that attention is deployed in two ways: bottom-up (BU) and top-down (TD). The bottom-up component of attention, aka endogenous or stimulus-driven, processes sensory information primarily in a feed-forward manner. Typically, a series of successive transformations are applied to the input visual signal to highlight the most interesting, important, conspicuous, or so-called *salient* regions (Itti and Koch 2001a; Koch and Ullman 1985). In contrast, in top-down attention, aka context-driven or goal-driven, information related to the ongoing behavior, task, or goal is selected (e.g., staying within the road lanes while driving (Land and Lee 1994)). The reader is referred to

Ballard et al. (1995), Borji et al. (2014), Hayhoe and Ballard (2005), Land and Hayhoe (2001), and Navalpakkam and Itti (2005) for reviews of top-down attention studies. Please see also the chapter on top-down attention in this encyclopedia (Schwedhelm and Treue 2015).

Conventionally, bottom-up attention models generate a 2D topographic saliency map, where a value at every location determines how salient that location is, relative to its neighbors. The goal in saliency modeling is then to transform an image into its spatially corresponding saliency map (static saliency), possibly also taking into account temporal relations between successive video frames of a movie (dynamic saliency) (Itti et al. 1998). Early computational saliency models were primarily concerned with identifying conspicuous regions due to low-level feature contrast (e.g., pop-out search). Gradually, however, saliency models have shifted from identifying low-level conspicuous image regions, regardless of where people look (as was the goal in Itti et al. (1998)), to predicting eye movements as a proxy for visual saliency (as was the goal in Bruce and Tsotsos et al. (2005)). Notice that eye movements are only one way of defining the saliency concept and testing saliency models. There is, however, a subtle distinction between the two. Please see Borji et al. (2013b) for a detailed discussion on this. Nonetheless, the recent trend in modeling bottom-up attention and saliency has encouraged researchers to collect increasingly larger eye movement datasets, in particular during free-viewing of natural scenes.

To frame the concepts and models of bottom-up attention so far into a broader picture, we refer to Fig. 1 as a possible anchor to help organize this review. The computational modeling effort will be reviewed in four phases:

- **Phase I:** This phase regards the early computational works (e.g., Koch and Ullman in 1985; Fig. 1a) closely built on top of behavioral hypotheses (e.g., the Feature Integration Theory by Triesman and Gelade).
- **Phase II:** Models in this phase extend and operationalize Phase I models to be applicable



Bottom-Up Attention, Models of, Fig. 1 (continued)

to an unconstrained variety of stimuli (e.g., Itti et al. model in 1998; Fig. 1b). The Itti et al. model spurred a lot of ideas resulting in a myriad of saliency models in phase III.

- **Phase III:** The spectral residual model by Hou and Zhang in 2007 is an example of models in this phase (see Fig. 1c for details on this model). It is a simple model and can be implemented in few lines of code.
- **Phase IV:** Recently, the resurgence and success of neural networks (NN) in computer vision and other areas has brought along a new wave of highly predictive saliency models (Phase IV; Fig. 1d). A notable example here is the SALICON model (Huang et al. 2015), proposed in 2015, in conjunction with the SALICON dataset (Jiang et al. 2015). It is the first model to be trained on a large scale attention dataset.

The principal emphasis in this chapter will be on computational models that can process any visual stimulus in the form of a still image and return a prediction map, the same size as the input image, that can be compared to human or animal behavioral or physiological responses (typically fixations during a task such as free viewing in the context of bottom-up attention) (Rothenstein and Tsotsos 2008). In addition to these models, some other types of models including abstract models, phenomenological models, or models specifically designed for a single task or for a restricted class of stimuli also exist, but will not be covered here

(see Gottlieb and Balan 2010; Itti and Koch 2001a; Rothenstein and Tsotsos 2008; Tatler et al. 2011).

Bottom-up attention models carry value for at least two main purposes. First, they present testable predictions that can be utilized for understanding human attention mechanisms at computational, behavioral, and neural levels. Indeed, a large number of cognitive studies have utilized saliency models for model-based hypothesis testing (e.g., Borji et al. 2013b; Parkhurst et al. 2002). Second, predicting where people look in images and videos is useful in a wide variety of applications across several domains (e.g., computer vision, robotics, neuroscience, medicine, assistive systems, healthcare, and human-computer interaction). Some example applications include gaze-aware compression and summarization, image enhancement, activity recognition, object segmentation, recognition and detection, image captioning, visual question answering, advertisement design, novice training, patient diagnosis, and surveillance. See Borji and Itti (2013) for a review.

In what follows, we first examine key concepts of early bottom-up attention models (section “Bottom-Up Attention Modeling: Pre Deep Learning Era”), followed by a brief overview of deep saliency models (section “Bottom-Up Attention Modeling: Deep Learning Era”), and a discussion of biological plausibility of deep and non-deep saliency models (section “Biological Plausibility of Classic and Deep Saliency

Bottom-Up Attention, Models of, Fig. 1 Four models from four different eras of saliency modeling. **(a) Phase I:** Koch and Ullman (1985) introduced the concept of a saliency map derived from bottom-up inputs from all feature maps, where a winner-take-all (WTA) network selects the most salient location for further processing. **(b) Phase II:** Itti et al. (1998) proposed a complete computational implementation of a purely bottom-up and task-independent model based on Koch & Ullman’s theory, including multiscale feature maps, saliency map, winner-take-all, and inhibition of return. **(c) Phase III:** A myriad of saliency models appeared between 1998 and 2013. Schematic representation of spectral residual model (Hou and Zhang 2007) by Hou and Zhang (2007). The log

spectrum $\mathcal{L}(f)$ is computed from the down-sampled image (with amplitude $\mathcal{A}(f)$ and phase $\mathcal{P}(f)$). From $\mathcal{L}(f)$, the spectral residual $\mathcal{R}(f)$ is obtained by multiplying $\mathcal{L}(f)$ with a local average filter and subtracting the result from itself. The saliency map is then the inverse Fourier transform of the exponential of amplitude plus phase (i.e., $\mathcal{S}(x) = \mathcal{F}^{-1}[\exp(\mathcal{R}(f) + \mathcal{P}(f))]$). **(d) Phase IV:** A new wave of saliency models has emerged with the resurgence of convolutional neural networks (CNNs). Huang et al. (Huang et al. 2015) proposed a deep saliency model, known as the SALICON, that combines information from two pretrained CNNs, each on a different image scale (fine and coarse). The two CNNs are then concatenated to produce the final saliency map

Models”). In section “[Benchmarks, Datasets, and New Data Collection Methodologies](#),” current saliency benchmarks, datasets, and new methodologies for collecting large scale data are explained. In section “[State-of-the-Art Performance](#),” we provide a quantitative comparison of a large number of deep and non-deep saliency models in their ability to predict eye movements during free viewing of natural scenes. Section “[Where Do Models Fail?](#)” explores what current models are missing. Finally, in section “[Discussion and Outlook](#),” we discuss the remaining challenges that need to be addressed in order to build better saliency models.

Bottom-Up Attention Modeling: Pre-deep Learning Era

Computational modeling of bottom-up attention dates back to the seminal theoretical works by Treisman and Gelade (1980), the computational architecture by Koch and Ullman (1985), and the bottom-up model of Itti et al. (1998). Itti et al.’s model was able to predict human behavior in visual search tasks (e.g., pop-out versus conjunctive search (Itti and Koch 2000)), demonstrate robustness to image noise (Itti et al. 1998), detect traffic signs and other salient objects in natural environments (Itti and Koch 2001b), detect pedestrians in natural scenes (Miau et al. 2001), locate military vehicles in overhead imagery (Itti et al. 2001), and – most importantly – predict where humans look during passive viewing of images and videos (Parkhurst et al. 2002; Peters et al. 2005). Note that visual salience does not only depend on the physical property of a visual stimulus. It is a consequence of the interaction of a stimulus with other stimuli, as well as with a visual system (biological or artificial). For example, a color-blind person may have a dramatically different experience of visual salience than a person with normal color vision.

Following initial success, many research groups started exploring the notions of bottom-up attention and visual salience, which gave rise to many computational models from 1998 to 2013. In 2013, we summarized 53 bottom-up models along 13 different factors (Borji and Itti 2013; Borji et al. 2013a). These models fall into

different categories (e.g., Bayesian, learning-based, spectral, and cognitive). The early models mainly computed visual salience from bottom-up features in several feature maps, including luminance contrast, red-green and blue-yellow color opponency, and oriented edges (Itti et al. 1998). Subsequent models incorporated mid- and higher level features (e.g., face and text (Cerf et al. 2009), gaze direction (Parks et al. 2015)) to better predict gaze. A thorough examination of all models in this period is certainly not feasible in this limited space. Instead, we list a number of highly influential static and dynamic saliency models as follows. These include both models that are strongly inspired by biological vision as well as other implementations of saliency that are based on more abstract mathematical definitions.

1. **Static saliency models:** Attention for Information Maximization (AIM) (Bruce and Tsotsos 2005), Graph-based Visual Saliency (GBVS) (Harel et al. 2006), Saliency Using Natural statistics (SUN) (Zhang et al. 2008), Spectral Residual saliency (SR) (Hou and Zhang 2007), Adaptive Whitening Saliency (AWS) (Garcia-Diaz et al. 2012), Boolean Map-based Saliency (BMS) (Zhang and Sclaroff 2013), and the Judd et al. model (Judd et al. 2009).
2. **Dynamic saliency models:** AWS-D (Leboran et al. 2017), OBDL (Hossein Khatoonabadi et al. 2015), Xu et al. (2017), PQFT (Guo et al. 2008), and Rudoy et al. (2013).

Bottom-Up Attention Modeling: Deep Learning Era

Deep learning has emerged as a very successful solution to a variety of problems across several computational domains (LeCun et al. 1998). A deep-learning architecture is a cascade of simple modules that compute nonlinear input–output mappings, and all (or most) of which are subject to learning. A certain type of deep architectures, known as convolutional neural networks (CNN, aka ConvNets) has been very popular. A typical CNN is composed of a series of convolutional layers and pooling layers, followed by one or more fully connected layers. The parameters of the entire network are learned via

backpropagation over a large scale labeled dataset for a certain task (e.g., object recognition). The overall architecture of CNNs resembles the LGN-V1-V2-V4-IT hierarchy of the visual ventral stream, and the convolutional and pooling layers are directly inspired by the classic notions of simple cells and complex cells in the cortex (e.g., Yamins and DiCarlo 2016).

The success of CNNs on large scale object recognition corpuses (Deng et al. 2009) has brought along a new wave of saliency models that perform markedly better than traditional saliency models based on hand-crafted features. To model bottom-up attention, researchers leverage existing deep architectures that are trained for scene or object recognition and repurpose them to predict saliency. Often some architectural novelties are also introduced. These models are trained in an end-to-end manner, effectively formulating saliency as a regression problem. To remedy the lack of sufficiently large scale fixation datasets, deep saliency models are often pretrained on large image datasets and are then fine-tuned on small scale eye movement or click datasets. This procedure allows models to reuse the object-level visual knowledge already learned in CNNs and successfully transfer them to the task of saliency prediction. A large number of deep saliency models have appeared in a relatively short period of time (2014–2018). A detailed discussion of these models goes beyond the scope of this chapter. Instead, we include a number of landmark static and dynamic deep saliency models and refer the reader to Borji (2018), for a comprehensive review. These models differ in their architectures and the way they are trained.

1. **Static saliency models:** eDN (Vig et al. 2014), DeepGaze I and II (Kümmerer et al. 2014), Mr-CNN (Liu et al. 2015), SALICON (Huang et al. 2015), DeepFix (Kruthiventi et al. 2017), SAM-ResNet (Cornia et al. 2016), and EML-Net (Jia 2018).
2. **Dynamic saliency models:** Two-stream network (Bak et al. 2018), Chaabouni et al. (2016), Bazzani et al. (2016), OM-CNN (Jiang et al. 2017), Gorji and Clark (2018), ACLNet (Wang et al. 2018), and SG-FCN (Sun et al. 2018).

To account for differences in viewing static and dynamic stimuli by human observers (Observers view images and videos differently. They have much less time to view each video frame (about 1/30 of a second) compared to 3–5 s over still images. Further, motion is a key component that is missing in still images but strongly attracts human attention over videos (See Rudoy et al. 2013)), traditional video saliency models pair bottom-up feature extraction with an ad hoc motion estimation method that can be performed either by means of optical flow or feature tracking. In contrast, deep video saliency models learn the entire process end-to-end, either by adding temporal information to CNNs (as in (Bak et al. 2018)), or developing a dynamic structure using recurrent neural networks (Hochreiter and Schmidhuber 1997) (as in (Bazzani et al. 2016)).

Biological Plausibility of Classic and Deep Saliency Models

How well do classic and deep saliency models agree with biological findings on visual attention mechanisms? To answer this question, we would like to highlight two key points. First, as explained above, previous research has shown that CNNs can explain the feed-forward mechanisms involved in rapid object recognition (Yamins and DiCarlo 2016). Second, since deep saliency models are built on top of CNNs, they inherit biologically plausible properties of CNNs (e.g., convolution operation). While it is not entirely clear how saliency is computed in these models and whether they work similar to traditional saliency models (e.g., by implementing center-surround operations, normalization, etc.; see Fig. 8), there is evidence that they may generalize classic models. To get an idea, consider a CNN with a single convolutional layer followed by a fully connected layer trained to predict fixations. This model generalizes the classic Itti model and also models built upon it that learn to combine feature maps (e.g., Borji 2012; Judd et al. 2009; Xu et al. 2014). The learned features in the CNN will correspond to orientation, color, intensity, etc., which can be combined linearly by a fully connected layer (or 1x1 convolutions in a fully convolutional neural network). To handle the

scale dependency of saliency computation, classic models often utilize multiple image resolutions. In addition to this technique (as in the SALICON model), deep saliency models concatenate maps from several convolutional layers (as in ML-Net), or combine input from earlier layers in the network with later layers (e.g., using skip connections) to preserve fine details.

Despite the above resemblances, the most evident shortcoming of classic models (e.g., the Itti model) with respect to today's deep architectures is the lack of ability to extract higher level features, objects, or parts of objects. Some classic models remedied this shortcoming by explicitly incorporating object detectors such as face or text detectors. The hierarchical deep structure of CNNs (e.g., 152 layers in the ResNet (He et al. 2016)) allows capturing complex cues that attract gaze automatically. This is perhaps the main reason behind the big performance gap between the two types of models. In practice, however, research has shown that there are cases where classic saliency models win over the deep models (Huang et al. 2015), indicating that current deep models still fall short in fully explaining low-level saliency (See Fig. 8). Further, deep models still fail in capturing some high-level attention cues (e.g., gaze direction, objects of action, relative importance of objects; See Fig. 7).

Our understanding of how saliency computation emerges inside deep saliency architectures and how the mechanisms involved in these models differ from those implemented in deep models for object recognition are still limited. In this regard, recent work on understanding the representations learned by CNNs for scene and object recognition can offer new insights to understand deep saliency models (e.g., He et al. 2019; Zhou et al. 2014).

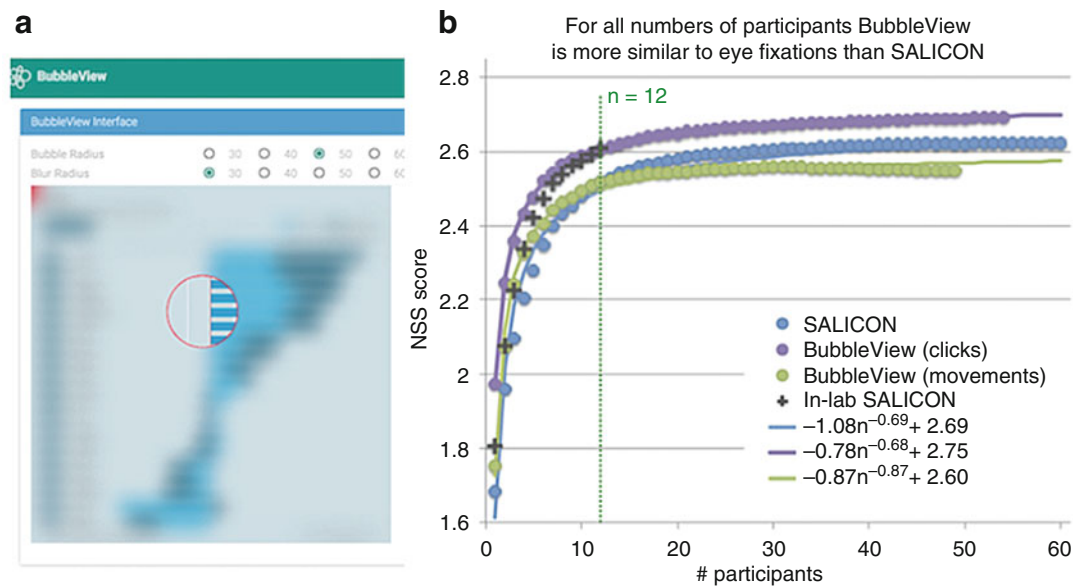
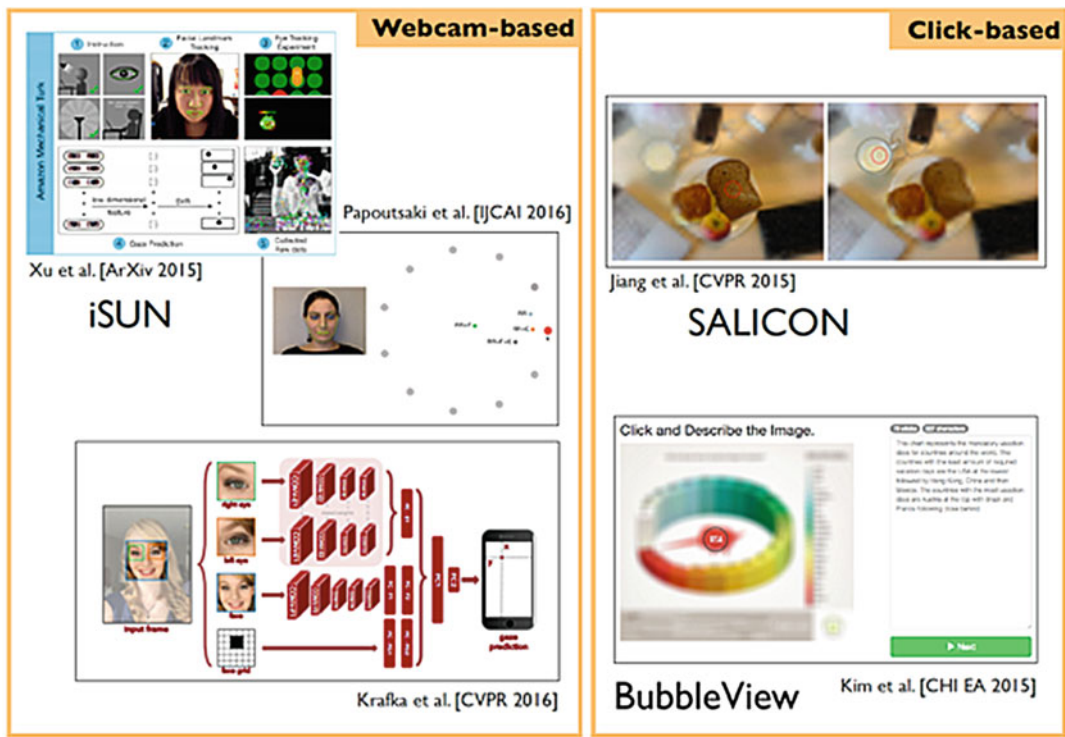
Benchmarks, Datasets, and New Data Collection Methodologies

Benchmarks have been instrumental for advances in computer vision (Borji 2018). In the saliency domain, they have sparked a lot of interest and have spurred a lot of interesting ideas over the past several years. Two of the most influential image-

based benchmarks include MIT (saliency.mit.edu) and SALICON (<http://salicon.net>).

The MIT benchmark is currently the gold standard for evaluating and comparing image-based saliency models. It supports eight evaluation measures for comparison and reports results over two eye movement datasets: (1) MIT300 and (2) CAT2000 (Borji and Itti 2015). As of October 2018, 85 models are evaluated over the MIT300 dataset, out of which 26 are NN-based models (~30% of all submissions). The CAT2000 dataset has 30 models evaluated to date (9 are NN-based). In addition, five baselines are computed on both datasets. The SALICON benchmark is relatively new and is primarily based on the SALICON dataset (Huang et al. 2015). It offers results over seven scores and uses the same evaluation tools as the MIT benchmark. These two benchmarks are complementary to each other. The former evaluates models with respect to actual fixations but suffers from small scale data. The latter fixes the scale problem but considers noisy click data as a proxy of attention. In this review, we provide an overview of the SALICON dataset, since it has been very useful for constructing saliency models, but focus on providing results over the MIT benchmark since fixations provide a closer link to visual attention mechanisms than mouse clicks (Tavakoli et al. 2017).

Traditionally, saliency models have been validated by comparing their outputs on small scale datasets composed of eye movements of humans or monkeys watching complex image or video stimuli (e.g., Bruce and Tsotsos 2005; Parkhurst et al. 2002). New large scale databases have emerged by following two trends: (1) increasing the number of images and (2) introducing new measurements to saliency by providing contextual annotations (e.g., image categories, regional properties, etc.). To annotate these large scale datasets, researchers have resorted to crowd-sourcing schemes such as gaze tracking using webcams (Xu et al. 2015) or mouse movements (Jiang et al. 2015; Kim et al. 2017) as alternatives to lab-based eye trackers (Fig. 2). Deep-supervised saliency models rely heavily on these sufficiently large and well-labeled datasets. Here, we provide an overview of the most recent and popular image



Bottom-Up Attention, Models of, Fig. 2 Left: New crowd-sourcing methodologies to collect attention data including TurkerGaze (Xu et al. 2015), SALICON (Jiang et al. 2015), and BubbleView (Kim et al. 2017). Right: (a) An illustration of BubbleView (Kim et al. 2017) paradigm, (b): The NSS score obtained by comparing mouse clicks and mouse movements to ground truth fixations on natural images on the OSIE dataset (Xu et al. 2014). Each point

represents the score obtained for a given number of participants, averaged over 10 random splits of participants and all 51 images used. It shows that BubbleView clicks better approximate fixations than SALICON mouse movements for all feasible numbers of participants ($n < 60$). It also shows that the clicks of 10 participants explain 90% of fixations (Figure compiled from Kim et al. 2017).

datasets for training and testing saliency models. For a review of fixation datasets pre-deep learning era please consult (Winkler and Subramanian 2013).

- **MIT300:** This dataset is a collection of 300 natural images from the Flickr Creative Commons and personal collections (Bylinskii et al. n.d.). It contains eye movement data of 39 observers, which results in a fairly robust ground-truth to test models against. It is a challenging dataset for saliency models, as images are highly varied and natural. Fixation maps of all images are held out and used by the MIT Saliency Benchmark for evaluating models.
- **CAT2000:** Released in 2015, this is a relatively larger dataset consisting of 2000 training images and 2000 test images spanning 20 different categories such as Cartoons, Art, Satellite, Low resolution images, Indoor, Outdoor, Line drawings, etc. (Bylinskii et al. n.d.). Images in this dataset come from search engines and computer vision datasets. The training set contains 100 images per category and has fixation annotations from 18 different observers. The test, used for evaluation, contains the fixations of 24 observers. Both MIT300 and CAT2000 datasets are collected using the EyeLink1000 eye-tracker.
- **SALICON:** It is currently the largest crowd-sourced saliency dataset. Images of this dataset come from the Microsoft COCO dataset and contain pixelwise semantic annotations. The SALICON dataset contains 10,000 training images, 5,000 validation images and 5,000 test images. Mouse movements are collected using Amazon Mechanical Turk via a psychophysical paradigm known as *mouse-contingent saliency annotation* (Fig. 2). Eye movements sometimes do not match mouse movements (Tavakoli et al. 2017). Nevertheless, this dataset introduces an acceptable and scalable method for the collection of additional data for saliency modeling. Currently, many deep saliency models are first trained on the SALICON dataset and are then fine-tuned on the MIT1000 or CAT2000 datasets for predicting fixations. A similar paradigm known

as the BubbleView (Kim et al. 2017) has also been proposed where a subject has to successfully click on a blurred image to reveal the story of the scene.

State-of-the-Art Performance

A quantitative comparison of static saliency models over the MIT benchmark is presented here (For detailed results please refer to (Borji 2018)). Since our concentration is on the ability of models to predict saliency measured via eye movements, we do not report results on the SALICON dataset.). The MIT benchmark has the most comprehensive set of traditional and deep saliency models evaluated over eight scores. We mainly focus on performances using the AUC-Judd and NSS scores since they provide a better model assessment than others (Bylinskii et al. 2018). The following five baselines are also considered:

1. **Infinite humans:** How well a fixation map of infinite observers predicts fixations from a different set of infinite observers, computed as a limit? See Bylinskii et al. (2018) for details. Prediction is still not perfect due to observer differences.
2. **One human:** How well a fixation map of one observer (taken as a saliency map) predicts the fixations of the other $n - 1$ observers. This is computed for each observer in turn, and averaged over all n observers. Different individuals are more or less predictive of the rest of the population, and so a range of prediction scores is obtained.
3. **Center:** This saliency model is computed by stretching a symmetric Gaussian to fit the aspect ratio of a given image, under the assumption that the center of the image is most salient (Tatler 2007).
4. **Permutation control:** For each image, instead of randomly sampling fixations, fixations from a randomly sampled image are chosen as the saliency map. This process is repeated five times per image, and the average performance is computed. This method allows capturing observer and center biases that are independent of the image (Koehler et al. 2014).

5. **Chance:** A random uniform value is assigned to each image pixel to build a saliency map. Average performance is computed over five such chance saliency maps per image.

Model Comparison over the MIT300 Dataset

Figure 3 shows the model performance over the MIT300 dataset. According to the AUC-Judd and NSS scores, the top five models are all NN-based. Using the AUC-Judd measure, DeepGaze II, and EML-NET models hold the top two spots. The *infinite humans* baseline performs the best. While models perform close to each other according to the AUC-Judd score, switching to NSS widens the differences. EML-NET has the highest score. The *infinite humans* baseline achieves the best NSS. The second and third ranks here belong to CEDNS and DPNSal models. BMS is the best-performing non-NN-based model and ranks better than the deep eDN model. The majority of models significantly outperform all the baselines, except the *infinite humans* baseline. Among baselines, *one human* and *center* predict fixations better than *permutation* and *chance*. For details please see Borji (2018).

Majority of the top 30 models are NN-based. Comparing the best results pre- and during the deep learning era shows significant improvements in terms of NSS and AUC scores. At the same time, the gap between the best model and the *infinite humans* baseline has also reduced.

Model Comparison over the CAT200 Dataset

Figure 4 shows the results over the CAT2000 dataset. According to the AUC-Judd measure, SAM-ResNet, SAM-VGG, and CEDNS are tied in the top but still below the *infinite humans* baseline. EML-NET, the winner on the MIT300 dataset, is ranked second here (tied with DeepFix). Switching to NSS, CEDNS performs slightly better than SAM-ResNet, SAM-VGG, and EML-NET. Among classic models, BMS (Zhang and Sclaroff 2013) and EYMOL (Zanca and Gori 2017) perform better than the others. Overall, models that do well over the MIT300 dataset perform well here as well.

There is a 3.5% improvement from the best non-deep model to the best deep model in terms

of AUC-Judd. The performance gap between the best non-deep model and the *infinite humans* upper-bound is 5.55% and shrinks to 2.22% using the best deep learning model (based on the AUC-Judd measure).

A qualitative comparison of model predictions over a sample image from the CAT2000 dataset is presented in Fig. 5. It shows large differences in appearance of the maps generated by different models. As it can be seen, recent deep models generate saliency maps that are very similar to the ground truth fixation map on this image, better than their non-deep predecessors.

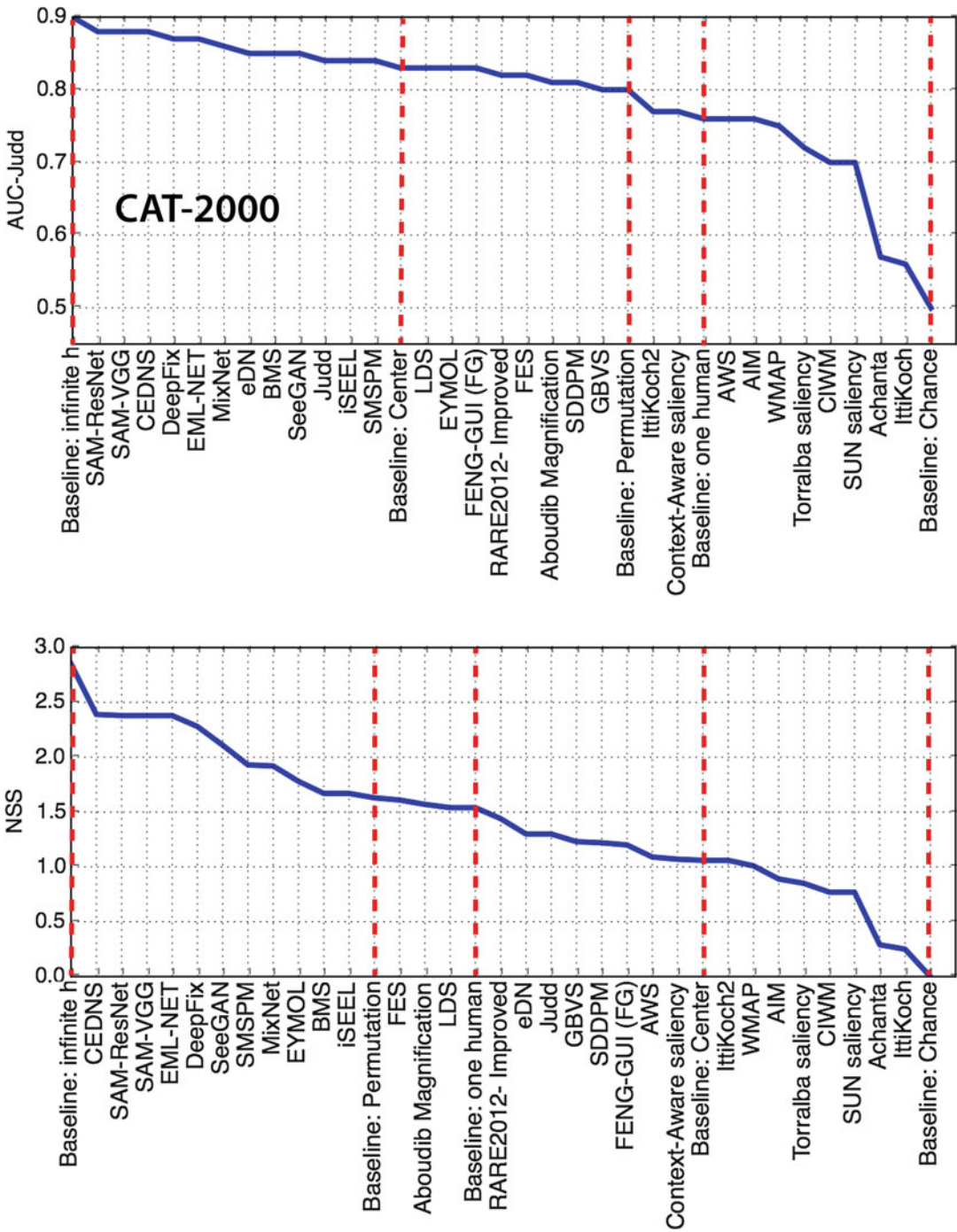
Overall, results show that new neural network-based saliency models have created a large gap in performance relative to traditional saliency models from the pre-deep learning era. However, they still fall short in performing at the level of humans on this task as is demonstrated in Fig. 6. Further, they suffer from several shortcomings that need to be addressed, and will be discussed next.

Where Do Models Fail?

As we saw above, deep learning models have shown impressive performance in saliency prediction. A deeper look, however, reveals that they continue to miss key elements in images (Fig. 7).

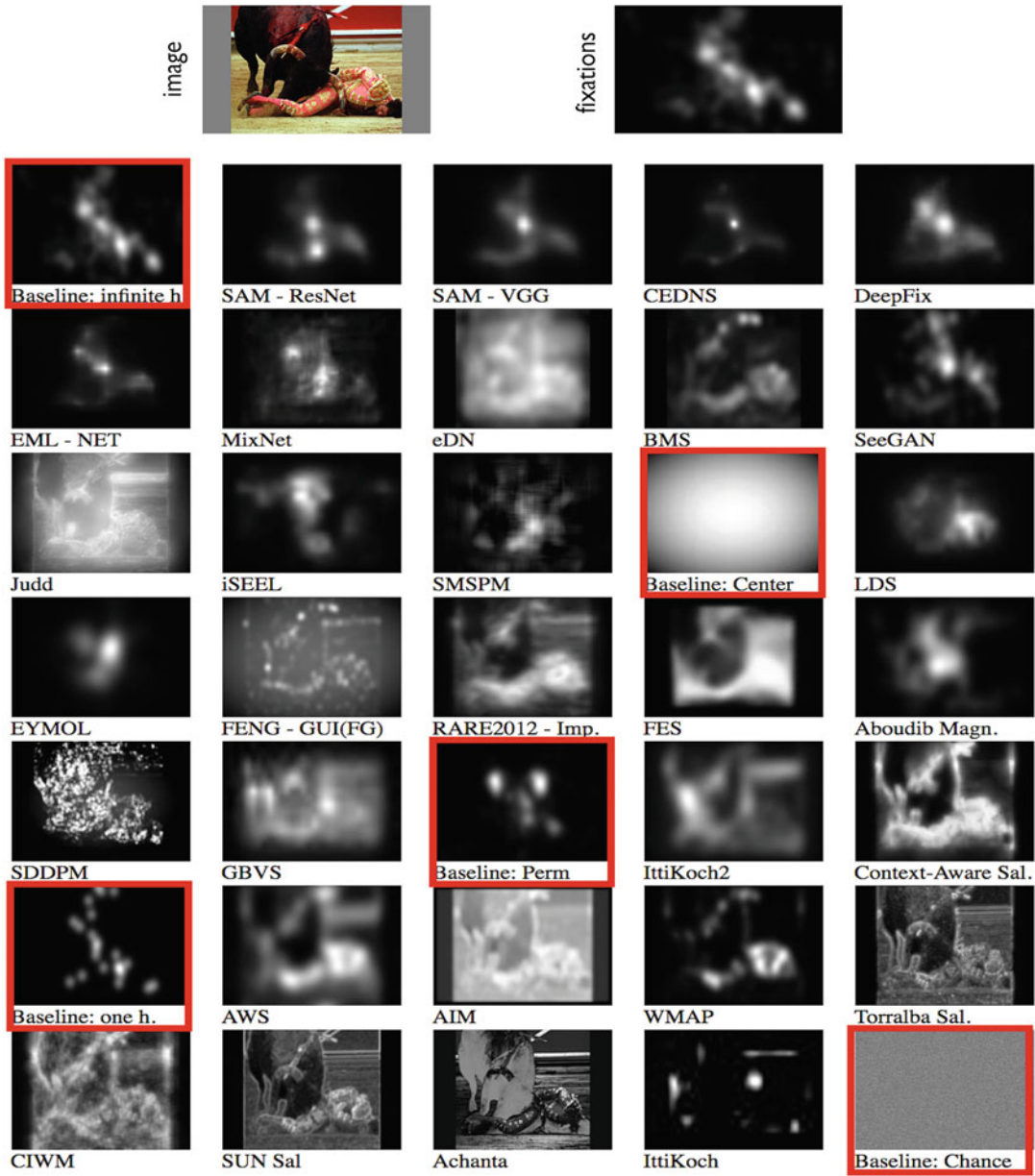
In Bylinskii et al. (2016), we investigated the state-of-the-art image saliency models using a fine-grained analysis on image types, image regions, etc. In a behavioral study, conducted via Amazon Mechanical Turk, workers were asked to label (1 out of 15 choices) image regions that fall on the top 5% of the fixation heatmap. Analyzing the failures of models on those regions shows that the majority of the errors made by models are due to failures in accurately detecting parts of a person, faces, animals, text, objects of action, and gaze direction. These regions carry the greatest semantic importance in images (Fig. 7a & b). One way to ameliorate such errors is to train models on more instances of faces (e.g., partial, blurry, small, or occluded faces, non-frontal views), more instances of text (different sizes and types), and animals. Saliency models may also need to be trained on different tasks, to learn to detect gaze and action and leverage this information for

B



Bottom-Up Attention, Models of, Fig. 4 Performance of 30 saliency models and 5 baselines (marked with dashed red lines) for fixation prediction over the CAT2000 dataset.

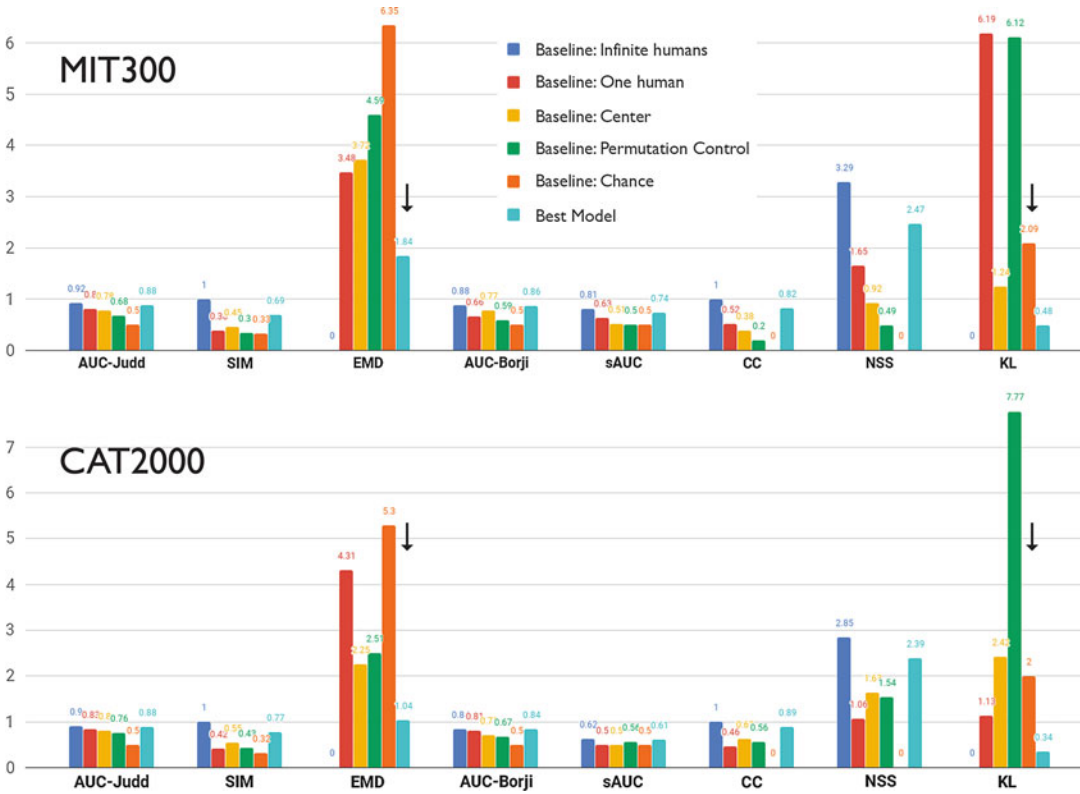
Models are sorted in terms of the AUC-Judd (top row) and NSS (bottom row) scores. Infinite h. stands for *infinite humans* baseline



Bottom-Up Attention, Models of, Fig. 5 Saliency prediction maps of 35 models (including 5 baselines) on a sample image from the CAT2000 dataset (See the MIT benchmark webpage: saliency.mit.edu). Red boxes illustrate baselines

saliency. Moreover, saliency models need to reason about the relative importance of image regions, such as focusing on the most important person in the room or the most informative sign on the road (Fig. 7c, d & e). Interestingly, when we added the missing regions to models, performance improved drastically (Bylinskii et al. 2016). This

has been corroborated by several other studies that showed augmented deep saliency models perform better than original models (e.g., Gorji and Clark 2017, 2018; Recasens et al. 2015). Previous research has also identified cases where deep saliency models produce counterintuitive results relative to models based on feature



Bottom-Up Attention, Models of, Fig. 6 Performance of five baselines and the best saliency model (can be different for each score) for predicting fixations over two eye movement datasets (MIT300 and CAT2000) using eight scores. For EMD and KL, the lower the better (downward arrows). As it can be seen, the best model

often wins over the baselines except *infinite humans* baseline, indicating a gap between the best models and humans in saliency prediction. The gap is wider for some scores (e.g., NSS, EMD) and narrower using some other scores (e.g., AUC-Borji, sAUC). This holds over both datasets

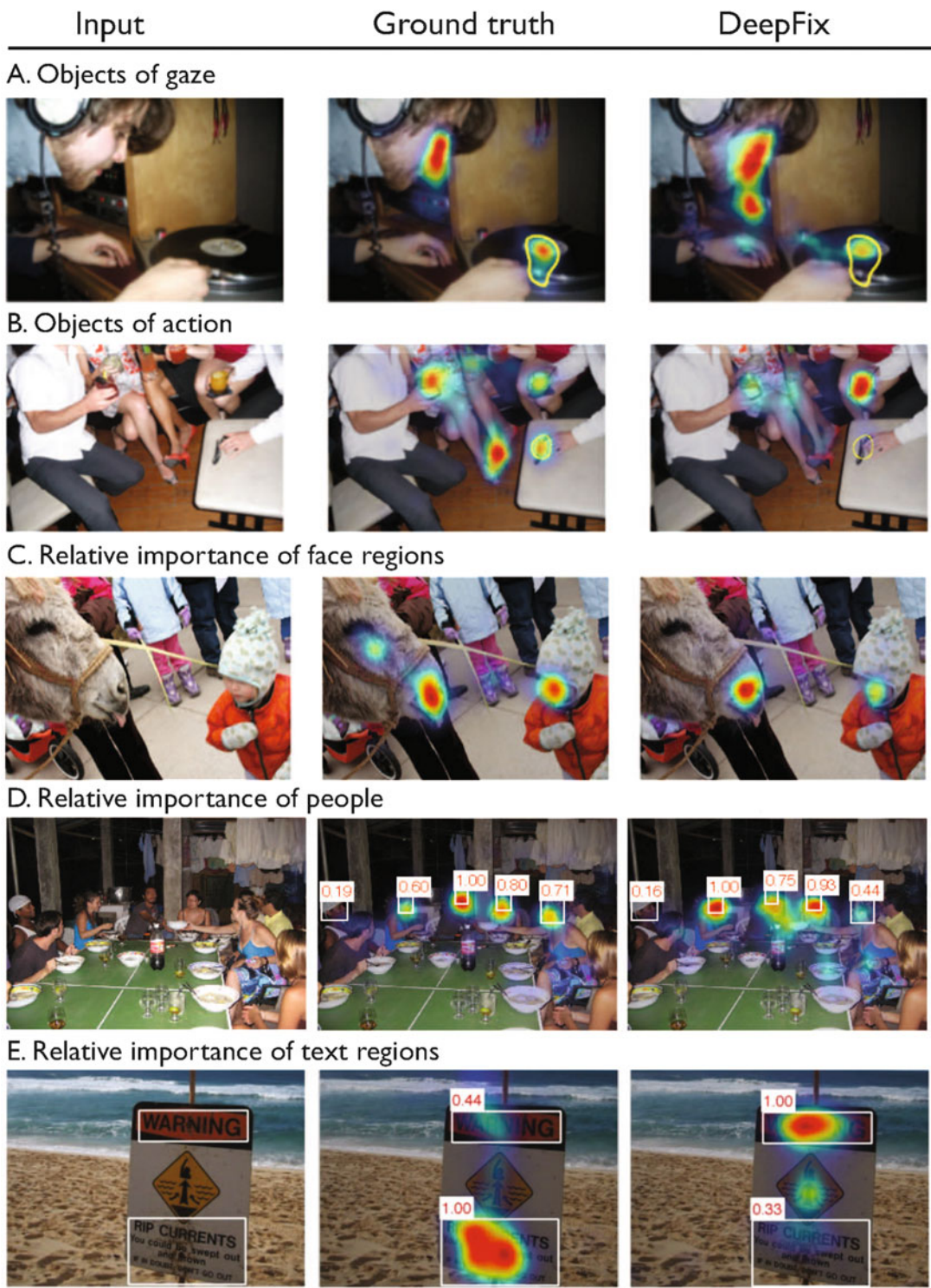
contrast. For example, Rahman and Bruce (2015) and Huang et al. (2015) showed that, unlike the classic Itti et al. model, new saliency models fail to highlight odd items in pop-out psychological patterns (Fig. 8).

Discussion and Outlook

Saliency prediction performance has improved dramatically in the last few years, in large part, due to deep supervised learning and large scale mouse click datasets. We also have a much better understanding of challenges pertaining to model evaluation than before. The new NN-based models are trained in a single end-to-end manner, combining feature extraction, feature integration, and saliency value prediction, and have created a large gap in performance relative to traditional

saliency models. The success of these saliency prediction models suggests that the high-level image features encoded by deep networks (e.g., sensitivity to faces, objects and text), as well as the ability of CNNs to capture global context are extremely useful for predicting fixation locations. Despite the immense recent progress, however, saliency prediction is far from being solved and there continues to be a big room for improvement. Some areas in which improvement can be made are discussed below:

- Saliency models based on deep learning are good face and text detectors, much better than their non-deep predecessors. The degree to which these models perform in face and text detection, compared to the state-of-the-art face



Bottom-Up Attention, Models of, Fig. 7 (continued)



B

Bottom-Up Attention, Models of, Fig. 8 Example stimuli where deep saliency models produce counterintuitive results relative to models based on feature contrast. Sometimes deep models neglect low-level image features (local contrast) and overweight the contribution of high-level features (e.g., faces or text). Some of the failure cases might be due to the fact that deep saliency models compute

absolute saliency and not relative saliency (See section “[Biological Plausibility of Classic and Deep Saliency Models](#)”). Although fixations are not recorded on these images, it is easy to predict where participants will typically fixate. See Huang et al. (2015); Rahman and Bruce (2015) for more details

and text detectors, still remains to be determined.

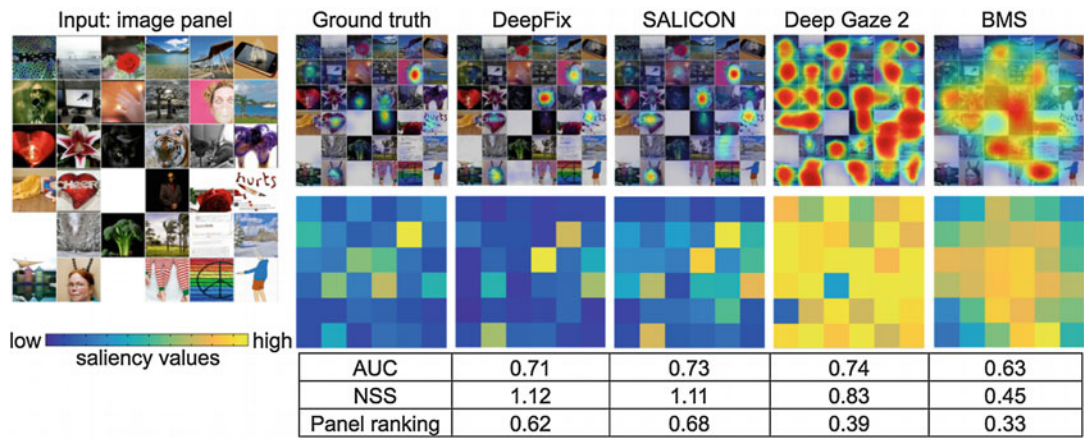
- Even the best saliency models tend to place a disproportionate amount of importance on face regions, humans, and text even when they are not necessarily the most semantically interesting parts of the image. Saliency predictors will need to reason about the relative importance of image regions, such as focusing on the most important person in the room or the most informative sign on the road (which is image- and context-dependent). Similarly, in the presence of several text regions in the image, some high-level understanding of meanings is necessary to prioritize different text regions (e.g., what is the warning sign about?).
- There has been a lot of progress in understanding the representations learned by CNNs for scene and object recognition in recent years (e.g., Zhou et al. 2014). Our understanding of what is learned by deep saliency models, however, is limited. The main questions here are how saliency computation emerges inside deep saliency architectures, and how the patterns in different network layers learned for saliency

prediction differ from those patterns learned for object recognition? We have recently started to look into this (See He et al. 2019).

- Fair saliency model comparison still remains an unsolved research problem today. Active research is ongoing to understand the pros and cons of the saliency measures (e.g., Kummerer et al. 2018). Many of the current saliency methods compete closely with one another at the top of the existing benchmarks and performances vary in a narrow band (See Figs. 3 and 4). Also, as we saw in section “[State-of-the-Art Performance](#),” some evaluation measures have begun to saturate and the produced rankings by different models are often inconsistent with each other. Thus, as the number of saliency models grows and score differences between models shrink, evaluation measures should be adjusted to a) elucidate differences between models and fixations (e.g., by taking into account the relative importance of spatial and temporal regions) and b) mitigate sensitivity to map smoothing and center-bias. Complementary to measures, finer-grained stimuli such as image

Bottom-Up Attention, Models of, Fig. 7 While deep learning models have shown impressive performance for saliency prediction, a finer-grained analysis shows that they miss key elements in images. Some example stimuli for which models (here DeepFix model (Kruthiventi et al. 2017)) under- or overestimate fixation locations due to gaze direction (a), or locations of implied action or motion

(b) are shown. Also, models fail to detect small faces or profile ones, and fail to assign correct relative importance to them (c). Cases for which models do not correctly assign relative importance to people (d), or text regions (e) in the scene are also shown. Please see text and Bylinskii et al. (2016) for further details



Bottom-Up Attention, Models of, Fig. 9 A finer-grained test proposed in Bylinskii et al. (2016) for determining how saliency models prioritize different subimages in a panel, relative to each other (left). A panel image from the MIT300 dataset (right). The saliency map predictions given the panel as an input image. The maximum response

of each saliency model on each subimage is visualized (as an importance matrix). AUC and NSS scores are also computed for these saliency maps. The panel ranking is a measure of the correlation of values in the ground truth and predicted importance matrices (Figure from our work in Bylinskii et al. (2016)).

regions in a collection or in a panel (as in Fig. 9 to measure how well models predict the relative importance of image content), psychophysical patterns (pop-out search arrays and natural oddball scenes), as well as transformed images can be used to further differentiate among models.

- Collecting large scale data for constraining, training, and evaluating attention models is crucial to progress. Bruce et al. (2016) pointed out that the manner in which data is selected, ground truth is created, and prediction error is measured (e.g., loss function) is critical to model performance. Large scale click datasets (Huang et al. 2015; Kim et al. 2017) have been highly useful to train deep saliency models and to achieve high accuracy. However, clicks occasionally disagree with fixations. Thus, separating good clicks from noisy ones can improve model training. Moreover, studying discrepancies between mouse movements and eye movements, collecting new types of image and video data, as well as refining available datasets can be rewarding.

In this review, we examined the recent progress in saliency prediction and proposed several

avenues for future research. In spite of tremendous efforts and huge progress, there continues to be room for improvement in terms of finer-grained analysis of deep saliency models, evaluation measures, datasets, annotation methods, cognitive studies, and new applications.

Cross-References

- [Attentional Top-Down Modulation, Models of](#)
- [Hierarchical Models of the Visual System](#)
- [Working Memory, Models of](#)

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Braided Electrodes

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Definition

Braided electrodes consist of multiple, independent fine wires that are braided around a stiff core or needle that is used to aid insertion.

Detailed Description

The braids are like a textile or fabric covering around a stiff core. This needlelike core is needed to shape the braid initially and can also be used as an aid for insertion into tissue. It is removed after insertion for chronic applications to allow the braid to move with the tissue and reduce its footprint in the tissue. Each wire in a braid is a separate conductor, i.e., microelectrode. These wires can be used for either recording or stimulation depending on the material used and the impedances of the active sites (Figs. 1 and 2).

Rationale for Braided Electrodes: Braided electrodes take advantage of two things: (a) the flexibility/compliance of ultrafine microwires and (b) the structure and strength of interwoven strands.

The stability of chronic electrode implants is influenced among other things by (a) the compliance, (b) the size, and (c) the biocompatibility and

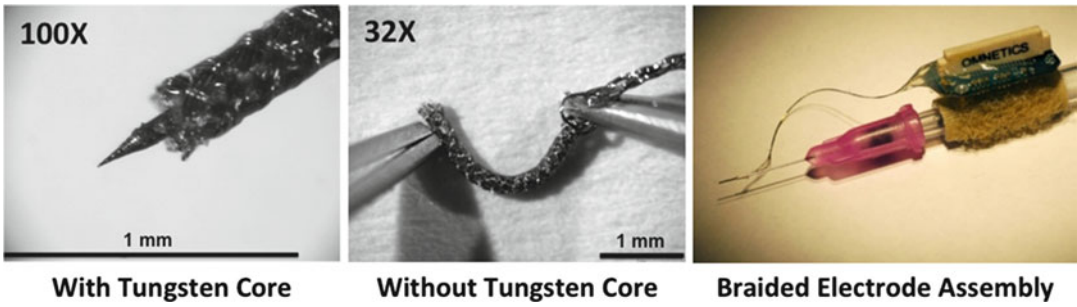
coatings of the implanted structure (Branner et al. 2004; Hochberg et al. 2006; Misra et al. 2013). The compliance of a single wire scales as the cube of the length over radius to the fourth power (e.g., Head et al. 1989; Kim et al. 2013). This means that the degree of stress and strain in the tissue surrounding an implanted electrode is reduced as electrode wires become thinner and longer. The conductance of the rodlike electrode members will only reduce as a function of the second power of radius reductions, so conductance is not an issue as wires get thinner.

Fifty micron wires are routinely used to record neural activity. Given the relationships mentioned above, creating a neural interface of a collection of independent 10 μm wires will significantly improve the compliance of the ensemble and increase recording electrode density while potentially preserving wire conductance within the operating range of current and conventional headstages and amplifiers used in single-unit recording.

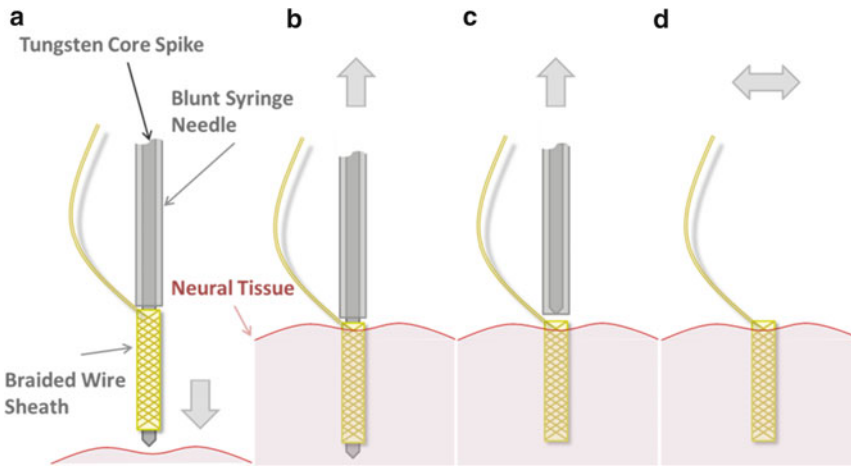
Mechanical Testing: Mechanical bending tests have shown that the implanted portion of braided microelectrodes consisting of either 12 or 24 ultra-fine wires (9.6 μm or 12.7 μm) had 4–21 times better mechanical compliance than a single 50 μm wire. The wired connections between an implant and a percutaneous connector also play a vital role in the long-term performance of an implant since these tethers can produce forces on the implant. The mechanical compliance of the bundles of ultrafine wires were 6–96 times better than the compliance of a single 50 μm wire (Kim et al. 2013).

Histology: Short Summary of Histology

Different Types of Braided Electrodes: Braids are made from various topologies of interwoven strands (Ko and colleagues, 4). The mechanical properties of precisely braided composites offer several advantages that are presently utilized in textiles and modern composite materials (e.g., various sports equipment and body armor). Examples of topologies for microelectrode braids are



Braided Electrodes, Fig. 1 Examples of braided electrode probe assemblies and springy flexibility of braided probes after core removal (From Kim et al. 2013 with permission)



Braided Electrodes, Fig. 2 Stages in braided probe insertion and deployment. (a) Assembly. (b) Insertion of assembly. (c) Removal of core leaving only braid. (d)

Remaining braid/tether probe after deployment (Reproduced from Kim et al. 2013, with permission)

(a) tubular braids, (b) 3D braids, and (c) figured braids:

- (a) Tubular braids form the simplest assemblies with symmetric repeating patterns. The recording sites are located at the ends of the wires which roughly puts them in a circular arrangement at a particular depth below the tissue surface.
- (b) 3D braids are similar to tubular braids as they consist of symmetric repeating patterns, but the recording sites for each wire in the braid are placed at varying locations throughout the braid. This allows a more distributed placement of recording sites in the tissue.

(c) Figured braids do not have a symmetric repeating pattern but have systematic alterations in the braid pattern through the structure to alter compliance or to assemble wires in specific groupings and to aid in the placement of recording sites along the braid.

Special Techniques Enabled by Braiding

Combinatorics

The two characteristics of combinatoric probes are that (a) each wire has multiple recording sites along its length and (b) the recording sites of different wires are organized in a patterned braid into unique combinations of electrodes such as

stereotrodes or multitrodes. Gerstein and Clark showed in 1964 that it was possible to record multiple classifiable single-unit action potentials from multiple 5–10 μm exposed recording points spaced along a single 10 μm Tungsten microelectrode (Gerstein and Clark 1964). We have also observed that two electrically connected electrodes in a Utah array can occasionally still record single units, but both channels record the same activity. Based on their results and our observations, and back-of-the-envelope calculations of theoretical electrical networks, signals from separate recording sites along one such electrode wire will roughly add (Fig. 3).

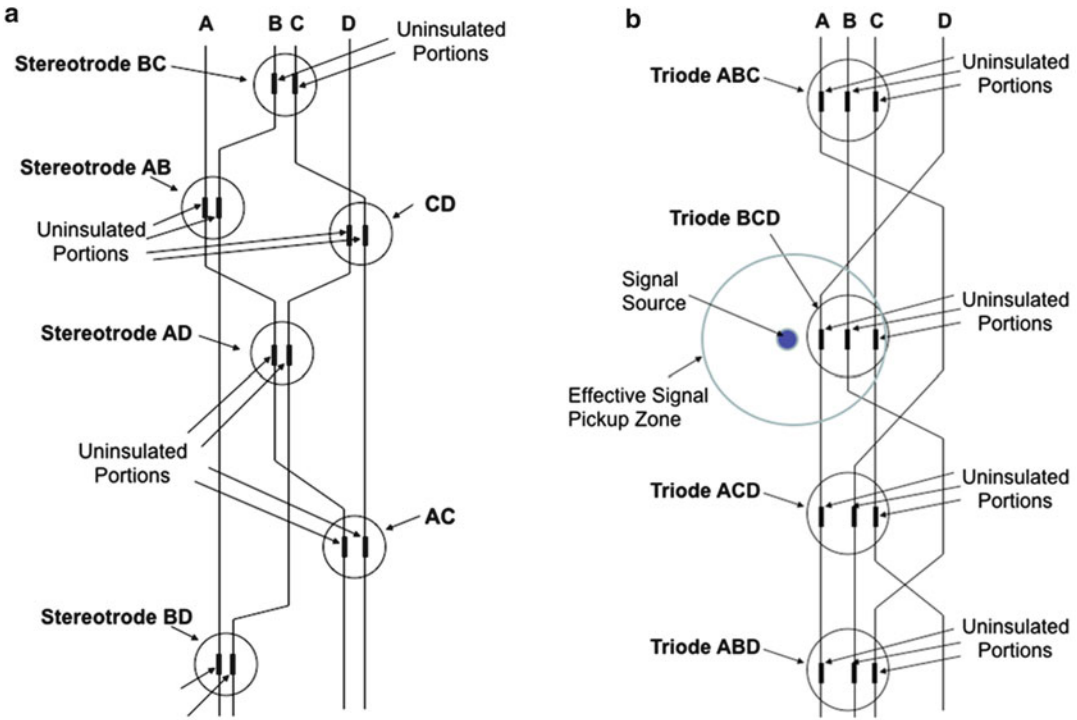
Under the assumption that most single-unit pickup near a spatial site will simultaneously co-occur on each of the wires that comprise the spatial site in a braid, a neuron in a combinatoric electrode will have a “signature.” That is, a unit can be spatially assigned based on the unique collection of wires on which it co-occurs. The combinatoric probe is thus an innovation that exploits principles

of stereotrode/tetrode methods (Gray et al. 1995) for multisite wires organized into a 3D combinatoric pattern. Because we know which electrodes picked up a particular event, cross-correlated patterns of recorded spikes can then be separated out into their location of origin on the probe in most instances. Some activity may remain spatially undefined in cases of limited (thus ambiguous) pickup. The improved yield of units in a combinatoric arrangement of n wires arranged in groups of k recording points per spatial site from combinations of recording points on multi-recording-point wires can potentially be huge.

$$nC_k \text{ or } \binom{n}{k} = \frac{n(n-1) \dots (n-k+1)}{k(k-1) \dots 1},$$

ie, $\frac{n!}{k!(n-k)!}$

The yield improvement arises from the process of arranging recording points on wires into many



Braided Electrodes, Fig. 3 Combinatorics concept examples. (a) A “4 choose 2” combinatorics probe with two recording points per wire, and six spatial location sites

AB, BC, CD, AC, AD, and BD. (b) A “4 choose 3” combinatorics probe with three recording points per wire, and four spatial location sites ABC, BCD, ACD, and ABD

or all of the possible combinations at spatial sites. For example, in Fig. 3a, we show four wires with four recording points each. In Fig. 3a, we obtain ${}_4C_2$ spatial sites ($4 \text{ choose } 2$) = 6 stereotrode sites. In Fig. 3b, we employ four wires, each with three recording points, used in triode groupings, and obtain ${}_4C_3$ ($4 \text{ choose } 3$) = 4 triode sites, compared to a single tetrode site. Accordingly, a braid of six wires allows ${}_6C_4$ spatial sites, which gives 15 tetrode sites, composed using only six multisite wires, each wire with ten recording points.

For this recording strategy to provide unambiguous unit data the firing must ideally be sparse, largely desynchronized on a millisecond time scale, and loss of data or spatial precision due to occasional collisions must be acceptable for the use and algorithms applied to recorded data. One determining factor for collision likelihood is the number of recording points per wire. A 24-count braid organized as tetrodes allows up to ${}_{24}C_4$, i.e., 42,504 uniquely coded spatial sites. The collision likelihood per wire in the probe with sufficient recording points to fully span the potential 42,504 separate spatial sites would clearly be unacceptably large. In contrast the number of spatial sites that are possible using 4–6 recording points per wire would still be an improvement compared with current conventional designs, while the likelihood of the collisions on a wire would probably be acceptable. For example, settling on limiting the design to only four recording points per wire allows 24 spatially separate tetrodes to be very simply constructed within the 24-wire tubular braid, allowing ~4 times the unit yield per wire compared with using six separate tetrodes. Optimized recording arrangements in this combinatoric design space will thus depend on the neural density, average firing frequency, and spatial firing pattern statistics and the collision tolerance of the applications and analysis algorithms using the data.

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Brain Architecture Management System (BAMS)

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Definition

The Brain Architecture Management System (BAMS; <http://brancusi.usc.edu>) is an online publicly accessible neuroinformatic platform designed to handle neurobiological information at different organization levels of the vertebrate central nervous system (CNS).

Detailed Description

BAMS Structure

The backend database of BAMS is implemented in the latest MySQL public version, MariaDB (<http://mariadb.org>). The backend structure of BAMS is modular, with the *Brain Parts* module

as the center of the system. Any brain part (gray matter regions, fiber tracts, and ventricles) are uniquely defined in BAMS by a tuple made of its name, the nomenclature used to identify and name it, the nomenclature version, and species. A neuroanatomical nomenclature is defined here as an internally consistent set of terms used to name a CNS part. The number of terms included in a nomenclature is variable (at least one), and the nomenclature version uniquely specifies the set. Usually, a brain nomenclature is associated with a neuroanatomical atlas, but this does not constitute a constraint for inserting it. The constraints that are considered are the internal consistency, whether the reference is original research, and the brain region names are associated with textual definitions, or at least depicted on a brain atlas (Bota and Swanson 2005).

The BAMS modules are *Connections*, *Relations*, *Cells*, and *Molecules*. The *Connections* module holds data and metadata about macroscopic neuroanatomical projections between gray matter regions. Any neuroanatomical connection is represented in BAMS by a set of more than 40 attributes (Bota et al. 2005). The *Relations* module stores qualitative (topological) spatial relations between brain regions in the same species and defined in different nomenclatures, as well as the supporting references as metadata. The *Cells* module allows insertion of names and definitions of neuron types and classes, as well as relations between them, as collated from the published literature. It records neuronal population attributes, such as topographical positions within brain regions, densities, and patterns of staining. It also includes a classification schema, which allows specification of criteria used to hierarchically organize neuron nomenclatures (Bota and Swanson 2007). Thus, the *Cells* module allows insertion of different neuronal nomenclatures, hierarchically organized. A unique feature of this module is the set of classification criteria that can be associated to any hierarchically organized neuron nomenclature (“is-a” relationship). BAMS includes more than 100 structural, hodological (inputs and outputs), electrophysiological, and functional criteria and sub-criteria, which can be used to specify the common features

and specific differences of neuronal classes and types (Bota and Swanson 2007). Any neuronal class or type captured in a hierarchically organized manner includes the specific sets of criteria, as well as the relevant metadata (textual definitions, associated references, and collators names).

The *Molecules* module represents data and metadata as collated from the literature and pertaining to brain regions or neurons that are recorded in two general classes of physiological states of the animals (subjects): “normal” and “manipulatedQ” Molecules are also classified in two general classes: “cell associated” and “releasable by neurons.” The “cell associated” class is further divided in classes accepted by the IUPHAR nomenclature (<http://www.iuphar-db.org/index.jsp>).

The *Molecules* module allows insertion of quantitative and qualitative attributes of molecules identified using the most used techniques used in neuroanatomy: radioactive tracers, immunohistochemistry, and expression of genes at the regional and neuronal levels. It also includes a comprehensive schema for metadata representation of experiments, from the details of the used antibodies to the plane of sectioning. This metadata schema allows insertion of data and metadata specific to each of the used techniques listed above. A full description of this module can be found in Bota and Swanson (2006).

BAMS Interfaces and Inference Engines

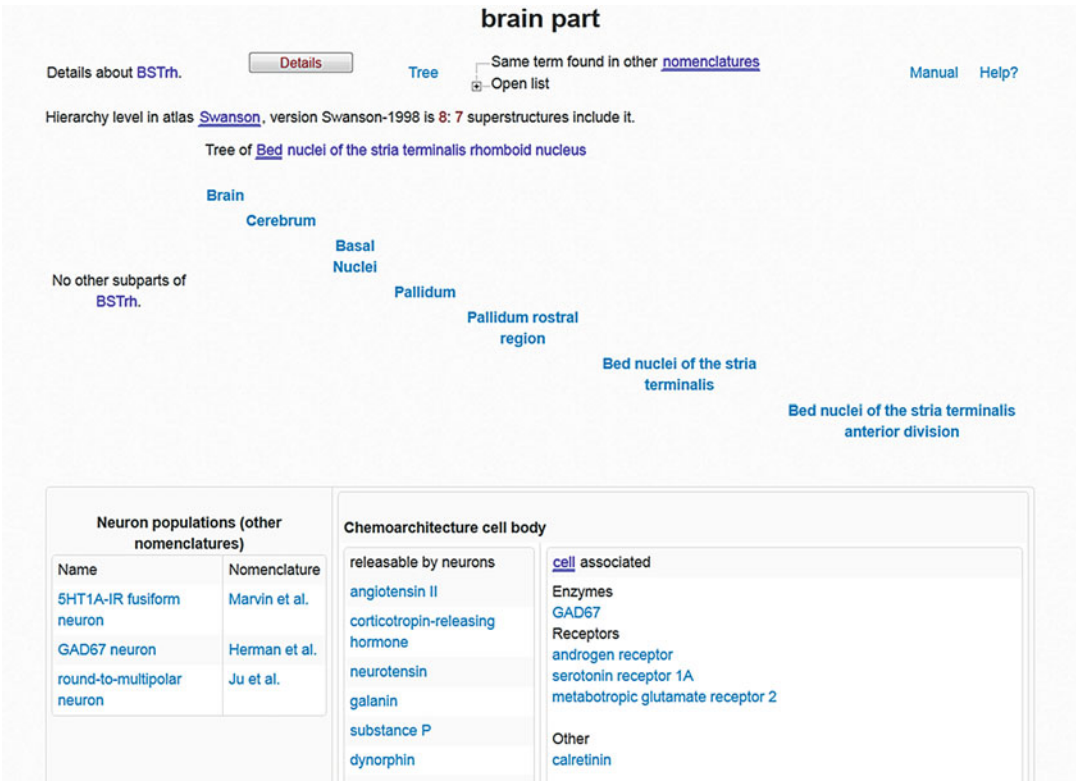
The Web BAMS interfaces are comprehensive and versatile, allowing users to search for information and manipulate inserted data and metadata in different way. Both interfaces and inference engines are implemented in PHP (<http://www.php.net/>), as well as JavaScript. The middleware PHP is continuously updated and upgraded, and at present we use its 5.5.x version. Generally, the outputs of searches are either text, tables, and images (PNG format). Each BAMS module described in the previous section can be searched for information in a different way. A complete description of search engines implemented in BAMS, as well as examples, can be found in its

Manual: http://brancusi.usc.edu/public/files/user_manual.pdf.

Two of the simplest ways to search for information in BAMS are by gray matter regions names and abbreviations. The results of these searches will be lists of regions with those names or abbreviations, respectively, which best match the searched strings. These lists are ordered in descending order of the relevance, as well as by the type of information that is associated in the system. Clicking on any of the retrieved results (gray matter regions names) will return the region information, recorded in BAMS, and links to the associated neurons, expressed molecules, and to its inputs and outputs (Fig. 1).

BAMS users have several options to create gray matter networks. First, they can use the input and output interfaces, choosing a certain set of regions of interest (Bota et al. 2005). The

connections between these regions will be first displayed in tabular formats. The interface that displays these tables of connections includes a link for extension of the networks with one more layer. Users will be asked to choose the regions of interest that are the targets of the afferent regions of the initial tables. Once this action is finished, the user-chosen networks will be displayed as extended tables, as well as in graphical formats. Examples of such complex networks that can be constructed by users can be found in BAMS' Manual and at the URL: <http://tinyurl.com/mf4jxws>. A second option to create gray matter regions networks is automated, and the users have to specify the first and the last region, as well as the number of intermediary layers (Bota et al. 2003, 2005). This engine infers all possible networks between the user-specified regions and with the preset number of layers (intermediary



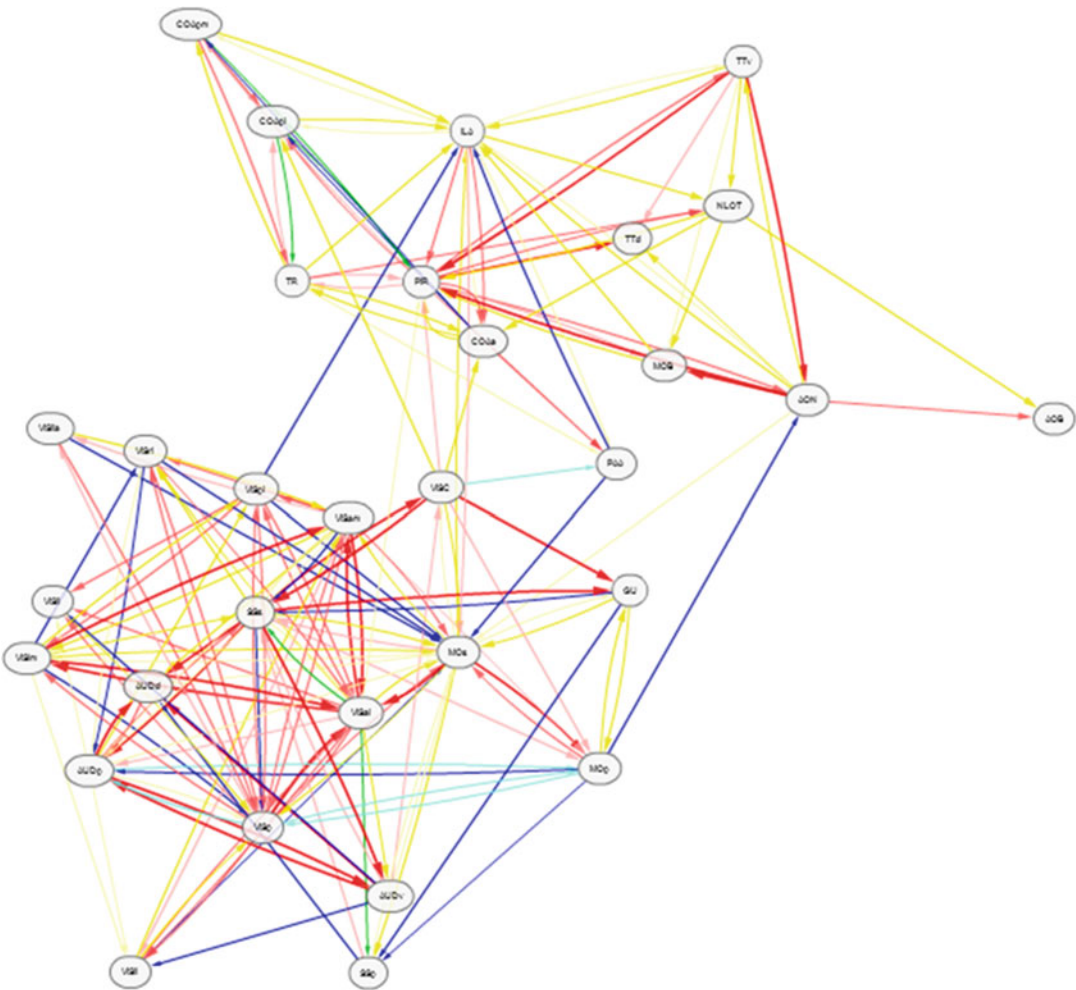
Brain Architecture Management System (BAMS), Fig. 1 The general output of search for brain regions in BAMS. See text for details

stations), from the connections data inserted in BAMS. To reduce the number of possible networks, this engine constructs only the forward ones and with at least moderate connections. The third and the newest way to construct and visualize networks uses a graphical interface constructed de novo in the second generation of BAMS, BAMS2 (see below). This functionality can be accessed from the “Connectome” tab of BAMS’ *Menu*. The networks that can be accessed by users are those that can be constructed using the rat Swanson-2004 neuroanatomical

nomenclature and hierarchy (Swanson 2004) and “custom” matrices, created by the curators of the system. The first set of networks is those of the major divisions of the rat CNS. An example of such network is shown in Fig. 2.

Additionally, users can search for connections of regions, using autocomplete forms that allow both names and abbreviations. These forms are implemented in BAMS2 (see below).

The *Molecules* module data and metadata can be accessed in two ways: a simple browse function of molecules by categories and an engine that



Brain Architecture Management System (BAMS), Fig. 2 The network representation of connections of the rat somato-motor cortex, as defined in the Swanson-2004

nomenclature (Swanson 2004), constructed automatically in BAMS

compares the experiments inserted in BAMS. BAMS includes both presence and absence of molecules in brain regions or neuron; therefore, this variable will be always showed. The state of the animal, “normal” or “manipulated,” is also always associated with each record. BAMS includes an additional function that of inference of the expression patterns of gray matter parts that include subparts, and these are associated with molecules data and metadata. A complete description of the *Molecules* module and its interfaces can be found in Bota and Swanson (2006).

The *Cells* module interfaces include a simple browsing function, which lists the names of neurons, the associated neuron nomenclature, their definitions, and the collators’ names. It also includes search forms by names of neurons and by brain regions. The former is divided in “BAMS Reference” and “Other.” The names of neurons tagged with “BAMS Reference” are the standard terms of the system, while those tagged “Others” are synonyms or partial correspondences. The criteria for choosing a neuron name as “BAMS Reference” are described and discussed in detail in Bota and Swanson (2007).

Additional search functionalities include those for references inserted in BAMS and search for brain regions by species and for relations between brain parts defined in different nomenclatures.

BAMS2

In 2010 we decided to upgrade BAMS to the second generation. Thus, we constructed de novo the entire infrastructure, structure, and interfaces of the new system, BAMS2.

BAMS2 uses both PostgreSQL as a classic relational database and RDF triples to store the data and metadata. The Web framework Django is used to create its interfaces. BAMS2 (<http://brancusi1.usc.edu>) is not a simple iteration of the older system, because it includes new functionalities, besides the ones already existent in BAMS. Secondly, the BAMS2 public data and metadata is encoded in RDF triplets and queried using

SparQL. Finally, we developed in BAMS2 a comprehensive and versatile *Personal Workspace* module, which allows rapid insertion of connections data annotated and collated directly from experiments. The *Workspace* data and metadata are stored in PostgreSQL relational database. Besides its extended functionality to handle and represent neuroanatomical data directly inserted by neuroanatomists, the *Workspace* also allows third-party systems anonymous access, to create tabular and graphical representations of their stored connections data. This novel functionality of BAMS2 Workspace is exemplified to date in the “Connectome” tab of the classical BAMS (see above).

BAMS: Inserted Information

BAMS includes to date about 1.25 million details, most of them manually inserted. It stores about 10,000 CNS parts in five species and 33 nomenclatures; about 70,000 connections reports, mostly in the rat CNS; 341 neuron identified names identified in more than 200 rat regions; and about 9000 molecule reports in both rat and mouse CNS and related to more than 100 molecules expressed in these species brains. These data and metadata have been collated from more than 700 published references, most of them original research articles.

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Brain Atlases

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Definition

An atlas is a collection of maps. Used in a geographic sense, an atlas refers to a collection of maps of an entire planetary body such as that of the Earth or the Mars. In an analogous manner, brain atlases are collections of brain image data where each collection typically spans across one (or more) whole brain. This article primarily provides pointers to other articles dealing with brain atlases. See the Cross-References/Related Terms below.

Cross-References

- [BrainMap](#)
- [Cell Centered Database](#)
- [Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)
- [Connectome, *Drosophila*](#)
- [Connectome, General](#)
- [Connectome, Mouse](#)
- [Human Connectome Project](#)

Brain Computer Interfaces

- [Brain-Machine Interface and Neuroimaging](#)

Brain Damage

- [Brain Ischemia and Stroke](#)

Brain Energy Metabolism

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Definition

The brain is an organ of great complexity, whose mystique is tightly guarded by several protecting layers, from the physical armor of the skull to the biochemical border of the blood–brain barrier. What fuels the brain to sustain a range of neurophysiological states is a question of great importance not only to advance our insight on how brain functions, but also to shed some light on how to treat patients with neurological and psychiatric conditions.

The electrophysiological activity of the brain, usually measured in terms of frequency of neuronal firing, is a process which cannot be sustained unless the underlying metabolism is able to provide the energy required for the process of depolarization and subsequent repolarization to take place, including the supporting role of glial cells. In this chapter, we give an overview of the modeling of brain energy metabolism and how it can be coupled to models for electrophysiological and cerebrovascular dynamics.

Our understanding of the brain keeps evolving, so no assumption about brain energy metabolism should be taken for granted, and even the fundamental roles of the different cell types keep being reassessed. For example, in the studies on energetic substrates other than glucose, astrocytes have emerged as playing a much more prominent role than originally thought. How fundamental glial cells are for brain electrophysiology and what portion of the energetic needs must be allocated for astrocytes' functions continues to be a topic of active research. Due to the limited volume inside the skull and the lack of myoglobin, brain metabolism depends crucially on the cerebral

blood flow for the delivery of glucose and oxygen, the principal substrates for energy production, and the removal of carbon dioxide, lactate, and other byproducts of the metabolism.

Cerebral hemodynamics has its share of open questions. Already in the nineteenth century, the physiologist Angelo Mosso measured a localized increase in blood flow following sustained neuronal activation, a phenomenon with numerous details for which several potential explanations have been proposed but still waiting to be fully settled. For example, a discovery three decades ago, the physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation has raised the question of what the reasons may be for the significant oversupply of oxygenated blood in activated brain regions. All these questions are tied to electrophysiology through metabolism, underlying its pivotal role in the process of integrating the different scales of the multiscale brain.

Detailed Description

The Energetic Cost of Brain

Electrophysiological Activity: Discoveries and Mysteries

Beyond the Naked Neuron: The Role of Astroglia
Traditionally, computational neuroscience has focused on a single neuron, or more generally, a network of neurons. From early on, however, experiments have verified that the behavior of neurons is strongly conditioned on the environment, and in particular, by the concentration of electrolytes in the surrounding environment: for example, it is well understood that a rise in extracellular potassium concentration triggers seizure like firing or bursting in neurons. This suggests that to understand how brain functions, it is necessary to go beyond the naked neurons to design models that take into account the regulatory factors of the environment and their interaction with neurons. In brain tissue, astroglia is the main regulator of the neuron's electrolytic environment, and the interplay between neurons and astrocytes with regard to energy metabolism is key for the glutamate–glutamine cycling between

the presynaptic neurons and astrocytes. The changed perception of astroglia in the past decades has been very dramatic, as they have gone from merely space filling connective tissue (The Greek meaning of glia is glue, revealing rather openly the initial impression) to being *the other brain* (Volterra and Meldolesi 2005; Fields 2009; Dienel 2017; Bak et al. 2018).

Cerebral Metabolism in Health and Disease

The brain is the most metabolically demanding organ in the human body: While an adult brain constitutes typically only approximately 2% of the total body weight, it accounts for approximately 20% of total oxygen consumption and 25% of total glucose consumption at awake resting state (Sokoloff 1999; McKenna et al. 2012). The complexity of the biochemistry of the brain and the difficulty in accessing this organ without major disruption in its functions contribute to the challenge of understanding cerebral metabolism. The price to be paid for the protection provided by the skull is that brain has no space to store any significant amount of energetic fuel to resort to in case of disruption in the blood flow, and the lack of myoglobin means that essentially all oxygen available to the brain must be provided through the cerebral blood flow. At resting state, most energetic needs of the brain go towards keeping the neuronal membrane potential at about -70 mV; these needs are met by the coordinated action of hemodynamics and metabolism. During neuronal activation, when additional energy is needed to ensure that the depolarized membranes return to the resting voltage, the cerebral blood flow increases to sustain the increased cerebral metabolic rate in a highly coordinated manner. Therefore, it should not come as a surprise that even a small perturbation of cerebral metabolism or hemodynamics will result in major disruption of the brain activity.

In recent years, there has been an increasing interest in understanding the underlying metabolic disruptions behind neurodegenerative disorders to direct the search for better pharmaceutical therapies and to suggest life style changes. While many neurodegenerative conditions may have a genetic basis, metabolic changes often occur before the onset of the disease, hence suggesting

that trying to return the metabolism to its healthy state may be a way to delay, if not offset, the disease. Given the brain's primary need for energy to sustain the membrane polarization, many diseases resulting in brain degeneration are associated with perturbations of the energy metabolism, affecting either the glucose metabolism or the processes leading to oxidative phosphorylation, a process responsible for ATP production in bulk.

Among today's aging population, Alzheimer's disease (AD) is one of the most prevalent and devastating age-related neurodegenerative conditions, affecting the ability to create new memories and to tend to even the most basic tasks. While the etiology is still for the most part elusive, impairment of glucose metabolism is such an invariant pathophysiological feature of AD to suggest that the consequences of glucose hypometabolism lead to neuronal degeneration and cognitive deficits (Chen and Zhong 2013). Because the occurrence of impairment of glucose metabolism in AD may precede the onset of cognitive dysfunctions by years (Cunnane et al. 2011), it may be considered part of the AD biomarker. Positron emission tomography (PET) studies using ^{18}F fluorodeoxyglucose (FDG) in AD patients during disease progression have shown that the severity of the symptoms correlates with the reduction of glucose metabolism in the parieto-temporal lobe, the posterior cingulate cortex, and the frontal areas, while the primary visual and motor cortex, the cerebellum, the thalamic and basal ganglia nuclei are less affected (Mosconi 2005); at first, the reduction in glucose metabolism arises in memory-related regions like the hippocampus and the entorhinal cortex. This is confirmed in Melrose et al. (2011) where it was shown that AD patients with hypometabolism suffer greater impairment in the right hemisphere, in particular in the frontal pole, the dorsolateral prefrontal cortex, the superior parietal lobule, the inferior parietal lobule, and the posterior superior and middle temporal gyri.

Cognitive deficits are a challenge for insulin-resistant type 2 diabetes mellitus patients, who are at increased risk of AD; vice versa, most AD patients show insulin resistance, hence prompting some researchers to label AD as *type 3 diabetes mellitus*, or brain insulin resistance. Incidentally, GLUT4, the glucose transporter into

hippocampus neuron, is insulin responsive (Apelt et al. 1999). The final steps of the metabolism of glucose occur in mitochondria where the glucose products enter the Krebs cycle to provide the substrates for oxidative phosphorylation producing the majority of ATP. Disruption in either of these pathways will interfere with complete glucose metabolism, in turn rendering the cell unable to provide the ATP required to meet the energy demands, with the result that the neuron may undergo apoptosis (Shoffner 1997). Deposition of β -amyloid in mitochondria contributes to the disruption of oxidative phosphorylation in mitochondria. In a chicken or the egg type of argument, lower neuronal activity in turn would decrease glucose metabolism, hence worsening the symptoms of AD. In a phase I trial, continuous deep brain stimulation of the fornix for one month triggered a local increase in glucose metabolism (Smith et al. 2012).

Epilepsy is another major neurological disease with known connections to metabolism. The generation of seizures is likely to be facilitated by deficient energy production leading to destabilization of membrane potential. Traditional anti-seizure drugs overcome the destabilization of membrane potential by sedation, i.e., inhibiting action potential transmission: This curbing of the energy demand may cause cognitive deficits and other unpleasant side effects. It has been known since the time of Hippocrates (Wheless 2008) that fasting can be used to treat epilepsy. A less drastic way to make the body produce acetone and beta-hydroxybutyric acid is to follow a diet rich in fat and poor of carbohydrates, usually referred to as ketogenic diet. The use of ketogenic diets to control epilepsy has been typically limited to pediatric epilepsy patients (Martin et al. 2006): Ketone bodies enter the Krebs cycle anaplerotically and are oxidized by the brain. Diets based on medium chain triglycerides replenishing the Krebs cycle anaplerotically have been shown to have anticonvulsant action without the heavy side effects of traditional drugs. A recent review (McDonalds et al. 2018) provides an overview of the known mechanisms perturbing oxidative glucose metabolism in epilepsy and discusses the benefits of a dietary regimes based on medium chain triglycerides in chronic epilepsy. If glucose metabolism is

unable to meet the highly increased energetic demand during seizure, the compensation mechanisms initiated by the brain in an attempt to increase ATP production may impair oxidative phosphorylation due to oxidative stress. The explanation of the effectiveness of the dietary changes requires a solid understanding of the brain cell metabolism.

The decrease in glucose and oxygen metabolism of brain cells, which is part of the normal aging process, becomes critical in the onset and progression of amyotrophic lateral sclerosis (ALS), Parkinson's (PD), and Huntington's (HD) diseases (Hoyer 1982). As is the case for AD, FDG-PET studies show a reduced glucose utilization in specific brain regions of PD, ALS, and HD patients; changes in blood-brain barrier and lower expression of glucose and monocarboxylate transporters have been found in patients with cognitive impairments; see, e.g., Camandola and Mattson (2017). In PD patients, the glucose hypometabolism may be caused by an alteration of an enzyme in the Pentose Phosphate Pathway (PPP) induced by environmental toxins (Lei et al. 2014). A deeper understanding of the metabolic disruption in the brain of PD patients may guide interventions to ameliorate the associated neuropathology and motor deficits.

ASL patients experience increased energy expenditure at rest (Funalot et al. 2009) and have been reported to suffer from multiple metabolic perturbations, including glucose intolerance, insulin resistance, high levels of fats in blood, as well as astrocyte end feet degeneration, suggesting that altered metabolism plays a significant role in ALS progression.

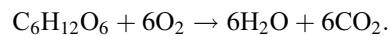
In HD, where early degeneration of neurons in the striatum results in involuntary motor movements, a decrease in striatum metabolism occurs well before the atrophy, and glucose hypometabolism is strongly correlated with the progression of the disease. Early stage HD patients have normal levels of glucose transporters but lower than normal glucose uptake. As in other neurodegenerative conditions, while the picture of the associated metabolic disruptions is not clear, intervention to boost neuroenergetics may

delay the onset or slow the progression of the disease.

Cortical spreading depression (CSD) occurring usually with migraine, stroke, and brain trauma (Lauritzen et al. 2011) is characterized by a failure of brain ion homeostasis: An increase of extracellular potassium leads to depolarization of the brain cells and increased extracellular glutamate concentration by an impaired glutamate uptake by astrocytes. The energetic need increases beyond the supply of glucose and oxygen, possibly because of a failure in the neurovascular signaling that normally would lead to hyperemia. A detailed picture of the chain of events during CSD, and in particular the causal sequence between electrophysiological activity, metabolism, and neurovascular signaling are topics of active study, underlining the importance of mathematical modeling and simulation.

Energy Metabolism from Top Down

This section contains a general overview of the brain energy metabolism. For a classic text on the topic, we refer to Siesjo (1978); see also Lajtha (2007). The energy supply of the brain is for the most part a product of the aerobic metabolism of glucose, whose complete oxidation process can be expressed as

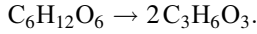


How completely the glucose entering brain tissue is oxidized can be expressed as the ratio of the cerebral metabolic rates, intended as the brain molar uptake, of glucose and oxygen, CMR_{glc} and CMR_{O_2} , or oxygen-glucose index (OGI) of the brain,

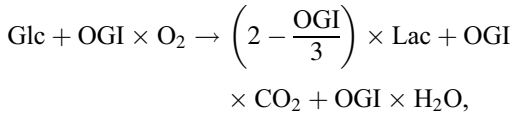
$$\text{OGI} = \frac{\text{CMR}_{\text{O}_2}}{\text{CMR}_{\text{glc}}}.$$

If all glucose entering the brain undergo complete oxidation, it follows from the stoichiometry that $\text{OGI} = 6$. In normal conditions, however, the typical observed OGI is of the order 5.2–5.4 with spatial and temporal variation (Vaishnavi et al. 2010), indicating that a small portion of the glucose undergoes a nonoxidative process, resulting

in the production of lactate (or lactic acid), the end product of anaerobic metabolism of glucose,



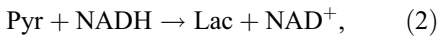
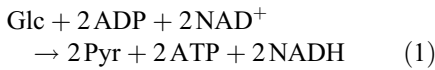
Therefore, the complete metabolic fate of glucose can be described in terms of these two processes, summarized by OGI,



where Glc and Lac denote glucose and lactate, respectively.

To understand what controls the OGI, we need to look at the metabolism of brain cells accounting separately for cytosol and mitochondria.

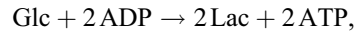
The most prominent cytosolic pathway in most living cells is glycolysis, a complex chain of enzymatic reactions converting glucose into pyruvate or lactate. Lumping a number of the detailed reactions together, we can break down glycolysis into two simplified steps,



where ATP and ADP denote adenosine triphosphate and adenosine diphosphate, respectively, NAD^+ denotes nicotinamide adenine dinucleotide, and NADH its reduced form, whose relevance for energy metabolism will be discussed later. ATP can be thought of as the energy currency, because the cleaving of one of its three phosphate groups provides energy for reactions or transports that would not otherwise take place. More specifically,

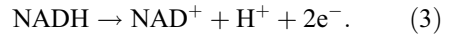


where P_i is an inorganic phosphate group, not accounted for in our lumped glycolysis description. If we lump further the reactions in glycolysis into the breakdown of glucose to lactate,

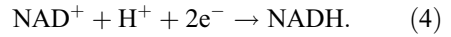


we see that glycolysis can produce energy in the amount of two moles of ATP per mole of glucose in an anaerobic fashion.

Before introducing oxidative metabolism, we point out that in the second step (2) of glycolysis, the role of NADH, nature's reducing agent, is to donate electrons needed for the reaction and become NAD^+ ,



Conversely, the electrons freed when the reaction occurs in the reverse direction are absorbed by the oxidizing agent NAD^+ , which turns into NADH,



In Eq. (2), pyruvate is reduced to lactate in a reaction facilitated by the enzyme lactate dehydrogenase (LDH). Since this reaction is reversible, the same enzyme catalyzes the oxidation of lactate to pyruvate, with the direction of the reaction depending, among other things, on the ratio of the concentrations of lactate and pyruvate; in normal condition, the equilibrium is towards lactate in a 10:1 ratio and is in near equilibrium with the ratio of NADH/NAD^+ (Mintun et al. 2004).

Glycolysis alone is not sufficiently effective to provide the energy needed by the brain, as can be seen from the following simple calculation. The brain consumes about 20% of the total energy of the human body, which, assuming a total energy consumption of 2000 kcal per day, amounts to 1680 kJ per day, the equivalent of about 20 Watts. If this energy were to come from glycolysis alone, about 27.5 moles of glucose would be required: This, with the molar mass of approximately 180 g per mole, would amount to about 5 kg! A much more efficient mode of energy production is through mitochondrial oxidative phosphorylation.

Pyruvate, a pivotal substance in energy metabolism, is produced in cytosol either from the processing of glucose (Eq. 1) or, occasionally,

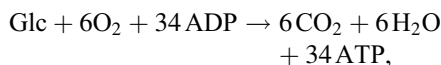
through oxidation of lactate. Pyruvate entering the mitochondrial matrix feeds a complex chain of reactions, known as the tricarboxylic acid (TCA) cycle, or Krebs cycle, which strips the carbons from pyruvate and produces NADH. From the point of view of NADH production, the Krebs cycle can be summarized approximately by the lumped reaction



emphasizing the fact that each pyruvate molecule produces five reducing equivalents inside the mitochondrion. In the presence of oxygen, reducing equivalents, i.e., NADH, become a great source of energy. A complex process, known as oxidative phosphorylation (OxPhos), taking place in the mitochondrial matrix, binds energy into ATP according to the approximate stoichiometry



In summary, following glucose from the beginning of glycolysis, into the TCA cycle to the end of oxidative phosphorylation, shows that through aerobic metabolism we have



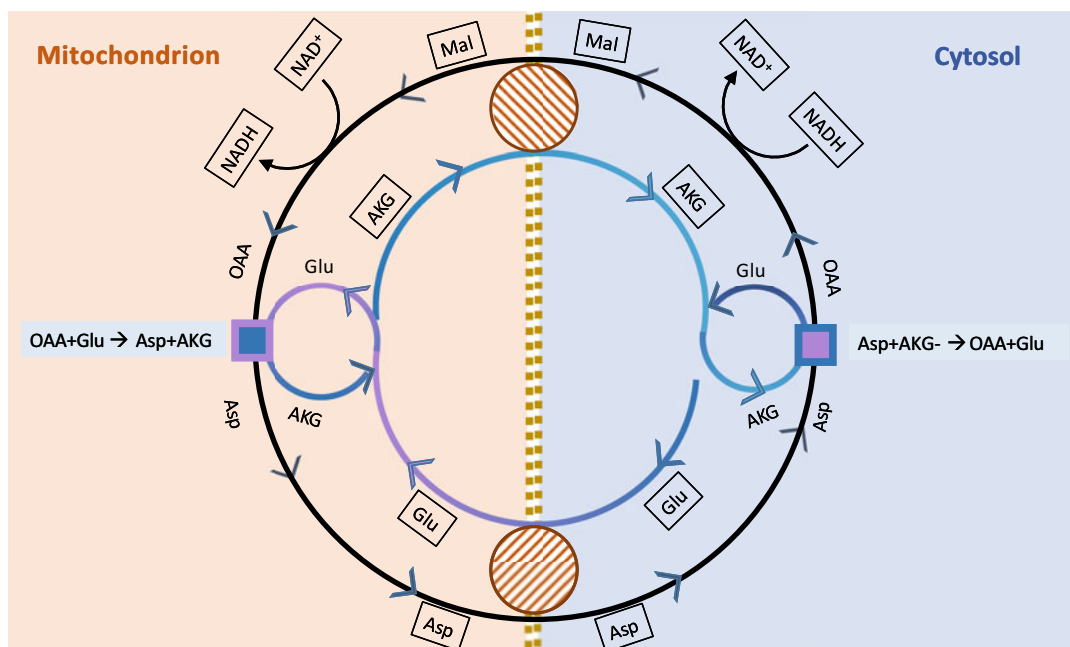
that is, 17 times more ATP per glucose is produced compared to anaerobic metabolism. This means that to satisfy the 20 Watt energy consumption of the brain, only about 300 g of glucose per day suffices.

Since ATP is produced in mitochondria, while most energy demand is for processes occurring in cytosol, there must be a way for ATP to be transferred from mitochondria to cytosol, as described in Klingenberg (1980) and Kunji et al. (2016). Only selected molecules can cross the mitochondrial membrane, which is impermeable, for example, to NADH and NAD^+ , important players in the coupling of glycolysis and

oxidative phosphorylation. The virtual movement of NAD^+ and NADH across the mitochondrial membrane is effected by the malate–aspartate shuttle (MAS), schematically summarized in Fig. 1, involving several metabolites (Lajtha 2007).

The balance of NADH and NAD^+ is crucial for cell functions. As NADH produced in the first part of glycolysis enters mitochondrion to participate in oxidative phosphorylation, the redox balance in cytosol shifts towards NAD^+ and lactate production in cytosol stops, hence decreasing the rate of anaerobic oxidation. On the other hand, if lack of oxygen stops oxidative phosphorylation, the slowing down of malate–aspartate shuttle triggers pyruvate reduction (Eq. 2) to lactate, increasing the rate of anaerobic metabolism (Mintun et al. 2004). While the basic control mechanism is well understood, indirect effects complicate the picture: The reactions (3) and (4) affect the pH of the environment, a factor that regulates several of the enzymes involved in the energy metabolism of the cell. Also, the MAS involves metabolites of the TCA pool, hence indirectly affecting the metabolic process in the mitochondrion. These observations underline the difficulty of building a reliable and comprehensive computational model that takes into account the fine details and feedback mechanisms that eventually regulate the balance between aerobic and anaerobic metabolism.

We conclude by pointing out that a lot of the communication between a cell and the surrounding environment is through the cross-membrane exchange of biochemical species. Some of the exchanged substances, e.g., gases, have been assumed to diffuse passively according to cross-membrane concentration gradients, while other molecules, most notably glucose and lactate, require the help of specific transporter proteins, e.g., glucose transport protein (GLUT) and monocarboxylate transport protein (MCT), both expressed in different isoforms. Thus, a dynamical system describing the metabolic processes in the cell is a complex nonlinear system with proper models for enzymatic reactions and passive and active transporters, as discussed in more detail later.



Brain Energy Metabolism, Fig. 1 The malate–aspartate shuttle, a mechanism whose net effects is equivalent to a NADH/NAD^+ exchange across the inner membrane of the mitochondrion (vertical line) that is impermeable to these cofactors. The shuttle depends on two membrane-bound proteins, the malate- α -ketoglutarate antiporter, and the aspartate–glutamate antiporter. The key MAS enzyme,

malate dehydrogenase (MDH), acts differently in cytosol and in mitochondrion by facilitating the reactions $\text{Mal} + \text{NAD}^+ \rightarrow \text{OAA} + \text{NADH}$ in the latter, and the reverse reaction in the former. Observe that the net effect is purely on the redox both sides of the membrane. Abbreviations: α -ketoglutarate (AKG), aspartate (Asp), glutamate (Glu), malate (MAL), oxaloacetate (OAA)

Zooming In: Neurons and Astrocytes

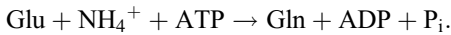
The description above makes no distinction between the metabolic processes in neuron and astrocyte. However, since these cell types have different roles in the signal processing of the brain, it is reasonable to expect differences in their metabolism also. Indeed, while many of the reaction chains can be found in both neuron and astrocyte, the enzymes and the cross-membrane transporters may have different concentrations and can be of different isoforms, and the regulatory factors in the two cell types may vary. In addition, the mitochondrial density in neuron and astrocyte is different and may even vary from one part of the cell to another. Moreover, neurons and astrocytes have different spatial configuration and geometry; hence, the surface areas are different. In fact, the role of the astrocytic end feet wrapped around the capillaries continues to be a topic of active research. In the light of these considerations, even

if the two cell types have for the most part the same reactions and transfers, we cannot assume that the reaction and transport rates are the same.

The V-Cycle: Glutamate–Glutamine Cycling The neuronal signal carried by the action potential propagates from presynaptic neuron to the postsynaptic neuron through a process which includes chemical signaling using excitatory neurotransmitters, whereas inhibitory neurotransmitters can stop the action potential propagation. The most common excitatory transmitter in brain, but not the only one, is glutamate, while γ -aminobutyric acid (GABA) is most commonly responsible for the inhibition of an action potential. We start by addressing the role of glutamate.

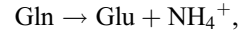
As the action potential reaches the end of an axon, the reversed membrane voltage potential causes the calcium channels to open, triggering a massive release of glutamate (Glu) into the synaptic cleft. The glutamate receptors in the dendrite of

the post-synaptic neuron sense the increased glutamate concentration, causing an opening of sodium channels and a triggering of an action potential that continues to travel down the dendrite. As long as the glutamate concentration remains significant in the cleft, the sodium channels remain open, so it is imperative that the transmitter is promptly removed from the cleft. Glutamate cleaning is done mostly by astrocytes (Anderson and Swanson 2000): After the uptake, the glutamate is amidated to glutamine (Gln) in the cytosol of the astrocyte by the astrocyte-specific enzyme glutamate synthetase (GS) according to the stoichiometry



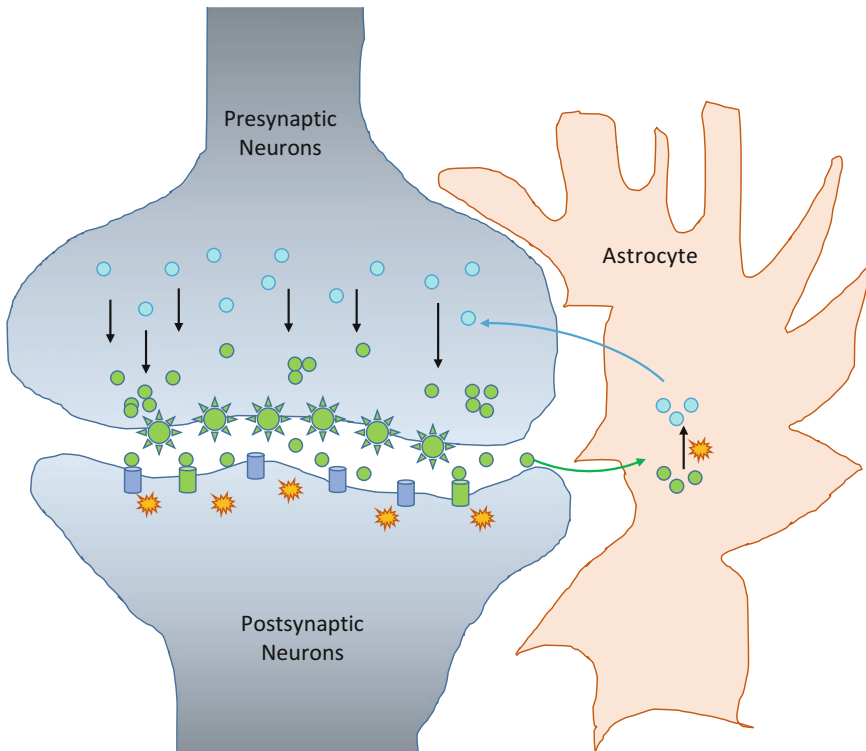
Glutamine is not excitatory and therefore can be returned to the presynaptic neuron without causing a trigger of action potential. In neuron, upon the cleaving of an ammonium, glutamine

becomes glutamate as the end product of the reaction



catalyzed by the phosphate-activated glutaminase (PAG) enzyme, believed to be located at the inner membrane of neuronal mitochondrion. A cartoon of the signal transmission and glutamate cycling for glutamatergic neuron is shown in Fig. 2.

The presence of GABA in the synaptic cleft inhibits the opening of the sodium channels, thus effectively stopping the action potential transmission. The fate of GABA parallels in many ways that of glutamate. After having been released into the synaptic cleft by GABAergic neurons, it is taken up by astrocytes and eventually returned to GABAergic neurons in the form of glutamine: Overall, the GABA cycle is more complex than the glutamate–glutamine cycle. GABA is



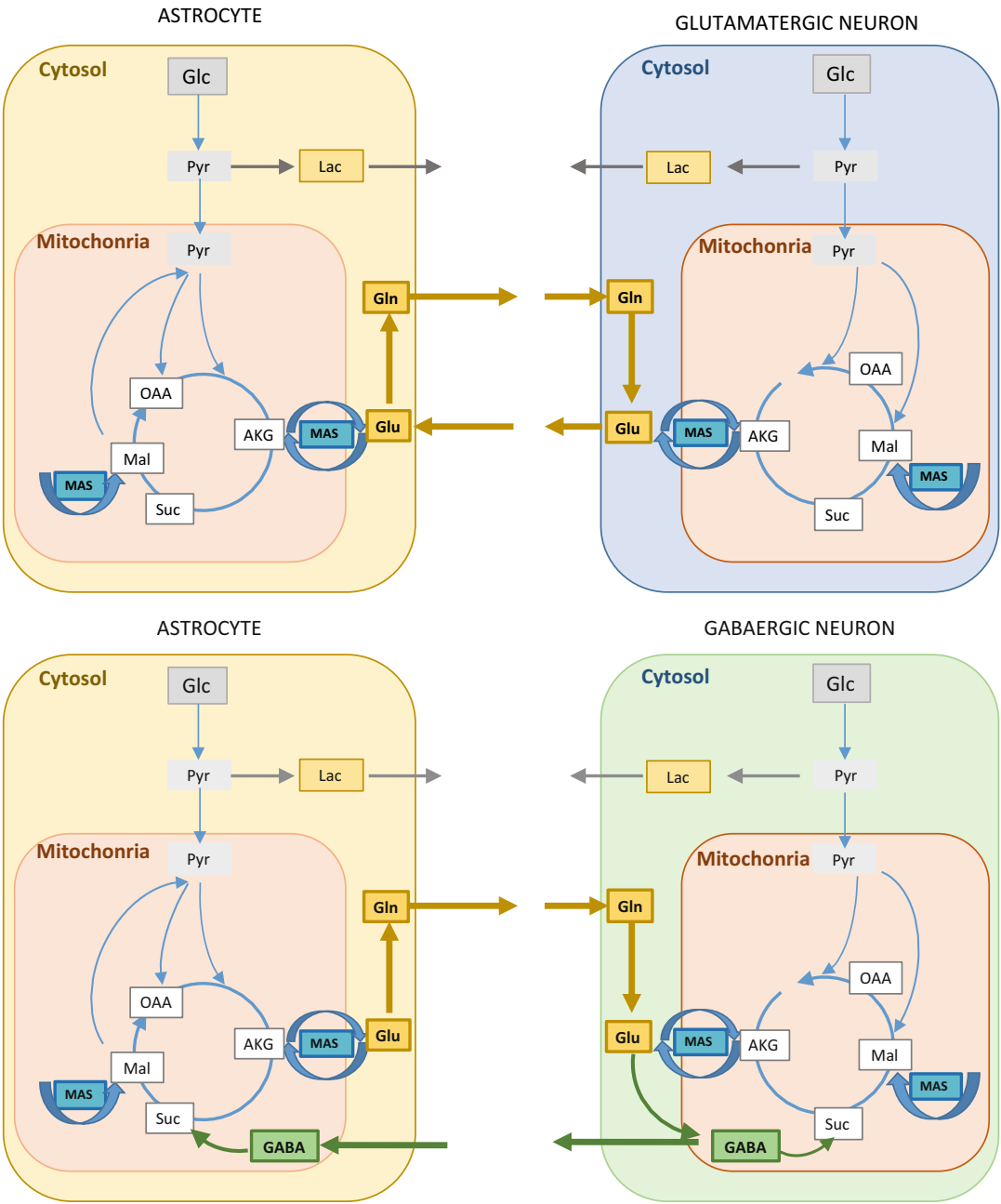
Brain Energy Metabolism, Fig. 2 Meeting at the synaptic cleft of glutamatergic neuron and astrocyte. Glutamate in presynaptic neuron is packed in vesicles that merge with the axon membrane, releasing the glutamate into the

synaptic cleft. The glutamate is immediately taken up by the astrocyte that amidates it to glutamine, a neutral substance from the point of view of neurotransmission, and can be safely diffused back to the presynaptic neuron

synthesized from glutamate by the glutamic acid decarboxylation (GAD) enzyme, present in different isoforms both in neuron and astrocyte.

A schematics of the neurotransmitter cycling in the context of an excitatory (top) and inhibitory (bottom) event is shown in Fig. 3.

B



Brain Energy Metabolism, Fig. 3 Schematic picture of the glutamate–glutamine–GABA cycling between neurons and astrocytes. (Top) Glutamatergic neuron and astrocyte with the glutamate–glutamine cycle, also known as V-cycle. (Bottom) GABAergic inhibitory neuron and

astrocyte. The figures indicate the main coupling sites with the metabolic processes, and in particular, the TCA cycle in mitochondria. The abbreviations are succinate (Suc), α -ketoglutarate (AKG), malate (Mal), oxaloacetate (OAA)

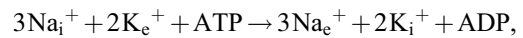
The glutamate–glutamine cycle and the GABA–glutamate cycle between neurons and astrocytes are only a part of the full picture of reactions involving glutamate that participates in the metabolic processes, including the malate–aspartate shuttle (Hertz and Chen 2017). Due to space limitation, we omit many details, some of which have not been fully resolved yet and continue to be the topic of active investigation, for example, the mechanisms by which the ammonium is returned from neuron to astrocyte (Cooper 2012; Calvetti and Somersalo 2013).

In presynaptic glutamatergic neurons, glutamate is packed into vesicles that in connection with the axonal action potential transmission merge with the cell membrane and lead to glutamate release. The articles (Attwell and Laughlin 2001; Howarth et al. 2012) contain a careful analysis of the energetic cost of glutamine–glutamate cycling. The estimated cost in astrocyte is approximately 2.33 ATP, with 1.33 for the uptake and 1 for the processing. The energetic cost of vesicle packing in neuron is only 0.33 ATP per glutamate molecule. The real cost incurred by the signaling takes place in the postsynaptic neuron: Each vesicle contains about 4000 glutamate molecules, and the release of one glutamate vesicle leads to the entry of 210 000 Na^+ ions in the postsynaptic neuron, which triggers also the signal in the dendrite traveling down towards the soma, all this requiring ATP to restore the membrane potential, as discussed below.

Transmembrane Ion Transport and Signal Propagation The most significant demand for ATP generated in neurons is for the ion pump action necessary to restore the membrane potential during signal propagation. It is well understood that the signal propagation along the neuronal cell membrane includes a process by which extracellular sodium enters the neuron (depolarization), followed by the outflow of intracellular potassium (repolarization), as accurately described by the classical Hodgkin–Huxley model (Keener and Sneyd 2009).

The major engine for the restoration of the membrane potential, which requires the

concurrent extrusion of excess sodium from the cell and intake of potassium, is the sodium–potassium pump, or Na^+/K^+ -ATPase, a protein in the plasma membrane that moves the ions against the concentration gradient by utilizing the energy released by the dephosphorylation of ATP. Denoting by K_e^+ and K_i^+ the extracellular and intracellular potassium, respectively, and using a similar notation for sodium ions, the pump action can be expressed as

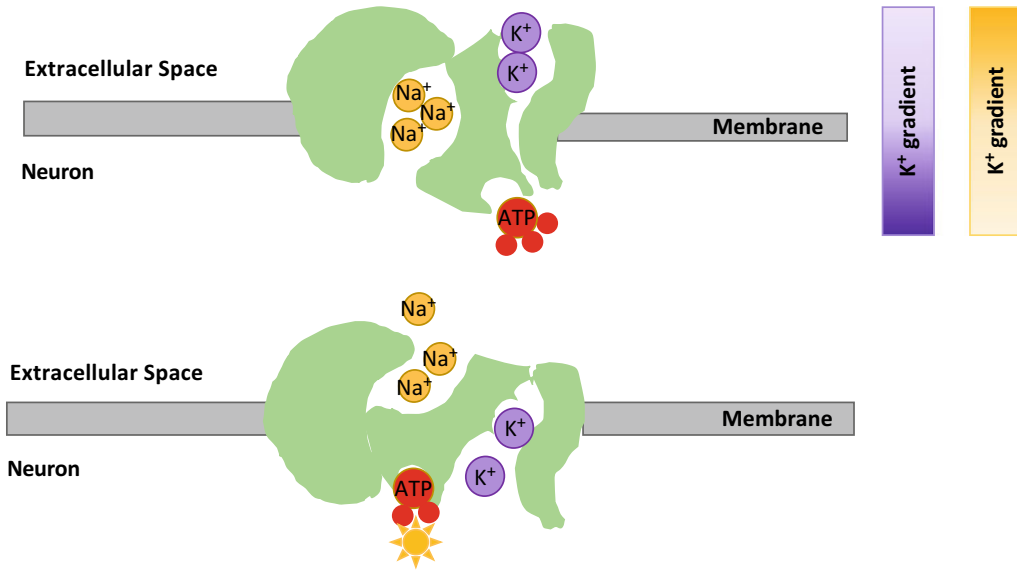


A schematic of the mechanism of the pumps is shown in Fig. 4.

Computational Models

The metabolism in neuron–astrocyte complex is usually described in terms of well-mixed homogenized multicompartment models. Well mixed means that within a compartment, every metabolite change is observed everywhere without a delay, implying restrictions on the size scale of the model. The number of compartments included in the model depends on the desired level of detail. Neuron, astrocyte, and extracellular space (ECS) are usually accounted for as separate compartments in models of cerebral cellular metabolism, as is blood, needed to replenish the supply of metabolites. In complex models of brain energy metabolism, the neuron and astrocyte are separated into cytosolic and mitochondrial subcompartments. For an overview of the current models in literature, we refer to Somersalo et al. (2012).

We begin our overview of mathematical models of brain energy metabolism with an outline of the design principles of spatially lumped models. Assume that the model comprises L compartments. A *metabolic network* consists of biochemical reactions R_j and transports T_k between compartments: For each metabolic reaction R_j , a corresponding reaction flux φ_j is assigned and, likewise, each transport T_k is associated with a transport flux ψ_k . These quantities are typically expressed in units of $\mu\text{mol}/\text{min}$,



Brain Energy Metabolism, Fig. 4 The sodium–potassium pump action. With the energy released from the dephosphorylation of the ATP, the pump moves three sodium ions out of the neuron, replacing them with two

potassium ions, the ion movement being executed against the concentration gradients to reconstitute the transmembrane resting potential

scaled to correspond to one gram of brain tissue. The reaction and transport fluxes are arranged into vectors,

$$\varphi = \begin{bmatrix} \varphi_1 \\ \vdots \\ \varphi_n \end{bmatrix}, \quad \psi = \begin{bmatrix} \psi_1 \\ \vdots \\ \psi_m \end{bmatrix},$$

n and m being the number of reactions and transports included in the model, respectively.

Each reaction depletes some metabolites and produces others; likewise, each transport moves metabolites from a compartment to another. Since the role of the same metabolite may change from one compartment to another, we identify metabolites by their chemical composition and the corresponding compartment, so that, e.g., cytosolic glucose in neuron is regarded as different from the cytosolic glucose in astrocyte. Given the complete list of compartment specific metabolites, for each reaction R_j we define the stoichiometric vector $\mathbf{s}_j$ specifying how many molecules of each

metabolite, accounted for with its compartment affiliation included, is produced (positive entry) or consumed (negative entry) by the reaction. Similarly, a transport T_k moves a metabolite from one compartment to another, and we define the associated stoichiometric vector $\mathbf{s}_k$ indicating the number of metabolites depleted (negative entry), or replenished (positive entry). The stoichiometric vectors corresponding to all reactions and transports in the model can be stored as column vectors of the stoichiometric matrix,

$$S = [\mathbf{s}_1 \quad \mathbf{s}_2 \quad \dots \quad \mathbf{s}_N] \in \mathbb{R}^{M \times N},$$

where $N = n + m$ and M is the number of metabolites included in the model, counted with the multiplicity of compartments.

To set up a dynamical model, tracking the changes of the metabolites over a time period, the relative volumes, intended as percentages of the total volume, of the compartments need to be included. Assuming that the model domain is a

unit volume, let η_ℓ denote the volume fraction of the ℓ th compartment, $\eta_1 + \dots + \eta_L = 1$. We define the

volume matrix $V \in \mathbb{R}^{M \times M}$ as a diagonal matrix with

V_{jj} = volume fraction of the compartment assigned to the j th metabolite.

Thus, if the first metabolite in the list is astrocytic glucose, V_{11} is the volume fraction of astrocyte. With these notations, the dynamical system governing the metabolic network can be written concisely as

$$V \frac{d\mathbf{X}}{dt} = \mathbf{S} \begin{bmatrix} \varphi \\ \psi \end{bmatrix} + \mathbf{r}, \quad (5)$$

where $\mathbf{X} \in \mathbb{R}^M$ is the vector of concentrations of all biochemical species, and the vector $\mathbf{r} \in \mathbb{R}^M$ is a vector containing all transports from outside the system. In practice, $\mathbf{r}$ comprises transports of metabolites through the blood flow and possibly losses through diffusion.

Observe that in order to solve the system, we need to know how the fluxes φ and ψ depend on the metabolite concentrations, which requires a good understanding of the biochemistry and physiology. In the following subsections, we elaborate further on their explicit expressions.

Flux Balance Analysis Flux balance analysis (FBA) refers to the analysis of the steady states in a metabolic network (Schilling et al. 2000; Kauffman et al. 2003). Because in a steady state the metabolite concentrations are time invariant, the derivative on the left hand side of the model (5) vanishes, leading to the linear system

$$\mathbf{S} \begin{bmatrix} \varphi \\ \psi \end{bmatrix} = -\mathbf{r}. \quad (6)$$

where the unknowns are the fluxes, whose values must fall inside physiological ranges to be meaningful. For this reason, a straightforward solution of the linear system, e.g., in the least squares sense, is typically useless.

In order for the system to respect the conditions for the cells to be alive, several of the fluxes have to be nonnegative. This is the case for those associated with irreversible enzymatic reactions, such

as those that are part of glycolysis or oxidative phosphorylation. The same holds for some of the transports. Furthermore, the maximum reaction flux or transport rate is regulated by the expression of the enzyme or transporter facilitating the reaction, hence is typically bounded from above. Hence, in order for the computed solution to have an interpretation in terms of cell physiology, a number of bound constraints need to be implemented as part of the flux balance analysis.

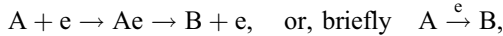
The second observation is related to the non-uniqueness of the solution. If the matrix $\mathbf{S}$ has more columns than rows, as is often the case, it has a nontrivial null space, consisting of all non-zero vectors that satisfy

$$\mathbf{S} \begin{bmatrix} \varphi_0 \\ \psi_0 \end{bmatrix} = 0.$$

Any vector from the null space can be added to any solution of the Eq. (6) without affecting the equilibrium. The presence of the null space may be interpreted as the necessary leeway of the system to adjust itself, should the conditions of the environment change, making this concept particularly useful from the point of view of understanding the capabilities and limitations of the system. Characterizing the null space under bound constraints in the flux balance analysis is not a trivial task due to the high dimensionality of the flux space. A systematic description of the set of all possible solutions requires the use of sampling methods to generate a significant ensemble of possible solutions by using Monte Carlo or quasi-Monte Carlo techniques. This ensemble can be summarized in terms of its mean and credibility intervals (Papin et al. 2004; Wiback et al. 2004; Heino et al. 2010) or used to find histograms of single fluxes, or correlations between fluxes. This approach has been applied to brain

energy metabolism: see, e.g., Occhipinti et al. (2007, 2008, 2010), Calvetti and Somersalo (2012), Massucci et al. (2013), Calvetti et al. (2016), and DiNuzzo et al. (2016); for an extension incorporating genomic information, see Becker et al. (2007) and Lewis et al. (2010).

Dynamic Models All biochemical reactions in cells are enzymatic. Enzyme kinetics is a vast topic (Marangoni 2003; Cornish-Bowden 2012), as different enzymes have their characteristic reaction facilitating mechanisms and regulating factors, such as the ambient pH. Quantitatively, however, enzyme kinetics models have some common features, most prominently maximum reaction rates dependent on the expression level of the enzymes, and characteristic saturation rates. One of the simplest mathematical descriptions of enzyme kinetics comprising these two features is the Michaelis–Menten model, which can be derived from different assumptions concerning the enzyme action. Denoting by e the enzyme, the simplest enzymatic reaction type can be written as



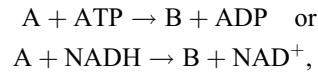
where the intermediate phase Ae typically represents a fast transient. The Michaelis–Menten expression for the associated reaction flux is of the form

$$\varphi = V_{\max} \frac{[A]}{K + [A]},$$

where $V_{\max}$ is the maximum reaction rate and K is the affinity constant indicating the concentration level $[A]$ of A at which the reaction rate is one half of the maximum. Smaller affinity constant means faster saturation of the reaction. The characteristic time constant of the reaction is proportional to the ratio $K/V_{\max}$.

Reactions requiring the participation of the facilitator pairs ATP/ADP or NADH/NAD⁺ are regulated by the availability of these cofactors. Detailed modeling of the dependency requires that the details of each reaction are well understood. A useful approximation is obtained by

following the principle that, qualitatively, when there is abundance of the needed cofactor, the reaction rate follows the Michaelis–Menten kinetics, while scarcity of the cofactor lowers the maximum reaction rate. Consider reactions of the type



and define the phosphorylation state p and the redox state r of the compartment where the reaction occurs by

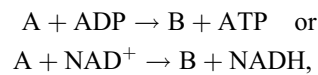
$$p = \frac{[\text{ATP}]}{[\text{ADP}]}, \quad r = \frac{[\text{NADH}]}{[\text{NAD}^]}.$$

Modifying the Michaelis–Menten kinetics model, we write the related reaction fluxes as

$$\varphi = V_{\max} \frac{p}{p + \mu} \frac{[A]}{K + [A]} \quad \text{or}$$

$$\varphi = V_{\max} \frac{r}{r + \nu} \frac{[A]}{K + [A]},$$

respectively, where $\mu > 0$ or $\nu > 0$ are the affinity constants of the phosphorylation or redox state. Conversely, reactions of the type



are quenched in the absence of ADP or NAD⁺, respectively; hence, the corresponding fluxes can be modeled, respectively, as

$$\varphi = V_{\max} \frac{1/p}{1/p + \mu} \frac{[A]}{K + [A]}, \quad \text{or}$$

$$\varphi = V_{\max} \frac{1/r}{1/r + \nu} \frac{[A]}{K + [A]}.$$

Some reactions may require both redox and phosphorylation cofactors. For instance, the flux

of the glycolytic reaction (1) in this modeling framework would take the form

$$\varphi = \frac{1/r}{1/r + v} \frac{1/p}{1/p + \mu} \frac{[\text{Glc}]}{K + [\text{Glc}]}.$$

The transport fluxes can be modeled in a similar manner. The transport of a substance A from compartment x to compartment y effectuated through a membrane-bound protein X may be viewed akin to an enzymatic reaction,



where A_x and A_y refer to the same metabolite in different compartment, and AX is the fast transient state corresponding to the membrane passage. A natural Michaelis–Menten type model for the flux of this transport is

$$\psi = T_{\max} \frac{[A_x]}{M + [A_x]},$$

where $T_{\max}$ is the maximum transport rate and M is the affinity. The above model assumes a unidirectional transport; in the case of bidirectionality, the net transport flux becomes

$$\psi = T_{\max} \frac{[A_x]}{M + [A_x]} - T'_{\max} \frac{[A_y]}{M' + [A_y]},$$

where the maximum transport rate $T'_{\max}$ and affinity M' of the reverse transport may or may not be equal to the ones of the forward transport.

Transport by passive diffusion through concentration gradient across the membrane is usually modeled by Fick's law,

$$\psi = \lambda([A_x] - [A_y]).$$

A major challenge of dynamic metabolic modeling using parametric models is the fact that the number of model parameters increases concomitantly with the complexity of the model, and finding reliable values for the parameters is not easy. Several factors contribute to the ambiguity about the values of the model parameters.

First, the expression levels of different enzymes and transporters are poorly known and vary widely; second, in vitro measurements may not translate reliably to the in vivo and in situ settings; third, the regulatory factors are numerous, variable, and poorly known. Other factors, like mitochondrial density, may also affect the model. At the moment there is not a complete agreement on how geometric factors such as the vicinity of astrocytic end feet to capillaries and the transport across the blood–brain barrier should be taken into account (Serlin et al. 2015).

Several dynamic metabolic models have been published in the past decades, but because of the reasons mentioned above, no one is considered the gold standard model. For details and specifics of each model, we refer to Gruetter et al. (2001), Aubert and Costalat (2002, 2005), Simpson et al. (2007), Cloutier et al. (2009), DiNuzzo et al. (2010), Calveti and Somersalo (2011), and Calveti et al. (2015).

Spatially Distributed Models In the literature, most of the metabolic models of the brain assume a well-mixed compartment structure. However, there are several reasons why a spatially distributed model could be of interest. One is that lumped models do not account for diffusion, in particular of oxygen, which may be a rate limiting factor for energy metabolism. Indeed, the classical investigations of A. Krogh suggested that the capillary density needs to be quite high in order for brain tissue to remain well oxygenated. A second argument is that assuming spatially invariant mitochondrial density could bias the balance between aerobic and anaerobic metabolism. A big challenge for designing a mathematical model that accounts for spatial inhomogeneity is the extremely complex and poorly known geometry of neurons and astrocytes. In Calveti et al. (2015), the geometric complexity was avoided by introducing an effective multidomain reaction-diffusion model, akin to the bidomain model widely used in modeling the myocardium.

An additional motivation for developing spatially distributed models is the fact that spatial distribution of the metabolic processes will play a significant role in understanding phenomena like the cortical spreading depression: The

depolarization wave is known to propagate through the brain tissue, and many important questions are related to the interplay of depolarization, metabolic activity, and hemodynamics. The challenges of building a realistic distributed model are significant.

Towards Coupled Metabolism and Electrophysiology The foundation of the mathematical description of neuronal signal propagation along the axon is the classical Hodgkin–Huxley model, governed by a system of coupled differential equations for the membrane voltage potential V and three gating functions regulating the sodium influx and potassium efflux (Keener and Sneyd 2009). An important assumption of the model, well justified in the famous experimental setup with the giant axon of the squid, is that the reversal potentials are constants. Using the Nernst equation, the reversal potentials are given in terms of the ion concentrations inside and outside the cell. For the squid giant axon, it is realistic to assume that these concentrations do not change, but in the microscopic environment of brain neurons, such assumption is no longer realistic: A small potassium flux out of the neuron can change significantly the potassium concentration in the very narrow extracellular space, and the astrocyte intervention is needed to restore it.

Models which couple ion concentrations to pump actions in neurons and astrocytes have recently appeared in the literature; in Cressman et al. (2009) and Barreto and Cressman (2011), the authors couple the extracellular and intracellular sodium and potassium concentrations through an algebraic equation, and account for the sodium–potassium pump effect as well as the glial potassium cleaning, and potassium diffusion out of the system. A step forward towards the coupling of the electrophysiology to metabolism was taken in Wei et al. (2014) where the authors add an oxygen-dependent regulator to the sodium–potassium flux of the neuron. This is tantamount to assuming that ATP production is based on aerobic metabolism and that the ATP level responds without a delay to oxygen availability: However, the details of metabolic processes are omitted, and the energetic need of the astrocyte is not included.

In the metabolic modeling literature, the idea of coupling of the metabolic needs of the neuron and the ion dynamics is not new: In Aubert et al. (2001), for example, the influx of sodium is used as an external trigger of the elevated metabolic rate; however, the feedback mechanism coupling the ion dynamics and metabolism has been included only recently. In Jolivet et al. (2015), the metabolic model of Aubert and Costalat (2002) is coupled with the basic Hodgkin–Huxley model. In Calvetti et al. (2018), the electrophysiological model of Cressman et al. (2009) was coupled with the neuron-astrocyte complex metabolic model in Calvetti and Somersalo (2011), including a phosphorylation state-dependent factor both in the neuronal sodium–potassium pump action and in the glial potassium flux. This implies that both neuron and astrocyte need a steady supply of metabolites to guarantee the ion balancing. While in neuron the energetic cost of the ATPase to sustain the sodium–potassium pump action is relatively well known, the energetic need of glia remains somewhat of a mystery. In particular, the potassium cleaning per se is not ATP-dependent, yet it is believed that in order to be functional, astrocytes use a significant percentage of the total energy budget of the brain (Hertz et al. 2007), justifying a phosphorylation level control in astrocyte also.

Integrating the Neurovascular Coupling

Much of our current understanding of the functioning brain is based on brain imaging methods, such as blood oxygenation level-dependent functional MRI (BOLD-fMRI), with the implicit assumption that elevated electrophysiological activity triggers an increase in the supply of oxygenated blood at the same location, so that an observed elevation in blood flow can be used as a proxy for elevated activity. While experiments confirm that the basic assumption is valid (Logothetis et al. 2001), the details of the neurovascular connection are not completely understood. It has been suggested that the vasodilation is due to a signal that could consist of increased extracellular potassium concentration (Filosa et al. 2006), astrocytic regulation through the end feet (Nortley and Attwell 2017), increased lactate concentration (Fox et al. 1988; Mintun et al. 2004), nitric oxides

from the neurotransmission related glutaminase (Lourenco et al. 2016), or a combination of all of them. Given that every one of the proposed mechanisms is directly related to the cell energy metabolism, instead of referring to neurovascular coupling, it would be more correct to use neuro-metabolic-vascular coupling to underline the crucial role of the energy metabolism.

Two classical models explaining qualitatively the origin of the BOLD signal are known as the balloon model (Buxton et al. 1998) and the Windkessel model (Mandeville et al. 1999; Kong et al. 2004). These models have been developed further since they were originally published, to better understand the coupling with neuronal activity: To this end it is important that the model is more specific in identifying the vascular compartment susceptible to activity-induced dilation. Unlike the arterial and venous vessels, the vascular walls of capillaries do not have smooth muscles; hence, it is natural to hypothesize that the main increase in blood volume following neuronal activation is accommodated by arteries and veins whose compliance increases, although capillary recruitment during activity is not ruled out. Current literature seems to be in favor of the hypothesis that the arterial compartment is mostly accommodating the increased blood flow.

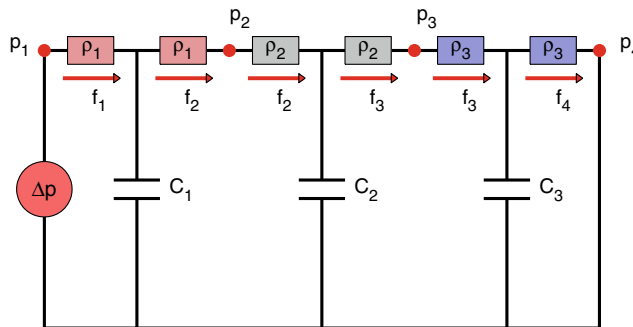
The blood flow has been incorporated from early on in some metabolic models in the literature, mostly to give an interpretation to the BOLD

signal in terms of the metabolic activity, see, e.g., Aubert and Costalat (2002). However, models integrating the blood flow and metabolism including a two-way feedback mechanism are still missing, although there has been some recent work towards integrating the oxygen dynamics in tissue with multicompartment vascular models (Zheng et al. 2005; Kocsis et al. 2006; Huppert et al. 2007).

In Barrett et al. (2012), the authors developed a three-compartment model for coupling the neurovascular stimulus and blood flow, without elaborating on what comprises the signal. The model exploits the analogy of the blood system with an electric circuit as shown in Fig. 5, whose governing equations can be deduced from the circuit theory,

$$p_j = \rho_j f_j + \frac{V_j}{C_j}, \quad \frac{dV_j}{dt} = f_j - f_{j+1}, \quad 1 \leq j \leq 3,$$

where $j = 1$ corresponds to arteries, $j = 2$ to capillaries, and $j = 3$ to veins, p_j is the entry blood pressure, V_j is the compartment volume, ρ_j is the resistance, C_j the compliance, and, finally, f_j the blood flow. The authors assume that the blood moves through the vascular system according to a Poiseuille flow, leading to a resistance model



Brain Energy Metabolism, Fig. 5 The analog electric circuit corresponding to the three compartment cerebral blood flow model. Each compartment is divided symmetrically in half, each half contributing equally to the resistance of the blood flow. The pressures p_j correspond to

voltages, the blood flows f_j correspond to electric currents, resistivities ρ_j correspond to electric resistances, volumes V_j of the compartments are treated as charges, and finally, compliances C_j of the compartments correspond to capacitances

$$\rho_j \propto \frac{1}{V_j^2},$$

while the viscoelastic properties of the vessels regulating their compliance are modeled as

$$C_j = C_j^* \left(\frac{\kappa_j - V_j/V_j^*}{\kappa_j - 1} - v_j \frac{dV_j}{dt} + s_j(t) \right),$$

$$1 \leq j \leq 3,$$

where C_j^* and V_j^* are the baseline compliances and volumes, κ_j is the stiffness, v_j is the viscoelastic constant and, most importantly, $s_j = s_j(t)$ is the vasodilatory stimulus associated to the compartment. The presence in the formula of the derivatives of the volumes makes this a nonstandard system which, in the cited articles, is treated as a differential-algebraic system. The explicit dependence of the model on the unspecified stimulus function provides a good starting point for coupling it with metabolic and electrophysiological models by establishing a connection through the stimulus function originating from the metabolic model, while coupling backwards the resulting blood flow to the metabolite supply. Such integrative process has been recently initiated in Capo Rangel et al. (2018), where the stimulus function is interpreted to be proportional to the potassium concentration in the extracellular space.

Cross-References

- Axon, Modeling
- Dynamical Systems: Overview
- Enzyme Kinetics, Modeling of
- Hodgkin-Huxley Model
- Modeling Ion Concentrations
- Modeling Synapses
- Sodium Channels

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Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery

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Synonyms

Extracellular compartment; Interstitial space; Interstitial volume

Definition

The extracellular space (ECS) comprises a system of contiguous narrow spaces interposed between the brain cells. It occupies approximately 20% of the brain tissue volume. Mathematical modeling quantifies the macroscopic parameters of the ECS from experimental data obtained with diffusion analysis and tests the hypotheses about the ECS microstructure.

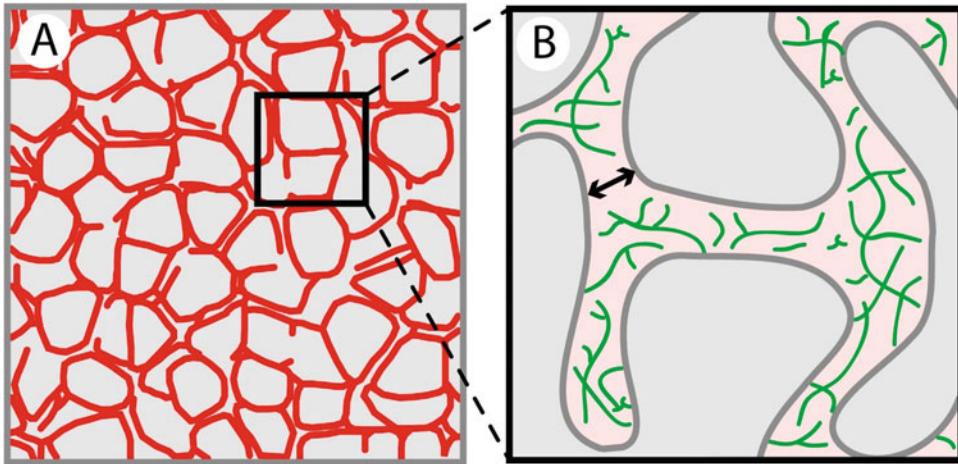
Detailed Description

The ECS is filled with ionic solution and macromolecules of the extracellular matrix. Its structure is determined by the shape of brain cells (neurons and glia) and their processes (axons and dendrites), the width of pores

between the cells, and the extracellular matrix (Fig. 1). The ECS is fundamentally important for the brain function as it complements neuronal and glial networks. Instead of merely filling the void between the brain cells, as its name might suggest, the ECS exerts a direct influence on many essential processes in the brain, including the diffusion of neurotransmitters and neuromodulators mediating intercellular communication, the distribution of ionic currents, the cellular homeostasis, the neurotrophic effects, the transport of nutrients, and the clearance of metabolites. From the perspective of patient care, ECS forms the final segment of a delivery route for therapeutics destined for the brain cells. Therapeutic agents enter the ECS across the blood-brain barrier at a capillary, from the cerebrospinal fluid, or they are released directly into the ECS. The efficacy of treatment depends on the compatibility between the drug or its carrier and the ECS microenvironment.

It has been recognized that the ECS structure undergoes dynamic reversible changes during brain activity as well as transitions between sleep and awake brain states (Nicholson and Hrabetova 2017). It is also changed profoundly, and often irreversibly, by many pathophysiological processes associated with neurological disorders and brain tumors (Sykova and Nicholson 2008). The results of ECS research are thus important for understanding the brain function and challenges to the chemical traffic and drug delivery when the ECS structure is altered by pathophysiological processes.

In this entry, we will focus on the role of ECS as a route for molecular transport. Once introduced into the ECS, substances are transported predominantly by diffusion because the ECS lacks any active transport mechanism. Physiological effects of substances diffusing in the ECS are governed by their concentrations and their arrival times, which in turn depend on the ECS structure affecting the diffusion. Biophysical parameters of the ECS have to be taken into account whenever quantitative understanding of any diffusion-mediated process is desired.



Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery, Fig. 1 Schematic of brain ECS. (a) Brain cells (gray) surrounded by the ECS (red). (b) Cell geometry (gray),

pore width (double arrow), and extracellular matrix (green) are key components of the ECS structure. (Modified from Hrabetova S, *diffusion-fundamentals.org* 16 (2011) 3, pp. 1–2)

Experimental Approaches

Research of the ECS is challenging, in part because the ECS structure cannot be easily visualized, the interstitial pores being below the resolution of light microscopy. Electron microscopy studies provide indispensable information on topology, but they require tissue processing methods known to diminish the ECS volume, and they also cannot quantify parameters of the extracellular matrix or visualize dynamic changes of the ECS structure (Sykova and Nicholson 2008). In contrast, emerging super-resolution imaging techniques that break the diffraction limit are beginning to provide much needed information on the ECS microstructure and nanoscale diffusion in the living brain tissue (Hrabetova et al. 2018).

Currently, the common experimental approach uses diffusion measurements to indirectly obtain information on the ECS structure (Nicholson 2001; Nicholson and Hrabetova 2017). In a diffusion experiment, molecules are released from a point source, and their subsequent ECS concentration is detected either by special ion-selective microelectrodes (Real-Time Ionophoretic method) or by optical imaging (Integrative Optical Imaging) and analyzed as a function of position and time. In diffusion experiments employing

small extracellular probe molecules, two macroscopic parameters of the ECS structure are quantified: the volume fraction and the hindrance. Volume fraction α is a proportion of the tissue volume occupied by the ECS ($\alpha = V_{\text{ECS}}/V_{\text{tissue}}$). Hindrance describes how much the diffusion process in an ECS environment slows down in comparison with an obstacle-free medium. It can be expressed as the diffusion permeability $\theta = D^*/D_{\text{free}}$, where D^* is an effective (i.e., averaged over a small neighborhood volume) diffusion coefficient in the brain tissue and D_{free} is a free diffusion coefficient (Hrabe et al. 2004) or as the tortuosity $\lambda = \theta^{-1/2}$ (Nicholson 2001). In an isotropic brain tissue, α is about 0.20, and θ is about 0.4 ($\lambda = 1.6$) (Sykova and Nicholson 2008). The ECS is a dynamic structure, and its volume fraction and hindrance change, often independently, during brain activity and in disease (Sykova and Nicholson 2008). For example, during a stroke, α is as low as 0.07 and θ decreases to 0.23 ($\lambda = 2.1$), while in malignant brain tumors α expands to 0.48 and θ decreases to 0.32 ($\lambda = 1.8$). The ECS volume and hindrance are two essential ECS parameters which determine concentration and arrival times of substances diffusing in the ECS.

Diffusion measurements that employ larger extracellular probe macromolecules are able to

separate the influence of complex ECS geometry from the constrictivity factor, which describes an additional hindrance due to frequent proximity of macromolecules to the cellular walls (Nicholson and Hrabetova 2017). According to the restricted diffusion theory, the constrictivity depends on the average width of the ECS pores, which can thus be estimated. This approach leads to an estimate in the range of 38–64 nm. Another approach combined diffusion measurements with the scaling theory developed in polymer physics to obtain an estimate of 31 nm. The individual ECS pores of a living brain tissue are therefore much wider than the 15–20 nm typically obtained with electron microscopy. The width of extracellular pores is an essential parameter for drug delivery strategies because it provides an upper limit for the size of particles (e.g., liposomal and viral drug carriers) that can uniformly penetrate the ECS and access cells in an unrestricted manner.

Computational Approaches

Computational approaches are indispensable in the ECS research. At a macroscopic level, an appropriate solution of the diffusion equation is fitted to the data obtained in a diffusion experiment to extract the ECS parameters. The most general form of the diffusion equation accounts for an anisotropic environment and allows both the volume fraction and the diffusion permeability (a tensor quantity in this case) to become inhomogeneous (Arranz et al. 2014):

$$\begin{aligned} \frac{\partial c(\vec{r}, t)}{\partial t} = & \frac{D_{\text{free}}}{\alpha(\vec{r})} \\ & \nabla \cdot \left[\alpha(\vec{r}) \boldsymbol{\theta}(\vec{r}) \cdot \nabla c(\vec{r}, t) \right] \\ & + \frac{s(\vec{r}, t)}{\alpha(\vec{r})} - \kappa(\vec{r}) c(\vec{r}, t), \end{aligned}$$

where $c(\vec{r}, t)$ is the concentration at position $\vec{r} = (x, y, z)$ and time t , D_{free} is the diffusion coefficient in obstacle-free medium, α is the ECS

volume fraction, $\boldsymbol{\theta}$ is the diffusion permeability tensor, s is the source strength, and κ is the non-specific linear clearance approximating a loss proportional to the concentration. This equation has to be solved numerically in this general form. However, several analytical solutions exist under simplifying assumptions often used in practical measurements.

The ECS parameters extracted from diffusion measurements are the result of macroscopic averaging of a geometrically complex microscopic environment and consequently do not provide information about the ECS features at a microscopic level. Very little is known about the local structure of individual ECS pores, their organization, and statistical distribution of their parameters. Monte Carlo simulations of molecular diffusion in simplified three-dimensional ECS models are used to test various hypotheses about the microscopic ECS features. One important simulation tool is the *MCell* (Monte Carlo Cell) package (Stiles and Bartol 2001; www.mcell.psc.edu). It was designed for biologically oriented users and uses a simple model description language to specify simulation components such as the cellular surfaces and reaction mechanisms.

Monte Carlo simulations have been used to simulate diffusion of molecules in media constructed of simplified cell shapes that allow tight packing (Tao and Nicholson 2004; Hrabec et al. 2004). They revealed that an extracellular environment with convex cellular elements cannot have diffusion permeability θ lower than $2/3$, which is far above the typical experimental value. This led to the development of a model of hindrance based on diffusion dwell times (Hrabec et al. 2004). More complex shapes were introduced, which included concave cellular geometries. The volume fraction α was divided into the well-connected (α_o) and dead-space (α_{ds}) parts. A new relationship between the θ and α was obtained, namely,

$$\frac{\theta}{\theta_0} = \frac{\alpha_o}{\alpha_o + \alpha_{ds}} = \frac{\alpha_o}{\alpha}.$$

This model of the ECS composed of both convex and concave cells can explain diffusional

hindrance measured in the brain under normal as well as some pathological conditions. It predicts that about 40% of the brain ECS under normal conditions is formed by dead spaces increasing to 60% in a stroke (Hrabetova and Nicholson 2004). In practice, the local ECS geometry probably varies continuously between the well-connected spaces and dead spaces, including features such as lake-like openings.

Another factor which manifests itself by increased hindrance is the fast reversible binding of molecules to the binding sites in the extracellular microenvironment. Comparing diffusion measurement with molecules of similar sizes but distinguished by their chemical interactions, it is possible to extract the respective reaction rates (Nicholson and Hrabetova 2017).

Conclusions

Brain ECS facilitates intercellular communication, nutrient and metabolite trafficking, and the delivery of drugs. ECS research combines diffusion experiments in the brain with computational modeling approaches to characterize the microstructure of the ECS and discover how it is regulated. The results are important for understanding the workings of the brain under physiological conditions and in various neuropathological states, which often affect the ECS properties and result in disrupted traffic of ions, signaling molecules, and nutrients. They are also essential for the design of effective drug delivery strategies in patients suffering from neurological disorders and brain tumors. The ultimate goal of the ECS research is to construct a dynamic three-dimensional model of the brain ECS.

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Brain Ischemia and Stroke

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Synonyms

Brain damage; Cerebrovascular disease; Oxygen deprivation

Definition

Cerebral ischemia, which occurs during stroke, is insufficient blood flow to the brain and leads to loss of oxygen and glucose supply. This severely compromises cellular respiration, causing neuronal damage. Cells move toward cell death, which can be simplified as being controlled, e.g., apoptosis, and uncontrolled, e.g., necroptosis, and as intrinsic (due to changes in the cell) or extrinsic (resulting from extracellular signals). There are more than 12 kinds of cell death, and inhibition of multiple death pathways may be necessary for neuroprotection (Fricker et al. 2018). Ischemic stroke is a multiscale phenomenon, involving a cascade of events at spatial scales from organelles (e.g., loss of mitochondrial membrane potential) to tissue and temporal scales from milliseconds generation of action potentials to years for the restructuring of networks. Ischemic insult also involves transcriptional changes to regulatory networks of genes. Taken together, modeling the molecular and genetic aspects of ischemia is fundamental to understanding how to modulate neuroprotective elements in the case of stroke, which is the primary therapeutic approach in saving at-risk tissue. Computer-based cellular modeling can assist in understanding the molecular changes involved, the decision and control points for various cell fates, and the potential for recovery with partial damage and help define the scope of the genetic and regulatory network changes that occur.

Detailed Description

The mechanisms by which cells accumulate damage, signal damage to neighboring cells, and eventually die all remain unclear. The geometric complexity of neurons makes it difficult to elucidate single-cell diffusive mechanisms in the ischemic signaling cascade. Further complexity occurs due to difficulties in disconnecting effects at the cellular level from effects at the tissue level, as well as effects due the synaptic interconnectivity of the neurons, which can lead to network

cascades in dying tissue. Compounding these difficulties is the fact that many signaling cascades are heavily interdependent on non-apoptotic, homeostatic mechanisms and have multiple non-linear dependencies. The intricacies of signaling pathways that are potentially involved in cell death, both intracellular and intercellular, make it useful to study neuronal ischemia using multi-scale modeling, which can describe the effects across subcellular and cellular levels.

Blood enters the brain via a complex arterial tree. When arteries or large arterioles are damaged through occlusion or rupture, blood supply is locally reduced, causing ischemic damage. The degree of damage is highly variable, depending on the extent and duration of the insult. Generally, we conceptualize two major separable regions: an *ischemic core* where blood flow is essentially zero and an *ischemic penumbra* where there is some residual blood flow. The ischemic penumbra is a region that is considered a target for rescue by appropriate treatment. At normal body temperature, full ischemia for 3–5 min is generally lethal to neurons. However, irreversible damage in the penumbra can occur over several hours following ischemia. The cellular and molecular changes in these regions have markedly different presentations (Lipton 1999). Damage in the penumbra will be highly variable across multiple time-scales. The duration of oxygen deprivation that triggers the ischemic cascade and the extent of damage will likely depend upon genetic and environmental factors in the individual and in the precise types of cells involved. In particular, it is hypothesized that larger cells such as Purkinje cells and cortical pyramidal cells may be particularly vulnerable.

Nutrient Delivery

Ultimately, all ischemia results from loss of substrates for the cell to generate adenosine triphosphate (ATP), its primary energy currency. Computer models of nutrient delivery at the level of blood and of extracellular tissue are therefore useful in providing the setting for effects on the individual cell. This nutrient modeling allows

us to better define molecular differences in types of ischemia that will be produced. Simplified ischemia models at this level represent brain tissue as a set of voxels which exchange O_2 , with influx and outflux of blood between the regions and oxygen consumption integrated at each simulation time-step (Hudetz et al. 1982). In a paper published in 2002, Duval et al. (2002) modeled four parameters: cerebral blood flow, rate of oxygen extraction from blood, metabolic rate of oxygen use by tissue, and the apparent diffusion coefficient of water. A survival delay variable was also used to quantify the decay of tissue in the penumbra from functional to salvageable to necrotic. This modeling suggested that the penumbra could take on two major forms: ischemic and edematous. Ischemic penumbra tissue was metabolically altered and generally not salvageable, whereas the edematous penumbra tissue appeared to retain greater recovery potential. This model represented a first step toward clarifying how extracellular nutrient parameters might affect the generation of penumbral regions. Other models have included blood flow parameters in molecular models as a way of developing more robust models of cellular networks (Dronne et al. 2006).

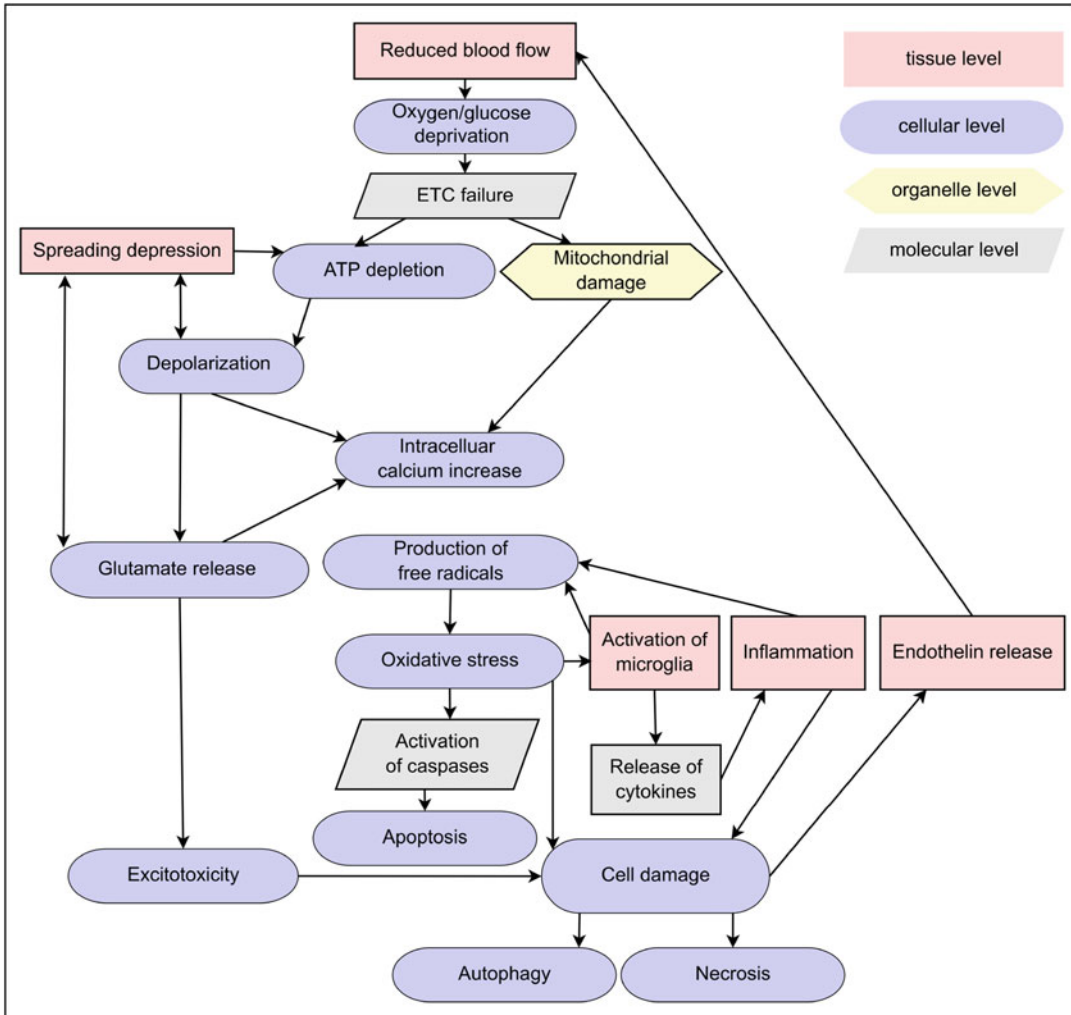
Several findings relevant for ischemic stroke have come from modeling ATP production and consumption in a motor neuron, used to study amyotrophic lateral sclerosis (Le Masson et al. 2014). The model demonstrates the link between ATP required for an action potential and the neuronal geometry. Low ATP production in the model leads to a deadly positive feedback loop as the neuron consumes more ATP, because Na^+-K^+ pump activity is reduced so the neuron gradually depolarizes and the firing rate increases. It shows that Ca^{2+} accumulation is a by-product of energy failure, relevant for many of the death pathways involved in ischemia. By modeling the morphology of the motor neuron including both the dendrites and axon, the model was able to show how an energy crisis in a localized microdomain, such as the end of the axon can generate ectopic action potentials and hyperexcitability.

Initiation of the Ischemic Cascade

After vascular damage, neuronal uptake of O_2 and glucose is reduced, leading to a sequence of metabolic and molecular changes that span spatial scales from subcellular to tissue (Fig. 1). An early result of nutrient loss is a reduction in ATP. The biochemistry of energy production in brain tissue utilizes the same reactions that are used in other cells of the body. However, neurons are run at high metabolic states in order to maintain the electrochemical gradient that enables neurons to fire action potentials. They have additional ATP delivery challenges associated with the presence of long, thin processes with large surface to volume ratios. With disruption in ATP production, plasma membrane ionic gradients will begin to decay, preventing neuronal electrical function and allowing excitotoxic damage via calcium entry due to depolarized membrane potential. Loss of ion homeostasis may precipitate the accumulation of reactive oxygen species and intracellular calcium dysregulation, both of which are primary perpetrators of cell death (Lipton 1999). Models of this process are similar to the early work done by Magnus and Keizer in pancreatic β -cells, another electrically excitable cell type (Keizer and Magnus 1989). This model demonstrated that increased glucose concentration could enhance burst spiking, generating an elevated intracellular Ca^{2+} and excitotoxicity. Later work by Magnus and Keizer focused on developing more robust models of mitochondrial Ca^{2+} signaling (Magnus and Keizer 1998).

Similarly, in neuronal cells, loss of ATP due to poor blood flow triggers a cascade of reactions leading to apoptosis or necrosis. Four major mechanisms are recognized (Lipton 1999):

1. Influx of Ca^{2+} ions through NMDA receptors and voltage-gated Ca^{2+} channels
2. Increased intracellular Na^+ causes glutamate efflux, which also eventually leads to increased intracellular Ca^{2+}
3. Decreased ATP/ADP ratio producing a fall in intracellular pH
4. Production of free radicals, particularly near mitochondrial membranes



Brain Ischemia and Stroke, Fig. 1 The cascade of some of the key events following ischemic stroke. (Adapted from *Drug Discovery Today: Disease Models*, Vol.

19, Adam J. H. Newton and William W. Lytton, *Computer Modeling of Ischemic Stroke*, pp. 77–83, 2016, with permission from Elsevier)

Ionic dysfunction is a hallmark of both necrotic and apoptotic cellular changes. This dysfunction is primarily manifest via abnormal Ca^{2+} fluctuations within the cell. The generation of free radicals and inability to manage pH may also be tied to Ca^{2+} dysregulation via Ca^{2+} -binding control proteins such as calmodulin, calbindin, and calpain (Saftenku and Friel 2012). The products from these early reactions are heavily involved in the cell's final fate.

Due to the importance of Ca^{2+} and Ca^{2+} buffering in determining cell fate, much attention in

ischemia research has focused on modeling this ion. Normally, there are very low resting levels of Ca^{2+} in the neuron. This would ideally use stochastic modeling, because small concentrations of ions cannot be identified as bulk units, which can be handled deterministically. Such a deterministic approach (e.g., rate laws) relies on the law of large numbers; for many aspects of Ca^{2+} signaling, the concentration is so low that this law does not apply. It has been suggested, in fact, that the cell uses chemistry as a computational tool and is able to harness stochastic Ca^{2+} fluctuations to generate

robust intracellular signaling networks. Ischemic cascades therefore involve stochastic events as well as deterministic events, and both involve considerable species diffusion through neurons and extracellular tissue space. Modeling allows us to explore Ca^{2+} fluctuations and species diffusion at a very small-scale level.

Disruption of Homoeostasis

Typically mathematical and computational modeling of neurons assume ion homeostasis. Ion pumps powered by ATP or exchangers driven by concentration gradients are able to limit any changes resulting from the neuron firing. Such assumptions may be valid for physiological neuronal behavior. However, during pathological conditions like ischemia or seizure, the demands placed on the cell exceed its capacity to meet them. This is seen dramatically during spreading depolarization. Spreading depolarization is a wave of breakdown in the ion gradients in neurons and astrocytes resulting in almost complete depolarization. Spreading depression (SD) is the corresponding silencing of electrical additivity that results from this depolarization. SD causes secondary lesion growth in focal ischemia, (reviewed Hartings et al. 2017), which has also been shown with a phenomenological model of cell death based on energy supply and calcium concentrations (Chapuisat et al. 2008). SD can be triggered by many insults such as seizure, migraines, and traumatic brain injury and may not cause cell damage in normally perfused tissue.

Several mathematical models have explored ion (Wei et al. 2014) and glutamate (Hubel et al. 2017; Conte et al. 2018) homoeostasis using three compartments: intracellular, extracellular, and astrocytic. These models include several mechanisms to restore ion concentrations, including the Na^+/K^+ pump and glutamate transporters. Some also allow the cell volume to respond to changes in ion concentrations, primarily related to Cl^- homoeostasis. Cl^- homoeostasis is maintained by passive leaks (Kay 2017) or a balance between the chloride potassium symporter (KCC2) which tends to transport Cl^- into the cell and Na^+/K^+ –

Cl^- cotransporter (NKCC1) which tends to remove it. The extracellular concentration is treated as a bath, with diffusion slowly restoring the concentrations. These models have been used to show the range of behaviors that can be produced by the cell by modifying ion concentrations, from regular spiking activity to spreading depression and anoxic depolarization. They have explored the role of astrocytes in buffering K^+ and glutamate, the interplay between the Na^+/K^+ pump and the glutamate transporter reversal, and their role in generating recurrent waves of SD.

Ion concentrations have also been modeled in multicompartment neurons with dendrites (Kager et al. 2002; Somjen et al. 2008). These models have shown SD is ignited in the apical dendrites in an all-or-none fashion if the membrane current turns inward, leading to a positive feedback loop where more K^+ was released from the dendrite leading to even greater depolarization. Both the onset and duration of SD are modulated by glia buffering of K^+ . A limitation of these biophysically detailed models is that they consider the neuron in isolation with their own ECS and astrocyte. By considering a 1D (Conte et al. 2018) or 2D continuum (Tuckwell 2008), it is possible to model the propagation of waves of SD, e.g., speed and duration, and the form of the waves such as spiral, reverberating, or recurrent waves. However, these continuum models lack the finer-scale details of the underlying neurons. Tools have recently been developed for multiscale modeling to incorporate biophysically detailed neurons in a 3D macroscopic model of ECS (Solbra et al. 2018; Newton et al. 2018).

Use of Boolean Networks in Ischemia Modeling

The changes in nutrients, in ATP, in Ca^{2+} , etc. detailed above are only the beginning of a large array of interconnecting molecular changes. One way to make sense of such a complex and large network has been to use a Boolean Network (BN) formalism to model system dynamics. By conceptualizing the molecules in the signaling

networks as having a discrete set of states (ON/OFF or activated/repressed), interaction rules can be defined for a particular set of reactions. Mai et al. used BNs to model aspects of apoptosis (Mai and Liu 2009). They found downstream redundancies, feedback loops, points of control, and steps leading toward irreversible commitment to this endpoint. Although this approach simplifies reaction dynamics to a 0/1 decision tree, it can provide valuable information on system properties and points of modulation within the apoptotic pathway.

Therefore, the type of information that can be gleaned from a model depends very much on how the model is designed. One alternative to BN modeling is to use ordinary differential equation (ODE) kinetics to model Ca^{2+} wave propagation and reactivity with a higher degree of precision. Within this context, one can also model Ca^{2+} wave propagation and define parameters for wave oscillation interactions with other elements in the single cell. Such an approach, however, does not link Ca^{2+} waves to network pathological processes within and without the cell. Recently, Kazemzadeh et al. used a combined Boolean and ODE approach to model network regulatory effects of apoptosis in a modified (cf. humanized) yeast model. Using databases to generate robust Boolean networks that could then be solved at time-steps enabled them to calculate steady states of complex apoptotic networks and to test the effects of genetic knockouts and variable ischemic insults (Kazemzadeh et al. 2012). Another set of experiments by McDermott et al. was aimed at using BN formalism to study regulatory gene networks in response to ischemic insult. They modeled clusters of functionally related gene elements in steady state and then perturbed this system by using various types of preconditioning insults, including mild ischemia, and a later more serious ischemic insult. Results between the various initial states were compared, and the functional significance of genetic contribution to neuroprotection was analyzed by looking at the robustness of cluster response to preconditioning (McDermott et al. 2012). Most of the results from the computer model were confirmed by previously published experimental data. BN formalism

is a reductionist view of network signaling, whereas simultaneous ODE solving at discrete time-steps gives a larger picture of intracellular signaling. Attempts to link these two modeling methods in studying apoptosis and ischemic cascades have been gaining popularity in computational neuroscience as well as systems biology (Bogda et al. 2013).

Future Considerations

Computer modeling affords several advantages in the study of ischemia. It allows us to accurately measure many reactants simultaneously in exceedingly complex environments. We can link top-down and bottom-up models of ischemia to create robust multicellular models. We have also begun to understand how genetic regulation and preconditioning effects may confer neuroprotection. And, importantly, we can identify control points for cascade modulation, which are appropriate targets for therapeutic intervention. Such research will likely provide proof of concept and system extrapolation for the development of new drugs to encourage recovery or enhance the duration of recoverability in the penumbra.

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Brain-Computer Interfaces

► [Functional Neuroscience: Cortical Control of Limb Prostheses](#)

BrainInfo

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Definition

BrainInfo can be thought of as a Web-based handbook of neuroanatomy. It is an authoritative resource for computational neuroscientists and others who need a quick in-depth orientation to specific structures in the central nervous system (CNS). BrainInfo has three components. The **BrainInfo Portal** provides extensive descriptive information and images of some 2500 brain structures; **NeuroNames** is a neuroanatomical ontology that provides standard English names for the structures plus 13,000 synonyms in eight languages; and **NeuroMaps** provides brain atlases of the macaque and mouse together with tools for mapping data and processing images for publication.

Detailed Description

The BrainInfo Portal (<http://braininfo.org>)

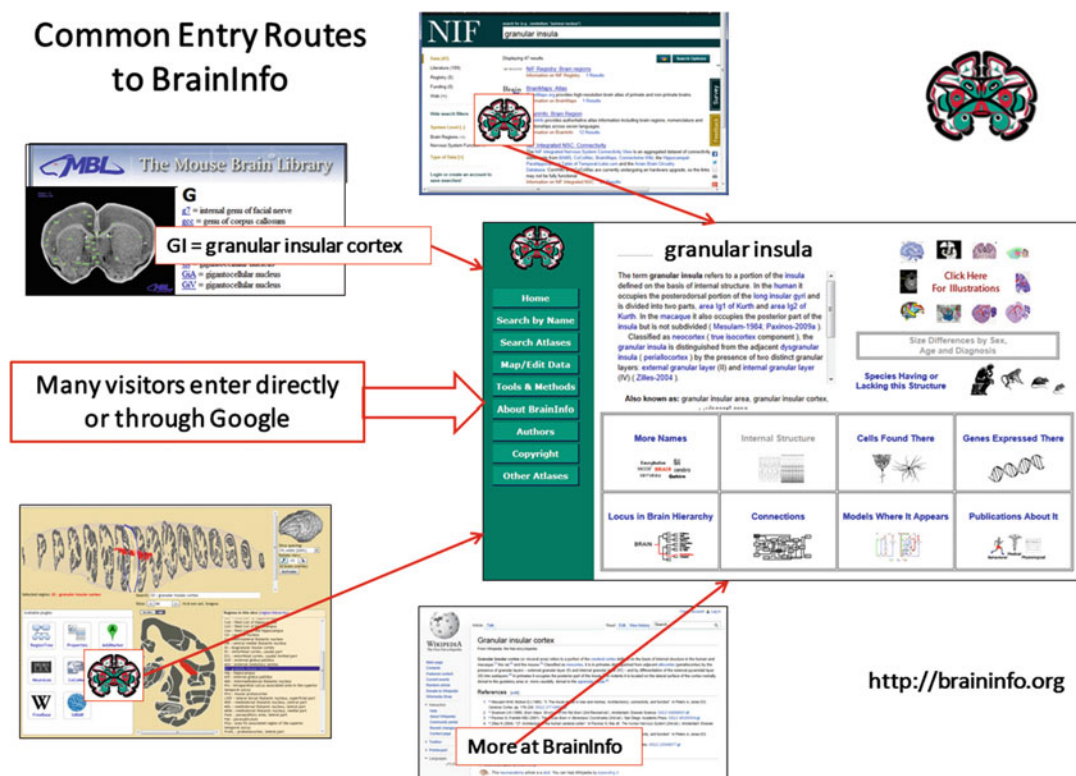
Users enter the Portal by several routes. Most enter via Google or via a page that they have previously bookmarked. Many also enter through

other websites that focus on a specific aspect of neuroanatomy, such as the brain of a particular species or the inputs and outputs, cell types, or gene expression in structures. Such sites link to BrainInfo to give users one-click access to a wider range of information on specific neural structures (Fig. 1). A guide to use of the Portal is found at Bowden and Dubach (2005).

BrainInfo, in turn, links out to pages in some 50 other websites to provide users access to information and illustrations of some 2500 structures and superstructures in the CNS of the four species most studied by neuroscientists: the human, macaque, rat, and mouse (Fig. 2, SPECIES). With more than a thousand distinct cell groups identified in the mammalian brain, mastering the neuroanatomy is a challenge. The challenge is magnified several times by variability across species, methods of identification, and nomenclature (Bowden and Martin 1997).

The Portal is designed particularly for neuroscientists who work in disciplines other than anatomy. It is for those whose knowledge of neuroanatomy is limited and who need rapid access to information that is scattered under a variety of names and across numerous publications and websites. The computational neuroscientist who comes upon an unfamiliar structure in a model system, or the psychiatrist who encounters an unfamiliar structure in reading about the neural mechanism of a classical disorder, can *Search by Name*, and BrainInfo will display the Central Directory to a wealth of text and images of the structure (Fig. 2).

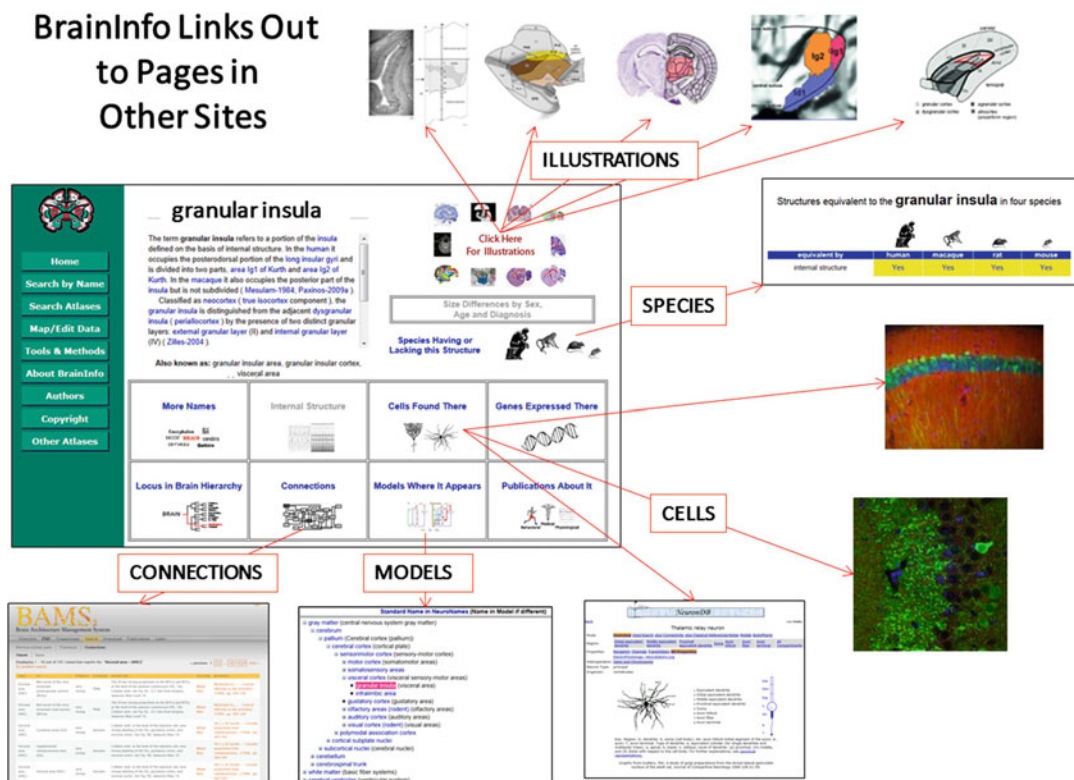
The geneticist or molecular biologist who finds gene expression in an unfamiliar brain area can *Search Atlases*, find the area, and click it, and BrainInfo will display the Central Directory for the structure together with its standard name, a



BrainInfo, Fig. 1 Visitors enter BrainInfo either directly, through Google, or through links from many other websites including the Neuroscience Information Network

(NIF), the Mouse Brain Library (MBL), the Scalable Brain Atlas, and Wikipedia

BrainInfo Links Out to Pages in Other Sites



BrainInfo, Fig. 2 The BrainInfo Portal links out to pages deep in some 50 other neuroscience websites that illustrate most accurately, clearly, and thoroughly the anatomical

relations and internal features of CNS structures in the human, macaque, rat, and mouse

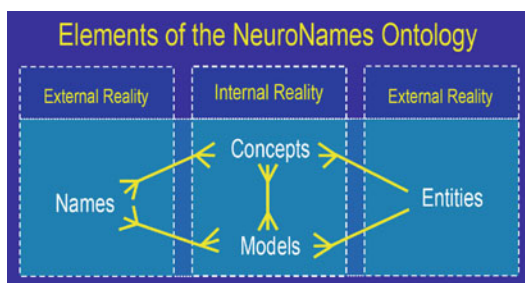
brief description, illustrations, kinds of neurons it contains, inputs, outputs, and so forth.

NeuroNames (<http://braininfo.rprc.washington.edu/Nnont.aspx>)

Neuroanatomical terminology is unusually confusing. Beginning in the late 1800s, scientists in multiple countries, studying the brains of many species, and publishing in multiple languages, contributed an overwhelming array of redundant and overlapping terms to the vocabulary (Bowden and Martin 1997). The typical brain structure has an average of six English and Latin names, many of which appear in the text and labels of today's publications and websites. The *standard nomenclature* of NeuroNames reflects an attempt to relate every name of a CNS structure in the neuroscience literature to a defined structure and to select one of those terms as its standard name.

All anatomical information in BrainInfo is indexed according to the standard nomenclature of the NeuroNames ontology. The ontology defines the relations between ~15,500 *names* (character strings), for ~2500 *concepts* (definitions) of the *entities* (structures) they represent in different *models* (hierarchies or networks) of CNS organization (Fig. 3).

The NeuroNames ontology allows visitors at the input interface of BrainInfo to *Search by Name* using not only the standard term but any synonym or homonym for the structure of interest. It includes all English terms for all structures and names for the most common ~1000 structures in seven other languages: French, German, Indonesian, Italian, Latin, Russian, and Spanish. On the output side, when BrainInfo sends a visitor to a website that uses a different name than the NeuroNames standard, a message box in the



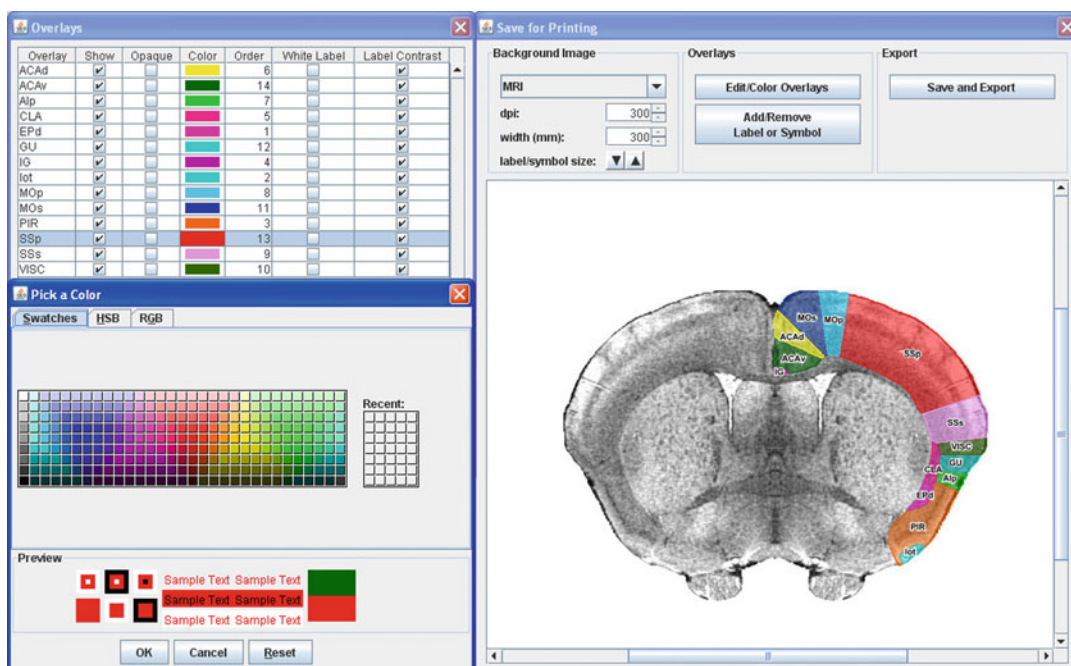
BrainInfo, Fig. 3 NeuroNames is an informatics tool for resolving neuroanatomical ambiguities (Bowden et al. 2012b). In neuroanatomy, the same name (*left panel*) can represent multiple concepts (the homonym problem); and the same structural concept, or model composed of structural concepts (*central panel*), can have multiple names (the synonyms problem). A given model includes multiple concepts, and the same concept can occur in multiple models. Different scientists can hold different concepts of the same entity (*right panel*) and can model a complex entity in different ways. The NeuroNames ontology resolves naming and conceptual ambiguities by assigning a unique standard name to each concept and specifying the relations of all other names (as synonyms or homonyms) to the standard name and its concept

sidebar informs the visitor, “Look for [*the local name*].”

Developers of other neuroscience websites use NeuroNames to index databases in the standard nomenclature and to allow visitors to enter their websites using any synonym for structures (Bowden et al. 2012a). The ontology is freely downloadable from BrainInfo in either XML or Excel format. Both versions include the web address (URL) of BrainInfo’s Central Directory for each structure, which allows developers to link their visitors to BrainInfo for more information (Fig. 1).

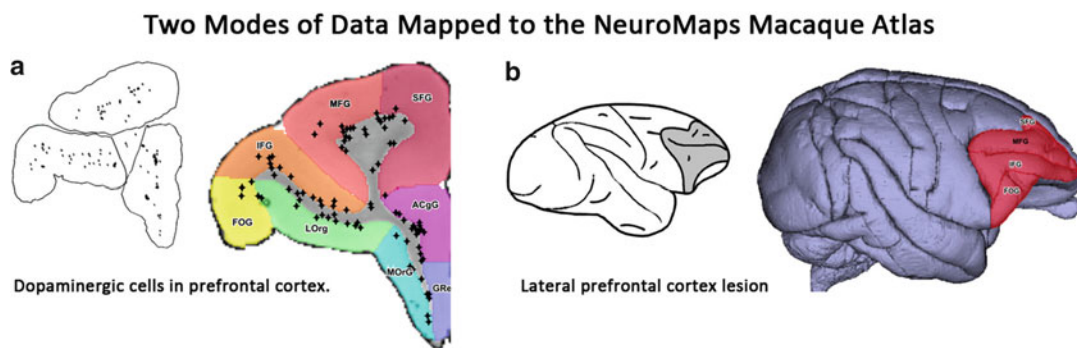
NeuroMaps (<http://braininfo.rprc.washington.edu/MapViewData.aspx>)

Neuroanatomy is the common ground of the various neuroscientific disciplines. All data, whether of gene expression, functional MRI activity, or neuronal firing patterns, are related through the site in the brain from which they are recorded. NeuroMaps provides standard atlases of the



BrainInfo, Fig. 4 The NeuroMaps image processor enables users to adjust the size, colors, labels, and resolution of images for projection and publication. Here, the boundaries of cytoarchitectural areas in the cerebral cortex

of the mouse in the Allen Brain Atlas (AIBS 2008) have been mapped to the NeuroMaps symmetrical version of the Waxholm mouse brain (Bowden et al. 2011)



BrainInfo, Fig. 5 NeuroMaps illustrations: (a) dopaminergic cells at the gray-white boundary of prefrontal cortex (Dubach 1994) and (b) a lesion of lateral prefrontal cortex

that produces a top-down attentional deficit in macaques (Rossi et al. 2007)

macaque and mouse brains to which investigators can map data of all modalities for comparison, projection, and publication.

Each NeuroMaps atlas is based on a high-resolution MRI (magnetic resonance image) oriented according to standard stereotaxic practice for the species; the left and right hemispheres are identical to ease comparison of data mapped to the two hemispheres (Bowden et al. 2011). NeuroMaps tools allow the investigator to slice, tilt, and rotate the atlas MRI to match the plane of section of tissue bearing the data. They allow the designation of unlimited pairs of registration points to match landmarks in the experimental image to landmarks in the atlas. The investigator draws boundaries around data areas in the experimental image. A mapping tool automatically transfers them by a nonlinear process to corresponding locations in the atlas. Image processing tools enable the investigator to size, color, label, and adjust the resolution (dpi = dots per inch) of the merged image to match specifications of the journal where it is to be published (Fig. 4).

The NeuroMaps image processor can display data in multiple formats. The cross-sectional display of areal data (Fig. 4; BrainInfo 2013a) is suitable for mapping fMRI activation, gene expression, lesions, injection sites, and projection areas. Similar cross-sectional displays are used for mapping point data: stimulation sites, recording sites, and individual neurons stained for specific enzymes, receptors, or neurochemistry (Fig. 5a).

The three-dimensional MRI model is suitable for mapping surface areas, such as architectonic areas and cortical lesions (Fig. 5b; BrainInfo 2013b).

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Brain-Machine Interface and Neuroimaging

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Synonyms

[Brain computer interfaces](#); [Neural prosthetics](#)

Definition

Brain machine interfaces (BMIs) directly connect brain activity and devices outside the brain for such purposes as sensory substitution, motor compensation and enhancement, neurorehabilitation, suppression of maladaptive neural circuits, and treatment for brain lesions and neurological and psychiatric disorders. A BMI usually consists of some of the following electrical, mechanical, and computing elements: a brain activity measurement system (electrodes, amplifier, AD converter, etc.), a computer for decoding brain information and/or controlling stimuli to the brain, an effector system (prosthetic limb, rehabilitation robot,

computer cursor, etc.), and a neural stimulation system.

Detailed Description

BMIs can be classified from at least the following three viewpoints. The first classification concerns which brain function is substituted, compensated, enhanced, or cured by BMI. Only three very basic functions are listed here: sensory processing, central decision-making, and motor control, which includes communication. The second addresses the BMI's objective: the substitution, compensation, and enhancement of lost or normal brain functions, or the cure, recovery, and rehabilitation of degraded brain functions. The third classification of BMI is whether it is invasive, i.e., whether it uses thin wire electrodes, semiconductor electrodes, electrocorticograms (ECoG; EEGs directly attached to the cerebral cortex surface), deep brain electrodes for brain activity measurement and/or electrical stimulation; or whether it is noninvasive, using scalp EEGs, fMRIs, NIRSSs, and so on. Theoretically, we have $3 \times 2 \times 2 = 12$ different BMI classes, but only a few have become practical. Below we explain some of the roughly two thirds that are actively being developed.

1. An artificial sensory organ or sensory BMI is an invasive system of sensory-function substitution for handicapped people. Artificial sensors, such as microphones or CCD cameras, measure auditory or visual signals and are transformed as inputs to a neural stimulation system with multiple electrodes that electrically stimulate the peripheral sensory nerves or the central nervous system. The oldest, most successful example, with 30 years of practical usage, is the cochlear implant. Artificial retinas have also nearly become practical. Visual cortex stimulation (artificial vision) and artificial vestibular systems are under active research and development.
2. A Brain Computer Interface (BCI) resembles a BMI in its wider definition, but in its narrower

- usage, it is a noninvasive BMI used to compensate for lost motor functions. An EEG-BCI uses such varied features as sensorimotor cortex μ rhythm, slow cortical potential, and the P300 to decode movement parameters including gaze direction and to control an interface, including controlling a computer mouse or selecting a character for communication (Birbaumer et al. 1999). Some BCIs are practical and/or commercially available. As rare examples of nonmedical BMI applications, inexpensive examples have been developed for gaming.
3. Neural prosthetics or BMIs in a narrow sense are an invasive BMIs used to compensate for lost or damaged motor functions. Proof of the concepts was demonstrated around 2000 in rodents and monkeys by pioneers such as Johan Wessberg (Wessberg et al. 2000), Andrew Schwartz (Taylor et al. 2002), and John Donoghue, and the technique was translated into human patients around 2005 (Hochberg et al. 2012). Invasive electrodes measure brain activity (several tens to a few hundred neurons), a decoder extracts the motor command information from neural signals, and finally an effector system is controlled by this extracted movement information. Users observe the results of the effector actions, and a loop is closed connecting the brain, the measurement system, the decoder and the effector, and the signals are returned to the brain. This is one of the most actively studied classes of BMI in the past 15 years. Subdural ECoG electrodes have recently attracted attention because they are more stable than the intracortical electrodes that are inevitably associated with scars. These less invasive BIM systems, which are not invasive to the brain itself, might be quite practical because decoding of the three-dimensional arm trajectory of monkeys using ECoG did not significantly deteriorate for a year or two (Chao et al. 2010), and ECoG-BMI can control a multi-joint robot arm and a hand system with exactly the same decoding parameters for over a week in humans (Yanagisawa et al. 2012).
 4. An EEG-BMI rehabilitation system is a noninvasive BMI used for the recovery of motor functions in stroke patients. This has opened up a quite promising newly-emerging BMI application field. With conventional rehabilitation protocols, useful (i.e., graspable) hands are restored in only 15% of stroke patients but that figure increases to around 80% with BMI rehabilitation. Pioneers Jun-ichi Ushiba and Meigen Liu recorded sensorimotor cortex μ rhythms from severe stroke patients whose extensor muscles could not even generate EMG, and decoded their movement intention based on the decrease in the μ power: event-related EEG desynchronization. When the decoder output was successful, both visual and kinesthetic feedback was given to patients via a robotic splint that extended their paralyzed wrists and fingers (Shindo et al. 2011).
 5. fMRI-decoded neurofeedback (DecNef) can be used as a noninvasive BMI system for treating abnormal central decision-making functions in psychiatric disorders (Kawato WFSBP Plenary talk 2013). Shibata, Watanabe, Sasaki, and Kawato developed DecNef, by means of which spatial activity patterns in a specific brain area can be noninvasively controlled through real-time fMRI neurofeedback (Shibata et al. 2011). First, a decoder is obtained that classifies BOLD signal patterns by visual attributes, emotional states or normal and pathological states in psychiatric disorders. In the induction stage, volunteers unconsciously control their brain activity so that a desirable pattern is produced while being guided by a real-time reward signal computed as the decoder output. Thus, three important elements of DecNef are decoding of information from fMRI brain activity, real-time neurofeedback of decoded information, and unconscious reinforcement learning by participants.
- In most BMIs, except the sensory substitution BMI, necessary brain information is first extracted from brain activity signals using a decoder. This information is transformed and fed back to users in some sensory modality with/without

reward signals, and finally BMI users learn to change their brain networks based on synaptic plasticity. In these three steps, computational neuroscience plays a critical role. For example, computational motor control models outline the neural prosthetics paradigm to record from many neurons, and use their firing frequencies to decode movement kinematics (Georgopoulos et al. 1982). Computational models also play important roles in non-invasive decoding algorithms (Miyawaki et al. 2008). Finally, neural operant conditioning in BMI users (Fetz 1969) can be understood from computational algorithms derived from supervised and reinforcement learning theories.

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Brain-Machine Interfaces

► [Functional Neuroscience: Cortical Control of Limb Prostheses](#)

Brain-Machine-Brain Interface

► [Recurrent Brain-Computer Interfaces](#)

BrainMap

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Definition

BrainMap is an online community database that archives the results of published functional and anatomical neuroimaging

experiments and their associated metadata (<http://brainmap.org>). Experimental results and metadata are archived into the database according to an expert-refined taxonomy developed to describe the experimental procedure employed in each publication within the database. Users may input publications and their associated neuroimaging results to the database using the *Scribe* application (<http://brainmap.org/scribe>) or search the database for publications of interest by applying filters in the *Sleuth* application (<http://brainmap.org/sleuth>). Coordinates of activation resulting from filtered searches may be downloaded and exported for further meta-analysis using the *GingerALE* application (<http://brainmap.org/ale>), which uses the activation likelihood estimation algorithm (ALE; Turkeltaub et al. 2002; Eickhoff et al. 2009).

Detailed Description

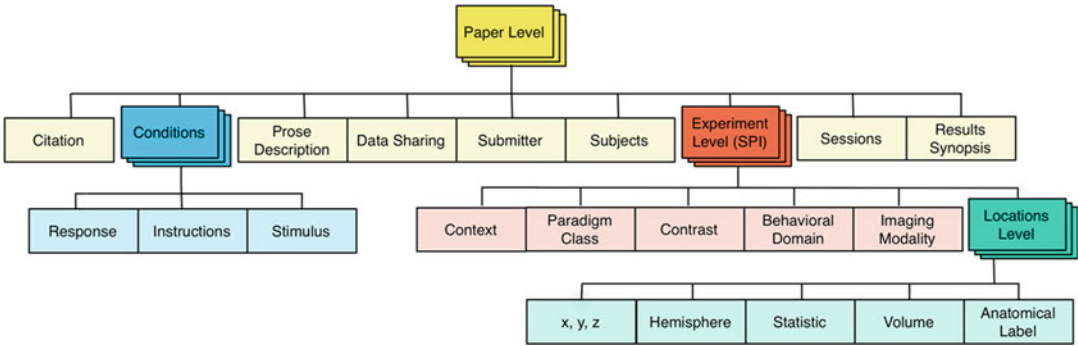
The advent of magnetic resonance imaging and positron emission tomography to acquire functional data of the human brain revolutionized the way scientists examined neural systems associated with cognition, perception, and action. Consequently, the volume of functional imaging publications has been increasing exponentially since in the early 1990s. Introduced over two decades ago, the BrainMap database (<http://brainmap.org>) was created to archive the results of the growing number of neuroimaging publications in a manner that leads to optimum accessibility (Fox et al. 1994; Laird et al. 2005, 2009). The BrainMap Project supports a database of functional neuroimaging experiments, as well as voxel-based morphometry database (VBM). Currently (as of October 2013), the BrainMap Functional Database includes 2336 publications, which reported the results of 11,103 functional activation experiments across a total of 45,188 subjects, while the BrainMap VBM Database includes 796 publications, which reported the results of 2444 structural neuroimaging experiments across a total of 55,222 subjects.

Standardized Coordinates

Neuroimaging experiments report locations of activation or deactivation as three-dimensional coordinates (x,y,z) in standard space. This practice allows for more precise quantitative localization of activation rather than qualitatively describing the structure associated with the activation. Due to the variability between each subjects' brain morphometry, activation coordinates are transformed into a common coordinate system for comparison across multiple subjects. The two best-known reference spaces for the human brain were developed by Talairach and Tournoux (Talairach and Tournoux 1988) and the Montreal Neurological Institute (MNI; Collins et al. 1994).

BrainMap Coding Scheme

A hierarchical taxonomy (Fig. 1) was developed for BrainMap such that the results of publications could be coded into the databases according to information about the subject population, task, imaging modality, or behavioral conditions associated with the experiment. The cataloguing of information in this manner not only provides consistent labeling of each experiment but also promotes rapid retrieval from the database. The publication is first coded according to citation information: publication journal and year, institution, and authors. Additional metadata fields include subject description (e.g., age, gender, handedness, ethnicity) and diagnosis (e.g., healthy or diseased), which are all fully described at the publication level. The published three-dimensional (x,y,z) coordinates extracted from statistical parametric images are archived from each experiment. Individual experiments are classified according to paradigm class, which describes the specific task being performed, and behavioral domain, which describes the cognitive construct being studied. The statistical contrasts of interest (e.g., "Task – Rest") producing the statistical parametric image are also archived at the experiment level (Fox and Lancaster 2002). When published coordinates are entered into the BrainMap database, MNI coordinates are



BrainMap, Fig. 1 Hierarchy of BrainMap coding scheme. Each publication consists of three levels of descriptors. At the highest level of each publication, general information about citation information, subjects, and summaries of the experimental design and results are

encoded. The condition level is composed of information about the behavioral stimulus, instructions, and response. The experiment level includes metadata fields that describe the contrasted brain images, with a tertiary level for archiving coordinate locations

transformed into Talairach space (Lancaster et al. 2007), and vice versa, providing the option for coordinate extraction in either coordinate system. Additionally, activation volume extent, statistical parameter, and significance level are all archived with each experiment.

Activation Likelihood Estimation

Since the results of neuroimaging experiments are typically reported as three-dimensional coordinates in standard space, the primary purpose of BrainMap is to support coordinate-based meta-analyses of functional and structural neuroimaging studies. Once a set of experimental results is identified in *Sleuth*, it is exported to *GingerALE* to perform a coordinate-based meta-analysis using the ALE algorithm. The ALE score determines the probability that a given location was reported active across the experiments selected. A permutation test has been implemented to test for statistical significance. The ALE method yields locations of consistent activation patterns across a set of similar neuroimaging experiments, which offers many benefits to simply reviewing the images on an experiment-by-experiment basis.

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Brainstem Auditory Evoked Potentials (BAEP)

► Auditory Brainstem Responses

Brainstem Motoneurons, Models of

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Definition

Brain stem motoneuron models are mathematical representations of the input–output properties of motoneurons located in the different motor nuclei of the brain stem.

Detailed Description

Several classes of mathematical models have been developed to describe the input–output properties of the resident motoneurons of the different motor nuclei of the brain stem (i.e., abducens, facial, hypoglossal, oculomotor, trigeminal, and trochlear). These models range in complexity from simple “black box” analytical models (Poliakov et al. 1997; Powers et al. 2005) to complete Hodgkin-Huxley-type ionic conductance-based models with reconstructed dendritic trees (Kulagina 2011). The choice of model type has been largely dictated by the question at hand, i.e., responses to synaptic inputs, intrinsic properties, aggregate or pool behavior, and contribution to neural circuits. In all variants, these models have proved extremely useful in the quantitative analysis of electrophysiological recordings from motoneurons and in the interpretation of studies of movements controlled by brain stem circuits (e.g., eye movements, breathing, and swallowing).

The analytical models typically involve recording the responses of brain stem motoneurons to electrical noise injected across the cell membrane through an intracellular electrode. The resultant spike trains are analyzed using systems identification techniques that typically yield two-stage cascade models, consisting of a linear input filter and a static nonlinearity (e.g., Poliakov

et al. 1997) or alternatively autoregressive-moving average models that differentiate the roles of input filtering and intrinsic spike-generating conductances in governing motoneuron discharge behavior (Powers et al. 2005). These models are useful in describing how brain stem motoneurons respond to the excitatory and inhibitory synaptic inputs they receive.

Partial Hodgkin-Huxley type ionic conductance-based models (Powers et al. 1999; Pierson et al. 2001; Purvis and Butera 2005) have been used to understand the mechanisms underlying spike-frequency adaptation of brain stem motoneurons and their responses to neuromodulators. More recently, complete Hodgkin-Huxley type ionic conductance-based models with reconstructed dendritic trees (Kulagina 2011) have been used to study how the topographic location of synaptic inputs and the presence of voltage-gated conductances in the dendritic membrane shape motoneuron discharge behavior.

To study the aggregate behavior of a pool of brain stem motoneurons, the individual cells are typically modeled as *integrate-and-fire* elements that begin discharging when a threshold input current is encountered and have their firing frequencies modulated in accord with a specified current-frequency transform. Such models may capture some of the variability inherent in a population of motoneurons by varying the threshold and current-frequency gains and are useful for determining the relative contributions of intrinsic electrical properties versus the distributions of specific synaptic input systems to motor output (Dean 1997). Integrate-and-fire representations of brain stem motoneurons are also useful in modeling brain stem circuits where the detailed physiology of the cellular elements is sublimated to the goal of understanding the behavior of the system (e.g., Scudder et al. 2002).

Cross-References

- [Hodgkin-Huxley Model](#)
- [Neural Population Model](#)
- [Spike Train Analysis: Overview](#)

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Brian Spiking Neural Network Simulator

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Definition

Brian (<http://briansimulator.org>) is an open source Python package for developing simulations of networks of spiking neurons (Goodman and Brette 2008, 2009). The design is aimed at minimizing users' development time, with execution speed as secondary goal. Users specify neuron and synapse models by giving their equations in standard mathematical form, create groups of

neurons, and connect them via synapses. The intent is to make the process as flexible as possible so that researchers are not restricted to using neuron and synapse models already built into the simulator. The entire simulator is written in Python, using the NumPy and SciPy numerical and scientific computing packages. Parts of the simulator can optionally be run using C++ code generated on the fly (Goodman 2010). Computationally, Brian uses vectorization techniques (Brette and Goodman 2011) so that for large numbers of neurons, execution speed is of the same order of magnitude as C++ code (Goodman and Brette 2008).

Detailed Description

Philosophy

The aim of Brian is to be, in order of priority:

1. Easy to learn, use, and understand.
2. Expressive and flexible.
3. Computationally efficient.

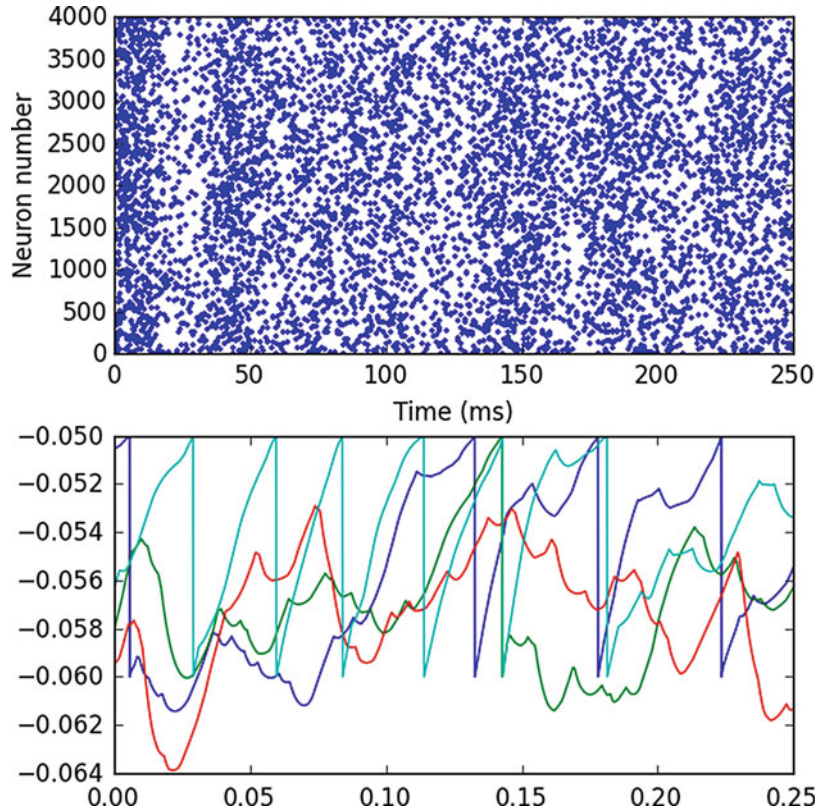
These choices were designed to both encourage correct and reproducible simulations and to minimize the development time of a simulation study as this is often much greater than the simulation time (Fig. 1).

Overview and Example

A simulation written with Brian is a Python module (script) that typically involves doing at least the following:

1. Import the Brian package.
2. Define parameters and equations.
3. Create groups of neurons with the NeuronGroup object.
4. Create synapses with the Connection or Synapses objects.
5. Specify variables to be recorded using SpikeMonitor and StateMonitor objects.
6. Run the simulation with the run function.
7. Analyze and plot the output.

Brian Spiking Neural Network Simulator,
Fig. 1 Example output of
 Brian simulator



The following example illustrates these steps
 (the output is shown below) (Fig. 1):

```
from brian import *
eqs = """
dv/dt = (ge+gi-(v+49*mV))/(20*ms) : volt
dge/dt = -ge/(5*ms) : volt
dgi/dt = -gi/(10*ms) : volt
"""
P = NeuronGroup(4000, eqs,
threshold='v>-50*mV', reset='v=-60*mV')
P.v = -60*mV+10*mV*rand(len(P))
Pe = P.subgroup(3200)
Pi = P.subgroup(800)
Ce = Connection(Pe, P, 'ge',
weight=1.62*mV, sparseness=0.02)
Ci = Connection(Pi, P, 'gi', weight=-9*mV, sparseness=0.02)
spikemon = SpikeMonitor(P)
statemon = StateMonitor(P, 'v',
record=range(4))
run(250*ms)
subplot(211)
raster_plot(spikemon)
```

```
subplot(212)
statemon.plot()
show()
```

Design

Brian is designed around equations: users specify neuron models in terms of differential equations in standard mathematical notation rather than using predefined neuron types, and event code such as threshold condition or reset code is also specified in terms of mathematical expressions or statements in standard notation. For example:

```
eqs = """
dv/dt = (ge+gi-(v+49*mV))/(20*ms) :
volt
dge/dt = -ge/(5*ms) : volt
dgi/dt = -gi/(10*ms) : volt
"""
```

The text after the colon on each line gives the units of the variable being defined (v, ge, gi here).

Equations are required to be dimensionally consistent.

Features

Brian has support for the following basic features:

- Define neuron models using arbitrary differential equations, threshold conditions, and reset codes.
- Define synaptic neuron models using arbitrary synaptic differential equations and propagation equations.
- Define parameter values using SI units.
- A library of standard neuron and synapse models.
- Record neuron activity, both spikes and traces.
- Plasticity (STDP, STP, arbitrary user-defined plasticity models).
- Gap junctions.
- Nonlinear synapses.

In addition, Brian comes with the following extension packages:

- Model Fitting (Rossant et al. [2010](#), [2011](#)). This package fits a user-specified neuron model to electrophysiological data. Fitting can be performed in parallel over multiple CPUs, multiple machines, and, if available, using graphics processing units (GPUs) for a speed improvement up to $60\times$.
- Brian Hears (Fontaine et al. [2011](#)). This package is for simple and efficient modeling of the auditory periphery. It consists of a base library for performing filter-based modeling, as well as implementations of many standard filter banks used in auditory periphery modeling.
- Electrophysiology. Models of electrodes and amplifiers, compensation, and analysis methods.

The online support for Brian consists of the following:

- Extensive documentation, including tutorials, examples, a manual, and a reference section.
- An online support mailing list, with feedback from developers and other users.

Cross-References

- [GENESIS, the GEneral Neural Simulation System](#)
- [MOOSE, the Multiscale Object-Oriented Simulation Environment](#)
- [NEST: the Neural Simulation Tool](#)
- [NEURON Simulation Environment](#)
- [PyNN: a Python API for Neural Network Modelling](#)
- [Software Tools for Modeling in Computational Neuroscience: Overview](#)

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Brute-Force Model Databases

- [Neuronal Model Databases](#)

Bursting in Neurons and Small Networks

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Definition

Bursting refers to patterns of neural activity consisting of episodes of relatively fast spiking separated by intervals of quiescence. Bursting neurons are ubiquitous in the nervous system and play important roles in the production of motor, sensory, and cognitive behaviors. Because bursting is the predominant mode of activity in *central pattern generator* (CPG) networks that underlie rhythmic motor activity, bursting neurons have been best characterized in invertebrate CPG networks. Bursting neurons fall into two classes, based on whether bursting is an intrinsic neuronal property, resulting solely from the interaction among ionic currents, or whether it is a network property, emerging from the interaction among ionic and synaptic currents.

Detailed Description

Introduction and Background

Bursting patterns consist of episodes of relatively fast spiking (bursts) separated by intervals of either quiescence or subthreshold activity such

as subthreshold oscillations (Kispersky et al. 2010; Malashchenko et al. 2011; Desroches et al. 2013). Bursting is ubiquitous in the nervous system and has been shown to play an important role in the generation of network rhythmic patterns (Nusbaum and Beenhakker 2002). Bursting neurons are of particular importance in rhythmically active CPG networks, which control the ongoing motor behaviors that underlie coordinated activity such as swimming, invertebrate heartbeat, feeding, and limbed locomotion (Friesen and Pearce 1993; Calabrese 1995; Calabrese et al. 1995; Marder and Calabrese 1996; Smarandache et al. 2009).

Extensive research into the mechanisms that generate network bursting activity and its role in motor behavior has been done in invertebrates (Calabrese 1995; Nusbaum and Beenhakker 2002; Selverston 2005). *Invertebrate CPG networks* are comprised of a relatively small number of neurons and, in many systems, the intrinsic properties of the participating neurons, and the network connectivity is well known. These networks produce multiple complex outputs that control similar behaviors as the much larger CPG networks of vertebrate animals (Marder and Calabrese 1996).

Bursting activity can be generated by individual neurons or through synaptic interactions within networks. *Endogenous bursting* in individual neurons emerges as the result of the interaction among participating ionic currents, often in the presence of tonic excitatory drive (Harris-Warrick and Flamm 1987; Guckenheimer et al. 1993). Endogenous bursting neurons are often pacemakers of the networks in which they are embedded, which rhythmically drive follower neurons (Selverston 2005). Bursting may also emerge as a network phenomenon through synaptic interactions of individual neurons that are not necessarily endogenous bursters (Selverston et al. 2009). In such networks, the rhythmic properties cannot be ascribed to any individual neuron but emerge as a result of synaptic organization. However, as described below, network bursting can also involve endogenous bursters.

While bursting is a stereotypical mode of neuronal activity, there are qualitatively different

types of bursting patterns that differ not only in the bursting attributes (e.g., burst frequency, number of spikes per burst, inter-burst interval, duty cycle) but also in the mechanisms that govern their generation. These mechanisms can be investigated from two different, but complementary, perspectives: membrane biophysics and dynamics. The *biophysical mechanisms* involve the participating ionic and synaptic currents and neuromodulators that interact to generate bursting activity. The *dynamical mechanisms* involve nonlinearities, time scales, and bifurcations that govern the initiation and termination of the bursts, the duration of the inter-burst intervals, and additional properties of the bursting patterns. There is no one-to-one correspondence between these two mechanisms. In fact, different sets of ionic currents can give rise to qualitatively similar bursting patterns by the same dynamical mechanism, and, similarly, the same sets of ionic currents can give rise to different bursting patterns. This article focuses on the dynamical mechanisms of bursting and some of the biophysical mechanisms underlying the dynamical behavior.

Endogenous Bursting in Individual Neurons

Bursting patterns can be considered as bursts of spiking activity in otherwise quiescent neurons or, alternatively, as persistent spiking which is periodically suppressed. These contrasting descriptions can be used to describe the main mechanistic features of bursting: the burst initiation and termination. Additionally, a complete description of bursting activity must include an analysis of spiking properties within a burst, in particular, what determines the intra-burst spike frequency, as well as the dynamical properties of the *inter-burst intervals* (IBIs).

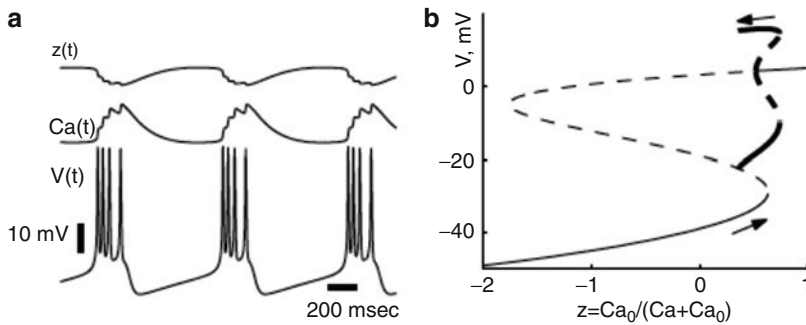
Classification of Bursting Neurons Using Bifurcation Theory

A classification of mechanisms of spike initiation and termination has been described in terms of bifurcations of dynamical systems (Izhikevich 2000b, 2007). Bifurcations describe the qualitative structural changes in the dynamics of the system. The dynamical systems analysis of neuron and network dynamics is based on the

assumption that the output of the system is the solution of a set of differential equations, based on the biophysical properties of the neurons and their synaptic connections. The number of variables in the differential equation is often referred to as the dimension of the system. From a mathematical viewpoint, these equations result in a stable solution trajectory (not necessarily solvable explicitly) that describe the time-dependent changes in the dynamical properties of the neurons, including the voltage trajectories. Using dynamical systems methods, these equations can be analyzed, often in a reduced form, by exploring the transitions between fast and slow kinetics. The *resting state* of a neuron, for example, may correspond to a stable *equilibrium* point of the dynamical systems equations. *Repetitive spiking*, in contrast, corresponds to a stable *periodic orbit* (limit cycle).

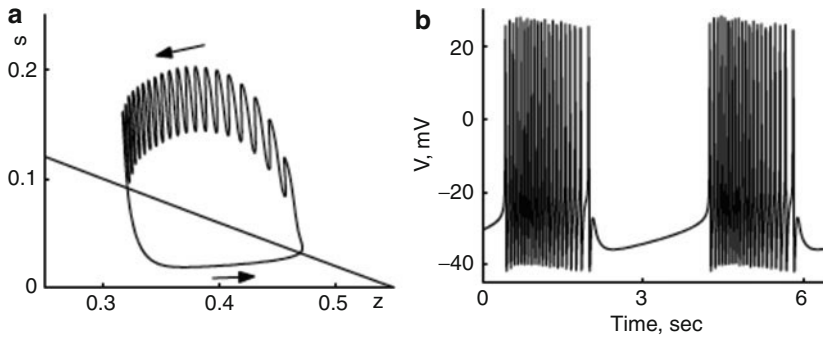
Dynamical systems often evolve in multiple time scales. For instance, the rest state of a neuron can, in a slow time scale, gradually drift to a more depolarized voltage and then suddenly transition to a spiking state. In the fast time scale, these transitions appear as sudden changes in the geometric properties of the system: a stable fixed point (rest state) suddenly changes into an unstable one, and a stable periodic orbit (spiking) appears. These transitions reflect the bifurcations of the underlying dynamical system. A thorough study of the bifurcations underlying the generation and termination of bursting activity can be found in Izhikevich (2000b).

In the classification of bursting dynamics, the underlying bifurcations of the fast dynamics can be used to describe the overall burst structure. For instance, a saddle-node (SN) bifurcation and a homoclinic (HOM) bifurcation govern burst initiation and termination, respectively, in *square-wave* bursters (Fig. 1). In contrast, both burst initiation and termination in *parabolic* bursters (Fig. 2) are governed by saddle-node on an invariant circle (SNIC) bifurcation (Rinzel and Lee 1987; Butera et al. 1996; Rinzel and Ermentrout 1998). *Elliptic* bursters involve a subcritical Andronov–Hopf bifurcation (**sub-AH**) and an SN bifurcation for burst initiation and termination, respectively (Izhikevich 2000a) (Fig. 4). To a large extent, these bifurcations also govern the



Bursting in Neurons and Small Networks, Fig. 1 *Square-wave bursting in the modified Morris-Lecar model.* (a) Slow negative feedback via calcium accumulates during the burst and slowly decays during the silent phase. The slow accumulation of calcium activates $I_{K(Ca)}$, which subsequently terminates the burst.

Calcium concentration is governed by $Ca' = \epsilon(-\mu g_{Ca} m \infty(V)(V - E_{Ca}))$, $Ca_0 = 10$, $\epsilon = 0.005$, $\mu = 0.2$. (b) Bifurcation diagram showing the region of bistability and bursting. The bifurcation parameter z is a function of calcium. Arrows indicate the direction of the change in z during silent and active phases of bursting



Bursting in Neurons and Small Networks, Fig. 2 *Parabolic bursting in the modified Morris-Lecar model.* Model is the same as in Fig. 1 with an additional slow variable s to generate the underlying slow oscillation: $I_{Ca,s} = g_{Ca,s}(V - E_{Ca})$. (a) Projection of the bursting trajectory onto the slow-variable plane. Direction of movement is indicated with arrows. The straight line

represents the boundary between equilibria and oscillation for the fast subsystem when the slow variables are fixed; it is where the SNIC bifurcation occurs. Below the low-voltage steady state is the only fast subsystem attractor (silent phase), whereas above this curve there is an oscillation of the fast subsystem (spiking). (b) Time course of parabolic bursting

dynamics of both the intra-burst spike frequency and the IBIs, for example, the shape and amplitude of spikes, spike-frequency adaptation, and bistability (Cymbalyuk et al. 2002).

From a dynamical systems viewpoint, a simple model that is able to generate oscillatory behavior is two-dimensional and involves the interaction of voltage and a recovery variable. Voltage increases due to a positive feedback effect on a relatively fast time scale, typically generated by calcium or sodium. The recovery variable opposes the changes in voltage on a slower time scale and, in biophysical models, corresponds to a state

variable of a voltage-gated ionic current such as a potassium current. Although the classical Hodgkin-Huxley model is four-dimensional (Hodgkin and Huxley 1952), the spiking behavior in this model can be reduced to a two-dimensional model (Kepler et al. 1992) without losing significant information.

A simple way to produce bursting activity in a model is to use a two-dimensional system that produces spiking and add one or two slow variables that modulate the spiking activity. The dynamical variables that make up a bursting neuron can then be separated into two subgroups: fast

(if they evolve on the time scale of a spike) and slow (if they evolve on the time scale of a burst, roughly determined by the IBI), thus giving these models their name, fast–slow bursters. The bursting model can then be written in the following form:

$$X' = F(X, Y)$$

$$Y' = \mu G(X, Y),$$

where X is a vector of at least 2 fast variables for repetitive spiking. Y is a vector of slow variables that modulates fast spiking. The small parameter $\mu \ll 1$ is a ratio of fast–slow time scales. To determine the type of bursting activity that the dynamical system will exhibit, the slow variable Y is treated as a constant parameter in the fast subsystem equation $X' = F(X, Y)$. The parameter Y is used to determine the bifurcations in the geometric properties of the fast subsystem which correspond to the transitions at the burst onset and termination.

The number of slow variables necessary to produce bursting in a model neuron depends on the underlying generic burst mechanisms that involve additional specific mechanisms of burst initiation and termination. A bursting neuron can be driven by one of the two generic mechanisms: a *hysteresis loop* such as in the square-wave burster (Fig. 1), or a *slow wave*, such as in the parabolic burster (Fig. 2). Hysteresis loop refers to the existence of bistable dynamics in the fast subsystem: if the slow variables are kept fixed at a constant value (within some range), the fast subsystem will exhibit two attractors (a stable equilibrium point and a periodic orbit) simultaneously. Hysteresis-loop bursting requires only one slow variable, resulting in three total variables as a minimal model for bursting. The slow variable allows the bistable fast subsystem to transition between its two stable states in either of two ways (Rinzel and Ermentrout 1998). For example, when the trajectory is near the stable fixed point of the fast subsystem, the slow variable grows until this fixed point becomes unstable (through a fast subsystem bifurcation) and the trajectory transitions to the stable periodic orbit. The slow variable then

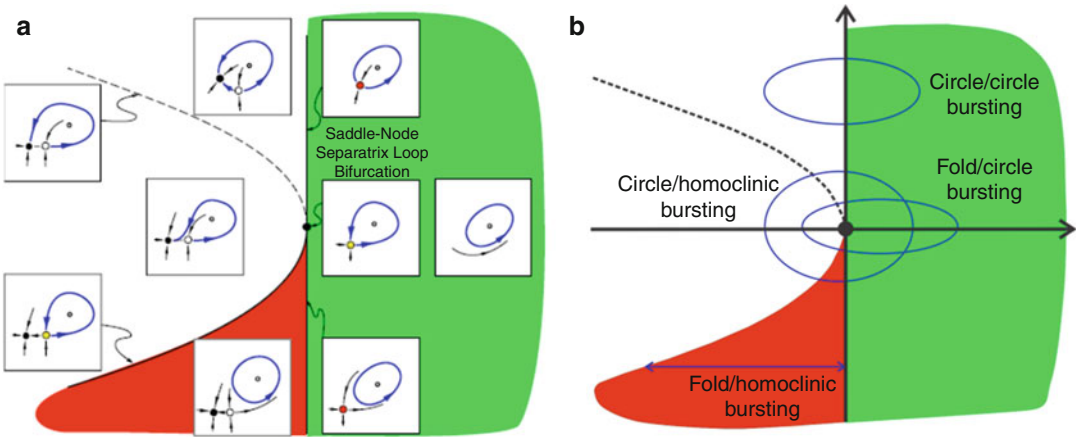
decays until the stable periodic orbit vanishes or becomes unstable (again through a fast subsystem bifurcation) and the trajectory transitions back to the stable fixed point and the cycle repeats.

In contrast, if the fast subsystem is monostable such as in the parabolic burster (Fig. 2), two slow variables will be necessary to generate bursting activity, resulting in a total of four variables for a minimal model of bursting. In this case, the slow subsystem requires two variables and exhibits an autonomous limit cycle attractor without feedback from voltage changes in the fast subsystem. The neuron bursts because the fast subsystem is driven periodically through SNIC bifurcations.

In what follows, we will think of a fast–slow burster as a slow system driving the fast system through various bifurcations that govern the initiation and termination of bursting activity. There are 16 possible pairs of bifurcations in hysteresis-loop bursters and 8 possible pairs of bifurcations in slow-wave bursters (Izhikevich 2000b). Each one of these bifurcations corresponds to a different topological bursting mode. Although not all these bifurcations have been found in biological neurons, this description has proved to be insightful. We discuss some of them in detail below (for additional information, see Izhikevich (2000b)).

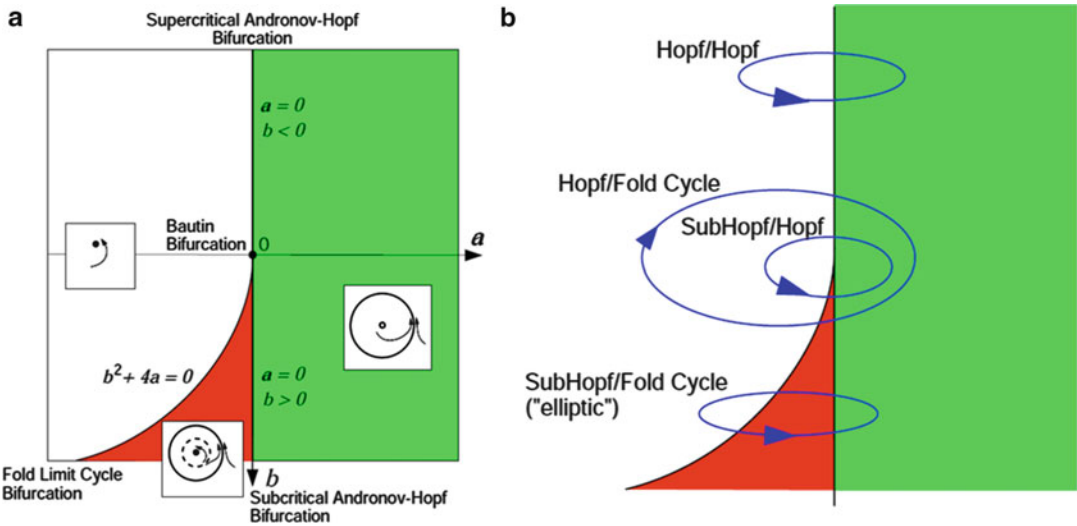
One of the 8 slow-wave bursters can arise from a pair of SNIC bifurcations (both burst onset and termination) and is also known as the circle–circle or parabolic bursting (Fig. 2). The topological type of the hysteresis-loop burster depends on whether the fast system is close to either an SN-homoclinic orbit or a Bautin bifurcation (Figs. 3 and 4). For instance, one of the 16 possible hysteresis-loop bursters involves sub-AH/fold combination of bifurcations to obtain an elliptic burster (Figs. 4 and 5).

The pairs of bifurcations that determine the initiation and termination of a burst can also be used to classify bursting neurons based on their intra-burst spike-frequency content. If the burst onset is through a SNIC bifurcation, the burst shows a progressive increase in spike frequency. If the burst termination is through a homoclinic orbit bifurcation, there is spike-frequency adaptation (a progressive lengthening of inter-spike intervals (ISIs)) near the end of the burst. This is



Bursting in Neurons and Small Networks, Fig. 3 Pairs of bifurcations in fast-slow hysteresis bursters with the fast subsystem near a saddle-node homoclinic orbit (SN-HOM) bifurcation. (a) Bifurcation diagram showing changes in the geometry of the fast subsystem as parameters are varied. (b) A system near

such an SN-HOM bifurcation may exhibit four different types of fast-slow bursting. Traversing from the red region to the green region leads to square-wave bursting in which burst initiation is through the fold (or SN) bifurcation and the burst termination is through a homoclinic orbit bifurcation

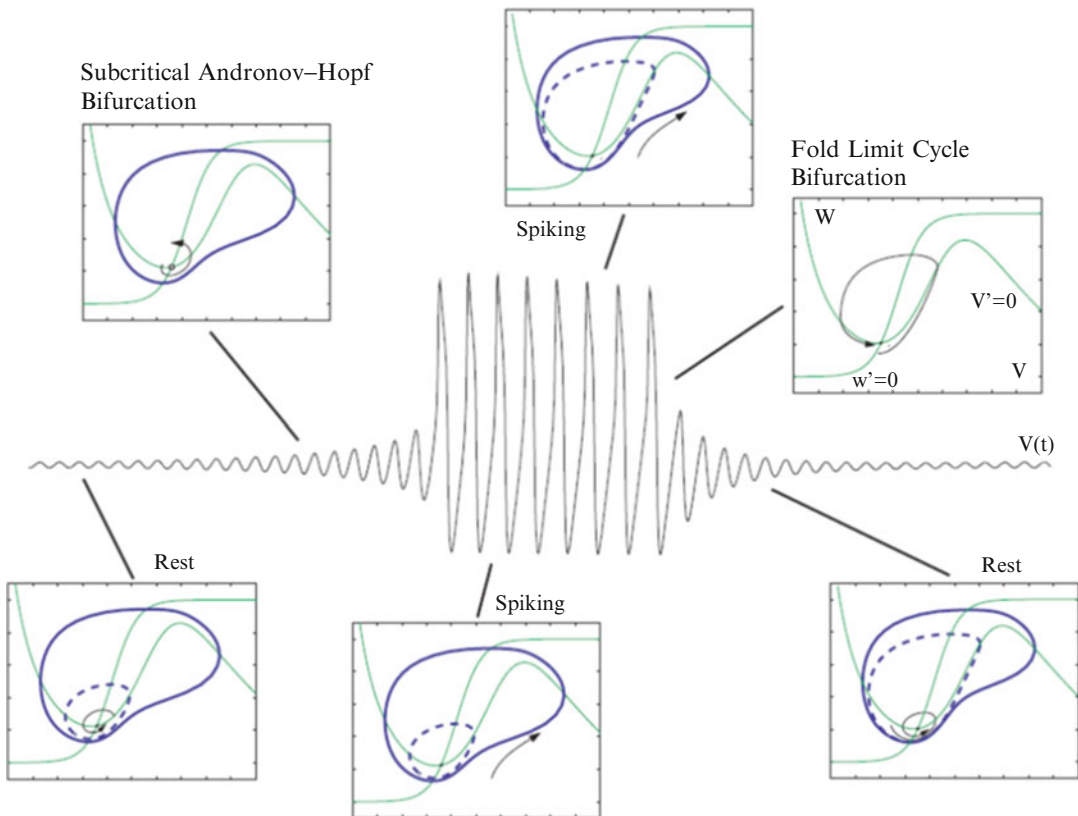


Bursting in Neurons and Small Networks, Fig. 4 Pairs of bifurcations in fast-slow hysteresis bursters with the fast subsystem near a Bautin bifurcation. (a) Bifurcation diagram showing changes in the geometry of the fast subsystem as parameters a and b in the topological normal form $z' = (a + i\omega) + b|z|^2 - z|z|^4$ are varied. When the system is near a Bautin (or Andronov-Hopf) bifurcation it may exhibit four types of bursting when the bifurcation parameters a and

b change. In the upper two quadrants, the bifurcation of the rest state takes place via the super-AH and in the lower two quadrants via the sub-AH bifurcation. (b) Four possible topological types of bursting with different bifurcations of the rest and spiking states. Traversing from the red region to the green region leads to elliptic bursting in which the burst initiation is through the sub-AH bifurcation and the burst termination is through the fold bifurcation

a prevalent feature in invertebrate bursting neurons. Guckenheimer et al. (1997) studied the scaling properties of ISIs at transitions associated with

a homoclinic bifurcation corresponding to the transition from spiking to quiescence. The homoclinic orbit bifurcation results in a spike frequency



Bursting in Neurons and Small Networks, Fig. 5 *Elliptic bursting in the Morris-Lecar model (variables V and w) with an additional $I_{K(Ca)}$. Green curves are nullclines $V' = 0$ and $w' = 0$ of the fast subsystem. As the neuron transitions from silence to bursting*

and back again, there is a clear sequence of changes in the geometry of the phase plane of the fast subsystem. These changes correspond to bifurcations. In the elliptic burster, burst initiation is through the sub-AH bifurcation, and burst termination is through the fold (or SN) bifurcation

that decreases as a function of the distance to the saddle. The proximity of homoclinic and a sub-AH bifurcation was used to explain the phenomenon of spike-frequency adaptation. The slow adaptation variable will cause the trajectories of the fast system to track a family of stable periodic orbits until the homoclinic bifurcation is reached, after which they become quiescent (Guckenheimer et al. 1997).

Models of Bursting Neurons

Bursting in neurons is a dynamical mechanism generated by the interplay of different types of ionic currents. There is not a one-to-one mapping between the sets of ionic currents and the stereotypical type of bursting patterns. Bursting mechanisms have been studied using biophysical

(conductance-based) models, which include a detailed description of the participating currents, or reduced models, capturing stereotypical bursting patterns in a relatively simple way, but lacking any correspondence to the underlying biophysics. Below, we briefly describe these two approaches with a special emphasis on biophysical models related to invertebrate systems.

Reduced Models

The simplest mechanism to generate bursting activity consists of a sinusoidally forced integrate-and-fire (IF) model (Lapicque 1907) where the subthreshold dynamics are linear. The sinusoidal input brings voltage above threshold for a portion of its period, thus causing persistent firing during an interval within this period and silence outside

it. This mechanism can be extended to include models with two- and three-dimensional linear subthreshold dynamics (with or without intrinsic subthreshold oscillations) and the quadratic integrate-and-fire models (Feng 2001). While the subthreshold dynamics in these models can be in principle connected to the biophysical properties of neurons, the spike initiation and termination mechanisms are ad hoc.

The integrate-and-fire-or-burst (IFB) (Smith et al. 2000) model is a generalization of the IF model to include an additional slow variable representing the de-inactivation of a simplified T-type calcium current (I_T) with instantaneous activation. The subthreshold dynamics are, therefore, two-dimensional. This additional current endows the model with the ability to exhibit post-inhibitory rebound (PIR). This model is able to generate bursts of activity when voltage is hyperpolarized enough to de-inactivate I_T . Since the threshold for de-inactivation is more depolarized than the resting voltage, the neuron can respond to a brief input with a burst of spikes. However, the intrinsic dynamics of the model does not produce enough hyperpolarization, and so periodic bursting requires an additional sinusoidal input current.

The FitzHugh–Rinzel (FHR) model (Rinzel 1986) is a three-dimensional generalization of the (two-dimensional) FitzHugh–Nagumo (FHN) model (Fitzhugh 1961; Nagumo et al. 1962; Fitzhugh 1969). The classical FHN forms the fast subsystem, which, to first approximation, produces oscillations when the (unstable) fixed point is located in the middle branch of the cubic V -nullcline. The transition from a stable fixed point to a stable limit cycle occurs through an Andronov–Hopf bifurcation as the tonic (DC) current is increased. In the FHR model, this control parameter is substituted by a slow variable, which governs the generation of elliptic bursting. Modifications to this model could, in principle, generate bursting activity by other mechanisms.

The Hindmarsh–Rose (HR) model (Hindmarsh and Rose 1984; Hindmarsh and Cornelius 2005) is also three-dimensional and slightly more complex than the FHR model. In contrast to the FHN

model, the fast subsystem of the HR model has a quadratic recovery-like nullcline that creates extra equilibrium points. This produces bistability through proximity to a saddle-node homoclinic orbit bifurcation. A slow adaptation variable provides the necessary negative feedback to generate square-wave bursting.

Minimal (Phenomenological) Biophysical Models

The two-dimensional version of the Morris–Lecar (ML) model (Rinzel and Ermentrout 1998) describes the generation of oscillatory activity as the result of the interaction of a non-inactivating calcium current with instantaneous activation and a delayed-rectifier potassium current. The mechanisms responsible for the generation of oscillations include the Andronov–Hopf and SNIC bifurcations and depend on the parameters describing the activation/inactivation curves and voltage-dependent time scales. The parameters of the basic ML model can be adjusted to simulate the envelope of bursting waveforms, which has been carried out in modeling the AB–PD neurons of the pyloric pacemaker in the crustacean stomatogastric ganglion (STG) (Skinner et al. 1994; Kopell et al. 1998). The substitution of a biophysical parameter (I_{app}) by a slow variable endows the ML model with the ability to generate bursting activity. One example is the bursting patterns generated by adding a calcium-activated K^+ current, $I_{K(Ca)}$:

$$I_{K(Ca)} = \tilde{g}_{K(Ca)} \left(\frac{Ca^p}{Ca^p + 1} \right) (V - E_K)$$

The modified ML model for bursting becomes

$$\frac{dV}{dt} = - \frac{(I_{Ca} + I_K + I_L + I_{K(Ca)})}{C}$$

$$\frac{dw}{dt} = \frac{\lambda[w_\infty - w]}{\tau(V)}$$

$$\frac{dCa}{dt} = \varepsilon(-\mu I_{Ca} - Ca)$$

As the calcium concentration varies, the system may become bistable so that the fast

subsystem can periodically switch back and forth between repetitive spiking and resting, thus producing bursting. The modified ML model is able to produce either *square-wave* or *elliptic* bursting patterns by changing parameter values that alters the type of bistability in the fast subsystem. Burst initiation by a sub-AH bifurcation produces an elliptic burster, whereas burst initiation by a saddle-node bifurcation produces a square-wave burster. To obtain the slow-wave oscillation underlying *parabolic* bursting in the ML model, the addition of one more variable is required to provide a slow positive feedback that counteracts the slow negative feedback of $I_{K(Ca)}$.

Biophysical Properties of Bursting Neurons

Bursting in neurons arises from a complex interaction between many ionic currents, where the actual ionic mechanisms may vary between different bursting neuron types. In most cases, bursting oscillations involve the presence of a slow inward ionic current. The current–voltage (IV) relationship of this inward current includes a negative slope region and results in an inverted bell-shaped structure which allows the inward current to become active regeneratively. Such currents include the persistent Na^+ current (I_{Nap}) and low-threshold inactivating calcium currents (I_{Ca}). Such currents can work together with other currents such as the slow calcium-activated non-selective cation current (I_{CAN}) and the hyperpolarization-activated inward current (I_h) to depolarize the membrane potential and produce a burst of action potentials. The activation of these inward currents, which leads to a burst of spikes, is counteracted by the slow activation of voltage- and calcium-dependent outward currents which terminate the burst. Moreover, some inward currents, such as the T-type calcium current, inactivate upon depolarization of the membrane potential, and this inactivation may also contribute to the termination of the burst.

Often neurons that do not burst in isolation can produce bursting activity in a network (as described in the next section). The pyloric network LP neuron does not burst endogenously but, in response to inhibitory input, can produce post-inhibitory rebound and plateau potentials

that support a burst of action potentials. These properties were described in detailed biophysical models of this neuron, first in a single-compartment model (Buchholtz et al. 1992; Golowasch et al. 1992) and, more recently, in a multi-compartment model that was used to explore how different ionic conductance levels can produce similar bursting output in this neuron (Taylor et al. 2009). In the biological network, the LP neuron receives periodic inhibition from the pacemaker neurons AB and PD which result in the production of bursting activity out of phase with the pacemaker bursts. Plateau potential generation is supported by a similar set of ionic currents as those that underlie bursting activity. For example, the low-threshold slowly inactivating I_{Ca} is substantially inactive at rest, but inactivation can be removed upon inhibitory input, thus promoting the plateau potential, often together with a burst of spikes. Zhang et al. (1995) showed that, in the dorsal gastric (DG) motor neuron of the STG, I_{CAN} , which is activated by calcium but is carried by Na^+ and K^+ , can underlie the plateau potential that results in a long after-depolarization and contributes to burst firing. The current usually acts alongside a low-threshold I_{Ca} , and the dynamical interaction can cause a strong regenerative current that supports plateau potentials.

The pacemaker AB neuron of the crustacean pyloric network is an endogenous burster whose bursting activity depends on the presence of extrinsic neuromodulatory inputs (Hooper and Marder 1987). Early attempts to dissect the ionic mechanism underlying endogenous bursting involved a plateau potential which is initiated and maintained by I_{Nap} and I_{Ca} and terminated by $I_{K(Ca)}$ (Gola and Selverston 1981). Burst frequency in AB is strongly dependent on calcium entry because burst frequency decreases with calcium entry and higher calcium entry results in a larger potassium-mediated post-burst hyperpolarization. The AB neuron employs different mechanisms for bursting under a variety of modulatory conditions (Harris-Warrick and Flamm 1987). A modeling analysis of the AB neuron bursting activity examined the mechanisms that generate and control bursting in this neuron and its electrically coupled partner, the PD neuron (Soto-

Trevino et al. 2005). This model demonstrated that the bursting in the AB neuron was crucially dependent on the modulator-activated inward current $I_{M\bar{D}}$, and, as discussed in the next section, the PD neuron greatly influences the duty cycle and dynamical range of bursting frequency in the pacemaker group.

Bursting can also occur solely due to the slow inactivation of I_{Ca} without the need for bistability. Two examples of ionic mechanisms underlying burst firing are the R15 neuron, located in the abdominal ganglion of the mollusk *Aplysia californica*, and the lobster cardiac ganglion interneurons. The essential ingredients for bursting in the R15 neuron are the negative slope region of I_{Ca} that determines the burst onset, together with the calcium-dependent inactivation of this current, which terminates the burst (Adams and Levitan 1985; Kramer and Zucker 1985). A biophysical model of the R15 neuron showed that $I_{K(Ca)}$ and I_{CAN} are not necessary for producing the parabolic-like bursting in this neuron (Canavier et al. 1991). This modeling study also demonstrated the presence of slow oscillations in the absence of action potentials, supporting the parabolic structure (Fig. 2) of the bursting. The parabolic nature of the R15 bursting was further supported by the nonuniform intra-burst spike frequency, even in the absence of $I_{K(Ca)}$. Similar to the R15 neuron, the lobster cardiac ganglion interneurons respond to a steady depolarizing input with slow-wave oscillations called driver potentials. These driver potentials are mediated by slow activation and calcium-dependent inactivation of an I_{Ca} (Tazaki and Cooke 1990).

Bursting in Networks of Neurons

Principles Underlying Rhythmic Bursting in Networks

CPG oscillations can arise either from pacemaker neuron activity or as a network property. In pacemaker-driven networks, one or more neurons can be identified that produce bursting oscillations even when synaptically isolated from the network. The rhythm generated by these pacemaker neurons is then propagated to the network through synaptic interactions. In pacemaker-driven

networks, the properties of the pacemaker neurons are the primary determinant of the rhythm frequency. In contrast to pacemaker-driven CPG networks, in other CPG networks, the rhythmic pattern generation is controlled by subnetworks of neurons and thus emerges as a network property. Although network-driven CPGs may also include endogenously bursting neurons, the network frequency in these CPGs is primarily determined by parameters that control the activity of the rhythm-generating subnetwork.

Half-Center Oscillators

Early studies of locomotion in cats by Graham Brown led him to suggest that the alternating activity of flexor and extensor muscles is controlled by a network of two neuron populations in the spinal cord, each of which inhibits the other to produce antiphase alternating activity. He termed these putative central networks that produce antiphase motor activity half-center oscillators (HCOs) (Graham Brown 1911). Later studies have found reciprocal inhibition to be a prevalent feature of CPG networks in both vertebrates and invertebrates (Marder and Calabrese 1996). In invertebrate CPGs, HCOs are often comprised of two neurons coupled through reciprocal inhibition. The two-cell HCOs provide the simplest network mechanism that is capable of generating stable bursts of alternating activity. Alternating bursting oscillations can arise in HCOs as an emergent network property even when the individual component neurons are not oscillatory (Wang and Rinzel 1992). When the HCO is composed of endogenous bursting neurons, mutual inhibition acts to stabilize the burst period, and bursting occurs over a much wider range of biophysical parameters (Cymbalyuk et al. 2002). Examples of CPG networks whose rhythm-generating mechanism involves HCOs include the CPGs that control leech swimming and heartbeat (segmental oscillators), the crustacean gastric mill network, and the swim networks in lamprey and the gastropod mollusk *Tritonia*.

Antiphase patterns in HCOs can be generated by various mechanisms that have been classified according to whether intrinsic or synaptic properties are involved and whether the inhibited cell

transitions to the bursting regime before or after the termination of inhibition by the other cell. The terms *intrinsic release/escape* and *synaptic release/escape* (Wang and Rinzel 1992; Skinner et al. 1994) have been used to describe these mechanisms. *Intrinsic release* refers to the inhibited cell initiating a burst only when the free cell reaches the end of its burst and turns off inhibition. *Intrinsic escape* refers to the inhibited neuron generating a burst while it is still inhibited and subsequently shutting off the free neuron. Post-inhibitory rebound (PIR) has been shown to initiate the inhibited cell burst when the neuron is non-oscillatory (Wang and Rinzel 1992), although it has also been shown that a PIR-like current is not required to generate oscillations in HCOs composed of non-oscillatory neurons (Skinner et al. 1994). *Synaptic release* refers to the free neuron membrane potential falling below the synaptic threshold, thereby allowing the inhibited neuron to transition to a burst. In contrast, *synaptic escape* refers to the inhibited cell membrane potential depolarizing and crossing a (low) synaptic threshold, thereby inhibiting the free cell. The description of these mechanisms assumes rather restrictive conditions: (i) synapses with well-defined synaptic thresholds and no dynamics and (ii) HCOs that are active in the relaxation regime (very fast transitions for burst onset and termination). When these conditions are relaxed, antiphase patterns may emerge as a result of combinations of escape and release such as in the HCO of the leech heartbeat timing network (Nadim et al. 1995a).

The Role of Electrical Coupling

Computational studies of electrical coupling have provided much insight into the role of gap junctions in networks especially because an inability to cleanly block gap junctions has led to a paucity of experimental data. Electrical coupling is known to promote synchrony in a network. However, more complex and nonintuitive behaviors can arise from electrically coupled networks (Sherman and Rinzel 1992; Chow and Kopell 2000). Electrical coupling between an oscillatory and a bistable neuron can result in a wide variety of behaviors that depend on both the intrinsic

biophysical properties and the coupling strengths (Sherman and Rinzel 1992; Kopell et al. 1998). Weak coupling between two identical neurons can induce antiphase oscillation, which extends far beyond the parameter range for oscillation in single neurons, thus making for a more robust oscillator (Sherman and Rinzel 1992). Electrical coupling can also produce oscillatory activity when neurons that are silent in isolation are coupled through gap junctions (Sherman and Rinzel 1992; Manor et al. 1997).

The properties of a non-oscillatory neuron can regulate features such as frequency and amplitude of a bursting neuron to which it is electrically coupled. However, the influence of a non-oscillatory through gap junctions on oscillations of a bursting neuron can be nonintuitive (Kepler et al. 1990). Kepler et al. examined the effect of the PD neuron on the bursting activity of the AB neuron and showed that the electrical coupling between these neurons can serve to either increase or decrease the oscillation frequency depending on the voltage waveform of the bursting AB neuron. This effect was further explored through a mathematical analysis of the effect of a bistable neuron coupled to an oscillatory neuron which showed how the network frequency is influenced by the relative voltages of the bistable neuron compared to the voltage range of oscillations in the oscillatory neuron. This influence is dependent on the strength of coupling in a nonlinear manner (Kopell et al. 1998). Using ML neurons in the relaxation-oscillation regime, the authors showed how the electrical coupling can “pin” the voltage trajectory to the low or high branches of the voltage nullcline than compared to the uncoupled oscillator, thus changing the frequency and shape of the oscillations. Unexpectedly, a coupling with higher strength may not necessarily be more effective at influencing the frequency.

The effect of electrical coupling has also been investigated in biophysically realistic model neurons. In the STG pyloric network, for example, electrical coupling between the AB and PD pacemaker neurons causes these neurons to fire in synchrony. Of the two, AB is the only neuron that is capable of endogenous bursting. These two neurons, by virtue of their electrical coupling,

fire burst in phase over a wide range of frequencies (Soto-Trevino et al. 2005). The frequency of the isolated AB neuron can be greater than 2 Hz but limited to 1 Hz in the intact network, i.e., when coupled to the PD neuron (Hooper and Marder 1987). Previous modeling work using reduced models had suggested that the role of the PD neuron in this coupled pair is to regulate the network frequency (Hooper and Marder 1987; Kepler et al. 1990; Abbott et al. 1991). The Soto-Trevino et al. multi-compartment model of the AB–PD pacemaker ensemble demonstrated that increasing the coupling strength caused the slow-wave oscillation and spikes to become near synchronized (Soto-Trevino et al. 2005). For large coupling strengths, the non-oscillatory PD neuron transitioned from tonic spiking to large-amplitude bursting. Coupling of the PD to the AB neuron also increased the frequency of AB oscillation compared to the isolated AB frequency. Thus, the network possesses a way to regulate bursting oscillations that is anatomically separate from the mechanism of the generation of the bursting.

Segmented Networks of Bursting Neurons

In segmented animals, locomotion and other motor functions often require that the movement of different body parts maintain a constant phase relative to adjacent parts, despite changes in frequency. In crayfish and leech, swimming is controlled by the coordinated bursting activity of distributed CPGs in which the undulatory movements appear as a traveling wave. This traveling wave is generated by segmental oscillators with intersegmental phase lags. The neural basis that accounts for the stable intersegmental phase differences has been modeled as linear chains of weakly coupled oscillators (Friesen and Pearce 1993; Skinner et al. 1997; Jones et al. 2003).

The crayfish swimmeret system is a good example of intersegmental coordination. The bursting activity that drives the alternating power and return strokes of individual swimmerets on each segment is driven by a local CPG module. Bursts of impulses in coordinating interneurons control the relative timings of intersegmental bursts and result in a very stable anterior-to-posterior phase progression of bursts that differ

in phase by about 90° between adjacent segments (Smarandache et al. 2009; Mulloney and Smarandache 2010).

Swimming in the leech is also involves intersegmental coordination and is characterized by a wave that travels rostral-caudally along the animal. The crests and troughs are produced by antiphase contractions in dorsal and ventral longitudinal muscles in body wall segments. Intersegmental phase lag in body movement is stable at $\sim 20^\circ$ (Friesen and Pearce 1993). Phase differences are also observed between segmental oscillators in the timing network of the leech heartbeat CPG.

The leech heartbeat pattern is bilaterally asymmetric: on one side, a rostral-caudal wave of muscle contractions causes the peristaltic flow of blood through the heart tube, whereas, on the contralateral side, all segments contract in synchrony. This asymmetric activity switches after 20–50 cycles. Rhythmic activity of the leech heartbeat CPG arises independently in pairs of HCOs located in the third and fourth ganglia (Nadim et al. 1995b; Hill et al. 2002). Rhythmic bursting arises from mutual inhibitory connections between two such neurons. These rhythm-generating subnetworks are coupled via coordinating interneurons from other segmental ganglia to produce a stable phase difference in the range 15–20% (Hill et al. 2002).

The theory of weakly coupled oscillators (Schwemmer and Lewis 2012) has been used to understand intersegmental coordination. This theory is used to predict phase differences between segmental oscillators under a mathematically described assumption of weak coupling. A chain of such oscillators with nearest-neighbor coupling can support a constant-speed traveling wave. The weak coupling implies that the intrinsic dynamics are dominant, so that the perturbed system remains close to the limit cycle and the coupling only affects the speed with which the neuron moves around its limit cycle. This limit cycle represents the oscillatory spiking activity in the case of a tonic spiking neuron or the slow-wave oscillations in the case of a bursting neuron (as in Jones et al. 2003). The dynamics of each neuron can be reduced to a single-phase equation that

describes the phase of the neuron in the limit cycle. This allows for the construction of phase models to investigate the pattern of timings of individual elements in a network and the collective properties of the system.

The key to reducing a high-dimensional model and exploiting the form of the phase equations is the computation of the phase interaction function H (Ermentrout and Kopell 1991; Schwemmer and Lewis 2012), which reduces the interaction between the oscillators to a function of their phase difference $\Delta\varphi$. Methods of singular perturbation theory can often be used as an approach for deriving the interaction function H (Hoppensteadt and Izhikevich 1997). The essential step in deriving H is the infinitesimal phase response curve (iPRC) and its relation to the solution to the adjoint equation. The iPRC quantifies the normalized shift due to an infinitesimally small perturbation delivered at any given phase on the limit cycle so that the oscillator responds in a linear fashion.

In the crayfish swimmeret system, the coupling functions H have been approximated experimentally to understand how multiple oscillator elements coordinate their activity to produce wavelike activity representative of swimmeret locomotion (Skinner et al. 1997; Jones et al. 2003). In this case, the iPRC was used to approximate the H function and the zeroes of the G function coupling two modules for a model containing two ascending and one descending connection predicted a stable phase difference of 90° . A good agreement with the experimental data showed that the effects of both excitatory and inhibitory ascending connections combine to promote a Stable 90° phase lag between power stroke neuron bursts in neighboring ganglia.

Different strategies are used to achieve the appropriate phase differences between neighboring segments. Phase differences generated by asymmetries in the coupling between segmental oscillators, where ascending and descending interneurons vary in strength and sign (Skinner and Mulloney 1998; Smarandache et al. 2009). On the other hand, the excitability gradient hypothesis states that phase differences arise from the intrinsic frequency or excitability

differences between segmental oscillators (Grillner et al. 1993). In the crayfish swimmeret CPG, stable phase differences arise due to the combined effect of excitation and inhibition from ascending and descending coordinating neurons (Jones et al. 2003). In contrast, in the leech heart-beat timing network, a stable phase difference seems to arise from coupling between segmental oscillators of different inherent frequencies. When two segmental oscillators with different intrinsic frequencies were coupled in a model network, the faster one dominated the network frequency and led in phase. The phase difference was directly correlated with the difference in periods (Hill et al. 2002). This phase difference arises because the faster segmental oscillator bursts before the slower one and thereby terminates the activity of the shared coordinating interneuron. There is a brief time in each cycle when the slower segmental oscillator is relieved of inhibition from coordinating interneurons before the faster segmental oscillator ends its burst. Thus, the slow segmental oscillator can be entrained by the fast segmental oscillator through the indirect action of the coordinating interneuron.

Summary

Bursting is a ubiquitous property of neurons in many systems. Bursting in single neurons often results from the interaction of voltage-gated ion channels at various time scales. Bursting can be modeled at different levels of complexity, from abstract reduced models to minimal two- and three-dimensional models and biophysical realistic conductance-based models, often with good agreement with the experimental activity. A bursting neuron is often described by a system of ordinary differential equations operating at two different time scales, also called fast-slow bursters. The different types of bursting in such systems have been classified according to dynamical systems theory in terms of the transitions between the silent and spiking states. The hysteresis-loop bursting is the simplest form of bursting that requires only one slow variable in

addition to the fast subsystem that can operate in two stable states: quiescent or tonic spiking. On the other hand, without such fast bistable dynamics, the slow-wave oscillation must be generated independent of the fast spiking and requires at least two slow variables. The classification of different bursting mechanisms is usually done by describing the transitions between the silent and active phases of bursting using bifurcation theory analysis of dynamical systems.

Many oscillatory networks include bursting neurons that are not endogenous bursters. These neurons respond to synaptic input with bursts of spikes that are generated by the activation of regenerative or hyperpolarization-activated inward currents. Even in a two-cell network, the coupling of a bursting neuron to a non-oscillatory neuron can result in phase-locked bursting. In this case, the properties of the non-oscillatory neuron can influence the network frequency and the oscillation amplitude, often in unexpected ways. Electrical coupling of a non-oscillatory neuron to a bursting neuron, for example, can lead to faster or slower bursting oscillations. On the other hand, reciprocally inhibitory coupling can lead to either alternating or synchronized oscillations. In larger networks of bursting neurons, such as those involved in the control of locomotion, the oscillatory activity can be analyzed as a chain of coupled oscillators. These oscillators often represent the bursting activity of the locomotor networks as recorded from the segments of the spinal cord. The theory of weakly coupled oscillators provides a powerful tool for the understanding of how phase-locked oscillations arise in chains of segmental oscillators and can be used to predict which cellular or synaptic parameters control the frequency of the network and the relative phase of the segmental oscillators.

Cross-References

- [Bifurcations Dynamics of Single Neurons and Small Networks](#)

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Cable Equation

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Definition

The cable equation is a mathematical equation derived from a circuit model of the membrane and its intracellular and extracellular space to provide a quantitative description of current flow and voltage change both within and between neurons, allowing a quantitative and qualitative understanding of how neurons function.

Detailed Description

Brief History of Cable Theory in Neuroscience

The origins of cable theory date back to 1855 to work by Lord (William Thomson) Kelvin, “On the Theory of the Electric Telegraph,” which provided the mathematical theory necessary for laying the transatlantic telegraph cable. The utility of this work for neuroscience, however, was not recognized until many years later, after nerve axons came to be regarded as “core conductors.” In the core conductor concept, nerve axons are considered to be long, thin, cylindrical tubes of membrane filled with an electrically conducting axoplasm and immersed in a highly conductive

medium. Because the resistance across the membrane is much larger than the resistance through the axoplasm, over short distances along the cylinder, electric current will preferentially flow down the core. In fact current will flow through the core for a considerable distance before the total amount of current that has leaked out through the membrane becomes significant. This “core conductor” concept was given a mathematical framework in the 1870s when Weber derived and solved steady-state equations in cylindrical coordinates for three-dimensional current flow in and around an axon. Nevertheless, it was not until around 1900 that Hermann and others explicitly recognized that the reduction of these equations from three spatial dimensions to one spatial dimension (distance along the axon or cable) led to an equation equivalent to Lord Kelvin’s cable equation.

Quantitative comparison of cable equation calculations to experimental results requires the use of single fiber preparations, but such preparations were not available until the 1930s. Given the current emphasis on cable theory for dendritic neurons, it might seem surprising to many today to learn that the first applications of cable theory were to determine the passive electrotonic properties of axons. Axons are however the prototypical cable. Hodgkin and Rushton in their classic 1946 paper derived solutions of the cable equation for an infinite cable. They noted that weak sub-threshold currents produce a voltage change that varies linearly with current, and they applied their

cable equation solutions to recordings of such responses to estimate membrane capacity, membrane resistivity, and axoplasm and extracellular resistivity in lobster leg axons. Hodgkin and Rushton argued that an analysis of this “passive behavior is essential to any theory of excitation,” it “provides an insight into the structure of the surface membrane,” and “such an analysis must precede an understanding of the more complicated electrical changes which make up the nervous impulse itself.” Several investigators applied cable theory to estimate passive cable parameters in a number of giant invertebrate axons, and results have been summarized by Rall (1977; Table 1).

In the 1950s, the advent of glass micropipettes made it possible to stimulate and record intracellularly from neurons having diameters much smaller than those of the large invertebrate axons. Some of the early recordings were made from the soma of large motoneurons or pyramidal cells. It had been known from the time of Ramón y Cajal that these neurons possessed extensive dendritic trees, and in the late 1950s it was verified with the electron microscope that dendrites and dendritic spines were sites of synapses. What role did dendrites play in neuronal excitability, and how did dendritic properties affect integration of synaptic inputs? The early answers to these questions, based on interpretations of somatic recordings, turned out to be incorrect. It took the application of cable theory to these recordings by Rall (1957, 1959, 1960), along with subsequent work by Rall and others, to provide a correct understanding of the role dendrites play in signaling (for a detailed history, see commentaries and original papers in Segev et al. (1995)).

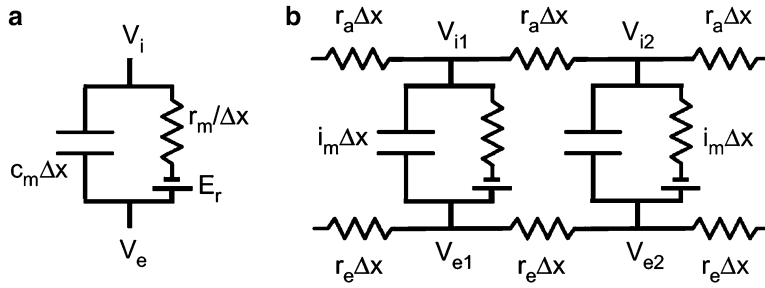
The application of cable theory to dendrites had to be different from the application to axons. First, while axons are long and can be effectively modeled as infinite cables, dendrites are much shorter, requiring solutions for a finite cable. Many such solutions are given by Rall (1959, 1960) and Jack et al. (1975). Second, axons tend to run for long distances without branching, but dendritic trees are highly branched. Solutions for branched dendrites are given in Rall (1959) and also Rall and Rinzel (1973) and Rinzel and Rall

(1974). Furthermore, Rall showed that under certain conditions a branched structure could be reduced to an “equivalent cylinder” allowing solutions for a finite cable to be applied to many cell types. Third, axons and dendrites play different roles in signaling, so the questions for cable theory to address are much different. For example, how far synapses are from the soma electrotonically is a fundamental question for dendritic neurons; simple electrotonic length formulas were derived by Rall (1969) to address this question, and much work in this area has been done by others since (for a review and references, see Rall and Agmon-Snir (1998)).

As information accumulates about voltage-dependent conductances in dendrites, one might question the relevance of passive cable theory to the study of dendritic neurons today. On this point, Rall and Agmon-Snir (1998) echo and extend the arguments for the importance of cable theory for axons given by Hodgkin and Rushton, quoted above, stating “the intuition and methods given by passive cable theory enhance our understanding of the integrative mechanisms even in excitable dendrites. The passive case is an important reference for the excitable case and helps us better understand the role of excitability. Moreover, the passive case is a useful approximation that, analyzed with powerful methods, gives rise to general rules concerning the role of the geometry of the dendritic tree and of passive biophysical properties.” Some of these general rules will be shown below.

The Cable Equation

Given that neurons can be represented as core conductors with a patch of membrane adequately approximated by an electric circuit (Fig. 1), the derivation of the cable equation is a straightforward application of Ohm’s law, Kirchhoff’s law, and the relationship $q = CV$. The most difficult part of the derivation is defining resistances, capacitances, and currents in the proper units and knowing how to convert these terms to specific resistances and capacitance. Given the circuit in Fig. 1, Ohm’s law leads to $\partial V_i / \partial x = -i_i r_a$ and $\partial V_e / \partial x = -i_e r_e$, Kirchhoff’s law provides $\partial i_i / \partial x = -i_m$ and $\partial i_e / \partial x = +i_m$, and $q = CV$ and Ohm’s law together give membrane current



Cable Equation, Fig. 1 Electric circuits for a membrane patch (a) and a neuron cable (b). r_m resistance of a unit length patch of membrane Ω cm, r_a axial resistance per unit length Ω /cm, c_m capacitance per unit length μ F/cm, i_m

membrane current per unit length mA/cm. Note membrane resistivity $R_m = r_m \pi d$ in Ω cm², membrane capacity $C_m = c_m / \pi d$ in μ F/cm², axial resistivity $R_a = r_a \pi d^2 / 4$ in Ω cm (also called R_i), and d diameter

$i_m = c_m \partial V_m / \partial t + (V_m - E_r) / r_m$. When these equations are combined, the result is the cable equation:

$$\frac{r_m}{r_a + r_e} \frac{\partial^2 V_m}{\partial x^2} = r_m c_m \frac{\partial V_m}{\partial t} + (V_m - E_r).$$

This equation can be rewritten as

$$\begin{aligned} \lambda^2 \frac{\partial^2 V}{\partial x^2} &= \tau \frac{\partial V}{\partial t} + V \quad \text{where } \lambda \\ &= \sqrt{\frac{r_m}{r_e + r_a}} \quad \text{and } \tau = r_m c_m \end{aligned}$$

with λ known as the space constant or length constant and τ known as the membrane time constant. In nondimensional form with $T = t/\tau$ and $X = x/\lambda$ this equation becomes

$$\frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} - V.$$

We usually neglect r_e (see Rall 1959) and express λ and τ in terms of specific resistances and capacitance as

$$\begin{aligned} \lambda &= \sqrt{\frac{R_m d}{4 R_a}} \quad \text{and } \tau \\ &= R_m C_m \quad \text{where } d \text{ is cable diameter.} \end{aligned}$$

Note that the above cable equation assumes current flow in one dimension, down the core of

the cable. This is a useful approximation because the length of axons and dendrites far exceeds the diameter making radial and angular flow of current negligible except in the immediate vicinity of a current source. A three-dimensional approach may be warranted when voltage changes in a large extracellular volume are of importance (Eisenberg and Johnson 1970), but in most cases, the one-dimensional cable equation is entirely appropriate.

Solutions for the Infinite Cable

For an axon, the assumption is that current is applied at a middle point $x = 0$, with the axon cable extending in both directions from this point to $\pm\infty$, with voltage being bounded. The solution obtained for these conditions by Hodgkin and Rushton (1946) and more directly by Jack et al. (1975) is

$$\begin{aligned} V(X, T) &= \frac{r_a I_0 \lambda}{4} \\ &\left\{ \exp(-X) \operatorname{erfc}\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right) - \exp(X) \operatorname{erfc}\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right) \right\} \end{aligned}$$

in nondimensional form, where I_0 is a constant current and erfc is the complementary error function. The solution above can be used to obtain two useful particular solutions – voltage at the stimulation site as a function of time, $V(0, T) = (r_a I_0 \lambda / 2) \operatorname{erfc}(\sqrt{T})$, and the steady-state voltage, $V(X, \infty) = (r_a I_0 \lambda / 2) \exp(-X)$. The former shows that voltage rises to 84% of its final value at $T = t/\tau = 1$ (compared to 63% for an

isopotential sphere), and the latter illustrates the usefulness of λ as a measure of voltage decay with distance.

Steady-State Solutions for Semi-infinite and Finite Cables

In the steady-state $\partial V/\partial t = 0$, reducing the cable equation to an ordinary differential equation,

$$\lambda^2 \frac{d^2 V}{dx^2} - V = 0.$$

This equation is easily solved, and the general solution can be expressed in various equivalent forms:

$$\begin{aligned} V(x) &= A_1 \exp(-x/\lambda) + A_2 \exp(x/\lambda) \\ V(x) &= B_1 \cosh(x/\lambda) + B_2 \sinh(x/\lambda) \\ V(x) &= C_1 \cosh((\ell - x)/\lambda) + C_2 \sinh((\ell - x)/\lambda) \end{aligned}$$

where ℓ is the length of the cable. The arbitrary constants depend on the boundary conditions (BC) which specify either the voltage or the current (derivative of the voltage) at the ends of the cable:

$$\begin{aligned} \text{Voltage BC : } V(0) &= V_0 \text{ and } V(\ell) \\ &= V_L \text{ or } V \text{ is bounded (not infinite).} \end{aligned}$$

$$\begin{aligned} \text{Current BC : } -\frac{1}{r_a} \frac{dV}{dx} \Big|_{x=0} &= i_i \text{ and } \frac{1}{r_a} \frac{dV}{dx} \Big|_{x=\ell} \\ &= i_e. \end{aligned}$$

Voltage boundary conditions are straightforward. The current boundary conditions come from Ohm's law and the convention that current is positive to the right, so one must be careful with the direction of the injected current, particularly at the end of the cable. This explains the lack of a minus sign for the current BC at $x = \ell$. Some commonly used current boundary conditions are:

$$\text{Sealed end : } -\frac{1}{r_a} \frac{dV}{dx} \Big|_{x=\ell} = 0.$$

$$\begin{aligned} \text{Leaky end : } -\frac{1}{r_a} \frac{dV}{dx} \Big|_{x=\ell} & \\ &= V(\ell) G_\ell \text{ e.g., } -\frac{1}{r_a} \frac{dV}{dx} \Big|_{x=\ell} \\ &= V(\ell) \left(\frac{\pi d^2}{R_m 4} \right) \text{ for an end cap.} \end{aligned}$$

$$\text{Current injection : } -\frac{1}{r_a} \frac{dV}{dx} \Big|_{x=0} = I_0.$$

Note that the leaky end condition would not have the minus sign if we considered leak at $x = 0$ because of the direction of the leak current. Simulation software packages typically assume a sealed end condition at terminations because the leak conductance, G_ℓ , through an end cap of membrane with the same membrane resistivity, R_m , as the dendrite turns out to be negligible.

Application of boundary conditions to the general solution leads to special solutions that provide significant insight. First, consider the semi-infinite cable where boundary conditions are $V(0) = V_0$ and $V(\infty)$ is bounded. These conditions lead to

$$V(x) = V_0 \exp\left(\frac{-x}{\lambda}\right).$$

For current input, I_0 , at $x = 0$, V_0 would be replaced by $r_a I_0 \lambda$ which is a factor of 2 larger than noted above for the infinite cable. This solution shows the significance of λ as a measure of voltage decay with distance in that voltage drops 1/e or 37% for each λ distance. It must be stressed that this result applies strictly only for semi-infinite and infinite cables – for finite cables with sealed ends, the decay is less.

As a second example, consider voltage clamp in a finite cable. Boundary conditions are $V(0) = V_0$ and sealed end at ℓ . The solution is

$$V(x) = V_0 \cosh\left(\frac{\ell - x}{\lambda}\right) / \cosh\left(\frac{\ell}{\lambda}\right).$$

One can use this expression to estimate how effective voltage clamp at the soma space clamps distal regions by considering the solution at $x = \ell$

or $V(\ell) = V_0/\cosh(\ell/\lambda)$. For cells with an electrotonic length $L = \ell/\lambda = 1$, the solution shows that the voltage change at the end of the cable is only 65% of the difference between V_0 and the resting potential. For transient inputs, the effective space clamp is considerably worse (Rall and Segev 1985).

A third useful case is the solution for current input in a finite cable. Boundary conditions are current input at $x = 0$ and sealed end at $x = \ell$. The solution is

$$V(x) = \frac{r_a \lambda I_0 \cosh((\ell - x)/\lambda)}{\sinh(\ell/\lambda)}.$$

This solution is useful for illustrating the dependence of input resistance, R_N , a measure of cell excitability, on various electrotonic and morphological factors:

$$\begin{aligned} V(0) &= \frac{r_a \lambda I_0}{\tanh(\ell/\lambda)} \text{ so } R_N = \frac{r_a \lambda}{\tanh(\ell/\lambda)} \\ &= \left(\frac{2}{\pi}\right) \frac{\sqrt{R_m R_a} d^{-3/2}}{\tanh(\ell/\lambda)}. \end{aligned}$$

The last expression shows the dependence of input resistance on $d^{3/2}$, a factor that proves to be important for branched case solutions and reduction of a branched tree to an equivalent cylinder. Note that as $\ell \rightarrow \infty$, $R_N \rightarrow r_a \lambda$ in agreement with the semi-infinite solution above. Alternatively, we say that the input conductance of a semi-infinite cylinder, $G_\infty = 1/(r_a \lambda)$. It is straightforward to convert the last expression above into the following useful equations:

$$R_N = \frac{R_m L}{A_D \tanh(L)} \quad \text{also} \quad R_m = \frac{R_N A_D \tanh(L)}{L}$$

where $L = \ell/\lambda$ is electrotonic length and A_D is the membrane area of the cable. The first of these expressions shows the dependence of input resistance on membrane area, electrotonic length, and membrane resistivity, and the second is useful for estimating R_m when input resistance, membrane area, and electrotonic length are known or alternatively for estimating membrane area when input resistance, membrane resistivity, and electrotonic

length are known. A means to estimate electrotonic length independently is described below.

Another useful case is current input at $x = 0$ and leaky end at $x = \ell$. In this case, the solution is

$$V(x) = \frac{r_a \lambda I_0 [\cosh((\ell - x)/\lambda) + (G_L/G_\infty) \sinh((\ell - x)/\lambda)]}{\sinh(\ell/\lambda) + (G_L/G_\infty) \cosh(\ell/\lambda)}$$

where G_L is the leaky end conductance and G_∞ is the conductance of an infinite extension of the cable (semi-infinite cylinder) as defined above. If $G_L = 0$ (sealed end), we get the solution shown earlier for current input into a finite cylinder. If $G_L = G_\infty$, then the leak is equivalent to an infinite extension of the cylinder and $V(x) = I_0/G_\infty \exp(-x/\lambda)$ as shown above for the semi-infinite cylinder. If $G_L = \infty$, then the solution represents the case where voltage at the end is clamped to 0. It is interesting to think about what other values of G_L/G_∞ might mean. A value of $G_L/G_\infty = 2$ might correspond to the attachment of an infinite extension of not one but two cylinders or perhaps flare in dendritic tree diameters; conversely, $G_L/G_\infty = 0.5$ might represent taper. Sample solutions for a number of different boundary conditions are shown in Fig. 2.

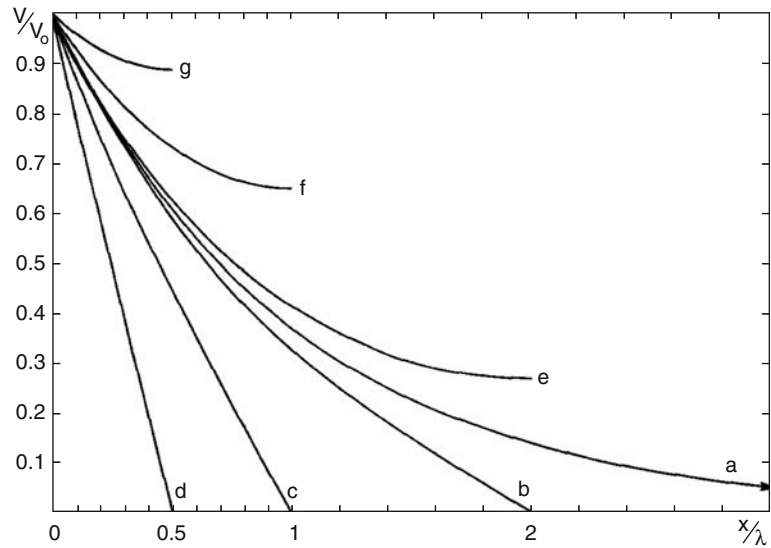
Steady-State Solutions for Branched Dendritic Trees

Steady-state solutions for branched dendritic trees can be obtained by letting each dendritic segment be represented by a finite cable and then connecting these cable segments at the branch points using continuity of voltage and conservation of current. It is useful to express the resulting equations in terms of the unknown voltages at the nodes – branch points, terminations, and the start. For a dendritic tree with n segments, the solution would require solving $n + 1$ simultaneous equations for voltages at the nodes. From these voltages, it is then possible to compute the voltage anywhere in the dendritic tree.

Another approach is to use the iterative algorithm proposed by Rall in 1959. In this algorithm, additional cylinders at branch points are considered as a leak conductance at the end of the parent cylinder and use is made of the leaky end solution of the cable equation given just above. The leak

Cable Equation,

Fig. 2 Voltage attenuation with distance. *a*, Infinite cylinder; *b*, *c*, *d*, voltage clamp to rest in cylinders with $L = 2$, 1, and 0.5; *e*, *f*, *g*, sealed end in cylinders with $L = 2$, 1, and 0.5. (From Rall (1959), Fig. 3 with permission from Elsevier)



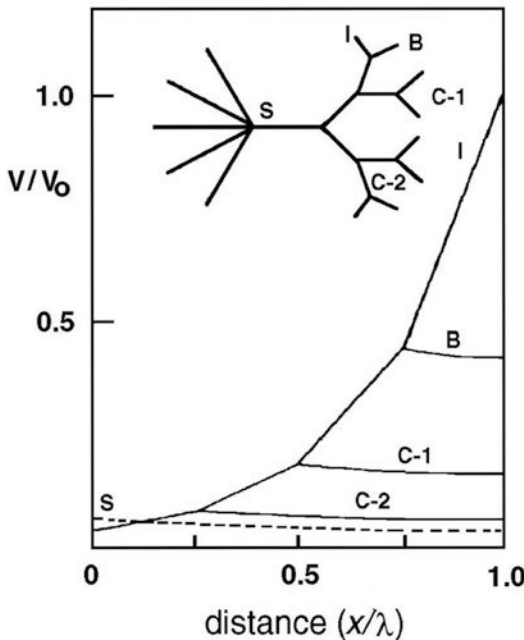
conductance of the initial cylinder equals the sum of the input conductances of attached cylinders, which each have a leak conductance equal to the sum of the input conductances of their attached cylinders, and so forth iteratively, until terminations are reached. The leak conductance at terminations is assumed to be known, typically zero or sealed end. Given the leak conductance at terminations, the input conductance of the terminating branches can be computed, and the sum of input conductances of terminating branches having the same parent becomes the leak conductance of the parent branches, which allows the input conductance of the parent branches to be computed, iteratively, back to the initial segment. With input conductance of the initial cylinder known, along with the leak conductances G_L and G_∞ for all three segments, the voltage can then be computed iteratively from the starting segment out to terminating segments. Numerical examples of this procedure are given in Rall (1959) and Jack et al. (1975).

Although the above approaches, along with compartmental modeling approaches, can be used to obtain steady-state solutions for cells with arbitrarily branched geometry, these solutions do not provide the understanding and insight that can be obtained with closed form mathematical solutions. Rall and Rinzel (1973) constructed an idealized branched neuron model

with suitable symmetry assumptions and equivalent cylinder constraints on branch diameters and were able to apply superposition to obtain mathematical solutions for the case when input was applied to only one distal branch of the dendritic tree. Explicit expressions were given for input resistance at the site of input and for voltage attenuation from the input location to the soma. Numerical illustrations showed how branch input resistance and voltage attenuation, factors important for the effectiveness of synaptic inputs, depend on certain morphological and electrotonic properties of the dendritic tree. A result of particular note is the asymmetric attenuation toward the soma compared with attenuation toward the periphery as shown in Fig. 3.

Transient Solutions to the Cable Equation

Transient solutions to the cable equation have been derived for various conditions. Mentioned above is the solution by Hodgkin and Rushton for the infinite cable, computed via Laplace transforms. A number of investigators have developed solutions with the use of Laplace transforms for various boundary conditions including Rall (1960), Jack and Redman (1971a, b), and others. The analysis from Rall (1960) was particularly important for showing that estimates of the membrane time constant from recordings of voltage



Cable Equation, Fig. 3 Asymmetric voltage attenuation. Steady-state voltage attenuation with input at location I (solid line) or with the same input at the soma (dotted line). Note the steep attenuation from I to the soma and the lack of much attenuation from any branch point toward the periphery. Note also that the soma voltage for input at I equals the voltage at I for input at the soma. This illustrates the reciprocity property of linear systems. (Figure reproduced from *The Book of Genesis* ©2003 James M Bower and David Beeman which was based on Fig. 4 from Rall and Rinzel (1973) reproduced with permission from Elsevier)

transients were much too small when dendritic trees were not considered appropriately. Other methods of solution make use of Green's functions.

Transient solutions for branched dendrites can become very complicated and not very insightful without some simplifying assumptions, as evidenced by solutions with the Laplace transform approach by several investigators. However, the development by Rall (1962) of the equivalent cylinder model allowed the analysis to be simplified significantly (see entry ► “Equivalent Cylinder Model (Rall)”). Briefly, Rall showed that with a certain set of assumptions, a highly branched dendritic tree could be reduced mathematically to a single equivalent cylinder. Solutions that make use of the equivalent cylinder assumption to

provide particularly insightful results have been obtained by Rall (1969) and Rinzel and Rall (1974) as we will now discuss.

Rall (1969) assumed that a neuron's dendritic tree could be approximated by an equivalent cylinder and used separation of variables to solve the cable equation, obtaining in nondimensional form:

$$V(X, T) = (A \sin(aX) + B \cos(aX)) \exp[-(1 + \alpha^2)T].$$

Boundary conditions and the initial condition are then used to evaluate the constants A, B, and α . Applying sealed end boundary conditions at both ends gives

$$V(X, T) = \sum_{n=0}^{\infty} B_n \cos\left(\frac{n\pi X}{L}\right) \exp\left[-\left(1 + \left(\frac{n\pi}{L}\right)^2\right)T\right]$$

where then B_n have to be obtained from the initial condition, $V(X, 0)$. Regardless of the initial condition, the exponential term in the above equation shows that the voltage will decay back to rest with an infinite number of time constants defined by

$$\frac{1}{\tau_n} = \left[\frac{1 + (n\pi/L)^2}{\tau_0} \right] \text{ or } \tau_n = \frac{\tau_0}{1 + (n\pi/L)^2}$$

where we have replaced T by t/τ and then include the factor $1 + (n\pi/L)^2$ to define the τ_n . Note that $\tau_0 = \tau_m$, the membrane time constant, when membrane properties are uniform. Then we can simplify our solution to:

$$V(X, t) = \sum_{n=0}^{\infty} C_n \exp(-t/\tau_n).$$

Rall called the τ_n “equalizing time constants.” In a cylinder, the initial voltage decay is fast, as it is governed by the fast time constants which describe how voltage “equalizes” among the dendrites, while the final slower decay is governed by the membrane time constant. A sphere or uniformly polarized cell has only one decay time constant, the slow membrane time constant. It was ignoring the fast time constants and trying to fit voltage transients with just one exponential

term that led to the significant underestimation of the membrane time constant by some investigators in the 1950s and early 1960s. Note that voltage charging is also faster in a cylinder than in a sphere. This may seem counterintuitive if the fast time constants are “equalizing time constants.” To explain this paradox, it must be remembered that in a sphere, the capacitance of the whole cell has to be discharged before significant current flows through the membrane, whereas in a cylinder, only local capacitance has to be discharged before there is local membrane current flow; consequently, voltage charging begins earlier.

The usefulness of this transient solution was pointed out by Rall who showed that if τ_0 and τ_1 could be estimated from an experimental transient, then the electrotonic length of the dendritic tree $L = \ell/\lambda$ can be estimated with the following formula:

$$L = \frac{\pi}{\sqrt{\tau_0/\tau_1 - 1}}.$$

In early studies, the time constants were estimated by a procedure called “exponential peeling,” but with the advent of sophisticated computers and software, nonlinear curve fitting methods are used. Estimates of L tell us if the cell is electrotonically compact or not. This is important for estimating the effectiveness of synaptic inputs and in particular the strength of distal inputs compared to identical proximal inputs and also for estimating the extent of space clamp during voltage clamp. There are a number of other formulas that can be used to estimate L , although the one given above is considered to be the most robust. A caveat is that L estimates made with this formula assume that the cell can be approximated as an equivalent cylinder; deviations from this assumption will influence τ_1 and will cause errors in the L estimate (see entry ► “[Electrotonic Length, Formulas and Estimates](#)”).

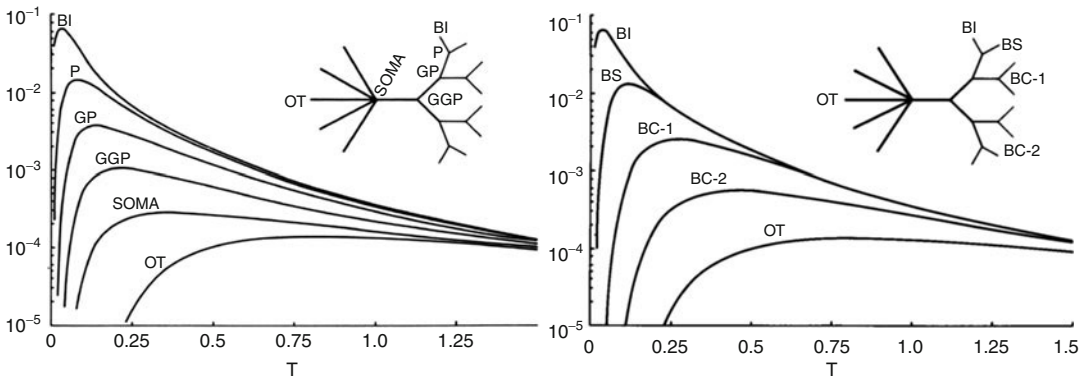
Rinzel and Rall (1974) developed a transient solution for a branched dendritic tree using the same idealized dendritic tree and similar symmetry assumptions and superposition methods as used in their steady-state solutions for a branched tree mentioned above. The mathematical

expressions derived were used to illustrate the attenuation and delay characteristics of the voltage peak caused by a transient input in a distal branch as it proceeds to the soma. While voltage attenuation of transient inputs from the input site to the soma was considerably more severe than that observed previously for steady-state inputs, a significant fraction (about half) of the input charge (the integral of the voltage change) was nonetheless delivered to the soma. Expressed another way, the attenuation of the integral of the voltage between the input site and the soma equals the steady-state attenuation between these two locations. These calculations also showed that the time to peak and half-width of the voltage response at the soma depend on the distance of the input from the soma. Some of these results are illustrated in Fig. 4.

Insights from Cable Equation Solutions

Cable equation solutions have provided considerable insight leading to a quantitative and qualitative understanding of how neurons function. Insights may have come from solutions for simplified neuron structures with particular assumptions about branching and diameters at branch points and passive membrane with (usually) uniform properties, but their applicability is general. The list below is long but is not meant to be exhaustive:

1. *Space constant* λ . The space constant (length constant) λ is a useful qualitative measure of voltage decay with distance along a cable. However, as a quantitative measure, λ is the distance over which the steady-state voltage decays to $1/e$ or 37% of its value at the origin *only* in infinite and semi-infinite cables. Electrotonic length and boundary conditions, as well as the presence of side branches, matter for steady-state voltage attenuation in finite cables.
2. *Membrane time constant* τ . The membrane time constant τ is a useful qualitative measure of how voltage decays in time. However, as a quantitative measure, τ is the time it takes for voltage to decay to $1/e$ or 37% of its initial value *only* in an isopotential or uniformly



Cable Equation, Fig. 4 Voltage attenuation for transient inputs. Input is at BI. *Left*: voltage attenuation to the branch points. *Right*: voltage attenuation to the terminals. Note how much less attenuation is from the branch points to the

terminals than between branch points. Compare with Fig. 3. (Reproduced from Rinzel and Rall (1974) Figs. 4 and 5 with permission from Elsevier)

polarized cell. Additional time constants affect the early voltage time course depending on morphology. Neglect of these additional time constants can lead to erroneous estimates of τ in dendritic neurons.

3. *Summation of inputs.* In a linear system, the solution for two current inputs is the sum of the solutions for each input. This is helpful for understanding spatial and temporal summation of synaptic inputs if they are small. However, it should be noted that synaptic inputs, being a conductance multiplied by a driving force, are not linear, so results should be interpreted with caution.
4. *Reciprocity.* In a linear system, the voltage response at the soma to current injection at a dendritic location will equal the voltage response at this dendritic location following the same current injection at the soma. This result applies generally for any two points in the cell and can be used to determine if a dendritic tree is passive or if blockers have made it so.
5. *Input resistance calculations.* Cable theory solutions can be used to calculate the input resistance in any passive branched dendritic tree. Input resistance can be much higher in distal dendrites than at the soma. The smaller diameter of the dendritic branch produces a larger voltage response to current injection. Boundary conditions also play a role.

6. *Steady-state voltage attenuation depends on cylinder electrotonic length and boundary conditions.* As mentioned above, steady-state voltage attenuation is described quantitatively by λ only for infinite and semi-infinite cables. For finite cylinders, both cylinder electrotonic length and boundary conditions affect attenuation. If the terminal boundary condition is a sealed end, attenuation with distance is less in electrotonically shorter cylinders than longer ones. If the terminal boundary condition is voltage clamp to rest, attenuation with distance is larger in electrotonically shorter cylinders than longer ones. The sealed end and voltage clamp to rest conditions represent two extremes that determine voltage attenuation (Fig. 2).
7. *Voltage attenuation is asymmetric.* A segment of dendrite within a dendritic tree will have a certain core resistance, but voltage attenuation across this core resistance will be asymmetric, depending on the boundary conditions at the ends of the segment. For an input in a distal branch, the boundary condition heading proximally toward the soma is a very leaky end, approaching a voltage clamp to rest condition, while the boundary condition heading distally is a not very leaky end, approaching a sealed end condition. Consequently, applying the previous point above, there will be severe attenuation heading

proximally, but little attenuation heading distally. This explains the asymmetric attenuation in Fig. 3. The degree of voltage attenuation across a segment depends on how much the terminal boundary condition in the direction current is flowing that resembles a “sealed end” or “clamp to rest” condition.

8. *Transient voltage attenuation is more severe.* Voltage attenuation is more severe for transient inputs than for steady-state inputs. Nevertheless, the attenuation of the integral of the voltage change over time, with the integral computed at the input site and at the soma, equals the steady-state voltage attenuation between these two locations.
9. *Dendritic filtering.* In passive systems, dendrites provide low-pass filtering of the voltage response to synaptic inputs. As the signal travels to the soma, the voltage response is attenuated and becomes spread out. A shape index which plots EPSP half-width vs. time to peak can be used to predict the electrotonic location of the synapse. Note however that the shape index will depend not only on the synaptic location but also on the time course of the synaptic conductance and the electrotonic length of the dendritic tree as well.
10. *The $d^{3/2}$ and signal attenuation.* If dendrite diameters at branch points satisfy the “3/2 rule,” $d_p^{3/2} = d_{d1}^{3/2} + d_{d2}^{3/2}$, where d_p is the diameter of the parent branch and d_{d1} and d_{d2} are diameters of daughter branches, then there is impedance matching at branch points, and the attenuation with electrotonic distance remains unchanged. However, if diameters at branch points do not satisfy this condition, attenuation will be steeper or less steep after the branch point depending on whether the exponent is less than 3/2 or greater than 3/2, respectively. Changes in the summed $d^{3/2}$ along dendrites control signal attenuation.
11. *Consequences for voltage clamp.* Attenuation out from soma is relatively small. Recall that the analytic solution for voltage at the end of a cylinder given voltage clamp at the origin is $V(L) = V(0)/\cosh(L)$. This equation allows us to estimate the extent of space clamp in the cell when the soma is voltage clamped. Although much of the voltage change at the soma is felt at the distal dendrites, the space clamp is far from perfect at distal locations, and this can be very important in interpreting results.
12. *Implications for placement of excitatory and inhibitory inputs.* The differences in input resistance at the soma and distal dendrites, the asymmetry of voltage attenuation, and the solution for voltage clamp at the soma have implications for the placement of excitatory and inhibitory inputs. Regarding inhibition, inhibition is most effective when placed at the soma because the effect is felt throughout the cell. Regarding excitation, soma input will not produce the large changes in voltage seen with more distal input, so excitation at the soma is less likely to activate voltage-gated conductances, suggesting that excitation might be better placed in the dendrites. If there are voltage-gated conductances in the dendrites, the large distal voltage changes could activate them and amplify the signal.
13. *Electrotonic length.* The electrotonic length, L , of the dendritic tree can be estimated from experimental measurements of τ_0 and τ_1 if the cell can be approximated as an equivalent cylinder. However, one must be careful in the interpretation of the time constants when the cell deviates from an equivalent cylinder. Most neurons have an electrotonic length of 1 or less.
14. *Dendritic spines.* Dendritic spines represent a special case of asymmetric voltage attenuation. Voltage attenuation will be steep from the spine head to the dendrite because the boundary condition at the spine-dendrite junction resembles a very leaky end. However, there will be negligible voltage attenuation from the dendrite to the spine head because the boundary condition at the tip of the spine head is practically a sealed end.
15. *Effect of reconstruction errors.* Cable theory can explain effects of reconstruction errors on parameter value estimates. Dendrite

diameters are notoriously difficult to measure accurately because diameters are near the optical resolution of the microscope. Length values can be inaccurate because of tissue shrinkage, particularly in the z-axis. Cable theory says if the reconstruction diameters are uniformly off by a factor of x , then the R_m , C_m , and R_a values used in models should be equal to the actual R_m multiplied by x , the actual C_m divided by x , and the actual R_a multiplied by x^2 . If reconstruction lengths are uniformly off by a factor y , then the R_m , C_m , and R_a values used in models should be equal to the actual R_m multiplied by y , the actual C_m divided by y , and the actual R_a divided by y .

16. *Optimal diameters.* Cable theory calculations suggest that a neuron can optimize the effectiveness of distal inputs with its morphology or electrotonic parameters. For a cylinder of given length, if diameter is small, input resistance is large, and attenuation is steep, whereas if diameter is large, input resistance is small, and there is much less attenuation. Because of this trade-off between input resistance and attenuation, there will be a diameter that will maximize the effectiveness inputs delivered at the end of the cable.
17. *Modeling cells as an equivalent cylinder.* To a first approximation, dendrites can be modeled as an equivalent cylinder. This approximation is useful for providing insights into how voltage changes in dendritic trees.

Cross-References

- [Electrotonic Length, Formulas and Estimates](#)
- [Equivalent Cylinder Model \(Rall\)](#)

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Cable Model(s)

- [Mammalian Motor Nerve Fibers, Models of](#)

Calcium Buffering: Models of

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Definitions

Neuronal Ca^{2+} dynamics are tightly controlled by endogenous calcium-binding proteins (CaBPs), which may bind one or more Ca^{2+} ions either in a cooperative or noncooperative manner. The binding of Ca^{2+} to buffers can be described kinetically by using binding and unbinding rate constants in ordinary differential equations (ODEs) or by using equilibrium constants. In addition to buffering, some CaBPs perform specific Ca^{2+} -dependent actions on downstream targets; these are termed Ca^{2+} sensors and are modeled similarly, except that target reactions are included. Finally, perturbations by Ca^{2+} indicator dyes, which are themselves buffers, can be addressed similarly.

Detailed Description

Background

Opening of Ca^{2+} permeable channels results in steep increases in the intracellular free Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) that can reach tens of micromol/liter at the entry site. Ca^{2+} buffers make a major contribution to reducing $[\text{Ca}^{2+}]_i$ to lower levels within milliseconds and to limiting the spatial extent of $[\text{Ca}^{2+}]_i$. Thus, buffering is central for maintaining a high temporal responsiveness to $[\text{Ca}^{2+}]_i$ signals, which is eminent for neuronal coding.

Second-Order Buffer Reaction

Chemical Reaction

The simplest reaction is binding of Ca^{2+} to a buffer (B) with only one binding site:



$$[\text{B}]_f = [\text{B}]_T - [\text{CaB}] \quad (2)$$

$$K_D = \frac{1}{K_A} = \frac{k_{\text{off}}}{k_{\text{on}}} = \frac{[\text{B}]_f [\text{Ca}]_i}{[\text{CaB}]} \quad (3)$$

$[\text{Ca}^{2+}]_i$, $[\text{B}]_f$, and $[\text{CaB}]$ are the concentrations of free Ca^{2+} , free buffer, and Ca^{2+} buffer complex, respectively. $[\text{B}]_T$ is the total buffer concentration. K_D and K_A are the equilibrium dissociation and association rate constants, respectively. In neuronal modeling, it is convenient to use K_D . Note that a higher K_D value implies that the buffer has a lower affinity for Ca^{2+} and is less easily saturated. Concentrations and K_D are in units of M (mol/liter). k_{on} (unit: $\text{M}^{-1} \text{s}^{-1}$) and k_{off} (s^{-1}) are the forward and backward binding rate constants, respectively, determining the velocity of the reaction.

Kinetic Model

The above reactions together with a Ca^{2+} influx can be converted to ODEs for each well-mixed compartment, assuming mass action kinetics (Markram et al. 1998; Schmidt et al. 2003):

$$\frac{d[\text{Ca}]_i(t)}{dt} = J + R \quad (4)$$

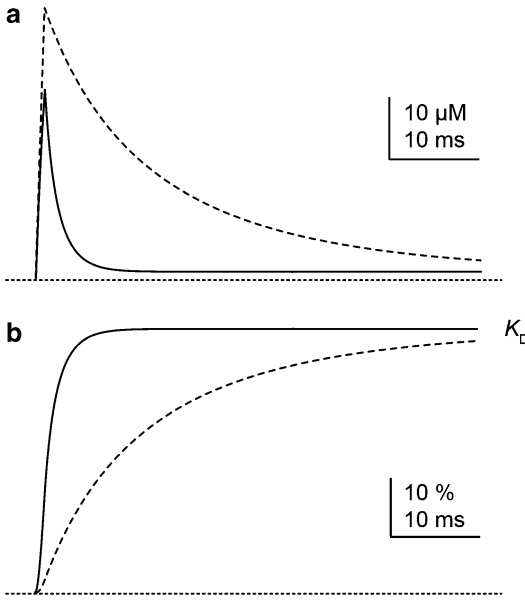
$$\frac{d[\text{B}]_f(t)}{dt} = R \quad (5)$$

$$\frac{d[\text{CaB}](t)}{dt} = -R \quad (6)$$

$$R = -k_{\text{on}}[\text{Ca}]_i(t) [\text{B}]_f(t) + k_{\text{off}}[\text{CaB}](t) \quad (7)$$

where R is the reaction term and J the Ca^{2+} influx, both in units of M/s. In order to solve the system numerically (► [Deterministic Reaction-Diffusion Simulators](#)), starting conditions for $t = 0$ are determined by assigning $[\text{Ca}^{2+}]_i(0) = [\text{Ca}^{2+}]_{\text{rest}}$ and by calculating $[\text{B}]_f(0)$ and $[\text{CaB}](0)$ from Eq. 3.

From a brief increase, $[\text{Ca}^{2+}]_i$ relaxes approximately exponentially to a value determined by K_D , and the fraction of Ca^{2+} bound buffer



Calcium Buffering: Models of, Fig. 1 $[Ca^{2+}]_i$ decay kinetics (a) and fractions of Ca^{2+} -bound buffers (b) after a 100 μM influx step in the presence of either a rapid (solid lines, $k_{on} = 10^8 M^{-1} s^{-1}$, $k_{off} = 100 s^{-1}$) or a slow (dashed lines $k_{on} = 10^7 M^{-1} s^{-1}$, $k_{off} = 10 s^{-1}$) buffer, both with a K_D of 1 μM and $[B]_T$ of 100 μM . Dotted lines indicate resting levels

increases concomitantly (Fig. 1). The time constant is determined by k_{on} , k_{off} , $[Ca^{2+}]_i$, and $[B]_f$ but can be approximated as $\tau \approx 1/(k_{on} [B]_f(\infty))$ (Markram et al. 1998).

Rapid Buffer Approximation (RBA)

The RBA is a steady-state simplification for binding in well-mixed compartments under the assumption of quasi-instantaneous equilibration of all reactants (Neher 1998). Although this assumption is not met during rapid signaling, the RBA is often useful. Combining Eqs. 2 and 3 ($[B]_f$ is typically unknown, whereas $[B]_T$ may be estimated experimentally) and rearranging yields.

$$[CaB] = \frac{[B]_T [Ca]_i}{K_D + [Ca]_i} \quad (8)$$

Using Eq. 8, the total Ca^{2+} concentration (free and bound Ca^{2+}) is given by

$$\begin{aligned} [Ca^{2+}]_T &= [Ca^{2+}]_i + [CaB] \\ &= [Ca^{2+}]_i + \frac{[B]_T [Ca]_i}{K_D + [Ca]_i} \end{aligned} \quad (9)$$

By differentiating $[CaB]$ with respect to $[Ca^{2+}]_i$ in Eq. 8, the “buffer capacity” (κ) is defined, which gives a dimensionless measure of how many Ca^{2+} ions are bound for each free Ca^{2+} . For example, κ of 100 (a typical value for neurons) implies that 100 Ca^{2+} are bound for each free Ca^{2+} :

$$\kappa = \frac{d[CaB]}{d[Ca]_i} = \frac{K_D [B]_T}{(K_D + [Ca]_i)^2} \quad (10)$$

By differentiating $[Ca^{2+}]_T$ with respect to $[Ca^{2+}]_i$ in Eq. 9 and inverting the result, the “buffering factor” (β) is defined, which is a number between zero and one and a measure of the fraction of Ca^{2+} remaining free:

$$\beta = \frac{d[Ca]_i}{d[Ca]_T} = \frac{1}{1 + \kappa} \quad (11)$$

The usefulness of κ and β becomes apparent when considering the sum of Eqs. 4 and 6 for the total Ca^{2+}

$$\frac{d[Ca]_T(t)}{dt} = J \quad (12)$$

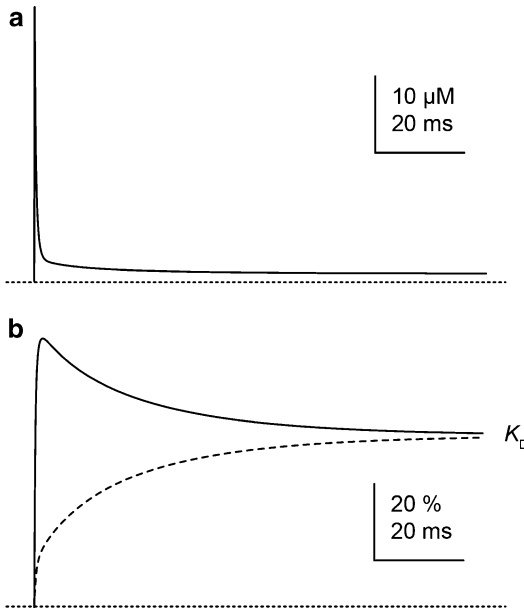
and then deriving the change in $[Ca^{2+}]_i$

$$\frac{d[Ca]_i(t)}{dt} = \frac{d[Ca]_i(t)}{d[Ca]_T(t)} \frac{d[Ca]_T(t)}{dt} = \beta J \quad (13)$$

Equation 13 quantifies the degree to which a very rapid buffer limits the impact of a Ca^{2+} influx J on $[Ca^{2+}]_i$ in a well-mixed compartment. Although κ and β are functions of Ca^{2+} , they can be regarded as constant if $[Ca^{2+}]_i \ll K_D$. On the other hand, if $[Ca^{2+}]_i \gg K_D$, then $\kappa \rightarrow 0$ and $\beta \rightarrow 1$, i.e., the buffer is saturated.

Competition Between Rapid and Slow Buffers

A neuron typically expresses multiple CaBPs (with different kinetics) that compete for Ca^{2+}



Calcium Buffering: Models of, Fig. 2 Competition of fast and slow buffer for Ca^{2+} . (a) $[\text{Ca}^{2+}]_i$ kinetics as in Fig. 1 but in the presence of both buffers. (b) Ca^{2+} bound fractions of the rapid (solid line) and the slow buffer (dashed line) as in Fig. 1 but now during competition. Note the difference in their binding behavior compared to Fig. 1

binding. In such a system, the amount of Ca^{2+} bound to a given buffer can initially deviate substantially from the equilibrium (Markram et al. 1998). A rapid buffer will initially bind more Ca^{2+} than predicted from equilibrium, while the slow buffer will bind less Ca^{2+} . Later on, Ca^{2+} liberated by the rapid buffer will be bound by the slow buffer, and both will relax to their equilibrium occupancy (Fig. 2). This generates multiphase $[\text{Ca}^{2+}]_i$ decay kinetics (Schmidt et al. 2003).

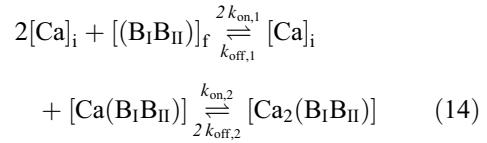
Competition Between Ca^{2+} and Mg^{2+}

CaBPs bind other divalent cations like Mg^{2+} . The competition is included by adding ODEs for Mg^{2+} similar to those for Ca^{2+} . This shifts the effective K_D for Ca^{2+} towards larger values (Fig. 3, Schmidt 2012).

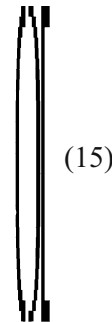
Higher-Order Buffering

Many CaBPs have several binding sites that may cooperate with each other, i.e., binding of Ca^{2+} to one site facilitates (positive cooperativity) or

hinders (negative cooperativity) binding of Ca^{2+} to other sites. This is expressed by different k_{on} and k_{off} for the individual steps. In a two-step reaction, for example, positive cooperativity means that $k_{\text{on},2} > k_{\text{on},1}$ and/or $k_{\text{off},2} < k_{\text{off},1}$, such that $K_{D,2} < K_{D,1}$. Calretinin is an example for positive cooperativity (Faas et al. 2007):



The corresponding reaction rate is



Replacing R by R_c in Eqs. 4, 5, and 6 yields the ODEs for the kinetic simulation.

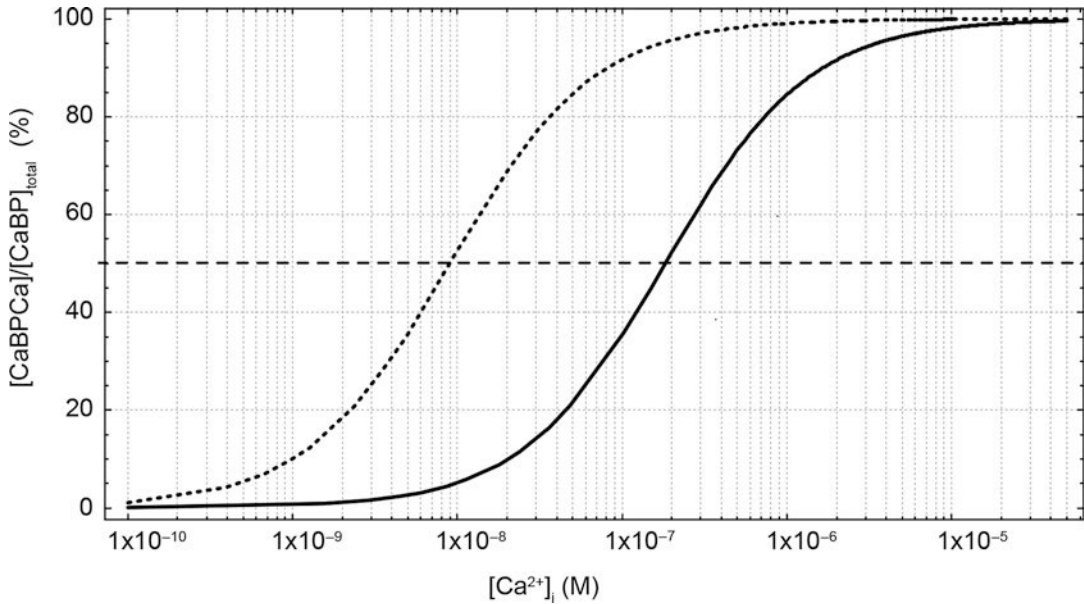
Spatial Resolution

Spatial resolution can be achieved by subdividing a well-mixed compartment into smaller compartments that are coupled by diffusion. This is obtained by introducing diffusion flux terms J_D (M/s) into Eqs. 4, 5, and 6 for each compartment n (Markram et al. 1998; Schmidt et al. 2013):

$$J_D = D_x \frac{A_{n,n+1}}{dV_n} ([X]_{n+1}(t) - [X]_n(t)) \quad (16)$$

where D_x (m^2/s) is the diffusion coefficient of species X, A the exchange surface area, d the distance between subcompartments, and V their volume.

Spatial resolution can also be obtained by converting Eqs. 4, 5, 6, and 7 to partial differential equations (PDEs) with the spatial coordinates as



Calcium Buffering: Models of, Fig. 3 Steady-state Ca^{2+} -binding curves for parvalbumin ($K_{D,\text{Ca}} = 9 \text{ nM}$, $K_{D,\text{Mg}} = 31 \text{ } \mu\text{M}$) in the absence (dotted line) and presence (solid line) of $600 \text{ } \mu\text{M}$ $[\text{Mg}^{2+}]_i$

additional independent variables. The independent variables are omitted in the following for clarity:

$$\frac{\partial [\text{Ca}]_i}{\partial t} = D_{\text{Ca}} \nabla^2 [\text{Ca}]_i + R + J \quad (17)$$

$$\frac{\partial [\text{B}]_f}{\partial t} = D_{\text{B}} \nabla^2 [\text{B}]_f + R \quad (18)$$

$$\frac{\partial [\text{CaB}]}{\partial t} = D_{\text{CaB}} \nabla^2 [\text{CaB}] - R \quad (19)$$

The system can be solved numerically by the method of finite elements, i.e., by breaking down the total geometry into a finite number of sub-compartments (meshing).

Limitations

Real chemical reactions are discrete events that depend on the collision of the reactants, i.e., they are stochastic and noisy. With larger numbers of molecules, the reactions are well described by the deterministic differential equations. For small molecule numbers, the effects of noise may become important, and it could be appropriate to use stochastic simulation. Such a Monte Carlo

simulation is more time-consuming, and it has to be carefully weighted whether it is really required. As a rule of thumb, a reaction with less than 100 molecules is likely to be more adequately described stochastically (Bhalla and Wils 2009).

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Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis

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Definition

Calcium is a key but a ubiquitous messenger in cell physiology. Yet direct electrophysiological or light imaging measurements are limited by the intrinsic small nano- to micrometer space where chemical reactions occur and also by the small number of molecules. Thus any fluorescence dye molecule added to measure the number of calcium ions can severely perturb the endogenous chemical reactions. Over the years, an alternative approach based on modeling, mathematical analysis, and numerical simulations has demonstrated that it can be used to obtain precise quantitative results about the order of magnitude, rate constants, the role of the cell geometry, and flux regulation across scales from channels to the cell level.

The aim of this ECN is to present physical models of calcium ions from the molecular description to the concentration level and to present the mathematical tools used to analyze the model equations. From such analysis, asymptotic formulas can be obtained, which are usually valid

for a certain range of parameters. However these formulas allow exploring at low cost the parameter space. The methods to analyze these equations are part of the classical analysis of partial differential equations and stochastic processes, which will not be reviewed here (see Schuss 1980, 2010a). We shall present several models related to diffusion, where formulas can be derived, and we shall specify how these formulas are used to extract parameters from experimental measurements. But in general models are far too complicated to lead to equations that can be analyzed, and most of the time, numerical simulations have to be built. Building rational simulations requires discretizing the physical equations and bridging the gap between the limits of the equations and the physical description that they account for. We will present here several stochastic simulations and their rules, limitations, and tricks that have been developed over the years. As we shall see here, any bottleneck in the equation can lead to heavy simulations running for days. In that case, coarse graining is a key step to reduce the complexity of the equation so that some analysis can be obtained and can be used to check in some limit the validity of the simulations.

All together physical modeling, mathematical analysis, numerical simulation, and their application to the statistical analysis of experimental data form an ensemble of approaches that are used today to better understand molecular interaction in nano- to microdomains. But the most striking convergence of these methods is to derive physiological laws from their first physical principles. We shall present (1) stochastic modeling of calcium ions and their trajectories, (2) modeling of local interactions with discussion of the rate constants, (3) derivation of asymptotic formulas for the residence of calcium in microdomains and dendritic spines, (4) modeling and simulation of diffusion in a crowded three-dimensional dendrite, (5) modeling of calcium in the spines, (6) modeling the CaM activation pathway, and (7) modeling of coarse-grained Markov chain to estimate the probability that the number of calcium ions bound to key molecule is reached. Finally, we shall discuss how these simulations can be used to study physiological processes

such as transient calcium ions in a dendritic spine, long-term potentiation induction, or what limits the spread of calcium following synaptic stimulations.

Detailed Description

Neuronal Microdomains

Neurons can be decomposed into several key microdomains involved in specific functions: dendrites integrate electrical signals, whereas dendritic spines are microcompartments receiving the postsynaptic terminal of excitatory synapses (Fig. 1). The presynaptic terminal is also a key compartment that controls calcium in relation to vesicular release. Dendrites further decompose into distal and apical dendrites which seem to have different electrophysiological properties that can be correlated with a difference in the structure. The soma and the axon are also separate compartments. We show in Fig. 1 different distinct compartments. Finally, it was found that aspiny neurons can confine calcium for a time scale comparable to a dendritic spine (Goldberg et al. 2003). Can organelles such as vesicles or endoplasmic reticulum control calcium concentration?

Diffusion in Neuronal Microdomains: Stochastic Modeling

We start with a Brownian description of calcium ions. Indeed motion due to thermal fluctuations is the main driving force for the motion of particles such as ions or molecules. Calcium motion has been well approximated as diffusion, which confirms that the ionic charge is screened. This is not the case for calcium influx through channels, where the nanometer space restriction is a dominant factor for the interaction between the channel charges and the ion (Benazzila 2000; Eisenberg et al. 1995). In cells, long distances are overcome mostly by the diffusion process. For example, free calcium ions diffuse in the dendritic spines or any neuronal microdomain in the dendrite or the axons (Korkotian et al. 2004). At the molecular level, diffusion of ions is described by a random walk. When an ion meets any plasma membrane, it is reflected or translocated inside an organelle at

pumps or exchangers. The transition from one region to another can be modeled by specifying absorbing conditions in specific boundary regions, such as the fictive separation between a dendrite and a spine.

Description of Calcium Stochastic Trajectories

A calcium ion trajectory is described by the Smoluchowski limit in the large damping approximation of the Langevin equation. The position x at time t satisfies the stochastic equation

$$\gamma[\dot{x} - V(x, t)] + F(x) = \sqrt{2\varepsilon\gamma}w. \quad (1)$$

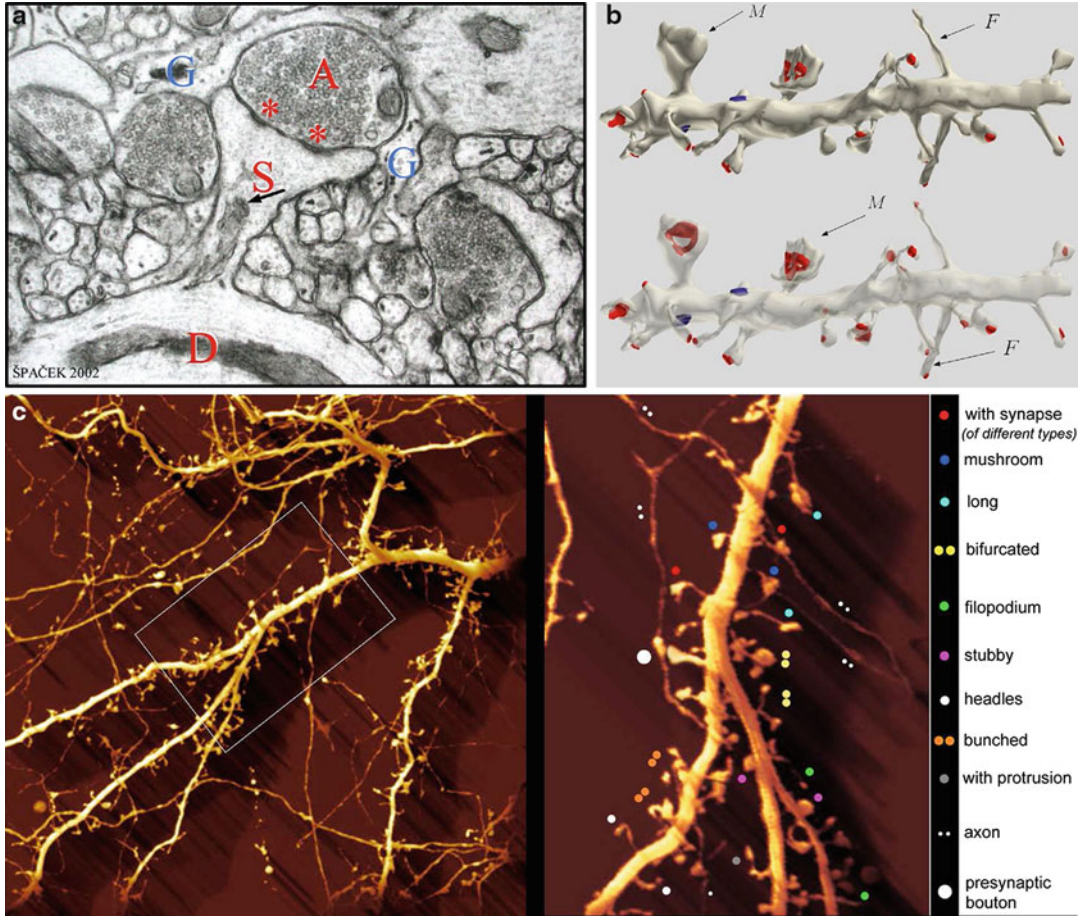
Here $\varepsilon = k_B T/m$, where T is the temperature and k_B the Boltzmann constant; $\gamma = 6\pi a\eta$ is the dynamical viscosity, where η is the viscosity coefficient per unit mass and a is the radius of the ion. w is a random white noise modeling the thermal fluctuations, and the electrostatic force is

$$F(x) = -ze\nabla_x U_0(x),$$

where U_0 is the potential created by the site where the proteins are located. In a first approximation, each protein creates a localized parabolic potential, where the depth can be calibrated by using the backward-binding rate and the radius by using the forward-binding rate (Korkotian and Segal 2006). The frictional drag force, $-\gamma[\dot{x} - V(x, t)]$, is proportional to the relative velocity of the ion and the cytoplasmic fluid. The field of fluid $V(x, t)$ induced by calcium ions will be discussed below.

The Langevin Equations

We shall here explain the physical consideration behind the reduction to Eq. 1. For a dendritic spine containing N ions of different species (e.g., Ca^{++} , Na^+ , Cl^- , and so on), $\mathbf{x}_i(t)$ is the displacement vector of the i -th ion, m_i is its mass, and z_i is its valence. $\tilde{\mathbf{x}} = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N)$ is the coordinate of the N ions in configuration space. We consider a given flow field $V(\mathbf{x}, t)$ (see description below) and that ions interact with a fixed potential of the charges on the proteins, $U_0(\mathbf{x})$, and with the variable potential of all other ions. The variable potential consists of both the electrostatic ion-ion interaction potential, $U_{ii}(\tilde{\mathbf{x}})$, and the potential of



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 1 Neuronal microdomains. (a) Electron microscopy of a synapse. The postsynaptic terminal is located on a dendritic spine (S) branched in the dendrite (D). Located around the axon (A) are the glial cells (G). (b) Three-dimensional EM reconstruction of two dendrites from the

hippocampus. The PSDs of excitatory synapses are marked in red and of inhibitory synapses in blue. Filopodia (marked F) and mushroom spines (marked M) are clearly seen. (c) All possible types of the dendritic spines, for example, a 3D reconstructed hippocampal dendrite, 3 weeks old in primary culture

Lennard-Jones-type repulsions, $U_{LJ}(\tilde{\mathbf{x}})$ (that represents the finite size of the ions). The force per unit mass on the i -th ion is

$$\mathbf{F}_i(\tilde{\mathbf{x}}) = -z_i e \nabla \mathbf{x}_i [U_0(\mathbf{x}_i) + U_{ii}(\tilde{\mathbf{x}})] - \nabla \mathbf{x}_i U_{LJ}(\tilde{\mathbf{x}}).$$

The dynamics of the i -th ion is given by the Langevin equation

$$\begin{aligned} \ddot{\mathbf{x}}_i + \gamma_i [\dot{\mathbf{x}}_i - \mathbf{V}(\mathbf{x}_i, t)] + \mathbf{F}_i(\tilde{\mathbf{x}}) \\ = \sqrt{2\epsilon_i \gamma_i} \dot{\mathbf{w}}_i, \end{aligned} \quad (2)$$

where $\epsilon_i = k_B T / m_i$, T is the temperature, $\gamma_i = 6\pi a_i \eta_i$ is the dynamical viscosity, η_i is the viscosity coefficient per unit mass, and a_i is the radius of the ion. The frictional drag force, $-\gamma_i [\dot{\mathbf{x}}_i - \mathbf{V}(\mathbf{x}_i, t)]$, is proportional to the relative velocity of the ion and the cytoplasmic fluid. The accelerations $\dot{\mathbf{w}}_i$ represent the thermal fluctuations of the fluid. The relation between the velocity diffusion constant and the friction coefficient,

$$D_i = \frac{k_B T}{m_i \gamma_i},$$

is Einstein's fluctuation-dissipation principle (Schuss 1980). In the Smoluchowski limit of large damping (Schuss 1980) the Langevin Eq. (2) reduces to

$$\gamma_i[\dot{\mathbf{x}}_i - \mathbf{V}(\mathbf{x}_i, t)] + F_i(\tilde{\mathbf{x}}) = \sqrt{2\epsilon_i\gamma_i}\dot{\mathbf{w}}_i, \quad (3)$$

When neglecting the ion-ion interactions, we set $U_{\text{LJ}}(\tilde{\mathbf{x}}) = U_{ii}(\tilde{\mathbf{x}}) = 0$, so that Eq. 3 becomes

$$\gamma_i[\dot{\mathbf{x}}_i - \mathbf{V}(\mathbf{x}_i, t)] + \mathbf{F}(\mathbf{x}_i) = \sqrt{2\epsilon_i\gamma_i}\dot{\mathbf{w}}_i, \quad (4)$$

where

$$\mathbf{F}(\mathbf{x}_i) = z_i e \nabla \mathbf{x}_i U_0(\mathbf{x}_i).$$

Since we are interested in tracing only one species in the spine, namely, the concentration of calcium, we assume that $\gamma_i = \gamma_{\text{Ca}^{++}}, m_i = m_{\text{Ca}^{++}}, z_i = z = 2$. Under these assumptions, equations in (4) are independent and identical, so that their transition probability densities are identical. We denote the transition probability density function (pdf) of each ion by $p(\mathbf{x}, t | \mathbf{x}_0, t_0)$ so that the calcium concentration is

$$c(\mathbf{x}, t) = \int_{\Omega_t} p(\mathbf{x}, t | \mathbf{x}_0, t_0) c_0(\mathbf{x}_0) d\mathbf{x}_0,$$

where $c_0(\mathbf{x}_0)$ is the initial calcium density.

Specification of the Hydrodynamic Flow

The flow of the incompressible cytoplasmic fluid in the spines is generated by the local contraction of actin-myosin complexes saturated by calcium ions. We assume that the flow field is derived from a potential $\phi(\mathbf{x}, t)$ (see, e.g., Landau and Lifshitz 1975),

$$\mathbf{V}(\mathbf{x}, t) = \nabla \phi(\mathbf{x}, t). \quad (5)$$

The incompressibility condition, $\nabla \cdot \mathbf{V}(\mathbf{x}, t) = 0$, reduces to the Laplace equation in the head $\Omega_H(t)$ of the spine at time t . The surface of the head, $\Sigma(t)$, is partitioned into the surface $\Sigma_H(t)$ of the spine head, that does include the surface common with the neck, and the cap $\Sigma_N(t)$ of the

surface of the head inside the neck, $\Sigma(t) = \Sigma_H(t) \cup \Sigma_N(t)$. The Laplace equation in $\Omega_H(t)$ is

$$\Delta \phi(\mathbf{y}, t) = 0 \quad \text{for } \mathbf{y} \in \Omega_H(t), t > 0, \quad (6)$$

with the boundary conditions

$$\begin{aligned} \left. \frac{\partial \phi(\mathbf{y}, t)}{\partial n} \right|_{\mathbf{y} \in \Sigma_H(t)} &= -V(t), \quad \left. \frac{\partial \phi(\mathbf{y}, t)}{\partial n} \right|_{\mathbf{y} \in \Sigma_N(t)} \\ &= F(V(t)), \end{aligned} \quad (7)$$

where $V(t)$ is the average velocity induced by the deformation of the head (see Eq. 8 below) (Holcman and Schuss 2004), due to the sum of all the local contractions, and $F(V(t))$ is the induced field velocity at the top of the neck $\Sigma_N(t)$: for a volume displaced per unit time equal to $4\pi R^2(t)V(t)$ in dimension 3 and $2\pi R(t)V(t)$, where $R(t)$ is the instantaneous radius of the head, then $R(t) = -V(t)$. The flux through Σ_N is $|\Sigma_N|v(t)$; hence

$$v(t) = F(V(t)) = \begin{cases} \frac{4\pi R^2(t)V(t)}{|\Sigma_N|} & \text{indimension 3} \\ \frac{2\pi R(t)V(t)}{|\Sigma_N|} & \text{indimension 2} \end{cases},$$

when the field is due to the contraction of myosin after 4 calcium ions are bound. The total number of sites bound to 4 calcium is $S^{(4)}(t)$ and can be obtained by solving a system of reaction-diffusion equations (Holcman and Schuss 2004). Finally the velocity at the boundary is given by

$$V(t) = v_Q S^{(4)}(t), \quad (8)$$

where v_Q is a constant velocity. The quantities $V(t)$ and $F(V(t))$ are stochastic processes, that are proportional to the number of saturated proteins at any given time t . The flow field can be expressed explicitly in terms of the functions $V(t)$ and $F(V(t))$ by Green's function for the Neumann problem for Poisson's equation in a sphere (or a disk) through Stokes' formula. Green's function $G(\mathbf{x}, \mathbf{y}, t)$ is the solution (defined up to a constant) of the equation

$$\begin{aligned}
-\Delta_{\mathbf{y}} G(\mathbf{x}, \mathbf{y}, t) &= \delta(\mathbf{x} - \mathbf{y}) - \frac{1}{|\Omega_0|} \quad \text{for } \mathbf{x}, \mathbf{y} \in \Omega_H(t) \\
\frac{\partial G(\mathbf{x}, \mathbf{y}, t)}{\partial n(\mathbf{y})} &= 0 \quad \text{for } \mathbf{x} \in \Omega_H(t), \mathbf{y} \in \Sigma(t).
\end{aligned}
\tag{9}$$

Multiplying Eq. 6 by $G(\mathbf{x}, \mathbf{y}, t)$ and Eq. 9 by $\phi(\mathbf{y}, t)$ and integrating with respect to $\mathbf{y}$ over the domain, using Stokes' theorem and the boundary condition (7), we get

$$\begin{aligned}
\phi(\mathbf{x}, t) &= \int_{\mathbf{y} \in \Sigma(t)} \frac{\partial \phi(\mathbf{y}, t)}{\partial n} G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} - \int_{\mathbf{y} \in \Sigma(t)} \frac{\partial G(\mathbf{x}, \mathbf{y}, t)}{\partial n} \phi(\mathbf{y}, t) dS_{\mathbf{y}} \\
&\quad + \frac{1}{V_H} \int_{\Omega_H(t)} \phi(\mathbf{y}, t) d\mathbf{y} \\
&= \int_{\mathbf{y} \in \Sigma(t)} \frac{\partial \phi(\mathbf{y}, t)}{\partial n} G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} + \frac{1}{V_H} \int_{\Omega_H(t)} \phi(\mathbf{y}, t) d\mathbf{y} \\
&= - \int_{\Sigma_H(t)} V(t) G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} + \int_{\Sigma_N(t)} F(V(t)) G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} \\
&\quad + \frac{1}{V_H} \int_{\Omega_H(t)} \phi(\mathbf{y}, t) d\mathbf{y} \\
&= -V(t) \int_{\Sigma_H(t)} G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} + F(V(t)) \int_{\Sigma_N(t)} G(\mathbf{x}, \mathbf{y}, t) dS_{\mathbf{y}} \\
&\quad + \frac{1}{V_H} \int_{\Omega_H(t)} \phi(\mathbf{y}, t) d\mathbf{y}.
\end{aligned}$$

The flow field is given by

$$\begin{aligned}
\nabla \phi(\mathbf{x}, t) &= -V(t) \int_{\Sigma_H} \nabla_{\mathbf{x}} G(\mathbf{x}, \mathbf{y}) dS_{\mathbf{y}} \\
&\quad + F(V(t)) \int_{\Sigma_N} \nabla_{\mathbf{x}} G(\mathbf{x}, \mathbf{y}) dS_{\mathbf{y}}.
\end{aligned}$$

In the neck, due to the symmetries and the uniform initial conditions, we simplify the flow field by assuming its velocity is parallel to the axis of the neck. It is given by

$$\nabla \phi(\mathbf{x}, t) = \mathbf{V}(\mathbf{x}, t) = F(V(t)) \mathbf{k},$$

where $\mathbf{k}$ is a unit vector along the axis of the neck. We note that according to Eq. 8, as the number of saturated proteins increases, the hydrodynamic flow begins to dominate the diffusion. In Holcman and Schuss (2004), and Holcman et al. (2004), we connected the strength of flow field to the number of bound myosin molecules induced by calcium. This results in nonlinear coupled partial

differential equations, that can be solved numerically by stochastic simulations.

Rate Constants and Molecular Dynamics

We shall now recall how to model chemical reactions, described by the backward- and the forward-binding rate, which are usually obtained in aqueous solution, where diffusion is not limited by space. In confined microdomains where the number of ions involved can be small, the binding rates have to be reinterpreted.

Backward-Binding Rate

The mean time that two molecules react chemically is modeled as the mean time the first molecule stays imprisoned in the potential well of the second. The random time interval between the binding and the reappearance of the binding molecule into the free state is exponentially distributed with a rate constant equal to the backward-binding reaction. The exponentially distributed waiting time for the backward reaction is based on Kramers' theory of activated barrier crossing,

as described in Matkowsky et al. (1982). Thus for transient chemical reactions, each molecule reacting with a calcium ion has two consequences: first, the molecule can become activated, and second, the time course of calcium is delayed. The unbinding events are modeled as Poissonian processes. Fixing a scale Δt , the probability to unbind is $k_b \Delta t$ (take a uniform variable and check whether it is above or below $k_b \Delta t$).

Forward-Binding Rate

The forward-binding rate K_{for} corresponds to the flux of particles to the binding sites. Contrary to the backward-binding rate, this rate does not contain local properties only, but includes the effect of the global geometry of the domain, where the chemical reaction occurs. Such a rate has been computed at equilibrium by Smoluchowski and can be converted as the effective radius R_a of a ball that mimics the binding site and so that the average probability that an ion meets such ball is equal to the forward rate. The radius is calibrated according to the formula

$$K_{\text{for}} = 2\pi R_a D [\text{Ca}^{2+}], \quad (10)$$

where $[\text{Ca}^{2+}]$ is the initial calcium concentration and D the diffusion constant. This calibration can also be used to estimate the effective radius of a binding molecule in a transient state, calibrated for the initial concentration condition. When the binding sites are located on the boundary, the narrow escape formula should be used (Holcman and Schuss 2013).

Modeling the Interaction of Calcium Ion with Surface or Receptors

We shall now specify the interaction conditions between a calcium ion and a receptor or a membrane, the model at a molecular and population level, and the physical laws that can be derived from elementary physical principles.

Absorption

Absorption at surface $\partial\Omega$ is the process by which a particle is removed after it hits $\partial\Omega$, which can be an artificial interface such as the one between the spine and the dendrite or an effective one such as a

channel. Indeed, during a simulation, when an ion hits such a surface, it disappears. In general, absorption on a surface is modeled by killing the trajectories when it encounters or passes over the surface $\partial\Omega$. Thus the probability density function to make a transition from $x \in \partial\Omega$ to any point y during time t is zero: $p(y, t|x) = 0$.

Partial Absorption

Partial absorption accounts for a probability that a particle arriving at a surface is reflected with a probability p or absorbed with probability $1 - p$. This condition can be calibrated to describe the interaction between the moving particle and the binding site of a receptor. This condition is formulated at a molecular level for stochastic simulations or with a probability density function to describe the macroscopic level. This condition is called also radiation or reactive or Robin boundary conditions and has been widely used to describe diffusion in a biological cell with chemical reactions on its surface (Andrews and Bray 2004; Batsilas et al. 2003; Berezhkovskii et al. 2004; Erban and Chapman 2007; Monine and Haugh 2005; Lamm and Schulten 1983; Tai et al. 2003; Zwanzig 1990).

Schematic Description

The overdamped Langevin equation can be written as a stochastic equation

$$\dot{x} = a(x, t) + \sqrt{2\sigma + (x, t)} \dot{w} \quad (11)$$

The process $x(t)$ defined by Eq. 11 with partially absorbing boundaries can be defined as the limit of Markovian jump processes generated by the Euler scheme

$$x_{\Delta t}(t + \Delta t) = x_{\Delta t}(t) + a(x_{\Delta t}(t), t)\Delta t + \sqrt{2\sigma(x_{\Delta t}(t), t)}\Delta + w(t, \Delta t) \quad \text{for } t \geq s \quad (12)$$

$$x_{\Delta t}(s) = x \quad (13)$$

in the interval $x > 0$, for $0 \leq t - s \leq T$, with $\Delta t = T/N$, $t - s = iT/N$ ($i = 0, 1, \dots, N$), where for each t the random variables $\Delta w(t, \Delta t)$ are normally distributed and independent with zero mean and variance Δt . In dimension one, with boundary at

0, the boundary behavior for the simulated trajectories that cross the boundary, identified by

$x_{\Delta t}(t) + a(x_{\Delta t}(t), t)\Delta t + \sqrt{2\sigma(x_{\Delta t}(t), t)}\Delta w < 0$ is described by

$$x_{\Delta t}(t + \Delta t) = \begin{cases} -(x_{\Delta t}(t) + a(x_{\Delta t}(t), t)\Delta t + \sqrt{2\sigma(x_{\Delta t}(t), t)}\Delta w) \text{ w.p. } 1 - P\sqrt{\Delta t} \\ \text{terminate trajectory otherwise.} \end{cases} \quad (14)$$

Thus the exiting trajectory is normally reflected w.p.

$$R = 1 - P\sqrt{\Delta t} \quad (15)$$

and is otherwise terminated (absorbed). The scaling of the termination probability with $\sqrt{\Delta t}$ reflects the fact that the discrete unidirectional diffusion current at any point, including the boundary, is $O(1/\sqrt{\Delta t})$ (Singer et al. 2008). This means that the number of discrete trajectories hitting or crossing the boundary in any finite time interval increases as $1/\sqrt{\Delta t}$.

Partial Reflecting Condition in Dimension Larger Than 2

The scheme (14) is generalized to diffusion with drift and anisotropic constant diffusion matrix $\sigma(t)$ in the half space, $x_1 > 0$, with partial oblique reflection. The Robin boundary condition is recovered if and only if trajectories are reflected in the direction of the unit vector

$$\mathbf{v} = \frac{\sigma \mathbf{n}}{\|\sigma \mathbf{n}\|}, \quad (16)$$

where $\mathbf{n}$ is the unit normal to the boundary. The radiation parameter $k(\mathbf{x}, t)$ in the d -dimensional Robin boundary condition and the absorption parameter

$P(\mathbf{x})$ are related by

$$\kappa(\mathbf{x}, t) = rP(\mathbf{x})\sqrt{\sigma_n(t)}, \quad x_1 = 0, \quad (17)$$

with $r = 1/\sqrt{\pi}$ and $\sigma_n(t) = \mathbf{n}^T \sigma(t) \mathbf{n}$. The relation (17) can also be adapted for curved boundaries and applied to the tangent plane at each point of the boundary. Indeed this is due to the fact that a smooth local mapping of the domain to a half

space with an orthogonal system of coordinates preserves the constant isotropic diffusion matrix, though the drift changes according to Itô's formula. In this case the vector $\mathbf{v}$ coincides with the normal $\mathbf{n}$.

The reflection law and the relation are new for diffusion in higher dimensions. The constant r for the Euler scheme is not the same as that for other schemes, e.g., for a discrete random walk with radiation boundaries, $r = 1/\sqrt{2}$. The reflection can be constructed explicitly. Indeed, the d -dimensional stochastic dynamic is

$$\dot{\mathbf{x}} = \mathbf{a}(\mathbf{x}, t) + \sqrt{2}\mathbf{B}(t)\dot{\mathbf{w}} \quad (18)$$

in the half space

$$\Omega = \{\mathbf{x} = (x_1, x_2, \dots, x_d) \in \mathbb{R}^d : x_1 > 0\}$$

where $\mathbf{w}$ is a vector of d independent Brownian motions and when we assume that the diffusion tensor $\sigma(t) = \mathbf{B}(t)\mathbf{B}^T(t)$ is uniformly positive definite for all $t \geq s$. We use henceforward the abbreviation $\sigma(t) = \sigma$. The radiation condition (35) becomes

$$-\mathbf{J}(\mathbf{y}, t|\mathbf{x}, s) \cdot \mathbf{n} = \kappa(\mathbf{y}, t)p(\mathbf{y}, t|\mathbf{x}, s), \text{ for } \mathbf{y} \in \partial\Omega, \mathbf{x} \in \Omega, \quad (19)$$

where the components of the flux vector $\mathbf{J}(\mathbf{y}, t|\mathbf{x}, s)$ are defined by

$$\begin{aligned} \mathbf{J}^k(\mathbf{y}, t|\mathbf{x}, s) = & -[a^k(\mathbf{y}, t)p(\mathbf{y}, t|\mathbf{x}, s)] \\ & + \sum_{j=1}^d \frac{\partial}{\partial y_j} [\sigma^{jk}p(\mathbf{y}, t|\mathbf{x}, s)] \end{aligned} \quad (20)$$

The Fokker-Planck equation for the pdf of $\mathbf{x}(t)$ can be written as

$$\frac{\partial p(\mathbf{y}, t | \mathbf{x}, s)}{\partial t} = -\nabla \mathbf{y} \cdot \mathbf{J}(\mathbf{y}, t | \mathbf{x}, s) \text{ for all } \mathbf{y}, \mathbf{x} \in \Omega \quad (21)$$

If $\mathbf{x} \in \Omega$, but

$$\mathbf{x}' = \mathbf{x} + \mathbf{a}(\mathbf{x}, t)\Delta t + \sqrt{2}\mathbf{B}(t)\Delta \mathbf{w}(t, \Delta t) \notin \Omega,$$

the Euler scheme for Eq. 18 with oblique reflection in $\partial\Omega$ reflects the point $\mathbf{x}'$ obliquely in the constant direction of $\mathbf{v}$ to a point $\mathbf{x}'' \in \Omega$, as described below. First, we denote by $\mathbf{x}_B'$ the normal projection of a point $\mathbf{x}'$ on $\partial\Omega$, that is, $\mathbf{x}_B' = \mathbf{x}' - (\mathbf{x}' \cdot \mathbf{n})\mathbf{n}$. Then we write the Euler scheme for Eq. 18 with partially reflecting boundary as

$$\mathbf{x}(t + \Delta t) = \begin{cases} \mathbf{x}' & \text{for } \mathbf{x}' \in \Omega \\ \mathbf{x}'' \text{ w.p. } 1 - P(\mathbf{x}_B')\sqrt{\Delta t}, & \text{if } \mathbf{x}' \notin \Omega, \\ \text{terminate trajectory w.p. } P(\mathbf{x}_B')\sqrt{\Delta t}, & \text{if } \mathbf{x}' \notin \Omega \end{cases} \quad (22)$$

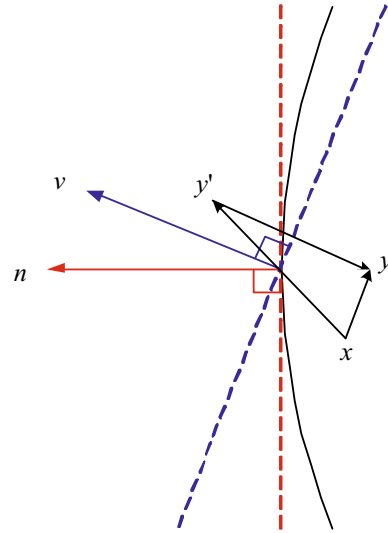
The value of the termination probability $P(\mathbf{x}_B')\sqrt{\Delta t}$, that varies continuously in the boundary, is evaluated at the normal projection of the point $\mathbf{x}'$ on the boundary. The oblique reflection in the direction of the unit vector $\mathbf{v}$ ($v_1 \neq 0$) is defined by

$$\mathbf{x}'' = \mathbf{x}' - \frac{2x_1'}{v_1} \mathbf{v}. \quad (23)$$

Note that $x_1'' = -x_1'$ guarantees that the reflected point of a crossing trajectory is inside the domain Ω . The fact that the normal components of $\mathbf{x}''$ and $\mathbf{x}'$ are of equal lengths makes the high-dimensional boundary layer analysis similar to that in one dimension. Normal reflection corresponds to $\mathbf{v} = \mathbf{n} = (1, 0, \dots, 0)$. We note that for a point $\mathbf{y} \in \Omega$, we can write $\Pr\{\mathbf{x}'' = \mathbf{y}\} = \Pr\{\mathbf{x}' = \mathbf{y}'\}$, where

$$\mathbf{y} = \mathbf{y}' - \frac{2\mathbf{y}' \cdot \mathbf{n}}{v_1} \mathbf{v} \quad (24)$$

is the oblique reflection of $\mathbf{y}'$ (see Fig. 2). If the scheme described above is not used, a paradox can arise (Singer et al. 2008): while the pdf of the



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 2

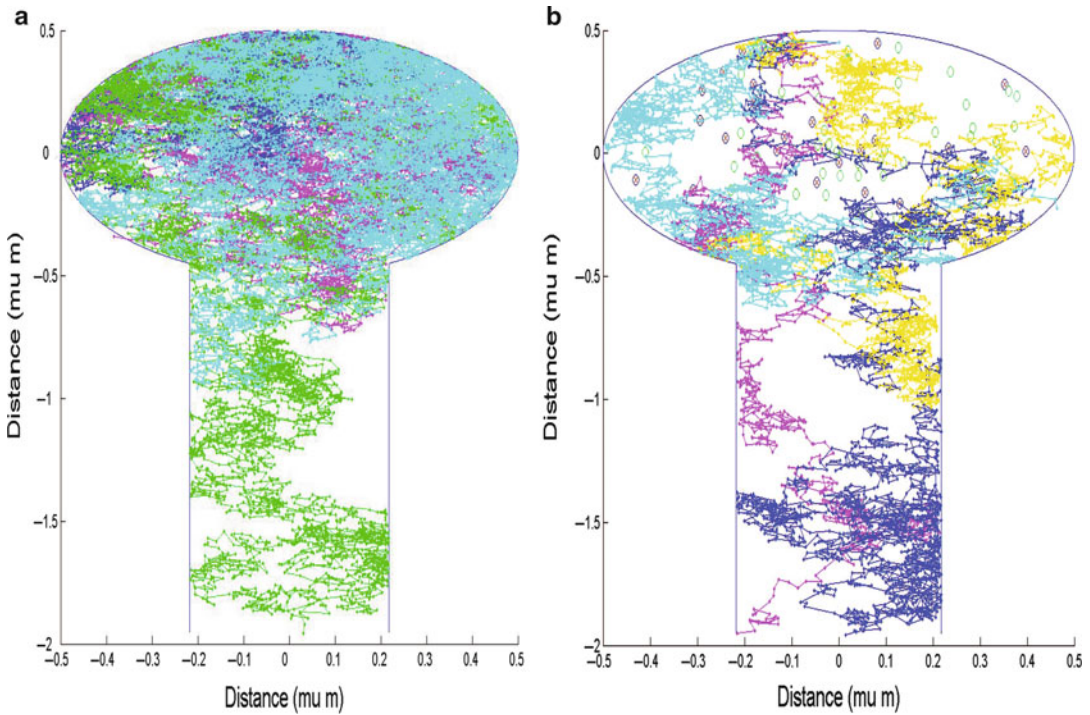
Reflection Scheme. A simulated trajectory can get from $\mathbf{x}$ to $\mathbf{y}$ in a single time step Δt in two different ways: (i) directly from $\mathbf{x}$ to $\mathbf{y}$, without crossing the boundary, and (ii) by crossing the boundary from $\mathbf{x}$ to $\mathbf{y}'$ and reflection in the oblique direction $\mathbf{v}$ with probability $1 - P(\mathbf{y}_B')\sqrt{\Delta t}$ to $\mathbf{y}$. The reflection law Eqs. 22–24 satisfies $v_1' = -v_1$

solution of Eqs. 12 and 13 converges to the solution of the FPE Eq. 32 and the initial condition Eq. 34, it does not satisfy the boundary condition Eq. 35, leading to a boundary layer, due to the diffusion approximations in the Markovian jump process (Fig. 3).

Generic Modeling of Calcium Ions at Pumps or Exchangers

Partial absorbing boundary condition can be used to model the behavior of calcium ion near a channel or a pump. However cooperativity should be implemented for each case at hand. For example, after entering inside an exchanger, an ion takes a certain time to exit: this is modeled by changing a partial reflecting boundary condition to a reflecting one as long as the ion is inside the exchanger.

Some pumps can work with several ions. As the intrinsic biophysical mechanism of permeability is not necessarily understood, there is no consensus for a universal coarse-graining scheme of



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 3 The filling of space by five random trajectories in the spine with no drift (a) and with drift (b). Each color corresponds to a trajectory. Proteins are uniformly distributed in the spine head and are represented by circles and crossed circles, respectively. A trajectory starts at the top of

the spine head where channels are located and continues until it is terminated at the dendritic shaft or at an active pump. The parameters for the simulation are $\delta_1 = 0.02 \mu\text{m}$, $\delta_2 = 0.01 \mu\text{m}$, $K_{\text{back}}^{\text{AM}} = 10^4 \text{ s}^{-1}$, $K_{\text{back}}^{\text{cal}} = 2.10^3 \text{ s}^{-1}$, $R = 0.5 \mu\text{m}$, $d/2 = 0.21794 \mu\text{m}$, $l = 1.5 \mu\text{m}$, $N_{\text{pumps}} = 10$

ion extrusion. If two ions are required, we propose that once the first ion enters the channel, it cannot move before another has hit the binding area. If the second ion enters while the first one is not returned (after an exponential waiting time), then the first one can be extruded. During that time, no other ions can enter the channel.

Modeling Calcium Influx from Channels: NMDA Receptors, AMPA Receptors, and VSCC

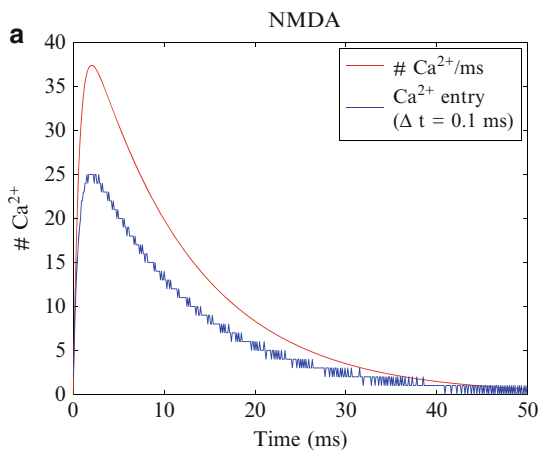
We shall now present examples of three classical channels such as NMDA, AMPAR (GluR2-calcium permeable), and voltage-sensitive calcium channel (VSCC) for simulating the flux of calcium inside neuronal cells. The flow of ions through open channels has been studied using Langevin equation (Eisenberg et al. 1995; Roux et al. 1995). The fluxes of ions can be implemented numerically as follows.

Calcium Influx Through NMDAR

Calcium influx through NMDA channels can be approximated by (Koch 1999, p. 99)

$$I_N(t) = g_N \frac{e^{-t/\tau_{N,1}} - e^{-t/\tau_{N,2}}}{1 + 0.33[Mg^{2+}]e^{-0.06V_m}} \times (V_m - E_N), \quad (25)$$

where the conductance is $g_N = 0.16 \text{ nS}$ and the Nernst potential $E_n = 0$, V_m is the membrane potential. When the potential V_m is fixed and the fraction of current carried by calcium ions is 15%, we can simulate such a flux by injecting particles at random times such that the instantaneous rate is the one obtained from relation Eq. 25. Indeed, the entrance is a Poissonian process with a time-dependent rate $\lambda(t + \Delta t) = \frac{I_{\text{Ca}}(t)\Delta t}{2e}$. The number of entering ions is $N(t)\Delta t = \frac{I_{\text{Ca}}(t)\Delta t}{2e}$, where



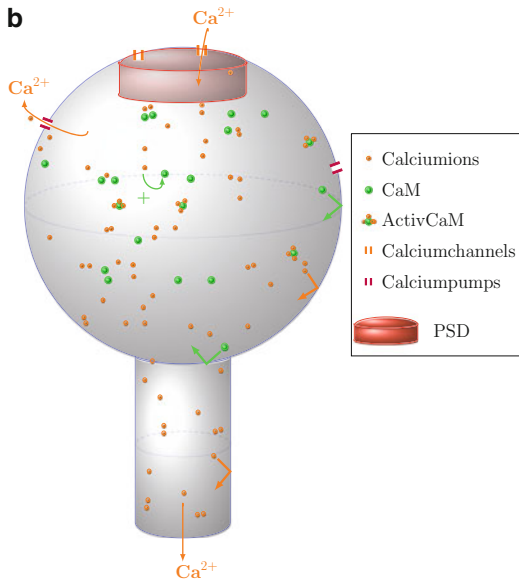
Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 4 Calcium entry and dynamics. (a) Time course of calcium entry inside a spine through an NMDA receptor.

$I_{Ca}(t)\Delta t = \int_t^{t+\Delta t} I_N(s)ds$. An example of stochastic calcium ion entry is presented in Fig. 4 (discretized at a time step $\Delta t = 0.1$ ms). In some dendritic spine models (Holcman et al. 2004; Holcman and Schuss 2004), the entrance dynamics is neglected and ions are initially placed at channels, located at the top of the dendritic spine head. Typically, the total charge is $Q_N = \int_0^\infty I(s) ds$; thus the fraction of calcium is $Q_{Ca} = 0.15 Q_N$ Coulomb. The number of calcium ions entering is $N_{N,Ca} = \frac{Q_{Ca}}{2e}$, where the e is the electron charge. Using parameters of Table 1, we obtain that $Q_N = 6.38pC$ and thus there are about $N_{N,Ca} = 3000$ ions entering in average inside a single NMDA receptor (for a fixed mean voltage $V_m = -65.1$ mV).

Calcium Influx Through AMPAR

The stochastic arrival of ions entering through an AMPAR is computed exactly with the same method as for NMDA, except that the mean flux is given by

$$I_A = g_A \frac{t}{\tau_A} e^{-t/\tau_A} (V_m - E_A), \tag{26}$$



(b) Schematic representation of the calcium and calmodulin (CaM) pathway inside a dendritic spine (Guerrier and Holcman 2014a)

Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Table 1 Calcium entry into dendritic spines

Parameter	Description	Value
	Fraction of NMDAR current carried by Ca^{2+}	15%
	Total charge entering I_N (NMDAR)	6.38×10^{-15} C
	Calcium ions entering through NMDAR	≈ 3000 ions
g_N	NMDAR conductance	0.16 nS
E_N	Equilibrium potential (NMDAR)	0 mV
$\tau_{N,1}$	NMDAR time constant	11.5 ms
$\tau_{N,2}$	NMDAR time constant	0.67 ms
	Fraction of AMPAR current carried by Ca^{2+}	1.4%
	Total charge entering I_A (NMDAR)	11.51×10^{-15} C
	Calcium ions entering through NMDAR	≈ 500 ions
g_A	Conductance (AMPA)	0.3 nS
E_A	Equilibrium potential (AMPA)	0 mV
τ_A	AMPA time constant	0.2 ms
	Total charge entering I_V (NMDAR)	0.64×10^{-15} C
	Calcium ions entering through VSCC	≈ 2000 ions

where $g_A = 0.3$ nS and the Nernst potential $E_a = 0$ mV. The fraction of AMPAR current carried by calcium ions is 1.4%; thus we find that the total charge is $Q_A = 11.51$ fC, leading to approximately 500 ions.

Influx Through VSCC

Calcium influx through VSCC requires computing the changes in the membrane potential depolarization. One possibility is to use the simplified Hodgkin-Huxley model (Hille 2001). The voltage change follows the dynamics

$$C \frac{dV}{dt} = -I_{Na}(V, n) - I_K(V, n) - I_L(V) \\ - I_{Ca}(V, m, h) - \gamma I_N - \eta I_A \\ \frac{dx}{dt} = 0.1\alpha_x(1-x) - \beta_x x, \text{ for } x = n, m, h.$$

where the currents are

$$I_{Na} = g_{Na}p^3(0.89 - 1.1n)(V - E_{Na}) \\ I_K = g_Kn^4(V - E_K) \\ I_{Ca} = g_{Ca}m^3h(V_m - E_{Ca}) \\ I_L = g_L(V - E_L)$$

with parameters

$$p = \frac{\alpha_p}{\alpha_p + \beta_p}, \alpha_k = \frac{1}{\tau_k} \frac{\theta_k - V_m}{e^{\frac{\theta_k - V_m}{\tau_k}} - 1}, \\ \beta_k = \eta_k e^{\frac{V_m + 65}{\sigma_k}}, \text{ for } k = n, m, h, p.$$

where γ and η are summarized in Table 1. The total charge becomes $Q_V = 0.6$ fC, which leads approximately to 2000 ions entering through VSCC.

Stochastic Simulation of Calcium in a Dendritic Spine

The major benefit of stochastic simulations is to access the total number of biochemical bonds induced by calcium ions on specific molecules and to quantify the amount of structural changes occurring at the spine level. There are many other consequences such as computing the hydrodynamic component that changes the nature of the

ion trajectories or distinguishing the periods of calcium dynamics. Novel coarse-grained equations are derived in (Holcman and Schuss 2004).

Space Exploration

The geometric characteristics of ionic trajectories with the hydrodynamic flow are distributed differently from pure diffusion (Holcman and Schuss 2004) (see Fig. 3). Not only the nature of the movement is different, but the hydrodynamic flow causes the ions to drift in the direction of the neck, and consequently the time they spend in the spine head is reduced. As a consequence, the probability of a trajectory to leave through a pump located in the head decreases. Similarly, the probability to return to the head from the spine neck is reduced if it has to diffuse upstream, against the hydrodynamic drag force. Thus the ionic trajectory stays inside the spine a shorter time in the presence of the hydrodynamic flow, as compared to the time without it. As discussed in (Holcman et al. 2004), the total number of bound molecules can change as much as 30% with and without the flow.

Two Stages of Calcium Concentration Decay

Two very distinct decay rates of the fast extrusion periods have been reported in (Majewska et al. 2000; Sabatini et al. 2001). The second decay period is identified as purely driven by random movement, and the time constant equals the first eigenvalue of the Laplacian on the spine domain, with the adequate boundary conditions. It was shown that the first period corresponds to a fast calcium extrusion, measured in (Majewska et al. 2000) with an exponential decay rate $\lambda = 0.14$ s⁻¹ and is due to the diffusion of saturated buffers, binding kinetics of endogenous buffers, diffusion of buffers, buffered calcium diffusion across the spine neck, and the effect of the pumps. The first period dynamics is defined by the fast binding to calcium stores (Majewska et al. 2000; Sabatini et al. 2001). On the other hand, in the simulation resulting from the model (Holcman et al. 2004), based on fast spine motility, the first time period has an exponential decay rate, constant $\lambda_t = 0.16$ s⁻¹ derived in Holcman and Schuss (2004). The decay seems to be a consequence of the

dynamics created by the push effect, since stores were neglected. Further studies that include large numbers of buffers should reveal the precise contribution of buffers to the calcium fast decay rate, as compared to the rate imposed by the spine contraction.

Multiscale Modeling of Connecting a Continuum Bath with Single Molecular Dynamics

There are various interesting multiscale modeling approaches where the goal is to connect a discreet description of Brownian particles with a continuum (Franz et al. 2013; Flegg et al. 2012). The conservation of fluxes at the connecting interface generates boundary layer behavior that needs to be specifically studied.

Recipe for a Successful Stochastic Simulation

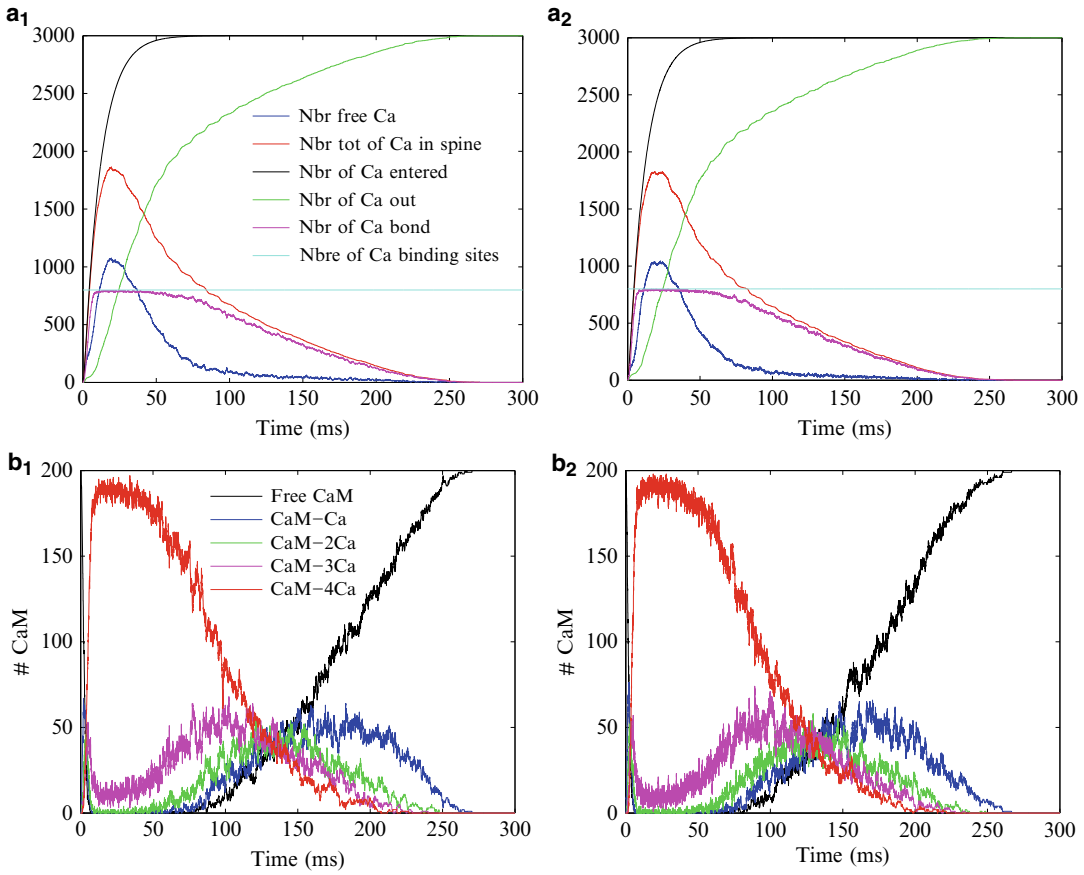
- **Choosing a time step for a simulation.** The time step of a simulation is critical: when it is too small, the simulations take forever, while if it is too large, then binding to buffers of a certain size a is missed. For a time step Δt and a diffusion coefficient D , a Brownian particle moving in three dimensions jumps to a distance $\Delta x^2 = 6D\Delta t$. Thus the constraint $|\Delta x| = a/4$ provides an estimate for the time step. In general the size of the smallest target defines the condition for the time step Δt . In most cases, where target sites are fixed, it is more interesting to refine the time step when a particle enters its neighborhood.
- **Positioning a particle that has unbound.** In the Smoluchowski limit equation (where there is no dynamic for the velocity), the coarse graining of a potential well is usually done by freezing the position of the particle at the binding position during an exponential waiting time, the rate of which is the backward rate (reciprocal of the mean time to escape the well). After the particle unbinding, where should the particle be positioned? Certainly not at the absorbing boundary defining the well; otherwise the particle is immediately absorbed, unless the boundary condition is changed from absorbing to reflecting during a certain refractory time. Another possibility is to position the particle outside the boundary

layer of the binding site: a small distance away from the site (3–4 radii away). This is possible if the sites are not surrounded by other absorbing sites. Inside a structure that contains a high concentration of binding sites, a different simulation approach is needed: either to derive a homogenized equation or the dynamics in the wells should not be coarse grained.

- **Partial absorption.** When there are many absorbing sites located at close proximity, non-linear effects should be taken into account. It is possible to derive homogenized boundary conditions (see for details (Taflia and Holcman 2011)).
- **Coarse graining a simulation with the narrow escape rate.** Instead of running a full Brownian simulation where the position of each calcium ion and calmodulin molecule is computed with the Euler scheme, it is possible to coarse grain it into a rate model based on the narrow escape theory (Schuss and Holcman 2013; Holcman and Schuss 2013). The gain of this procedure is to avoid lengthy simulation imposed by the smallest length. In a Brownian simulation, due to the small calmodulin-binding site of radius $R_{\text{CaM}} = 2$ nm, in order to ensure that the process does not jump over the site, the MSD formula leads to a time step of 10^{-6} ms (with $D_{\text{Ca}} = 200 \mu\text{m}^2 \text{ms}^{-1}$), which would lead to days of simulations. To circumvent this difficulty, it is possible to compute directly the rate of arrival of calcium ions to one of the free calmodulin-binding sites. The mean first binding time τ_B of a Brownian particle diffusing with diffusion coefficient D_I in a spherical domain Ω , to a small spherical target (radius r) diffusing with coefficient $\tau_B = \frac{|\Omega|}{4\pi(D_1+D_2)r}$. Due to the small size r , the binding times are exponentially distributed with a mean $\lambda_1 = 1/\tau_B$. For N -independent calcium ions diffusing within Ω , the first binding time T_b to a calmodulin site is distributed with rate

$$\lambda(N) = \lambda_1 N. \quad (27)$$

Thus, the probability that a binding event occurs between time t and $t + \Delta t$ is $\mathbb{P}(t \leq T_b < t +$



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 5 Calcium dynamics: comparing a Brownian simulation with a coarse-grained rate model for binding to calmodulin. **A₁** and **A₂**: Time course of calcium for 3000 ions entering a dendritic spine through NMDA receptors containing 200 calmodulin. The Brownian time step is $\Delta t = 3 \cdot 10^{-6}$ ms (**A₁**). For the rate model, $\Delta t = 10^{-4}$ ms (**A₂**). Ions diffuse freely in the synapse (*dark blue*), can be

bound to calmodulin (*magenta*), or can leave the spine (*green*). The curves are compared with the total number of ions (*black*) and the total amount of calcium in the spine (free plus bound) (*in red*). **B₁** and **B₂**: Activation of calmodulin during the Brownian simulation (**B₁**) and the rate model (**B₂**). A calmodulin molecule can have zero, one, two, three, or four calcium ions bound (*black, dark blue, green, magenta, and red* respectively)

$\Delta t) = \lambda(N)\Delta t$. An application consists in replacing the Brownian movement of calcium ions in a spine head by the binding rate $\lambda(N)\Delta t$ at each calmodulin site. We thus need to compute at each time step the number N of free calcium in the spine. Furthermore, calcium ions can escape a dendritic spine head Ω_{head} through small pumps. To model this calcium escape, we use a similar method as described above where we approximate the binding of calcium to a pump by using the mean first passage time of a diffusing ion to a

small target located on the boundary. When there are N calcium ions, the first binding time is

$$\mu(N) = \frac{4R_{\text{pump}}D_{\text{Ca}}N}{|\Omega|_{\text{head}}}. \quad (28)$$

It is also possible to account for the competition with escaping through the spine neck using the narrow escape formula for a spine (Eq. 45). This procedure accelerates the simulations and gives excellent results (Fig. 5).

In Figs. 4 and 5, we present a simulation of calcium entry in a dendritic spine binding to calmodulin (Guerrier and Holcman 2014a).

Diffusion Laws in Microdomains with Small Openings

Synaptic input creates calcium transients in single dendritic spines and dendrites (Fig. 6). We shall now present the modeling approach used to study calcium transients.

Probability Density Function of an Ion

The stochastic nature of the calcium motion requires a probabilistic approach. Indeed, the

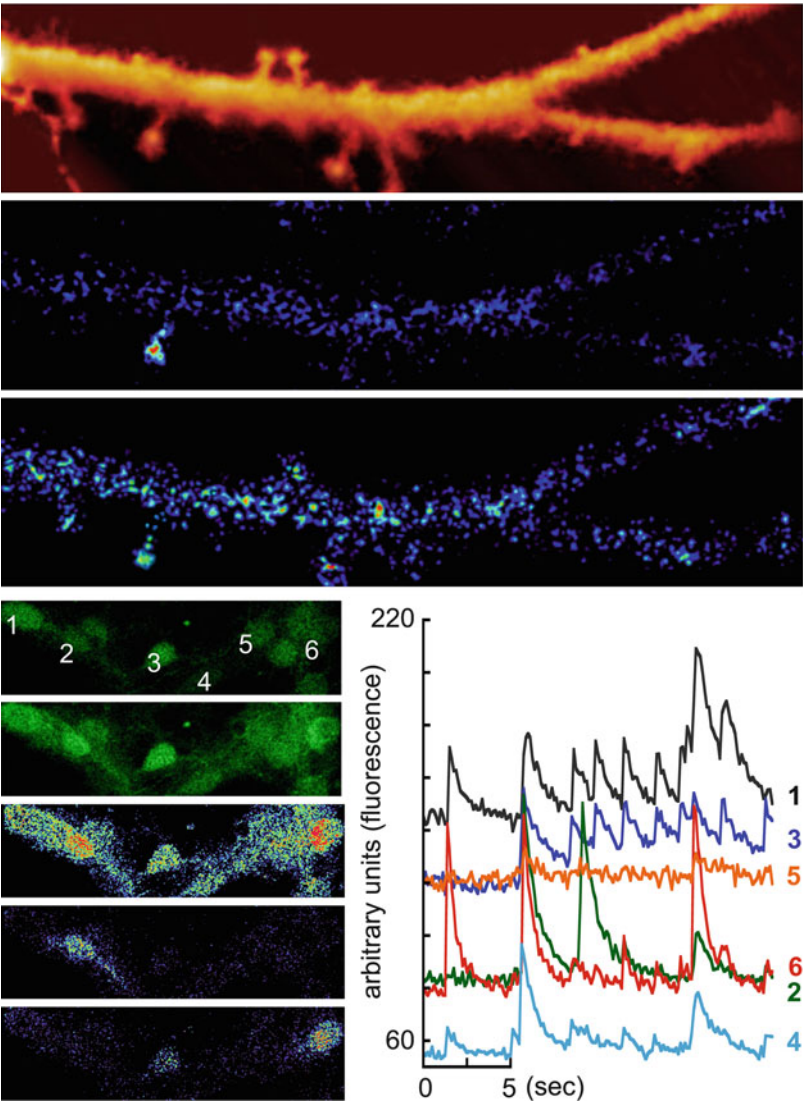
location of an ion is not certain, and the probability $p(x,t)$ to find an ion at time t at a position x satisfies the standard Fokker-Planck or diffusion equation

$$\frac{\partial p}{\partial t}(x,t) = D\Delta p(x,t), \tag{29}$$

where Δ is the Laplacian operator and D is the diffusion constant in the cytoplasm. The solution of Eq. 29 requires specifying initial and boundary conditions and allows the entire characterization of a transient regime or the steady state distribution of a single ion. For a general domain, the

Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 6

Upper: Isolated calcium transients in a single dendritic spine. Synaptic activity generates a transient calcium change in a spine and a whole dendritic segment, triggered by a back-propagating action potential. *Lower:* Spontaneous calcium activity in neurons. Synchronized and not synchronized activity as well as small (probably EPSPs), larger (probably single spike), and very large events (burst of several spikes). The decay phase of calcium is approximated by exponentials or sum of exponentials



solution cannot be derived analytically, but it is possible to obtain long- and short-time asymptotic estimations. As we shall see, these expressions provide the dependency with respect to many geometrical parameters. When necessary, numerical simulations are used to obtain the missing information. They are usually tedious to obtain and require careful discretization of the domain, especially when small and large scales are present.

For many independent calcium ions, the concentration $c(x, t)$ is given by $c(x, t) = Np(x, t)$, where N is the initial number of ions. Ignoring at this stage the effect of any chemical reaction, the microdomain geometry Ω is the main determinant of the characteristic time scale involved in diffusion. When the boundary decomposes into two parts, $\partial\Omega_a$ the absorbing part, made of key fast-binding elements, and $\partial\Omega_r$ the reflective part, then it is usually a critical aspect to quantify the mean time $\mathbb{E}(\tau)$ for an ion to reach $\partial\Omega_a$. The boundary conditions are

$$\begin{aligned}\frac{\partial p(x, t)}{\partial n} &= 0 \text{ on } \partial\Omega_r, \\ c(x, t) &= 0 \text{ on } \partial\Omega_a.\end{aligned}$$

The general solution of the diffusion equation can be formally expanded as

$$c(\mathbf{x}, t) = \sum_{k=1}^{\infty} c_k u_k(\mathbf{x}) \exp(-\lambda_k t) \quad (30)$$

where $\lambda_k > 0$ are the eigenvalues; u_k , $k = 1$, are the eigenfunctions; and c_k are the constants. The general explicit computation of the solution of diffusion equations can be found in Carslaw and Jaeger (1959) and Crank (1975). Although expression (30) justifies fitting a sum of exponentials to experimental data, connecting the eigenvalues with the precise geometry is in general very difficult, except in a few cases where the geometry contains a narrow passage or small hole. This is the case of a dendritic spine or a narrow domain in dendrites. When $|\partial\Omega_a| \ll |\partial\Omega_r|$, the reciprocal of the mean time to escape a domain $\mathbb{E}(\tau)d$ is the first eigenvalue (Schuss et al. 2007). Indeed, $\frac{1}{\lambda_0}$ is usually very large, so that there is a large gap

with the rest of the eigenvalue $\lambda_0 \ll \lambda_1$, and thus the solution 30 can be further approximated by a single exponential for a time $t \gg \frac{1}{\lambda_1}$,

$$c(\mathbf{x}, t) \approx c_0 \exp(-\lambda_0 t). \quad (31)$$

We conclude that for domains with narrow neck, the arrival of diffusing particles to the small domain is almost Poissonian. This is a consequence of the geometry.

Transition Probability Density Function with Partial Reflecting Boundary Condition

The transition probability density function (pdf) of the limit process 11, $p(y, t|x, s) = \Pr\{x(t) = y|x(s) = x\}$, is the solution of the FPE

$$\begin{aligned}\frac{\partial p(y, t|x, s)}{\partial t} &= -\frac{\partial[a(y, t)p(y, t|x, s)]}{\partial y} \\ &+ \frac{\partial^2[\sigma(y, t)p(y, t|x, s)]}{\partial y^2},\end{aligned} \quad (32)$$

or equivalently,

$$\frac{\partial p(y, t|x, s)}{\partial t} = -\frac{\partial J(y, t|x, s)}{\partial y} \text{ for all } y, x > 0,$$

where

$$\begin{aligned}J(y, t|x, s) &= a(y, t)p(y, t|x, s) \\ &- \frac{\partial[\sigma(y, t)p(y, t|x, s)]}{\partial y}\end{aligned} \quad (33)$$

is the flux. The initial condition is

$$p(y, t|x, s) \rightarrow \delta(y - x) \text{ as } t \downarrow s, \quad (34)$$

and the radiation boundary condition is

$$-J(0, t|x, s) = \kappa p(0, t|x, s), \quad (35)$$

where κ is a constant related to the constant c and to the values of the coefficients at the boundary. The no flux and Dirichlet boundary conditions are recovered if $\kappa = 0$ and $\kappa = \infty$, respectively. The relation between the reactive “constant” $\kappa(t)$ and the absorption parameter P for the dynamics

(Eq. 11) on the positive axis with drift and with a variable diffusion coefficient is

$$\kappa(t) = rP\sqrt{\sigma(0,t)}, \quad r = \frac{1}{\sqrt{\pi}}. \quad (36)$$

The relation Eq. 36 is true for diffusion with variable coefficients. The value $r = 1/\sqrt{\pi}$ is different than values obtained for other schemes, e.g., than the value $r = 1/\sqrt{2}$, predicted by the discrete random walk theory of radiation boundaries (Collins and Kimball 1949). Values of r for other schemes are given in Erban and Chapman (2007).

Exit Diffusion Rate from Dendritic Spines

We summarize in this section the approach used to derive asymptotic formulas for the rate of diffusional exit from the spines. A dendritic spine with a narrow neck has very degenerate geometry (Andrews and Bray 2004), but the exit time of a diffusing particle, which is the reciprocal of the first eigenvalue, can be directly measured from fluorescence imaging. We shall now recall the main formula for the exit rate that was obtained in the context of the narrow escape (NET) and dire strait (DST) theory (Holcman and Schuss 2014; Schuss and Holcman 2014).

A free Brownian particle moves in a bounded domain $D \subset \mathbb{R}^d (d = 2, 3)$, whose boundary $\partial\Omega$ is sufficiently smooth (the analysis in higher dimensions is similar to that for $d = 3$). The Brownian trajectory $x(t)$ is reflected at the boundary, except for a small hole $\partial\Omega_a$, where it is absorbed, as shown in Fig. 7. The reflecting part of the boundary is $\partial\Omega_r = \partial\Omega - \partial\Omega_a$. The lifetime in Ω of a Brownian trajectory that starts at a point $\mathbf{x} \in \Omega$ is the first passage time τ of the trajectory to the absorbing boundary $\partial\Omega_a$. The NET

$$v(\mathbf{x}) = \mathbb{E}[\tau | \mathbf{x}(0) = \mathbf{x}] \quad (37)$$

is finite under quite general conditions (Schuss 2010b). As the size (e.g., the diameter) of the absorbing hole decreases to zero, but that of the domain remains finite, the NET increases indefinitely. A measure of smallness can be chosen as the ratio between the surface area of the absorbing

boundary and that of the entire boundary, for example,

$$\varepsilon = \left(\frac{|\partial\Omega_a|}{|\partial\Omega|} \right)^{1/(d-1)} \ll 1, \quad (38)$$

provided that the isoperimetric ratio remains bounded:

$$\frac{|\partial\Omega|^{1/(d-1)}}{|\Omega|^{1/d}} = O(1) \text{ for } \varepsilon \ll 1 \quad (39)$$

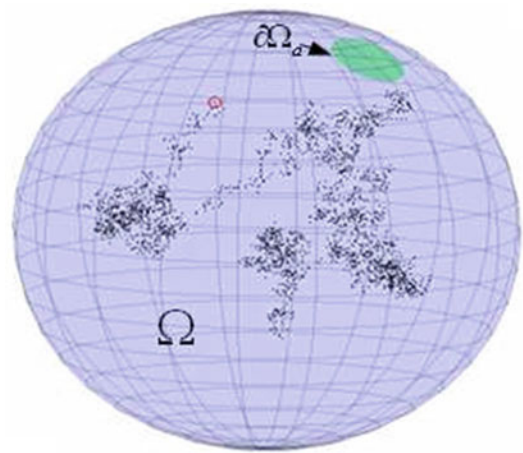
The NET $v(\mathbf{x})$ can be obtained by solving the Pontryagin-Andronov-Vitt (PAV) mixed boundary value problem for Poisson's equation (Pontryagin et al. 1933; Pontryagin et al. 1989; Schuss 2010b)

$$\Delta v(\mathbf{x}) = -\frac{1}{D} \text{ for } \mathbf{x} \in \Omega \quad (40)$$

$$v(\mathbf{x}) = 0 \text{ for } \mathbf{x} \in \partial\Omega_a \quad (41)$$

$$\frac{\partial v(\mathbf{x})}{\partial n(\mathbf{x})} = 0 \text{ for } \mathbf{x} \in \partial\Omega_r, \quad (42)$$

where D is the diffusion coefficient and $\mathbf{n}(\mathbf{x})$ is the unit outer normal vector to the boundary at $\mathbf{x} \in \partial\Omega$. For a circular window of radius $a \ll |\partial\Omega|^{1/2}$ (Fig. 7),



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 7 Brownian escape from a spherical window

$$\mathbb{E}_\tau = \frac{|\Omega|}{4aD \left[1 + \frac{L(0)+N(0)}{2\pi} a \log a + o(a \log a) \right]}$$

for $a \ll |\partial\Omega|^{1/2}$.

(43)

The MFPT to the absorbing boundary at the end of the funnel of a solid of revolution obtained by rotating the symmetric planar domain composed of a bulky head connected to a narrow neck formed by two tangent circular arcs of radius l_+ separated by a distance a' (see Fig. 8 in Holcman and Schuss (2013)) is given by

$$\tau = \frac{1}{\sqrt{2}} \left(\frac{l_+}{a'} \right)^{3/2} \frac{V}{l_+ D} (1 + o(1))$$

(44)

for $a' \ll l_+$,

where $V = |\Omega'|$ is the volume of the domain. The NET $\tau_{x \rightarrow \partial\Omega_a}$ of a diffusing particle from a three-dimensional domain ' Ω ' with a bottleneck in the form of a narrow circular cylinder of cross-sectional area πa^2 is given by

$$\tau_{x \rightarrow \partial\Omega_a} = \begin{cases} \frac{|\Omega_1|}{4aD} \left[1 + \frac{a}{\pi R} \log \frac{R}{a} \right] + \frac{O(1)}{D} + \frac{L^2}{2D} + \frac{|\Omega_1|L}{\pi a^2 D} & \text{solid spherical head of radius } R \text{ connected to the neck at a right angle} \\ \frac{|\Omega_1|}{4aD} \left[1 + \frac{L_2 + R_2}{2\pi} \left| \frac{\partial\Omega_a}{\pi} \right|^{1/2} \log \sqrt{\frac{|\partial\Omega_1|}{|\partial\Omega_a|}} + O \left(\sqrt{\frac{|\partial\Omega_a|}{|\partial\Omega_1|}} \log \sqrt{\frac{|\partial\Omega_a|}{|\partial\Omega_1|}} \right) \right] & \\ + \frac{L^2}{2D} + \frac{|\Omega_1|L}{\pi a^2 D} & \text{a general head connected to the neck at a right angle} \\ \frac{1}{\sqrt{2}} \left(\frac{R_c}{a} \right)^{3/2} \frac{|\Omega_1|}{R_c D} (1 + o(1)) + \frac{L^2}{2D} + \frac{|\Omega_1|L}{\pi a^2 D} & \text{a general head connected smoothly to the neck by a funnel,} \end{cases} \quad (45)$$

where R_c is the curvature at the cusp. The asymptotic expression is derived in Holcman and Schuss (2011). The order 1 term can be computed for the sphere using the explicit expression of the Neumann-Green function (Cheviakov et al. 2010). When the spine radius is small, the leading order term for the mean exit time (which is also the rate of diffusion extrusion) was initially presented in Svoboda et al. (1996). This term accounts for the many returns of an ion between the spine neck and head (Biess et al. 2007). This term is not present when an ion cannot return to the head once it enters the neck (Korkotian et al. 2004). Because the other terms in formula 45 diverge to infinity, their contribution cannot be neglected and they affect significantly the residence time of a diffusing particle in a dendritic spine (see Fig. 8). We conclude from these

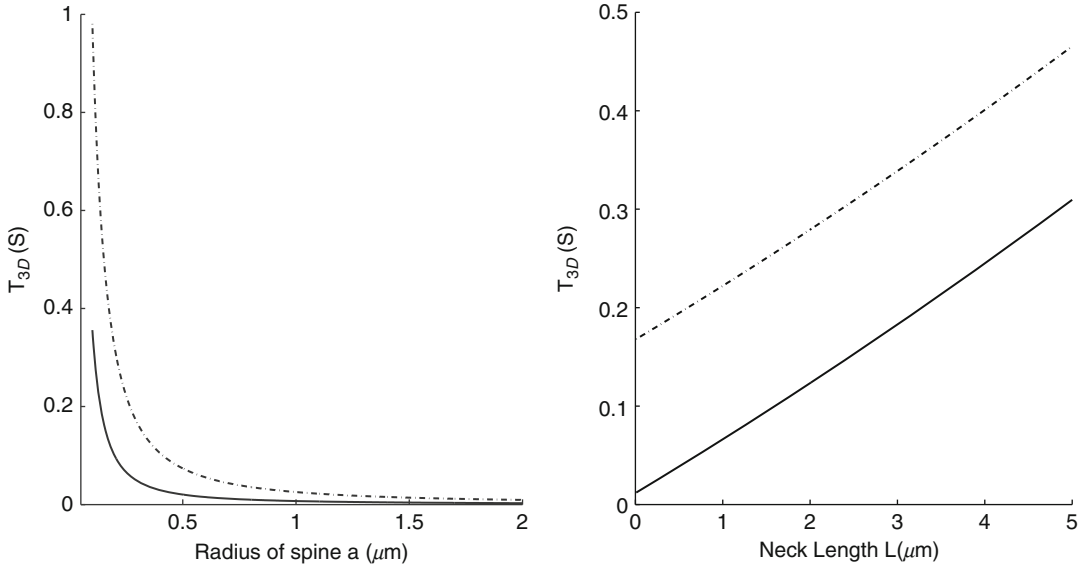
analytical formulas that the spine connection determines the rate of extrusion. For short spines, all terms are significant.

Remarks

The presence of a spine apparatus inside the spine might affect the extrusion of calcium or any other diffusing molecules. In addition, molecular binding affects calcium extrusion, and the rate is no longer Poissonian.

Influence of Calcium Buffers on the Residence Time of Calcium in Microdomains Such as the Dendritic Spines

The residence of calcium in a spine can be influenced by other mechanisms than pure diffusion. Binding and unbinding to calcium buffers affect the time course. In that case, the entire



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 8 Residence time of calcium in a dendritic spine.

Left: mean residence time of calcium τ_{3D} as a function of the spine radius a . *Right:* τ_{3D} is plotted as a function of the spine length L

system of partial differential equations (PDE) describing the process should be solved. Only numerical simulations are available. The generic example is

$$Ca + B_{\text{free}} \xrightleftharpoons[k_b]{k_f} Ca - B, \quad (46)$$

which leads to the PDE system of equations

$$\begin{aligned} \frac{\partial c}{\partial t}(x, t) = D\Delta c(x, t) - k_{\text{in}}c(x, t)B(x, t) \\ + k_b[c - B](x, t), \end{aligned} \quad (47)$$

$$\begin{aligned} \frac{\partial [c - B]}{\partial t}(x, t) = D_B\Delta c(x, t)B(x, t) \\ + k_{\text{in}}c(x, t)B(x, t) \\ - k_b[c - B](x, t). \end{aligned} \quad (48)$$

$c - B$ is the bound calcium that can diffuse with diffusion coefficient D_B , but stays confined in the spine head, while the calcium can be extruded at pumps or at the spine neck, which translates into the following boundary conditions:

$$\begin{aligned} \frac{\partial c(x, t)}{\partial n} &= 0 \text{ on } \partial\Omega_r, \\ c(x, t) &= 0 \text{ on } \partial\Omega_a, \\ \frac{\partial [c - B](x, t)}{\partial n} &= 0 \text{ on } \partial\Omega_r. \end{aligned}$$

when there is cooperativity at pumps, more elaborated boundary conditions are needed (Hille 2001) and will be discussed later on. There is no general solution of such equations. If binding is fast, since $c(x, t) + [c - B](x, t) = N_0 e^{-\lambda_1 t}$, the decay rate depends on the unbinding time, such that for a long enough time (so that binding occurred), the asymptotic decay rate is well approximated by a sum of two exponentials

$$c(x, t) = Ae^{-\lambda_1 t} + Be^{-k_b t}, \quad (49)$$

where A and B are constants.

Residence Time of Calcium in the Dendritic Spines with a Hydrodynamic Flow

Dendritic spines can change shape in a few hundred milliseconds (Fischer et al. 1998; Holcman

et al. 2004), after calcium ions flow in. This fast change of shape decreases the spine head volume. Spine motility was proposed by Blomberg et al. (1977), and the fast twitching movement of the spine was anticipated by F. Crick in (1982). Spine fast contraction was attributed to actin-myosin molecules or troponin C, which were observed inside the spine head. As in muscle cells, high concentrations of actin molecules indicate that rapid movement can follow the arrival of calcium ions. It has been proposed in Holcman et al. (2004) that calcium ions set the spine in motion by initiating the contraction of actin-myosin (AM) as they bind at active sites. Each molecule is assumed to give rise to a local contraction. In a simplified model, all contractions add up to achieve a global contraction, neglecting anisotropic contraction due to a delay interval between each molecule contraction. Once calcium ions enter the spine, they arrive to the binding sites by diffusion and can bind there. When four calcium ions bind to a single troponin C protein, a local contraction of the protein occurs. Adding all local contractions at a given time produces a global contraction and induces a hydrodynamic movement of the cytoplasmic fluid. Calcium trajectories are no longer pure Brownian, but contain a drift, and thus the probability to reach the dendritic shaft through the spine neck is increased (Holcman et al. 2004). The model requires feedback of a flow field $\mathbf{v}(\mathbf{x}, t)$ on the velocity. The flow field can be computed using Green's function of the spine domain (Holcman et al. 2004). Adding the effect of diffusion and hydrodynamics, the transient escape rate is not necessarily a single exponential. The concentration inside the spine follows:

$$c(x, y, z, t) = C \exp \left\{ -\lambda_1 t + \frac{\dot{v}_0^2}{4D} t \right\},$$

where the hydrodynamic decay time is

$$\tau = \frac{4D}{\dot{v}_0^2}, \quad (50)$$

where v_0 is the initial average velocity (Holcman et al. 2004). Figure 3 illustrates the effect of

adding a hydrodynamic drift on pure diffusion for the exploration of the spine head. Contrary to the effect of buffer, the hydrodynamic effect shifts the extrusion rate, but does not lead to a sum of exponentials.

Crowding Model of a Dendrite

Molecular crowding reduces diffusion, and this effect can be estimated by computing the effective diffusion coefficient of a Brownian particle moving between obstacles in dimension 2. For obstacles positioned periodically, the effective coefficient of diffusion decays nonlinearly with the density of obstacles (Holcman et al. 2011). This decay also depends on the shape of the obstacles. The effective diffusion coefficient can be computed asymptotically by conformal mapping (Holcman et al. 2011). In addition, when obstacles are positioned with additional variabilities, local narrow passages, funnels, or dead ends can be observed that lead to heterogeneity in the diffusion trajectories (Ghosh et al. 2012; Holcman and Schuss 2012, 2013). However due to the complexity of obstacle geometry, there is no achieved theory of diffusion with obstacles in three dimensions.

We present here a local model and numerical simulations to study calcium diffusion in a dendrite. The dendrite cytoplasmic medium is highly heterogeneous and filled with many organelles. Thus the motion of a diffusing particle is affected by many interactions with its environment. The functional consequences of these interactions are difficult to access directly experimentally due to ubiquitous pathways especially for calcium dynamics. In a reduced model of diffusion in dendrites, the one-dimensional effective diffusion equation and an effective diffusion constant account for the presence of heterogeneity in the medium.

Modeling Diffusion in a Heterogeneous Dendritic Cytoplasm

To characterize diffusion in a heterogeneous dendrite, containing various organelles such as mitochondria, spine apparatus, endoplasmic reticulum, and other structures, one method (Biess et al. 2011) consists of coarse graining a three-dimensional

cylindrical dendrite into a one-dimensional effective diffusion equation in the limit where the space between organelles is small. Diffusing ions can still move inside a dendritic domain Ω , and the nature of the motion is not impaired and is well approximated by the Smoluchowski limit of the Langevin equation (Schuss 2010a): a particle at position $\mathbf{X}(t)$ at time t is described by

$$\dot{\mathbf{X}} + \frac{1}{\gamma} \nabla \Phi(\mathbf{X}) = \sqrt{2D} \mathbf{w}(t), \quad (51)$$

where Φ is a potential per unit of mass, γ is the friction coefficient, D is the aqueous diffusion constant, and $\mathbf{w}(t)$ is the Gaussian white noise. The potential Φ represents the effective force on the particle. When a moving molecule hits impenetrable organelles O_i , it is reflected.

The distribution of independent molecules is characterized by the probability density function (pdf) $p(\mathbf{x}, t)$ which satisfies the Fokker-Planck equation

$$\frac{\partial p}{\partial t} = D \Delta p + \nabla \cdot \left[\frac{1}{\gamma} (\nabla \Phi(\mathbf{X})) p \right] \quad (52)$$

in the domain $\tilde{\Omega} = \Omega \setminus \cup_i O_i$ and a zero flux condition on the organelles and the dendritic membrane $\partial \tilde{\Omega}$:

$$\mathbf{J} \cdot \mathbf{n} = -D \frac{\partial p}{\partial n} + \frac{p}{\gamma} \frac{\partial \Phi}{\partial n} = 0, \quad (53)$$

where $\mathbf{J}$ is the flux and $\mathbf{n}$ the outer normal of the domain $\tilde{\Omega}$.

To account for the overall effect of crowding on diffusion, we adopt an approach based on a compartmentalization of the dendritic domain and the narrow escape theory (Holcman and Schuss 2013), which provides the mean time for a Brownian particle to exit a domain through a small absorbing opening. The dendrite is divided into periodic compartments of length l and volume V , separated from their neighbors by a reflecting cross section, except for a small opening of radius a . This compartment should be large enough so that the organelle density is the same in each of them. The small openings allow

diffusing molecules to move across compartments. In contrast to previous models where crowding has been described by spherical obstacles (Biess et al. 2011) that pose barriers to diffusing molecules, crowding is modeled as a sequence of periodic compartments and small openings at the boundaries of neighboring compartments. A compartment k starts at position x_k and ends at position x_{k+1} . The number $N_k(t)$ of particles in compartment k changes according to the net flux across the small windows. The flux is estimated by the small hole approximation (see Biess et al. (2011) for details).

The concentration $c(x, t) = N(x, t)/V(x, t)$ satisfies

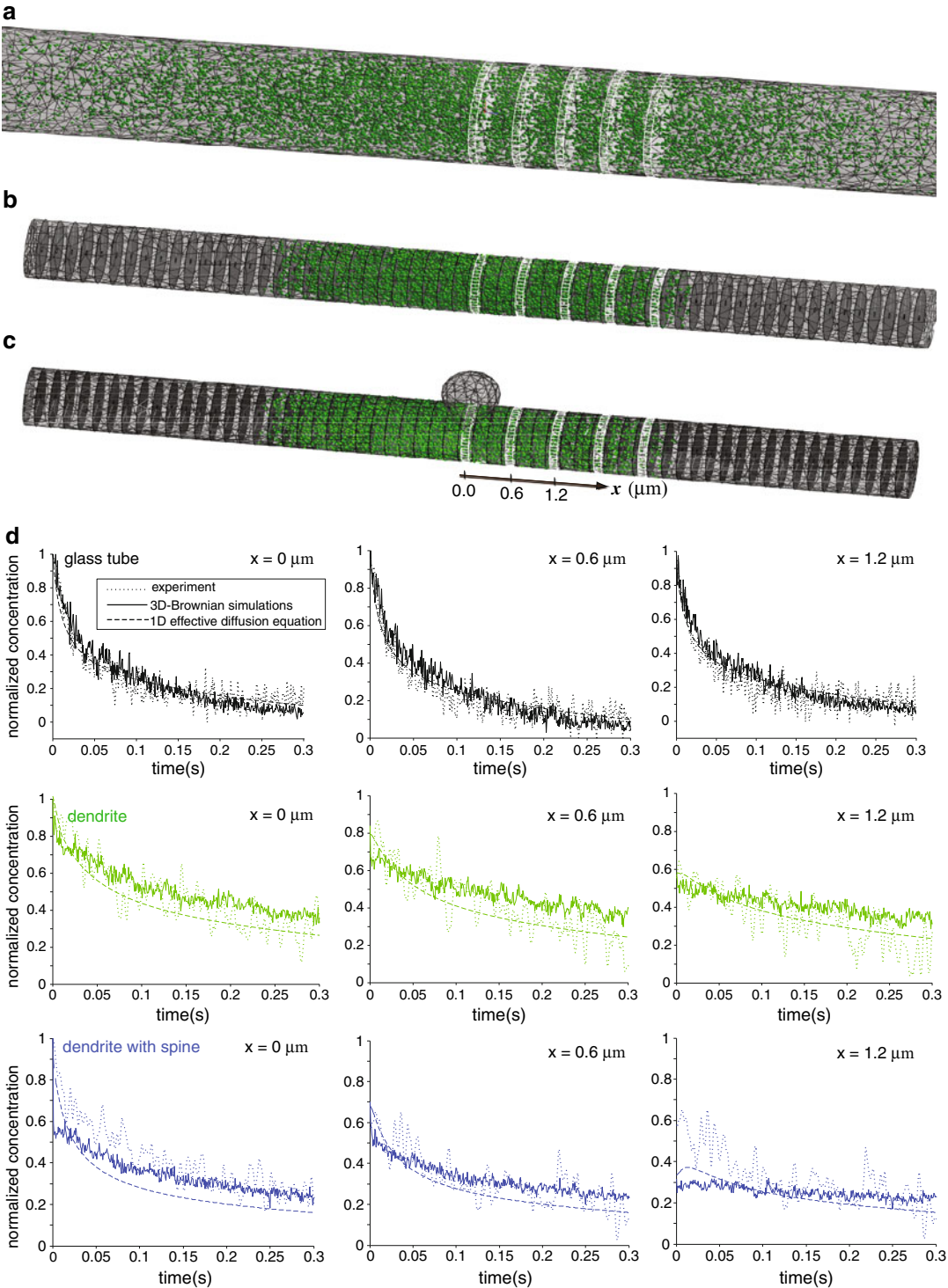
$$\frac{\partial c(x, t)}{\partial t} = \frac{4l^2 D}{V(x)} \frac{\partial}{\partial x} \left[a(x) \frac{\partial}{\partial x} C(x, t) \right]. \quad (54)$$

Similar equations have been derived in other contexts (Zwanzig 1990; Biess et al. 2007; Berezhkovskii et al. 2004). When the parameters $a(x)$ and $V(x)$ are spatially independent, Eq. 54 simplifies to

$$\frac{\partial c(x, t)}{\partial t} = D_{\text{eff}} \frac{\partial^2 c(x, t)}{\partial x^2}, \quad (55)$$

where $D_{\text{eff}} = \frac{4la}{S} D$, the effective diffusion constant, and $V = Sl$, with S the cross-sectional area. The effective diffusion constant depends on two parameters: the compartment length l and the size of the opening a .

The model parameters are determined by (i) measuring the ratio of diffusion constants D_{eff}/D and (ii) a calibration condition of the form $l/a = 4$. The calibration condition expresses that the parameters l and a do not necessarily have direct physiological meanings, and we can thus set one parameter arbitrarily within the limits of the small hole approximation. Additional measurements of the diffusion constant will then fix the other parameter. A Brownian simulation of diffusing ions around an obstacle is presented in Fig. 9. Other applications of reducing equations are to compute the mean time for calcium ions or diffusing molecules to travel along crowded dendrites or axons.



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 9 Brownian simulations of uncaging experiments. (a) Model glass pipette. Shown is the initial particle distribution as taken from the experimental data and the sampling volumes (white cylindrical disks) at

Calcium Spread Following High-Frequency Stimulation

The one-dimensional effective diffusion equation presented in the last paragraph allows analyzing calcium spread originating from localized inputs such as synapses. At dendritic synapses calcium can enter through NMDA receptors. To estimate calcium spread as a function of the synaptic input frequency, Ca^{2+} influx was simulated in the middle of a dendritic segment (Fig. 10) with buffers and pumps (see Biess et al. (2011) for the reaction-diffusion equation). The different input frequencies are $f = 5, 10, 20, 50, 80$ Hz. Interestingly, for input frequencies larger than 20 Hz, the calcium signal in the dendrite reaches a stationary value. For high input frequencies (≥ 20 Hz) calcium spread does not exceed $2.5 \mu\text{m}$ ($= 0.5 \times \text{FWHM}$) as measured from the input source. Buffers and pumps limit calcium spread to a few micrometers (Biess et al. 2011).

Calcium Extrusion Along a Cylinder: Homogenization of Hole into a Killing Rate

Computing the final distribution of calcium ions between two possible fates is a generic problem. It can be the proportion of bound calcium ions versus the number extruded or the fraction that reached the dendrite versus the fraction that got pumped. We present a general approach based on homogenization to reduce the complexity of this computation.

Homogenization of Perforated by Partially Reflecting Boundary

We approximate the flux through a reflecting boundary, perforated by many small independent absorbing holes (Berg and Purcell 1977;

Berezhkovskii et al. 2004). For diffusion, the problem can be solved using the eigenvalues of the Laplace equation in the domain Q with mixed Neumann boundary conditions on $\partial\Omega - \partial\Omega_A$ and Dirichlet conditions on $\partial\Omega_A = \cup_{i=1}^N A_i$. If the holes A_i are sufficiently far apart, the smallest eigenvalue λ_1^A is asymptotically the sum of the eigenvalues $\lambda_1^{A_i}$ of the Laplace operator in Ω with mixed Neumann-Dirichlet boundary conditions on $\partial\Omega - A_i$ and A_i , respectively, which can be calculated from the narrow escape theory (Holcman and Schuss 2013). For circular holes with fixed radius ε , we have the formula

$$\lambda_1^{A_i} \approx \frac{4\varepsilon D}{|\Omega|}, \lambda_1^A = \frac{4\varepsilon DN}{|\Omega|}. \quad (56)$$

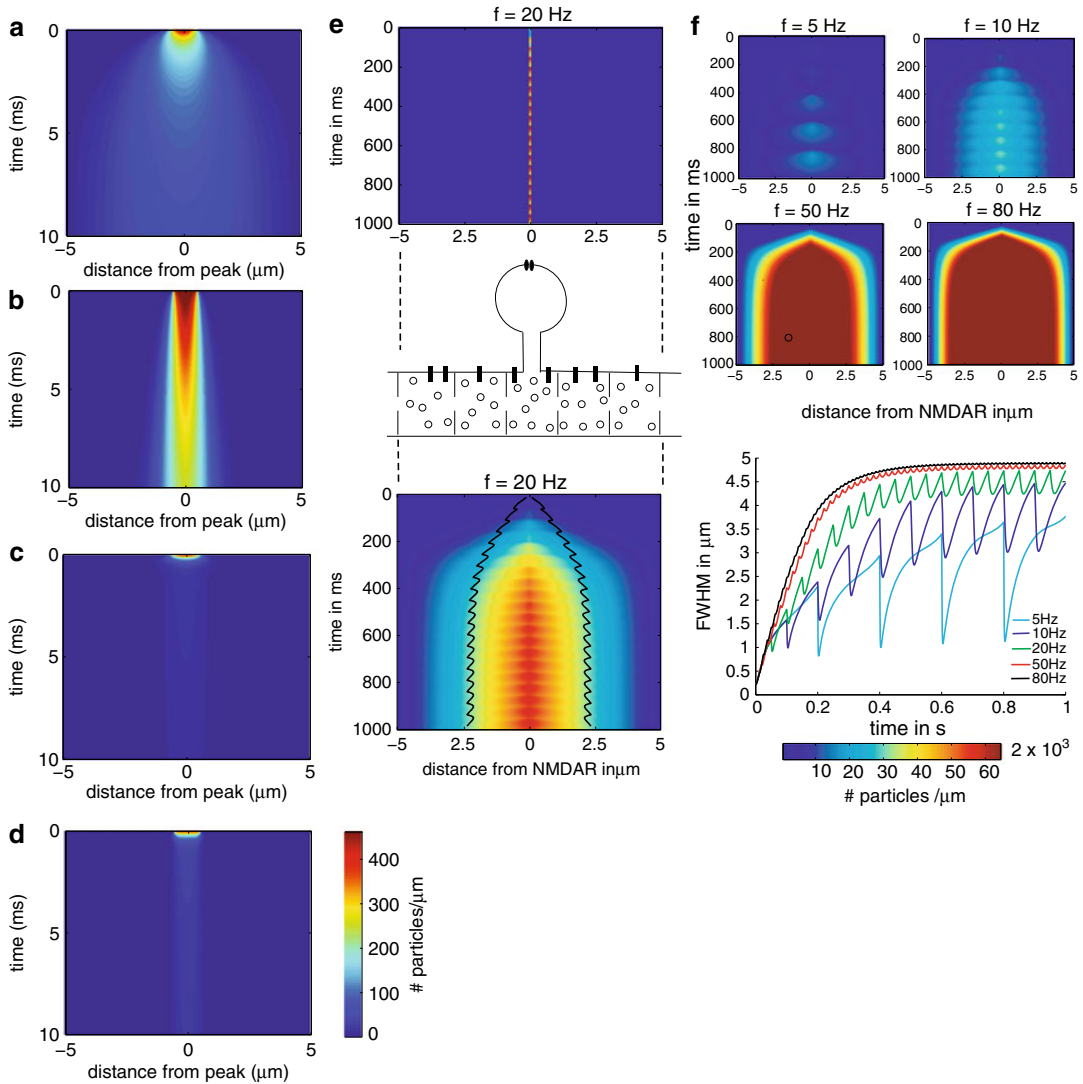
The pdf of the Brownian motion in the perforated domain relaxes to a quasi-steady state and can be described by a single exponential decay in time with rate λ_1^A and a uniform quasi-steady state distribution in Ω , except in boundary layers near A_i . The total absorption probability flux on the boundary, λ_1^A , is partitioned among the holes with probabilities $P_i = \frac{\lambda_1^{A_i}}{\sum_{i=1}^N \lambda_1^{A_i}}$. If the holes are distributed with surface density $n(\mathbf{x})$ on $\partial\Omega$, the normal absorption flux density is

$$\mathbf{J}(\mathbf{x}) \cdot \mathbf{v}(\mathbf{x}) = \frac{4\varepsilon D n(\mathbf{x})}{|\Omega|}. \quad (57)$$

The homogenization procedure consists in replacing the perforated holes by a radiation condition that preserves asymptotically the same quasi-steady state distribution. We replace the leading eigenfunction and eigenvalue of the

← **Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 9** (continued) different locations from the uncaging spot. **(b)** Compartmentalized model dendrite. **(c)** Compartmentalized model dendrite with attached spine (dendrite geometry as in B with spine neck radius $0.3 \mu\text{m}$, spine neck length $0.2 \mu\text{m}$, spine head radius

$0.4 \mu\text{m}$). **(d)** Comparison of 3D Brownian simulations with the uncaging experiments and the results derived from the solutions of the 1D effective diffusion equation. The normalized concentration profiles are shown for the glass tube **(a)**, the dendrite **(b)**, and the dendrite with attached spine **(c)** at three locations from the uncaging spot. (Adapted from Biess et al. (2011))



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 10 Lateral extent of calcium driven by high-frequency stimulation. (a) Calcium diffusion in an aqueous solution contained in a pipette. (b) Calcium diffusion in a crowded dendrite. The initial concentration is equal to about 600 particles and evaluates to about 470 particles per micron for a dendrite. (c) Same settings as in (a) but with additional buffers (medium buffer concentration) and pumps. (d) Same settings as in (b) but with additional buffers (medium buffer concentration) and pumps. (e) Calcium was injected at 20 Hz for 1 s at the location of the

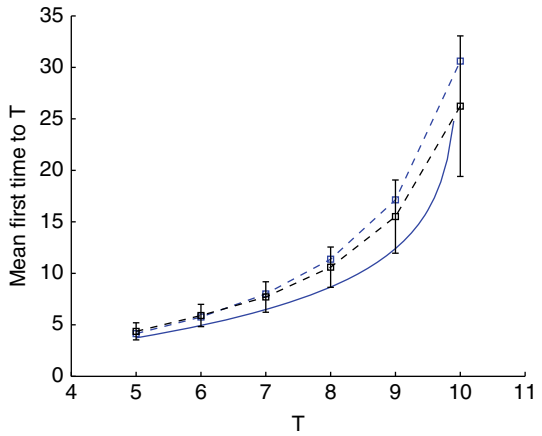
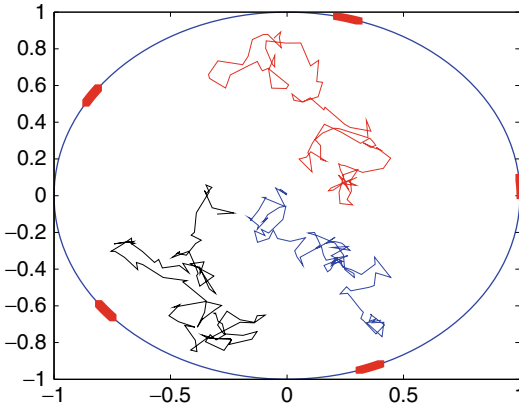
NMDAR in the middle of the dendritic segment as shown in the upper and middle panel. The resulting spatiotemporal profile in the dendrite is shown in the lower panel. (f) Spatiotemporal profiles in the dendrite for different influx frequencies at the location of the NMDAR. (g) Corresponding calcium spread in the dendrite as measured by the full width at half maximum (FWHM) of the calcium signal. (Adapted from Biess et al. (2011)). Figure 11 shows the plot of $\tau_{\tau}^{\text{irrev}}$ for several values of the threshold T , compared to Brownian simulations in a circular disk $\Omega = D(R)$ with reflecting boundary, except at the targets

Robin problem by a Laplace equation with a small radiation function $k(\mathbf{x})$:

$$D\Delta p(\mathbf{x}) = -\lambda p(\mathbf{x}) \text{ for } \mathbf{x} \in \Omega \quad (58)$$

$$D \frac{\partial p(\mathbf{x})}{\partial \nu} = -k(\mathbf{x})p(\mathbf{x}) \text{ for } \mathbf{x} \in \partial\Omega \quad (59)$$

Matching the flux density in Eqs. 57 and 59, we obtain in dimensional coordinates



Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis, Fig. 11 The MFTT. *Left*: trajectories of diffusing molecules in a microdomain containing five binding sites on the boundary. *Right*: the time τ_T^{irrev} is plotted as a function of the threshold T . We present the Brownian

simulations (*dotted blue line*, variance in black), the theoretical formula 74 (*dotted black line*), and its approximation 75 (*continuous blue line*) for a circular disk in the irreversible case ($k_{-1} = 0$). The other parameters are $S_0 = 15$, $M_0 = 10$, $\varepsilon = 0.05$, $D = 0.1 \mu\text{m}^2\text{s}^{-1}$, and the radius of the disk $R = 1 \mu\text{m}$ (200 runs)

$$k(\mathbf{x}) = 4\varepsilon D p_o(\mathbf{x}) n(\mathbf{x}) + O\left(\frac{\varepsilon^2}{L^2} \log \frac{\varepsilon}{L}\right). \quad (60)$$

The quasi-steady state pdf is

$$p_o(\mathbf{x}) = \frac{(1 + o(k_o))}{|\Omega|},$$

except in boundary layers near A_i .

After the first homogenization which consists in replacing a three-dimensional diffusion with total and/or partial absorption by a reduced diffusion equation in dimension one, with a killing rate k , the case of a cylindrical geometry can be treated immediately. The one-dimensional case of a diffusion with uniform killing inside an interval (Holcman et al. 2005) with reflecting and absorbing endpoints has a survival pdf of a particle satisfying the equation

$$\begin{aligned} \frac{\partial p(x, t)}{\partial t} &= -\nabla \cdot J(x, t) - k p(x, t) \\ p(L, t) &= 0, p(x, 0) = \rho(x), \end{aligned} \quad (61)$$

where the probability flux density is given by

$$J(x, t) = -D \frac{\partial}{\partial x} p(x, t) + b(x) p(x, t). \quad (62)$$

For long-time asymptotic, the solution of Eq. 61 is approximated by the first eigenfunction:

$$p(x, t) = p_o(x) c^{-\lambda_o t} + O(c^{-\lambda_o t}), \quad (63)$$

normalized by

$$\int_0^L p_o(x) dx = 1 \quad (64)$$

When the killing term k is a constant, the eigenvalue problem

$$\begin{aligned} D \frac{\partial^2 p(x)}{\partial x^2} - k(x) p(x) &= -\lambda p(x) \\ p(L) &= 0, \frac{\partial p(0)}{\partial x} = 0. \end{aligned} \quad (65)$$

In case that $k(x) = k = \text{const}$, the first eigenfunction and eigenvalue are

$$p_o(x) = \Omega \frac{\cos(\Omega x)}{\sin(\Omega L)}, \Omega = \frac{\pi}{2DL}, \lambda_0 = D \frac{\pi^2}{4L^2} + k.$$

The total flux J of killed diffusing particles is given by

$$J = \int_0^L k(x)p_o(x)dx = k.$$

Particles Splitting: Absorbed Versus Arrived

To quantify how ions split between pumps located on the surface of a cylinder and the ones that arrive at the end, we use the ratio

$$\begin{aligned} R_s &= \frac{\int_{\partial\Omega_a} \mathbf{J}(\mathbf{x}|\mathbf{y}) \cdot \mathbf{v}(\mathbf{x}) dS_x}{\int_{\Omega} k(\mathbf{x}) p(\mathbf{x}|\mathbf{y}) d\mathbf{x}} \\ &= \frac{\int_{\partial\Omega_i} \Phi(\mathbf{x}) dS_x - \int_{\Omega} k(\mathbf{x}) p(\mathbf{x}|\mathbf{y}) d\mathbf{x}}{\int_{\Omega} k(\mathbf{x}) p(\mathbf{x}|\mathbf{y}) d\mathbf{x}} \end{aligned} \quad (66)$$

that can be computed in the limit of a very thin cylinder. The flux and the killing term are computed from solving the steady state using Fokker-Planck

$$0 = D\Delta p(\mathbf{x}|\mathbf{y}) - k(\mathbf{x})p(\mathbf{x}|\mathbf{y}) \text{ for } \mathbf{x}, \mathbf{y} \in \Omega \quad (67)$$

The boundary conditions are

$$\begin{aligned} p(\mathbf{x}|\mathbf{y}) &= 0 \text{ for } \mathbf{x} \in \partial\Omega, \mathbf{y} \in \Omega_a \\ \mathbf{J}(\mathbf{x}|\mathbf{y}) \cdot \mathbf{v}(\mathbf{x}) &= 0 \text{ for } \mathbf{x} \in \partial\Omega - \partial\Omega_a \\ &\quad -\partial\Omega_i, \mathbf{y} \in \Omega, t > 0. \\ \mathbf{J}(\mathbf{x}|\mathbf{y}) \cdot \mathbf{v}(\mathbf{x}) &= -\Phi(\mathbf{x}) \text{ for } \mathbf{x} \in \partial\Omega_i. \end{aligned}$$

The time-independent flux is $\Phi(\mathbf{x}) \geq 0$. The external steady-state flux of absorbed particles is

$$J_a = \int_{\partial\Omega_a} \mathbf{J}(\mathbf{x}|\mathbf{y}) \cdot \mathbf{v}(\mathbf{x}) dS_x. \quad (68)$$

The total inward flux is

$$J_i = \int_{\partial\Omega_i} \mathbf{J}(\mathbf{x}|\mathbf{y}) \cdot \mathbf{v}(\mathbf{x}) dS_x = \int_{\partial\Omega_i} \Phi(\mathbf{x}) dS_x. \quad (69)$$

If the killing measure is uniform in the interval $[0, L]$, then $R_S(L) = \frac{1}{\cosh(bL)-1}$, where $b = \sqrt{\frac{N_A}{D}}$. The case where the killing is a Dirac $k(\mathbf{x}) = k\delta(\mathbf{x} - \mathbf{x}_1)$, located at a single point $\mathbf{x}_1$, and k is a constant has been treated in Holcman et al. (2005). Interestingly, changing the distribution of killing

from uniform to concentrated at one point has a drastic effect on the final repartition of ions (see Fig. 2, Holcman et al. (2005)).

Calcium Cascade Initiating Cellular Activation

The molecular implementations that describe the transformation of a transient signal to cell activation are still unclear. We shall here present a threshold-based model: when the number of bound molecules equals a given number, we suppose that a cellular change is initiated. We present a Markov chain model that reduces the geometrical complexity based on the narrow escape rate formula (Schuss et al. 2007).

Probability to Bind a Fixed Number of Molecules During a Transient Process

To illustrate the need of a multiscale approach to bridge the molecular to the cellular scale, we recall that during long-term potentiation (LTP) induction, a transient calcium signal is converted into a long-term change in the synaptic properties (Bliss and Collingridge 1993; Malenka and Nicoll 1999; Lee et al. 2009; Lisman et al. 2012). This process specifically involves a class of kinases (CaMKII) that have complex local cooperative binding sites organized into a ring structure.

However, the first problem is to define the meaning of activation. For example, it can either be a single binding by a $\text{CaM}(\text{Ca})_3$ or $\text{CaM}(\text{Ca})_4$ molecules, several bonds, or one to six phosphorylations. Once a criterion is chosen, it becomes a computational question to estimate the probability P_k that k CaMKII molecules are activated and also compute statistical quantities such as the mean number $\langle N_{\text{act}} \rangle$ of CaMKII that are activated following a transient calcium entry.

More complicated calcium patterns are also generated where calcium ions are flowing inside a synapse. In that case, it is worthwhile to compute the number of bound molecules before an arbitrary time t or the probability $P_{\text{act}}(t)$ and the mean number $\langle N_{\text{act}}(t) \rangle$ of activations before time t . These quantities are in practice difficult to compute and depend on many parameters such as the dendritic spine geometry, the intrinsic property rate constants, the

binding site interaction forces, their localization, and so on. There are two complementary approaches:

1. **Coarse-grained Markov models:** this approach is based on the narrow escape methodology, where instead of accounting for the entire time dynamics within the complex geometry organization of the microdomain, a Poissonian rate of arrival to small targets is used to approximate the target search and finding. Various quantities of interest such as the activation probability and the statistic for the number of bound CaMKII can be estimated (Holcman and Schuss 2005; Dao Duc and Holcman 2010, 2012; Holcman et al. 2014).
2. **Brownian simulations.** Contrary to the previous approach, it is not possible to obtain the exact dependency of the probability; rather this approach is tedious and allows estimating any moment of interest for a given set of parameters.

For a microstructure such as a dendritic spine, there is no equilibrium, because the steady state is zero. Thus the relaxation time is the time for a diffusing particle to be extruded by diffusion, which is in the range of tens of ms (see Holcman and Schuss 2011). The probability for N CaMKII to be activated and the time to induction is the mean time for this to happen during a repetitive stimulation. Because the calcium to CaMKII pathways requires CaM intermediates, there is no coarse-grained model yet (Guerrier and Holcman 2014a). To present the threshold method, we shall now present a simplified model where a diffusing molecule can bind to a ligand. The probability to reach a threshold has been developed in Dao Duc and Holcman (2010) and is reviewed here briefly.

Coarse-Grained Markov Models

Traditional chemical kinetics, based on mass-action laws or reaction-diffusion equations, give

an inappropriate description of the stochastic chemical reactions in microdomains, where only a small number of substrate and reactant molecules is involved. A reduced Markovian description of the stochastic dynamics of the binding and unbinding of molecules is given in Holcman and Schuss (2005) and applied in Dao Duc and Holcman (2010, 2012). Specifically, consider two finite species, the mobile reactant M that diffuses in a bounded domain Ω and the stationary substrate S (e.g., a protein) that binds M . The boundary $\partial\Omega$ of the domain Ω is partitioned into an absorbing part $\partial\Omega_a$ (e.g., pumps, exchangers, another substrate that forms permanent bonds with M , and so on) and a reflecting part $\partial\Omega_r$ (e.g., a cell membrane). In this model, the volume of M is neglected. In terms of traditional chemical kinetics, the binding of M to S follows the law



where k_f is the forward-binding rate constant, k_b is the backward-binding rate constant, and S_{free} is the unbound substrate. We assume in our model of the reaction that the M molecules diffuse in Ω independently and, when bound, are released independently of each other at exponential waiting times with rate k_{-1} .

To calculate the average number of unbound (or bound) sites in the steady state, the following reduced model is used. The number $k(t)$ of unbound receptors at time t is a Markovian birth-death process with states $0, 1, 2, \dots, \min\{M, S\}$ and transition rates $\lambda_k \rightarrow k+1 = \lambda_k$, $\lambda_k \rightarrow k-1 = \mu = k_{-1}$. The boundary conditions are $\lambda_S \rightarrow S+1 = 0$ and $\lambda_0 \rightarrow -1 = 0$. Setting $P_k(t) = \Pr\{k(t) = k\}$, the Kolmogorov equations for the transition probabilities are given by (Holcman and Schuss 2005).

$$\begin{aligned} \dot{P}_k(t) = & -[\lambda_k + k_{-1}(S - k)]P_k(t) + \lambda_{k+1}P_{k+1}(t) + k_{-1}(S - k + 1)P_{k-1}(t) \\ \text{for } k = & (S - M)^+ + 1, \dots, S - 1 \end{aligned} \quad (71)$$

with the boundary equations

$$\begin{aligned}\dot{P}_{(S-M)^+}(t) &= -k_{-1}SP_{(S-M)^+}(t) + \lambda_1 P_{(S-M)^++1}(t) \\ \dot{P}_S(t) &= -\lambda_S P_S(t) + k_{-1}P_{S-1}(t)\end{aligned}$$

and initial condition $P_{k,q}(0) = \delta_{k,S}\delta_{q,0}$. In the limit $t \rightarrow \infty$ to the model (71) gives the average number

$$\langle k_\infty \rangle = \sum_{j=(S-M)^+}^S jP_j,$$

where $P_j = \lim_{t \rightarrow \infty} P_j(t)$. Similarly, the stationary variance of the number of unbound sites is $\sigma^2(M, S) = \langle k_\infty^2 \rangle - \langle k_\infty \rangle^2$, where $\langle k_\infty^2 \rangle = \sum_{j=(S-M)^+}^S j^2 P_j$. The rates λ_k are modeled as follows. For a single diffusing molecule, the time to binding is the first passage time to reach a small absorbing portion $\partial\Omega_a$ of the boundary, which represents the active surface of the receptor, whereas the remaining part of $\partial\Omega$ is reflecting. Due to the small target and to the deep binding potential well, the binding and unbinding of M to S are rare events on the time scale of diffusion (Schuss et al. 2007). This implies that the probability distribution of binding times is approximately exponential (Schuss 2010b) with rate $\lambda_1 = 1/\mathbb{E}\tau_1$, where the NET $\mathbb{E}\tau_1$ is the MFPT to $\partial\Omega_a$. When there are S binding sites, $k(t)$ of which are unbound, there are $N = [M - S + k]^+$ free diffusing molecules in Ω , where $x^+ = \max\{0, x\}$. The arrival time of a molecule to the next unbound site is well approximated by an exponential law with state-dependent instantaneous rate (see discussion in Holcman and Schuss (2005))

$$\lambda_k = \frac{Nk}{\mathbb{E}\tau_1} = \frac{k(M - S + k)^+}{\mathbb{E}\tau_1}.$$

The results of the Markovian model (71) are

$$\begin{aligned}P_S &= \frac{1}{1 + \sum_{k=1}^{S-(S-M)^+} \frac{\prod_{i=S-k+1}^S i(M - S + i)^+}{k!(\mathbb{E}\tau_1 k_{-1})^k}} \\ \langle k_\infty \rangle &= P_S \sum_{k=S-1}^{(S-M)^+} (S - k)^+ \frac{\prod_{i=S-k+1}^S i(M - S + i)^+}{k!(\mathbb{E}\tau_1 k_{-1})^k} \\ \langle k_\infty^2 \rangle &= P_S \sum_{k=S-1}^{(S-M)^+} [(S - k)^+]^2 \frac{\prod_{i=S-k+1}^S i(M - S + i)^+}{k!(\mathbb{E}\tau_1 k_{-1})^k} \\ \sigma_S^2(M) &= \langle k_\infty^2 \rangle - \langle k_\infty \rangle^2\end{aligned}\tag{72}$$

(see Holcman and Schuss (2005) for further details).

These formulas are used to estimate the fraction of bound receptors in photoreceptor outer segments and also to interpret the channel noise measurement variance in Holcman and Schuss (2005). In Holcman and Triller (2006) this analysis was used to estimate the number of bound AMPA receptors in the postsynaptic density. A similar gated Markovian model was proposed in Bressloff and Earnshaw (2009).

The reduced Markovian model is used for the calculation of the mean time of the number of bound molecules to reach a given threshold T (MFTT). In a cellular context, the MFTT can be used to characterize the stability of chemical processes, especially when they underlie a biological function. Using the above Markov chain description, the MFTT can be expressed in terms of fundamental parameters, such as the number of molecules and ligands and the forward- and backward-binding rates. It turns out that the MFTT depends nonlinearly on the threshold T . Specifically consider M Brownian molecules that can bind to immobile targets S inside a microdomain, modeled generically by Eq. 70. The first time the number $[MS](t)$ of MS molecules at time t reaches the threshold is defined as

$$\tau_T = \inf \{t > 0 : [M|S](t) = T\},\tag{73}$$

and its expected value is τ_T . Consider the case of an ensemble of the targets initially free and distributed on the surface of a closed microdomain and assume that the backward rate vanishes ($k_{-1} = 0$) and $k_f > 0$. The dynamical system for the transition probabilities of the Markov process $MS(t)$ is similar to that above, but for the absorbing boundary condition at the threshold T , which gives Eq. 71 (Dao Duc and Holcman 2010). When the binding is irreversible ($k_{-1} = 0$), τ_T is the sum of the forward rates

$$\begin{aligned}\tau_T^{\text{irrev}} &= \frac{1}{\lambda_0} + \frac{1}{\lambda_1} + \dots + \frac{1}{\lambda_{T-1}} \\ &= \frac{1}{\lambda} \sum_{k=0}^{T-1} \frac{1}{(M_0 - k)(S_0 - k)}\end{aligned}\tag{74}$$

In particular, when $M_0 = S_0$ and $M_0 \gg 1$, Eq. 74 becomes asymptotically $\tau_T^{\text{irrev}} \approx T/\lambda$ ($M_0(M_0 - T)$). In addition, when the number of

diffusing molecules greatly exceeds the number of targets ($M_0 \gg S_0, T$), (74) gives the asymptotic formulas

$$\tau_T^{\text{irrev}} \approx \begin{cases} \frac{1}{\lambda M_0} \log \frac{S_0}{S_0 - T} & \text{for } M_0 \gg S_0, T \\ \frac{1}{\lambda S_0} \log \frac{M_0}{M_0 - T} & \text{for } S_0 \gg M_0, T \\ \frac{T}{\lambda M_0 S_0} & \text{for } M_0, S_0 \gg T. \end{cases} \quad (75)$$

Discussion and Conclusion

We have summarized here biophysical models at a molecular level, mathematical analysis, and coarse-graining models to study calcium dynamics in cellular microdomains. The present approach can be implemented to better understand how calcium dynamics can induce sophisticated processes such as long-term potentiation or depression, cellular process that are responsible for long-lasting changes in physiological properties. Yet what calcium is doing at synapses still remains unclear: where calcium is accumulating, what is the number of activated CaMKII (it is not exactly clear what is the meaning of being activated; it can be that a single site is phosphorylated), and what other calcium-activated molecules are important. We presented as an example of complex calcium feedback how spine twitching can be described at a molecular level. We also described Brownian and simplified simulation of calcium and the CaMKII pathway. The CaMKII molecule can be modeled as a simplified ring made of six balls. A calibration procedure is then use to determine the radius a of a sphere or disk in that matches the Smoluchowski formula. We have not reviewed the presynaptic terminal, which is a critical microdomain where calcium modulates the release of vesicles. Vesicular release is triggered by calcium entrance at specific calcium channels (Holderith et al. 2013). The exact steps from the calcium entrance to the vesicular release are still under investigation. The steps of calcium diffusion have been investigated both experimentally and numerically. In particular the distance from the channel to the vesicle is a

key parameter. Channel clustering also would be interesting to investigate. The possibility that channels are not fixed and the membrane is constantly remodeled shows that this process is quite complex. Interestingly, the release probability can be modulated by six orders of magnitude (Kochubey et al. 2011; Schneggenburger et al. 2012). Simulations of presynaptic calcium are based on numerically solving partial differential equations (Matveev et al. 2004; Zucker and Regehr 2002; Zucker 1993); however, it is hard to account for the cusp nature of the region between the vesicles and the plasma membrane (Neher 2010). Analyzing diffusion in cusps can be studied by mapping locally the cusp conformally to a nonsingular domain or to use analytical computation (Holcman and Schuss 2012; Guerrier and Holcman 2014b). Another difficulty is to account for various varicosities, leading to divergences, and a multiscale analysis should be developed. Modeling approaches are already shedding a new light on the unsolved debate about the role of the dendritic spines in regulating electrical versus chemical activity. It is certainly time to revisit the electrical properties of the spines based on solving the full Poisson-Nernst-Planck equation. Chemical properties should consider surface receptors trafficking as a chemical reservoir.

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Calcium Dysregulation in Neurodegenerative Diseases

Haroon Anwar

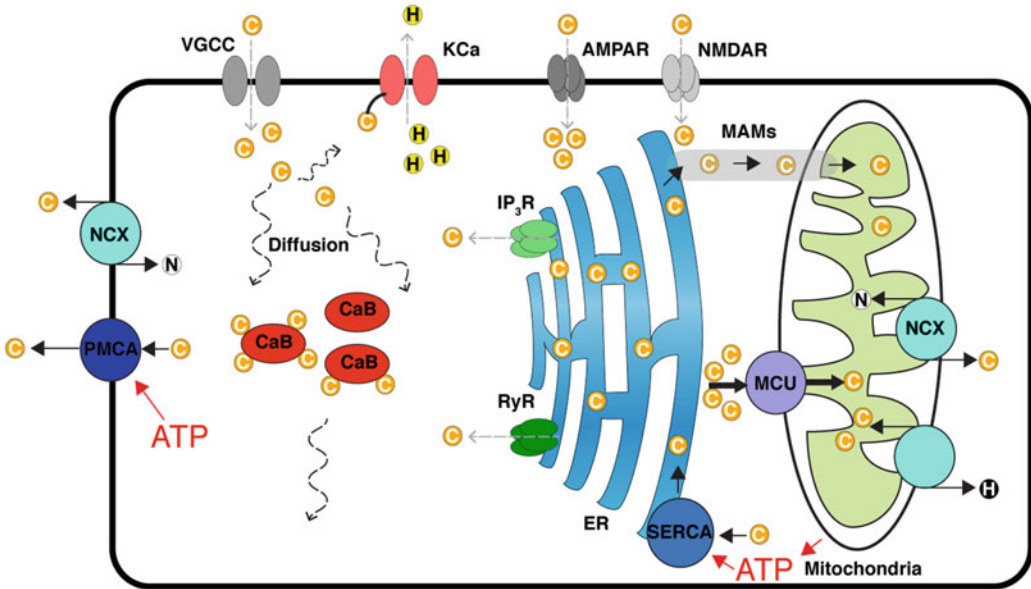
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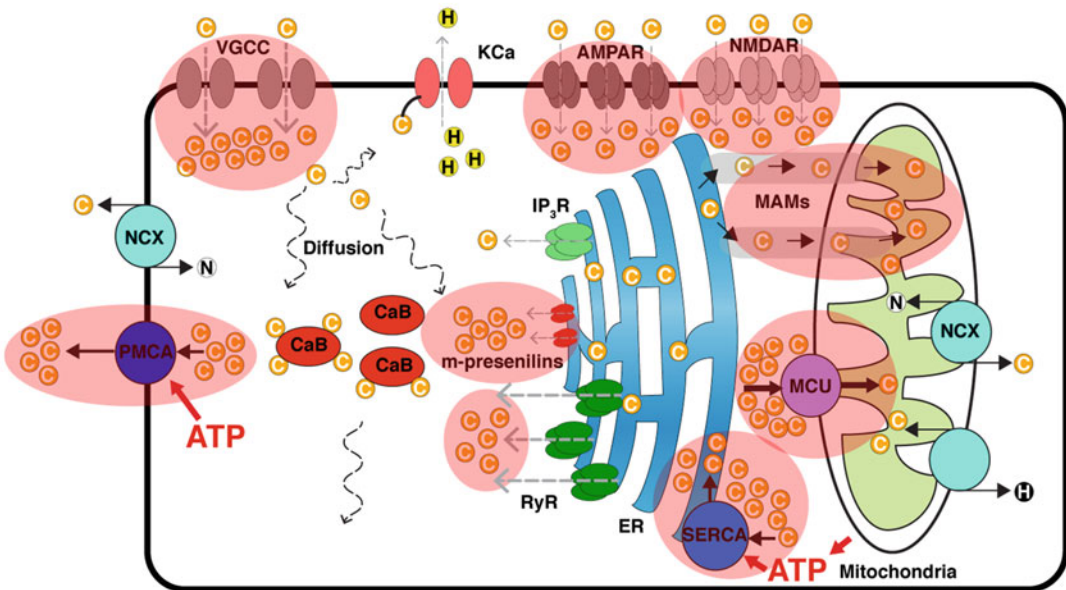
Definition

Intracellular Ca^{2+} is controlled by a complex network of Ca^{2+} -binding proteins, voltage-gated Ca^{2+} channels (VGCC), pumps, transporters, and intracellular stores (see Fig. 1). A large number of resources allocated for proper handling of intracellular Ca^{2+} levels manifest the significance of Ca^{2+} regulation in the lifecycle of a cell. The disruption in proper handling of intracellular Ca^{2+} can alter the excitability properties and synaptic connectivity (Koffie et al. 2011; Scheff et al. 2007) resulting in a loss of functional neural networks, which may cause severe motor and cognitive disabilities (DeKosky and Scheff 1990). Furthermore, Ca^{2+} dysregulation may trigger molecular events that can eventually lead to neuronal death. Because these effects are typically observed in neurodegenerative disease, it is obvious that the malfunctioning of Ca^{2+} regulatory mechanisms is related to these disorders. In the past, many studies have proposed different hypotheses regarding disease onsets and propagation and have tried to relate the malfunctioning of Ca^{2+} handling mechanisms to the disease. However, because of interdependence of the molecular pathways, the role of individual mechanisms and the causality between Ca^{2+}

Ca²⁺ regulation under physiological conditions



Ca²⁺ dysregulation in neurodegenerative diseases



Calcium Dysregulation in Neurodegenerative Diseases, Fig. 1 A schematic comparing Ca²⁺ handling in healthy vs diseased neuron. The highlighted regions (in red) in the lower panel show enhanced cytosolic Ca²⁺ due to upregulation of Ca²⁺ permeable channels (VGCCs, AMPARs, NMDARs, RyRs), altered dynamics of these channels (indicated by thicker arrows), and addition of

Ca²⁺ leak channels in ER (m-presenilins). In response to increase in cytosolic Ca²⁺ levels, PMCA and SERCA increase their activities and need more ATP to maintain the Ca²⁺ levels in physiological range, which causes oxidative stress in mitochondria. Furthermore, enhanced Ca²⁺ transport to mitochondria has been reported in neurodegenerative diseases via MAMs and MCU

dysregulation and disease onset and propagation remains unclear. We hope that computational modeling capturing Ca^{2+} regulatory mechanisms and Ca^{2+} -dependent signaling pathways can help establish the basis of disease onset and progression and eventually could allow uncovering the possible targets for intervention and prevention.

In this chapter, first I will discuss mechanisms of Ca^{2+} dysregulation in a few neurodegenerative diseases (see Fig. 1 lower panel) and then will review existing computational models of neurodegenerative diseases with emphasis on Ca^{2+} dynamics.

Detailed Description

Mechanisms Underlying Ca^{2+} Dysregulation in Neurodegenerative Diseases

Ca^{2+} dysregulation in Alzheimer's is triggered by abnormal aggregation of beta amyloids ($\text{A}\beta$), which in turn either enhances Ca^{2+} leak from endoplasmic reticulum (ER) into cytosol (Tu et al. 2006) via mutant presenilins (Bezprozvanny 2013) or via upregulation of ryanodine receptors (RyR) (Bruno et al. 2012; Kelliher et al. 1999) or enhances mitochondrial-ER cross talk via mitochondria-associated membranes (MAMs) (Area-Gomez and Schon 2016; Area-Gomez et al. 2018; Hedskog et al. 2013). Additionally, a shift in the balance between Ca^{2+} -calmodulin-dependent kinase II (CaMKII) and Ca^{2+} -dependent phosphatase calcineurin (CaN) at the synapses may disproportionally enhance long-term depression (LTD) (Reese et al. 2011). As a result, synapses get weakened and eventually eliminated. Ca^{2+} imbalance may also be triggered by extracellular block of K^+ channels by $\text{A}\beta$ that can lower the threshold of spiking and enhances the excitability of the neuron (Good 1996). Moreover, protein aggregation and misfolding may directly or indirectly affect the Ca^{2+} permeability of VGCCs, AMPARs, and NMDARs or result in decrease affinity of plasma membrane Ca^{2+} -ATPases (PMCAs), sarco/endoplasmic reticulum Ca^{2+} -ATPases (SERCAs), Na^+ - Ca^{2+} exchangers

(NCXs), and Ca^{2+} buffers. Handling increased loads of Ca^{2+} , and breakdown of increased toxic proteins may cause oxidative stress (Aliev et al. 2014) and trigger autoimmune response (Eikelenboom et al. 2010) leading to homeostatic imbalance, loss of network connectivity, and neuronal death. More details can be found in recent review articles (Gibson 2017; Popugaeva et al. 2017; Wang et al. 2017).

In Parkinson's disease (PD), dopamine-releasing neurons within substantia nigra (SN-DA) are particularly vulnerable to the degeneration compared to other dopaminergic neurons. The Ca^{2+} regulatory mechanisms are not only crucial for the dopamine release within a physiological range but also modulate their mitochondrial (Davey and Bolaños 2013) and lysosomal activity (Tofaris 2012), their metabolic stress levels, and their vulnerability to degeneration. It is not clear what make SN-DA neurons vulnerable to PD. It has been hypothesized that low levels of Ca^{2+} -binding proteins in SN-DA neurons like calbindin increase susceptibility of these neurons to the disease. Because Ca^{2+} in SN-DA neurons is mainly removed from cytosol by uptake into ER via SERCA pumps and by mitochondria via MCU or mitochondria $\text{Ca}^{2+}/\text{H}^+$ exchanger or indirectly via MAMs (Cali et al. 2012; Guardia-Laguarta et al. 2014), slight disruption in any of the Ca^{2+} regulatory process can lead to increased Ca^{2+} levels, which can trigger downstream processes eventually leading to cell death. Recent studies have implicated aggregation of α -synuclein in enhanced activation of SERCA pumps (Betzer et al. 2018) and L-type Ca^{2+} channels in Parkinson onset (Lieberman et al. 2017) resulting in increased oxidative stress and mitochondrial dysfunctioning. More details can be found in recent review articles (Dolgacheva et al. 2018; Ludtmann and Abramov 2018; Post et al. 2018).

In Huntington's disease, GABAergic medium-sized striatal spiny projection neurons are considered to be the main target for the disease onset. In addition to synaptic dysfunction in these neurons, Huntington disease gene (Htt) alters Ca^{2+} homeostatic regulation by disrupting mitochondrial and

ER function. Htt directly interacts with the mitochondrial membrane reducing its ability to sequester Ca^{2+} (Panov et al. 2002). Bezprozvanny and colleagues showed that mutant Htt (mHtt) sensitized the $\text{IP}_3\text{R1}$ to IP_3 , thereby enhancing Ca^{2+} release in response to activation of metabotropic glutamate receptors (Tang et al. 2003). Subsequent studies indicated that inhibition of $\text{IP}_3\text{R1}$ function by genetic knockdown interfering peptides or pharmacological agents could protect striatal neurons from glutamate-mediated apoptosis (Tang et al. 2005, 2009). In a recent study, Bezprozvanny group showed that striatal dendritic spine loss could also be rescued by inhibition of the store-operated Ca^{2+} entry (SOCE), which is observed to be overactive in response to a depletion of ER Ca^{2+} stores because of the higher basal activation of $\text{IP}_3\text{R1}$ induced by mHtt (Wu et al. 2016). RyR mediate Ca^{2+} -induced Ca^{2+} release in response to influx through plasma membrane channels; however, RyR can also act as a source of Ca^{2+} “leak” into the cytosol at rest elevating the basal intracellular Ca^{2+} concentration (Guerrero-Hernández et al. 2014). In neurons, such chronic increases in intracellular Ca^{2+} can alter responsiveness of a large number of signaling pathways, shifting threshold for synaptic plasticity, survival/growth, and other signaling essential for the neurons’ role in circuit function. (Read (Mackay et al. 2018; Naia et al. 2017) for more details).

Mitochondrial dysfunction and alteration in ER-mitochondria cross talk have been observed in amyotrophic lateral sclerosis (ALS)-affected motor neurons (Cozzolino and Carri 2012) (also see review (Manfredi and Kawamata 2016)). Excessive mitochondrial Ca^{2+} accumulation can cause the opening of the mitochondrial permeability transition pore, which has been associated with activation of cell death pathways (Rasola and Bernardi 2011). It was demonstrated experimentally that altering the physical distance between the opposing membranes affect Ca^{2+} flow from ER to mitochondria and cell viability (Csordás et al. 2006). The most evident ER abnormality described in ALS is ER stress accompanied by upregulation of the unfolded protein response (UPR). This phenomenon has been amply

described in ALS patients (Kiskinis et al. 2014), as well as in cellular and animal models of ALS (Walker et al. 2013; Zhang et al. 2014). However, it is unclear what exactly triggers the activation of UPR. It is likely that proteostasis dysregulation is involved in the activation of UPR. The experimental evidence suggests that MAMs- and ER-mitochondria communications, especially lipid metabolism and Ca^{2+} signaling between the two organelles, are logical points of interaction in the pathogenesis of different forms of ALS. Decreased ER-mitochondria interaction could result in insufficient Ca^{2+} transfer from the ER stores to mitochondria and defective bioenergetic coupling. It could also alter the autophagic process, because of impaired vesicle biosynthesis. However, abnormally increased or persistent ER-mitochondria contact might result in enhanced Ca^{2+} flux into mitochondria, triggering mitochondrial permeability transition and apoptosis. RyRs could also be potentially dysregulated in ALS causing abnormal cytosolic and mitochondrial Ca^{2+} influx (Grosskreutz et al. 2010). Sensitivity to Ca^{2+} dysregulation may be affected by Ca^{2+} -binding proteins, since motor neurons have lower amount of these proteins compared to ALS-spared neurons (Bernard-Marissal et al. 2012). More details can be found in recent review articles (Bernard-Marissal et al. 2018; Raymond 2016; Smith et al. 2017).

Computational Models of Neurodegenerative Diseases with Ca^{2+} Dynamics

The existing computational models of neurodegenerative diseases lack the detailed description of mechanisms controlling intracellular Ca^{2+} levels that would be required to make these models useful for better understanding the diseases. Most of the models only validate the experimentally proposed hypothesis related to diseases. The computational models investigating the effects of synaptic dysregulation and homeostatic regulation on network connectivity (Anastasio 2014; Romani et al. 2013; Rowan et al. 2014) were too simple to extend their usefulness beyond revealing mechanistic details. Some of these models provide insights into disease onset, disease progression, and its effects on behavior of

subcellular organelles, individual neurons, and neural networks, but the results were mostly attributed to a single factor. In contrast, the neurodegenerative diseases cause disruption of many interacting processes. A few computational models of neurodegenerative diseases with Ca^{2+} dynamics captured at different scales are briefly described below.

A computational model of protein aggression developed by De Caluwé and Dupont (2013) qualitatively described the interactions between intracellular Ca^{2+} and $\text{A}\beta$. The rise and decay of intracellular Ca^{2+} and $\text{A}\beta$ level were captured by a single rate constant for each. The activation of $\text{A}\beta$ synthesis by Ca^{2+} was represented by a hill term with a maximal rate V_{ω} , half-saturation constant K_{ω} , and a Hill coefficient n . They also considered that $\text{A}\beta$ oligomers induce Ca^{2+} entry into the cell, putatively by provoking an increase in plasma membrane permeability. This process was characterized by a cooperativity coefficient m and a rate constant k_{β} . Using that model the authors showed that a “steady state” characterized by low levels of Ca^{2+} and amyloids coexist with “pathological state” where the levels of both compounds are high. Thus, a large enough perturbation in either amyloid metabolism or up regulation of Ca^{2+} homeostasis could trigger AD onset.

A model proposed by Good et al. (1996) showed in cultured hippocampal neurons that $\text{A}\beta$ could block fast inactivating K^{+} currents without affecting its kinetics. Later Good and Murphy (1996) proposed a mathematical model of hippocampal neuron showing $\text{A}\beta$ -mediated block of A-type K^{+} channels could result in increased intracellular Ca^{2+} levels and increased membrane excitability. Their model had an immobile Ca^{2+} buffer with a single binding site, a Ca^{2+} extrusion pump (using Michaelis-Menten kinetics), Ca^{2+} diffusion, and several VGCCs to regulate intracellular Ca^{2+} levels. They showed that an increase in Ca^{2+} buffering capacity or decrease in density of VGCCs could reduce the $\text{A}\beta$ -mediated effects causing less increased Ca^{2+} levels and excitability.

Morse and colleagues (Morse et al. 2010) used a multi-compartment computational model of hippocampal pyramidal neuron to show that oblique apical dendrites are more vulnerable to

$\text{A}\beta$ during back propagating action potential because of their proximity to the axosomatic region in contrast to apical tuft dendrites and the smaller dendritic diameters. The excitability of the model neuron is enhanced by $\text{A}\beta$ -mediated block of A-type K^{+} channels. The model suggested that the less attenuated back propagating action potential in oblique dendrites may activate larger number of VGCCs causing larger influx of Ca^{2+} into the cytosol, which will result into much larger concentrations of intracellular Ca^{2+} due to the larger surface-to-volume ration in oblique dendrites (Morse et al. 2010).

Only recently, some efforts were put toward constructing somewhat detailed computer model of a motor neuron linking electrical activity with ATP pathways (Le Masson et al. 2014). The model included the plasma membrane $\text{Na}^{+}/\text{K}^{+}$ ATPases, PMCA, SERCA, plasma and mitochondrial NCX, MCU, and mitochondrial dynamics for converting ADP into ATP to meet the cell's energy demands. The multi-compartmental neuron model included I_{h} , Na^{+} , K^{+} , VGCCs, and K_{Ca} channels. Using this model, the authors proposed that a reduction in ATP availability can lead the neuron to prolonged depolarization, causing massive influx of Ca^{2+} , leading to cell death. The authors showed that this process involved a positive feedback loop in which small deficits in available ATP lead to small ion imbalances that, in turn, caused a higher energy demand on the neuron, which lead to worse imbalances. This study provided theoretical evidences that bioenergetics could be a critical determinant of motor neuron differential susceptibility in ALS. Based on the findings of their model, they suggested that any therapeutic strategies aimed at supporting bioenergetics might enhance the capacity of motor neurons to withstand pathological insults, thereby prolonging the lifespan of ALS patients.

Mitochondrial dysfunction is observed in almost all neurodegenerative diseases. It is known that aggregated proteins such as $\text{A}\beta$ and α -synuclein alter the dynamics of MAMs. Malfunctioned MAM can induce ER-mitochondria cross talk. Therefore including MAM dynamics in the computational model of diseases will provide a much better understanding of the emergent

behavior of the interactions of several dysfunctional Ca^{2+} regulatory mechanisms. Such an effort has been made by Szopa and colleagues by constructing a model of ER-mitochondria cross talk to investigate its effects on Ca^{2+} oscillations (Szopa et al. 2013). This model was extended from the existing model (Marhl et al. 2000) to capture Ca^{2+} regulation by ER, mitochondria, and the interaction between ER and mitochondria. The Ca^{2+} influx into mitochondria was modeled via mitochondrial Ca^{2+} uniporters (MCU) located in MAMs sensing elevated Ca^{2+} concentrations in ER and Ca^{2+} uniporter located outside MAMs sensing cytosolic Ca^{2+} levels. The Ca^{2+} release from mitochondria into cytosol was represented by $\text{Na}^+/\text{Ca}^{2+}$ and $\text{H}^+/\text{Ca}^{2+}$ exchangers with the rate of Ca^{2+} efflux regulated by the cytosolic Ca^{2+} concentrations. The Ca^{2+} influx into ER was modeled using a SERCA pump, whereas the Ca^{2+} release into the cytosol from ER was modeled using a Ca^{2+} leak channel and $\text{IP}_3\text{Rs/RyRs}$. A single Ca^{2+} -binding protein was included in the model to bind free cytosolic Ca^{2+} . The model produced Ca^{2+} oscillations where the period of oscillations depended on the Ca^{2+} permeability through MAMs. The model predicted that for sufficiently large Ca^{2+} permeability, the oscillations disappeared resulting into high Ca^{2+} levels in mitochondria, which could be interpreted as early step in an apoptotic pathway.

Recently, Matsuzawa et al. presented a multiscale model exploring the effects of $\text{A}\beta$ on synaptic plasticity using computer simulations (Matsuzawa et al. 2017). Ca^{2+} influx was modeled using NMDA current, whereas intracellular Ca^{2+} was modeled using a simple exponential decaying pool. The parameters of a phenomenological synaptic weight model were fitted to a more realistic kinetic model of synaptic plasticity involving insertion/removal of AMPARs. Both LTP and LTD were modeled using a sigmoid function dependent on intracellular Ca^{2+} . The effect of $\text{A}\beta$ was implemented by altering the threshold of activation of LTP and LTD based on $\text{A}\beta$ concentration. The model supports the hypothesis that $\text{A}\beta$ interacts with the phosphorylation/

dephosphorylation pathways of AMPAR at multiple molecular substrates occasionally in opposing manner, eventually resulting in enhanced LTD. Another detailed model of Alzheimer's analyzes the interaction among $\text{A}\beta$ depositions, Ca^{2+} signaling and mitochondrial function was published recently (Ranjan et al. 2018). This model shows that $\text{A}\beta$ accumulation causes an increase in intracellular Ca^{2+} levels and dysregulation of Ca^{2+} channel receptors on the ER. For more details see Ranjan et al. (2018).

Conclusions

The main motivation to study neuroscience is to understand how molecular and cellular mechanisms give rise to functional neurons and neural networks underlying behavior, so that we can understand the causes of psychiatric and neurodegenerative diseases in hope to intervene and cure, prevent, or slow down its progression. The main challenge we face today is because of the ability of subcellular processes, neurons, and neural networks to self-regulate with dynamics that can adapt variably to different levels of perturbation. Because most of these homeostatic processes are Ca^{2+} dependent, it is evident that Ca^{2+} dysregulation in neurodegenerative diseases alter the dynamics of homeostatic regulation. This means that any sort of intervention would require a precise control over homeostatic regulation in the brain. Thus far, I am unaware of many studies quantifying dynamics of molecular pathways underlying homeostasis. That leaves a big space for computational neuroscientists to intervene. However, to succeed with this challenge, a community effort and collaboration with experimentalists would be required to setup a framework to properly explore the parameters and validate with experiments. Without including multiscale homeostatic regulation descriptions in computational models of diseases, these models will remain limited in their usefulness, as has been the case in the past. Future models of neurodegenerative disorders must incorporate detailed Ca^{2+}

dynamics along with the factors that cause the disease onset and the downstream signaling pathways affecting the motor control and memory and lead to psychosis.

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Calcium Pumps, Models of

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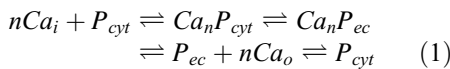
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Definition

Calcium pump is the general term that refers to molecules that extrude or remove calcium from the cytosol. The calcium may be pumped into the extracellular space, or pumped into organelles such as the smooth endoplasmic reticulum or mitochondria, both of which function as calcium stores. Some of these pumps directly utilize ATP as an energy source and are known as calcium ATPases. Other pumps rely on concentration gradients and thus are exchangers.

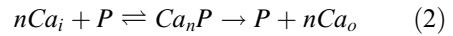
Detailed Description

So far only three different types of calcium pumps have been used in computational models. Two of them are calcium ATPases: the smooth endoplasmic reticulum ATPase (SERCA) pump and the plasma membrane calcium ATPase (PMCA) pump (e.g., Morgans et al. 1998). Both of these are typically modeled as an enzyme reaction, e.g.,



This indicates that n calcium molecules from the cytosol bind to the pump when the binding

sites are facing the cytosol, i.e., in the P_{cyt} conformation. Next, the conformation changes so that binding sites are facing the extracellular space or lumen of the organelle (P_{ec} conformation), and then the calcium molecules dissociate to the extracellular space or internal organelles. This reaction scheme can be modeled as explained for enzyme reactions. Reaction Scheme 1 already simplifies the enzyme reaction which involves ATP hydrolysis and thus involves additional states. A 12 state model includes more detail and varying degrees of cooperativity among calcium ions (Tran et al. 2009). Alternatively, reaction scheme can be simplified further by assuming that the conformational changes are instantaneous:



This enzyme reaction can be modeled either stochastically or deterministically as a system of three elementary reactions, but usually they are simplified further using the Michaelis-Menton formulation, which gives calcium flux, Φ :

$$\Phi = \frac{V_{\max}[Ca^{++}]^n}{[Ca^{++}]^n + K_D^n} \quad (3)$$

For the smooth endoplasmic reticulum calcium ATPase (SERCA) pump, K_D is 0.1 μM (Li and Rinzel 1994), and $n = 2$. For the plasma membrane calcium ATPase (PMCA) pump, K_D is 1.0 μM (Enyedi et al. 1994), and $n = 1$. There is some evidence that the pumps can be modified by calcium. For both pumps, $V_{\max}$ is typically adjusted to effect and is proportional to membrane surface area.

This formulation results in a basal calcium concentration of 0, thus a compensatory leak back into the cytosol is typically included:

$$\Phi = \frac{V_{\max}[Ca^{++}]^n}{[Ca^{++}]^n + K_D^n} - J_L([Ca_{ec}^{++}] - [Ca^{++}]) \quad (4)$$

The second term on the left hand side is a compensatory leak; J_L is adjusted such that net

calcium flux from the organelle lumen (or the extracellular space for the PMCA) is zero at the desired basal calcium value. This formulation is widely used, both in models of neurons (e.g., Blackwell 2002; Amini et al. 1999) and cardiac myocytes (e.g., Jafri et al. 1998; Korhonen et al. 2008).

The other pump is the sodium-calcium exchanger (NCX), which depends on both internal and external sodium and calcium concentration. Because this exchanger derives energy from the sodium concentration gradient, it exhibits a dependence on membrane voltage. Several different formulations of this exchanger have been proposed in an attempt to capture all dependencies on ion concentration. One formulation (Gall et al. 1999) calculates dependence on membrane potential from the reversal potential for calcium and sodium and also has an additional

term describing the sigmoid dependence on internal calcium concentration:

$$\Phi_{NCX} = \frac{V_{NCX}}{F} \cdot \text{area} \cdot \left(\frac{[Ca^{++}]^n}{[Ca^{++}]^n + K_{NCX}} \right) \cdot (V_M - V_{NaCa})$$

$$V_{NaCa} = \frac{R \cdot T}{F} \left(m \ln \frac{[Na^+]_o}{[Na^+]_i} - \ln \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \right) \quad (5)$$

The factor of m in the equation for Φ_{NCX} represents a stoichiometry of $m Na^+$ to $1 Ca^{2+}$, which is typically 3 or 4 (Fujioka et al. 2000; Blackwell 2004; Kang and Hilgemann 2004). V_{NCX} is the exchanger capacity, V_M is membrane potential, T is temperature, R is the ideal gas constant, and F is Faraday's constant.

A different formulation was derived to account for the currents observed in bull-frog cardiac atrial cells (Campbell et al. 1988).

$$I_{NCX} = V_{NCX} \frac{([Na^+]_i^3 [Ca^{++}]_o \exp \frac{\gamma(r-2)V_M F}{RT} - [Na^+]_o^3 [Ca^{++}]_i \exp \frac{-(1-\gamma)(r-2)V_M F}{RT})}{1 + d_{NaCa} ([Na^+]_i^3 [Ca^{++}]_o + [Na^+]_o^3 [Ca^{++}]_i)} \quad (6)$$

This formulation has been used in several models (Amini et al. 1999; Rasmusson et al. 1990). Since the driving potential for calcium depends on sodium, these models often include equations for the sodium-potassium exchanger.

Due to the importance of calcium for excitation-contraction coupling, many models of cardiac myocytes have even more elaborate models of the NCX that are based on an influential model (DiFrancesco and Noble 1985):

$$I_{NCX} = V_{NCX} \frac{([Na^+]_i^3 [Ca^{++}]_o \exp \frac{\gamma V_M F}{RT} - [Na^+]_o^3 [Ca^{++}]_i \exp \frac{-(1-\gamma)V_M F}{RT})}{(K_{m,Na}^3 + [Na^+]_o^3) (K_{m,ca} + [Ca^{++}]_o) (1 + K_{sat} \exp \frac{-(1-\gamma)V_M F}{RT})} \quad (7)$$

In addition to dependence on membrane potential and concentration gradients, this equation also has terms representing saturation of the exchanger by external sodium concentration and calcium concentration. This equation has been used in models to show that enhanced activity of the NCX contributes to prolongation of the cardiac AP (Priebe and Beuckelmann 1998), to show that

genetic alterations of NCX can indeed account for alternations in excitation contraction coupling (Korhonen et al. 2008), and to demonstrate how force generation is altered by changes in heart rate (Jafri et al. 1998).

An even more elaborate equation was developed (Weber et al. 2001) to account for allosteric modulation of NCX. That equation also has been

used in several models of cardiac action potentials (Rovetti et al. 2010; Hund and Rudy 2004).

A different approach is to use Markov kinetic models to describe activity of the exchanger (Omelchenko and Hryshko 1996; Haase and Hartung 2009; Kim and Matsuoka 2008). The goal of this approach is to understand state transitions of the molecule and to completely capture effects of voltage and ion concentration on exchanger current for a wide range of conditions.

In summary, the large number of studies and models reflects the importance of control of calcium concentration for cell function.

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Calcium Release, Models of

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Definition

Intracellular Ca^{2+} levels control nearly all cell functions. To adequately fulfill its physiological

roles, cytosolic Ca^{2+} concentration is thus dynamically regulated by channels mediating Ca^{2+} exchanges with the extracellular medium or with intracellular stores, by proteins acting as Ca^{2+} buffers and by diffusion. In neurons, as in other electrically excitable cells, Ca^{2+} changes are mainly carried by Ca^{2+} entry from the exterior, through voltage-dependent Ca^{2+} channels. These channels are able to generate large increases in cytosolic Ca^{2+} in a few milliseconds. In contrast, in electrically non-excitable cells, the main source for Ca^{2+} is the endoplasmic reticulum (ER). Release of Ca^{2+} from the ER occurs through the inositol 1,4,5-trisphosphate receptor (InsP_3R) or through the ryanodine receptor (RyR) in response to a hormonal stimulation (Fig. 1).

However, also in neurons, release of ER Ca^{2+} can be triggered during an action potential and thereby modulate Ca^{2+} -activated plasma membrane channels and affect neuronal excitability. Thus, Ca^{2+} exchanges between intracellular organelles and the cytoplasm need to be accurately modelled when describing the signaling activity of neurons. Of particular importance is the fact that Ca^{2+} can be released from the ER in a regenerative manner, through the so-called Ca^{2+} -induced Ca^{2+} release regulation. This autocatalytic regulation, mediated by either the InsP_3R or the RyR , allows for an excitable process additional to plasma membrane electrical activity. Other factors control cytoplasmic Ca^{2+} changes in a way that is

independent from the electrical properties of the plasma membrane, such as buffers, ATP-driven Ca^{2+} pumps, Ca^{2+} exchangers, InsP_3 metabolism, mitochondria, or store-operated Ca^{2+} entry (Keener and Sneyd 2009). Factors that control Ca^{2+} dynamics in a voltage-independent way are reviewed here below, both from a biological and a modelling point of view.

Detailed Description

Calcium Channels

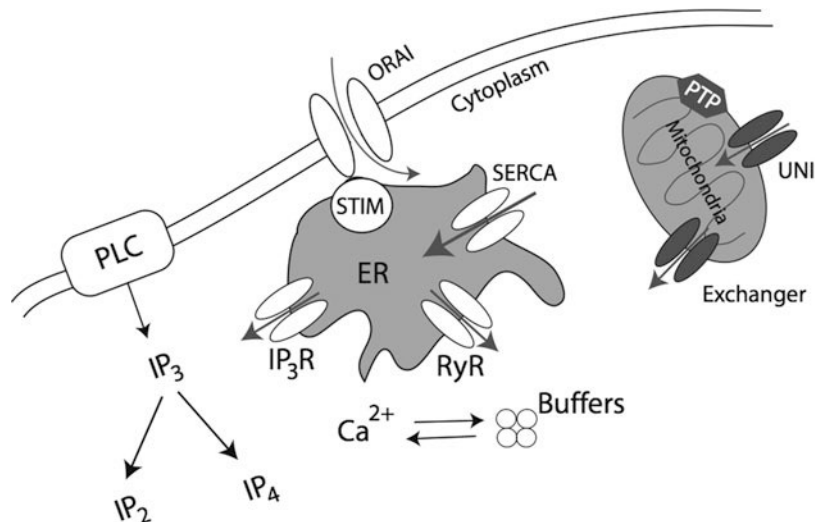
At rest, Ca^{2+} concentration is low (30–100 nM) in the cytoplasm and mitochondria and high (0.5–1 mM) in the extracellular medium and ER. These gradients allow for a rapid increase in cytosolic Ca^{2+} following the opening of specific Ca^{2+} channels when required for the signaling function of the cell. On the other hand, maintenance of these gradients occurs through active, ATP-dependent pumping.

InsP3 Receptor

The InsP_3 receptor is a tetrameric protein located in the membrane of the ER, although the presence of this receptor has also been reported in the perinuclear or plasma membrane (Parys and De Smedt 2012). This receptor is a Ca^{2+} channel that, when opened, lets Ca^{2+} flow along its gradient. Its Ca^{2+} -releasing activity is not only regulated by

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Fig. 1 Schematic representation of the main processes regulating cytosolic Ca^{2+} concentration in electrically non-excitable cells



InsP3 but also by the Ca^{2+} concentration at the cytoplasmic terminal: Ca^{2+} concentrations up to ~300 nM tend to open the channel, while higher concentrations inhibit Ca^{2+} release, albeit on a slower time scale. The activation, acting as an autocatalytic regulation through which Ca^{2+} activates its own release in the cytoplasm, plays a major role in the occurrence of the well-known Ca^{2+} oscillations observed in most non-excitable cell types (Berridge 2012).

Deterministic Model

Models can describe sequential activation and inhibition by assuming that the InsP3 receptor possesses 3 types of binding sites: one for InsP3, one for Ca^{2+} with an activatory effect, and one for Ca^{2+} with an inhibitory effect, characterized by a lower affinity for Ca^{2+} . These detailed models for the receptor (see Thul et al. 2008, for review) can accurately describe the properties of the channel and are easily implemented to perform stochastic simulations (Falcke 2004). When the cellular behavior is the subject of interest, such models can be simplified on the basis of the different time scales of the activatory and inhibitory processes (Dupont et al. 2011). The evolution of the fraction of inhibited channels can be described by a unique differential equation:

$$\frac{dR_i}{dt} = k_+ C^{ni} \frac{1 - R_i}{1 + \left(\frac{C}{k_{act}}\right)^{na}} - k_- R_i$$

where k_+ and k_- are the kinetic constants of Ca^{2+} association to and dissociation from the inhibitory Ca^{2+} binding site of the receptor, C represents the concentration of cytosolic Ca^{2+} , and K_{act} is the dissociation constant of Ca^{2+} binding to the activating Ca^{2+} binding site of the InsP3 receptor. Thus, Ca^{2+} can be released from the ER through the InsP3 receptor when it is active (i.e., open); the fraction of open channel is related to the fraction of inhibited receptor by the following algebraic equation:

$$IR_a = (1 - R_i) \frac{C^{na}}{(K_{act})^{na} + C^{na}} \frac{IP^3}{(K_{IP})^3 + IP^3}$$

Even at basal InsP3 concentration, the InsP3R/ Ca^{2+} channel can release Ca^{2+} through its

autocatalytic activation and amplify Ca^{2+} entry through voltage-gated Ca^{2+} channels.

A more accurate description of InsP3-induced Ca^{2+} fluxes can be obtained when taking into account the existence of the isoforms of this receptor/channel. Three isoforms have been identified (InsP3R1, InsP3R2, and InsP3R3), and their levels of expression are largely tissue specific. Experiments where the levels of expression of these isoforms have been modified (overexpress or knockdown) clearly indicate that their proportions significantly affect the time course of cytosolic Ca^{2+} concentration (Hattori et al. 2004). Although all the InsP3 receptor subtypes display similar permeation properties, they differ significantly in their regulatory properties due to different interactions with accessory proteins, various modes of regulation by ATP, or phosphorylation (Parys and De Smedt 2012). The characteristics of one specific receptor subtype can be considered in a model by assigning the appropriate values to the dissociation constants for IP3 binding, Ca^{2+} binding to the activatory site, and Ca^{2+} binding to the inhibitory site. Although still controversial, putative values are summarized in the table below:

	Type 1(μM)	Type 2(μM)	Type 3(μM)
K_{IP}	0.50	0.20	4.00
K_{act}	0.50	0.50	0.50
K_{inh}	0.50	0.25	1.15

In this table, the dissociation constant for Ca^{2+} on the inhibitory site corresponds to

$$K_{inh} = \left(\frac{k_-}{k_+}\right)^{1/ni}$$

As another difference, the evolution equation for the fraction of inhibited receptor has to be slightly modified to reproduce the behavior of the InsP3R1: it is assumed that InsP3 inhibits Ca^{2+} binding to the inhibitory site, which is necessary to account for the observation that for type 1 receptors, inhibition occurs for higher concentrations of cytosolic Ca^{2+} when the concentration

of InsP3 increases (Dupont and Combettes 2006). The appropriate equation is then

$$\frac{dR_i}{dt} = k_+ C^{ni} \frac{1 - R_i}{1 + \left(\frac{C}{k_{oct}}\right)^{na}} \frac{(K_{IP})^3}{(K_{IP})^3 + IP^3} - k_- R_i$$

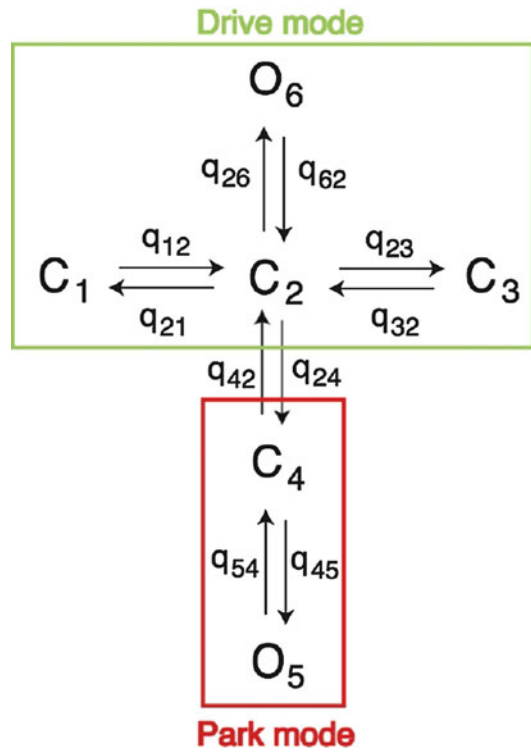
Stochastic Model Accounting for Mode Changes
Deterministic models do a very good job in simulating global Ca^{2+} changes and in reproducing most characteristics of signal-induced Ca^{2+} oscillations. However, in order to understand measurements of time-dependent single-channel currents through an InsP3R (Ionescu et al. 2007; Mak et al. 2007), stochastic models describing the transitions between many channel states need to be considered.

In particular, recent experiments revealed that the InsP3R exhibits mode changes: the average open probability indeed jumps between two levels even when ligand (Ca^{2+} , InsP3, or ATP) concentrations are kept constant. These modes are referred to as drive (highly active) and park (inactive) modes by Siekmann et al. (2012). In each of these modes, the receptor can exist in different open or closed states. By comparing fits of Markov models with different numbers of states and different topologies, it was found that the drive mode is best represented by a model with one open and three closed states, while the best model for the park mode only has one open and one closed state (Fig. 2).

Inside each mode, rate constants are ligand independent. Some of these constants are different for the type I and the type II InsP3R. Only the transition rates between both modes, q_{24} and q_{42} , are fitted by different values depending on the concentrations of Ca^{2+} , IP3, and ATP. These values are given for a large set of conditions in Siekmann et al. (2012). Interestingly, the park and drive times depend only on the rates exiting the modes:

$$t_{park} = \left(1 + \frac{q_{45}}{q_{54}}\right) \frac{1}{q_{42}}$$

which can be approximated by $\frac{1}{q_{42}}$ since the ratio $\frac{q_{45}}{q_{54}}$ is low for both types I and II InsP3R.



Calcium Release, Models of, Fig. 2 Drive and Park Markov model for the InsP3R developed by Siekmann et al. (2012)

$$t_{drive} = \left(1 + \frac{q_{21}}{q_{12}} + \frac{q_{23}}{q_{32}} + \frac{q_{36}}{q_{62}}\right) \frac{1}{q_{24}}$$

An important point to remember at this point is that in such type of models, the channel states and connections between them are not related to any underlying reaction scheme. Rather, they represent the most complex model that can be built unambiguously from statistical analysis of single-channel data.

Ryanodine Receptor

Deterministic Model

The ryanodine receptor (RyR) much resembles the InsP3 receptor. It is expressed in all excitable cells. It is responsible for excitation–contraction coupling in muscle cells. The main activator is Ca^{2+} itself, and, as for the InsP3 receptor, excess Ca^{2+} has an inhibitory effect on the RyR, although

the level of Ca^{2+} required for inhibition much depends on the receptor subtype. Other factors that modulate the activity of the RyR are caffeine, ryanodine, and the second messenger cyclic ADP ribose, which may be the endogenous activator of the channel, in the same way as IP3 for the IP3 receptor.

The RyR can be modelled the same way as the InsP3 receptor, although simpler kinetic expressions are also adequate. Modelling studies indeed suggest that inactivation does not play a significant role for RyR-mediated Ca^{2+} release. Indeed, describing this flux by a very simple Hill-type expression, the following sigmoidal function of cytosolic Ca^{2+}

$$V_{\text{RyR}} = \left(k_1 + k_2 \frac{C^3}{(K_o)^3 + C^3} \right) \cdot (C_{\text{ER}} - C)$$

gives excellent agreement with observations in bullfrog sympathetic neurons (Friel 1995). However, simulations of the RyR should take into account the prominent opposition of RyR with plasma membrane Ca^{2+} channels, and more especially L-type Ca^{2+} channels, as geometry is crucial for the Ca^{2+} dynamics (Thul et al. 2012).

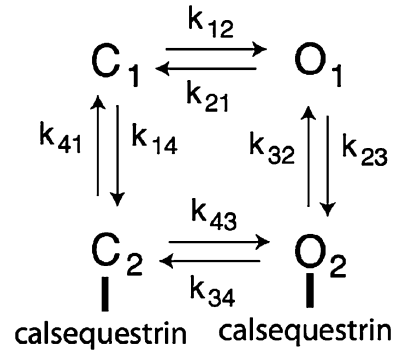
Stochastic Model Including Regulation by Ca^{2+} in the ER

A striking property of RyRs is that their activity spontaneously terminates after a few tens of milliseconds. This strongly suggests the existence of an inactivated state. Experimental evidences also show that high levels of Ca^{2+} in the ER increase the open probability of the RyR (Shannon and Bers 2000). A plausible molecular mechanism could involve an interaction between calsequestrin, a widespread ER Ca^{2+} buffer, and the RyR (Györke and Terentyev 2008).

This dual regulation of the RyR by cytosolic and by Ca^{2+} /calsequestrin is taken into account in the model of Restrepo et al. (2008) that assumes the existence of 2 open (O) and 2 closed (C) states (Fig. 3):

Transition from C1 to O1 and from C2 to O2 (Fig. 3) is activated by cytosolic Ca^{2+} . Thus,

$$k_{12} = K_u C^2$$



Calcium Release, Models of, Fig. 3 Model for the RyR and its regulation by calsequestrin developed by Restrepo et al. (2008)

and $k_{43} = K_b C^2$. Calsequestrin regulates the passage from C1 to C2 and from O1 to O2. In fact, only the calsequestrin monomers interact with RyR. Calsequestrin dimerization is favored by high ER Ca^{2+} . Thus, C2 and O2 states are predominant when ER Ca^{2+} is low. Assuming a fast equilibrium between calsequestrin monomers and dimers, Restrepo et al. (2008) have derived an algebraic equation for transition rates:

$$k_{23} = k_{14} = M(C_{\text{ER}})t_b^{-1}$$

where M is an increasing function of C_{ER} .

Other rates are constant. Importantly, $k_{12} > k_{43}$, which means that unbinding of calsequestrin induced by dimer formation at high ER Ca^{2+} leads to an increase in the RyR open probability, as observed experimentally.

Influx

In non-excitable cells, influx of Ca^{2+} is thought to occur through two possible mechanisms, depending on the filling state of the endoplasmic reticulum. Such an influx is thus said to occur through “store-operated Ca^{2+} channels (SOCs).” When the ER is only slightly depleted, the rate of influx is small and proportional to the level of agonist stimulation through a mechanism that may involve arachidonic acid (Shuttleworth 2009). Arachidonic acid is produced by diacylglycerol, a membrane compound that is produced by the same reaction as InsP3. Thus,

this stimulated influx is modelled in the simplest possible way by assuming that the rate of Ca^{2+} entry increases linearly with the level of cell stimulation (Keener and Sneyd 2009).

In most situations, the major molecular components of SOC_s are STIM and Orai. STIM resides in the ER membrane, not far from the plasma membrane where Orai channels are expressed. STIM is able to sense the filling state of the ER (through an EF-hand motif in its N-terminus). Upon Ca^{2+} dissociation, it changes its conformation, which allows self-association of STIM molecules. When aggregated, STIM molecules interact with Orai at plasma membrane junctions. Orai then allows the entry of Ca^{2+} in the cytosol.

A simple model for Ca^{2+} entry based on the STIM–Orai interaction has been proposed by Liu et al. (2010). Ca^{2+} flux through SOC channels is given by

$$V_{IN} = V_{SOC}[SO] \frac{C_{ex}}{K_{ex} + C_{ex}}$$

where $[SO]$ represents the fraction of open SOC_s and V_{SOC} the maximal rate of Ca^{2+} entry of extracellular Ca^{2+} (C_{ex}) through SOC channels. Open SOC_s correspond to STIM–Orai complexes. Thus, $[SO]$ must be computed as the ratio between the concentration of STIM–Orai complexes and the total concentration of Orai. Its time evolution is simply given by the balance between STIM–Orai binding and unbinding, i.e.,

$$\frac{d[SO]}{dt} = f_0(1 - [SO])[STIM] - b_0[SO]$$

where $[STIM]$ represents the concentration of ER Ca^{2+} -free STIM. Thus,

$$\begin{aligned} \frac{d[STIM]}{dt} = & -f_S[STIM](C_{ER})^{ns} \\ & + b_S([STIM]_{tot} - [STIM]) \end{aligned}$$

When solved at steady state, this simple model gives an excellent agreement with the experimental data about store-operated Ca^{2+} entry in human Jurkat T cells (Luik et al. 2008).

Inositol 1,4,5-Trisphosphate Metabolism

Inositol 1,4,5-trisphosphate metabolism is overlooked in most models for intracellular Ca^{2+} dynamics, although it is well known that the level of this messenger has a profound influence on the level of cytosolic Ca^{2+} . It makes no doubt that variations in the concentration of InsP3 will modify the Ca^{2+} flux of Ca^{2+} from the ER through the InsP3 receptor.

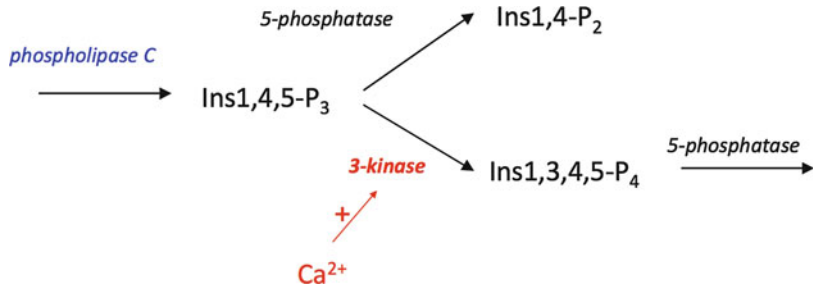
InsP3 originates from the receptor-activated hydrolysis of phosphoinositides through well-characterized signaling cascades. The ultimate enzyme of this cascade is membrane-bound phospholipase C. This enzyme possesses several isoforms (β , γ , δ , ϵ , and ζ) differing by the signaling pathway in which they are involved and by their Ca^{2+} sensitivity. PLC β is activated by protein G-coupled receptors, PLC γ by tyrosine kinases, PLC δ by PIP2 and Ca^{2+} , PLC ϵ by Ras, and PLC ζ by Ca^{2+} . Concerning its degradation, InsP3 can be either dephosphorylated by a 5-phosphatase into IP2 or phosphorylated by a 3-kinase into InsP4. The 3-kinase is stimulated by an increase in Ca^{2+} as binding of Ca^{2+} and calmodulin enhances its activity. The stimulation factor varies from 2 to 10 depending on the isoform (Dupont and Erneux 1997). Thus the InsP3-induced Ca^{2+} release leads to a decrease in InsP3 concentration. Another level of complexity comes from the fact that the product of InsP3 phosphorylation by 3-kinase, InsP4, is a competitive inhibitor of the other InsP3-metabolizing enzyme, the 5-phosphatase (Fig. 4).

Because of this network of intertwined regulations, it is difficult to apprehend the interplay between Ca^{2+} and InsP3 concentrations in an intuitive manner. Models taking these regulations into account have proven useful to understand experimental results and make theoretical predictions (Dupont and Erneux 1997; Dupont et al. 2003). Using enzyme kinetics, the evolution of the concentrations of InsP3 and InsP4 can be described as

$$\begin{aligned} \frac{dIP_3}{dt} = & \gamma \cdot V_{PLC} - V_k \frac{IP_3}{K_k + IP_3} \frac{C^4}{(K_o)^4 + C^4} \\ & - V_{P1} \frac{IP_3}{K_{P1} \left(1 + \frac{IP_4}{K_{\phi 2}}\right) + IP_3} \end{aligned}$$

Calcium Release, Models of, Fig. 4

Inositol 1,4,5-Trisphosphate (Ins 1,4,5-P₃) metabolism



$$\frac{dIP_4}{dt} = V_k \frac{IP_3}{K_k + IP_3} \frac{C^4}{(K_o)^4 + C^4} - V_{P2} \frac{IP_4}{K_{P2} \left(1 + \frac{IP_3}{k_{\phi 1}}\right) + IP_4} - k \cdot IP_4$$

The level of Ca²⁺ in the mitochondria thus results from the balance between entry through the uniporter and efflux via the Na⁺-Ca²⁺ exchanger and possibly the permeability transition pore:

$$\frac{dC_m}{dt} = -J_{Na,ex} + J_{uni} + J_{PTP}$$

Mitochondria

Mitochondria also affect cytoplasmic Ca²⁺ signals. They can both buffer cytosolic Ca²⁺ changes and release Ca²⁺. At rest, intramitochondrial and cytosolic Ca²⁺ concentration are similar, of the order of 100 nM. Ca²⁺ entry in the mitochondria occurs through a multistep mechanism. By extruding protons out of the mitochondria, the respiratory chain creates a large inside-negative potential difference across the inner mitochondrial membrane. This ΔΨ_m, which is harnessed by the ATP synthase in the production of ATP, allows a uniporter to transport Ca²⁺ inside the mitochondria when cytosolic Ca²⁺ locally reaches high concentrations, which arises in the close vicinity of ER Ca²⁺ release sites. Ca²⁺ entry then depolarizes the mitochondria, thus reducing its own driving force. When cytosolic Ca²⁺ returns to its basal value, extrusion of Ca²⁺ out of the mitochondria occurs mainly through the rather slow Na⁺-Ca²⁺ exchanger (Santo-Domingo and Demaurex 2010; Rizzuto et al. 2012). In addition to the uniporter/exchanger pathway for Ca²⁺ cycling between the cytosol and the mitochondria, an important increase in matrix Ca²⁺ can also lead to opening of the permeability transition pore (PTP), a voltage-dependent, high-conductance channel behaving as a large pore allowing solutes with a molecular weight less than about 1,500 kDa to equilibrate across the inner membrane.

All fluxes depend on cytosolic Ca²⁺, mitochondrial Ca²⁺, and mitochondrial potential in a complex manner. Detailed, accurate kinetic expressions can be found in the literature (Oster et al. 2011).

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Calcium Waves, Models of

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Definition

A calcium wave is a transient rise in cytosolic calcium concentration that propagates spatially within the cell. It has the property that it is regenerative and is followed by a refractory period. It is believed that the wave carries a signal from one part of the cell to another.

Detailed Description

Calcium ions play an important role in a variety of cellular functions that impact nearly all aspects of cellular life. In fact, the calcium signal is one of the most versatile and universal signaling agents of the human body that controls almost everything we do – Ca^{2+} ions contribute to egg activation upon fertilization, muscle contraction, enzyme secretion, neurotransmitter release, how our brains process information and store memories, wound healing, and apoptosis. Calcium ions play such an important role in so many biological processes that it has been branded as the “life and death signal” (Berridge et al. 1998).

At rest, intracellular calcium concentration remains low, about 0.1 μM . Transient increases of intracellular Ca^{2+} concentration influence different cellular processes across a variety of different cells. This transient rise can peak at 0.5–3.0 μM depending upon the cell type and signal. The change in Ca^{2+} concentration transmits information through an organized set of spatiotemporal changes (Adkins and Taylor 1999). When considering the inositol 1,4,5-trisphosphate (IP_3) receptor channel that is found on the endoplasmic reticulum, release occurs as localized

blips, puffs, transients, oscillations, and waves (Fig. 1). When considering the ryanodine receptor (RyR) that is found in the sarcoplasmic reticulum, the internal calcium store in muscle, release occurs in the form of quarks (a fundamental opening event) and calcium sparks which are the elementary unit of calcium release which sum up to the calcium transient. The calcium transient can propagate to carry a signal from one part of the cell to another in a calcium wave.

Basic Mechanism of Ca^{2+} Signaling

In the cell cytosol, Ca^{2+} can enter from two sources: (1) from extracellular sources through a variety of plasmalemmal Ca^{2+} channels such as voltage-operated channels (VOCs), receptor-operated channels (ROCs), or store-operated channels (SOCs) or (2) from intracellular Ca^{2+} stores such as the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). The endoplasmic reticulum (ER) comprises up to 20 % of the cell; it is the major Ca^{2+} storage organelle in many cell types (Foskett et al. 2007). The extracellular calcium concentration is in the mM range,

whereas the internal concentration in ER is of the order of a few hundred μM and may reach up to mM (Falcke 2004). This provides a large driving force for calcium entry into the cytosol which is much lower. This low concentration of Ca^{2+} is maintained by pumps and other Ca^{2+} transporters located on the ER membrane and plasma membrane (Foskett et al. 2007) as well as intracellular calcium-binding proteins which serve as Ca^{2+} buffers. Hence, a finely tuned mechanism regulates cytosolic calcium.

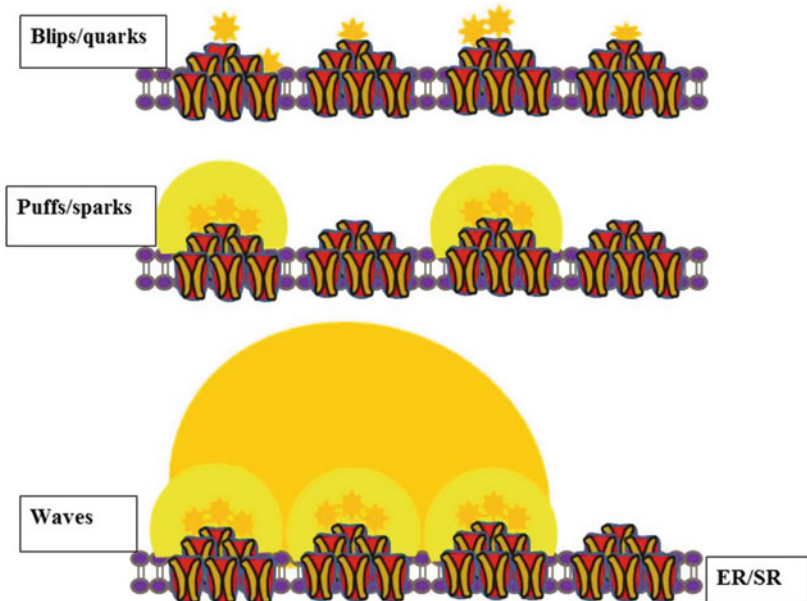
Mechanisms of Calcium Waves

The specific mechanism of calcium waves can vary depending upon cell type and condition. Mathematically they all have some common features. First, the system must be excitable which means that an increase in calcium above a threshold will trigger additional calcium release. This requires positive feedback of calcium release (such as calcium-induced calcium release) that is possible with systems that contain the IP_3 receptor or the RyR. These can be described as components of a system of coupled differential equations

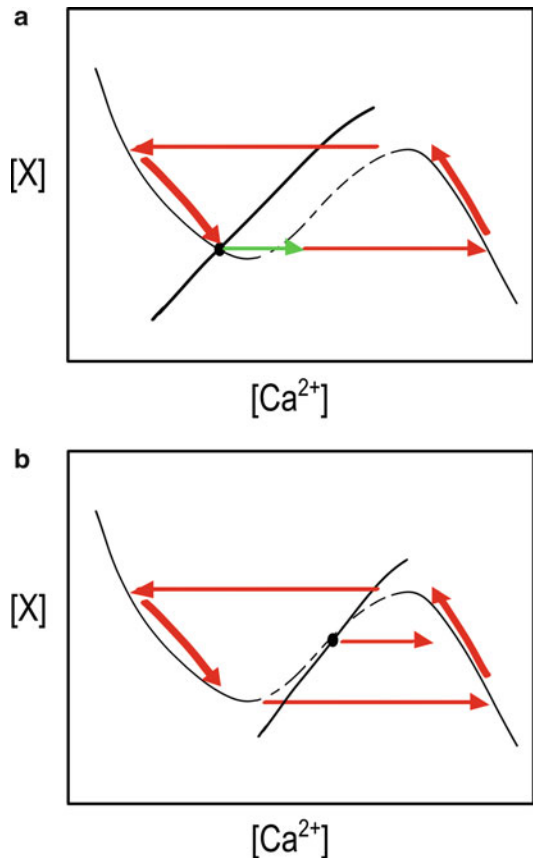
Calcium Waves,

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Fig. 1 Calcium blips (or quarks in the case of RyR clusters) are considered to be openings of one or a few IP_3 receptor channels (*top*). Calcium puffs (or sparks in the case of RyR clusters) reflect the opening of a cluster of IP_3 receptor channels (*middle*). When calcium release propagates from one cluster to another, a calcium wave results (*bottom*)



giving the ability to analyze the mechanism of calcium waves. Mathematically a system of differential equations can be studied two variables at a time using a phase plane diagram that explores the values of the derivatives at different values of the variables. The phase plane considers the nullclines (the curves where each derivative is zero), and the values of the derivatives at other points (vector field) define the trajectories of possible solutions. The system can be characterized by an n-shaped nullcline and a second nullcline that is relatively straight that crosses the other at a stable steady state (Fig. 2a). A steady state is the point where the derivatives are all equal to zero. The dashed portion of the n-shaped nullcline is the unstable portion, and the solid portions are the stable portions. A trajectory will move toward the stable portions of the nullcline and away from the unstable portion. At rest, the system will be at its stable steady state shown by the solid black circle. If the perturbation is small and does not cross the dashed portion, the trajectory will return to the steady state. A sufficient perturbation (green arrow) will move the trajectory past the unstable portion of the n-shaped nullcline. The trajectory will then proceed to the right to the stable part of the nullcline (red arrow). The trajectory will then track along the n-shaped nullcline (thick red arrow on right) until it falls off the nullcline and moves left until it finds the other stable part of the n-shaped nullcline (left pointing red arrow). The trajectory will then follow the nullcline back to the steady state (thick red arrow on left). Detail of this mechanism can be found in the model developed by Sneyd and coworkers (Girard et al. 1992). If the “straight” nullcline is shifted so that it crosses the unstable portion of the n-shaped nullcline, oscillations occur (Fig. 2b). Any small perturbation off the unstable steady state (solid black circle) will move to the stable portion of the n-shaped nullcline, and the red trajectory will be followed in an oscillatory fashion, unable to return to the stable point. In models of agonist-induced calcium wave and oscillations, changing the IP_3 concentration would shift the “straight” nullcline. Hence for a range of values of IP_3 (when the “straight nullcline crosses the unstable portion of the n-nullcline (dashed)), oscillations will occur.



Calcium Waves, Models of, Fig. 2 The dynamics of the system of differential equations can be studied with a phase plane diagram that characterizes the trajectories of solutions for two system variables using the vector field (values of derivatives for different values of the variables). (a) An excitable system has this characteristic n-shaped nullcline crossed by a second “straight nullcline” establishing a stable steady state (black circle) so that sufficient perturbations from the stable steady state (green arrow) cross the unstable portion of the n-shaped nullcline. The trajectory then follows the red arrows generating a transient rise in the independent variable of the plot. (b) When the nullclines cross, yielding an unstable steady state (black circle), perturbations off the steady state result in an oscillatory trajectory

Classification of calcium waves into five categories can be accomplished by the mechanism giving rise to the waves: (1) membrane depolarization-triggered calcium waves, (2) agonist-induced calcium waves, (3) fire-diffuse-fire calcium waves, (4) calcium phase waves, and (5) kinematic calcium waves. A common feature of these mechanisms is that they all involve calcium release from

the endoplasmic reticulum which is an intracellular calcium store. These calcium waves can be found in single cells as well as multicellular systems.

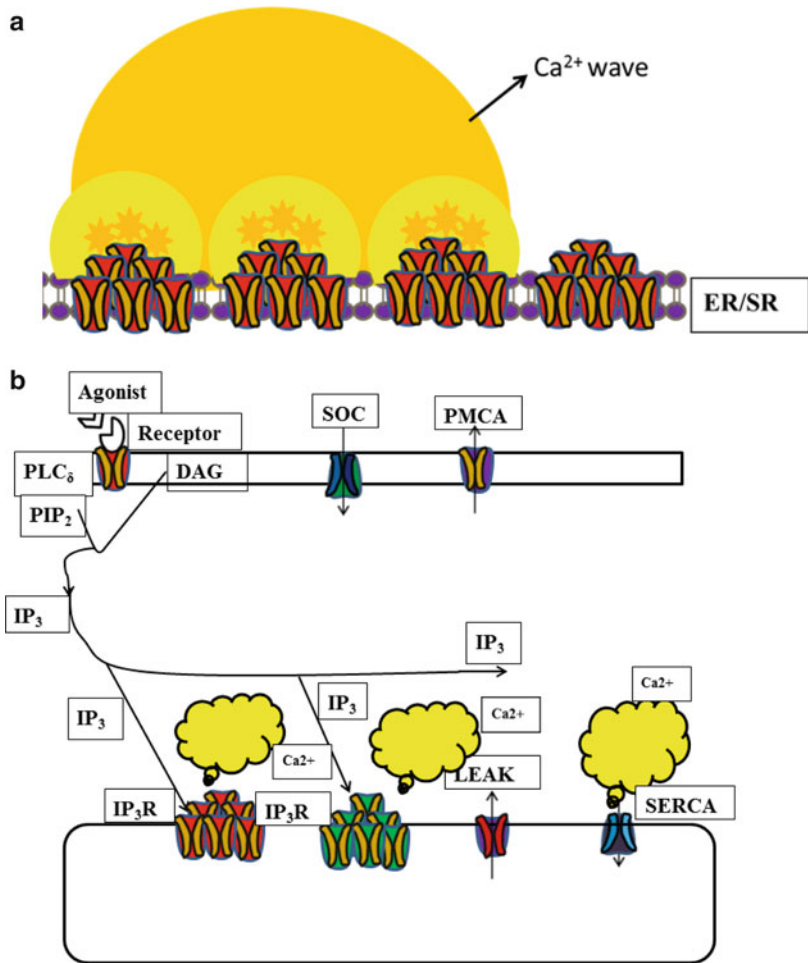
Membrane Depolarization-Triggered Calcium Waves – In this type of wave, a propagating signal triggers release of calcium from internal stores resulting in calcium waves. For example, membrane depolarization, as seen during an action potential, results in the opening of voltage-gated calcium channels. The wave of depolarization triggers calcium release from the intracellular stores in two ways. In the case of ryanodine receptor type 1 (RyR1) in skeletal muscle, the conformational change in the voltage-gated L-type calcium channel during opening triggers a conformational change in the adjacent RyR1 causing calcium release from the sarcoplasmic reticulum. On the other hand, in

cardiac myocytes which contain ryanodine receptor type 2 (RyR2), the calcium entry through these plasmalemmal calcium channels can trigger calcium release from the internal stores through a calcium-induced calcium-release mechanism. These waves are quite fast as in an action potentials the depolarization propagates very rapidly across the plasmalemma. In networks of neurons, the rapid spread of depolarization between neurons or astrocytes can trigger a wave of calcium elevation in these cells. In other cells, this can involve either ryanodine receptors, IP₃ receptors, or both.

Agonist-Triggered Calcium Waves – A wave of IP₃ has been observed to trigger a wave of calcium release from the endoplasmic reticulum in oocytes during fertilization. This occurs as IP₃ binds to the IP₃ receptor in the ER-releasing calcium (Fig. 3a).

Calcium Waves, Models of,

Fig. 3 Schematic diagram of mechanisms of calcium waves. (a) Agonist-triggered calcium wave. (b) Fire-diffuse-fire calcium wave



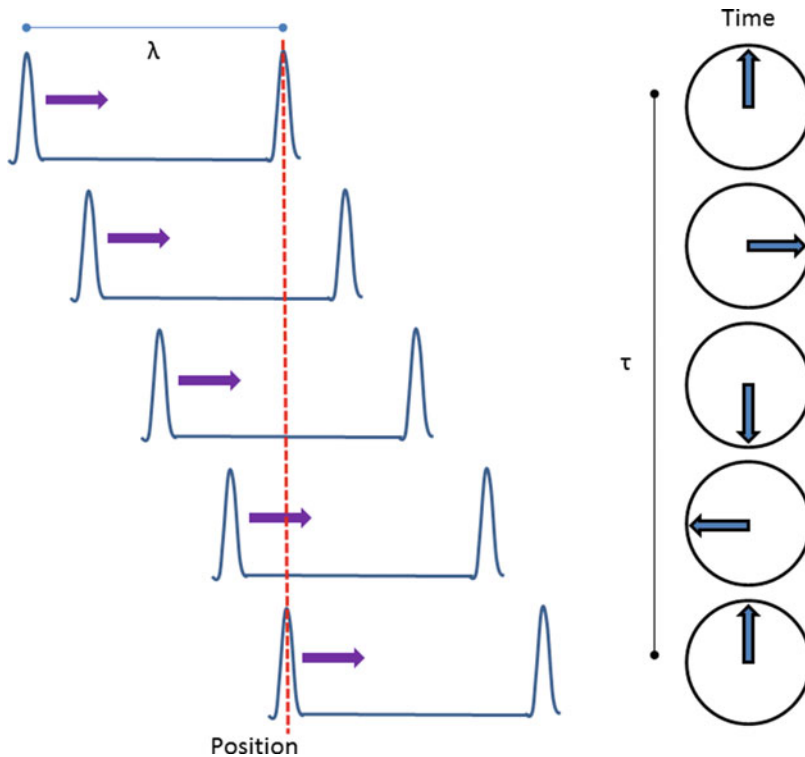
The calcium activates IP_3 production allowing the wave of IP_3 to propagate (Fall et al. 2004). Another example is the calcium waves observed in airway epithelium cells where calcium waves depend upon IP_3 diffusion (Sneyd et al. 1995). The speed of these waves is governed by the propagation speed of the wave of IP_3 which is controlled by the IP_3 diffusion rate and its dynamics.

Fire-Diffuse-Fire Calcium Waves – In this type of calcium wave (Fig. 3b), calcium released from the endoplasmic reticulum through channels, such as the IP_3 receptor or ryanodine receptor, diffuses to adjacent channels and triggers release from these sites through calcium-induced calcium release (Atri et al. 1993; Jafri and Keizer 1995). The wave speed (c) of this type of waves is proportional to the square root of the effective

diffusion constant, D_{eff} , for calcium divided by a characteristic time, T_1 :

$$\text{i.e., } c^2 = D_{\text{eff}}/T_1.$$

Calcium Phase Waves – Phase waves result from a series of spatially adjacent oscillators in which there is a slight phase delay between oscillators as one moves down the chain of oscillators. For example, during receptor stimulation by an agonist, IP_3 is produced which induces calcium oscillations. The initial gradient of IP_3 can initiate calcium oscillations sequentially from sites moving down the initial gradient. As these sites fire in sequence, it appears that a wave of calcium actually propagates even though there is no diffusion of calcium (and no net movement of calcium). Instead, there are localized cycles of uptake and release that give the appearance of a wave (Fig. 4).

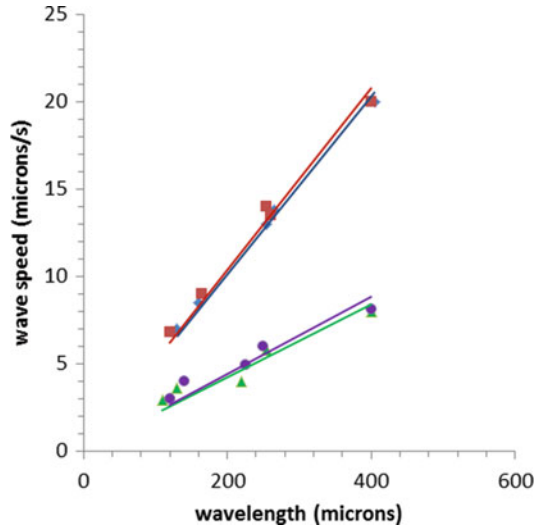


Calcium Waves, Models of, Fig. 4 The spatial length between two waves is the wavelength (λ), and the time between two successive transients is the period between oscillations (τ). The phase of the oscillation for the spatial point shown by the red dashed line is shown by the clocks on the right. When the arrow is pointing up, a calcium transient occurs as a cycle of local calcium uptake and

release. As the phase progresses, the waves propagate to the right as shown by the purple arrows even though there is no calcium diffusion. As the phase advances through one period (from top to bottom on right), the wave advances to the right by one wavelength (left). Hence the wave speed is the ratio of wavelength do period, i.e., $c = \lambda/\tau$

For these waves, the wave speed is equal to the ratio of the wavelength to the period of oscillation (Jafri and Keizer 1994; Jafri and Keizer 1995).

Kinematic Calcium Waves – Kinematic waves are related to phase waves but actually have weak diffusion of calcium. Murray provides a mathematical description of kinematic waves (Murray 1993). As calcium is highly buffered, calcium diffusion in cells is slow and can be considered weak. Hence, with oscillatory calcium dynamics, kinematic waves are observed. Waves propagate as a result of local cycles of uptake and release with little diffusion. This was first suggested for calcium waves by Jafri and Keizer (Jafri and Keizer 1994; Jafri and Keizer 1995, 1997). This type of wave has been observed experimentally in astrocytes by Russell and coworkers and has been described by a model (Roth et al. 1995). As with phase waves, the wave speed is equal to the ratio of the wavelength to the period of oscillation (Fig. 5). Experimental data from oocytes under certain conditions also support this relation (Lechleiter et al. 1998).



Calcium Waves, Models of, Fig. 5 The wave speed is equal to the oscillation wavelength divided by the oscillation period ($c = \lambda/\tau$). Changing the level of IP_3 alters the oscillation frequency ($1/\tau$) and alters the slope of the line. Shown are data points from simulations. Normal diffusion with $[IP_3] = 0.52 \mu M$ (red squares). No diffusion with $[IP_3] = 0.52 \mu M$ (blue diamonds). Normal diffusion with $[IP_3] = 0.26 \mu M$ (purple circles). No diffusion with $[IP_3] = 0.26 \mu M$ (green triangles). Lines represent linear curves fitted for data going through the origin. (The figure is reproduced from data in Jafri and Keizer (1994).)

Example of Deterministic Model for Ca^{2+} Waves

The Jafri-Keizer model provides an example of a computational model for calcium waves that produces fire-diffuse-fire calcium waves, phase waves, and kinematic waves. The model consists of five differential equations for the dynamic variables: cytosolic calcium concentration ($[Ca^{2+}]_{cyt}$), endoplasmic reticulum calcium concentration ($[Ca^{2+}]_{ER}$), cytosolic IP_3 concentration ($[IP_3]$), and the fraction of channels in the open and closed states of the IP_3 receptor (X_{100} and X_{101} , respectively). The dynamics of the cytosolic calcium concentration is described by the contributions of diffusion ($J_{diffusion}$), ER calcium leak (J_{leak}),

calcium release from the IP_3 receptor ($J_{release}$), and sequestration back into the ER by the ER calcium pump (J_{pump}). These fluxes are buffered by native and exogenous molecules (fluorescent indicator dyes):

$$\frac{\partial [Ca^{2+}]_{cyt}}{\partial t} = \beta_{cyt} [J_{diffusion} + J_{leak} + J_{release} - J_{pump}]. \quad (1)$$

The buffering of calcium (β_{cyt}) is described by the rapid buffering approximation (Wagner and Keizer 1994):

$$\beta_{cyt} = \left\{ 1 + \frac{[B_s]_{cyt} K_s^{cyt}}{(K_s^{cyt} + [Ca^{2+}]_{cyt})^2} + \frac{[B_m]_{cyt} K_m^{cyt}}{(K_m^{cyt} + [Ca^{2+}]_{cyt})^2} + \frac{[B_e]_{cyt} K_e^{cyt}}{(K_s^{cyt} + [Ca^{2+}]_{cyt})^2} \right\}^{-1}, \quad (2)$$

where $[B_i]_{\text{cyt}}$ is the total concentration of cytosolic calcium buffer i and K_i^{cyt} is its disassociation constant for calcium with the subscripts $i = s, m, e$ represent native stationary buffer, native mobile buffer, and exogenous buffers, respectively. The

diffusion of calcium ($J_{\text{diffusion}}$) and the contributions to calcium diffusive flux due to calcium bound to mobile buffers (native, m , and exogenous, e) are described by

$$J_{\text{diffusion}} = (D_{\text{Ca}}^{\text{cyt}} + \gamma_m^{\text{cyt}} D_m^{\text{cyt}} + \gamma_e^{\text{cyt}} D_e^{\text{cyt}}) \nabla^2 [Ca^{2+}]_{\text{cyt}} - 2 \left(\frac{\gamma_m^{\text{cyt}} D_m^{\text{cyt}}}{K_m^{\text{cyt}} + [Ca]_{\text{cyt}}} + \frac{\gamma_e^{\text{cyt}} D_e^{\text{cyt}}}{K_e^{\text{cyt}} + [Ca]_{\text{cyt}}} \right) \nabla [Ca]_{\text{cyt}} \cdot \nabla Ca_{\text{cyt}}, \quad (3)$$

where D_i^{cyt} is the diffusion constant for calcium, native mobile buffer, and exogenous buffers ($i = \text{Ca}, m, e$, respectively) and γ_i^{cyt} is ($i = m, e$, respectively)

$$\gamma_i^{\text{cyt}} = \frac{[B_i]_{\text{cyt}} K_i^{\text{cyt}}}{(K_i^{\text{cyt}} + [Ca]_{\text{cyt}})^2} \quad (4)$$

These equations are also derived from the rapid buffer approximation (Wagner and Keizer 1994).

The release of calcium from the IP_3 receptor is described by

$$J_{\text{release}} = c_1 v_1 X_{110}^3 ([Ca^{2+}]_{\text{ER}} - [Ca^{2+}]_{\text{cyt}}), \quad (5)$$

where c_1 is the ER/cytosol volume ratio and v_1 is the maximal calcium ion flux through the channel.

There is also a passive leak out of the ER given by

$$J_{\text{leak}} = c_1 v_2 ([Ca^{2+}]_{\text{ER}} - [Ca^{2+}]_{\text{cyt}}), \quad (6)$$

with maximal rate v_2 . The pump that sequesters calcium back into the ER is described by

$$J_{\text{pump}} = \frac{v_3 [Ca^{2+}]_{\text{cyt}}^2}{[Ca^{2+}]_{\text{cyt}}^2 + K_3^2}, \quad (7)$$

with v_3 being the maximal pump rate and K_3 the binding constant for calcium.

The balance equation for ER calcium mirrors that of cytosolic calcium except that the transmembrane fluxes have the opposite effect and the buffers and diffusion are those of the ER:

$$\frac{\partial [Ca^{2+}]_{\text{ER}}}{\partial t} = \beta_{\text{ER}} \left[\left(D_{\text{Ca}}^{\text{ER}} + \gamma_m^{\text{ER}} D_m^{\text{ER}} [Ca^{2+}]_{\text{ER}} - 2 \frac{\gamma_m^{\text{ER}} D_m^{\text{ER}}}{K_m^{\text{ER}} + [Ca]_{\text{ER}}} \nabla Ca_{\text{ER}} \nabla Ca_{\text{ER}} - (v_2 + v_1 X_{110}^3) \right) * ([Ca^{2+}]_{\text{ER}} - [Ca^{2+}]_{\text{cyt}}) + \frac{1}{c_1} \frac{v_3 [Ca^{2+}]_{\text{cyt}}^2}{[Ca^{2+}]_{\text{cyt}}^2 + k_3^2} \right], \quad (8)$$

where

$$\beta_{\text{ER}} = \left\{ 1 + \frac{[B_s]_{\text{ER}} K_s^{\text{ER}}}{(K_s^{\text{ER}} + [Ca^{2+}]_{\text{ER}})^2} + \frac{[B_m]_{\text{ER}} K_m^{\text{ER}}}{(K_m^{\text{ER}} + [Ca^{2+}]_{\text{ER}})^2} \right\}^{-1} \quad (9)$$

and

$$\gamma_m^{ER} = \frac{[B_m]_{ER} K_s^{ER}}{(K_m^{ER} + [Ca]_{ER})^2}. \quad (10)$$

The dynamics of IP_3 are described by

$$\begin{aligned} \frac{\partial [IP_3]}{\partial t} &= D_{IP_3} \nabla^2 [IP_3] \\ &+ I_r([IP_3] * -[IP_3]), \end{aligned} \quad (11)$$

where D_{IP_3} is the diffusion constant for IP_3 and I_r is the relaxation rate of IP_3 to its steady-state value $[IP_3]^*$. The state of the IP_3 receptor is given by

$$\begin{aligned} \frac{dX_{100}}{dt} &= -a_2 [Ca^{2+}]_{cyt} X_{100} \\ &- a_5 [Ca^{2+}]_{cyt} X_{100} + b_5 X_{110}, \end{aligned} \quad (12)$$

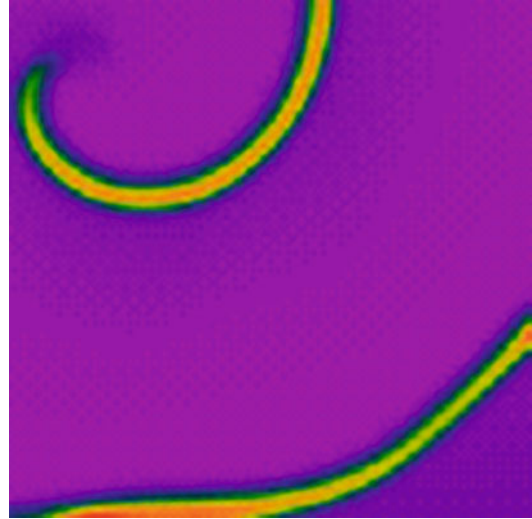
$$\begin{aligned} \frac{dX_{110}}{dt} &= -a_2 [Ca^{2+}]_{cyt} X_{110} + b_2 c_2 [IP_3] \\ &+ a_5 [Ca^{2+}]_{cyt} X_{100} + b_5 X_{110}, \end{aligned} \quad (13)$$

with the transition rate constants a_i and b_i and the proportionality constant c_2 for X_{111} (the state with IP_3 , activating and inactivating calcium bound) binding to IP_3 . The model for the IP_3 receptor was first described by DeYoung and Keizer as an eight-state system and reduced to a two-state system used here (De Young and Keizer 1992; Keizer and De Young 1994).

To demonstrate the model, a simulated spiral wave based upon this model (Jafri and Keizer 1995) is shown here (Fig. 6).

Example of a Stochastic Model for Ca^{2+} Wave

The physiological events that underlie calcium waves are the stochastic opening and closing of ion channels. Experiments have observed this stochastic behavior as calcium blips, puffs, and waves. Hence to understand the dynamics of these molecular events that underlie calcium waves, stochastic models are needed. As an example, a model of a



Calcium Waves, Models of, Fig. 6 Spiral calcium wave produced by the Jafri and Keizer model for agonist-induced calcium waves in *Xenopus laevis* oocytes (click for movie)

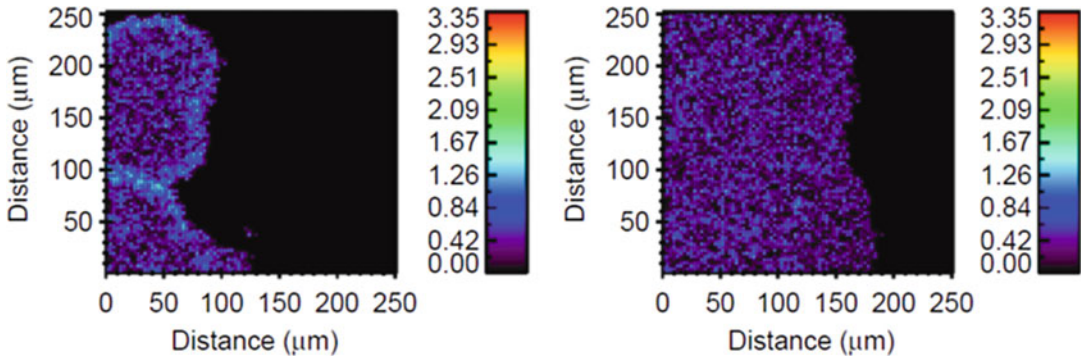
calcium wave in the mature *Xenopus laevis* oocyte is presented (Ullah 2011). For the simulation, each single IP_3 channel was modeled with four equal and independent subunits, where the kinetics of each subunit is determined by the simplified version of Sneyd and Dufour model (Sneyd and Dufour 2002). The channels were clustered into groups of 20 channels. The spatiotemporal Ca^{2+} dynamics are described by the following equation:

$$\frac{dc}{dt} = D_{cyt} \nabla^2 c + J_{cluster} \delta(\vec{x} - \vec{x}_n) - J_{serca} + J_{leak'} \quad (14)$$

$$\begin{aligned} \frac{dc_{ER}}{dt} &= D_{ER} \nabla^2 c_{ER} \\ &+ \gamma (J_{serca} - J_{cluster} \delta(\vec{x} - \vec{x}_n) - J_{leak}), \end{aligned} \quad (15)$$

$$\frac{dp}{dt} = D_p \nabla^2 p + \beta(p^* - p) + J_{stim} + J_{PLC\delta}, \quad (16)$$

where “c” is the cytosolic calcium concentration; c_{ER} denotes the concentration of calcium in the ER; D_{cyt} and D_{ER} are the effective diffusion



Calcium Waves, Models of, Fig. 7 Snapshots of Ca^{2+} wave after injecting an IP_3 stimulus. The wave propagates to the *right*; the calcium released in the cytosol provides positive feedback for the propagation of the Ca^{2+} wave across the cytosol through further activation of IP_3R . IP_3 receptors are modeled with 20 channels per cluster at a distance of $3\ \mu\text{m}$ uniformly distributed throughout the two-

dimension grid. The global Ca^{2+} wave is generated by applying an IP_3 stimulus J_{stim} in Eq. 13, along a line at the *left edge* of the grid. It activates the IP_3 receptors and initiates the Ca^{2+} wave. The IP_3 then diffuses to the cytosol, activates the internal IP_3Rs , opens up the channels, and releases more Ca^{2+} from the internal store ER to generate the self-sustaining wave

coefficients of calcium in the cytosol and in the ER, respectively; and D_p is the diffusion coefficient of IP_3 . The parameter γ denotes the ratio of the cytoplasmic volume to the ER volume and is used to account for different volumes of two compartments. The term J_{cluster} represents the Ca^{2+} of an IP_3 receptor containing a small cluster of channels. The magnitude of this flux depends on both the number of open channels within the cluster and the Ca^{2+} gradient across the ER membrane:

$$J_{\text{cluster}} = N_{\text{open}} \pi r^2 v_{\text{channel}} (c_{\text{ER}} - c), \quad (17)$$

Here r represents the channel cross-sectional radius. N_{open} is the number of open channels, and v_{channel} is the maximum Ca^{2+} flux per channel. N_{open} is obtained from the kinetics of the IP_3 receptors, which are modeled stochastically, i.e., the number of open channels is random, as each channel can open and close stochastically.

The leak term J_{leak} represents the loss of Ca^{2+} through the ER membrane, into the cytosol. Similar to the cluster's flux, the leak flux also depends on a concentration gradient, as well as v_{leak} the maximum leak conductance:

$$J_{\text{leak}} = v_{\text{leak}} (c_{\text{ER}} - c). \quad (18)$$

As cell function is highly dependent on a high Ca^{2+} gradient across the ER membrane, the

cell requires ATP-driven SERCA pumps (sacro-/endoplasmic reticulum Ca^{2+}) to be distributed across the ER membrane. The J_{serca} term in Eq. 11 represents this mechanism and follows a similar form as Eq. 7:

$$J_{\text{serca}} = v_{\text{serca}} \frac{c^2}{(k_{\text{serca}}^2 + c^2)} \quad (19)$$

Phospholipase C (PLC_δ) in the plasma membrane stimulates production of IP_3 upon increasing cytosolic Ca^{2+} levels, i.e.,

$$J_{\text{PLC}_\delta} = V_{\text{PLC}_\delta} \frac{c^2}{(k_{\text{PLC}_\delta} + c^2)}. \quad (20)$$

PLC_δ is an important signaling effector as it increases sensitivity to IP_3 and facilitates an intracellular calcium wave (Fig. 7).

Conclusions

In summary, calcium waves are ubiquitous throughout biological systems. They allow the spatial and temporal control of calcium in different parts of the cell. As calcium waves are complex nonlinear phenomena, mathematical models have played an important role in understanding their dynamics.

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Calcium-Dependent Potassium Channels

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Synonyms

BK channels (KCa1.1); SK channels (KCa2.x)

Definition

Calcium-dependent potassium channels are potassium-permeable channels whose gating is regulated by the intracellular calcium concentration. Small-conductance (10–20 pS) calcium-activated (SK) channels are purely gated by calcium, while the opening probability of large-conductance (> 100 pS) calcium-activated (BK) channels is a complex function of both membrane potential and intracellular calcium concentration (Fig. 1). Both SK and BK channels are composed of four subunits. Intermediate-conductance (IK) channels, which are not expressed in neurons, are not considered further here.

Detailed Description

Gating Properties

SK channels activate at relatively low calcium concentrations (100 nM to 1 μM , Fig. 1, left).

Their opening is regulated by the interaction between calcium ions and calcium-binding proteins (calmodulins), which are constitutively associated with each subunit. Main sources of calcium include voltage-dependent calcium (CaV) channels, NMDA receptors, and various types of intracellular stores. The time constant of SK channel activation (5–15 ms) is much faster than the calcium oscillations involved in pacemaking of most neurons. These channels can therefore be considered as rapid “calcium followers.” As a consequence, their intrinsic kinetics is generally modeled as instantaneous.

BK channels are solely active during the repolarizing phase of the action potential, because they need both a rather strong depolarization and a large calcium concentration to activate (Fig. 1, right). In addition, they deactivate very quickly. Therefore, they modulate the action potential duration and are able to generate a fast (few milliseconds) afterhyperpolarization. Because of their large hyperpolarizing effect, they are able to modulate the availability of other voltage-dependent channels. They have no significant

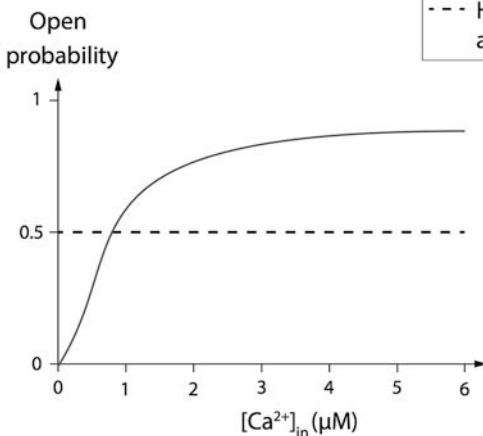
role during most of the interspike interval, contrary to SK channels.

Effect on Intrinsic Neuronal Excitability

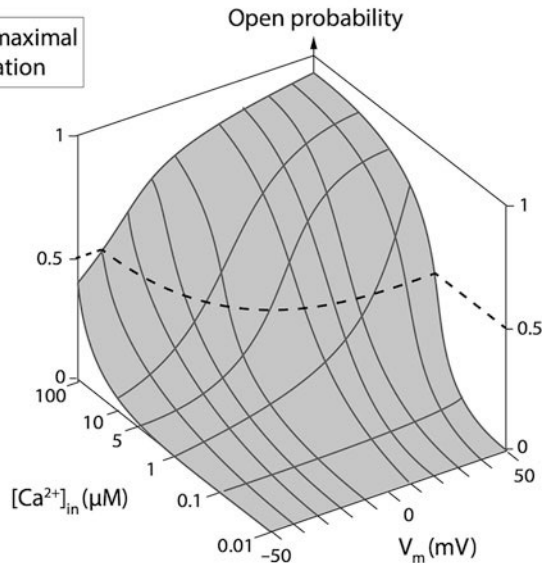
In pacemaker neurons, SK channel activation promotes regular interspike intervals (ISIs). In many cases, application of SK blockers has been shown to deregulate firing and/or induce bursting behavior, both in vitro and in vivo (see, e.g., Feng and Jaeger 2008 and Waroux et al. 2005) (Fig. 2). In these neurons, SK channels produce a large afterhyperpolarization (AHP), whose duration varies depending on the kinetics of the calcium oscillations. Because the conductance involved is rather large, the neuron is very insensitive to incoming noise during this event, preventing the generation of premature action potentials.

The importance of the regularity promoting effect of SK channels has been emphasized in the case of cerebellar Purkinje neurons. Indeed, a loss of precision of pacemaking in these cells is

SK Channels

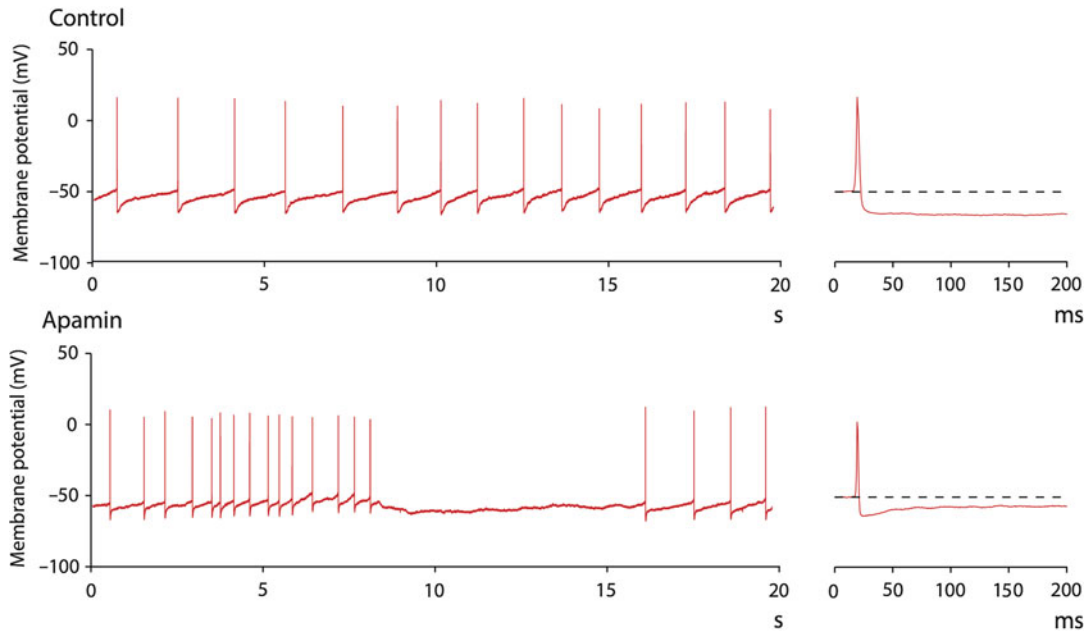


BK Channels



Calcium-Dependent Potassium Channels, Fig. 1 *Left:* Calcium-dependent activation of SK channels (Modified from Stocker 2004). *Right:* Calcium- and

voltage-dependent activation of BK channels (Modified from Blatz and Magleby 1986)



Calcium-Dependent Potassium Channels, Fig. 2 Effect of the SK channel blocker apamin on intrinsic dopamine neuron excitability (intracellular recording in a rat brain slice by J. Scuvée-Moreau)

observed in a model of a disease called episodic ataxia type 2 (Alviña and Khodakhah 2010). In the mouse model of the disease, a loss of function is observed in the CaV channels which activate SK channels of Purkinje neurons. Interestingly, regularizing the firing rate through the use of positive modulators of SK channels produces beneficial effects.

In pyramidal neurons, SK channels have been shown to at least contribute to the medium duration AHP and thereby to underlie the phenomenon known as spike frequency adaptation (Hille 2001). In other types of neurons, it has been shown that SK channels contribute to the termination of bursts, such as in Aplysia R15 neurons (Plant and Kim 1976).

BK channels operate during and immediately after the action potential. They have been shown to control action potential width (Bean 2007) and therefore to promote the ability of high-frequency firing. In particular, they prevent incremental inactivation of voltage-gated sodium channels. This action is also performed by other potassium channels (e.g., Kv3) in some neurons. As pointed out

by Bean, the strong repolarizing effect of BK channels explains the counterintuitive observation of a broadening of action potentials during blockade of some CaV channels. In addition, their progressive inactivation may contribute to frequency-dependent broadening of action potentials.

Effect on Synaptic Transmission

Some studies have found evidence for the presence of some SK channel subtypes in axon terminals, but there is scarce information on their physiological roles at this level.

Postsynaptically, SK channels have been found on the soma and dendrites of many neurons. Three roles have been proposed for them: first, they may be in close contact with NMDA receptors on spines of pyramidal neurons. In this case, they may produce a negative feedback in the sense that their activation by calcium influx through NMDA channels will provide a local hyperpolarizing drive that will inhibit further NMDA

receptor activation. Thus, their activation will decrease the likelihood of NMDA-dependent long-term potentiation (Adelman et al. 2011). Second, SK channels have also been reported to contribute to dendritic integration in pyramidal-type neurons. More precisely, they seem to contribute to the repolarization of plateau potentials induced by glutamate. Third, they have been shown to underlie a slow inhibitory postsynaptic potential following activation of Gq-coupled metabotropic receptors, synthesis of inositol triphosphate, and ensuing release of intracellular calcium.

BK channels are present in presynaptic terminals of several types of neurons. By modulating the action potential width, they may have a major effect on the amount of released neurotransmitter.

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Calmodulin, Models of

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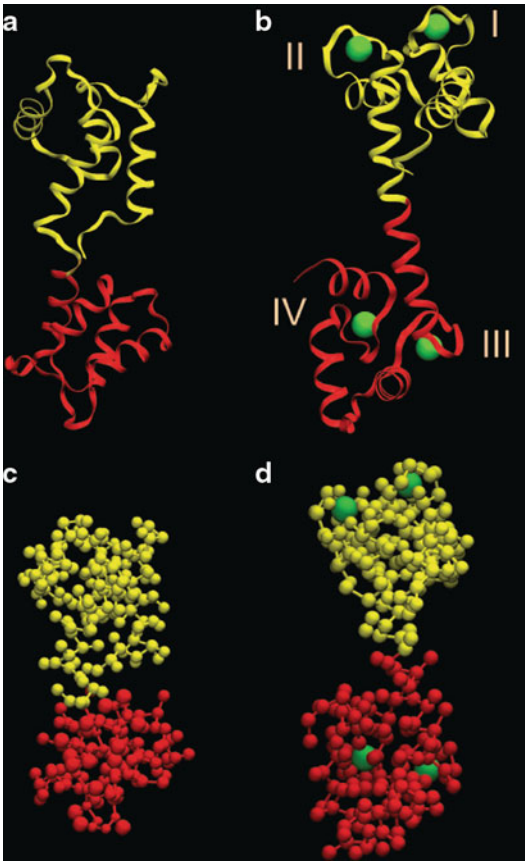
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Definition

Calmodulin (CaM) is a small (148 amino acid) ubiquitous protein responsible for decoding oscillatory changes in intracellular calcium and transducing the signal to downstream targets. Four separate calcium (Ca^{2+})-binding sites are distributed into two globular domains (the N- and C-lobes) tethered together by a linker whose structural flexibility is essential for interactions with its multiple target proteins. So, despite its small size, there are significant complexities in building quantitative mathematical models to accommodate the multitude of different structural (liganded) states that ultimately dictate CaM's functions. Detailed molecular modeling is beginning to advance our understanding for how this single protein can interact with several unique target proteins in both Ca^{2+} -bound (holoCaM) and Ca^{2+} -free (apoCaM) states.

Detailed Description

CaM is typically described as a dumbbell-shaped protein with two globular domains connected through a central helix (Crivici and Ikura 1995). Each globular domain contains two EF hand Ca^{2+} -binding sites, and the affinity of each site for Ca^{2+} and their binding kinetics is fairly well characterized (Linse et al. 1991; Bayley et al. 1996; Gaertner et al. 2004; Putkey et al. 2008; Faas et al. 2011). The N-domain sites are labeled 1 and 2 and those in the C-domain are labeled 3 and 4 (Fig. 1), and the experimentally determined macroscopic binding constants can be found in Table 1. Ca^{2+} binding between site



Calmodulin, Models of, Fig. 1 Structures of CaM in the absence (a and c) and presence (b and d) of Ca²⁺. The N- and C-terminus of CaM are colored in yellow and red, respectively, and Ca²⁺ ions are represented by green spheres. Ribbon representations of apoCaM and holoCaM are shown in (a) and (b) and the C_α side-chain representations of the same structures are shown in (c) and (d).

Calmodulin, Models of, Table 1 Ca²⁺binding to CaM

Site	K _d (μM)	K _{off} (s ⁻¹)	K _{on} (μM ⁻¹ s ⁻¹)
1	40	20,000	500
2	2.5	3000	1200
3	12.6	5100	408
4	0.25	9.1	36.4

1 and site 2 and between site 3 and site 4 exhibits cooperativity. Under steady-state conditions, the C-lobe has a ~ 5- to six-fold greater average binding affinity for Ca²⁺ (~1.7 μM) than the N-lobe (~10 μM), indicating that the C-lobe is preferentially occupied under steady-state conditions.

However, since cellular Ca²⁺ levels are constantly fluctuating and under these rapidly varying Ca²⁺ conditions, the kinetics of association and dissociation dictate the probability of N-lobe or C-lobe saturation. The N-lobe binds Ca²⁺ quickly and releases it quickly, while the C-lobe binds and releases Ca²⁺ more slowly. In this way, the N-lobe has the capacity to respond in a switch-like manner to brief Ca²⁺ transients, while the C-lobe kinetics lead to slower activation and longer duration occupancy, loosely analogous to a capacitor. As a consequence, Ca²⁺ binding to the C-lobe of CaM is the rate-limiting step for full occupancy when starting from the apoCaM state. From the intracellular perspective, both the level of resting Ca²⁺ and the shape, amplitude, and frequency of Ca²⁺ oscillations will influence the overall Ca²⁺ occupancy of the different lobes of CaM. Different modeling strategies have been developed to address the complexities of the four separate Ca²⁺-binding sites on CaM (Holmes 2000; Keller et al. 2008; Saucerman and Bers 2008; Stefan et al. 2008; Kubota and Waxham 2010; Faas et al. 2011). Minimally these models incorporate the different K_d and on and off rates for Ca²⁺ binding to the N- and C-lobes of CaM. Coupling factors have been incorporated to accommodate the known cooperativity of Ca²⁺ binding into some models, while others employed the strategy to model each site within each domain independently with a specific on and off rate for Ca²⁺ binding.

In addition to Ca²⁺ binding, CaM can interact with hundreds of target proteins to regulate numerous biochemical, metabolic, and cellular processes (Yamniuk and Vogel 2004; Choi and Husain 2006). Some of these target proteins interact preferentially with apoCaM, while others prefer holoCaM. In both cases, the mutual interactions of specific amino acid residues in CaM and the target molecule dictate target selectivity. From the many CaM/target protein structures available, a few generalizations about binding can be made. The highly malleable structure of CaM is critical, where a helical linker connects the two lobes with notable structural flexibility (Crivici and Ikura 1995; Hoeflich and Ikura 2002; Bhattacharya et al. 2004; Slaughter et al. 2005; Homouz et al. 2009; Price et al. 2010).

Unwinding of the central helix permits the N- and C-lobes to adjust their orientation and relative distance to each other to accommodate unique structural features in the target molecules.

Computer simulations allow the investigation of CaM dynamics involving inter- and intra-domain movement in solution that is a prerequisite to model the intricacies of target interactions. Molecular dynamics simulations are typically employed to study protein dynamics at an atomic detail but are limited to time scales shorter than many biologically relevant conformational changes and by the size (number of atoms that can be simulated) of the protein of interest (Shaw et al. 2010). Therefore, it is computationally intractable to explore the extensive conformational fluctuations CaM undergoes to interact with target molecules by using all-atomistic molecular dynamics simulations. An alternative strategy is to employ a physics-based approach that utilizes low-resolution protein models to simulate the motion of CaM (and its targets). In this approach, each amino acid (except glycine) is represented by two beads: a α bead used to capture the trace of the protein backbone and a second bead that represents the size and chemical nature of the amino acid side chain (See Fig. 1). The van der Waals interaction between a pair of side-chain beads follows the Lennard-Jones potential, and their strength of interaction depends on the amino acid sequence (chemical environment). The interaction between α beads captures the hydrogen bonding between the two intervening backbones. The potential for the backbone retains partial information from the experimentally determined structures. The Brownian motion of individual atoms within the model is described by the Langevin equations of motion where the effect of solvent is implicitly represented through friction and agitation:

$$m \frac{d^2 X(t)}{dt^2} = -\nabla U(X) - \gamma \frac{dX(t)}{dt} + R(t).$$

In this formula, X is the position of the beads at time t , m denotes the mass of the bead, $U(X)$ is the potential of the system, γ is the friction coefficient, and $R(t)$ is the random force caused by the agitation of solvent at a certain temperature. The trajectories

can be computed by the integration of the equations of motion. This coarse-grained molecular simulation can be employed to efficiently explore a wide range of structures in solution while still preserving information of protein conformation pertinent to a global minimum on the folding energy landscape. This level of detail is indispensable to capture the conformational fluctuations employed by CaM as it searches for binding to individual targets.

The modeling strategy is further expanded with quantum chemistry calculations to capture the charge distribution of residues in the Ca^{2+} -bound state of CaM (holoCaM) (Wang et al. 2011). Additionally, computations can be made of the electrostatic interactions between charged residues modulated by the ionic strength in solution. The electrostatic interaction V_{ij} is represented by a Debye-Hückel (Debye and Hückel 1923) term in the potential of the system:

$$V_{ij} = \frac{z_i z_j}{4\pi r \epsilon_0 \epsilon_r} e^{-r} / \sqrt{\epsilon_r \epsilon_0 k_B T / 2eI}.$$

Z_i (Z_j) is the partial charge on each bead i (j), r is the separation between beads i and j , ϵ_0 is the permittivity of free space, ϵ_r is the relative dielectric constant, k_B is the Boltzmann constant, T is the temperature, e is the charge of an electron, and I is the ionic strength of the aqueous solution. In employing such simulations, it was shown that at higher ionic strength electrostatic repulsions are screened which results in stability increases and a more extended conformation of CaM. In this situation, CaM would more likely bind to target molecules that favor the extended conformation, a determinant in the process of ultimately dictating target selectivity.

Because of the computational efficiency of this strategy, it is also possible to address issues such as how the effect of excluded volume of surrounding macromolecules (Minton 1981) would impact the distribution of CaM conformations. As one example, incorporating Ficoll 70, an inert, nonpolar polymer, into the simulation environment can simulate macromolecular crowding. In this example, a simple hard-sphere model of Ficoll 70 (impenetrable hard spheres with a radius of 55 Å) is utilized to reduce the computational

demand while efficiently retaining its excluded volume effect. Coarse-grained molecular simulations showed that, at levels of crowding comparable to those predicted inside cells, apoCaM favors a more compact conformation and as a consequence would favor binding to targets where CaM must adopt a more compact form (Homouz et al. 2009).

Based on a combined approach of coarse-grained molecular simulations, energy landscape theory, and experiments, it will be possible to determine the number and probability distribution of unique conformations that will dictate how CaM chooses to distribute among the many possible intracellular targets. Ultimately, multi-scale computational models will be needed that can combine the oscillatory nature of the Ca^{2+} fluctuations and subsequent binding to CaM with the molecular level simulations of CaM and target protein structural fluctuations.

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Capacitance, Membrane

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Definition

The membrane capacitance results from the fact that the plasma membrane acts as a capacitor: the

phospholipid bilayer is a thin insulator separating two electrolytic media, the extracellular space and the cytoplasm. The membrane capacitance is proportional to the cell surface area and, together with the membrane resistance, determines the membrane time constant which dictates how fast the cell membrane potential responds to the flow of ion channel currents.

Detailed Description

Membrane capacitance is the electrical capacitance associated with a biological membrane, expressed in units of Farads (F). The electrical capacitance of a biological membrane results from the membrane composition of a bilayer of mostly phospholipids that form an insulating matrix to which proteins are attached or embedded. The total membrane capacitance c_m of a cell is a quantity directly proportional to the membrane surface area and the dielectric properties of the membrane, provided that the thickness of the membrane is constant. Thus, the total membrane capacitance is $c_m = C_m A$, where C_m is the specific membrane capacitance (typically expressed in units of $\mu\text{F}/\text{cm}^2$) and A is the area.

Because of its linear relationship with cell surface area, capacitance is often measured experimentally as a way of determining cell area and thus cell size if the cell geometry is simple, for example, spherical or cylindrical (Streit and Lux 1987), or changes in membrane surface area (Neher and Marty 1982). These changes can be global or local, for example, when cells grow dendritic branches or add or remove membrane due to endocytosis or exocytosis at a synapse. Cell capacitance may also change due to local membrane thickness variations at lipid rafts, which are $\sim 10\%$ thicker than non-raft membranes (Alberts et al. 2008).

Because membrane capacitance determines the time constant of a neuron ($\tau_m = r_m c_m$), it plays an important role in the integration of the electrical inputs a neuron receives. It also determines the propagation velocity of action potentials which is inversely proportional to c_m (Matsumoto and Tasaki 1977). Finally, cell capacitance is a crucial parameter in detailed conductance-based

computational models, which are widely used to understand the activity and output of complex neuronal systems (Koch 1999).

To determine the exact surface area of a cell, a precise value of the specific membrane capacitance is required. A number of different methods can be used to determine the exact capacitance value, but in such calculations the fact that cell membrane surface – particularly in neurons – is rarely restricted to simple shapes should always be considered. In fact, the area of neurons is almost always distributed over surfaces that are intricate and complex, which affects the accuracy of capacitance measurements.

Measurement of Membrane Capacitance

A capacitor accumulates charge proportional to the voltage across it:

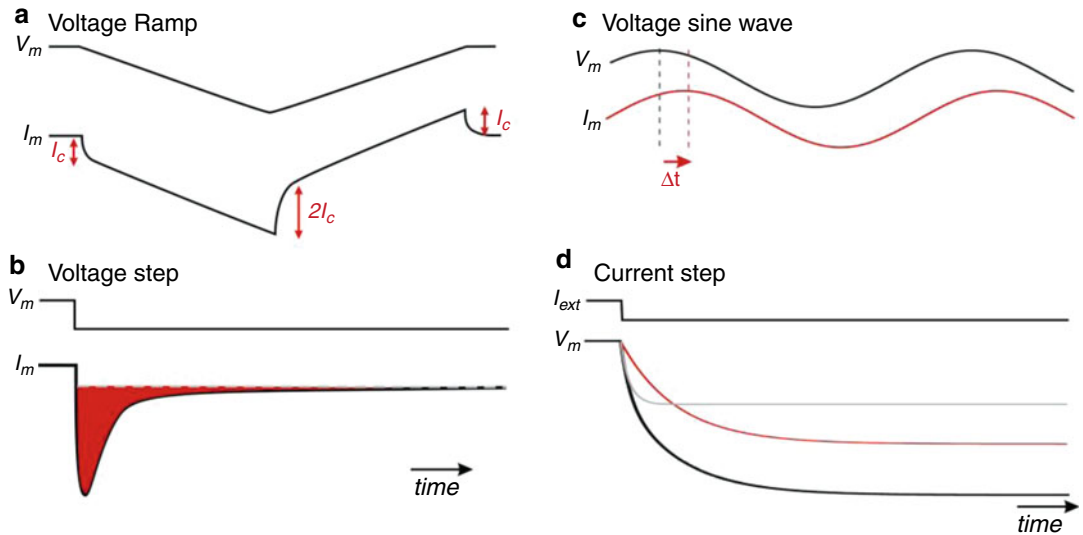
$$Q = c \cdot \Delta V \quad (1)$$

The rate of change of the capacitive charge is the capacitive current:

$$\left[I_c = \frac{dQ}{dt} = c \frac{dV}{dt} \right] \quad (2)$$

From this basic concept, several time-domain methods have been derived to measure the capacitance of a neuron, which essentially measure I_c under voltage clamp conditions.

1. Voltage ramp method. If a voltage ramp with slope dV/dt is applied to a capacitor in parallel with a resistor (an RC circuit), the current response generated includes a step whose amplitude is equal to the capacitive current I_c (Fig. 1a, red), followed by a ramp proportional to the conductance ($1/R$) of the circuit (Fig. 1a). From eq. 2, c can then be calculated.
2. Voltage step method. If a brief voltage step is applied, an initial current transient will be generated which is primarily the current that charges the capacitor (Fig. 1b). By integrating the area under the curve of this transient current ($\int I_c dt$, Fig. 1b, red), the charge Q can be measured and then used to determine c from Eq. 1.



Capacitance, Membrane, Fig. 1 *Capacitance measurement protocols. Top traces show stimulation waveform. (a–c), voltage clamp protocols. (d), current clamp protocol. Time scales for the different protocols differ, with (a) and*

(d) typically being slower (seconds) than (b) and (c) (tens to hundreds of milliseconds). Red indicates the response element relevant for the measurement of capacitance

3. Voltage sine wave method. If a sinusoidal voltage waveform is applied to an RC circuit, the current response will also be sinusoidal but shifted relative to the voltage input by a constant time (Δt , Fig. 1c, red). The resulting phase change is related to the capacitance of the circuit (Neef et al. 2007). Lock-in amplifiers in combination with voltage clamp devices generate outputs that are proportional to both impedance and phase, and thus capacitance can be determined (Neher and Marty 1982; Neef et al. 2007).

All voltage clamp methods give accurate measurements of capacitance in cells that are electrically compact (isopotential) and therefore can be described as single-compartment RC circuits. This is the case for many cell types, but is almost never true for neurons whose extensive processes (dendrites and axon) render them non-isopotential. For non-isopotential cells all these methods are inaccurate. Intuitively, the reason for this inaccuracy is that, at locations distal from the point of current injection (i.e., the site of electrode impalement), the membrane voltage decays along the processes relative to the

command voltage. The inability to maintain a constant voltage throughout the cell is referred to as the space clamp problem.

As an example, for a simple cell that can be represented by two compartments, one near and one far from the point of current injection, connected by a resistor, r_a , the total capacitance measured with voltage clamp methods can be approximated by

$$\left[c_m = c_n + c_f \frac{1}{(1 + r_a/r_f)^2} \right] \quad (3)$$

where c_n is the capacitance of the compartment near the point of current injection and c_f and r_f are the distal compartment capacitance and membrane resistance, respectively (Golowasch et al. 2009). Thus, the farther the distal compartment, and the lower its membrane resistance, the bigger the error in total capacitance. For cells with more complex morphological structure than two connected compartments, the measured capacitance deviates from the approximation given by Eq. 3. An estimate of the capacitance measured in voltage clamp in cells of more complex morphology is provided by Taylor (2012).

Current clamp method. A much more accurate method for measuring capacitance is current clamp pulses. It is appropriate even for cells that have their capacitance distributed over several distal compartments (Golowasch et al. 2009). The principle behind this method is that during a current pulse currents rapidly flow axially along the different cable-like structures of a cell and “equalize” the voltage. These currents generate voltage changes that can be described by multiple exponential terms with short time constants (Rall 1977; Holmes et al. 1992). Meanwhile, the membrane is slowly charged homogeneously over the entire surface of the cell, a process that can be characterized by an additional exponential change of the membrane potential, which has the slowest time constant of all the exponential terms. Thus, the membrane potential V_m can be described as a sum of exponential terms plus the resting potential V_{rest} :

$$V_m(t) = V_{rest} + \sum_{i=0}^{\infty} V_i \left(1 - e^{-t/\tau_i}\right) \quad (4)$$

By dividing Eq. 4 through by the external current I_{ext} , one obtains a series of resistive terms $R_i = V_i/I_{ext}$. The time constant of the slowest exponential term τ_0 is equal to the product $\tau_m = r_m c_m$, and r_m can be determined as the resistive component of the slowest exponential term (R_0), and $c_m = \tau_m/r_m$ (Golowasch et al. 2009).

All these methods rely on manipulating voltage in a range where only passive properties of the cell are involved. Any activation of voltage-gated currents will introduce significant errors in the capacitance estimate (Golowasch et al. 2009; White and Hooper 2013).

Specific Membrane Capacitance

The value most used is $1 \mu\text{F}/\text{cm}^2$, which most likely stems from the first measurements ever made in the famous series of experiments of Hodgkin, Huxley, and Katz published in 1952 (Hodgkin and Huxley 1952; Hodgkin et al. 1952). They in fact measured values over a range of 0.8 and $1.5 \mu\text{F}/\text{cm}^2$, with a mean of 0.9

$\mu\text{F}/\text{cm}^2$ (Hodgkin et al. 1952), but then used $1 \mu\text{F}/\text{cm}^2$ to simplify the complex calculation used for their final and seminal paper (Hodgkin and Huxley 1952). Later on it was shown that most cells do not have a smooth membrane whose area can be measured optically by making a simplifying geometric assumption (e.g., a perfect cylinder or a perfect sphere). Instead, most cell membranes have a certain degree of rugosity (lack of smoothness), which could lead to an overestimate of the specific membrane capacitance value. Using an inflation method in the whole-cell patch clamp configuration, Solsona and collaborators (Solsona et al. 1998) determined the specific membrane capacitance value to be closer to $0.5 \mu\text{F}/\text{cm}^2$. Furthermore, it has been established that cell capacitance does not significantly vary as a function of ion channel density (Gentet et al. 2000), and the value of $0.5 \mu\text{F}/\text{cm}^2$ obtained from inflated cells is close to that measured in artificial lipid bilayers although this value also depends on lipid composition (Niles et al. 1988).

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Cardiac Excitable Tissue Pathology (Ion Channels)

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Definition

The generation of the heartbeat is generated by cellular level electrical activity in the form of action potentials that arises as a result of timed opening

and closing of a variety of cardiac ion channels. When this tightly coupled interplay of ion channels is perturbed by any number of varied mechanisms including, but not limited to, genetic perturbations, altered Ca^{2+} signaling, deranged subcellular signaling, disruptions in cell ultrastructure or coupling, ionic dysregulation, or direct insult, an arrhythmogenic substrate can develop.

Detailed Description

Ionic Mechanisms of Cardiac Action Potential

Action potentials can be divided into non-contractile pacemaker cells and contractile cells that require an external stimulus, such as atrial and ventricular cells (Demir 2004). Numerous action potential morphologies exist and vary depending on the location in the myocardium. The action potential of contractile cells generally has 4 phases. Phase 0 is the rapid depolarizing phase resulting from fast Na^+ channel activation that causes rapid depolarization of the cell membrane potential. Phase 1 occurs when Na^+ channel inactivate, and K^+ ions pass outward through I_{to} (transient outward currents, which underly the notch found in some ventricular cell types). Phase 2 is marked by a phase of high resistance corresponding to the action potential plateau that is maintained by inward T-type and L-type Ca^{2+} currents and outward delayed rectifier K^+ currents. This critical phase permits the phenomenon of Ca^{2+} -induced Ca^{2+} release that couples electrical activity to cardiac contraction. Phase 3 is marked by inactivation of Ca^{2+} currents and larger K^+ currents that bring on the final repolarization phase of the action potential, allowing the cell to return to its resting potential in phase 4.

Perturbations in Ion Channels and Associated Processes Cause Disease

A wealth of basic scientific investigations have revealed that aberrant ion channel gating can result from naturally occurring mutations in the genes encoding cardiac ion channels leading to cardiac arrhythmias (Noble and Rudy 2001;

Priori et al. 1999a, b). Importantly, ion channels also interact with, and are regulated by, accessory proteins that dynamically influence the action potential. Many such examples of indirect perturbations underlying disease exist over the wide range of cardiac ion channels. Since they cannot all be covered in this brief overview, we will describe some perturbations affecting cardiac Na^+ current mutations as paradigms for the types of perturbations that have been linked to cardiac electrophysiologic pathology.

Since 1995 (Bennett et al. 1995), more than 200 mutations have been linked to SCN5A, the gene encoding the cardiac Na^+ channel α subunit on chromosome 3p21 (Wang et al. 1995). Initially segregated into distinct disease phenotypes such as long-QT3 syndrome (LQT3), Brugada syndrome (BrS), progressive cardiac conduction defect (PCCD), sick sinus syndrome (SSS), atrial fibrillation, and dilated cardiomyopathy (DCM), it is now known that multiple genetic defects can lead to overlapping syndromes with multiple clinical characteristics existing in one patient (Ruan et al. 2009).

LQT3 is a subset of the congenital long QT syndrome and is characterized by a delay in cardiac cellular repolarization, leading to cardiac arrhythmias and sudden death, often in young people. It has been proposed that delayed ventricular repolarization promotes a substrate for triggered activity via early afterdepolarizations (EADs), which result from reactivation of L-type Ca^{2+} channels (Thomas et al. 2007; Viswanathan and Rudy 1999; Lankipalli et al. 2005).

The first identified mutation in SCN5A, consequently shown to be a LQT3 variant, was ΔKPQ , a 3 amino acid deletion (lysine, proline, glutamine at positions 1505–1507) in the linker region between domains III and IV (Bennett et al. 1995). This motif is known to be critical for fast inactivation of the Na^+ channel, and this mutation results in persistent non-inactivating current (Bennett et al. 1995) (termed channel “bursting”) during normal cellular repolarization.

While the ΔKPQ mutation is one example of altered gating, evidence suggests that mutation-induced gain of function in cardiac I_{Na} can exist in at least three distinct forms. In addition to channel

bursting, a second abnormality in Na^+ channel gating that has been elucidated and linked to phenotype results from steady-state channel reopening called window current (Ruan et al. 2009; Wang et al. 1996). Window currents arise as a result of reopenings that occur over voltage ranges where steady-state inactivation and activation overlap. A third original mechanism was demonstrated in channels containing the I1768V mutation, which does not result in an obvious gain of channel function. However, experiments and mathematical simulations revealed that under nonequilibrium conditions during repolarization, channel reopening results from faster recovery from inactivation at membrane potentials that facilitate the activation transition (Clancy et al. 2003).

In each of these mechanisms, pathologic late Na^+ current due to channel reopening causes severe prolongation of the AP plateau (demonstrated on the body surface ECG as QT interval prolongation) and sets the stage for potentially deadly arrhythmic triggers (Clancy et al. 2003).

In contrast to LQTS-associated mutations that cause a gain of Na^+ channel function, mutations that have been identified in patients with congenital forms of Brugada syndrome (BrS) result in a loss of Na^+ channel function (Tateyama et al. 2004; Vecchietti et al. 2007; Liu et al. 2002). BrS is an arrhythmic syndrome characterized by right bundle branch block, ST-segment elevation on the ECG, and ventricular tachyarrhythmias that result in sudden death (Brugada et al. 1998). The reduction in I_{Na} has been shown to occur by several mechanisms in BrS, including reduced rates of recovery from inactivation, faster inactivation subsequent to channel opening, and protein trafficking defects (Clancy and Kass 2002; Grant et al. 2002; Tan et al. 2001; Bebarova et al. 2008).

BrS may result in heterogeneity of repolarization across the right ventricular myocardial wall. Repolarization in the epicardial cell layer is thought to be more sensitive to suppression of the peak Na^+ current due to a more prominent transient outward K^+ current (I_{to}) (Yan and Antzelevitch 1999). Mutations in SCN5A that reduce the peak I_{Na} could selectively hasten the repolarization in the epicardium, leading to a loss of the epicardial action potential plateau phase and an increased propensity

towards reentrant arrhythmias. This theory may explain the ST-segment elevation resulting from a dispersion of action potential plateau potentials observed in patients with BrS.

Another proposed mechanism underlying the Brugada syndrome phenotype is that loss of Na^+ current, observed as a depolarizing shift of the channel activation curve, may result in sufficiently slow conduction such that some areas of the myocardium are undergoing repolarization, while others are still depolarizing (Zhang et al. 2007). Indeed, a simulation-based investigation of this mechanism was investigated and shown to be plausible and account for the observed ST-segment elevation in these patients (Zhang et al. 2007; Petiprez et al. 2008; Miyoshi et al. 2005).

Heterogeneity of Ion Channel Expression in the Heart: Dispersion of Action Potential Morphology Leading to Arrhythmia

It has been shown experimentally that the myocardium displays distinct cell types that are heterogeneous in ion channel expression across the ventricular wall. This heterogeneity plays a key role in the normal sequence of ventricular excitation and in arrhythmogenesis (Noble and Rudy 2001; Antzelevitch et al. 1999). Potassium currents (I_{Kr} and I_{Ks}) in particular, which are essential in ventricular repolarization, show marked differences in expression between endocardial, mid-myocardial, and epicardial cells (Liu and Antzelevitch 1995). Midmyocardial cells, for example, have reduced I_{Ks} density and display longer APD than other cell types, and these differences in multicellular models can give rise to transmural heterogeneity which may contribute to the arrhythmogenic potential in long-QT syndrome (Viswanathan and Rudy 1999, 2000).

Mutations Can Result in Multiple Phenotypes

The relationship between genetic mutations and clinical syndromes is complex, as the revelation of

novel mutations suggests paradoxical phenotypic overlap or exclusivity. Multiple loci in the cardiac Na^+ channel have been identified where the same mutation can result in different disease phenotypes. An insertion of an aspartic acid residue (1795insD) in the carboxy terminus of $\text{Na}_v1.5$ can result in either BrS or LQTS (Bezzina et al. 1999). Additionally, mutation of the same residue to a histidine (Y1795H) or cysteine (Y1795C) results in BrS and LQTS, respectively, indicating the proximal region of the C-terminus as a potentially important structure in sodium channel function (Roden et al. 1996). Further review can be found in Moreno and Clancy (2009).

Calcium Dynamics and its Regulation of the Na^+ Channel

The changing dynamics of calcium during the cardiac action potential is a complex and highly coupled system that includes L- and T-type Ca^{2+} currents, ryanodine receptors, $\text{Na}^+/\text{Ca}^{2+}$ exchangers and SERCA pumps, Ca^{2+} -binding proteins and buffering with calmodulin and troponin, and multiple sarcoplasmic reticulum (SR) subspaces (Rice and Jafri 2001). Each of these processes has the potential to alter electrophysiological homeostasis and lead to arrhythmia.

Ca^{2+} modulation of the Na^+ channel has been demonstrated after direct binding sites for Ca^{2+} (Wingo et al. 2004), and the Ca^{2+} -binding protein calmodulin (CaM) (Mori et al. 2000) was found on the carboxy terminus of the Na^+ channel. These discoveries led to studies that revealed inactivation of I_{Na} can be modulated by Ca^{2+} , CaM, and/or the Ca^{2+} /CaM/CaM-kinase signaling cascade (Undrovinas and Maltsev 2008; Wagner et al. 2006; Maltsev et al. 2008).

In studies examining the interaction of the Na^+ channel and I_{NaL} with CaMKII, it was found that CaMKII coimmunoprecipitates and phosphorylates Na^+ channels (Wagner et al. 2006). Overexpression of CaMKII δ_C in rabbit myocytes (acute) and transgenic mice (chronic) led to (1) enhanced I_{NaL} , (2) slowed fast inactivation (but enhanced intermediate inactivation), (3) slowed recovery from inactivation, (4) shifted

steady-state availability in hyperpolarizing direction that was Ca^{2+} dependent, and (5) a rise in intracellular Na (Undrovinas and Maltsev 2008; Wagner et al. 2006); importantly, these results were reversible with CaMKII inhibition (acute only). Interestingly, Bers and Grandi (2009) note the striking similarity of these CaMKII-induced changes with the LQT3- and Brugada-linked mutant 1795insD (Bezzina et al. 1999). Maltsev and Undrovinas (Maltsev et al. 2008) found that in both normal and failing canine ventricular myocytes, the Ca^{2+} /CaM/CaMKII signaling cascade increased I_{NaL} and Na^+ influx by slowing inactivation kinetics, but conversely found a positive shift in the steady-state availability curve (Undrovinas and Maltsev 2008; Maltsev et al. 2008). Evidence of CaMKII upregulation has been confirmed in other studies examining the effects of CaMKII in the heart failure setting (Ai et al. 2005; Currie et al. 2004; Kirchhefer et al. 1999).

Conclusions

Understanding how perturbations to cardiac ion channels emerge as altered behavior in higher dimensions of cardiac tissue and lead to pathophysiology including cardiac arrhythmia and heart disease is a critical area of research. The ubiquity of ion channels throughout all excitable tissue and the myriad mutations that lead to disease that have thus far been discovered have provided a tremendous substrate for a fundamental understanding of ion channel biophysics. The challenge continues to be integration of fundamental mechanisms at the ion channel scale to the complex emergent phenomena of arrhythmia in higher dimensions.

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Cardiac Excitable Tissue Pathology (Ischemia)

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Definition

Ischemia is a condition that results when tissue is inadequately perfused with blood, leading to insufficient delivery of oxygen and necessary components, as well as impaired removal of metabolic waste products. In the context of cardiac tissue, ischemia can produce derangements of electrical activity, reduced mechanical pumping ability, myocardial infarction, and sudden cardiac death.

A wealth of experimental data has been generated describing the fundamental structural and functional changes that occur in cardiac tissue during ischemia. However, it is increasingly clear that the many complex changes that occur during the time course of ischemia and their resultant effects on emergent electrical and mechanical functioning in the heart cannot be fully observed or readily predicted via study of constituent elements alone. For this reason, a number of modeling and simulation studies have been undertaken to reveal fundamental biological principles and mechanisms of functional changes observed in cardiac ischemia and to predict how interactions between system components contribute to pathological electrical and mechanical changes in cardiac cells and tissue. Modeling and simulation have also been used to predict emergent disease processes and treatment effects in ischemia. At present, there is no alternative, efficient, and cost-effective experimental or clinical strategy that can achieve these goals. Enabling computationally based investigations are advances in numerical techniques and computing (Nivala et al. 2012; Abramson et al. 2010; Rocha et al. 2011; Neic et al. 2012), the implementation of customizable solvers such as Continuity (<http://www.continuity.ucsd.edu/Continuity>), modeling platforms like CHASTE and OpenCMISS

(Bernabeu et al. 2009; Bradley et al. 2011), and infrastructures aimed at facilitating standardization, interoperability, and dissemination of models (e.g., CellML and FieldML) (Bernabeu et al. 2009; Bradley et al. 2011; Christie et al. 2009; Quinn et al. 2011; Wimalaratne et al. 2009).

Detailed Description

Effects of Derangements to pH and Phosphometabolites

During ischemia, one of the initial changes in the cardiac cell is the acidification of both the intra- and extracellular compartments (Carmeliet 1999). This acidification is the result of increased proton production inside the cell as it undergoes a shift from mitochondrial to glycolytic ATP production, which is exacerbated as proton-absorbing phosphocreatine (PCr) is depleted. Some increased proton production is compensated for by the sodium-hydrogen exchanger (NHE), which moves sodium into the cell and exports protons, a process that promotes extracellular acidification. Shaw and Rudy initially developed mathematical models that incorporated electrophysiological intracellular pH modulation of membrane components to investigate pH effects on excitability of cardiac cells and tissues (Shaw and Rudy 1997a, b).

More recently, Crampin and Smith developed a computational model of cardiac acidosis that includes a dynamical model of pH regulation via inclusion of model representations of NHE as well as the sodium-bicarbonate symporter (NBC), anion exchanger (AE), and chloride-hydroxide exchanger (CHE) – all of which respond to changes in pH (Crampin and Smith 2006). The model simulations predicted effects of changes in pH on the time course of key ionic species during acidosis, including intracellular protons, sodium, and calcium. The Crampin and Smith model also incorporated dynamic models of direct and allosteric regulation of subcellular components by pH, including the sodium-calcium exchanger (NCX), sodium-potassium pump (NaK), SERCA pump, and ryanodine receptors (RyRs), which all exhibit decreased function at subnormal pH. In addition, the model integrated experimentally

observed pH-dependent changes in the conductance and/or gating kinetics of key cardiac ionic currents (e.g., I_{Na} , I_{Ca} , I_{to} , I_{Kr} , I_{Ks} , I_{K1}). This model was then used to make predictions about the effect of acidosis on electrophysiology and calcium cycling, the latter of which is a surrogate readout for excitation-contraction coupling (Crampin and Smith 2006; Crampin et al. 2006). Simulations suggested that critical to suppressed contractility are elevated sodium, inhibition of sodium-calcium exchange, and the direct interaction of protons with the contractile machinery.

A key calcium cycling component from the Crampin and Smith model, the cardiac sarcoplasmic/endoplasmic calcium (SERCA) pump, was subsequently modeled in more detail with particular inclusion of multiple phosphate species (MgATP, MgADP, and Pi) to allow detailed computational investigations on effects of altered metabolic function on the SERCA pump (Tran et al. 2009). Model predictions from this study showed that binding of MgATP had a large inhibitory effect on the maximal reverse rate of the SERCA pump. During ischemia, when ATP availability is low, reverse SERCA flux would be more prominent. This pathological effect is expected to contribute to calcium overload and resultant calcium-dependent arrhythmias observed in ischemia.

Another pH derangement in ischemic tissue is impaired proton removal that is exacerbated by the sustained presence of carbon dioxide in ischemic tissue (Carmeliet 1999). The recent modeling and simulation study by Roberts and Christini incorporated dynamic concentration changes for extracellular carbon dioxide and bicarbonate into the Crampin and Smith model (Crampin and Smith 2006) and then utilized the model to show how NHE inhibitors, which have been expected to reduce ischemia-reperfusion injury through normalization of Na homeostasis, made things worse by prolonging intracellular acidosis because of impaired proton removal. The resulting prolonged acidosis was predicted to inhibit multiple subcellular components, especially NaK (which is responsible for removing sodium), with the unintended and paradoxical consequence of perpetuating sodium overload (Roberts and Christini 2011).

Roberts and Christini also applied a comprehensive ischemia-reperfusion model that incorporates both pH- and phosphometabolite-dependent effects to dissect out specific roles for pH- or phosphometabolite-related processes in generating changes in excitability and action potential morphology that are associated with ischemia-linked development of cardiac arrhythmias (Roberts and Christini 2012). The model predictions suggested that phosphometabolites played a larger role than pH changes in persistent shortening of APD, reduction of action potential amplitude (APA), and depolarization of the resting membrane potential. Reduced phosphometabolite availability and pH recovery were predicted to affect multiple ion channels and exchangers. Some of these effects were the result of direct modulation by phosphometabolites and/or acidosis, while others resulted from elevated sodium and calcium loads during reperfusion. The results from Roberts and Christini suggested that therapies directed at increasing phosphometabolites availability during reperfusion may be more beneficial than aiding pH recovery with regard to mitigating action potential changes that increase the likelihood of reentrant arrhythmias.

Accumulation of Extracellular K

One of the hallmark indicators of ischemia in cardiac tissue is an increase in extracellular potassium that arises from impairments in cellular metabolism and predisposes the heart to lethal arrhythmias (Kleber 1983; Cascio et al. 1992). Hyperkalemia depolarizes the resting membrane potential, which reduces sodium channel availability and cell excitability. The consequent depression in upstroke velocity, coupled with decreased cellular coupling in response to low pH and ATP availability (Sugiura et al. 1990; Swietach et al. 2007), leads to a significant – and potentially proarrhythmic – reduction of tissue conduction velocity (Kagiyama et al. 1982; Carmeliet 1999).

Shaw and Rudy developed an ionic-based theoretical model of the cardiac ventricular cell to simulate conditions of acute ischemia including accumulation of extracellular potassium, acidosis,

and anoxia and to predict and examine their effects on ion concentrations, ionic currents, and the cardiac action potential (Shaw and Rudy 1997a). They used the model to predict the underlying ionic mechanisms responsible for reduced excitability and shortening of the action potential duration. Shaw and Rudy showed that extracellular potassium accumulation was the primary effector of cell excitability by depolarizing resting membrane potential and reducing sodium channel availability. Additional depression of excitability was induced by acidosis. Major changes in action potential duration were predicted by the model to be caused by anoxia-dependent opening of the ATP-sensitive potassium current ($I_{K(ATP)}$), consistent with predictions from an earlier simulation study by Ferrero Jr et al. (1996).

Potassium accumulation exhibits a multiphasic time course resulting from a presumed combination of three mechanisms that includes (1) increased K(+) efflux, (2) decreased K(+) influx, and (3) reduction in the volume of the extracellular space. Because the relative contributions of each of these mechanisms have been challenging to determine experimentally, modeling and simulation studies have been undertaken to predict how ionic mechanisms contribute to accumulation of extracellular potassium. Terkildsen et al. (2007) developed a model that was used to simulate changes in metabolite concentrations during acute global ischemia and investigate their effects in a dynamic model of cellular electrophysiology. The model incorporated a metabolically sensitive description of the Na(+)-K(+) pump and ATP-sensitive potassium current, in addition to cell volume regulation to allow a quantitative description of ischemic hyperkalemia. Simulations predicted that reduced NaK activity plays the largest role in extracellular potassium accumulation, followed by increased potassium efflux via $I_{K(ATP)}$ and a shrinking extracellular space due to cell swelling.

Reactive Oxygen Species

Reactive oxygen species (ROS) play a role in ischemic tissue pathology and result from increased production (e.g., increased free radical

generation) coupled with reduced availability of scavenging compounds (Murphy and Steenbergen 2008). ROS can damage the cell membrane via lipid peroxidation and increased leakiness and has been implicated in the collapse of mitochondrial function (Akar and O'Rourke 2011; Xie and Akar 2010; Akar et al. 2005; Aon et al. 2006, 2009). Modeling and simulation have been important tools to investigate how metabolic dysfunction that originates in the mitochondria can disrupt cardiac electrophysiology and lead to arrhythmias (Zhou and O'Rourke 2012). Zhou et al. formulated a model of the cardiac action potential in which a novel link between the membrane potential of the mitochondrial and the cellular membrane was established (Zhou et al. 2009). The model predictions suggested that effects of oxidative stress on mitochondrial membrane potential are a primary mechanism for shortening of the cellular action potential duration and suppression of cellular electrical excitability (Zhou et al. 2009).

Zhou et al. subsequently developed a reaction-diffusion mathematical model of ROS-induced ROS release in the mitochondrial network and demonstrated that such a model was sufficient to reproduce the experimentally observed emergent macroscopic properties of the mitochondrial network (Zhou et al. 2010). Model simulations were also used to confirm experimental observations that suggested depolarization waves of the mitochondrial membrane potential could arise (similar to cell membrane in cardiomyocytes) following stimulation with localized laser-flash or antioxidant depletion. Moreover, the model predicted similar sensitivity of the wave propagation rate to changes in quantities including superoxide, diffusion, production, and free radical scavenging to that observed experimentally. Finally, the model predicted novel mechanisms for synchronization of electrical activity, arising from clusters of oscillating mitochondria that entrain neighboring mitochondria.

Oxidative stress that occurs during ischemia can also result in modification of ionic components both directly and indirectly through activation of modulatory cell signaling pathways. Because these networks of interactions are

extraordinarily complicated and typically studied in isolation in experiment, computational modeling approaches have been used to predict effects of ischemia-linked oxidation on emergent properties of cardiac cells and tissues. Christensen and coauthors undertook a modeling and simulations studies that predicted effects of alterations in the cardiac Na current by oxidized calmodulin kinase II (CaMKII) (Christensen et al. 2009). The model predicted that phosphorylation of Na channels by oxidation-activated CaMKII causes a reduction in Na channel availability, a reduction in cellular excitability, and a slowing of conduction velocity of excitatory waves in tissue, increasing the likelihood of conduction block in the ischemic border zone.

Wagner et al. subsequently used a combined experimental and computational approach to probe the role for ROS-activated CaMKII effects on Na overload that is commonly observed in ischemia (Wagner et al. 2011). The model showed that although ROS-activated CaMKII effects on Na current may play a role in Na overload in the cells, the model suggested that this mechanism alone was not sufficient to account for the large increases in Na observed experimentally.

Disruption of Electrical Function and Arrhythmia Triggers

A number of modeling studies have been undertaken to better understand how single-cell electrical changes translate to tissue-level pathologies during ischemia (Shaw and Rudy 1997b; Romero et al. 2009; Rodriguez et al. 2004; Jie and Trayanova 2010). Shaw and Rudy carried out simulations in a multicellular one-dimensional ventricular fiber representation to determine mechanisms of slowed conduction and conduction failure during acute ischemia (Shaw and Rudy 1997b). They simulated conditions of elevated extracellular potassium, acidosis, and anoxia. The model predictions suggested that elevation in extracellular potassium was the major determinant of conduction, causing supernormal or depressed conduction, and was the only factor that could singularly cause conduction block when extracellular potassium varied within the

range reported for acute ischemia. This study demonstrated the potential for cardiac L-type Ca^{2+} current to support conduction of excitatory waves and defined a “safety factor” for conduction that accounts not only for various ionic currents but also the source-sink relationship in coupled tissue.

The source-sink relationship and its link to reentry vulnerability were explored in another modeling and simulation study by Romero et al. (2009). These simulations suggested that the source-sink relationship was the ultimate cause of the unidirectional conduction block that can lead to reentrant arrhythmias.

The most dangerous arrhythmias that arise during ischemia are ventricular tachycardia and fibrillation. These arrhythmias can be caused either by rapid repeated activation of an abnormal (ectopic) self-exciting region, or they can manifest as reentrant arrhythmias. During ischemia, afterdepolarizations can give rise to spontaneous excitatory waves if they excite a large enough region. Reentrant arrhythmias require such a trigger and are perpetuated by slowed conduction and unidirectional conduction block, mechanisms that have all been explored in quantitative detail using modeling and simulation approaches (Starmer 1997; Quan and Rudy 1990; Cherry et al. 2012; Jie and Trayanova 2010; Qu et al. 2006; Jie et al. 2008).

Mechanical Dysfunction

Ischemia produces profound effects on cardiac contractile function. Ischemia can produce an increase in diastolic pressure due to contracture, as well a reduction or absence of developed pressure (Allen and Orchard 1987). Mathematical models that contain explicit representations of cross-bridge formation and tension development have been used to better understand how ischemic metabolic pathology leads to impaired contractile force (Rice et al. 2008; Crampin and Smith 2006; Tran et al. 2010; Loiselle et al. 2008; Campbell et al. 2010; Ch'en et al. 1998).

Tran et al. developed a thermodynamically consistent and metabolite-sensitive model of cardiac cross-bridge cycling to explore the influence

of ischemic metabolites on force production under normal and ischemic conditions (Tran et al. 2010). The model recapitulated many of the experimentally observed effects of MgATP, MgADP, Pi, and H^+ on force development and retained the force/length/ Ca^{2+} properties of earlier models upon which the formulation is based (Rice et al. 2008; Crampin and Smith 2006; Loiselle et al. 2008; Ch'en et al. 1998). The model simulations suggested that the force-MgADP relationship (positive or negative) depends on the concentrations of the other metabolites and $[H^+]$.

During ischemia, afterdepolarizations can give rise to a spontaneous excitatory wave, and if the ectopic focus spreads to a large enough region, it can trigger a lethal arrhythmia. A three-dimensional tissue model incorporating mechanosensitive channels and regional ischemia has been used to study how mechanoelectrical feedback can trigger premature ventricular beats and have the potential to trigger reentry (Jie and Trayanova 2010; Jie et al. 2010).

Conclusions

Understanding how ischemia-induced alterations in multiple cardiac components emerge as altered behavior in higher dimensions of cardiac tissue and cause pathophysiology—including cardiac arrhythmia and mechanical dysfunction is a critical area of research. The ubiquity of pathological ischemia as a disease process affecting most excitable tissue and the myriad perturbations that occur simultaneously make this a disease that can benefit from modeling and simulations approaches to improve the fundamental understanding of the disease process and to reveal experimentally testable targets for therapy.

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continuous range, the potential set of possible behavioral options is discrete. The neuroscientific study of decision-making draws heavily on the fields of psychology, economics, statistics, and ecology. Neuroscientific approaches to decision-making aim to reveal computational principles that can be mapped onto their neurobiological implementation.

There are two dominant traditions in neuroscience and psychology to study categorical decisions: perceptual and value-based decision-making. Perceptual decision-making focuses on how accurate decisions are reached by resolving perceptual uncertainty. In value-based decision-making, the stimuli themselves are not ambiguous, rather the value or utility of different options needs to be estimated based on prior experience. In both cases, the goal is to systematically manipulate different features of the environment in order to understand how they guide behavior.

Categorical Decisions

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Definition

Categorical decision-making is the process of committing to a particular option from a discrete set of alternatives.

Detailed Description

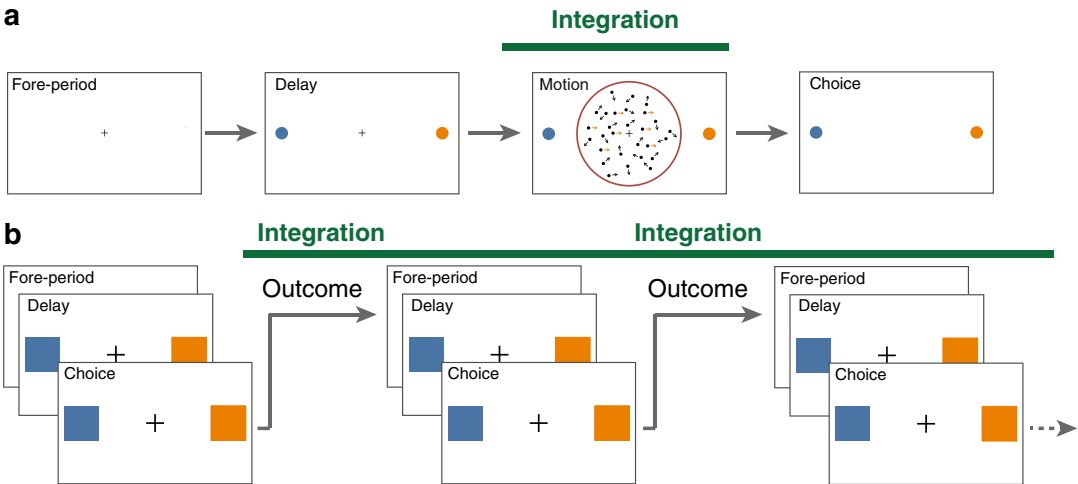
Introduction

Studies of categorical decision-making attempt to understand behavior by probing how different features of complex and changing environments guide the selection of choices. While the parameters underlying these features often span a

Behavioral Tasks for Studying Categorical Decisions

Both traditions of decision-making have extensively used two-alternative forced choice (2AFC) task designs. 2AFC is the simplest task in which the process of a decision between alternatives can be studied. In a 2AFC task, the subject is forced to make a choice between two alternatives based on the stimulus she has experienced.

An example of a widely used perceptual decision-making task is the visual random dot task (Newsome et al. 1989; Gold and Shadlen 2007). In this task an ambiguous perceptual stimulus is instantiated by a cloud of moving dots. Subjects are asked to report whether the apparent motion is to a given direction or its opposite. A random process controls the moment-to-moment movement of individual dots. The strength of apparent motion and hence stimulus discriminability are controlled by the fraction of coherently moving dots. To perform correctly on the task, subjects need to view the stimulus over some period of time to extract the direction of coherent motion.



Categorical Decisions, Fig. 1 (a) Schematic of the random dot task. Foreperiod: a fixation point appears at the center of the screen. Delay: once the subject fixates the point, the two saccade targets appear on either side of the fixation point. The trial is ready to start. Motion: the cloud of randomly moving dots appears. A subset of these dots moves coherently in the direction of one of the saccade

targets. Choice: the subject makes a saccade to one of the two targets. In this paradigm, the integration of evidence occurs during the stimulus presentation. (b) Schematic of matching task. Foreperiod and delay: same as in (a). Choice: the subject makes a saccade to one of the two targets. In this paradigm, the integration of evidence occurs by integration over the previous outcome history

An example of a value-based decision-making task is the matching paradigm in which subjects have to choose between two options that differ in the probability and size of rewards (Platt and Glimcher 1999; Sugrue et al. 2004). Both reward probability and size are set by the experimenter and change across trial blocks. Here a subject has to integrate across trials (and not across time within a trial) to infer the value of the stimuli and make the correct choice (Fig. 1).

Models of Decision-Making

Computational studies of decision-making in neuroscience often focus on algorithmic descriptions of the decision process and attempt to describe both behavior and its neural correlates.

Models of perceptual decision-making describe how ambiguous perceptual information is processed and leads to the selection of a choice. At every instant, a subject extracts some features from the stimulus that will form the evidence that guides the decision-making process. One popular class of models that have been proposed to describe how the evidence is used is based on sequential sampling

(Bogacz et al. 2006). They have been chiefly motivated by sequential probability ratio test, in which the ratio of the probability of possible alternatives is computed as evidence is accumulated. These models can be solved as a first passage time problem; a commitment to a decision occurs once the probability ratio reaches a set value. As shown in Eq. 1, the decision variable $V(t)$ is updated by integrating the momentary evidence $e(t)$. Once the decision variable reaches a set bound B , the corresponding alternative is chosen and the response is initiated (Eq. 2). More complex models have been developed taking into account physiological characteristics such as adaptation and the role of time in the decision process (Drugowitsch et al. 2012; Brunton et al. 2013).

Accumulation:

$$\frac{dV}{dt} = e(t) + \text{noise} \quad (1)$$

Decision rule:

$$V(t) \geq B \quad (2)$$

These models have been popular, as they can account for the dependence on the stimulus of

both the choice and the reaction time (t_{choice} where $V(t_{\text{choice}}) = B$). They also explain the widely observed trade-off between the speed and accuracy of decisions. A lower threshold B implies that less accumulation of evidence is necessary to commit to a decision, which leads to faster reaction times at the expense of reduced accuracy. Neural recordings have revealed evidence for the existence of such accumulators in neural circuits implicated in perceptual decision-making (Gold and Shadlen 2007).

In value-based decision-making, models have used ideas from *reinforcement learning*. In a matching task, even if a full model of the task structure is not available to the subject, a reinforcement-learning algorithm can estimate the values of the stimulus features. The value of a stimulus is the subjective utility of its outcome, which needs to be estimated based on experience. There is a large class of reinforcement-learning model, but the simplest and most often used one is *temporal difference learning* (TDRL). As shown in Eq. 3, the update rule for the value $V(T)$ of each alternative after trial T has two terms. The first is an update term that depends only on the previous outcome history. It is a *temporal discount*, proportional (with a constant γ) to the value of the previous trial $V(T - 1)$. The second term is the *prediction error* δ , which is proportional (with a constant α) to the difference between the outcome $r(T)$ and the expected outcome computed from the outcome history $V(T - 1)$. Once the value of each option is computed, the choice is made using a decision rule that optimizes the behavior according to the task contingencies. The decision rule often represents a trade-off between exploiting the currently available evidence that leads to larger reward (e.g., selecting the option with the highest value, $\text{choice} = \text{argmax}(V_i)$) and balancing exploitation with exploration using a probabilistic decision rule (e.g., selecting an option with a probability given by a softmax rule where $P_{\text{Choose } R} = e^{V_R/\beta} / (e^{V_R/\beta} + e^{V_L/\beta})$, and β controls the trade-off between exploration and exploitation, or by a relative value rule where $P_{\text{choice} = R} = (V_R / (V_R + V_L))$ (Lee et al. 2012).

TD learning:

$$V(T) = \gamma V(T - 1) + \alpha \delta(T) \quad (3)$$

$$\delta(T) = r(T) - V(T - 1) \quad (4)$$

Decision rule:

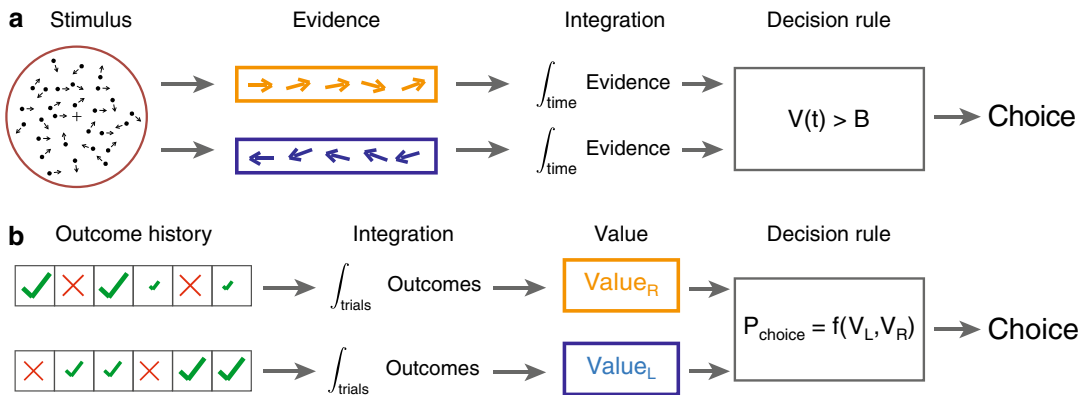
$$P_{\text{Choice} = R} = \max(V_R, V_L) \text{ or } \frac{e^{V_R/\beta}}{e^{V_R/\beta} + e^{V_L/\beta}} \text{ or } \frac{V_R}{V_R + V_L}$$

Despite its simplicity, this model is able to predict trial-to-trial variation in behavior in value-based decision-making tasks. For instance, an implementation of TDRL with the relative value decision rule ($P_{\text{Choose } R} = (V_R / (V_R + V_L))$) can account for the observation that the ratio of responses matches the ratio of inferred stimulus values (Sugrue et al. 2004). Importantly, fitting these models to behavior has enabled researchers to extract decision variables that can be mapped onto neural activity (Lee et al. 2012). For example, activity in the dopaminergic system correlates with the prediction error signal (Schultz et al. 1997), and activity in the lateral intraparietal cortex correlates with stimulus value in a matching task (Platt and Glimcher 1999; Sugrue et al. 2004).

These models describe the computations performed during the decision-making process but not their implementation at the neuronal level. Attractor networks, neural networks composed of spiking neurons connected through synapses, have been proposed as a biologically plausible implementation of these computations (Wang 2012). These neural networks implement dynamical systems on which sensory stimuli act as perturbations. Depending on their strength, these perturbations can push the network toward different attractor states leading to a categorical decision (Fig. 2).

Open Questions and Future Directions

Decisions are, given the available evidence, not always perfect. Understanding the sources of error, the sources of noise, and uncertainty in the behavior will be essential to understanding how



Categorical Decisions, Fig. 2 (a) Stimulus: the stimulus is being sampled. Evidence: the relevant parameters from the stimulus are extracted to obtain the momentary evidence at a given time. Integration: the evidence is integrated over time to obtain the decision variable. Race to bound: once the decision variable reaches a predetermined bound the corresponding action is selected. (b) Outcome

history: the subject has an internal representation of the outcome history. Integration: the outcome history is integrated over past trials to obtain a decision variable. Value computation: the value of each alternative is computed using the integrated outcome history. Decision rule: the probability of making a given choice is a function of the computed values that depends on the decision rule used

decisions are computed in the brain. In the two frameworks presented above, noise has distinct origins. In perceptual decision-making, the sensory perception itself can be noisy. In value-based decision-making, the external world environment can be stochastic, or the internal model of the task contingencies may be incorrect (Beck et al. 2012), leading to suboptimal behavior. Stochastic behavior, however, can also be advantageous in competitive environments so that competitors are not able to predict choice behavior. Understanding the contribution of different sources of noise to decisions is an exciting direction in the field.

Although reaction time is often used as a critical constraint for models of decision-making, there are multiple processes contributing to it, including non-decision time, such as the time required for movement planning. Clever behavioral manipulations can be used to separate different components of reaction time and reveal that simple discriminations can unfold in as little as 30 ms (Stanford et al. 2010).

The goal of models is to provide trial-by-trial accounts for behavioral outputs rather than just fitting averages and observed distributions of decision variables. Models, however, may be underconstrained when only using categorical choices as behavioral readouts of graded decision

variables. Additional variables, such as reaction time (Gold and Shadlen 2007), confidence report (Kepecs and Mainen 2012), or changes of mind (Resulaj et al. 2009), can be used to further constrain models. Using these variables can improve trial-by-trial fits, identify different sources of noise, and help us understand the computational processes supporting decision-making.

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Cav1.1–4 “Long-Lasting” Type (L Type)

- [High-Voltage-Activated Calcium Channels](#)

Cav2.1 “Purkinje” Type (P/Q Type)

- [High-Voltage-Activated Calcium Channels](#)

Cav2.2 “Non-L Type” (N Type)

- [High-Voltage-Activated Calcium Channels](#)

Cav2.3 “Residual” Type (R Type)

- [High-Voltage-Activated Calcium Channels](#)

Cav3

- [Low-Voltage-Activated Calcium Channels](#)

CCDB

- [Cell Centered Database](#)

Cell Centered Database

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Synonyms

CCDB

Definition

The Cell Centered Database (CCDB; <http://ccdb.ucsd.edu>) project was launched in 2002 to provide online repository of high-resolution 3D light and electron microscopic reconstructions of cells and subcellular structures (Martone et al. 2002, 2003, 2008). The CCDB was designed to complement the structural databases of gene, protein, and tissue structure by hosting data in the dimensional range known as the “mesoscale,” roughly encompassing the structures that sit between gross morphology and molecular structure, e.g., cellular networks, cellular and subcellular microdomains along with their macromolecular constituents. The study of mesoscale structures continues to present a challenge to experimentalists, because to build a comprehensive understanding of complex tissues in this dimensional range requires the ability to aggregate data obtained by multiple researchers across techniques and spatial scales.

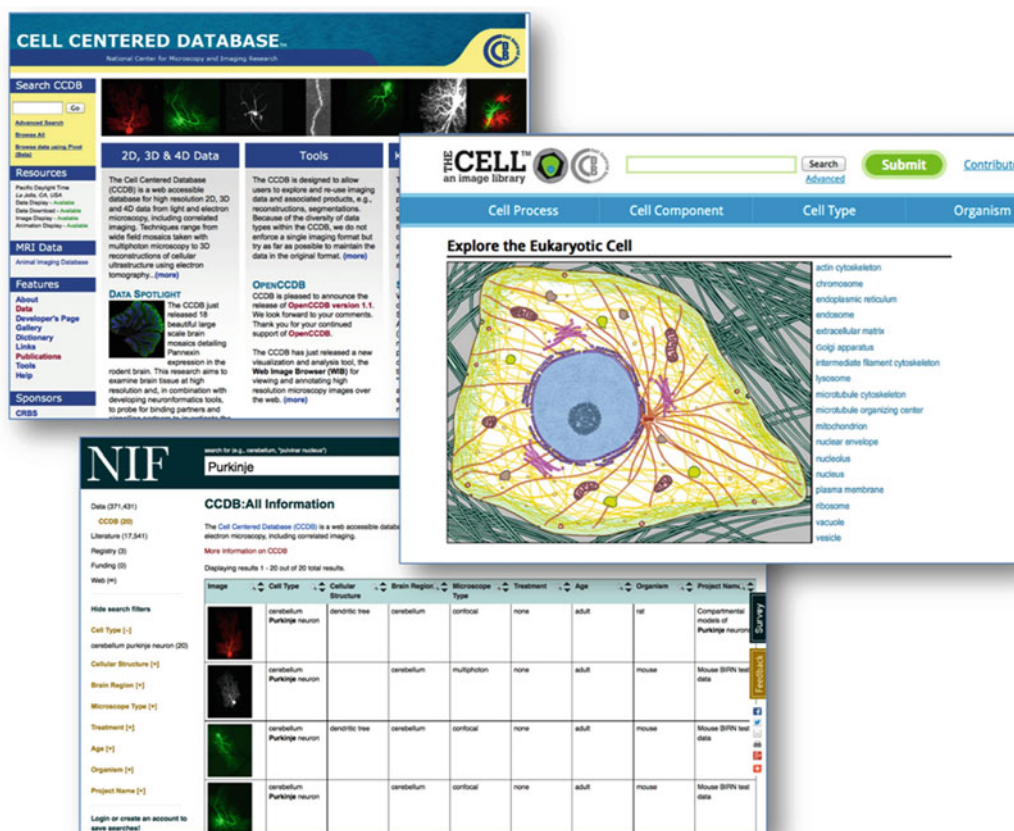
Detailed Description

The types of imaging data stored in the CCDB are quite heterogeneous, ranging from large-scale maps of protein distributions taken by confocal

(Orloff et al. 2013) microscopy to 3D reconstruction of individual cells, subcellular structures, and organelles reconstructed using electron tomography, time series of subcellular dynamics, and a growing collection of serial block face electron microscopic datasets (e.g., <http://ccdb.ucsd.edu/sand/main?mpid=8244&event=displaySum>). While many of the datasets in the current CCDB derive from the nervous system, reflecting our own area of expertise, the schema of the CCDB is essentially agnostic with regard to cell type.

From its inception, the CCDB envisioned that it would be part of a series of distributed databases that could be cross-queried and navigated and has worked actively to integrate with other relevant resources. In 2012, the CCDB joined with the Cell

Image Library (CIL: <http://cellimagelibrary.org>), developed by the American Society of Cell Biology. All public CCDB data is now available directly through the CIL and through CIL's cell-centered interface (Fig. 1), which additionally hosts over 10,000 additional images of cells and tissues. The CIL provides an easy to use graphical interface, where users can browse contents by clicking on various organelle systems in a graphic of a eukaryotic and prokaryotic cell. Datasets in the CIL are annotated with terms from 14 different ontologies in 16 different fields as well as a basic description and technical details. CCDB is also registered with the Neuroscience Information Framework (<http://neuinfo.org>) as part of its extensive data federation. Currently, the CCDB



Cell Centered Database, Fig. 1 The CCDB may be accessed through its home page (upper left), via the Cell Image Library interface (middle panel) or via the

Neuroscience Information Framework (bottom). Through CIL and NIF, CCDB data is linked to other relevant data at different scales and systems

and CIL are maintained as separate resources, but we are working to merge the front and back ends to provide a unified resource for cellular imaging data.

In addition to the public CCDB, the CCDB also maintains a private space available via the CCDB portal (<http://ccdb-portal.crbs.ucsd.edu/>). Private space is used for the data management pipeline for the National Center for Microscopy and Imaging Research (<http://ncmir.ucsd.edu>). Private space is also used for registration of datasets prior to publication. Once data are approved, they are released to the public site.

Although the predominant data type housed within the CCDB is imaging data, the CCDB

was not designed to be a simple image repository, that is, the data model is not designed for the storage of individual images. Rather, it is designed around the process of 2D, 3D, and 4D reconstruction from light or electron micrographs, capturing key steps in the process from experiment to analysis. At the center of the CCDB data model is the “microscopy product” table. The microscopy product refers to a set of related 2D images taken by light (epifluorescence, transmitted light, confocal, or multiphoton) or electron microscopy (conventional or high-voltage transmission electron microscopy). For each type, the images comprising a single microscopy product are systematically related to each other along a single

CELL CENTERED DATABASE™
National Center for Microscopy and Imaging Research

Data | Search | Gallery | Dictionary | Publications | Tools | MyCCDB | Data Download | Help

Home • Search result • nmodel • Summary Information

Data Set Information

Summary

Details

- All information
- Project
- Specimen preparation
- Microscopy product
- Imaging product type
- Specimen description
- Imaging parameters

2D image

Reconstruction

Segmentation

Map Location

Add to MyLabBench Download dataset Show project tree Show product in Pivot

Summary Information

Microscopy product ID: 8244
Image basename: nmodel

Summary

Project ID	P2023
Leader	Mark Ellisman, Stephen Larson (Other projects)
Collaborators	Sarah Maynard, Eric Bushong, Maryann Martone
Project Description	The Whole Brain Catalog™ is a ground-breaking, open-source, 3-D virtual environment developed by a team of researchers from UC San Diego under the Whole Brain Project™. The Catalog aims to connect members of the international neuroscience community to facilitate solutions for today's intractable challenges in brain research through cooperation and crowd sourcing. CCDB provides the backend services for very large scale image data sets on mouse brain derived from high resolution light and electron microscopy
Experiment Purpose	To prepare specimens with suitable contrast for whole cell reconstruction of stained cells using serial block face SEM
Species	Mouse
System	central nervous system
Organ	brain
Region	neocortex
Cell type	neocortex pyramidal neuron
Structure	
Product Type	SERIAL SECTION
Instrument	FEI Quanta 200 FEG SEM with Gatan 3 View

New Search

Search home

Keyword Go

Accession # Go

Project ID Go

If you want to search for some keywords in a detail info, page, just simply highlight the keywords, right click over the selected text and click "Search CCDB"

Browse Products

- All records ([Data statistics](#))
- Brain mosaics
- Correlated light microscopy & electron microscopy
- Electron tomography
- Filled cells
- Live imaging
- Protein localization
- Serial blockface
- View project tree structure

Cell Centered Database, Fig. 2 Organization of search results through the CCDB interface. Users are shown thumbnails for the types of data available for each

microscopy product. In this case, the 2D dataset, 3D reconstruction, and segmentation are all available

dimension. For example, a tilt series contains images that are related to each other through a tilt angle; a mosaic contains images that are related through X, Y coordinates, and optical section, through focus and serial section series contain images that are related through Z depth. A given set of data may be more than one product, for example, it is possible for a set of images to be both a mosaic and a tilt series.

Linked to each microscopy product are any reconstructions and analysis products, e.g., segmentations and models, created from either the raw data or the reconstruction. The CCDB makes the 2D image datasets, reconstructions, and segmentations available for viewing and download (Fig. 2). Because each project may have different aims, the CCDB does not require that all types of products be available for each dataset. The microscopy product identifier serves as the accession number for the CCDB. This value was chosen because a given dataset may only be taken once, and therefore, each microscopy product represents a unique dataset. In contrast, multiple reconstructions may be derived from a single microscopy product, and multiple segmentations may be derived from a single reconstruction.

The CCDB was designed with an eye towards encouraging reanalysis and reuse of mesoscale data and for mining the content of these datasets. Towards this end, the CCDB provided not only the final data product, usually a 3D reconstruction, but the raw data, specimen preparation details, the imaging parameters, and any derived data products created as a result of analysis of the reconstruction. Thus, the schema of the CCDB ensures that researchers can trace the provenance of a piece of data and understand the specimen preparation and imaging conditions that led to it while making raw and derived data available for reanalysis.

Data from the CCDB/CIL is available free of charge for browsing online and for download and reuse through a CC-BY license. Users should cite the CCDB accession number and acknowledge both the CCDB and the data contributor in any subsequent use. CCDB/CIL encourages submissions from the biological imaging community and accepts high-quality imaging data regardless of

whether they are part of a published study. Submitted data are curated and annotated by staff prior to release. If data are part of a published study, the CCDB/CIL can provide an accession number and private review space for use during the review process. Data will be released to the public upon publication.

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CellML

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Definition

CellML is a format for specifying mathematical models, focusing on the needs of systems biology, but applicable to a broader range of fields that use mathematical modeling. It focuses on models that are formulated as ordinary differential equation (ODE) systems and differential algebraic equation (DAE) systems. Please see Miller et al. [2013](#) for more details. (Note that the article mentions some of the tools that were available for working with

CellML at the time it was written. Specifically, it mentions OpenCell and COR. Since then, these two projects have been merged into a single project called OpenCOR.)

Further Reading

Miller AK, Britten RD, Lloyd CM, Nickerson DP, Nielsen PM (2013) CellML. In: Dubitzky W, Wolkenhauer O, Cho K, Yokota H (eds) *Encyclopedia of systems biology*. Springer, New York, pp 378–381

Center-Surround Modulations

► [Center-Surround Processing, Computational Role of](#)

Center-Surround Processing, Computational Role of

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Synonyms

[Center-surround modulations](#); [Contextual integration](#); [Contextual processing](#); [Nonclassical receptive fields](#)

Definition

Center-surround processing (CSP) describes the integration of localized “center” with contextual (“surround”) information into a more global representation. It has been studied mostly as a sensory computation, in particular in the early visual system (Carandini et al. 2005). Although center and surround are often defined in space, CSP is a more general processing in the sense that it is also

performed in other physical dimensions such as in the auditory domain or in time (Schwartz et al. 2007). In neuroscientific contexts, CSP is defined rather mechanistically as the difference between the processing of localized and extended stimuli. Signatures for CSP are found in many different brain areas, where the responses of neurons to a localized stimulus are strongly and often nonlinearly influenced by its context. Computationally, these processes are thought to be essential for constructing complex, global representations in higher brain areas (i.e., the perception of “objects”) from simple, local features forming the sensory input.

Detailed Description

CSP can be introduced and studied from two different perspectives:

- From neurophysiological and psychophysical evidence: Experiments reveal a rich repertoire of cases where the surround of a stimulus influences the brain’s processing of the center of a stimulus. Important examples are antagonistic (► [Retinal Neurophysiology](#)) receptive fields (► [Spectrotemporal Receptive Fields](#) ► [Receptive Field Modeling](#)) of retinal ganglion cells (► [Retinal Neurophysiology](#)) which have different polarities in center and surround (e.g., Geffen et al. 2007), non-classical receptive fields in the visual cortex (► [Hierarchical Models of the Visual System](#)) revealing strong nonlinearities in the integration of center and surround (e.g., Freeman et al. 2001), and enhanced or reduced visibilities of target stimuli induced by the presence of flanking elements in psychophysical studies (e.g., Polat et al. 1998).
- From theory and first principles: Information integration becomes necessary if “global” information is distributed over many “local” channels such that the knowledge of information in one local channel is not sufficient to recover the “global” information in an unambiguous way. CSP is a special form of information integration, with the additional

requirements that there must be some form of topology (in order to define center and surround) and that there is a limited range over which information can be integrated. This perspective on CSP is explored in normative approaches (► [Bayesian Approaches in Computational Neuroscience: Overview](#); ► [Cortical Function, Normative Models of](#); ► [Visual Illusions, Models of](#)), e.g., probabilistic modeling, with strong conceptual cross-links to Gestalt psychology (► [Visual Illusions, Models of](#)).

The definition of center and surround strongly varies among studies – it can be defined in terms of the stimulus components used in an experiment, in terms of the synaptic input fields of a neuron (or population), in terms of a cell's response properties or receptive field organization, or in terms of the modulation of the neuronal response by stimuli presented outside the receptive field (the “nonclassical receptive field”). CSP is not restricted to concentric arrangements, even if the name suggests this specific form for center-surround (CS) interactions.

The following paragraphs will explain various aspects of CSP within different concepts and theoretical approaches, in an attempt to structure research on CSP. Note that these aspects are not isolated from each other but have mutual cross-links.

From Image Processing to Object Recognition

In (applied and neural) image processing, CSP plays a fundamental role in both preprocessing and in higher-order computations performed on a visual scene. The simplest CS computations can be expressed as linear spatial filters applied to an input. For example, a Mexican hat (► [Center-Surround Processing, Network Models of](#); ► [Flicker-Induced Phosphenes](#)) filter, which can be realized as a Difference-of-Gaussians (DOG) (► [Center-Surround Processing, Network Models of](#); ► [Flicker-Induced Phosphenes](#)) M (Fig. 1a) defined as

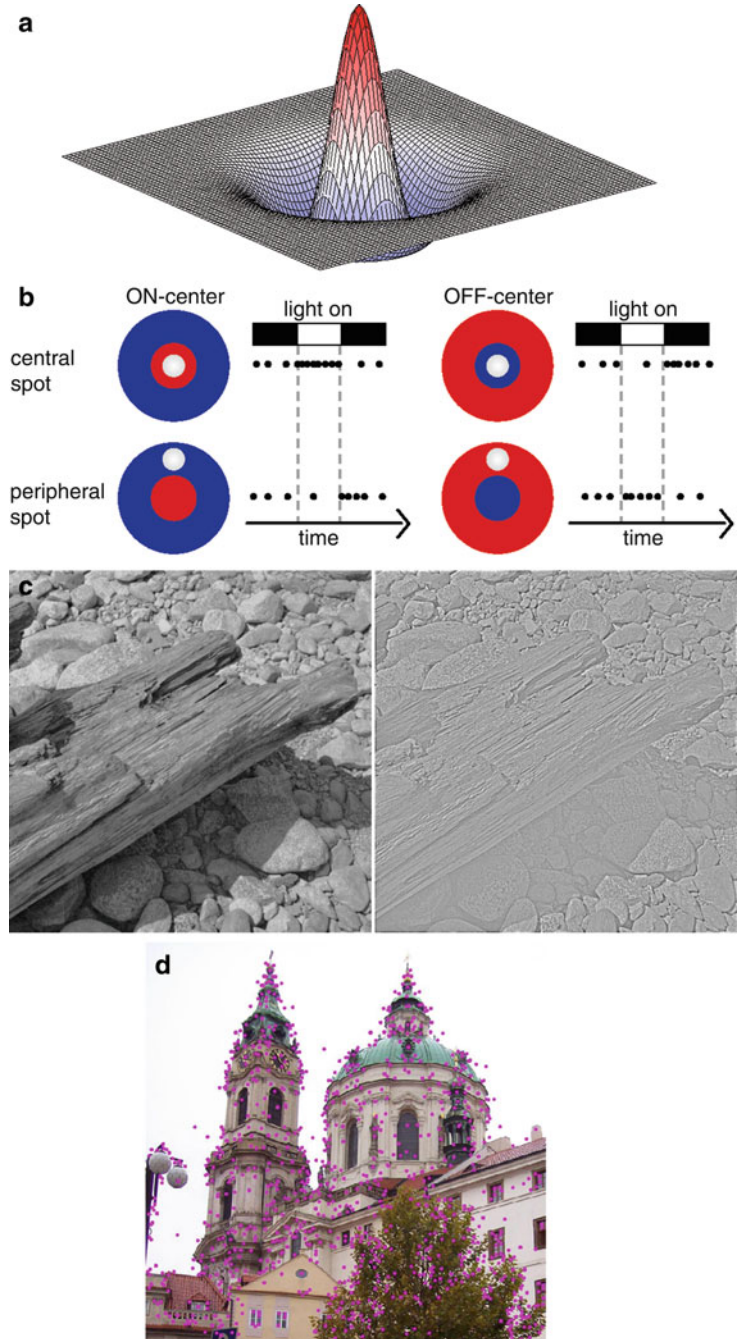
$$M(x) = A_+ \exp\left(-\frac{|x|_2}{2\sigma_+^2}\right) - A_- \exp\left(-\frac{|x|_2}{2\sigma_-^2}\right)$$

can be used for edge enhancement, data compression, decorrelation (► [Sensory Coding, Efficiency](#)), and whitening (► [Independent Component Analysis of Images](#)):

- Edge enhancement: Mexican hat with zero integral, applied to images, completely suppress regions with homogeneous content, as, e.g., uniformly painted walls or open sky. Edges or any other discontinuities, however, are enhanced by this filter (Fig. 1c). In discrete representation, the Mexican hat acts like a Laplacian operator which computes the second spatial derivative (curvature) of a two-dimensional function.
- Data compression (e.g., Zhaoping 2006): If an image is composed of many regions with homogeneous content (see paragraph above), as is typical for natural scenes, the output of a DOG filter will yield few values which are substantially different from zero, namely, at locations with discontinuities. The image representation will thus become compressed or sparsified (► [Independent Component Analysis of Images](#)) (Olshausen and Field 1996). The term sparse denotes a representation in which only few units (or neurons) are active, while all other units are (almost) silent (e.g., Rozell et al. 2008).
- Decorrelation (spatial and temporal): In most natural image ensembles the light intensities of neighboring locations are highly correlated, even over long distances. DOG filters reduce these spatial correlations as well as temporal variations in light intensities which are shared by a region of pixels in an image.
- Whitening (e.g., Graham et al. 2006): Natural images typically have power spectra exhibiting power law characteristics. DOG filters with increasing amplitudes for higher spatial frequencies can be used to decompose the image into spatial frequencies and then to selectively enhance higher-frequency image content to achieve a flat power spectrum whitening (► [Independent Component Analysis of Images](#)), Fig. 1c).

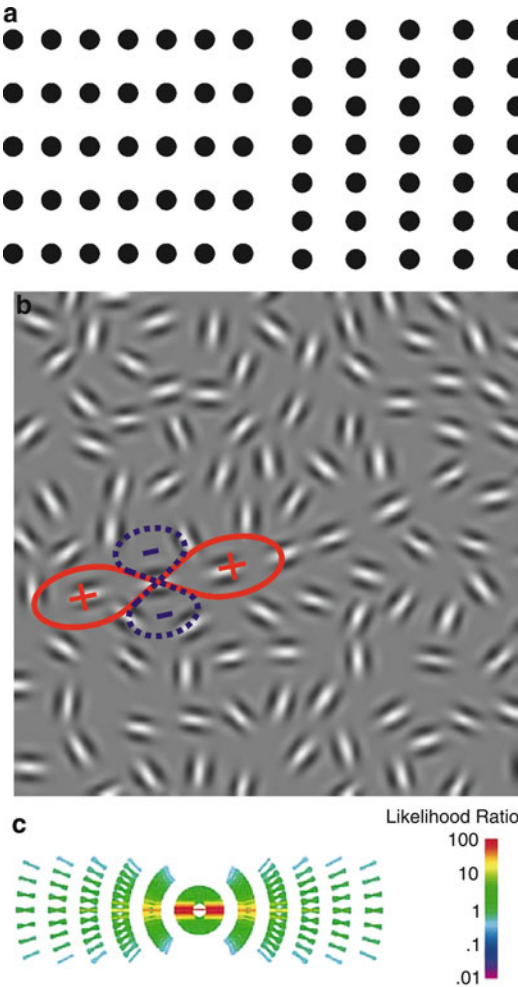
**Center-Surround Processing,
Computational Role of,**

Fig. 1 From image processing to object recognition. **(a)** Mexican hat function (difference of Gaussians) which is positive in the center (*red*) and negative in the surround (*blue*). **(b)** ON- and OFF-center receptive fields of retinal ganglion cells. Stimulating with a bright spot in the RF's center leads to an increased firing rate for the ON center and to a decreased firing rate in the OFF-center cell. Conversely, stimulating with a bright spot in the surround leads to a decreased firing rate in the ON center and to an increased firing rate in the OFF-center cell (Kretzberg and Ernst 2013) (Textbook Neurosciences, Springer 2013, Box 18.2a). **(c)** Comparison between a whitened image (*right*) to the original image (*left*). The whitened image contains far less pixel values that are different from the background level than the original image (Olshausen and Field 1996) (<http://redwood.berkeley.edu/bruno/sparsenet/>). **(d)** Example for image spots selected by the SIFT algorithm as suitable, characteristic descriptors for a visual scene (Wikipedia, accessed 6 Oct 2013, http://en.wikipedia.org/wiki/Scale-invariant_feature_transform. The image was published under the Creative Commons License)



More complex operations are achieved by non-linear CSP. Robust image processing often requires computations to be invariant against changes in illumination, spatial scale, contrast, or other properties of a scene which are unimportant for a certain (recognition) task. One example is divisive normalization (► [Color](#)

[Vision, Computational Methods for](#); ► [Computation with Population Codes](#)) or inhibition where the output of a unit processing the “center” is divided by the summed output of units processing the surround. Divisive normalization plays an important role for achieving contrast-invariance of a preceding filter operation, which is, e.g.,



Center-Surround Processing, Computational Role of, Fig. 2 Feature integration and Gestalt psychology. (a) Dot pattern visualizing the Gestalt law of proximity. In the left pattern, the horizontal spacing of the dot grid is smaller than the vertical spacing. In consequence, the dots are perceived as being grouped in horizontal lines. The effect reverses in the right pattern, where spacing in the vertical dimension is smaller. (b) Stimulus used to study contour integration (Emst et al. 2012): in a background of randomly oriented edge elements (*Gabor patches*), a horizontal contour of colinearly and cocircularly aligned edges has been embedded. Superimposed is an association field, which visualizes the typical interactions needed to integrate the local edge elements into the global percept of a contour. (c) Association field computed from natural image statistics. This association field was derived from the pairwise edge statistics of contours labeled by human observers as belonging to the same object. The color denotes the likelihood ratio of having an edge with the corresponding orientation and distance to a horizontal edge in the center of the association field which belongs to the same contour, versus the same configuration

realized in neural responses to visual input patterns.

Most applied image-processing algorithms make heavy use of CSP in a hierarchical manner. Algorithms inspired by properties of the visual system include HMAX (Riesenhuber and Poggio 1999), SIFT, and HOG (Dalal and Triggs 2005). As an example, the Scale Invariant Feature Transform (SIFT) (► [Color Vision, Computational Methods for](#)) algorithm (Fig. 1d) builds on a sequence, or chain, of center-surround operations (Lowe 2004; Lindeberg 2012). Parts of this procedure are (a) DOG filtering on different spatial scales to find the so-called keypoint candidates (i.e., characteristic points of interest in a scene), then (b) detection of corners by inspection of the keypoint candidates' surrounding regions, and finally (c) the generation of “descriptors” by computing the differences between the local orientation of the image patch at a keypoint and the orientations of the surrounding patches. These CS operations realize the computational principles of (a) scale-invariance, (b) selection of salient features, and (c) orientation-/rotation-invariance, respectively.

Feature Integration and Gestalt Psychology

In the 1920s, a group of psychologists around Max Wertheimer (*1880, +1943) expressed a set of principles (Todorovic 2007) according to which basic image features (e.g., dots, edges, lines) are grouped by our visual system to facilitate higher-order cognitive functions such as figure-ground segregation or object recognition. For example, if dots are arranged on a regular grid, and if the horizontal (vertical) distance between these dots is slightly larger than the vertical (horizontal) distance, the dots are perceived as arranged in columns (rows). This phenomenon refers to the Gestalt law of “proximity” (Fig. 2a). Gestalt laws are linked to CSP by the fact that the surround of a feature (in the

← **Center-Surround Processing, Computational Role of, Fig. 2** (continued) occurring in the plain edge statistics (Geisler et al. 2006) (Geisler, Super, Perry and Gallogly, Vision Research 41 (2001), pp 711, Figure 3f)

above example, the proximity of neighboring elements) determines how the central part of a stimulus is perceived. Also in Gestalt psychology, surround refers not only to the dimension space but also to other dimensions such as time: Elements having the same motion vector (i.e., a “common fate”) are also likely to be grouped together. In the literature, such grouping processes often run under the terms feature integration or binding (see also Herzog 2009).

While Gestalt psychologists defined criteria of feature integration mostly in an empirical way, more recent work strives to ground Gestalt principles in natural scene statistics which then implies specific forms of CSP (Geisler et al. 2001; Sigman et al. 2001; Simoncelli and Olshausen 2001). Central idea is that the laws according to which the surround of a local image patch influences its processing shall be determined by the statistical properties of objects in natural scenes (if object recognition is the ultimate goal of visual processing). A good example for the close match between Gestalt processing and natural image statistics is contour integration ► “Somatosensory Cortex: Neural Coding of Shape”. Contour integration refers to the (cognitive) process which links oriented line segments that are aligned in colinear and cocircular way (thus obeying the Gestalt law of “good continuation”) (Fig. 2b). Computationally, contour integration can be performed using an association field that quantifies which particular configurations of two oriented edges are to be linked together (Field et al. 1993). Association fields extracted from psychophysical experiments closely match the pairwise edge statistics computed from human-labeled natural scenes (Fig. 2c) (Geisler et al. 2001).

Models emerging from the feature integration perspective on CSP are predominantly “bottom-up,” seeking to implement empirically observed principles of CSP in suitable neural architectures (Li 1998), but see also Ernst et al. (2012) for a normative approach.

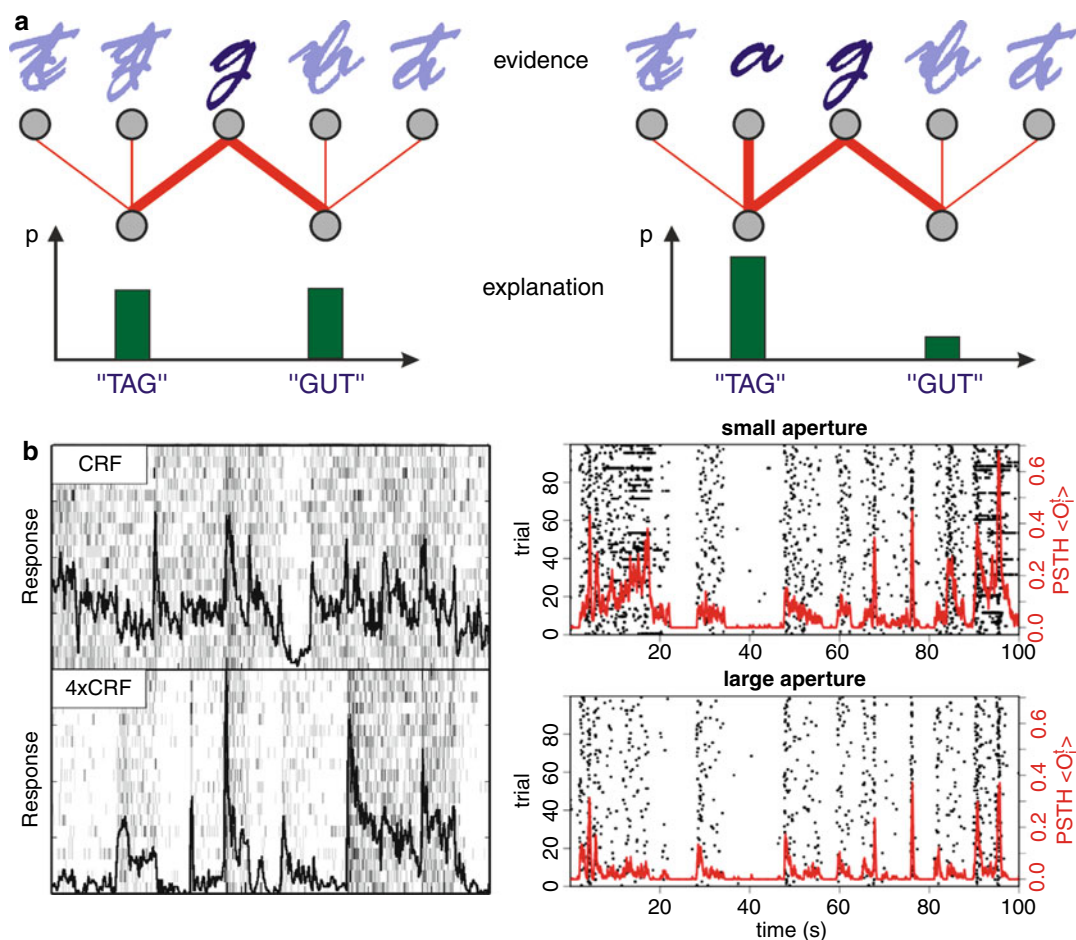
Normative and Probabilistic Approaches

A different perspective on CSP emerges from normative frameworks for understanding brain

function. They predict properties of CSP from general principles for neural computation and cognition. A prominent example for a normative framework is the hypothesis that the brain holds an internal model of the outside world (von Helmholtz 1856) which is constantly matched to the signals received by our sensory system. Such an internal model could consist of the statistical properties of objects and their composition in natural scenes which are used to infer the presence (or absence) of these objects in a stream of action potentials (► Hodgkin-Huxley Model; ► Excitability: Types I, II, and III) from the retina.

In the framework of ► Bayesian Inference with Spiking Neurons, CSP emerges as a competition between neurons with input fields that overlap in their surrounds (Fig. 3a): Both neurons would respond equally when only the optimally matching center stimuli were presented alone, giving the same evidence for two potential explanations (Fig. 3a, left). The additional appearance of a surrounding stimulus would disambiguate the situation by giving more evidence for the first of the two explanations (Fig. 3a, right). In consequence, the responses will become modulated accordingly – the second explanation is made less probable and thus “explained away,” and the first explanation becomes more likely. This effect can account for a range of experimentally observed CS modulations.

While the objective of Bayesian frameworks is to perform statistical inference as best as possible, other objectives as, e.g., the goal to obtain a “sparse” representation also imply specific forms of CSP. In neurophysiological contexts, a sparse representation is beneficial to reduce the number of action potentials transmitted and thus energy consumption. On a conceptual level, sparsity is a suitable constraint for situations in which a scene that is represented by a flood of signals on the sensory levels can be equally well described by the presence of typically only a small number of objects efficient coding (► Efficient Population Coding) (Fig. 3b). Interestingly, requiring a sparse representation and performing optimal inference lead to similar dynamics in CSP (Lochmann et al. 2012; Zhu and Rozell 2013).

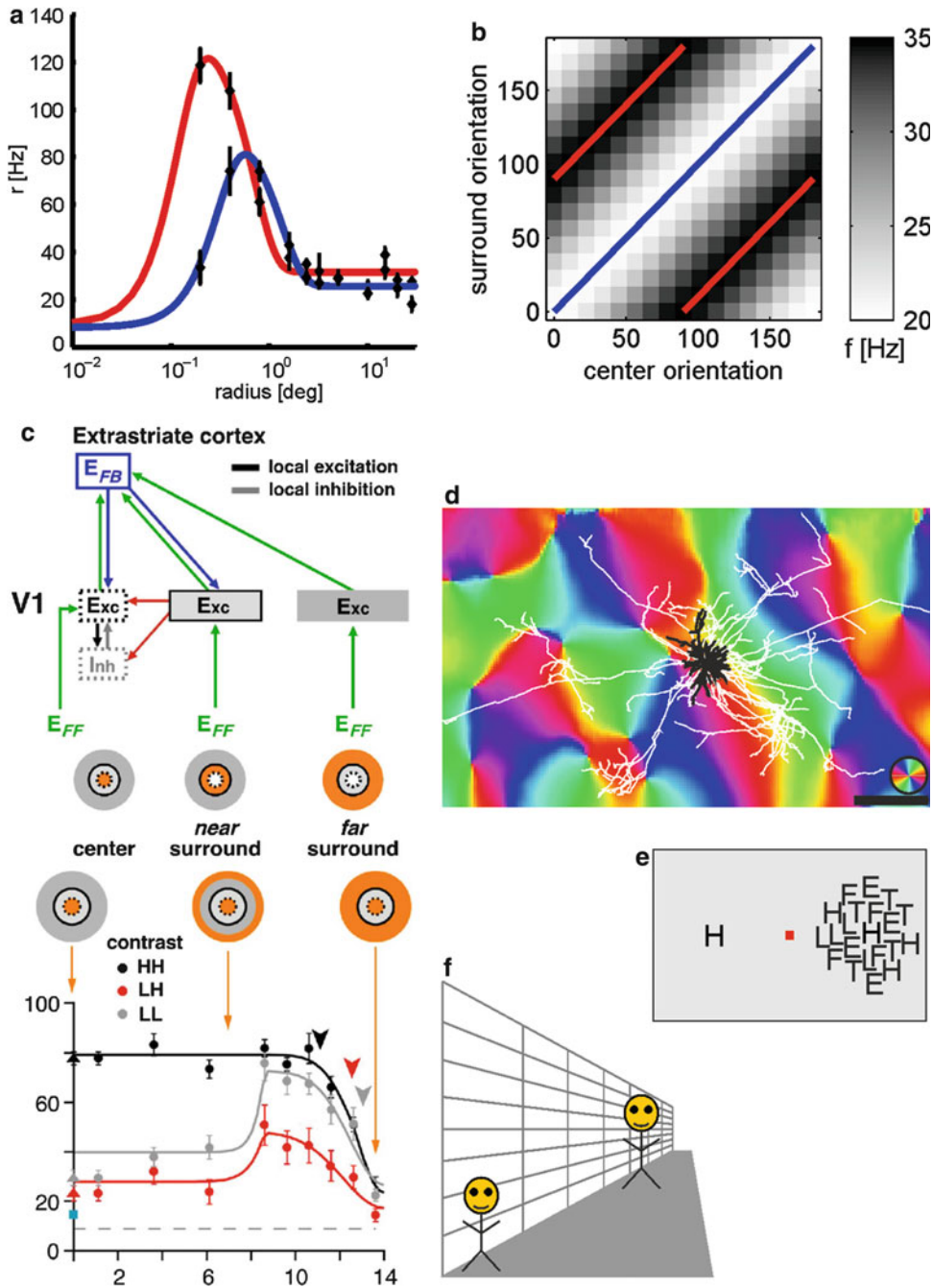


Center-Surround Processing, Computational Role of, Fig. 3 Normative and probabilistic approaches. (a) Contextual information integration and “explaining away.” In this simplified scheme, a generative model is shown with two possible causes (explanations) for a stimulus (observation): the presence of the words “tag” and “gut,” each having three letters. Given the clear evidence of only one letter “g,” these two explanations are equally likely (*left*). The additional, contextual evidence of the letter “a,” however, disambiguates the situation and increases the likelihood for the presence of “tag.” At the same time, this increased likelihood for “tag” explains away the presence of the letter “g” as evidence for “gut,” thus decreasing

its likelihood. **(b)** While neurons fire with high rates and more regular when stimulated locally within their classical receptive field (*top, left and right*), their activity becomes more sparse and more irregular for a (natural) stimulation which extends beyond their cRF (*bottom, left and right*), thus resembling more the typical activation patterns observed *in vivo* in a natural environment. This experimental observation (*left*, Vinje and Gallant 2000) (Vinje and Gallant, Science 18 (2000), 1273ff, Figure 1b/c) has recently been explained by “explaining away” in a normative model for contextual processing (*right*, Lochmann et al. 2012) (Lochmann, Ernst and Deneve, J. Neurosci 32 (2012), Figure 4d)

Taken together, one of the major factors shaping CSP in normative approaches is competition. Competition is realized by different mechanisms as, e.g., divisive and subtractive inhibition and unspecific and input-targeted inhibition (e.g., Carandini and Heeger 1994), and leads not only to suppression but also to enhancement of neural

responses. Together with the statistical properties of the elementary building blocks of natural scenes, normative frameworks currently provide a comprehensive account for CSP as performed in the early stages of the visual system (Srinivasan 1982; Rao and Ballard 1999; Spratling 2010; Lochmann et al. 2012; Zhu and Rozell 2013).



Center-Surround Processing, Computational Role of,
Fig. 4 Neurophysiological and psychophysical evidence for CSP. (a) Response of a V1 cell to circular gratings of increasing diameter, for low stimulus contrasts (blue) and high contrasts (red). Surround suppression thus depends on contrast, with the preferred stimulus size being larger for low contrasts (Shushruth et al. 2009) (Textbook Neurosciences, Springer 2013, Box 18.7c). (b) Typical,

idealized response pattern for an orientation-contrast sensitive cell as in Sillito et al. 1995, with the orientation of the center on the horizontal axis, and the orientation of the surround annulus on the vertical axis. Highest firing rates are observed if center and surround are orthogonal (red lines), lowest firing rates if center and surround have same orientations (blue line). (c) Contextual influences from the surround are seldom homogeneous, but can be divided into

Neurophysiological and Psychophysical Evidence for CSP

(a) Physiological Correlates

The response characteristics of neurons are often described in terms of their receptive fields (RFs) (► [Spectrotemporal Receptive Fields](#); ► [Receptive Field Modeling](#)). One distinguishes between the “classical” and “extra-classical” (or “nonclassical”) part of a RF (cRF and ncRF). Heuristically, the cRF describes the neuron’s response to localized and simple stimuli, while the ncRF characterizes the response characteristics for extended and complex stimuli. Technically, the cRF is obtained by using stimulation with sparse or dense noise stimuli and applying reverse correlation (► [Spike Triggered Average](#)) methods to compute the RF of a cell under a linearity assumption (i.e., that the response to arbitrary combinations of localized stimuli is the sum of responses to these stimuli presented in isolation). In essence, ncRFs are response properties which are not explained by this simple model – in particular, modulations of the neural response to stimulus components inside the cRF by stimulus components outside the cRF, which would give no response when presented alone (e.g., Sillito et al. 1995; Levitt and Lund 1997; Cavanaugh et al. 2002; Freeman et al. 2001; Series et al. 2003).

cRFs of neurons often reveal a concentric organization of their spatial receptive fields, in

particular neurons of the early visual system. A prominent example is retinal ganglion cells or neurons from the lateral geniculate nucleus (Fig. 1b). They are organized either in an ON-OFF or in an OFF-ON (antagonistic) layout, meaning that these cells respond preferentially to a bright spot on a dark background or to a dark spot on a bright background, respectively. Mathematically, such cRFs can be described with Mexican hat functions (see above). Antagonistic cRFs are not limited to vision, e.g., also neurons in the auditory system possess RFs in frequency space which resemble a one-dimensional cross section of a Mexican hat (Machens et al. 2004; Theunissen et al. 2000).

ncRFs come in many different varieties, and although they have extensively been studied in the visual system, there is yet no coherent empirical classification scheme. The following examples illustrate some prominent effects that were confirmed by different experimental studies, and for which normative (see above) or bottom-up modeling can provide a unifying account:

- Surround suppression (Fig. 4a): If a stimulus localized in feature space is made larger, the neural response initially grows, but then becomes more and more suppressed (e.g., Shushruth et al. 2009; Solomon et al. 2006). Typically, suppression is most pronounced when the stimulus extends beyond the cRF borders. If the stimulus consists of oriented features (i.e., gratings, bars), surround

Center-Surround Processing, Computational Role of, Fig. 4 (continued) “near surround” and “far surround.” On the left, model scheme for explaining the origin of differences between near- and far-surround interactions. On the right, responses of a V1 cell to a stimulus composed of a center grating and an annulus of same (preferred) orientation with decreasing inner radius, eliciting far-surround facilitation from about 8-deg. annulus width (Ichida, Schwabe, Bressloff, Angelucci, J. Neurophysiol 98, 2168ff(2007), Figures 1b and 2a right). (d) Orientation preference map and layout of horizontal connections of a layer II pyramidal cell in cat A17. Preferred stimulus orientation is coded according to the color palette in the lower right corner; the black bar corresponds to 500 μ m in

the cortex. The dendrites of the cell are shown in black, and its axon in white (This figure is courtesy of Dr. Zóltan Kisvarday and Ms. Kitti Csorba) (Textbook Neurosciences, Springer 2013, Box 18.8). (e) Example for crowding: the letters “H” have the same size and visual eccentricity from the red fixation spot. However, the right “H” is more difficult to perceive because of the presence of contextual information, i.e., the other letters. (f) Famous visual illusion, demonstrating the contextual influence of the lines in the background, suggesting depth in space, on size perception of the figures – although being of the same physical size, the right figure is perceived as being bigger than the left one

suppression is the strongest if these features are similar and the weakest or even opposite if these features are different. This effect might also depend on stimulus strength (or contrast). Changing the contrast can reverse the polarity of the modulation.

- Contrast enhancement (Fig. 4b): If the stimulus consists of components that are different (or orthogonal) in the surround, neural responses often become enhanced or disinhibited (e.g., Sillito et al. 1995). Computationally, contrast enhancement is similar to edge enhancement by DOG filtering, but extends to more complex feature combinations such as oriented gratings (corner detection).
- Sparsity of neural representation for natural scenes (Fig. 3c): Signatures of CSP are also revealed when stimulating visual cortical neurons with natural scenes. Responses are strong and sustained when neurons are stimulated with natural scenes seen through a circular aperture with a diameter matching their cRF. However, when the aperture is widened, the responses become weaker, more transient, and sparse, thus better matching the neural dynamics observed *in vivo* (Vinje and Gallant 2000).
- Near and far surround (Fig. 4c): In the visual cortex, the surround is further subdivided into a “near surround” and a “far surround.” These can have differential influence on firing rates, e.g., the far surround exerts an enhancement of neural activity, while the near surround suppresses neural responses (e.g., Schwabe et al. 2006; Ichida et al. 2007).

Note that this list is not complete and that there typically is a large amount of variability in ncRF properties even for neurons of one type in one particular brain area.

(b) Anatomical Correlates

CSP is at least partly mediated by the topology of anatomical connections between neurons within and between cortical areas. Typically, axons or dendrites extend radially from neural

populations and have different ranges for excitatory and inhibitory connections. This property naturally causes antagonistic response profiles in the afferent cells. Furthermore, connections were shown to be response specific: For example, excitatory long-ranging horizontal axons in the primary visual cortex preferentially connect neurons with similar cRFs (“neurons that fire together, wire together”) (Fig. 4d). Depending on the effective sign of these interactions, they might mediate surround suppression (see above), but also enhancement of colinear stimulus configurations as would be necessary for integrating contours.

(c) Psychophysical Evidence

Signatures of CSP are extensively studied with psychophysical methods (see paragraph above: Feature Integration and Gestalt Psychology). In the corresponding literature, these effects figure under various terms such as masking (the perception/visibility of localized stimuli depends on their spatial and temporal context), crowding (detection and identification of localized stimuli depends on the nature and density of flanking elements) (Fig. 4e), popout (a much higher saliency of certain feature combinations which are embedded in surrounding elements), fill-in (complementing missing sensory information by the brain), and others. Many visual illusions yield good examples for CSP (Bach 2013). At a first glance, they might be regarded as glitches of the visual system, but indeed are signatures that the brain does “its best” to make sense of artificially composed stimulus arrangements with a content that does not match normal experience or natural image statistics (Fig. 4f).

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Bayesian Inference with Spiking Neurons](#)
- [Center-Surround Processing, Network Models of](#)
- [Color Vision, Computational Methods for](#)

- ▶ Computation with Population Codes
- ▶ Cortical Function, Normative Models of
- ▶ Efficient Population Coding
- ▶ Excitability: Types I, II, and III
- ▶ Flicker-Induced Phosphenes
- ▶ Hierarchical Models of the Visual System
- ▶ Hodgkin-Huxley Model
- ▶ Independent Component Analysis of Images
- ▶ Receptive Field Modeling
- ▶ Retinal Neurophysiology
- ▶ Sensory Coding, Efficiency
- ▶ Somatosensory Cortex: Neural Coding of Shape
- ▶ Spectrotemporal Receptive Fields
- ▶ Spike Triggered Average
- ▶ Visual Illusions, Models of

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Center-Surround Processing, Network Models of

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Synonyms

[Models of end-stopped cells](#); [Models of lateral inhibition](#); [Network models of contextual effects](#)

Definition

Surround modulations of neuronal responses by stimuli outside the receptive field are omnipresent

in sensory systems, and network models seek to explain them as an emergent network phenomenon. They are particularly useful because recurrent networks often behave counterintuitive, i.e., different from the neural dynamics assumed by phenomenological models.

Detailed Description

Lateral inhibition is an example of center-surround (CS) processing. As a perceptual phenomenon, it was already known to Ernst Mach in the mid-nineteenth century (Yantis 2014). The so-called Mach bands are a visual illusion, where the border between adjacent luminance-defined areas appears to have higher contrast than it actually has. Phenomenological models of this perceptual effect share the common idea of spatial filtering the input image (the visual sensory signal) with a symmetric center-surround kernel (Pessoa 1996). Such a filter-based description is agnostic regarding the actual neural mechanism, but network models with short-range excitation and long-range inhibition are plausible candidates for implementing them. End-stopped neurons in primary visual cortex (V1), first described by Hubel and Wiesel in 1965 (Hubel and Wiesel 1965), are another example, where the spatial surround of the receptive field modulates the strength and selectivity of orientation-tuned responses. Recent modeling studies emphasize the role of strong local and balanced intracortical feedback in surround modulation (e.g., Ozeki et al. 2009) and how it may interact with interareal feedback connections (Shushruth et al. 2012) in CS processing. Strongly recurrent neural networks can exhibit counterintuitive emergent properties that are not anticipated by the often implicitly assumed circuitry underlying, e.g., filter-based or other computational approaches to CS. The role of CS processing in perception could be the amplification of relevant stimulus features in noisy and cluttered environments such as figure-ground segmentation in vision. Hence, the explicit integration of different pathways in network modeling CS processing is a promising approach to understand how sensory systems

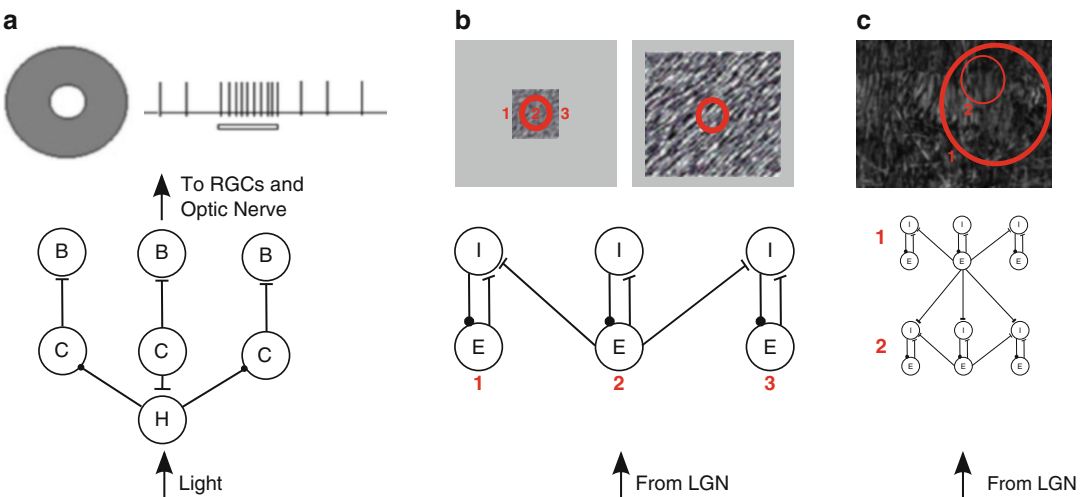
extract relevant information from noisy and cluttered environments.

Models of Center-Surround Processing in Early Vision

The signaling cascades in the retina triggered by photons impinging on photoreceptors are well characterized. For example, light falling onto cones leads to their hyperpolarization and a decrease in glutamate release onto bipolar cells. In response to this decrease, on-center bipolar cells depolarize, which leads to an increase of the glutamate they release onto retinal ganglion cells (RGCs). As a consequence, these RGCs are on-center cells that increase their spike discharge. Horizontal cells, contacted by the photoreceptors, inhibit neighboring photoreceptors. This explains

why a full illumination (causing lateral inhibition) leads to less RGC spikes than a spatially restricted illumination (with less or no lateral inhibition). Figure 1a illustrates the increase in RGC spike discharges in response to a visual stimulus and shows how cone photoreceptors, C, are connected to horizontal cells, H, and bipolar cells, B. This basic motif, namely, realizing suppression of responses to a large stimulus via inhibition of neighboring cells, has been very influential and was thus employed to explain surround suppression in the cortex as well.

Figure 1b (top) shows two image patches of different size. Within these patches the texture is dominated by an oblique orientation, a stimulus feature that triggers responses of orientation-selective neurons in primary visual cortex (V1). Interestingly, however, is the observation that orientation-selective V1 neurons with their



Center-Surround Processing, Network Models of,

Fig. 1 Illustration of three center-surround effects, each with a possible underlying network model. (a) The frequency of spike discharges of retinal ganglion cells (RGCs) increases when the center of the RGC's receptive field (RF) is illuminated (white dot) and returns to the pre-stimulus baseline when the illumination is turned off. When the center and the surround of the RF are illuminated, then the spike discharge does not increase (not shown). A retinal circuit model explains this selectivity via lateral inhibition: Light falls onto the cones, C, which triggers lateral inhibition of neighboring cones with horizontal cells, H. The on-center bipolar cells forward this signal to RGCs. (b) Responses of orientation-selective

neurons with RF center at location 2 (in the visual field) in primary visual cortex (V1) are suppressed when the size of the oriented texture is increased. The retinal circuit for lateral inhibition, Fig. 1a, is not directly applicable, because the horizontal connections in V1 are made only by excitatory cells. Those need to contact local inhibitory neurons to implement a "sign switch" that realizes the lateral inhibition. (c) Interconnected lateral inhibition circuits across different visual areas. The feedback connections from areas downstream to V1 are known to be spatially more extensive than the horizontal connections within V1 (Fig. 1b). Via such pathways the lateral inhibition can affect neurons with very distant RF centers

receptive field (RF) center at location 2 (Fig. 1b) *decrease* their spike discharges when the texture is increased in size. Hubel and Wiesel first described such a phenomenon in V1 of cats in 1965 (Hubel and Wiesel 1965). Qualitatively, this is the same phenomenon as the selectivity to illumination in the RF center of on-center RGCs: When the stimulated area in the visual field is increased, the response decreases. Experimental studies even support another analogy to the retinal circuit, namely, that the observed surround suppression in V1 may be inherited partly by surround suppression in the LGN (Webb et al. 2005) (as the suppression of RGCs is inherited from the lateral inhibition acting between their presynaptic cells).

Network models of surround suppression in V1 make use of the idea of lateral inhibition. In V1, however, the lateral connections to neighboring neurons (in terms of distinct neighboring RF centers) are made only by excitatory cells. One proposal has been that these lateral connections target local inhibitory neurons (Somers et al. 1998), which then perform a “sign switch” of this excitatory and horizontally propagating signal (Fig. 1b). The detailed layout of the topographic map in V1 determines how long such horizontal connections need to be in order to link neurons with different RF centers. Intracortical long-range connections (up to 2–3 mm in macaque V1) are widely believed to carry this horizontal signal, but much shorter connections (up to 0.25 mm) have been proposed as a potential substrate as well (Wieland and Sajda 2006). These shorter connections may account for some forms of surround suppression, but they fail to account for physiologically observed response suppression for large stimuli in which the surround is way beyond the reach of these short-range connections.

The role of short-range connections received renewed interest after a modeling study (Ozeki et al. 2009) that emphasized an apparently counterintuitive property of strongly recurrent networks of excitatory and inhibitory neurons (see the local coupling between E and I neurons in Fig. 1b). It was shown that an increased excitation of inhibitory neurons from outside the local recurrent circuitry, such as via the long-range horizontal connections, ultimately leads to a decrease of

both the excitatory *and* inhibitory responses, which can easily be understood using phase-plane analysis (Ozeki et al. 2009). While this study is still compatible with horizontal connections as the substrate of surround suppression in V1, it shows that network models need to be set up explicitly and analyzed rigorously to overcome the potentially too simplistic intuition that worked for simple circuits (e.g., Fig. 1a) but fails for strongly recurrent systems. Recently, this model has been used to investigate the orientation tuning of surround suppression (Shushruth et al. 2012).

Models of Center-Surround Processing Across Multiple Cortical Areas

For some forms of surround suppression observed in V1, the long-range horizontal connections may even be too short. Feedback connections from downstream cortical areas into V1 have been proposed as the substrate of lateral inhibition in cases when the stimulus in the surround is beyond the reach of the V1 horizontal connections (Schwabe et al. 2006), because this feedback is spatially even more extensive. Moreover, it may play a crucial role in center-surround processing in other conditions as well, in particular during natural vision. Figure 1c shows an image of a tiger almost hidden behind grass and the spatial extent of a RF in a visual area downstream to V1 (large red circle). The larger RF encloses a smaller RF in V1, which is located at the barely visible neck of the tiger. Surround suppression is known to enhance the responses to borders such as inside the RF of the V1 neuron. Due to the barely visible border, a global-to-local integration of spatially adjacent cues will be beneficial to enhance responses to elongated borders (the tiger’s neck) in cluttered scenes.

Modeling Techniques

For most of the effects described here, mean-field models that describe the dynamics of the average neural activity in a population of neurons are often sufficient. Some studies employ large-scale

simulations of networks of spiking model neurons. They are often biologically more appropriate as they can account for aspects that are hard to integrate into mean-field models such as heterogeneity of parameters.

Discussion and Future Directions

Given that strongly recurrent networks can have counterintuitive properties (Ozeki et al. 2009; Shushruth et al. 2012), it may be important to employ them as building blocks for larger models, including the neural mass models used in brain imaging. In particular, studying how adaptation at various time scales and via multiple mechanisms affects the effective network connectivity and hence the resulting center-surround computations is an important task for future studies. Finally, we need to understand how interconnected cortical areas collaborate in center-surround computations at each stage.

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Central Vestibular Signal Processing

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Definition

The *vestibular nuclear complex* (VNC) is a major site of central vestibular processing and traditionally consists of four major neuroanatomical regions: *medial*, *lateral*, *superior*, and *descending* (*spinal*) vestibular nuclei. However, recent cellular and molecular studies indicate that further subdivisions, based on more detailed analyses, better describe *functional groups* within these nuclei. The distribution of *calcium-binding proteins* and *marker genes* is redefining the VNC into specific regions with identifiable functional implications.

Detailed Description

The mammalian vestibular system is responsible for our sense of balance and can be divided into *peripheral* and *central* components (Goldberg et al. 2012). The *peripheral vestibular system* is located in the inner ear and composed of five sense organs (three semicircular canals and two otolith organs) that collectively generate signals in

response to rotational and translational head movements. These “balance” signals are then transmitted, via the eighth cranial nerve, to various targets in the central nervous system (CNS). Collectively, these CNS targets comprise the *central vestibular system* and are responsible not only for creating our perception of balance but also for contributing to the remarkably precise stabilization of gaze and posture, as well as general motor control (Cullen 2012; Goldberg et al. 2012).

Subdividing the Vestibular Nuclear Complex

Precisely how these complex and demanding functions are accomplished, particularly by the central vestibular system, is not understood. This is due in large part to our rudimentary understanding of the functional neuronal groups that constitute the central vestibular system. This lack of knowledge is best illustrated by the vestibular nuclear complex (VNC), a critically important brainstem region that distributes incoming peripheral vestibular signals to other parts of the brainstem, cortex, cerebellum, and spinal cord. Despite it being a major site for multisensory processing, we know very little about this region beyond the classical neuroanatomical studies that first described four major divisions or *vestibular nuclei* (Brodal and Pompeiano 1957). This lack of detailed knowledge is because it has been difficult to identify, classify, and manipulate functionally distinct cell types that are often spatially intermingled within the VNC (Kodama et al. 2012). In the last decade, however, immunohistochemical and molecular studies, together with electrophysiological analyses, have begun to identify discrete subdivisions within these individual vestibular nuclei and support the notion of a vastly more complex functional organization that has been long suspected (Scudder and Fuchs 1992; Bagnall et al. 2007).

Analysis of the Medial Vestibular Nucleus

Revealing the complexity of both functional organization and connectivity within the VNC

provides a much-needed cellular basis for understanding this pivotal central vestibular region. For example, one division of the VNC, the *medial vestibular nucleus* (MVN), can itself be further subdivided simply based on the individual neuron’s projection target. These targets include ocular motor neurons, cerebellar neurons, and local neurons within the ipsi- and contralateral VNCs (Highstein and Holstein 2006). Further subdivisions have also been described based on specific differences in intrinsic excitability across MVN neurons with different axonal projections and neurotransmitter (Takazawa et al. 2004; Sekirnjak and du Lac 2006; Bagnall et al. 2007; Kolkman et al. 2011a, b; Shin et al. 2011). Still other subdivisions have been demarcated by immunoreactivity (ir) to functionally important calcium-binding proteins (CBPs) such as *calbindin* (CB) and *calretinin* (CR). Subdivisions based on these CBPs have proved consistent across a number of species including rodents, cat, monkeys, and human (Resibois and Rogers 1992; Rogers and Resibois 1992; Kevetter 1996; Baizer and Baker 2005, 2006; Baizer and Broussard 2010) strongly suggesting a conserved purpose. While the function of these distinct CBP regions has yet to be determined, it has been suggested that regions with dense CB-ir represent a zone of dense cerebellar input (Baizer et al. 2013) and thus may play a role in adaptive modifications of reflexive eye movements (Rambold et al. 2002). While the CR-ir region is likely to receive direct peripheral vestibular input and project to other parts of the VNC and suggests a coordinating rather than command role in eye movement generation.

Functional Organization of the MVN Revealed by Combined Studies

Molecular studies are beginning to uncover further complexities in the internal organization of the VNC. In addition to classifying neurons into distinct subdivisions, molecular studies have the added advantage of ascribing these subdivisions particular functions. In a recent study by Kodama et al. (2012), using single-cell expression profiling

of genes related to neurotransmitters and ion channels, they were able to demonstrate candidate molecular markers that subdivided MVN into six distinct types. By combining this approach with anterograde and retrograde labeling techniques, they were able to determine the functional role of four out of the six molecularly defined classes of MVN neurons. The six types were identified as three classes of excitatory neurons (E1, E2, E3) and three classes of inhibitory neurons (I1, I2, I3), each associated with a specific set of marker genes. For example, E1 were large glutamatergic MVN neurons that uniquely expressed gene markers *Spp1* (*secreted phosphoprotein 1*) and *Slc17a6* (*vesicular glutamate transporter 2*) and projected to oculomotor or abducens motor nucleus, while glutamatergic E2 neurons expressed *Crh* (*corticotropin-releasing hormone*) and *Slc17a7* (*vesicular glutamate transporter 1*) and projected to the cerebellar flocculus.

Future Studies of the Central Vestibular System

As proposed by Kodama et al. (2012), this strategy of classifying neurons into functionally distinct groups could also be applied to any heterogeneous neuronal population, including those regions associated with central vestibular system. For example, quantitative single-cell transcript analyses, in situ hybridization, immunohistochemistry, and electrophysiological studies could be used to identify functional organization of neurons in the cerebellar and ocular motor nuclei, as well as higher cortical centers processing vestibular information. With the expanded knowledge promised by these combined studies, the chances of understanding how the central vestibular system unobtrusively achieves the extraordinary feat of creating our sense of balance and its attendant actions are becoming a realistic possibility.

Cross-References

- [Peripheral Vestibular Signal Processing](#)
- [Vestibular System: Overview](#)

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Cercal System

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Definition

The cercal system is a mechanosensory system in orthopteran insects, which mediates the detection, localization, and identification of air currents surrounding the animals. The receptor organ for this modality is a pair of antenna-like appendages called *cerci* at the rear of the abdomen, covered with mechanosensory hairs like the bristles on a bottlebrush (Fig. 1). Air currents in the animal's immediate environment move these hairs and, thereby, activate the receptor neurons at the base of the hairs. The cercal system is implemented around an internal representation of stimulus direction and dynamics that demonstrates the essential features of neural maps found in more complex systems, including mammalian visual and auditory systems. Over the last several decades, this system of the cricket has been used as a simple “model system” for investigations of development, mechanoreceptor biomechanics, neural maps, and neural coding (Jacobs et al. 2008).

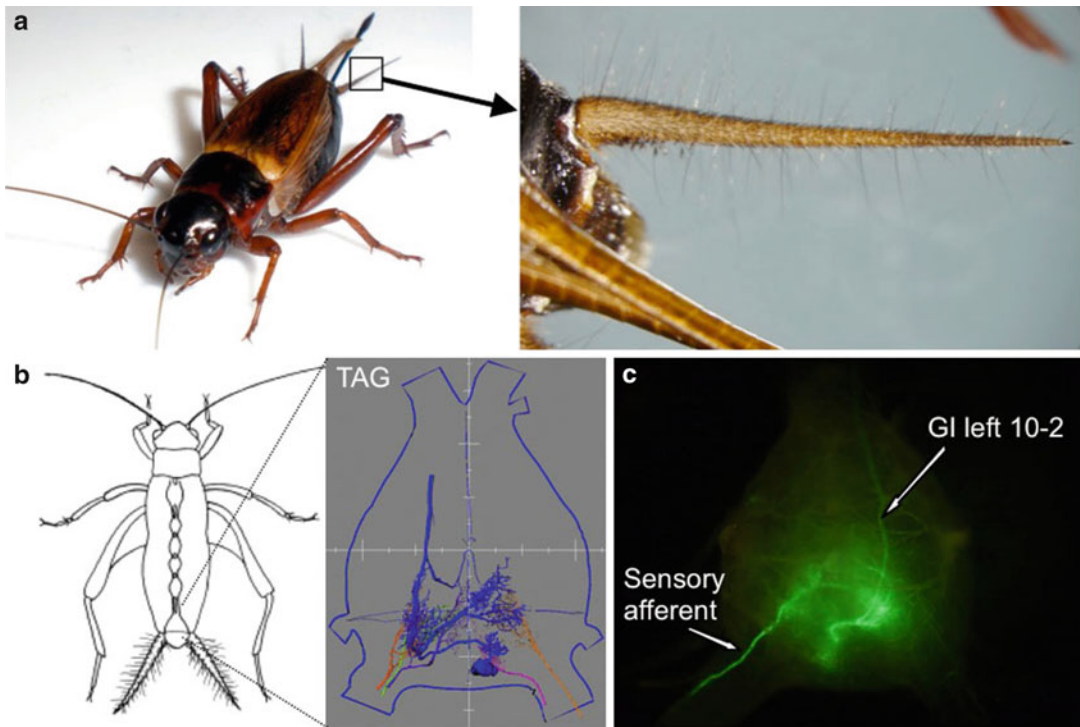
Detailed Description

Overview

The cercal system was shown in early studies to be of critical importance for the oriented escape response to air puffs (Hoyle 1958; Camhi 1980; Boyan et al. 1986). However, it is a considerable oversimplification to class this system as an “escape system.” Rather, the cercal system should be thought of as functioning as a low-frequency, near-field extension of the animal's auditory system. Air particle displacement directed at the cerci can elicit at least 14 distinct responses, including evasion, flight, offensive reactions, scanning, freezing, and various reactions during male stridulation, and response can depend on the behavioral state of the animal as well as the context of the environment (Baba and Shimozawa 1997; Casas and Dangles 2010). In addition to the filiform receptors sensitive to air particle displacement, bristle hairs, clavate hairs, and campaniform sensilla are distributed on the cercus. The cercal system is, therefore, also responsible for mediating behavior related to orientation relative to gravity as well as a variety of touch and chemotactic sensations via other types of sensors on the cerci (Murphey 1985; Sakaguchi and Murphey 1983; Heusslein and Gnatzy 1987). The detailed description of this topic will be limited to the sensory-processing system on direction and dynamics of airflow mediated by filiform receptors.

Functional Organization of the Mechanosensory Hair Array

In *A. domesticus*, the species used for most of the studies in the past, each cercus is approximately 1 cm long in a normal adult cricket and is covered with 500–750 filiform mechanosensory hairs (Palka et al. 1977; Miller et al. 2011). These hairs range in length from 50 μ m to 1.5 mm. Each hair is supported at its base by a viscoelastic socket that enables the hair to pivot within its socket, rather than bending along its shaft (Keil and Steinbrecht 1984). Each hair's directional movement axis is determined by the orientation of a hinge-like structure in the socket. The 750 hairs on each cercus are arrayed with their movement axes in diverse orientations within the



Cercal System, Fig. 1 The cricket cercal system. (a) *Gryllus bimaculatus* (female). The cerci are the two antenna-like structures, covered with fine hairs, extending from the rear of the abdomen. (b) Computer reconstruction of the outline (blue) of a terminal abdominal ganglion (TAG) with several reconstructed nerve cells.

A reconstruction of a single identified giant interneuron (GI right 10–3) is shown in blue, and several filiform sensory afferent arbors are shown in other colors. (c) Micrograph of the GI left 10–2 and a filiform afferent stained with fluorescent dye

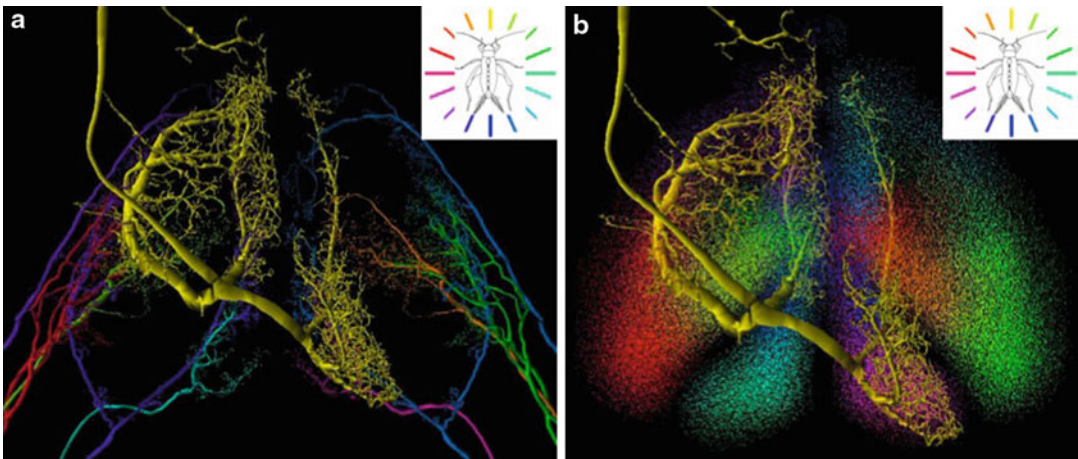
horizontal plane. On a global scale, the directionality of hairs is organized in bands along the long axis of the cerci. There is a systematic rotation in the movement directions of the hairs around the circumference of each cercus, and there is a non-uniform distribution of hair densities along the length of the cercus, with greater density nearer the base than near the tip (Palka et al. 1977; Miller et al. 2011). This global organization of the array insures that air currents of sufficient velocity will deflect *all* of the filiform hairs to some extent: each hair will be deflected from its rest position by an amount that is proportional to the cosine of the angle between the air current direction and the hair's movement axis.

Each mechanosensory hair is innervated by a single spike-generating mechanosensory receptor

neuron. These receptors display directional and dynamical sensitivities that appear to be derived largely from the mechanical properties of the hairs themselves (Shimozawa and Kanou 1984). The amplitude of the response of each sensory receptor cell to any air current stimulus depends upon the velocity and direction of that stimulus, and the directional tuning curves of the receptor afferents are well-described by cosine functions (Landolf and Jacobs 1995; Landolf and Miller 1995).

Representation of Stimulus Direction

The sensory afferents of filiform sensilla project in an orderly array into the terminal abdominal ganglion to form a continuous representation of the direction of air currents in the horizontal plane (Bacon and Murphey 1984; Jacobs and



Cercal System, Fig. 2 Anatomical prediction of synaptic connectivity between filiform sensory afferents and interneurons. **(a)** A reconstruction of GI right 10–2 shown in yellow and afferent arborizations from 12 different filiform hair receptors shown in different colors. The color of each

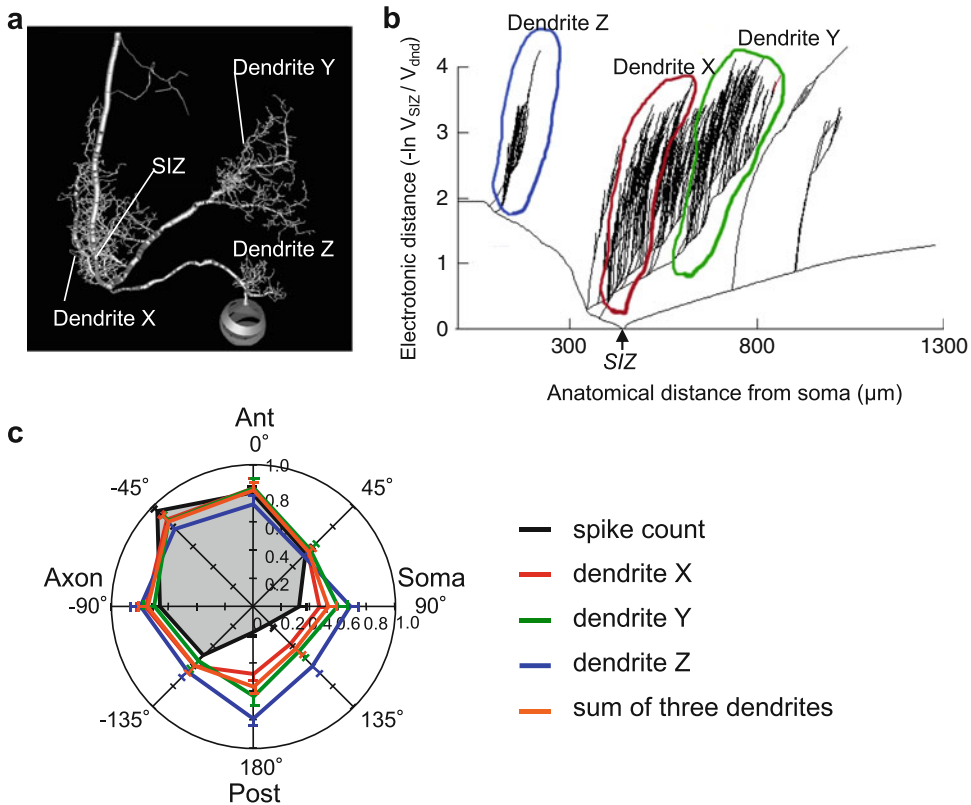
afferent corresponds to its direction of peak activation. **(b)** A reconstructed dendrites of GI right 10–2 within the afferent neural map of direction. The neural map is predicted by the “statistical cloud” corresponding to the density of synaptic terminals for that stimulus direction

Theunissen 1996, 2000; Paydar et al. 1999). The synaptic terminals from afferents having similar peak directional sensitivities arborize in adjacent areas, and the spatial segregation between afferent arbors increases as the difference in their directional tuning increases. A representation of the stimulus direction in a three-dimensional neural map of the entire filiform afferents has been developed, based on anatomical and physiological measurements taken from a large sample of individual afferents (Fig. 2; Troyer et al. 1994; Jacobs and Theunissen 1996; Paydar et al. 1999). By combining the predicted responses of each class of afferents with this information about the spatial location of their terminal arborizations within the neural map, predictions have been made of the spatial patterns of synaptic activation that would result from sustained, unidirectional air currents (Jacobs and Theunissen 2000; Paydar et al. 1999; Troyer et al. 1994). The predictions were consistent with spatial patterns of ensemble activity of filiform afferents visualized by calcium imaging experiments (Ogawa et al. 2006).

Dendritic Integration in the Giant Interneurons (GIs)

The 1500 sensory afferents synapse with a group of approximately 30 local interneurons, and

approximately ten pairs of identified ascending interneurons project their axons to motor centers in the thorax and integrative centers in the brain. These ascending interneurons have been called “giant interneurons” due to their large-diameter axons which enable very rapid conduction of action potentials to the higher ganglia. Like the afferents, these interneurons are also sensitive to the direction and dynamics of air current stimuli (Jacobs et al. 1986; Miller et al. 1991; Ogawa et al. 2004; Theunissen and Miller 1991; Theunissen et al. 1996). The directional sensitivity of the ascending interneurons is primarily based on the relative positions of their dendrites within the afferent map of the mechanosensory afferents (Fig. 2; Jacobs and Theunissen 2000). However, the overall directional tuning and dynamical sensitivity of each individual interneuron also depends on the spatial distribution of synapses onto the complex geometry of the dendritic arbors (Fig. 3; Ogawa et al. 2008). The frequency sensitivity of each interneuron depends on two independent factors: (a) its inherent frequency-filtering properties that are a function of intrinsic membrane properties and synaptic transmission characteristics and (b) the position of its dendrites within the afferent map.



Cercal System, Fig. 3 Relationship between electrotonic geometry of the dendritic arbor and directional tuning of dendritic Ca^{2+} responses in GI 10–3. **(a)**, images showing the compartment models of GI 10–3 with the spike-initiation zone (SIZ) indicated. **(b)**, plots of inward electrotonic distance (ED) versus path distance relative to the SIZ in the model of GI 10–3. The X axis is the path distance from the soma to the compartment along each process. **(c)**, polar plots indicate the mean number of spikes

(black line), and the mean amplitude of Ca^{2+} increases at three different dendrites X, Y, and Z (red, green, and blue lines, respectively). Each value of the Ca^{2+} - and action-potential responses was scaled to the maximal responses of each measurement. The curve shown by the orange line was predicted by calculating the weighted sum of the tuning curves of the individual dendritic responses based on electrotonic distances

Dendritic Ca^{2+} Elevation and Ca^{2+} -Mediated Adaptation

The excitation of GIs causes cytosolic Ca^{2+} elevation in their dendrites (Ogawa et al. 2000). Similar to the firing responses, dendritic calcium responses to the airflow stimuli also show direction sensitivity, which varies in their selectivity and preference direction depending on the dendritic location (Ogawa et al. 1999, 2004, 2008; Ogawa and Oka 2015). This detectable calcium elevation is mainly due to the influx of Ca^{2+} through voltage-gated Ca^{2+} channels activated by action potentials back-propagating into the dendritic arbor (Ogawa et al. 2000). Therefore,

the spatial heterogeneity of direction sensitivity in dendritic Ca^{2+} response is considered to be due to changes in the location of the spike-initiation site and/or the intra-dendritic spike-propagation dynamics depending on the airflow direction (Ogawa et al. 2002a, 2002b; Ogawa and Mitani 2015). Heterogeneous Ca^{2+} dynamics induces local Ca^{2+} accumulation during repetitive stimulation, which causes direction-specific attenuation of the GI's response via transient synaptic depression (Ogawa et al. 2001; Ogawa and Oka 2015). This mechanism provides a neural basis for direction-specific adaptation of the escape behavior to repetitive airflow stimulation.

Neural Encoding and Transmission

Some or perhaps all of the 20 projecting sensory interneurons in this system represent the general parameters of air currents via an ensemble coarse-coding scheme. For example, four GIs in a well-studied group (the left and right GIs 10–2 and 10–3) have been shown to be tuned broadly to the direction and velocity of bulk airflow movements and project a coarse-coded image of these parameters to higher centers that is accurate to approximately 8 degrees (Theunissen and Miller 1991; Theunissen et al. 1996). More recent research has demonstrated that these same four GIs (and perhaps all of the other projecting GIs) also respond with high sensitivity to complex dynamic multidirectional features of air currents on a smaller spatial scale than the physical dimensions of the cerci (Mulder-Rosi et al. 2010), using a coding scheme that is more complex than simple linear encoding (Aldworth et al. 2011). The velocity threshold for these features is lower than the threshold for simple unidirectional bulk flow stimuli used in previous studies. Thus, in addition to participating in the ensemble encoding of bulk air flow stimulus characteristics, the projecting GIs are also tuned to detect complex dynamical signal features that may correspond to important naturalistic stimuli such as approaching predators. Four main factors underlie the specialized feature sensitivity of these interneurons: (1) the specific characteristics of the distribution of mechanosensory hairs along the two cerci, (2) the operation of the cerci as delay lines for the sensory afferent inputs located at different distances out along the cerci (Mulder-Rosi et al. 2010), (3) the highly organized nature of the afferent terminal arborizations into a map of directional and dynamical stimulus parameters within the terminal abdominal ganglion, and (4) the architecture of the interneurons' dendritic branches within this afferent map.

Response Properties in Natural Condition

Most studies of the cercal sensory system GIs have been carried out in laboratory settings using carefully controlled stimuli. Using a piston mimicking the natural airflow of an approaching predator, Dupuy and colleagues recorded neural

activity of GIs through the abdominal connectives from the terminal abdominal ganglion of freely moving wood crickets (*Nemobius sylvestris*) in a semi-field situation (Dupuy et al. 2012). A cluster analysis of spike amplitudes revealed six different subsets of cercal interneurons. No spontaneous activity was recorded for the units of larger amplitude corresponding to the largest giant interneurons. Many of the smaller cercal units were already activated by background noise, sometimes only weakly, and the approach of a predator was signaled by an increase in their activity, in particular for the larger-amplitude units. A scaling law predicted that the cumulative number of spikes is a function of the velocity of the flow perceived at the rear of the cricket, including a multiplicative factor that increases linearly with piston velocity.

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Cerebellar Long Term Depression

- Long Term Depression in the Granule Cell-Purkinje Cell Synapse

Cerebellar LTD

- Long Term Depression in the Granule Cell-Purkinje Cell Synapse

Cerebrovascular Disease

- Brain Ischemia and Stroke

Channelopathy

- [Epilepsy: Abnormal Ion Channels](#)
- [Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation](#)

Chaos, Neural Population Models and

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Definition

Nonlinear dynamic systems, even if completely described by deterministic equations, may exhibit unpredictable behavior, in that arbitrarily small deviations in the initial conditions, after sufficient time has passed, lead to completely different behavior. This is referred to as deterministic chaos and has been shown to arise in neural population models (NPM).

Detailed Description

Chaotic Systems

Deterministic chaos occurs in systems completely described by deterministic differential equations. These systems may be quite simple, but they have to be nonlinear and live in phase spaces of at least three dimensions (Poincaré-Bendixson theorem). Chaos means that arbitrarily small differences in initial conditions nevertheless lead to strongly diverging trajectories of system behavior after some time. Consequently, under any realistic conditions the system's long-term behavior is unpredictable. In spite of the impossibility to predict the system's behavior in any single case, the chaotic dynamics are often not entirely arbitrary, but can be described by so-called strange attractors. Just like fixed points or limit cycles, strange attractors eventually attract all trajectories

that start within their basin of attraction. However, unlike those simple forms of attractors, strange attractors are not simply points or closed orbits, but form complex manifolds of fractal dimension in phase space. In spite of their spatial extent, they fill only an infinitesimally small fraction of the phase space. Examples are the Lorenz attractor (Lorenz 1963), which describes a simple hydrodynamic system, and the Rössler attractor (Rössler 1976), which was inspired by a taffy puller machine.

The rate with which nearby trajectories converge or diverge is described by the Lyapunov spectrum, comprising one Lyapunov exponent per phase space dimension (Politi 2013). If the largest Lyapunov exponent (LLE) is positive, the system is chaotic (in case of more than one positive Lyapunov exponent, one speaks of hyperchaos), while zero or negative LLEs indicate phase space contraction, that is, trajectories from a certain region in phase space tend to converge.

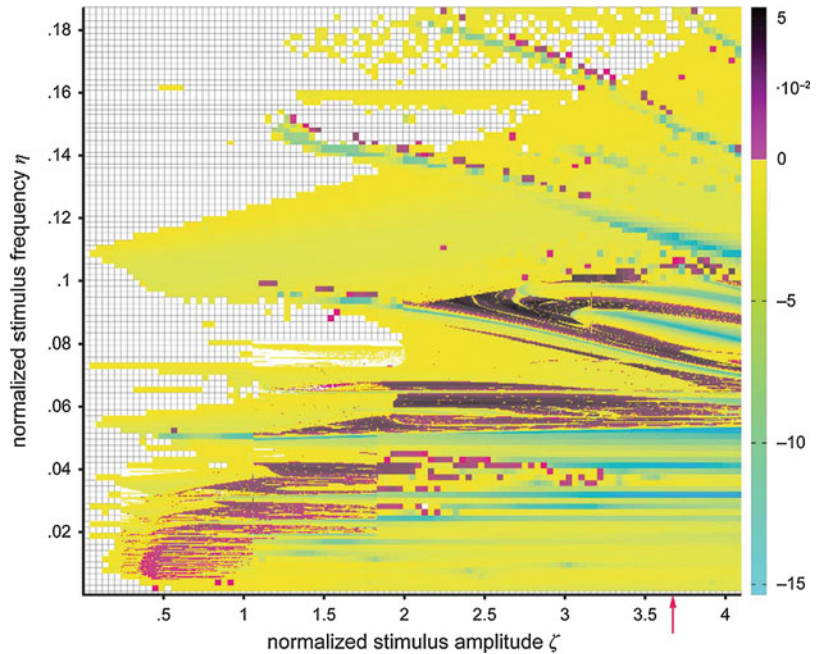
Whether or not a system is chaotic may depend on system parameters. The transition from deterministic to chaotic asymptotic behavior upon change of one or several system parameters is referred to as *route to chaos*. Very often this happens through an infinite succession of period-doubling bifurcations of decreasing spacing (Feigenbaum 1978). The chaotic region is usually interrupted by islands of stability in a fractal fashion.

Chaos in NPMs

In several types of NPMs, chaotic dynamic behaviors have been demonstrated. Freeman (1987) constructed an NPM of the olfactory system and demonstrated different chaotic regimes. More recently, Dafilis et al. (2001, 2009) investigated the parameter space for a cortical model of two neural populations, one excitatory and one inhibitory (Liley model). They showed that chaos can occur, when the excitatory input to the inhibitory population does not greatly exceed the excitatory input to the excitatory population. They also showed that chaotic and non-chaotic regions in parameter space form a complicated, apparently fractal, pattern. The time series and frequency

Chaos, Neural Population Models and,

Fig. 1 Largest Lyapunov exponent of a periodically driven Jansen-Rit model, as a function of stimulus amplitude and frequency. Positive exponents (magenta to black) reflect diverging trajectories and thus chaos. Zero exponents (white) indicate neutral stability, and negative exponents (cyan to yellow) reflect frequency locking. Several parameter regions with scattered, presumably fractal, patterns of chaotic regime are shown at a finer resolution. (From Spiegler et al. 2011)



spectra corresponding to the chaotic dynamics closely resembled real EEG in the gamma range (30–100 Hz).

Spiegler et al. (2011) investigated a periodically forced Jansen-Rit model and observed, when varying amplitude and frequency of the input, a complicated, presumably fractal, pattern of chaotic and non-chaotic regimes (Fig. 1). Interestingly, they showed that this pattern matches the estimated chaoticity (in terms of the LLE) of the time series of EEG under stimulation with light flicker of variable frequency.

Brain Dynamics: Stochastic Processes or Deterministic Chaos?

Time series of functional brain measurements, for example, electroencephalography or magnetoencephalography, feature a high degree of irregularity and unpredictability. There has been a discussion whether stochastic processes or deterministic chaos is the main reason for this behavior (Stam 2005). Both can clearly explain the observations in terms of time series and spectra. Stochastic elements in functional activity could originate from stochastic input from the outer and inner environments and from the very high number of relatively independent processes that

are present in the brain at any given time, while deterministic chaos can originate from the intrinsic dynamics of the neural circuits, as shown above. While stochasticity would be simply an epiphenomenon of brain function, chaos could play an important role in information processing (Skarda and Freeman 1987). Experimentally, chaos has been shown to exist at the single-cell level. There is, however, growing evidence for the existence of chaos at all levels of brain function and for its role as part of the neural code. For an extensive discussion, refer to Korn and Faure (2003).

Cross-References

- [Bifurcation Analysis](#)
- [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- [Bifurcations, Neural Population Models and Jansen-Rit Model](#)
- [Neural Population Model](#)
- [Pattern Formation in Neural Population Models](#)
- [Phase Transitions, Neural Population Models and](#)

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Characterization of Motor Learning in Continuous Tracking Tasks

► [Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)

Chloride Channels

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Definition

Chloride channels play an important role in regulating neuronal excitability, especially in the

context of fast synaptic inhibition mediated by GABA_A and glycine receptors. But in order for chloride channels to reduce excitability, chloride driving force must be maintained via transporters that extrude chloride from the cell. Other transporters load chloride into the cell. The complicated and dynamic balancing of chloride influx and efflux, which also involves a variety of other ion species, directly affects how chloride channels regulate excitability.

Detailed Description

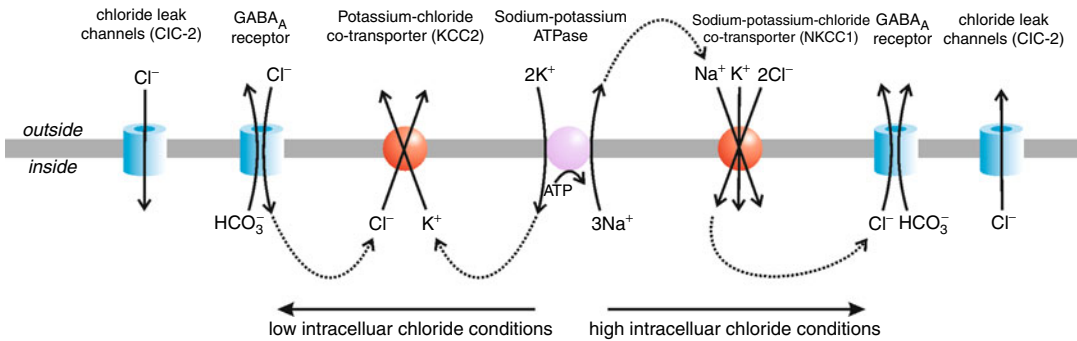
Function

Chloride ions participate in many cellular functions, from helping regulate cellular excitability to helping regulate cell volume. Those functions are mediated through a variety of chloride channels and transporters (Duran et al. 2010; Fig. 1). The regulation of neuronal excitability garners the most attention among neuroscientists. As the dominant charge carrier through GABA_A and glycine receptors, chloride is directly implicated in the efficacy of fast synaptic inhibition. Therefore, if chloride regulation is compromised, which occurs under a variety of pathological conditions including epilepsy and neuropathic pain (Kahle et al. 2008; Price et al. 2009), the efficacy of fast synaptic inhibition can be compromised with disastrous effects.

Understanding (and modeling) synaptic inhibition requires that we understand (and correctly account for) chloride flux. Synaptic inhibition is most often modeled as a simple current. But keeping in mind that chloride current reflects chloride flux and that chloride flux can sometimes deplete the chloride gradient, explicitly modeling chloride flux is sometimes necessary (Doyon et al. 2011).

Chloride Flux and the Electrochemical Gradient

The magnitude and direction of chloride flux across the cell membrane depends on the electrochemical chloride gradient. That gradient is described by the driving force, which is the difference between membrane potential and chloride reversal potential E_{Cl} . E_{Cl} is dictated by the ratio of intracellular and extracellular concentrations,



Chloride Channels, Fig. 1 Cartoon depicting membrane proteins that contribute to chloride flux. Channels (blue) let chloride move down its electrochemical gradient. Importantly, chloride can move in either direction through those channels depending on the direction of the gradient, notwithstanding rectification of the channel. The chloride

gradient is maintained by cotransporters (red) and exchangers (not shown) that harness the gradient of another ion species to move chloride against its gradient. Maintenance of the other ion gradients ultimately relies on the sodium-potassium pump (mauve). Numerous other proteins involved in chloride flux are not shown

$[Cl^-]_i$ and $[Cl^-]_o$, as explained by the Nernst equation. Under normal conditions (i.e., low $[Cl^-]_i$ and membrane potential between resting level and spike threshold), opening a chloride channel will allow chloride to flow down its electrochemical gradient and into the neuron. This influx represents an outward current since the direction of current is defined by the direction in which positive charge flows.

Notably, physiological conditions are often deliberately violated for the purpose of experimental testing. For example, in whole cell patch clamp recordings, high levels of chloride are sometimes included in the pipette solution (which will dialyze the cell) in order to increase the chloride driving force so as to improve the detection and measurement of chloride currents. Likewise, voltage can be clamped at values that, under normal conditions, would occur only briefly during a spike. Under these artificial conditions, chloride may flow in the direction opposite to what it would normally. To be clear, there is nothing wrong with such experiments, but one must consider the relevant factors when interpreting the results.

Chloride Transporters and Chloride Homeostasis

The ability of chloride to reduce excitability requires that chloride leak into the neuron. Passive movement of chloride down its gradient and into the cell would eventually deplete the chloride

gradient were it not for other mechanisms that serve to replenish the gradient by extruding chloride from the cell. (Notably, passive chloride flux can deplete the gradient, but it cannot reverse it, which is a topic we will return to later). The most important chloride extruder in central neurons is the potassium-chloride cotransporter KCC2 (Payne et al. 2003). KCC2 harnesses the potassium gradient such that chloride ions can piggy-back potassium ions out of the neuron through an electroneutral process (Fig. 1). Cotransport is not equivalent to pumping: Pumping is active (i.e., it depends directly on ATP hydrolysis), whereas cotransport is only secondarily active (i.e., it depends on ion gradients established and maintained by pumps).

The sodium-potassium-chloride cotransporter NKCC1 is also expressed in neurons and serves to load chloride into cells via the sodium gradient. In central neurons, KCC2 expression increases during development, whereas NKCC1 expression decreases (Ben-Ari et al. 2012). The same is not true for peripheral neurons, which is why GABA is depolarizing (although nonetheless inhibitory because of processes like sodium channel inactivation) in mature peripheral neurons.

Other proteins not depicted in Fig. 1 can also contribute to chloride homeostasis. These include sodium-dependent and sodium-independent anion exchangers. Exchangers, or antiporters, function like cotransporters in that they move one ion against its gradient by harnessing the

energy of a different gradient, but unlike cotransporters that move both ion species in the same direction, exchangers move each ion species in opposite directions.

It has also been suggested that certain rectifying leak channels, like ClC-2 , serve as one-way valves that selectively let chloride out of the cell. However, a passive leak process can only ever let chloride flow down its gradient, unlike cotransport, which moves chloride against its gradient by harnessing a different ion gradient. In short, the role of ClC-2 channels is context dependent, but they probably work in mature, healthy, central neurons to regulate excitability by leaking chloride into the cell. But to make this matter more confusing, certain members of the ClC family actually function as exchangers rather than as channels (Duran et al. 2010).

One should appreciate that there are other chloride channels not shown in Fig. 1. For instance, many neurons express chloride channels that are activated by increased intracellular calcium (Duran et al. 2010; Hartzell et al. 2005). Of particular clinical importance, the cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride channel involved in regulating water flow across epithelia; mutations in this channel lead to, among other problems, dehydrated mucus that is excessively viscous and which therefore blocks ducts, leading to cystic fibrosis (Gadsby et al. 2006). Beyond their involvement in phasic synaptic transmission, GABA receptors can (depending on their subunit composition) be exquisitely sensitive to GABA, remaining open even in response to ambient levels of extracellular GABA and thus contributing a tonic chloride conductance to the cell (Lee and Maguire 2014; Sigel and Steinmann 2012). In all cases, channels rely on the passive movement of chloride down its electrochemical gradient.

Synaptic Inhibition and Chloride Flux

As already explained, synaptic inhibition by GABA_A receptors relies on chloride influx to produce an outward current. However, GABA_A receptors are often described as mediating shunting inhibition because they prevent the depolarization caused by concurrent excitatory

input rather than causing gross hyperpolarization. This occurs because the GABA reversal potential is close to the resting membrane potential, which means that chloride driving force is small, especially in the absence of a depolarizing event. Shunting inhibition works by GABA_A receptors mediating a chloride-based current that is proportional yet opposite in direction to the inward cation-based current mediated by AMPA/NMDA receptors. To be clear, cations entering via AMPA/NMDA receptors do not escape via the open GABA_A channels, contrary to what one might assume based on the term “shunting.” Consequently, even shunting inhibition involves chloride influx and, therefore, is not immune to the effects of chloride dysregulation.

Notably, GABA_A channels do not always mediate chloride influx. For example, in immature neurons and mature peripheral neurons that maintain a high intracellular chloride concentration through the actions of NKCC1 , GABA_A receptor activation leads to depolarization caused by chloride efflux. This is in contrast to the depolarizing GABA responses that occur in central neurons after pathological reduction of KCC2 and/or during sustained inhibitory input. Under conditions in which chloride extrusion capacity is reduced (but chloride is not actively loaded into the neuron, e.g., by NKCC1), chloride influx can rapidly deplete the chloride gradient, especially in small compartments like dendrites that have a high surface area-to-volume ratio (Doyon et al. 2011), but chloride flux does not reverse direction; instead, GABA-induced depolarization occurs because the associated bicarbonate efflux becomes dominant relative to chloride influx (Grover et al. 1993). The relative permeability of GABA_A channels to chloride versus bicarbonate is about 4:1 and should be accounted for by calculating the “GABA” reversal potential by using the Goldman-Hodgkin-Katz equation (which can accommodate multiple ion species) rather than the Nernst equation (which accommodates only one ion species). Because of the bicarbonate component, the functional reversal potential for GABA_A channels is usually several millivolts less negative than E_{Cl} .

Summary

Chloride plays a crucial role in helping regulate neuronal excitability, especially in the context of fast synaptic inhibition. Inhibition normally relies on chloride moving into the neuron, and inhibition may thus fail if chloride is allowed to accumulate intracellularly. Indeed, the direction and magnitude of chloride flux depend on the electrochemical chloride gradient, which in turn depends on the regulation of intracellular chloride levels. A variety of transporters work to regulate intracellular chloride levels, implicating other ion species in the process. This dynamic balancing of chloride influx and efflux is transparent under normal conditions, but the complex interplay between processes must be accounted for when any one of those processes goes awry.

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Choice Behavior

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Synonyms

Consumer behavior; Decision-making; Preference mapping.

Definition

The pattern of response allocation when making a selection among several choice alternatives.

Detailed Description

Choice behavior – the description of response allocation patterns when making a selection among several choice alternatives, as well as the identification of the choice-underlying psychological and neural mechanisms and their evolutionary origins – has been the topic of study in many scientific disciplines. Economics, mainly micro- and macroeconomics, has generated formal models of choice behavior that are designed to make accurate predictions of (aggregate) human behavior while making as few assumptions as possible and while being agnostic about the choice-underlying mental mechanisms. Psychologists are traditionally more concerned with describing and explaining the observable reality of human decision, but psychological theory is often also tested with animal models as approximations of specific, isolated aspects of human

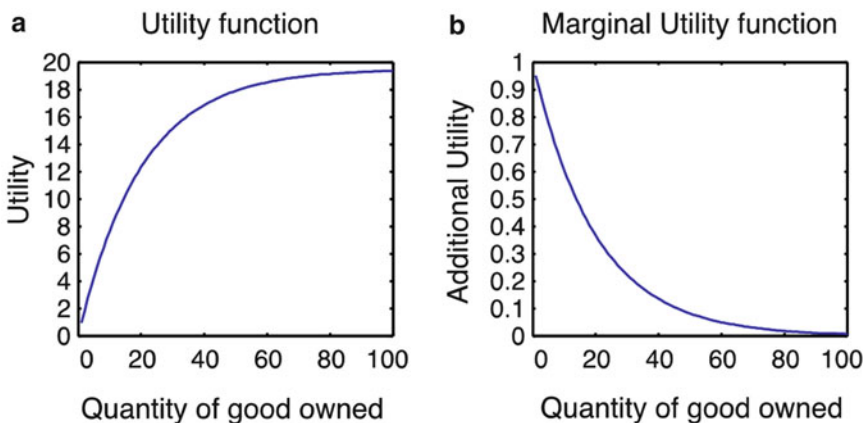
behavior. Biologists are interested in choice behavior, too. Optimal foraging theory, for instance, prescribes and explains how animals should make optimal foraging decisions in variable environments if they were to maximize Darwinian fitness. Neuroscientists have started to reveal the neural mechanisms underlying choice behaviors in animal and human models. Thus, despite a superficially obvious dominance of economic theory in the study of human decision making, the science of choice behavior comprises many different approaches from different schools of thinking and applies to human as well as animal subjects. This entry is meant to give an overview of the different approaches to animal and human choice behavior.

Choice Behavior in Microeconomics: Revealed Preferences

In economic theory, choices, measured as the response distribution among a range of alternatives, are the observable behavioral output of a process that draws upon *preferences*. Preferences are unobservable cognitive structures specific to an individual in a particular context. It is usually assumed that a decision maker behaves *as if* he or she was maximizing a utility function. A utility

function is a mathematical construct linking objective quantities of a (single) good A to the subjective value (utility) it renders (Fig. 1a). This utility function is usually assumed to be concave and decelerating, meaning that the additional utility gained per unit of A decreases as a function of the amount of A already owned. For example, increasing the wealth of a very poor beggar by \$100 yields a very large additional utility to the beggar, whereas adding \$100 to the fortune of a very rich person yields little additional utility. The increase in utility as a function of goods already owned is called *marginal utility*. The *marginal utility function* (Fig. 1b), obtained by plotting the increase in utility due to receiving an additional unit of A, follows an exponential decay (Friedman and Savage 1948; Bernoulli 1954; Kahneman and Tversky 1979).

Preferences and utility functions are not visible, but can only be inferred from observable choices. In the analysis of consumer choice behavior, preferences are often inferred by pitting against each other two or more bundles, consisting typically of different quantities of good A and good B and observing the pattern of responses of the consumer. These choices or *revealed preferences* are thought to reflect the outcome of the consumer's internal decision-making processes and are an inherently *relative*



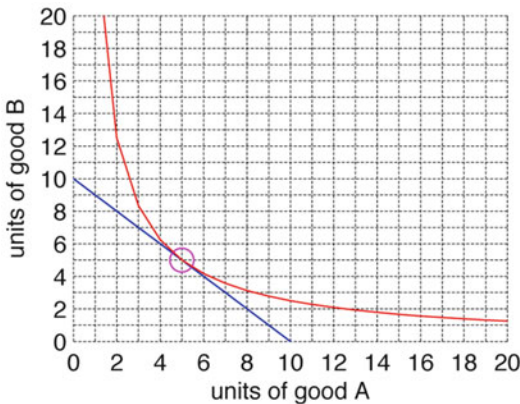
Choice Behavior, Fig. 1 Utility and marginal utility functions. (a) A utility function links objective quantities of a good with the subjective pleasure ("utility") derived from these goods. The concave, decelerating function

captures the notion that a small increase given a poor reference is more valuable than a similar small increase against a wealthy background. (b) Each additional unit of a good thus confers less additional or *marginal* utility

property. The consumer is assumed to maximize her/his *utility* (Von Neumann and Morgenstern 1944), or subjective pleasure, derived from obtaining each of the alternatives within her/his *budget* constraints. This is illustrated by plotting revealed preferences on a budget line diagram (Fig. 2). (Although the concept “*utility*” is often equated with subjective pleasure, this is an imprecise paraphrase of its historical meaning, since economic theory is agnostic about the actual mental mechanisms producing choice. Thus, strictly speaking, the term *utility* is inherently descriptive and does not refer to any actual hedonic or emotional states.) When asked to spend her/his budget between goods A and B within the allotted budget, the consumer reveals her/his preferences between A and B by selecting a certain bundle on the budget line. This bundle represents the best possible alternative available to the consumer within the budget. The weak axiom of revealed preferences (WARP; Samuelson 1938) states that the selected bundle is at least as good or better than other bundles on the budget line and strictly preferred over all other bundles that contain less goods

than the chosen bundle (every bundle inside the triangle). This prediction is derived from the assumption that, if the consumer prefers A over B, he or she cannot simultaneously prefer B over A and that more of a good thing is better than less of a good thing (cf. Glimcher 2010). WARP is an appealing theory with only minimal assumptions, but has little predictive power outside the revealed preference set. WARP has been extended to GARP, the generalized axiom of revealed preferences, refined, and shown to be a necessary and sufficient condition for choice data to be consistent with the maximization of a continuous, concave, and monotonic utility function (Houthakker 1950; Afriat 1967; Harbaugh et al. 2001). Satisfying GARP implies internally consistent decision making and transitivity, i.e., the preservation of a preference order, presumably corresponding to an at least ordinal utility ranking of the choice alternatives.

The chosen bundle is also informative about the consumer’s relative preference between A and B. More precisely, one could ask which bundles other than the chosen one would be equally valuable (i.e., render equal utility) to the consumer. Let us assume a consumer wanted to buy fruit and chose a bundle containing 4 apples and 3 oranges. And let us now assume that one apple is taken away from this bundle. How many oranges would we need to add to this new bundle to make it equally valuable to the old bundle? Removing one apple may be compensated by adding, say, one orange. However, the less apples the consumer has in his bundle, the more valuable each apple becomes (evident from the concave shape of utility functions), so if yet another apple is removed, one may have to add 2 additional oranges to make the next bundle equally attractive. Such equally valued bundles can be linked with an *indifference curve* (Fig. 2), a function that is convex to the origin, tangential to the originally chosen bundle, and represents combinations of good A and good B that render equal utility. The rate at which a consumer is willing to give up one unit of A in favor of one unit of B is called the *marginal rate of substitution* and can be read out from the slope of the indifference curve.



Choice Behavior, Fig. 2 Revealed preferences, the budget line, and indifference curve. If a consumer is asked to spend a budget of 10 units between good A and good B, both priced at 1 unit per good, her/his chosen bundle (purple circle on the blue budget line) reveals her/his preference. The indifference curve (red) links hypothetical bundles that would render equal utility to the chosen bundle. The marginal rate of substitution moves away from 1:1 as either good A or good B becomes scarcer and the utility attached to each unit of the scarce good increases

Choice Behavior in Animals: Optimal Foraging

It is very likely that evolution has shaped the way in which people make decisions. The evolution of decision making can be investigated by studying animal choice behavior. Biologists usually assume animals forage for food, choose mating partners, or make other decisions affecting their fitness. According to this view, natural selection has favored the development of specific choice behaviors that maximize the decision maker's Darwinian fitness, e.g., that optimize their energy intake and reproduction success (Kalenscher and van Wingerden 2011). Thus, like humans, animals encounter a plethora of choices in relation to food intake and energy expenditure. In the field of behavioral ecology, *optimal foraging theory* is a normative theory that prescribes that animals should make foraging decisions that maximize their *fitness*, operationalized as the ratio of food intake over expenditure to ensure survival (Charnov 1976) or reproductive success (Hamilton 1964a, b). When taking into account that a given food patch becomes depleted over time and obtaining additional energy intake therefore is associated with progressively larger amounts of energy spent foraging, the *marginal rate of energy intake* mirrors the shape of the marginal utility function. Indeed, animals are sensitive to the marginal rate of energy intake when making foraging decisions.

Choice Distribution: Herrnstein's Matching Law

When making repeated decisions between options A and B, a decision maker should consistently choose the option that represents the highest utility. Typically, however, this is not how animals behave in such a choice situation. Since the *reward rate* associated with a given option might change over time, it pays to switch between exploitation and exploration of choice options. The *matching law* (Herrnstein 1961) states that animals distribute their responses across choice options to match the relative rates of reward obtained from those options. So, for instance, if

option A provides three units of reward and option B provides one unit, then option A is typically chosen three times as often as B. Indeed, when given a choice, animals do explore the alternatives as predicted by the matching law (Kalenscher et al. 2003; Sugrue et al. 2004).

Choice Behavior Under Risk: Expected Utility

Often, the outcome associated with a choice option is not deterministic, but probabilistic. Probabilistic outcomes can be drawn from a distribution with known variance (such as a dice toss), in which case economists say that the outcomes are subject to *risk*. Thus, risk is often defined as outcome variance. Risk contrasts with *ambiguity*, which occurs when the variance in the outcome distribution is not (yet) known (Burke and Tobler 2011). In addition, uncertainty, defined as the inverse of predictability of the outcome, has been shown to affect decision making too. Risk, probability, and uncertainty are related concepts, as illustrated in the following example. Assume a decision maker chooses between the following gambles:

(A) Win \$90 or \$110 with equal probability ($p = 0.5$).

or

(B) Win \$50 or \$150 with equal probability ($p = 0.5$).

Both alternatives have equal expected value (the sum of the products of the probabilities times reward magnitudes is \$100 in both cases). However, alternative (B) has the higher outcome variance and is therefore the riskier alternative. For each alternative, the uncertainty of each outcome is maximal because $p = 0.5$. Changing the reward probabilities would skew the outcome distribution and would affect the alternatives' expected values. Uncertainty decreases towards the probability extremes and is zero at $p = 0$ or $p = 1$.

Risk also seems to play a role in animal foraging decisions. For example, the actual caloric

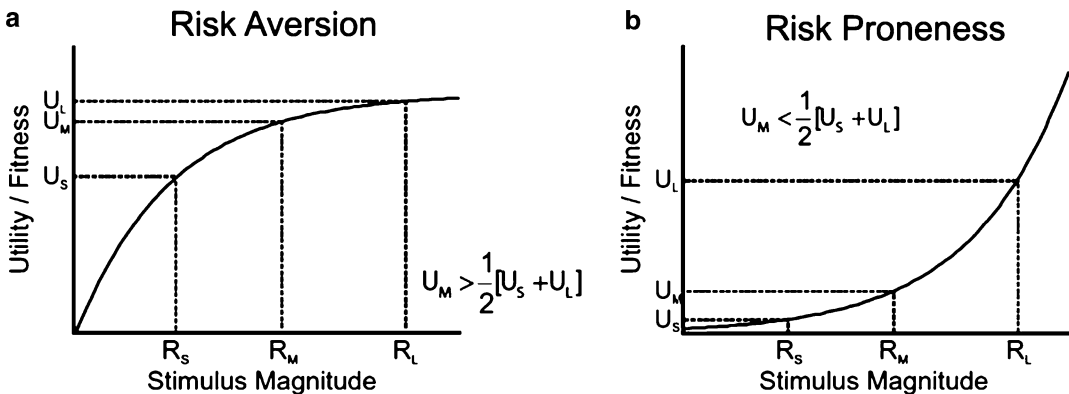
yield associated with hunting a certain type of prey varies depending on the specifics of the prey and the amount of energy spent during the hunt. A predator could opt for initiating a hunt subject to high risk with regard to the actual outcome or rather pursuing a low-risk foraging strategy with a tighter outcome distribution. In humans, risk and probabilities can be simultaneously or independently instructed, whereas animals typically have to sample the outcome distribution to arrive at estimates of outcome risk and probabilities (Schultz et al. 2008, 2011; Tobler et al. 2009; O'Neill and Schultz 2010).

The most prominent normatively flavored framework for understanding decision making under risk in humans is the *expected utility theory* (EUT; Von Neumann and Morgenstern 1944). EUT states that a decision maker should integrate the utilities of all possible outcomes of a decision weighted by their probabilities into an expected utility estimate, which can then be used to compare option alternatives. EUT proposes a set of mathematical equations to describe choice behavior based on four axioms that define a rational decision maker (rational in this case means that the decision maker exhibits stable preferences and behaves consistently with respect to them). These

axioms are completeness, continuity, transitivity, and independence. The first three prescribe that a decision maker can and will rank option alternatives consistently, while the fourth ensures that alternatives are evaluated independently, such that, for instance, the rank of an alternative should not be affected by the availability of an inferior alternative. If the axioms of EUT are met, option A should be preferred over option B if and only if $U(A) > U(B)$, that is, if the utility derived from option A exceeds that obtained from option B. If a consumer's choices imply a concave utility function, EUT predicts risk aversion if the choice is between a risky outcome (i.e., equiprobable low and high payouts) versus a safe outcome (certain, medium-sized outcome, Fig. 3). Due to the decreasing rate of marginal utility implied in concave utility functions, high outcomes are discounted more relative to small outcomes, so that

$$U_{\text{high}} + U_{\text{low}} < 2 * U_{\text{med}}$$

resulting in net risk aversion. In the study of foraging decisions, the concept of outcome variance has been captured in risk-sensitive foraging theory by assuming that energy intake is



Choice Behavior, Fig. 3 Risk aversion and risk proneness. Utility functions can explain risk attitude according to expected utility theory and risk sensitivity theory. (a) Utility (for humans) or Darwinian fitness (for animals) as a function of the magnitude of a commodity. The utility/fitness curve is concave and is a decelerating function of the current level of stimulus magnitude (wealth/amount) because the marginal utility/fitness increment decreases

with increasing level of stimulus magnitude. A concave utility/fitness function predicts risk aversion when choosing between a medium-sized, certain reward (R_M) and a risky option offering large or small rewards (R_S and R_L) with equal probabilities. (b) A convex function predicts risk proneness. (Taken from Kalenscher and van Wingerden (2011), with permission)

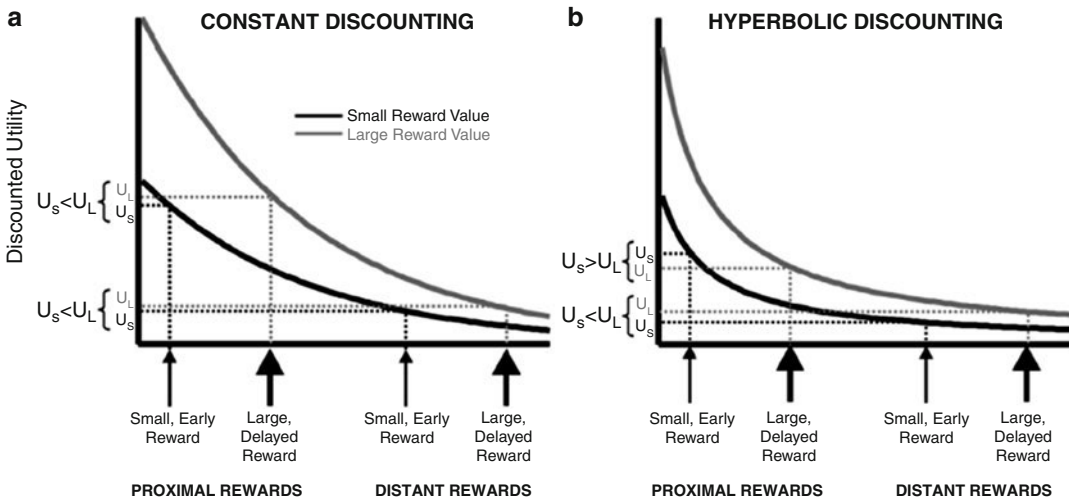
nonlinearly coupled to Darwinian fitness, resulting in a decreasing rate of marginal fitness that in turn predicts risk aversion (Kacelnik and Bateson 1996; Kacelnik 1997; Stephens 2008). Indeed, humans and animals are mostly risk averse in many domains and situations, although they occasionally exhibit risk-seeking behavior (Friedman and Savage 1948; McCoy and Platt 2005; Tobler et al. 2007; Glimcher 2008).

Choice Behavior with Delayed Outcomes: Discounted Utility

Besides outcome variance, delay to reward is another important factor affecting choice behavior. Humans and other animals, when given a choice between two equally sized but differentially delayed outcomes, will prefer the sooner reward to the later reward (Samuelson 1937; McDiarmid and Rilling 1965; Rachlin and Green 1972; Ainslie 1974; Kalenscher and van

Wingerden 2011). This process, called *delay discounting*, has been formalized in the normative economic framework of *discounted utility theory* (DUT; Samuelson 1937; Koopmans 1960; Prelec and Loewenstein 1991; Kalenscher and Pennartz 2008). DUT states that the value of a delayed reward decreases with the duration of the delay according to a discount function. Therefore, in maximizing the utility of her/his choices, a decision maker should take into account the *discounted utility*, derived by reducing the utility of each of the alternatives according to this time-dependent discount factor.

The shape of the discount function has been the subject of debate. Originally, a decreasing exponential with a constant discount factor was proposed (Samuelson 1937). An exponential discount function predicts that preferences are stationary, i.e., that the addition of a common delay to both alternatives in an intertemporal choice task should not interfere with the preference order (Fig. 4a; Koopmans 1960). Formally



Choice Behavior, Fig. 4 Constant vs. hyperbolic discounting. Constant vs. hyperbolic discounting of future events. The figure describes a choice between a small, short-term outcome or a large, long-term outcome (proximal) and another situation in which both outcomes are deferred into the future by the same time interval (distant). (a) Constant (here: exponential) utility function of a large, delayed (gray line) and small, short-term commodity (black line). With exponential discounting, preference stationarity holds when the rewards are deferred by the same time interval into the future. (b) People seem to

place a premium on short-term availability of rewards, deflecting the discount into an upward direction for temporally close rewards. The resulting hyperbolic discount function can explain preference reversals over time. Due to the steeper utility decay for short delays, the utility of the small, short-term commodity is higher than that of the large, delayed reward for temporally proximal outcomes, but the utility order reverses when both outcomes are deferred into the future. (Taken from Kalenscher and Pennartz (2008), with permission)

put, if a decision maker is indifferent between option A delivered at time t_1 and option B delivered at time $t_1 + \Delta t$, that is, choosing both options about 50% of the time, then preference stationarity states that he or she should also be indifferent between option A delivered at a later time t_2 and option B delivered at $t_2 + \Delta t$ (Eq. 1):

$$\text{If } A(t_1)\tilde{B}(t_1 + \Delta t) \text{ then } A(t_2)\tilde{B}(t_2 + \Delta t) \quad (1)$$

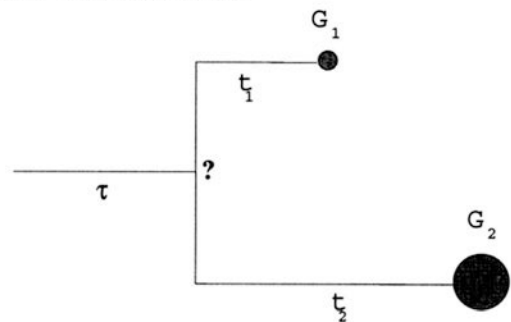
However, empirical evidence shows that in many situations, decision makers exhibit *time-inconsistent preferences* (see ► “Decision-Making, Bias”). This means that a decision maker prefers $A(t_1)$ over $B(t_1 + \Delta t)$ but $B(t_2 + \Delta t)$ over $A(t_2)$ after the addition of some common delay $t_2 - t_1$ (Ainslie 1975; Green et al. 1994; McClure et al. 2004). Given this evidence, a hyperbolic discount function, which can explain preference reversals after adding common delays, has been proposed (Fig. 4b; Ainslie 1975; Mazur 1984, 1988; Rachlin et al. 1991; Green et al. 2010). The tendency of humans and other animals to put a premium on the short-term availability of rewards has been called *impulsivity* or *failure of self-control* (see ► “Decision-Making, Bias”).

Ecological Rationality: Sequential Background-Foreground Choices

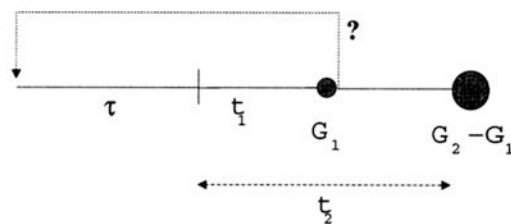
It has been argued that the (binary) choice between two differentially delayed alternatives is an artificial testing situation that does not correspond to the contexts in which animals make, and arguably preindustrial age humans made, their decisions. Stephens (2008) and coworkers have emphasized the use of sequential choice paradigms to approach foraging behavior, using *patches* as canonical units of foraging. A patch constitutes a finite-sized resource that can be exploited more than once. Importantly, the marginal rate of return decreases with each subsequent extraction until the patch is depleted. The foraging animal thus faces a sequential stream of choices to either stay and further exploit the patch or go and explore another source, which likely

depends on parameters such as the current rate of return given the patch depletion state and the travel time to the next patch. This type of sequential choice has a background-foreground structure in which the forager default or *background strategy* is to explore the environment for food, which can be temporarily put on hold to follow the *foreground strategy* of exploiting the current foraging options, such as gathering additional nectar or attacking a prey. Stephens et al. model intertemporal choice behavior using a patch paradigm by splitting the large, delayed reward in two smaller rewards. After receiving an initial small reward, the animal can choose to stay for an additional delay, resulting in the delivery of the second reward, or go and start a new trial (Fig. 5).

Self-control paradigm



Patch-use paradigm



Choice Behavior, Fig. 5 Self-control and patch-foraging paradigms. Two “equivalent” decision contexts. In the self-control paradigm, the subject makes a binary choice between a small immediate outcome (G_1 after t_1) and a large delayed outcome (G_2 after t_2). In the patch paradigm, the forager’s choice has equivalent consequences, but the forager decides whether to stay in the patch and collect $G_2 - G_1$ additional units of food after $t_2 - t_1$ or to leave immediately after obtaining the small amount G_1 . In the latter, but not the former case, the inter-trial interval (τ) is part of a key delay to the next reward opportunity. (Taken from Stephens and Anderson (2001))

By adjusting the time delays in the patch preparation to the delays typically used in the self-control or intertemporal choice paradigm, the mean outcome rates over time associated with the choice options can be matched precisely (Stephens and Anderson 2001). Whereas animals typically make many “impulsive” decisions in the binary intertemporal choice paradigm, resulting in a sub-optimal rate of energy intake, they attain much higher energy intake rates in the economically equivalent patch paradigms. Modeling choice behavior through decision rules, Stephens and Anderson show that the identical “shortsighted” decision rules produce optimal choices, in the sense of maximizing energy intake rates over time, in one paradigm (the patch situation), but very clearly not in the other paradigm (the binary intertemporal choice situation). Specifically, in the patch paradigm, the inter-trial interval becomes a key delay, included in the stay/leave decision, so that the short-term and long-term optimality of the choice for the larger, delayed reward becomes aligned (see ► [“Decision-Making, Bias”](#)).

Neural Correlates of Choice Behavior

Economic theory is traditionally agnostic regarding the mental mechanisms underlying choice behavior, but is only concerned with accurately describing and predicting choices. As a consequence, a common notion in economics is that a decision maker behaves “as if” he or she was maximizing a utility function, but economic theory does not assume that there actually is such a thing as a mental representation of a utility function. Recently, this agnostic view has been challenged by advances in the neurosciences aimed at investigating whether there actually is a neural representation of (cardinal) utility in the brain. This new “neuroeconomics” paradigm (Glimcher and Rustichini 2004) has proven quite fruitful in finding correlates of inferred utilities and, conversely, in predicting choice from neural data, supporting the validity of an underlying utility function guiding choice behavior.

The neural correlates of value-based decision making (as distinct from, e.g., perceptual decision

making or categorization) have been investigated in both humans and animals. A well-established finding in the research on value coding in the brain is that frontal brain regions such as the orbitofrontal cortex (OFC), lateral prefrontal cortex (IPFC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC) show differential levels of activity with regard to the (expected) value of a stimulus (see recent reviews by Rangel and Hare 2010; Louie and Glimcher 2012). Though the values associated with stimuli and actions influence neural processing in many other cortical and subcortical brain regions, electrophysiological recordings made from primate OFC (area 11/13, which has homologues in rodents and humans; Wallis 2012) indicate that neural representations of value associated with outcomes found in that brain region are independent of the action required to obtain the said outcome, its physical location, and, to some degree, its sensory features (Padoa-Schioppa and Assad 2006, 2008; Padoa-Schioppa 2007). When monkeys were faced with a binary choice, some neurons showed variation in firing rate that correlated with the derived subjective utility estimate of the chosen alternative, called *chosen value* correlates. Such an abstract representation of subjective value in a *goods-based model* (Padoa-Schioppa 2011) of choice alternatives approximates economic value as defined in normative frameworks such as EUT or DUT (see above). In humans, similar representations of expected and obtained value, which could inform decision-making processes and decision evaluation, are present in the ventromedial prefrontal cortex (Kable and Glimcher 2007, 2009; Kahnt et al. 2010) and ventral striatum (Knutson et al. 2001; Tobler et al. 2007; Rolls et al. 2008; Christopoulos et al. 2009).

Neural Coding of Risk, Probability, and Delays Associated with Outcomes

As outlined above, risk/outcome variance, probability/uncertainty, and delay to reward all influence choice behavior. Assuming that revealed preferences reflect internal decision-making

processes using the ordinal utility ranking of choice alternatives and that these processes rely on cardinal representations of value in the brain, it follows that neural signals in some brain areas should be sensitive to these parameters (Burke and Tobler 2011).

Risk

In humans, signals of risk, defined as outcome variance or reward volatility, can be found as BOLD activity correlates in the anterior cingulate cortex (Behrens et al. 2007; Christopoulos et al. 2009), OFC (Tobler et al. 2007), and VStr (Kuhnen and Knutson 2005). In nonhuman primates, a population of neurons recorded from macaque OFC and posterior cingulate cortex (CGp) show firing rates that correlate with risk levels. When given a choice between safe and risky outcomes, under certain conditions, these animals prefer the risky outcome, with their preference increasing as the risk increases (McCoy and Platt 2005; O'Neill and Schultz 2010); however, this risk-seeking behavior is linked to the objective levels of reward, so it reverses to risk-neutral or risk-averse behavior when higher outcomes are at stake. In macaques, these neuronal risk signals occur separately from expected value signals present in other OFC neurons, but in rats, risk does modulate reward-related neuronal responses (Roitman and Roitman 2010). Dopamine neurons also code a tonic risk signal in the delay interval between stimulus and outcome (Fiorillo et al. 2003, 2005; Tobler et al. 2005). It thus appears that the brain maintains an isolated measure of outcome variance, tracking the volatility of the reward environment. From an efficient coding perspective, this measure of risk should influence the neuronal representation of outcomes by scaling these representations to their mean (expected outcome) and variance (risk) to facilitate reward discrimination (Schultz et al. 2011; Louie and Glimcher 2012). Recordings of neural activity in primate and human OFC and primate lateral intraparietal area (LIP) show that this is indeed the case (Elliott et al. 2008; Padoa-Schioppa 2009; Louie et al. 2011; Louie and Glimcher 2012).

The neural basis of risk attitudes has recently been investigated, indicating that value signals related to risky outcomes in lateral prefrontal

cortex are modulated by individual risk attitudes (Tobler et al. 2009). The value signal of risky options was attenuated by increasing risk in risk-averse participants, but increased in risk-seeking participants. In addition, anticipation of risk differentially modulated neuronal activity in ventral striatum (VStr) and anterior insula (AI) for risk seekers and risk avoiders (Rudorf et al. 2012).

Probability

While a neural correlate of risk associated with a certain stimulus is informative for tracking the volatility of the expected outcome stream, a stimulus that predicts reward with $p = 0.75$ should clearly be valued higher than a stimulus that predicts reward with $p = 0.25$, in spite of equal risk associated with both stimuli. In contrast to humans, who can be instructed on probabilities, animals have to experience the outcome distribution. As probabilities associated with stimuli become known through repeated sampling, neural signals of outcome probabilities could emerge. Platt and Glimcher (1999) presented monkeys with pairs of stimuli that differed in the probability of associated reward, while recording the activity from neurons in LIP. They found that LIP neurons coded the action (a saccade) required to obtain the reward and that these neuron's firing rates were modified by both the probability of receiving a reward and its magnitude. When the probability of reward varied, animals exhibited matching behavior (see above), mirrored by neural activity in LIP that tracked the expected reward associated with each saccade target across trials (Sugrue et al. 2004). Dopamine neurons in the ventral tegmental area (VTA) of macaques also seem to incorporate probability in coding an expected outcome signal at the time of stimulus onset, in line with EUT (Fiorillo et al. 2003). In rats, neural activity in OFC single cells and ensembles discriminates between different probabilities (Van Duuren et al. 2009). In monkeys, firing rate modulation by outcome probability was found in ACC, OFC, and lateral prefrontal cortex by Kennerley et al. (2009) and Wallis and Kennerley (2011). Interestingly, the OFC contained a larger proportion of neurons that seemed to code an isolated probability signal, whereas this parameter was more

often integrated with other decision parameters in ACC and IPFC.

Delay

Humans and other animals prefer immediate over delayed rewards (see above). One view on the neural basis of these time preferences holds that immediate and delayed rewards are actually processed by different neural systems that compete for behavioral control. The so-called β system is placed in the mesolimbic reward areas such as VStr and OFC and is thought to process the immediate value of reward, while the δ system, located in prefrontal and parietal regions, performs basic exponential discounting of delayed rewards (McClure et al. 2004, 2007). Together, the β/δ system combines into a hyperbolic-like discounting function consistent with theoretical and experimental data (Ainslie 1975; Mazur 1984, 1988; Rachlin et al. 1991) with more steep discounting in the β than the δ network. Although the view that discounting is the consequence of two separate neural choice systems has been criticized (Kable and Glimcher 2007), recent models posit that the discounted future reward value is neutrally represented as a singular signal in ventromedial prefrontal cortex which, however, can be modified by activity in brain structures that were associated with the δ system, mainly dorso-lateral prefrontal cortex (Hare et al. 2009; Figner et al. 2010). In primates, single neurons in LIP (Louie and Glimcher 2010), OFC (Roesch and Olson 2005), and striatum (Cai et al. 2011) encode subjective value modulated by delay to reward. Likewise, single-neuron activity in the PFC homologue of pigeons (Kalenscher et al. 2005) and in rat OFC (Roesch et al. 2006) and other limbic structures (reviewed in Roesch and Bryden 2011) is sensitive to delay. However, in pigeons, the reward signal integrates delay to reward with magnitude, whereas this is not the case in rat OFC, amygdala, and ventral striatum.

The importance of the OFC for the representation to delayed rewards is underlined by the numerous lesion studies that have implicated this region, sometimes with opposing effects (Mobini et al. 2002; Winstanley et al. 2004; Rudebeck et al. 2006; Mar et al. 2011). In rats, Mar et al.

found that the exact anatomical locus of the lesion differentially affected delay discounting, with lateral OFC lesions increasing and more medial lesion decreasing discounting, respectively.

Neural Representation of Value in Foraging

As reviewed earlier, the binary choice context presented in most of the studies discussed above might not reflect the choices for which neural processes have presumably been adapted in the course of evolution (Stephens 2008; Kalenscher and van Wingerden 2011). If choice behavior relies partly on evolutionarily old adaptations to the stay/leave decisions made during foraging, it follows that the relative value of these alternatives should be represented, perhaps separately, in phylogenetically older brain structures. The challenge in foraging can be conceptualized as calculating the relative outcome rate of the current foreground environment versus the mean outcome rate of the background. Recent work in humans and primates indicates that dorsal ACC seems to code signals that relate to stay/go decisions in patch-foraging paradigms (Hayden et al. 2011; Kolling et al. 2012). While the OFC/vmPFC seems mainly concerned with current or chosen value, dACC activity scales with the relative level of reward in the background in both humans and macaques, possibly serving as a reference estimate for stay/leave foraging decisions.

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Chronic Electrical Stimulation

► [Parkinson's Disease: Deep Brain Stimulation](#)

Clone Nomenclature

► [Nomenclature of Ion Channels \(IUPHAR Scheme\)](#)

Closed-Loop Experiments

► [Adaptive Stimulus Optimization](#)

Closed-Loop Neuroprosthesis

► [Recurrent Brain-Computer Interfaces](#)

Cochlear Implant

► [Auditory Prosthesis](#)

Cochlear Inner Hair Cell, Model

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Synonyms

[Auditory sensory receptor cell, model](#); [Auditory transducer, model](#)

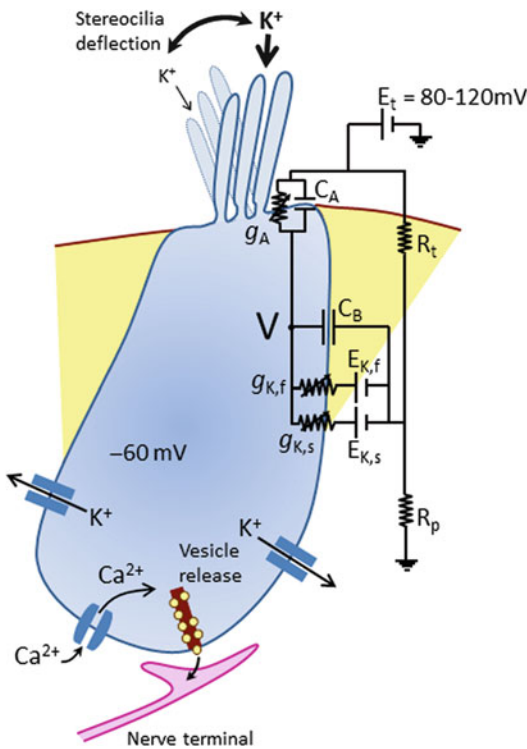
Definition

An algorithmic description of how deflections of the stereocilia in an auditory sensory receptor cell, or cochlear inner hair cell, cause fluctuations in the cell's intracellular voltage or receptor potential.

Detailed Description

Cochlear inner hair cells (IHCs) are auditory sensory receptor cells located in the organ of Corti. They have stereocilia that deflect following mechanical motion of the organ of Corti (Fig. 1). The fluid surrounding the stereocilia bundle, the endolymph, has a positive electrical potential (80–120 mV), while the electrical potential within the IHC is negative at rest (around –60 mV). Stereocilia deflection toward the tallest cilium in the bundle increases the inward flow of positive ions, mostly potassium (K^+), and thus increases the cell's intracellular potential. This mechanism effectively transduces a mechanical signal (stereocilia motion) into an electrical signal (the IHC intracellular or receptor potential). This mechanism is important because the IHC receptor potential controls the influx of calcium ions (Ca^{2+}) through voltage-gated channels, and intracellular calcium triggers the release of neurotransmitter from within IHC to the synaptic cleft, which then triggers action potentials in nearby auditory nerve terminals.

Increasing the amount of stereocilia deflection increases the proportion of open transducer channels and the magnitude of the receptor potential. The rate of increase is nonlinear due to two mechanisms: the saturation of transducer current (Lukashkin and Russell 1998) and the outward flow of K^+ through the IHC basolateral membrane (Kros and Crawford 1990). While stereocilia deflection in one direction increases the receptor potential, deflection in the opposite direction closes transducer ion channels and prevents the inward flow of K^+ ions to the cell. This asymmetric and saturating gating of transducer channels explains why the receptor potential shows an AC and a DC component. It also



Cochlear Inner Hair Cell, Model, Fig. 1 An inner hair cell and its equivalent electrical circuit model. Stereocilia deflection toward the tallest cilium increases the inward flow of K^+ , which increases the cell's intracellular potential (V). In the model, this is described by a conductance (g_A) in the apical portion of the cell's membrane, which is typically assumed to be the sum of a mechanically sensitive K^+ conductance and leakage conductance (not shown). The "excess" of intracellular K^+ is reduced by an outward K^+ current through voltage-gated basolateral channels. In the model, this is described by fast-activating ($g_{K,f}$) and slow-activating ($g_{K,s}$) basolateral K^+ conductances. The cell's intracellular voltage (V) controls the inward flow of calcium (Ca^{2+}), which controls the release of neurotransmitter vesicles from within the cell. The intracellular voltage also depends on other parameters: E_t endocochlear potential; R_t , R_p epithelium resistances; C_A , C_B capacitance of the apical and basal portions of the cell's membrane, respectively; $E_{K,f}$ and $E_{K,s}$ reversal potentials of the fast and slow basolateral K^+ currents, respectively. (Model adapted from Lopez-Poveda and Eustaquio-Martin 2006)

explains why the IHC is said to operate as a saturating, half-wave rectifier.

The IHC receptor potential is also determined by the resistor-capacitor effect of the IHC membrane and by the homeostasis of the organ of Corti. The amplitude ratio between the AC and

DC receptor potential components decreases with increasing stimulus frequency (Russell and Sellick 1978), which explains the common notion that the IHC operates as a low-pass filter. Less acknowledged, however, is that the AC receptor potential alone shows a band-pass response tuned at a frequency around 500 Hz (Sellick and Russell 1980) or 1 kHz (Dallos 1985) for low stimulus intensities. The rising slope of the AC frequency response probably results from receptor potential responding to the velocity of vibration of the organ of Corti for frequencies below approximately 200–500 Hz and to its displacement above that frequency (Sellick and Russell 1980).

The IHC responds nonlinearly also in time. The time-dependent activation of basolateral K^+ channels induces nonlinear, time-dependent adaptation of the receptor potential which could contribute partly to auditory nerve adaptation (Kros and Crawford 1990; Kros 1996).

Approaches to Model the IHC Transfer Function

IHC models aim at simulating the cell's receptor potential in response to a time-varying signal describing stereocilia motion. Traditionally, the IHC transfer function has been modeled using biophysical analogs and signal-processing analogs, as reviewed elsewhere (Meddis and Lopez-Poveda 2010).

Signal-processing models consider the IHC as a cascade of an asymmetric, saturating, nonlinear gain, which accounts for the growth of the transducer current with increasing stereocilia motion, followed by a low-pass filter, which accounts for the resistor-capacitor filtering of the IHC membrane. The order and cutoff frequency of this filter are chosen so as to mimic as closely as possible the physiological low-pass characteristics of the IHC. These models are easy to implement and fast to evaluate and require very few parameters. They, however, neglect important aspects of IHC processing and are limited in scope. For instance, they disregard the voltage and time dependence of activation of basolateral K^+ currents that could be significant for hearing brief and intense sounds

(Kros 1996). Another shortcoming of these models is that their parameters do not represent physiological variables; hence, these models may be inappropriate to model hearing impairment associated with IHC dysfunction.

Biophysical IHC models are electrical circuit analogs of the full organ of Corti (an early review is given by Mountain and Hubbard 1996). Figure 1 illustrates an example model of this type by Lopez-Poveda and Eustaquio-Martin (2006). It consists of several elements that describe the electrical properties of the apical and basal portions of the IHC and its surrounding fluids. It is assumed that the IHC intracellular space is equipotential and thus can be represented by a single node (V). It is also assumed that the IHC intracellular potential is primarily controlled by the interplay of a transducer, variable (inward) K^+ current that results from stereocilia deflections, and a basolateral (outward) K^+ current that eliminates the excess of intracellular K^+ from within the IHC. The magnitude of the transducer current is calculated from stereocilia displacement using a Boltzmann function that describes the gating of transducer channels. The excess of intracellular K^+ is eliminated through two basolateral voltage- and time-dependent nonlinear activating conductances: one ($g_{K,f}$) with fast and one ($g_{K,s}$) with slow-activation kinetics. The activation of these two conductances is modeled using a Hodgkin-Huxley approach. The reversal potential of each of the currents involved is accounted for by a shunt battery ($E_{K,s}$ and $E_{K,f}$). The capacitive effects of the IHC membrane are modeled with a single capacitor ($C_A + C_B$). The receptor potential also depends on the endocochlear potential (E_t), which is simulated with a battery. The values of the model parameters are typically set to physiological values or are optimized to reproduce physiological data. This relatively simple electrical circuit accounts for a wide range of well-reported in vitro and in vivo IHC response characteristics (Lopez-Poveda and Eustaquio-Martin 2006).

There exist simpler biophysical models that consider voltage- and time-independent basolateral K^+ currents (Shamma et al. 1986). There also exist more sophisticated models that incorporate the role of transmembrane chloride

and sodium currents and pumps in shaping the IHC intracellular potential (Zeddies and Siegel 2004).

Applications

Both signal-processing and biophysical IHC models have been used successfully in composite models of the peripheral auditory system and related applications (reviewed by Meddis et al. 2010). In this case, it is typically assumed that the input to the IHC model is basilar membrane motion rather than stereocilia motion, and a high-pass filter is used to couple between the two (Shamma et al. 1986). This high-pass filter is important to mimic the abovementioned band-pass behavior of the AC receptor potential, which could be significant for low-frequency hearing (Lopez-Poveda et al. 2007). Recent evidence suggests that the motion of the reticular lamina would be a more accurate mechanical input to the IHC than basilar membrane motion (Guinan 2012).

Cross-References

- [Anatomy and Physiology of the Mammalian Auditory System](#)
- [Auditory Sensing Systems: Overview](#)
- [Auditory-Nerve Response, Afferent Signals](#)

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Further Reading

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Cocktail Party Problem

- [Auditory Perceptual Organization](#)

Coding Accuracy of Neural Populations

- [Efficient Population Coding](#)

Coding Efficiency of Neural Populations

- [Efficient Population Coding](#)

Coexistence of Bursting Regimes

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Definition

Coexisting bursting solutions are exhibited in some models of bursting (link) neurons. Such solution regimes manifest themselves as a large number (typically three or more) coexisting stable periodic solutions. These solutions coexist at a given fixed parameter set, persist indefinitely, and can be switched by between external perturbations.

Detailed Description

Overview

Many biological dynamical systems exhibit multistability. Such systems have two or more stable attractors for a fixed set of parameters. Multistable periodic systems exhibit two or more oscillatory attractors for a fixed set of parameters. Examples of multistability can be found in vertebrate motoneurons (e.g., Hounsgaard and Kiehn 1989, where two distinct spike firing rates of action potentials coexist), invertebrate neurons (e.g., Lechner et al. 1996, coexisting bursting and spiking oscillations), and small networks of coupled neurons (e.g., Kleinfeld et al. 1990). Outside of neuroscience, such multistable oscillations can be found in models of intracellular calcium oscillations (Haberichter et al. 2001) and coupled genetic oscillators (Koseska et al. 2007).

Bursting pacemaker neurons are single neuron oscillators with a unique oscillatory state – they alternate between an active episode comprised of a series of two or more action potentials and a silent phase characterized by a lack of the firing of action potentials. Such oscillations are autonomous and exhibited by neurons in a variety of neural systems. These include invertebrate neurons (Kandel 1979),

cortical neurons (Chagnac-Amitai and Connors 1989), and brainstem neurons (Smith et al. 1991). Such properties are considered to be common to neurons involved in either central pattern generation or neurosecretory functions.

Bursting neurons can have multiple stable solutions. The most common and simplest case is coexistence of silent, bursting, and/or periodic spiking solutions. The coexistence of two such states is often referred to as bistability. Coexistence of periodic spiking and bursting solutions has been suggested in computational (Butera et al. 1995) and experimental (Lechner et al. 1996) studies of Aplysia neuron R15. Bursting neurons are often described as having their dynamics on two distinct time scales, one fast, underlying the firing of action potentials, and one slow, underlying the slow dynamics. The slower dynamics of a bursting system are often studied in the lower-dimensional space of the slower state variables (e.g., Butera et al. 1997).

Canavier et al. (1993) have shown for the first time that a modeled bursting neuron can exhibit a large number of stable coexisting bursting solutions. These solutions all exist at the same fixed parameter set. The occurrence of a given solution is dependent on the choice of initial conditions, and an appropriate well-timed single perturbation can switch the oscillation from one stable solution to another. Simulated neuromodulators can alter the number of stable attractors (Canavier et al. 1994). Two unique properties are exhibited by these solutions. First, the distinct bursting oscillations are *concentric* when viewed in the state space of the slow variables. Second, each distinct bursting oscillation *has a distinct number of action potentials per cycle*. Some of the stable bursting solutions were limit cycles, while others were chaotic attractors. Appropriately timed transient inputs are capable of switching the trajectory from one attractor to the other, but otherwise the attractors are stable, as well as robust to a modest amount of noise.

Necessary Components

This phenomena was further investigated in a reduced 4-variable ion-channel-based model (Butera 1998), and necessary components were identified that give rise to multistability. These

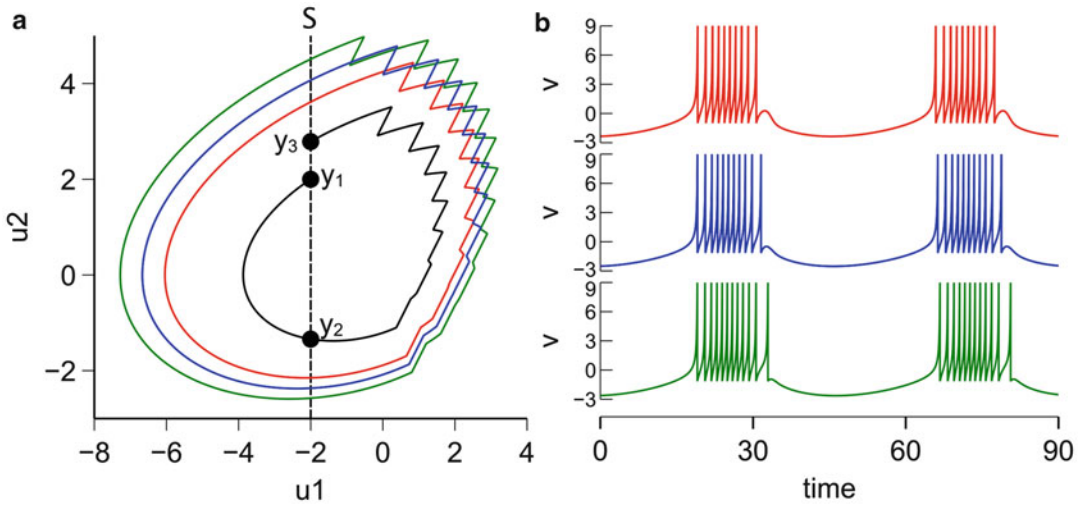
assumptions were validated in a simplified 3-variable model. Further studies (Newman and Butera 2010) generalized the 3-variable model to one that is scalable to an arbitrarily large number of stable solutions and demonstrated experimental responses of bursting neuron R15 to transient input that are consistent with these mechanisms. Several key components underlie these solutions in all computational models studied:

1. The solution trajectory, during the silent phase of the burst, converges to a low-dimensional manifold (two dimensional in the examples studied).
2. A first-return map constructed on this manifold possesses a series of discontinuous solutions, with each continuous set corresponding to all solution trajectories with the same number of action potentials.
3. The first-return map can be decomposed into two distinct maps – a contractile map corresponding to the silent phase of the burst on the low-dimensional manifold and an expansive map which is discontinuous, with each distinct set of points corresponding to bursts with the same number of action potentials.

Computational Example

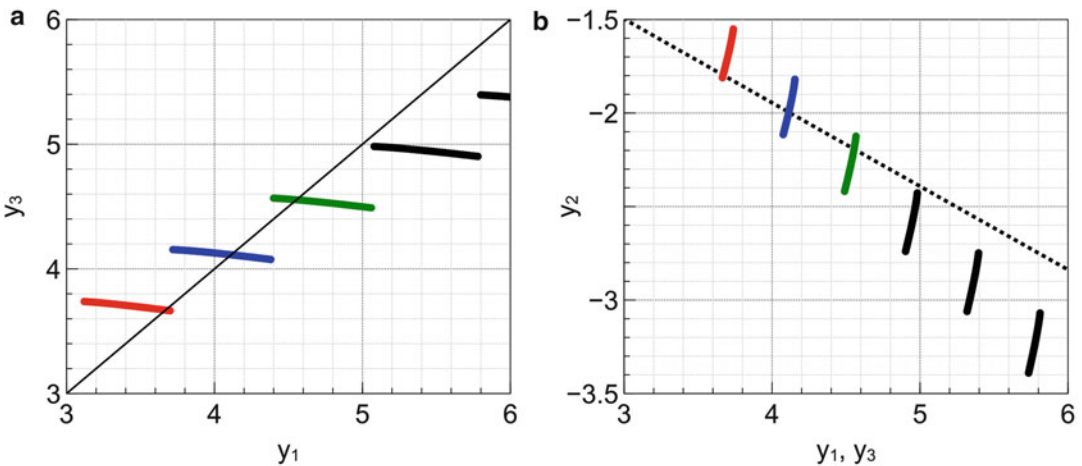
Figure 1 illustrates an example of a multistable bursting model. The model consists of two slow variables u_1 and u_2 and a quadratic integrate-and-fire-type model for the membrane potential variable v . At this parameter set (identical to those used in Fig. 2 of Newman and Butera 2010), three coexisting bursting solutions exist. Panel A illustrates the (u_1, u_2) phase space of the three solutions, all of which are stable limit cycles. The trajectories wind counterclockwise. When u_1 is at a sufficiently high value, the model starts firing action potentials, and with each firing of an action potential, the slow variables u_1 and u_2 are discretely perturbed. Panel B illustrates the time course of the three limit cycle solutions plotting v versus time. The solutions in panel B are color coded to correspond to the three phase-plane solution projections in panel A.

The dynamics of such a model can be studied by choosing a Poincare section (LINK) that spans



Coexistence of Bursting Regimes, Fig. 1 Multistability in a minimal bursting model. Model is from Newman and Butera (2010), with parameters identical to those used in Fig. 2 of that paper. (a) Phase-plane projection of the two slow variables of the model for

the three stable limit cycle solutions that coexist. (b) Plot of voltage versus time for the three stable limit cycle solutions, color coded to link to the identical solution trajectories in panel (a)



Coexistence of Bursting Regimes, Fig. 2 Mappings for understanding multistability in bursting models. (a) First-return map calculated by choosing initial conditions corresponding to positive y values on the Section S in Fig. 1. This is the mapping $y_1 \rightarrow y_3$, indicated by the example trajectory in Fig. 1. (b) Decomposed first-return map. The dotted line represents the mapping of all points y_1

to the corresponding crossing of S indicated by y_2 on Fig. 1. The dots represent the mapping of all points y_2 to the second cross of S indicated by y_3 on Fig. 1. This map is inverted so that both maps share y_2 on the y -axis. The color coding associates these maps with the solution trajectories in Fig. 1 that have the same number of action potentials as all the trajectories in these maps

all possible trajectories during the silent phase of the burst cycle. One such section is chosen and indicated by the line labeled S in Fig. 1. Initial conditions on this section y_1 are systematically chosen, and subsequent crossings of the section

in positive (y_2) and negative (y_3) direction are recorded. Using such an approach, a return map can be constructed. Figure 2a plots a return map of initial conditions along Section S in Fig. 1, plotting y_3 versus y_1 . Note the discontinuous nature of

the maps – each continuous family of solutions corresponds to all trajectories with the same number of action potentials during a burst. The data points corresponding to the same number of action potentials as the limit cycle solutions in Fig. 1 are colored accordingly.

To understand how the fast and slow processes interplay, the map can be decomposed into two separate maps. The map of $y_1 \rightarrow y_2$ represents the silent phase of the burst. This map is continuous, since action potentials do not fire, and is plotted by the dotted line in Fig. 2b. The map of $y_2 \rightarrow y_3$ highlights the effect of the action potentials in breaking up the map into discontinuous regions based on the number of action potentials fired. This is also plotted in Fig. 2b, only inverted, so that both maps share y_2 on the y-axis of the map. The intersection of these two maps is identical to the fixed points in the first-return map of panel A. By studying the effects of parameters on these maps, one can deduce how various components of the model contribute to modulating the map into having fewer or additional intersections, controlling the amount of multistability in the system.

Implications

The experimental validation of such models is challenging, as neurons exist not in isolation, but in complex networks. Newman and Butera (2010) illustrated experimental responses from bursting neuron R15 whose dynamics in response to transient inputs are consistent with the dynamics described by this class of models. They further postulate that this class of multistability can exist in a large number of bursting neuron models with circle/circle dynamics (Izhikevich 2007) and that even if only one attractor exists, such topology can give rise to complex transient responses to transient input.

While speculative, this type of bursting could underlie a form of memory not dependent on a slow time-scale process, but rather inherent in the stability of the attractors. Canavier et al. (1994) showed how neuromodulators could alter the number and stability of the attractors.

The feasibility of this idea has also been demonstrated in analog circuit implementations of these dynamics (Butera et al. 2002). Other dynamical

systems that exhibit such large-scale multistability typically rely upon the role of delayed feedback and have been demonstrated in neural systems (Foss et al. 1996) and engineered optical (Aida and Davis 1991) and digital (Aida et al. 1994) systems.

Cross-References

► [Multistability in Neurodynamics: Overview](#)

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Coexistence of Pathological and Functional Neuronal Regimes

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Definition

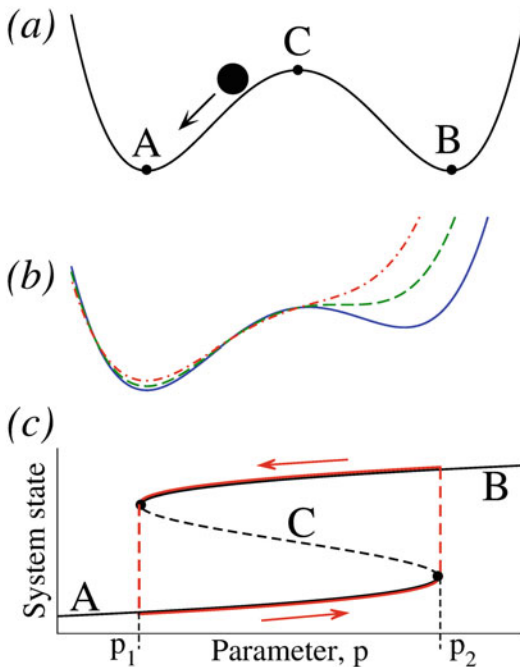
Coexistence of pathological and functional neuronal regimes designates a situation for the neural networks, where at least two regimes of the brain dynamics coexist related to either normal physiological (healthy) functioning or a pathological state. In other words, the corresponding neural populations demonstrate multistability of healthy and pathological attractors. Among pathological brain regimes one can distinguish several cases resulting in a number of neurological disorders

like epilepsy, Parkinson's disease, tinnitus, paroxysmal attacks of pain and muscle spasms, and bipolar disorders (Baldissera et al. 1991; Milton and Jung 2003; Foffani et al. 2003; Hammond et al. 2007; Roberts et al. 2010; Coggan et al. 2011; Goldbeter 2011; Raoul et al. 2012; Cloutier et al. 2012). Also, for the physiological regimes, several different attractors may coexist as found, for example, for multistable visual perception, central pattern generators in the context of motor control, resting states of the brain, memory and cognitive processes, etc. (Schöner et al. 1990; van Emmerik and Wagenaar 1996; Leopold and Logothetis 1999; Moreno-Bote et al. 2007; Briggman and Kristan 2008; Haken 2008; Sterzer et al. 2009; Deco et al. 2009; Lewis et al. 2009; Braun and Mattia 2010; Freyer et al. 2011). Multistability of pathological and functional regimes is by no means restricted to brain dynamics. Rather, both scientifically and clinically relevant multistability-related concepts are found in the field cardiac physiology. In fact, cardiac tissue supports several coexisting spatio-temporal dynamical patterns which can possibly be involved in the transition from reentrant tachycardia to fibrillation (Glass 2005; Hwang et al. 2005). The basis of such a complex phenomenon as multistability is a highly nonlinear character of the corresponding real systems, which implies the development and utilization of sophisticated modeling approaches and extensive computational and theoretical investigations.

Detailed Description

Introduction

A simple case of multistability, where two stable states coexist (bistability), is schematically illustrated in Fig. 1 (Hale and Kocak 1991; Strogatz 1994; Kuznetsov 1998; Thompson and Stewart 2002). If the system state is represented as a ball rolling in an energy landscape, then the latter may have the form of a double-well potential, see Fig. 1a. Two minima *A* and *B* stand for coexisting attractors which are separated by an unstable state *C*. The ball will approach one of the attractors if it is placed in the corresponding basin of attraction,



Coexistence of Pathological and Functional Neuronal Regimes, Fig. 1 Schematic illustration of bistability. (a) Energy landscape in the form of a double-well potential, where the system state is represented by a rolling ball. (b) Possible evolution of the potential when a selected parameter varies. (c) One-parameter bifurcation diagram where the stable and unstable states are depicted by black solid and dashed curves, respectively. Bistability emerges for parameter $p \in (p_1, p_2)$, and the red curves show a hysteresis when the parameter changes in the directions indicated by arrows

which reflects an appropriate choice of the initial conditions. If system parameters vary, the potential may undergo transformations, for example, one of the attractors may lose its stability or disappear (Fig. 1b). Such transitions, called bifurcations, can be illustrated by a one-parameter bifurcation diagram, when the limit system states are plotted versus the bifurcation parameter, see Fig. 1c. For parameter $p < p_1$ or $p > p_2$ the system is monostable and only one attractor exists, A or B, respectively. For the parameter range $p \in (p_1, p_2)$ the attractors A and B coexist and the system demonstrates bistability, see also Fig. 1a. Figure 1c illustrates just one of a number of possible bifurcation scenarios for the appearance of bistability of, for example, steady states (Hale and Kocak 1991; Strogatz 1994; Kuznetsov

1998; Thompson and Stewart 2002): When parameter p increases a stable state B and unstable state C emerge via a saddle-node bifurcation at $p = p_1$ in addition to the existing stable state A. The latter can then collide with C and annihilate in, again, a saddle-node bifurcation at $p = p_2$. Another possible scenario emerges when A is a steady state, and B and C are limit cycles. In this case the bifurcations at $p = p_1$ and $p = p_2$ are a saddle-node bifurcation for limit cycles and a subcritical Andronov-Hopf bifurcation, respectively. In this case the steady state A continues to exist for $p > p_2$, but gets unstable. The latter scenario can be realized, for instance, in the famous Hodgkin-Huxley (HH) model of action potentials in squid giant axons (Hodgkin and Huxley 1952; Rinzel and Miller 1980; Guckenheimer and Labouriau 1993), where the spiking behavior (supported by a stable limit cycle) coexists with a silent regime (supported by a stable steady state).

One of the indications of bistability is the observation of hysteresis (Hale and Kocak 1991; Strogatz 1994; Kuznetsov 1998; Thompson and Stewart 2002), where the system exhibits a delayed response to low, for example, cyclic changes of parameters and, hence, demonstrates a dependence on its history. In the framework of the bifurcation diagram shown in Fig. 1c, the system remains at the stable state A if the parameter slowly increases up to $p = p_2$. Then the system jumps to the state B since A either loses its stability or disappears. If parameter p then slowly decreases, the system will follow the evolution of attractor B even if p becomes smaller than p_2 . The return to attractor A takes place only for $p < p_1$. The following increase of the parameter will repeat the hysteresis loop, see Fig. 1c (red curves).

Multistability occurs at different levels of neuronal systems and constitutes a powerful repertoire of adaptive neuronal dynamical regimes.

Multistability in Single Neurons

Multistability has been observed and investigated for single neurons, both in experimental and modeling studies. Two coexisting stable steady states for the membrane potential have been

found in the squid giant axon under tetraethylammonium chloride (Tasaki and Hagiwara 1957). In the potassium-rich environment short depolarizing pulses can induce an abrupt transition from a lower state of the transmembrane potential to an upper state, and hypopolarizing pulses can reverse the transition (Tasaki 1959). The bistability of tonic spiking and silence has been demonstrated in the squid giant axon under low Ca^{2+} bath concentration, where a single current pulse can induce a transition between these two states (Guttman et al. 1980). More precisely, the repetitive firing can be annihilated by a brief depolarizing or hyperpolarizing pulse, whereas non-annihilating perturbations induce a phase reset. Moreover, the nerve was shown to exhibit a hysteresis when the current is slowly varied through the bistability range. The studies mentioned above provide experimental evidence of bistability of different regimes of the membrane potential in the squid giant axon and a possibility to switch between them under external perturbations, when the system is shifted into the corresponding basin of attraction, see also a theoretical study by Best (1979). The related HH model demonstrates a complicated bifurcation diagram including the coexistence of stable steady states and limit cycles supporting silent and spiking regimes, respectively (Hodgkin and Huxley 1952; Rinzel and Miller 1980; Guckenheimer and Labouriau 1993).

The neurons in the subthalamic nucleus (STN) in rat have been found to exhibit rich patterns of activity including a resting hyperpolarization (down state), a quiescent depolarization (up state), a rhythmic bursting, and a tonic firing (Kass and Mintz 2006). In such a way the STN neurons are quadristable, which also suggests different algorithms for integration and processing of incoming synaptic inputs. A bistable behavior was reported for α -motoneurons in cat, where a brief intracellular depolarizing current pulse can induce a sustained firing which can be terminated by a hyperpolarizing current pulse (Hounsgaard et al. 1984). Such “on”- and “off”-stimuli can switch the neurons between the two coexisting stable states. Moreover, for a slowly increasing and then decreasing depolarizing current a well-

pronounced hysteresis was observed for the firing frequency of the neuron. The stimulation current may thus play a role of a bifurcation parameter leading to different oscillatory regimes, see Fig. 1c. Bistability and hysteresis disappear even under sub-anesthetic doses of barbiturate or ketamin. However, the bistable behavior of the motoneurons can be observed in anesthetized cats during penicillin-induced seizures (Schwindt and Crill 1980).

Emergence and properties of multistability of neural dynamics have extensively been studied by modeling, where the advantages of bifurcation theory (Hale and Kocak 1991; Strogatz 1994; Kuznetsov 1998; Thompson and Stewart 2002) can be used to a great extent. The bifurcation analysis of a 19-compartment hippocampal pyramidal cell model under high-potassium conditions, a related two-compartment reduced model, and the HH equations reveals a parameter region of bistability characterized by repetitive firing and a quiescent state (Hahn and Durand 2001). For the HH model the bistability region is bounded by a fold-cycle bifurcation (saddle-node bifurcation for limit cycles), after which limit cycles disappear, from one side, and a subcritical Andronov-Hopf bifurcation, where the fixed point gets unstable, from another side, see also Guckenheimer and Labouriau (1993) for a review of bifurcations in the HH model. For the two-compartment reduced model, the regimes of stable spiking, low-amplitude oscillations, rest state, and repetitive bursting have been found with the bistability of the latter two, which is mediated by a subcritical Andronov-Hopf and a torus bifurcation (Hahn and Durand 2001). The bistability of a rest state and a firing mode in cerebellar Purkinje cells has been shown to be mediated by a saddle-node bifurcation of steady states in the transition from rest to firing and a saddle homoclinic bifurcation from firing to rest (Fernandez et al. 2007). The behavior of the cell and its model can be switched from rest to firing and from firing to rest by a brief and strong enough input (Loewenstein et al. 2005; Fernandez et al. 2007). The bistability of tonic firing and bursting was also found and studied in a detailed two-compartment conductance-based cortical neuron model for elevated extracellular

potassium concentration (Fröhlich and Bazhenov 2006).

A generic biophysical mechanism underlying the emergence of different dynamical regimes in a leech heart interneuron and its model has been studied by Cymbalyuk et al. (2002). A bistability of bursting and silence, bursting and tonic spiking, and tonic spiking and silence has been illustrated in a two-parameter bifurcation diagram. The coexistence of stable tonic spiking and bursting behaviors can be explained by the Lukyanov-Shilnikov bifurcation of a saddlenode periodic orbit with noncentral homoclinics (Shilnikov et al. 2005). A detailed bifurcation analysis of the bistability of the bursting and silence regimes of a model of a leech heart interneuron revealed that the bistability range in leak current parameter space is bounded by a subcritical Andronov-Hopf bifurcation of a steady state and a homoclinic bifurcation for a saddle periodic orbit of unstable hyperpolarized subthreshold oscillations (Malashchenko et al. 2011). The stable manifold of the latter separates the basins of attraction of the stable bursting and silence regimes. Six types of multistability have been reported for a low-dimensional neural model of a single leech heart interneuron based on slow calcium current (Malashchenko et al. 2011). There may coexist spiking and silence, spiking and subthreshold oscillations, spiking and bursting, bursting and subthreshold oscillations, bursting and silence as well as bursting, subthreshold oscillations, and silence.

As follows from the above brief overview, multistability is a generic phenomenon already at the level of single neurons. This is also supported by study of Marin et al. (2013), where a large database of isolated leech heart interneuron models was examined with respect to coexisting stable states. It appears that in 91% of 2223 cases of unique endogenous bursters, the multistability of bursting and silent regimes is present in some range of the leak conductance parameter. Such a prevalence of multistability in models of single neurons has to be taken into account at the investigation of neural networks, where the multistability can further be enhanced or even created by interactions.

Multistability in Neural Networks

When a population of bistable units gets weakly coupled in a network, the intrinsic bistability of individual nodes is translated into a pronounced multistability of stable states of the network as proved by Mackay and Sepulchre (1995) for a large class of interaction types. However, even for a monostable dynamics of individual elements, the interactions can induce additional attractors coexisting in the state space of coupled neurons. A single HH model neuron in a monostable regime can nevertheless demonstrate a great multistability if a self-interaction is introduced via a recurrent delayed loop (Foss et al. 1996). This has also been observed experimentally for a periodically spiking aplysia motoneuron reciprocally connected to a computer (Foss and Milton 2000).

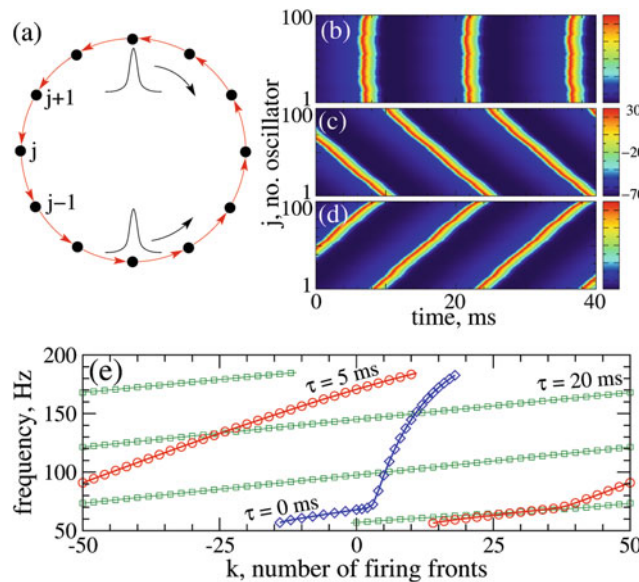
Two (or more) phase oscillators, each exhibiting simple periodic oscillations, can synchronize at different phase differences and synchronization frequencies depending on initial conditions if coupled with delay (Schuster and Wagner 1989; Lysyansky et al. 2008; D’Huys et al. 2008; Popovych et al. 2010). Two neurons with self- and mutual-inhibition and receiving a common excitatory input demonstrate several distinct firing patterns which change in discrete steps as the stimulus frequency varies (Harmon 1964). The considered network motif of reciprocally inhibiting pairs of neurons can control the antagonistic muscular systems, is able to store several patterns of motion, and exhibits a hysteresis at the transition between them. Coexisting polyrhythmic synchronization of three monobursting neurons has been found in simple network motifs of reciprocally inhibitory connections (Shilnikov et al. 2008), which can serve as building blocks for larger inhibitory-excitatory networks of, for example, central pattern generators (Briggman and Kristan 2008).

For a more complex coupling topology, the presence of at least one positive loop is a necessary (but not sufficient) condition for the emergence of multiple states (Thomas 1981; Cinquin and Demongeot 2002), which is of particular importance for the analysis of biological systems (Ferrell and Machleder 1998; Laurent and

Kellersohn 1999). This property can be illustrated on a simple network of oscillatory neurons coupled in a feed-forward loop (Fig. 2a) which seems to be a generic coupling topology in the nervous system (Alexander et al. 1986; Ahissar and Kleinfeld 2003) and has been investigated in the context of pathological neural dynamics (Volkman et al. 1996; Bergman and Deuschl 2002; Fogelson et al. 2006; Hammond et al. 2008), excitable cardiac tissue (Courtemanche et al. 1993), orientation tuning in visual cortex (Ben-Yishai et al. 1997), and central pattern generators (Golubitsky et al. 1999). For such systems a multitude of stable states may coexist which include in-phase synchronized states, where the neurons fire nearly simultaneously (Fig. 2b), as well as traveling waves with one or more firing fronts propagating either in the direction of coupling (Fig. 2c) or in opposite direction (Fig. 2d) (see Refs. Ermentrout 1985; Dodla et al. 2004; Perlikowski et al. 2010; Popovych et al. 2011). In spite of the monostable dynamics of the individual

neurons which can fire only at a single frequency, the ring-coupled neurons (Fig. 2a) synchronize and, depending on initial conditions, can spike with different phase shifts between neighboring neurons and also at very different synchronization frequencies selected from a certain interval (Fig. 2e). Including a communication delay in the coupling significantly enhances the multistability, where several firing patterns of the same spatial configuration (the same number of firing fronts), but with different oscillation frequency can coexist (Fig. 2e).

The intrinsic multistability of coupled neurons enables to select particular firing patterns of the network out of a repertoire of existing stable patterns. This can for instance be done by a brief transient perturbation shifting the system from one basin of attraction to another (Fig. 1a). The parameters of the stimulation signal, such as intensity, duration, and timing, have to be appropriately calibrated, which can be achieved with the use of the phase response curves (PRC)



Coexistence of Pathological and Functional Neuronal Regimes, Fig. 2 (a) Ring of unidirectionally coupled neurons. (b–d) Periodic spatiotemporal patterns appearing for identical synaptic weights and communication delays: (b) in-phase synchronization, (c) and (d) traveling waves with one firing front propagating along ($k=1$) and against ($k=-1$) the direction of coupling, respectively, see (a). The membrane potential V_j is encoded in color versus time

and oscillator number. (e) Co-existence of multiple stable traveling waves, where the spiking frequency of synchronized neurons is depicted versus the number of firing fronts k for different values of the delay τ in the coupling as indicated in the plot. (First published in Popovych et al. (2011). Copyright (2011) by the American Physical Society)

(Schultheiss et al. 2011), as suggested by Canavier et al. (1999). Other approaches include a stabilization of a targeted traveling wave by a delayed feedback stimulation (Montgomery and Silber 2004) or designing and stabilization of a desired firing pattern by an adjustment of communication delays or/and synaptic weights (Popovych et al. 2011; Yanchuk et al. 2011).

Feedback mechanisms are essentially involved in the function of a biological switch which can guide the transition of a biological system to particular functional regimes, for example, for the expression of one or another gene and protein production, or even make an irreversible turn into one of several possible distinct evolution pathways as, for example, for cell differentiation (Ferrell and Machleder 1998; Laurent and Kellersohn 1999; Cinquin and Demongeot 2002). A biological switch is a bistable (multistable) system which can remember a stimulus long after the stimulus has been removed and behaves like a light switch – once it is flipped, it will stay on (Ferrell 1998), see hysteresis in Fig. 1c. A simple biological switch has been discussed by Cherry and Adler (2000), where two coupled subsystems negatively regulate each other. Such a switch has two stable states, one in which the first element is in “on-state” and the second is in “off-state,” and another in which these states are reversed. A transient input signal can force the system into a particular steady state which persists after the input is removed. In such a way the system “remembers” what kind of input signal it was last exposed to, although it is composed from elements that themselves have no memory. Such a switch may be a simple component of a more complex regulatory network. The multistability of a system with feedback can be deduced from the behavior of the open-loop system when the feedback is blocked by a simple graphical method as suggested by Angeli et al. (2004).

The neurons in the brain are highly interconnected through a complicated coupling topology on both intra- and inter-population levels (Sporns 2011). Such a complexity has also been reflected in a variety of neural model networks of different architectures and levels of

detailing (Arbib 2003). Hence, one can anticipate a great multistability of many dynamical regimes in such networks. For example, an experimental study by Sasaki et al. (2007) investigated the spontaneous CA3 network activity in hippocampal slice cultures with functional multineuron calcium imaging. Several network states were revealed, where the system stabilizes and stays for tens of seconds in a certain configuration with sudden jumps to the next state. Such a behavior can suggest that the network dynamics is governed by local attractor-like dynamics with transitions from one attractor to the next. Repeated patterns of spontaneous neural activity have been found in cortical slice cultures, which can be maintained by the underlying neural network for many hours of observation (Beggs and Plenz 2004).

Functional Regimes

The multistability of neural populations may comprise healthy as well as pathological dynamical regimes. Examples of multistable functional regimes include multistable perception, varieties of motor patterns in the context of motor control, spontaneous neuronal activity of the brain at rest, etc. (Schöner et al. 1990; van Emmerik and Wagenaar 1996; Leopold and Logothetis 1999; Moreno-Bote et al. 2007; Briggman and Kristan 2008; Haken 2008; Sterzer et al. 2009; Deco et al. 2009; Lewis et al. 2009; Braun and Mattia 2010; Freyer et al. 2011).

Multistable perception can be explored when, for example, an ambiguous sensory stimulus (e.g., ambiguous picture such as the Necker cube, face-vase or young-old woman illusions) is presented, or when the eyes view two incongruent images in the framework of binocular rivalry (Ditzinger and Haken 1989; Leopold and Logothetis 1999; Sterzer et al. 2009; Braun and Mattia 2010). The perception will switch back and forth from one to another appearance and interpretation of the stimulus, which continues as long as the pictures are perceived, and the transitions with episodes of mixed or intermediate appearance also include self-transitions (Brascamp et al. 2006). Multistable perception is not restricted to the visual system. In fact, striking similarities in the

multistable behavior have also been observed for auditory and tactile sensory domains (Pressnitzer and Hupe 2006; Carter et al. 2008).

In multistable visual perception, the neurons in the visual system get strongly modulated during perceptual alternations such that a kind of competition between central stimulus representations can be hypothesized (Leopold and Logothetis 1999), see also Ditzinger and Haken (1989). Neuronal activity of different brain areas supports the sustained perceptual dominance of a certain pattern or participates in perceptual changes (Tong et al. 1998; Lumer et al. 1998; Sterzer et al. 2009). In this way, the brain seems to form different states of activity corresponding to the perception of different stimuli and switch between them when viewing ambiguous or dissimilar images. Macroscopic models for such processes were developed by Ditzinger and Haken (1989). It was found that such switches in the perception have a stochastic character and contrasted to the reciprocal-inhibition models of bistable perception in which fatigue initiates perceptual reversals (Taylor and Aldridge 1974; Leopold and Logothetis 1999). The statistical distribution of time intervals spent on each percept is unimodal and asymmetric and can be fitted by the gamma distribution, and subsequent intervals appear to be largely independent of each other (Fox and Herrmann 1967; Borsellino et al. 1972).

The dynamics observed in the context of perceptual multistability can be compared with that of the decision-making processes, where the framework of coexisting different attracting states is used (Deco et al. 2009; Braun and Mattia 2010). It can be explained by models having several stable states (attractors) representing different percepts (Fig. 1a), and the system visits one or another attractor under the action of random perturbations (Brascamp et al. 2006). Such an approach has successfully been applied to detailed mean-field and network models of spiking neurons extended by a weak adaptation process (Moreno-Bote et al. 2007), see also Gigante et al. (2009) for a more complex representation of attracting states for multistable perception. The attractor mechanism is also supported by results of Kim et al. (2006) showing that binocular rivalry

can exhibit the phenomenon of stochastic resonance (Moss et al. 2004). Random perturbations of the neural dynamics can, for instance, originate from a sporadic signal loss at the level of signal processing in the brain, eye saccades and blinking, finite-size induced fluctuations in neural networks, spiking variability, internal or external noise, etc. Randomness can even have a functional role, when the brain intentionally introduces perturbations of the vision in order to reorganize the sensory input and its processing and archive a more stable exploration and representation of the surrounding world (Carpenter 1999; Leopold and Logothetis 1999; Brascamp et al. 2006).

Multistability is a common phenomenon in the motor system which can generate a variety of recognizably different patterns of behavior (Schöner and Kelso 1988; Marder and Calabrese 1996; Briggman and Kristan 2008). Distributed control and modular organization of the motor circuits greatly contribute to multistable dynamics. The building blocks properties of the pattern generating circuits can be collected into a certain “alphabet” on the cellular, synaptic, and network levels, which essentially contribute to the functions and to the multitude of possible regimes produced by such systems (Getting 1989). These properties and, as a result, the dynamics of the neural circuits can be modified to a great extent by synaptic inputs or neuromodulators (Marder and Calabrese 1996; Briggman and Kristan 2008). The organizational principles of neural networks indicate that a single anatomical set of neurons may perform multiple tasks, which leads to the notion of multifunctional pattern-generating circuits (Getting 1989; Briggman and Kristan 2008).

A detailed examination of the flight behavior of the blowfly revealed a few discrete and distinct patterns of the neuronal spike trains controlling the corresponding muscle activity (Wyman 1966). During the flight, several different motor units of a single muscle receive repeated sequences of spikes from motoneurons, where the phase relations between spikes across different spike trains are stably preserved independently of the oscillation frequency. Occasionally, a transition to a different firing pattern can happen such that any

inter-unit sequential ordering of the spikes is possible. The group of motoneurons controlling the flight thus demonstrates a kind of “phase multistability” of a few stable output patterns corresponding to different possible combinations of preferred phase positions of the spikes (Wyman 1966). Another example of multistability in the motor system is provided by the central pattern generator (CPG) of the lobster involved in the generation of the “pyloric” motor rhythm (Russell and Hartline 1982). The motoneurons of the lobster CPG can be switched from the rest state to the bursting and back by brief depolarizing and hypopolarizing current pulses, respectively, in an all-or-none fashion. This fundamental feature of bistability of the motoneurons may play a role in the formation of the pyloric motor rhythm when neurons interact with the synaptic network of the CPG.

In experiments on voluntary cyclic movements of two hands or fingers, an abrupt transition from asymmetrical, anti-phase mode to symmetrical, in-phase mode of oscillations has been reported when the oscillation frequency was continuously increased (Kelso 1984; Kelso and Scholz 1985). While only one (symmetrical, in-phase) mode can be observed beyond the transition, both modes coexist for slow oscillations, and the system stays in the symmetrical mode and does not return to its initially prepared (asymmetrical, anti-phase) state when the cycling frequency is reduced. The observed hysteresis phenomenon, see Fig. 1c, and bistability were investigated in modeling studies (Haken et al. 1985; Schöner et al. 1986). Under the influence of random forces, the phase transition is characterized by two important properties referred to as *critical fluctuations* (Haken 1983), where the variables exhibit enhanced fluctuations close to the transition, and *critical slowing down* (Haken 1983), where the system demonstrates an increased relaxation time to the mode that turns unstable at the transition (Kelso and Scholz 1985; Schöner et al. 1986). These properties can serve as an indication of the bifurcation and can be assessed in experimental setups, where the noise is inevitable. Overall, these findings indicate the important role of the self-organization processes in motor control (Kelso 1997; Haken 2008).

In a neuronal model of the spinal pattern generator for the swimming in the lamprey, a multistability of a silent regime (steady state) and oscillatory behavior (limit cycle) can be mediated by saddle-node bifurcations of the fixed points and limit cycles (Jung et al. 1996). The most effective network models of CPG for walking can be decomposed into dynamical modules which demonstrate a well-pronounced multistability and enable a switching between multiple stable output configurations (Chiel et al. 1999; Beer et al. 1999). To describe the gaits of the quadrupedal locomotion for, for example, horses, a set of collective variables of the relative phases can be introduced, where the stable gait patterns are represented as attractors (Schöner et al. 1990). In this framework, continuous and abrupt gait transitions can be investigated, where the latter can be accompanied by stability loss of the corresponding attractors and the presence of hysteresis. Similar transitions, multistability, and hysteresis can also occur in human bipedal walking (van Emmerik and Wagenaar 1996).

Spontaneous activity of the brain at rest, which can be defined as the firing of neurons measured in the absence of (sensory) stimuli or task activations (Ringach 2009; Deco and Corbetta 2011), is a further example for the emerging of multistability of functional regimes. There is converging evidence for spontaneous activity being highly structured in both space and time, which suggests the existence of underlying attractor states (Plenz and Thiagarajan 2007; Ringach 2009; Deco and Corbetta 2011). The ongoing neural activity of resting brain states also demonstrates the presence of several attracting states and a spontaneous and irregular switching between them. For example, the instantaneous power of the human electroencephalographic (EEG) data exhibits erratic switching in the alpha band (~10 Hz) between low- and high-power modes as time evolves (Freyer et al. 2011). A sophisticated corticothalamic mean-field model predicts that these fluctuations arise from the noise-induced jumps between two distinct probability distributions with overlapping tails which emerge from a coexisting stable steady state and a limit cycle perturbed by noise. The latter includes additive

as well as state-dependent (multiplicative) components. The bifurcation diagram has the form as in Fig. 1c, where state *A* is a stable equilibrium bifurcating via a subcritical Andronov-Hopf bifurcation, and *B* and *C* are stable and unstable limit cycles, respectively (Freyer et al. 2011).

For spontaneous brain activity at rest, several large-scale resting state networks (RSN) can be identified by functional magnetic resonance imaging (fMRI), which include distinct brain areas being functionally connected by a significant correlation of their fMRI signals (Deco and Corbetta 2011). Since the topography of RSNs closely resembles the structure of jointly task-activated brain networks, different RSNs can be viewed as sets of attractor states shaped during repetitive activation by the task performance and maintained by intrinsic dynamics at rest (Lewis et al. 2009; Deco and Corbetta 2011). The measured spontaneous fluctuations of the macroscopic resting activity can be modeled by the dynamics of an ensemble of Wilson-Cowan mean-field models (Wilson and Cowan 1972) weakly coupled with time delay (Deco et al. 2009). Noise can induce a switching between multistable states of enhanced synchronization of either of the subnetworks with characteristic effect of stochastic resonance (Moss et al. 2004). These active fluctuations of the spontaneous activity between multistable states can set up the brain for external signals that can trigger the activation of one of the available multistable states (Deco et al. 2009; Deco and Corbetta 2011): “Metaphorically speaking, the resting state is like a tennis player waiting for the service of his opponent. The player is not static, but continues to move with small lateral jumps left and right to be able to react more promptly to a fast ball.”

Pathological Regimes

Several neurological disorders attracted large attention of the modeling studies, which can contribute to a better understanding of the mechanisms of pathological neuronal dynamics. In many cases such a dynamics involves the coexistence of two or more attracting states, where the brain switches between them in generating abnormal activity. Epilepsy is one of these diseases. The nonstationarity in time series from intracranial

depth and subdural EEG recordings of patients with temporal lobe epilepsy can be explained by transitions between two states of the mesoscopic collection of neurons contributing to the measured signals, and the transition probability increases as a seizure is approached (Manuca et al. 1998). Neuronal networks involved in epilepsy can be considered to possess a multistable dynamics consisting of, at least, two states: An interictal one characterized by normal ongoing activity, and another one that is characterized by the paroxysmal occurrence of synchronous oscillations (seizure) (da Silva et al. 2003a, b). The transitions between these two attractors can be caused by different endogenous or exogenous factors resulting in random fluctuations of some variables or variation of critical parameters. Such fluctuations lead to either sudden jumps between attractors or their gradual interchanging deformations (da Silva et al. 2003a, b; Breakspear et al. 2006). Several studies were devoted to an irregular dynamics of the “seizure” attractors characterized by positive Lyapunov exponents, which indicates the presence of chaotic regimes, and the dimension of such attractors may be significantly reduced as compared to “normal” ones (Babloyantz and Destexhe 1986; Kowalik et al. 2001).

Multistability comprising physiological sparse and pathological tonic-clonic activity was demonstrated in a realistic model network of two-compartment conductance-based neurons including extracellular potassium concentration dynamics (Fröhlich et al. 2010). For the same parameters and identical afferent input level, transient perturbations can switch the cortical network between these two states inducing, in this way, a long-lasting change in brain dynamics and replacing the functional regime by a pathological one. In the above framework of a “multistability-mediated dynamic repertoire,” the ictal state is characterized by a different behavior and its underlying mechanism as compared to the inter-ictal states. For example, the synaptic efficiency can be depressed during seizure contrary to its behavior in the non-seizure states, which can contribute to the mechanism of seizure termination (Vincent et al. 2011).

Also for Parkinson's disease (PD) there is an evidence of multistable dynamics. For instance, the recording of local field potentials (LFP) from the STN of patients with PD clearly demonstrates the emergence of a 300-Hz rhythm after levodopa administration, which is dopamine- and movement-dependent (Foffani et al. 2003). No such consistent rhythm has been found in the pathological regime in the absence of dopaminergic medication at rest, which could contribute to movement abnormalities in PD and reflect a bistable compound of nuclear activity at its transition to physiological functioning. Moreover, also in the two other major frequency bands, theta band (< 8 Hz) and beta band (8–30 Hz) (Brown and Williams 2005) pathological neuronal synchrony may occur. While beta band activity is related to akinesia and rigidity (Kühn et al. 2006), theta band oscillations are connected to tremor (Wang et al. 2005; Reck et al. 2009; Tass et al. 2010). Abnormal synchronization processes in these frequency bands served as targets for the development of stimulation techniques for desynchronization (Tass 1999, 2003b), ultimately aiming at an unlearning of abnormal synchrony by shifting the affected neural systems to more favorable attractors (Tass and Majtanik 2006), see below.

Furthermore, a repertoire of activity patterns of STN neurons (Kass and Mintz 2006) can support the emergence of multistable dynamics at the network level. The neurons in the pedunculopontine nucleus (PPN), which has been suggested as a target for deep brain stimulation (DBS) to improve gait and postural instability (Plaha and Gill 2005), exhibit a bistable behavior of fast and slow spiking (Lourens et al. 2011). DBS of PPN neurons in the pathological case can assist them to return to their natural oscillations, which in turn facilitates locomotion and postural control. The effect of STN DBS on rigidity, one of the cardinal symptoms of PD, can also be accounted for by multistability of motoneuron firing, see Hounsgaard et al. (1984). The stimulation can reduce the neuromodulatory input to the motoneurons which in turn switch from the state of persistent inward current characterized by self-sustained firing to the state, where the inward current is decreased or even suppressed, and the

rigidity is suppressed as well (Raoul et al. 2012). The pathogenesis of PD has been modeled at the molecular level, where a feedback-induced biochemical bistability was suggested to play a central role at the transition from a “healthy” homeostatic state to alternative “disease” state with stable high concentrations of molecules associated with PD (Cloutier et al. 2012). The presented simple bistable bifurcation diagram as in Fig. 1c allows a plausible interpretation of the impact of a variety of risk factors on susceptibility, severity, and multi-timescale progression of the disease.

The motoneurons' multistability (Hounsgaard et al. 1984) is involved in long-lasting epochs of muscle cramps which can regularly be evoked in patients by a short-lasting excitatory input to motoneurons and continues for more than 1 min (Baldissera et al. 1991). It has been suggested that such a perturbation shifts the motoneurons to a self-sustained depolarization and repetitive firing, which provokes the cramps. A suprathreshold stimulation was shown to terminate this activity by repolarizing the motoneurons and shift the motoneurons back to their low-level state. This result suggests that the mechanism which generates the cramps is intrinsic to the motoneurons' somata and based on the bistability of motoneuronal membrane (Baldissera et al. 1991) observed in other experiments (Hounsgaard et al. 1984). The susceptibility of the motoneurons to such a bistability can be enhanced by factors that modify the potassium equilibrium potential or conductance. The post-stimulation electromyographic (EMG) afterdischarges, which were observed in patients with peripheral neuropathies and with muscle cramps as compared to patients without cramps (Parisi et al. 2000), further support the importance of the above bistable dynamics of motoneurons in the generation of cramps. The afterdischarges are considered to be the result of a hyperactive bistable state of motoneurons which may occur spontaneously or may be triggered by a brief muscle contraction as well as by a repetitive stimulation of the peripheral nerve (Parisi et al. 2000).

The modeling of afterdischarges (continued spiking after a brief stimulus) in the framework

of paroxysmal symptoms, such as paroxysmal attacks of pain or muscle spasm, can reveal possible mechanisms of the underlying bistability that was found to be caused by slow positive feedback (Coggan et al. 2011). Perturbations can shift the system from the basin of attraction of a steady state (silent regime) to the basin of attraction of coexisting stable limit cycle (spiking regime), in this way initiating afterdischarges. In this state, an even slower negative feedback, such as intracellular sodium accumulation, is activated and destroys the attractor, which terminates the afterdischarges (Coggan et al. 2011).

Another example of multistable behavior related to pathological regimes can be the case of bipolar disorders which are characterized by recurrent and alternating episodes of mania and depression (Goldbeter 2011). A spontaneous and recurrent switching between mutually exclusive states of the disorder can be observed and explained by a model of two neural circuits that inhibit each other. Multistability has also been discussed in the context of human cancer by identifying bistable biological switches which could lock the networks of protein-protein interactions and gene regulations in a disease state, where some sets of genes could be abnormally overexpressed or repressed (Shiraishi et al. 2010).

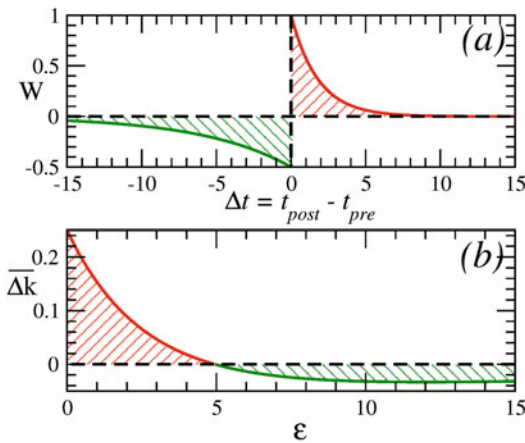
Time-Varying Parameters

Multistability is defined as coexistence of several stable states (attractors) for fixed parameter values (Fig. 1a), and perturbation of system variables can elicit sudden changes of the system's behavior by switching between different attractors. If parameters vary, the system can undergo transitions between qualitatively different dynamics, when a single attractor bifurcates, but this can, however, happen also in a monostable case. On the other hand, the parameters of complex biological systems are not fully frozen, but rather undergo a certain degree of variation while adapting to changes in the environment, input, underlying activity, etc. In the multistable situation a cyclic parameter variation may lead to the manifestation of hysteresis and sequential emergence of

different regimes corresponding to different attractors (Fig. 1c). This mechanism is the basis of burst generation involving a cyclic transition between two attractors: a stable steady state (hyperpolarized state) and a limit cycle (spiking) (Izhikevich 2000). In this case a slowly varying parameter depends on system's dynamics and is considered as one more dynamical variable.

Dynamics acting on different time scales are, in fact, of fundamental importance to biology (Haken 1992; Izhikevich 2000). For instance, in the context of the multistable perception, a specific set of so-called attention parameters was introduced (Ditzinger and Haken 1989). The latter become time dependent because of a saturation of synaptic connections (Ditzinger and Haken 1989). In this framework oscillations of the perception naturally arise, which are in excellent agreement with experimental findings (Ditzinger and Haken 1989). For epileptic tonic-clonic brain activity, a cyclic variation of a certain parameter may induce transitions between pathological and normal states in a hysteresis-like manner (Breakspear et al. 2006), and the state-dependent depression of synaptic efficiency may serve as a mechanism of seizure termination (Vincent et al. 2011).

It is well-known that synapses are involved in adaptation processes, where their efficacy is governed by spike timing-dependent plasticity (STDP) (Gerstner et al. 1996; Markram et al. 1997; Feldman 2000; Wittenberg and Wang 2006; Caporale and Dan 2008). An example of the STDP function is illustrated in Fig. 3a (see also Refs. Bi and Poo 1998; Bi 2002). The synaptic weights are updated in a point-like process by the increment $W(\Delta t)$ after pre- or post-synaptic neurons fired. For such a plasticity rule the synaptic weight is potentiated or depressed depending on whether the post-synaptic firing follows or advances the pre-synaptic firing, respectively. STDP can lead to multistability where states with different connectivity and different collective dynamics may coexist. If, for instance, the initial coupling is weak, the neurons get desynchronized, and the spiking time differences Δt get broadly (e.g., uniformly) distributed. Then STDP (Fig. 3a) leads to a further



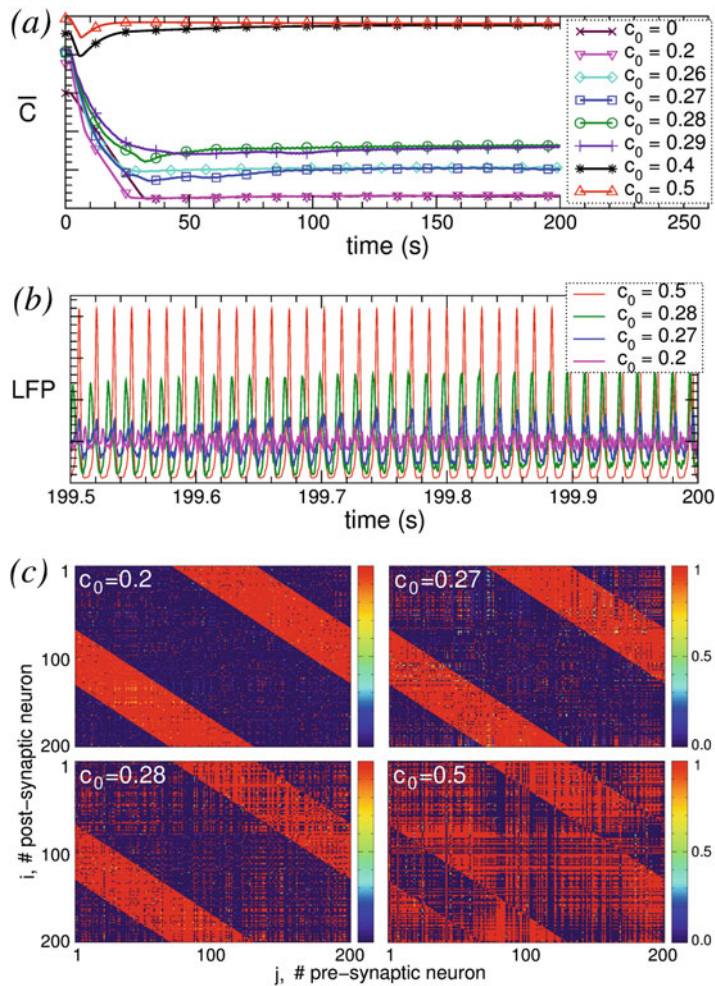
Coexistence of Pathological and Functional Neuronal Regimes, Fig. 3 (a) Normalized plasticity function versus the difference of the spike/burst timing of post- and pre-synaptic neuron $\Delta t = t_{\text{post}} - t_{\text{pre}}$. (b) The average update rate of synaptic weights $\Delta k(\epsilon) = \int W(\xi)\rho(\xi)d\xi$ for the uniform distribution density $\rho = 1/2\epsilon$ of $\Delta t \in [-\epsilon, \epsilon]$

suppression of the coupling, see Fig. 3b for large ϵ where $\Delta k < 0$, the neurons remain desynchronized, and a weakly coupled desynchronized state gets stabilized (Fig. 4). On the other hand, if the initial coupling is strong, the neurons fire synchronously, that is, their spiking time differences are narrowly distributed around zero, see Fig. 3b for small ϵ where $\Delta k > 0$, and the synaptic weights get further potentiated. Such initial conditions result in a strongly coupled synchronized state (Fig. 4). Along with the two regimes, some other states with intermediate coupling strength and synchronization may coexist as well (Fig. 4).

Neuronal synchronization is essentially involved in normal brain function, ranging from sensory information processing to cognitive and motor function (Singer 1993; Engel et al. 2001). Abnormal neural synchrony, on the other hand, can significantly impair neural processes and is a hallmark of several neurological disorders like Parkinson's disease or tinnitus (Hammond et al. 2007; Roberts et al. 2010). Hence, it was suggested to specifically counteract abnormal neural synchrony by desynchronization achieved with computationally designed stimulation techniques (Tass 1999). Accordingly, methods for

synchronization control developed with methods of dynamical systems (Tass 1999, 2001, 2003b; Rosenblum and Pikovsky 2004; Popovych et al. 2005; Popovych and Tass 2010) may turn out to have significant clinical applications. Desynchronizing stimulation can induce a rewiring of the synaptic connections in which the synaptic weights get depressed (Tass and Majtanik 2006). After sufficiently long stimulation, the amount of coupling in the network is significantly reduced, and the neural population is shifted to a healthy model attractor with a weakly coupled and desynchronized regime (anti-kindling) (Tass and Majtanik 2006).

The anti-kindling process in a neural network with STDP is illustrated in Fig. 5 for coordinated reset (CR) stimulation suggested for desynchronizing electrical DBS (Tass 2003a, b; Tass and Majtanik 2006) and for the treatment of tinnitus by noninvasive acoustic stimulation (Tass and Popovych 2012). For both stimulation modalities, that is, for somatic electrical and synaptically mediated (e.g., sensory) stimulation, there exists a range of stimulation intensities, where CR stimulation can effectively shift the collective dynamics of the stimulated neural network to a weakly coupled and desynchronized regime which stably persists after cessation of stimulation (Fig. 5, green curves) (Popovych and Tass 2012). This corresponds to long-lasting therapeutic effects of CR stimulation, which has been confirmed by several pre-clinical and clinical studies. CR-induced long-lasting desynchronization has experimentally been verified in rat hippocampal slice rendered epileptic by magnesium withdrawal (Tass et al. 2009). In addition, electrical CR stimulation of the STN was tested in a non-human primate model of parkinsonism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque monkeys, where sustained therapeutic long-lasting aftereffects on motor function in MPTP monkeys were observed after low-dosage CR stimulation (Tass et al. 2012a). Lasting aftereffects of electrical CR stimulation of the STN were observed in Parkinson patients (Adamchic et al. 2014). Moreover, noninvasive sensory (acoustic) CR stimulation has already been



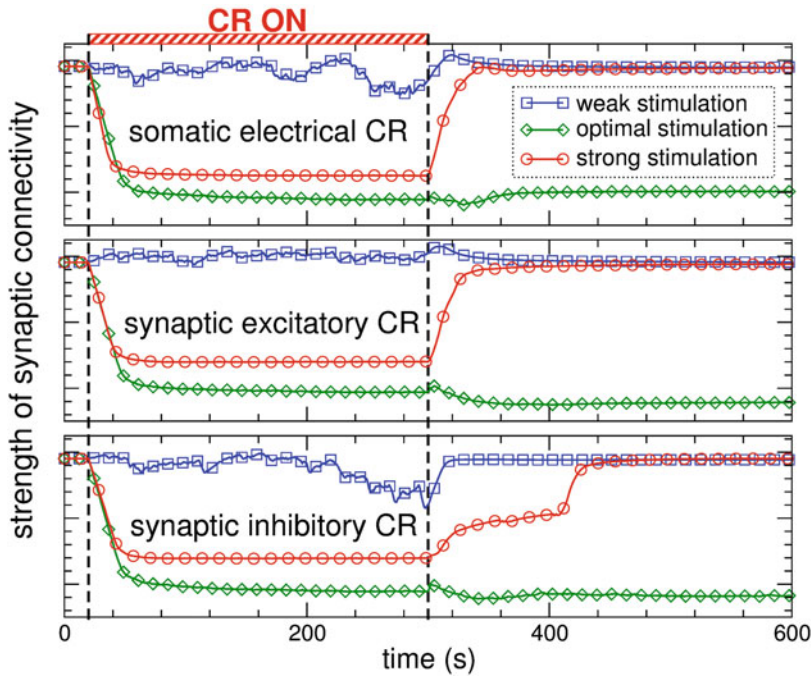
Coexistence of Pathological and Functional Neuronal Regimes, Fig. 4 Plasticity-induced multistability of synchronized and desynchronized states in a neural network with STDP. **(a)** Time courses of the mean (averaged across the network) synaptic weights $C(t)$ for different initial coupling matrices $\{c_{ij}(0)\}$ whose elements are Gaussian distributed around the mean value c_0 indicated in the legend. **(b)** Time courses of the LFP of four different stable regimes observed for the initial coupling matrices with mean value c_0 indicated in the legend. LFP

oscillations of different amplitude reflect the extent of synchronization among neurons. **(c)** The corresponding coupling matrices developed in the neural ensemble due to STDP for four different stable states. The initial mean values c_0 are indicated in the plots. The closely (distantly) located neurons interact via excitatory (inhibitory) connections according to the Mexican hat spatial profile with periodic boundary conditions, see Popovych and Tass (2012) for details

applied for the treatment of chronic subjective tinnitus and is turned out to significantly counteract both tinnitus symptoms and the underlying pathological neuronal synchronization (Tass et al. 2012b) by normalizing the effective brain connectivity and restoring the functional patterns of activity (Silchenko et al. 2013; Adamchic et al. 2013).

Summary

The theoretical framework of attractors and multistability established for nonlinear dynamical systems can effectively be applied to the analysis of realistic biological systems, in particular, to the investigation of neuronal dynamics. Multistability enables to switch system from one state to another



Coexistence of Pathological and Functional Neuronal Regimes, Fig. 5 Stimulation-induced rewiring and desynchronization of the neural ensemble with STDP by desynchronizing coordinated (CR) stimulation. The time courses of the mean synaptic weights $C(t)$ are plotted for weak, optimal, and strong stimulation intensities as indicated in the legends. The stimulation time interval is

indicated by a red bar and by vertical dashed lines for direct electrical CR stimulation, indirect excitatory CR stimulation, and indirect inhibitory CR stimulation (as indicated in the plots) administered to a strongly coupled and synchronized regime as in Fig. 4 for $c_0 = 0.5$, see Popovych and Tass (2012) for details

appropriate perturbation. The emergence of hysteresis, which can be induced by a cyclic parameter variation, provides further evidence for co-existing attractors. To understand the mechanisms underlying the neuronal dynamics, it is important to figure out whether the observed behavior belongs to a “parameter-mediated dynamic repertoire” or to a “multistability-mediated dynamic repertoire” (Fröhlich et al. 2010). In the latter case, a brief appropriate stimulus may suffice to switch the system to another, possibly more preferable state as explained above, whereas to control parameters is a much more difficult task, in particular, in neuronal networks of the brain. The modeling approaches at different levels of complexity significantly help in solving the above problem, where the study of bifurcation mechanisms as well as other properties of attractors and the structure of the state space can

substantially contribute as illustrated above. In this way, the model-based development of control methods with the use of methods from nonlinear dynamics and especially the phenomenon of multistability can result in effective techniques for the treatment of a variety of neurological diseases.

Glossary

Attractor An attractor is a closed invariant set in the state space of a system to which many initial conditions (configurations) of the system converge as time evolves. The union of all initial conditions approaching an attractor constitutes its basin of attraction and has a positive measure, that is, it occupies a positive volume of the state space. An attractor cannot be

decomposed into smaller attractors with distinct basins of attraction. In the theory of dynamical systems a number of different types of attractors have been discovered including steady states, limit cycles, and chaotic attractors, where the latter two are characterized by periodic and irregular oscillations, respectively.

Bifurcation A bifurcation denotes a sudden qualitative change of the system's dynamics as one or more parameters vary over a bifurcation point. A number of local and global bifurcations are known including saddle-node (fold), Andronov-Hopf, period-doubling (flip), transcritical, pitchfork, Neimark-Sacker (torus), saddle-node on invariant circle (SNIC), blue sky catastrophe, homoclinic, and hereoclinic bifurcations. Bifurcations can involve steady states (fixed points), periodic orbits (limit cycles), or more complicated objects like chaotic attractors. Bifurcation theory describes the bifurcation conditions and dynamics of the system before and after the bifurcation. The bifurcation transition gets more complicated with increasing codimension of a bifurcation which is the number of varying parameters necessary for the bifurcation to occur.

Multistability Multistability is a property of a system to have two (in the case of bistability) or more different attractors which coexist in the state space for the same values of system parameters. These states can be realized for different initial conditions or under perturbations shifting the system state to the corresponding basins of attraction. In biological systems multistability is a common phenomenon.

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Cognition and Control

► Embodied Cognition, Dynamic Field Theory of

Cognition, Bayesian Models of

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Synonyms

Probabilistic models of cognition; Rational models of cognition

Definition

Bayesian models provide a principled way to deal with uncertainty. In cognitive tasks the uncertainty is mainly in how to represent the observed

data, as there is usually not enough data to uniquely determine the representation. Bayesian models of cognition implement a general method for dealing with representational uncertainty which can be applied to explain human performance in various cognitive tasks.

Detailed Description

Cognitive tasks are full of uncertainty. From deciding what to call a new object, to determining what causes what in the environment, to learning a language, there is generally not enough information to uniquely determine the answer. Bayesian models of cognition provide a principled way to deal with this uncertainty, using probability theory to evaluate hypotheses and produce responses. Below, I briefly review three key areas in which Bayesian models of cognition have been applied: categorization, learning and causal inference, and language.

Categorization

Studies of categorization investigate how people group stimuli and generalize from previous experience to new situations. Classically, categories were defined by a set of necessary and sufficient conditions that determined whether an object was a member of the category. However, all-or-none category membership clashes with empirical investigations demonstrating that in human categorization, objects are more or less members of a category (Rosch 1973; Rosch and Mervis 1975).

Bayesian models of cognition provide a link between the classical definition and empirical observations. People might assume that a necessary and sufficient set of conditions describe the category, but do not know the exact set of conditions. For example, it might be unclear exactly what wavelengths of light define the category of red. Uncertainty about the boundary can be dealt with in a Bayesian model, which produces a graded category as a result of combining sets of more or less likely conditions (Shepard 1987; Tenenbaum and Griffiths 2001).

Another classic representational question in categorization is whether categories are represented by prototypes or exemplars. Prototype representations compare new stimuli to a single abstract example, while exemplar representations compare new stimuli to all previously observed examples (Medin and Schaffer 1978; Nosofsky 1986; Reed 1972). Each representation is appropriate for different problems, and Bayesian models have been used to combine these representations together, weighting representations by how well they suit the problem (Anderson 1991).

Learning and Causal Inference

Learning research has a long history in cognition, with initial investigations focusing how animals were able to associate stimuli such as tones and lights with particular rewards. Although early work investigated associations, the demonstrated power and flexibility of animal learning indicated that more complex representations were used (Rescorla 1988).

This type of learning has been modeled in a Bayesian framework as causal inference, in which the animal attempts to determine the causal structure of the environment in order to make predictions (Courville et al. 2006). Learning a causal structure is extremely difficult, and for some learning problems even infinite observations of outcomes are not enough to uniquely determine the structure. Bayesian models deal with this uncertainty and can even take into account vast spaces of possible structural forms (Kemp and Tenenbaum 2008).

Language

In language learning a difficult problem is to work out what is and is not grammatical, and this is another problem for which too few examples exist to uniquely determine the answer (Gold 1967). Learning grammaticality is difficult: while people almost always observe only correct examples of language use, they learn both grammatical rules and also the exceptions to the rule. An example of this is the dative alternation: for most verbs it is grammatical to alternate between the

constructions “He threw the ball to me” and “He threw me the ball,” but an exception is the verb *carried* (Baker 1979).

While the absence of observing “He carried me the ball” is not proof that this construction is ungrammatical (it could be just rarely employed), it is evidence for the hypothesis that *carried* is an exception. By adjusting the weights on the hypotheses given the observed data, Bayesian models of language are able to make sensible inferences despite uncertainty about how language should be represented (Perfors et al. 2010).

Cross-References

► [Perception, Bayesian Models of](#)

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Coherence and Granger Causality Spectral Analysis

► [Spectral Interdependency Methods](#)

Coherence of Local Field Potentials

► [Local Field Potential, Synchrony of](#)

Collations of Connectivity Data on the Macaque Brain (CoCoMac)

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Synonyms

[Compilation of published tracer injection studies in the Macaque brain; Macaque axonal projection matrix; Macaque brain wiring diagram](#)

Definition

Collations of Connectivity Data on the Macaque Brain (CoCoMac) is a database that contains the results of hundreds of publications in which tracer substances are injected into macaque brains to

reveal the afferent and efferent projections of neurons in the injection zones. The goal is to get complete coverage of the brain, so that a full axonal projection matrix can be extracted from the database.

The injected tracer substances diffuse from the extracellular space into the neurons and are then driven by active transport mechanisms toward the axon terminals (anterograde tracer) or toward the soma (retrograde tracer). For each tracer injection, the core information to record is (i) the location of the injection zone, (ii) whether the tracer is anterograde or retrograde, (iii) which locations in the brain are labeled by the tracer after the incubation period, and if available (iv) the laminar distribution of labeled sites and (v) quantitative measures.

This information is collated from the literature by manually parsing figures and textual statements, in which locations are expressed as brain region names. What makes the task challenging is that the relevant literature spans many decades and that nomenclatures and brain parcellations (atlases) vary widely both in time and across research groups. CoCoMac uses transformations based on spatial relations (Stephan et al. 2000) to map data onto a user-specified set of brain regions.

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Collision Avoidance Models, Visually Guided

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Definition

Visually guided collision avoidance models (VGCAMs) describe the operation of sensory

and motor neuronal circuits detecting potential collisions and producing motor avoidance responses. To describe these sensory–motor transformations, VGCAMs usually begin as phenomenological descriptions of responses and then focus on the study of associated neural circuits and biophysical mechanisms. At the sensory level, several biophysical processes operate in parallel to shape and tune the visual response of collision detecting neurons. VGCAMs also generate descriptions about the operation of intermediate circuits linking sensory input and motor output, when experimental data about these intermediate circuits is incomplete.

Detailed Description

Visually Guided Collision Avoidance Behaviors

Most visual animals are highly effective at detecting and avoiding collisions, which may occur either by encounters with obstacles during navigation (Tammero and Dickinson 2002b) or by moving objects that directly approach them (e.g., predators; Rind and Simmons 1999; Gabbiani et al. 2004; Simmons et al. 2010; Fotowat and Gabbiani 2011; Card 2012). In both cases, an important visual cue to predict a potential collision is the expansion of the approaching surface or object. The detection of this visual cue triggers motor programs controlled by neural circuits to generate quick and reliable avoidance responses. To be effective, the associated maneuvers need to be executed in a timely and accurate manner, which implies that the approaching object must be precisely monitored in real time. For this reason, most animals possess movement detector neurons specially tuned to detect objects approaching on a collision course. Thus, visually guided collision avoidance behaviors (VGCABs) provide a favorable model for studies of sensory coding and sensory–motor transformations.

Looming Stimuli

To describe the visuomotor transformation that begins in sensory neurons and ends in the animal's muscles, one needs well-controlled stimulation

conditions. If we stimulate the animal monocularly, approaching objects can be simulated using their two-dimensional projection on a computer screen (Gabbiani et al. 1999). Such *looming stimuli* usually represent dark circles or squares of various sizes approaching at constant speeds on a direct collision course with the animal (Fig. 1a). Let l denote the object half-size and x the object position with respect to the animal eye, i.e., $x > 0$ before collision, and $x = 0$ at collision. Defining $t = 0$ as the time of expected collision and $t < 0$ as the time before collision, the position of an object approaching at constant velocity v is described by the equation:

$$x(t) = v \cdot t. \quad (1)$$

According to these conventions, the velocity v is negative, reflecting the fact that the object is approaching. The angular size of the object at the retina, $\theta(t)$, is given by

$$\theta(t) = 2 \cdot \tan^{-1} \frac{l}{v \cdot t}. \quad (2)$$

The square drawn on the monitor screen (Fig. 1a) has a half-size, $l_{\text{screen}}(t)$, that depends

on the distance from the monitor to the eye of the animal, $x_{\text{eye-screen}}$, and the angular size, $\theta(t)$, as

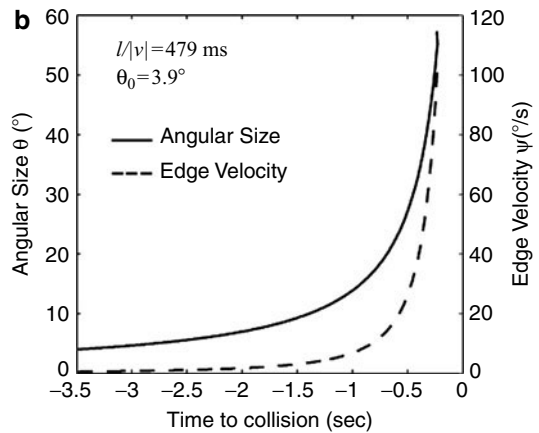
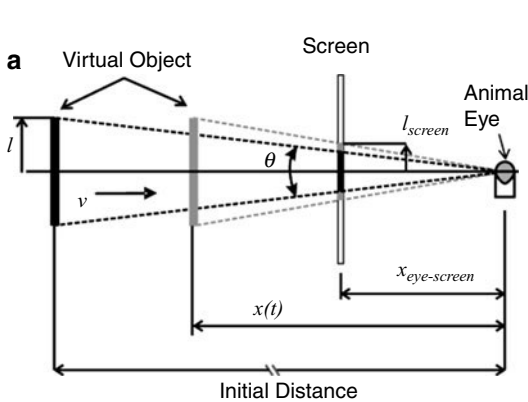
$$l_{\text{screen}} = x_{\text{screen-eye}} \cdot \tan(\theta(t)/2). \quad (3)$$

The angular edge velocity of the object, $\psi(t)$, is defined as

$$\psi(t) = \frac{1}{2} \frac{d\theta}{dt} = \frac{\theta(t)'}{2} = \frac{l/v}{(l/v)^2 + t^2}. \quad (4)$$

As follows from Eqs. 2 and 4, the optical variables $\theta(t)$ and $\psi(t)$ are nonlinear functions of time and depend only on the ratio $l/|v|$ between the object's half-size l and its approach speed v . For a given object size, a faster approach speed implies a faster expansion rate and a smaller $l/|v|$ ratio. Varying the $l/|v|$ ratio thus allows investigators to manipulate the temporal dynamics of the looming stimulus.

For the stimulus to be uniquely determined by the parameter $l/|v|$, simulations must begin from an angular size smaller than the minimum one detected by the animal. If the object starts from a higher angular size, the initial angular size, θ_0 , is another independent parameter characterizing the stimulus (Oliva and Tomsic 2012).



Collision Avoidance Models, Visually Guided, Fig. 1 Looming stimuli. (a) Simulation of an object's approach at constant speed. The eye of the animal is stimulated from the left side by simulating squares of half-size l approaching at a constant speed v towards the center of the eye. The figure shows the virtual object at two different times during the simulated approach. $x(t)$ is the

position of the object in a reference system centered at the animal's eye, $\theta(t)$ is the angle subtended by the object at the animal's eye, and l_{screen} is the square half-size on the monitor screen. (b) Time course of $\theta(t)$ and of the angular edge velocity $\psi(t)$ as a function of time before collision for an approach with $l/|v| = 479$ ms and $\theta_0 = 3.9^\circ$. Both functions are nonlinear in time; see Eqs. 2–4

VGCABs in Invertebrates

Invertebrates are important models for the neurobiology of visually guided behaviors due to their accessible nervous systems and easily quantifiable behavioral output (Reichardt et al. 1983; Egelhaaf et al. 1989; Borst and Haag 2002; Srinivasan and Zhang 2004). Phenomenological descriptions usually rely on input–output functions assuming that the *motor output* is regulated by an *input optical variable*. The input optical variable may, for example, be the angular size of the object, $\theta(t)$, or its time derivatives like the angular velocity, $\theta'(t)$, or the angular acceleration, $\theta''(t)$ (Fig. 1b). A simple but useful such variable is time-to-contact, $\tau(t)$, which can be computed when θ is small and when the approach velocity is constant: $\tau \sim \theta(t)/\theta'(t)$. Time-to-contact gives a running estimate of the time before collision that could trigger a motor reaction at a constant delay prior to the anticipated collision (Gibson 1958; Lee and Reddish 1981; Wagner 1982; Wang and Frost 1992).

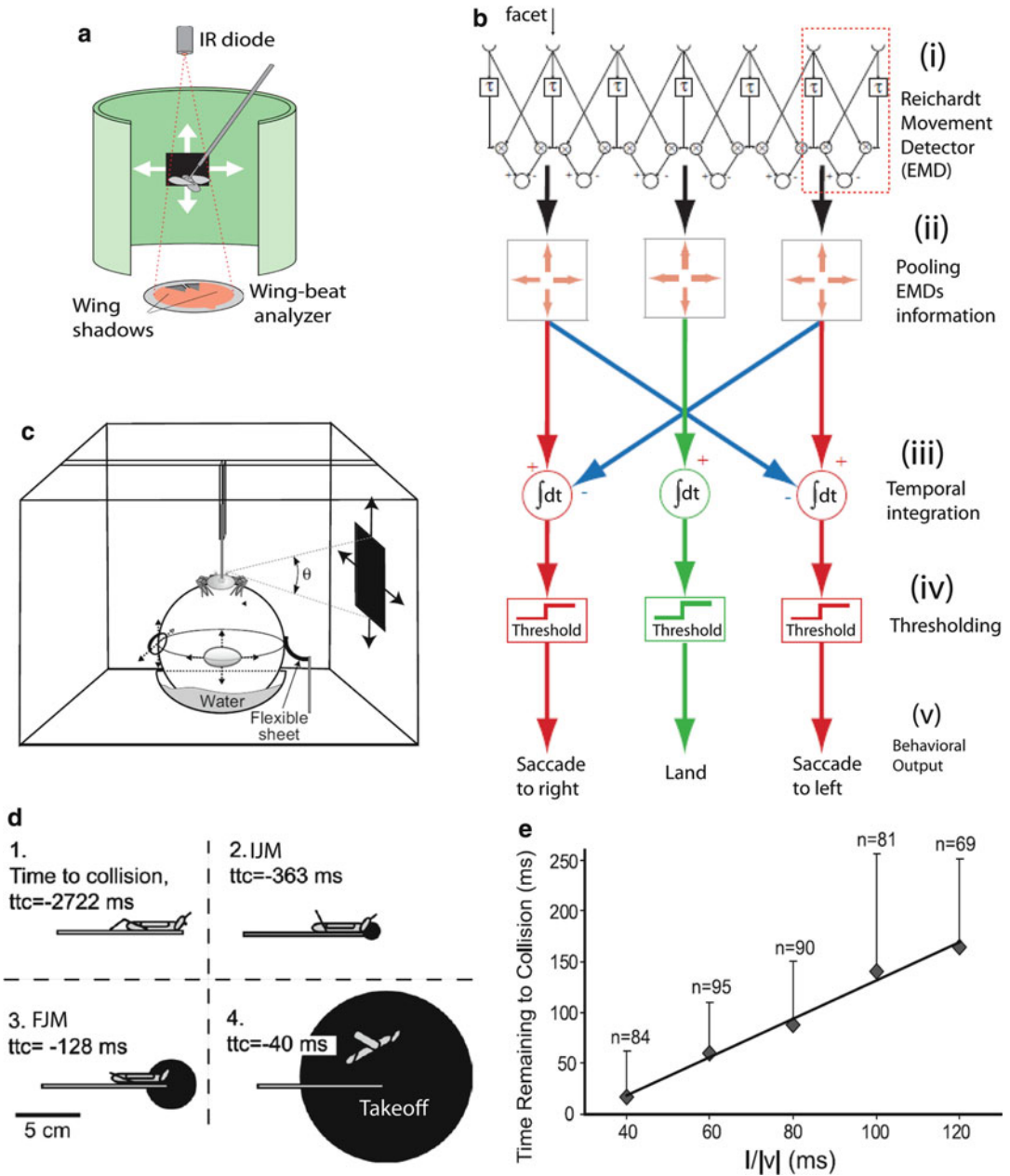
Invertebrate VGCABs vary considerably depending on the animal's motor system, locomotion mode, and living environment. Some VGCABs can be described as all-or-none threshold responses, triggered when an optical variable exceeds a certain value, after which the animal displays a pre-programmed motor response. This type of VGCAB was described in the crayfish defensive reflex (Glantz 1974a) and in flies (leg extension reflex for landing, Borst and Bahde 1988; Tammero and Dickinson 2002a; saccades in free flight, Tammero and Dickinson 2002b). Other avoidance responses are continuously adjusted to account for modifications of the trajectory and/or velocity of obstacles and predatory attacks. Such behaviors have been studied in the context of animal navigation (e.g., Srinivasan and Zhang 2004) and less frequently in the context of predator avoidance (Land and Layne 1995; Oliva and Tomsic 2012). Finally, there are behaviors where the avoidance response is composed of distinctive preparatory stages, each one being triggered when an optical variable reaches a particular threshold. Examples of such multistage responses are observed in locusts (e.g., Santer et al. 2005b; Fotowat and Gabbiani 2007; Fotowat et al. 2011),

flies (Card and Dickinson 2008; Fotowat et al. 2009), and crabs (Nalbach 1990; Hemmi and Pfeil 2010).

Figure 2 illustrates behavioral responses to looming stimuli in invertebrates. They exemplify ballistic-like, regulated, and multistage responses in systems where neural and behavioral analyses have been carried out.

Ballistic-Like Escape Behaviors: Fig. 2a shows a device designed to study the collision avoidance and landing responses to looming stimuli in *Drosophila* (Tammero and Dickinson 2002a). Tethered flies were placed inside an arena in which stimuli of varying trajectories and angular rates of expansion were applied (ψ constant for each stimulus). Flies have two types of responses to these stimuli: leg extensions, which are typical of the “landing response,” and a change in their wing-stroke amplitude, characteristic of collision avoidance responses. An expanding stimulus elicits both landing and collision avoidance responses, but two different pathways appear to mediate the reactions. The azimuthal position of the stimulus affects the probability of the two behaviors: the probability of the landing response is greater when stimuli are applied frontally, while the probability of a collision avoidance reaction is strongest laterally. Both the latencies and sensitivities of the two responses differ as a function of the angular velocity of expansion.

These experiments and knowledge about motion-detection circuits in flies have inspired a computational model to describe collision avoidance and landing responses (Fig. 2b). According to this model, the fly estimates optic flow during flight using a two-dimensional array of Reichardt motion detectors (Fig. 2bi) (Borst and Egelhaaf 1989). The motion information is pooled such that image expansion in the two lateral fields and in the frontal fields of view is calculated (Fig. 2bii). The outputs of these three expansion calculations are then temporally integrated and passed through threshold detectors (Fig. 2biii–iv). Expansion detected laterally triggers a collision avoidance response in the opposite direction, while frontal image expansion causes a landing response. Note that lateral expansion on one side inhibits the opposite expansion-detecting pathway,



Collision Avoidance Models, Visually Guided, Fig. 2 VGCAB in invertebrates. (a) Schematized experimental setup for measuring a fly's response to image expansion. During tethered flight, the fly's wing-stroke amplitude and frequency are measured by optically tracking the shadows cast from an infrared (IR) diode by each of the wings on an optical wing-beat analyzer. The difference between the amplitudes of each wing stroke controls the visual display, allowing the fly to orient actively towards the position of the $15^\circ \times 15^\circ$ square. At periodic intervals, the square symmetrically expands, eliciting a behavioral

response. (Adapted from Tammero and Dickinson (2002a)). (b) Computational model to describe collision avoidance and landing responses in flies. (See text for details; Adapted from Tammero and Dickinson (2002a)). (c) Measurement of the escape response in the crab *Neohelice granulata*. Locomotor activity was studied in a walking simulator consisting of a Styrofoam ball that could be freely rotated by the animal. The crab was held in position by a weightless rod attached to its carapace that could slide up and down within a guide located above the animal. Locomotion was assessed by recording the

preventing a turn from being immediately followed by another one in the opposite direction (Fig. 2bv).

Other insects, such as locusts, also present collision avoidance responses during flight. When looming stimuli are presented, flying locusts may, for example, produce a gliding behavior to evade aerial predators (Santer et al. 2005a).

Continuously Regulated Escape Behaviors: Fig. 2c shows a system designed to study collision avoidance responses to looming stimuli of initial size θ_0 in the crab *Neohelice granulata* (Oliva et al. 2007). The escape response consists of a threshold-type decision for initiating the escape run, followed by a visually regulated mechanism for continual control of the escape speed (Oliva and Tomsic 2012). The escape decision and the regulated speed mechanism can be described by a phenomenological input–output function f_{IO} that describes the crab speed, $v_c(t)$, as a function of an optical variable, $u_2(t - \delta)$, evaluated δ milliseconds earlier:

$$\begin{aligned} v_c(t) &= f_{IO}[u_2(t - \delta)] \text{ if } u_2 \\ v_c(t) &= 0 \text{ if } u_2(t - \delta) \leq 0. \end{aligned} \quad (5)$$

The optical variable $u_2(t)$ is the product of the angular increment since the onset of expansion, $\Delta\theta(t) = \theta(t) - \theta_0$, and of the stimulus angular velocity, $\theta'(t)$:

$$u_2(t) = (\Delta\theta(t) - \Delta\theta_{esc}) \cdot \theta'(t). \quad (6)$$

The parameter $\Delta\theta_{esc}$ is a threshold independent of looming stimulus dynamics. In addition to regulating the speed of escape (Eqs. 5 and 6), the crab makes continuous adjustments to the escape

direction as a function of the path of the object approach (Land and Layne 1995). Thus, the predator is maintained laterally and the crab runs in the opposite direction.

Multistage Escape Behaviors: Fig. 2d shows a looming-evoked multistage escape behavior in locusts (Santer et al. 2005b; Fotowat and Gabbiani 2007). The locust jump consists of several distinct phases, during which the animal orients itself away from the approaching object using its middle legs and stores the energy required for takeoff in the elastic elements of its hind legs (Heitler 1974; Burrows 1996). By monitoring the position of the hind leg femur–tibia joint, Fotowat and Gabbiani (2007) showed that after an initial flexion of the tibia, the joint moves to align the leg parallel to the body. This stage is called the *initial joint movement* (IJM). Subsequently, the flexor and extensor muscles of the hind legs contract simultaneously to store the mechanical energy required for the jump, a stage known as *co-contraction*. This leads to a *final femur–tibia joint movement* (FJM), which is followed by cessation of activity in the flexors, also known as *triggering*. After this, the energy accumulated in elastic hind leg elements is released and *takeoff* occurs.

Figure 2e shows a linear relationship between the mean takeoff time and the value of the looming stimulus parameter $l/|v|$. This linear relationship is equivalent to takeoff occurring with a fixed offset relative to the time the stimulus has reached a fixed angular threshold size on the retina (Gabbiani et al. 1999). Fotowat and Gabbiani (2007) studied the execution times for the IJM and FJM, also showing a linear relationship for t_{IJM} and t_{FJM} as a function of $l/|v|$. Thus, the initial

Collision Avoidance Models, Visually Guided, Fig. 2 (continued) rotations of the ball with two computer mice. The looming stimuli were applied from the right. (Adapted from Oliva and Tomsic (2012)). (d) Looming-evoked multistage escape behavior in locust. Drawing of four frames of a looming stimulus with $l/|v| = 60$ ms. *Frame 1* corresponds to the first stimulus frame. *Frames 2* and *3* correspond to the average timing of the first two preparatory stages of the jump escape behavior (*IJM* and *FJM*; see

main text). The last frame corresponds to the average timing of takeoff [time to collision (tc) is negative before takeoff]. (Adapted from Fotowat and Gabbiani (2007)). (d) Mean timing of takeoff and SD relative to expected collision (time remaining to collision positive before expected collision). Locusts were presented looming stimuli at $l/|v| = 40, 60, 80, 100$, and 120 ms (n indicates number of jumps recorded across all animals. (Adapted from Fotowat and Gabbiani (2007))

and final preparatory phases and takeoff are triggered when the approaching object crosses successive threshold angular sizes on the animal's retina. A similar study conducted for the jumping escape response of *Drosophila melanogaster* to looming stimuli found again a linear relationship between the mean takeoff time and $l/|v|$ (Fotowat et al. 2009).

Another important aspect of visually guided jumping escape responses is related to the control of the escape's direction. Using high-speed videography, Santer et al. (2005b) showed that, after the start of co-contraction, locusts produce tilting postural movements mediated by the pro- and mesothoracic legs. These movements rotate the long axis of the locust towards the direction of jump up to 50° to either side of their long axis. In addition, escape circuitry allows locusts to control the timing, distance, and elevation of these jumps (Santer et al. 2005b; Simmons et al. 2010).

In another series of studies on escape's directionality, Card and Dickinson (2008) described the escape behavior of the fruit fly, *Drosophila*, showing that the fly's escape response is composed of different stages occurring while the object is approaching: (1) freeze, (2) a body lean or leg postural adjustment, (3) wing elevation, and (4) jump. They found that flies can use visual information to plan a jump directly away from a looming threat by a series of postural adjustments that determine the direction of their escape. This is accomplished by regulating the position of their center of mass in relation to the middle leg points of contact. Thanks to this strategy, the extension of the middle legs pushes them away from the expanding visual stimulus.

Collectively, the results from these studies suggest that the invertebrate central nervous system is capable of mapping particular azimuthal positions in visual space to a set of trajectories in motor space. Furthermore, it was proposed that independent descending pathways with different thresholds of activation regulate these visuomotor transformations (Santer et al. 2008; Card and Dickinson 2008; Card 2012).

These behavioral data raise the question: What information do visual neurons encode to regulate these VGCABs? In the next section, we describe a

set of neurons specially tuned to detect stimuli on a collision course. These neurons are important elements of the descending pathways that regulate VGCABs.

Looming-Sensitive Neurons in Invertebrates

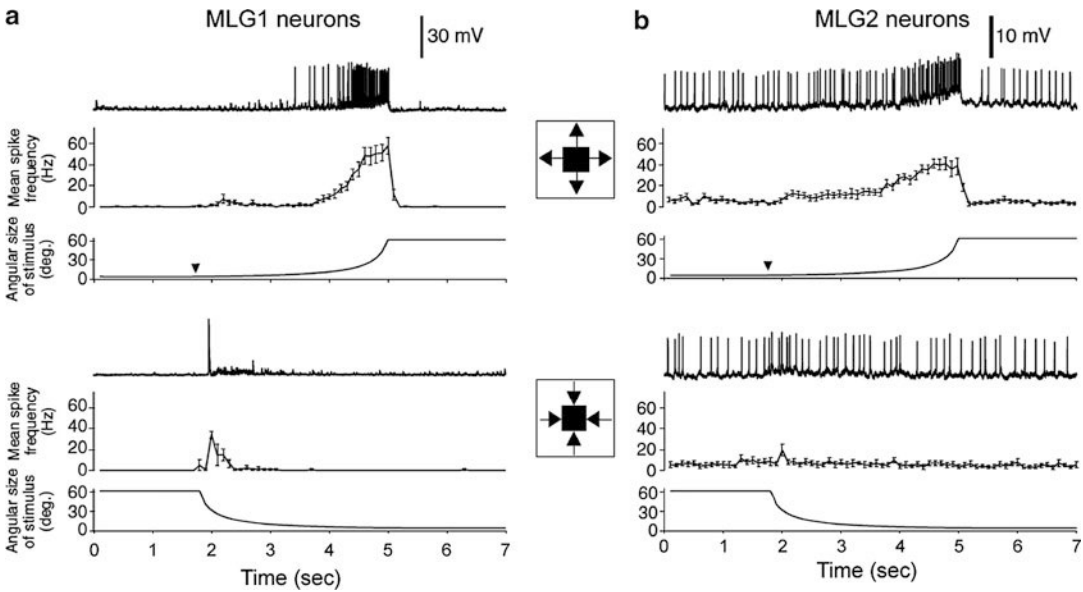
Neurons tightly tuned to detect objects approaching on a direct collision course, called looming-sensitive neurons (LSNs), have been characterized in locusts (Schlotterer 1977; Rind and Simmons 1992; Gabbiani et al. 1999; Gray et al. 2010), flies (Borst 1991; Fotowat et al. 2009), praying mantis (Yamawaki and Toh 2009), crayfish (Glantz 1974a), and crabs (Medan et al. 2007; Oliva et al. 2007).

The most important property of LSNs is their preferential response to looming rather than to receding or translating stimuli. For example, Fig. 3a shows the response to looming and receding stimuli of the motion detector neurons MLG1 and MLG2 in the crab *Neohelice granulata*. Both stimuli have the same value of $l/|v|$ and therefore act on the same number of photoreceptors but with a temporarily reversed photoreceptors' activation dynamics. As seen in the figure, the response to expansion is much larger than that to contraction.

In contrast to neurons involved in optomotor response behaviors, such as those broadly studied in the fly (Borst and Haag 2002), LSNs have a weak response or are inhibited by whole field motion (Rind and Simmons 1992; Gabbiani et al. 2002; Medan et al. 2007). Furthermore, LSNs do not have a strong directional sensitivity across their visual field (Krapp and Gabbiani 2005; Medan et al. 2007), respond to small object movement, and have large receptive fields (Rowell et al. 1977).

Some LSNs exhibit adaptation processes inhibiting their response to stimuli that are constant over time. This phenomenon generates selectivity to looming stimuli (which produce a temporal increase in excitation), as opposed to translating movements that produce constant excitation (Peron and Gabbiani 2009b, c).

Another phenomenon observed in many LSNs is the reduction of their responses to repetitive stimulation (known as habituation; Glantz 1974b; O'Shea and Rowell 1975; Tomsic et al.



Collision Avoidance Models, Visually Guided, Fig. 3 Response of crabs' MLG1 and MLG2 neurons to looming and receding stimuli. (a) Responses to a black looming and receding stimulus for MLG1 neurons. (b) Same as (a) for MLG2 neurons. Sample recordings from a single MLG1 and a single MLG2 neuron illustrate the type of responses of these neurons. Peristimulus time

histograms show the mean spike rate recorded from 11 MLG1 and 13 MLG2 neurons from different animals (one trial per stimulus per neuron). Data is subdivided into 100 ms bins and is plotted as mean $\pm$ s.e.m. The angular size of the looming and receding object is given in the bottom traces of each panel. Arrowheads signal the beginning of the stimulus. (Adapted from Oliva et al. (2007))

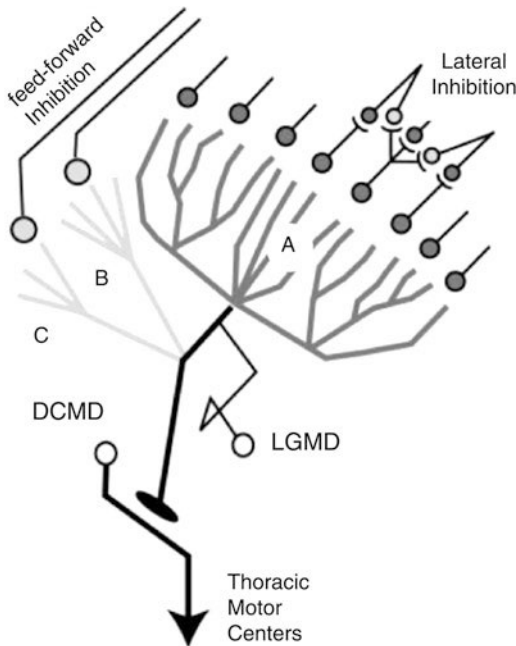
2003; Gray 2005). This property is expected, since if these neurons are an important part of the warning and escape system, the animal must have mechanisms to protect against repetitive stimulation that is harmless. Furthermore, LSNs must possess mechanisms to avoid habituation to wide-field motion stimuli experienced during locomotion; lateral presynaptic inhibition is thought to represent one such mechanism (O'Shea and Rowell 1975).

How do sensory circuits encoding looming stimuli work and what are the biophysical processes tuning LSNs to looming stimuli? To date, the most complete answers to these questions have been obtained in the lobula giant motion detector (LGMD) neuron of the locust. In the following section, we will see that various biophysical processes work in parallel to shape its visual responses.

LGMD/DCMD Neurons in Locust

The lobula giant motion detector (LGMD) is an identified neuron in the third visual neuropil of the

locust optic lobe (lobula) that responds vigorously to objects approaching on a collision course (Fig. 4). The locust LGMD is an extensively studied looming-sensitive neuron (O'Shea and Rowell 1976; Rowell et al. 1977; Schlotterer 1977; Rind and Simmons 1992; Hatsopoulos et al. 1995; Judge and Rind 1997; Gabbiani et al. 1999, 2002; Krapp and Gabbiani 2005; Guest and Gray 2006; Santer et al. 2008; Peron et al. 2009; Peron and Gabbiani 2009a, b; Fotowat and Gabbiani 2011; Jones and Gabbiani 2012b). It makes a strong synapse with another identified neuron, the descending contralateral movement detector (DCMD; Rowell 1971; O'Shea and Williams 1974). The synaptic contact between the LGMD and the DCMD is so powerful that LGMD's spikes are transmitted in a 1–1 manner to the DCMD. Thus, under visual stimulation, each spike in the DCMD is caused by a spike in the LGMD. The DCMD large axon travels down the animal's contralateral nerve cord and contacts motor and interneurons involved in generating jumps and flight steering (Burrows and Rowell



Collision Avoidance Models, Visually Guided, Fig. 4 Schematics of LGMD circuitry. The lobula giant movement detector (LGMD) receives excitatory synaptic inputs (circles shaded in dark gray) on a large dendritic field (A). An important characteristic of this pathway is the presence of a lateral inhibitory network between excitatory afferent fibers presynaptic to the LGMD (inhibitory synapses are illustrated by circles shaded in light gray). ON and OFF feedforward inhibition impinges on two separate dendritic fields (B and C, respectively). The LGMD makes a strong synapse with the descending contralateral movement detector (DCMD) that contacts motor and interneurons involved in generating jumps and flight steering. (Adapted from Gabbiani et al. (2005))

1973; O'Shea et al. 1974; Simmons 1980). Therefore, the LGMD/DCMD neurons provide an excellent system for studying the sensory-motor transformations that occur during looming-evoked collision avoidance behaviors (Fotowat and Gabbiani 2011).

As in many LSNs, the LGMD responds to the movement of small objects irrespective of the object's location in the neuron's receptive field. This response is small and weakly directionally selective. The neuron is also inhibited by whole field motion and, as previously mentioned, it is vigorously excited by objects approaching on a collision course with the animal (Schlotterer

1977; Rind and Simmons 1992; Hatsopoulos et al. 1995; Gabbiani et al. 1999).

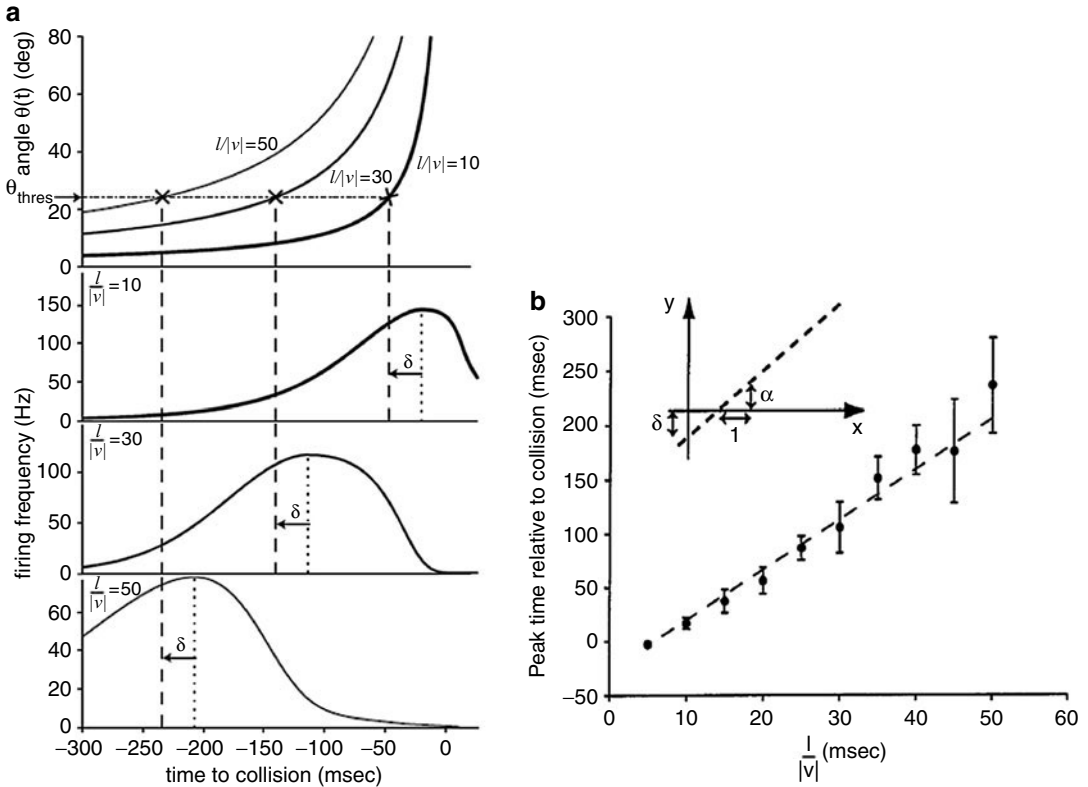
The LGMD neuron has three dendritic subfields that integrate different processes (O'Shea and Williams 1974). The main subfield (A) receives ~15,000 cholinergic excitatory synapses arranged retinotopically. The remaining two dendritic subfields (B and C) receive ~1000 feedforward GABAergic inhibitory synapses (Rowell et al. 1977; Gabbiani et al. 2005). Current evidence is consistent with subfields B and C providing phasic ON and OFF inhibition, respectively (Gabbiani et al. 2004).

Figure 4 shows a proposed model for the LGMD/DCMD circuit (Rowell et al. 1977; Rind and Bramwell 1996; Gabbiani et al. 1999). In this model, excitatory presynaptic inputs arriving at dendritic subfield A experience lateral inhibition (LI) that reduces LGMD responses to wide-field stimuli. On the other hand, there are also feedforward inhibitory (FFI) processes acting on subfields B and C, which increase with the size of the moving object, generating the selectivity of this neuron to small object movement and controlling the rapid saturation to looming stimuli.

LGMD/DCMD Responses to Looming Stimuli

Figure 5a shows the typical response of the LGMD neuron to looming stimuli as the looming parameter $l/|v|$ is varied over one order of magnitude (5–50 ms; Gabbiani et al. 1999). The overall time course of the LGMD's firing rate consists of an increase followed by a peak and a subsequent decrease. A feature of the LGMD response to looming stimuli is that the peak firing time consistently shifts towards collision as the parameter $l/|v|$ is reduced. Plotting peak firing time relative to collision, t_{peak} , as a function of $l/|v|$ reveals a relation that can be fitted by a linear function with slope, α , and intercept, δ (Fig. 5b). Thus, the LGMD's peak firing time acts as an *angular threshold detector*, signaling, with a delay of δ ms, the time at which an object reaches a fixed angular size $\theta_{thres} = 2 \tan^{-1}(1/\alpha)$ on the retina (Fig. 5a; Gabbiani et al. 1999).

Using data from electrophysiological and anatomical characterizations of the LGMD (Palka 1967; Rowell et al. 1977) and the linear relation



Collision Avoidance Models, Visually Guided, Fig. 5 LGMD response to looming stimuli. (a) Peak firing rate signals that an angular threshold was exceeded δ ms earlier. The time course of angular size is depicted in the top panel for three approaches at different values of $l/|v|$. The mean angular size subtended by the object δ ms prior to the peak for each approach is indicated by the crosses. The corresponding time course of the instantaneous firing rate is illustrated in the bottom three panels

(with each panel corresponding to a different value of $l/|v|$). The position of the peak firing rate is indicated by the dotted lines while the dashed lines indicate the moment in time preceding the peak by δ ms. Note that the value of θ_{thres} is independent of $l/|v|$, as read from the ordinate θ_{thres} on the top panel. (b) Relation between the time of peak firing rate and $l/|v|$ is linear. The parameters δ and θ_{thres} are obtained from the linear fit (see inset). (Adapted from Gabbiani et al. (1999))

from Fig. 5b, Gabbiani et al. (1999) proposed an input-output function, f , describing the firing rate of the LGMD and DCMD neurons that should satisfy the following three assumptions: (1) f should depend only on the angular size $\theta(t)$ and angular edge velocity $\psi(t)$ of the approaching object. These two variables are thought to be represented in the form of inhibitory (size-dependent) and excitatory (motion-dependent) inputs to the various dendritic subfields of the LGMD. (2) The firing rate at time t depends only on the value of θ and ψ at time $t - \delta$. (3) The peak of $f(t)$ should satisfy the linear relation between t_{peak} and $l/|v|$ shown in Fig. 5b. These assumptions

imply that f must be described by the following phenomenological model:

$$f(t) = g\left(\psi(t - \delta) \cdot e^{-\alpha \cdot \theta(t - \delta)}\right), \quad (7)$$

where $g(\eta)$ is a static nonlinearity that characterizes the transformation between the kinematic variable $\eta = \psi(t - \delta) \cdot e^{-\alpha \cdot \theta(t - \delta)}$ equation and the firing rate.

Gabbiani et al. (2001) investigated the dependence of this angular threshold computation on several stimulus parameters that alter the spatial and temporal activation patterns of inputs of the LGMD. It was shown that the same angular

threshold computation was implemented by the LGMD in three different locust species and that the computation was invariant to changes in target shape (from solid squares to solid discs), to changes in target texture (checkerboard and concentric patterns), and to changes in contrast (Gabbiani et al. 1999). Finally, the angular threshold computation did not depend on object approach angle, over at least 135° in the horizontal plane.

These findings raise the question: How does the LGMD implement the multiplicative operation between angular edge velocity ψ and angular size θ in Eq. 7? The proposed scheme is based on excitation being logarithmically related to angular velocity and added to inhibition signaling angular size, followed by an approximate exponentiation at the spike initiation zone (SIZ) that converts membrane voltage to firing rate (Gabbiani et al. 2002). Together, these steps result in a multiplication of the excitatory and inhibitory inputs to the LGMD, as summarized in Eq. 8:

$$f(t) = g[\exp[\log(\psi(t - \delta)) - \alpha \cdot \theta(t - \delta)]]. \quad (8)$$

The model of Eqs. 7 and 8 accurately describes the LGMD/DCMD firing rate around the time of maximum activity (t_{peak}). However, for the prediction to be accurate at all times, it is necessary to relax the second assumption and add a dependency to the static nonlinearity g , with respect to the parameter $l/|v|$ (Gabbiani et al. 1999):

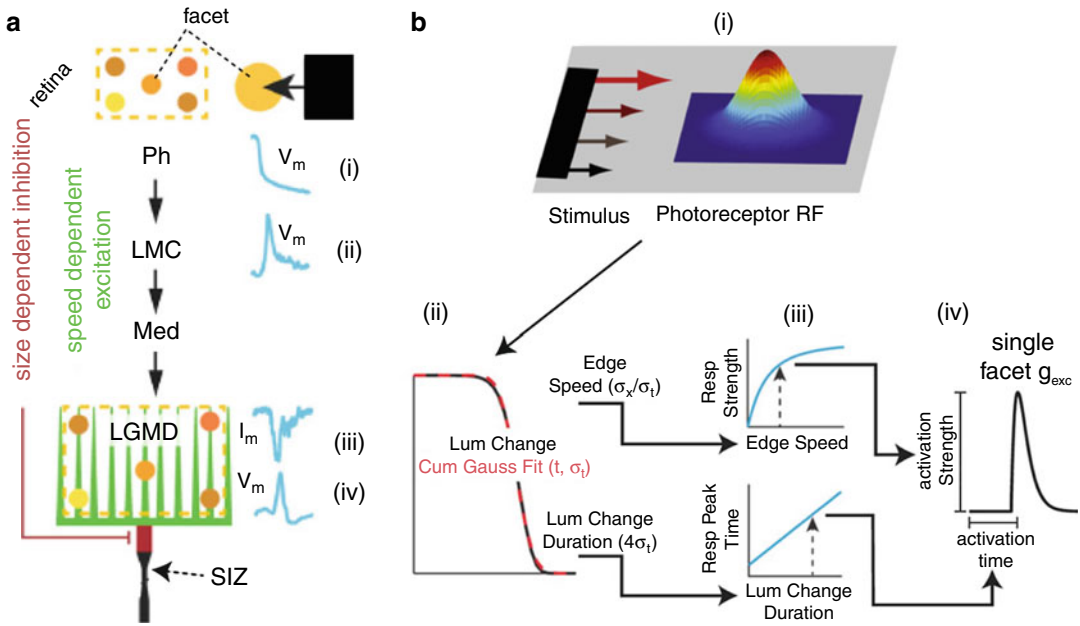
$$f(t) = g_{l/|v|}[\psi(t - \delta) \cdot e^{-\alpha \cdot \theta(t - \delta)}]. \quad (9)$$

This dependence of the g on $l/|v|$ is attributable both to the properties of the conductances shaping the response of the LGMD and to its presynaptic elements that were not taken into account in the derivation of Eqs. 7 and 8 (Gabbiani et al. 1999). Although the proposed computation (Eqs. 7–9) has a high predictive power and provides insight into the LGMD computation, we will see next that many biophysical processes act in parallel to shape and tune the LGMD response to looming stimuli.

Experimental Characterization and Computational Modeling of Presynaptic Circuitry and Feedforward Excitation to the LGMD Subfield A

The LGMD receives retinotopic excitatory input from an entire visual hemifield (see Figs. 4 and 6a). Using electrophysiology, in vivo imaging, and pharmacology, it has been shown that this excitatory projection activates calcium-permeable nicotinic acetylcholine receptors and preserves retinotopy down to the level of a single ommatidium (Peron et al. 2009). Figure 6bi shows the proposed mechanism that results in speed sensitivity of the LGMD's excitatory input (Jones and Gabbiani 2010). When a translating edge stimulus is applied, the figure's edges move with angular velocity ψ through the array of facets on the animal's eye (Fig. 6ai). The faster the movement of a dark edge across a facet (Fig. 6bi), the more rapidly the luminance encountered by the underlying photoreceptors will decrease (Fig. 6bii). More specifically, an edge traveling at a constant speed ψ , and sweeping through a Gaussian receptive field of width σ_x , will produce a local, time-dependent luminance change that has the functional form of a cumulative Gaussian with a duration determined by its standard deviation (SD), $\sigma_t = \sigma_x/\psi$. Below photoreceptors, the most likely next stage in the visual pathway is the large monopolar cells (LMCs) in the lamina (Fig. 6aii; James and Osorio 1996; Rind and Bramwell 1996). Recordings from LMCs revealed that these neurons responded to these luminance changes with increasing depolarization proportional to $1/\sigma_t$, yielding a local response proportional to the stimulus speed $\psi = \sigma_x/\sigma_t$ and consistent with the high-pass filtering properties reported in other insect species (Laughlin and Hardie 1978). Another effect was that the latency of the peak response in LMCs cells decreased as the stimulus duration became shorter (or as the edge velocity was increased).

Because recording from the transmedullary neurons that synapse onto the LGMD is not yet technically feasible, Jones and Gabbiani (2010) measured the effect of that stage of the excitatory pathway by voltage clamping the LGMD to resolve excitatory postsynaptic currents elicited by single-facet stimulation (Fig. 6aiii–iv).



Collision Avoidance Models, Visually Guided, Fig. 6 Circuitry, physiology, and modeling of the excitatory presynaptic circuit to the LGMD. (a) Recordings from photoreceptors, LMCs, and the LGMD in both voltage (I_m) and current (V_m) clamp to single-facet stimuli (right, cyan traces) enable analysis of how edge speed is coded along the pathway. Five facets on the eye (top, dashed square) mapped onto five distinct locations within the excitatory dendritic field (matching square and hues) symbolize its retinotopic organization. (ai) Photoreceptors (Ph) hyperpolarize (right, cyan trace) as dark edges cross their receptive fields over single facets on the eye (top, yellow circles). (aai) Subsequently, that information propagates along an excitatory pathway comprising LMCs and medullary interneurons (Med), terminating onto the

LGMD's large excitatory dendritic field (green rake). (iii–iv) Voltage and current clamping the LGMD to resolve postsynaptic currents. In addition, the LGMD receives inhibition related to stimulus size onto distinct dendrites (red line). (b) Model of velocity encoding by single photoreceptors and its relation with the LGMD excitatory synaptic conductance's strength and latency. (bi) As a dark object crosses the Gaussian-shaped receptive field, it produces a luminance (Lum) change whose duration depends on stimulus speed (bii). (biii) The luminance change duration ($LD = 4 \cdot \sigma_t$) and the edge velocity ψ determine the LGMD excitatory synaptic conductance's strength and latency (biv). (Adapted from Jones and Gabbiani (2010, 2012b))

Based on these experiments, Jones and Gabbiani (2012b) described the excitatory synaptic conductance's strength and latency as a function of the edge velocity ψ and of the luminance change duration ($LD = 4 \cdot \sigma_t$), respectively (Fig. 6biii).

To construct a computational model of the LGMD excitatory current to looming stimuli, it is necessary to incorporate information about the spatial distribution of ommatidia on the locust eye (Krapp and Gabbiani 2005). Based on this information, the luminance input to each facet can be calculated as a function of time, and, using the model for the excitatory conductance (Fig. 6biii–iv), the excitatory postsynaptic current in the

LGMD compartment associated with facet number n , $i_{exc,n}$, is described by

$$i_{exc,n}(t) = g_{exc,n}(t) \cdot (V_n(t) - E_{exc}), \quad (10)$$

where $V_{dend,n}$ is the dendritic compartment potential in the region associated to the facet, E_{exc} is the excitatory synaptic reversal potential, and $g_{exc,n}$ is the excitatory conductance (current and conductance are expressed per unit area).

Finally, another effect related to the latency reduction for faster luminance changes, defined as the synchronization effect, was characterized in the LGMD (Jones and Gabbiani 2010). By selectively stimulating an array of neighboring

photoreceptors, latency reduction (Fig. 6biii) favors summation of inputs activated sequentially throughout the looming sequence, making the neuron maximally sensitive to looming stimuli. Therefore, the LGMD's selectivity arises partially from presynaptic synchronization of a large population of inputs during a looming stimulus and subsequent postsynaptic detection within the LGMD neuron.

Experimental Characterization of Lateral Inhibition (LI) and Feedforward Inhibition (FFI) in LGMD to Looming Stimuli

To analyze separately the action of LI and FFI, Rowell et al. (1977) conducted intracellular recordings between dendritic field A and the LGMD's SIZ. When measuring membrane voltage in this region, IPSPs associated with the FFI could be observed to evaluate their effect on the LGMD firing rate.

Through this approach, it was shown that LI or FFI can be selectively activated with a translating square-wave grating stimulus. If the grating has wavelength λ and angular velocity ω , the contrast frequency is defined as $fc = \omega/\lambda$. For contrast frequencies below 12 Hz, there was a reduction in the LGMD firing rate, but no IPSPs were observed. In this range of frequencies, the grating stimulus preferentially activates presynaptic LI. For frequencies greater than 12 Hz, IPSPs were observed, which indicated the activation of FFI.

A subsequent experiment was designed to analyze the influence of LI on looming stimuli (Gabbiani et al. 2002). In this experiment, looming and a low-frequency wide-field drifting grating were simultaneously applied. As indicated above, LI was thus preferentially activated. By comparing the difference between the response to this stimulus and the response to a looming stimulus alone, it was shown that the effect of LI was mainly produced for angular sizes $\theta < 23^\circ$.

As we saw earlier, the phenomenological model (Eqs. 7–9) assumes that inhibition depends on the angular size, $\exp(-\alpha \cdot \theta)$, and is mainly produced by FFI on LGMD's dendritic fields B and C. To test this hypothesis experimentally, FFI was inactivated through the local application of a GABA antagonist (picrotoxin) in these

dendritic subfields (Gabbiani et al. 2002, 2005). After blocking feedforward inhibition by means of picrotoxin injection, the duration of LGMD responses to looming stimuli was greatly prolonged. This manipulation also increased the number of spikes and peak firing rates relative to control trials. These results suggested that feedforward inhibition plays an important role in controlling feedforward excitation. Based on these experimental results, it was concluded that the multiplicative operation is most likely caused by the interaction between postsynaptic feedforward excitation and inhibition within the LGMD itself, rather than through presynaptic inhibition.

Although LI does not have a significant influence on the LGMD response to looming stimuli for angles greater than 23° , this inhibition is important to protect the LGMD against habituation to visual stimuli that the animal experiences while walking or flying (O'Shea and Rowell 1975). Furthermore, it can strongly influence the response of this neuron to the movement of small stimuli (Rind and Simmons 1999; Peron and Gabbiani 2009b). A biologically inspired computational model of LI was developed in Rind and Bramwell (1996).

Spike-Frequency Adaptation Process and Its

Influence in the LGMD Tuning to Looming Stimuli Another biophysical process that affects the tuning of the LGMD to looming stimuli is spike-frequency adaptation (SFA). SFA is a reduction of a neuron's firing rate to a stimulus of constant intensity. The LGMD exhibits rapid adaptation to both constant current injection (Gabbiani and Krapp 2006) and to translating objects moving at constant angular speed (Peron and Gabbiani 2009a, b). Using pharmacology and Ca^{2+} imaging techniques, Peron and Gabbiani (2009a) showed that SFA is mediated by a Ca^{2+} -dependent K^+ current I_{AHP} governed by a large influx of calcium in the region between the spike initiation zone (SIZ) and the excitatory dendritic field (see Fig. 6a). Intracellular block of this current minimally affected the LGMD's response to looming stimuli but substantially increased its response to translating ones. Thus, SFA contributes to the

neuron's tuning by selectively decreasing its responses to non-preferred stimuli, such as translating and receding stimuli (Peron and Gabbiani 2009b). Peron and Gabbiani (2009a, b) constructed a computational model with three compartments that simulate the dendrites, the region where I_{AHP} was localized, and the axon. This computational model could explain several aspects of the LGMD responses to visual stimuli, current pulses, and pharmacological treatments (Peron and Gabbiani 2009a). Furthermore, it was shown that SFA acts as a selectivity filter for specific temporal input profiles. In the context of time-varying stimuli, adaptation is least effective at suppressing spikes in response to stimuli where not only the first but also the second derivative of the input's intensity is positive. Looming stimuli exhibit precisely this property, and this may explain the insensitivity of the LGMD's looming response to SFA. In conclusion, SFA provides an example of how a membrane conductance can tune a neuron for specific time-varying stimuli (Peron and Gabbiani 2009b).

Computational/Biophysical Model of LGMD Response to Looming Stimuli

The biophysical processes involved in the LGMD computation described phenomenologically (Eqs. 7–9) could be understood in a detailed computational/biophysical model (Jones and Gabbiani 2012b). The model took into account the morphology of the neuron (Peron et al. 2007) and the action of different intrinsic and synaptic currents acting on the LGMD (Fig. 6a). The model neuron had a rake-like dendritic tree, where it received excitatory synaptic inputs (see Eq. 10). It also possessed active conductances implementing realistic SFA within the SIZ. In addition to the time-varying excitatory input, the model included inhibitory inputs stimulated with a fixed magnitude and delay after the stimulus had reached each new facet. Therefore, the size-dependent inhibitory synaptic current acting on the LGMD (Fig. 6a), i_{inh} , was described by

$$i_{inh}(t) = g_{inh}(t) \cdot (V_m(t) - E_{inh}). \quad (11)$$

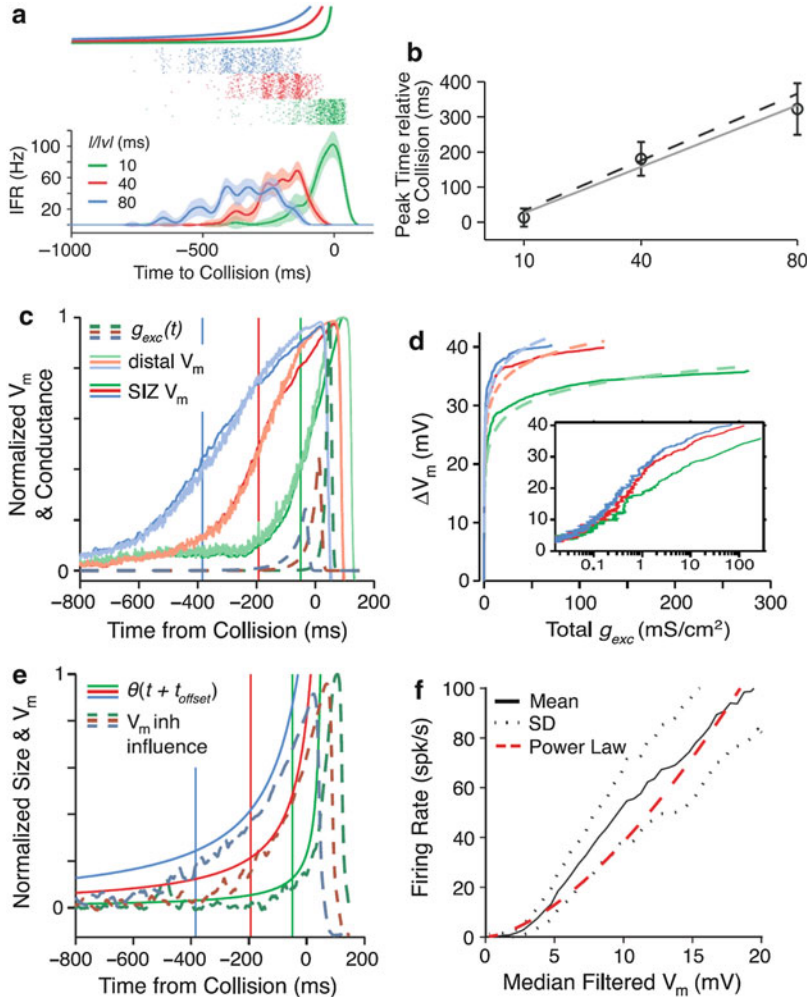
Here, V_m is the dendritic compartment potential, E_{inh} is the inhibitory synaptic reversal

potential, and g_{inh} is the inhibitory conductance. Due to these assumptions, the synaptic inhibition was approximately proportional to the area covered by the looming stimulus, consistent with previous descriptions of feedforward inhibition onto the LGMD (Hatsopoulos et al. 1995; Gabbiani et al. 2005). Finally, the SIZ compartment contained Hodgkin–Huxley active conductances for spike production, and synaptic noise in the model was adjusted to fit the variability of experimental data to single-facet stimulation (Jones and Gabbiani 2012a, b).

As seen in Fig. 7a and b, the model displayed looming responses similar to those observed in vivo and reproduces the linear relationship between t_{peak} and $1/|v|$ described above. But, how does the LGMD implement the logarithmic transformation of angular edge velocity ψ and the multiplication with angular size θ in Eqs. 7–9?

The biophysical/computational model addressed these questions by examining how signals at different levels of the circuit and in different compartments of the model were interrelated and how they were related to the angular speed and size of the looming stimulus. To evaluate the signal transformations in the context of the proposed computation, Jones and Gabbiani (2012b) first quantified the relationship between angular velocity, the total excitatory synaptic conductance to the LGMD model, and the dendritic and SIZ membrane voltage.

Figure 7c shows the normalized excitatory synaptic conductance and both the dendritic and SIZ V_m during looming. Because the dendritic and SIZ V_m are similar to one another, it was concluded that the velocity tuning transformation occurs locally within the dendrites of the model and that the SIZ V_m was a close reflection of the local dendritic V_m . Using the data in Fig. 7c, the excitatory conductance and resulting V_m at the SIZ were plotted against each other (Fig. 7d), and from this figure, we observe that the transformation between the two signals can be described as a logarithmic compression. The light dashed lines show logarithmic fits to the curves and the inset shows that the relationship is approximately linear when displayed on a logarithmic abscissa. To understand how the logarithmic compression



Collision Avoidance Models, Visually Guided, Fig. 7 Computational/biophysical model of LGMD response to looming stimuli. (a) Spiking responses of the LGMD model to looming stimuli. *Top* traces show the stimulus angular size for $l/|v| = 10, 40$, and 80 ms. The rasters show spiking in 50 simulated presentations for each $l/|v|$ value, and *bottom* traces show the mean instantaneous firing rates of the model computed by convolution of individual spike trains with a Gaussian filter (SD, 20 ms). Envelopes show SEM. (b) The timing of the model LGMD peak firing rate (circles, error bars show SEM) depends linearly on $l/|v|$ (black dashed line). This corresponds with the peak response occurring 14.7 ms after the stimulus has reached a constant angular size of 23.7° . The gray line shows the best fit linear relationship found in Jones and Gabbiani (2010). (c) Membrane potential over time in multiple locations. *Lighter* traces show the membrane potential over time in a dendritic compartment corresponding to the center of the visual field, while the

brighter solid traces are the V_m near the SIZ. For comparison, the time course of $g_{exc}(t)$ is plotted. (d) The relationship between $g_{exc}(t)$ and the resulting membrane potential near the SIZ. Colors show responses to different looming stimuli as in (a). *Solid lines* show the observed relationship, while *dashed lighter lines* show fitted functions of the form $V_m = A \cdot \log(B \cdot g_{exc})$. The *inset* shows the data on a logarithmic x-axis, demonstrating that the relationship is approximately linear with a slight dependence on the $l/|v|$ parameter. (e) Time course of the V_m inhibitory influence is shown, plotted with the angular size of the stimulus. Signals are all normalized to their maximum across $l/|v|$ values. (f) Instantaneous firing rate function for the model. The *solid black line* depicts the averaged relationship between median filtered SIZ V_m and IFR, while the *dotted lines* are one SD away from it. The *red dashed line* shows the best fitting power-law function. (Adapted from Jones and Gabbiani (2012b))

occurs, Jones and Gabbiani analyzed the dendritic membrane potential, concluding that the cause of the compression was due to a reduction in the driving force of synaptic excitatory currents as an increasing number of synapses are activated by the looming stimulus (see Eq. 10).

On the other hand, simulations showed that, unlike the excitatory process, the size-dependent inhibitory conductance was more subtly transformed. Since the reversal potential of inhibitory inputs were only 10 mV below the resting potential, the best way to measure the effect of inhibition on the output of the model was to consider the difference in V_m of simulations with and without inhibition; they called this difference: $V_{m\text{inhibitory influence}}$. Figure 7e shows its time evolution with the angular size of the stimulus. This time course was consistent with the feedforward inhibition observed experimentally in the firing rate of LGMD (Gabbiani et al. 2005).

The observation that the excitatory synaptic conductance activated by a looming stimulus is compressed nearly logarithmically in the membrane potential of the model, while the inhibitory influence remains much closer to signaling angular size, matches the proposed phenomenological model that excitatory and inhibitory inputs are effectively multiplied by an addition in logarithmic coordinates. The subsequent approximate exponentiation is then implemented via a non-linear transformation at the SIZ of the LGMD (Eq. 8; Gabbiani et al. 2002).

Figure 7f shows the transformation between membrane potential at the SIZ and instantaneous firing rate. This relation was fit with a power law, suggesting that this supralinear transformation plays a role similar to the exponentiation proposed in Eq. 8 (Gabbiani et al. 2002).

In conclusion, this computational model (Jones and Gabbiani 2012b) suggests a plausible biophysical implementation of the computation performed by the LGMD: the total excitatory input to the LGMD is expansively dependent on angular velocity but is logarithmically compressed by local reduction of the driving force in the dendrites, resulting in membrane potential changes that are a saturating function of velocity. In the main dendritic trunk, this excitatory signal is summed with an inhibitory signal related to the stimulus' angular size; in the biophysical model, this inhibitory influence tracks angular size sub-linearly. The resulting membrane potential is transformed by a final nonlinear, expansive spike-thresholding step at the LGMD's SIZ. The output firing rate thus reflects a multiplication between the stimulus' angular velocity and a negative exponential of its angular size.

Phenomenological Models in Other LSNs

Studies to characterize other LSNs have been carried out in different animal species. Table 1 summarizes some phenomenological models describing LSN responses to collision stimuli. These models use input–output functions of the type $R(t) = g(z(t - \delta))$, where z is an input optical variable, $R(t)$ is the neuronal firing rate, and δ is the delay time. The examples in Table 1 show that the optical variables most commonly used are the angular velocity $\theta'(t)$ and the angular size $\theta(t)$. Using this information, an animal could compute in parallel several variables of interest, such as the time to collision τ and the η function. This seems to be the case of pigeons, in which extracellular recordings in the optic tectum showed three types of neurons (called ρ , τ , and η) that encode information on collisions (Sun and Frost 1998; Laurent

Collision Avoidance Models, Visually Guided, Table 1 Phenomenological models in LSNs

Animal	Neuron	Optical variable	References
Crayfish	Jittery movement fibers	θ'	Glantz (1974a)
Locust	LGMD/DCMD	$\eta = \theta' \cdot e^{-\alpha \cdot \theta}$	Gabbiani et al. (1999)
Pigeon	Neurons η , ρ , τ	$\rho = \theta'$	Sun and Frost (1998)
		$\tau = \theta/\theta'$	
		$\eta = \theta' \cdot e^{-\alpha \cdot \theta}$	
Goldfish	Mauthner cell	$\kappa = \theta \cdot e^{-\alpha \cdot \theta}$	Preuss et al. (2006)

and Gabbiani 1998). These results indicate that the pigeon's brain reconstructs objects approaching using several computations. Each variable provides a different piece of information about the state of the environment, and the animal presumably makes an informed decision on the basis of these different inputs. Moreover, given the results of Table 1, it will be interesting to investigate whether the biophysical processes described in the LGMD neuron (see previous section) can be generalized to other species.

Linking Sensory Coding and Behavioral Responses

In recent years, significant progress has been made in understanding the function of sensory circuits and in the phenomenological description of behavioral and neuronal responses to looming stimuli. However, important aspects are still unknown about the mechanisms that nervous systems use to decide whether, when, in which direction, and how intensely to perform an escape response (Santer et al. 2008; Fotowat and Gabbiani 2011; Hemmi and Tomsic 2012; Card 2012; Herberholz and Marquart 2012).

One approach to study these issues (generally used when experimental data about intermediate circuits is incomplete) is to use VGCAMs to propose feasible descriptions about the operation of intermediate circuits linking sensory input and motor output. For example, Glantz (1974a) proposed a model for the crayfish's defensive reflex. Using the fact that crayfish LSNs encode the angular velocity of expansion (see Table 1), the existence of a firing rate integrator was proposed, such that the behavioral response was displayed when an accumulated number of spikes exceeded a threshold value. This model could explain that the behavioral response was produced when the angular size increased by a fixed value of 8° .

Another example of this approach is the computational model for eliciting collision avoidance and landing responses in flies (Tammero and Dickinson 2002a, b) (see Fig. 2b). It is noteworthy that these VGCAMs can be used to frame hypotheses about circuitry, which can be directly tested by current or future experiments.

To study experimentally how sensory information control decisions and generate different motor escape patterns, it is extremely useful to have an experimental preparation which allows the measurement of neural activity in sensory neurons and interneurons, electromyographic activity in important muscles, and behavioral response in a freely behaving animal. In this direction, Santer et al. (2008) studied looming behavior in tethered locusts walking on a ball, where locusts perform pre-takeoff leg adjustments, but do not complete the final hind leg extension for the takeoff jump. Nevertheless, using simultaneous high-speed videography and extracellular recording, it was possible to correlate DCMD responses with the timing of hind leg flexion.

Recently, a study which simultaneously measured the DCMD neuron activity, muscle activity in the hind legs, and the animal's acceleration was conducted in freely behaving locusts (Fotowat et al. 2011). It used a miniature telemetry system to transmit data output to a remote receiver wirelessly (Harrison et al. 2011). This system permitted study of how variability in the DCMD response affects the final motor output on a trial-by-trial basis (Fotowat et al. 2011).

These experiments found little evidence for an involvement of the DCMD in the initial preparatory movements leading to the jump. The DCMD firing rate threshold predicted only 36% of the variance of co-contraction onset, indicating that other neurons still play an important role at this stage. This result is not surprising since, as we saw in Section 2 escape responses can require complex calculations prior to initiation.

Nevertheless, the DCMD activity played an increasingly important role as collision became imminent. For instance, after co-contraction onset, the number of DCMD spikes precisely predicted the hind leg's motoneuron activity. The number of DCMD spikes from co-contraction onset was highly predictive of jump occurrence. Additionally, the time of DCMD peak firing rate could predict 75% of the trial-to-trial variability of the jump time from the DCMD peak firing time. In conclusion, the transformation of sensory activity into the motor program leading to visually guided jumps appears to rely on distinct attributes of a

neuron's time-varying discharge from a specific time point (co-contraction onset).

Is the DCMD the sole source of looming information to the jump motor circuitry, or are there other parallel visual pathways that could generate escapes? Ablating the DCMD altered the flexion timing but did not eliminate it, a fact that suggested that pathways beyond the DCMD must necessarily be involved (Santer et al. 2008). Locusts possess, besides the DCMD, a second pathway called the descending ipsilateral motion detector (DIMD) found in the ipsilateral nerve cord, which has near identical looming responses to those of the DCMD (Fotowat et al. 2011). In the absence of these two neurons, locusts still flex their hind legs in preparation for co-contraction; however, they rarely take off, and when they do, it is after projected collision. These results suggest that the activity of the DCMD or DIMD is likely not necessary for the initial flexion stage but plays a critical role in generating correctly timed jump takeoffs.

Conclusion

Understanding how sensory stimuli are processed by the nervous system to generate complex behaviors is a central goal of systems and computational neuroscience. In view of their biological importance, visually guided collision avoidance behaviors (VGCABs) provide a favorable model for studies of sensory coding, sensory-motor transformations, and decision-making processes, as many animals have developed specialized neural circuitry to sense and execute them. Furthermore, these behaviors must be controlled by rather simple neural circuits to generate quick and reliable avoidance responses. At the sensory level, VGCAMs usually begin as phenomenological descriptions and then focus on the study of associated neural circuits and biophysical mechanisms for implementing these computations. In this sense, an outstanding example is the case of the locust's LGMD/DCMD neurons, whose properties have been studied for over 40 years (Burrows 1996). Using experimental techniques such as electrophysiology, pharmacology, calcium

imaging, and computational modeling techniques, this work has shown that different biophysical processes work in parallel to tune the LGMD response to looming stimuli.

At the behavioral level, studies in invertebrates showed that VGCABs vary considerably depending on the animals' motor structure and living environment, ranging from ballistic-like or multistage to continually adjusted behaviors. For this reason, we need comparative studies across different species to determine the generality of the discovered mechanisms. VGCABs require computations integrating information from different sensory channels to decide whether, when, in which direction, and how intensely to perform an escape response. Therefore, it will be interesting to study how downstream circuits interpret these sensory messages in order to make an appropriate motor decision. Finally, VGCAMs can be used to frame hypotheses about circuitry, which can be directly tested by techniques such as calcium imaging and electrophysiological recordings in freely behaving animals.

Cross-References

- [Decision-Making, Models](#)
- [Optic Flow Processing](#)
- [Reduced Morphology Models](#)
- [Visual Motion Detection in *Drosophila*](#)
- [Visual Processing in Free Flight](#)

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Color Computational Vision

► [Color Vision, Computational Methods for](#)

Color Vision, Computational Methods for

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Synonyms

Color computational vision; Computational neuroscience of color

Definition

The study of color vision has been aided by a whole battery of computational methods that attempt to describe the mechanisms that lead to our perception of colors in terms of the information-processing properties of the visual system. Their scope is highly interdisciplinary, linking apparently dissimilar disciplines such as mathematics, physics, computer science, neuroscience, cognitive science, and psychology. Since the sensation of color is a feature of our brains, computational approaches usually include biological features of neural systems in their descriptions, from retinal light-receptor interaction to subcortical color opponency, cortical signal decoding, and color categorization. They produce hypotheses that are usually tested by behavioral or psychophysical experiments.

Detailed Description

Although the sensation of hue is an invention of our brains, it nevertheless allows us to identify objects by one of their key physical features: their color. Our cortical neurons receive information about the world “out there” and process it in highly nonlinear ways to make sense of the environment, highlighting and grouping important items over the rest. In the case of color, this information is carried by the distribution of energy

in the photons (wavelength distribution) of the light reflected by objects. Our visual system captures these photons through a very sophisticated mechanism in our retinas, one that converts wavelength information into neural spikes and ultimately into the vivid sensation we experience. However, the result of this process bares only a small resemblance to the physical characteristics of the light originally falling on our retinas. For instance, two objects whose reflected light may differ by only a few more energetic photons may be assigned completely different color categories by our brain. The opposite may also occur: two objects reflecting remarkably different photon/energy distributions may look as having the same color to us. Our perception of color at a point in space may depend not only on the physical characteristics of the light reflected from that point but also on that of the points surrounding it. The origins of these mechanisms are deeply rooted in the lifestyles of our primate ancestors and their need to avoid predators, find suitable mates, and forage for nutritious fruits and leaves in the African forest. These tasks and a changing visual environment may have determined the properties of our color vision and its drive to collect information about the part of the environment that changes the least: the surfaces of objects. This knowledge may help categorize the objects (edible? dangerous?) and therefore improve our chances of survival. In view of this, it is easy to understand why our brain has evolved its nonlinearities to favor a representation of the world that enhances and improves on the mere physics of the visual environment.

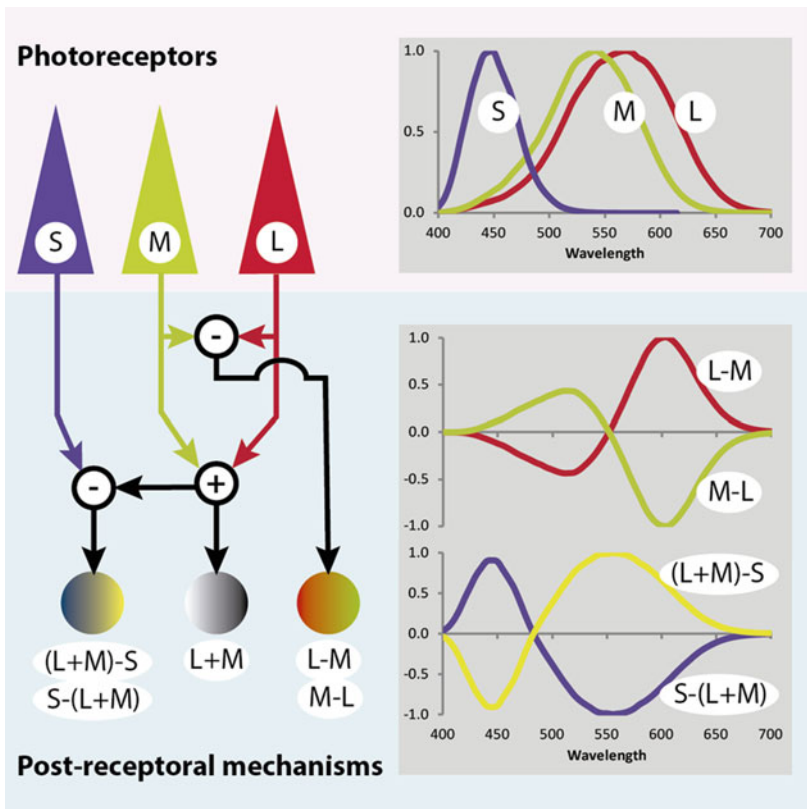
The very properties that aid survival also make the problem of predicting color sensation from the wavelength patterns of light stimulating our retinas very complex and mathematically difficult to address. Color vision scientists have made a great deal of advance, making sense of what is in essence a complex nonlinear problem. Each subdiscipline studies the phenomenon from its own unique perspective, with computational approaches contributing to our understanding at every level, from neurophysiology to behavior.

The Retina

The retina is perhaps the best known part of our visual system. It contains three types of photoreceptors or cones that are selectively stimulated by photons according to their energy (wavelength). These receptors (named *L*, *M*, and *S* because of their preferences for long, medium, and short wavelengths, respectively) are light-sensitive neurons which fire electrical impulses when exposed to light of wavelengths near their preferred value. Their sensitivity has been quantified (Stockman and Sharpe 2000) in the form of three spectral sensitivity functions (see Fig. 1). Notice that since each of the cones could be stimulated by

photons with energies within a wide range, long-wavelength-preferring cones could be stimulated by medium-wavelength light. Given that cones also respond to light intensity, intense light of suboptimal wavelength can produce the same firing rate as low-intensity light of optimal wavelength. This is the reason why many (in fact infinite) wavelength distributions can produce similar outputs from the cones. Two lights of different wavelength distributions that produce the same retinal output are called *metamers*.

Receptor and post-receptor mechanisms were anticipated in the nineteenth century (well before any physiological observation) in the form of a trichromatic theory by Young (1802) and



Color Vision, Computational Methods for, Fig. 1 Schematics of the chromatic signal processing in the retina. The figure on the *left* shows the three human photoreceptors and how they connect to form the three post-receptoral mechanisms by addition and subtraction. Chromatic information is obtained by sampling the spectrum around different wavelengths and comparing the

output of at least two different types of photosensitive neurons. Two of the post-receptoral mechanisms are chromatically opponent and one ($L + M$) is achromatic. Panels on the *right* show the spectral sensitivity of each chromatic mechanism. The terms $L + M$, $L - M$, etc. refer to the sign of the operation and do not represent the weight of each mechanism in the sum

Helmholtz (1867) and a color opponent theory by Hering (1875). The first postulates that color vision is based on three fundamental mechanisms as illustrated at the top of Fig. 1, and the second postulates that color vision arises from the workings of three opposed mechanisms: red green, blue yellow, and light dark (see bottom of Fig. 1). Each theory was an attempt to explain different phenomena such as how mixtures of colored light create a different color or the observation that some opposing pairs of sensations cannot be simultaneously experienced (e.g., there is no reddish-green color) and afterimages (illusory colors that appear after our retinas have been overexposed to colored stimuli) (Gregory 1998). Our current knowledge of the interaction between cone photoreceptors and light can be expressed mathematically as the integral of the product between the electromagnetic power distribution of the light and each of the cones' spectral sensitivity functions (L , M , and S curves shown in Fig. 1):

$$\varepsilon_i = \int_{\lambda} S_i(\lambda)P(\lambda)d\lambda \quad (1)$$

In Eq. 1, ε_i represents the excitations of the three classes of cones ($i = L, M, S$), $S_i(\lambda)$ is their corresponding spectral sensitivity, and $P(\lambda)$ is the spectral power distribution of the light falling on them. Since in real life light measurements are only available at a series of finite wavelengths, the integral in Eq. 1 is generally approximated to a finite sum over the visible spectrum (400–700 nm).

Computational Methods for the Retina

In practice, it is unlikely that we know the full spectrum of the light falling on the retina. It is more common to operate retinal models based on images obtained by commercial cameras. These are also modeled by Eq. 1, but their sensor sensitivities are usually unknown. Some devices are capable of producing images in standard, device-independent color spaces such as the CIE1931 XYZ system or the sRGB color standard, which are easily convertible following a simple set of

formulae (Poynton 2003; Green and MacDonald 2002). Once we know the XYZ coordinates, we can obtain the chromaticity coordinates x, y using the following:

$$\begin{aligned} x &= \frac{X}{X+Y+Z} \\ y &= \frac{Y}{X+Y+Z} \end{aligned} \quad (2)$$

From there, it is possible to obtain the cone excitations using Y (luminance) and the following transformation (Wyszecki and Stiles 1982a):

$$\begin{aligned} \varepsilon_L &= Y[0.15514x/y + 0.54312 - 0.03286(1-x-y)/y] \\ \varepsilon_M &= Y[-0.15514x/y + 0.45684 - 0.03286(1-x-y)/y] \\ \varepsilon_S &= Y[0.00801(1-x-y)/y] \end{aligned} \quad (3)$$

In the case of Eq. 3, ε_i values correspond to the Smith and Pokorny cone fundamentals (Smith and Pokorny 1975) and the chromaticities ought to be derived from the Judd-modified CIE1931 standard color matching functions (Judd 1951). The plot at the top of Fig. 1 shows an example of cone fundamentals, with the sensitivity of each cone plotted as a function of wavelength. Color matching functions are obtained from psychophysical experiments where subjects have to visually match the sensation produced by spectrally narrowband stimuli to a mixture of three spectrally broadband lights. It is possible to mathematically obtain cone fundamentals from such experiments, given certain assumptions (Wyszecki and Stiles 1982b). Although Smith and Pokorny did not specify the coefficient necessary to obtain ε_s , the value of 0.00801 was chosen to take into account the relative strengths of the two post-receptor neural opponent mechanisms (see below).

Equation 3 provides a good approximation for transforming the output of cameras and monitors once we can express it in the CIE1931 XYZ system. However, in most cases this is not possible, and devices such as cameras and monitors need to be characterized to convert their outputs to cone excitations. There are several methods for characterizing cameras which include gamut mapping between a known target and the camera

output (Cheung et al. 2004; Parraga et al. 2010), estimation of the camera's sensor sensitivities (Westland and Ripamonti 2004; Barnard and Funt 2002), and mixtures (Parraga et al. 2010). They transform the output of a commercial digital camera into a device-independent color space such as the CIE1931 XYZ.

Receptoral Gain Control Mechanisms

In the retina, there is a nonlinear relationship between the input and the output of the cone photoreceptors, which is often characterized as a gain control mechanism (output signals are modified by signals from the same or different cones). This mechanism converts cone excitations into a contrast representation such as

$$C_i = \frac{\Delta \varepsilon_i}{\varepsilon_i^b - \varepsilon_i^0}; \text{emi} = L, M, S \quad (4)$$

where ε_i^b represents the cone excitation produced by the background (the adaptation state), ε_i^0 is a constant, and $\Delta \varepsilon_i$ represents the excitation difference between the cone considered and the background (Stockman and Brainard 2010). The i subindex discriminates between the three types of photoreceptors.

One of the reasons for this normalization is to reduce the massive intensity range present in the visual environment (in a typical sunny day, variations in intensity between shaded and illuminated objects can reach 9 orders of magnitude), which cannot be encoded directly by the output of single neurons (e.g., retinal neurons can encode ranges of approx. 50–1) (De Valois 2004).

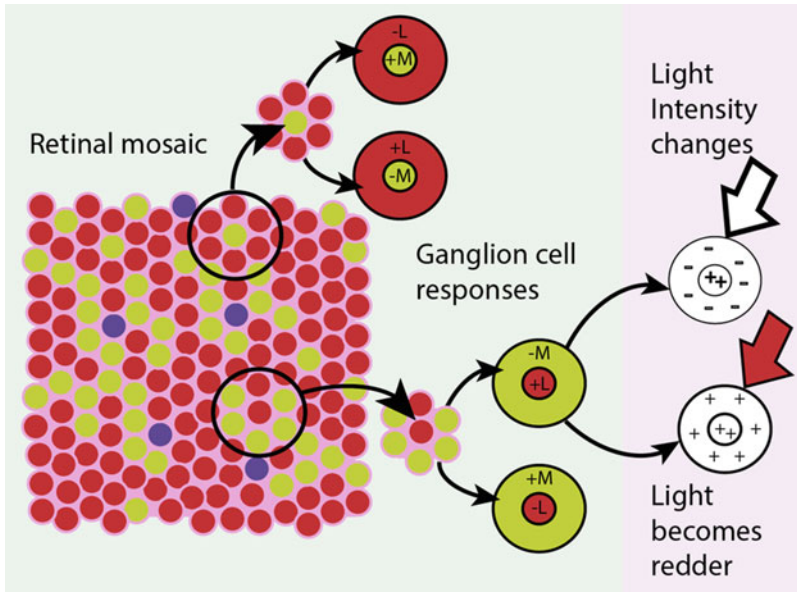
Post-Receptoral Color Processing

The signals transmitted by cones are combined and encoded in a series of steps by neurons in the retina (the last processing layer is formed by neurons called ganglion cells) and transmitted to an area inside the thalamus called the lateral geniculate nucleus (LGN). The majority of these signals (80% of the fibers reaching the LGN)

passes through a layer of ganglion cells called *parvocellular* (or parvo) cells (De Valois 2004). At this stage, the information is organized both spatially and chromatically in opponent signals. For example, a parvo cell in the central retina may receive input from a single L or M cone and weight it against input from a small group of surrounding cones (see Fig. 2).

Each ganglion cell is stimulated by light falling on a physical part of the retina that contains the cones to which it is connected (its receptive field). As a result of the wiring shown in Fig. 2, parvo cells output a signal that is spatially and chromatically opponent and conveys both intensity (i.e., brightness) and wavelength information (i.e., color) from the light falling on its receptive field. Thus parvo cells perform a “double duty,” carrying information about both intensity and color. The right part of Fig. 2 shows how intensity changes in light increase the cell's antagonism, conveying information about the smallest possible unit (a cone), while chromatic changes produce a synergistic response in the center and surround, thus increasing the number of cones contributing to the signal. For this reason, parvo cells in Fig. 2 convey finer detail information (higher spatial frequencies) about intensity than for color. In other words, when light varies spatially in color, the same cells can only carry information about its coarse spatial distribution (lower spatial frequencies). This imbalance has been confirmed psychophysically by our greater ability to detect fine patterns of achromatic light and coarse patterns of colored light (De Valois and De Valois 1988) and matches the information content of natural scenes (Parraga et al. 2002). This combination of spatial and chromatic opponency in parvo cells appears to be a sophisticated mechanism to optimally extract information from the visual environment, carrying both chromatic and achromatic signals over different spatial frequency bands (multiplexing).

Computationally, it is common to model the center-surround receptive field structure by convolving the color opponent representations with Gaussian kernels of opposite sign and different standard deviations (difference of Gaussians). For example, one kernel is applied to the L-cone



Color Vision, Computational Methods for, Fig. 2 Schematics of the spatiochromatic opponent processing in the retina. Parvocellular ganglion cells collect input from a single cone and compare it with a pool of surrounding cones. In the case of $L - M$ opponency, this leads to four possible combinations, as illustrated in the figure. The *right* part of the figure shows an example of

how the same cell can carry information about both intensity and color. If the light falling on the cell's receptive field changes its intensity, both center and surround are stimulated, therefore increasing their antagonism. If the same light changes its color toward *red*, the center is stimulated and the surround is depressed, contributing less to reduce the ganglion cell output signal (therefore the + sign)

representation and another (of greater standard deviation) to the M-cone representation and the results are subtracted from each other. This process is equivalent to subtracting a blurred version of the M-cone-excitation image (the surround) from another slightly blurred version of the L-cone excitation (the center). A similar algorithm can be applied to obtain $S - (L + M)$ opponency. Similarly to parvo, there exist in the retina two other types of ganglion cells. The *koniocellular* (or konio) cells that carry information about S-cone excitation relative to their surrounds ($S - (L + M)$ and $-S + (L + M)$) and the *magnocellular* (or magno) cells that receive excitatory output from all three types of cones, therefore, are insensitive to color (De Valois 2004). Figure 1 illustrates this opponency from a spectral point of view.

The three types of ganglion cells described above connect to specialized layers of neurons in the LGN. The presence of these LGN cells representing different aspects of the light captured

by cones has inspired the creation of color spaces based on the properties of these neurons. The best known is the MacLeod–Boynton cone-excitation space (MacLeod and Boynton 1979) which is based on the coefficients of Eq. 3 plus an arbitrary condition that the relationships among the sensitivities of the three receptor mechanisms at 400 nm (see Fig. 1) will be given by Eq. 5:

$$S_L(400) + S_M(400).36em = .36emS_S(400) \quad (5)$$

where $S_i(400)$ is the sensitivity of each cone photoreceptor at 400 nm. To obtain the coordinates of the MacLeod–Boynton receptor space, it is necessary to convert the L -, M -, and S -cone excitations to coordinates l -, m -, and s -, respectively, using the following transformation:

$$l = \frac{L}{L + M}; emm = \frac{M}{L + M}; ems = \frac{S}{L + M} \quad (6)$$

The normalization provided by Eq. 5 constrains the value of s in Eq. 6 between 0 and 1.

An extension of cone-excitation spaces are cone-contrast spaces, which address the issues posed by the receptor gain control mechanisms described in Eq. 4. Two popular cone-contrast spaces were created by Derrington et al. (1984) and Boynton (1986) following different assumptions about the neutral points (crossings of the $L - M$ and $S - (L + M)$ functions of Fig. 1). Cone-contrast representations take into account the cone excitation produced by the background and rescale the signal accordingly. The new coordinates become

$$C_i = \frac{\Delta \varepsilon_i}{\varepsilon_i^b}; \text{emi} = L, M, S \quad (7)$$

where $\Delta \varepsilon_i$ is the cone-excitation difference between the signal and a given reference level (the background). ε_i^b is the cone excitation produced by the background. In this new representation, the background excitation becomes the origin of the new system. Cone-contrast spaces provide a representation of the input signal arriving at later stages in the visual pathway.

Cortical Color Processing

LGN neurons project to the primary visual cortex in the occipital part of the brain (also known as striate cortex or area V1). From there, visual information is sent to the so-called extrastriate visual cortical areas (named V2, V3, V4, and V5). Each part of the retina is mapped into V1 with a very precise correspondence between the

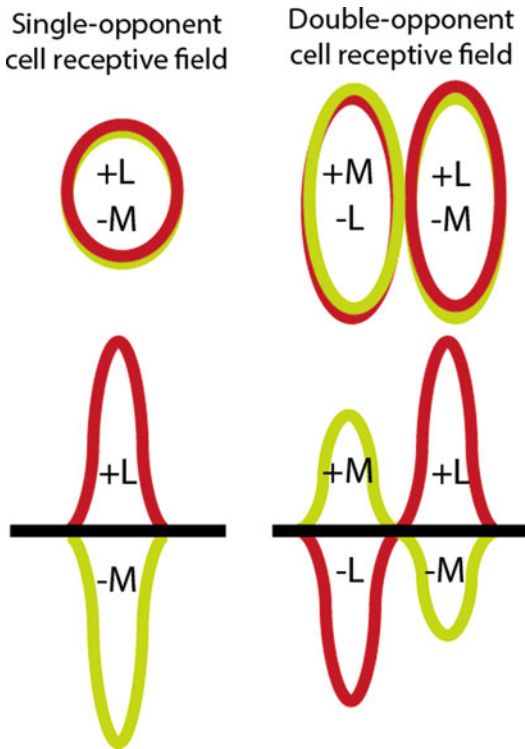
visual field and its related location in the primary visual cortex. A large portion of V1 is dedicated to the center of the retina, where the abundance of cones is highest and the receptive field smallest. In contrast to the well-defined, opponent-color information-carrying neurons found in the retina and LGN, color-sensitive cortical neurons respond to many other properties of the visual stimulus such as contrast, object orientation, shape, etc. This is thought to be the reason behind many illusory phenomena where the color of the area we gaze is influenced by patterns of the surrounding area (chromatic induction, see Fig. 3) and color constancy (Brainard 2004).

Originally, color processing in the visual cortex was thought to be modular and separated from other forms of perception. This view was supported by studies in cerebral achromatopsia (a lesion in the brain that causes loss of the ability to recognize colors without loss of form and motion perception) and others (Zeki 1993). Today's prevalent view is that V1 is strongly stimulated by color, with about 50% of its neurons responsive to some kind of chromatic stimulus, with $L - M$ being the preferred direction (Shapley and Hawken 2011). Areas V2 and V4 also respond to color; however, many of their neurons respond equally to achromatic patterns. Two intriguing classes of color-processing neurons were found in the primary visual cortex: single- and double-opponent cells (Shapley and Hawken 2011; Hurlbert 2003; see Fig. 4). The former respond best to large areas of color, while the latter have preference for color boundaries,

Color Vision, Computational Methods for, Fig. 3

The figure shows the influence of surrounding patterns on the perceived color of a central area. In both figures, the inverted “U” bar has the same RGB values, but it is perceived differently according to its surroundings. This phenomenon is called “chromatic induction”





Color Vision, Computational Methods for, Fig. 4 Cartoon examples of single-opponent and double-opponent color-processing cells. Single-opponent cells are insensitive to edges and do not prefer any oriented stimuli. They respond strongly to colored patches. On the other hand, double-opponent cells are strongly selective for chromatic edges and have a preferred orientation

patterns, and textures. Both types of neurons have been linked to the perceptual phenomena shown in Fig. 3.

There have been reports in the literature about a spatial segregation of color-selective neurons in V1 and V2. A number of optical imaging electrophysiological and microelectrode studies have found the presence of clusters of color-selective neurons, although there are still negative results and the issue has not been definitively resolved (Shapley and Hawken 2011).

Computational Models of Color Processing in the Visual Cortex

Computational models of cortical processing can be categorized as either primarily

phenomenological, i.e., trying to capture the observed phenomena in a convenient mathematical form, or mechanistic, i.e., trying to show how observed phenomena arise from biologically grounded neural mechanisms. A typical color vision model contains a preprocessing stage where the input image is converted to an L -, M -, or S -cone-excitation representation, a cone opponency stage that weights the output of cones to produce opponent signals, and other post-receptoral stages which may include normalizations by neighboring units and weighting parameters. The center-surround receptive field interaction is usually modeled via a pyramid of 2-dimensional Gaussian or Gabor operators that convolve the image to obtain chromatic and achromatic information at different spatial scales and orientations. A final layer can also be implemented to account for single- and double-opponent cell processing.

Chromatic induction demonstrations like those shown in Fig. 3 have inspired some computational attempts to model color processing in the visual cortex, trying to predict the effects of surround stimuli on the perceived color of a central patch. Examples of these are the models of Singer and D’Zmura (1995) and Spitzer and Barkan (2005) and Otazu et al.’s CIWaM (2010). The latter consists of a cone-receptor stage that separates the input into two chromatic and one achromatic channels: a wavelet pyramid to model spatiochromatic processing in the cortex, including normalization effects by neighboring neurons (divisive normalization) (Heeger 1992), and a weighting function to mimic the spatial filtering of the human visual system. A later version of CIWaM was capable of predicting unconstrained eye movements in human subjects (Murray et al. 2011).

A family of computational approaches to color processing takes advantage of the tools currently available in computer science for tasks such as object recognition. For example, one approach consists of applying shape-based descriptors such as scale-invariant feature transform (SIFT) on the post-receptoral color representations. SIFT will learn “interesting features” of an object in a set of training images which can

be later used to identify the object in the dataset. Other approaches involve a set of shape-based descriptors computed from gray-scale pixel intensities, which are in turn concatenated with hue histograms. An improvement has been proposed by Van de Weijer and Schmid who concatenated a hue histogram with gray-scale SIFT image descriptors (Gevers 2012), while Zhang et al. (2012) described a hierarchical model of color processing inspired in the primate visual cortex. They produced chromatically opponent channels using operators that resemble single- and double-opponent cells and outperformed the object recognition of previous approaches.

Color Constancy

The human visual system has the ability to perceive objects as having a well-defined color despite the fact that they reflect light according to their own pigmentation, geometry, and the wavelength content of the illumination. During a typical day, natural daylight changes its color quite dramatically, but we are mostly unaware of its full effect on the surfaces of objects. As we have seen before, the distribution of power as a function of wavelength in the light reaching our retinas determines how we perceive color. In the case of light reflected from objects, this power distribution depends on several factors. Equation 8 provides a simplified description of the problem (Brainard 2004):

$$C(\lambda) = E(\lambda)R(\lambda) \quad (8)$$

Here $C(\lambda)$ is the spectral power distribution of the light reaching our retina, $E(\lambda)$ is the spectral power distribution of the illumination, and $R(\lambda)$ is the spectral reflectance of the surface. Equation 8 assumes that the illumination is spatially uniform and surfaces are Lambertian (diffusely reflective, with no specularities). Of these factors, only $R(\lambda)$ is intrinsic to the objects, while $E(\lambda)$ changes according to the type of illumination, physical location, time of the day, etc. In summary, to produce a stable scene in

terms of color, the human visual system disentangles the two factors at the right side of Eq. 8. This is a mathematically ill-posed problem, given that there are infinite possible combinations of illumination and reflectance that produce the same reflected light. To solve it, the human visual system may resort to information from previous experience, scene features such as specular reflections and interreflections, memory of colors, etc.

The problem of illumination removal is ubiquitous. For example, in computer vision, there are applications that require illumination stability in order for algorithms to work. In photography, users expect the image to represent the scene “as they saw it,” not the actual physical values. Many popular computational approaches try to solve this problem by taking into account the information intrinsic to the image, rather than the physiological or anatomical mechanisms of the visual system. For practical reasons, methods were developed to return an image that approximately represents the intrinsic color of objects, discounting the effects of the illumination (canonical image). This image can be then “reilluminated” to create conditions close to the observer’s perception. Illuminant removal methods contain different statistical hypothesis, the most popular being the “gray world” assumption, which states that the *average reflectance of a scene is achromatic*. Another popular hypothesis (called “MAX-RGB”) takes advantage of some properties of white surfaces and specular reflections and is based on the assumption that *the maximum reflectance of a scene is achromatic*. Once a hypothesis is introduced, the computational algorithm returns an image that meets the hypothesis. Many of these solutions are strongly dependent on whether the input image complies with the hypothesis and are prone to fail in particular cases. For example, a “gray world” algorithm may fail when the average color of the scene is not gray. The main drawback of this family of computational approaches is that they do not provide much insight about the mechanisms that are behind color constancy. See Gevers (2012) for a comparison of illuminant removal methods.

Color Appearance

The models and the physiologically based color spaces described above have been created to handle the perception of colors viewed in isolation and in controlled, fully adapted conditions. However, the perceptual appearance of colors in naturalistic viewing conditions depends on so many external factors (surround, background, illuminant, etc.) that a series of sophisticated models have been created to account for them. These so-called color appearance models are not constrained by attempts to incorporate elements of the physiology (Fairchild 1998).

Cross-References

- [Center-Surround Processing, Computational Role of](#)
- [Center-Surround Processing, Network Models of](#)
- [Computational Neuroanatomy: Overview](#)
- [Cortex: Overview](#)
- [Lateral Geniculate Nucleus \(LGN\) Models](#)
- [Visual Illusions, Models of](#)

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Comparative Analysis of Half-Center Central Pattern Generators (CPGs)

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Definition

CPGs are networks of neurons that can produce rhythmic activity, featuring a stereotyped sequence of phases that repeats in a periodic-like manner, without receiving rhythmic inputs from an outside source. Half-center CPGs, also known as half-center oscillators, are CPGs consisting of two components connected by reciprocal synaptic inhibition. While the coupled network exhibits a two-phase pattern, with one component exhibiting a high activity level and the other at a low activity level in each phase, the individual components are not able to switch between sustained high and low activity phases in isolation. Comparative analysis of half-center CPGs is the study of how specific features of half-center CPGs translate into particular properties.

Detailed Description

A half-center CPG consists of a pair of components and the coupling between them. Each component may be an individual neuron or a population of neurons. In a half-center oscillation, each component switches back and forth between sustained low activity and high activity states. The level of activity in a neuron is related to its membrane potential. Transmembrane currents allow ions to pass through channels into or out of a neuron, altering its membrane potential or voltage. These channels may be blocked by two types of gating processes, and changes in the extent of blockage are called (de)activation or (de)inactivation, depending on the gating type. Many of these ion currents are intrinsic to a neuron, meaning that the extent to which they flow is determined by the neuron's own voltage and the ion concentrations in the extracellular medium surrounding the neuron, independent of the activity of other neurons nearby. Other currents are synaptic and are induced by the activity of other neurons. When active, neurons release neurotransmitters that activate synaptic currents in other neurons, their postsynaptic targets. In half-center CPGs, these synaptic currents are inhibitory. If the voltage of a postsynaptic neuron is at a typical physiological level, then such a current lowers its voltage, making it harder for the postsynaptic neuron to activate in the short term. Thus, the primary features of a half-center CPG consist of the sets of ion currents intrinsic to its components; the time scales, voltage dependences, strengths, and other characteristics of these currents; the pattern of synaptic connections between its components; and the characteristics of the synaptic currents that these connections induce. To compare properties of different half-center CPGs efficiently, however, it is useful to group together various half-center CPGs with common emergent features that lead to similar properties.

Classifying Half-Center CPGs: Low and High Activity States and Transitions Between Them

For simplicity, it is convenient to refer to components of CPGs as individual neurons, although the

following discussion can be generalized to cases where the components are neuronal populations. The activity level of a neuron can be quantified using its membrane potential or its rate of generating spikes, which are brief pulses of elevated potential also known as action potentials. Usually high potentials are associated with high rates of spike generation, although there are circumstances in which this link does not hold. An isolated neuron can be in a low activity state, in a high activity state, or in a regime where it spends a significant time in each state with rapid transitions between states. By definition, the neuronal components of a half-center CPG cannot be in the latter state in isolation, as can be checked experimentally by preventing the induction of synaptic currents, although they must enter this rhythmic state once they are coupled synaptically (Hooper 2001). For an isolated neuron to maintain a low activity state, there must be a low voltage at which its intrinsic ion currents are balanced. A high activity state may correspond to the balancing of a neuron's intrinsic currents at a high voltage or to sustained spike generation, without extended pauses between spikes. If we represent a neuron by a system of ordinary differential equations encoding the relations between membrane potential and ion current flows, ignoring spatial effects and stochasticity, then states of balanced current are equilibrium points of the system, while a state of sustained spiking is a periodic solution. If a biological neuron or mathematical model neuron tends to one of these states over time from an appropriate set of starting conditions, then the attained state is an attractor for the system.

These ideas lead to a classification of half-center CPGs in terms of which attractors are present in the absence of inputs, assuming these are unique. Theoretically, the possibilities are:

- L-L: both neurons have attracting equilibrium points in low activity states in the absence of inputs
- L-H: one neuron has an attracting equilibrium point at a low activity state, and one has an attracting high activity equilibrium point or oscillation in the absence of inputs
- H-H: both neurons have attracting high activity states, either equilibrium points or oscillations, in the absence of inputs

In each case, when the neurons are coupled with inhibition, both must transition repetitively between low and high states, taking turns being active, for a CPG rhythm to result. Thus, it is important to check that this alternation is possible in each of the cases in this classification. To keep things relatively simple, it is helpful to assume that the synaptic inputs from a neuron turn on quickly when that neuron's activity level becomes sufficiently high and turn off quickly when its activity level is sufficiently low, although theoretical work has considered slower input changes as well. It turns out that there are certain types of transitions between states that can occur in each case and that the most useful classification is in terms of these transition mechanisms, taking into account both intrinsic and synaptic properties of a model, rather than in terms of the intrinsic attractors of model units alone.

A transition-based classification of half-center CPG models uses the categories of *intrinsic escape*, *intrinsic release*, *synaptic escape*, and *synaptic release* (see Wang and Rinzel 1992; Skinner et al. 1994), defined in terms of which neuron and which processes associated with that neuron control the transitions between activity states. To set up and understand this classification, it is useful to note that certain processes associated with voltage changes are relatively fast while others are relatively slow. The former group includes changes in activation or inactivation of certain currents in response to changes in voltage as well as changes of voltage itself in response to changes in availability of currents, while the latter includes changes in other (in)activation levels as well as changes in concentrations of certain ions within a neuron.

- In *intrinsic escape*, the slow processes of the neuron in a low activity state allow it to make a transition to a high activity state. In doing so, its inhibition to the other neuron turns on, causing the other neuron to make a high-to-low transition

- In *intrinsic release*, slow processes of the neuron in a high activity state cause it to make a transition to a low activity state. In doing so, its inhibition to the other neuron turns off, causing the other neuron to make a low-to-high transition
- In *synaptic escape*, the threshold for activation of synaptic inputs is low. The neuron in a low activity state undergoes small increases in voltage due to its slow processes. Due to the low synaptic activation threshold, this voltage increase is enough to introduce some inhibition of the high activity neuron. This inhibition suffices to induce a high-to-low transition in the high activity neuron, and the resultant loss of inhibition of the low activity neuron causes it to switch to a high activity state
- In *synaptic release*, the threshold for activation of synaptic inputs is high. The neuron in a high activity state undergoes small decreases in voltage due to its slow processes. Due to the high synaptic activation threshold, this voltage decrease is enough to relieve some inhibition of the low activity neuron. This loss of inhibition suffices to induce a low-to-high transition in the low activity neuron, and the resultant inhibition of the high activity neuron causes it to drop to a low activity state

This classification is simplest if it is assumed that the two neurons in the half-center CPG model are identical. More generally, it makes sense under the assumption that both transitions in the network are of the same type. A generalization of the classification would allow for two different transition types within one network oscillation; one neuron might activate through intrinsic escape, for example, while the other neuron might activate through intrinsic release. Another observation is that none of these transition types explicitly specifies a particular timing between the transition of one neuron and the corresponding transition of the other neuron. For example, one neuron might undergo a high-to-low transition intrinsically, releasing the other neuron from inhibition. This change might be enough to induce an immediate low-to-high

transition in the released neuron. On the other hand, additional time might be needed before the released neuron could activate.

Finally, note that this classification is related to the classification based on single neuron attractors. This relation can be illustrated using examples involving particular currents.

Example 1 – L-L/intrinsic release with I_T . Suppose that both neurons have attractors at low activity states without inputs and have T-type calcium currents, I_T , which are inactivated at these attracting states. If one neuron is placed in a high activity state and the other in a low activity state, the low activity neuron is inhibited, and its voltage is reduced. I_T is a positive inward current that slowly deinactivates at low voltages. Thus, if the high state neuron transitions to a low state, the rapid release from inhibition combined with the enhanced availability of I_T can allow the formerly inhibited neuron to activate, inhibiting its partner, in a process called *post-inhibitory rebound*. The whole cascade can repeat periodically and sustain a half-center oscillation.

Example 2 – H-H/synaptic release with I_{K-Ca} . Suppose that both neurons have attracting high activity states without inputs and have a calcium-dependent outward potassium current, I_{K-Ca} , which is activated at these attracting states. If one neuron is put into a low activity state in the absence of inputs, it will transition to high activity on its own, but suppose that the other neuron has just been allowed to become active and supplies sufficient inhibition to block this transition. Over time, the active neuron's I_{K-Ca} activates, and this outward current reduces its voltage. If this voltage reduction is sufficient, it may reduce the inhibition level to the other neuron. As a result, the other neuron may become active and inhibit its partner, causing a high-to-low transition in the formerly active neuron.

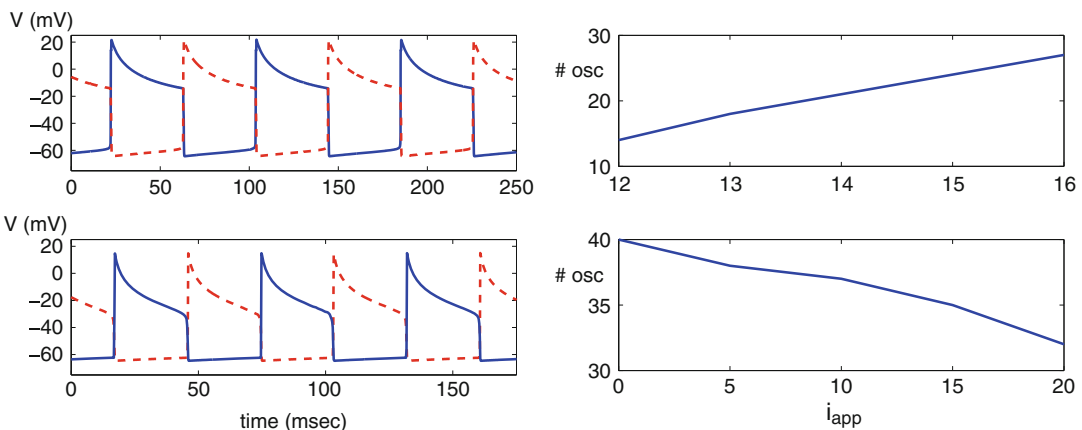
Example 3 – H-H/intrinsic escape with I_{K-Ca} . In the above scenario, it is also possible that the neuron in the low activity state can escape without any reduction of inhibition, because its I_{K-Ca} deactivates over time. Depending on

model parameters, this effect may be enough to allow it to transition to the high state and suppress the formerly active neuron.

Several subtle yet important points arise from this type of analysis: (1) Different transition mechanisms can arise even from the same intrinsic neuron features, depending on the quantitative details. Once neurons are coupled into a network, their individual properties can become masked or overshadowed by network interactions (Ausborn et al. 2018; Rubin and Smith 2019). (2) Certain combinations of intrinsic neuron features and transition mechanisms are possible, while others are not. That is, neurons' intrinsic dynamic properties can constrain which types of network dynamics can emerge (Ausborn et al. 2018). (3) The same transition mechanism can result despite the involvement of different neuron features. In particular, distinct current types can be associated with the same transition mechanism; for example, the depolarization-activated outward current I_{K-Ca} or the depolarization-inactivated inward current I_T can be replaced by the depolarization-inactivated inward current I_{NaP} in the above examples, as long as model parameters are tuned appropriately (Fig. 1, left; cf. Izhikevich 2007).

Transition-Dependent Properties of Half-Center CPGs

A classification of half-center CPGs in terms of transition mechanisms is useful because various properties are determined, or predicted to be determined, by which transition mechanism is present. Consider a theoretical half-center CPG composed of two identical neurons with low activity attractors and with transitions by intrinsic release. Suppose that an equal excitatory current, which raises voltage, is applied to both neurons. Whichever neuron is active controls the next phase transition in the coupled network, and therefore the effect of this current will be determined by its impact on the neurons when they are active, as long as the current is not so large that it changes the transition mechanism (Skinner et al. 1993; Curtu et al. 2008). Since the current is excitatory, it will delay the high-to-low transition of each active neuron, prolonging the period of the CPG oscillation (Fig. 1, right bottom). Alternatively, suppose that the neurons in the CPG have high activity attractors and that the CPG rhythm involves transitions by intrinsic escape. In this case, whichever neuron is suppressed controls the next phase transition in the coupled network. If an excitatory current is applied equally to



Comparative Analysis of Half-Center Central Pattern Generators (CPGs), Fig. 1 Half-center oscillations with transitions by escape and release. (Left) A two-neuron model with reciprocal inhibition and persistent sodium current generates half-center oscillations using escape (top row) or release (bottom row). (Right) Number of

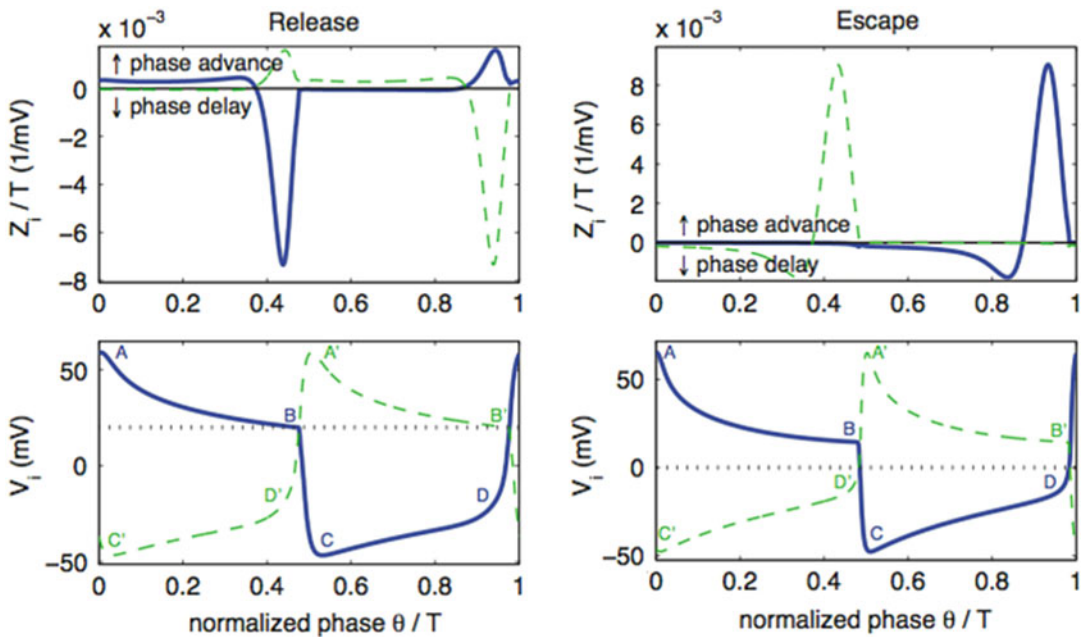
completed oscillations in a 1 s simulation with applied current I_{app} when transitions are by escape (top row) or release (bottom row). For example, five oscillations mean that one cell oscillated three times and the other two times during the simulation

both neurons, this current will raise their voltages and thus accelerate the escape of the suppressed neuron. This effect shortens the period of the CPG oscillation (Fig. 1, right top). In a half-center CPG with a moderate synaptic threshold such that transitions remain intrinsic, a switch from intrinsic release to intrinsic escape may be achieved by applying progressively stronger excitatory current, shifting the neurons' attractors from low activity to high activity states; this switch may be abrupt or may be interrupted by a current range lacking oscillations, in which release is blocked but escape is not yet possible. In either case, the dependence of CPG period on applied current level is non-monotonic.

A more complicated situation is the application of unequal excitatory current levels to the two neurons in a half-center CPG (Daun et al. 2009; Ausborn et al. 2018). This scenario is likely functionally relevant, as modulatory inputs to CPGs may target distinct components differently. In a CPG with transitions by intrinsic escape, the neuron receiving a stronger current will escape faster, but, under fairly general conditions, the network equilibrates such that the duration of the other neuron's suppressed phase remains approximately constant. In contrast, if transitions occur through intrinsic release, then current availabilities tend to equilibrate such that little change in either oscillation phase duration results. If transitions occur through synaptic release, then the low-to-high transition of the neuron with greater stimulation is accelerated, but that of the other neuron is delayed, such that both phase durations are altered. Thus, of these possibilities, only intrinsic escape allows for independent modulation of the durations of the two activity phases in a half-center oscillation (Daun et al. 2009), as would appear to be desirable to maximize the flexibility of behaviors driven by CPG rhythms and is observed in data on fictive locomotion and simulations that reproduce it (Yakovenko et al. 2005; Rybak et al. 2006).

A third scenario that can yield different response properties of half-center CPGs is the application of transient stimulation. Suppose

that a CPG is oscillating with a period T . Assign time 0 to correspond to the time when the voltage of one cell increases through some fixed level. Under this time labeling, the time at which this same event next occurs is time T . For each $t \in [0, T]$, define a phase $\phi = t/T \in [0, 1]$. A phase response curve (PRC) can be defined by plotting the advance or delay in phase introduced by a transient current injection as a function of the oscillation phase at which the injection occurs (Ermentrout and Terman 2010). The PRCs that result when the transitions within an oscillation are due to escape are quite different from the PRCs for release-based transitions (Fig. 2; Zhang and Lewis 2013). For example, label the voltages of neurons in a half-center CPG as v_1, v_2 . Suppose that $\phi = 0$ occurs when the voltage v_1 reaches its maximum. If the two neurons are identical, then v_2 reaches its maximum at $\phi = 1/2$. If transitions occur by escape, then stimulation of neuron 1 at $\phi \in (0, 1/2)$ will have little impact, since the next phase transition relies on the escape of unstimulated neuron 2. Stimulation at $\phi \in (1/2, 1)$, when neuron 1 is suppressed, may accelerate its escape and hence advance the phase of the oscillation, although details relating to the timing, amplitude, and duration of stimulation matter. If transitions occur instead by release, then stimulation of neuron 1 at ϕ in some range within $(0, 1/2)$ will help it continue to suppress neuron 2 and hence cause a delay, especially if v_1 is dropping toward synaptic threshold when the stimulation arrives. Stimulation at $\phi \in (1/2, 1)$ in this case arrives when neuron 1 is suppressed and has little effect on when neuron 2 releases neuron 1 and hence relatively little impact on phase. In summary, the advance or delay in oscillations induced by a transient stimulation at a known oscillation phase depends on whether the transitions in a network are by escape or release. A major phase delay can only arise in the release case, and stimulation in the later part of the active phase of the neuron being stimulated is particularly well suited to distinguish escape (little change in phase) from release (significant phase delay) (Zhang and Lewis 2013).



Comparative Analysis of Half-Center Central Pattern Generators (CPGs), Fig. 2 PRCs for half-center oscillations depend on whether transitions occur by release (left) or escape (right). Top curves (solid blue or dashed green) show Z_1/T , a measure of phase advance or delay, as a

function of the phase at which stimulation is applied to the neuron with a voltage trace of the corresponding type shown in the *bottom* panels. (Figure reproduced from Zhang and Lewis (2013) with permission of Springer-Verlag)

Cross-References

- [Bursting in Neurons and Small Networks](#)
- [Invertebrate Pattern Generation: Overview](#)
- [Phase Response Curves: Overview](#)
- [Sensory Input to Central Pattern Generators](#)
- [Stability and Homeostasis in Small Network Central Pattern Generators](#)
- [Synaptic Dynamics: Overview](#)
- [Vertebrate Pattern Generation: Overview](#)

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Compartment Model for Nuclear Medicine

► [Kinetic Models for PET/SPECT Imaging](#)

Compartmental Models of Spinal Motoneurons

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Definition

Compartmental neuron models represent the complex geometry of a neuron as a set of electrically connected compartments, each of which is considered to be isopotential (i.e., the membrane voltage does not vary along the length of the compartment). Compartmental models of spinal motoneurons can be divided into three groups based on the extent to which they rely on a simplified version of dendritic morphology: (1) detailed compartmental models, which attempt to accurately represent the dendritic morphology based on anatomical reconstructions of stained motoneurons; (2) cable models, in which the branching structure of the dendritic tree is collapsed into one or more equivalent cables; and (3) two-compartment models, in which the dendritic tree is represented by a single lumped compartment that is connected to a compartment representing the soma and initial portion of the axon.

Detailed Description

Motoneurons have the largest dendritic trees of any neuron in the mammalian central nervous system (Kernell 2006). Unlike pyramidal and Purkinje neurons, whose dendritic trees primarily project in a single plane, motoneuron dendrites typically project radially from the soma in all directions and branch extensively. As a result, it is extremely difficult to record directly from motoneuron dendrites, and our understanding of the properties of motoneuron dendrites is based almost exclusively on indirect evidence. Compartmental models of motoneurons are therefore useful tools to infer dendritic properties based on intracellular and whole-cell recordings from the soma.

Equivalent Cylinder Representation of the Dendritic Tree

Early compartmental models of motoneurons represented the dendritic tree as an equivalent cylinder. Wilfrid Rall showed that if dendritic branching followed certain rules, the entire dendritic tree could be collapsed into a single equivalent constant diameter cylinder. This allowed the use of linear cable theory to derive analytical solutions for the effects of injecting current at one point on the cable on the current and voltage measured at other points along the cable (Jack et al. 1975; Koch 1999; Rall 1977; Rall et al. 1992). This theory provided estimates of the electrical length of the dendrites based on measurements of the decay of somatic membrane voltage following a brief pulse of injected current. The distal ends of motoneuron dendrites were estimated to be an average of 1–2 length constants (λ) away from the soma. (A length constant is distance over which the voltage produced by a steady-state injection of current applied at one point on the cable falls to 1/e of its value at the point of current injection.) These estimates implied that distal synapses could exert an appreciable effect on the somatic membrane potential, contrary to earlier suggestions (Eccles 1964). The

theory also was used to estimate the relative location of synapses based on the size and time course of synaptic potentials measured at the soma.

Formulation of Compartmental Models

Although the equivalent cylinder approximation and linear cable theory were extremely useful in providing information about the basic electrical properties of motoneurons as well as the flow of synaptic current in the absence of voltage-dependent conductances, the compartmental representation is needed to model current and voltage changes along the cable in the presence of voltage-dependent conductances. In the compartmental representation, the cable (or branched dendritic tree) is divided into discrete compartments, each of which is assumed to be isopotential along its length. This representation replaces the cable equation, which is partial differential equation that is first order in time and second order in space, with a set of coupled, ordinary first-order differential equations describing current flow in each compartment and between adjacent compartments.

The basic equation describing current flow in a compartment is based on Kirchhoff's current law, which states that for each compartment the net current through the membrane (i_m) is equal to the net longitudinal current that enters and leaves the compartment through the interior of the compartment. The membrane current is in turn composed of capacitative current and ionic current. The membrane equation for compartment j , connected to compartments $j - 1$ and $j + 1$, is thus

$$c_{m_j} dV_j/dt + I_{ion_j} = g_{j-1,j}(V_{j-1} - V_j) - g_{j,j+1}(V_j - V_{j+1}),$$

where V_{j-1} , V_j , and V_{j+1} are the membrane potentials across compartments $j-1$, j , and $j+1$; c_{m_j} is the capacitance of compartment j ; and $g_{j-1,j}$ and $g_{j,j+1}$ are the coupling conductances (reciprocal of the axial resistances) between adjacent compartments (Segev et al. 1989). If we divide the ionic current into that following across a voltage-independent leak conductance (g_L) and that flowing across a number of different voltage-dependent conductances ($\Sigma g_i(V)$) and rearrange terms, the basic differential equation is

$$dV_j/dt = (1/c_{m_j}) \left(-g_L(V_j - V_L) - \sum g_k(V_j)(V_j - V_i) + (V_{j-1} - V_j) + g_{j-1,j}(V_{j-1} - V_j) - g_{j,j+1}(V_j - V_{j+1}) \right),$$

where V_L is the resting (leak) conductance and the V_i s are the reversal potentials for ions flowing through the voltage-dependent conductances. The voltage-dependent conductances are the product of a fixed maximal conductance and one or more state variables that describe how the proportion of open channels changes with voltage and time. A separate set of differential equations describes the evolutions of the state variables, generally of the following form:

$$dm/dt = (m_\infty(V) - m)/\tau_m(V),$$

where $m_\infty(V)$ is the steady-state voltage dependence of channel open probability and $\tau_m(V)$ is the voltage-dependent time constant. Channels can

also be gated by internal calcium (or sodium), and in these cases additional differential equations are needed to represent the buffering, extrusion, and diffusion of calcium (or sodium).

Early Models of Action Potential Generation and Repetitive Firing

Dodge and Cooley (1973) adapted the Hodgkin and Huxley (1952) description of the gating of the sodium (Na) and potassium (K) conductances underlying the action potential in squid axons to model the generation of action potentials in spinal motoneurons. The motoneuron was represented as a series of cylindrical compartments representing the proximal axon and soma, and

the dendritic tree was represented as an equivalent cylinder divided into 30 compartments. The model provided a good match to experimentally recorded action potentials and somatic voltage-clamp recordings when Na and K channels were confined to the soma and axon initial segment. In addition, in order to match the experimental data, the voltage dependence of sodium channels on the initial segment was shifted to 10 mV more hyperpolarized than those on the soma, and the densities of Na and K channels on the initial segment were roughly nine- and six-fold times those on the soma. The increased density and lower threshold of channels on the initial segment are common features of compartmental models of motoneurons (and other neurons as well) and fit well with the available experimental evidence (Bender and Trussell 2012).

Until recently, it was generally assumed that normal motoneuron dendrites are passive, i.e., they have no voltage- or calcium-dependent channels. As described later, it is now clear that motoneuron dendrites have a variety of active conductances. However, even early recordings of motoneuron properties indicated that following axotomy motoneurons develop a number of features, such as all-or-none partial spikes superimposed upon synaptic potentials (Kuno and Llinas 1970), which are consistent with the presence of active dendritic conductances. The input–output properties of motoneurons are also altered following axotomy. In normal motoneurons the relation between injected current and firing rate is composed of up to three linear segments: a shallow primary range at lower levels of injected current and a steeper, secondary range at higher levels, followed in some cases by a shallow tertiary range at the highest levels of injected current (Kernell 2006). Following axotomy, the frequency–current (F–I) relation is characterized by a single linear range whose slope is similar to that of the secondary range in normal motoneurons (Heyer and Llinas 1977).

Traub and Llinas (1977) explored the potential mechanisms underlying the differences in repetitive firing in normal and axotomized motoneurons using compartmental models of varying complexity, ranging from a single cable representation of

motoneuron dendrites to up to four branching dendrites. An essential feature of all of the models was the inclusion of a slow potassium conductance underlying the medium-duration afterhyperpolarization (mAHP). This conductance is activated by the influx of calcium through calcium channels that are opened during the spike. Both the calcium (Ca) and calcium-activated potassium channels (KCa) were placed in compartments corresponding to the proximal dendrites, and Na channels were extended to the proximal dendrites to provide sufficient depolarization to activate the calcium channels. The authors examined the effects of several different spatial distributions of Na and KCa channels on model behavior and found a range of distributions that could reproduce the F–I behavior of normal and axotomized motoneurons. Secondary range firing resulted from a decrease in action potential-induced dendritic depolarization at higher levels of injected current, resulting in a decrease in KCa activation. The behavior of axotomized motoneurons was reproduced by lowering the Na density on the proximal dendrites (leading to secondary range firing at low levels of injected current) and putting hot spots of Na channels at $0.6\text{--}0.7\lambda$ from the soma. The distal Na hot spots mediated local spikelike depolarizations in response to synaptic inputs that propagated decrementally to the soma, leading to the spikelike partial responses superimposed on the synaptic potentials recorded at the soma.

Although the mechanism for partial responses proposed by Traub and Llinas (1977) is consistent with the available experimental evidence (Sernagor et al. 1986), secondary range firing does not seem to depend upon a saturation or reduction of the KCa-mediated mAHP (Schwindt and Calvin 1973). More recent compartmental models based on an alternative mechanism of secondary range firing are considered later.

Synaptic Integration in Passive Dendritic Trees

Both cable models and models with a detailed representation of the dendritic tree have been

used to investigate the relation between the structure and specific membrane properties of motoneuron dendrites and the delivery of current from dendritic synapses to the soma. The best-studied synaptic input to spinal motoneurons is the monosynaptic excitatory input from primary muscle spindle (Ia) afferents. Somatic recordings of excitatory postsynaptic potentials (EPSPs) evoked by electrical stimulation of multiple Ia afferents (composite Ia EPSPs) or from the stretch-evoked activation of single Ia afferents (unitary or single-fiber Ia EPSPs) provided a number of lines of evidence that the synaptic terminals of Ia afferents are distributed widely across the dendritic trees of motoneurons (see Burke 1967, and references therein). Single-fiber Ia EPSPs exhibit a wide variety of shapes that can be quantified by plotting the EPSP width at half amplitude (half-width) versus the time to peak. EPSPs with short times to peak and half-widths were presumed to arrive from proximal synapses, whereas distal synapses were thought to underlie those with long time to peak and half-widths. Simulations with a 10-compartment cable model (Rall et al. 1967) could reproduce the experimentally recorded range of EPSP shapes if it was assumed that single Ia afferents gave rise to a number of synaptic terminals at different distances from the soma, an assumption that was later validated by experimental evidence (Burke and Glenn 1996). This model was also able to account for a number of other experimental findings related to the summation of Ia composite EPSPs, their sensitivity to changes in somatic membrane potential and the ability to detect changes in membrane impedance during the EPSP.

The acquisition of detailed anatomical data on the structure of motoneuron dendrites and the projection of single Ia afferent fibers have guided the development of models that provide a much more precise representation of the structure and specific membrane properties of motoneuron dendrites as well as the spatial distribution of Ia afferent synaptic terminals. Detailed models of reconstructed spinal motoneurons have shown that the experimentally recorded voltage responses to pulses and steps of current injected into the soma can only be reproduced if the

specific membrane resistivity is lower in the soma than in the dendrites (Clements and Redman 1989; Fleshman et al. 1988). Although part of this decrease in somatic resistivity may arise from the leak induced by penetration of the soma with a sharp electrode, this is unlikely to be the only factor contributing to variations in membrane resistivity (see Sect. 3.3.2 in Powers and Binder 2001). Unfortunately, there are a number of different spatial distributions of specific membrane resistivity that can reproduce the experimental data; for example, a step distribution (low in the soma and high and uniform in the dendrites) and a sigmoidal distribution (resistivity rises as a sigmoidal function of distance from the soma) give equally good fits to the experimental data. Somewhat surprisingly, when Ia afferent terminals are distributed onto the models in accordance with the available anatomical data, the step and sigmoidal models give equally good fits to the experimentally recorded EPSPs (Segev et al. 1990). Nonetheless, the spatial distribution of voltage changes produced by activating Ia afferents will depend upon the exact spatial distribution of specific membrane resistivity; this may be particularly important when considering how synaptic inputs are modified by voltage-dependent dendritic conductances.

Limited Charge Transfer in Passive Dendritic Trees

Although analysis based on both cable theory and compartmental models indicates that a significant fraction of the charge entering through even the most distal synapses on motoneurons can reach the soma, that situation changes as more and more synapses are activated. The total conductance of a patch of membrane (in the absence of voltage-dependent conductances) is the sum of the resting conductance and the conductance contributed by activated synapses, and even at relatively low levels of synaptic activation, the total conductance begins to be dominated by the synaptic conductance term (Barrett 1975). This increased conductance together with a decrease in driving force as the membrane is depolarized toward the synaptic reversal potential reduces the amount of synaptic

charge reaching the soma. Barrett (1975) concluded that physiological levels of activation of excitatory input to motoneurons could deliver enough current to produce high rates of repetitive discharge, but recent simulations using detailed compartmental models suggest that this may not be the case.

Korogod et al. (2000) calculated synaptic charge transfer for synapses throughout the dendritic tree in detailed compartmental models of reconstructed motoneurons at different levels of tonic synaptic input (simulated by changing the effective membrane resistivity). In models of cat spinal motoneurons, all of the synapses exhibited high transfer effectiveness (i.e., they transmitted at least 50 % of their charge) at rest. However, at high levels of tonic synaptic activity, only the most proximal synapses were effective. Cushing et al. (2005) used compartmental models of reconstructed motoneurons to explicitly estimate the total amount of synaptic current that could be delivered to the soma during increasing activation of excitatory dendritic synapses. The relation between the effective synaptic current (i.e., the portion of current that reached the soma) and the level of excitatory drive was highly nonlinear, due to increases in membrane conductance and decreases in synaptic driving force as increasing numbers of synapses were activated. The effective synaptic current produced by high-frequency (100 Hz) activation of all of the excitatory synapses was well below that needed to maximally drive motoneurons. This result fits with the experimental finding that the effective synaptic currents produced by high-frequency activation of various peripheral and descending inputs to motoneurons were rather modest (Powers and Binder 2001).

Repetitive Firing and Synaptic Integration in Motoneuron Models with Active Dendritic Trees

Many of the early experimental studies of synaptic integration and repetitive firing in motoneurons were based on recordings obtained in anesthetized animals. An alternative preparation is the unanesthetized, decerebrate animal, which

has been used for over a century to study spinal and postural reflexes. In this preparation, the cerebrum is removed under anesthesia, rendering the animal insensate, obviating the need for further anesthetic. In the absence of anesthetic and inhibitory inputs from the cortex, monoaminergic neurons in the brainstem that project to the spinal cord exhibit tonic activity. This tonic monoaminergic drive facilitates the activation of a number of voltage-sensitive channels, including those present on motoneuron dendrites (Heckman et al. 2003). Under these conditions, motoneurons exhibit a number of behaviors that are not observed in anesthetized preparations, and these same behaviors occur in *in vitro* preparations in the presence of monoamines (Heckman et al. 2003). These behaviors include the following: (1) bistable discharge, the motoneuron continues to discharge after the cessation of a brief excitatory stimulus; (2) hysteresis, in response to a triangular injected current waveform, the motoneuron stops discharging at a lower level of injected current than is required to recruit the motoneuron on the ascending limb of the command; and (3) voltage-dependent synaptic amplification, excitatory synaptic currents are increased with depolarization. All of these behaviors are thought to be mediated by persistent inward currents (PICs) generated primarily by low-threshold calcium channels on the dendrites (Heckman et al. 2003).

PIC-mediated behaviors can be replicated by a variety of compartmental models that place the spike-generating (Na and K) conductances on or near the soma compartment and PIC-generating conductances on the dendrites. These include two-compartment models (Booth et al. 1997; Kim and Jones 2010; Venugopal et al. 2011), cable models (Carlin et al. 2009; Powers et al. 2012a,b; Shapiro and Lee 2007), and detailed compartmental models (e.g., Bui et al. 2006; Elbasiouny et al. 2005, 2006). The consensus view based on these simulations is that the bistable behavior and hysteresis observed in somatic recordings arise from a plateau depolarization in the dendrites following voltage-dependent activation of the PIC. The PIC acts in combination with the leak conductance (and probably voltage-dependent K conductances) to give

rise to a dendritic current–voltage (I–V) relation that is N-shaped, reflecting the contribution of the leak current at hyperpolarized voltages (leading to a positive slope in the I–V relation) and the predominance of the PIC at intermediate voltages (leading to a negative I–V slope), followed by a predominance of outward currents at more depolarized voltages (Heckman et al. 2003). This N-shaped relation has two stable steady-state voltages: one near the resting potential and one corresponding to a depolarized plateau potential. Bistable behavior occurs when injected or synaptic current produces a dendritic plateau that persists when the excitatory input stops, since the plateau depolarization represents a stable state. In response to a triangular injected current waveform, the onset of the dendritic plateau leads to an increase in the slope of the F–I relation (secondary range firing), followed by a decrease in slope (tertiary range firing) once a stable plateau is reached (Elbasiouny et al. 2006; Powers et al. 2012a,b). Hysteresis in the F–I relation occurs because the site of the dendritic plateau is at a significant electrical distance from the soma, so that the plateau is turned off at a lower somatic voltage that was required to initiate the plateau.

Simulations based on detailed compartmental models suggest that the best matches to the experimental data are obtained when the Ca channels responsible for the plateaus are restricted to a relatively narrow range of distances centered at roughly 0.5λ away from the soma, although the exact length and location of these dendritic “hot spots” depend somewhat on which types of experimental data (both electrophysiological and anatomical) are used to constrain the models (Bui et al. 2006; Elbasiouny et al. 2005; Grande et al. 2007b). The presence of multiple hot spots of Ca channels may allow motoneurons to amplify synaptic inputs in a graded manner as synaptic input is increased, since the effective thresholds for activating Ca channels may vary along the dendritic tree as a result of variations in the local geometry (Bui et al. 2006; Elbasiouny et al. 2006; Carlin et al. 2009). A nonuniform distribution of Ca channels also can allow differential amplification of different synaptic inputs, with increased amplification occurring as the spatial

distributions of synaptic terminals and Ca channels show increasing overlap (Bui et al. 2008; Grande et al. 2007a).

There is also evidence that dendritic (as well as somatic and axonal) Na channels contribute to PICs and synaptic amplification (Heckman et al. 2003; Powers et al. 2012a,b). One intriguing possibility, based on a recent simulation study with a two-cable compartmental model, is that bistable firing and synaptic amplification arise in different parts of the dendritic tree with different PIC-generating channels (Shapiro and Lee 2007). In this model, all-or-none plateau generation by Ca channels gives rise to bistable behavior, whereas graded activation of Na channels produces synaptic amplification.

Although there is not enough experimental and simulation data to specify the spatial distribution of Na and Ca channels mediating PIC, the data do support the idea that most of the PIC is derived from dendritic channels (Heckman et al. 2003), and this has important implications for the synaptic control of motoneuron firing rate. Since most of the synaptic input is on the dendrites, the dendritic plateaus have a lower threshold for activation (as measured at the soma) when driven by excitatory synaptic input than by current injected into the soma (Bui et al. (2006) in fact used experimental data of this type to set their channel distributions). As a result, in both cable (Powers et al. 2012a,b) and detailed compartmental models (Elbasiouny et al.), an increase in excitatory drive can lead to a rapid increase in firing rate as soon as the motoneuron starts to fire (secondary range firing), followed by a much shallower increase in rate with further increases in excitation (tertiary range firing). Similar patterns of firing are seen in human motor units during slowly increasing isometric contractions, supporting the hypothesis that PICs provide an important contribution to motoneuron discharge during a variety of motor behaviors (Heckman et al. 2008).

Limitations

As is true of almost all compartmental models, the experimental data is not sufficient to constrain the

parameters (channel properties and channel distribution) of compartmental models of spinal motoneurons. This limitation is particularly severe for motoneuron models due to the lack of direct dendritic recordings and the limited immunocytochemical data on the dendritic distribution of different channel types. As a result, the actual spatial distribution of a particular channel may be significantly different from the one that provides the best fit to experimental data for a given model, since the optimal distribution is likely to vary with the channel properties and the presence of other channels. Nonetheless, the spatial separation of spike-generating and plateau-generating conductances is a common feature of many different types of compartmental models of spinal motoneurons and at this point appears to provide a fairly accurate representation of a range of motoneuron behaviors.

Cross-References

- [GENESIS, the GEneral NEural Simulation System](#)
- [NEURON Simulation Environment](#)

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Further Reading

Genesis <http://www.genesis-sim.org>

Neuron <http://www.neuron.yale.edu/neuron>

Compilation of Published Tracer Injection Studies in the Macaque Brain

► [Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)

Complex Auditory Brainstem Response (cABR)

► [Auditory Frequency-Following Responses](#)

Complex Network Theory in Neuroscience

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Compulsory Averaging

► [Peripheral Vision, Models of](#)

Computation with Dopaminergic Modulation

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Definition

Dopamine (DA) is a neuromodulator released by midbrain neurons with widespread projections

throughout the brain. Dopaminergic modulation has diverse effects on cellular, motor, and cognitive functions, including reinforcement learning, working memory, and attention. Dysregulation of dopamine also plays a central role in the breakdown of these functions in disorders such as Parkinson's disease and schizophrenia.

Detailed Description

Dopamine Basics

DA is a neuromodulator released by neurons in two nuclei of the midbrain: the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). The axons of these neurons project to a large number of cortical and subcortical areas. Prefrontal cortex, motor cortex, and the striatum are among the most densely innervated areas. DA release tends to be fairly homogeneous across DA neurons, by virtue of electrical coupling between the axons of adjacent neurons, which induces highly synchronous firing. As pointed out by Paul Glimcher, these properties suggest that DA neurons “cannot say much to the rest of the brain but what they say must be widely heard” (Glimcher 2011).

DA affects its targets primarily by two classes of receptor – D1 and D2 – and the distinct properties of these receptors have functional consequences which are discussed below. D2 receptors tend to be activated earlier, and at lower concentrations, than D1 receptors (Lapish et al. 2007; Schultz 2007). As a consequence, D2 receptors are more sensitive to phasic (transient) DA release than D1 receptors, with the opposite pattern for tonic (background) DA release (Grace 1991). D1 and D2 receptors also have different postsynaptic effects: D1 receptor activation increases both NMDA (excitatory) and GABA (inhibitory) currents, whereas D2 receptor activation decreases them (Trantham-Davidson et al. 2004).

Reinforcement Learning Models

One of the most influential hypotheses about DA is that it plays an integral role in a system that learns to predict future reward. This hypothesis

can be formalized in terms of the theory of reinforcement learning (RL) first developed in computer science (Sutton and Barto 1998). At each time t the agent occupies a state s_t (e.g., the agent's location or the surrounding stimuli) and receives a reward r_t . The goal of an RL system is to estimate the *expected discounted future return*, or *value*, of visiting a sequence of states starting in state s_t :

$$V(s_t) = E \left[\sum_{k=0}^{\infty} \gamma^k r_{t+k} \right], \quad (1)$$

where γ is a *discount factor* that accounts for the fact that distal rewards are less valuable than proximal rewards. The expectation E represents an average of the quantity inside the brackets over stochastic sequences of states.

If we make certain assumptions about the environment (specifically, that it is a *Markov decision process*; see Sutton and Barto 1998), then the value can be estimated by a simple learning rule known as *temporal difference learning*:

$$\hat{V}(s_t) \leftarrow \hat{V}(s_t) + \alpha \delta_t, \quad (2)$$

where α is a *learning rate* and δ_t is a *prediction error* defined as:

$$\delta_t = r_t + \gamma \hat{V}(s_{t+1}) - \hat{V}(s_t). \quad (3)$$

Intuitively, if the prediction error is greater than zero, then more reward was received than was predicted, and hence $\hat{V}(s_t)$ is increased. If the prediction error is less than zero, then $\hat{V}(s_t)$ is decreased. Another implication of this learning rule is that prediction errors will gradually propagate backwards in time as values at earlier time points come to reflect reward received at later time points.

Schultz et al. (1997) observed that the phasic firing of DA neurons in an appetitive conditioning experiment was conspicuously consistent with a hypothetical prediction error. In these experiments, a conditioned stimulus (CS, e.g., a tone) is repeatedly followed by an unconditioned stimulus (US, e.g., juice reward). Schultz et al. noticed that DA firing increased in response to an

unexpected reward (e.g., in early training trials). After multiple training trials, if the reward is delivered following the CS, then DA firing is at baseline following reward delivery but increases following the CS onset. In this case, the reward is expected and hence the prediction error at the time of reward is zero, whereas the prediction error at the time of the CS is greater than zero due to the temporal propagation described above. Finally, if the reward is omitted following the CS, DA firing pauses (decreases below baseline), consistent with the occurrence of a negative prediction error.

In addition to its role in predicting reward, DA plays an important role in selecting actions to increase reward. For example, electrophysiological studies have shown that DA responses to reward are sensitive to actions (Morris et al. 2006; Roesch et al. 2007), and DA receptor antagonism in the striatum suppresses the initiation of reward-seeking actions (Berridge and Robinson 1998). According to RL theory, there are a number of ways to use prediction errors to estimate the value of actions, some of which have been integrated into models of DA (e.g., Frank 2005; Houk et al. 1995; Montague et al. 1996; Suri and Schultz 1998).

Since the seminal work of Schultz et al. (1997), the prediction error theory of DA has been corroborated by converging evidence from humans and other animals (see Glimcher 2011 for a review). At the same time, it is clear that such a simple theory is unable to account for many of the complexities of DA function. These lacunae have stimulated a number of significant extensions of the theory, some of which are described below. Interestingly, these extensions mirror the technical development of RL theory in computer science. Biological and artificial agents face similar challenges in optimizing reward – and may have even arrived at similar solutions.

One development of the prediction error theory concerns the phasic DA firing in response to novel stimuli (e.g., Horvitz et al. 1997). The original prediction error theory fails to anticipate this finding, since novelty does not by itself predict reward. However, as pointed out by Kakade and Dayan (2002), novelty responses can be rationalized by considering the problem of optimizing

reward. All agents face a dilemma between *exploiting* the currently best option and *exploring* other options that might be potentially better (Cohen et al. 2007). One way to encourage exploration is by initializing the values of all states to be greater than zero. As shown by Kakade and Dayan, this has the effect of generating positive prediction errors when these states are visited for the first time, consistent with the DA novelty response.

A second development has been to incorporate timing variability and partial observability into the TD model (Daw et al. 2006). The original prediction error theory (Montague et al. 1996; Schultz et al. 1997) used a delay line to represent different temporal epochs as distinct states. Daw et al. (2006) replaced the delay line with two assumptions: (1) States are occupied for some random amount of time before a transition occurs (timing variability); and (2) states are not directly observed, but must be inferred from noisy sensory data (partial observability). Daw et al. showed that these extensions could account for a number of timing properties of phasic DA firing. For example, if a reward is delivered early or late, a phasic DA burst is observed (Hollerman and Schultz 1998), contrary to the delay line model, which predicts a negative prediction error (i.e., a pause in firing). The Daw et al. model correctly predicts a positive prediction error, because it infers that a transition to the “reward state” has occurred early or late.

A third development of the theory concerns the role of tonic DA. It has long been recognized that tonic levels of DA appear to be regulated independently of phasic levels (Grace 1991). In particular, increased tonic DA has been associated with the invigoration of behavior (Schultz 2007), and the depletion of tonic DA results in a loss of vigor (Salamone et al. 2001; Sokolowski and Salamone 1998). To account for these observations, Niv et al. (2007) proposed that tonic DA signals an estimate of an environment’s average reward. When the average reward is high, it is rational for an agent to respond more vigorously (since more reward can be collected), whereas when the average reward is low, the energetic costs may outweigh the benefits of responding. This model predicts not only a lower rate of

responding with depleted tonic DA but also a longer latency to respond, consistent with experimental evidence (Denk et al. 2005).

A fourth development has been to integrate the prediction error theory into more biologically detailed models of RL in the basal ganglia. For example, Frank (2005) proposed a model in which DA differentially affects the “direct” and “indirect” pathways of the basal ganglia. The direct pathway striatal neurons in the direct pathway primarily express D1 receptors, whereas striatal neurons in the indirect pathway primarily express D2 receptors. The net effect of DA in the striatum is to increase activity in the direct pathway and suppress activity in the indirect pathway, resulting in disinhibition of action selection in the frontal cortex via modulation of basal ganglia output pathways. One consequence of this differential effect is that neurons in the direct pathway undergo long-term potentiation following a DA burst, whereas neurons in the indirect pathway undergo long-term depression. Another contribution of this model is a division of error-driven learning into positive and negative components: D1-expressing neurons learn more from positive prediction errors, whereas D2-expressing neurons learn more from negative prediction errors. Thus, the model of Frank (2005) provides a neurally plausible mechanism by which DA can influence action selection in corticostriatal circuits.

Gain Modulation and Working Memory

The sensitivity of a neuron to stimulation can be enhanced by the application of DA, without changing the spontaneous firing rate (Clarke et al. 1987; Foote and Morrison 1987). In other words, DA increases the signal-to-noise ratio of a neuron. Servan-Schreiber et al. (1990) introduced a connectionist implementation of this idea by positing that DA increases the gain β of a sigmoidal activation function:

$$a = \frac{1}{1 + e^{-\beta x - b}}, \quad (4)$$

where x is the synaptic input of the neuron, b is the baseline membrane potential, and a is the firing

rate. This basic schema for dopaminergic gain modulation has been reproduced in much greater biological detail by a number of authors (e.g., Durstewitz et al. 1999; Moyer et al. 2007).

An important function of gain modulation is to support active maintenance in working memory: If a group of neurons are recurrently connected to form an attractor network, increasing the gain will increase the stability of high activity states (i.e., actively maintained memories) while suppressing low activity states corresponding to spontaneous background activity. Consistent with this idea, DA appears to play an important role in supporting active maintenance of working memory representations in the prefrontal cortex (Cohen et al. 2002).

DA has been hypothesized to play a complementary role in updating working memory (Braver and Cohen 1999; Durstewitz et al. 1999; O'Reilly and Frank 2006). According to these models, a phasic burst of DA acts as a “gating” signal, transiently amplifying afferent inputs while suppressing local inhibitory signals. The effect of this gating signal is the encoding of afferent input into the current attractor state. O'Reilly and Frank (2006) have proposed a biologically detailed refinement of this idea, whereby “stripes” in the prefrontal cortex (groups of neurons connected to distinct areas of the basal ganglia). Levitt et al. (1993) encode representations in working memory that are updated by phasic DA bursts. This model uses an RL mechanism to learn when to gate, providing a link to the models of corticostriatal plasticity described above.

How can the active maintenance and updating roles of DA be reconciled? One suggestion is that these roles are mediated by different receptors. Specifically, Cohen et al. (2002) have suggested that phasic DA activity primarily affects updating via D2 receptors, whereas tonic DA activity primarily affects active maintenance via D1 receptors. These two modes interact, with tonic DA inhibiting phasic DA by regulating presynaptic autoreceptors (Grace 1991). This hypothesis is consistent with the observation that prolonged pharmacological elevation of tonic DA results in perseverative and stereotyped behavior (Arnsten

1998; Sawaguchi and Goldman-Rakic 1991), which could arise from a failure to update due to reduced phasic DA.

Computational Modeling of Dopamine-Associated Disorders

The models reviewed above furnish a set of hypotheses about the etiology of psychiatric disorders arising from DA dysfunction. This section focuses on the two most well-studied examples: schizophrenia and Parkinson's disease.

A number of authors have proposed that many cognitive deficits in schizophrenia can be explained by a breakdown in the regulation of gating (Braver and Cohen 1999; Durstewitz and Seamans 2008; Frank 2008; Waltz et al. 2007). The gain modulation view leads Braver and Cohen (1999) to propose that reduced prefrontal DA in schizophrenics results in a lower signal-to-noise ratio; combined with noisier DA signaling, this produces gating of irrelevant information into working memory and can cause psychotic episodes in schizophrenia. Another view, proposed by Frank and colleagues (Frank 2008; Waltz et al. 2007), is that striatal D1 receptor function is compromised in schizophrenia, resulting in impaired learning from positive prediction errors but spared learning from negative prediction errors.

The model of Frank and colleagues also sheds light on the cognitive deficits in Parkinson's disease (Frank 2005; Moustafa et al. 2008b; Wiecki and Frank 2010). Unmedicated patients with Parkinson's disease appear to be better at learning from negative outcomes compared to positive outcomes, and this pattern is reversed by DA medication (Cools et al. 2006; Frank et al. 2004; Moustafa et al. 2008a). Frank et al. explained these findings in terms of the effects of DA levels on D1 and D2 receptors in the striatum: Depleted DA in unmedicated patients results in D2 dominance (as in schizophrenia), whereas elevated DA in medicated patients results in D1 dominance. This account may explain the nature of cognitive deficits following DA medication, such as failures to avoid non-rewarding or punishing stimuli

(Cools et al. 2006; Frank et al. 2004; Moustafa et al. 2008a) and susceptibility to pathological gambling and addiction (Dagher and Robbins 2009).

In addition to these cognitive deficits, Parkinson's disease is associated with bradykinesia, an overall slowing of movements, and this deficit is relieved by DA medication. However, Parkinson's patients can learn to make movements at a task-specified velocity and with the same level of accuracy as controls; the key difference is that Parkinson's patients take longer to reach the performance criterion (Mazzoni et al. 2007). The tonic DA model of Niv et al. (2007) offers a perspective on these findings: since tonic DA is reduced in Parkinson's disease, the average reward will be perceived as lower, thus reducing the opportunity cost of not responding. Thus, bradykinesia may actually reflect an optimal decision by the motor system based on incorrect information about average reward provided by tonic DA (Niv and Rivlin-Etzion 2007).

Cross-References

- [Computational Models of Neuromodulation](#)
- [Reward-Based Learning, Model-Based and Model-Free](#)

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Computation with Population Codes

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Definition

Population coding is a computational theory postulating that information is represented and processed by a large number of neurons. In such a coding scheme, each neuron on its own encodes only a small amount of the information that is distributed across the population. Population coding provides robustness, because even if individual neurons are noisy or fail altogether, the population code still processes information effectively.

Detailed Description

Fundamentals of Computation

To understand how a population code computes, we will first start by describing the basics of computation by analyzing silicon-based computers. There are two essential ingredients to

computation: representation and transformation. Information in computers is represented using discrete binary digits, called bits. A bit is often thought of as a “yes” or “no” response or a “1” or “0”. A bit represents two states and is the simplest form of information. A computer is built by utilizing a large number of bits to represent information. The number of elements that can be represented grows exponentially with the number of bits that are used. Eight bits (a “byte”) can represent up to 256 (2^8) different values. Large numbers are represented by more and more bits: an integer is typically represented by 32 bits, and a “double” is a decimal number that is represented by 64 bits. A computer can represent anything by using more and more bits of information. A 2-h movie, for example, is currently represented with about 8 billion bits.

Computation is in essence the transformation of information from one representation to another. For instance, a computer represents – or “encodes” – each letter in this text by a byte (8 bits). For you to read this text, the computer must transform each letter into an image, which is made of pixels that are also represented by bits. The computer transforms the byte that represents each letter into a different sequence of bits that represents the pixel colors. The specific rules of the transformation are called the “algorithm.” The monitor then “decodes” the bits that represent the pixel colors and creates an image. A computer can perform “universal” computation, which means that it has the ability to transform any string of bits into any other arbitrary string of bits. This ability is what makes a computer so powerful, because it can transform any type of information in one representation into any other representation.

The brain, too, must represent a large number of variables produced by the sensory environment or intrinsic states. To perform their functions, neurons in the brain must be able to encode, transform, and decode this information. However, unlike the bits on a computer, neurons are intrinsically noisy. The failure of a single bit in a computer could have catastrophic effects on the entire system, but by design there is virtually no noise in a computer, so these types of failures are rare. Biological systems, on the other hand, have a

great deal of noise of many sorts – both from the intrinsic properties of the component neurons and from ongoing neural activity from sources other than the signal of interest. The neurons must perform their computations in the face of many potential failures caused by this noise. The brain appears to solve this noise problem by distributing information across a large population of neurons. Having more neurons entails robustness to the encoded information, because a large number of independent neurons represent the information. By spreading the information about different variables across many neurons, very little information is lost if a single neuron misfires or even dies.

Theoretical work in systems neuroscience has developed the “population coding” framework of neural computation, based on this premise that information is processed across a large population of neurons. Population coding computes differently than a computer, but it still must perform the same fundamental operations of information processing: representation and transformation. The brain receives information from the outside world and must represent this information in the activity of neurons. The brain then transforms this information in different brain regions to other representations that are useful for perception or behavior. For instance, to grab a baseball, your brain transforms visual information that is stored in an eye-centered coordinate system into a body-centered coordinate system. The same information is stored in both coordinate systems, but with different representations. The motor cortex then uses the body-centered coordinate system to generate a motor sequence that contracts and relaxes the correct muscles to reach out while opening the hand and then stop the reaching and close the hand as it envelopes the baseball. For the brain to perform such a behavior, it must have a representation of all the relevant information, as well as the ability to transform one representation into another.

Representation of Single Variable in Population Codes

The first step for a population code is to represent information through the activity of neurons.

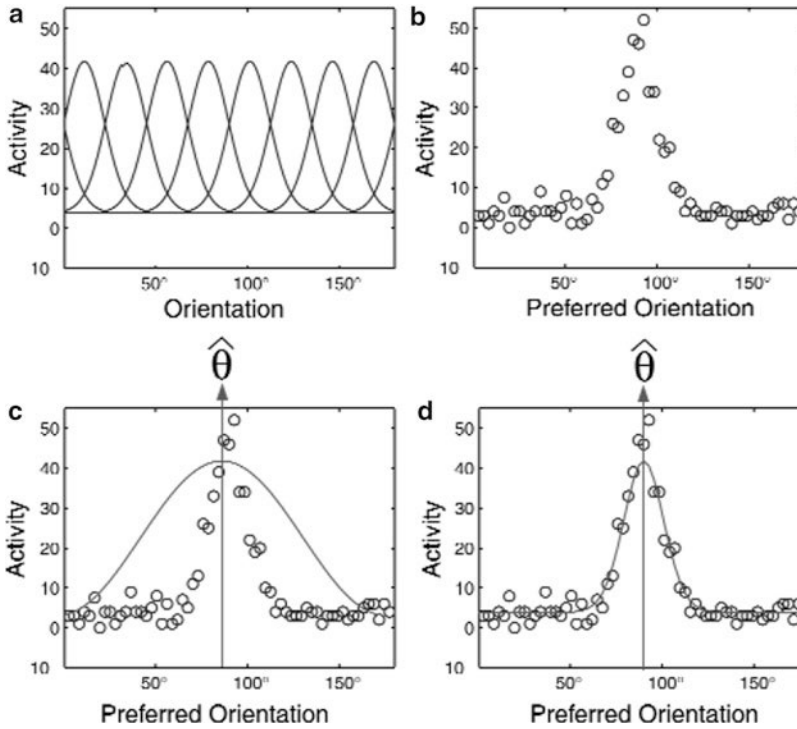
A good way to understand how a population code can represent information is to decode a single variable from neural responses. A classic example of population coding is provided by determining how a simple cell in visual cortex responds to bars oriented at different angles. A given simple cell responds maximally to a bar that is oriented at the neuron’s “preferred” angle, but this neuron also responds to orientations that are close to this preferred angle. The relationship between the stimulus and the firing rate of the neuron creates the neuron’s “receptive field,” which peaks at the preferred angle and decays as the stimulus angle moves away from the preferred angle. The receptive field is typically a bell-shaped curve, often taken to be Gaussian for nonperiodic variables and a cosine function for periodic variables (Deneve et al. 1999).

A large number of neurons make up the population, where each neuron has its own receptive field. The preferred orientations of each neuron are spread out across the full stimulus space. Figure 1a shows several example receptive fields from eight different neurons; each bell-shaped curve is the receptive field of a different neuron. These receptive fields partially overlap and are centered at different preferred angles. When a stimulus is presented, all neurons respond based on their receptive fields. When an oriented bar is presented that has an angle of $\theta = 90^\circ$, then several neurons with preferred orientations close to 90° will fire (Fig. 1b). The closer the neuron’s preferred orientation is to 90° , the higher the neuron’s firing rate, but noise can make the firing rate variable for a given stimulus presentation. The activity of the population is described by

$$r_j = f_j(\theta|\Theta_j) + \epsilon \quad (1)$$

where r_j is the firing rate of neuron j , Θ_j is the preferred orientation of neuron j , f_j is a function that describes the neuron’s receptive field, and ϵ is noise. This is the “standard model” of population coding.

There are various approaches used to come up with an estimate, $\hat{\theta}$, of the orientation of the stimulus encoded by the firing rates of the population of neurons. All approaches obtain an



Computation with Population Codes, Fig. 1 The standard model of population coding. (a) A population of neurons have receptive fields that are sensitive to different orientations. Each bell-shaped curve is from a different neuron, and the neuron's preferred orientations are spread out across the stimulus space. Y-axis: spikes per second. (b) When an orientation of $\theta = 90^\circ$ is presented, the

neurons respond based on their receptive fields shown in a. (c) The population vector estimator is a voting method that decodes the orientation from the neural activities by fitting a cosine function to the responses. (d) The maximum likelihood estimator fits a template derived from the receptive field shapes (From Deneve et al. 1999)

estimate by computing a function from the activity across the population R , where $R = (r_1, r_2, \dots)$. Because of noise, the response across the population varies during different presentations of the same identical stimulus. This variability means that the estimate, $\hat{\theta}$, is a random variable. Different techniques for decoding the estimate from the population activity have been developed, each with different tradeoffs: in bias (whether the $\hat{\theta}$ is right on average), variance (how close $\hat{\theta}$ is to θ on average), computational efficiency, and biological plausibility (Pouget et al. 1998).

One interpretation of the population code representation is that each neuron “votes” for its preferred stimulus. Such schemes are typically computationally efficient and biologically plausible, but have higher variances than other decoding methods (they are only optimal under specific conditions as discussed below). Three

commonly used voting schemes are the following.

Population Vector Estimator (PVE)

Bar orientation is a spatially periodic variable, and the PVE decodes such periodic variables by fitting a cosine function (Fig. 1c) to the activity patterns, R :

$$\hat{\theta}_{\text{PVE}} = \text{phase}(z) \quad (2)$$

where

$$z = \sum_j r_j e^{i\theta_j} \quad (3)$$

Optimal Linear Estimator (OLE)

Because the PVE works only for periodic variables, other measures must be used for

nonperiodic variables. A standard algorithm for decoding a nonperiodic variable from a population code is the OLE:

$$\hat{\theta}_{\text{OLE}} = \sum_j \Theta_j r_j \quad (4)$$

Center of Mass Estimator (COM)

A simple extension of the OLE, the COM can account for the background firing (one form of noise) by comparing the neural responses when the stimulus is presented to the background rate and when the stimulus is absent:

$$\hat{\theta}_{\text{COM}} = \frac{\sum_j \Theta_j (r_j - b)}{\sum_j (r_j - b)} \quad (5)$$

where b is the spontaneous activity of the neurons. All three of these estimators are “voting methods,” because each spike from a neuron is like a vote for that neuron’s preferred stimulus feature, and the estimate is a simple combination of all of the votes. Unlike these voting methods, other estimators can decode the population activity optimally, which means the variance of the estimate is minimized and there is no bias. These estimators are less biologically plausible, however, and less computationally efficient than the voting methods.

Maximum Likelihood Estimator (ML)

This estimator finds the value of θ that maximizes the conditional probability of the population response, $P(R|\theta)$, and is optimal when θ is uniformly distributed:

$$\hat{\theta}_{\text{ML}} = \arg \max_{\theta} P(R|\theta) \quad (6)$$

The ML estimator is similar to the PVE in that it is effectively fitting a template to the population response (Paradiso 1988) (Fig. 1d). However, the PVE assumes that the shape of the template is a cosine, whereas the ML derives the template directly from the receptive fields of the neurons, which means that the decoder must have knowledge of the receptive field shapes of the encoding neurons. This may be a biological implausibility, but it is also possible that the receptive field shapes are learned over time (Sanger 2003).

Maximum a Posteriori Estimator (MAP)

This estimator is an extension of the ML estimator that can incorporate the prior distributions of R and θ . The MAP estimate maximizes the full posterior distribution of the encoded variable, $P(\theta|R)$, which is derived from the conditional probability through Bayes’ theorem:

$$\hat{\theta}_{\text{MAP}} = \arg \max_{\theta} P(\theta|R) \quad (7)$$

$$P(\theta|R) = \frac{P(R|\theta)P(\theta)}{P(R)} \quad (8)$$

This is a useful modification if certain values of θ are more likely than others, e.g., if horizontal orientations are seen more frequently than vertical orientations. If the prior distribution is flat – meaning that all values of θ are equally likely – then the MAP estimate is identical to the ML estimate.

High-Dimensional Population Codes

The activity of a population of neurons can be considered to form a high-dimensional response space: two neurons would form a two-dimensional space (a plane), three neurons would form a three-dimensional space, etc. If the activity of three neurons is plotted as the x , y , and z coordinates in a three-dimensional Cartesian system, then a particular stimulus activates these neurons in a particular firing pattern, which would correspond to a point, called the “population vector,” in three-dimensional space. Each additional neuron would add a dimension to this response space. As the firing rate of neuron j increases, the population vector would move up in the j th dimension. If we had ten neurons representing the 1-dimensional orientation, then each presentation of a particular orientation would activate the ten neurons in a specific way that would correspond to a population vector in the 10-dimensional response space. Each orientation would cause a different pattern of activation, which would correspond to a different population vector in the 10-D space. Together, the responses to all possible orientations would form a 1-D “manifold” (a curvy line) in the 10-D response space.

In addition to representing information about one stimulus variable, a population of neurons can encode multiple variables simultaneously. A signal could have several feature dimensions, all of which are encoded by the brain. For instance, a population of neurons could simultaneously encode both the orientation and the thickness of a bar stimulus. In this population, each neuron would have a two-parameter receptive field that has both a preferred orientation and a preferred thickness:

$$r_j = f_j(\theta, \phi | \Theta_j, \Phi_j) + \epsilon \quad (9)$$

where Φ is the thickness of the bar and Φ_j is the thickness preferred by neuron j . In this representation, each combination of orientation and thickness would correspond to a single point in the high-dimensional response space (with each dimension again corresponding to the activity of one neuron). All possible combinations of bar orientation and bar thickness would form a 2-dimensional manifold (a curvy plane). In one direction along this manifold, the information about orientation is represented, and in another direction information about thickness is represented. In general, the population can encode multiple dimensions of the stimulus, where each neuron can be sensitive to any combination of stimulus dimensions:

$$r_j = f_j(\theta, \phi, \psi, \dots | \Theta_j, \Phi_j, \Psi_j, \dots) + \epsilon \quad (10)$$

An individual neuron can have a preference for an arbitrary combination of each of the stimulus dimensions. The preferred orientation and thickness of a given neuron can be chosen independently. For instance, a neuron with a preferred orientation of $\Theta_j = 90^\circ$ could be just as likely to respond to a thick bar as a thin bar.

The information about a particular feature of the stimulus does not necessarily correspond to the firing of a particular neuron. In the population code, the neurons represent stimuli through their joint activities. When representing multiple stimulus dimensions, the neurons are activated by all features of the stimulus with different strengths.

The orientation of a stimulus would thus be only one of many components of the response for a given neuron. The information about orientation is encoded in the combination of activities across the population. This can be thought of as a particular direction in the high-dimensional space, but not as the firing of a particular neuron.

Just as adding more neurons adds more dimensions to the population code, adding more features to the stimuli would increase the number of dimensions in the manifold representing those features. In general, the larger the number of dimensions (i.e., neurons), the larger the number of features that a particular neuronal population can represent. This relationship between the number of neurons and the number of features that can be encoded requires a consideration of “basis sets.”

Basis Sets

For the same neurons to encode more than one feature, the activity of the neuronal population must create a “complete basis set” for these features. To understand what such a requirement means, consider a particular set of neurons with receptive fields that respond to both orientation and thickness, but these receptive fields are actually perfectly correlated: neurons that prefer 90° orientations also prefer thick bars, and neurons that prefer 0° also prefer thin bars. If the receptive fields are correlated in such a way, then there are different combinations of orientations and thicknesses that activate the population in exactly the same way. If the population response is the same to two different stimuli, then there is less information about the stimulus available in the activity. Technically, this inability of the population to fully encode the two features arises because we have intentionally made the receptive fields “linearly dependent.” For the neurons to represent all the dimensions of the stimulus, they must form a complete basis of the stimulus space: the manifold determined by the neurons’ firing rates in the response space must have as many dimensions as the number of features. Because we have made the receptive fields perfectly correlated,

every combination of thickness and orientation no longer forms a 2-dimensional manifold, but instead forms a 1-dimensional manifold. Every point in the 1-dimensional manifold represents different combinations of the two dimensions, which means that the information about both features is not present in the population activity.

To form a complete basis of a stimulus space with d dimensions, there must be at least d neurons with receptive fields that are “linearly independent.” This means that no receptive field could be made out of a linear combination of the other receptive fields. The number of stimulus dimensions that a population code could possibly represent is less than or equal to the number of neurons. Typically a signal can be fully characterized by only a few features, and the number of neurons responding to a stimulus is usually much greater than the number of stimulus dimensions. If there are d stimulus dimensions, and N neurons in the population, and $N > d$, then the population code is a d -dimensional manifold in an N -dimensional space. To form a complete basis of a d -dimensional stimulus, there must be at least d neurons with receptive fields that are linearly independent. Not all of the neurons need to be linearly independent, however; with N neurons, some of the receptive fields can be linear combinations of others, as long as there is a subset of at least d linearly independent receptive fields.

If the stimulus dimensions (d) are low compared to the number of neural dimensions (N), the neurons can form an “overcomplete basis set” of the stimulus space. There are at least d neurons with linearly independent receptive fields in an overcomplete basis set, but the other neurons can be linearly dependent. The overcomplete basis gives robustness to the population code because redundant information about the stimulus is duplicated across many neurons in the N -dimensional space. Even if one of the N neurons completely failed, the $N-1$ neurons would still form a complete basis of the d -dimensional stimulus space, and no information about the stimulus would be lost. An interesting feature of this robustness is that none of the $N-1$ receptive fields needs to be exactly the same as the neurons that failed. The information carried by the failed neuron is also

represented by some linear combination of the $N-1$ neural responses. This property means that no two neurons are necessarily “redundant” – every neuron could have a unique response to a stimulus – but there is redundant information in the population vector. This redundancy helps the neuronal population maintain all of the information even in the presence of large amounts of noise.

The receptive field functions (f_j) play a critical role in the formation of a basis set. The receptive field shapes considered so far are Gaussian (aka, bell-shaped curves), because these types of functions match many biological receptive fields and because these types of functions are capable of forming a basis set. There are other types of receptive field functions (such as sigmoids or threshold-linear) that can also form basis sets, and it is possible to have different types of basis functions together in a single population code. The key property is that the basis set must be able to represent (or closely approximate) any type of nonlinear function by a linear combination of the basis functions:

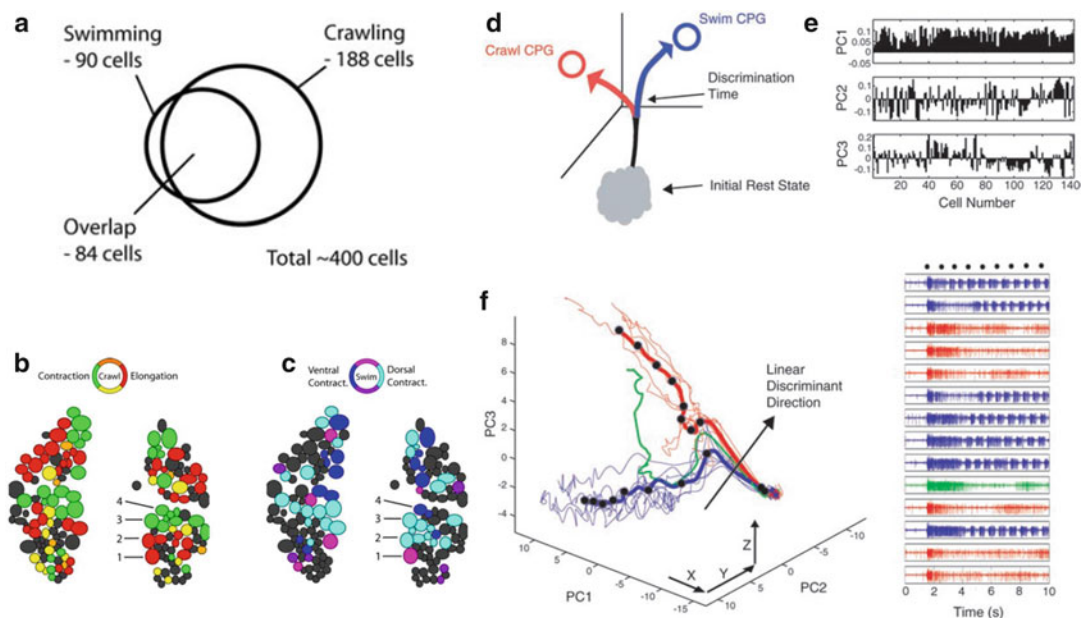
$$g(\theta) = \sum_j w_j f_j(\theta | \Theta_j) \quad (11)$$

where w_j are the coefficients and $g(\theta)$ is some nonlinear function. This requirement of a basis set is similar to the decomposition of a signal by a Fourier transform, where a linear combination of sines and cosines can closely approximate any nonlinear function. Some receptive field functions do not have this property. For instance, if all the receptive fields were linear, then any linear combination of them would also be linear. This means that nonlinear functions cannot be fully represented, which means that a population code based entirely on linear receptive fields could not fully represent any signal.

Nervous systems can utilize the population coding framework beyond representing extrinsic features of the stimulus. The brain must represent intrinsic information about decisions and motor-commands as well. The nervous system of the leech has provided insights into how the same population of neurons can encode different

modalities of information. The leech has a very simple nervous system, where the activity of a significant fraction of cells (>100) can be recorded simultaneously with voltage-sensitive dyes (VSDs). These recordings show that almost every cell in the leech nervous system is multifunctional: each neuron responds to many different stimuli and during several different behaviors. In effect, each neuron has a high-dimensional receptive field that is sensitive to many of the sensory, motor, and intrinsic variables. Neurons in the leech encode the sensory environment using a population code. The local bend response is a reflex in which the leech bends its body away from a stimulus. Local bending requires

information about the stimulus location to be propagated through the nervous system. The neurons involved in this behavior have overlapping receptive fields, each with preferred touch locations, and encode the information about touch location just like the orientation information in the standard model (Lewis and Kristan Jr 1998; Fig. 1a). Neurons are also encoding information about the motor patterns. For instance, virtually all the neurons that respond while the leech swims also respond while the leech crawls (Briggman and Kristan Jr 2006; Fig. 2a). Swimming and crawling are both oscillatory behaviors, and many of the neurons' voltages oscillate with the muscle contractions at different phases



Computation with Population Codes, Fig. 2 Populations encode multiple modalities of information. (a) Neurons that oscillate with the swimming and crawling behaviors were observed with voltage-sensitive dyes. Virtually all neurons are multifunctional: those involved in swimming were also involved in crawling. (b, c) Image of the dorsal side of the leech ganglion where neuron somas are shown as circles. Neurons involved in crawling (b) and swimming (c) are colored based on the relative phase of their oscillations. (d) The swimming and crawling central pattern generators (CPG) are encoded as different population vectors in the high-dimensional neural space. The population begins at an initial rest state and then makes an excursion to one of the CPGs after a stimulus. (e) The first three principal components of neural responses. This allows the high-

dimensional neural space to be reduced to 3 dimensions, which can be visualized. (f) Trajectories of the neural responses in PCA space during swimming and crawling behaviors (left). The black dots indicate equally spaced intervals in time. These behaviors can be predicted from the population response using linear discriminant analysis, which chooses the direction that maximally separates the population vectors during the two behaviors (arrow). The decision to swim or crawl can be determined before the motor patterns start (right): the traces show the firing of several motor neurons during swimming (blue) or crawling (red). In one outlier, the population vector appeared to head in the swim direction, but changed course and went to the crawl pattern (green) (From Briggman et al. 2005; Briggman and Kristan Jr 2006)

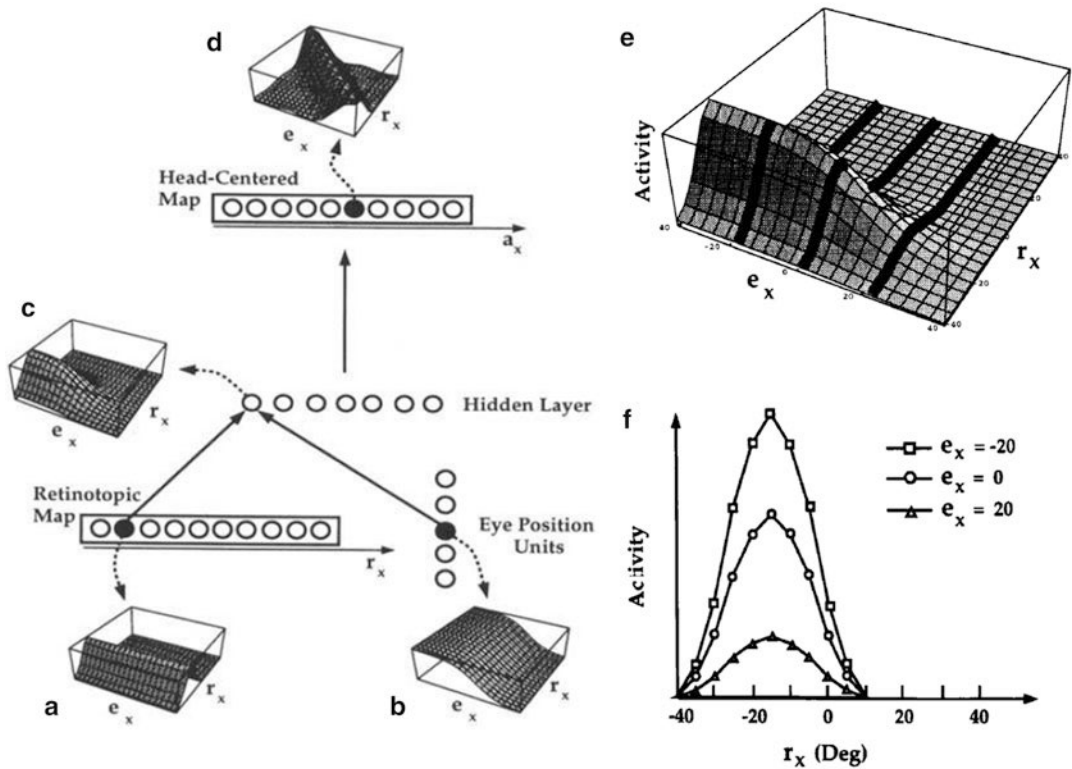
(Fig. 2b, c). There is no correlation between the phase at which a neuron oscillates during swimming and the phase at which it oscillates during crawling. This may be a consequence of the population forming a complete basis of all the motor patterns, because uncorrelated responses can arise from linearly independent receptive fields.

The swim and crawl motor patterns are represented as different population vectors in the high-dimensional response space of neural activity (Fig. 2d). The swim motor pattern is off in one direction, and the crawl motor pattern is off in another. To visualize the population code recorded through VSD imaging, the high-dimensional neural activity was reduced to three dimensions using principal components analysis. Each principal component corresponds to different combinations of activity patterns across all the neurons (Fig. 2e). The combinations of activity that are most correlated are chosen as the first three principal components, and the population vector can be visualized as a point in three-dimensional space. By plotting the population vector over time, the two behaviors can be distinguished in the neural activity (Fig. 2f). In fact, the neural activity predicts the future behavioral state before the swim or crawl behavior actually begins. If the leech is stimulated at a particular site, it “chooses” to swim or crawl with equal probability. This decision can be decoded from the population activity before the motor pattern can be seen. The information about the decision is encoded by the same population of neurons and can be decoded as a particular direction in the high-dimensional space. By finding the point in time where the population vectors during swim and crawl separate, the decision direction can be decoded as the linear discriminant that maximally separates the two classes of behavior. The decision direction is actually a different direction than the information about either motor pattern (Briggman et al. 2005). This shows that the leech nervous system encodes all of the pertinent information as different directions along a manifold in high-dimensional space, regardless of whether the information is sensory, motor, or intrinsic.

Transformations with Population Codes

Each area of the brain represents information using its own population code by combining information from the population codes of its inputs. Decoding a population code with an estimator is a strategy for an experimentalist to get an understanding of how information is represented by neuronal activity. In the brain, however, the stimulus dimensions are never directly extracted from a population code of neural activity. Instead, one population code is mapped directly onto another population code. This mapping is still effectively an estimation problem, because the direct mapping is equivalent to decoding the relevant information from the inputs and then encoding them into the local code.

Mapping one population code onto another requires nonlinear transformations. An excellent example of this problem is the transformation of a retinotopic map onto a head-centered map (Pouget and Sejnowski 1997; Fig. 3). As the eyes move around, neurons that receive information from the retina have receptive fields that move with the eyes. These neurons encode the visual scene in retinotopic coordinates. Another population of neurons encodes the position of the eyes. With the information from these two populations, the brain can encode the visual input in reference to the head position, which would be useful if an object was moving towards your head and you wanted to move your head out of the way. The goal is to transform the population code in the retinotopic coordinates into a population code in head-centered coordinates by combining the retinotopic information with the eye position information. For simplification, we will consider a model of only the horizontal spatial dimension of the stimulus, x . In this model, each neuron in the retinotopic population has a receptive field that is based on where the stimulus falls on the retina. For these receptive fields, the relevant stimulus dimension is the position on the retina, r_{x_i} , and each neuron has a preferred retinal position (Fig. 3a). A second population encodes the position of the eyes, e_x (Fig. 3b). The eye position neurons were given sigmoidal receptive fields, which were chosen because of their



Computation with Population Codes, Fig. 3 Transformation of population codes. (a) A population of neurons form a retinotopic map of the visual world, with individual neurons having receptive fields based on where the stimulus falls on the retina (r_x). (b) Another population of neurons encode the position of the eyes (e_x). (c) The hidden layer combines information from the retinotopic map and eye position units and forms a population code that is a complete basis set of the input

information. (d) The head-centered reference frame can be decoded from the hidden layer with a linear transformation. (e, f) The receptive field of a neuron in the hidden layer (same as panel C) has a receptive field that is gain modulated by the eye position units. This allows the hidden layer to form a complete basis set of the inputs. (e) Full 2-D receptive field. (f) Slices of the receptive field shown in black from (e) (From Pouget and Sejnowski 1997)

biological relevance; each of these neurons has a different inflection point (similar to a preferred stimulus) in their receptive fields, and they too form a population code.

To combine the information from the retina (r_x) and the eye position (e_x), an intermediate (“hidden”) layer was added (Fig. 3c) that forms a population code to represent the combined information about retinal activity and eye position. The key to the transformation was to make the population code of the hidden layer have a complete basis set of the information from both input populations. This projected the two dimensions of the stimulus (retinal position and eye position Fig. 3a, b) onto a 2-dimensional manifold

in high-dimensional space (Fig. 3c). This transformation allowed the relevant dimension of head-centered coordinates (Fig. 3d) to be a simple linear combination of the population code formed in the hidden layer, which could easily be read out by the next neuronal population. The advantage of using a population code with a complete basis set is that any reference frame is just a linear combination away.

In fact, information about eye position, head position, body position, joint position, etc. can all be combined into a single population code. With such a code, different motor systems can read out the information about visual space with different reference frames all from the same population

(Pouget and Sejnowski 1997) with just a simple linear transformation. Further, the information about each reference frame can be decoded by these motor systems in parallel, because the population code is representing all of the necessary information simultaneously.

The key to forming this basis set was to find how the activity in the two population codes should be combined. It is standard procedure that synaptic connections can compute linear transformations of the inputs $\left(r_j = \sum_i w_{ij} r_i\right)$, i.e., the synaptic strengths multiply the input firing rates to produce the downstream firing rates. But this modification alone was not sufficient to form a complete basis set of the data; gain control was also needed. Gain control is a scaling of the post-synaptic firing rate and is seen in many different biological neural circuits. Gain control is a non-linear operation, which meets the necessary conditions for forming a basis set (other nonlinearities are also possible, but gain control is the most biologically plausible (Pouget and Sejnowski 1997)). Figure 3e, f shows how neurons in the hidden layer are gain modulated by the eye position, where the receptive field shape is maintained, but the amplitude is altered. These neurons are inspired by the activity of neurons in parietal cortex.

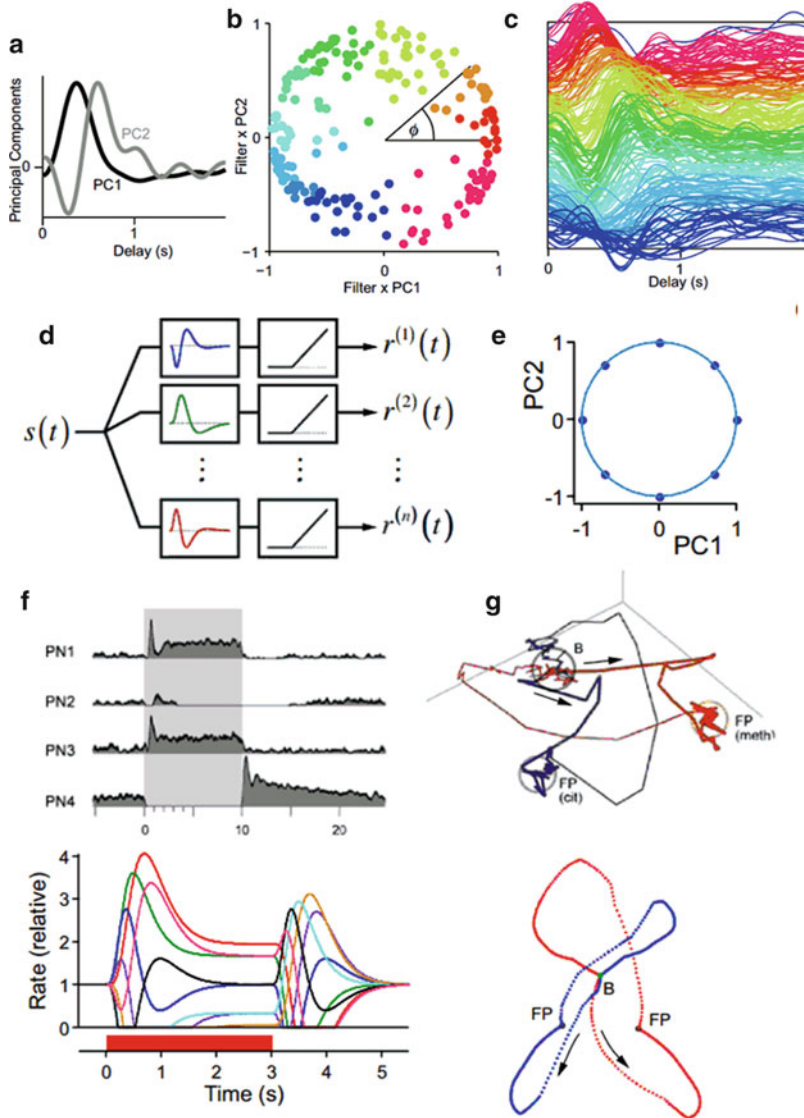
The mechanism of gain control in neurons is still controversial. Early studies postulated that shunting inhibition could be the mechanism of such multiplicative transformations (Blomfield 1974; Vu and Krasne 1992). Shunting inhibition alters the resistance of the neuron by opening inhibitory channels with a reversal potential that is the same as the resting potential. Changing the resistance of the neuron scales the voltage (and thus the firing rate) through Ohm's law ($V = IR$). More recent studies have suggested that this mechanism is not sufficient when spiking dynamics are considered and that shunting inhibition acts additively (Holt and Koch 1997). Many alternatives use neural circuitry to implement gain control (Baca et al. 2008; Salinas and Abbott 1996). However, shunting inhibition is receiving renewed interest as the mechanism for gain

control, as models show that adding noise (Doiron et al. 2000; Chance et al. 2002) or using multi-compartmental neurons (Capaday and van Vreeswijk 2006) can implement multiplicative operations in spiking neuron models.

Population Coding in Time

Many signals that the brain processes change in time. This temporal information can also be encoded by population codes. To encode temporal information, the receptive fields must also vary in time. An illustration of how temporal population coding is implemented by the nervous system comes from studies of olfactory processing in the insect antennal lobe. While randomly puffing pulses of odor, several neurons were recorded as they responded to the fluctuating odor stimulus. Neurons respond with different activity patterns during such an odor stimulus; some neurons respond immediately when the odor turns on and then go silent, some neurons stay on while the odor is present, and still other neurons respond only when the odor turns off. The firing rates of these neurons were approximated by a "linear-nonlinear model" and closely matched the recorded rates. This model found a "temporal receptive field" that describes a preferred temporal fluctuation in the odors where the neuron fires maximally. Just like receptive fields considered before, temporal fluctuations in the stimulus that are close to the preferred temporal fluctuation also cause the neuron to fire. The temporal receptive field integrates the fluctuation pattern of the odor stimulus over time (this is the linear part of the model), and this sum is then passed through a nonlinear function (which is a threshold-linear filter).

The temporal receptive fields found for all of the neurons can be well described by only two main components (Fig. 4a). These components are determined by normalizing the responses and calculating the principal components across time for all of the temporal responses of the neurons. Each neuron's receptive field is effectively explained as a linear combination (i.e., a weighted



Computation with Population Codes, Fig. 4 Population coding in time. (a) The first two principal components (PC1, PC2) of the temporal receptive fields of many neurons in the insect antennal lobe. (b) The coefficients of the first two components for each receptive field. The receptive fields are spread out uniformly around the unit circle as different combinations of the two main components. The colors are based on the angle of the coefficients around the circle (Φ). (c) All normalized receptive fields plotted and sorted vertically based on the angle from (b). (d, e) A simple model of the insect antennal lobe population code. (d) The signal ($s(t)$) is encoded by the responses of a population of neurons ($r^{(n)}(t)$) with different temporal receptive fields and a threshold-linear filter. (e)

The receptive fields were chosen based on eight different combinations of the principal components derived in (a). (f) Responses of four antennal lobe projection neurons (PN1-4) to a step of odorant (top, gray-shaded area), compared with the responses of the model (bottom) that shows similar patterns of activation. (g) The population vector trajectories in PCA space of the recorded neurons from (f) (top) when two different odors were presented. The population vector encodes the odorant presence and recent fluctuation history. The model neurons show a similar pattern (bottom). B indicates the baseline when no odor is present; FP indicates fixed points of the population vector when different odors are present (From Geffen et al. 2009)

sum) of just two components. Figure 4b shows the weights of the two components that best match the derived filters from the data, where the weights for each component are spread out at every angle, mainly along the edge of the unit circle. Figure 4c shows the shapes of all of the filters sorted based on the angle, which shows how the filters for all the neurons vary smoothly as combinations of the two components. These neurons represent temporal variations of the odor signal as a two-dimensional manifold in the high-dimensional neural space. The neurons' receptive fields are spread out almost uniformly, which creates an overcomplete basis set that is minimally redundant and maximally robust. These types of receptive fields allow the neurons to encode a representation of some temporal history of the signal in the population code.

This encoding of temporal history in the population response can be seen in a simple model of these neurons (Fig. 4d). In the model, a population of neurons are randomly given one of the eight receptive fields made out of different combinations of the two main components (Fig. 4e). When the population is given a step odor stimulus, the neurons respond differently based on their receptive fields. Just like the responses seen in the antennal lobe, the model neurons go through different fluctuations when the stimulus comes on and when it goes off (Fig. 4f). The stimulus information is encoded as a point in the high-dimensional activity space, which in this case moves in time (Fig. 4g). Before the onset of the odor step, the population is at some equilibrium (denoted as B). After the step, the population vector makes a rapid excursion from baseline and eventually reaches a fixed point (FP), which indicates that the firing rates have reached a steady state. When the odor is turned off, the population vector leaves the fixed point, makes another excursion, and settles back to the original baseline. If a different odor is given, then the neurons progress through a similar pattern, but along a completely different trajectory.

Each point along these trajectories encodes the recent history of the odor fluctuations. Since the

odor filters are responsive only to a window of a few seconds, the information in the population code contains only a few seconds of history. At the fixed point after the odor turns on, the population vector represents the presence of a particular odor and the fact that the odor has not changed in the last few seconds. During the excursion, the population vector continuously encodes the odor presence and the sudden change in odor that occurred when the odor step turned on. Different odor fluctuations would move the population vector along different trajectories in the high-dimensional space, and the recent history of the stimulus fluctuations can be decoded by the immediate position of the population vector.

Alterations in the neural responses over longer timescales would be required to encode a longer history of temporal information. Other types of temporal fluctuations seen in nervous systems may be serving this purpose. A full range of different time scales could be implemented by various neural mechanisms. For instance, adaptation or neuromodulators can encode information on the order of seconds, short-term plasticity could be involved in representing information on the order of tens of seconds, and long-term plasticity could encode even larger temporal scales.

Conclusion

Population coding is a powerful framework for neural computation. By spreading information across a large population of neurons, the brain solves many of the problems posed by biology. Noise is mitigated by coding information in the joint activities of many neurons, instead of individual neurons that can easily fail. Further robustness is achieved by coding with an overcomplete basis set, which contains redundant information that can compensate for information lost due to noise. An overcomplete basis set enables a population of neurons to represent all of the features of the stimulus, the intrinsic states, and/or motor activity as well as the recent history of these states simultaneously. This facilitates parallel

processing from downstream systems, since they can decode different reference frames from the same population. Population codes can be arbitrarily transformed into other representations and combined with information from other population codes in a biologically plausible manner. Population coding is a promising theoretical basis for universal computation in the nervous system and a necessary foundation for generating the wide variety of perceptual, cognitive, and behavioral states seen in the brain.

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Computation with Serotonergic Modulation

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Synonyms

5-hydroxytryptamine (5-HT)

Definition

Serotonin is an aminergic neuromodulator found throughout nervous systems of invertebrate and vertebrate animals. Serotonergic modulation of neural circuits plays an important role in a multitude of neural functions ranging from motor control, memory systems, decision-making, and sensory processing.

Detailed Description

Introduction

Serotonin (5-HT) is an ancient neuromodulator fundamentally tied to the evolution, development, and optimal function of the nervous system of animals. 5-HT and serotonergic receptors (5-HTRs) are found throughout the body and influence almost every aspect of animal physiology, ranging from autonomic functions such as cardiovascular/smooth muscle tone and thermoregulation to higher-level processes such as sensory processing, cognitive control, memory, and emotion. The role of 5-HT is complex and multifaceted, in part due to a variety of properties of the

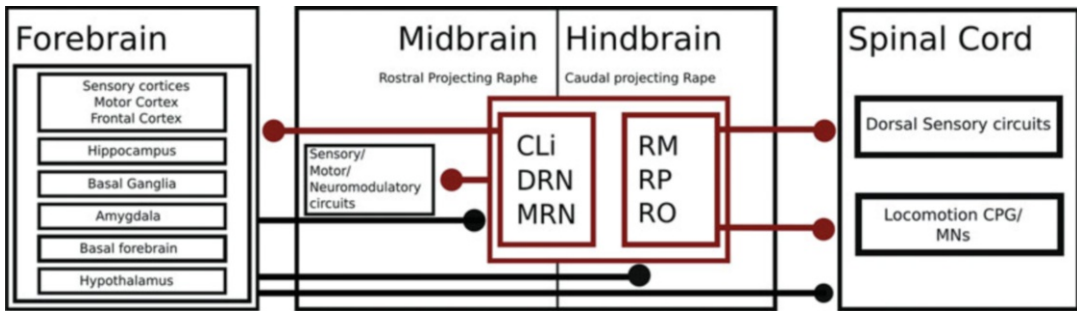
serotonergic system. In both invertebrate and vertebrate species, serotonergic fibers project throughout the nervous system releasing 5-HT at synapses and non-synaptically through a process known as volume transmission, a common feature of neuromodulatory transmission (Zoli et al. 1999; Dayan and Huys 2009). There are many different types of 5-HTRs (at least 17 different receptors within humans), many of which exert opposing and/or complementary effects on neuronal physiology and act on the order of milliseconds to minutes (Bockaert et al. 2006). Lastly, in recent years, there has been a growing understanding of the functional heterogeneity of serotonergic neurons in central nervous system, suggesting the existence of specific serotonergic subsystems, which modulate specific neural structures and behavior in a context- and brain state-dependent manner (Hale and Lowry 2011). Given the biochemical and behavioral complexity of the serotonergic system, it is difficult to discern an underlying principle that governs its role, as has been attempted for other neuromodulators (Doya 2002; Montague et al. 2004; Ashton-Jones and Cohen 2005; Bouret and Sara 2005; Hasselmo and Sarter 2011).

Early neurophysiology experiments performed in invertebrate preparations have shown that 5-HT modulates the intrinsic membrane properties of neurons, altering action potential waveforms and membrane conductances, through the activity of 5-HTR-dependent signaling pathways (Kleinhaus and Angstadt 1995; Katz 1998). Through these same pathways, 5-HT has been shown to play a role in the modulation of synapses, where it is capable to augment or attenuate the strength of synapses within a neural circuit. While 5-HT alters the properties of neurons and synapses within particular neural circuits, it also plays a role in the interactions between distinct neural structures, modulating the relative strengths of opposing circuits, leading to changes in brain state and production of adaptive behaviors (Brezina 2010; Dayan and Huys 2009). Most recently, computational neuroscientists, influenced by computational theories of learning and decision-making, have argued that given the widespread presence of 5-HT in the vertebrate

brain, 5-HT might act as a global signal, reporting behaviorally relevant state information (i.e., reward, hunger, arousal, punishment) to the rest of the brain, facilitating the formation of both aversive and appetitive cognitive states. Finally while many scientists have proposed many theories for a single function of 5-HT (Soubri  1986; Deakin and Graeff 1991; Jacobs and Fornal 1999; Tecott 2007; Cools et al. 2007; Dayan and Huys 2009), it is important to note that 5-HT does not act in a “neurochemical vacuum” and there are many important interactions between the serotonergic and other neuromodulatory systems both at the cellular and network level (Katz and Harris-Warrick 1990; Daw et al. 2002; Marder and Thirumalai 2002). I will here briefly review the main functions ascribed to 5-HT modulation in (1) rhythmic motor networks and (2) modulation of sensory systems. Note that this is by no means a complete or exhaustive review of 5-HT function in the central nervous system, but rather an overview of the best described roles of 5-HT modulation.

5-HT and Rhythmic Motor Networks

Serotonin plays a prominent role in the initiation and coordination of rhythmic motor behaviors in both invertebrate and vertebrate nervous systems (Jacobs and Fornal 1993; Katz 1998; Jordan and Slawinska 2011). Rhythmic motor behaviors (i.e., swimming, breathing, walking) are driven by the activity of biological neural networks known as central pattern generators (CPGs). These networks generate stable, repetitive motor outputs even in the absence of sensory feedback or extrinsic cues. Neuromodulators alter CPGs by altering both intrinsic membrane properties and synaptic interactions among neurons within the CPG. Modulatory inputs play an essential role in normal network function. In many experimental systems, the removal of neuromodulatory inputs through a variety of methods can significantly impair or completely abolish rhythmic motor activity (Harris-Warrick 2011). In vertebrates, 5-HT plays an important role in the generation of rhythmic locomotion



Computation with Serotonergic Modulation, Fig. 1 Schematic of the mammalian 5-HT system. Serotonergic neurons (shown in red) are restricted to the midbrain and hindbrain, where they are divided into two distinct populations. A rostral-projecting group projects to the forebrain and midbrain structures (caudal linear nucleus, *CLi*; dorsal raphe nucleus, *DRN*; median raphe nucleus, *MRN*). The majority of serotonergic axonal fibers travel to the forebrain through the forebrain bundle, a

major axon tract of the mammalian brain. Serotonergic neurons are found throughout the forebrain where they modulate sensory processing, motor cortex, and cognitive function. A caudal-projecting group projects to hindbrain and spinal cord structures where it modulates transmission of sensory signaling, locomotor central pattern generators (CPGs), and autonomic functions (raphe magnus, *RM*; raphe pallidus, *RP*; raphe obscurus, *RO*)

behaviors (Fig. 1). In the neonatal rodent spinal, bath application of 5-HT is reliable and commonly used method to induce in vitro fictive locomotion. Several 5-HT₂ or 5-HT₇ receptors prevent the initiation of fictive locomotion following brainstem stimulation. Conversely pharmacological activation of 5-HT₂ and 5-HT₇ receptors induces rhythmic outputs within the spinal cord that resembles electrically driven locomotion. Within spinal CPG neurons, 5-HT alters intrinsic membrane properties through the modulation of particular membrane currents. 5-HT lowers the voltage threshold of activation of the hyperpolarization-activated cation current (I_h) and persistent sodium current (I_{NaP}), inducing a depolarization from rest (Jordan and Slawinska 2011). Computational modeling of the spinal CPG suggests that the spinal locomotion is organized by the activity of two interconnected levels of a half-center oscillator, a rhythm-generating layer and a pattern-forming layer (McCrea and Rybak 2008). 5-HT is thought to modulate excitatory and inhibitory neurons within these two functional layers, providing tonic excitatory drive and important flexibility to perform coordinated rhythmic movements (Harris-Warrick 2011; Jordan and Slawinska 2011).

Serotonergic Modulation of Sensory Systems

Just as in the motor networks mentioned above, neuromodulators also continuously modify sensory circuits to appropriately guide behaviors (Birmingham and Tauck 2003; Hurley et al. 2004; Devore and Linster 2012). Neuromodulatory neurons effecting sensory processing may either be intrinsic to an affected sensory circuit or located in distal brain regions providing centrifugal inputs to many brain regions (sensory or non-sensory) concurrently. Rather than transmitting information about ongoing stimuli, neuromodulatory inputs instead are thought to dynamically filter neural representations in a manner related to environmental events and/or the brain's internal state (Hurley et al. 2004; Devore and Linster 2012). 5-HT is an important mediator of these functional changes.

In vertebrates, the majority of sensory circuits receive centrifugal serotonergic inputs from the median raphe (MRN) and dorsal raphe nuclei (DRN) located along the midline of the brainstem. Interestingly, DRN neurons receive inputs from many sensory processing regions, including the retina and vestibular nuclei (Kawano et al. 1996; Ye and Kim 2001). It should be noted that the majority of DRN inputs are not from sensory

structures but instead from other raphé nuclei, midbrain, and cortical structures (Hornung 2010). Tonic DRN activity is tied to the phase of the sleep-wake cycle, with activity highest during the waking state. Compared to alert waking states, DRN neurons show decreased tonic activity during quiet waking states, even less activity during slow-wave sleep, and are completely silent during rapid-eye movement (REM) sleep (Jacobs and Fornal 1999). DRN neurons also respond transiently to particular types of sensory stimuli (Heym et al. 1982; Ranade and Mainen 2009). Lastly, recent work has suggested that DRN neurons may be transmitting signals related to features of behavioral paradigms such as reward, aversion, and executive control (Miyazaki et al. 2012; Nakamura 2013).

5-HT has been shown to modulate sensory responses across a number of neural structures across species and sensory modalities (Andersen and Dafny 1982; Kloppenburg and Erber 1995; Mooney et al. 1996; Hurley and Pollak 1999; Xiang and Prince 2003; Kloppenburg and Mercer 2008; Dacks et al. 2009). In many regions of the brain, patterns of neuromodulatory input are highly heterogeneous and differentially target particular neuron types within specific sensory circuits (McLean and Shipley 1987; Klepper and Herbert 1991; Mooney et al. 1996; Kang et al. 2001; Paspalas and Papadopoulos 2001). Through complex innervation patterns and the multitude of 5-HTRs expressed within sensory circuits, 5-HT induces a variety of effects on sensory representations from gross attenuation (Petzold et al. 2009) or enhancement (Hurley and Pollak 2001; Deemyad et al. 2013) to alteration of receptive field structure (Hurley and Pollak 1999; Dacks et al. 2009) and changes in neural sensitivity to environmental cues (Kloppenburg and Mercer 2008; Yokogawa et al. 2012).

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Computational Analysis of Rodent Spinal CPG

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Definition

The production of patterned locomotor output by the rodent neuromuscular system is regulated by the central pattern generator(s) of the spinal cord. The rodent spinal CPG is capable of producing a wide range of gaits, and in particular the default “fundamental locomotor rhythm” of walking.

Fictive locomotor experiments and transgenic rodent lines have produced a wealth of information about the neuronal constituency and synaptic organization of the rodent spinal CPG, but many neuronal subpopulations have yet to be identified and the full synaptic architecture is far from being definitively mapped out. A few mathematical and computational models have been proposed which (1) integrate experimental results into a unified, interrogable conceptual framework and (2) enable the testing of various hypotheses of CPG organization in silico. The ultimate goal of computational modeling and analysis of the rodent spinal CPG is to link specific network structures and intrinsic neuronal properties to experimentally observed features of locomotor output.

Detailed Description

Background

In order for it to walk effectively, a rodent's forelimb and hind limb muscles must repeatedly flex and contract in the correct sequence and with the correct timing (onset and duration) of flexion and contraction. In rodents and other mammals, the basic patterning of such locomotor activity is generated and maintained by the neuronal networks in the spinal cord, which are most likely organized into one or more central pattern generators (CPGs).

Early experiments with decerebrate cats established that higher order input from the brain is not needed for locomotion: Cats whose brainstems have been transected at the level of the mesencephalic locomotor region (MLR) will walk with the proper gait and speed when placed on a moving treadmill. (If the brainstem is transected above the MLR, the cats will walk spontaneously; if the transection is made below the MLR, the electrical or pharmacological stimulation of the brainstem is required to produce walking.) Thus, the circuitry which patterns neuromuscular activity for walking, as well as other basic gates such as hopping and jumping, must be located below the brainstem in the spinal cord.

The closely related phenomenon of "fictive locomotion" has been studied in experiments on rodents. In these preparations, the whole spinal cord is removed from the animal and then stimulated either electrically or using neuromodulatory agents, e.g., serotonin, NMDA, dopamine, or acetylcholine. The stimulation evokes neural activity among the interneurons and motoneurons of the cord, and the observed firing patterns correspond closely to the activity patterns observed in intact, locomoting animals, as explained below. Motoneuron activity is measured at the dorsal roots, the proximal ends of bundles of motoneuron axons that innervate the muscles of the intact animal, and typically occurs in rhythmic bursts. The motoneurons (and interneurons) active during locomotion are located in the lower thoracic and lumbar spinal segments; those active during hind limb movement are found in lumbar segments L1–L6, with the strongest coordinated activity often measured from L2 and L5. Firing of L2 motoneurons corresponds to hind limb flexor muscle activity, while firing of L5 motoneurons corresponds to hind limb extensor muscle activity.

The phasing of motoneuron bursts – between the L2 and L5 segments and between the left and right sides of each segment – takes one of four forms: total (contralateral) intra- and (ipsilateral) intersegmental synchrony, (contralateral) intrasegmental alternation with (ipsilateral) intersegmental synchrony, (contralateral) intrasegmental synchrony with (ipsilateral) intersegmental alternation, and simultaneous (contralateral) intrasegmental alternation with (ipsilateral) intersegmental alternation. These modes correspond to tonic-clonic seizing, rhythmic left-right alternation, hopping, and fictive locomotion (in experimental preparation) or walking (in the intact animal). This last mode, simultaneous ipsilateral flexor-extensor antisynchrony and contralateral flexor-flexor/extensor-extensor antisynchrony, is also called the fundamental locomotor rhythm of the spinal locomotor CPG. Since the rhythmic neural firing patterns evoked in fictive locomotor experiments occur in the absence of sensory feedback, it may be inferred that the neural programs for basic locomotor gates, and the mechanisms for switching between them, are encoded in the circuitry of the spinal locomotor CPG.

Neurobiology of the Rodent Spinal CPG

The neurons of the rodent spinal CPG may be divided into four major functional classes: motoneurons (MNs), ipsilateral coordinating interneurons (ICNs), commissural interneurons (CINs), and rhythmogenic interneurons (RGNs).

Motoneurons directly innervate the flexor or extensor muscles on a single side of the animal, and their axons form the ventral roots of each spinal segment. Though they act primarily to excite muscular contraction, they may also limit their own firing by exciting Renshaw cells which in turn inhibit the motoneurons. The most significant flexor-related motoneuron clusters are found in L1 and L2, and the main extensor-related motoneuron clusters are located in L5 and L6.

The rhythmogenic interneurons appear to be a heterogeneous group of interneurons which act in different ways to support the rhythmic (oscillatory) drive that underlies the locomotor pattern. Neither the composition nor the location of the RGN population is known with much certainty. Each lumbar segment has some rhythmogenic capacity, as does each side of a given segment, but some segments exhibit stronger rhythmogenic activity than others in fictive locomotion experiments. Some RGNs, i.e., those in the Hb9 and V2a subclasses, may be able to burst endogenously and may thereby effect direct rhythmic excitation of MNs. But quite likely there are other, as yet unidentified, subpopulations of RGNs, perhaps organized in a half-center oscillator configuration, which contribute to the generation of the rhythmic motor pattern.

Experiments using transgenic rodent (mainly mouse) lines have provided the most detailed picture of the intra-segmental connectivity of the spinal cord. A small number of ICN subpopulations have been identified to date, including the Renshaw cells already mentioned, as well as Ia, V1, and V2b interneurons. These interneurons act via inhibition to enforce alternation between extensor-associated and flexor-associated neuron groups on a single side of the midline. Some subtypes, in particular V1, help regulate locomotor speed.

The axons of commissural interneurons cross the midline of the spinal cord and may synapse

onto neurons in the same spinal segment or several segments away. CINs mediate all cross-cord communication and play a central role in coordinating the rhythmic alternation of flexion and extension between the left and right sides. As with the ICNs, our most detailed knowledge of spinal cross-cord connectivity comes from transgenic rodent studies. The main CIN pathways are inhibitory: some run from L1, L2, and L3 to L4, L5, and L6, and vice versa, while others connect opposite sides of the same spinal segments. Presumably all of these connections work to enforce the contralateral flexor-flexor and extensor-extensor antisynchrony needed for walking. Some experimental work has also indicated that there are excitatory CIN connections within and between segments (e.g., mediated by V0 Dbx1 and V3 interneuron subpopulations), but less is known about them, and the evidence that they play a significant role in cross-cord coordination is indeterminate. It is known that contralateral MNs are the postsynaptic targets of some CINs, but for many CIN pathways the targets are not known precisely, and the overall organization of CIN connections is only incompletely understood.

Computational Models

Computational models of the rodent spinal CPG have two main goals: (1) to integrate the myriad experimentally determined neurobiological details into a unified, comprehensible framework and (2) to help researchers investigate hypotheses regarding CPG organization under simulated experimental conditions. There are also two competing imperatives which inform the construction of any computational neuroscience model: comprehensive inclusion of all known experimental data in the pursuit of biological realism and the simplification of messy details, imperfect data, and biological complexity in order to improve model comprehensibility and to make model analysis tractable. Extant models of the rodent spinal CPG resolve the tension between these competing aims at different balance points.

Coupled Cell Networks

Most simplified are coupled cell network models, originally developed by Golubitsky et al., which are defined solely in terms of generic oscillator cells and their connections (Buono 2001; Buono and Golubitsky 2001; Golubitsky et al. 1999; Stewart et al. 2003). In the locomotor CPG context, they aim to answer the question, given a particular arrangement of (generic) neurons and synaptic connections, which locomotor gaits are even theoretically possible? Few, if any, assumptions are made about the cells' intrinsic dynamics or the properties of the connections. The cell networks' dynamics are described purely in terms of their constituent cells' phases, and model analysis relies on the symmetry properties of the network. This approach is essentially mathematical, rather than computational, and eschews almost all biological details. It is quite powerful, however, in that it can establish definitively the complete set of possible phase relationships which can exist in a network of oscillators with a given symmetric coupling structure. It can also be used to determine whether the set of possible outputs of two different networks is functionally identical. Although real CPGs have many cell types with complicated cellular dynamics, as well as a variety of synaptic and electrical couplings, and may not be fully symmetric, often their structures do appear to conform (at least roughly) to the results of the mathematical theory. Especially relevant to the modeling of the rodent spinal locomotor CPG are results which establish the minimal network structures (minimal in the sense of least number of oscillatory cells and connections) which are capable of producing all known bipedal and quadrupedal gaits. In particular, eight coupled oscillatory cells arranged in two rings of four cells (a two-layer network) are needed to produce all primary and secondary gaits in quadrupeds.

Rybak Et al. Model

Over the past decade, Rybak and collaborators have developed a large-scale model of the mammalian CPG which incorporates a great deal of experimental data from both cat and rodent preparations, achieving remarkable biological realism

at the expense of some analytic tractability (Ivashko et al. 2003; Dietz et al. 2013; McCreary and Rybak 2007; Rybak et al. 2006a, b). The model is discussed in detail in the article (Two-Level Model of Mammalian Locomotor CPG); here we present only a brief summary. The Rybak et al. model comprises a few 100 Hodgkin-Huxley-style model neurons, divided into classes aligned with the rubric of MNs, ICNs, CINs, and RGNs described above. Where possible, the intrinsic properties of the model neurons are tuned to match those of identified subpopulations of the mammalian spinal CPG. Experimental data on synaptic connectivity also inform the model's synaptic architecture. However, some features of the model's neuronal and synaptic components are, of necessity, hypothetical.

The chief distinguishing feature of the Rybak et al. model is its two-layer architecture: there is a clear partitioning of interneuronal subnetworks into a rhythm-generating layer and a pattern formation layer. The rhythm-generating layer has a synaptic architecture that supports rhythmogenesis via a standard half-center oscillator dynamic, but it also includes model neurons capable of intrinsic bursting. The output of the rhythm-generating layer feeds forward (primarily excitation, but also with a few inhibitory pathways) to the pattern formation layer. The pattern formation layer includes reciprocal inhibitory circuits which enhance and modulate the flexor-extensor alternation communicated from the rhythm-generating layer. The output of the pattern formation layer feeds forward to the motoneurons, acting via direct excitation on motoneurons as well as via polysynaptic inhibition. There is no direct pathway from the rhythm-generating layer to the motoneurons. Both the rhythm-generating and pattern-generating layers may receive direct tonic excitation, simulating input from the MLR. In its original incarnation, the model was used to simulate the CPG network of a single hemicord of the decerebrate cat preparation, and it admitted afferent feedback at each neuronal layer. The model was later modified to model the rodent fictive locomotor preparations described above. The modified model includes two hemicord CPG

units connected at the rhythm-generating level via both inhibitory and excitatory CINs, and it omits the tonic drive from the MLR and afferent feedback.

When properly tuned, the Rybak et al. model successfully reproduces the basic fictive locomotor rhythms found in the cat and rodent spinal preparations, with good matches to the oscillation periods and duty cycles recorded in experiments. Perturbation experiments with the model show that it is capable of recovering from phase-resetting perturbations rapidly and with minimal interruption of the locomotor rhythm. Furthermore, the model reproduces the phenomenon of deletions, spontaneous omissions of a motoneuron pool's activity during a phase of the locomotor rhythm when it is normally active. In most cases, deletions do not change the overall phase of the locomotor rhythm once the deleted motoneuron pool rejoins the rhythm, and they are thus termed "non-resetting deletions." A small minority of deletions do lead to a shift in the phasing of the fundamental locomotor rhythm and are called "resetting deletions." The dual layer architecture of the Rybak et al. model can explain the origin of the two types of deletions: failures at the rhythm-generating layer produce resetting deletions, while failures at the pattern-generating layer produce non-resetting deletions.

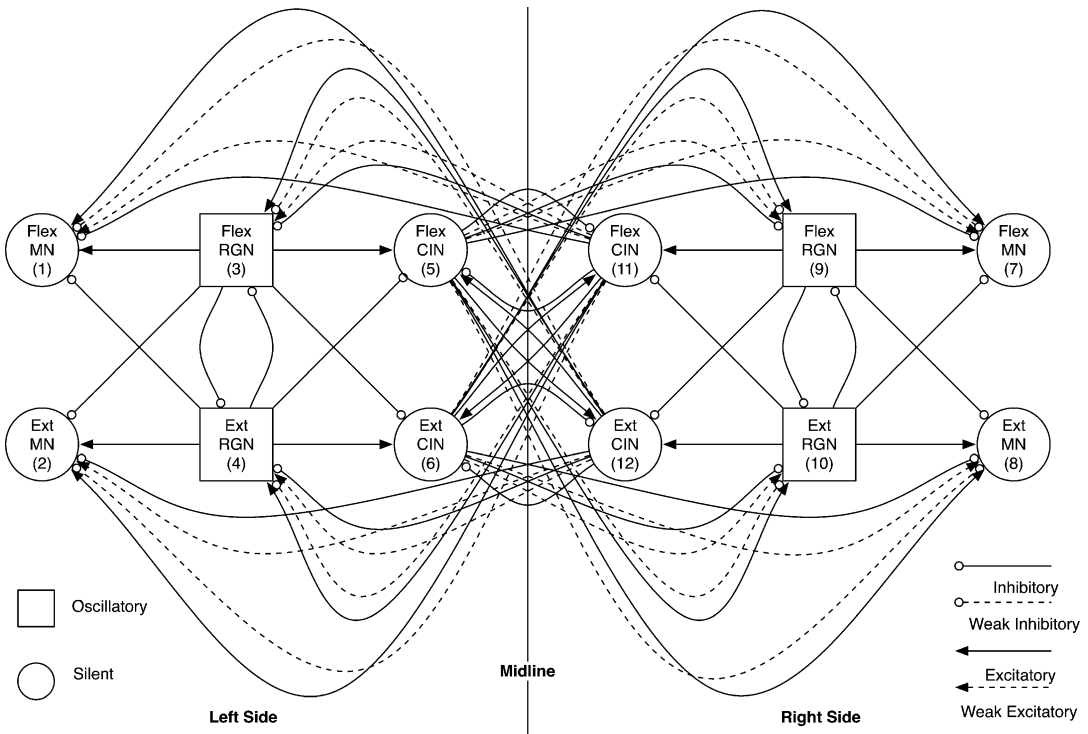
Sherwood et al. Model

Intermediate in biological realism and analytic tractability is the model of Sherwood et al. for the rodent spinal hind limb CPG (Sherwood et al. 2011). It uses Hodgkin-Huxley-style neurons and dynamic synapses (with parameters and properties parameters similar to those of corresponding cells in the Rybak et al. model), and it is informed by experimental data on the neurobiology of the rodent spinal CPG circa 2008. It was developed, however, with the mathematical results from coupled cell network theory in mind, and to this end it represents various populations of MNs, CINs, and RGNs by single representative model neurons (as per the methods of coupled cell network theory, the ICNs were functionally subsumed into the synaptic connections between the other three categories of

neuron). Furthermore, it is organized as a single layer with multiple symmetries; all synaptic connections known or hypothesized at the time were included. A key departure from conventional CPG architectures (i.e., half-center oscillators) is that each RGN bursts endogenous, so that rhythmogenesis is an intrinsic neuronal property, rather than a network property. In many respects, the Sherwood et al. model is a "minimal" biologically realistic model of the rodent spinal CPG (see Fig. 1).

While it was known from theoretical considerations that such an architecture is capable of producing each of the fictive locomotor gaits seen experimentally, Sherwood et al. sought to investigate how effectively the fundamental locomotor rhythm was achieved by the CPG when starting from an unorganized state, how the CPG responded to perturbations of the locomotor rhythm, and how the distribution of synaptic weights affected these two aspects of CPG output. Emphasis was placed on understanding the role of CINs in organizing simultaneous ipsilateral flexor-extensor antisynchrony and contralateral flexor-flexor/extensor-extensor antisynchrony (the walking rhythm). To this end, they explored the space of symmetric synaptic weightings in the CPG model extensively and also studied the phasing properties of functionally significant subnetworks (related to quotient networks in coupled oscillator theory) of the full CPG model.

Among the findings was that a multitude of synaptic weightings produced functionally equivalent CPG output, echoing results from studies of invertebrate CPGs (cf. Prinz et al. 2004). Strong inhibitory connections were required to produce the fundamental locomotor rhythm, while small amounts of interfering cross-cord excitation could destabilize it. In all configurations leading to the fundamental locomotor rhythm, the model CPG recovered very slowly from perturbations, much more slowly than could be biologically plausible. Analysis of CPG subnetworks revealed that the endogenous bursting properties of the coupled RGNs dominated the phasing and synchronization properties of the CPG network. This was a major cause of the slow network phase resetting in



Computational Analysis of Rodent Spinal CPG, Fig. 1 Diagram of the full CPG model of Sherwood et al. *Flex* flexor, *Ext* extensor (From Sherwood et al. 2011)

response to perturbation. It was surmised that rhythmogenesis by single endogenously bursting neurons was not functionally equivalent to – and was in some way more fragile than – rhythmogenesis by conventional half-center oscillator networks. Subsequent investigation of the phase response properties of endogenously bursting neurons revealed that such neurons have a much richer phase response structure than tonically firing neurons and thus more complicated synchronization behavior in some network architectures, such as that of the Sherwood et al. CPG model (Fig. 1).

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Computational Glioscience

► Neuron-Glial Interactions

Computational Maps

► Cortical Maps, Activity-Dependent Development

Computational Model-Based Development of Novel Stimulation Algorithms

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Definition

In the context of this entry, the model-based development of stimulation algorithms designates a process of creation and computational testing of new techniques for control and modulation of undesirable (pathological) neuronal dynamics. Abnormal brain activity has been observed in several neurological disorders

including Parkinson's disease, essential tremor, epilepsy, tinnitus, and others. Brain stimulation is used for the therapy of patients suffering, for example, from Parkinson's disease, epilepsy, or mental disorders. Brain stimulation is called deep brain stimulation (DBS) if structures deeply inside the brain are targeted, cortical stimulation (intracortical or epicortical) if the electrical contacts of the stimulator are positioned within the cortex or on its surface, or noninvasive transcranial stimulation if the neurons are stimulated by electrical currents induced across scalp by either external magnetic field (transcranial magnetic stimulation, TMS) or electrical current administered via scalp electrodes (transcranial direct-current stimulation, tDCS). Apart from direct brain stimulation, other stimulation forms and targets may also be used, such as spinal cord stimulation (e.g., for the treatment of pain), vagus nerve stimulation (for the treatment of epilepsy), or acoustic stimulation (for the treatment of tinnitus). Novel, model-based approaches, which use methods from synergetics, nonlinear dynamics, and statistical physics to specifically restore brain function and connectivity, demonstrate how insights into the dynamics of complex systems contribute to the development of novel therapies.

Detailed Description

In the nervous system synchronization processes play an important role, e.g., in the context of information processing (Singer 1989) and motor control (Andres and Gerloff 1999). However, pathological, excessive synchronization may strongly impair brain function and is a hallmark of several neurological disorders like Parkinson's disease (PD), essential tremor, epilepsy, and tinnitus (Alberts et al. 1969; Elble and Koller 1990; Nini et al. 1995; Llinas et al. 1999; Milton and Jung 2003; Smirnov et al. 2008; Roberts et al. 2010). For example, parkinsonian resting tremor appears to be caused by a pacemaker-like population of neurons which fires in a synchronized and periodic manner (Alberts et al. 1969; Smirnov et al. 2008). In contrast, under healthy conditions,

these neurons fire in an uncorrelated, i.e., desynchronized manner (Nini et al. 1995). Permanent deep brain stimulation (DBS) at high frequencies (>100 Hz) is the standard therapy for medically refractory PD and essential tremor (Benabid et al. 1991, 2002; Blond et al. 1992). High-frequency (HF) DBS has been developed empirically, mainly based on experimental results, clinical observations, and animal experiments (Bergman et al. 1990). DBS was approved by the Food and Drug Administration (FDA) as a treatment for essential tremor in 1997, for Parkinson's disease in 2002, and for dystonia in 2003. The treatment of severe neurological and psychiatric diseases with DBS is a rapidly growing and promising field. However, in spite of many beneficial effects, in some patients, DBS may not help or may cause side effects, or the therapeutic effects may disappear over time (Tasker 1998; Volkmann 2004; Rodriguez-Oroz et al. 2005; Deuschl et al. 2006).

With the objective of finding more effective stimulation techniques with less side effects, a model-based development of novel stimulation methods has been initiated (Tass 1999, 2002a, b, 2003b; Rosenblum and Pikovsky 2004a; Hauptmann et al. 2005b; Popovych et al. 2005, 2006a; Tass et al. 2006; Hauptmann et al. 2007c; Tukhlina et al. 2007; Popovych and Tass 2010). In these studies, relevant neuronal target populations were modeled mathematically, and stimulation techniques have been developed utilizing principles from nonlinear dynamics and statistical physics (Tass 1999). One goal of this approach is to control the pathological neural dynamics appropriately in order to achieve a mild and efficient relief of symptoms (Tass 1999). The second, more ambitious goal is to stimulate in a way that the formerly affected neuronal populations unlearn their pathological connectivity and, hence, their tendency to produce pathological synchronization (Tass and Majtanik 2006). Put otherwise, the very goal of this approach is to induce long-lasting therapeutic effects which outlast the cessation of stimulation. To this end, stimulation algorithms have been developed and optimized to exploit dynamic self-organization principles and plasticity rules (Tass and Majtanik 2006; Tass and Hauptmann 2006, 2007, 2009; Hauptmann and Tass

2007, 2009, 2010; Tass and Popovych 2012; Popovych and Tass 2012).

Several novel stimulation techniques have computationally been developed in the past. In this entry, four of these control methods will be presented in detail: coordinated reset (CR) stimulation (Tass 2003a, b), multisite linear delayed feedback (MLDF) stimulation (Hauptmann et al. 2005a, b, c, 2007a, b), nonlinear delayed feedback (NDF) stimulation (Popovych et al. 2005, 2006a, b, 2008; Popovych and Tass 2010), and proportional-integro-differential feedback (PIDF) stimulation (Pyragas et al. 2007). These techniques have the common objective of reducing the extent of synchronization of the target population by reestablishing a normal desynchronized physiological activity in a formerly highly synchronized population of neurons. For other stimulation methods, we refer to Rosenblum and Pikovsky (2004a), Tukhlina et al. (2007), Kiss et al. (2007), Luo et al. (2009), Danzl et al. (2009), and Nabi and Moehlis (2011).

CR stimulation, in its original realization, uses short electrical pulse trains to subsequently reset subpopulations of the neuronal network, which induces a desynchronized state (Tass 2003a, b). The stimulation is applied through a small number of stimulation sites which are equally spaced within the neuronal population. Desynchronization is achieved by utilizing self-organization principles, in particular, the slaving principle induced by the pathological neuronal interactions (i.e., interactions which have the potential to induce a pathological synchronization) (Tass 2003a, b). Several studies addressed the optimal parameter calibration of CR stimulation (Lysyansky et al. 2011a, 2013; Lücken et al. 2013) and also suggested CR stimulation for activation of inactive or hypoactive neuronal population by multi-frequency and phase-shifted activation of the stimulated neuronal networks (Lysyansky et al. 2011b).

MLDF (Hauptmann et al. 2005a, b, c, 2007a, b) and NDF (Popovych et al. 2005, 2006a, b, 2008; Popovych and Tass 2010) stimulation use delayed feedback for stabilizing a desynchronized state which is intended to be as close to the physiological mode of action as possible. Here, the local field potential (LFP) of the target population is

measured, amplified, delayed, and fed back into the ensemble. The PIDF (Pyragas et al. 2007) utilizes an instantaneous LFP and is designed for a particularly difficult situation characterized by a separate registration and stimulation setup.

It has been shown experimentally that synaptic plasticity enhances neuronal synchronization (Nowotny et al. 2003). From the kindling phenomenon in the context of epilepsy, it is well known that neural networks may learn pathological strong interactions (Speckmann and Elger 1991; Morimoto et al. 2004). The novel desynchronizing stimulation protocols are designed to invert this pathological process, so that the affected neuronal populations unlearn their pathological connectivity, and physiological neuronal activity is reestablished on a long-term basis (Tass and Majtanik 2006; Hauptmann and Tass 2007, 2009, 2010; Tass and Hauptmann 2007; Tass and Popovych 2012; Popovych and Tass 2012). In a nutshell, the novel stimulation techniques aim at a well-directed employment of fundamental principles of dynamic brain action to induce long-lasting therapeutic effects.

Standard High-Frequency Stimulation

For high-frequency (HF) deep brain stimulation (DBS), the golden standard for the therapy of medically refractory movement disorders, depth electrodes are chronically implanted in the thalamic ventralis intermedius nucleus or the subthalamic nucleus (STN) (Benabid et al. 1991, 2002), and permanent HF (>100 Hz) periodic electrical pulse-train stimulation is applied. HF DBS has been developed empirically, mainly based on intraoperative observations, and, as yet, the mechanism of HF DBS is not sufficiently understood (McIntyre et al. 2004b). HF DBS strongly alters the neuronal firing and mimics the effect of tissue lesioning, e.g., by suppressing neuronal firing, which, in turn, suppresses the symptoms (Benabid et al. 2002; Filali et al. 2004; McIntyre et al. 2004b; Volkmann 2004). However, HF DBS is a reversible technique and has a much lower rate of side effects than lesioning with thermocoagulation (Schuurman et al. 2000).

HF DBS seems to induce a regular bursting in STN neurons during stimulation and a transient suppression of the neuronal activity mediated by a synaptic-independent blockade of the intrinsic voltage-gated currents after its cessation (Beurrier et al. 2001, 2002). Another hypothesis is that HF DBS appears to block neuronal activity in relevant target areas during stimulation (Benabid et al. 2002). In single-compartment conductance-based biophysical models of isolated STN neurons, the HF stimulation may cause a suppression of neuronal activity on an elementary membrane level, where a neuron's resting state or low-amplitude subthreshold oscillations can get stabilized (Pyragas et al. 2013). The obtained theoretical results resemble the clinically observed relations between stimulation amplitude and stimulation frequency required to suppress parkinsonian tremor (Benabid et al. 1991). Several contributing mechanisms resulting in the observed effects of HF DBS might be membrane inhibition, jamming, excitation of excitatory and inhibitory afferents, excitation of efferents, and plasticity (Benabid et al. 2005). In particular, HF stimulation of afferent axons projecting to STN can account for a therapeutic effect of HF DBS within STN (Gradinaru et al. 2009).

To precisely evaluate the contribution of these different mechanisms, spatially extended multi-compartment neuron models were used to demonstrate the effects of extracellular stimulation on the different structures of the stimulated neuronal population (Grill and McIntyre 2001). Depending on the stimulation amplitude and the shape of the stimulation pulses, either the cells were activated directly or fibers mediating excitatory or strong inhibitory action were activated (Grill and McIntyre 2001). Modeling studies indicate that already at the level of single neurons, the activation of a larger number of structures can take place with different and possibly conflicting impacts on the single neuron dynamics (Grill and McIntyre 2001).

Experimental and modeling studies also reveal that the globus pallidum interior (GPi) – one structure of the basal ganglia – might strongly be involved in the mechanisms of DBS (Hashimoto et al. 2003; Rubin and Terman 2004; Miocinovic

et al. 2006). HF stimulation of the STN regularizes GPi firing (Hashimoto et al. 2003), and this restores the responsiveness of the thalamus (Rubin and Terman 2004). Accordingly, one may distinguish between local and nonlocal effects of HF stimulation. Locally, in the vicinity of the stimulation electrode, axons rather than cell bodies (somas) get activated (McIntyre et al. 2004a), while the latter can even be effectively inhibited by HF stimulation (Benabid et al. 2002; Welter et al. 2004; Meissner et al. 2005). The stimulation-induced axonal activity propagates antidromically and orthodromically (Hammond et al. 2008) and can change the firing in the output structures downstream to the neuronal target population. The pathological discharge patterns in the target population can be replaced by HF spiking or suppressed depending on whether the efferent fibers of the stimulated nucleus are excitatory or inhibitory, respectively (Hashimoto et al. 2003; Anderson et al. 2003; McIntyre et al. 2004b). In other words, local and nonlocal effects of HF DBS may differ considerably.

HF DBS, although being clinically beneficial and widely used, still has a number of limitations. On the one hand, HF DBS may cause adverse effects like dysarthria, dysesthesia, cerebellar ataxia, and memory decline (Volkman 2004; Rodriguez-Oroz et al. 2005; Freund 2005). On the other hand, HF DBS may be ineffective, or its therapeutic effect may wear off over time (Kumar et al. 2003; Rodriguez-Oroz et al. 2005). For instance, 11–15 % of PD patients have unsatisfactory outcomes although their depth electrodes are properly placed (Limousin et al. 1999). This initiated the development of new stimulation algorithms with an extensive use of mathematical models and methods from nonlinear dynamics and statistical physics (Tass 1999).

Coordinated Reset Stimulation

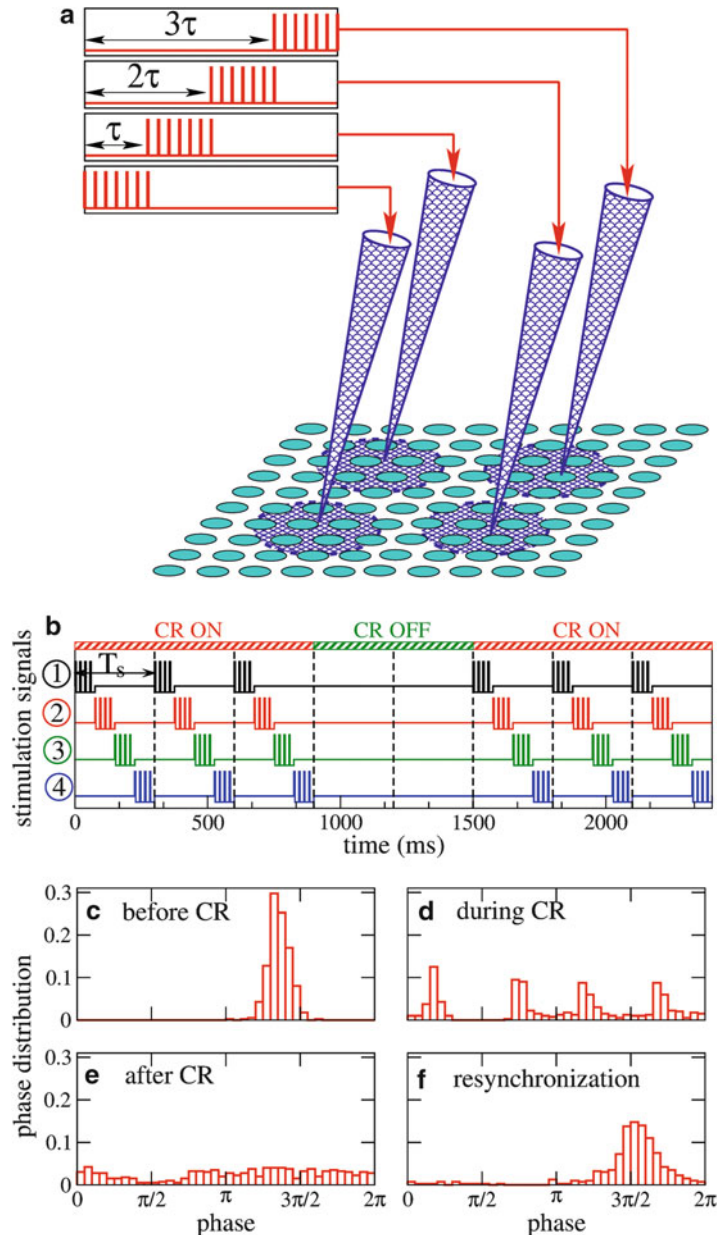
Coordinated reset (CR) stimulation was designed to specifically counteract pathological synchrony by desynchronization (Tass 2003a, b). The idea behind CR stimulation (Tass 2003a, b) is to robustly shift the stimulated population into a

dynamical state which is not the desired desynchronized state, but sufficiently close to it. Close in the sense that due to the pathologically strong coupling, the population automatically relaxes into the desired desynchronized state. The scheme of the stimulation setup is presented in Fig. 1a. Several stimulation sites are placed within the target network, and weak resetting stimulation signals are administered via these

stimulation sites. In this way the oscillatory population is divided into several subpopulations, where each of them is assigned to the corresponding stimulation site and receives the stimulation signal mostly from that stimulation site. CR stimulation means that a synchronized population of neurons is stimulated with a sequence of brief resetting stimuli (typically brief HF stimulus trains; see Fig. 1b) via the

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Fig. 1 Stimulation setup of CR stimulation method. (a) Brief and mild resetting stimuli are administered at different sites at subsequent times and effectively divide the stimulated population into several, say four, subpopulations. (b) Stimulation signals of CR stimulation in the form of short charge-balanced pulse trains. (c–f) Snapshots of the phase distribution density histograms before, during, and after (poststimulation desynchronizing transient) CR stimulation and during resynchronization as indicated in the plots. In (d), the phases ψ_j of the stimulation neurons form four phase clusters equidistantly (or close to that) distributed over the period of oscillations. In (e), a nearly uniform distribution of the oscillator phases is formed during the poststimulation transient. Plots (c–f) are adapted from Lysyansky et al. (2013)



different sites. The delay between the subsequent resetting stimuli can be chosen as $\tau = T/n$ with respect to that at the preceding site (Fig. 1a), where n is the number of stimulation sites, and T approximates the mean period of the collective dynamics of synchronized oscillators (Tass 2003a, b).

The subsequent reset of the different subpopulations induces a so-called cluster state, i.e., the whole population divided into n subpopulations which differ with respect to their mean phase. This effect is illustrated in Fig. 1d where a snapshot of the distribution of the phases ψ_j of the stimulated oscillators is shown. The phases of the population of oscillators stimulated via, e.g., four sites form four phase clusters equidistantly (or close to that) distributed over the oscillation period. To estimate the extent and type of synchronization of the whole population of N oscillators, the cluster variables

$$Z_m(t) = R_m(t)e^{i\psi_m(t)} = \frac{1}{N} \sum_{j=1}^N e^{im\psi_j(t)}, \quad (1)$$

can be used. $R_m(t)$ and $\Psi_m(t)$ are the corresponding real amplitude and real mean phase, where $0 \leq R_m(t) \leq 1$ for all time t (Daido 1992; Tass 1999). Cluster variables are convenient for characterizing synchronized states of different types: Perfect in-phase synchronization corresponds to $R_1 = 1$, whereas an incoherent state, with uniformly distributed phases, is associated with $R_m = 0$, $m = 1, 2, 3, \dots$. Small values of R_1 combined with large values of R_m are indicative of an m -cluster state consisting of m distinct and equally spaced clusters, where all oscillators within the same cluster have similar phases. In Fig. 1c–d, for instance, the variables R_1 and R_4 approximately attain the following values, respectively: (c) 0.98 and 0.72, synchronization; (d) 0.07 and 0.55, stimulation-induced four-cluster state; (e) 0.17 and 0.08, poststimulation desynchronization transient; and (f) 0.75 and 0.2, resynchronization.

From the cluster state, the neurons typically relax to a uniformly desynchronized state (Fig. 1e) before they revert back to the in-phase synchronized state (Fig. 1f), if left unperturbed. To understand how a stimulus-induced clustering leads to an effective desynchronization, the

dynamics of the leading modes $Z_1, Z_2, \dots$, can be considered. When the coupling among oscillators becomes sufficiently large, e.g., it exceeds a certain critical value, Z_1 from Eq. 1 becomes an order parameter (Kuramoto 1984), which according to the slaving principle (Haken 1983) governs the dynamics of the other, stable modes Z_m ($m = 2, 3, \dots$) on the center manifold (Pliss 1964): The order parameter Z_1 acts on a slow timescale, whereas the stable modes Z_m act on a fast timescale and relax to values given by the order parameter Z_1 (Wunderlin and Haken 1975; Haken 1983). In a system with large number of oscillators, this relationship reads (Tass 1999):

$$R_m \propto R_1^\nu \text{ with } \nu \geq 2, \quad m = 2, 3, 4, \dots \quad (2)$$

Small values of R_1 in the stimulation-induced cluster state lead to small values of other order parameters and to onset of desynchronization during the poststimulation transient. Stimulation-free neurons will eventually resynchronize if left unperturbed for sufficiently long time (Fig. 1f). Hence, to maintain a desynchronized neuronal firing, CR stimuli have to be administered repetitively.

CR stimulation exploits transient responses which are due to the oscillators' (pathologically strong) interactions. The general stimulation protocol of the intermittent CR stimulation (Tass et al. 2009; Lysyansky et al. 2011a) is illustrated in Fig. 2. Here, the collective dynamics is visualized by considering the collective firing of the neurons. A single firing/bursting model neuron fires/bursts whenever its phase is close to zero (modulo 2π) (Kuramoto 1984; Ermentrout and Kopell 1991; Grannan et al. 1993; Hansel et al. 1993; Tass 1999). The collective firing can be illustrated with the *relative number of neurons producing an action potential or burst at time t* given by

$$n_{\text{fire}}(t) = \frac{\text{number of neurons with } \cos \psi_j > 0.99}{N}. \quad (3)$$

$0 \leq n_{\text{fire}}(t) \leq 1$ for all t . $n_{\text{fire}}(t) = 0$ means that no neuron fires/bursts, while all neurons fire/burst at time t if $n_{\text{fire}}(t) = 1$. Varying the threshold

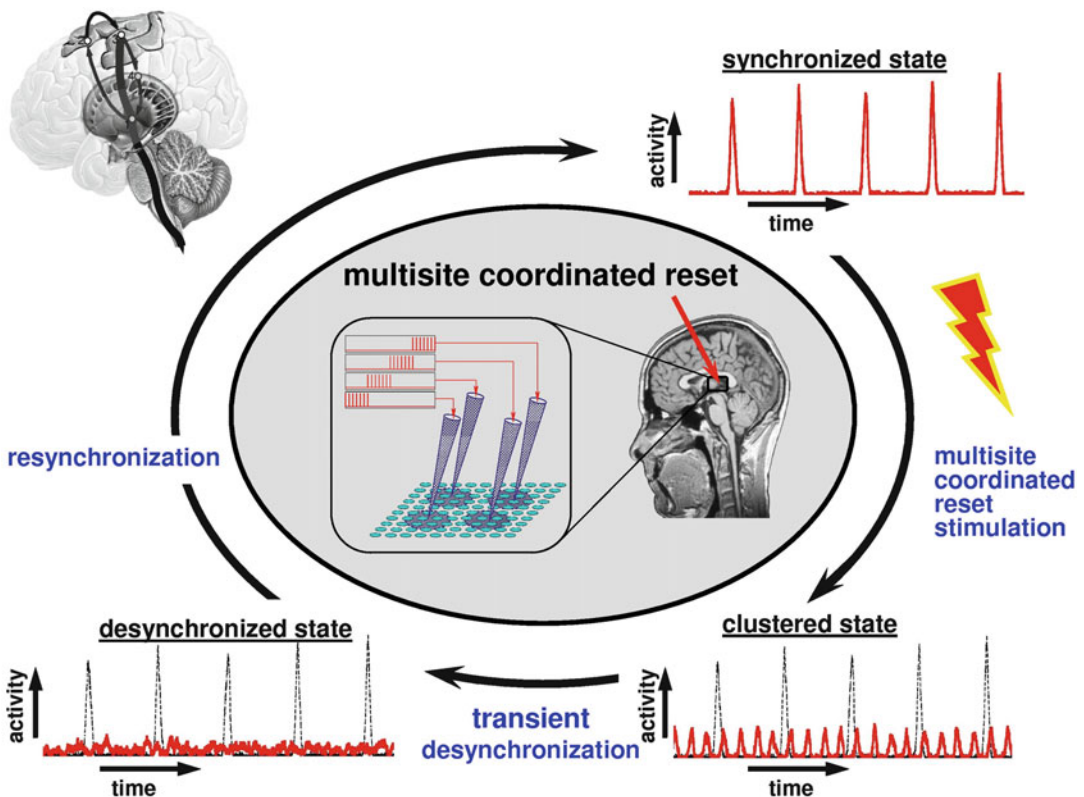
parameter 0.99 in a reasonable range does not change the results.

As shown in Fig. 2, stimulation starts when the neurons are synchronized, and the collective firing demonstrates high-amplitude rhythmic oscillations (upper-right insert in Figs. 2 and 1c). After a few periods of stimulation (Fig. 1b), the oscillatory population is shifted into a cluster state (bottom-right insert in Figs. 2 and 1d). Then the stimulation is switched off (Fig. 1b) and the ensemble returns to a synchronized state on this way passing through a uniformly desynchronized state (bottom-left insert in Figs. 2 and 1e, f). And the procedure is repeated (Fig. 1b) such that the ensemble is kept in a transient desynchronized state. The relaxation to a clustered state is due to the system being attracted by the center manifold as characterized by Eq. 2. By imposing a cluster state, the stimulation does only half of the

desynchronizing work. The rest, namely, approaching a uniformly desynchronized state, is done by the system itself. In this way, the coupling, which causes the synchronization, is used for improving the desynchronizing effect. In summary, by shifting the system into an unstable cluster state, the system reacts by automatically running through a transient desynchronized state.

The effectively desynchronizing intermittent CR stimulation (Fig. 1b) can be used to prevent from resynchronization. For this, the repetitive stimulus administration can be organized either regardless of the state of the stimulated ensemble (open-loop control) or in a demand-controlled way (closed-loop control), where the following three different control strategies can be utilized:

- (i) *Periodic administration of CR stimuli*: The most simple, open-loop type of stimulation is



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 2 A general scheme of the intermittent CR stimulation. Desynchronized firing of

neurons is maintained by repetitive administration of CR stimuli intermingled with epochs of no stimulation

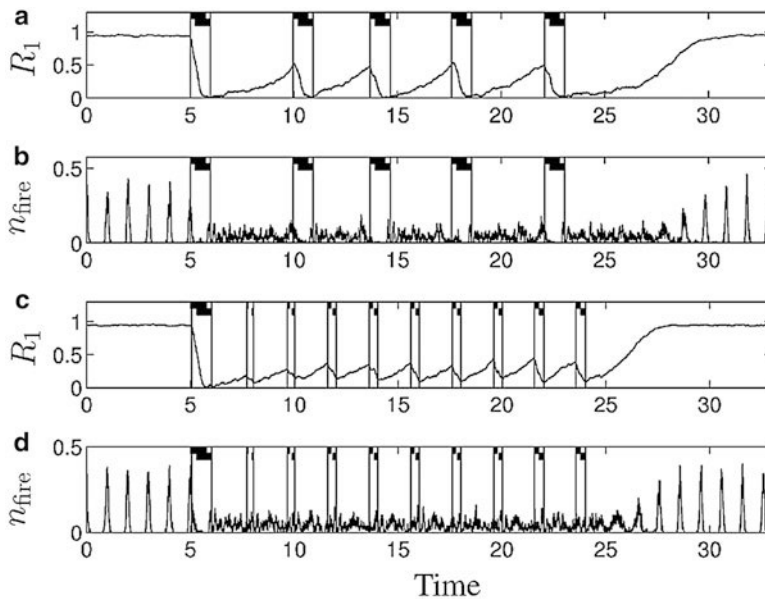
a periodic administration of CR stimuli. Here, the time intervals of fixed length of CR stimulation (ON cycles) are typically recurrently followed by time intervals of fixed length where the stimulation is switched off (OFF cycles) (Fig. 1b).

- (ii) *Demand-controlled timing of the administration of identical stimuli*: Whenever the population tends to resynchronize, the same stimulus is administered (Fig. 3). The stronger the synchronization among the neurons is, the more often a stimulus has to be administered to maintain an uncorrelated firing. In an experimental application, ideally, one has to observe the synchronized oscillation during a sufficiently long period of time in order to perform a frequency analysis which yields the period T of the population in the absence of stimulation and, thus, the critical stimulation parameter τ (the time delay between successive HF pulse trains administered via different stimulation sites; see Fig. 1). Alternatively, one can also choose T according to

the known frequency range of the pathological oscillation.

- (iii) *Periodically administered HF pulse trains of demand-controlled length*: The stimuli are periodically administered with offset times $t_k = kvT$, where $k = 0, 1, 2, 3, \dots$ is the index labeling the different stimuli, $T = \bar{T} + \varepsilon$ is a time interval in the range of the period $\bar{T}$ of the population without stimulation, and v is a small integer such as 2 or 3. This means that a 1: v entrainment of the four subpopulations is performed, where the spontaneous frequency of the neurons is approximately v times larger compared to the frequency of stimulus administration. The smaller the $|\varepsilon|$, the smaller is the stimulation strength necessary to achieve an entrainment.

The closed-loop variants (ii) and (iii) require that the ensembles activity can be measured appropriately. Here, either the start times of identical CR stimuli or the length of periodically administered stimuli is calculated from the values



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 3 Desynchronizing effect of the demand-controlled intermittent CR stimulation. Time course of R_I from Eq. 1 (a, c) and of n_{fire} from Eq. 3 (b, d) during different types of stimulation. Demand-controlled timing of stimulus administration (a,

b): As soon as the amplitude R_I of the recovering order parameter reaches the value of 0.5, the stimulus is administered again. Periodic stimulation with demand-controlled length of HF pulse train (c, d): The stimulus is administered periodically, where the length of the HF pulse trains is adapted to R_I (First published in Tass (2003b))

of R_1 . For example, in the case (ii), the stimulation is started if R_1 becomes larger than a certain threshold (Fig. 3, upper two plots), whereas in the case (iii), the stimulation period is longer for larger values of R_1 measured at the onset of the stimulation (Fig. 3, bottom two plots); see references (Tass 2003a, b) for details.

Applying the standard, permanent HF stimulation (Benabid et al. 1991; Blond et al. 1992) (in a first approximation) corresponds to stimulating each neuron with the same HF pulse train. During a permanent HF stimulation, a high-frequency entrainment of the order parameter Z_1 captures Z_1 in a small portion of the complex plane (Tass 2001), so that the individual neurons' firing is stopped, but no desynchronization occurs (see also Pyragas et al. (2013)). In contrast, during stimulation, R_1 can be even larger compared to its pre-stimulus level, and after stimulation, the synchronous firing continues immediately. To suppress the firing with such a simple pulse train persistently, it has to be administered permanently. The number of single pulses used to suppress the firing in the case of the standard permanent HF pulse-train stimulation is about five and eight times larger than that used for blocking the resynchronization in Fig. 3a, b and 3c, d, respectively. This illustrates the effectiveness of the demand-controlled CR stimulation. The latter can effectively desynchronize stimulated oscillators with a significantly smaller amount of stimulation current compared to the standard permanent HF pulse-train stimulation.

The efficacy of CR stimulation can further be improved by an optimal choice of the stimulation parameters. Several computational studies on neuronal models of different complexity have addressed this problem and showed that intermittent $m:n$ ON-OFF CR stimulation, where m cycles with stimulation ON are recurrently followed by n cycles with stimulation OFF, is most effective for a weak stimulation intensity and short ON intervals (Lysyansky et al. 2011a). The stimulation-induced cluster state leads to the longest desynchronized poststimulation transient which can further be prolonged for nonuniform timing of the stimuli onsets (Lücken et al. 2013). The number of stimulation sites is another important

stimulation parameter, and its optimal choice essentially depends on the properties of the neuronal tissue (Lysyansky et al. 2013). For a weak (strong) spatial decay rate of the stimulation current with distance to the stimulation site, CR stimulation can optimally be delivered via small (large) number of stimulation sites.

Spike Timing-Dependent Plasticity

It is well known that synapses in the brain are involved in the adaptation process, where their efficacy is governed by spike timing-dependent plasticity (STDP) (Gerstner et al. 1996; Markram et al. 1997; Feldman 2000; Wittenberg and Wang 2006; Caporale and Dan 2008). Plasticity is a fundamental property of the nervous system: In order to learn and to adapt to sensory inputs, neurons continuously regulate the strength of their synaptic connections in relation to the mutual timing properties of their firing or bursting (Hebb 1949; Gerstner et al. 1996; Markram et al. 1997; Debanne et al. 1998; Kilgard and Merzenich 1998; Abbott and Nelson 2000; Feldman 2000; Song et al. 2000; van Hemmen 2001; Zhou et al. 2003). However, plasticity may not only lead to desired learning and optimization processes. Rather neuronal populations can learn pathologically strong interactions which may lead, e.g., to the emergence of epilepsy (Morimoto et al. 2004; Speckmann and Elger 1991). This is well known from the so-called kindling phenomenon (Goddard 1967), where preparatory stimulation induces the spontaneous production of epileptic seizures without gross morphological changes (Morimoto et al. 2004).

An example of the STDP function is illustrated in Fig. 4a (see also references Bi and Poo (1998) and Bi (2002)), and the synaptic weights are updated in a point-like process by the increment $W(\Delta t)$ as soon as the pre- and postsynaptic neurons fire. For such a plasticity rule, the synaptic weight is potentiated or depressed depending on whether the postsynaptic firing follows or advances the presynaptic firing, respectively. STDP can lead to multistability where states with different connectivity and different collective dynamics may

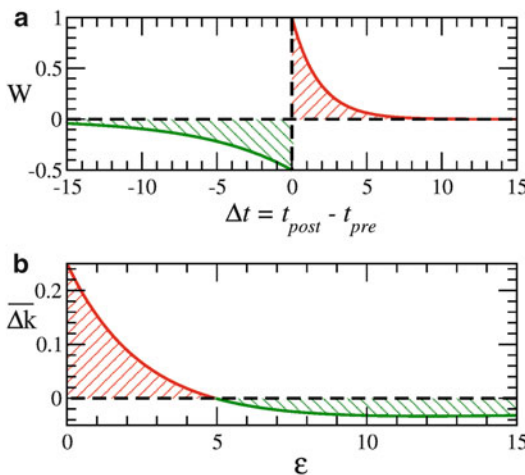
coexist. If, for instance, the initial coupling is weak, the neurons get desynchronized, and the spiking time differences Δt get broadly (e.g., uniformly) distributed. Then STDP (Fig. 4a) leads to further suppression of the coupling (see Fig. 4b for large ε where $\overline{\Delta k} < 0$), the neurons remain desynchronized, and a weakly coupled desynchronized state stabilizes. On the other hand, if the initial coupling is strong, the neurons fire synchronously, i.e., the spiking time differences are narrowly distributed around zero (see Fig. 4b for small ε where $\overline{\Delta k} > 0$), and synaptic weights get further potentiated. Such initial conditions result in a strongly coupled synchronized state. Along with the two regimes mentioned above, some other states with intermediate coupling strength and synchronization may coexist as well.

The impact of plasticity on synaptic weights and collective neural dynamics has been accounted for by several theoretical studies on desynchronizing stimulation methods (Tass and Majtanik 2006; Hauptmann and Tass 2007; Tass and Hauptmann 2007). They have initiated an approach which is targeted on unlearning pathologically strong synaptic interactions by desynchronizing brain

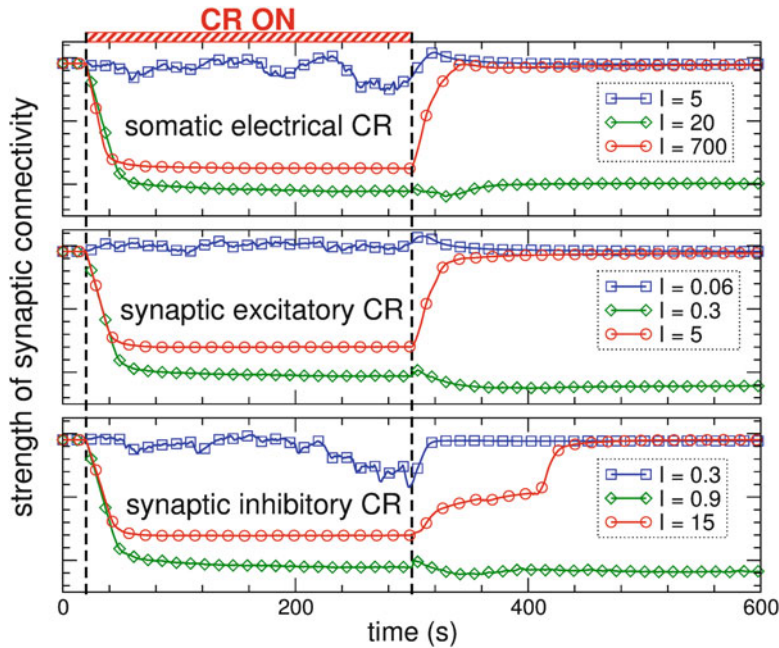
stimulation and which has further been developed in subsequent papers (Hauptmann and Tass 2009, 2010; Tass and Popovych 2012; Popovych and Tass 2012). This approach exploits plasticity in two different ways: On the one hand, due to plasticity, desynchronizing stimulation may decrease the strength of the neurons' synapses by decreasing the rate of coincidences. On the other hand, neuronal networks with synaptic plasticity may exhibit bi- or multistability (Seliger et al. 2002; Tass and Majtanik 2006; Hauptmann and Tass 2007; Tass and Hauptmann 2007; Maistrenko et al. 2007). Accordingly, by decreasing the mean synaptic weight, desynchronizing stimulation may shift a neuronal population from a stable synchronized (pathological) state to a stable desynchronized (healthy) state, where the neuronal population remains thereafter, if left unperturbed.

In PD neuronal populations of the basal ganglia are strongly synchronized (Beurrier et al. 2002; Schnitzler et al. 2006; Timmermann et al. 2007). By the same token, abnormal neural synchrony is a hallmark of tinnitus (Llinas et al. 1999; Weisz et al. 2005; Roberts et al. 2010; Adamchic et al. 2013). In the synchronized regime, synaptic plasticity results in a further amplification of the synchronized activity by a strengthening of the synaptic connections (Nowotny et al. 2003). Properly designed stimulation may be used to break this vicious circle and to induce an anti-kindling (Tass and Majtanik 2006; Hauptmann and Tass 2007, 2009, 2010; Tass and Hauptmann 2007; Tass and Popovych 2012; Popovych and Tass 2012), which finally may reestablish the normal level of connectivity, associated with a mostly uncorrelated neuronal activity. In this way a sustained long-lasting desynchronization can be achieved, and therapeutic aftereffects can be established after the cessation of desynchronizing stimulation as predicted computationally (Tass et al. 2012a, b).

The anti-kindling process in neural networks with STDP is illustrated in Fig. 5 for CR stimulation for two stimulation modalities: somatic electrical and synaptically mediated (e.g., sensory) stimulation, which were suggested for desynchronizing electrical DBS (Tass 2003a, b; Tass and Majtanik 2006) and for the treatment of



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 4 (a) Normalized plasticity function versus the difference of the spike/burst timing of post- and presynaptic neuron $\Delta t = t_{\text{post}} - t_{\text{pre}}$. (b) The average update rate of synaptic weights $\overline{\Delta k} \varepsilon = W(\xi)\rho(\xi)d(\xi)$ for the uniform distribution density $\rho = 1/2 \varepsilon$ of $\Delta t \in [-\varepsilon, \varepsilon]$



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 5 Stimulation-induced rewiring and desynchronization of the neural ensemble with STDP by desynchronizing coordinated (CR) stimulation. The time courses of the mean synaptic weights $\bar{c}(t)$ are plotted for different stimulation intensities I as indicated in the legends. The stimulation time interval is

indicated by the red bar and by the vertical dashed lines for direct electrical CR stimulation, indirect excitatory CR stimulation, and indirect inhibitory CR stimulation (as indicated in the plots) delivered to a neuronal population in a strongly coupled and synchronized regime; see (Popovych and Tass 2012) for details (Adapted from Popovych and Tass (2012))

tinnitus by noninvasive acoustic stimulation (Tass and Popovych 2012), respectively. For both stimulation modalities, there exist a range of stimulation intensities, where CR stimulation can effectively change the collective dynamics of the stimulated neural network to a weakly coupled and desynchronized regime which stably persists after the stimulation is completely switched off (Fig. 5, green curves; Popovych and Tass 2012). Desynchronizing CR stimulation results in an anti-kindling of the pathological connectivity, and, finally, the physiological weakly coupled and desynchronized state is reestablished. This may lead to long-lasting therapeutic effects of CR stimulation. On the other hand, too weak or too strong CR stimulation does not cause long-lasting effects, and the synaptic connectivity returns to the pre-stimulation level after cessation of stimulation (Fig. 5, blue and red curves, respectively). In the latter case, however, CR stimulation

may induce an acute (during stimulation) normalization of abnormal connectivity.

The theoretical findings on the properties of CR stimulation have been verified experimentally. The resetting impact and the induced transient desynchronization of an electrical short-pulse stimulation, on which the CR technique is based, have been reported *in vivo* for coupled neuronal bursters in paddlefish (Neiman et al. 2007). Taking into account STDP, the long-lasting desynchronizing effects of CR stimulation have been investigated in detail in theoretical studies (Tass and Majtanik 2006; Tass and Hauptmann 2007; Hauptmann and Tass 2007), and the results have been confirmed experimentally *in vitro* in rat hippocampal slice (Tass et al. 2009). The beneficial therapeutic long-lasting aftereffects of the weak electrical CR stimulation have been observed in the MPTP-treated macaque monkeys, in contrast to a stronger CR stimulation and to

standard HF DBS (Tass et al. 2012b). It was shown that unilateral CR stimulation delivered to the STN of parkinsonian MPTP monkeys for only 2 h per day during 5 days leads to significant and sustained therapeutic aftereffects for at least 30 days, while standard 130 Hz DBS and strong CR stimulation have no aftereffects (Tass et al. 2012b).

Computational studies revealed that CR stimulation is effective for a number of stimulation setups and demonstrates a great applicability. CR stimulation has been suggested for counteraction of a cerebral hypoactivity found in a number of diseases (Candy et al. 1983; Wolkin et al. 1992; Salehi et al. 1994; Kishimoto et al. 1998; Bearden et al. 2001), without promoting pathological synchronization, by a multifrequency and phase-shifted activation of the stimulated neuronal networks (Lysyansky et al. 2011b). Other computational studies showed that CR stimulation can be effective in inducing desynchronization for direct somatic stimulation and as well as for excitatory or inhibitory synaptically mediated stimulation (Popovych and Tass 2012); see Fig. 5. The latter stimulation setup might correspond to stimulation of afferent or efferent fibers or sensory stimulation where the stimulation signals arrive at the neural target population as postsynaptic potentials. Sensory CR stimulation has been suggested for desynchronizing the neural synchrony underlying tinnitus (Tass and Popovych 2012) and successfully verified in a clinical proof of concept study in tinnitus patients treated with noninvasive acoustic CR stimulation (Tass et al. 2012a; Silchenko et al. 2013; Adamchic et al. 2013). It turned out that acoustic CR stimulation can significantly counteract both tinnitus symptoms and the underlying pathological neuronal synchronization by normalizing the effective connectivity and restoring the functional patterns of activity (Tass et al. 2012a; Silchenko et al. 2013; Adamchic et al. 2013).

Multisite Linear Delayed Feedback

Similarly as in the case of CR stimulation, multisite linear delayed feedback (MLDF) (Hauptmann

et al. 2005a, b, c, 2007a, b) is administered via several stimulation sites, e.g., via four sites as illustrated in Fig. 1a. The individual stimulation signals $S_m(t)$ of each of the stimulation sites are however derived from the delayed mean field $Z(t)$ of the stimulated ensemble using different time delays for different stimulation signals. The mean field characterizes the collective macroscopic dynamics of the oscillators and can be viewed as the ensemble average of the signals $z_j(t)$, $j = 1, \dots, N$, of individual oscillators, $z(t) = N^{-1} \sum_{j=1}^N z_j(t)$.

For n stimulation sites, the stimulation signals are calculated as $S_m(t) = KZ(t - \tau_m)$, $m = 1, \dots, n$, where K is the amplification parameter, and the values of delay τ_m , for example, for $n = 4$ are calculated from the following relation

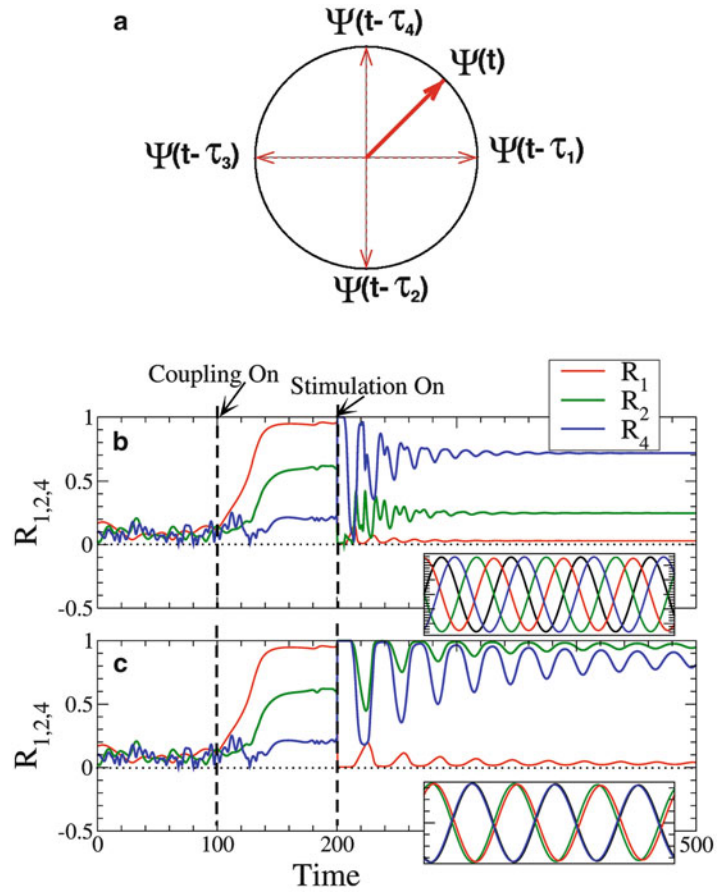
$$\tau_m = \frac{11 - 2(m - 1)}{8} \tau, \quad m = 1, 2, 3, 4 \quad (4)$$

The delays τ_m are symmetrically distributed with respect to the main delay τ , where the smallest time delay between neighboring stimulation sites is chosen as $\tau/4$. In the case $\tau = T$ (mean period of the ensemble), the delays τ_m are uniformly distributed over the mean period T . In another realization, instead of four delays τ_m , $m = 1, \dots, 4$, one can use only two of them, e.g., τ_1 and τ_2 . One can put $\tau_3 = \tau_1$ and $\tau_4 = \tau_2$, where the polarity of the stimulation signals $S_3(t)$ and $S_4(t)$ is reversed: $S_3(t) = -S_1(t)$ and $S_4(t) = -S_2(t)$. Assuming that the mean field of the ensemble uniformly oscillates with period $T = \tau$, the alternating polarity of the signal corresponds to a shift in time by half a period. Therefore, under this condition, the stimulation signal $S_3(t) = -S_1(t) = -KZ(t - \tau_1)$ approximates the stimulation signal $S_1(t + \tau/2)$ which is shifted in time by half of the period, which, in turn, is equal to $KZ(t - \tau_3)$, where τ_3 is calculated according to Eq. 4. Analogous arguments are applicable to the stimulation signal $S_4(t) = -S_2(t) = -KZ(t - \tau_2)$.

If the phase $\Psi(t)$ of the mean field $Z(t)$ (see also Z_I from Eq. 1) uniformly rotates with a constant frequency $\Omega = 2\pi/\tau$, the phases $\Phi_m(t) = \Psi(t - \tau_m)$ of the stimulation signals $S_m(t)$ are equidistantly distributed over the unit circle as illustrated in Fig. 6a. Then the phases $\psi_j(t)$ of the stimulated

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Fig. 6 Control of synchronization by multisite linear delayed feedback (MLDF) stimulation. **(a)** Distribution of the phases $\Phi_m(t)$ of the stimulation signals $S_m(t)$ administered via four stimulation sites (as in Fig. 1a), with the delayed mean phase, $\Phi_m(t) = \Psi(t - \tau_m)$, with delays τ_m from Eq. 4 for $\tau = T$. **(b, c)** Time courses of the amplitudes of the cluster variables (Eq. 1) the order parameters R_1 , R_2 , and R_4 . In the subplots, four trajectories from each of the four stimulated subpopulations assigned to each of the four different stimulation sites are shown for $t \in (320, 340)$. Parameter $\tau = T$ in **(b)** and $\tau = 2T$ in **(c)**

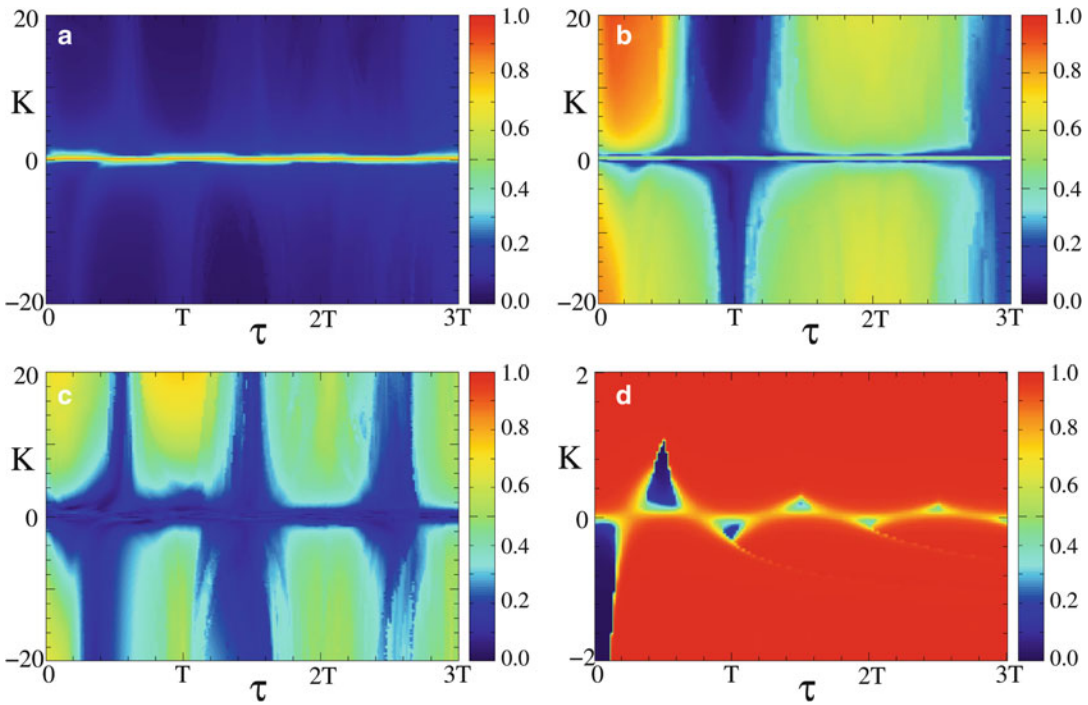


neuronal subpopulation assigned to the stimulation site m are attracted to the phase $\Psi(t - \tau_m)$ of the corresponding stimulation signal. Hence, the phases of all oscillators stimulated with MLDF become symmetrically redistributed on the circle $(0, 2\pi)$ in a cluster state. The order parameter $R_1(t)$ is thus minimized. Depending on the value of the delay τ , the stimulation can induce different cluster states in the stimulated ensemble, where the corresponding order parameter R_m attains large values.

As shown in Fig. 6b, c, the in-phase synchronization in the stimulated ensemble is effectively suppressed (for time $t > 200$, where both coupling and stimulation are switched on), where the order parameter $R_1(t) = |Z_1(t)|$ from Eq. 1 attains small values (Fig. 6b, c, red curve). This indicates a symmetrical redistribution of the oscillator phases $\psi_j(t)$ over the unit circle. For the parameter τ close

to the mean period T of the stimulation-free ensemble, a four-cluster state is induced by the stimulation, where the order parameters R_1 and R_2 are small, whereas R_4 is relatively large (Fig. 6b). In the inset showing four trajectories from each of the stimulated subpopulations, the emerging four-cluster state induced by MLDF is illustrated. For τ closer to, for example, $2T$, the stimulation induces a two-cluster state, where R_1 is small, whereas R_2 and R_4 are large (Fig. 6c). The oscillators thus split into two clusters, which is also illustrated in the inset in Fig. 6c.

MLDF robustly suppresses in-phase synchronization as shown in Fig. 7a, where the time-averaged order parameter $\langle R_1 \rangle$ attains small values for a broad range of parameters τ and K . On the other hand, depending on system and stimulation parameters, MLDF can induce either a two-cluster state, where the second order



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 7 Impact of the MLDF stimulation versus parameters τ and stimulus amplification K . The time-averaged order parameters $\langle R_1 \rangle$, $\langle R_2 \rangle$ and $\langle R_4 \rangle$ are depicted in plots (a–c), respectively, and encoded in color ranging from 0 (blue) to 1 (red). In plot (d), the

impact of the single-site linear delayed feedback (SLDF) on the oscillatory population is illustrated, where the values of the order parameter $\langle R_1 \rangle$ are depicted in color versus parameters τ and K (First published in Popovych et al. (2006a,b))

parameter R_2 attains relatively large values (e.g., for $\tau \approx 2T$; see Fig. 7b), or a four-cluster state, where R_2 becomes small and the fourth order parameter R_4 increases (e.g., for $\tau \approx T$; see Fig. 7c). Therefore, the whole stimulated population splits into two or four distinct subpopulations. Within the phase clusters, the individual oscillators have phases close to each other, while the different phase clusters are equidistantly distributed on the circle. Hence, depending on the values of the parameters τ and K , MLDF with four stimulation sites may cause either a two-cluster state, where R_1 is close to zero and R_2 is large, or a four-cluster state, where both R_1 and R_2 are small, but R_4 is large. The cluster states become less pronounced, and the phases redistribute on the circle even more uniformly if a local coupling as well as a spatially decaying profile of the current spread is taken into account (Hauptmann et al. 2005a).

In Fig. 7d a similar two-parameter diagram for the averaged order parameter $\langle R_1(t) \rangle$ is presented for a single-site linear delayed feedback (SLDF) suggested for synchronization control in references (Rosenblum and Pikovsky 2004a, b). The stimulation is performed via one stimulation electrode in such a way that all oscillators of the ensemble (in a first approximation) receive the same stimulation signal $S(t)$. In this case the stimulation signal $S(t)$ attains the form $S(t) = KZ(t - \tau)$. For stimulation with SLDF, in the corresponding two-parameter diagram (Fig. 7d), islands of perfect desynchronization are complemented by areas of stimulation-enhanced synchronization. In the limit $N \rightarrow \infty$, the order parameter $R_1 = 0$ in the desynchronization regions, where the phases are uniformly distributed on the circle $(0, 2\pi)$ (Rosenblum and Pikovsky 2004a, b). This is the state of complete desynchronization, where the stimulated

oscillators rotate with different frequencies indicating an absence of any cluster state whatsoever. The island-like structure of desynchronization regions in parameter space of SLDF (Fig. 7d) was also experimentally confirmed for arrays of coupled electrochemical oscillators (Zhai et al. 2008).

The important property of the stimulation with the multi- and single-site linear delayed feedback is the inherit demand-controlled character of the methods. As soon as the desired desynchronized state is achieved, the values of the order parameter $R_I(t)$, i.e., the amplitude of the mean field, become small. Along with the order parameter, in the desynchronized state, the amplitude of the stimulation signal $S(t)$ vanishes as well. Stimulation with multi- and single-site linear delayed

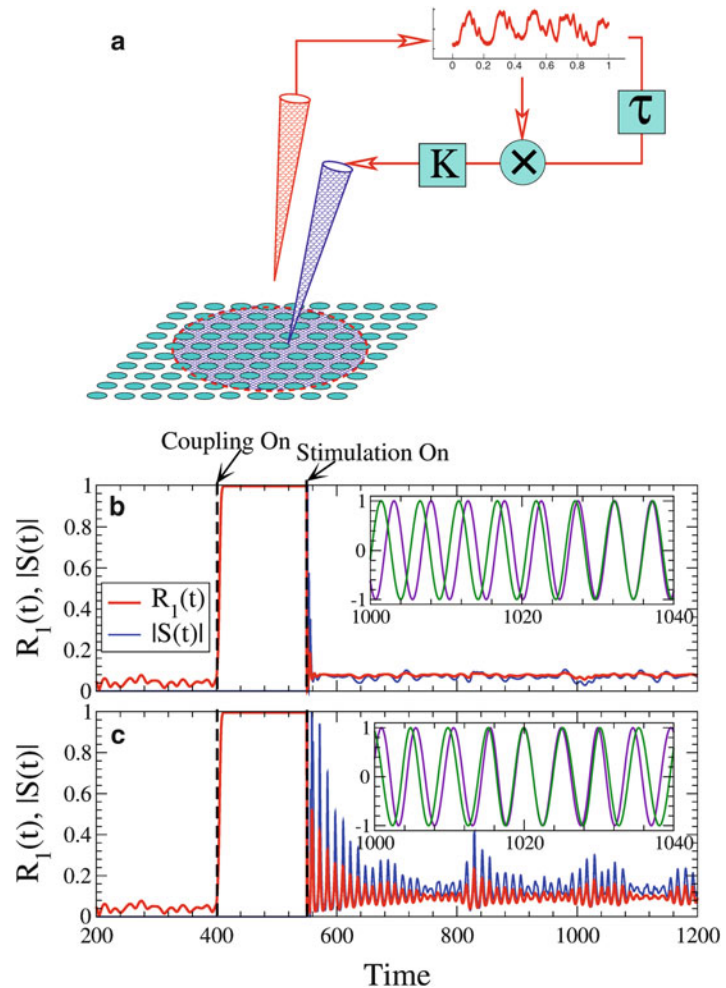
feedback thus represents a noninvasive control method for desynchronization of coupled oscillators. The stimulated ensemble is then subjected to a highly effective control at a minimal amount of stimulation force.

Nonlinear Delayed Feedback

As in the case of the single-site linear delayed feedback, for the stimulation with nonlinear delayed feedback (NDF), only one registering and one stimulating site is required; see Fig. 8a. All stimulated oscillators receive the same stimulation signal $S(t)$ which is constructed from the measured mean field of the ensemble. It is assumed that the measured mean field $Z(t)$ of the

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Fig. 8 Control of synchronization by nonlinear delayed feedback (NDF) stimulation. (a) The macroscopic activity (mean field) of the controlled population is measured, delayed, nonlinearly combined with the instantaneous mean field, amplified, and fed back via a single stimulation site. (b, c) Desynchronization of strongly synchronized oscillators by NDF. Time courses of the order parameter $R_I(t)$ (red curves) and the amplitude of the stimulation signal $|S(t)|$ (blue curves) are plotted for delays (b) $\tau = T/2$ and (c) $\tau = T$, where T is the mean period of the stimulation-free ensemble. In the insets, trajectories of two selected oscillators are depicted in the stimulated regime (First published in Popovych et al. (2008))



ensemble has the form of a complex analytic signal $Z(t) = X(t) + iY(t)$, where $X(t)$ and $Y(t)$ are the real and imaginary parts of $Z(t)$, respectively. If only the real part $X(t)$ of the mean field is measured, the imaginary part can be calculated, e.g., with the Hilbert transform (Pikovsky et al. 2001). The stimulation signal is then constructed by a nonlinear combination of a delayed complex conjugate mean field with the instantaneous mean field (Popovych et al. 2005, 2006a, b, 2008; Popovych and Tass 2010)

$$S(t) = KZ^2(t)Z^*(t - \tau) \quad (5)$$

where K is a stimulus amplification parameter, τ is a time delay, and the asterisk denotes complex conjugacy.

The desynchronizing effect of the stimulation with NDF is illustrated in Fig. 8b, c. NDF (with onset at $t = 550$) desynchronizes the stimulated oscillators, and the order parameter R_I reaches values of approximately the same order of magnitude as in the uncoupled regime ($t < 400$). This indicates a high level of desynchronization. The stimulation does not destroy the normal oscillatory activity of the individual oscillators. In the insets in Fig. 8b, c, individual trajectories of two selected oscillators of the stimulated ensemble are plotted. The stimulated oscillators rotate with different individual frequencies just as in the coupling- and stimulation-free regime.

As soon as a desynchronized state is achieved, the stimulation force decreases, and the stimulated system is subjected to a highly effective control with a minimal amount of stimulation force. Also, as soon as the oscillators resynchronize, the mean field starts to exhibit large-amplitude oscillations, and the stimulation signal increases in amplitude and brings the ensemble back to a desynchronized state. This demand-controlled character of the nonlinear delayed feedback is illustrated in Fig. 8c where the onsets of resynchronization (increase of $R_I(t)$, red curve) at times around $t \approx 850, 1050$, and 1200 lead to an increase of the amplitude of the stimulation signal $|S(t)|$ [blue curve], which in turn results in a suppression of the resynchronization.

The impact of the nonlinear delayed feedback on the stimulated oscillators is twofold. On the

one hand, the stimulation can effectively desynchronize even strongly interacting oscillators within a large range of values of the stimulus amplification K ; see Fig. 9a. This effect is very robust with respect to a variation of the delay τ and, as a result, with respect to a variation of the mean frequency Ω of the stimulated ensemble. On the other hand, in a weakly coupled ensemble, the stimulation can induce synchronization in island-like regions of small values of the stimulus amplification K complemented by domains of desynchronization; see Fig. 9b.

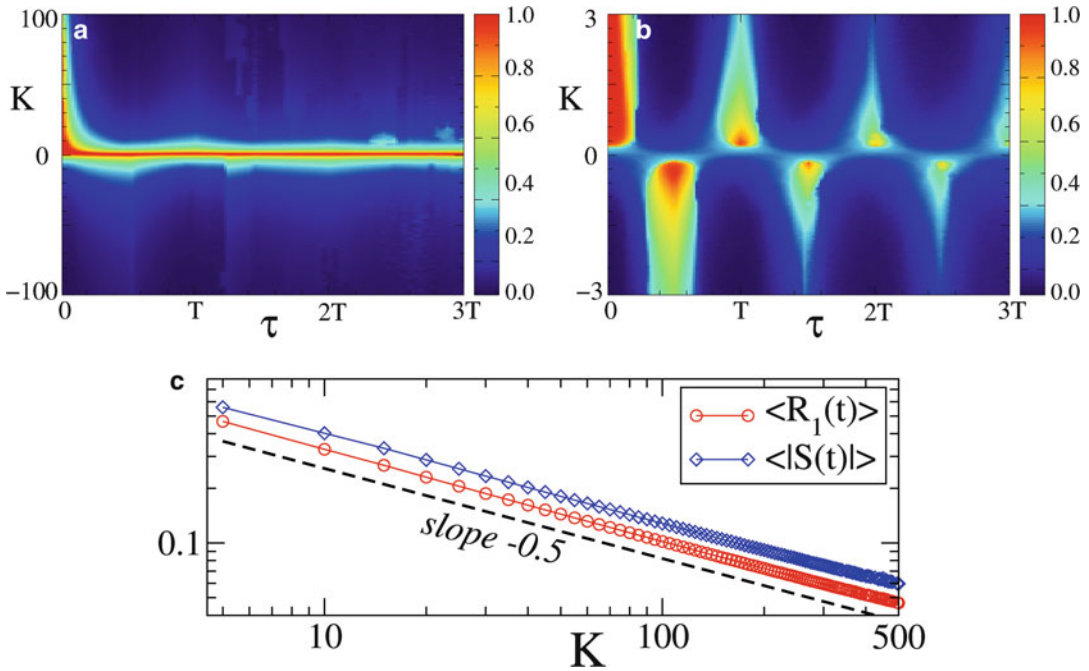
An increase of the stimulus amplification parameter K results in a gradual decay of the order parameter R_I for both strongly and weakly coupled oscillators, which indicates the onset of desynchronization in the stimulated ensemble. Simultaneously, the amplitude of the stimulation signal $|S(t)|$ decays as well, indicating the demand-controlled character of the nonlinear delayed feedback stimulation. For a fixed delay $\tau > 0$, the order parameter and the amplitude of the stimulation signal decay as $|K|$ increases according to the following power law (Fig. 9c):

$$R_I \sim |K|^{-1/2}, |S| \sim |K|^{-1/2}. \quad (6)$$

For large values of K , all stimulated oscillators rotate with different frequencies close to the natural frequencies (Popovych et al. 2005, 2006a, 2008). The oscillators thus exhibit a uniform desynchronous dynamics without any kind of cluster states. In addition, depending on the values of the delay τ , the nonlinear delayed feedback can significantly change the mean frequency Ω , i.e., the frequency of the mean field $Z(t)$ of the stimulated ensemble (Popovych et al. 2005, 2006a, 2008). The macroscopic dynamics can thus be either accelerated or slowed down, whereas the individual dynamics remains close to the original one. This enables an approach for frequency control of the oscillatory population stimulated with NDF.

Mixed Nonlinear Delayed Feedback

The NDF method can also be applied for desynchronization and decoupling of two (or more) interacting oscillator populations. For



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 9 Robustness of the NDF effects. (a) Stimulation-induced desynchronization and (b) stimulation-induced synchronization in ensembles of (a) strongly coupled and (b) weakly coupled oscillators. The time-averaged values of the order parameter $\langle R_1 \rangle$ are

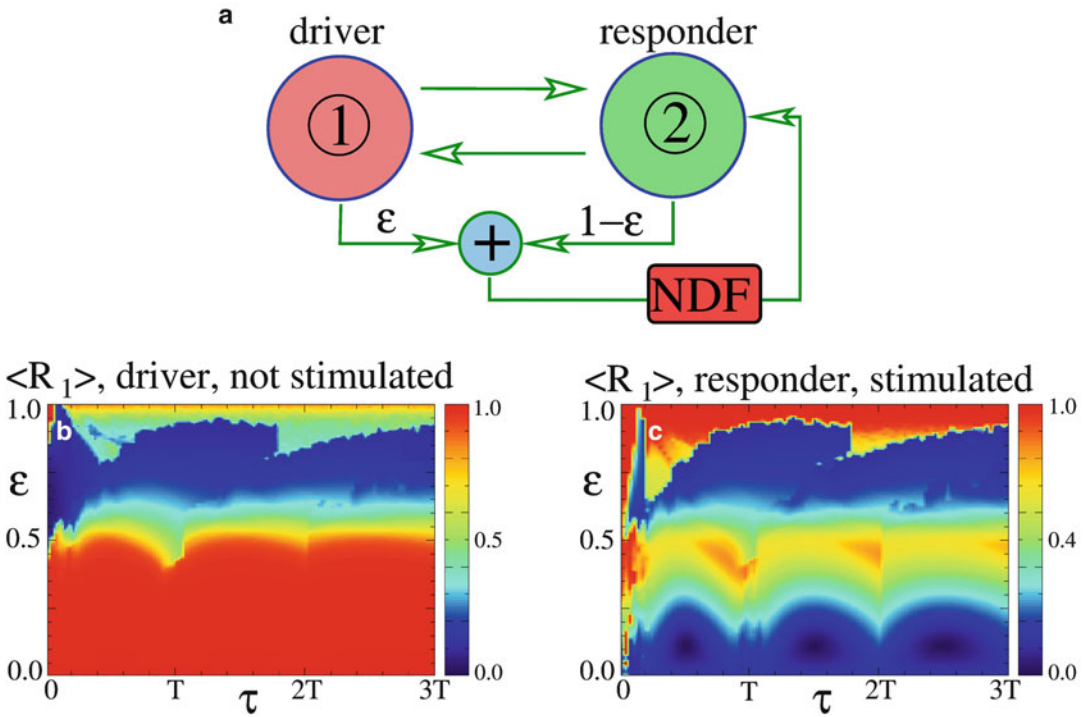
encoded in color ranging from *red* (synchronization) to *blue* (desynchronization) versus delay τ and stimulus amplification K . (c) Log-log plot of the time-averaged order parameter $\langle R_1 \rangle$ and amplitude of the stimulation signal $\langle |S(t)| \rangle$ versus K . The *dashed line* has the slope -0.5 and is given for comparison

this, mixed NDF can be used (Popovych and Tass 2010), see Fig. 10a. For a drive-response coupling scheme, the coupling within population 2 is assumed to be weak, so that, being isolated from population 1, no synchronization emerges in population 2. In contrast, the coupling in population 1 is strong enough to cause synchronization within population 1. It then drives the second population, which synchronizes because of the driving and sends a response signal back to population 1. The second ensemble is stimulated with signal $S(t)$, which is constructed from the mixed mean field Z_ε according to the rule of NDF from Eq. 5. The mixed mean field $Z_\varepsilon = \varepsilon W_1 + (1 - \varepsilon)W_2$ is a linear combination of the mean fields W_1 and W_2 of populations 1 and 2, respectively.

The level of mixing of the mean fields W_1 and W_2 within the stimulation signal is given by the parameter ε . Depending on ε the mixed NDF can have different desynchronizing effects on populations 1 and 2.

- *Small ε* : Mostly population 2 contributes to the stimulation signal. The mixed NDF desynchronizes the driven and stimulated population 2 (Fig. 10c), but the driving ensemble 1 remains unaffected and exhibits strongly synchronized dynamics (Fig. 10b). The populations get effectively decoupled from each other.
- *Intermediate ε* : Both populations equally contribute to the stimulation signal. Both ensembles remain synchronized (Fig. 10b, c).
- *Large ε* : Mostly population 1 contributes to the stimulation signal. Both ensembles are effectively desynchronized by the mixed NDF (Fig. 10b, c).

In the latter case, the desynchronization induced by the mixed NDF in the driven and stimulated population 2 propagates to the drive population 1 which is not directly stimulated. This is indicative of an indirect control of synchronization by the mixed NDF.



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 10 Desynchronization and decoupling of interacting populations by the mixed NDF. (a) Stimulation setup: The measured mean fields of populations 1 and 2 are linearly combined into a mixed mean field, processed by the NDF algorithm (Eq. 5) and fed back to the target population 2. (b, c) Time-averaged

order parameter $\langle R_1 \rangle$ of (b) intrinsically synchronized, drive population 1 and (c) stimulated population 2 driven into a synchronized state by population 1 versus time delay τ and mixing parameter ϵ . The color coding as in Fig. 9 (First published in Popovych and Tass (2010), copyright (2010) by the American Physical Society)

Proportional-Integro-Differential Feedback

For a particularly difficult situation, where measurement and stimulation are not possible at the same time and at the same place, there is another control method which is based on a proportional-integro-differential feedback (PIDF). The scheme of this stimulation protocol is sketched in Fig. 11a, see also Fig. 10a for $\epsilon = 1$ except for the measured signal being processed by a PIDF algorithm. The controlled ensemble of N coupled oscillators is divided into two separate subpopulations of N_1 and $N_2 = N - N_1$ oscillators, one being exclusively measured and the other being exclusively stimulated. In this way a separate stimulation-registration setup is realized, where the recording and stimulating sites are spatially separated and the measured

signal is not corrupted by stimulation artifacts. The observed signal is considered to be the mean field W_1 of the measured subpopulation. Below, the main attention will be paid to the proportional-differential (PD) feedback only (for more details, see reference Pyragas et al. 2007). Then, the stimulation signal $S(t)$ administered to the second, stimulated subpopulation is constructed as

$$S(t) = PW_1(t) + DW_1(t), \quad (7)$$

where the parameters P and D define the strength of the proportional and differential feedback, respectively.

The effect of the stimulation with PD feedback is illustrated in Fig. 11b. As the strength of the feedback (parameters P and D) increases, the stimulation results in a complete desynchronization of

the whole ensemble. The threshold of the onset of desynchronization depends on the relative splitting $N_1:N_2$ of the oscillators between subpopulations and on the mean frequency Ω : The threshold is larger for the smaller number of oscillators N_2 in the stimulated populations or for larger frequency Ω . The latter dependence can be eliminated if an integral component is included in the stimulation signal; see reference (Pyragas et al. 2007). Moreover, if the coupling in the ensemble is rather weak, the desynchronization can be achieved by applying the proportional feedback only. In contrast, in the case of strong coupling, the stimulation signal additionally requires the differential feedback for robust desynchronization. As illustrated in the two-parameter diagrams in Fig. 11c, d, there exists a certain threshold in parameters P and D values, where the stimulation with PIDF desynchronizes both subpopulations in the target ensemble: stimulated subpopulation (Fig. 11d) and also measured, non-stimulated subpopulation (Fig. 11c). In this sense, the PIDF stimulation method appears to be very effective even for a complicated stimulation protocol with a separate stimulation-registration setup.

Closed-Loop DBS

The standard setup of HF DBS utilizes an open-loop stimulation protocol where a permanent HF electrical pulse train is administered to the target nucleus (Benabid et al. 1991; Volkmann 2004). Systematic investigations of the influence of the stimulation parameters were performed with a focus on the optimization of standard HF DBS via an appropriate parameter calibration (Rizzzone et al. 2001; Moro et al. 2002; Rubin and Terman 2004) including computational approaches toward a closed-loop optimization setup (Feng et al. 2007a, b).

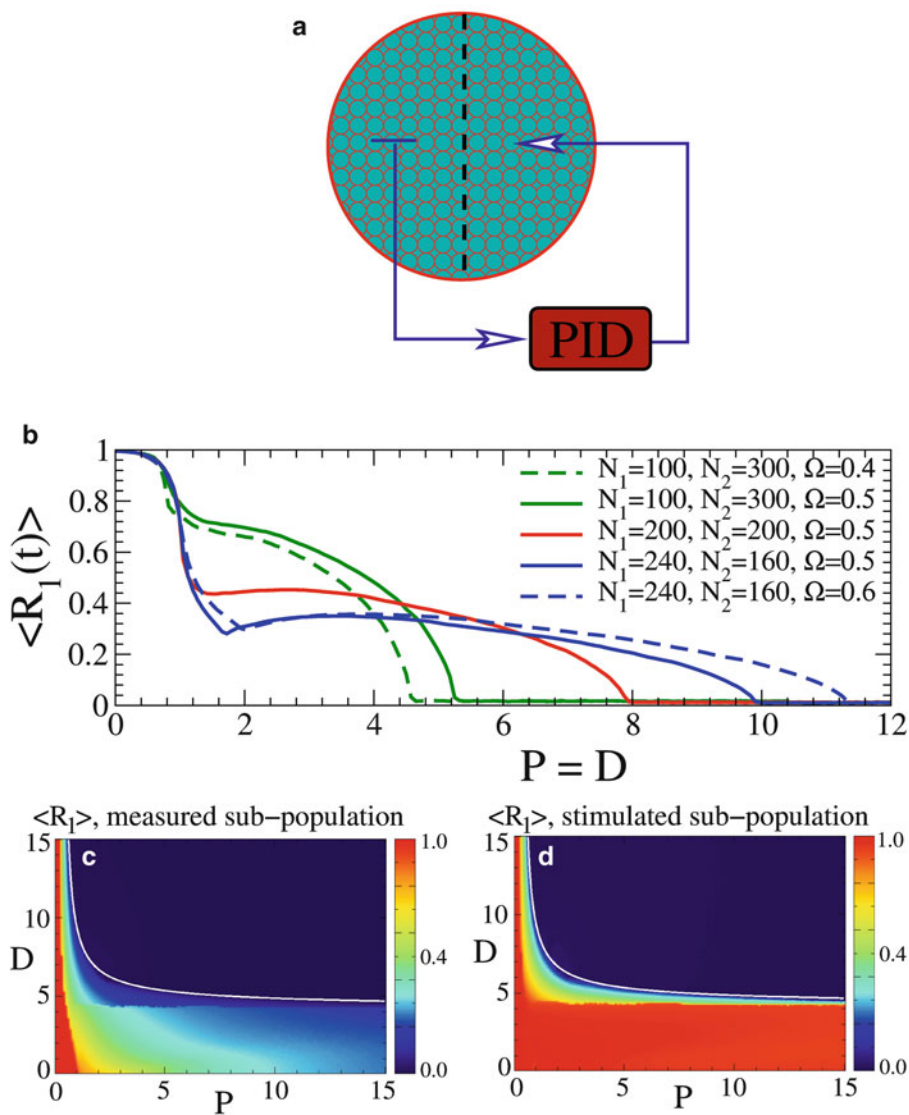
In monkeys rendered parkinsonian with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a closed-loop DBS was tested under acute conditions (Rosin et al. 2011). To this end, a short train (comprising seven pulses at 130 Hz) was delivered through a pair of electrodes located in the GPi at a predetermined, fixed latency (80 ms) following each action potential

recorded through an electrode placed in the primary motor cortex (M1). This type of stimulation caused a strong decrease of the firing rate of pallidal neurons together with a pronounced decrease of the oscillatory neuronal activity at the tremor frequency (4–7 Hz) and at the double tremor frequency (9–15 Hz) along with an amelioration of the MPTP-induced akinesia. After cessation of this type of closed-loop DBS, the initial firing pattern reverted back, i.e., pallidal firing rate and pallidal oscillatory activity attained pre-stimulus levels (Rosin et al. 2011). In contrast, standard continuous 130 Hz DBS caused a less pronounced decrease of the pallidal firing rate, the oscillatory neuronal activity, and the amelioration of the akinesia (Rosin et al. 2011).

Another study (Little et al. 2013) confirmed the efficacy of the closed-loop adaptive DBS (aDBS) in PD patients, where the onsets and offsets of HF stimulation were triggered by a threshold crossing by LFP in beta band measured via the same stimulation electrode implanted in STN. The stimulation trigger threshold for the LFP amplitude was heuristically determined in such a way that a reduction of the stimulation time of approximately 50 % was achieved while maintaining clinical effect. The onset of HF stimulation was delayed by 30–40 ms after the crossing of the threshold by LFP, and the stimulation was sustained until beta amplitude fell below the threshold again (Little et al. 2013). For the same stimulation intensity and stimulation frequency (130 Hz), the aDBS can be about 30 % more effective than standard continuous HF DBS, while less than 50 % of the total electrical energy is delivered in the aDBS mode as compared to continuous HF DBS. Moreover, despite of the used fixed beta threshold, the triggered stimulation duration (per 10-s block) progressively drops over time during stimulation in the aDBS mode, which suggests that aDBS may lead to positive adaptive effects in pathological parkinsonian networks (Little et al. 2013).

Summary

High-frequency deep brain stimulation is the standard therapy for the treatment of medically



Computational Model-Based Development of Novel Stimulation Algorithms, Fig. 11 PIDF control: (a) The mean field is measured in one part of the controlled ensemble and, after processing according to proportional-integro-differential feedback (PIDF) algorithm, administered to the other part of the ensemble. (b) The time-averaged order parameter $\langle R_1 \rangle$ of the whole ensemble versus the strength of the PD feedback (with $P = D$) for different splitting N_i :

N_2 and different mean frequencies Ω . (c, d) The time-averaged order parameters $\langle R_1 \rangle$ (encoded in color) of (c) the measured subpopulation and (d) stimulated subpopulation versus stimulation parameters P and D . The white curve is the parameter threshold for the onset of desynchronization in the subpopulations (First published in Pyragas et al. (2007), used with permission from EPL)

refractory movement disorders (Benabid et al. 1991; Volkmann 2004). To overcome limitations of this type of therapy, a model-based development of novel deep brain stimulation techniques has been initiated (Tass 1999). The ingredients of

this approach are dynamic neuronal self-organization principles combined with fundamental plasticity rules of the nervous system (Tass 2003a, b; Tass and Majtanik 2006; Tass and Hauptmann 2006, 2007; Hauptmann and Tass

2007, 2009, 2010; Tass and Popovych 2012; Popovych and Tass 2012).

The control methods discussed in this entry differ with respect to the stimulation setup and stimulation effects as well as other properties such as robustness and applicability. For example, CR stimulation, in an open-loop protocol, is simple to apply, does not require sophisticated calibration, and effectively causes desynchronization of the stimulated oscillators. As mentioned above, a number of computational and experimental studies confirmed the applicability and efficacy of CR stimulation under different stimulation modalities.

Other smart feedback methods are more difficult to realize conceptually and technically and await experimental proof of concept. In modeling studies, they effectively result in a sustained desynchronized regime. The feedback methods can be applied under a variety of conditions and possess an intrinsic demand-controlled character, where the stimulation signal is significantly reduced or even vanishes as soon as desynchronization is achieved. The experimental and clinical realization of these methods is a challenging task, first of all, from the technical side, since stimulation signals have to fulfill all safety aspects like charge density limits. These limits strongly affect the applicability of the slow feedback signals, i.e., slow compared to the timescales of HF and CR pulses. In this way, the application conditions of the methods have to be handled with care, and stimulation setups and effects have to clearly be distinguished for different feedback methods. Otherwise, one can come up with misleading conclusions and erroneous interpretations of the efficacy of feedback methods; see the computational study (Dovzhenok et al. 2013) where nonlinear and linear techniques were not properly distinguished. To this end, only an experimental proof can finally assess the applicability and performance of the control methods.

In forthcoming studies, the mathematical modeling needs to be refined to incorporate further anatomical and physiological details, for instance, contributions of glial cells (Silchenko and Tass 2008). By the same token, control techniques have to be optimized and further

developed. As currently done for CR stimulation, clinical studies are necessary to evaluate the therapeutic effects of the novel stimulation techniques under real conditions. This interdisciplinary endeavor might finally provide superior therapies for patients with neurological or psychiatric diseases.

Glossary

Coordinated reset stimulation Coordinated reset (CR) stimulation is an effectively desynchronizing control technique, where a population of synchronized oscillators is stimulated via several stimulation sites in such a way that spatially and timely coordinated phase reset is achieved in subpopulations assigned to each of the stimulation sites. This method is suggested for counteraction of abnormal neuronal synchronization characteristic for several neurological diseases and amelioration of their symptoms. It has successively been verified in a number of experimental and clinical studies.

Deep brain stimulation Electrical deep brain stimulation (DBS) is the standard therapy for medically refractory movement disorders, e.g., Parkinson's disease and essential tremor. It requires a surgical treatment, where depth electrodes are chronically implanted in target areas like the thalamic ventralis intermedius nucleus or the subthalamic nucleus. For standard DBS, electrical high-frequency (>100 Hz) stimulation is permanently delivered via depth electrodes. More sophisticated deep brain stimulation techniques are in the process of being established for clinical use.

Delayed feedback Delayed feedback is a method for the creation of a closed-loop forcing, where a portion of the measured output signal of a system is time delayed, linearly or nonlinearly processed, and fed back into the system. This approach is often used to control the dynamic behavior of complex systems. In this entry, delayed feedback is used to control synchronization in ensembles of coupled oscillators, e.g., neurons.

Order parameter The order parameter is a quantity characterizing a phase transition or phase change in the transformation of a complex system from one phase (state) to another. The order parameter is convenient for characterizing the onset and extent of synchronization in larger ensembles: Perfect phase synchronization corresponds to a large value of the order parameter, whereas an incoherent (desynchronized) state is associated with a small value of the order parameter. In synergistics it has been shown that the dynamics of complex systems may be governed by only a few order parameters.

Synchronization Synchronization (from Greek *syn* = the same, common and *chronos* = time) means the adjustment of rhythms of self-sustained oscillators due to their weak interaction. The interacting oscillators can be regular (periodic) or chaotic. There are several different forms of synchronization including phase, complete, generalized, and lag synchronization, etc. In this entry, we focus on phase synchronization. In the simplest form, the oscillators, rotating with the same frequency, become phase synchronized (phase locked) to each other, if the difference of their phases remains bounded, e.g., constant. In the presence of noise, phase synchronization is characterized by the presence of one or more prominent peaks of the distribution of the phase difference. Put otherwise, the oscillators adjust their rhythms, while their amplitude dynamics need not be correlated.

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Computational Modeling of Olfactory Behavior

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Definition

Computational modeling is an essential tool for developing an understanding of how nervous systems compute. This is particularly so for questions that span levels of analysis, attempting to integrate cellular, neuromodulatory, and electrophysiological data with behavioral performance. In neuroscience, computational techniques are used to study the mechanisms underlying neuronal or network responses to simple and complex inputs, analyze interactions among the parameters governing the properties of a neuron or network, and determine the coordinated mechanisms that underlie experimentally observed rich phenomena such as coherent oscillations or synaptic plasticity. In particular, computational modeling has been successful in associating neural activity with behavioral function, proposing neurophysiological mechanisms for observed behavioral capabilities, and generating novel, testable hypotheses. In our lab, computational models of behavioral phenomena have enabled us to elucidate relationships among odorant physical properties, top-down neuromodulatory signals, olfactory neural network operations, and odor perception. We here briefly review this approach and highlight some examples from the last ten years.

Computational Modeling

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)
- [Polypeptide and Protein Modeling for Drug Design](#)

Detailed Description

Our standard approach to modeling olfactory behavior is as follows: (1) determine via behavioral pharmacology or similar experiments which

olfactory brain areas are likely to underlie a certain aspect of olfactory perception; (2) create a computational simulation of those brain areas, incorporating as much constraining experimental detail as possible given the level of modeling chosen; (3) use the model to simulate specific relationships between neural activity patterns and perception, generating testable hypotheses; and (4) based on these hypotheses, perturb both experimental and computational variables via lesions, training parameters, pharmacology, and other experimental tools. The outcome of these studies then serves to inform the computational models and help determine the direction of future study.

One critical aspect of this process is the selection of the level of detail at which to build the model. Our modeling is nearly all based on specific neural systems – as opposed to generic neural networks – but the level of detail implemented must be appropriate given the available experimental data in order for the model to contribute meaningfully to this research approach. More abstract models of particular networks, made with relatively reduced, single-compartment neurons, are appropriate when the data include general information about neurons being excitatory or inhibitory, reasonable estimates of synaptic connectivity patterns, and neuromodulator effects that are thought to excite, inhibit, and/or affect the excitability of particular cell types. Building simpler models with fewer free parameters enables a relatively efficient exploration of what such a network can do, and how the different effects of neuromodulators, for example, could combine to produce a functional outcome that corresponds to behavioral data. Following up on hypotheses generated by such models can increase the efficiency of experimental design, ultimately producing data sufficient to build the richer and more complex biophysical models.

Biophysical models require considerably more experimental data in order to be useful. They define physical membrane properties such as surface area, capacitance, and cell morphology, model many individual mechanisms such as sodium channels, calcium diffusion, and NMDA receptors, deploy these mechanisms into or with

respect to the cell membrane, and often are morphologically multicompartmental. Oligocompartmental model neurons, in particular, are built using perhaps 2–20 compartments that may serve to accurately model spike propagation times, segregate electrotonically distant parts of the neuron, construct cells with heterogeneous channel distributions, and/or implement other phenomena in which spatial heterogeneity matters. (Neuron models with hundreds of compartments, in contrast, usually are constructed to replicate the arbor of a specific neuron measured from imaging data.) If there are constraining data for enough of these parameters, then such models are singularly powerful, as they are able to implement underappreciated computational elements like shunt inhibition, intrinsic resonance properties, and the partial isolation of spines, and at their best they can predict the network-level consequences of, for example, localized effects on ion channel properties. In the absence of sufficient data, however, such models lose most of their predictive value, as they simply contain too many free parameters which, if unconstrained, can enable meaningless fits to many datasets; simpler models should be used in such situations. Irrespective of the level of complexity, however, useful models usually do not simply replicate established data but employ their capacity to quantify and juxtapose diverse datasets in order to explain what is known and explore what that might imply. Models can range from being quite tightly based on cellular data (e.g., Li and Cleland 2013, 2017) to being more speculative (e.g., Linster and Cleland 2010), but in either case the task is to understand how best to ask the next question. While models that stand the test of time are laudable, models that are subsequently superseded by new data have served their scientific purpose well.

Over the past quarter century, we have developed computational models of many behavior-related processes within olfaction, including the cholinergic, noradrenergic, and dopaminergic modulation of bulbar circuitry (Linster and Gervais 1996; Hasselmo et al. 1997; Linster and Hasselmo 1997; Linster and Cleland 2002; Linster et al. 2003; Mandairon et al. 2006a; Escanilla et al. 2009; Linster et al. 2011; Devore

and Linster 2012; Devore et al. 2012; de Almeida et al. 2013; Li and Cleland 2013; Devore et al. 2014; de Almeida et al. 2015; Li et al. 2015; de Almeida et al. 2016), perceptual learning (Mandairon et al. 2006b), mixture processing in the olfactory bulb (Linster and Cleland 2004), the bulbar mechanisms regulating differentiation among similar odors (Cleland and Sethupathy 2006; Cleland et al. 2007; Cleland et al. 2012), the role of spike synchronization in antennal lobe odor processing (Linster et al. 1994; Linster and Cleland 2001) and synaptic plasticity in olfactory bulb and cortex (Linster et al. 2007; Linster et al. 2009; Linster and Cleland 2010; Mandairon et al. 2014), the dynamical mechanisms underlying lateral communication and synchronization across the bulbar circuit (David et al. 2008, McIntyre and Cleland 2016; Li and Cleland 2017), and the multiple concerted processes required to enable concentration invariance in odor perception (Cleland and Linster 1999; Cleland et al. 2007; Cleland et al. 2012). In each case, a critical factor affecting model validity has been the comparison between model output and behavioral results. How does one determine whether and how the values of model output variables correspond to measured indices of behavior? While this is always ultimately an experimental question, we have determined several behavioral indices that can be reliably predicted by specific output metrics from our computational models, including perceptual similarity, discrimination performance, learning rate, memory capacity, and memory persistence. For example, we first demonstrated that the pairwise overlap in neuronal activation patterns across the olfactory bulb input layer could predict pairwise perceptual similarity (Linster et al. 2001; Cleland et al. 2002). To the extent that this result is generalizable as a basic principle of olfactory coding, one then can, in subsequent studies, compare changes in pairwise overlap within the computational model to behavioral changes in perceptual discrimination. This in turn enables, for example, the effects of neuromodulators on olfactory discrimination to be modeled and tested against behavioral data (e.g., Mandairon et al. 2006a). Importantly, while this principle of pattern overlap among

glomeruli has been largely supported experimentally, its basis is inductive and it cannot be reliably extrapolated; e.g., it may not extend reliably to spatial patterns among mitral cells, or within piriform cortex. Like theoretical models in general, these models serve to organize our understanding of complex data sets until a superior theory can be constructed.

We here describe three specific examples of the modeling of olfactory behavior that provided useful insights into the underlying neural mechanisms. First, an abstract model of spike timing and oscillations in the honeybee antennal lobe explained how neuronal synchronization patterns could underlie seemingly paradoxical behavioral generalization effects observed across different odor concentrations (Linster and Cleland 2001; Cleland and Linster 2002; Linster and Cleland 2010). Second, a large-scale, reduced model of olfactory bulb outlined a feedback normalization network enabling concentration invariance in bulbar output, consistent with behavioral performance (Cleland et al. 2007). Third, a moderately detailed computational model of cholinergic modulation in the olfactory bulb glomerular layer predicted coordinated network-level and behavioral outcomes from the properties and localization of nicotinic cholinergic receptors in the olfactory bulb (Mandairon et al. 2006a; de Almeida et al. 2013; Devore et al. 2014; de Almeida et al. 2016).

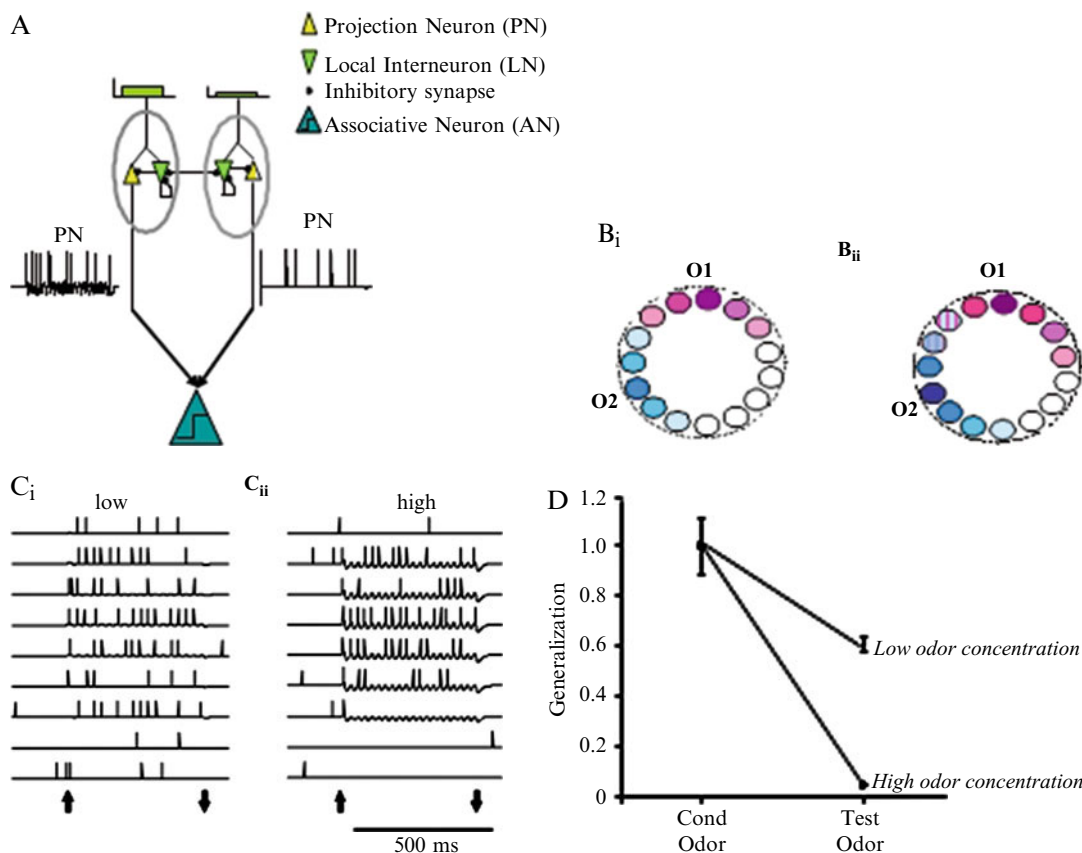
Example 1: Odor Concentration and Spike Timing in the Insect Antennal Lobe

Honeybee olfaction is an important model system for olfactory learning due to its well-developed and efficient behavioral conditioning paradigms and the relatively well-understood neural circuits involved in odor learning. The behavioral relevance of spike timing regulation in olfaction was first demonstrated in the honeybee antennal lobe, in which it was demonstrated that stimulus-evoked synchronous spiking was necessary for fine odor discrimination. Specifically, in combined electrophysiological and behavioral experiments, when fine-scale spike synchrony was disrupted, bees' odor discrimination performance was impaired, even though the overall profile of

evoked activity in antennal lobe neurons remained intact (Stopfer et al. 1997; Stopfer et al. 2003). Using the same behavioral paradigm, it subsequently was demonstrated that honeybees discriminate odors better when they are presented at high concentrations than when they are presented at lower concentrations (Bhagavan and Smith 1997). Neurophysiologically, this result was counterintuitive because calcium imaging studies have shown that higher concentration odor stimuli activate correspondingly larger and more overlapping areas of the antennal lobe (Strauch et al. 2012), which, given that overlap predicts perceptual similarity, should result in poorer discrimination. Computational modeling resolved this behavioral conundrum by combining the findings of these two lines of research (Linster and Cleland 2001; Cleland and Linster 2002). The model exhibited oscillations and spike synchronization patterns similar to those recorded in the antennal lobe and demonstrated that while higher-intensity odor inputs would evoke broader neural activity overall, an increasingly narrow subpopulation of neurons within this broad ensemble would be increasingly strongly synchronized. Synchrony-sensitive follower neurons and plasticity processes responding selectively to these highly synchronous inputs would therefore interpret higher-concentration inputs as more discriminable from one another, matching behavioral observations, while blocking these synchronization processes would impair fine odor discrimination. In contrast, lower-concentration inputs would evoke weaker synchrony among antennal lobe projection neurons and generate less activity or plasticity in follower cells (Fig. 1). This work illustrated how computational modeling can fuse separate datasets derived from a common system to explain seemingly unrelated results, constructing a common theoretical basis upon which subsequent experiments can be based. Since this time, the study of spike synchronization processes within olfactory coding research has grown substantially, particularly with the elaboration of timing-dependent synaptic plasticity algorithms in the brain (Song et al. 2000; Gao and Strowbridge 2009; Linster and Cleland 2010).

Example 2: The Problem of Concentration Invariance in the Olfactory Bulb

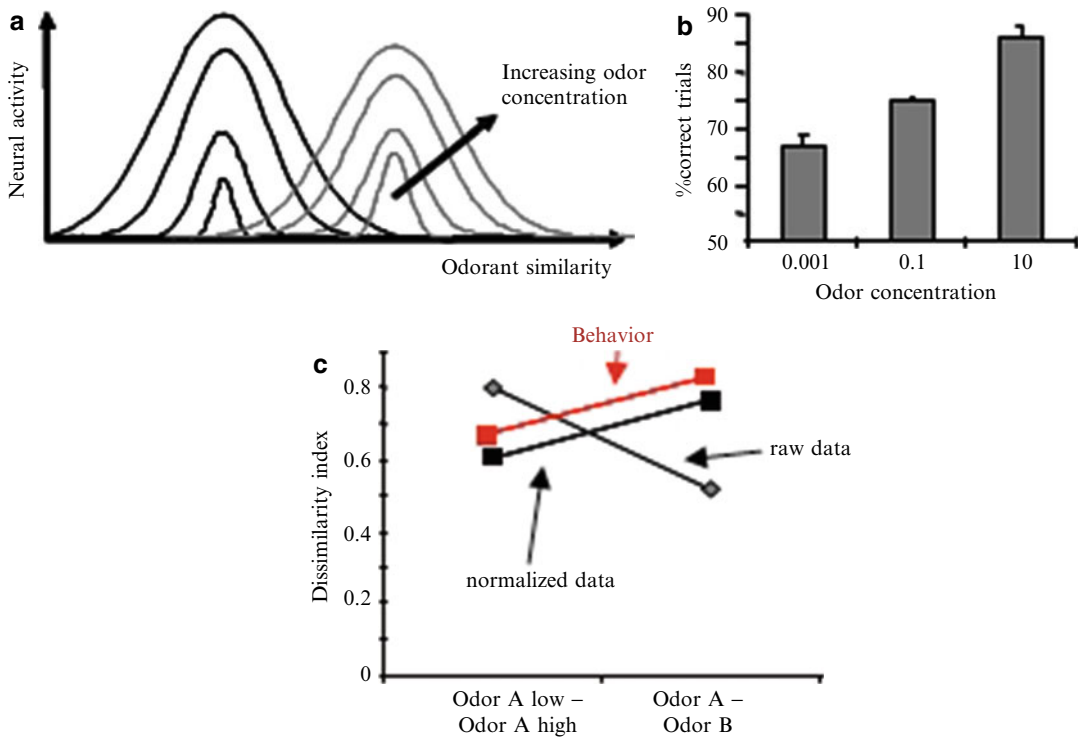
Odorants elicit widely distributed patterns of activity across the olfactory bulb input layer, as evidenced by 2-deoxyglucose activity mapping (Johnson and Leon 2000), intrinsic imaging (Meister and Bonhoeffer 2001), and other imaging techniques. These activation patterns are substantially altered when odor concentration is changed (Johnson et al. 1999; Johnson and Leon 2000; Meister and Bonhoeffer 2001), to the extent that the pattern evoked by a given odor may more closely resemble that of a different odor than that of itself when presented at a different concentration (Cleland et al. 2007). Despite this fact, animals can identify a given odor over a reasonable concentration range, and – critically – neural response patterns at the output of the olfactory bulb are less affected by odor concentration than are those measured at the input. Interestingly, simple normalization (z-scoring) of these odor-evoked patterns rendered them reasonably consistent across concentrations (Johnson et al. 1999; Johnson and Leon 2000), and behavioral tests measuring the pairwise perceptual similarities of odorants showed that perception was better predicted by normalized activity patterns than by nonnormalized activity (Cleland et al. 2007) (Fig. 2). These results, together with physiological demonstrations that mitral cell spike rates do not monotonically increase with odor concentration (Harrison and Scott 1986; Wellis et al. 1989; Meredith 1986), suggested that these odor-specific patterns are actively normalized within olfactory bulb circuitry. Computational modeling based on these data, and on contemporary understandings of cellular properties in the olfactory bulb, demonstrated how these neural circuits in the olfactory bulb glomerular layer could perform such a normalization function. Specifically, a laterally interconnected network of interneurons, then believed to be excitatory, synapsing onto local inhibitory interneurons and with a broad distribution of lateral projection distances estimated from anatomical data (Aungst et al. 2003), was shown capable of performing feedback normalization uniformly across the bulb (Cleland et al. 2007). These simulations showed that a



Computational Modeling of Olfactory Behavior,

Fig. 1 Synchronization and odor perception in the honeybee antennal lobe. **(a)** Network diagram of honeybee antennal lobe model. The network was created based on known neuron types and was capable of generating odor-evoked, GABAergic neuron-dependent field potential oscillations that shaped spike timing as described experimentally. Briefly, input from olfactory sensory neurons (SNs) directly activates projection neurons (PNs) as well as inhibitory local interneurons (LNs). Local interneurons are reciprocally connected with each other in a feedback network which generates synchronous oscillations when activated. Local interneurons also inhibit projection neurons and are capable of synchronizing projection neuron spikes with respect to these network oscillations. Because local interneurons in the model have higher activation thresholds than projection neurons, highly activated glomeruli oscillate more strongly and the corresponding projection neurons are most strongly synchronized. The associative neuron (AN), corresponding to the reward-activated neuron VUMmx1 in honeybees, is sensitive to synchronized spike inputs. **(b)** In the model, increasing odor concentration at the input of the antennal lobe generates more widespread activation patterns and hence increased overlap among odor representations (Bi designates a lower concentration odorant, Bii a higher

concentration odorant). Each circle represents a glomerulus receiving input from sensory neurons expressing a shared olfactory receptor; darker colors symbolize stronger activation and striped glomeruli indicate glomeruli substantially activated by both inputs. Glomeruli are mapped onto a hypothetical one-dimensional circular axis of receptive field similarity (Cleland and Linster 2002). O1 and O2 denote the centers of the glomerular patterns activated by two different odors. **(c)** Increased odor concentration also generates stronger oscillations in activated glomeruli, resulting in greater synchrony among a narrower population of the most strongly activated projection neurons. **(d)** Increased synchrony leads to reduced generalization between two odors presented at higher concentrations than when presented at lower concentrations, despite their larger overlap at the input to the antennal lobe. Odor conditioning was simulated by presenting a conditioning odor stimulus to the model at a low (25% of maximum activation) or high (100% of maximum activation) intensity and training the network on the odor. Subsequently, the network was presented with a novel odor and the degree of overlap between the representations of the conditioned and novel odors was calculated (generalization). The graph shows the degree of generalization to the novel test odor after conditioning at low and high stimulus intensities. (Figures adapted from Cleland and Linster (2002))



Computational Modeling of Olfactory Behavior, Fig. 2 Normalization in the olfactory bulb glomerular layer. **(a)** Schematic depiction of odor representations in the olfactory bulb glomerular layer. Odorants are ordered along a hypothetical axis of similarity onto which individual glomeruli can be mapped. Note that this is purely for representational purposes and that such orderly mapping does not exist in the system. Glomerular activation becomes stronger and spreads by activating additional glomeruli as odor intensity increases; consequently, the overlap between two odor representations increases. **(b)** Despite the increase in overlap between odorants at higher concentrations, rats and mice can differentiate odorants better as concentration increases. The graph shows the percent correct trials in a forced choice go/no-go task in rats as a function of odor concentration (Wei et al. 2006).

(c) In certain cases, the raw and normalized activation patterns evoked by a given odorant at different concentrations are more different from one another than they are to the representation of an entirely different odorant. The graph depicts (black lines) indices of dissimilarity between glomerular activation patterns, calculated from raw or normalized 2-deoxyglucose uptake data, computed between a single odor **(a)** presented at two concentrations and between that odor and a different odor **(b)**, both presented at the same concentration (Cleland et al. 2007). For comparison, the graph also depicts (red line) the corresponding behavioral results (i.e., degree of perceptual dissimilarity) in response to the same odor pairs. The normalized activation patterns predict behavioral perception, whereas the raw data do not

partially localized network of microcircuits could underlie a nonlocalized, uniform effect, utilizing this small-world effect to normalize mitral cell odor responses in order to render them more concentration-invariant. In this example, behavioral experiments were necessary to validate the basis for the computational model by demonstrating that global normalization correctly predicted perceptual similarities. Interestingly, in subsequent experimental studies, the role of these laterally projecting interneurons in broadly

inhibiting mitral cells across the olfactory bulb was confirmed (Banerjee et al. 2015), even though the interneurons themselves since have been shown to be GABAergic and dopaminergic, rather than glutamatergic as was previously believed (Kiyokage et al. 2010). That is, the 2007 model proved correct at Marr's (1982) computational level (normalization at this level of the olfactory bulb network was required in order to explain experimental results) but not at the implementation level (the mechanism by which this

normalization is achieved was incorrect in that model). This provides an excellent example for how a model can serve its purpose, being correct at a certain level and enabling the coordinated interpretation of diverse datasets, while also becoming outdated by experimental progress and requiring update or replacement. It is also important to emphasize that computational operations in neural circuits are necessarily embedded in broader networks that can enhance, impair, or prevent their function. Concentration tolerance in olfaction, for example, is not mediated solely by this single circuit; rather, its operation depends on multiple prior circuit computations that establish important prerequisites for its success (Cleland et al. 2012).

Example 3: Effects of Nicotinic Receptor Activation on Odor Discrimination – Behavioral Experiments and Biophysical Modeling

The cellular effects of nicotinic cholinergic receptor activation in the olfactory bulb are relatively well understood (Castillo et al. 1999; Pressler et al. 2007). Nicotinic cholinergic activation opens cation currents both in mitral cells, exciting them and increasing their odor-evoked activation levels, and in GABAergic periglomerular cells, increasing their inhibition of mitral cell primary dendrites. Hence, nicotinic receptor activation simultaneously excites and (indirectly) inhibits mitral cells in the bulb – two effects that initially might appear to cancel one another out. However, computational modeling of these two neuron types embedded within their glomerular microcircuit showed that, rather than canceling each other out, these two effects complement one another (Linster and Gervais 1996; Linster and Hasselmo 1997; Linster and Cleland 2002). Specifically, while the increased inhibition on mitral cell primary dendrites sharpens mitral cell responses to odorants by suppressing weak responses, the concomitant excitation near the soma maintains or enhances the strength of response within this narrower receptive field. As a consequence, receptive fields are sharper but stronger (Mandairon et al. 2006a; de Almeida et al. 2013; Devore et al.

2014; de Almeida et al. 2016; Li and Cleland 2013). When comparing ensemble responses to multiple odorants in this model, the overlap in mitral cell activation patterns is reduced when nicotinic receptors are activated, separating the representations of highly similar odors and predicting that they would become easier to discriminate. We tested this prediction behaviorally and found that, indeed, the blockade of nicotinic cholinergic receptors in the olfactory bulb reduced rats' capacity to differentiate between perceptually similar odorants, whereas it did not affect the perception of chemically and perceptually dissimilar odor pairs. Moreover, enhancing cholinergic modulation during behavior improved rats' ability to differentiate between perceptually similar odorants (Mandairon et al. 2006a; Chaudhury et al. 2009) (Fig. 3). In this study, the known cellular effects of nicotinic receptor activation were sufficient to predict perceptual effects once constructed into an appropriate network model, suggesting that the computational model captured the essence of this neuromodulatory process. Subsequent behavioral and computational studies further suggested that this reduced overlap in bulbar representations enables more rapid cortical learning and that cortical and bulbar cholinergic modulatory responses act in concert to establish efficient and stable learning processes (de Almeida et al. 2013; de Almeida et al. 2015; de Almeida et al. 2016).

Conclusion

Computational modeling of the neurons and networks of the brain provide essential tools and frameworks for understanding the neural mechanisms underlying animal behavior. By juxtaposing diverse experimental results within appropriate theoretical frameworks, constructing functional scenarios, and assessing the likelihood and consequences of each, modeling facilitates the theoretical analysis of complex datasets and the construction of testable hypotheses, providing an essential link between physiology and behavior.

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Computational Models of 3D-Cue Integration

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Definition

Depth cue integration is the process by which the brain derives a three-dimensional property (e.g., depth, slant and curvature) from distinct image measurements, often referred to as depth cues. Individual depth cues are thought to result from independent processes of image formation. The goal of a computational model of cue integration is to describe the brain mechanisms which combine different depth cues into a single estimate of a 3D property. A valid model must be based on a testable normative theory identifying (1) the nature of the 3D information provided by separate modules, (2) the goal of the computation, (3) the computational algorithms that underlie integration, and (4) a plausible neural implementation in a biological system.

Detailed Description

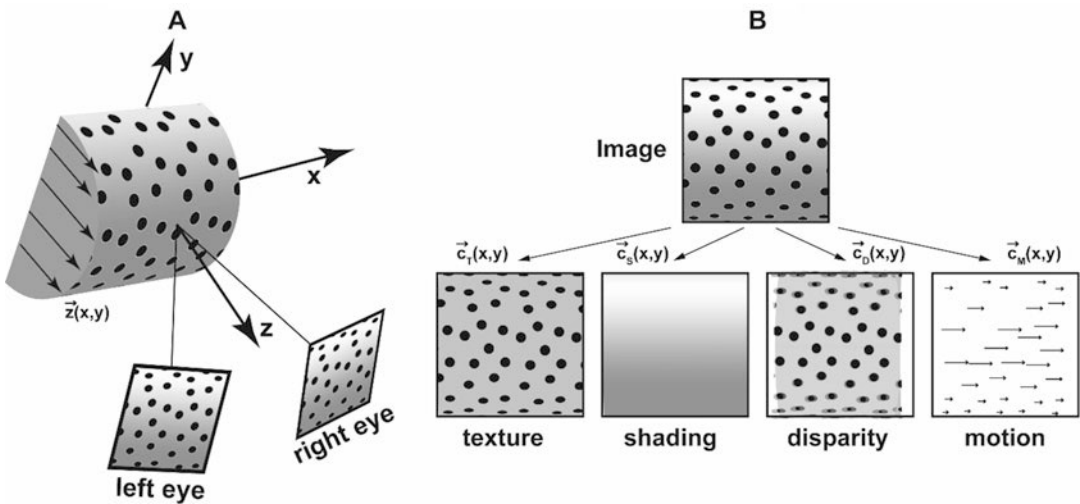
Depth Cues and Multiple Processes of Image Formation

The light reflected by surfaces of environmental objects projects patterns to the point of observation that are registered as retinal images. The structure of these images depends on the complex interplay of several factors related to the material composition of the projecting surfaces and their spatial relationship relative to the point of observation. These factors are responsible for independent processes of image formation that only have in common the 3D structure of the object from which they generate. To illustrate this, consider Fig. 1a. The material composition of the 3D object is such that its surface is covered with circular texture elements. The retinal projections of these elements are ellipses whose aspect ratio and orientation depend on the slant and tilt of the underlying 3D surface (Fig. 1b). This pattern of elliptical shapes – the texture gradient – therefore carries information about the 3D surface. This aspect of image formation is distinct from the

one also shown in Fig. 1b which derives from the same 3D structure but results in a different image information: shading. If the object surface is composed of a uniform matte material, then the relative orientation between local surface patches and the direction of the illuminant determines the intensity of the light that these patches reflect. For the smooth surface, the variation in local surface orientation relative to the illuminant and viewing direction results in the familiar smooth variation of light intensity (shading) observed on the image projection (Fig. 1b).

The image patterns arising from these distinct aspects of image formation are often referred to as depth cues. Texture and shading are examples of depth cues arising from static *monocular* image formation processes resulting from the specific relationship between viewpoint, surface shape, material composition, and ambient light. In contrast, two other depth cues (binocular disparity and motion parallax) depend on image formation processes deriving solely from the relative shift in the image of projected points between two distinct views. For binocular disparities, this shift is

C



Computational Models of 3D-Cue Integration, Fig. 1 (a) A 3D surface projects images onto the retinae of the left and right eye (represented by planar surfaces). z represents the observer's gaze direction, (x, y) the frontoparallel plane, and $\vec{z}(x, y)$ the depth-map. (b) The

retinal images (top) can be decomposed into distinct sets of image measurements, commonly referred to as depth cues, capturing independent processes of image formation (bottom)

recorded instantaneously through a comparison of the right and left retinal images. For retinal motion, the shift is registered monocularly between two instants of time.

Depth Cues and Mappings to External 3D Structure

3D structure can be operationalized in terms of either the first-order property of a “depth map” of discrete points, or higher order properties such as the slant of a planar surface, or the curvature of a nonplanar surface. Depth cues result from a mapping from these 3D properties to two-dimensional retinal image patterns. However, as suggested above, the information carried by this mapping is also mediated by other factors that are independent from the 3D structure of objects, such as material properties, illuminant characteristics, location, and motion of the observer. We define these as scene parameters.

If we define a 3D property, for example, a depth map $\vec{z}(x, y)$, and a set of scene parameters $\vec{p}_i$, a depth cue i can be formally specified as a set of image measurements $\vec{c}_i(x, y)$ defined at each image location (x, y) resulting from an image formation process $\vec{c}_i(x, y) = f_i(\vec{z}(x, y), \vec{p}_i)$. Unless the scene parameters $\vec{p}_i$ (e.g., material property, illuminant) are specified, depth cues are inherently ambiguous.

Consider, for example, the texture cue, which can be defined as a set of orientations, sizes, aspect ratios, and distributions of image texels $\vec{c}_T(x, y)$. The relevant scene parameters for the texture cue are the texel properties on the 3D surface $\vec{p}_T(x, y)$. Without some knowledge of $\vec{p}_T(x, y)$, it is impossible to recover or infer $\vec{z}(x, y)$, since the shape and distribution of image texels depend both on the surface structure and the shape and distribution of surface texels. In the example of Fig. 1, the smooth variation of orientations and aspect ratios of image texels can only be mapped back to the generating 3D structure if surface texels are assumed to be circular and uniformly distributed over its surface. Similarly, other cues are also intrinsically ambiguous: the shading cue is ambiguous since the image luminance gradient depends on the rate of variation of the local surface orientation as well as the material composition of the

object and the characteristics of the ambient illumination; patterns of retinal motion depend on the observer’s speed of motion; binocular disparities for a given object depend on the square of the distance to the object from the observer.

Assuming that each image measurement type $\vec{c}_i(x, y)$ derives from an independent and distinct neural process, the problem is to understand how the visual system analyzes and combines the inferred 3D structure from each measure (depth cue) to achieve a unique 3D interpretation.

Normative Theories of Cue Integration

In the tradition of the computational approach introduced by David Marr (Marr 1982), it is important to specify both the goal of the visual system and the algorithmic process when encoding 3D information. Vision scientists mostly agree that locating objects within the scene and estimating their 3D structure mainly serves the purpose of allowing efficient interactions with the environment. An obvious solution is to postulate that the visual system derives accurate (unbiased) estimates of 3D properties from retinal projections. In reference to the previous formulation, this means deriving the actual depth map $\vec{z}(x, y)$ from the depth cues. However, we saw that without knowledge of the scene parameters, $\vec{p}_i$, depth cues underspecify $\vec{z}(x, y)$. Depending on the specific cue and the viewing conditions, knowledge of the scene parameters is either partial or depends on having learnt the statistical regularities of the environment.

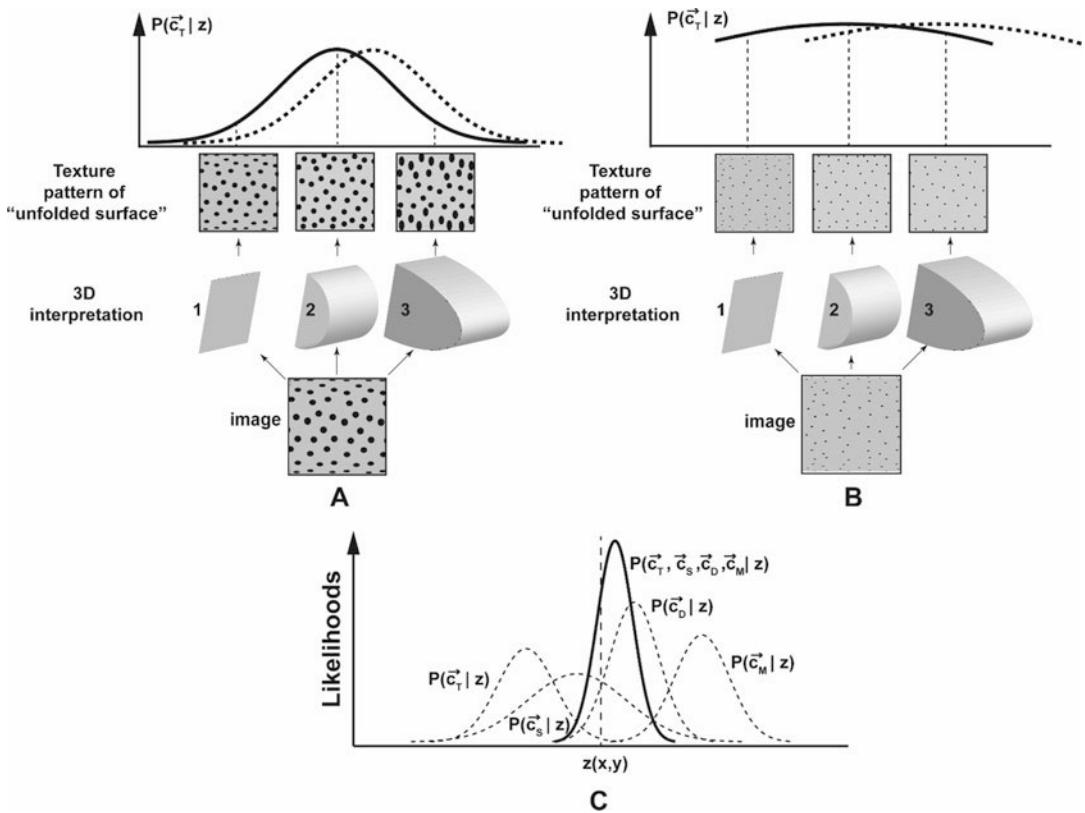
The analysis of single cues in terms of world to image mapping was inspired by Gibson’s seminal analysis of image gradients and how such gradients can directly specify certain aspects of the 3D structure of the external environment (Gibson 1950, 1966). Much of the detailed computational analysis and development occurred in the field of machine vision and first wave artificial intelligence. For example, Horn and Takeuchi’s analysis of the shading cue (Horn 1986) was followed on by other work on texture, motion, and disparity (see Howard and Rogers 2002). These deterministic models identified the dependence of the mapping on a range of viewing parameters and the necessity of underling uniformity assumptions

(e.g., isotropy, surface continuity, and uniform reflectance) necessary for restricting possible solutions of the inherent one-to-many mapping.

An alternative algorithmic approach to deriving the 3D object structure is based on a probabilistic formulation of the problem. Consider again the texture cue example shown in Fig. 2. The retinal image depicted at the bottom of Fig. 2a could be interpreted as a flat surface (interpretation 1) across which texture elements systematically vary in shape (texture elements are idiosyncratically compressed and denser at the edges). Although this interpretation is correct (the surface on which this

figure is printed/displayed is indeed flat), we perceive the pattern as a curved surface. This is presumably because the visual system prefers a 3D interpretation (interpretation 2) where the shapes of texture elements are inferred to be similar to each other in size and orientation (uniformity) and distributed evenly (isotropically) across a surface (Knill 1998).

This preference could arise from learning the most common properties of textures present in the world. The visual system is said to prefer interpretation 2 because it represents a texture pattern that is more probable to exist in the world than the



Computational Models of 3D-Cue Integration, Fig. 2 A texture pattern measured on the image can be projected back onto a range of possible 3D interpretations. In the subset depicted, one interpretation corresponds to the image plane (1), one to the veridical solution (2), and one to a more elongated object (3). The texture pattern resulting from the back-projection can be analyzed in terms of how probable it is according to the natural statistics of the environment. If knowledge of these statistics is accurate, then the most likely 3D interpretation is, on average, veridical (solid curve). However, any given

image instance will yield a likelihood function peaked at a non-veridical solution (dotted curve), such deviation being smaller for a reliable texture pattern (a) than an unreliable texture pattern (b). (c) When multiple cues are present on the image, the likelihood functions $P(\vec{c}_i|z)$, where $i = T, S, D, M$ will be peaked at different values (dotted curves) that all deviate from the veridical solution (vertical dotted line). However, the joint likelihood distribution $P(\vec{c}_T, \vec{c}_S, \vec{c}_D, \vec{c}_M|z)$ (solid curve) is more precise and peaked at a value closer to the veridical solution

one implied by interpretation 1, although both are equally plausible from a theoretical standpoint. Similarly, an interpretation of a very deeply curved surface (interpretation 3) is also considered less probable because it would imply an underlying surface texture pattern that is also non-uniform and nonisotropic. In other words, the problem can be cast as determining the most likely 3D interpretation based on the statistical likelihood in the external world of different patterns of texture elements implied by the “unfolded” surface for each interpretation.

If the visual system has accurate knowledge of the statistical distribution of scene parameters and their mappings to retinal images (e.g., Likelihood distributions of texture patterns), then this 3D interpretation will on average correspond to the accurate 3D structure (i.e., it will be unbiased). Note, however, that given the stochastic nature of this postulated process, any given 3D estimate will necessarily deviate from the accurate solution. In Fig. 2a, the solid curve represents the ideal case in which the likelihood distribution is peaked at the accurate 3D solution. In practice, the likelihood function will be peaked at a different value (dotted curves in Fig. 2) because, for example, texture elements on an actual 3D surface will never perfectly match the criteria of homogeneity and isotropy. Over a large number of estimates of similar 3D structure, or multiple trials in a laboratory experiment where the surface textures are generated by the same random process (as for the object in Fig. 1), the distribution of estimates $P(\hat{z}|z)$ will match that of the unbiased likelihood function represented by the solid curve. The variability of trial-by-trial estimates will depend on the specific nature of the surface texture patterns. For example, the image in Fig. 2b (bottom) results from the projection of a surface composed of random points rather than circular dots (Fig. 2a). When back-projected on possible 3D interpretations, the distributions of the resulting “unfolded surfaces” are statistically similar, hence the flat likelihood function. In this case, any given estimate based on the likelihood distribution will deviate substantially from the accurate solution (Fig. 2b, dotted line).

The above analysis leads to a formulation of the problem of cue integration as that of finding the most probable 3D interpretation given multiple image measurements. The debate in the early 1990s was largely about whether this process involved a nonlinear and interactive process dubbed “strong fusion” or a modular and linear combination process dubbed “weak fusion” (see Clark and Yuille 1990). While some early research suggested a nonlinear regularization model (e.g., Bülthoff and Mallot 1988), later work championed the linear model which was developed and validated based on an approach using Bayesian probability theory (Landy et al. 1995; Clark and Yuille 1990).

The Bayesian approach allows a formal definition of the problem of inference of 3D structure from individual image cues in probabilistic terms. Given a set of image measurements $\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n$, the probability of a 3D interpretation $\vec{z}$ is:

$$P(\vec{z}|\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n) = \frac{P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n|\vec{z})P(\vec{z})}{P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n)}$$

$P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n|\vec{z})$ is the likelihood function, which quantifies the probability of making the observed set of image measurements given a specific interpretation $\vec{z}$. $P(\vec{z})$ is the prior probability of the given 3D structure $\vec{z}$ in the environment independent of the image data. $P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n)$ is the probability of making the set of image measurements, which is a constant since it does not depend on the depth map $\vec{z}$. Given this formulation, the problem of finding the Euclidean structure that has generated a given image is to seek $\hat{\vec{z}} = \underset{\vec{z}}{\operatorname{argmax}} P(\vec{z}|\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n)$, defined as the Maximum A Posteriori (MAP) estimate. In absence of knowledge about the a priori probability of 3D structures in the environment, the term $P(\vec{z})$ is non-informative (uniform distribution). In this case, this process reduces to finding the most likely solution $\hat{\vec{z}} = \underset{\vec{z}}{\operatorname{argmax}} P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n|\vec{z})$, defined as Maximum Likelihood Estimate (MLE).

If $\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n$ are conditionally independent, that is, the scene parameters affecting one cue are independent from those affecting another (e.g., the surface material is independent from the motion of the observer or the direction of the illuminant), then the likelihood function of the image can be expressed as the product of the likelihood functions $P(\vec{c}_i|\vec{z})$ associated with each individual cue:

$$P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n|\vec{z}) = P(\vec{c}_1|\vec{z})P(\vec{c}_2|\vec{z}) \dots P(\vec{c}_n|\vec{z})$$

In this simplified version of the problem, finding the most likely 3D interpretation requires that individual modules estimate the actual likelihood functions, which requires a knowledge of the image formation function and the distribution of scene parameters.

If the likelihood functions are Gaussian distributions peaked at $\hat{\vec{z}}_i$ with variance σ_i^2 then the combined likelihood $P(\vec{c}_1, \vec{c}_2, \dots, \vec{c}_n|\vec{z})$ is peaked at $\hat{\vec{z}} = \sum_{i=1}^n w_i \hat{\vec{z}}_i$, where $w_i \propto 1/\sigma_i^2$ and $\sum_{i=1}^n w_i = 1$. Importantly, the combined estimate $\hat{\vec{z}}$ is closer to the accurate (unbiased) solution than each single-cue estimate and the variance of the combined likelihood smaller than the variances of the single-cue likelihoods. Specifically: $1/\sigma_c^2 = \sum_{i=1}^n 1/\sigma_i^2$ (see Fig. 2c).

This equation provides a possible heuristic implementing MLE cue combination: individual MLEs are combined through a weighted average, where each weight is inversely proportional to the variance of the likelihood function. Figure 2c illustrates the Bayesian cue combination regime in graphical form. Each cue measurement of the image leads to an estimate of the underlying depth structure, where each estimate will deviate from the accurate solution due to stochastic noise (even though the underlying likelihood function for each cue estimator is unbiased), but the combined estimate will converge on the accurate solution.

The MLE model has been tested by assuming independent unbiased estimates of texture and disparity, texture and motion, disparity and motion in the visual modality, as well as

integration of 3D information between the sensory modalities (Landy et al. 2011). This method can be generalized to dependent cues (motion and disparity), to non-Gaussian functions with long tails, and to the full Bayesian model when the image data is unreliable (see Landy et al. 2011). Other additional rules to deal with special cases have also been proposed. For example, in the case of cue inconsistency, the robustness rule suggests that when two cues have very different reliabilities, the more precise cue could overrule the less precise one (Landy et al. 2011).

Challenges of the Bayesian Approach

The strength of the Bayesian framework is that it provides a clearly reasoned normative theory of cue integration. However, there are challenges to this framework posed by both theoretical and empirical considerations. From a theoretical perspective, the basic assumption of the Bayesian approach is that the visual system has learnt an accurate mapping between single cues and 3D properties. This requires the internalization of the accurate statistics of the object-to-image mappings, material and spatial properties of objects, etc., through a process of implicit or explicit learning. The internalization of object-to-image mappings presupposes access to error signals, such as arising from incorrect motor executions. While such error signals may be readily available within the graspable region of the agent, it leaves open the question of how information beyond this region is learned, where such feedback is not always available but where vision still delivers useful 3D information.

A further assumption of this model is that it requires on-line instantaneous access to unbiased probability distributions of the mappings (likelihood functions) between a large variety of possible 3D interpretations and 2D patterns. There have been some preliminary proposals on how this might occur (Knill 1998; Landy et al. 2011) and recent advances in machine learning suggest that vast numbers of mappings can indeed be learnt. The challenge, however, is to show whether such learning systems can generalize to

complex domains and be made compatible with the overall algorithmic structure of Bayesian integration.

Other complications for the Bayesian approach come from empirical observations that seem at odds with its basic assumptions and predicted outcomes. First, the main assumption of unbiased estimates from individual cues does not seem to hold in a large number of studied examples in shape from texture (Todd 2004), shape from motion (Domini and Caudek 2003), and shape from disparity (see Howard and Rogers 2002, on depth constancy). Moreover, studies show that even when multiple cues are combined, they lead to systematic biases in perceptual judgments (Bülthoff and Mallot 1988; Todd 2004). Though some of these results may be interpreted in the Bayesian framework by considering the influence of priors (e.g., the “flatness” prior), such priors are invoked in an ad-hoc manner.

A ubiquitous example of a departure from the prediction of the Bayesian approach is the perception of pictorial depth when viewing depictions of 3D scenes rendered on a flat surface (e.g., photographs). Within the Bayesian framework, the information present in this stimulus can be represented by two likelihood functions, one for depth estimates from monocular cues taken together and another from binocular disparity. The latter is sharply peaked at zero depth since disparity specifies a flat surface. The combined likelihood function predicts a depth interpretation (or combined peak) lying somewhere between zero depth and the peak from the monocular information, but biased more toward the zero-depth interpretation, because disparity is usually the most reliable signal. This implies that depth should appear significantly flatter or squashed in the *z*-direction yielding distortions in perceived 3D object and layout compared to viewing the real scene. Removing the disparity cue by closing an eye should shift the peak to that specified by monocular cues causing the perception of significantly increased depth and changes in perceived 3D shape/layout more closely matching the real scene. However, consistent with informal observation, this prediction has been disconfirmed in multiple experimental paradigms (see Vishwanath 2014).

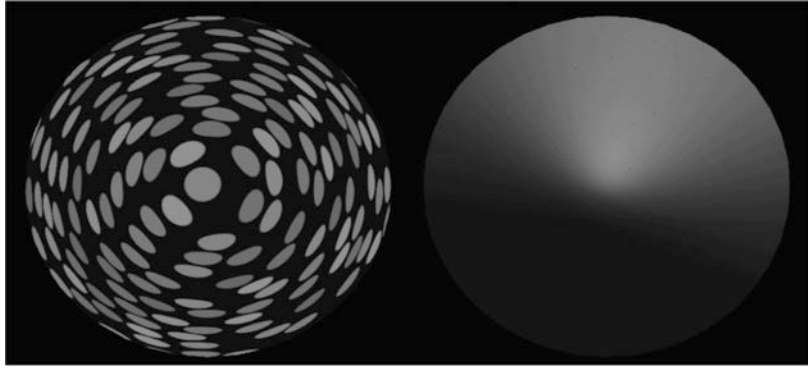
More generally, the Bayesian approach’s assumption that the aim of depth cue integration is to derive a single accurate depth map of the 3D scene does not appear to comport with empirical evidence that suggests multiple depth representations or maps that are invoked under different behavioral conditions (see Loomis et al. 1992; Glennerster et al. 1996). For example, while observers can accurately blind-walk to two pre-viewed markers at different distances (up to a range of at least 20 m), their visual estimates of the depth separations between the same two markers is highly underestimated (Loomis et al. 1992). Another vivid example of the potential for multiple dissociated representations and associated biased estimation is demonstrated in Fig. 3 (Di Luca et al. 2010). Here, it is evident that different cues deliver widely different but stable percepts of curvature, slant and depth even when the underlying 3D structure from which the images are generated is identical. This suggests that different cues may be specialized towards derivation of different and distinct aspects of 3D structure such as 3D curvature or slant, rather than the generic derivation of a single depth map. This could explain specific biases in 3D judgments with specific cues.

A significant challenge to computational approaches that aim to explain the psychology of 3D vision is that they must ultimately be compatible with important aspects of the appearance and phenomenology of 3D objects and space. In the Bayesian approach, the theoretical assumption that depth cue integration derives from a stochastic process underlies the empirical assumption that the variability in subject responses to multiple presentation of a stimulus arises from the random sampling of an underlying likelihood probability distribution (Landy et al. 2011). This implies that perceptual estimates of depth or 3D shape from the very same stimulus (single or multi-cue) with fixed viewing parameters are necessarily different from instance to instance. This does not seem to comport with our phenomenology in most cases of stable 3D structure for a given stimulus.

Computational approaches must also ultimately provide explanations for the compelling differences in the appearance of 3D space under

Computational Models of 3D-Cue Integration,

Fig. 3 Rendering of the same 3D paraboloid when it is specified by only texture or shading information. The textured object appears significantly deeper than the shaded one, and yet the latter looks “pointier” (higher curvedness at the tip) than the former



different conditions; for example, the vivid immersive and tangible depth that is induced under binocular but not monocular viewing of real scenes. Because the Bayesian approach regards all cues (monocular and binocular) to be functionally and computationally equivalent at the stage of integration (Landy et al. 1995) and assumes the derivation of a single 3D representation, it struggles to account for differences in appearance across different viewing and stimulus conditions.

Alternative Models

Alternative models must replicate empirical results that seem to support the Bayesian model predictions, such as the claim that combined-cue estimates are more reliable (less noisy) than individual cue estimates. But they must, in addition, provide a theoretical framework which can account for widespread perceptual biases in a non-ad hoc way, and which can accommodate a more parsimonious and realistic framework for learning object-to-image mappings. They must also be able to point to ways in which other aspects such as multiple representations and features of visual appearance can be accounted for.

An alternative approach to the modelling of cue integration is to drop the notion that it is aimed at deriving a single accurate (unbiased) reconstruction of the scene, but that, instead, the system simply learns mappings between image measures and physical structure through trial and error as a results of repeated interactions with

physical objects. Formally, the visual system learns independent mappings relating image measurements $\vec{c}_i$ to 3D estimates $\vec{z}_i$ such that these estimates are proportional to the 3D property: $\vec{z}_i = f_i(\vec{c}_i) = \lambda_i \vec{z}$. These mappings are learnt in ideal conditions, that is, (1) within the personal space of the agent, where errors arising from unsuccessful motor actions can modify the mapping and (2) within typical ranges of scene parameters such as the motion of the observer, the material properties of objects, and the illuminant. When the ideal conditions for cue i are met, the proportionality factor λ_i takes on a value close to one. For example, λ_i is close to one for disparity processing when the object is at the most frequent grasping distance and for motion when the observer moves at an average speed. In contrast to the Bayesian approach, each module does not provide an unbiased estimate of 3D properties, but an estimate proportional to the 3D property through an unknown proportionality factor λ_i .

If single-cue mappings are assumed to be learnt simultaneously as components of a general mapping, we can define the function $\vec{z}_c = F_c(f_1(\vec{c}_1), f_2(\vec{c}_2), \dots, f_n(\vec{c}_n)) = F_c(\lambda_1 \vec{z}, \lambda_2 \vec{z}, \dots, \lambda_n \vec{z})$ characterizing this mapping based on normative criteria. The criteria are (1) that this function is maximally sensitive to variations in the value of the 3D property $\vec{z}$ relative to variations of the scene parameters λ_i and (2) it is proportional to the 3D property $\vec{z}$. These criteria can be met by finding the function $F_c(\lambda_1 \vec{z}, \lambda_2 \vec{z}, \dots, \lambda_n \vec{z}) = \lambda_c \vec{z}$ maximizing $\frac{\lambda_c}{\sigma_{\lambda_c}}$, where σ_{λ_c} is the standard deviation of λ_c . Note

that the variability of λ_c depends on the variability of the scene parameters, quantified in terms of variances $\sigma_{\lambda_i}^2$. It can be shown that $\frac{\lambda_c}{\sigma_{\lambda_c}}$ is maximized if:

$$\begin{aligned}\hat{\vec{z}} &= \beta \sqrt{\sum_i \frac{f_i(\vec{c}_i)^2}{\sigma_{\lambda_i}^2}} = \beta \sqrt{\sum_i \frac{(\lambda_i \vec{z})^2}{\sigma_{\lambda_i}^2}} \\ &= \lambda_c \vec{z}\end{aligned}$$

where β is a constant. This model of 3D cue integration differs from Bayesian models in two ways. First, since the unknown proportionality factor λ_c is most often *not* equal to 1, the model output is in general biased, except when the visual system is operating within the ideal scene conditions on which the system parameters have been learned. Second, it is a deterministic and not a stochastic model, in that, given a visual input, it provides a single estimate, not a probability distribution. In contrast to the MLE, the variances $\sigma_{\lambda_i}^2$ are not associated with likelihood distributions derived for each specific stimulus estimated in real time, but are fixed parameters slowly learned and modified through interactions with the environment. The alternative approach described here is an adaptation of a model of cue integration termed the Intrinsic Constraint (IC) model (Domini and Caudek 2011, 2013).

Can such a model account for the main achievement of the Bayesian approach, namely, predicting the reduced depth-discrimination thresholds from single-cue stimuli to combined-cue stimuli? According to the Bayesian approach, this reduction is due to the shift in variability in trial-to-trial responses from single cues to combined cues and, particularly, the improvement in reliability when cues are combined. A pervasive technique for estimating the variability of a sensory estimate within the MLE approach is the Two-Interval Forced Choice (2IFC) psychometric procedure, where on a given trial a fixed standard stimulus is compared to a variable comparison stimulus. Using this method, the standard deviation of the underlying single and combined cue likelihoods are estimated as the Just Noticeable Difference (JND) in responses (the depth difference between comparison (z_C) and standard (z_S))

yielding an 84% discrimination rate (see Fig. 4a)). If JND_i are single-cue estimates of the noise standard deviation, then MLE predicts that the combined stimulus should give rise to: $1/JND_c^2 = \sum_{i=1}^n 1/JND_i^2$ as indeed verified in several studies (see Landy et al. 2011)).

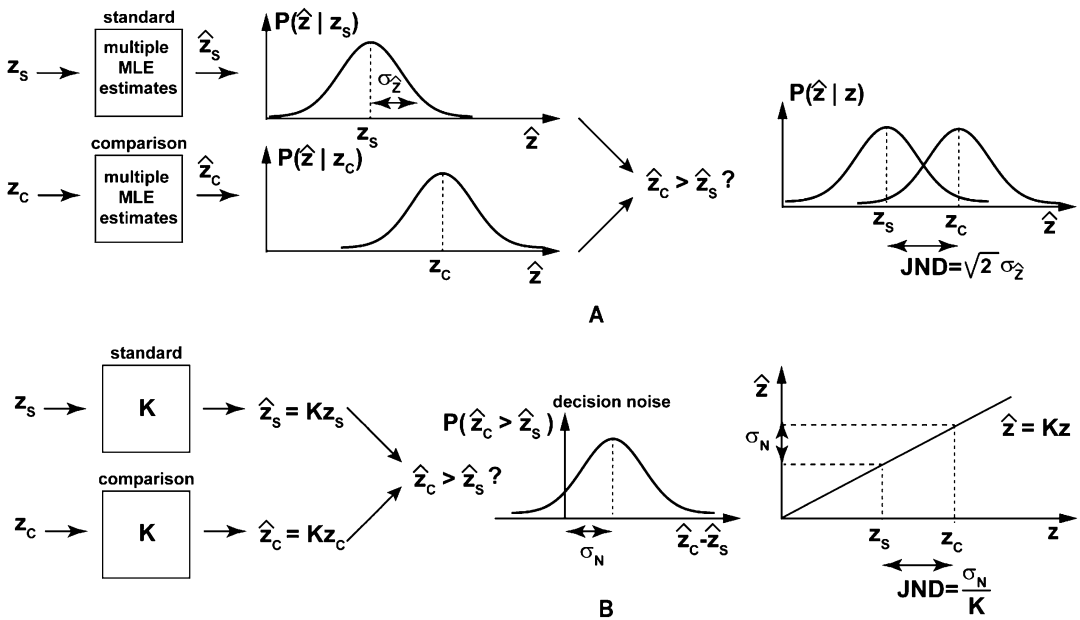
Unlike the MLE approach, where this prediction is modelled to arise from variability in the cue-specific depth estimator from trial to trial, the IC model proposes that variability in a 2IFC task arises from response variability as a result of task demands (e.g., retaining in memory a perceived 3D property for two interval comparisons). This variability is a function of the depth gain relating each cue (or combination thereof) with depth estimates. To understand this, consider again the previous equation. Since β , λ_i , and $\sigma_{\lambda_i}^2$ are unknown parameters, considering the depth between two points (not the entire depth map), the equation can be rewritten as:

$$\hat{z} = \sqrt{\sum_i (k_i z)^2} = Kz$$

where k_i are unknown gains associated with each cue and $K = \sqrt{\sum_i k_i^2}$ is the gain of the combined stimulus. In this case, the difference between the estimated depths of the comparison and standard stimuli need to yield $\Delta \hat{z} = \sigma_N$, where σ_N is the standard deviation of the task-related noise. Since $\Delta \hat{z} = K \Delta z = K(z_C - z_S)$ the JND (defined as $z_C - z_S$) is inversely proportional to the gain: $JND = \frac{\sigma_N}{K}$ (Fig. 4b). Since for single cues $JND_i = \frac{\sigma_N}{k_i}$ and for combined cues $JND_c = \frac{\sigma_N}{\sqrt{\sum_i k_i^2}}$ it follows that: $1/JND_c^2 = \sum_{i=1}^n 1/JND_i^2$, matching the prediction of the Bayesian model.

In general, for conditions where there are only small conflicts between depth cues, this model makes exactly the same predictions as the MWF, that is, weighted cue combination where the weights are inversely proportional to the squared JNDs.

Although this model makes the same predictions as the Bayesian models regarding discrimination thresholds, there are important differences. First, the Bayesian probabilistic approach



Computational Models of 3D-Cue Integration, Fig. 4 (a) The MLE approach predicts that the distribution of responses resulting from repeated viewing of the same 3D object $P(\hat{z}|z)$ matches the likelihood function $P(\vec{c}_i|z)$. If the likelihood function is Gaussian, the Just Noticeable Difference (JND) between a fixed standard stimulus z_s and a comparison stimulus z_c is a measure of the standard deviation of the likelihood function. (b) According to the IC approach, repeated viewing of the

same 3D object leads to a negligible variation of the percept. Instead, the variability in the responses of a comparison task is the result of decision noise that for similar stimulus magnitude has a fixed standard deviation σ_N . Since according to IC model, the 3D estimates $\hat{z}$ are related to the world property z through a gain K that in general is different from unity, the JND is an indirect measure of the gain ($JND = \frac{\sigma_N}{K}$)

assumes the existence of underlying cue likelihood distributions that can be directly inferred from JND measurements for specific stimuli. The alternative deterministic approach does not require the existence of likelihood functions and JND measurements are not claimed to represent noise in the underlying estimates or likelihood distributions, but instead in the psychophysical decision process. Second, it makes different predictions regarding biases in 3D estimates. For example, it predicts that combined stimuli always look deeper than single-cue stimuli, since depth estimates are added through the Pythagorean sum (Domini and Caudek 2011, 2013) so that the gain of the combined stimulus is always larger than the gain of the single-cue stimuli. This property of the model, combined with the new interpretation of JNDs, leads to a second counterintuitive prediction: the perceived depth of two stimuli is the

same when the ratio between the simulated depths matches the ratio between the JNDs of the two stimuli (Domini and Caudek 2013).

Another paradox in depth cue integration (mentioned in the previous section) that can be predicted within the IC framework is the case of pictorial depth perception where the integrated depth estimates in pictorial space appear unaffected by the strong binocular disparity signal specifying zero depth (flatness). Specifically, judged pictorial depth does not change between monocular and binocular viewing (see Vishwanath 2014), contrary to the prediction of the Bayesian (MLE) model. The IC model predicts no perceived depth difference between monocular and binocular viewing of pictorial images since monocularly the disparity gain is zero ($k_d = 0$), and binocularly, disparity specified depth is equal zero ($z_d = 0$), such that the disparity

term in the Pythagorean sum is zero in both cases and does not contribute to the depth interpretation.

The model is also compatible with the observation described previously (Fig. 3) that perceived 3D shape for a given object appears different depending on the underlying cue specifying 3D shape. The IC model can explain these differences in terms of gain. When depth or slant is concerned, the gain of the texture stimulus is much higher than the gain of the shading stimulus, presumably because shading does not encode depth directly, and therefore a larger depth (higher slant of sides) is perceived. On the other hand, the gain for curvature is larger for the shading than the texture cue, since shading encodes curvature directly (Di Luca et al. 2010), and therefore the tip of the shaded stimulus appears pointier.

Future Directions

Looking to future, beyond accurately modeling quantitative judgments of 3D properties, any comprehensive computational theory of cue integration must also be able to provide an operational understanding of the significant differences in visual appearance of three-dimensionality under different combinations of depth cues. For example, human observers report a vivid, tangible, and immersive appearance to objects and the spaces between them viewing real objects binocularly (where depth cues are consistent) compared to viewing a high-resolution pictorial depiction of the same scene (depth-cue conflict), despite the fact that the perception of 3D shape and layout in the two cases are very similar (Vishwanath 2014). One way in which these differences may be accommodated within a computational model of depth-cue integration is to drop the assumption of the Bayesian model that the visual system derives a single 3D map. Instead, depth-cue integration is directed at creating two distinct depth maps: a “relative” depth map that encodes 3D properties only up to a uniform scaling factor and a “scaled”

depth map where 3D properties are scaled in units relevant to the motor plant. Recent evidence suggests that such a model can more effectively explain variations in qualitative appearance as well as how differences in qualitative appearance are correlated with the efficacy of the representations for 3D shape judgments and motor interaction (Vishwanath 2005, 2014).

Summary

The most widely accepted model of depth cue integration claims that the computational goal of depth cue integration is the reconstruction of a single accurate representation of the visual scene. It assumes that estimates from single cues are stochastic samples from underlying probability distributions (likelihood functions) and that the distributions arise from unbiased scene-to-image (cue) mappings. The theoretical challenges to this model remain as to how vast numbers of stimulus-specific unbiased likelihood mappings are learned and accessed and how probabilistic variability in depth estimates can be reconciled with the stable perception of 3D objects and layout. The empirical challenges are in explaining the evidence showing a ubiquity of biases in 3D judgments, evidence of multiple distinct 3D representations, and the inability of the Maximum Likelihood approach to address differences in visual appearance under different cue combination regimes. Alternative approaches that rely on a deterministic multi-representation cue integration regime may provide clues to how these challenges can be met.

Cross-References

- [3D Shape Perception, Models of](#)
- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Cognition, Bayesian Models of](#)
- [Perception, Bayesian Models of](#)
- [Stereo Vision, Models of](#)

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Computational Models of Auditory Stream Segregation

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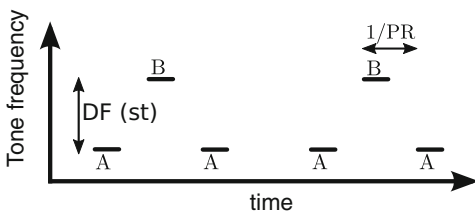
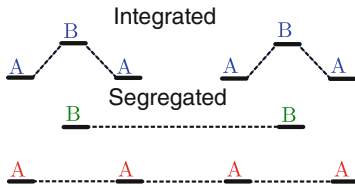
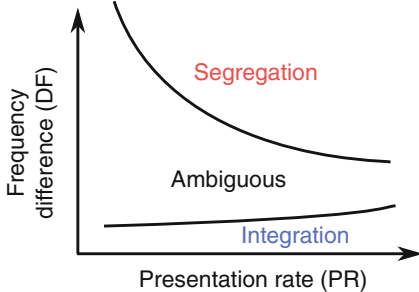
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Definition

Auditory stream segregation is a fundamental process that allows us to segregate and focus on distinct sound streams (e.g., voices) in a dynamic noisy environment. Stream segregation has been widely studied with the auditory streaming paradigm, a relatively idealized stimulus for which two sequences of pure tones can be segregated in different streams. Our understanding – still far from complete – of this process is informed by a wealth of behavioral experiments, electrophysiology, brain imaging, and theoretical modelling. This review will highlight modelling efforts that have advanced our understanding of this important dynamical process.

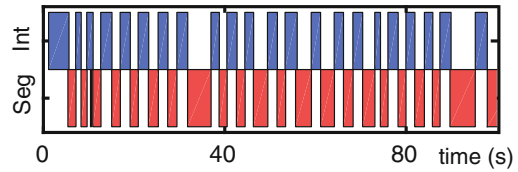
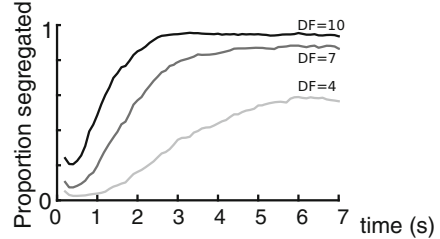
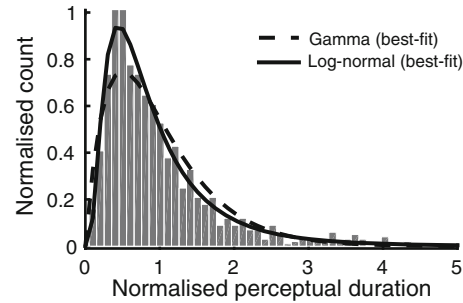
Detailed Description

Auditory scene analysis involves segregating a complex scene into objects or streams (recent reviews: Bendixen (2014) and Snyder and Elhilali (2017)). A valued paradigm involves segregating two interleaved sequences of A tones and B tones repeating in an ABA_n pattern and separable by a perceived difference in pure tone frequency and timing (auditory streaming, Fig. 1a) (van Noorden 1975). The sequence can be perceived as integrated into one or as segregated into two streams (Fig. 1b). The initial percept is typically integration, but as time proceeds (over ~10 s), a

A Auditory streaming: ABA_sequence**B** Perceptual interpretations (percepts)**C** van Noorden organisation (redrawn; van Noorden 1975)

Computational Models of Auditory Stream Segregation, Fig. 1 Behavioral characteristics of auditory streaming experiments. (a) Stimulus paradigm where low-frequency A tones, high B tones (separated by the difference in tone frequency DF), and silences () each of 100 ms repeat in an ABA_triplet pattern with a presentation rate PR = 10 Hz. (b) Stimulus is perceived as either one integrated stream ABA_ABA... or two segregated streams A_A_A_A... and _B_B_B_B... (c) Schematic diagram of the perceptual regions in terms of PR and DF, redrawn after van Noorden (1975). Predominantly integration for small DF and segregation for large DF (with dependence on PR), while either is possible (ambiguous) at intermediate ranges. (d) Perceptual reports for 90 s of a single trial. Initial percept is integrated (bias to integration)

perceptual transition to segregation becomes more likely, a phenomenon called “buildup” (Anstis and Saida 1985). Buildup occurs more rapidly with a large difference in tone frequency (DF) between A and B (Fig. 1e) and at faster presentation rates. The bias in perception toward

D Percept reports (human data, Rankin et al 2015)**E** Trial-averaged build-up function (model, Rankin et al 2017)**F** Distribution of perceptual durations (human data N=15, Rankin et al 2015)

followed by a switch to segregated within first ~10 s (buildup phase). Subsequently perception alternates every ~2–5 s between integrated and segregated (bistability) if DF is not too large or small (Data from Rankin et al. (2015)). (e) Buildup function with initial bias to integration (proportion of segregation is low initially). Trial averaging across abrupt switches results in a smooth buildup function. Probability of segregation builds up over time (faster at large DF). Converges to the proportion of segregation in post-buildup alternations (Panel reproduced from Rankin et al. (2017)). (f) Stochasticity is characterized by a log-normal distribution of perceptual durations (data normalized by the mean duration for each individual to account for intersubject variability) (Panel reproduced from Rankin et al. (2015))

integration at low DF, segregation at high DF, and ambiguity at intermediate values was characterized in the so-called van Noorden diagram (Fig. 1c). The first perceptual switch, typically from integrated to segregated, is followed by persistent alternations between the two interpretations

(auditory bistability) (Fig. 1d). Pressnitzer and Hupé (2006) showed that auditory bistability shares the characteristics of perceptual bistability: exclusivity (one percept at a time), inevitability (of switches), and randomness (of percept durations) (Leopold and Logothetis 1999). The stochasticity of switching times is characterized by a log-normal distribution (Fig. 1f). These characteristics hold for a broad class of bistable visual stimuli including binocular rivalry (Leopold and Logothetis 1999), ambiguous figures (Long and Toppino 2004), moving plaids (Hupé and Rubin 2003), and gratings (Meso et al. 2016).

Electrophysiology has revealed the neural activity underlying auditory streaming. Trial-averaged recordings with short stimulus presentations (< 20 s) show a dependence on DF and PR in the primary auditory cortex (A1) in awake monkeys (single-electrode recordings) (Fishman et al. 2001, 2004; Micheyl et al. 2005) and in anesthetized rodents (voltage-sensitive dye imaging) (Farley and Noreña 2015). In a data-driven statistical model, A1 responses were interpreted using neurometric functions that mimic the time course of buildup in Micheyl et al. (2005); Pressnitzer et al. (2008); see (Deike et al. 2012) for a discussion of the computation of buildup functions. Recently, imaging approaches have shed light on the network of brain areas involved in streaming with fMRI (Kashino and Kondo 2012), the effects of attention on neural representations of streams with MEG (Billig et al. 2018) or with magnetic resonance spectroscopy (Kondo et al. 2018), and the role of oscillations in encoding streams with EEG (Costa-Faidella et al. 2017) (comprehensive review: Snyder and Elhilali (2017)).

This review explores the various modelling approaches used to study auditory streaming, from signal processing and temporal coherence to neuronal competition and statistical models.

Signal Processing and Temporal Coherence

Various models have been proposed that exploit multiple stages of processing with filter banks and

nonlinear transformations to model auditory stream segregation (e.g., Beauvois and Meddis (1991), McCabe and Denham (1996), Elhilali and Shamma (2008); review: (Szabó et al. 2016)). While the different stages in these models are often mapped to different stages of processing in the auditory pathway, the computations performed do not have a firm link to neural computations. A central focus of these studies has been to reproduce the dependence (van Noorden 1975) of perceptual bias (toward integration or segregation) on DF and presentation rate (Elhilali and Shamma 2008), the dynamics of buildup (McCabe and Denham 1996), or both (Beauvois and Meddis 1991). These frameworks have been extended to incorporate a representation of temporal coherence (the common onset of auditory events) (Elhilali et al. 2009; Ma 2011), which is a strong cue for the integration of streams. Several of these frameworks have been used to explore auditory scene analysis for stimuli that are significantly more complicated than the example of ABA_triplets shown in Fig. 1a. For example, the crossing-bouncing illusion reported in van Noorden (1975) (rising and falling sequences of tones are perceived as crossing over or bouncing) has been explored with models (Elhilali and Shamma 2008; McCabe and Denham 1996). Recently the temporal coherence framework was used to explore the segregation of complex sound sources, including speech (Krishnan et al. 2014).

Neuronal Competition

Competition-based models proposed for visual bistability (e.g., binocular rivalry) incorporate mutual inhibition, slow adaptation, and noise (Laing and Chow 2002). In noisy competition-based dynamics, a slow adaptation process sets durations and produces switch statistics (Shpiro et al. 2009). The phenomenological model presented in Mill et al. (2013) treats buildup and subsequent bistability separately. The pattern discovery stage addresses algorithmically the formation of the different perceptual patterns during buildup, and the initial bias to integration

emerges from this process (albeit without a link to neural computations). Abstracted units assigned to each discovered perceptual pattern enter into competition through the mechanisms described above.

Our recent study introduced the first neuromechanistic competition model of auditory bistability (Rankin et al. 2015), a departure from percept-based rivalry models (Laing and Chow 2002; Shpiro et al. 2009). Dynamic inputs are linked to sensory features by mimicking the neuronal responses from electrophysiological recordings (awake macaque, A1) (Micheyl et al. 2005). Based on a conceptual description proposed in Fishman et al. (2001), the model considers competition downstream of A1. It captures the switching statistics of bistable auditory perception for long stimulus presentations and their dependence on DF (Rankin et al. 2015). A governing principal for asymmetric input manipulations in binocular rivalry (Levelt's proposition II (Brascamp et al. 2015; Levelt 1968); generalized for several visual modalities in Moreno-Bote et al. (2010)) was shown to hold for auditory streaming. It was shown in new experiments that as DF is varied, the durations of the stronger percept (dominant for a larger proportion of time) are affected more than the durations of the weaker percept, as predicted by the model.

An extension of the work accounts for early bias to integration and buildup (Fig. 1e) (Rankin et al. 2017). Our model demonstrates that broader tonotopic responses in A1 before rapid adaptation on a timescale of 500 ms biases toward integration, while the slower timescale of buildup (~ 10 s) emerges from competition downstream. It is the first treatment – through a direct link to observed neurophysiological responses – to explain both the initial bias for integration and the apparent disparity between adaptation timescales. The model can also account for new findings that while stimulus perturbations such as pauses are known to reset streaming to the integrated percept (Anstis and Saida 1985; Rogers and Bregman 1993), unexpected additional tones can promote the segregation of streams.

Other Neuronal Frameworks

In a modelling competition across a tonotopically organized feature space, Almonte et al. (Almonte et al. 2005) reproduced the van Noorden organization of perceptual bias. An advantage of this framework was the possibility to consider time-varying stimuli, which allowed for the crossing-bouncing illusion to be studied. Such a framework would be a good candidate to explore the time-varying stimuli used in van Noorden's experiments to determine the boundaries in terms of PR and DF for perceptual bias. Wang and Chang (2008) used an oscillator network and reproduced the van Noorden organization, but not the dynamics of buildup. The relatively abstract model includes a 2D array of oscillators across tone frequency and time (delay line) dimensions. This structure with significant redundancy is unlikely to be found in auditory brain regions.

Statistical and Bayesian Frameworks

The statistical properties of percept durations for auditory streaming share features across a range of bistable perceptual phenomena (Cao et al. 2016; Pressnitzer and Hupé 2006). Recent studies have shown that the distribution of perceptual durations is better described by a log-normal, rather than gamma (Pressnitzer and Hupé 2006), distribution (Rankin et al. 2015; Denham et al. 2018) (Fig. 1f). Two models based on probabilistic switching schemes (Barniv and Nelken 2015; Steele et al. 2015) can reproduce the characteristic distributions of perceptual durations. The statistical model of Steele et al. (2015), based on an alternating renewal process, reproduces the main features of buildup and alternations, but not observed switch time correlations. A dynamic Bayesian model for alternations using an evidence accumulation process (Barniv and Nelken 2015) succeeds in reproducing correlations. In these models the initial bias to integration is set by specifying a priori initial conditions (Barniv and Nelken 2015; Steele et al. 2015). A Bayesian inference framework has also been used to study streaming, focusing on the PR and DF dependence of

perceptual bias (Yates et al. 2017) and the crossing-bouncing illusion (Cusimano et al. 2018). A scaling property revealed in Cao et al. (2016) of the distribution of perceptual durations (constant ratio of the coefficient of variation and skewness) applies across a wide range of perceptually bistable phenomena, including auditory streaming. An abstracted statistical process can account for this property based on a finite birth-death process accumulating toward a threshold; however, this has yet to be captured in a model specific to auditory streaming (or any other bistable stimulus).

Discussion

Many of the modelling studies described here were successful in reproducing the characteristics of perceptual bias described by the van Noorden organization (Fig. 1C) (Almonte et al. 2005; Elhilali and Shamma 2008; Wang and Chang 2008; Yates et al. 2017). However, comparisons with van Noorden are often made without taking into account three important aspects of the original experiments: (1) time-varying stimuli, (2) attentional effects (e.g., instruction to “hold integration”), and (3) the termination of trials at the first perceptual switch. While some models account for the dynamics of buildup, e.g., Beauvois and Meddis (1991) and McCabe and Denham (1996), they ignore the fact that buildup accumulates after 5–10 s toward the steady-state probability of segregation for bistable alternations (Fig. 1d and e). More recently, models have focused on understanding these bistable alternations (Rankin et al. 2015; Steele et al. 2015) and, in some cases, account for buildup (Barniv and Nelken 2015; Mill et al. 2013; Rankin et al. 2017). While (Rankin et al. 2015, 2017) successfully bridged between available neurophysiological data from macaque A1 (Fishman et al. 2001; Micheyl et al. 2005) and behavior in humans (Pressnitzer and Hupé 2006), future insights are likely to be informed by a closer link to imaging work in humans (say, related to the effects of attention (Billig et al. 2018; Costa-Faidella et al. 2017; Kondo et al. 2018)), as yet unexplored in

models). For example, the importance of attention for binocular rivalry has been explored with imaging (EEG) (Zhang et al. 2011) and successfully modelled in a divisive normalization framework incorporating neuronal competition mechanisms (Li et al. 2017). Elsewhere, a recent model of beat perception (Large et al. 2015) is geared toward comparisons with and informative for imaging experiments (Tal et al. 2017). The next generation of models should make predictions testable with imaging experiments and focus on complex, dynamic stimuli approaching real-world situations.

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Computational Models of Deep Brain Stimulation (DBS)

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Definition

DBS is a procedure in which a device is implanted within the brain and used to deliver pulses of electrical activity to the surrounding tissue. While parts of the device may extend elsewhere, the electrical stimulation is delivered in the interior of the brain, rather than outside of it or on its surface. Computational models of DBS are systems of equations representing some aspects of the DBS process, such as the electric field generated by a certain form of DBS or the predicted voltage responses of neurons impacted by this field, for which a computer can be used to obtain high accuracy approximate solutions. These predicted neural responses to DBS can then be introduced into network models of brain circuits, enabling theoretical investigation of the effects of DBS on brain activity.

Detailed Description

While DBS is being used or tested for use in treating a variety of conditions, computational models of DBS to date have primarily focused on DBS for Parkinson's disease (PD) and related states (collectively known as parkinsonism). Therefore, this review will focus on DBS models related to parkinsonism.

DBS for Parkinsonism

In DBS, a set of electrodes is surgically implanted into a brain area selected based on patient symptoms. The electrodes are linked to a subcutaneous

pulse generator outside of the brain, which causes electrical stimulation to be delivered through the electrodes with a prescribed frequency, amplitude, and timing. These stimulation parameters can be tuned externally to try to optimize the therapeutic results of DBS.

The mechanisms underlying the therapeutic efficacy of chronic high frequency (~100 Hz) brain stimulation remain mysterious and controversial. Recent research efforts have focused on the concept that disorders treated with DBS are fundamentally disorders of a specific brain network, as opposed to a specific neuron type, ion channel, or molecule (McIntyre and Hahn 2010). The basic working hypothesis is that DBS interacts with the diseased network to eliminate or subdue the underlying pathological neural activity (Rubin et al. 2012). Computational models have played an important role in the evolution of this hypothesis, suggesting that changes in the underlying dynamics of the stimulated brain networks may represent the core mechanisms of DBS and that those basic dynamical changes can be achieved via activation, inhibition, or lesion.

Computational Models of the Electric Field Associated with DBS for Parkinsonism

Computational modeling of DBS has established itself as a useful tool for investigating therapeutic mechanisms and designing techniques to optimize clinical application of DBS technology (McIntyre et al. 2007). A prime example comes from patient-specific DBS models, and the corresponding electric field generated by human DBS electrodes. The last decade has seen these models evolve from point source electrodes in an infinite homogeneous medium, to clinical electrodes in the human brain, to detailed representations of the electrode-tissue interface (Chaturvedi et al. 2010). The electric field predictions from modern DBS models have been validated against experimental measurements in the brains of nonhuman primates (Miocinovic et al. 2009) and electrophysiological measurements in human patients (Chaturvedi et al. 2010).

Patient-specific DBS models have had their greatest clinical impact in analysis of the target of the stimulation. In the case of subthalamic

nucleus (STN) DBS for PD, patient-specific models have demonstrated that activation of the white matter dorsal to the STN is most associated with therapeutic benefit (Maks et al. 2009; Butson et al. 2011). Further, when this region is explicitly targeted via surgical electrode placement (Plaha et al. 2006) or stimulation parameter selection (Frankemolle et al. 2010), outcomes improve relative to stimulation concentrated on the STN itself.

More recently, patient-specific DBS models have concentrated on the integration of connectomic data (models of structural or functional connectivity) into their stimulation analyses (Horn 2019). These models have highlighted to role of directly stimulating cortical connections to the deep brain surgical targets in the generation of therapeutic effects (Akram et al. 2017; Gunalan et al. 2017).

Computational Models Focusing on the Network Response to DBS for Parkinsonism

There are several different characteristics that can be used to classify those existing models that focus on the network response to DBS for parkinsonism. Computational models are generally motivated by an *underlying hypothesis for the central mechanism of DBS efficacy*, although such hypotheses need not be mutually exclusive. Depending on which hypothesis is under study, models may vary in their *mathematical formulations*, *level of abstraction of model neurons*, *selection of brain structures modeled*, and *representation of DBS inputs*.

For example, a common general hypothesis is that DBS works by eliminating pathological synchrony in basal ganglia structures. This idea can be explored using model equations representing many individual neurons or using models in which variables correspond to entire populations of neurons (e.g., one equation for each basal ganglia area). In the former approach, which allows the timing of individual neuron spikes to be considered, neurons have been represented as either abstract oscillators or as more biophysical units. In the latter approach, model equations can track phase density, with synchronization corresponding to a peaked phase distribution

(Tass 2002). Alternatively, the population approach can be based on firing rate or some other measure of net activity, which only allows for the analysis of synchrony between populations, not within a population. Similarly, both of these frameworks can be utilized to consider alternative hypotheses not emphasizing synchrony. They have been used, for example, to consider DBS-induced changes in burstiness (Rubin and Terman 2004; Modolo et al. 2008; Hahn and McIntyre 2010) or firing rates (Moroney et al. 2008; Humphries and Gurney 2012) within various basal ganglia nuclei. In particular, models have been used to consider the specific hypothesis that DBS can replace pathologically bursty and irregular firing with more regularized outputs. Some of these models include additional brain structures such as thalamic nuclei downstream from the basal ganglia, so that predictions can be made about the impact that altered basal ganglia firing patterns have on activity outside of basal ganglia (Rubin and Terman 2004), have considered effects of DBS applied directly to thalamic targets (Grill et al. 2004), or have included some form of cortical inputs (Hahn and McIntyre 2010). Finally, neurons need not be modeled explicitly at all; instead, they can be represented as stochastic processes yielding discrete spiking events, which may be useful for considering hypotheses about differences in correlations, information transfer, or signal propagation with and without DBS (Reitsma et al. 2011; Rosenbaum et al. 2014). One interesting idea is that DBS may eliminate pathological structure in basal ganglia outputs by inducing stochastic short-term depression (due to synaptic dynamics and axon failure), and this has been modeled using stochastic processes as well as single-compartment biophysical neuron models (Rosenbaum et al. 2014).

DBS inputs themselves are represented simply as applied currents within many computational models. These currents may be delivered at multiple sites, with various timings, or may be derived from computationally generated feedback signals (Hauptmann et al. 2005). Alternatively, a more involved field model of DBS may be coupled to a detailed neuronal model for consideration of

spatial effects (Yousif et al. 2012). Some computational modeling studies have circumvented the need for an explicit representation of DBS by incorporating experimentally recorded data from basal ganglia structures, collected with and without DBS, as inputs into a computational model (Guo et al. 2008; Dorval et al. 2008; Meijer et al. 2011; Cleary et al. 2013). Even without experimental recordings or modeling of DBS currents, DBS effects may also be included in a model through a phase resetting curve, which is a mathematical representation of how neurons respond to general inputs (Wilson et al. 2011), or through altered probability of spike generation in stochastic process models of neuronal circuits (Rosenbaum et al. 2014).

Cross-References

- ▶ [Computational Model-Based Development of Novel Stimulation Algorithms](#)
- ▶ [Computational Models Supporting Parameter Finding for Deep Brain Stimulation](#)
- ▶ [Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation](#)
- ▶ [Deep Brain Stimulation \(Models, Theory, Techniques\): Overview](#)
- ▶ [Parkinson's Disease: Deep Brain Stimulation](#)
- ▶ [Spinal Stimulation for Parkinson Treatment](#)

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Computational Models of Mammalian Respiratory CPG

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Definition

Rhythmic breathing movements in mammals are produced by a central pattern generator (CPG), consisting of specialized neuronal networks located in the brainstem that are capable of endogenously producing patterned rhythmic activity. This activity emerges from the intrinsic biophysical properties and synaptic interconnections of spatially distributed neuron populations within the pontine–medullary circuits comprising the CPG. These circuits are embedded in a larger respiratory neural control system engaging various central nervous system (CNS) and peripheral afferent inputs that regulate the neural activity patterns including the oscillation period and amplitude of the output rhythmic motor activity to adjust it to the internal and/or external environment for sensorimotor integration and physiological homeostasis of O₂ and CO₂ in the body. Computational models of the brainstem respiratory CPG that incorporate various levels of biological and mathematical detail have been in development for several decades with the objective of explaining the dynamical operation of the CPG neurons and circuits, particularly to

delineate mechanisms of respiratory rhythm and pattern generation. Recent data-driven models that have explored functional architecture of the CPG circuits and advanced understanding of these mechanisms are reviewed.

Detailed Description

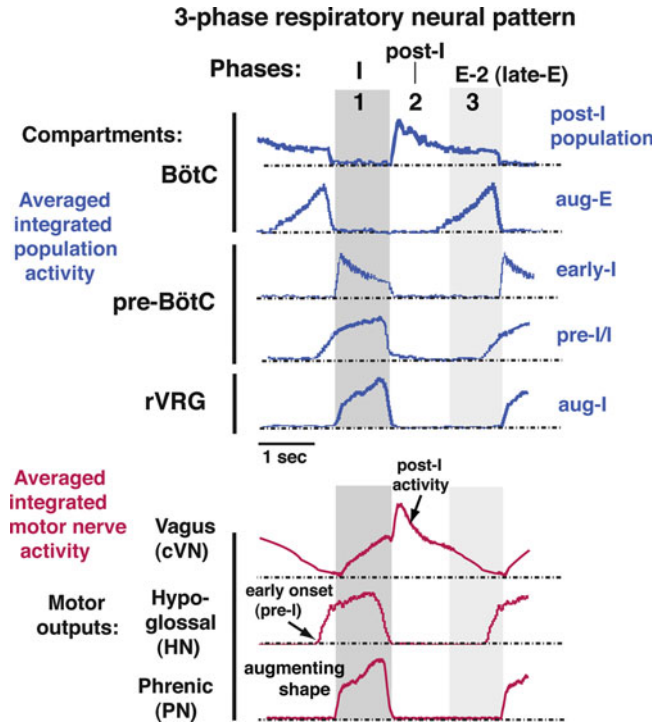
Respiratory Motor Patterns and CPG Activity: Neurophysiology

A major objective of the models described in this entry is to reproduce experimental data and provide mechanistic explanations for the activity patterns and operation of identified or postulated key components of the brainstem respiratory CPG and associated motor output patterns during the normal respiratory cycle. The basic activity patterns of brainstem–spinal neurons and efferent motor behaviors of the CPG to be explained have been established experimentally from electrophysiological recording studies (see Lindsey et al. 2012 for a comprehensive review). Essential neurophysiological features as they are presently understood that need to be taken into account in computational modeling analyses are summarized below.

During normal breathing in mammals, the rhythmic motor pattern consists of three neural activity epochs or “phases”: inspiration (I, phase 1), post-inspiration (post-I, phase 2), and the later second stage (called E-2) of expiration constituting phase 3 of the respiratory cycle (Richter and Smith 2014) (Fig. 1). This three-phase motor pattern is phylogenetically conserved in all mammalian species from rodents to humans and reflects the coordinated activity of numerous populations of brainstem and spinal motoneurons that are driven and controlled by the output of the brainstem CPG circuits. At the brainstem level, the cranial motoneurons control musculature of the upper airways (e.g., hypoglossal, glossopharyngeal, laryngeal muscles), and motoneurons at the spinal cord level innervate muscles of the respiratory pump (diaphragm, thoracic, abdominal musculature). This neural pattern is also reflected in the activity profiles of the antecedent interneuron populations (Fig. 1) in specific

anatomically defined regions of the medulla oblongata and pons generating the three-phasic rhythmic drive. That is, there are distinct populations of neurons that are predominantly active with some temporal dispersion during the inspiratory phase or during the post-I or later E-2 phase of expiration. This has been determined experimentally by extracellular recording and mapping of single neuron or neuron population activity, including with large arrays of microelectrodes enabling simultaneous recordings at multiple brainstem sites for temporal correlation of activity, allowing inferences about network connectivity to guide computational analyses of circuit interactions (Lindsey et al. 2012). There have also been numerous intracellular recording studies that reveal the spiking activity and underlying synaptic inputs or biophysical properties of the different neuron types, which are critical for conductance-based modeling analyses of neuronal circuit activity and neuronal interactions (Richter and Smith 2014).

Each phase of the respiratory cycle is functionally and behaviorally distinct. During inspiration, medullary inspiratory premotoneurons (i.e., bulbospinal neurons with direct monosynaptic connections to spinal motoneurons, see Fig. 2) drive the activity of phrenic motoneurons that control contraction of the diaphragm via the phrenic nerve (PN) to inflate the lungs. Medullary inspiratory neurons also drive cranial hypoglossal motoneurons (Fig. 2) to activate via hypoglossal nerves (HN) tongue protrussor muscles to prevent obstruction of the oropharyngeal airway during inspiration. Other cranial motoneurons with projecting axons in branches of the vagus nerve innervate laryngeal muscles that control abduction of the glottis and vocal cords to maintain upper airway patency. The post-I phase of motor output is evident in recordings from the recurrent laryngeal or central vagus nerves (cVN) (e.g., Richter and Smith 2014) and is essential for controlling musculature regulating the caliber of the upper airway during expiration as well as integrating breathing with several other orofacial motor behaviors including vocalization and swallowing. During this phase the larynx is initially partially adducted (closed), which stalls airflow to provide



Computational Models of Mammalian Respiratory CPG, Fig. 1 Patterns of neuronal population activity from extracellular recordings in the medulla and motor output patterns recorded from spinal (PN) and cranial nerves (central vagus, cVN, and hypoglossal, HN) during the three-phase respiratory cycle. Neuronal population recordings have been obtained in key structural–functional compartments (BötC, pre-BötC, and rVRG, refer to Fig. 2). Recordings were obtained from juvenile rat brainstem–spinal cord preparations and are integrated and averaged over multiple cycles to show relative timing and activity profiles during the three-phase cycle. The active

inspiratory (I) and expiratory (E) neurons are typically classified with nomenclature based on profiles of their firing patterns (e.g., decrementing, augmenting spiking frequency) and their predominant activity phase. As depicted, pre-I/I neurons in the pre-BötC start firing before and continue into inspiration; early-I neurons have peak spiking in early-I followed by a decrementing pattern; rVRG aug-I neurons have an augmenting (also called ramping) firing pattern; post-I neurons, a decrementing firing pattern; and aug-E neurons, an augmenting firing pattern during E-2 (After Smith et al. 2009)

more time for gas exchange, and then slowly abducted (opened) to allow exhalation. In the premotor network producing this activity (Fig. 1), this phase is also critical for dynamically off-switching inspiration in the core microcircuits. During the E-2 phase of expiration, the active medullary expiratory bulbospinal neurons drive spinal thoracic and lumbar motoneurons (Fig. 1) to produce low levels of intercostal and abdominal muscle activity during normal (quiet) breathing. At higher levels of respiratory motor activity, such as when levels of carbon dioxide (CO_2) are elevated or levels of oxygen (O_2) are reduced, forced or active exhalation occurs during this phase,

which engages new circuit elements (Abdala et al. 2009; Rubin et al. 2011).

CPG Network Architecture and Circuit Components

Respiratory CPG circuits like all other GPG (and CNS) circuits are constructed from core sets of interacting excitatory (glutamatergic) and inhibitory (glycinergic and/or GABAergic) populations of interneurons whose activity is transmitted via mono- and polysynaptic circuits to motoneurons. The critical populations and their circuit



transmission circuits in the rVRG. BötC excitatory post-I neurons generate the post-I phase activity transmitted to cranial vagal motoneurons (I/E Mns, *brown*), which also receive inspiratory inputs from excitatory pre-BötC and rVRG neurons. The pre-I/I excitatory neurons of the pre-BötC are the excitatory “kernel” circuit neurons that project via premotor circuits to cranial motoneurons including hypoglossal and vagal motoneurons (*brown*) and to rVRG excitatory aug-I bulbospinal premotor neurons with projections to spinal cord inspiratory phrenic motoneurons (IMn, *brown*). Excitatory bulbospinal aug-E expiratory neurons of cVRG and driven by BötC aug-E excitatory neurons project to thoracic intercostal (IC) and abdominal (Abd) spinal expiratory motoneurons (EMns). Circuit neurons within these compartments receive tonic and in some cases phasic/rhythmic excitatory drive from the pontine, RTN/pFRG, and raphé compartments, where the latter two drives are in part chemosensory signals dependent on the blood/brain CO₂ level. Additional descriptions of the roles of the different populations of excitatory and inhibitory respiratory neurons are in the main text (After Smith et al. 2009)

populations to produce appropriately coordinated circuit activity and motor output patterns.

A central hypothesis in the respiratory neurobiology field is that these key populations of interneurons, which constitute the neural machinery for generating the three phases of the respiratory cycle, are bilaterally distributed in three anatomically defined and functionally distinct

compartments in the ventrolateral medulla (Fig. 2): the so-called Bötzing complex (BötC), pre-Bötzing complex (pre-BötC), and rostral ventral respiratory group (rVRG), which collectively are components of a more extensive rostro-caudally distributed “ventral respiratory column” (VRC) on each side of the brainstem (Smith et al. 2013; Fig. 2). Electrophysiological recording studies have shown that major populations of inspiratory neurons are concentrated in the pre-BötC (pre-I/I and early-I neurons, see Fig. 1 for nomenclature) and rVRG (aug-I neurons), while populations of expiratory neurons are in the BötC (post-I neurons, aug-E neurons active during the E-2 phase) and more caudally in the cVRG (aug-E). This spatial segregation of neuron types, although not exclusive, suggests a specific compartmental organization of mechanisms producing inspiratory and expiratory activity and that these populations form microcircuits that interact within and between these compartments. These microcircuits, depicted in Figs. 2 and 3, are postulated to represent key neural building blocks of the CPG network (Smith et al. 2007, 2013).

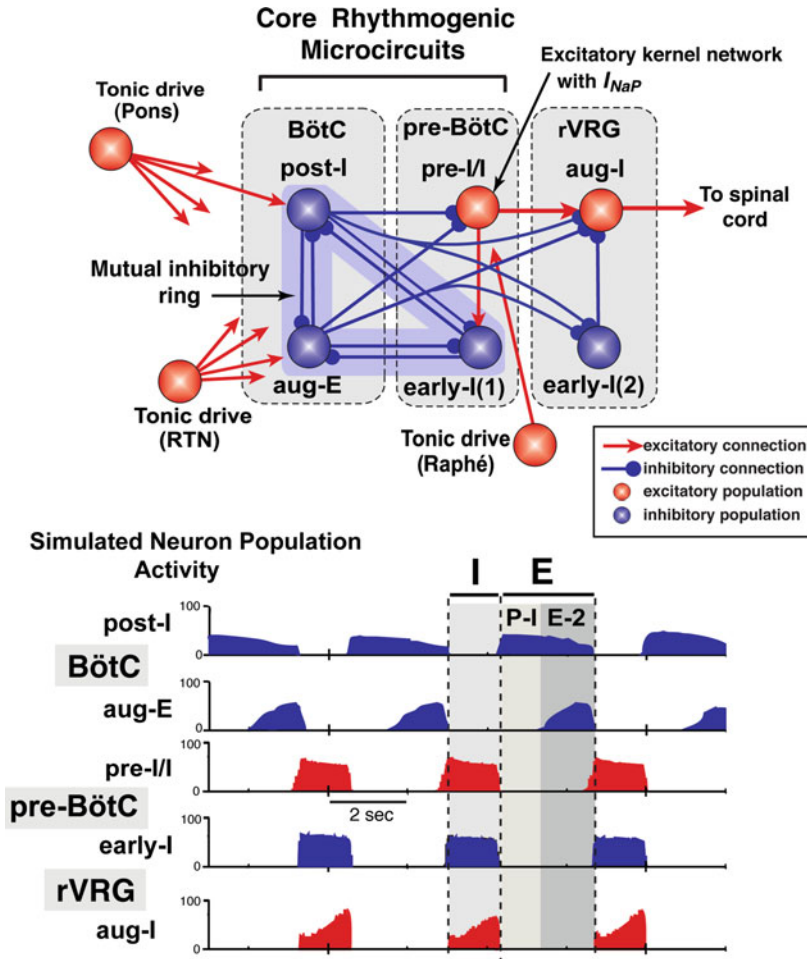
Experimental results also suggest that (1) the BötC contains neuronal machinery essential for generating expiratory activity, including populations of inhibitory neurons active during the post-I and E-2 expiratory phases; (2) the pre-BötC, a critical CPG component, has excitatory circuits that constitute the kernel inspiratory oscillator, these neurons have local intrinsic mechanisms for inspiratory rhythm generation, and there are also pre-BötC inhibitory interneurons driven locally by the excitatory neurons and are thus also active during inspiration; (3) the rVRG contains the main population of excitatory premotor bulbospinal inspiratory neurons that are driven by pre-BötC rhythmogenic excitatory neurons and project to phrenic motoneurons as well as cranial motoneurons so that activity of this population produces phrenic nerve (PN) inspiratory motor output and the inspiratory activity of cranial nerves (e.g., the laryngeal nerve innervating the upper airway); (4) generation of the normal three-phase respiratory pattern requires pontine circuits in the rostral brainstem, specifically excitatory

inputs to more caudal compartments especially the BötC to control generation of the post-I activity phase; and (5) other excitatory inputs such as from the retrotrapezoid nucleus or parafacial respiratory group (RTN/pFRG) in the more rostral medulla, which is a major source of chemosensory (CO_2/pH and O_2 -related) afferent input for homeostatic respiratory regulation, adaptively adjust the core CPG circuit activity in response to various metabolic demands. Other brainstem sources of afferent input are from the serotonergic raphé nuclei (also with CO_2 chemosensory properties, Fig. 2) and the nuclei of the tractus solitarius (NTS), which also project to the RTN and pons conveying mechanosensory signals and input from peripheral chemoreceptors (sensing O_2) (Smith et al. 2013).

Based on this spatial and functional organization, the current neurophysiological concept is that the respiratory rhythm and normal three-phase inspiratory–expiratory pattern emerge from circuit-based dynamic interactions between (1) the inhibitory neuronal populations in the BötC that are active during expiration, (2) the inhibitory neuron populations in the pre-BötC active during inspiration, and (3) the excitatory populations in the pre-BötC and rVRG that generate inspiration. The operation of this circuitry is controlled in part by other compartmentalized network components located in the more rostral medulla and pons that provide neural input “drives,” regulating dynamic behavior of the core CPG circuitry. The compartmental network organization is thought to be a basic design principle allowing flexible multilevel control of different circuit components for regulation of inspiratory and expiratory phase activity (Smith et al. 2013), giving rise to a repertoire of respiratory motor behaviors. The recent models described below attempt to computationally represent these processes.

Recent Computational Models: Overview

A basic problem in understanding the operation of the postulated core CPG circuits described above



Computational Models of Mammalian Respiratory CPG, Fig. 3 Circuit configuration of the conductance-based neuronal population model, incorporating the core mutual inhibitory ring-like structure within pre-BötC–BötC microcircuits and the inspiratory pre-BötC excitatory kernel circuits composed of pre-I/I spiking neurons with I_{NaP} functioning as an important conductance mechanism. Each neuronal component is represented in the model by a population of neurons. In the model simulations, all of these circuit components received tonic

excitatory synaptic drive from the sources depicted. Representative simulated integrated activities of the main populations of BötC, pre-BötC, and rVRG during the three-phase respiratory cycle are illustrated at the bottom. Integrated population activities are total number of spikes per sec/number of neurons ($n = 50$ neurons per population). Detailed descriptions of the model components and their interactions are in the main text (From Smith et al. 2009)

is to define how the intrinsic biophysical/electrophysiological properties of the constituent neuron populations, and population connectivity/synaptic interactions within specific circuit architectures, generate the spatiotemporal patterns of neuronal activity required for the three-phase organization of the respiratory motor pattern. Computational models of the brainstem respiratory CPG that incorporate various levels of biological and

mathematical detail have been in development for decades, exploring various facets of the dynamical operation of the GPG neurons and circuits. For a comprehensive review including historical perspectives, see Lindsey et al. (2012). Two types of recent models are described below – conductance-based and activity-based models of CPG circuits. These models incorporate the most recent experimental information on the structural–

functional organization of pontine–medullary network components (Fig. 2), as identified from neuroanatomical reconstruction or electrophysiological connectivity studies, and key biophysical/electrophysiological properties inferred from neuronal recording studies. The models represent at different levels of complexity how the inhibitory and excitatory network interactions and intrinsic biophysical mechanisms within the core circuitry, operating under control by external excitatory inputs such as from RTN/pFRG and the pons, contribute to rhythmic pattern generation in different network states. In addition to explaining circuit dynamics generating the normal three-phase respiratory pattern, these models have explored a number of other dynamical features of CPG operation. This includes rhythmogenic mechanisms embedded within the interacting pontine–medullary circuits that generate different experimentally observed motor patterns underlying distinct (patho)physiological respiratory behaviors (see Lindsey et al. 2012; Smith et al. 2013 for recent reviews).

Conductance-Based Computational Models

The conductance-based models developed by Rybak et al. (2007), Smith et al. (2007), and Rybak and Smith (2009) are extensions of their earlier models that incorporate synaptically coupled populations of inspiratory and expiratory spiking single-compartment neurons with biophysical properties and ion channel kinetics of membrane currents/conductances modeled in the Hodgkin–Huxley style. These model formulations incorporate experimentally characterized or postulated biophysical properties for respiratory neurons. The model neurons are assembled into individual populations for each functional type of inspiratory or expiratory neuron with heterogeneity of neurons built into individual populations by random distributions of some neuronal biophysical parameters and simulation conditions. Excitatory or inhibitory synaptic interactions among populations are modeled by incorporating

postsynaptic conductances in target neurons that are activated by spiking of neurons providing the activity-dependent synaptic inputs. The model circuitry, shown schematically in Fig. 3, also includes the tonically spiking neurons representing those identified electrophysiologically in the pons, RTN, and raphé nuclei that provide excitatory synaptic drive to the postulated microcircuits in the three major medullary compartments (BötC, pre-BötC, and rVRG) as described below.

The BötC compartment model microcircuit contains two populations of rhythmically active inhibitory expiratory neurons, the post-inspiratory (post-I) and the augmenting expiratory (aug-E) neurons active during the E-2 phase. These populations inhibit neuronal populations within the pre-BötC and rVRG and reciprocally inhibit each other (Fig. 2). The BötC compartment contains an excitatory post-I population (post-I(e)) that contributes to the simulated central vagus (cVN) cranial motor output. All BötC neurons have intrinsic spike frequency adaptation properties defined by a high-voltage-activated calcium (I_{CaL}) with calcium flux activating calcium-dependent potassium currents ($I_{K,Ca}$, see Eq. 2 below).

The pre-BötC compartment in the model includes two rhythmically active inspiratory neuronal populations: pre-I/I and early-I(1) (Figs. 1 and 2), where the pre-I/I population is the key excitatory population of pre-BötC serving as a major source of network inspiratory activity. This population projects to the aug-I population of premotor inspiratory neurons of the rVRG and via an excitatory hypoglossal premotor neuronal population to the hypoglossal motor output (HN) (see Fig. 2; not shown in Fig. 3). Motoneuron populations are not explicitly incorporated in the model, and the activity of premotoneuron populations is considered to be representative of motor outputs since the activity patterns of motoneurons have been shown electrophysiologically to generally follow the activity of premotoneurons providing excitatory monosynaptic inputs. The pre-I/I populations of excitatory neurons, which are synaptically coupled by mutual excitatory

connections, play a critical role in generating the inspiratory rhythm. In the model, as found experimentally, some of these cells have intrinsic oscillatory bursting properties dependent on a persistent sodium current (I_{NaP}) – an experimentally established conductance mechanism underlying membrane voltage-dependent intrinsic rhythmogenic behavior of pre-BötC circuits in which endogenous oscillatory bursting is a function of the level of neuronal excitability or tonic excitatory drive (Smith et al. 2007; Richter and Smith 2014). All pre-BötC excitatory neurons in this model have I_{NaP} . Earlier conductance-based models of I_{NaP} -dependent bursting in a network model of isolated pre-BötC excitatory circuits (Butera et al. 1999a, b; see also Butera et al. 2005 for review) have shown that an increase in the average neuronal excitability or in external excitatory drive increases the inspiratory burst frequency over a large dynamic range (Purvis et al. 2007) and ultimately switches population activity to a mode of tonic asynchronous spiking. In the CPG model, where the pre-BötC circuits are embedded in the larger network providing inhibitory and excitatory inputs, under normal conditions, most neurons of the pre-BötC excitatory population are assumed to operate in a tonic-spiking mode due to high tonic excitatory input and are phasically inhibited by the expiratory neurons (post-I, aug-E) (discussed in Smith et al. 2007).

The early-I(1) population within the pre-BötC compartment is a population of inhibitory interneurons with adapting properties (also governed by I_{CaL} and $I_{K,Ca}$) and receives excitation from the pre-I/I population. In the modeled network, this population serves as a major source of inhibition of all expiratory neurons during inspiration (see Fig. 2).

Thus an important circuit architectural feature of this model is that the minimal core structure of the CPG is represented by BötC inhibitory expiratory (post-I and aug-E) neurons and the inhibitory inspiratory neurons in the pre-BötC, coupled in a ring-like network with mutual inhibitory interactions (Fig. 3). This inhibitory network interacts with the key excitatory kernel network

of pre-BötC inspiratory neurons to coordinate the generation of inspiratory and expiratory activity patterns. In this model synaptic inhibition is essential for orchestrating phase transitions to generate the three-phase respiratory pattern.

The rVRG compartment contains the aug-I excitatory, and early-I(2) inhibitory, populations. Aug-I represents the rhythmically active population of premotor inspiratory neurons projecting to and exciting phrenic motoneurons. Activity of this population in the model represents PN output and contributes to the inspiratory component of cVN discharge. The role of the inhibitory early-I (2) population of adapting neurons in the model is in shaping the ramping patterns of aug-I neurons. The tonic excitatory drives to these neurons contribute importantly to the augmenting activity pattern.

Single Model Neuron Conductance Descriptions and Population Modeling: Mathematical Formulations

Neurons in this model are represented as single-compartment cells with ionic currents for membrane channels described following the classic Hodgkin–Huxley formulation as summarized below, following closely the description given in the original papers (Rybak et al. 2007; Smith et al. 2007). The simplified ionic current (I) equation for the pre-BötC excitatory neurons is

$$C \cdot \frac{dV}{dt} = -I_{Na} - I_{NaP} - I_K - I_L - I_{SynE} - I_{Syn} \quad (1)$$

and the early-I (1, 2), aug-I, post-I, and aug-E neurons are modeled by

$$C \cdot \frac{dV}{dt} = -I_{Na} - I_K - I_{CaL} - I_{KCa} - I_L - I_{SynE} - I_{Syn} \quad (2)$$

where V is the membrane potential, C is the membrane capacitance, and t is time. The ionic currents represented on the right side of these current

balance equations are I_{Na} [fast (transient) sodium current], I_{NaP} [persistent (slow inactivating) sodium current], I_K (delayed rectifier potassium current), I_{CaL} (high-voltage-activated calcium-L current), I_{KCa} (calcium-dependent potassium current), I_L (leakage current), and I_{SynE} and I_{SynI} (excitatory and inhibitory synaptic currents, respectively). Expressions for individual currents are as follows:

$$\begin{aligned} I_{Na} &= g_{Na} \cdot m_{Na}^3 \cdot h_{Na} \cdot (V - E_{Na}); \\ I_{NaP} &= g_{NaP} \cdot m_{NaP} \cdot h_{NaP} \cdot (V - E_{Na}); \\ I_K &= g \cdot m_K^4 \cdot (V - E_K); \\ I_{CaL} &= g_{CaL} \cdot m_{CaL} \cdot h_{CaL} \cdot (V - E_{Ca}); \\ I_{KCa} &= g_{KCa} \cdot m_{KCa}^2 \cdot (V - E_K); \\ I_L &= g_L \cdot (V - E_L); \\ I_{SynE} &= g_{SynE} \cdot (V - E_{SynE}); \\ I_{SynI} &= g_{SynI} \cdot (V - E_{SynI}), \end{aligned} \quad (3)$$

where E_{Na} , E_K , E_{Ca} , E_L , E_{SynE} , and E_{SynI} are the reversal potentials and g_{Na} , g_{NaP} , g_K , g_{CaL} , and g_{KCa} are maximum conductances of the corresponding channels; g_{SynE} and g_{SynI} are excitatory and inhibitory synaptic conductances, respectively, and g_L is the constant leak conductance.

The kinetics of the activation and inactivation gating variables m_i and h_i (indexes indicate individual ionic currents), respectively, are described as

$$\begin{aligned} \tau_{mi}(V) \cdot \frac{d}{dt} m_i &= m_{\infty i}(V) - m_i; \\ \tau_{hi}(V) \cdot \frac{d}{dt} h_i &= h_{\infty i}(V) - h_i. \end{aligned} \quad (4)$$

The expressions for steady-state activation and inactivation variables, time constants, value of maximal conductances for individual neuron types, and the sources of experimental data from which model parameters were obtained are presented in the original papers (Rybak et al. 2007; Smith et al. 2007).

For currents gated by the internal calcium concentration in the model (I_{KCa}), the kinetics of intracellular calcium concentration Ca is described as follows:

$$\begin{aligned} \frac{d}{dt} Ca &= -k_{Ca} \cdot I_{CaL} \cdot (1 - P_B) \\ &+ (Ca_0 - Ca)/\tau_{Ca} \end{aligned} \quad (5)$$

where the first term constitutes influx (with the coefficient k_{Ca}) and buffering (with the probability P_B) such that $P_B = B/(Ca + B + K)$, where B is the total buffer concentration and K is the rate parameter. The second term describes kinetics of a calcium pump with resting level of calcium concentration Ca_0 and time constant τ_{Ca} . The calcium reversal potential in the model is a function of Ca :

$$E_{Ca} = 13.27 \cdot \ln(4/Ca) \text{ (at rest } Ca = Ca_0 = 5 \cdot 10^{-5} \text{ mM and } E_{Ca} = 150 \text{ mV)} \quad (6)$$

For modeling multiple neuronal populations and their synaptic interactions, each functional type of neuron (pre-I/I, early-I, post-I, aug-E) is represented by a population of 50 neurons. Connections between populations in this model are specified so that if a population A was assigned to receive an excitatory or inhibitory input from a population B or external excitatory drive d , then

each neuron of population A received the corresponding excitatory or inhibitory synaptic input from each neuron of population B or from d , respectively. The excitatory (g_{SynE}) and inhibitory postsynaptic (g_{SynI}) conductances are activated by the network activity-dependent excitatory or inhibitory inputs, respectively, formulated as

$$\begin{aligned} g_{SynEi}(t) &= g_E \cdot \sum_j S\{w_{ji}\} \cdot \sum_{t_{kj} < t} \exp(-(t - t_{kj})/\tau_{SynE}) + g_{Ed} \cdot \sum_m S\{w_{dmi}\} \cdot d_{mi} \\ g_{SynIi}(t) &= g_I \cdot \sum_j S\{-w_{ji}\} \cdot \sum_{t_{kj} < t} \exp(-(t - t_{kj})/\tau_{SynI}) + g_{Id} \cdot \sum_m S\{-w_{dmi}\} \cdot d_n \end{aligned} \quad (7)$$

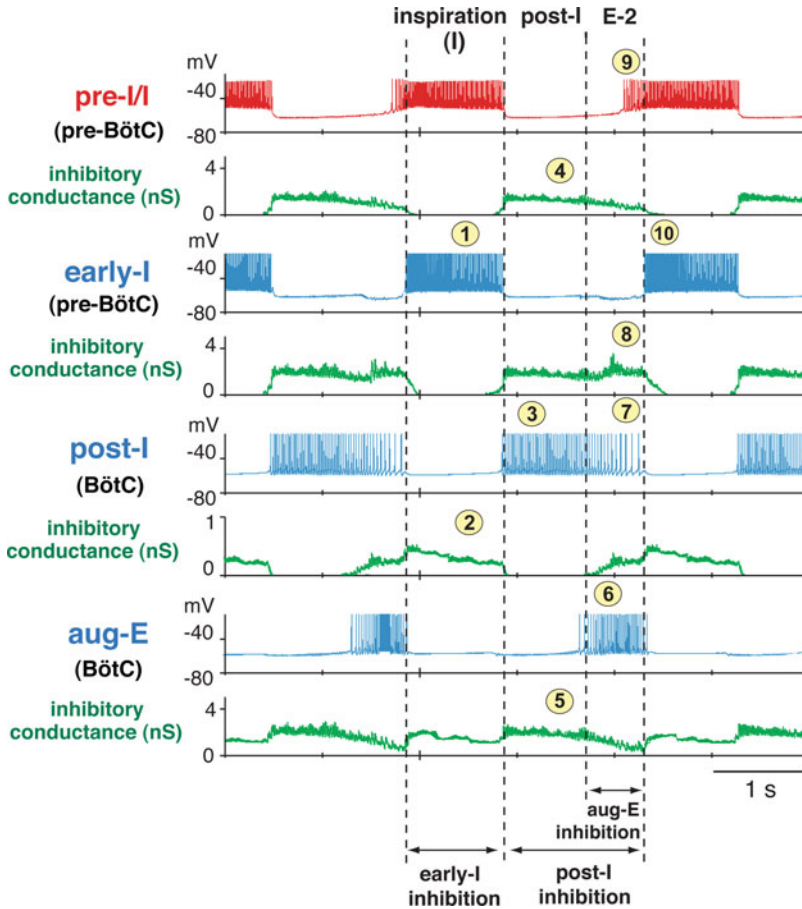
where the function $S\{x\} = x$, if $x \geq 0$, and 0 if $x < 0$. The first terms in the above two Eq. 7 describe the dynamics of integrated synaptic inputs from other network neurons. The second term describes the integrated inputs from external drives d_{mi} . The activity dependence of these inputs is handled by considering that each action potential arriving to neuron i from neuron j at time t_{kj} increases the excitatory synaptic conductance by $g_E \cdot w_{ji}$ if the synaptic weight $w_{ji} > 0$ or increases the inhibitory postsynaptic conductance by $g_I \cdot w_{ji}$ if the synaptic weight $w_{ji} < 0$. The parameters g_E and g_I define the increase in the excitatory or inhibitory synaptic conductance, respectively, produced by one action potential arriving for $|w_{ji}| = 1$, and t_{SynE} and t_{SynI} represent the decay time constants for the excitatory and inhibitory conductances, respectively. In the second term of Eq. 7, the parameters g_{Ed} and g_{Id} define the increase in excitatory or inhibitory postsynaptic conductance, respectively, produced by external input drive $d_{mi} = 1$ with a synaptic weight of $|w_{dmi}| = 1$. In the original model, $g_{Id} = 0$. The relative weights of synaptic connections (w_{ji} and w_{dmi}) during the three-phase operation and other states of the network are provided in the original publications. Heterogeneity of neurons to account for biological variability within each model population was incorporated by a random distribution of E_L (mean values $\pm$ SD) as well as the initial conditions for values of membrane potential, calcium concentrations, and channel conductances.

Dynamical Operation of Model Core Circuitry

Examples of the simulated output of this model are shown in Figs. 3 and 4, which illustrate neuron population activity patterns (Fig. 3) and the membrane potential trajectories (Fig. 4) including spiking patterns and the temporal profiles of postsynaptic inhibitory conductances in single representative neurons from each of the four main neuron populations in the pre-BötC and BötC circuitry. The integrated population activities are comparable to electrophysiological recordings (Fig. 1) obtained from an experimental preparation (in situ perfused brainstem–spinal

cord preparation from juvenile rat) (Smith et al. 2007, 2009), which spontaneously generates the three-phase respiratory pattern that is recorded at the neuron population level in medullary compartments and from cranial and spinal nerves monitoring motor output. The model parameters chosen and model simulations were designed to reproduce experimental data obtained from this preparation (see Smith et al. 2007 for details). The simulations have reproduced some essential temporal features of the three-phase organization of the neuron population activities and network outputs. This correspondence has been interpreted to imply that the minimal architecture for the core pre-BötC and BötC circuits represented in the model defines essential excitatory and inhibitory population interactions for generating the three-phase rhythmic pattern. In additional tests of this model, simulations could mimic a number of experimental observations including results from experiments examining (1) pharmacological perturbations of the cycle frequency and amplitude of population activity by blocking I_{NaP} , (2) disruptions of network activity by reducing inhibitory synaptic conductances, and (3) transformations of CPG network activity, motor patterns, and underlying rhythmogenic mechanisms as the network was physically reduced and functionally reconfigured. Regarding the latter, this model has delineated mechanistically how the core CPG components could be built hierarchically by assembling the postulated local pre-BötC and BötC microcircuits with their particular electrophysiological properties and their regulation by external excitatory drive inputs. Thus the model has shown that this type of circuit assembly has the capability for functional reorganization under different (patho)physiological conditions, which is considered an important property of the CPG.

The membrane trajectories and postsynaptic inhibitory conductances from representative single model neurons (Fig. 4) serve to illustrate in principle the dynamical operation of the core rhythmogenic microcircuits, particularly how the mutual inhibitory interactions within the ring-like architecture of circuit connections can orchestrate phase transitions to produce the three-phase respiratory pattern. Sequential events (numbered in the figure) beginning with the inspiratory (I) period



Computational Models of Mammalian Respiratory CPG, Fig. 4 Simulated membrane potential trajectories and time courses of inhibitory postsynaptic conductances in single neurons from the four major populations of the core pre-BötC and BötC circuitry in the conductance-based model with connections as depicted in Fig. 3. Sequential events beginning with the inspiratory (I) period are numbered and correspond to the stepwise

description given in the text, which provides an explanation of the dynamical operation of these microcircuits. This explanation emphasizes the roles of synaptic inhibition and intrinsic cellular biophysical properties in orchestrating phase transitions and neuronal rhythmic activity patterns underlying generation of the three-phase respiratory pattern (The figure is from Smith et al. 2013 with permissions)

are as follows. **(1)** During the inspiratory phase, activity of the pre-BötC early-I inhibitory population declines due in part to intrinsic spike frequency adaptation. This enables slow disinhibition of the BötC post-I neurons, evident in the trajectory of the post-I neuron inhibitory conductance **(2)**. Spiking of post-I inhibitory neurons **(3)** initiates inhibition of inspiratory activity by the abrupt rise of inhibitory conductance in pre-I/I **(4)** and early-I neurons, terminating the inspiratory phase. Simultaneous inhibition of BötC aug-E neurons **(5)** with the rapid onset of

inhibitory postsynaptic conductance also silences these neurons. Activity of the aug-E neuron population **(6)** is disinhibited and develops later in expiration, forming the second expiratory (E-2) phase, as the post-I neuron spiking frequency declines (adaptation). Aug-E neuron activity causes inhibitory conductance in post-I neurons to further reduce their spike frequency **(7)**, while the simultaneous inhibition of early-I neurons **(8)** transiently prevents reactivation of these neurons. The pre-I/I neurons in pre-BötC are only weakly inhibited in the model during the E-2

phase and receive high tonic excitatory drive, which in combination with the recovery from I_{NaP} inactivation in these cells enables escape from inhibition and onset of pre-inspiratory phase spiking activity (9) initiating a wave of synaptic excitation in the network. The resultant strong excitation to the early-I inhibitory neurons and their rapid onset of spiking (10) initiates strong inhibition of post-I and aug-E neurons, completing the E-to-I transition and initiation of the next cycle. These model-based descriptions for the generation of the three-phase respiratory pattern are generally in accord with classical descriptions of Richter and colleagues, but in the current model, involvement of specific compartmental microcircuits and their more recently elaborated electrophysiological properties are considered (see Richter and Smith 2014 for recent review).

Some Model Limitations

This model, as noted above, is a highly simplified representation of microcircuits within the CPG that attempts to define key features of the architecture and dynamics of postulated core circuitry incorporating simplified sets of neuronal biophysical properties. A key feature of the model is the asymmetric strengths of mutual synaptic interactions within the ring-like inhibitory connectome. In combination with strong intrinsic spike frequency adaptation properties of two of the inhibitory populations (post-I and early-I), this connectome enables the orderly progression of the cycle activity phases. Such asymmetry has not yet been examined and verified experimentally. Furthermore, all neurons in this model are assumed to receive tonic excitation that facilitates the phase transitions. The mapping of excitatory input drives onto the circuitry and the relative strengths of drives have also not been analyzed and confirmed experimentally. Some of the inputs from the sources represented in the model may in fact be rhythmic, and some models have attempted to explicitly incorporate state-dependent phasic inputs (Rubin et al. 2011; Lindsey et al. 2012). The interacting processes

leading to stable transitions between each activity phase are dynamically complex (see section “Activity-Based Computational Models” below), and the processes operating in the real network are undoubtedly not fully represented in the model. As shown from electrophysiological recordings, the three phases of the cycle are not strictly sequential with some temporal overlap, reflected by the spiking activity profiles of population neurons, particularly subsets of post-I neurons that spike into the E-2 phase, and pre-I/I neurons that begin spiking in the E-2 phase. These features are present in the model simulations. However, there is also temporal dispersion in the spiking patterns of different neurons within a population active during a given phase. For example, it has been established experimentally that there are also expiratory neurons with spiking confined primarily to the post-I phase. Currently it is not clear whether this reflects heterogeneity of synaptic inputs and/or electrophysiological properties within a given neuronal population, which is a feature of the current model, or if this reflects functionally distinct subpopulations.

This model assumes that the essential circuit interactions generating the respiratory rhythm are distributed between the BötC and pre-BötC regions, which is consistent with current experimental information but not yet definitively established. The spatial segregation of neurons with particular spiking patterns is not exclusive. For example, post-I spiking neurons are also located in the pre-BötC, which may imply that some of the inhibitory circuit interactions leading to inspiratory phase termination occur locally within this compartment. Regardless of the particular spatial arrangements, the circuit motifs and dynamic processes inherent in the present model are a plausible solution to the general problem of identifying canonical circuit architecture and neuronal interactions for generating the three-phase activity pattern. The mutual inhibitory connectome appears to be an important architecture for orchestrating the three-phase rhythmic pattern. More complex architectures with distinct subpopulations of glycinergic and GABAergic inhibitory neurons and their postulated network

interactions, but retaining key features of the inhibitory circuit interactions represented by the model described here, have been explored (Shevtsova et al. 2011). For more biophysically complex conductance-based models of pre-BötC excitatory circuit neurons, incorporating additional sodium- and calcium-based mechanisms for inspiratory rhythm generation, see for example Jasinski et al. 2013.

Activity-Based Computational Models

Activity-based (non-spiking) models of the core pre-BötC–BötC circuitry that incorporate the essential spike frequency adaptation properties of inhibitory neurons and I_{NaP} -dependent intrinsic burst generation mechanisms of pre-BötC excitatory neurons in a more simplified format have been developed by Rubin et al. (2009, 2011). These models have been used for computational studies of circuit dynamics in various states, including during the three-phase rhythmic pattern generation state as well as structurally reduced states of the CPG network that are considered to be functionally important. Activity-based neural models (Ermentrout and Terman 2010) are an established general form of models and have particular utility for (1) testing if the dynamical processes operating as described by more complex conductance-based models, such as for the core circuitry of the respiratory CPG as described above, can be adequately represented by a more minimal construct within a dynamical system's analytical and computational framework – this could imply that the basic circuit architecture and the proposed key dynamical properties of circuit elements can be a robust representation of the essential dynamical processes that are not a function of parameter tuning in the very large, complex parameter sets of the conductance-based model – and (2) applying numerical methods including bifurcation analysis, phase plane analysis, and fast–slow variable decomposition methods to analyze dynamic mechanisms underlying transitions between respiratory phases. These approaches have also enabled analyses of how gradual

changes of excitatory drives to particular cells in the network can control oscillation period and phase durations, which is an important physiological problem. In addition, transitions to other oscillatory regimes, such as experimentally established two-phase and one-(active) phase rhythmic activity states underlying important respiratory motor behaviors might be explained more rigorously, as well as the emergence of intermediate activity patterns in transitions between rhythmic states that have been observed experimentally.

This model was constructed with the same spatially organized network architecture as the conductance-based model and correspondingly contains four neurons ($i \in \{1, 2, 3, 4\}$), representative of the same neuronal populations, and three sources of excitatory drive ($dk; k \in \{1, 2, 3\}$). The four neurons include one excitatory pre-I/I ($i = 1$) and one inhibitory early-I ($i = 2$) neuron, for these neuronal types in the pre-BötC as in the conductance-based model, and two inhibitory neurons, post-I ($i = 3$) and aug-E ($i = 4$), representing these populations in the BötC.

Each type of neuron in this model is described by the dependent variable V_i , which represents an average voltage for that (i -th) population, and each output $f(V_i)$ ($0 \leq f(V_i) \leq 1$) represents an averaged or integrated population activity at the corresponding average voltage. It is assumed that the dynamics of the average voltages can be represented in the model by a conductance-like analytical framework since regimes in which neurons within each population are synchronized are considered (Rubin et al. 2009). Thus, the model was formulated to also explicitly represent dynamics of ionic currents so that the role of I_{NaP} causing oscillatory activity and current causing neuronal adaptation properties could be incorporated. In essence, this is an interesting novel, hybrid form of activity-based models that is meant to capture some of the essential dynamics of conductance-based models.

Following closely the description given in Rubin et al. (2009), the membrane potential of the I_{NaP} -containing excitatory pre-I/I neuron, V_1 , is described by the differential equation:

$$C \cdot \frac{dV_1}{dt} = -I_{\text{NaP}} - I_K - I_{L1} - I_{\text{SynE}1} - I_{\text{SynI}1} \quad (8)$$

$$C \cdot \frac{dV_1}{dt} = -I_{\text{NaP}} - I_K - I_{L1} - I_{\text{SynE}1} - I_{\text{SynI}1} \quad (9)$$

The other three neuron types ($i \in \{2, 3, 4\}$) in the circuit explicitly have dynamic adaptation of the depolarized voltage trajectory defined by the outward potassium current I_{ADi} . Each of these neurons has a membrane potential V_i that evolves as

In the above equations, C is the neuronal capacitance, I_K represents the potassium delayed rectifier current, and I_{Li} ($i \in \{1, 2, 3, 4\}$) is the leakage current. $I_{\text{SynE}i}$ and $I_{\text{SynI}i}$ ($i \in \{1, 2, 3, 4\}$) are the excitatory and inhibitory synaptic currents, respectively, described by

$$\begin{aligned} I_{\text{NaP}} &= g_{\text{NaP}} \cdot m_{\text{NaP}} \cdot h_{\text{NaP}} \cdot (V_1 - E_{\text{Na}}), \\ I_K &= g_K \cdot m_K^4 \cdot (V_1 - E_K), \\ I_{ADi} &= g_{AD} \cdot m_{ADi} \cdot (V_i - E_K), \\ I_{Li} &= g_L \cdot (V_i - E_L), \\ I_{\text{SynE}i} &= g_{\text{SynE}} \cdot (V_i - E_{\text{SynE}}) \cdot \sum_{k=1}^3 c_{ki} \cdot d_k, \text{ for } i \neq 2, \text{ and} \\ I_{\text{SynE}2} &= g_{\text{SynE}} \cdot (V_2 - E_{\text{SynE}}) \cdot \left(a_{12} \cdot f_1(V_1) + \sum_{k=1}^3 c_{ki} \cdot d_k \right), \\ I_{\text{SynI}i} &= g_{\text{SynI}} \cdot (V_i - E_{\text{SynI}}) \cdot \sum_{\substack{j=2 \\ j \neq i}}^4 b_{ji} \cdot f_j(V_j). \end{aligned} \quad (10)$$

In these equations g_{NaP} , g_K , g_{AD} , g_L , g_{SynE} , and g_{SynI} are the maximum conductances of the corresponding currents and E_{Na} , E_K , E_L , E_{SynE} , and E_{SynI} are the corresponding reversal potentials; a_{12} defines the weight of the excitatory synaptic input from the pre-I/I to the early-I neuron (see Fig. 5); b_{ji} defines the weight of the inhibitory input from neuron j to neuron i ($i \in \{1, 2, 3, 4\}$, ($j \in \{2, 3, 4\}$); and c_{ki} defines the weight of the excitatory synaptic input to neuron i from drive k (d_k , $k \in \{1, 2, 3\}$). The asymmetries in synaptic weights for the mutual inhibitory interactions between early-I, post-I, and aug-E neurons (e.g., $b_{23} > b_{32}$, $b_{34} > b_{43}$, but $b_{24} = b_{42}$) specify the order in which these cell types generate action potentials to produce the three-phase rhythmic pattern. For the analysis of effects of total independent excitatory drives (D_i , $i \in \{1, 2, 3, 4\}$) to different target neurons, D_i were varied without decomposition into weighted sums of drives d_k . In

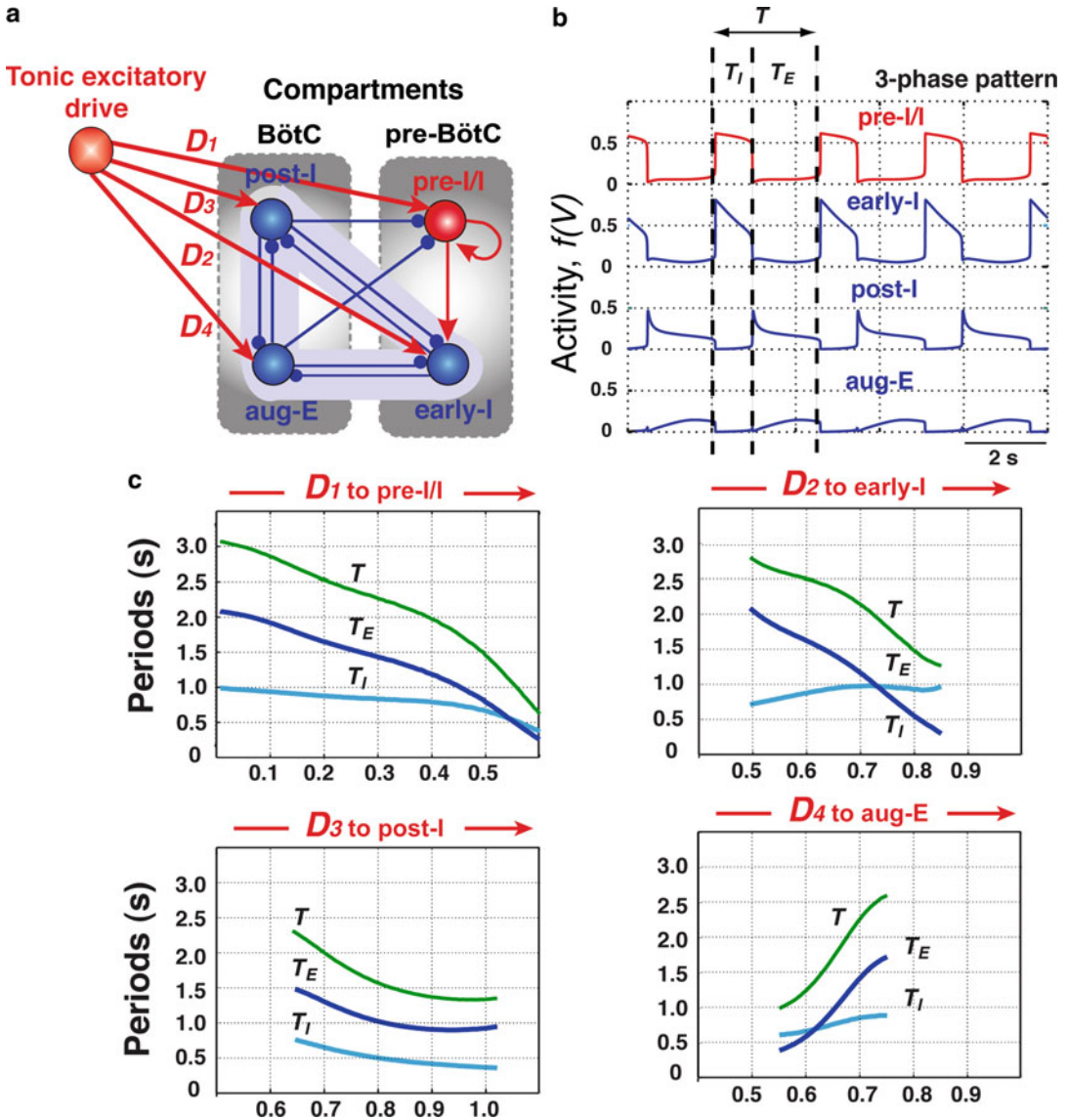
these cases, in the equations for $I_{\text{SynE}i}$ and $I_{\text{SynI}i}$ of the system (Eq. 10), the term $\sum_{k=1}^3 c_{ki} \cdot d_k$ was replaced in the model with D_i (see Fig. 5).

The output activity of each neuron type (indirectly representing the rate of spiking activity) is defined by the nonlinear function $f_i(V_i)$

$$f_i(V_i) = 1 / (1 + \exp(-(V_i - V_{1/2})/k_{Vi})), \quad i \in \{1, 2, 3, 4\} \quad (11)$$

where $V_{1/2}$ is the half-activity voltage and k_{Vi} defines the slope of the output function for each neuron.

The two slow variables in the model (h_{NaP}), representing the slow inactivation of I_{NaP} in neuron 1 (pre-I/I), and m_{ADi} ($i \in \{2, 3, 4\}$), defining the time course of adaptation in the other three



Computational Models of Mammalian Respiratory CPG, Fig. 5 Activity profiles of the four main types of neurons in the pre-BötC–BötC microcircuitry and control of respiratory cycle period and phase durations by tonic excitatory drives from simulations with the activity-based model of Rubin et al. (a) The distinct populations of inspiratory and expiratory neurons of the core circuitry within the BötC and pre-BötC compartments provide multiple nodes that may be targeted by external drives for control of cycle period and phase durations. (b) Simulations show activity profiles of each neuron type of the core circuitry producing a three-phase activity pattern with respiratory cycle period (T) and durations of

inspiration (T_I) and expiration (T_E) with $T = 2.5$ s, $T_I = 0.9$ s, and $T_E = 1.6$ s that are within the observed experimental range. The voltage trajectories show adaptation properties of post-I and early-I neurons, slow depolarizing drift in voltage of pre-I/I neurons, and augmenting activity profile of aug-E neurons. Compare the profiles with integrated population activities of the conductance-based model shown in Fig. 3. (c) Dynamic ranges of T , T_I , and T_E with changes in total drive selectively to each neuron type $D_1 \dots D_4$, where the excitatory postsynaptic input to each neuron has been weighted in proportion to the drive (Modified from Rubin et al. 2009)

neurons (each with fixed time constant τ_{ADi} and maximal adaptation), are defined by k_{ADi} :

$$\begin{aligned} \tau_{hNaP}(V_1) \cdot \frac{d}{dt} h_{NaP} &= h_{CoNaP}(V_1) - h_{NaP}, \\ \tau_{ADi} \cdot \frac{d}{dt} m_{ADi} &= k_{ADi} \cdot f_i(V_i) - m_{ADi}^* \end{aligned} \quad (12)$$

Voltage-dependent activation and inactivation variables and time constants for I_{NaP} (based on the I_{NaP} kinetic model of Butera et al. 1999a) and activation of I_K channels in the pre-I/I neuron are described as follows:

$$\begin{aligned} m_{NaP} &= 1 & (1 + \exp(-(V_1 + 40)/6)), \\ h_{\infty NaP} &= 1 & (1 + \exp((V_1 + 48)/6)), \\ \tau_{hNaP} &= \tau_{hNapmax} & \cosh((V_1 + 48)/12), \\ m_K &= 1 & (1 + \exp(-(V_1 + 29)/4)). \end{aligned} \quad (13)$$

Rubin et al. noted that at most points in the eight-dimensional phase space representing the eight variables of this model, the voltages $V_1, \dots, V_4$ evolve much faster than the inactivation variable h_{NaP} and the adaptation variables m_{ADi} ($i = 2, 3, 4$). Accordingly, the voltages represent the fast variables, and the system of differential equations for $V_1, \dots, V_4$ represent the fast subsystem. Equilibrium points of this subsystem occur where the right-hand sides of all equations in the fast subsystem are zero and typically form smooth equilibrium surfaces. These investigators accordingly used bifurcation analysis to identify fast subsystem equilibrium surfaces and phase transitional features by numerically tracking the fast subsystem equilibrium surfaces along which the fast system variables are relatively constant and detecting bifurcation curves, where solutions jump away (“fast jumps”) from each surface. Thus, they demonstrated how bifurcation diagrams (see Rubin et al. 2009) can be created by treating the variables h_{NaP} and m_{ADi} as fixed parameters and following curves of equilibrium points of the differential Eqs. 8 and 9 for the voltages $V_1, \dots, V_4$. They also demonstrated that

in certain cases, bifurcation curves could be generated by simultaneously varying two activation variables while holding the other two fixed, whereas in other cases, all four activation variables could be varied simultaneously along a one-dimensional curve in four-dimensional space. The dynamics of the model phase transitions, analyzed with this approach, yielded new insights into the operation of the circuit in different states.

Dynamical Operation During Three-Phase Rhythmic Pattern Generation: New Insights

The three-phasic operation of this activity model, as illustrated in Fig. 5, generates stable oscillations with period T , duration of inspiration T_I , and duration of expiration T_E , which, as the model was parameterized, are within the physiological ranges observed experimentally in the brainstem–spinal cord preparations of juvenile rats whose activity the model was intended to mimic (as with the conductance-based model). The voltage trajectories show characteristic slow adaptation properties of post-I and early-I neurons, depolarizing drift in voltage of pre-I/I neurons during the expiratory period due to slow recovery from inactivation of I_{NaP} , and the augmenting activity profile typical of aug-E neurons, all of which are comparable to the temporal profiles of integrated population activities in the conductance-based model (see Fig. 3). During the expiratory phases, the adapting (decrementing) activity of the post-I neuron, which is defined by the dynamic increase in its adaptation variable m_{AD3} (see Eqs. 9 and 12), causes a decline in inhibition from the post-I neuron that shapes the augmenting profile of aug-E neuron activity and produces slow depolarization of the pre-I/I and early-I neurons. Simultaneously, the pre-I/I neurons are depolarizing due to the slow recovery from inactivation of I_{NaP} (slow increase of h_{NaP} , Eq. 12) so that at some moment the pre-I neurons rapidly activate, providing excitation of the early-I neurons. This inhibits both post-I and

aug-E neurons, completing the switch from expiration to the inspiratory phase in accord with the conductance-based descriptions. The analysis indicates that the moment of pre-I/I activation occurs when the system reaches a bifurcation curve along the post-I/aug-E equilibrium surface, allowing the fast voltage variables to evolve quickly until they again reach an equilibrium surface, yielding a fast jump to the inspiratory phase.

During the inspiratory phase, according to this analysis, the system drifts near a new equilibrium surface, with its dynamics governed by Eq. 12. The early-I neuron, with its adapting activity, is defined by the dynamic increase in its adaptation variable m_{AD2} (Eqs. 9 and 12). The associated decline in inhibition from this neuron produces the slow depolarization of the post-I and aug-E neurons, and eventually, the system reaches another bifurcation curve, and a second fast jump occurs. Within this fast jump, the post-I neuron rapidly activates and inhibits both inspiratory neurons (pre-I/I and early-I) and the aug-E neuron initially, producing the inspiratory to expiratory phase transition. The model analysis indicates that this transition is always facilitated by *release* (as distinguished from *escape*), with m_{AD2} growing during inspiration.

As discussed above for the conductance-based model, it is important to emphasize that although the expiratory period can be conditionally subdivided into post-inspiratory (with a dominant post-I neuronal activity) and late E-2 expiratory (with reduced post-I and increasing aug-E activity) phases, as the model is constructed, there is no distinct switching between post-I and aug-E neuron activity phases in the so-called three-phase rhythmic pattern. Mathematically, there are only two fast jumps observed by bifurcation analysis, and accordingly the rhythmic pattern is not strictly three-phase, although functionally this is the case, leading these investigators to term the normal respiratory pattern as a “bio” three-phase rhythm. Nonetheless, in the model V_1 and V_2 are able to escape from this complex temporal pattern of expiratory phase inhibition for the transition to the inspiratory phase, as occurs naturally. A novel interesting result of the analysis is that with a higher excitatory drive to the network, the

early-I neurons can release from inhibition first and initiate the transition to the inspiratory phase. Thus this model in general has delineated possible contributions of escape and release mechanisms to various phase transitions during the cycle.

Results of these computational analyses have also generally suggested that the basic architecture and key properties of the core circuit neurons, as represented in both the simplified activity-based model with reduced parameter sets and the more complex conductance-based model, constitute a robust dynamical structure. The mutual inhibitory ring-like architecture interacting with the embedded excitatory kernel intrinsically gives rise to stable phase transitions. This bolsters the conclusion that this represents a plausible canonical circuit arrangement within the CPG for generation of the three-phase rhythmic pattern.

Control of Oscillation Period and Phase Durations in the Three-Phase Rhythm-Generating State

One important problem in respiratory neural control addressed with this model is to delineate mechanistically how the excitatory drives from various sources (signaling changes in physiological conditions) control the frequency and durations of inspiratory–expiratory phase activity. Rubin et al. (2009) noted that each of the inhibitory and excitatory populations of the pre-BötC–BötC circuitry potentially represent nodes for control of period and phase durations in the intact respiratory network. To theoretically investigate this control with the activity-based model, the effects of variations in the total excitatory drive D_i to each neuron on the oscillation T and on the durations of T_I and T_E have been analyzed. Some of the results are summarized in Fig. 5.

In general this model showed that variations in drive to the different network cells impact the inspiratory and expiratory phase durations, and the overall oscillatory period, differently with the model operating in the regime generating the three-phase pattern (Fig. 5). For example, increasing the drive to aug-E neurons lengthened T (reduced respiratory frequency) by ~ 2.5 times

by prolonging T_E and by a small increase in T_I . The prolongation of T_E results from a stronger aug-E inhibition of inspiratory neurons that necessitates a greater recovery from adaptation and inactivation before the inspiratory phase can initiate, causing a delay in the onset of this phase. In contrast elevated drive to post-I neurons slightly decreased T (increase frequency) as T_E becomes shorter because the additional drive to post-I leads to stronger inhibition on aug-E. The resulting weaker activation of aug-E leads to a net weaker inhibition of pre-I/I and early-I neurons, allowing a slightly earlier escape to initiate the inspiratory phase.

With the drive targeting neurons in the pre-BötC, the cycle period can be reduced and frequency increased by a factor of 4 from its initial value with increasing drive to the pre-I/I excitatory neurons. This occurs primarily by shortening T_E because the increase in drive to the pre-I/I neuron allows this neuron to escape from inhibition earlier. Increasing drive to the pre-BötC early-I inhibitory neurons can also reduce T by a factor of ~ 2 but by reducing T_I and shortening of T_E , which results from an earlier escape of the early-I neuron from inhibition and corresponding earlier switch to the inspiratory phase. Interestingly, as noted above, with a sufficient increase in drive, the early-I cell can replace the pre-I/I cell as the initiator of the transition to inspiration. Experimental manipulation of neuron excitability within the pre-BötC modulates respiratory cycle frequency over a substantial dynamic range and reinforces the basic concept that the pre-BötC is a key rhythmogenic structure. According to the modeling results, both the excitatory and inhibitory neuron populations in the pre-BötC can play a role and represent different mechanisms for control of respiratory frequency and phase durations. This new insight points to potentially distinct mechanisms at this level of the circuitry.

These modeling results illustrate in principle how the inspiratory and expiratory neuron populations can be distinct nodes for differential control of period and phase durations. As pointed out by Rubin et al. (2009), the significant changes in the oscillation period following changes in drives to particular neurons revealed by the

model are not typical for classical mutual inhibitory half-center models. Mathematically, the different effects on period observed relate in part to the asymmetry between decrementing and augmenting activity patterns in different cells. Phase transitions in the model occur via combinations of adaptation, release from inhibition, and recovery from adaptation (or from I_{NaP} inactivation in the pre-I/I neurons) that provides the escape mechanism. Importantly, the activity-based modeling approach allowed the simulated changes in phase durations and oscillation periods to be linked mathematically to the different balances of escape and release from inhibition and the contributions of neuronal spike frequency adaptation, all of which collectively underlie the phase transitions. Thus, the modeling results generally demonstrate how activity patterns of different cell types in the CPG (1) dictate the forms of the transition curves between phases and underlie the distinctive role each cell population plays in the phase transitions and (2) govern the effects that changes in excitatory drive have on the phase transition curves and overall respiratory activity pattern.

In other results from this theoretical analysis, it has been demonstrated that the different nodes in the circuitry can not only differentially provide control of oscillation period and phase durations but also can allow for control of the mode of rhythmic pattern generation by the external drives. The detailed treatment of this aspect is presented in Rubin et al. (2009). This analysis has generally reinforced the conclusion from the conductance-based model that the core CPG circuits appear to contain multiple functionally embedded oscillatory mechanisms, ranging from mutual inhibitory network-based interactions between pre-BötC and BötC circuits resembling classical inhibitory half-center type structures to conductance-based endogenous rhythmogenic mechanisms within the pre-BötC, with important physiological implications. Another important extension of this activity-based model has been the inclusion of an additional state-dependent oscillatory mechanism for homeostatic regulation, in the RTN/pFRG, that becomes active under conditions of high respiratory drive (i.e., by

elevated CO₂ in the system) and dynamically interacts with pre-BötC–BötC oscillator to produce forced expiration – a respiratory motor behavior distinct from the normal three-phase motor output that occurs at normal resting levels of CO₂. Again, the application of analytical methods from dynamical systems theory has elucidated possible mechanisms and dynamic synchronization of these oscillators. These computational studies are reviewed by Molkov in this volume.

Summary Perspectives

The brainstem respiratory CPG has provided unique opportunities to experimentally unravel how cellular and circuit properties are integrated in the mammalian CNS to produce rhythmic motor behavior. Some of the properties of key components of this CPG have been experimentally investigated in extraordinary detail, yet many aspects of neuronal and circuit structural–functional properties remain to be established (Smith et al. 2013). The data-driven computational modeling approaches described have been instrumental in exploring plausible canonical circuit architectures and the dynamical operation of postulated core microcircuits of the CPG. With the recent advent of new connectomics and optogenetics approaches for reconstructing circuit structure–function, increasingly more detailed experimental information will become available. As with all CNS circuits, CPG circuit dynamics cannot be easily intuited even when circuit organization has been definitively established. Many opportunities therefore exist for future concerted experimental and computational studies investigating the operation of this vital CPG.

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Computational Models of Modulation of Oscillatory Dynamics

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Definition

The term refers to a wide range of spiking neural network models that not only exhibit oscillatory behavior but also simulate neural effects and/or processes underlying ongoing changes in the oscillatory dynamics. These changes in the oscillatory dynamics, often referred to as modulations, can be of different nature: (i) quantitative where the key parameters of oscillations, e.g., amplitude or dominant frequency, vary over the course of a simulation and/or (ii) qualitative where the oscillatory regime undergoes state transitions. Modulatory mechanisms that underlie changes in the oscillatory behavior of a model could also be of various origins ranging from an external stimulus, entraining input, and specific excitatory/inhibitory drive to simulated neuromodulation or attentional effects.

Detailed Description

Background and Scope

Oscillations constitute an inextricable aspect of neural dynamics. Their origins and underlying mechanisms at a cellular as well as population level have been under investigation using both experimental and theoretical approaches. The

importance of oscillatory effects in the brain can largely be explained by abundant biological evidence for their correlations with various aspects of cognition and behavior. In this light, task- or function-dependent modulations of oscillatory dynamics bear special relevance to understanding the mechanisms, role, and nature of this prevalent phenomenon manifested at different scales of neural system organization. Computational models that capture such modulatory effects and demonstrate their impact on the ongoing neural dynamics and/or elucidate their functional implications on a circuit or system level serve as a valuable tool in unraveling the mystery of oscillations. The emphasis is here on spiking neural network models that simulate biologically relevant processes involved in dynamical modulation of ongoing neural activity in the brain. In other words, experimental scenarios where the effect of static manipulations of model parameters on the emergent oscillatory dynamics is tested in independent simulations lie outside the definition of the term of computational models of modulations adopted here.

The most common manifestations of modulatory effects are quantitative changes in parameters of neural rhythms, such as amplitude or peak frequency, and qualitative shifts of the oscillatory regime including synchronization effects. There is a wide range of mechanisms exploited in computational models to simulate modulations of oscillations. For example, the transitions between different oscillatory states in a multi-stable model can be induced by an external stimulus (e.g., Battaglia and Hansel 2006; Börgers et al. 2008; Herman et al. 2013; Lundqvist 2013a, b) or endogenously controlled by intrinsic cellular or network dynamics (Herman et al. 2013). Alternatively, a periodic modulation of oscillations can be imposed by varying noise conditions or other changing sources in order to study implications of changes in oscillatory dynamics (Lundqvist et al. 2013a). From a functional perspective, modulation of oscillatory phenomena in computational models is commonly studied in the context of neuromodulatory (Destexhe et al. 1994; Liljenström and Hasselmo 1995; Li and Cleland 2013) and attentional effects (Börgers

et al. 2005, 2008; Buia and Tiesinga 2006; Gu and Liljenström 2007; Buehlmann and Deco 2008) as well as perceptual and working memory processes (Lundqvist et al. 2012, 2013a, b; Herman et al. 2013). Then, depending on the modeling context, simulated modulation is most often related to cortical or hippocampal dynamics.

Since gamma rhythm with the peak frequency above 20–30 Hz constitutes the most prevalent spectral component of activity of oscillatory spiking network models, it is worth recalling its origin (Buzsaki and Wang 2012). The key neural mechanism involved is slow and fast feedback inhibition on a network level (Brunel and Hakim 1999; Whittington et al. 2000) or feedback inhibition on a cellular level (adaptation and other slow hyperpolarizing activity-dependent currents, e.g., Rotstein et al. 2005; Lundqvist et al. 2006; Herman et al. 2013). The network-level feedback inhibition can be exhibited either between excitatory and inhibitory cells leading to gamma-like oscillations at around 30 Hz (Brunel and Hakim 1999; Whittington et al. 2000) or between inhibitory neurons resulting in faster oscillations at frequencies higher than 60 Hz. In vivo both types of interactions are likely to contribute to the broadband gamma (Ainsworth et al. 2011).

Stimulus- or State-Dependent Modulations of Oscillatory Dynamics

Neural computation theories assume that in the macroscale brain processes information depending on incoming stimuli and its current dynamical as well as functional state. In the same spirit, modulation of the dynamics exhibited by network models often results from an external input/stimulus they receive and/or some intrinsic endogenous state transitions they undergo. Some computational studies attribute functional interpretation to different dynamical states of models. In this regard, special credit should be given to earlier work on spiking attractor networks (Amit and Brunel 1997; Compte et al. 2003; Lundqvist et al. 2010a, b) used to simulate a so-called

memory delay period when humans and primates held one or several items in working memory. The network dynamics during memory-coding interval is qualitatively different from that exhibited beforehand. More recently, the abundant work on cortical attractor models by Lundqvist and Herman (Lundqvist et al. 2011, 2013a, b, c; Herman et al. 2013) deserves here special attention since their biophysically detailed networks have been used to simulate a wide range of memory processes and perceptual phenomena with strong oscillatory correlates in agreement with biological data. In Lundqvist et al. (2011) and Herman et al. (2013), endogenous periodic switching between different network states with distinct spectral manifestations and functional meaning was reported. In particular, transitions from a memory-coding state accompanied by elevated spectral power in theta and gamma bands to a noncoding idling regime with increased alpha-band activity and suppressed theta-gamma correlates, and vice versa, serve as a prime example of intrinsically driven modulation of the model's oscillatory dynamics. It should be added here that such switching dynamics mediated by neural adaptation as well as short-term synaptic plasticity (depression and augmentation) can be linked to a so-called periodic memory replay phenomenon implicated in working memory maintenance (Sandberg et al. 2003; Fuentemilla et al. 2010; Lundqvist et al. 2011; Herman et al. 2013). Another modulatory effect in attractor network models simulating working memory is associated with varying oscillatory power in theta, alpha, and gamma frequency bands depending on the memory load, i.e., the number of memory items to be replayed by the network (Herman et al. 2013). This phenomenon has been widely reported in experimental studies (e.g., Raghavachari et al. 2001; Jacobs and Kahana 2009). All these effects can be explained by the so-called bistability of the network dynamics (it can exhibit two qualitatively different regimes of operation), controlled by the interaction of excitatory and inhibitory cells, and by synaptic (Wang et al. 2006; Mongillo et al. 2008) and neural mechanisms regulating lifetime of memory-coding states.

Changes or transitions of the dynamical regime of neural network models can also be induced by external stimuli. As a result, a stimulus drives the modulation of the model's ongoing oscillatory dynamics. This was the original approach to simulating a memory delay period (Amit and Brunel 1997; Compte et al. 2003; Lundqvist et al. 2006), where the stimulus forced cells in the targeted cell assembly to fire at an elevated rate, simultaneously suppressing the activity in other cells not belonging to the given assembly. This suppression is usually mediated by disynaptic inhibition via a population of interneurons. As mentioned earlier, in a biologically detailed version of such attractor networks (Lundqvist et al. 2006, 2010a, b, 2013a, b, c; Herman et al. 2013) interactions between pyramidal and basket cells in layers 2/3 mediate the competition between different memory patterns and produce at the same time gamma-like oscillations following a stimulus presentation. There have also been other detailed models devised to study the impact of stimulation on oscillatory power changes (Jones et al. 2009). However, they did not have a clear functional interpretation.

Imposed Rhythmic Modulation of Neural Dynamics in Computational Models

A study on functional and dynamical implications of infra-slow fluctuations in a cortical model (Lundqvist et al. 2013a) serves as one of the most representative examples of imposing rhythmic modulation in a network by an external source. The authors used an attractor network to simulate a threshold-stimulus detection task and imposed a slow sinusoidal modulation (~ 0.1 Hz) of excitatory noise onto each principal cell with the aim of generating a slowly varying oscillatory component in the synthesized field potentials. This allowed for investigating its effect on processing weak stimuli. Since the original network without a sinusoidal noise source produces oscillatory activity in three distinct frequency bands roughly corresponding to electrophysiological theta, alpha, and gamma depending on the current

functional and dynamical state, as a result of introducing the aforementioned fluctuating component, a strong phase-amplitude coupling emerged. In other words, a modulatory effect of the phase of the slow fluctuations on the power of faster rhythms (>1 Hz) was obtained in agreement with experimental data (Monto et al. 2008) and in line with the concept of nested oscillations (cf. section “Models of Nested Oscillations”).

Another prominent example of inducing oscillatory behavior in a model and studying the emergent modulatory dynamics is a combined simulation and experimental study by Jones et al. (2009). In their laminar model of somatosensory cortex, both feedforward and feedback pathways were stimulated with exogenous 10 Hz spiking input mimicking Rolandic mu rhythm. For the feedforward pathway layer 4 served as the target, whereas for the feedback pathway, the input was delivered to distal dendrites of layer 2/3 cells. By manipulating the relative timing of these inputs, the authors could study properties of the total modulated rhythmic activity and its effect on evoked sensory responses in a simulated somatosensory task.

Models of Nested Oscillations

Nested oscillation is a phenomenon where the phase of underlying slow rhythm modulates the power of faster oscillations. It has been a prominent finding for theta and gamma rhythms, particularly in memory tasks (e.g., Chrobak and Buzsaki 1998; Canolty et al. 2006; Jensen and Colgin 2007; Kendrick et al. 2011). This classical example of cross-frequency modulatory dynamics has received some attention in the computational neuroscience community. It has been modeled in both hippocampal networks (White et al., 2000; Rotstein et al. 2005; Neymotin et al. 2011) and cortical models (Kendrick et al. 2011; Herman et al. 2013). The origin of oscillatory nesting is still a matter of debate. In modeling work the emphasis has so far been on the role of intrinsic properties of interneurons (White et al. 2000; Tiesinga et al. 2001; Rotstein et al. 2005;

Neymotin et al. 2011). For generating a slower theta rhythm, Neymotin et al. (2011), Rotstein et al. (2005), and White et al. (2000) relied on a specific subtype of interneurons with slow synaptic dynamics (oriens lacunosum moleculare) due to their prevalence in hippocampus. In Rotstein et al.'s (2005), their coupling with fast-spiking interneurons was needed to sustain synchronized rhythmic activity at a population level. Then, as a result of special tuning of the coupling parameters to avoid interneurons firing without phasic excitation and with introduction of AMPA-mediated excitation, the authors managed to obtain the effect of nested oscillations. A similar circuit of interneurons with fast and slow synaptic dynamics was proposed by White et al. (2000) as main contributors to hippocampal rhythms. Neymotin et al. (2011), on the other hand, introduced an additional external driving input to oriens lacunosum moleculare interneurons from medial septum. Then, to generate gamma-band activity, classical basket-pyramidal cell loop was exploited, also enhanced by medial septum. Modulatory effect of theta rhythm with respect to the amplitude of gamma oscillations was obtained due to the coupling between two different types of interneurons in certain analogy to Rotstein et al.'s (2005) and White et al.'s (2000) minimalistic models. Similarly, the neural network model developed by Kendrick et al. (2011) exhibited theta-nested gamma as a result of combining fast and slow inhibitory interneurons. Interestingly, the model allowed the authors to investigate functional consequences of changing the ratio between theta and gamma, as a potential effect of learning. Their simulation results suggested that shallow nesting of gamma on theta, reported experimentally in inferotemporal cortex in a learning scenario, optimized coupling between the two rhythms and maximized responses in the downstream neurons.

A different approach to phase-amplitude modulation was adopted in a cortical laminar model proposed by Kramer et al. (2008). The authors suggested that layer interactions lead to the emergence of lower-beta rhythm as a result

of period concatenation of simultaneous faster rhythms. In another cortical model the occurrence of theta-gamma coupling in layer 2/3 was obtained as a result of the attractor dynamics mediated by recurrent connectivity (Herman et al. 2013). While the neural mechanism underlying gamma-band activity was analogous to the other models, i.e., local inhibitory-excitatory loop, the slower rhythm reflected the activation of a distributed memory pattern in the network stored by means of the aforementioned long-range recurrent connections. Most importantly, due to this functional aspect of the dynamics of theta-gamma modulation, Herman et al.'s (2013) model lends itself to an interpretation of a computational role of nested oscillations. In the context of memory and learning, one could hypothesize that slow and spatially coherent rhythm would provide a window for bursting and synaptic wiring of cell assemblies whereas the local populations constituting an assembly would exhibit activity on faster timescales corresponding to gamma rhythm. In that framework, gamma oscillations would mediate local computations, possibly of competitive nature.

Attentional and Neuromodulatory Effects on Oscillatory Dynamics in Computational Models

Neuromodulation provides another dimension to the dynamics of neural networks by modifying intrinsic properties of neurons and synapses (Marder and Thirumalai 2002; Marder 2012). Although there have been a number of computational studies that attempt to enhance our understanding of the computational role of neuromodulation (Fellous and Linster 1998), less attention in modeling work has been given to its implications for the oscillatory dynamics in neural circuits. Historically, it is important to mention theoretical studies on extrinsic neuromodulation of thalamic reticular cells (Destexhe et al. 1994) and the effects of cholinergic modulation on the olfactory cortex (Liljenström and Hasselmo 1995). Destexhe

et al. (1994) illustrated that a neuromodulator starts a cascade of cellular processes that leads to burst activity of single neurons, which generates population oscillations in the frequency range of spindle waves. Liljenström and Hasselmo (1995) contributed to the understanding of the implications of acetylcholine effects at the cellular level for cortical oscillations. In a rather simple model of EEG and field potentials recordings from the piriform cortex, they managed to explain the mechanism of altered evoked gamma oscillations and demonstrated how suppression of both neural adaptation and intrinsic excitatory synaptic transmission coupled with the activation of inhibitory interneurons mediated dynamical shifts between non-oscillatory and theta rhythmic regimes. More recently, the mechanism underlying cholinergic neuromodulation in the olfactory system was scrutinized in a biophysical model of the olfactory bulb (Li and Cleland 2013). Muscarinic neuromodulation was shown to strengthen the gamma-band oscillatory component in the synthesized bulbar local field potential.

A neuromodulation phenomenon has also been linked to attentional modulation of the neural dynamics. In a few computational studies, the effect of attention on basic stimulus processing has been demonstrated using a biased competition approach. The basic idea is that a slight additional external input to one of the competing neural populations (attended) is amplified and the activity in the other population (non-attended) is suppressed (Deco and Thiele 2009). A desirable feature of these attention models is the emergence of synchronization of neural activity in the gamma band consistently with experimental data (Fries et al. 2001). Such attention-induced effects of synchrony enhancement can be obtained by decreasing neural adaptation, which could reflect cholinergic modulation (Börgers et al. 2005). Alternatively, cholinergic-mediated reduction of inhibitory drive on excitatory cells can be used as a biasing mechanism (Buia and Tiesinga 2006; Börgers et al. 2008). Gu and Liljenström (2007) simulated different effects of cholinergic modulation on extracortical and

intracortical projections in a multilayer cortex and obtained the effect of attentional increase of gamma-band synchronization in the superficial layers.

Cross-References

- [Attentional Top-Down Modulation, Models of](#)
- [Computational Models of Neuromodulation](#)
- [Gamma Rhythm, Neural Population Models of the](#)
- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Neuromodulation: Overview](#)

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Computational Models of Motor Pools

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Definition

The *motor unit* comprises the motoneuron, its axon, and all the muscle fibers innervated by the axon's terminal branches (Heckman and Enoka 2012). The muscle fibers for one motor unit are sometimes referred to as the *muscle unit*. Each muscle is innervated by a pool of motoneurons in the ventral portion of the spinal cord or, for the face and neck, in the brainstem. Thus, the *motor unit pool* comprises all the motoneurons in one motor nucleus and the muscle innervated by those motoneurons. In contrast, a *motor pool* only includes the motoneurons.

Detailed Description

The motor unit pool has long been an appealing target for computational modeling of a neural network. Efforts at modeling this fundamentally important system date back more than 50 years, to Wilfred Rall's early interest in the input–output relations of the monosynaptic reflex arc (Rall 1955). But the system is inherently a neuromechanical one and the first models of motor unit pools in the 1960s and 1970s, Henneman and Burke, were based solely on recruitment of motor units at their maximum

forces to clearly illustrate the neuromechanical nature of the system (Kernell 2006). The key point is the great diversity of motor unit properties and their organization via Henneman's size principle (Henneman and Mendell 1981). Burke defined motor unit types to express this diversity (S (slow), FR (fast, fatigue resistant), and FF (fast, fatigable)) (Burke 1981), but all electrical and mechanical properties exhibit a continuous variation (Heckman and Enoka 2012). S motor units have motoneurons with low thresholds to synaptic activation, innervate relatively few muscle fibers, and thus produce small force. These fibers are all slow but have tremendous fatigue resistance. FRs and FFs have progressively higher thresholds for their motoneurons, greater forces and speeds, but lower fatigue resistances for their muscle units. These differences are not small: threshold varies tenfold, force more than tenfold, speed fivefold, and fatigue more than tenfold (Kernell 2006). The recruitment models by Henneman established that this sequence is optimal for fatigue resistance, energy efficiency, and precision of motor output. Burke and colleagues used this recruitment model approach to show how usage of motor units compared to the forces and speeds required in a wide range of movements. Posture can be accomplished by recruitment solely of S units, while FF units only become important for high speeds and forces.

More detailed models of motor unit pools by Heckman and Binder (1991) and by Fuglevand et al. (1993) in the early 1990s included rate modulation and revealed that the overall form of the motor pool input–output function was sigmoidal, with progressive recruitment of larger motor units at low levels giving way to saturation of forces at high levels. The Heckman and Binder work was designed to understand how the organization of synaptic input to the system affected motor output; this approach continues and has led to improved understanding of how neuromodulatory inputs that alter the electrical properties of motoneurons are fundamental in shaping normal motor output (Heckman and Enoka 2012). The work by Fuglevand and colleagues has inspired many studies of the structure

of the output in human subjects, such as relations between force and EMG (Heckman and Enoka 2012). Models have now progressed to where the distortions in motor units that occur in injury and neurodegenerative diseases are beginning to be explored (e.g., Elbasiouny et al. 2010; Venugopal et al. 2011). In all these efforts, a major advantage of this system is the close correspondence between theory and experiment that it affords. Many of the key parameters of motoneurons can be measured by intracellular recordings in animal preparations, while all of the output variables, including not only muscle force and EMG but also firing patterns of single motor units, can be measured in humans. Thus, motor pool computational models continue to provide unique insights into the structure of motor commands in both normal and pathological states.

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Computational Models of Neural Retina

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Synonyms

[Biophysical models](#); [Computational models of retinal function](#); [Retinal network models](#)

Definition

Computational models of the neural retina are extremely useful in the understanding of normal and abnormal retinal responses to light. They can also be for investigating retinal responses to artificial stimuli such as electrical stimulation by a vision prosthesis. Depending on the aims, complexities, and physiological assumptions on which the model is based, computational models of the retina may be classified into six broad types: single-compartment, morphologically realistic, block-compartment, discrete-neuronal network, continuum, and empirical models of retinal function.

Introduction

The retina is an elaborate architecture of neurons interconnected through gap junctions and synapses. At the outer retina, an array of rod and cone photoreceptors converts the incident light to neural responses. These signals then pass through approximately ten types of cone and one type of rod bipolar cell before arriving at the output neurons in the inner retina – the retinal ganglion cells (RGCs). RGC axons that form the optic nerve then transmit the signals in the form of action potentials to the brain (Masland 2012; Roska and Meister 2014). In addition to this vertical excitatory pathway, the retina also contains two lateral inhibitory pathways. In the outer retina, the

horizontal cells provide inhibitory feedback onto the photoreceptors and inhibitory feedforward onto the bipolar cells. In a similar scheme, the amacrine cells in the inner retina provide inhibition of the bipolar cells and the RGCs (Masland 2001).

Existing anatomical and neurophysiological knowledge of retinal function has permitted computational models to reproduce aspects of retinal responses to either visual or artificial electric stimuli at various levels of complexity. In turn, these models have helped sharpen our understanding of retinal function, particularly in how intrinsic biophysical and morphological properties at the cellular level, and integration of synaptic inputs at the network scale, contribute to retinal function. Over several decades, computational models provided important insights in understanding the response dynamics and computations of single retinal neurons, along with their functional contributions in the larger neural network.

Despite these major advances, significant aspects of retinal function remain to be described. For instance, experimental studies increasingly indicate that the function of many retinal neuron types is more intricate than originally thought (Zhang et al. 2012; Hosoya et al. 2005; Freed 2001; Fried et al. 2002; Masland 2012; Gollisch and Meister 2010; Baden et al. 2016). Similarly, at the frontiers of retinal electrostimulation, the mechanisms underlying the large diversity in retinal neuronal responses to artificial electrical stimulation are still being investigated (Twyford et al. 2014; Freeman et al. 2011; Felsen and Dan 2005; Guo et al. 2018; Yang et al. 2018).

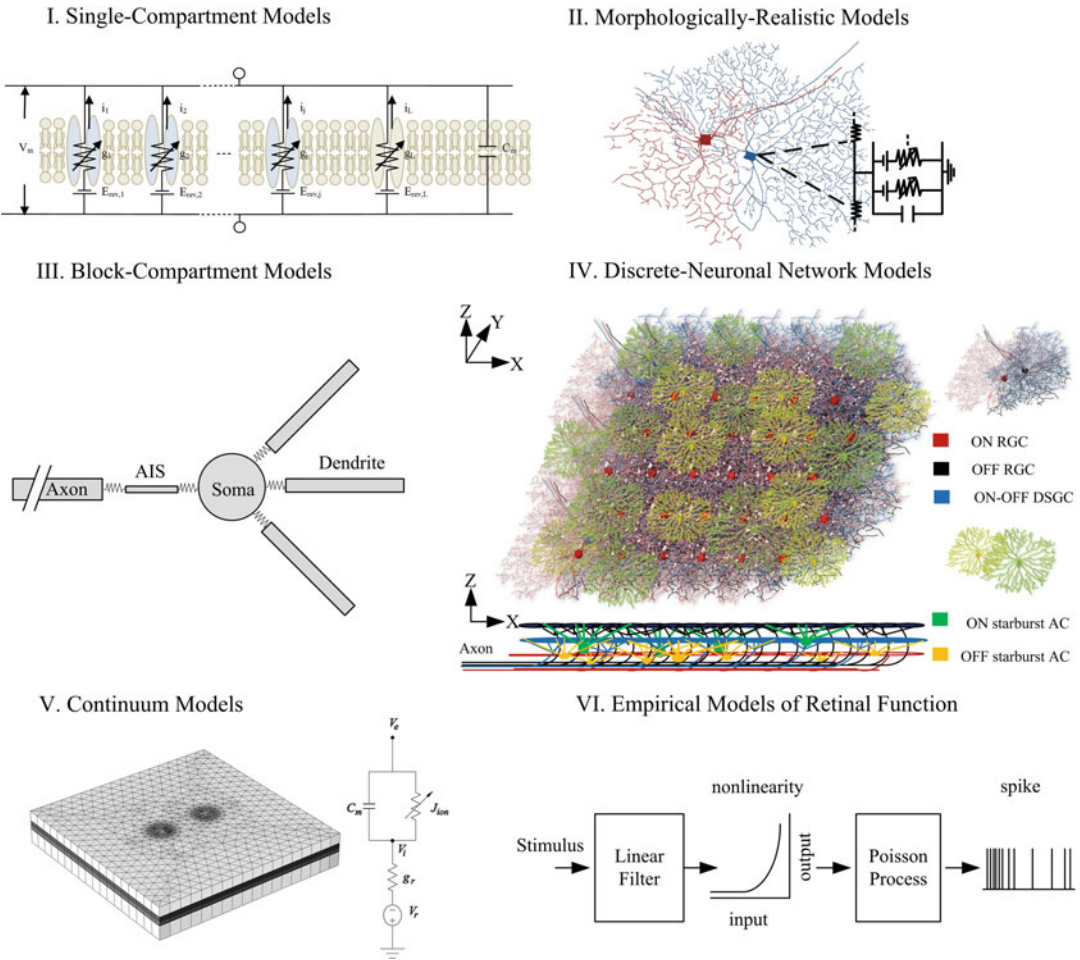
On a microscale, retinal neurons extract their preferred visual information; process this information, often with the help of other neurons; and then transfer the results to downstream neurons. A single neuron can be represented by either a single-compartment model, a morphologically realistic model, or via a block-compartment approach, depending on the aims, complexities, and physiological assumptions on which the model is based. Such models integrate electrophysiological current/voltage clamp recordings and biophysical principles into a mechanistic understanding of individual neuronal properties,

reconstructing ionic mechanisms hidden in the data, as well as utilizing new experimental information to improve existing model structures.

On a larger scale, visual information is arrayed across large inhomogeneous populations of neurons within each retinal layer. One approach of representing such neuronal networks involves bringing together individual neurons, each being a complete model capable of stand-alone execution, and connecting them together with the computational representation of synapses. As such, these models are generally mechanistically detailed, but computationally expensive to run. Alternatively, empirical models could also be used to construct large-scale models of the retinal function. Unlike the aforementioned approach, these models aim to capture only the input-output relationship of the neuron/network by treating the constituent neurons as black boxes (Pillow et al. 2005; Pillow et al. 2008). By omitting neuronal morphological details, and often the associated ionic biophysics too, these approaches have the advantage of computational efficiency. These large-scale tissue- or network-based models have been used to investigate how each retinal neuron contributes to a particular subcircuit or entire retinal tissue and how they work together to collectively encode visual input. Irrespective of the modeling techniques, they offer a better understanding of the growing amount of experimentally recorded retinal responses to light or electrical stimuli and can be used to make testable predictions. For clinical applications, some of these models also provide valuable insights into the development of effective stimulation strategies for visual prostheses (Luo and Da Cruz 2014; Halupka et al. 2017; Barriga-Rivera et al. 2017; Loizos et al. 2018; Tsai et al. 2017; Yang et al. 2018). This chapter examines the current state of the art of computational models of the neural retina, across different scales, and discusses their advantages, limitations, and future potential.

Single-Compartment Models

Single-compartment models (see Fig. 1, level I) have been used to simulate nearly all retinal



Computational Models of Neural Retina, Fig. 1 Six types of computational models typically used in retinal neuron modeling. I. Single-compartment models, II. morphologically realistic models, III. block-compartment models, IV. discrete-neuronal network models (adapted from (Publio et al. 2009)), V. continuum models, and VI. empirical models of retinal function (adapted from (Halupka et al. 2017)). Depending on the study aim, a single-compartment neuron model can be extended to any biophysical model type (II, III, IV, V), by

adding new assumptions such as anatomical structure, synaptic, or interneuron coupling information. Conductance-based models (i.e., types I, II, and III) can be used as individual neuron elements in both continuum models and discrete-network models. Empirical models are often used in building retinal networks or the whole visual system. Large-scale network models can capture the essential function of photoreceptors, bipolar cells, and RGCs, as well as the contribution of retinal heterogeneity in visual information processing

neuron types, including photoreceptors (Kamiyama et al. 1996; Publio et al. 2006; Kourennyi et al. 2004), horizontal cells (Aoyama et al. 2005; Usui et al. 1996b; Shirahata 2008), bipolar cells (Usui et al. 1996a), amacrine cells (Steffen et al. 2003; Shirahata 2011), and a range of RGC types (Fohlmeister and Miller 1997a; Fohlmeister et al. 1990; Guo et al. 2012; Kameneva et al. 2011; Qin et al. 2017). These

models approximate the structure of the neural excitable membrane using a capacitance to mimic the membrane phospholipid bilayer, in parallel with several conductors to mimic transmembrane channels composed of proteins. The relationship between the transmembrane potential and membrane currents is described by the following ordinary differential equation (ODE):

$$J_m = C_m \frac{dV_m}{dt} + J_{\text{ion}} + J_{\text{stim}} = 0 \quad (1)$$

where J_m denotes total membrane current density (current per unit membrane area), V_m represents membrane potential, C_m represents membrane capacitance per unit area, and J_{ion} represents the total ionic current density (Aidley 1979). A single-compartment model assumes no net current across the cell membrane ($J_m = 0$), since all current flowing through the ionic channels charges the membrane capacitance. This is also known as the space-clamped condition. Furthermore, the neuron may be activated by an intracellular stimulus current density (J_{stim}) delivered into the cell, to mimic experimental manipulation during intracellular recordings.

Since ionic mechanisms of retinal neurons are far more complex than those of the classic Hodgkin-Huxley ionic model of the squid giant axon (Hodgkin and Huxley 1952), many modelers have chosen to modify the classic model, extending it to replicate the known ionic mechanisms in various retinal neurons. Among the first ionic models developed for the retina were those for the RGCs. Their all-or-none spiking behaviors are close to the classical notion of neurons and are thus easily modeled by modifying existing Hodgkin-Huxley-type formulations. A landmark in RGC modeling was the Fohlmeister-Coleman-Miller (FCM) formulation (Fohlmeister et al. 1990; Fohlmeister and Miller 1997a, b). This model was based on voltage clamp studies in the tiger salamander retina. It contained five intrinsic ion currents underlying RGC spiking. Prior to these studies, experimental knowledge of detailed ion channel kinetics or their neuronal distribution was rarely used in retinal neural modeling. The FCM model also included intracellular calcium dynamics responsible for temporal spiking properties. With more optimized Na^+ and K^+ gating kinetics, the FCM model demonstrates many advantages over the original Hodgkin-Huxley formulation in terms of impulse encoding flexibility (Fohlmeister 2009), revealing its ability in reconstructing a large range of neuronal spiking behaviors. Since its publication, this model and its derivatives have led to further quantitative understanding of many dynamical phenomena in RGCs, including spike-frequency

adaptation (Fohlmeister and Miller 1997a), rebound activation (Guo et al. 2012; Kameneva et al. 2011), burst firing (Kameneva et al. 2011), and subthreshold activities (Kameneva et al. 2011).

Moreover, the single-compartment FCM model was also validated in higher-dimensional simulations with detailed anatomical information or network interactions. To the best of our knowledge, Fig. 2 illustrates nearly all applications and extensions based on FCM formulations in the last two decades. Its morphological-, tissue-, and network-based extensions are discussed in the following sections.

Despite the reported functional significance of all five ionic currents in the FCM model, relatively simpler ionic models were still used to study specific RGC response properties when accurate impulse generation was not required (Carras et al. 1992; Al Abed et al. 2013; Boinagrov et al. 2010), as well as for other retinal neurons (e.g., photoreceptors or bipolar cells) (Taylor et al. 1995; Aoyama et al. 2005).

The advantage of simplicity in a single-compartment model is also its weakness. Certain disparities between the single-compartment FCM model and known biological RGC behavior cannot be reconciled by optimizing the model parameters alone (Fohlmeister and Miller 1997a). Having additional neuronal compartments that differ in both size and ionic channel density could also produce more realistic spike generation and propagation (Carras et al. 1992). Recent brain cell studies suggest that models cannot capture subtle response characteristics, such as fast depolarization during action potentials, without incorporating representations of axons and dendrites and the propagation of current along these neurites (McCormick et al. 2007; Mainen and Sejnowski 1996; Herz et al. 2006). Therefore, rather than simply incorporating intrinsic properties at a single point, spatial anatomical information and ionic channel distribution are also required for accurate neuronal modeling.

Morphologically Realistic Models

Toward the goal of creating models that represent their biological counterpart more closely,

morphologically realistic models (see Fig. 1, type II) are based on detailed anatomical representations of the physical structural components in biological neurons, including soma, axon initial segment (AIS), axon hillock (AH), the distal axon, and dendrites. Such models are ideal for studying how cell morphologies and nonuniform distributions of ionic channels contribute to neuronal response dynamics and how these affect function. Morphologically realistic models provide a good approximation of biological neuronal behavior and have been largely used to build structurally “complex” retinal neurons such as amacrine cells and RGCs. These models can sometimes include more than 1000 morphological segments to ensure accurate spatial resolution (Fohlmeister et al. 2010).

In morphological cable models, membrane potential is both space and time-dependent, necessitating the modification of Eq. (1) as follows:

$$\begin{aligned} J_m &= \frac{\partial}{\partial s} \left(\frac{r\sigma_i}{2} \frac{\partial V_m}{\partial s} \right) \\ &= C_m \frac{\partial V_m}{\partial t} + J_{\text{ion}} + J_{\text{stim}} \end{aligned} \quad (2)$$

where s is the arc-length distance along the neuron, r is the local radius of the neuron which can vary with s , and σ_i is the intracellular conductivity.

In practice, Eq. (2) is approximated by separating the neuron into multiple discrete regions, each region associated with its own ionic properties and connected with neighboring compartments by axial conductors. The more compartments are used, the closer the model tends toward the biological neuron.

An advantage of this type of model is that it can also simulate cell responses to extracellular electrical stimulation, as opposed to only intracellular stimulation in the single-compartment model (a single-compartment model assumes no net current across the cell membrane). In this situation, membrane potential is calculated by taking the difference between intracellular potential V_i and extracellular potential V_e :

$$V_m = V_i - V_e \quad (3)$$

where V_i is derived from

$$\frac{\partial}{\partial s} \left(\frac{r\sigma_i}{2} \frac{\partial V_i}{\partial s} \right) = C_m \frac{\partial V_m}{\partial t} + J_{\text{ion}} \quad (4)$$

and the extracellular voltage distribution can be simulated by either a monopolar point source (Greenberg et al. 1999; Jeng et al. 2011) or a disk electrode (Greenberg et al. 1999; Tsai et al. 2012; Jeng et al. 2011), modeled as

$$V_e = \rho_e I / 4\pi r \quad (5)$$

$$\text{or } V_e = \frac{2IR_s}{\pi} \arcsin \left(\frac{2R}{\sqrt{(a-R)^2 + z^2} + \sqrt{(a+R)^2 + z^2}} \right) \quad (6)$$

where ρ_e denotes the resistivity of the retinal extracellular solution; I is the extracellular stimulus current; r is the distance between the stimulating electrode and the point at which the voltage is being computed; a and z are the radial and axial distance, respectively, from the center of the disk for $z \neq 0$; R is the radius of the disk; and R_s is the electrode transfer resistance. Note that Eqs. (5) and (6) are applicable to infinite and semi-infinite homogeneous media, respectively.

In some cases, the extracellular voltage distribution has been coupled to the local membrane potential (Abramian et al. 2011) and given by

$$\frac{\partial}{\partial s} \left(-\frac{r\sigma_e}{2} \frac{\partial V_e}{\partial s} \right) = C_m \frac{\partial V_m}{\partial t} + J_{\text{ion}} \quad (7)$$

where σ_e denotes the extracellular conductivity.

Neuronal morphology can influence the flow of intracellular currents between neighboring compartments through the cell membrane and by intracellular conductance. As a result, morphology may also contribute to the unique spiking behavior of different RGC types (Sheasby and Fohlmeister 1999). Although dendritic morphologies and stratifications of RGCs have been examined extensively, their contribution to RGC spiking patterns is not well understood, owing to the difficulty of isolating and manipulating such

properties in the experimental preparation. However, the morphologically realistic modeling approach can quantitatively control a variety of cellular properties, including morphology, and isolate their contributions in shaping firing patterns (Guo et al. 2013b, c).

Notable examples of morphologically realistic retinal neuron models include (a) the FCM (1997) model (Fohlmeister and Miller 1997b), which is the first morphologically detailed RGC formulation, able to closely reconstruct action potential shapes and spiking properties; (b) the Sheasby-Fohlmeister (1999) realistic RGC encoder (Sheasby and Fohlmeister 1999), used to explore the effect of regional ionic channel distributions along the cellular morphology; (c) the Schachter et al. (2010) model (Schachter et al. 2010), able to explain the mechanisms of active dendritic processing of synaptic inputs in direction-sensitive RGCs; and (d) the Jeng et al. (2011) sodium channel band model (Jeng et al. 2011) that enabled the determination of the factors underlying action potential initiation site in response to electrical stimulation of RGCs.

These morphologically detailed modeling approaches offer important information on how their channel distributions influence RGC firing patterns and how the interaction between different cell regions influences the neural coding. The recent morphologically realistic model of Abbas et al. (Abbas et al. 2013) suggested that dendritic ionic channels provide RGCs with the ability to code “looming” motion. Another recent study by Maturana et al. (Maturana et al. 2013) focused on how physical properties of RGCs contribute to their specific spiking response patterns in response to electrical stimulation.

Experimental findings have also suggested that RGC dendrites exhibit regenerative spikes, as opposed to being simply passive neurites (Velte and Masland 1999; Oesch et al. 2005; Sivyver and Williams 2013). The detailed dendritic structure of morphologically realistic models can provide the framework for investigating dendritic signal processing, since the physical properties can be precisely controlled in these models. Furthermore, the dendritic active conductances can be modulated *in silico*, to study their effects on RGC

spiking properties (Guo et al. 2013c). In summary, the realistic neuron modeling approach provides a promising tool for studying soma-dendritic interactions, assisting in interpreting experimental studies in dendritic patch-clamp recordings, fluorescent imaging, and immunocytochemical channel localization techniques.

Other than their application to RGCs, morphologically realistic models have also been applied to amacrine cells. These cells also demonstrate a large diversity in functional properties (Vigh et al. 2000; Yang et al. 1991). A morphologically realistic starburst amacrine cell model was developed by Fohlmeister et al. to study mechanisms underlying local dendritic processing (Fohlmeister et al. 1990). By testing different artificial morphologies, another amacrine modeling study by Tukker et al. (Tukker et al. 2004) suggested that directional sensitivity may mainly depend on a sufficient number of synaptic inputs at the distal dendrites rather than the dendritic morphology itself. Another amacrine modeling study by Miller et al. (2006) suggested that various amacrine cell spiking properties could be reproduced by a RGC model with minimal parameter adjustment (Miller et al. 2006), revealing the close ionic relationships between some amacrine cells and RGCs.

Although certain morphologically realistic retinal neuron models have also been used in constructing accurate models of local circuits or the whole-tissue retina, to study neuronal interactions during electrical stimulation (Greenberg et al. 1999; Resatz and Rattay 2004; Rattay et al. 2003; Rattay and Resatz 2004; Loizos et al. 2014, 2016, 2018), their huge computational demand has resulted in their restricted use for population-based simulations, especially in large-scale network modeling.

Block-Compartment Models

An alternative modeling strategy, block-compartment modeling (see Fig. 1, type III), represents only a few neuronal regions. This is a compromise between computational efficiency and biological realism. These models can be considered as a simplified version of the morphologically realistic approach,

extracting the most essential anatomical information to provide high computational efficiency with minimal neural structure.

The simplest model in this genre is a two-compartment system coupled by a linear conductor, representing a soma and a dendritic or axonal compartment. In this way, Eq. (2) can be updated as follows:

$$\begin{aligned} \frac{G_c}{p}(V_x - V_s) &= C_m \frac{dV_s}{dt} + J_{\text{ion},s} \\ \frac{G_c}{1-p}(V_s - V_x) &= C_m \frac{dV_x}{dt} + J_{\text{ion},x} \end{aligned} \quad (8)$$

where V_s and V_x represent the membrane potential in the soma and connected compartment, respectively, G_c is the coupling conductance between compartments, p is the percentage of the cell membrane area taken up by the soma, and $J_{\text{ion},s}$ and $J_{\text{ion},x}$ are the membrane potentials of the soma and connected compartment, respectively.

This morphology-reducing process depends largely on the motivation of specific studies, as well as the ionic mechanisms involved. Previous findings have suggested that reasonably realistic RGC spiking patterns, comparable to experimental recordings and simulations from morphologically realistic models, can be obtained using only four neuronal compartments (dendrites, soma, thin segment, and axon) (Fohlmeister and Miller 1997b). A single unbranched dendritic compartment, which allowed regionally specific activation of individual channel subtypes, was shown to be sufficient to elicit summation of excitatory postsynaptic potentials (EPSPs) in RGCs (Abbas et al. 2013). In addition, a simplified axonal activation model was able to successfully predict RGC experimental threshold profiles, as well as the initial activation location in response to electrical stimulation (Abramian et al. 2011). In another model investigating the origin of AP initiation in RGCs, the dendrites were reduced to unbranched cables of uniform diameter (Carras et al. 1992). Moreover, another such simplified RGC-structure model was used to investigate how epiretinal electrical stimulation could result in the production of punctate phosphenes, as

opposed to diffuse or streaked perceptions that would be consistent with the recruitment of axons from distant RGCs (Schiefer and Grill 2006). In a more recent tissue-based retinal model, each point in the RGC layer was represented by an active soma and a passive dendritic compartment, with a synaptic input into dendrites included to approximate the underlying neural structure (Al Abed et al. 2013).

Apart from RGC models, equivalent cable representations have also been used to simulate starburst amacrine cells (Poznanski 1992; Enciso et al. 2010; Tukker et al. 2004). These models incorporated various levels of simplified cylindrical dendritic structures and were helpful in elucidating the influence of morphological structure on the mechanisms underlying directional sensitivity in starburst amacrine cell networks.

Block-compartment models have also been applied to morphologically simple neurons such as photoreceptors (Taylor et al. 1995), bipolar cells (Mennerick et al. 1997), and horizontal cells (Usui et al. 1996b; Smith 1995) (see Table 1). Most of these retinal neuron types do not demonstrate a significant morphological diversity and only require a simple physical structure such as a cylindrical soma connected to an axon terminal.

One question that must be answered in block-compartment models is to what extent can retinal neurons be simplified without compromising realistic cell behavior? A general principle is that models should be at the simplest level required to reproduce desired behavior of a physical system. This also raises another question: to what extent does neural morphology contribute to its response? A recent study by Guo et al. (2013b) provided an example showing the contribution of morphology to cell responses. They showed that RGC models could reproduce distinct variations in spiking patterns in response to intracellular current injection by solely varying their morphology, with all biophysical parameters describing voltage-gated channel kinetics and distributions remaining unchanged. In addition, the spatial distribution of membrane ion channel densities among the various neural compartments also contributes to the neuronal response.

Computational Models of Neural Retina,

Table 1 Different types of retinal neurons can be characterized into multiple model types. RR, CR, HC, and BC models are largely limited to single-compartment and block-compartment models due to their relatively simple morphology. Morphologically complex neurons such as

ACs and particularly RGCs are represented at all types. Empirical models can reproduce the functional input-output relationship between light stimulus inputs and cell responses in nearly every retinal neuron type without considering the detailed biophysical structure of the neuron

Neuron type	Model type			
	Single-compartment model	Morphologically realistic model	Block-compartment model	Empirical model
Rod photoreceptor (RR)	Kamiyama et al. (1996), Kourennyi et al. (2004), Ogura et al. (2003), Publio et al. (2006)		Taylor et al. (1995)	Hood et al. (1993), Hamer et al. (2005), Lamb and Pugh (1992)
Cone photoreceptor (CR)	Baylor et al. (1974), Kourennyi et al. (2004), Vallergera et al. (1980), Publio et al. (2009)		Smith (1995), Taylor et al. (1995), Tsai et al. (2017)	van Hateren and Snippe (2007), Teeters et al. (1997), Shah and Levine (1996a), Shah and Levine (1996b)
Horizontal cell (HC)	Usui et al. (1983), Aoyama et al. (2005), Shirahata (2008)		Usui et al. (1996b), Smith (1995), Tsai et al. (2017)	
Bipolar cell (BC)	Publio et al. (2009), Usui et al. (1996a)		Mennerick et al. (1997), Werginz et al. (2015)	Robson and Frishman (1996), Robson and Frishman (1995)
Amacrine cell (AC)	Publio et al. (2009), Shirahata (2011), Steffen et al. (2003), Smith and Vardi (1995)	Velte and Miller (1997), Miller et al. (2006)	Enciso et al. (2010), Poznanski (1992), Tukker et al. (2004)	Saglam et al. (2009)
Retinal ganglion cell (RGC)	Fohlmeister et al. (1990), Fohlmeister and Miller (1997a), Guo et al. (2012), Kameneva et al. (2011), Publio et al. (2009), Boinagrov et al. (2012), Qin et al. (2017)	Fohlmeister et al. (2010), Fohlmeister and Miller (1997b), Guo et al. (2013a), Jeng et al. (2011), Sheasby and Fohlmeister (1999), Tsai et al. (2012), Greenberg et al. (1999), Maturana et al. (2013), Schachter et al. (2010), Schiefer and Grill (2006), Velte and Miller (1995), Carras et al. (1992), Rattay and Resatz (2004), Rattay et al. (2003), Resatz and Rattay (2004), Abbas et al. (2013), Publio et al. (2012), Yang et al. (2018), Guo et al. (2019)	Abramian et al. (2011), Carras et al. (1992), Al Abed et al. (2013), Abbas et al. (2013), Fohlmeister and Miller (1997b), Werginz et al. (2014)	Cai et al. (2007), Keat et al. (2001), Victor (1987), Victor (1988), Hosoya et al. (2005), Pillow et al. (2005)

Since there is no generally clear simplification approach in block-compartment neural modeling, an alternative approach comprises iterative morphometric simplification, wherein the reducing process is stopped when the model fails to reproduce biological cell responses. Although the influence of systematic morphologic perturbations in neuronal behavior has been reported in several brain cell studies (van Elburg and van Ooyen 2010; Mainen and Sejnowski 1996), no similar approach has been used yet in retinal neuron modeling. A morphometric simulator was developed recently to study how dendritic intersections, branching points, and terminal tips contribute to correct classification of RGC images (Ristanovic et al. 2009). One could imagine, for example, the integration of such a morphometric generator into a modeling framework, to create a platform for exploring the ramifications of RGC morphological variations (Wong et al. 2012; O'Brien et al. 2002; Rockhill et al. 2002).

Discrete-Neuronal Network Models

The retinal network can also be simulated by grouping discrete retinal neuron elements, based on techniques described earlier, with excitatory and inhibitory synaptic interactions. In addition to neural properties and stimulus parameters, these discrete-neuronal network models (see Fig. 1, type IV) also take into consideration the influence of forward and feedback connections among neurons, as well as the physical architecture of the retina.

A discrete-neuronal network model can represent either the entire retinal structure (Wohrer and Kornprobst 2009) or a retinal subsystem, including the cone-rod network (Smith et al. 1986), the rod bipolar network (Robson and Frishman 1996), the cone-horizontal cell circuit (Smith 1995), the horizontal cell layer (Usui et al. 1996b), the rod pathway (Publio et al. 2009), the cone pathway (Arguello et al. 2013; Cottaris et al. 2005; Teeters et al. 1997), the amacrine network (Smith and Vardi 1995), bipolar-RGC interactions (Rattay et al. 2003), and RGC layer (Publio et al. 2012).

Most discrete-neuronal network models do not focus on physiological precision in individual neurons but on the functional output of the retina on a large scale. They are generally constructed using non-biophysical neuron formulations such as cascaded models. This allows them to include a large number of cells with multiple visual pathways rather than specific local microcircuits while remaining computationally tractable. As such, these models can be very effective for investigating complex neural networks containing a large number of cells of different types. For example, one large-scale retinal model, comprising up to 10^5 neuron elements, was able to achieve both accurate physiological behavior and reasonable computational efficiency (Wohrer and Kornprobst 2009). Another study examined the contribution of different cell subclasses in a large RGC population, facilitating the development of testable population-based hypotheses (Bomash et al. 2013). In addition, these functional network models have also been used to provide a comprehensive description of electroretinogram (ERG) generation using only local rod bipolar circuits (Robson and Frishman 1996). They can also qualitatively explain various types of adaptation during visual information processing (Hosoya et al. 2005).

Some discrete-neuronal network models also incorporate detailed descriptions of retinal connectivity in successive neural layers, with these connections modeled by conductance-based formulations with a full set of cellular and synaptic parameters. For example, a detailed network model by Hennig et al. (Hennig et al. 2002) was used to test the influence of various retinal cell classes and subcircuits on the unique response pattern in each identified RGC type. Another model of the cone-horizontal cell network was used to study the biological origin of recorded damped oscillations in the retinal network (Tsai et al. 2017).

More recently, a discrete-neuronal network model was used to study the effects of electrical stimulation in the degenerated retina (Loizos et al. 2018). In this model, the retina was degenerated

by simulating anatomical and functional remodeling which occurs in the early stages of retinal degeneration. The deceased retinal network connectivity was based on high-speed automated electron optical images recorded from animal models (Marc et al. 2013).

It is important to note that detailed morphologically realistic models are not typically used for discrete-neuronal network modeling, mainly due to computational efficiency, except in those studies focusing on local microcircuit stimulation. Examples of the latter include (1) ionic models of rod/cone photoreceptors, bipolar cells, amacrine cells, and RGCs in an accurate network retinal description (Publio et al. 2009); (2) morphological-detailed RGC and bipolar layers in a computational model of retinal degeneration (Loizos et al. 2018); (3) a morphological RGC model in a local bipolar-RGC circuit (Resatz and Rattay 2004; Rattay and Resatz 2004); and (4) a recent model of the RGC layer represented by morphologically realistic models with dendrodendritic gap junctions (Publio et al. 2012).

Continuum Models

Continuum models (see Fig. 1, type V) have been used to simulate the response of bulk retinal tissue activation in an averaged spatial sense, without explicit representation of the constituent neurons. Continuum bidomain (intra- and extracellular domains) formulations have been proven useful in cardiac (Roth and Wikswo 1994; Henriquez 1993) and neural tissue simulation (Altman and Plonsey 1990; Martinek et al. 2008). These models are able to simulate bulk active or passive current flow across neuronal membranes into the extracellular space, perturbing the extracellular potential, as has been observed experimentally dating back several decades (Brindley 1956). This advantage allows the continuum bidomain approach to be an ideal tool for simulating the spatial extent of retinal activation due to extracellular electrical stimulation, as well as investigate the influence of electrode configuration, position, and stimulus parameters on retinal tissue responses.

In continuum retinal models, the dynamics of both extracellular and intracellular potentials are considered:

$$\begin{aligned} J_m &= \nabla \cdot \left(-\frac{r\sigma_e}{2} \nabla V_e \right) = \nabla \cdot \left(\frac{r\sigma_i}{2} \nabla V_i \right) \\ &= C_m \frac{\partial V_m}{\partial t} + J_{\text{ion}} \end{aligned} \quad (9)$$

where $V_m = V_i - V_e$ and σ_e is the extracellular conductivity. Some formulations adopt a “pseudo-bidomain” approach (Yin et al. 2010), by tying the intracellular potential to a remote resting potential:

$$J_m = \nabla \cdot \left(-\frac{r\sigma_e}{2} \nabla V_e \right) = g_r (V_r - V_i) \quad (10)$$

where V_r is the intracellular potential of a “remote” neural compartment and g_r is an intracellular conductance tying the intracellular potential to this remote compartment. The effect of the latter parameter is to prevent the intracellular potential from floating freely with changing extracellular potential, due to an applied stimulus.

The first such description of retinal electric simulation was the Dokos et al. (2005) model, comprising a vitreous and an active RGC layer (Dokos et al. 2005). It represented a “genuine bidomain” formulation (i.e., Eq. (9)) and was used to simulate the retinal response to a bipolar electrode configuration using various stimulus waveforms. This model was then extended by adding further retinal layers, including a passive inner plexiform layer, nuclear layer, subretinal space, retinal pigment epithelium, and choroid (Joarder et al. 2011). A similar model was also used to investigate the threshold of neuronal activation and the spatial extent of activation, thus providing valuable information regarding stimulus thresholds and localization of activation (Abramian et al. 2011). The subsequent retinal model by Abramian et al. was used to investigate multielectrode array stimulation (Abramian et al. 2014). This model examined the advantages of the so-called “quasi-monopolar” stimulation compared to bipolar or monopolar stimulation, combining the low thresholds of monopolar

stimulations with the focal spatial activation of hexapolar configurations (Matteucci et al. 2013).

Continuum models can be also be further extended by adding network effects, as in the retinal model of Yin et al. (Yin et al. 2010) which included excitatory input from bipolar cells and inhibitory input from wide-field amacrine cells. This model was subsequently refined by adding a dendritic compartment and synaptic currents to account for presynaptic influences on RGC activation (Al Abed et al. 2013). A further model utilizing microcircuitry of the ON cone pathway was formulated to investigate the network response to large and small spots of light (Yin et al. 2011).

These retinal models can be used to study the spatial activation profile of electrical stimulation. They provide a promising modeling framework which could be easily extended by incorporating newly identified ionic currents and synaptic connections. A more recent extension of the continuum approach was a multi-domain formulation to represent the major RGC compartments, including soma, dendrites, and AIS (Alqahtani et al. 2017).

Empirical Models of Retinal Function

Apart from the aforementioned biophysically detailed models, a black box approach may be used to represent the retinal network. The goal of these models is to capture statistical relationships between light stimuli and cell firing rates without describing detailed neural structure, biophysics, and network connectivity. A popular approach for implementing these block-structured models, also known as “cascaded models” (see Fig. 1, type VI), involves representing the retina as a series of linear and nonlinear temporal filter elements (Pillow et al. 2005, 2008). These models can closely reproduce responses of the retina to simple laboratory light stimuli using only a few free parameters. Empirical models do not attempt to accurately reconstruct biophysical aspects of real retinal neurons. However, they can provide enough overall functional characteristics to cover both the computational aspects of individual

retinal neurons and the collective capabilities of large-scale neural networks. They are thus very popular in modeling local neural circuits (Curlander and Marmarelis 1987), the larger retinal network (Teeters et al. 1997; Wohrer and Kornprobst 2009), or even the entire visual system (Halupka et al. 2017).

Empirical models of neural function were largely used to simulate behavioral characteristics of outer retinal neurons, the cones (van Hateren and Snippe 2007; Shah and Levine 1996a; Shah and Levine 1996b), and rods (Hamer et al. 2005; Lamb and Pugh 1992). Despite their high degree of simplicity, these phenomenological models have been successfully applied to investigate specific physiological mechanisms, including those underlying normal and abnormal rod-receptor activity affected by retinodegenerative disease (Hood et al. 1993), as well as nonlinear synaptic dynamics between photoreceptors and downstream neurons (Juusola et al. 1995).

In empirical models, the specific neural spiking behaviors were reproduced by their unique transfer functions, characterizing linear and nonlinear spatial summation mechanisms in various types of RGCs in the retina (Victor 1988, 1987). A generic spike-train simulator was also able to accurately reconstruct spiking responses in a large range of functionally identified RGCs from different species (Keat et al. 2001).

These functional models have also been popular for studying retinal motion detection and anticipation (Table 2). In one study, motion extrapolation in many species was reproduced by block structures representing the spatially extended receptive field, the biphasic temporal response, and a nonlinear contrast gain control (Berry et al. 1999). Another model of object motion-sensitive circuitry was able to predict the neuronal response at each stage of the circuit (Baccus et al. 2008), revealing the contribution of specific retinal interneurons in global motion detection.

However, the mechanisms underlying visual information processing can be far more complex than a series of temporal filters. Functional computation in a real retinal neuron is also highly related to its physical structure, ionic channel

Computational Models of Neural Retina, Table 2 Task-specific applications of various retinal neuron modes and the biological species each model is based on

Task	Biological species a model is based on
Modeling retinal neuron physiology	
Action potential initiation	Rabbit RGC: (Abramian et al. 2011; Jeng et al. 2011; Schiefer and Grill 2006) Mudpuppy RGC: (Carras et al. 1992) Tiger salamander RGC: (Werginz et al. 2014)
Dendritic processing	Rabbit starburst amacrine cell: (Velte and Miller 1997; Poznanski 1992; Enciso et al. 2010) Tiger salamander amacrine cell: (Miller et al. 2006) Rabbit OFF RGC: (Guo et al. 2013c) Rabbit direction selective RGC: (Schachter et al. 2010) Turtle direction selective RGC: (Borg-Graham 2001) Tiger salamander RGC: (Publio et al. 2012) Cat ON alpha RGC: (Freed et al. 1992) Mudpuppy RGC: (Velte and Miller 1995)
Motion detection and anticipation	Rabbit direction selective RGC: (Schachter et al. 2010) Tiger salamander and rabbit RGC: (Berry et al. 1999) Cat RGC: (Hennig and Worgotter 2007) Fly visual system: (Borst et al. 2005) Tiger salamander/rabbit retina: (Hosoya et al. 2005) Tiger salamander retina: (Baccus et al. 2008)
Effects of ionic channel distribution	Tiger salamander RGC: (Fohlmeister and Miller 1997a, b; Fohlmeister et al. 2010) Bullfrogs rod photoreceptor: (Ogura et al. 2003) Rabbit ON and OFF RGC: (Guo et al. 2013a) Rabbit starburst amacrine cell: (Velte and Miller 1997) Mouse dopaminergic amacrine cell: (Shirahata 2011) Tiger salamander amacrine cell: (Miller et al. 2006) Goldfish horizontal cell: (Aoyama et al. 2005) Lower vertebrate bipolar cell: (Usui et al. 1996a) Rat RGCs: (Qin et al. 2017)
Effect of new ionic mechanisms	Rabbit ON and OFF RGC: (Guo et al. 2012, 2013a, b, c) Mouse ON and OFF RGC: (Maturana et al. 2013; Kameneva et al. 2011) Mammalian rod photoreceptor: (Publio et al. 2009) Rat ON RGC: (Abbas et al. 2013) Mouse dopaminergic amacrine cell: (Steffen et al. 2003)
Effects of physical properties	Tiger salamander RGC: (Fohlmeister and Miller 1997b; Sheasby and Fohlmeister 1999) Mudpuppy RGC: (Velte and Miller 1995) Rabbit ON and OFF RGC: (Fohlmeister and Miller 1997b; Guo et al. 2013a, b, c; Tsai et al. 2012) Mouse ON and OFF RGC: (Maturana et al. 2013) Rabbit starburst amacrine cell: (Velte and Miller 1997; Poznanski 1992) Tiger salamander amacrine cell: (Miller et al. 2006)
Modeling retinal response to electrical stimulation	
Effects of extracellular stimulation waveform	Tiger salamander RGC: (Rattay et al. 2003; Resatz and Rattay 2004; Boinagrov et al. 2010; Werginz et al. 2014; Boinagrov et al. 2012; Barriga-Rivera et al. 2017)
Effects of electrode size/location	Mouse and monkey RGC: (Tsai et al. 2012) Tiger salamander RGC: (Greenberg et al. 1999; Schiefer and Grill 2006; Werginz et al. 2014)
Effects of multielectrode configuration	Tiger salamander and rabbit RGC: (Abramian et al. 2011) Tiger salamander RGC: (Cao et al. 2015; Dokos et al. 2005; Abramian et al. 2014; Joarder et al. 2011)
Differential activation of retinal neurons	Rat bipolar cells: (Werginz et al. 2015) Tiger salamander RGC: (Kameneva et al. 2016; Yang et al. 2018)
Electrical stimulation of degenerated retina	Tiger salamander RGC, lower vertebrate bipolar cell: (Loizos et al. 2018)
Electrical stimulation of retinal network	Tiger salamander cone, rabbit horizontal cell: (Tsai et al. 2017)

expressions, and synaptic interactions. In this regard, empirical models are not ideal for relating high-level response characteristics of neurons, or of a neural network, to the underlying mechanisms from which these characteristics arise. Although there have been a few examples of empirical models in simulating nonlinear interactions of multielectrode stimulation of the retina (Maturana et al. 2018) and visual cortex (Halupka et al. 2017), these models cannot easily simulate cellular responses to extracellular or intracellular electrical stimulation, limiting their utility in modeling retinal activation by artificial electric stimulation, as in the case of visual prostheses.

Outlook on Retinal Modeling

Among all retinal neuron types, the mechanisms underlying morphologically complex retinal neurons such as amacrine cells or RGCs are still unclear (for a review see Masland (2012)). There are more than 30 RGC types in the mammalian retina (Baden et al. 2016). A definitive description of these cells has not yet been made due to their rich diversity in both intrinsic electrophysiological and morphological properties. Limited experimental information on ion channel kinetics and distributions in identified cell types also makes cell-type-specific model parameter optimization a difficult task. Prior models of these neurons have been largely limited to identification of individual types, regardless of the diversity of the cellular morphology and membrane channel distributions/kinetics in each cellular region, despite the fact that the correlation between neuronal function and inherent biophysical properties is highly significant, as suggested by experimental studies (O'Brien et al. 2002; Wong et al. 2012). On the other hand, despite far less morphological diversity, there are still many debates about the functional classification and mechanisms of horizontal cells and bipolar cells. New knowledge about these “preprocessing” neurons continues to be found (Herrmann et al. 2011; Klaassen et al. 2011; Jackman et al. 2011; Freed 2000; Dreosti et al. 2011). Therefore, further model

validation based on newly found experimental evidence is still required to quantitatively identify and define these cells.

At the single-cell level, the composition of ion channels in retinal neuron models continues to be refined. The initial FCM model with five active membrane currents appears to be oversimplified, with the identification of new ionic channels in retinal neurons (Miller et al. 2002; Tabata and Ishida 1996; Lee and Ishida 2007). Ionic channel formulations are generally based on voltage clamp experimental data. The properties of these new currents and their regional distributions in different neuron types may significantly contribute to the overall neural response. With the likely discovery of more ionic mechanisms in retinal neurons, there still remains substantial room for improvement of the single-cell models.

In whole-retina models, the functional significance of cell morphology has not been systematically studied, despite of its importance being recognized in brain neuron network modeling (Traub et al. 2005). Why do retinal neurons present a large range of morphological diversity? It appears that morphological factors play some role in mediating neuronal function. Cell-specific morphological information will therefore play an increasing role in the development of future tissue or network-based models of retinal function.

Finally, the ability of existing retinal neuron models to reproduce experimental data under degenerative conditions is still unclear. Experimental studies (Chua et al. 2013; Kalloniatis et al. 2016; Nivison-Smith et al. 2013; Jones and Marc 2005) have shown that retinal neurons undergo remodeling in degenerative disease, leading to altered synaptic connections and neurotransmitter release, as well as functional changes (Cho et al. 2016). These retinal network changes will influence the RGC response to electrical stimulation. However, detailed biophysical mechanisms underlying retinal remodeling are still under debate (Trenholm and Awatramani 2015; Margolis and Detwiler 2011; Tsai et al. 2017). Thus, a computational model that can simulate critical stages

of retinal network remodeling during degenerative disease will be a major contribution to this area.

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Computational Models of Neuromodulation

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Definition

Neuromodulatory systems serve a special meta-processing role in the brain. Due to their anatomical privileges of having massively extensive arborization patterns throughout the central and peripheral nervous systems and to their physiological capacity of finely controlling how other neurons communicate with each other and plasticize, they are ideally positioned to regulate the way information is acquired, processed, utilized, and stored in the brain. As such, neuromodulation has been a fertile ground for computational models for neural information processing, which have strived to explain not only how the major neuromodulators coordinate to enable normal sensory, motor, and cognitive functions but also how dysfunctions arise in psychiatric and neurological conditions when these neuromodulatory systems are impaired.

Detailed Description

Although much still remains unknown or opaque about neuromodulatory functions, a computationally sophisticated and coherent picture is beginning to emerge on the back of recent modeling works (Dayan 2012). The four major neuromodulators that have received most theoretical treatment are dopamine, serotonin, acetylcholine, and norepinephrine. They all play important roles in regulating cortical functions such as inference, learning, and decision-making. Broadly speaking, dopamine and serotonin appear to be critical for the processing of stimuli and events with salient affective value, such as rewards and punishments, and the learning and execution of actions that lead to greater subjective utility (more rewards or fewer punishments); in contrast, acetylcholine and norepinephrine appear to be most critical for signaling various forms of uncertainty that plague cortical computations, arising from intrinsic neuronal processing noise, external environmental changeability, as well as imperfect sensory observations.

Reward and Punishment

One of the best understood computational functions of neuromodulation is the role of dopamine (DA) in signaling reward prediction errors (Montague et al. 1996; Schultz et al. 1997), associated with a reinforcement learning algorithm known as temporal difference learning (Sutton 1988), which can learn not only which stimuli predict future rewards but also the temporal delay until such a reward appears. Computational models have suggested reward prediction error to be important for at least three different functions. First, the most obvious, is the learning of environmental cues that predict future rewards as well as actions that lead to greater or lesser amount of reward. There is evidence that D1 dopamine receptors in the direct or “go” pathway in the striatum mediate the facilitation of actions with surprisingly good outcomes or positive prediction errors, whereas D2 dopamine receptors in the indirect or “no-go” pathway in the striatum

underlie the inhibition of actions that lead to negative prediction errors (Gerfen et al. 1990; Smith et al. 1998; Frank et al. 2004; Frank 2005; Cohen and Frank 2009; Kravitz et al. 2012). A second role suggested for dopamine, related to the theory of incentive salience (Berridge and Robinson 1998; McClure et al. 2003) and potentially via D1 receptors in the nucleus accumbens (Murschall and Hauber 2006; Frank 2005; Surmeier et al. 2007; Surmeier et al. 2010), is that it controls the expression of Pavlovian approach responses associated with the prospect of reward (Ikemoto and Panksepp 1999), in turn facilitating the initiation and learning of instrumental responses that boost reward (Satoh et al. 2003; Nakamura and Hikosaka 2006; Talmi et al. 2008). A third role suggested for the dopamine-mediated prediction error is that over the long term, the average prediction error reflects the average reward rate, which represents an opportunity cost that can drive the level of response vigor (Niv et al. 2007) or the trade-off between speed and accuracy (Dayanik and Yu 2012).

While animals need to seek out rewarding circumstances and actions, they also need to avoid punishing or threatening ones. The learning of avoidance behavior, or behavioral inhibition, appears to depend on both dopamine and serotonin (5-HT). Unexpected punishments (Ungless et al. 2004; Cohen et al. 2012) and the nondelivery of expected reward (Schultz et al. 1997) have both been shown to activate the dopaminergic system, which enable the learning of avoidance behavior via D2 receptors in the indirect pathway of the striatum (Frank et al. 2004; Kravitz et al. 2012). Complementing the dopaminergic system, serotonin has been suggested to play an opponent role, by signaling prediction errors associated with future “version” rather than reward (Deakin 1983; Daw et al. 2002; Cools 2011; Boureau and Dayan 2011). The suggestion is that initial hint of future aversion would activate the serotonergic prediction error (Schweimer and Ungless 2010) but that once the threat of that aversive outcome is avoided due to actions or circumstances, then the dopaminergic neurons would be activated by the associated reward prediction error, signaling safety, and thus reinforce the avoidance action

(Johnson et al. 2001; Moutoussis et al. 2008; Maia 2010). Aside from learning avoidance actions, serotonin has also been thought to be important for mitigating impulsivity and enabling general behavioral inhibition, such as delaying actions in order to receive a larger reward (Miyazaki et al. 2011; Doya 2002).

Uncertainty

Uncertainty of various forms plagues the brain's interactions with the environment. In a Bayesian statistical framework, optimal inference and prediction, based on unreliable observations in changing contexts, require the representation and utilization of different forms of uncertainty. For example, in the context of multimodal cue integration, uncertainty about the state of the world induced by unreliability of a cue should lead to the relative downgrading of that source of information relative to other more reliable cues (Ernst and Banks 2002; Battaglia et al. 2003). Analogously, in the context of integrating top-down and bottom-up information, uncertainty about the validity of an internal model of the environment should lead to relative suppression of top-down expectations in relation to bottom-up, novel sensory inputs (Yu and Dayan 2003; Körding and Wolpert 2004; Yu and Dayan 2005b). On the other hand, uncertainty about the predictive or other statistical properties of a stimulus or event should upregulate the *learning* accorded to that stimulus/event, relative to other better understood aspect of the environment (Yu and Dayan 2005b; Behrens et al. 2007; Nassar et al. 2012). Strictly speaking, exact Bayesian statistical computations need not distinguish among the various forms of uncertainty, as they are all reflected as probability distributions, or properties of distributions, of the relevant random variables under consideration. However, the brain can hardly be expected to implement arbitrarily precise and complex Bayesian computations, given its limited processing hardware, and thus needs to represent the most common and critical aspects of uncertainty so as to achieve near-optimal but efficient computations (Yu and Dayan 2003, 2005a, b).

Based on a wealth of physiological, pharmacological, and behavioral data implicating acetylcholine (ACh) and norepinephrine (NE) in specific aspects of a range of cognitive processes, it has been proposed that they respectively signal expected and unexpected uncertainty, with the former associated with known stochasticity or ignorance in the current environment and the latter arising from unexpected gross changes in the environment that require drastic revision of internal representation of the behavioral context (Yu and Dayan 2005b). The two forms of uncertainty are expected to be partly synergistic and partly antagonistic: a rise in unexpected uncertainty should lead to an increase of expected uncertainty (due to known ignorance), while expected uncertainty in turn has a suppressive influence on unexpected uncertainty, since the level of evidence for a fundamental change induced by a certain magnitude of prediction error should be normalized by the degree of expected variability (prediction error) (Yu and Dayan 2005b). Consistent with this, Sara and colleagues have found similarly antagonistic interactions between ACh and NE in a series of learning and memory studies (Sara 1989; Ammassari-Teule et al. 1991; Sara et al. 1992; Dyon-Laurent et al. 1993, 1994). They demonstrated that learning and memory deficits caused by cholinergic lesions can be alleviated by the administration of clonidine (Sara 1989; Ammassari-Teule et al. 1991; Sara et al. 1992; Dyon-Laurent et al. 1993, 1994), a noradrenergic α -2 agonist that decreases the level of NE (Coull et al. 1997).

In recent years, a number of experimental studies have confirmed major aspects of the uncertainty-based account of acetylcholine and norepinephrine functions. Pupil diameter, known to be correlated with noradrenergic neuronal activation level (Aston-Jones and Cohen 2005), has been shown to be, on the one hand, correlated with the discarding of previous beliefs and strategies and the exploration of novel ones (Gilzenrat et al. 2010; Jepma and Nieuwenhuis 2011) and, on the other hand, reflective of subjects' unexpected uncertainty beyond predicted variability (Preusschoff et al. 2011). Moreover, there is evidence that pupil

diameter is reflective of unexpected uncertainty (operationalized here as change point probability) and accompanies the discarding of previous beliefs and the incorporation of new data into a novel belief state (Nassar et al. 2012). Interestingly, pupil dilation is controlled by two muscles, the sphincter for contraction and the dilator for dilation, which are respectively innervated by acetylcholine and norepinephrine (Hutchins and Corbett 1997). The administration of cholinergic antagonists, scopolamine (muscarinic) and mecamylamine (nicotinic), increases pupil size in normal elderly volunteers (Little et al. 1998). Moreover, Alzheimer's disease (AD) patients, who have a severe and specific cholinergic deficit, have larger pupil size than controls both tonically and in response to light, while AD patients medicated with acetylcholinesterase inhibitor, which increases the endogenous level of acetylcholine, show a pupil response much closer to controls (Fotiou et al. 2009). This raises the intriguing possibility that the pupil dilation results might reflect the joint influence of both norepinephrine and acetylcholine. Separately, pharmacological and lesion studies directly manipulating acetylcholine levels have also produced behavioral results consistent with the cholinergic expected uncertainty hypothesis (Thiel and Fink 2008; Córdova and Chiba 2004).

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Computational Models of Painful Loading

► Biomechanical Model of Low Back Pain

Computational Models of Retinal Function

► Computational Models of Neural Retina

Computational Models of Visual Illusions

► Visual Illusions, Models of

Computational Models Supporting Parameter Finding for Deep Brain Stimulation

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Definition

Deep brain stimulation is a surgical therapy involving electrical stimulation of the brain via chronically implanted electrodes.

Once implanted, there are a number of stimulation parameters which must be set by the clinician in order to suppress the pathological symptoms, while not inducing any unwanted side effects.

Computational models can be used to estimate the optimal parameter settings for DBS to aid this process.

Detailed Description

Deep Brain Stimulation

Over 20 years ago (Benabid et al. 1987), deep brain stimulation (DBS) was introduced as a clinical therapy for a number of neurological and more recently psychological disorders. The treatment involves chronic electrical stimulation via quadripolar electrodes implanted into various regions of the human brain in a disorder-specific manner. Most commonly, DBS is used to treat a range of movement disorders such as essential tremor, Parkinson's disease, and dystonia (Vidailhet et al. 2005; Deuschl et al. 2006; Kupsch et al. 2006), with electrodes typically implanted into regions of the thalamus or the basal ganglia.

The treatment works well, and 70–80% of patients experience benefit from the treatment (Parkinson's UK).

Parameter Settings

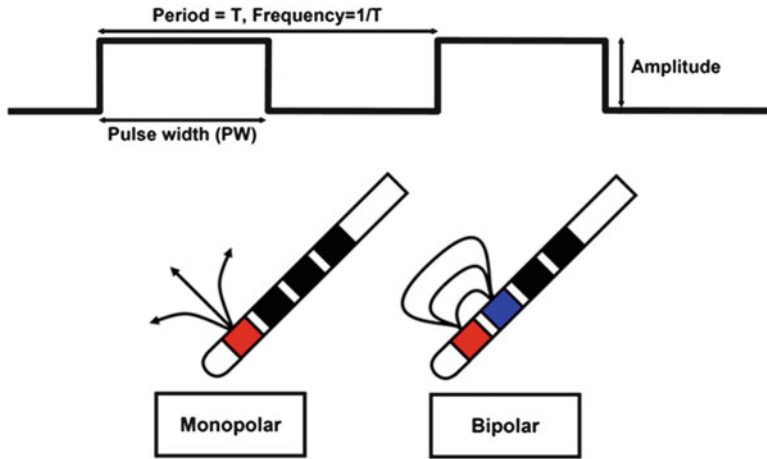
Despite the success of the treatment, however, there remains a lack of understanding of how this electrical current changes neuronal activity to lead to the observed therapeutic benefits (Benabid 2007; Kringelbach et al. 2007). This lack of understanding in turn restricts the clinical efficacy of DBS, further development of the technology, and identification of novel clinical applications. Of particular importance to the patient and clinician, however, is the identification of the optimal set of parameters for stimulation. These parameters include stimulation frequency, pulse width, amplitude, and contact configuration (see Fig. 1). This process of parameter selection for an individual patient is time consuming and difficult (Rizzone et al. 2001; Moro et al. 2002; Kuncel and Grill 2004), relying mostly on trial and error and the intuition of an experienced clinician. If we knew how DBS was achieving the clinical improvement at the neuronal level, patients' symptoms could be better targeted.

FEM Models

In recent years, computational models have been used to investigate this issue (Wei and Grill 2005; Yousif and Liu 2009; Butson et al. 2011) via a two-step approach: first, the spread of the electric field is modelled in a 3-dimensional model of the electrode and the surrounding tissue in a finite element method (FEM) model (Fig. 2a). The potential distribution induced by stimulation can then be calculated by solving the Laplace equation within the geometry.

Neuronal Models

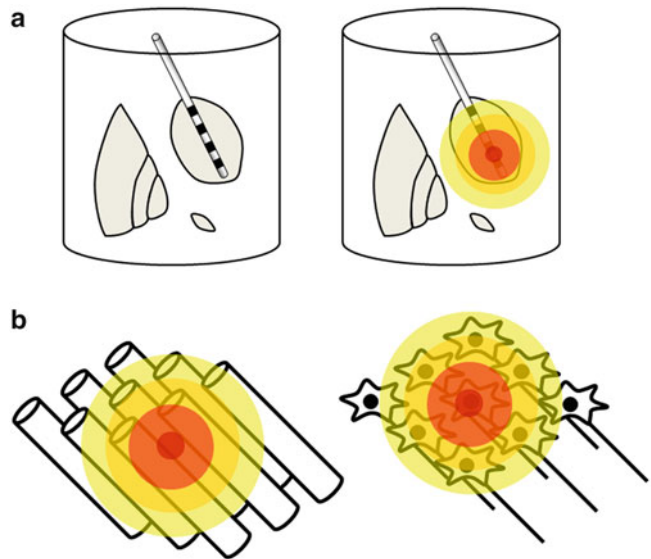
For the second step, the electric field estimation is applied to a model of neuronal structures (Fig. 2b) to predict the effect that stimulation has on the



Computational Models Supporting Parameter Finding for Deep Brain Stimulation, Fig. 1 Once the quadripolar DBS electrodes are implanted, an optimal set of parameters must be chosen by the clinician. The three parameters are stimulation frequency, pulse width, and amplitude of the waveform. In addition, the electrode can

be configured in different ways. If monopolar stimulation is selected, a single contact is used as the cathode, and the case of the stimulator, which is usually implanted in the chest, is used as the return electrode. If bipolar stimulation is selected, two contacts are used, and a near-field dipole is created

Computational Models Supporting Parameter Finding for Deep Brain Stimulation, Fig. 2 To model the impact of DBS on the human brain, a two-step approach is typically taken. (a) The geometry of interest is modelled in 3-dimensions and the equation of interest solved over this geometry to give a potential distribution (schematized here in color). (b) This potential distribution can then be applied to a dynamic model of neural activity, typically axons or neurons



firing properties in the surrounding tissue. At present, the vast majority of such models focus on arrays of unconnected axons, but recent work has shown that by modelling single neurons and networks of neurons, we can observe subtle effects of DBS on neural activity which would be overlooked by axon models (Yousif et al. 2010, 2012a, b). It has also been shown that using neuron models compared to axon models predicts that a much

smaller region of surrounding tissue will be activated, which will clearly impact on the use of such models for predicting parameter settings.

Making Predictions

Previously, there have been attempts to link the predictions made by FEM models to clinical

studies or observations (Butson and McIntyre 2007; Frankemolle et al. 2010; Chaturvedi et al. 2010). Similarly a limited amount of work has been done in order to link model results to measurements of the electric field in the macaque brain (Miocinovic et al. 2009). This not only allows the correlation of results with the observed clinical improvement but can also constrain the model parameters as the DBS-induced electric field can be directly measured. This process of validation is crucial for the success of these models in aiding the understanding of DBS and for establishing their credibility to clinicians who will ideally use such models in clinical practice.

In recent work, the use of such models to visualize the impact of specific parameter settings for an individual patient has emerged. Yousif et al. reported a clinical case where a bipolar setting was not tolerated by a patient with essential tremor during the first DBS programming session (Yousif et al. 2012). However, when the polarity of the same two contacts was reversed, the patient was able to tolerate a 70% increase in amplitude. By utilizing a computational modelling approach to visualize the effect of the two settings on the firing of neural fibers, it was possible to confirm that reversing the polarity, stimulated fibers of the nearby internal capsule. Stimulation of this fiber bundle has been reported to induce side effects from a thalamic electrode (Limousin et al. 1999). Hence, such an approach was used to help the clinician to understand why one configuration was superior to another, when simple consideration of the electric field induced by each would indicate them to be equivalent.

Future work should take a prospective approach to parameter settings. For each patient that is treated with DBS, an anatomically accurate model of the current spread can be produced and coupled to axon and/or neuron models. Prior to the process of clinically finding parameters, such a model can then be simulated at different parameter settings, to maximally activate axons or change the firing rate of neurons within the target brain structure. In this way, a set of parameters can be found which will guide the clinician's search for the optimal set of parameters. Such systems have now started to emerge from commercial

companies. In conclusion, such a method which theoretically predicts a set of parameters would streamline the process, reduce the stress and discomfort to patients and reduce the time required for tuning, checking, and adjusting parameters.

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Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation

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Definition

A computational model used to optimize electrodes and waveforms for deep brain stimulation (DBS) is typically composed of two separate models: a volume conductor model of an electrode in brain tissue used to calculate electrical potential distributions and cable models of neural elements (e.g., axons, local cells) used to calculate the response of neurons to the imposed stimulation. The integrated model is interfaced with an optimization algorithm to search for solutions that

increase the performance of DBS, where performance could be related to the efficiency, selectivity, and/or safety of stimulation. The results from the two models are combined to evaluate a specified cost function, and the optimization algorithm searches for a set of parameters that minimize the cost.

Detailed Description

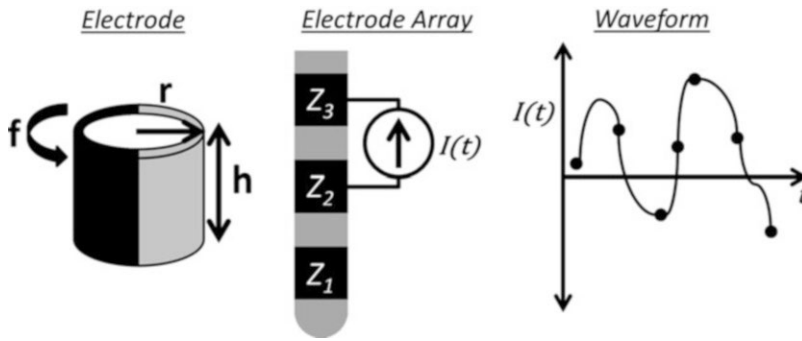
DBS is an established therapy for treating neurological disorders, in which an implanted array of cylindrical electrodes is used to deliver rectangular waveforms of electrical pulses to specific regions of the brain. Trial and error experimentation is not an efficient approach to design improved electrodes or waveforms and is unlikely to lead to an optimal result. Therefore, model-based design is being used to develop improved DBS electrodes (Butson and McIntyre 2006; Keane et al. 2012) and waveforms (Sahin and Tie 2007; Yousif et al. 2008; Foutz and McIntyre 2010; Wongsarnpigoon and Grill 2010).

Parameterization of Electrodes and Waveforms

There are an infinite number of possible electrode designs and waveform shapes. In real DBS systems, however, practical limitations exist, such as limitations on the size and number of electrodes and the maximum rate of change (slew rate) of the output voltage in the implantable stimulator. Therefore, the choice of parameterization should define as large a number of electrodes or waveforms as possible using the least number of parameters while keeping practical limitations in mind. Figure 1 gives an example.

Volume Conductor Models of Electrodes in Brain Tissue

The first step in the optimization process is calculating the electric field ($\vec{E}$) generated by the



Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation,

Fig. 1 Parameterization of an electrode (array) and waveform. An individual cylindrical electrode (*left*) can be parameterized by its radius (r), height (h), and the fraction of its surface that is conductive (f). In addition, the configuration

of the array (*middle*) can be parameterized by the positions of the individual electrodes along the shaft ($z_1 - z_3$). Waveforms (of voltage or current) applied to each contact – or between contacts – can be parameterized either by using the coefficients of a number of splines to define the waveform (*right*) or by discretizing the waveform into a finite time series

passage of current through brain tissue. Although the electrical properties of brain tissue vary with frequency, it is valid to assume that the capacitive, inductive, and wave propagation effects can be ignored for typical DBS parameters (Bossetti et al. 2008). Under quasi-static conditions, brain tissue can be treated as purely resistive, and $\vec{E}$ is derived from the gradient (∇) of the scalar potentials (Φ):

$$\vec{E} = -\nabla\Phi \quad (1)$$

It is also valid to assume that the resistivity (ρ) of brain tissue is linear or independent of Φ (Nicholson and Freeman 1975). Therefore, $\vec{E}$ is directly proportional to the current density distribution ($\vec{J}$):

$$\vec{E} = \rho \cdot \vec{J} \quad (2)$$

Substitution of Eq. 2 – Ohm's law – into Eq. 1 and taking the divergence of the result yields Poisson's equation:

$$\nabla^2\Phi = -\nabla \cdot (\rho \cdot \vec{J}) \quad (3)$$

which is the partial differential equation solved in the forward field problem for DBS.

The electrical properties of brain tissue are highly inhomogeneous (position dependent) and

anisotropic (direction dependent). Therefore, Poisson's equation cannot be solved analytically, and numerical methods are required to approximate a solution. The finite element method (FEM) is the preferred choice for modeling DBS because it can be readily applied to the complex geometries of the brain. For example, patient-specific FEM models are the current state of the art: The geometries of brain structures are defined by individual brain images, and the tensor conductivities of each brain region are determined using diffusion-tensor magnetic resonance imaging (Butson et al. 2007; Chaturvedi et al. 2010). Patient-specific models show good agreement with clinical results, but this performance comes at the expense of complexity and associated computational time.

In cases where an iterative optimization process requires solving Poisson's equation hundreds to thousands of times, simplified analytic and semi-analytic solutions offer a compromise between the predictive capabilities of the model and computational time. For example, if brain tissue is approximated as an infinite homogeneous medium with a single bulk ρ , then cylindrical harmonics (i.e., Bessel functions) can be used to calculate semi-analytically the potentials generated by the DBS electrode array. Although this method requires solving a system of unknowns, it can still be used to evaluate the effect of the electrode geometry on Φ . However, if electrode

geometry is not important and only the temporal dynamics matter, then the DBS electrode can be approximated as a point source of current (Zhang and Grill 2010), which yields the following analytic solution (Li and Uren 1998):

$$\Phi(x, y, z) = \frac{\|p_{i,j}\|^{1/2}}{4\pi(\rho_{11}x^2 + \rho_{22}y^2 + \rho_{33}z^2 + \rho_{11}x^2y^4 + \rho_{1,3}^{yz+\rho_{23}}yz)^{1/2}} \quad (4)$$

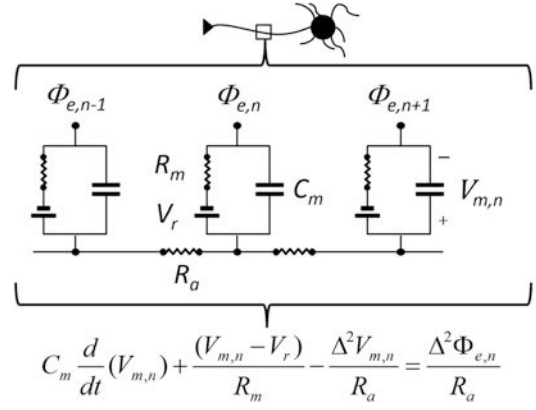
where I is the stimulus current, $\| \cdot \|$ is the determinant operator, $\rho_{i,j}$ is the resistivity tensor, and x, y , and z are the spatial coordinates relative to the point source (4) minimizes computational time and can be combined with the method of images to account for simple inhomogeneities in the brain tissue.

Cable Models of Neural Elements

The second step in the optimization process is simulating the response of target neural elements to the electric potentials calculated with the volume conductor model. Axons and dendrites are much longer than they are wide and azimuthally symmetric about their longitudinal axis, so they are modeled as a one-dimensional cable of cylindrical membrane compartments, each with circuit elements modeling the membrane and axoplasm. If the soma is also approximated as a series of cylindrical compartments, then the flow of charge through the entire neuron can be described using the cable equation (Fig. 2). The cable equation can be solved numerically using the finite difference method (Carnevale and Hines 1997).

Optimization Algorithms

The final step in the optimization process is using the results from the computational model of DBS to evaluate and minimize a cost function via a numerical optimization algorithm. The choice of cost function depends on the goal of the optimization. If the goal is to extend the battery life of the



Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation, Fig. 2 Modeling neural elements with the cable equation.

An isolated patch of membrane on a neuron (*top*) is modeled using a one-dimensional cable (*middle*). In that cable, the flow of charge is quantified using the cable equation (*bottom*), where V_m is the membrane voltage, V_r is the resting voltage, R_m is the membrane resistance, C_m is the membrane capacitance, R_a is the axoplasmic resistance, Φ_e is the external potential, and n denotes the index of the compartment

device, efficiency is increased by minimizing the transferred electrical energy (E):

$$E = \int IVdt, \quad (5)$$

where I and V are the applied voltage and applied current, respectively. If the goal is to reduce the risk of tissue damage, then the injected charge (Q),

$$Q = \int Idt, \quad (6)$$

is minimized because Q is correlated with tissue injury (McCreery et al. 1990; Shannon 1992). Or, if the goal is to mitigate the sensitivity of clinical outcomes to the malposition of the electrode, selectivity is increased by constructing a curve, $p(x)$, of the proportion of a nontarget population activated versus selected proportions of a target population and minimizing the area (A) under the curve:

$$A = \int p(x) dx \quad (7)$$

The cost function must be minimized numerically, as there is no guarantee that it will be continuously differentiable over the parameter space defining the electrode and/or waveform. Using iterative methods (e.g., Newton's method and conjugate gradient) to minimize cost is impractical because they require approximating a Jacobian and/or Hessian, which may or may not exist for all space. Therefore, stochastic search algorithms are used to identify solutions that minimize cost, including simulated annealing, genetic algorithm, and particle swarm – inspired by the natural processes of crystallization, evolution, and the collective behavior of self-organized systems, respectively.

Optimal Electrodes and Waveforms

Computational studies of DBS show that rectangular waveforms are the most energy efficient for pulse widths (PWs) $\leq 40 \mu s$ (Sahin and Tie 2007). For all other PWs, Gaussian waveforms and triangular waveforms are the most energy efficient; and the PW that minimizes E depends on a number of factors, including the spatiotemporal distribution of the potentials and the geometry, position, orientation, and electrophysiology of the target neural element (Foutz and McIntyre 2010; Wongsarnpigoon and Grill 2010).

Although little work has been done on optimizing electrodes for DBS, emerging work shows that the same factors that impact waveform efficiency (see above) are also important in designing more efficient and selective electrode geometries (Howell and Grill 2013).

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Computational Neuroscience of Color

- [Color Vision, Computational Methods for](#)

Computational Olfaction

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Definition

In natural environments, airborne chemical stimuli are distributed unpredictably in time and space, and odorants from innumerable sources intermix freely. The olfactory system must perform computations to detect potential signals of interest within these noisy signals, extract these signals, form representations, compare these to those of previously experienced, differentiate relevant from irrelevant stimuli, and cue an appropriate response. Computational modeling suggests that subnetworks of the olfactory system may be dedicated to perform specific computations underlying these functions.

Detailed Description

Neural Networks Involved in Olfactory Computation

Computational models of the olfactory system have contributed immensely to the framing of experimental problems and the construction of complex hypotheses regarding its function. Computational models from detailed biophysical to large-scale simple neuron models have proposed how olfactory networks compute the functions necessary to extract and recognize important chemical signals.

Signal-to-noise ratio in the olfactory system is inherently low at the level of olfactory sensory neurons (OSN), which are broadly tuned to odorants. OSNs sharing a common response profile to odorants project their axons to specific glomeruli within the olfactory bulb (Mombaerts et al. 1996), with a very high convergence. This high

convergence ratio has been proposed to improve the signal-to-noise ratio during odorant detection (van Drongelen et al. 1978).

Mitral cells, along with middle and deep tufted cells, are the principal output neurons of the olfactory bulb. They are directly postsynaptic to OSNs and as such the pattern of mitral/tufted cell activation across the bulb constitutes the output representations. Besides input from a single class of OSNs, mitral/tufted activation pattern also depends on the activity of several classes of bulbar interneurons. For example, some form of *normalization of stimulus concentrations* is clearly evident in the concentration-response profiles of mitral cells; this function has been proposed to be the role of an extensive network of excitatory and inhibitory neurons in the glomerular layer (Cleland et al. 2007). *Contrast enhancement*, the effects of which have been directly observed in the olfactory bulb (Yokoi et al. 1995), can be functionally defined as a process of competition between neurons expressing similar response profiles. Simplified models of the olfactory system have been able to implement contrast enhancement using lateral inhibition between glomeruli (Cleland and Linster 2002; Linster and Cleland 2001; Linster and Gervais 1996; Linster and Hasselmo 1997, 1999; Linster and Smith 1997). Alternatively to these highly simplified representations, non-topographical models of contrast enhancement are also capable of distributing inhibition in proportion to receptive field similarity but use local computations and broad feedback inhibition to create contrast (Cleland and Sethupathy 2004).

The net activation of mitral cells is then translated into trains of action potentials, the precise *timing* of which appears to be regulated by coordinated *oscillations* measurable in field recordings across the OB. These bulbar oscillations are thought to depend on an extensive excitatory-inhibitory network of mitral cell secondary dendrites and granule cell interneurons, as well as reciprocal cortical connections that modulate bulbar activity according to behavioral state (Kay 2003; Lagier et al. 2004; Martin et al. 2004;

Ravel et al. 2003). Mitral cell spike synchronization patterns can mediate a second level of feature extraction to the odor representation (David et al. 2009), as follower neurons in diverse central olfactory structures (Linster and Cleland 2003) process incoming mitral cell spikes via synaptic learning rules, the best known of which rely upon precise spike timing (Cleland and Linster 2002; Song et al. 2000). The mechanisms of oscillations have been the focus of a number of computational modeling efforts, some proposing oscillators governed by an excitatory-inhibitory feedback loop, others proposing intrinsic oscillations in mitral cells synchronized by slow common inhibitory inputs (Bathellier et al. 2006, 2008; David et al. 2009; Erdi et al. 1993; Freeman 1987; Li and Hopfield 1989).

Even though some models propose *associative memory* functions for olfactory bulb (Erdi et al. 1993; Hendin et al. 1998), olfactory associative memory functions have been more commonly attributed to the piriform cortex, one of the targets of mitral cell axons projecting from the olfactory bulb. Specifically, the piriform cortex has been proposed to mediate the associative memory functions necessary for odor-context learning (de Almeida et al. 2013; Haberly 2001; Haberly and Bower 1989; Hasselmo et al. 1990) and hierarchical clustering (Ambros-Ingerson et al. 1990). For example, cortical short-term synaptic depression can be employed to filter out stable background odorants, whereas long-term synaptic plasticity can store associations between neurons responding to the same odor stimuli. Indeed, the extensive intrinsic feedback network in this cortex and its integration with afferent inputs closely resembles the structure of traditional theoretical associative memory networks as first described by Marr (Marr 1971).

Conclusions

Computational models have an established and growing role within systems neuroscience. As our understanding of neural processing and

interactions becomes more sophisticated, computer models of these systems are increasingly necessary in order to understand and interpret experimental results. In the olfactory system in particular, computational modeling will no doubt be essential to understanding the integration of the many factors influencing the construction and transformation of odor representations.

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Further Reading

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Computational Psychiatry

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Definition

Computational psychiatry is a heterogeneous field at the intersection of computational neuroscience and psychiatry. Incorporating methods from psychiatry, psychology, neuroscience, behavioral economics, and machine learning, computational psychiatry focuses on building mathematical models of neural or cognitive phenomena relevant to psychiatric diseases. The models span a wide range – from biologically detailed models of neurons or networks to abstract models describing high-level cognitive abilities of an organism. Psychiatric diseases are conceptualized either as an extreme of normal function or as a consequence of alterations in parts of the model.

As in computational neuroscience more generally, the building of models forces key concepts to be made concrete and hidden assumptions to be made explicit. One critical function of these models in the setting of psychiatry is their ability to bridge between low-level biological and high-level cognitive features. While many neurobiological alterations are known, the exclusively atheoretical focus of standard psychiatric nosology on high-level symptoms has as yet prevented an integration of these bodies of knowledge. David Marr pointed out that models at different levels of description may be independent (Marr 1982). Nevertheless, algorithmic details may constrain functions at the computational level. The models used in computational psychiatry make these constraints explicit and thereby aim to provide normative conduits between the different levels at which neural systems are analyzed (Stephan et al. 2006; Huys et al. 2011; Hasler 2012; Montague et al. 2012). This in turn allows for a principled approach to study dysfunctions and indeed may allow the dysfunctions observed in psychiatry to inform neuroscience in general.

Practically, it underpins hopes that computational techniques may facilitate the development of a psychiatric nomenclature based on an understanding of the underlying neuroscience. Computational models enhance experimental designs by allowing more intricate neural and/or cognitive processes to be inferred from complex features of the data, often via Bayesian inference. These aspects motivate hopes that it may facilitate the development of clinical treatment and decision tools informed by advances in neuroscience.

Detailed Description

This entry describes four types of models applied to psychiatric diseases. The earliest models were connectionist (McClelland et al. 1986) or dynamical (King et al. 1984) and emphasized properties of the brain as a neural network. The second,

and now most common, class is models of reinforcement learning (Montague et al. 1996; Schultz et al. 1997; Sutton and Barto 1998). The third and fourth classes emphasize explicit model-based planning or social cognitive processes, respectively.

Connectionist and Neural Network Models

Connectionist approaches model psychological functions using a neural network in which particular neurons take on specific computational roles, for instance, representing a sensory input. Key aspects of the neural networks are based on particular features derived from biology (or known to be involved in psychopathology). This allows the consequences of these features for complex computation to be probed and hence is one direct approach to examining the link between Marr's levels. In psychiatry, connectionist models have been prominently applied to schizophrenia.

Patients with schizophrenia or mania can characteristically display rapidly changing, loose associations in their speech. Early work examined how parameters governing the dynamics of associative networks might reproduce this. An increase in noise, corresponding to a decrease in the dynamic gain, led to less specific memories, mirroring a broadening of associations in schizophrenia, and less stable, constantly altering memories, possibly mirroring the pressure of speech observed in mania. Spurious memories reminiscent of hallucinations arose when overloading the network with memories beyond its capacity (Grossberg and Pepe 1970; Hoffman 1987).

Patients with schizophrenia also show impairments in cognitive flexibility and control tasks that require the inhibition of a prepotent response. Cohen et al. (1996) used a connectionist network partitioned into four modules to model this. One module represented stimuli, another other responses, and a third the prefrontal cortex. A fourth module integrated the inputs from all

modules. The prefrontal cortex had a critical function in maintaining representations of task-relevant variables. When this memory function was impaired by a reduction in its gain, the network could accurately capture the impairments in performance seen in schizophrenia. As the gain was thought to depend on dopaminergic input, this work correctly predicted a prefrontal reduction of dopamine in schizophrenia. Later work further refined the role of dopamine in gating of information into the prefrontal cortex (Braver et al. 1999; Frank 2005).

Many psychiatric disorders are relapsing-remitting, with periods of well-being punctuated by times of illness. This is prominent in bipolar disorder, which can cycle rapidly between phases of depression and mania. Conversely, loss of diurnal sleep-wake rhythms is also common. These phenomena can be described by dynamical systems models of neural networks with feedback loops and delays interacting to produce oscillatory phenomena at various timescales (Mackey and Milton 1987; Milton 2010). The complexities of the local circuit, with synthesis, breakdown, and reuptake, can add substantial further complexity and facilitate the emergence of highly variable, chaotic solutions potentially relevant to multiple disorders (King et al. 1984).

Reinforcement Learning Models

Reinforcement learning (RL; Sutton and Barto 1998) describes a set of techniques aimed at choosing that action which maximizes the long-term expected reward. In terms of applications to psychiatric diseases, it is useful to differentiate between two approaches to solving this problem (Daw et al. 2005): a model-based and a model-free one. In the *model-based* approaches, the agent has a model $\mathcal{M}$ of the world that describes the consequences of actions and the desirability of the consequences. For instance, a player may know the rules of chess. The best move can then be inferred by considering all moves, their consequences, and the subsequent moves iteratively.

For most problems of interest, this model-based decision procedure is computationally unachievable. *Model-free* approaches replace computation by experience, maintaining a lookup table $Q(s, a)$ of the expected reward (and hence goodness) of each behavior a in situation s . This can be iteratively updated online with new experience by computing a prediction error (PE) δ which compares the obtained with the expected future reward $Q(s, a)$. This expectation $Q(s, a)$ can then be updated by letting $Q(s, a) \leftarrow Q(s, a) + \epsilon \delta$, where $0 \leq \epsilon \leq 1$ is a learning rate that determines how rapidly the qualities are allowed to change over time. That is, rather than inferring decisions from an understanding of the world, model-free choices are the result of repeated trial-and-error learning. This motivates the characterization of habits as model-free (Daw et al. 2005). Seminal work has shown that phasic signals by dopaminergic neurons are proportional to this PE δ (Montague et al. 1996; Schultz et al. 1997).

The application of reinforcement learning models to psychiatric diseases is motivated by a trio of facts. First, decisions are central to psychiatric disorders, and reinforcement learning techniques allow for a principled approach to decision-making. Decisions are the final common pathway preceding many aberrant behaviors, and poor decisions can have profound consequences for affected individuals. For instance, around a third of the life stress associated with major depressive disorder is due to poor decisions by individuals (Kendler et al. 1999). Second, many psychoactive substances and clinically useful medications influence neuromodulators: dopamine (antipsychotics such as haloperidol or clozapine and stimulants such as methylphenidate), serotonin (selective serotonin reuptake inhibitors, tricyclic antidepressants), noradrenaline (tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors), or acetylcholine (certain antipsychotics, cholinesterase inhibitors). Third, and unifying the first two, these same neuromodulators are central to computational models of decision-making. This is particularly clear for phasic

dopamine, which appears to report a signal akin to the PE δ used for learning in model-free RL (Montague et al. 1996; Schultz et al. 1997; Sutton and Barto 1998).

Predominantly Model-Free RL Accounts of Psychiatric Diseases

The simplest application of reinforcement learning models is in examining anhedonia, a central component of *depression*. Anhedonia describes a reduced ability to experience pleasure and is usually measured by verbal reports. People who report such a lack of pleasure are less likely to choose the more rewarding stimulus in a variety of standard learning (Costello 1972; Henriques et al. 1994; Pizzagalli et al. 2005) and stimulus reactivity (Bylsma et al. 2008) tasks. Decisions in some of these tasks can be captured by simple model-free reinforcement learning. Depression interferes with this learning by reducing the PE signal δ (Steele et al. 2007; Kumar et al. 2008; Chase et al. 2010a, b; Gradin et al. 2011), leading to reduced expectations of rewards over time. The PE δ is composed of the difference between expected reward and obtained reward, and anhedonia appears to reduce the former, while alterations of tonic dopamine affect the latter (Chowdhury et al. 2013; Huys et al. 2013).

Addictive substances release dopamine either directly or indirectly and modify dopamine receptors chronically (Volkow et al. 2009). This might simply suggest that addictive substances thereby result in overly large values of the drug-taking action by adding an irreducible floor to the PE signal δ . This would result in a persistent signal for learning, increasing the value of drug-taking actions without bound (Redish 2004; Dayan 2009). Other reinforcement learning models address the transformation from hedonic to compulsive drug taking (Everitt and Robbins 2005) by emphasizing the difference between model-free and model-based reinforcement learning (Redish et al. 2008). Drugs of abuse are known to lead to a

shift toward habitual behavior (Dickinson et al. 2000; Nelson and Killcross 2006), which can be captured by a shift from model-based to model-free decision-making (Daw et al. 2005). Neurobiologically, this shift might be accompanied by a progressive engraining of drug-taking actions through progressively more dorsal corticostriatal loops (Belin and Everitt 2008) and impairments of orbitofrontal function (Lucantonio et al. 2012).

Parkinson's disease is characterized by a progressive reduction of dopamine-producing cells in the midbrain and treated with dopamine precursors or agonists. Clinically, it results in a pronounced slowing (bradykinesia) and experimentally in facilitated learning of action omission compared to action production (no-go rather than go learning) that is normalized by dopaminergic medication. The effects of dopamine on *go* and *no-go* learning are accounted for by biologically detailed computational models of the basal ganglia (Frank 2005). Two critical structural aspects of the basal ganglia inform these models: (a) the presence of parallel corticobasal ganglia-thalamocortical loops for go and no-go learning and (b) the prevalence of activating D₁-type dopamine receptors on the go and inhibiting D₂-type receptors on the no-go loop (Maia and Frank 2011). Positive prediction errors are thus linked with go and negative prediction errors with no-go learning (Frank et al. 2007; Guitart-Masip et al. 2012). Such considerations are also relevant for *schizophrenia*, *Tourette's syndrome*, and *attention-deficit hyperactivity disorder* (Maia and Frank 2011). The work on Parkinson's disease is remarkable in that it has informed understanding of the function of the basal ganglia and dopamine in the healthy brain.

Finally, dopamine also plays a particular role in *schizophrenia* research because (a) the positive symptoms of psychosis respond to dopaminergic D₂ antagonists such as haloperidol (Seeman et al. 1976; Kapur et al. 2000; Laruelle et al. 2003) and because of (b) findings of increased dopamine synthesis, release, and synaptic levels in psychotic states (Heinz 2002; Kapur 2003) from the first

episode onward (Egerton et al. 2013). Model-free reinforcement learning models that link phasic dopamine to prediction error signals have been instrumental in relating the dopaminergic dysfunctions to cognitive phenomena. They have provided detailed accounts of the effects of dopamine manipulations on both learning and expression of learned contingencies in preclinical animal models such as the conditioned avoidance response and latent inhibition (Smith et al. 2004, 2005, 2007; Moutoussis et al. 2008). In humans, reinforcement learning models of decision-making have been combined with fMRI to examine the correlates of putatively dopaminergic PEs. Schizophrenia patients have a reduced response to prediction errors in striatal and midbrain regions (Juckel et al. 2006; Corlett et al. 2007; Jensen et al. 2008; Murray et al. 2008) that is normalized by treatment with second-generation antipsychotic medications (Juckel et al. 2006).

Passivity phenomena are another important characteristic feature of schizophrenia, where movements or sensations are experienced as not originating from oneself. Incorrect expectations about the consequences of one's own actions may lead to the assignment of the sensory consequences of one's own actions to external sources (Gray et al. 1991; Fletcher and Frith 2009). This may arise from an impaired connectivity between areas generating the predictions and those assessing the input (Ford et al. 2007), speaking to a generalized notion of PEs that is less directly related to phasic dopaminergic prediction errors (Rao and Ballard 1999) but rather to the consequences of dopamine in modulating synaptic plasticity (Friston and Frith 1995; Stephan et al. 2006; Friston 2008; Stephan et al. 2009).

Predominantly Model-Based Accounts of Psychiatric Diseases

Higher-level cognitive aspects of psychiatric diseases are captured by reinforcement learning models in which decisions are the product of searching an explicit model of the task at hand.

These have been applied to the concept of helplessness in depression, to the role of serotonin, and to delusional belief formation in schizophrenia.

In depression research, the concept of *helplessness* – a perception of lack of control – arose from animal behavior and describes animals who fail to escape from shocks after experiencing other stressors that were not under their control (Seligman and Maier 1967). Similar findings exist in humans (e.g., Miller and Seligman 1975). The simplest mathematical formulation of controllability is as a low action-outcome contingency $p(o|a)$ (Maier and Seligman 1976). More detailed accounts view controllability as relating not to individual available actions but to the average achievability of different outcomes by different choices of actions (Dayan and Huys 2009). This definition is close to the definition of control in control systems theory. The psychological construct whereby controllability is related to particular desirable outcomes can be captured by defining controllability as the fraction of rewards reliably achievable through appropriate action selection (Dayan and Huys 2009). These definitions of controllability can be used as prior beliefs and thereby account qualitatively for learned helplessness and chronic mild stress (Willner 1997) effects (Dayan and Huys 2009). Further refinements accounting specifically for generalization issues and for the computational costs of goal-directed decisions allow for more quantitatively detailed accounts (Lieder et al. 2013).

Serotonin plays an important role in research on depression because selective serotonin inhibitors (SSRIs) are first-line pharmacotherapeutic agents (Gelder et al. 2006) and because dietary manipulations that are thought to acutely reduce serotonin (acute tryptophan depletion) can lead to a rapid recurrence of symptoms in formerly depressed patients (Smith et al. 1997). However, animal work has related increased serotonin to behavioral inhibition, aversive expectations, and expression of helplessness (Soubrié 1986; Maier and Watkins 2005), suggesting that a reduction in serotonin should improve depressive symptoms.

Reinforcement learning models have linked the inefficient avoidance of negative events due to serotonin in a model-free system with an increased exposure to more negative events. These experiences might in turn underlie more negative moods due to serotonin reductions (Dayan and Huys 2008; Boureau and Dayan 2011; Dayan 2012). Further work has characterized the interaction of this model-free behavioral inhibition with internal cognitive planning models and has suggested that serotonin might also inhibit internal thought processes. This would be instrumental in facilitating planning by pruning overly large decision trees to a computationally manageable size (Huys et al. 2012). While serotonin is also central to helplessness, this computational relationship has not yet been examined.

“Jumping to conclusions” is a phenomenon that aims to capture *delusional belief formation*. It describes a tendency for patients with *paranoid ideation* to declare a strongly held belief based on data that should not be sufficient to warrant such strong beliefs (Garety et al. 2005). However, a model-based reinforcement learning model of the standard task used to measure jumping to conclusions (the “beads-in-a-jar” task) suggested that the reason patients with schizophrenia jumped to conclusions was not due to aberrantly strong beliefs but due to taking into account their future inability to exploit further data (Moutoussis et al. 2011).

Game-Theoretical Approaches to Social Dysfunction

Psychiatric disorders have a profoundly detrimental effect on social function. Social interactions are extremely complex and therefore difficult to investigate directly. Game-theoretical approaches allow interpersonal cognition to be probed parametrically because the social communication channel is highly restricted yet functional. Economic games benefit from having been extensively examined both theoretically and experimentally in economics (Camerer 2003).

Borderline personality disorder (BPD), which is characterized by unstable personal relationships and inappropriate emotional responses, leads to a breakdown of cooperation in *trust tasks*. In this task, the first participant (the investor) chooses which fraction of an endowment to invest. The investment is multiplied, and the trustee chooses what fraction of the multiplied amount to return to the investor. When played over multiple rounds, both players are best off when they cooperate (i.e., when the investor invests and the trustee faithfully returns a substantial fraction). However, this cooperation is easily broken. Healthy participants maintain cooperation by repairing lost trust through signals (e.g., by investing a large fraction to signal willingness to cooperate; King-Casas et al. 2005). Patients with BPD fail to recognize social signals used to repair social bonds after temporary ruptures, potentially due to a failure of the insula to respond (King-Casas et al. 2008). *Autistic spectrum disorder (ASD)* on the other hand does not affect the maintenance of cooperation in the trust task, but the cingulate cortex does not tag “self”-responses accurately (Tomlin et al. 2006; Chiu et al. 2008). In related cooperative games (e.g., the “stag hunt” game), ASD patients have a less rich representation of the other’s strategic abilities (Yoshida et al. 2008, 2010a, b). Responses of healthy volunteers to patients with a variety of psychiatric disorders in the trust task fall into distinguishable classes (Koshelev et al. 2010). This might allow the use of healthy volunteers as “biosensors” and formalizes one important aspect and use of empathy or even countertransference in psychiatric clinical practice. Formally, these tasks are partially observable Markov decision problems and can be modeled as such (Yoshida et al. 2008; Ray et al. 2009).

Limitations

Computational approaches to psychiatric disorders focus on decision-making, valuation, and cognition. While this is critical to many psychiatric disorders, immunological, endocrine, or

vegetative dysfunctions are so far largely beyond these accounts.

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Computational Structural Biology

► Polypeptide and Protein Modeling for Drug Design

Computational Synthesis of Motoneuron Morphology

► Algorithmic Reconstruction of Motoneuron Morphology

Computer Generation of Motoneuron Morphology

► Algorithmic Reconstruction of Motoneuron Morphology

Concentration-Response Functions

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Conductance Co-regulation

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Conductance Scaling

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Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons

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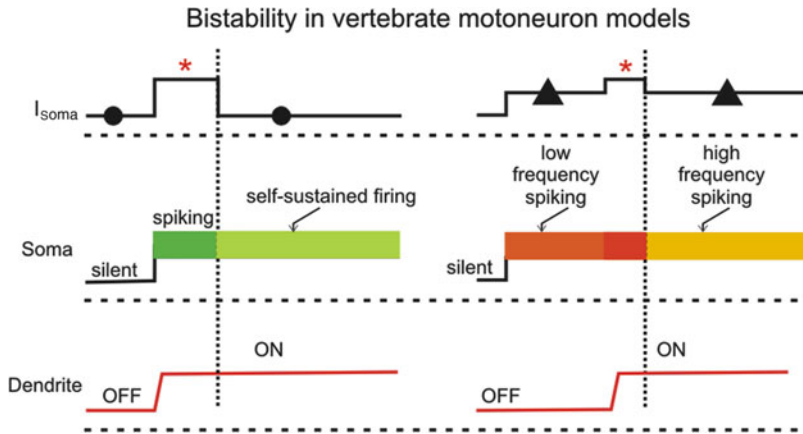
Definition

The term “conductance-based models of nonlinear dynamics in vertebrate motoneurons” refers to conductance-based motoneuron models that capture the complex nonlinear membrane

properties (e.g., bistability) of vertebrate motoneurons observed both in vivo and in vitro under certain conditions. Numerous conductance-based motoneuron models with widely varying morphological complexities and different ionic current composition exist that reproduce the experimentally observed nonlinear membrane properties. This article focuses on models that assume minimally required morphological complexity (e.g., two compartments) and ionic conductances. The resulting reduced set of equations and parameters describing such models have enabled detailed analyses of model behavior using geometric dynamical systems methods to provide insight into the basis of nonlinear membrane properties in vertebrate motoneurons.

Detailed Description

Dynamics of vertebrate motoneurons are phylogenetically conserved sharing common phenomenology from turtles to humans (Hornby et al. 2002). Under certain experimental conditions, these neurons display nonlinear membrane properties such as bistability (Bennett et al. 2001; Hounsgaard and Kiehn 1985; Schwindt and Crill 1977; Sigvardt et al. 1985; Lee and Heckman 1998a). Physiologically, bistability arises due to plateau potentials that develop and persist on a slower timescale (order of seconds to minutes) relative to the millisecond timescale action potential events. In most adult vertebrates, plateau potentials are generated by noninactivating “persistent inward currents” (Lee and Heckman 1998b) predominantly composed of low-voltage-activated L-type calcium and to a lesser extent by persistent sodium currents (Lee and Heckman 1996; Li and Bennett 2003). It is generally accepted that such currents are of dendritic origin (Carlin et al. 2000). When activated, they produce a persistent plateau in the somatic membrane voltage that can be sufficient to sustain action potentials even after the removal of plateau producing depolarizing input – also known as “self-sustained firing” (see Fig. 1). Additionally, activation of plateau potentials can induce higher-frequency



Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons, Fig. 1 Bistable membrane behavior in vertebrate motoneurons. *Left:* Somatic current injection (I_{soma}) marked by red asterisk induced somatic spikes (dark green) that in turn also activates dendritic plateau (dendrite switches from OFF to ON state). This dendritic plateau persists even after the somatic current returns to its initial level (demarcated by vertical dotted line) at which the soma was silent. This sustained plateau now drives somatic spikes resulting in self-

sustained firing (light green). Black circles indicate zero I_{soma} . *Right:* Figure shows the two levels of I_{soma} , low current (black triangle) that initially induces a low-frequency firing in the soma (orange) but does not activate the dendrite followed by a brief high I_{soma} (red asterisk) that turns on the plateau. Subsequent return of I_{soma} to its initial value (black triangle) results in a higher-frequency firing (yellow) due to the additional persistent depolarization by the dendritic plateau

firing for the same depolarizing current injection that produced a low-frequency firing before plateau activation (see Fig. 1).

generate physiologically realistic membrane voltage responses and firing behavior in the specific motoneurons being modeled (e.g., Booth et al. 1997; Kurian et al. 2011; Venugopal et al. 2011, 2012).

Models of Motoneuron Bistability

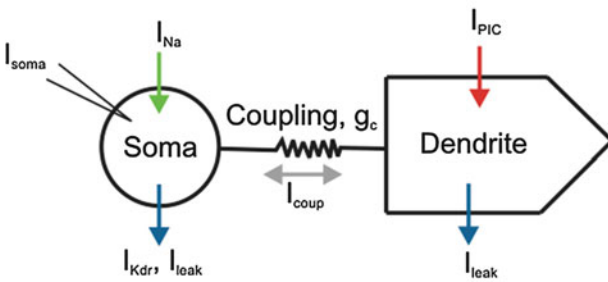
Models of motoneuron bistability have faithfully captured the nonlinear dynamics arising at the soma in experimental settings.

There are two basic features of these models that are critical for reproducing the experimentally observed bistable membrane properties in motoneurons. They include (1) the presence of at least two *weak/moderately* coupled compartments and (2) sufficiently disparate membrane properties between the compartments (e.g., dendritic localization of persistent inward currents). A classic two-compartment conductance-based model that first explored the phenomenology of vertebrate motoneuron bistability is the Booth-Rinzel model (Booth and Rinzel 1995) that included dimensionless equations. Similar two-compartment models incorporated more realistic biophysically based ionic conductances to

A Minimal Motoneuron Model for Understanding Bistable Membrane Behavior

Figure 2 shows the model schematic of a minimal two-compartment vertebrate motoneuron. The equations guiding this minimal model are given below:

Shown here are minimal set of ionic currents that include fast sodium (I_{Na}) and delayed rectifier potassium (I_{Kdr}) in the soma for action potential generation, a voltage-dependent persistent inward current in the dendrite (I_{PIC}) that mediates dendritic plateau, a leak current (I_{leak}) in both the compartments to maintain the resting potential, a coupling current (I_{coup}) that arises due to the electrotonic coupling of the compartments whose magnitude depends on the coupling conductance



Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons, Fig. 2 Minimal motoneuron model of bistability. *Left:* A schematic showing the morphological and electrophysiological components of the model consisting of two electrotonically coupled

Somatic compartment:

$$\frac{dV_S}{dt} = -I_{Na} - I_{Kdr} - I_{leak} + I_{coup} + I_{soma}$$

$$\frac{dw_S}{dt} = \phi_S \frac{w_S^\infty - w_S}{\tau_w}$$

Dendritic compartment:

$$\frac{dV_D}{dt} = -I_{CaP} - I_{leak} + I_{coup}$$

$$\frac{dm_{CaP}}{dt} = \frac{\varepsilon_D (m_{CaP}^\infty - m_{CaP})}{\tau_{CaP}}$$

compartments, namely, soma and dendrite. *Arrows* show the directions of inward and outward currents (see text for description of currents). *Right:* Equations guiding the membrane voltage dynamics in somatic and dendritic compartments

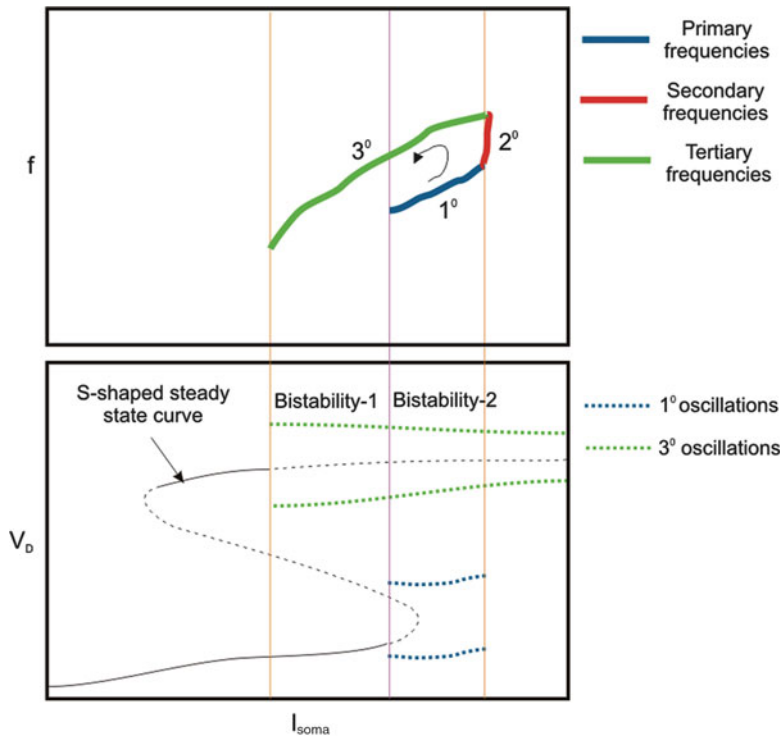
(g_c), and the proportion of area (p) suggested to be occupied by the soma. The term I_{soma} refers to somatic current injection. The somatic and dendritic voltages are given by V_S and V_D , respectively. For a detailed description of the model, see (Booth and Rinzel 1995). Note that these form a general set of equations and conductances guiding the somatic and dendritic compartments and one can easily incorporate additional terms for ionic currents as well as increase the morphological complexity as relevant. Alternatively, such minimal models could guide the development of artificial motoneurons that may act as bistable switches in neuromorphic circuits.

Hysteresis in the Frequency-Current Relationship and Mechanism Underlying Bistability

Motoneuron bistability described above can give rise to a counterclockwise hysteresis in the injected current firing frequency relationship (f-I) (see Fig. 3, *top*) although existence of f-I hysteresis itself is not sufficient for bistability.

Of importance in the f-I curve shown are the three ranges of firing frequencies, (1) primary, (2) secondary, and (3) tertiary ranges (see Kernell 1965; Schwindt 1973 for the first descriptions), that together lead to a counterclockwise hysteresis

to the f-I relationship. Use of geometric dynamical systems methods has provided insight into the mechanism of bistability and the emergence of the three frequency ranges. Figure 3 (*bottom*) shows a typical bifurcation structure of the dendritic voltage V_D with I_{soma} as the parameter. In the class of two-compartment models described above, this corresponds to an S-shaped curve for a range of coupling conductances characterized as weak-moderate (e.g., see Booth and Rinzel 1995; Kurian et al. 2011). The lower branch (dendrite OFF) consists of stable fixed points (non-spiking steady states/resting) and a stable oscillatory regime. The upper branch (dendrite ON) also consists of stable fixed points (non-spiking plateau state) and a stable oscillatory regime. The height and width of the S shape as well as that of the regimes described are dependent on the properties of the ionic conductances considered (e.g., note differences among the various models Booth et al. 1997; Kurian et al. 2011; Venugopal et al. 2011). Superimposing the dendritic voltage changes during a somatic triangular ramp current injection in the model clarifies that (1) the primary firing frequencies correspond to the oscillatory frequencies emerging at the lower branch, (2) tertiary frequencies correspond to the oscillatory frequencies emerging at the upper branch, and (3) secondary frequencies would arise during plateau development and are transitory see (Venugopal et al.



Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons, Fig. 3 Bifurcation analyses of emergence of f-I hysteresis and bistability. *Top:* Schematic of f-I relationship in response to a somatic triangular ramp current injection (I_{soma} trace not shown, but see *curved arrow* showing direction of I_{soma} changes). Spiking begins in the soma in the primary frequency range (*blue*) and continues into a steeper secondary range (*red*) as I_{soma} ramps up. On the descending I_{soma} ramp, tertiary frequencies (*green*) give rise to a counterclockwise hysteresis in the f-I relationship. *Bottom:* Bifurcation curve showing the various steady-state regimes. The *bold lines* in the steady-state *S-shaped curve* indicate stable fixed points and *broken lines* indicate unstable fixed points. *Blue dotted*

lines demarcate the amplitude of dendritic oscillations due to soma firing in the primary range (only stable oscillations are shown here). *Red dotted lines* demarcate the amplitude of dendritic oscillations due to soma firing in the tertiary range. Note that there are no stable steady-state oscillations for the secondary range in this diagram suggesting that these frequencies are transitory. Bistability-1 (region between *left orange* and *magenta vertical lines*) marks the region where tertiary firing and (stable) non-spiking state can coexist underlying self-sustained firing described earlier. Bistability-2 (region between *magenta* and *right orange vertical lines*) marks the region where primary and tertiary firing can coexist as described earlier in Fig. 1 (*right*)

2011). The same is illustrated using the steady-state bifurcation diagram (see Fig. 3) of dendritic voltage in response to I_{soma} clarifying that only 1° and 3° frequencies are stable oscillatory states, while the secondary range arising during plateau development is not evident as a stable steady state. This critical insight suggests the possible window of modulation of the plateau by synaptic inputs in turn regulating motoneuron firing frequencies and muscle output.

In summary, conductance-based mathematical models of vertebrate motoneurons have been

useful platforms to examine nonlinear dynamics in these neurons and have provided important insights into the basis of experimentally observed membrane properties in this important class of cells in the nervous system.

Cross-References

- [Compartmental Models of Spinal Motoneurons](#)
- [Morphologically Detailed Cellular and Pool Motoneuron Models](#)

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Connectionist Models of CPG Networks

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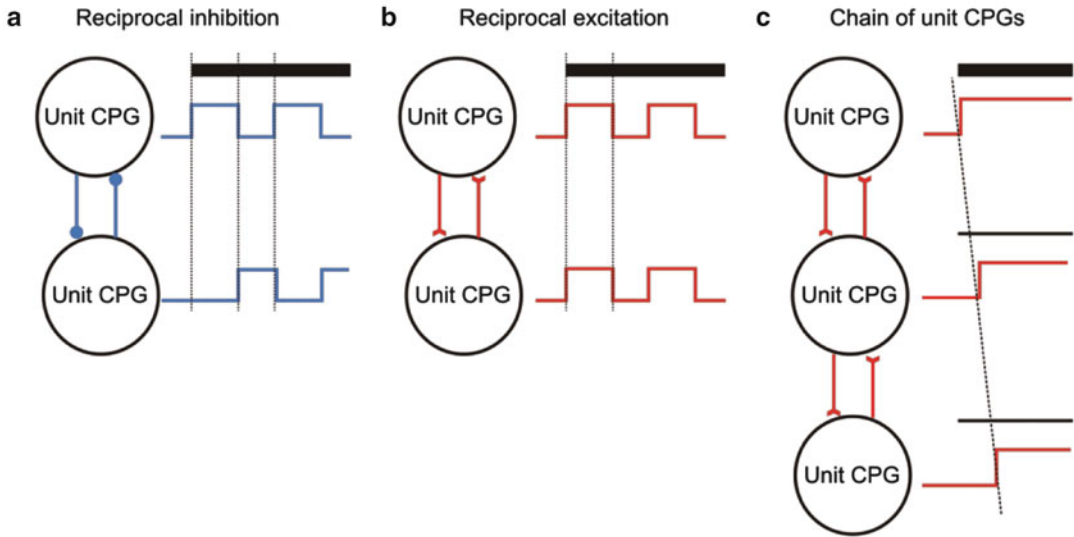
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Detailed Description

Central Pattern Generators (CPGs) are neural networks that can produce coordinated patterns of rhythmic activity to orchestrate repetitive behaviors such as feeding, locomotion, and respiration. CPGs are known to be composed of phylogenetically conserved connectional units that are typically organized into chains to enable coordinated activation of the effector organs (muscles). Through integration of experimental and computational approaches at the cellular and network levels, essential connectional elements of CPGs have been revealed (Grillner 2006).

Network Topology At the connectional level, a CPG network consists of “unit CPGs” representing the nodes of the network, and the reciprocal connections between unit CPGs correspond to the branches of the network. Physiologically, a unit CPG represents a group of neurons that can generate a recurrent burst of activity (Grillner 2006).

Simple inputs such as tonic excitation can produce rhythmic outputs in these networks. Increasing the stimulus strength typically increases the frequency of the network rhythm. Two unit CPGs are reciprocally coupled by mutual inhibition to generate alternating activity patterns (Fig. 1a) or by mutual excitation to generate synchronized bursts (Fig. 1b). Many unit CPGs connected in a chain with mutual excitation can generate a progressive phase lag in the bursts of activity along the CPG chain (Fig. 1c). It is generally accepted that rhythmogenesis is intrinsic to the neurons forming the unit CPG.



Connectionist Models of CPG Networks, Fig. 1 Schematic of typical connective elements of a CPG network. Unit CPGs with (a) reciprocal inhibitory (blue) and (b) reciprocal excitatory (red) connections are shown. (c) A chain of unit CPGs with reciprocal excitatory connections. The thick black lines in a, b, and c represent

the duration of CPG drive signal, and blue and red waveforms represent out-of-phase (a) and in-phase (b) activity. In (c), the *thin black lines* indicate reduced drive to the corresponding unit CPGs such that the top unit leads and subsequent phase lags are produced in the onset of activity as we go down the chain

However, connectionist models of CPG networks have unequivocally demonstrated that rhythmic patterns can be a resultant of a topology of connections among unit CPGs (Buchanan 1992). Hence, based on the nature of connections between unit CPGs, a CPG network can generate and shape patterns of activity.

Reconfiguration of CPGs Central pattern generators can reconfigure to switch from one activity pattern to another to produce multiple forms of the same behavior (e.g., walking, running, and galloping as different forms of locomotion) or functionally distinct behaviors (e.g., normal breathing versus gasping). Mathematical and simulation models suggest that the mechanisms underlying the reconfiguration of CPGs may include (1) altered strength and duration of the excitatory drive to the CPG network (e.g., Jung et al. 1996), (2) altered strength and duration of the mutual connections between unit CPGs (e.g., Venugopal et al. 2007), and (3) recruitment and

de-recruitment of unit CPGs (e.g., Nasse et al. 2008). Such reconfiguration of a given CPG network architecture can confer multifunctionality.

Unit CPG Models Biophysical models of unit CPGs are typically based on conductance-based Hodgkin-Huxley formalism to model the constituent neurons with one or more compartments (e.g., see review Grillner et al. 2005). In models that exclusively focused on network properties, nonlinear oscillators have been widely used to represent unit CPGs (e.g., see review Ijspeert 2008). It appears that the network activity pattern of interest can be produced irrespective of the type of the oscillator model (e.g., Collins and Richmond 1994). This provides various options for choosing a suitable oscillator to represent the unit CPGs/nodes, particularly when mathematical analyses are adopted for gaining mechanistic insight into network behavior. Moreover, simple oscillator models are suitable choices for prosthetic and/or robotic applications.

Parameter Tuning in CPG Networks Identification of intrinsic and synaptic properties/parameters of CPG networks that produce the shape and the nuances of activity patterns is at the core of neurobiological investigation of CPGs. Biophysical models of CPGs often adopt brute force methods for parameter tuning within physiological ranges (Prinz et al. 2004). Alternatively, artificial CPG networks for engineering applications have utilized artificial neural network learning algorithms to estimate network parameters (e.g., Ijspeert 2008).

Cross-References

► [Pulse-Coupled Oscillators](#)

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Connectivity Analysis in Normal and Pathological Brains

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Synonyms

[Connectomics](#); [Graph analysis](#); [Network science](#)

Definition

Connectivity analysis focuses on the neural network basis of the brain and characterizes topological and other aspects of brain network organization that appear relevant for understanding normal and pathological brain function.

Detailed Description

Brains as Networks

The network perspective of the brain integrates aspects of local versus distributed brain function, combining *segregation* and *integration* of components. Brain connectivity can be intuitively represented as *graphs*, where *nodes* represent neural elements, ranging in scale from individual cells to large-scale neural populations (e.g., cortical areas) and *links*, representing structural or functional associations between the nodes. This simplifying approach is based on the assumption that neural elements are intrinsically homogeneous and that their interactions are determined by anatomical connections.

Several types of connectivity can be distinguished (Friston 2004):

- *Structural*: the physical coupling of neural elements by neuronal connections.
- *Functional*: statistical dependencies in the dynamics of neural elements.
- *Effective*: the dynamic or functional impact exerted by one neural element on another.

Node elements can be defined by morphological, anatomical, or functional criteria, for instance, anatomical landmarks, cytoarchitectonic characterization, or functional activation patterns, respectively. Moreover, nodes can also be parcellated by their characteristic connectional fingerprint. Importantly, the way in which node parcels are defined also affects the density and topological features of the studied networks (de Reus and van den Heuvel 2013).

Structural connectivity is mostly derived from invasive approaches in animal models (histochemical or viral pathway tracing, polarized light imaging (PLI) of fibers, or optogenetic manipulation of projection neurons) and noninvasive investigations of the human brain (indirect characterization of tracts by diffusion-weighted magnetic resonance imaging, dwMRI). Depending on the studied type of connectivity and empirical constraints, one can consider *directed* versus *undirected* connectivity. For instance, human brain structural connectivity derived from diffusion-based MR imaging is typically undirected, whereas histochemical tracing in animal models allows identifying the origins and terminations of projections. Another distinction can be made of *binary* versus *weighted* networks. The former contain information on the existence or absence of links, while the latter also include information on the strength of edges (Rubinov and Sporns 2011).

Network organization matters functionally, in the ultimate sense that there are systematic connectivity differences between the brains of healthy subjects and patient groups (Bullmore and Sporns 2012). Central aspects of connectivity organization are network *geometry* (i.e., the spatial embedding of networks) versus *topology* (nonspatial features of connectional organization) (Bullmore and Sporns 2009; Sporns et al. 2004).

Topological Features of Brain Connectivity

Topology describes the connectional organization of a brain network, independent of its spatial arrangement. Topological features can be loosely ordered from more local to more global aspects. Some features are summarized in the following list. They are described in more detail in the recent research literature (Kaiser 2011; Rubinov and Sporns 2010; Sporns 2011; Stam and Reijneveld 2007).

Node Features

- *Degree*: the total number of incoming (afferent, in-degree) and outgoing (efferent, out-degree) links of a node; the *degree distribution* of nodes is a characteristic indicator of different classes of networks.
- *Strength*: the graded degree of weighted connections.
- Further node indices can be defined, such as the proportion between incoming and outgoing projections (Kötter and Stephan 2003).

Circuit Features

- *Motifs* or circuits are subnetworks consisting of relatively few nodes or links; motif spectra appear to be characteristic for different classes of biological networks (Milo et al. 2004).
- *Paths* are ordered sequences of unique edges, while *walks* are sequences of nonunique edges; *cycles* are paths leading back to the same node; the length of *shortest paths* (or its inverse, *local efficiency*) is frequently taken as an indicator for the potential length of minimal interaction distances in a network.
- Local *clustering* (cliquishness): the proportion of existing connections among the neighbors of a node.

Global Network Features

- Overall *density* of wiring: the total number of existing links in a network, out of all possible ones.

- The average shortest path (or its inverse, global efficiency).
- Network *diameter*: the longest shortest path.
- Further features can be considered at the scale of the whole network including *assortivity*: the similarity of the degree of linked nodes, as well as averages of node or circuit-based indices, such as clustering.
- Existence, number, and size of *modules*, which are formed by nodes that are more frequently or densely linked with each other than with the rest of the network.
- *Hubs*, which can be identified by a variety of measures, such as the node degree, node *centrality* (in terms of representation in the network paths), or vulnerability, and which may be *global* or *provincial* hubs depending on their placement in the network.
- *Hierarchy*: the encapsulation of features within features (e.g., modules of modules in *hierarchical modular networks*); however, hierarchy can also be defined in various other ways, e.g., by the local versus global access of nodes in a network (Müller-Linow et al. 2008).

It is important to note that network features at the same or different scales may be interrelated. For instance, dense networks may result in densely wired motifs.

Benchmark Networks

Benchmark networks can be based on the degree distribution of nodes. In so-called *Erdős-Rényi* or *random* networks, the probability, $p(k)$, of nodes possessing an edge degree k follows a Gaussian distribution, whereas the degree of nodes is constant in *regular* or *lattice* networks. *Small-world* networks can be seen as regular networks with a fraction of random links; they possess clustering comparable to regular networks and average shortest paths similar to random graphs. In *scale-free* networks, $p(k)$ follows a power law; thus, these networks lack a characteristic scale. Benchmark networks can also be constructed for a variety of other topological measures, for

instance, yielding *random modular* graphs or different types of hierarchical networks (Kaiser 2011).

There are also several established datasets for biological *connectomes*, in particular for cortico-cortical connections in the cat (Scannell et al. 1999), the rhesus macaque (Felleman and Van Essen 1991; Markov et al. 2014) as well as mesoscopic connections of the human brain based on diffusion MRI (Hagmann et al. 2008). Moreover, connectomes or partial connectomes at the cellular level exist for *Caenorhabditis elegans* (Varshney et al. 2011), drosophila (Chiang et al. 2011), and zebra fish (Stobb et al. 2012). From these datasets, further benchmarks can be derived, such as randomized versions preserving features, for example, the degree distribution, or pairwise degree distribution.

Geometry of Brain Connectivity

Brain networks are spatially embedded. The distance among neural elements may influence physiological and functional parameters through delays and metabolic costs and place constraints on the existence and strength of links. Consequently, it is a popular idea that brain networks should have compact wiring. However, other structural, functional, metabolic, or evolutionary constraints might also be important and there may be trade-offs between various, partly antagonistic constraints on brain connectivity (Chen et al. 2013; Kaiser and Hilgetag 2006).

Pathological Brain Connectivity

Aberrations in brain function arise from perturbations of local neural structures and mechanisms (i.e., node perturbations) as well as perturbed interactions between remote regions. The latter pathologies can be considered as *disconnexion* (disrupted connectivity) (Geschwind 1965) or *dysconnection* (maladjusted connectivity) syndromes (Stephan et al. 2009). Systematic differences in structural and functional connectivity

have been found between healthy controls and different patient samples, for example, with *autism* or *schizophrenia* spectrum disorders (Bullmore and Sporns 2012).

A well-studied example of the network perspective is *Alzheimer's disease* (AD), in which highly connected hub nodes of human functional brain connectivity show high metabolic activity as well as an affinity for the accumulation of *beta-amyloid* protein, thus, becoming the origin for the propagation of AD (Buckner et al. 2009).

Generally, however, it is currently unclear which network features contribute causally to different aspects of network dynamics or function.

Cross-References

- [Connectome, General](#)
- [Human Connectome Project](#)
- [Multiscale Brain Connectivity](#)
- [Neuropathologies and Networks](#)
- [Wiring Principles, Optimization](#)

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Further Reading

- Special issue: connectivity (2012) *NeuroImage* 62(4). <http://www.sciencedirect.com/science/journal/10538119/62>
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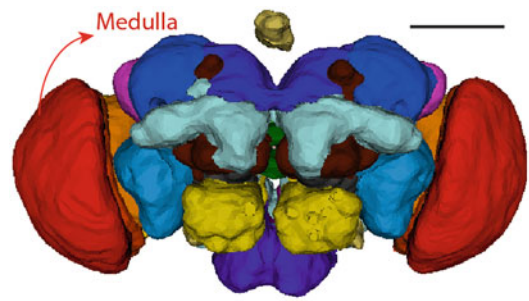
Connectome, *Drosophila*

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Definition

The *Drosophila* connectome is a comprehensive description of all the connections between subunits comprising the central nervous system (CNS) of the fruit fly, *Drosophila melanogaster*.

The CNS of *Drosophila* consists of the brain and ventral ganglion. It has a volume of $\sim 0.07 \text{ mm}^3$ (see Rein et al. 2002, Table 1). To compare, this is similar to the volume of a single cortical column in mouse barrel cortex ($\sim 0.09 \text{ mm}^3$) (Lefort et al. 2009; Hooks et al. 2011). The *Drosophila* brain can be subdivided into smaller neuropil compartments (Fig. 1), identified through anatomical boundaries (Ito et al. 2014), as well as the overlapping arborizations of the neurons constituting each neuropil compartment (Chiang et al. 2011; Jenett et al. 2012). In total, across these compartments, the *Drosophila* brain is thought to contain $\sim 90,000$ cells, of which $\sim 90\%$ are neurons. These neurons can be classified into



Connectome, *Drosophila*, Fig. 1 *Drosophila* brain with anatomically identified neuropil compartments individually colored (www.flybrain.org (AB00122)). Scale bar: 100 μm

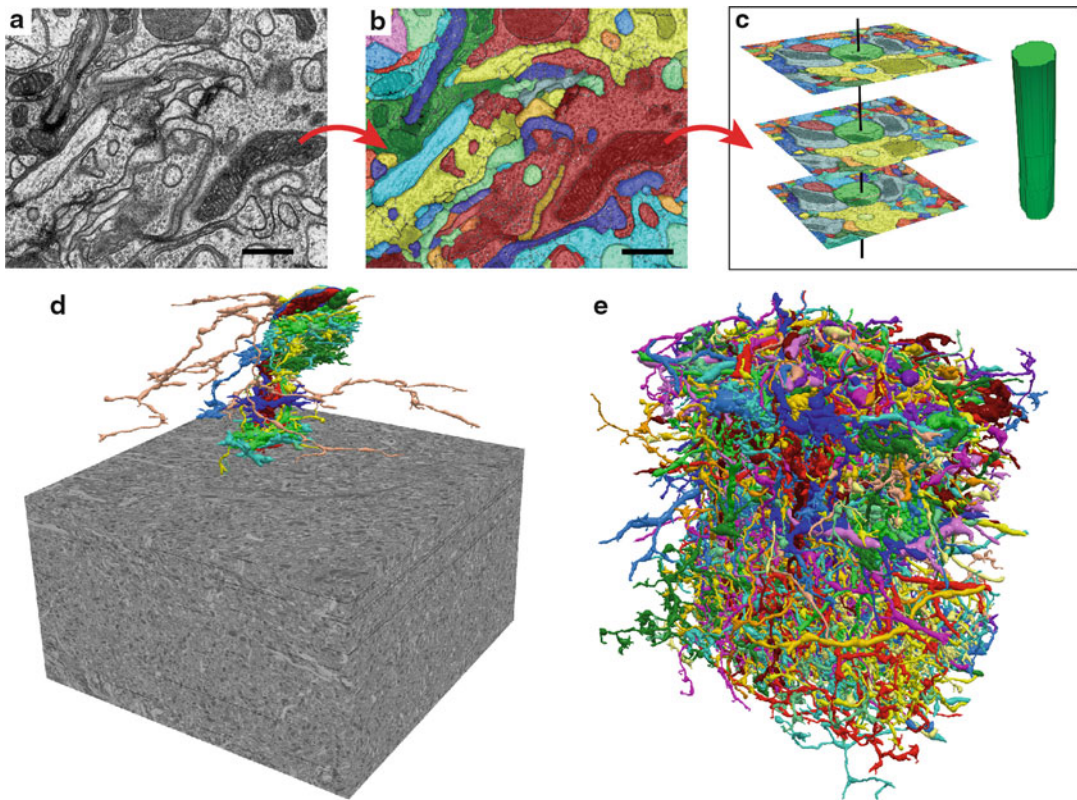
discrete cell types, with stereotypical shapes and synaptic connections, using both human observation and genetic reporter lines that label individual types.

A *Drosophila* connectome, within the brain, can be constructed at different levels of resolution. At low resolution, a connectome can be said to comprise neuropil compartments, with connections between them defined by neural pathways, as identified by light microscopy. In contrast, at high resolution, a connectome comprises individual neurons and all the chemical synapses between them. The components of such a cellular connectome are identified through electron microscopy (EM).

As of 2013, neuropil-level connectomes have been constructed for the entire *Drosophila* brain (Chiang et al. 2011), but only partial cellular connectomes have been reported. In particular, cellular connectomes have been reported for a cartridge of the lamina (Meinertzhagen and O'Neil 1991; Rivera-Alba et al. 2011) and a column of the medulla (Takemura et al. 2013), the first and second neuropil compartments, respectively, within the fly optic lobe (transmitting visual information). Despite their incomplete nature, these partial connectomes have already provided valuable insights into the computational functions of neuronal circuits.

Existing Neuropil-Level Connectomes

Large-scale, compartmental maps of the *Drosophila* brain have been obtained through the use of genetic reporters imaged by light microscopy (Chiang et al.



Connectome, *Drosophila*, Fig. 2 Reconstructing a cellular connectome using ssTEM. (a) TEM image of part of a 40-nm-thick section, 1 of 2769 sections imaged to reconstruct the medulla connectome. (b) Applying computational segmentation algorithms, followed by human proofreading on the TEM images, is necessary to isolate

neuronal cross sections (neurite profiles in single colors). (c) Profiles in consecutive sections (left) are linked to construct 3D neurites (right). (d) A subset of reconstructed neurons, embedded within the imaged neuropil. (e) Rendering of neurites belonging to 379 reconstructed neurons. Scale bar: 500 nm (a, b)

2011). Each reporter line fluorescently labels a sparse subset of neurons (Jenett et al. 2012; Ito et al. 2013). Aligning images from multiple lines to a standard *Drosophila* brain, the overlapping arbors of locally arborizing neurons are used to define individual compartments: local processing units (LPUs) (Chiang et al. 2011). The connections between these LPUs are found by identifying neurons projecting between them. In total, the resulting connectome contains 58 tracts between the 41 identified LPUs, a sparse subset (<10%) of the 820 numerically possible LPU-LPU connections.

Cellular Connectomes and EM

A neuropil-level connectome, generated from light microscopy, has insufficient resolution to

identify synapses and hence cannot detail the true connections between neurons. The large-scale, dense identification of all synapses within a region of neuropil requires higher resolution EM-based methods, typically serial-section transmission EM (ssTEM) (Fig. 2). However, these techniques are labor intensive and time-consuming. Therefore, only a few partial cellular connectomes have been reconstructed, specifically for two *Drosophila* optic lobe neuropils.

Optic Lobe Cellular Connectomes

The optic lobe of flies has been the subject of experimental interest for over 50 years, driven by the advanced visual behaviors of flies (Heisenberg

and Wolf 1984). Despite the large size of the optic lobe, encompassing almost 50% of the total CNS volume (Rein et al. 2002), the modular structure of its underlying neuropil compartments, corresponding to the ommatidia array of the compound eye, is highly amenable to connectomics.

Within the optic lobes, synapses are divergent polyads (Fig. 3), i.e., each presynaptic specialization (or “T-bar”) is typically associated with four to six postsynaptic dendrites. This divergence is expected to generalize to non-optic lobe neuropils, though the number of postsynaptic targets may vary across neuropils.

Lamina

The lamina receives most of its input directly from photoreceptors in the retina. It is thought to be mostly responsible for encoding contrast and for light adaptation. A cellular connectome of the repeating unit of the lamina, the lamina cartridge, has been reconstructed twice, in two different wild-type strains (Meinertzhagen and O’Neil 1991; Rivera-Alba et al. 2011). Both reconstructions are similar, with most differences apparently introduced by improvements in reconstruction quality and by differences in the interpretation of some

postsynaptic elements. The consensus lamina connectome contains the terminals of six photoreceptors, along with 12 types of neurons (Rivera-Alba et al. 2011; Tuthill et al. 2013). In total, each cartridge contains ~480 presynaptic sites, contacting ~1250 postsynaptic sites.

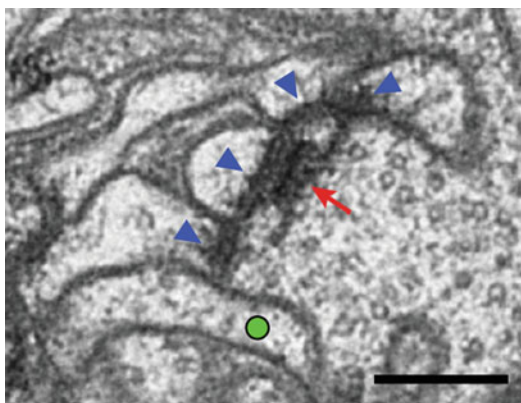
Medulla

Directly downstream of the lamina, the medulla is the single largest neuropil of the fly’s brain and receives visual input both through the lamina and directly from a subset of photoreceptors. It is thought to be responsible for (1) the computation of local visual motion, by the comparison of inputs from different points in space, and (2) color vision, utilizing the direct inputs from spectrally tuned photoreceptors.

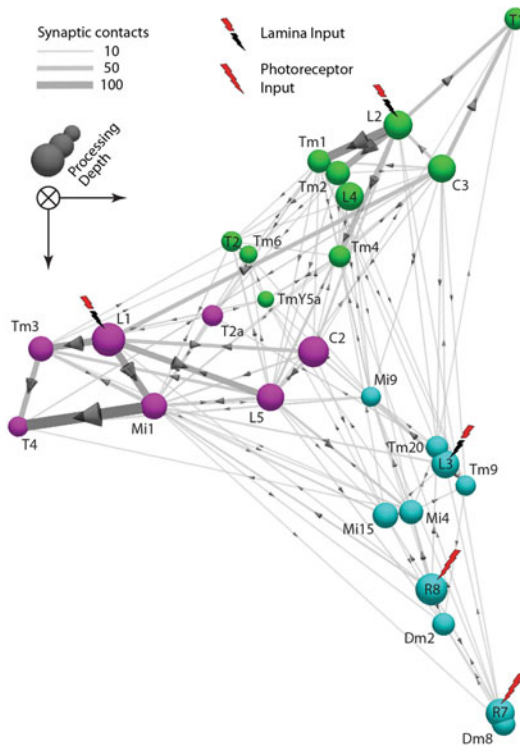
A connectome of the repeating unit within the medulla, the column, was reconstructed recently (Takemura et al. 2013) (Fig. 4). It reports the connections between 56 identified cell types, of which 27 are modular (contained in every column). As in the lamina, each presynaptic site contacts multiple postsynaptic elements (~3.8 on average). Within a column, the modular cell types are connected by ~2500 synaptic contacts. However, this is only a subset of the ~5800 synaptic contacts that these same modular cell types make in total, showing clearly that there are far more cross-column connections in the medulla than in the lamina (Rivera-Alba et al. 2011).

Characteristics of the *Drosophila* Connectome

Presynaptic terminals within the existing connectome reconstructions are typically of uniform size, and the number of synaptic contacts between different neuron pairs ranges over more than two orders of magnitude (1–150). Hence the synaptic weight for any pair is thought to be well approximated by the number of synapses in parallel. However, it is not known if it will be possible to generalize this quantitative assumption to the rest of the *Drosophila* connectome.



Connectome, *Drosophila*, Fig. 3 Divergent polyadic synapse. The presynaptic process, identified with a T-bar (red arrow), is associated with four postsynaptic dendrites (blue arrowheads). These postsynaptic processes can be distinguished from adjacent, unconnected processes (e.g., green circle) by their postsynaptic densities. Scale bar: 250 nm



Connectome, *Drosophila*, Fig. 4 3D graph of a connectome module: the connections between neurons found in every medulla column. The dominant direction of signal flow is oriented into the page. Cell types with stronger connections are positioned closer to each other. The colors identify three spatially segregated groups of neurons and, hence, three pathways of information transmission within the medulla

Synapse numbers for identified neurons are consistent across neurons of the same type in the lamina and medulla. However, as has been seen in both the antennal lobe (Chou et al. 2010) and the mushroom body (Murthy et al. 2008; Caron et al. 2013), this may not generalize to other parts of the brain. In general, learning associated or other forms of plasticity may decrease the stereotypy in the numbers of synaptic contacts, thereby increasing the difficulty of obtaining a single, defined connectome.

The Utility of Connectome Information: Functional Studies

One rationale for compiling a cellular connectome is to gain insight into the neuronal implementations

of behavior. The existing optic lobe connectomes have already demonstrated such utility. They have been used to direct the attention of genetic experiments toward a specific neuron(s) (Gao et al. 2008) and to provide the neuronal circuit substrates for computational analyses (Takemura et al. 2013). For example, the comprehensive nature of the cellular connectome reconstruction in the medulla allowed the identification of candidate neurons comprising a circuit computing local motion, a computation that had been intensely studied for more than 50 years (Borst et al. 2010), yet with limited prior insight.

In Progress

As of 2013, ongoing *Drosophila* reconstruction projects include the larval CNS connectome (Cardona et al.) and the connectome for seven medulla columns, utilizing a new imaging technique: focused ion beam milling scanning EM (FIB-SEM). FIB allows improved z-axis resolution, enabling more complete tracing of neurites thinner than the section thickness. This results in a more complete connectome, given that only 50% of the postsynaptic sites could be traced to an identified neuron in the ssTEM dataset. Further, by including multiple columns, the resulting connectome should also allow an estimate of the variation between columns, as well as the exploration of color vision circuits (Franceschini et al. 1981).

The Future

We are obviously at the early stages of assembling the components of the *Drosophila* cellular connectome. However, from the current rapid pace of improvements in sample preparation, imaging, and software tools for reconstruction, it seems possible that the cellular connectome will become available for the entire fly's CNS. This will require improvements in staining and sample preparation, increased reliability and speed of imaging, and improved automated image analysis algorithms. Additionally, information on the

polarity of synaptic transmission, and the presence of electrical synapses, neither visible from EM, must be incorporated from other techniques (Meinertzhagen and Lee 2011). However, even prior to the completion of the entire connectome, the demonstrated utility of the existing pieces of the *Drosophila* connectome suggests that each additional reconstruction should provide valuable biological insight.

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Connectome, General

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Definition

Connectome is the full connection matrix (or the full wiring diagram) of all neurons in the brain (Sporns et al. 2005). Current efforts in connectomics (study of the connectome) can be grouped along two axes, one based on scale (macro [or regional] vs. micro [or cellular] connectome) and the other based on research focus (data acquisition technology vs. theoretical frameworks and analysis). The end goal of connectomics is to understand how the brain works based on its intricate circuitry, i.e., to go from complete structure to detailed function. See Seung (2012) and Sporns (2011, 2012) for a general overview of connectomics.

Detailed Description

The main underlying assumption in connectomics is that the brain's connective architecture determines in large part its function (Sporns 2012; Seung 2012). This assumption can be put in an evolutionary

context, as noted by Swanson (2003): Evolution from simple neuronal networks in primitive animals to complex brains of animals like humans happened mostly in its architecture, not in its components.

Current Status of Connectomics

Connectomics aims to obtain the connectome from the whole brain and analyze it in full detail at subcellular resolution. However, because of technological limitations, current efforts are focused on either small volumes (on the order of 100 μm) of nm resolution samples or large volumes (whole brain) at hundreds of μm resolution. Connectomes at these two different scales are called micro (or cellular) connectome and macro (or regional) connectome, respectively (see, e.g., DeFelipe 2010).

Currently, the only full connectome that is available is that of the nematode *Caenorhabditis elegans*. All 302 neurons, their connections, and other somatic cells have been mapped out fully (White et al. 1986). Various connectivity analysis (e.g., Watts and Strogatz 1998; Kaiser and Hilgetag 2006; Sohn et al. 2011) and open-source simulation efforts (OpenWorm, <http://openworm.org>) are based on the *C. elegans* connectome data.

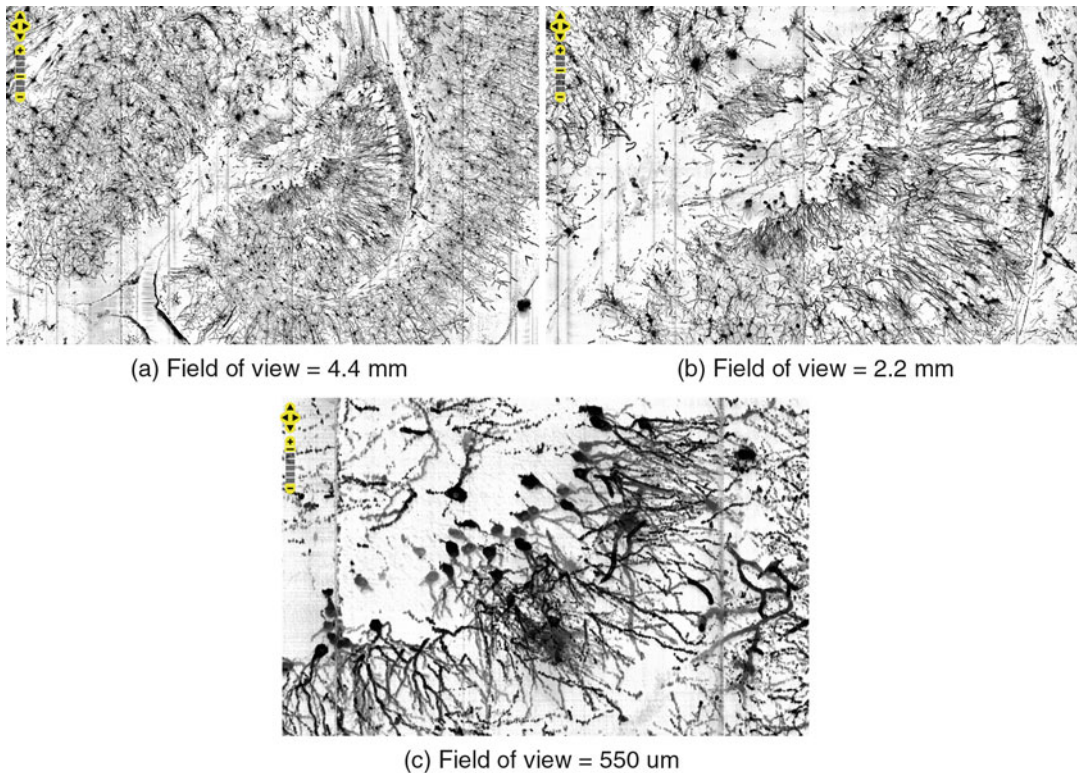
The *Drosophila* connectome has also been extensively mapped (379 neurons and 8637 chemical synapses) in the medulla of the optic lobe (Takemura et al. 2013). However, due to the complexity of the *Drosophila* brain compared to that of the *C. elegans* ($\sim 90,000$ cells in its brain, of which $\sim 90\%$ are neurons), the full connectome has not been mapped. See ► “Connectome, *Drosophila*” for details.

Cellular-level connectome (nm resolution) of larger animals seems to be beyond the horizon at the moment, although technologies for obtaining such data are actively being developed. For an overview of such methods, see ► “Physical Sectioning Microscopy,” especially those employing electron microscopy, e.g., serial block-face EM (Denk and Horstmann 2004) and automated tape-collecting ultramicrotome (Hayworth et al. 2006). These techniques have been used to map small volumes of neural circuitry ($\sim 100^3 \mu\text{m}^3$) at

nm resolution (on the order of 10 nm), for example, the mouse retina (Helmstaedter et al. 2013) or the rabbit retina (Anderson et al. 2011). At a similar scale, Bock et al. (2011) combined functional imaging (two-photon calcium imaging) and serial transmission EM to image 450 μm wide and 350 μm deep volume from the mouse visual cortex (this data set is available through the Open Connectome Project <http://openconnectomeproject.org>). In a similar vein, Mishchenko et al. (2010) studied the ultrastructure of rat hippocampal neuropil from serial sectioning transmission EM images (45–50 nm thick sections, 2.2 nm in-plane resolution).

At the μm scale, light microscopy techniques are being developed for connectomics, with the aim of obtaining local circuits based on histological stains (e.g., knife-edge scanning microscopy and related techniques; Mayerich et al. 2008; Chung et al. 2011; Li et al. 2010a; Fig. 1) and long-range projections based on tracer injections (Hintiryan et al. 2012; Mitra 2012). The typical volume that can be imaged with these methods is $\sim 1 \text{ cm}^3$ at the resolution of $\sim 1 \mu\text{m}$. See ► “Physical Sectioning Microscopy” and Kleinfeld et al. (2011) for related approaches such as array tomography, serial two-photon tomography, and all-optical histology. Optical sectioning techniques such as scanned light-sheet microscopy (Keller et al. 2008) are also promising, especially when combined with tissue-clearing methods like CLARITY (Chung and Diesseroth 2013). Fluorescence probes are routinely used to label distinct neuronal types or molecular signatures such as presynaptic vs. postsynaptic densities for the detection of synaptic connections. Most of the above techniques have been applied to mouse brain imaging (see ► “Connectome, Mouse” for publicly available data). However, the available data are only partial and in many cases geometric reconstructions are not available; thus analysis based on the data is scarce. Some reconstructions are available for small volumes of the mouse neuromuscular junction connectome ($\sim 100^3 \mu\text{m}^3$ at $\sim 0.2 \mu\text{m}$ resolution), where the brainbow technique was used (Srinivasan et al. 2010).

At the highest spatial scale, neuroimaging methods are used to map the macro (or regional)



Connectome, General, Fig. 1 Circuits in the mouse hippocampus. Screenshot from the Knife-Edge Scanning Microscope. Brain Atlas <http://kesm.org>, inverted and contrast enhanced (Chung et al. 2011; Mayerich et al. 2008).

The Golgi data set shown is an overlay of thirty 1 μm -thick sections at an interval of 2 μm , representing a tissue thickness of 60 μm . The voxel resolution is 0.7 $\mu\text{m} \times 0.6 \mu\text{m} \times 1.0 \mu\text{m}$

connectome. These techniques are mostly based on diffusion magnetic resonance imaging (dMRI; Park et al. 2008; Hagmann et al. 2007, 2008; Johansen-Berg and Rushworth 2009), with the exception of 3D-polarized light imaging (3D-PLI; Axer et al. 2011). Major white matter tracts can be imaged using these approaches. The volume covered by these techniques is often as large as the human brain (on the order of 10^3 cm^3), but the imaging resolution is low, about 2 mm for dMRI and about 30 μm for 3D-PLI. Serial sectioning has been employed on whole human brain at 20 μm sectioning thickness with in-plane resolution of 10 $\mu\text{m} \times 10 \mu\text{m}$, but the histological stain used only labeled cell bodies; thus, connectivity could not be established (Amunts et al. 2013). Although the resolution is low, data from this scale has been analyzed most intensely compared

to connectomes at different spatial scales. It is also notable that connectivity matrices derived from tracer injection methods are available at this scale, such as that of the macaque (► “[Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)”; Felleman and Van Essen 1991) and the cat (de Reus and van den Heuvel 2013). Simulation of an entire thalamocortical network of the human brain based on dMRI connectivity data (Izhikevich and Edelman 2008) and extensive connectivity analysis exists at this scale (see Chap. 5, The Connectome at the Macroscale, in Sporns 2012, and ► “[Human Connectome Project](#)”).

Across the multiple scales, connectomics research is already producing deep insights into the organization and function of the brain, e.g., (1) discovery of new cell types based on

morphology and connectivity (Helmstaedter et al. 2013), (2) organizing principles such as the “rich club” (nodes with high connectivity are more heavily connected among themselves; van den Heuvel and Sporns 2011; de Reus and van den Heuvel 2013), (3) emergence of activation patterns and sensitivity of the pattern to small local changes (Izhikevich and Edelman 2008), (4) wiring optimization principles (see ► “[Wiring Principles, Optimization](#)”), (5) changes in the connectome due to neurodegeneration (Zhou et al. 2012), and (6) identification of functionally distinct neuronal populations based on connectivity (Sohn et al. 2011).

From Raw Data to Geometry, Connectivity, and Databases

The imaging data obtained using the techniques outlined above are prone to noise and distortions; thus, noise and artifact removal using image processing algorithms is a necessary first step. Next, denoised images need to be registered so that an aligned 3D volume can be constructed (note that some methods do not require such a registration step). The last step of assembling the connectome is to reconstruct the geometry of all neurons and their connections from the image volume (see ► “[Reconstruction, Techniques and Validation](#),” and ► “[Reconstruction, Electron Microscopy](#)”). This is no trivial task, and researchers are exploring (1) manual (e.g., Fiala 2005), (2) automated (Jain et al. 2010; Bebis et al. 2010; Edwards et al. 2013), (3) crowd-sourcing-based (e.g., the EyeWire Project <http://eyewire.org>; Helmstaedter et al. 2013), and (4) a hybrid of automated and manual methods (Chklovskii et al. 2010; Mishchenko et al. 2010).

Once the full geometric description of all neurons is known, the connectivity needs to be established. In electron microscopy (EM) data, synapses can be inferred based on synaptic densities and synaptic vesicles and by locating gap junctions (Xu et al. 2013). Several manual and automated methods have been developed for this, e.g., Chklovskii et al. (2010), Xu et al. (2013), and Kreshuk et al. (2011). Aside from

EM data, exact connectivity cannot be established, unless molecular markers such as synaptophysin-GFP are used to explicitly mark the synapses (Li et al. 2010b). For example, data based on light microscopy typically show only a fraction (~1% for Golgi) of the entire population of neurons. In this case, we need to estimate connectivity. Methods like those proposed by Kalisman et al. (2003) can be used. One way to test the validity of such an approximation is as follows. First, conduct a systematic simulation study with a full synthetic circuit to establish a baseline. Next, drop a certain proportion of connections and observe the resulting change in behavior. The degree of redundancy in the connections (both for real and synthetic circuits) will play an important role here.

Informatics is also an important component in connectomics: how to represent and organize the image data and reconstructed geometry and connectivity. Standards for describing neuronal morphology such as ► “[NeuroML](#)” and classification and taxonomy schemes such as the Foundational Model of Connectivity (FMC) are being developed (Swanson and Bota 2010). Due to the massive amounts of data regardless of the imaging modality or scale, connectome data are generally made available through web-based multi-scale visualization environments (see Chung et al. 2011; Hintiryan et al. 2012; Mitra 2012; Mikula et al. 2007).

Analysis and Utilization of Connectome Data

Once the connectome is reconstructed and connectivity established, we need to analyze the data to gain new insights in brain structure and function.

Graph Theoretical Analysis With a full connectivity matrix, we can use standard graph theoretic measures such as in-degree, out-degree, clustering index, etc. (Barabasi 2002; Bullmore and Sporns 2009; Rubinov and Sporns 2010) and look for motifs (Watts and Strogatz 1998). See Kaiser (2011) for a tutorial.

Basic Circuit Analysis Stereotypical patterns of local circuits are a hallmark of brain architecture. These patterns are called basic circuits, and using these as a building block, large-scale circuit analysis can be conducted (Shepherd 2004). Connectome data can also enable systematic discovery of new basic circuit patterns.

Estimating Dynamic Parameters Certain dynamic parameters such as conduction delay can be estimated based on axon length and diameter. Simply calculating the delay distribution can already provide great insights into brain function. For example, Thiel et al. (2003) showed that the complexity of network dynamics critically depends on the delay distribution. (Also see Sporns et al. (2000) on the relationship between neuroanatomy and brain dynamics.) Compared to connectivity data, collections of delay data are relatively scarce, with few exceptions being the works by Lamme and Roelfsema (2000) and Nowak and Bullier (1997).

Bridging the Gap Between Structure and Function The connectome is fundamentally a static structure. How can physiological properties be inferred from just the structure? Toledo-Rodriguez et al. (2004) show a possibly powerful solution to this problem: use gene expression data (also see Markram 2006). They found that gene expression and electrophysiological properties are closely correlated. For approaches like this, existing gene expression data (e.g., the Allen Brain Atlas (Lein et al. 2007) and techniques that combine molecular and EM imaging serve as great resources (e.g., array tomography (Micheva and Smith 2007)) are great resources for this kind of approach. These approaches can also help determine the sign and strength of the synaptic connections (together with dynamic parameters discussed right above) which are important properties that influence function. For example, the function of a circuit can instantly become nontrivial to analyze when inhibition is involved, e.g., in various circuits that incorporate disinhibition.

Linking with Dynamic Data To obtain a more complete picture of the brain, eventually we will

need to combine structural and functional imaging of the brain. Near real-time calcium imaging of whole animals such as the zebra fish is already possible (Ahrens et al. 2013), and at the higher spatial scale, neuroimaging methods like magnetoencephalography (MEG) can be used (Larson-Prior et al. 2013). Functional and effective connectivity estimated using functional MRI (Friston 2011) could also be compared and contrasted with connectomics data. Some of the limitations of functional and effective connectivity estimation can be addressed through optogenetics (Lee et al. 2010).

Inter- and Intra-Specimen Variability Estimation Simply measuring the morphological variability among the same class of neurons can provide valuable insights into how redundant or specialized the functions are (Gerald Edelman, personal communication, 2009). Even when connectivity is not known, just examining the dendritic trees can give deep insights into neural computation (Mel 1994; Polsky et al. 2004).

Brute-Force Parameter Search and Simulation Of course a straightforward yet potentially valuable approach is to start with computational simulations based on detailed neuronal morphology (cf. the Blue Brain Project, Markram 2006). The reconstructed geometry can be used to construct multi-compartment models (see, e.g., Dayan and Abbott 2001). Appropriate parameters such as channel conductance, capacitance, etc. need to be figured out. Tools like NEURON, GENESIS, neuroConstruct, NeuGEN, Netmorph, etc. can be used for multi-compartment simulation and parameterized synthetic circuit generation/simulation/analysis (Hines and Carnevale 1997; Bower and Beeman 1998; Gleeson et al. 2007; Koene et al. 2009; Koene 2007; Ascoli et al. 2001; Eberhard et al. 2006). Connectomics data can help narrow down on the range of various parameters for these simulations (for parameter constraining procedures, see Druckmann et al. 2008).

Investigate the Effect of Link Fidelity A great matter of debate in connectomics is whether

individual connections matter (detailed EM info needed) or whether they can be averaged (diffusion MRI is enough). Some results suggest that dropping even a single spike in the initial condition can have a global effect on the entire cortex within 0.5 s (see Izhikevich and Edelman's (2008) large-scale simulation study of the thalamocortical system based on diffusion MRI data). However, considering that the brain in a normal operating environment is always anchored to the present input stimulus thus constantly resetting the initial condition, this may not be a serious issue. Issues like these can be studied based on circuit data estimated from the connectomics data sets.

Investigate Changes in the Connectome in Brain Disorders An important practical application of connectomics is to understand how brain disorders change or deteriorate the connectome. Preliminary work in this direction has already appeared: Zhou et al. (2012) showed how connectivity in health predicts regional vulnerability to disease (note: in this work, fMRI-based functional connectivity was studied, not structural connectivity). See ► [“Neuropathologies and Networks”](#) for details.

Novel Visualization Methods for Discovery The amount of connectome data that already exists surpasses our capability to analyze and understand them. In most cases, the connectome data are stored as numerical values, and humans are not good at dealing with such data directly. To enable discovery, novel real-time visualization methods may be necessary. Visualization should not be confined to rendering the geometry – various forms of filtering and statistical summary visualization based on local and global geometric properties (such as orientation, anisotropy, etc.) need to be developed. See Margulies et al. (2013) on visualizing dMRI human connectome data and Mayerich and Hart (2007) on visualizing serial EM data. Visual analytics for abstract information extracted from the connectome will also be necessary (see Meyer et al. 2010 for a discussion on visual analytics in general).

Challenges and Open Questions

A hotly debated open question in connectomics is regarding the scale: What level of detail is enough to completely replicate the architecture and function of the brain (Koene 2012)? This question arises partly due to the incompleteness of various data acquisition technology operating at scales ranging across several orders of magnitude, from EM to dMRI. There is no definite answer to this problem. In the next decade or so, for practical reasons, we will have to live with a patchwork of connectomics data from various scales, so we need to invent novel approaches to register and integrate connectome data from different imaging modalities at different scales.

One of the ultimate goals of connectomics is to construct a high-fidelity computer simulation of the brain (Whole Brain Emulation; Koene 2012). We can consider an interesting open question: Is it possible that we can have such a high-fidelity computer simulation of the brain but cannot understand what is going on in the simulation? This is a real possibility. Based on this, some might even argue that modeling and simulation do not give you any additional understanding about the phenomena that you are studying. However, we need to consider that simulations give us two very important tools: (1) full access to the system state (readout) and (2) full control over the system state (intervention). With a completely replicated simulation, we can conduct a full battery of experiments, including a unique opportunity to selectively damage or turn off parts of the system, which is an important requirement for inferring causality in a complex system (see Pearl 2001 for the importance of intervention for such an inference). Furthermore, high-fidelity simulations can lead to a rather exotic possibility of allowing the simulation itself to experiment on itself to objectively study subjective phenomena such as consciousness (note that whether brain simulations can cause mind is a whole separate issue; see, e.g., Searle 1980).

Some may argue that simulating the brain is not enough. That is, the entire body must be

simulated. This kind of argument can be based on philosophical grounds, e.g., the criticism of brain-body dualism by Bennett and Hacker (2003) (also see the counterpoint raised by Churchland 2005). However, the argument can also be based on practical grounds. All sensorimotor organs and the extensive peripheral nervous system form a major chunk of the animal nervous system, and these nervous networks define the environment-to-body interface. Without understanding this interface, it would be difficult to understand the function of the brain.

Finally, an important question is about the role of theory in the analysis of connectomics data. Connectomics research is data-driven by its nature, so one of the hopes is that data can lead us to principles of brain organization and function. However, due to the massiveness of the data, without theoretical guidance, it would be difficult to make progress. This is a classical chicken-or-egg problem: We want to study the connectome to get to the theory, but without theory we get lost in the data. There is some skepticism about connectomics research due to problems like this, but as argued by Lichtman and Sanes (2008), the human genome project had similar concerns yet the data ultimately led to spectacular scientific discoveries, and similar results are expected from connectomics. Since very specific theories can often be misleading unless grounded on detailed data, it would be better to start with broader perspectives, such as the importance of action and the sensorimotor loop (Llinás et al. 1994; Fuster 1997; Choe et al. 2007), the role of time and prediction (Choe et al. 2012), the evolutionary origin of brain (Humphrey 1992; Kwon and Choe 2009; Chung and Choe 2011), and the developmental processes that shape the brain (Weng et al. 2001; Miikkulainen et al. 2005).

Cross-References

- ▶ [Connectome, *Drosophila*](#)
- ▶ [Connectome, Mouse](#)

- ▶ [Determining Network Structure from Data: Nonlinear Modeling Methods](#)
- ▶ [Human Connectome Project](#)
- ▶ [Multiscale Brain Connectivity](#)
- ▶ [Network Theory in Neuroscience](#)
- ▶ [Neuropathologies and Networks](#)
- ▶ [Wiring Principles, Optimization](#)

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Connectome, Mouse

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Definition

The mouse connectome is a collection of all neuronal connections in the mouse brain, i.e., a complete wiring diagram of the mouse brain.

Detailed Description

The concept of connectome (Sporns et al. 2005; Seung 2012; Sporns 2012) has rapidly grown into a central theme in neuroscience and specifically in computational neuroscience and computational neuroanatomy. So far, as of 2013, the only existing connectome is that of the nematode *C. elegans* (White et al. 1986). Once obtained, the connectome of the mouse is expected to have significant scientific and clinical impact, due to (1) strong architectural and genetic similarities between the mouse and humans, (2) the extensive body of experimental studies involving the organism, and (3) the availability of a large array of transgenic, knockin, and knockout variants and molecular probes to infer function from the connectome structure (Chinwalla et al. 2002).

Acquisition of the Mouse Connectome

Rapid development in imaging technology in the past decade is taking us ever closer to the completion of the mouse connectome. See ► [“Physical Sectioning Microscopy”](#) for a detailed review of such imaging technologies.

Public Data Sources

Here, we will review existing public data sources relevant to mouse connectome research. As mentioned above, to date, a complete mouse connectome does not exist. The existing data collections focus on different aspects of the mouse connectome and are in many ways complementary to each other, especially due to the different scales and the size of the tissue volume represented in each data: cellular (or micro) connectome (sections [“Knife-Edge Scanning Microscope \(KESM\) Brain Atlas”](#) through [“Mouse Brain Architecture Project”](#) below) versus regional (or macro) connectome (section [“Electron Microscopy Data”](#) below).

Knife-Edge Scanning Microscope (KESM) Brain Atlas

The Knife-Edge Scanning Microscope (KESM) is a physical sectioning microscope that enables submicrometer-resolution imaging of whole small animal brains (Mayerich et al. 2008). The KESM Brain Atlas is an online atlas (<http://kesm.org>) at Texas A&M University that serves whole mouse (C57BL/6) brain data acquired using the KESM (Chung et al. 2011). Currently, three data sets are available, two from mouse brains stained with Golgi (neuronal morphology) and one with India ink (vasculature). The two Golgi data sets provide rich neuronal morphology data spanning the entire mouse brain with a voxel resolution of $0.6 \times 0.7 \times 1.0 \mu\text{m}$. Due to the sparse nature of the Golgi stain, exact synaptic connections and long-range projections are not visible in these data sets. However, the overall architectural plan of the

mouse brain can be studied, based on the diverse patterns of dendritic arbors across different regions of the mouse brain and major projection pathways such as the various commissures and the radiating projections within the striatum.

Allen Mouse Brain Connectivity Atlas

The Allen Mouse Brain Connectivity Atlas (<http://connectivity.brain-map.org>) provides axonal projection data from ~300 regions in the mouse brain, associated with C57BL/6 J mice and ~100 Cre driver lines backcrossed to the C57BL/6 J mice (Allen Institute for Brain Science 2012). For this atlas, conventional and viral tracers were used to label the projections, and serial two-photon tomography (Ragan et al. 2012) was used to section and image the prepared whole mouse brains. The resolution of the data sets is $0.3 \times 0.3 \mu\text{m}$ on the imaging plane, with a z-stack interval of 100 μm . The resulting image stacks are registered to the reference atlas of the Allen Mouse Brain Atlas and the Mouse Brain in Stereotaxic Coordinates (Paxinos and Franklin 2001). Quantitative data from the projections along with detailed annotations of the injection site are entered into an online neuroinformatics platform for public use. The platform also includes search and visualization tools for an extensive analysis of the axonal projection patterns in the mouse brain.

The Mouse Connectome Project

The Mouse Connectome Project (<http://mouseconnectome.org>) at the University of California, Los Angeles, hosts long-range projection data similar to the Allen Mouse Brain Connectivity Atlas. The collection hosts 245 injection cases (125 viewable at the moment, with a projected total case of 400 [as of July 2013]), with each case containing two injection sites using anterograde and retrograde tracers. All the brains used for data acquisition were that of the C57BL/6 J mice and were counterstained with a fluorescent

Nissl stain for cytoarchitectural registration. Injection sites were systematically chosen from a regular grid rather than anatomically identified regions. The prepared brains were sectioned coronally to 50 μm thick sections and imaged using a virtual slide scanner. All the data can be explored online using an interactive visualization tool called iConnectome. Detailed specimen preparation and data acquisition methods and case studies focusing on the pathways in the mouse olfactory bulb are available in Hintiryan et al. (2012). Latest work from the same project include a mouse neocortical connectivity atlas based on manual reconstruction (Zing et al. 2014).

Mouse Brain Architecture Project

The Mouse Brain Architecture Project (MPA, <http://brainarchitecture.org>) at the Cold Spring Harbor Laboratory also hosts long-range projection data similar to the Allen Mouse Connectivity Atlas and the Mouse Connectome Project. The MPA includes anterograde and retrograde tracer data from 235 regions in the mouse brain, with the majority of the injection sites in the cerebrum (218). The basic methodology is similar to that of the other long-range projection atlases: inject tracer in C57BL/6 mouse brain, slice (cryosection), whole-slide digital imaging (alternating slices processed with conventional histology and tracer detection, respectively), and make the processed data available online (Mitra 2012). However, one main feature distinguishes the MBA project from other atlases: the choice of injection coordinates. In MBA, the injection sites are determined by an algorithm to sample the brain in “the most homogeneous way compatible with separation of brain regions” (Grange and Mitra 2011). Injection sites in the cerebral cortex are selected based on a separate algorithm adapted to the geometry of the cortex.

Electron Microscopy Data

Electron microscopy (EM) data from selected regions of the mouse brain and nervous system are also available to the public.

The Open Connectome Project (<http://www.openconnectomeproject.org/>) hosts several EM image stacks, which include data from the mouse visual cortex (Bock et al. 2011). The data set was acquired using a custom Transmission Electron Microscope (TEM), spanning a volume $\sim 450 \times 350 \times 52 \mu\text{m}$, at a resolution of $<50 \text{ nm}$ in depth and $<5 \text{ nm}$ in the imaging plane.

The Whole-Brain Ultrastructural Mapping Project (<http://connectomes.org>) hosts EM data that spans an entire mouse coronal section at 80 nm voxel resolution, acquired using block-face electron microscopy. The data was made possible by a whole-brain EM staining method reported in Mikula et al. (2012).

Summary and Future Prospects

In this article, we reviewed mouse connectome data that are publicly available online. As we have seen, a complete connectome of the mouse is not yet available. However, data from multiple scales and different imaging modalities allow us to piece together an initial draft of the mouse connectome. Such a draft, although rough, can provide a valuable roadmap for the acquisition of the full mouse connectome.

Looking into the future, we can consider the acquisition of the raw connectome data as only a first step toward the understanding of mouse brain function. The immediate issue would be the geometric reconstruction of the neuronal morphologies and projections. Next, synaptic connections need to be established. Based on this, we can have a full wiring diagram. Inferring function from this wiring diagram would require a coordinated effort to integrate a vast amount of experimental research on mouse brain function – physiological, molecular, genetic, behavioral, and ecological – into the mouse connectome.

Cross-References

- [Connectome, General](#)
- [Physical Sectioning Microscopy](#)

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Connectomics

- [Connectivity Analysis in Normal and Pathological Brains](#)

Consumer Behavior

- [Choice Behavior](#)

Contamination by Spikes

- [Local Field Potential, Relationship to Unit Activity](#)

Context-Dependent Processing in Auditory Cortex

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Definition

Context-dependent processing refers to the experimental finding that a neuron may respond to the same stimulus in different ways, depending on the state of the animal and/or the recent history of stimulation. Context dependence differs from plasticity in that the changes in response properties are fast and reversible.

Detailed Description

Examples of state-dependent modulation of neuronal responses abound in the auditory system. Thus, auditory responses may depend on whether an awake rat is engaged in a task (Otazu et al.

2009) or whether she is running or standing (Schneider et al. 2014). However, most studies of context-dependent processing in auditory cortex deal with a sensory context – the history of previous stimulation.

Context dependence in that sense occurs at multiple time scales. Already at the level of the auditory nerve, firing rate adaptation constitutes a simple form of context dependence, where context duration is a few ms or a few tens of ms (Eggermont 1985). An intensively studied example of context dependence consists of the suppression of the responses to a stimulus that is preceded shortly beforehand by another similar stimulus (often called “forward masking”). Forward masking at the level of the mechanical vibrations of the cochlea may account for most properties of psychoacoustical forward masking (Plack and Oxenham 1998). At the level of the inferior colliculus (IC), neural forward masking has been used to account for the precedence effect, in which the first arriving waveform dominates spatial perception (Litovsky et al. 1999).

As early as the IC, there are processes that adapt neuronal response properties to the statistics of the incoming sound streams (Dean et al. 2005). Thus, for example, in the IC (and to some extent even in the auditory nerve), sound level coding adapts to the statistics of the sound levels to which the animal is exposed. Roughly speaking, neurons shift their level responses so that the steepest part of their dynamic range overlays the sound level range that occurs most frequently. Similarly, temporal response properties of auditory neurons may change with changes in the noise level. For example, in the IC, at good signal-to-noise levels, neurons are mostly temporally band-pass, but in the presence of noise, they become low-pass (Lesica and Grothe 2008). Such changes may occur over a few hundreds of ms. Changes with similar flavor have been also documented in song birds (Nagel and Doupe 2006).

In auditory cortex, sensory context dependence may last as long and longer. For example, forward masking is prominent and may last hundreds of ms after the offset of the sound, far beyond psychoacoustical forward masking (Wehr and Zador 2005; Nakamoto et al. 2006). Such effects

have been characterized in terms of changes in gain – the same change in sound level produces different changes in the firing rate depending on some features of previous stimulation. Rabinowitz et al. (2011) described such effects in terms of contrast adaptation, while Ahrens et al. (2008) and Williamson et al. (2016) developed a concept of a context gain field that modulates the input gain of each frequency band by summing up information from nearby frequency channels, again with temporal extents of a few hundreds of ms.

A major type of context dependence studied in the vertebrate auditory system is called “stimulus-specific adaptation” (SSA). SSA is the reduction in the response to a repeated sound which does not generalize, or generalizes only partially, to other, even very similar sounds (Khouri and Nelken 2015). SSA is usually studied using oddball sequences composed of two stimuli, one of which is common (usually appearing in 80–95% of all tone presentations) and the other rare. By presenting two oddball sequences, with the role of the two stimuli switched, it is possible to compare the responses to the same stimulus when common and when rare. As a rule, the response to the same stimulus when rare is larger than when it is common. While SSA has been most often studied with tone pips of varying frequencies, it can be elicited by complex sounds as well (Nelken et al. 2013). SSA has been demonstrated in all major mammalian models of the auditory system and in nonmammalian vertebrates (barn owls) as well (Gutfreund 2012).

Two mechanisms that have been invoked to account for context sensitivity in auditory cortex are synaptic depression (Yarden and Nelken 2017) and firing rate adaptation (Malmierca et al. 2014). However, there is evidence for dependence on context that lasts many seconds, even tens of seconds (Asari and Zador 2009; Yaron et al. 2012), probably requiring mechanisms beyond these two.

At the long end, context sensitivity may be indistinguishable from fast plasticity, such as that documented in ferret auditory cortex (Fritz et al. 2003). In these experiments, the responses to a tone frequency have been rapidly and

selectively enhanced once that frequency became behaviorally relevant. These changes could occur within a minute or so, about the same time scale studied by Yaron et al. (2012).

In summary, context sensitivity in the auditory system is related to a number of separate processes that influence sound coding. While some of them are well studied, their overall effects on sound coding and the interactions between them are not, and this continuum of time scales, which span the range from milliseconds to minutes, remains an important frontier of auditory neuroscience.

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Contextual Integration

- [Center-Surround Processing, Computational Role of](#)

Contextual processing

- [Center-Surround Processing, Computational Role of](#)

Continuum Spine Model

- [Dendritic Spines: Continuum Theory](#)

Continuum Spine Theory

- [Dendritic Spines: Continuum Theory](#)

Continuum Theory for Active Spines

► [Dendritic Spines: Continuum Theory](#)

Control of Aquatic and Terrestrial Gaits in Salamander

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Synonyms

[Swimming and walking modes of the salamander](#)

Definition

Salamanders are amphibian animals that are capable of several aquatic and terrestrial gaits. These gaits are in large part controlled by central pattern generator (CPG) networks in the spinal cord. These networks can be modeled at several levels of abstraction from detailed models based on Hodgkin-Huxley type of neurons to abstract systems of coupled oscillators. The models have been instrumental in testing some hypotheses concerning gait generation and gait transition in the salamander. One of the main hypotheses is that the salamander CPG is constructed out of two main subnetworks: a lamprey-like swimming CPG for the axial musculature and slower CPGs for the limbs. Some of the models have been tested on a salamander-like robot and demonstrated their ability to make transitions between swimming and walking gaits by varying the level of tonic input applied to the CPGs.

Detailed Description

Locomotion in Salamanders

Salamanders are key animals from an evolutionary point of view. Their body plan is close to early terrestrial tetrapods (Cohen 1988; Edwards 1977), and they offer an interesting opportunity to study the transition from aquatic to terrestrial locomotion. Also they provide a useful link between popular animal models for studying vertebrate locomotion such as on one hand swimming animals like the lamprey and zebra fish and the other hand mammal tetrapods like the rat and cat.

In water, salamanders typically use an anguilliform swimming gait, i.e., a gait in which a traveling wave of lateral undulation is propagated all along the body from head to tail (see Fig. 3, bottom). The wavelength of the undulation is kept more or less constant and is close to one body length. The animal can change speed by modulating the frequency of the undulation, and the swimming frequency range is relatively high, e.g., 2.22–4.49 Hz (mean: 3.09 Hz) in *Pleurodeles waltl* (Delvolvé et al. 1997).

On ground, salamanders switch to either walking trot gaits (i.e., a gait in which diagonal pairs of limbs are moved in synchrony) or diagonal sequence walking gaits (see Fig. 3, top, for a walking trot). The frequencies are significantly lower, e.g., 0.58–2.17 Hz (mean: 1.23 Hz) in *Pleurodeles waltl* (Delvolvé et al. 1997), and in a given animal do not overlap with those of swimming. A review of the kinematics of salamander locomotion can be found in Karakasiliotis et al. (2013). Note that these two gaits are only two out of several others (the most frequent ones), and the animal exhibits a large movement repertoire.

Like many other vertebrate animals, the periodic and coordinated activations of axial and limb muscles are produced by central pattern generators (CPGs) located in the spinal cord (Grillner 1981). One can distinguish an axial CPG that activates the axial musculature in the trunk and tail and limb CPGs that activate limbs muscles. Both types of CPGs are composed of multiple-coupled oscillators, i.e., neural pools that can oscillate independently (Cheng et al. 1998,

2002) and that are coupled through projections between interneurons for producing coordinated activity patterns. For instance, it has been shown that surgically isolated segments and hemisegments of the axial CPG can produce rhythmic activity when pharmacologically activated (Ryczko et al. 2010a). Like the lamprey, the axial CPG is therefore a double chain of oscillators with reciprocal inhibition to produce left-right alternation. The limb CPG appears to be composed of a set of independent oscillators for flexor and extensor muscles, which are coupled with inhibition in parallel with weaker excitation (Cheng et al. 1998, 2002).

One can therefore hypothesize that the salamander axial CPG has been inherited from older, swimming vertebrates like the lamprey (Edwards 1977; Cohen 1988; Delvolvé et al. 1997; Ijspeert 2001) and that the circuit has been extended during evolution by phylogenetically more recent networks controlling the limbs. This hypothesis is consistent with the observation that salamanders and lampreys share the same anguilliform swimming mode. For homologies between lamprey and salamander, see Ryczko et al. (2010b).

A very interesting property of the salamander locomotor network is that electrical stimulation of the mesencephalic locomotor region (MLR, a part of the brain stem that controls the initiation and maintenance of locomotion; Dubuc 2009) in a decerebrated salamander will induce gait transitions depending on the level of stimulation (Cabelguen et al. 2003). The level of activation of that region determines the frequency and the mode of locomotion, with (slow) stepping movements at low intensity and (faster) swimming movements at high intensity (Cabelguen et al. 2003). Interestingly, a gradual increase of stimulation will lead to an abrupt switch of gaits when a certain stimulation threshold is reached. From a dynamical systems point of view, the MLR and spinal cord can therefore make a bifurcation between two very different regimes under the control of a simple tonic (i.e., non-oscillating) signal. Similar gait transitions under MLR stimulation have been observed in other vertebrates, e.g., transitions between walking, trotting, and galloping in decerebrate cats (Shik et al. 1966).

More detailed reviews of salamander locomotion and neurophysiology can be found in Chevallier et al. (2008), Karakasiliotis et al. (2013), and Bicanski et al. (2013a). While we now have a good grasp of the general organization and functioning of the salamander locomotor networks, many aspects still require more investigation and can strongly benefit from computational studies. In particular the following questions need to be addressed:

1. What are the mechanisms of rhythm generation and how are the local oscillators implemented, i.e., which types of interneurons are involved and how are they interconnected?
2. How are the oscillators of the whole network, i.e., axial and limb CPGs, coupled together?
3. How much does sensory feedback affect pattern generation?
4. What are the mechanisms of gait transition, in particular the switch between walking and swimming under MLR stimulation?
5. What is the interplay between multiple descending pathways and the spinal circuits that allows the animal to produce its large movement repertoire?

As we will see next, computational models can play a significant role in helping answering these questions and decoding the mechanisms of gait generation and gait transition. Note that many of these questions are relevant for vertebrate animals in general.

Using Numerical Models and Robots to Decode the Gait Generation Mechanisms

Different types of models have been developed to address the questions listed above. As will be briefly described later, the models vary in their level of abstraction, from detailed models composed of Hodgkin-Huxley-like neurons (Bicanski et al. 2013b) to integrate-and-fire neurons (Knüsel et al. 2013), to leaky-integrator neurons (Ijspeert 2001; Ijspeert et al. 2005), and to abstract models made of coupled phase oscillators (Ijspeert et al. 2007; Knüsel et al. 2013). Some models have

been tested together with a model of the body either in simulation or on board of a real robot (Ijspeert 2001; Ijspeert et al. 2005, 2007). See Bicanski et al. (2013a) for a review. The next sections will present two models, one based on coupled oscillators and one based on Hodgkin-Huxley-like neurons.

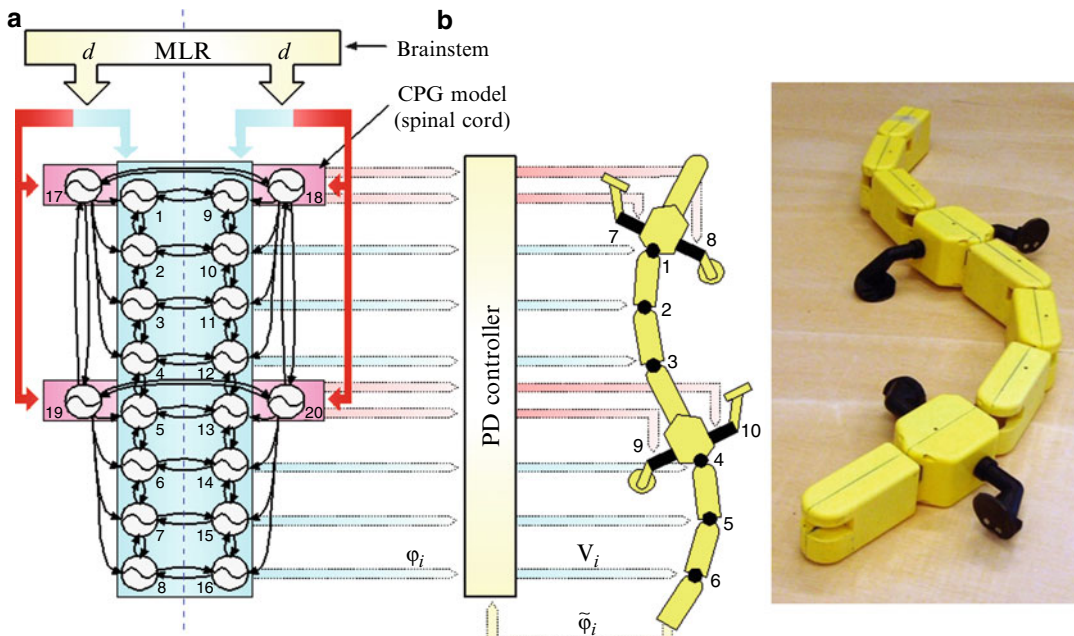
Oscillator Models of the Salamander Locomotor Circuit

Models made of abstract oscillators are useful to investigate and test hypotheses concerning the general topology of the couplings between neural oscillators and the mechanisms of gait transition, i.e., questions 2 and 4 as listed above.

These models are based on the assumptions that the rhythm generation ability of a local network of neurons can be represented by a simple oscillator model, without the need to model the

many individual neurons that compose the local network (in the order of several hundreds, the exact number is not known), and that the global dynamics of the coupled oscillator network is mainly dependent on high-level properties such as intrinsic frequencies of the oscillators, topology of inter-oscillator couplings, and strengths of couplings rather than on the local rhythm generation mechanisms. Such an approach is based on dynamical systems theory and has been useful to help understand the dynamics of the lamprey swimming network (Kopell 1995).

A model based on coupled oscillators was used to investigate the spinal mechanisms underlying the gait transition between stepping and swimming (question 4 above). To compare characteristics of the resulting gaits with those of the salamander, the mathematical model was coupled with a mechanical model of the body, i.e., an amphibious salamander-like robot *Salamandra robotica* (Fig. 1 right) (Ijspeert et al. 2007).



Control of Aquatic and Terrestrial Gaits in Salamander, Fig. 1 Configuration of a CPG model based on coupled oscillators (a) and salamander robot (b) (From Ijspeert et al. (2007)). The robot is driven by 10 DC motors, which actuate six hinge joints for the spine (black disks in the schematic view of the robot) and four rotational joints for the limbs (black cylinders). The CPG is composed of a

body CPG – a double chain of 16 oscillators with nearest neighbor coupling for driving the spine motors – and a limb CPG, four oscillators for driving the limb motors. The CPG model receives *left* and *right* drive signals d from the MLR region in the brain stem. The velocity, direction, and type of gait exhibited by the robot can be adjusted by modifying these two signals

The model represents the rhythmic activity of a local neural oscillator using the so-called amplitude-controlled phase oscillator. It is an oscillator with two state variables: the phase and the amplitude of oscillations. Its time evolution of an oscillator i is governed by the following equations:

$$\dot{\theta}_i = 2\pi v_i + \sum_j r_j w_{ij} \sin(\theta_j - \theta_i - \phi_{ij}) \quad (1)$$

$$\ddot{r}_i = a_i \left(\frac{a_i}{4} (R_i - r_i) - \dot{r}_i \right) \quad (2)$$

$$x_i = r_i (1 + \cos(\theta_i)) \quad (3)$$

where θ_i and r_i represent the phase and amplitude of the oscillator i , v_i and R_i determine the intrinsic frequency and amplitude (i.e., the frequency and amplitude toward which the oscillator converges when isolated), and a_i is a positive constant.

Oscillators are coupled together with diffusive coupling with a coupling weight w_{ij} and a phase bias ϕ_{ij} . The phase bias determines the phase lag that the coupling tends to induce between oscillators. The positive oscillatory signal x_i represents the periodic bursts produced by the oscillator. Such an oscillator is essentially a Kuramoto oscillator (Strogatz 2000) for the phase, extended with a critically damped second-order linear differential equation for the amplitude. An isolated oscillator will converge to a steady-state regime with sinusoidal output $x_i \propto \sin(v_i t + \theta_0)$ with frequency v_i and amplitude R_i : $x_i \propto (1 + \cos(v_i t + \theta_0))$.

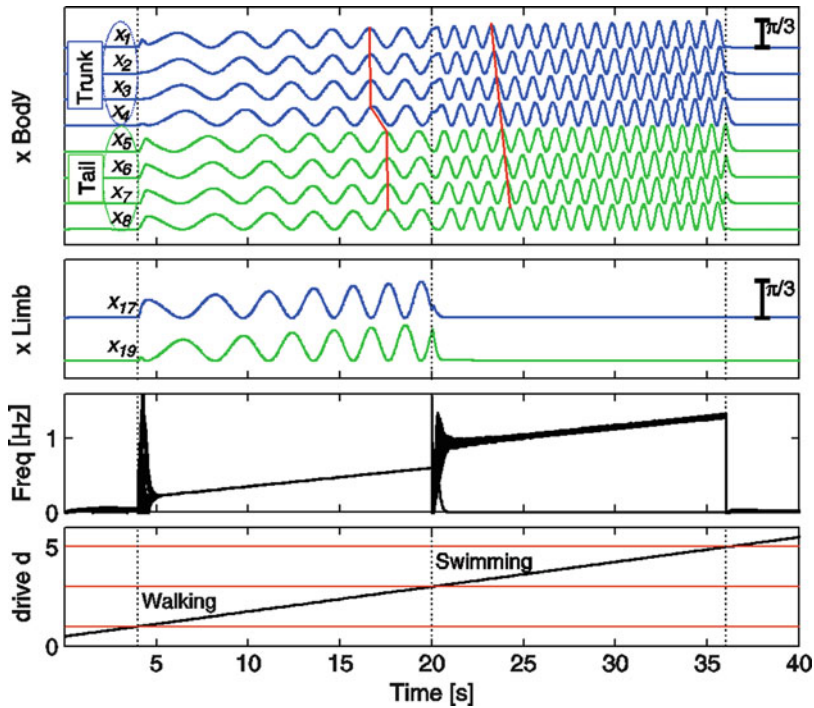
The CPG model is used to test four hypotheses: (1) the axial CPG of the salamander is organized like that of the lamprey, i.e., as a double chain of oscillators that produces traveling waves when activated. (2) A strong coupling from limb oscillators to axial oscillators allows the limb oscillators to impose their (slower) frequency on the axial network when limbs are activated. (3) The limb oscillators cannot oscillate at high frequencies, i.e., they saturate and stop oscillating at high levels of stimulation. (4) Limb oscillators have a lower intrinsic frequency than the axial oscillators for the same level of drive.

Following these hypotheses, the model is made of 20 coupled oscillators, 16 for the axial CPG and

4 for the limb CPGs (Fig. 1, left). The topology and strengths of couplings satisfy hypotheses 1 and 2. The so-called saturation function is implemented to adjust the intrinsic frequency and amplitude of limb and axial oscillators depending on the drive (representing the descending stimulation coming from the MLR) according to hypotheses 3 and 4. The equations of the coupled differential equations are numerically integrated on board of a microcontroller of the robot.

When a low drive is applied to the model, it leads to salamander-like stepping movements, with periodic motions of the limbs that are in antiphase between fore- and hind limbs and with a standing wave of trunk and tail undulation (Fig. 2). When the drive is increased, both frequency and amplitude of the lateral undulation are increased leading to faster stepping. When the drive passes the saturation threshold of the limb oscillators, these stop oscillating, and the axial oscillators rapidly switch to a traveling wave regime. Also because of the saturation, the limb oscillators do not impose anymore slower frequencies, and the frequency of oscillations then rapidly increases, similarly to what is observed in the real animal. The model therefore correctly replicates the abrupt gait transition induced by MLR stimulation (Cabelguen et al. 2003). It also provides an explanation of why swimming frequencies are systematically higher than stepping frequencies in kinematic recordings of freely moving animals (Frolich and Biewener 1992; Delvolvé et al. 1997).

Interestingly, despite the robot being only an approximation of the salamander body (e.g., in terms of number of joints and the simplified limb design), the movements produced by the robot are strikingly similar to those of the animal both in water and on ground (Fig. 3). By adjusting the drive level, the speed of locomotion can be adjusted both during stepping and swimming, and rapid switches between the two gaits can be performed. By providing more drive to the axial oscillators on one side compared to the other, turning movements can be induced. The higher drive on one side leads to higher amplitude of bending toward that side.



Control of Aquatic and Terrestrial Gaits in Salamander, Fig. 2 Transition from stepping to swimming. The transition occurs when the drive applied to the CPG model is linearly increased (From Ijspeert et al. (2007)). Below the first threshold, the circuit is silent. Once passing this first threshold (at $t = 4$ s), the CPG produces stepping-like patterns with a standing wave in the axial CPG (*top*) and periodic activation of the limb CPGs (*second from top panel*). When reaching the limb saturation threshold ($t =$

20 s), the limb oscillators stop oscillating, and this releases a traveling wave in the axial CPG as needed for anguilliform swimming. The gait transition is accompanied by a jump in instantaneous frequency, with low frequencies for stepping and high frequencies for swimming (*third panel from top*). Note that the large variations in instantaneous frequencies at $t = 4$ s and $t = 20$ s are due to short transient periods during which the phases of oscillators rapidly change before reaching steady-state regimes

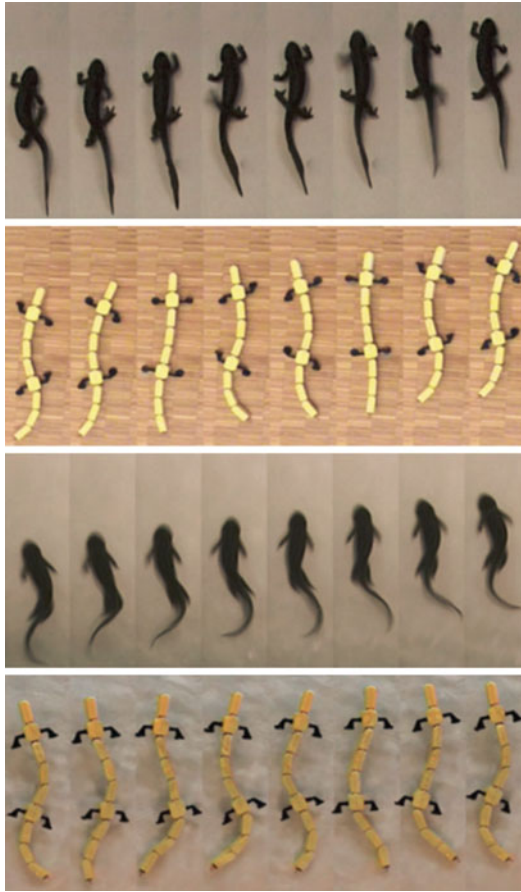
Hodgkin-Huxley Models of the Salamander Oscillatory Circuits

Models based on Hodgkin-Huxley (HH) neuron equations are useful to investigate the mechanisms of rhythm generation in the salamander (Question 1). Unlike the lamprey, the types of interneurons involved in the local oscillator networks of the salamander and the topology of their coupling are yet unknown. However, various experiments have shown that salamander and lamprey segmental circuits share many similarities (Ryczko et al. 2010b).

Models of the salamander segmental circuitry can therefore be developed with lamprey-like spinal hemisegments (i.e., oscillator networks on one side of the axial CPG) containing sparsely

connected excitatory and inhibitory neuron populations (Bicanski et al. 2013b). Hemisegments in the same segment are connected through both excitatory and inhibitory contralateral projections (Fig. 4). The model matches a large range of experimental findings, in particular the pharmacological stimulation by NMDA (*N*-methyl-d-aspartate) of isolated axial hemisegments and segments (Fig. 4, bottom). The model reproduces most of the effects of various pharmacological experiments (Ryczko et al. 2010a) that have been performed on isolated salamander spinal cords (e.g., the blockade of AMPA synapses, glycinergic synapses, calcium-activated potassium current, persistent sodium current, and h-current).

The model can not only replicate NMDA-induced oscillations, which are typically slower



Control of Aquatic and Terrestrial Gaits in Salamander, Fig. 3 Stepping and swimming gaits in the salamander and the robot. *Top two panels:* walking trot gait where the fore- and hind limbs are in antiphase and with the trunk and tail performing a standing wave. *Bottom two panels:* anguilliform swimming gait with the body making a lateral undulation traveling from head to tail (Adapted from the supplementary material of Ijspeert et al. (2007))

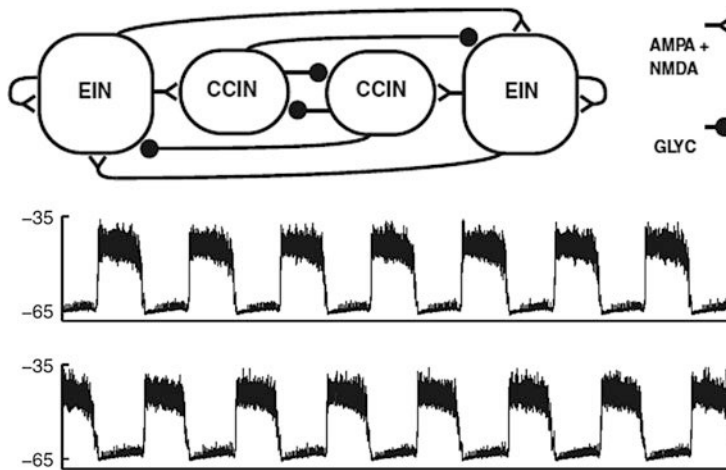
than *in vivo*, but also the range of *in vivo* frequency when receiving excitatory input from a population of simulated brain stem neurons (i.e., a more realistic way of stimulating spinal cord circuits). By slightly adjusting the conductances involved in burst termination, neural oscillators with different frequency ranges can be implemented, suggesting that the same circuit can be used both to represent slower limb oscillators and faster axial oscillators. When a slower limb oscillator is coupled to a faster axial oscillator, it can impose its slower frequency as needed

during stepping and similarly to the oscillator model above. The model therefore suggests that a lamprey-like segmental network can potentially serve as a building block for the axial and limb oscillators in salamanders.

Sensory Feedback, Rich Motor Skills, and Descending Pathways

The models above do not include sensory feedback, and it is likely that (multimodal) sensory feedback plays an important role in shaping the motor patterns and in adjusting their timing during locomotion. For instance, the difference of interaction forces between water and ground could possibly explain difference between traveling and standing waves in axial CPG during swimming and stepping. This was shown in a neuromechanical simulation that combined a simplified musculoskeletal model with a CPG model based on leaky-integrator neurons (Ijspeert et al. 2005). In the model, a simulated swimming salamander placed on dry ground tends to have lateral undulations that are close to a standing wave even when the CPG produces a traveling wave. In other words, the isotropic friction forces on dry ground imposed the standing wave of body movements. When sensory feedback from simulated stretch-sensitive cells was added to the circuit, the CPG activity was transformed into a standing wave that resembles the standing waves of EMG patterns recording during stepping on ground (Delvolvé et al. 1997). This illustrates how physical interaction with the environment together with sensory feedback can modulate CPG patterns.

Note that the coupled oscillator model described above (Ijspeert et al. 2007) relied on long-range couplings from limb to axial oscillators, with the forelimb oscillators sending projections to all trunk oscillators and the hind limb oscillators sending projections to all tail oscillators. Such a *global* coupling from limb to axial oscillators meant that a standing wave was imposed on the axial CPG as soon as the limb CPGs were active. Since then, experiments on isolated spinal cords have shown that the axial CPG can produce traveling waves even when the



Control of Aquatic and Terrestrial Gaits in Salamander, Fig. 4 Salamander neural oscillator model made of HH neurons. *Top*: topology of the circuit made of populations of excitatory (EIN) and inhibitory (CCIN) neurons. Each drawn neural unit represents a population of neuron models: 50 EINs and 30 CCINs per

hemisegment, i.e., a total of 160 neurons for the whole segmental network. *Bottom*: a representative average membrane potential trace in mV of the *left* and *right* hemisegmental EIN populations (Adapted from Bicanski et al. (2013b))

limb CPGs are rhythmically active (Ryczko et al. 2009). The frequencies of limb and axial CPGs are then identical and slow, supporting the idea of strong couplings from limb to axial CPGs (hypothesis 2 in the coupled oscillator model). But the fact that traveling waves are then observed instead of standing waves suggests that the coupling from limb to axial CPGs is only *local*, close to the girdles, and not global as in Ijspeert et al. (2007). It is therefore likely that the standing waves of EMGs during stepping are due either to sensory feedback or to modulation from descending pathways (rather than a central effect based on global couplings).

An important topic that remains to be addressed is how the salamander produces its large repertoire of movements (Question 5 above). In addition to anguilliform swimming and walking trots described above, the salamander can perform a large variety of movements such as backward walking, paddling limbs in phase, aquatic stepping, etc. The mechanisms underlying this large repertoire remain to be decoded, but it is most likely that they involve adding more descending pathways and more complex spinal circuits to the models presented above. Preliminary studies show that multiple different motor behaviors can be

generated by simply being able to activate subparts of the circuits differentially through different independent pathways (e.g., by providing different levels of drives to the neck, trunk, and tail oscillators in the axial CPG). But clearly the models will require modeling more complex circuits and more sensory streams to account for the richness of salamander motor skills. In particular the limb circuits are so far oversimplified and require more detailed studies. Continuing to combine experiments in neurophysiology together with modeling and robotic studies will be instrumental in making progress in this exciting field.

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Control of Breathing, Integration of Adaptive Reflexes

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Definition

Models of respiratory regulation – as with many physiological control systems – have traditionally invoked the Sherringtonian reflex paradigm (Sherrington 1906) in which the response to any afferent input is assumed to follow a static stimulus–response relationship that adds to other stimulus–response relationships to produce the overall response. Such a reductionist analysis has set the foundation for our understanding of various respiratory control mechanisms, such as central and peripheral chemoreflex, lung inflation and deflation reflexes, and exercise reflex via various chemical

and mechanical afferent feedbacks and feedforward commands. Under this Sherringtonian framework, such feedback and feedforward controls are taken as a combination of simple reflex drives acting in parallel that are integrated algebraically by the brainstem respiratory controller in determining the resultant respiratory rhythm (inspiratory/expiratory duration) and motor pattern (tidal volume) in response to various exogenous and endogenous stimuli. However, this simplified reductionist framework of respiratory control has been challenged by recent evidence indicating that such stimulus–response relationships are not merely mediated by static reflexes in the form of classical proportional feedback and feedforward controls but may involve adaptive neural mechanisms that conform to adaptive control systems in modern engineering control theory.

According to Sherrington (1906), reflexes are animal instincts evolved through natural selection to serve specific survival purposes in adaptation to challenging environments, hence the term “adaptive reflex.” On the other hand, it is now well recognized that many reflexes in lower animals (e.g., Aplysia gill and siphon withdrawal reflex) and mammalian higher brain mechanisms (e.g., eye-blink reflex) may also adapt in real time to modify the stimulus–response relationships through nonassociative and associative learning, two forms of use-dependent (activity-dependent) neural plasticity that contribute importantly to brain intelligence. This entry will focus on the roles of nonassociative and associative learning in adaptive modulation of chemoreflex, mechanoreflex, and exercise reflex control of breathing.

This entry is organized as follows. The next section presents the notion of *nonassociative learning* in respiratory control. Nonassociative learning is the progressive decrease (short-term depression, STD) or increase (short-term potentiation, STP) in the evoked response upon continued or repetitive afferent stimulation, evidencing use-dependent plasticity (Poon and Schmid 2012). Two traditional forms of nonassociative learning (*habituation* and *sensitization* evidencing STD and STP, respectively) have been extensively studied in the classic experiment of Aplysia gill and siphon withdrawal reflex (Hawkins et al.

1998). A third form of nonassociative learning called “*desensitization*” – also evidencing STD but is expressed in a secondary pathway – was first discovered in the pontine modulation of the Hering–Breuer reflex in rats (Siniia et al. 2000). The three forms of nonassociative learning – habituation, sensitization and desensitization – have been shown to have significant computational relevance and can be formulated as a *neural integrator/differentiator* that modulates the stimulus–response relationship in a time-dependent manner.

The third section discusses the role of *associative learning* in respiratory control. Associative learning such as classical (Pavlovian) conditioning differs from nonassociative learning in that the plasticity is not only use dependent but also pairing specific, requiring the interaction of two coincident afferent inputs called the conditioned and unconditioned stimuli. A canonical example of classical conditioning is the mammalian eye-blink reflex (Thompson and Steinmetz 2009). Another form of associative learning is operant conditioning (also called instrumental conditioning or reinforcement learning), in which the response to a stimulus may be modified by feedback of the resultant response in a closed loop in order to optimize certain performance measure (Hawkins et al. 2006). Experimental observations suggest that associative learning may play an important role in modulating the respiratory controller gain through integration of a variety of respiratory afferent information. This suggests that the respiratory controller may not simply add multiple stimuli linearly but may integrate them in a nonlinear, time-dependent manner to bring out an optimal response in the face of changing environmental challenges. Such optimal respiratory control suggests a close correlation between homeostatic regulation in physiology and the internal model principle in engineering (Poon et al. 2007) – which states that a feedback regulator under external disturbances may maintain regulation and stability provided a suitably reduplicated (internal) model of the disturbance signal is adapted in the feedback path (Francis and Wonham 1975). The notion of internal model is now well recognized in sensorimotor integration

(Davidson and Wolpert 2005; Tin and Poon 2005). This section concludes with a discussion of the relevance of internal model learning in respiratory control.

Detailed Description

Nonassociative Learning in Vagal–Mechanical Reflex and Chemoreflex Adaptation

Nonassociative learning with activity-dependent STP and STD of neurotransmission is prevalent in respiratory control. For instance, during hypoxia or sustained carotid sinus nerve stimulation, STP is evidenced by a progressive increase in the amplitude of respiratory motor response, followed by a gradual decay (afterdischarge) of the heightened response upon removal of the stimulus (Poon et al. 1999; Song and Poon 2009b). Such neural plasticity phenomena have important computational implications.

Nonassociative Learning as Neural Integrator and Differentiator

Functionally, the temporal patterns of STP and STD in response to a stimulus can be modeled respectively as a neural integrator and neural differentiator, or equivalently a low-pass and high-pass filter (Poon and Siniaia 2000). This analogy provides a strong mathematical foundation that underpins nonassociative learning in the perspective of adaptive control. Numeric integration and differentiation are elemental calculus operations. They also underlie all temporal dynamics and kinematics phenomena in Nature. An analog integrator or differentiator is any physical process with observable input and output signals that demonstrate integral or differential transformation in real time, respectively. Analog integrators and differentiators are limited by their *leakages*, i.e., physical bypasses that offset the integration and differentiation processes. Leaky integrators or low-pass filters are commonly used in electrophysiology experiments to obtain a moving time average of neuronal firing, which gives an analog “neurogram” of spike frequency as an output.

In the time domain, a leaky integrator’s response to a constant-step input exhibits

exponential saturation during on-transient and exponential decay during off-transient, whereas the corresponding response of a leaky differentiator demonstrates exponential decay from an initial overshoot during on-transient and exponential recovery from rebound undershoot during off-transient (Fig. 1a). As such, STP and STD are closely related to neural integrator/differentiator as they display characteristic integral/differential responses. A first-order neural integrator or differentiator can be readily described by the following state-space model (Poon and Young 2006):

$$\begin{aligned}\dot{x} &= -ax + bu \\ y &= cx + du\end{aligned}\quad (1)$$

where x and $\dot{x}$ are the state variable and its time derivative, respectively; y and u are the output and input of the integrator or differentiator; a , b , c , and d are the system parameters with $a > 0$ to guarantee stability.

With a constant-step input, $u = u_0$ for $0 < t \leq T$, where T is the duration of stimulation, Eq. 1 can be solved analytically for $x(t)$ (and hence $y(t)$) assuming $x(0) = 0$:

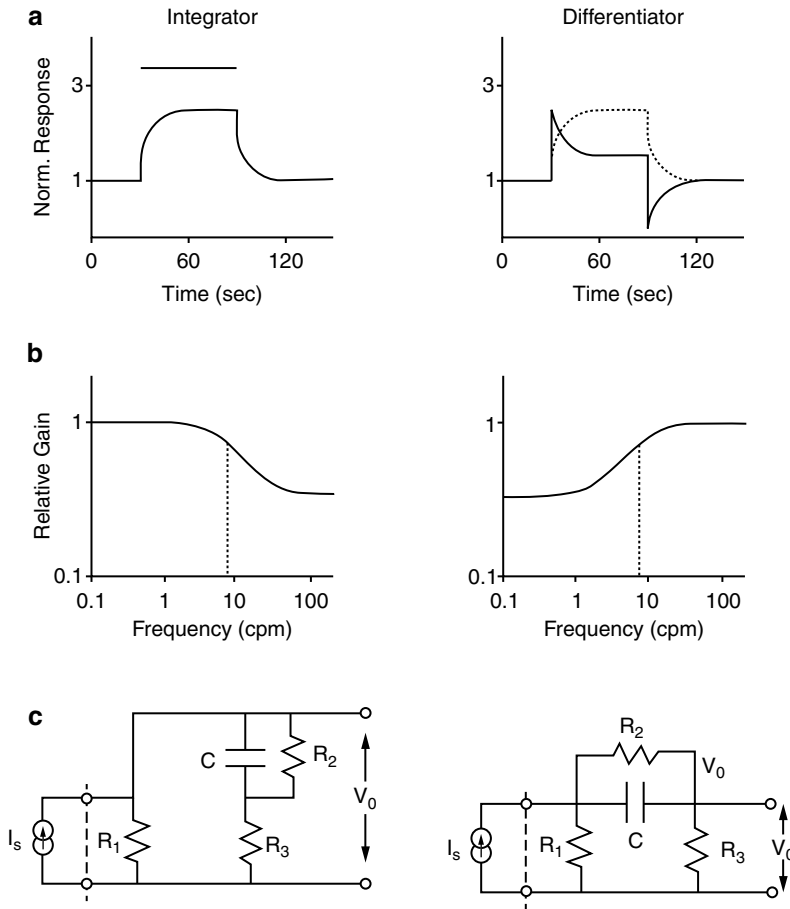
$$y(t) = du + \frac{cbu}{a}(1 - e^{-at}) \text{ for } 0 < t \leq T \quad (2)$$

The response $y(t)$ corresponds to a neural integrator if both terms on the right-hand side of Eq. 2 have the same sign, or a neural differentiator if they have opposite signs. Similarly, their afterdischarge during off-transient can be modeled by the following equation:

$$y(t) = (y(T) - y(0))e^{-at} \text{ for } y > T \quad (3)$$

Hence, neural integrator and differentiator can be characterized by the above exponential functions in the time domain. Higher-order integrator and differentiator can be achieved by combining multiple exponentials with different gains and time constants.

From linear time-invariant systems theory, neural integrator and differentiator can also be expressed in frequency domain using Laplace transform. In this regard, they perform low-pass and high-pass filtering to the input signal. The



Control of Breathing, Integration of Adaptive Reflexes, Fig. 1 Time and frequency response characteristics of integrator (*left panels*) and differentiator (*right panels*). (**a**) The temporal response of a leaky integrator to a constant-step stimulus (horizontal bar) consists of abrupt reflex increase/decrease of the response at stimulus onset/cessation followed by exponentially increasing/decaying (potentiation/afterdischarge) on-/off-transients. A leaky differentiator has similar reflex components but with exponentially decaying/rebound-increasing (accommodation/aftercharge) on-/off-transients, which are opposite to those of an integrator (*overlying dotted lines*). In both cases the off-transients may be rectified, with the response becoming monophasic (not shown) instead of biphasic. The time scales chosen are typical of oculomotor integrator and respiratory integrator. (**b**) In the

frequency domain, an integrator/differentiator behaves like a low-pass/high-pass filter. The passband in both cases is the frequency range where the transmission gain (normalized to unity) is highest and relatively constant. The high and low cutoff frequencies (*vertical dotted lines*) of these filters are inversely proportional to the time constants of the corresponding integrator and differentiator shown in **a**. (**c**) Examples of RC integrator ($C = 3.77$, $R_1 = 1.60$, $R_2 = 24.0$, $R_3 = 0.73$) and differentiator ($C = 1.0$, $R_1 = 1.75$, $R_2 = 24.0$, $R_3 = 10.2$) circuits with a current source (I_s) input and voltage (V_0) output. Units are arbitrary and RC values correspond to parameter values as defined in Eq. 1 for integrator ($a = 0.125$, $b = 0.125$, $c = 1$, $d = 0.5$) and differentiator ($a = 0.125$, $b = 0.125$, $c = -1$, $d = 1.5$) (Adapted from Poon and Young (2006))

time constant of a leaky integrator or differentiator is inversely proportional to the cutoff frequency of the equivalent low-pass or high-pass filter, respectively. In addition to frequency filtering, a leaky integrator/differentiator also introduces phase

shift (phase lag/phase lead) in the input–output relationship (Fig. 1b, c).

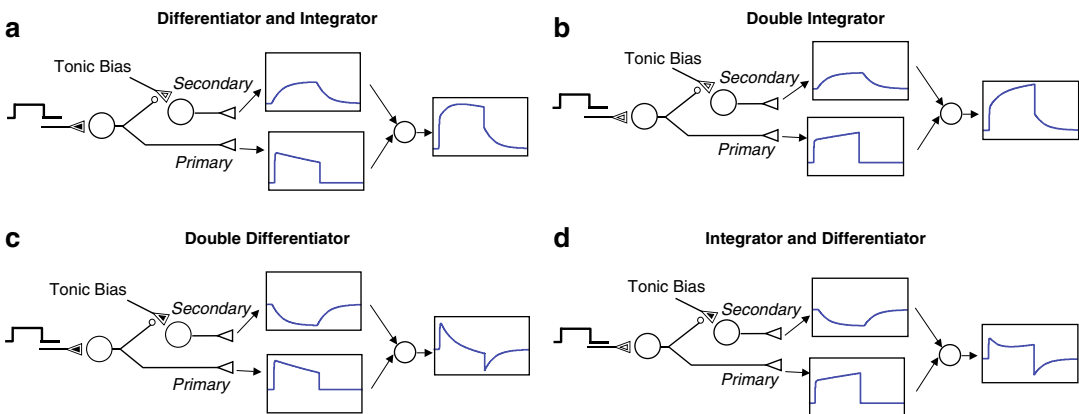
An integrator or differentiator that sustains an off-transient response with short-term memory decay upon removal of the stimulus is said to be

biphasic (or else, monophasic); it is termed inverted if the gain is negative. Under these broad definitions, nonassociative learning may be classified into four basic forms depending on whether the corresponding neural integrator or differentiator response is monophasic or biphasic (Poon and Young 2006). The STD or STP induced in a *primary* stimulus–response pathway (i.e., one that is directly activated by the primary stimulus) is necessarily monophasic, in that all reflex and adaptation effects mediated by that pathway must vanish abruptly and any associated memory effects become latent once the primary stimulus ceases (Fig. 2). *Habituation* and *primary sensitization* are monophasic STD and STP expressed in the primary stimulus–response pathway. The monophasic effects reflect the fact that the primary pathway is disfacilitated (gated off) once the primary stimulus ceases. Hence, habituation and primary sensitization act not only as a high-pass or low-pass filter in the frequency domain but also as a temporal filter in the time domain that

gates off any residual memory effect of the STD and STP in the primary pathway once the primary stimulus is removed.

Alternatively, the primary stimulus may induce STP or STD of neurotransmission indirectly in a collateral (*secondary*) pathway which is driven by another (secondary) input (Fig. 2). In this event the resulting integrator/differentiator response is *biphasic* with a post-stimulus short-term memory response, as the secondary input keeps the secondary pathway active after the primary stimulus ends. Such a post-stimulus response provides a simple marker for discriminating the memory effects in the primary and secondary pathways. The nonassociative learning effects corresponding to STD and STP mediated by a secondary pathway have been termed *desensitization* and *secondary sensitization*, respectively, in contradistinction to their counterparts (habituation and primary sensitization) that are mediated by the primary pathway.

A primary stimulus may induce STP and/or STD in the primary and secondary pathways



Control of Breathing, Integration of Adaptive Reflexes, Fig. 2

Compound neural integrator and differentiator models. Boxes show model simulations in arbitrary units and parameter values. (a) Primary differentiator–secondary integrator is realized by activity-dependent habituation–sensitization in corresponding primary–secondary pathways. Step application of primary input at a constant firing rate (*inset*) induces synaptic STD and STP (*filled* and *open inner triangle*) in primary and secondary pathway, respectively, with corresponding temporal differentiation and integration of the transmitted signals (*upper* and *lower boxes*). Primary differentiator is monophasic (with abrupt termination of response due to auto-chopping at end of stimulus train), whereas secondary

integrator is biphasic. Resultant response (*last box*) at output neuron shows a compound differentiator–integrator characteristic. (b) A double integrator may arise from STP in both primary and secondary pathways. (c) A double differentiator is similar to a double integrator but with STD instead of STP in both pathways. (d) A primary integrator–secondary differentiator can be realized in a similar fashion with a STP–STD combination. Structurally, primary differentiator (a, c) and secondary differentiator (b, d) are comprised of the primary reflex in conjunction with an inverted primary and secondary integrator, respectively, demonstrating the complementarities of integrator and differentiator (Adapted from Poon and Young (2006))

simultaneously to form compound integrator/differentiator. The dynamical order of a compound integrator/differentiator is the number of integrators/differentiators it is composed of, and its memory order is the number of component integrators/differentiators that are biphasic with short-term memory. The four possible second-order compound integrator/differentiator configurations are summarized in Fig. 2. Under this framework, the classical dual-process theory of nonassociative learning with concurrent habituation and secondary sensitization (Groves and Thompson 1970) is a special case of the second-order compound integrator/differentiator structure.

Short-Term Depression of Vagally Mediated Hering–Breuer Reflex

The classic Hering–Breuer inflation reflex describes the inspiration inhibition and expiration prolongation consequent to lung inflation, which is sensed by slowly adapting pulmonary stretch receptors in the airways and conveyed by the vagus nerve to the respiratory controller. This “reflex” is presumed to protect the lungs from potential damages due to overexpansion. However, new data accumulated over the past decade suggest that such a reflex is not static but is dynamic and adaptive, conforming to non-associative learning (MacDonald et al. 2009; Poon et al. 2000; Siniiaia et al. 2000).

During sustained lung inflation or electrical vagal stimulation in vagotomized rats, the immediate Hering–Breuer reflex response is countered by an ensuing STD that gradually lessens the initial lengthening of expiratory duration (T_E) and decrease of respiratory frequency (f_R). This is followed by a rebound shortening of T_E and increase of f_R upon termination of lung inflation or vagal stimulation before these post-stimulus STD responses gradually die out. The on- and off-transient STD responses in T_E and f_R resemble a biphasic differentiator. In both cases, the on-transients are best fitted by second-order exponential functions, while the off-transients are best fitted with a first-order exponential. The curve-fitting results suggest a second-order differentiator with monophasic STD (habituation) in the primary pathway and biphasic STD (desensitization) in a

secondary pathway (Fig. 2). Studies show that the biphasic STD component is abolished by NMDA receptor blockade or lesioning of the Kölliker–Fuse nucleus in the pontine pneumotaxic region in vagotomized rat, but similar interventions have no effect on the monophasic STD component (Poon et al. 2000; Siniiaia et al. 2000). The latter is thought to be mediated by relay neurons in the nucleus tractus solitarius, which demonstrate afferent-induced phasic STD that is NMDA receptor independent as well as long-term depression that is NMDAR receptor dependent (Zhou et al. 1997). The biphasic STD component with a post-stimulus rebound response that is dependent on NMDA receptor activity effectively discriminates the adaptive modulation of the Hering–Breuer reflex due to desensitization in the secondary (pontine) pathway from that due to habituation in the primary pathway. Pontine desensitization of the Hering–Breuer reflex in vagal-intact animals plays an important role in restoring entrainment of the respiratory rhythm to cyclical mechanical ventilation upon changing ventilator frequency and/or end-expiratory airway pressure (Dutschmann et al. 2009; MacDonald et al. 2007).

Short-Term Potentiation and Depression of Peripheral Chemoreflex

In addition to pulmonary stretch receptor afferents mediated by the vagus nerve, the respiratory control system also senses arterial partial pressures of (CO_2 (P_{aCO_2})) and O_2 (P_{aO_2}) and arterial pH through central and peripheral chemoreceptors in order to regulate blood gas concentrations and acid–base balance to maintain homeostasis. Abrupt exposure to hypoxic gas or brief electrical stimulation of the carotid sinus nerve (CSN) in animal models elicits complex peripheral chemoreflex response of inspiratory and expiratory variables that vary in a time-dependent manner (Poon et al. 1999, 2000; Song and Poon 2009b). These include a biphasic STP of inspiratory amplitude (with post-stimulus afterdischarge) and STD-like shortening of inspiratory duration (T_I) resulting in a STP-like progressive increase of f_R , as well as rapid shortening of T_E followed by a biphasic STP-like lengthening of T_E , resulting in post-hypoxic decline of respiratory frequency. The hypoxia-/CSN-induced

STP and STD of inspiratory variables resemble a biphasic neural integrator, whereas the corresponding STP of the T_E response in combination with an initial rapid shortening of T_E at the onset of hypoxia/CSN stimulation resembles a biphasic neural differentiator. These nonassociative learning effects provide low-pass and high-pass filtering of the peripheral chemoreceptor afferent input as discussed in the previous section.

Detailed analysis of the dynamics of the peripheral chemoreflex response to CSN stimulation delivered repetitively breath-by-breath during either the inspiratory or expiratory phase of the respiratory cycle reveals that peripheral chemoafferent signaling is relayed by parallel integrator/differentiator central pathways that independently modulate inspiratory amplitude, T_I and T_E with varying time constants (Young et al. 2003). These include biphasic fast–slow compound integrator pathways that mediate the successive augmentation of inspiratory amplitude and shortening of T_I , and biphasic fast–slow compound integrator/differentiator pathways that mediate the initial shortening and subsequent prolongation of T_E . These biphasic integrator/differentiator pathways also account for the off-transients of all these response components.

Blockade of NMDA receptor slows down the dynamics of the inspiratory-related neural integrators (Poon et al. 1999) and abolishes the slow expiratory-related neural differentiator response (Poon et al. 2000). Lesioning of lateral parabrachial nucleus selectively attenuates the rapid shortening of T_E during hypoxia, but presents no observable effects on the hypoxic response of other respiratory variables (Song and Poon 2009b). Similarly, lesioning of lateral parabrachial nucleus selectively attenuates the shortening of T_E and increase of inspiratory amplitude during hypercapnia, but presents no observable effects on the hypercapnic response of T_I (Song and Poon 2009a).

Long-Term Facilitation of Vagal–Mechanical Reflex and Peripheral Chemoreflex

In addition to short-term adaptive modulation of vagal–mechanical reflex and peripheral chemoreflex with STP and STD in primary and

secondary pathways following sustained afferent stimulations, long-term adaptive modulation of these reflexes may ensue when the afferent activations become repetitive. Specifically, repeated exposures to alternating episodes of hypoxia and hyperoxia in humans and animal models may induce long-term facilitation of respiratory (phrenic) motor output as well as hypoglossal (particularly genioglossal) and laryngeal adductor motor outputs that serve to increase upper airway patency (Fuller et al. 2000; McGuire et al. 2007; Xing et al. 2013). Similarly, episodic modulation of vagally mediated mechanical feedback induces long-term facilitation of hypoglossal motoneuron activity (Tadjalli et al. 2010). It is believed that such long-term adaptive modulations of the vagal respiratory reflex and peripheral chemoreflex are protective responses to obstructive sleep apnea, which is characterized by repeated episodes of hypoxemia and disruption of vagal feedback.

Associative Learning in Vagal–Mechanical Reflex and Chemoreflex Adaptation

In associative learning, the learning process is dependent on the pairing of two coincident inputs. Its significance in respiratory control has traditionally been underappreciated in favor of the Sherringtonian framework. However, recent evidence increasingly points to the existence of associative learning in respiratory control similar to classical studies in *Aplysia* (Glanzman 1995) and cerebellum (Thompson 1988). Specifically, vagal–mechanical input and central and peripheral chemoafferent inputs may indeed interact associatively (rather than linearly) in modulating the resultant ventilatory output.

Associative Learning in Central–Peripheral Chemoreceptor Interaction

A generally accepted simplification in current mathematical models of respiratory control is that feedback signals from central and peripheral chemoreceptors add linearly to determine the total “reflex” response (Cunningham et al. 1986; Gray

1946; Grodins et al. 1954), an assumption that is supported by indirect evidence (e.g., (Mardimae et al. 2012)). However, a significant number of reports in the literature present conflicting observations indicating that the interaction of central and peripheral chemoreceptor inputs may not be purely additive but could range from hypoadditive on one end of the spectrum to hyperadditive on the other. A recent study in awake dogs (Blain et al. 2010) provides one of the strongest evidence for hyperadditive peripheral–central chemoreceptor interaction, by abruptly stimulating the central chemoreceptor while holding the peripheral chemoreceptor activity constant at varying background levels. On the other hand, other studies (Day and Wilson 2007, 2009; Tin et al. 2012) demonstrate hypoadditive interaction when the peripheral chemoreceptor is stimulated while the central chemoreceptor activity is held constant at varying background levels. In particular, (Tin et al. 2012) showed that the responses in inspiratory amplitude and T_E (and hence f_R and neural ventilation) to hypoxia varied inversely with the background CO_2 level in spontaneously breathing (vagal–intact or vagotomized) and mechanically ventilated rats. The results show a hypoadditive hypercapnic–hypoxic interaction *in vivo* that resembles the reported hypoadditive central–peripheral chemoreceptor interaction *in situ* for these respiratory variables in the rat (Day and Wilson 2007, 2009), regardless of differences in vagal feedback, body temperature and ventilation method.

Collectively, these reports point to a complex nonlinear interaction of peripheral and central chemoreceptor inputs that contradicts the traditional Sherringtonian paradigm. The mechanism and site of such nonlinear interaction remain to be investigated.

Associative Learning in Mechanical–Chemical Interaction

Another limitation of the classical chemoreflex/mechanoreflex model under the Sherringtonian paradigm is that it cannot explain the control of ventilation during muscular exercise. In this case, ventilation increases directly with increasing metabolic demands (in terms of metabolic

CO_2 output, $\dot{V}_{CO_2}$) without any appreciable increases in P_{aCO_3} and arterial pH, i.e., without apparent activation of the chemoreflex mechanism. This discrepancy has led to the postulation of some exercise-induced feedforward signal that drives respiratory ventilation in proportion to metabolic demands with near constancy of arterial CO_2 and pH levels (Grodins et al. 1954). However, despite extensive search over the past century, none of the hypothesized feedforward or feedback mechanisms has been demonstrated conclusively as the true “exercise stimulus” that is obligatory to exercise hyperpnea (Poon et al. 2007). Much of the confusion lies in the fact that feedback mechanisms such as chemoreflex and skeletal muscle afferent feedback exert only transient effects on the exercise ventilatory response but do not materially contribute to the steady-state exercise hyperpnea response (Poon and Tin 2013). This persistent lack of conclusive evidence of a feedforward exercise stimulus as hypothesized under the Sherringtonian reflex paradigm raises serious questions regarding the validity of such oversimplified models for exercise hyperpnea.

Optimization Model of Exercise Hyperpnea and CO_2 Breathing

In contrast to Sherringtonian reflex, it has long been conjectured that many respiratory control phenomena may boil down to the general idea of optimality implied in natural selection (Priban and Fincham 1965). Poon (1987) first introduced the following mathematical cost function to integrate the chemical and mechanical components of breathing:

$$J = J_c + J_m = [\alpha(P_{aCO_3} - \beta)]^2 + \ln \dot{W}_o^2 \quad (4a)$$

$$\text{where } \dot{W}_o = \dot{V}_E^2 / (1 - \dot{V}_E / \dot{V}_{max})^2 \quad (4b)$$

The terms J_c , J_m in Eq. 4a represent the competing chemical and mechanical costs of breathing (α , β are parameters) in conformance to Steven’s power law and Weber–Fechner law of psychophysics, respectively. The term $\dot{W}_o$ that defines J_m is a measure of the work rate of

breathing as perceived by the respiratory controller subject to the mechanical limitation of the respiratory system. This is given by the mechanical plant equation (4b), where $\dot{V}_{max}$ is the maximal ventilation that could be sustained by the respiratory pump and the factor $(1 - \dot{V}_E/\dot{V}_{max})^2$ represents the pump's neuromechanical efficiency. The chemical cost J_c is a function of total chemical feedback. At rest and during moderate exercise it is determined primarily by P_{aCO_2} , which is constrained by the pulmonary gas exchange (chemical plant) equation:

$$P_{aCO_3} = P_{ICO_3} + \frac{863\dot{V}_{CO_2}}{\dot{V}_E \times \left(1 - \frac{V_D}{V_T}\right)} \quad (5)$$

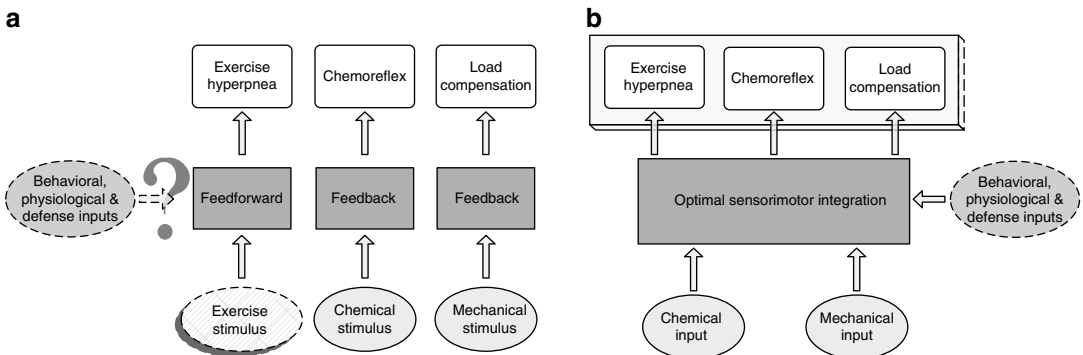
In Eq. 5, V_D/V_T is the physiological dead space-to-tidal volume ratio and is a measure of the inefficiency of pulmonary gas exchange, and P_{ICO_2} is the partial pressure of CO_2 in the inspired air during CO_2 inhalation ($P_{ICO_2} = 0$ when breathing room air).

The optimal total ventilation $\dot{V}_E$ is one that minimizes J (Eq. 4a) subject to the pulmonary gas exchange process (Eq. 5) and mechanical constraint (Eq. 4b), thus weighing the chemoafferent feedback against respiratory mechanical feedback, giving:

$$\dot{V}_E = \frac{\dot{V}_{E0}}{1 + \dot{V}_{E0}/\dot{V}_{max}} \quad (6a)$$

$$\text{where } \dot{V}_{E0} = 863\alpha^2(P_{aCO_3} - \beta) \times \frac{\dot{V}_{CO_2}}{\left(1 - \frac{V_D}{V_T}\right)} \quad (6b)$$

Equation 6 simulates the linear $\dot{V}_E = P_{aCO_3}$ relationship during CO_2 inhalation and proportional $\dot{V}_E - \dot{V}_{CO_3}$ relationship during exercise at constant P_{aCO_3} level. Thus, the optimization model successfully reproduces normocapnic exercise hyperpnea and hypercapnic CO_2 response by simply adopting an optimal control law (Eq. 4a) in place of the Sherringtonian reflex control law, without the need of an explicit feedforward exercise stimulus. In more general terms, the model addresses the important question of how the respiratory controller balances multiple competing objectives in order to optimize the work of breathing while striving to maintain homeostasis of arterial CO_2 and pH levels in a unified framework (Fig. 3). The form of the optimal solution (Eq. 6a & 6b) implies that the respiratory controller is responsive to an apparent metabolic CO_2 load $\dot{V}_{CO_3}/(1 - V_D/V_T)$ which tracks not only the actual metabolic CO_2 load $\dot{V}_{CO_3}$ but also the inefficiency of pulmonary gas exchange (V_D/V_T) that adds to the overall challenge of CO_2 elimination. This is in close agreement with the observation of heightened exercise ventilation at normal P_{aCO_3} in patients with increased physiological V_D/V_T , such as in congestive heart failure. The



Control of Breathing, Integration of Adaptive Reflexes, Fig. 3 Two views for respiratory control. (a) Classical reflex model assumes additive, reducible, and superposable characteristics of chemical, mechanical, and

exercise stimuli. (b) The optimization model integrates various afferent-efferent signals in a single model to characterize the complex interactions among these signals (Adapted from Poon et al. (2007))

controller's responsiveness to an apparent metabolic load that is influenced by inefficiency of pulmonary CO_2 elimination caused by physiological V_D/V_T is indicative of its ability of cognition and perception (Poon and Tin 2013). This is analogous to temperature sensing, where the perceived (or "real-feel") temperature is determined not only by the ambient temperature but also by environmental factors (humidity, wind chill, etc.) that affect body heat dissipation.

On the other hand, for any sizable external dead space load added in series with the airway, CO_2 elimination is also impaired by an elevated series V_D/V_T with resultant increase in the apparent metabolic CO_2 load like in congestive heart failure patients. However, because the increase in V_D/V_T now comes with rebreathing of dead space CO_2 , the controller may (at the beginning of each inspiration) mistake the dead space load for an airway CO_2 load (at $P_{ICO_3} \approx P_{aCO_3}$) that remains until the dead space is cleared toward late inspiration. This ambiguity may render the controller with an illusion of a *virtual* $P_{ICO_3}(\hat{P}_{ICO_3})$, which amounts to a virtual airway CO_2 load (Poon and Tin 2013). Hence, the effect of external dead space loading is equivalent to a combination of airway CO_2 loading and parallel dead space loading. Such illusive perception caused by CO_2 rebreathing provides a plausible explanation of the hypercapnic effect of dead space loading as opposed to the eucapnic state of increased physiological V_D/V_T in congestive heart failure.

In addition, Eq. 6b predicts a synergetic CO_2 –exercise interaction such that the slope of the $\dot{V}_E - \dot{V}_{CO_3}$ relationship is increased at increasing P_{aCO_3} levels while inhaling CO_2 , as demonstrated experimentally (Poon et al. 2007; Poon and Tin 2013). In contrast, the traditional Sherringtonian reflex model would predict an additive CO_2 –exercise interaction with a parallel shift of the $\dot{V}_E - \dot{V}_{CO_3}$ curve by CO_2 inhalation instead (Poon 1987). On the other hand, Eq. 6a shows that the magnitude of CO_2 –exercise interaction is also influenced by mechanical constraints. The term $\dot{V}_{max}$ in Eqs. 4 and 6a represents a hypothetical maximum ventilation that can be sustained by the respiratory muscles, such that the effect of mechanical limitation intensifies as $\dot{V}_E$ approaches

$\dot{V}_{max}$ resulting in a less than multiplicative CO_2 –exercise interaction at increasing $\dot{V}_E$ levels (Poon 1987). In this event, the resultant $\dot{V}_E - \dot{V}_{CO_3}$ curve would demonstrate an apparent additive component with a positive y-intercept. Hence, mechanical limitation due to a finite $\dot{V}_{max}$ provides a plausible explanation of the apparent additive CO_2 –exercise interaction component found in experiments that include moderate to high exercise $\dot{V}_E$ levels (Poon and Greene 1985) or in patients with pronounced ventilatory limitations (Paoletti et al. 2011).

Optimization Model of Mechanical Load Compensation

A remarkable property of the respiratory controller is its capability to compensate for ventilatory loading and unloading at rest and during moderate exercise, a phenomenon known as ventilatory load compensation. In normal subjects, this is achieved by adopting an optimal respiratory pattern that minimizes the increases in mechanical work rate of breathing caused by the ventilatory load, provided the latter is not mechanically limiting at the ventilatory levels of interest (i.e., at $\dot{V}_E \ll \dot{V}_{max}$) (Poon 1987, 1989a, b). This capability is also evidenced in patients with early stages of certain cardio respiratory diseases such as pulmonary fibrosis and emphysema. The optimization model provides a conceptual framework for understanding this behavior. To model the integrative control of $\dot{V}_E$ and respiratory pattern, Eq. 4a has been extended by expressing $\dot{W}_o$ explicitly in terms of the isometric respiratory driving pressure $P(t)$ (Poon et al. 1992). The mechanical plant in this case is defined by the following equation of motion:

$$P(t) = \dot{V}(t)R_{rs} + V(t)E_{rs} \quad (7)$$

whereby all ventilatory variables can be derived successively from the $P(t)$ waveform as follows:

$$P(t) = \dot{V}(t), \quad V(t) \rightarrow V_T, V_I, T_E \rightarrow \dot{V}_E \quad (8)$$

where R_{rs} , E_{rs} are respectively the total (extrinsic and intrinsic) respiratory resistance and elastance; $\dot{V}(t)$, $V(t)$ are instantaneous respiratory airflow and volume; and T_I and T_E are inspiratory and

expiratory durations. The resultant $\dot{V}_E$ is given by the variables V_T , T_I and T_E . This integrated model captures both the optimal ventilatory response characteristics of Eq. 6 and the corresponding optimal respiratory pattern. The strength of ventilatory load compensation is dependent on the type and magnitude of the ventilatory load relative to those of the background ventilatory stimulus. The parameters R_{rs} and E_{rs} can explicitly model the effects of resistive, elastic, and threshold loading, which have been studied singly and in combination, as well as under the influence of chemical stimulus and exercise (Poon 1989a, b; Sidney and Poon 1995). Computer simulations with the optimization model have proved to be consistent with the experimental observations (Poon et al. 1992). In all cases, ventilatory loading provokes compensatory inspiratory, postinspiratory, and expiratory motor responses that fully or partially restore $\dot{V}_E$ to the control level in normal or disease states or when ventilation is stimulated by chemical or exercise inputs.

Internal Model Paradigm in Respiratory Control

Traditional Sherringtonian reflex models of homeostatic regulation rely mainly on feedback, feedforward, and set-point operations. These classical control engineering schemes have limited predictive power for complex behaviors, such as integrative physiological control at multiple levels of organization, and are nonrobust to disturbances (Poon 1996). In contrast, the optimization model suggests that the respiratory controller may be self-adapting, continuously maintaining optimality in the presence of unknown disturbances.

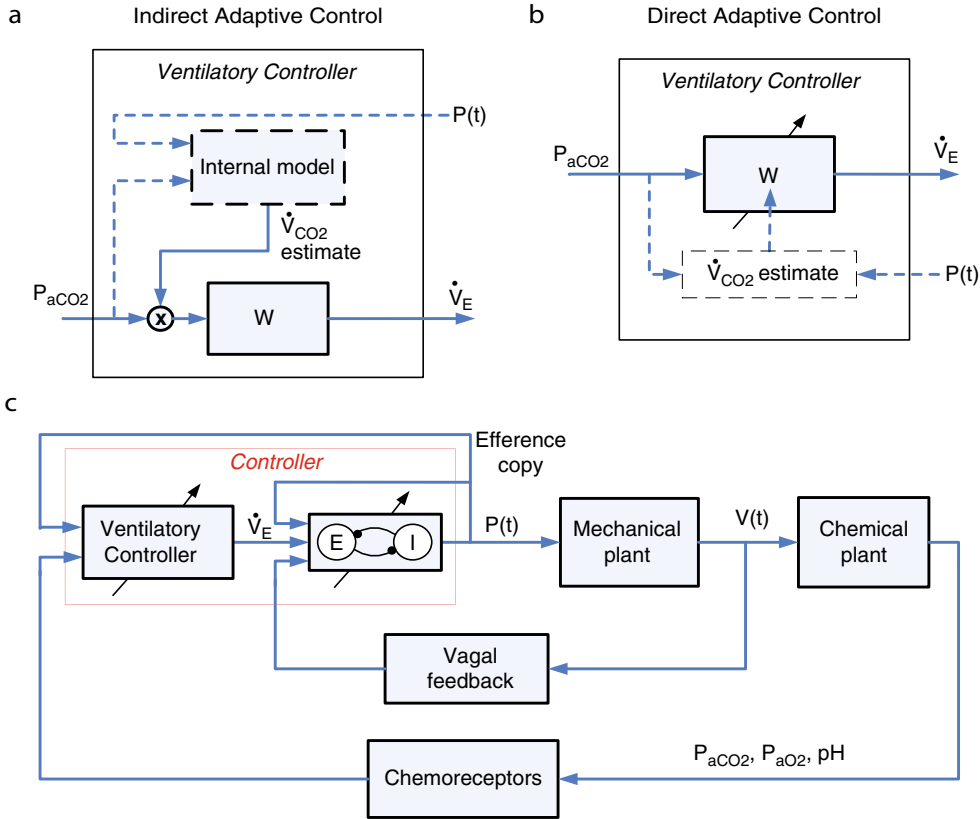
In this context, the homeostatic regulation problem in physiology is closely related to the internal model principle in modern control systems engineering, which states that a feedback regulator under external disturbances may maintain regulation and stability provided a suitably reduplicated model of the disturbance signal is adapted in the feedback path (Francis and Wonham 1975). Such a reduplicated model of the disturbance is called “internal model.” It is now well recognized that forward and inverse internal models (models of the external

environment and its inverse) are widespread in many types of sensorimotor integration in the mammalian brain (Davidson and Wolpert 2005; Tin and Poon 2005).

The optimal solution (Eq. 6) suggests that the respiratory controller may be tracking an apparent metabolic CO_2 load $\dot{V}_{CO_2}/(1 - V_D/V_T)$ instead of the actual metabolic CO_2 load $\dot{V}_{CO_2}$, perhaps through continuous algorithmic identification of the causal relationship of the controller output and resultant chemical–mechanical afferent feedbacks. The projected estimate of this apparent metabolic CO_2 load may take the form of some controller drive signals (indirect adaptive control) or modifiable gain parameters (direct adaptive control), like in engineering adaptive control theory (Fig. 4). Either way, the “exercise stimulus” may amount to some “mental percept” signal emergent from optimal sensorimotor integration rather than an explicit feedforward signal to the controller. Similar internal model sensorimotor integration architecture may also underlie the optimal adaptation of the respiratory pattern to changes in ventilatory mechanical loads.

Hebbian Feedback Covariance Learning and Direct Internal Model Control

Hebbian synaptic plasticity was first postulated by D.O. Hebb over 50 years ago as a mechanism of learning and memory (Hebb 1949). In its original form, Hebb suggested that a synaptic connection can be strengthened if pre- and postsynaptic activities coincided during a short time interval. To circumvent limitations to the classical Hebbian model such as instability and saturation and the lack of reinforcement feedback dynamics in the learning mechanism, Young and Poon (1998) have introduced a Hebbian feedback covariance adaptive control algorithm as a novel paradigm for direct internal model adaptation and reinforcement learning (operant or instrumental conditioning). Unlike classical adaptive control laws which operate deterministically, the feedback covariance adaptive control law is driven by the intrinsic fluctuations of the control signal (such fluctuations are ubiquitous in physiological signals) and resultant covariation of the feedback signal that is



Control of Breathing, Integration of Adaptive Reflexes, Fig. 4 Hypothetical internal model structures for self-tuning adaptive control of respiration. (a) In indirect adaptive control, the metabolic level is continuously estimated by the controller based on an internal model of the causal relationship between the respiratory motor output and chemical feedback. The resultant neuronal estimate provides an indirect “feedforward” signal to the feedback

controller (with fixed gain W) to generate the ventilatory drive. (b) In direct adaptive control, the estimate is directly incorporated in the controller as a variable feedback gain. (c) Two-tier respiratory control system structure with (central and peripheral) chemoreceptor afferent feedback driving an adaptive ventilatory controller and vagal volume-related feedback driving an adaptive central pattern generator signals (Adapted from Poon et al. (2007))

routed back to the controller through the plant dynamics. In its simplest form, the controller gain, w , that determines the optimal input–output relationship is computed by correlating the corresponding intrinsic fluctuations of the control (efferent) signal u and feedback (afferent) signal y :

$$\frac{dw}{dt} = k(\delta y \cdot \delta u) \quad (9)$$

where k is the adaptation constant and δu and δy are the temporal variations of the afferent and efferent signals, respectively, about their corresponding mean values. The adaptation law states that the controller gain (or synaptic weight),

w , will be potentiated if δu and δy are positively correlated and will be weakened otherwise. The parameter w thus encodes an inverse internal model that may track any disturbances in the plant dynamics, such as changes in the metabolic $\dot{V}_{CO_2}$ in the chemical plant of the respiratory system. Young and Poon have shown that, with suitable modifications of the adaptation rule (Eq. 9) to account for the dynamics and delays in the feedback loop, this feedback covariance-based internal model paradigm allows robust direct adaptive control of a general class of linear and nonlinear dynamical systems with stability and convergence guaranteed by Lyapunov theory.

In summary, multiple lines of evidence have strongly suggested that mammalian respiratory control possesses rich adaptive signal processing capabilities in the form of both nonassociative learning and associative learning, which have been ignored in the traditional Sherringtonian framework. New paradigms of adaptive respiratory control will potentially open up new opportunities for more in-depth understanding of homeostatic regulation and sensorimotor control in general.

Cross-References

- [Computational Models of Mammalian Respiratory CPG](#)
- [Hebbian Learning](#)
- [Learning Rules: Overview](#)
- [Pre-Botzinger Complex Rhythm Generation](#)
- [Reward-Based Learning, Model-Based and Model-Free](#)
- [Short-Term Plasticity, Biophysical Models](#)

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Control of Locomotion and Scratching in Turtles

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Definition

The spinal cord contains central pattern generators, which are networks of neurons that can generate coordinated patterns of activity in motor neurons (motor patterns) in the absence of sensory feedback. The turtle spinal cord contains central pattern generators for several kinds of limb movements and is convenient to study physiologically because turtles, being diving animals, have evolved mechanisms to keep tissue healthy under low-oxygen (hypoxic) conditions. Turtle locomotion includes swimming and stepping. Spinal cord central pattern generators have been demonstrated in turtles for forward swimming and

for three forms of scratching, a rhythmic behavior in which the same-side (ipsilateral) hind limb repeatedly rubs against a specific location on the body surface that has been irritated or tickled. Stimulation in a transition zone, at the border of the receptive fields for two forms of scratching, or simultaneous two-site stimulation for two forms of scratching, or for one form of scratching plus forward swimming, can evoke motor pattern blends. Blends may be switches, in which consecutive cycles alternate between two different motor patterns, or hybrids, in which each cycle exhibits characteristics of both motor patterns. The ability of the turtle spinal cord to produce blends suggests that the corresponding central pattern generators are partly shared or that there are strong interactions between components of each. The spinal cord on the opposite (contralateral) side to the scratching limb contributes to generating scratching motor patterns, specifically to the hip-extensor phase of scratching; this circuitry may be part of a bilateral network that contributes to flexor-extensor and left-right coordination for both swimming and scratching. Many spinal interneurons, which are neurons contained entirely within the spinal cord, are multifunctional, meaning that they generate action potentials rhythmically during forward swimming and all three forms of scratching, often bilaterally, and are often activated during limb withdrawal (flexion reflex) as well. Multifunctional interneurons may be components of multiple central pattern generators. Other spinal interneurons, however, are behaviorally specialized: scratching-specialized neurons and flexion reflex-selective neurons are not active, and often are inhibited, during other kinds of motor patterns, and may play a special role in selecting or generating one type of motor pattern.

Detailed Description

Why Study Locomotion and Scratching in Turtles?

Turtles have been used as a model system to study the control of locomotion and scratching in vertebrates since the 1970s. One major reason for their

use is that turtles, being diving animals, have evolved cellular and molecular mechanisms to maintain tissue health under conditions of reduced oxygen (hypoxia) (Lutz and Milton 2004). Such conditions often occur during physiological experiments on reduced or *in vitro* animal preparations, which are often required to study neuronal mechanisms. Thus, researchers are often able to acquire useful physiological data from healthy turtle tissue for about three times as long as they could from comparable mammalian tissue (Hounsgaard and Nicholson 1990).

It is also relatively easy to evoke both locomotion and scratching in turtles, even in reduced preparations and without using exogenous drugs (Stein 2005). The forms of locomotion that have been studied behaviorally include forward swimming, backward swimming (or backpaddling), and forward stepping. Of these, brainstem and spinal cord mechanisms have been studied for forward swimming.

There Are Three Forms of Turtle Scratching

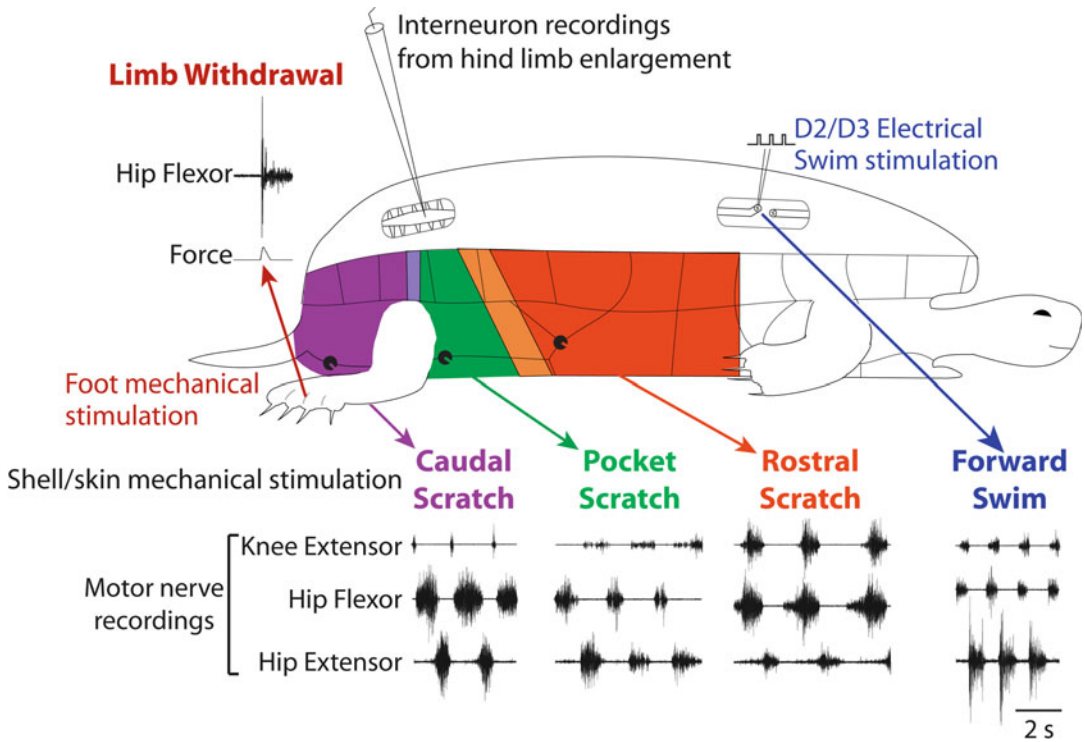
In addition, there are three forms of scratching performed by each hind limb in response to irritation or tickling of the skin or shell (which has sensory innervation). In each form of scratching, the hind limb rubs against a distinct region of the body surface (Fig. 1). A different part of the hind limb and a different knee-hip synergy are used in each form, to target the different regions of the body surface (Mortin et al. 1985). The different synergies required to reach each region are analogous to the different ways humans use to scratch the upper and lower back. In both cases, biomechanical constraints necessitate the use of different limb muscle synergies. Also in both cases, there is a narrow transition zone at the borders of the receptive fields for different forms of scratching. An irritating stimulus within a transition zone can evoke either of the two forms of scratching or sometimes a blend of the two forms. Blends can be switches, in which the limb changes forms on a cycle-by-cycle basis, or hybrids, in which each cycle includes elements of the two

forms. Both switches and hybrids can result in successful rubbing. The receptive fields for rostral and pocket scratching are innervated by contiguous spinal cord segments (i.e., their dermatomes are adjacent and partly overlapping) (Mortin and Stein 1990). The spinal cord segments that provide sensory innervation of the caudal scratch receptive field, however, are more caudal and are not contiguous with the segment innervating the pocket scratch receptive field, being separated by segments that provide sensory innervation of the hind limb instead.

The Turtle Spinal Cord Contains Central Pattern Generators for Swimming and Scratching

The turtle spinal cord can produce the different forms of locomotion and scratching even when all input from the brain is removed. Forward swimming movements of the opposite hind limb can be evoked by electrical stimulation in a region of the spinal cord white matter (the lateral funiculus) in post-cervical spinal cord segments (Lennard and Stein 1977). This stimulation is thought to generate action potentials in the descending axons of reticulospinal neurons (which have been cut off from their cell bodies). Selective lesion of the white matter in this region reduces or eliminates voluntary swimming in otherwise intact turtles.

It has been found in limbed vertebrates generally that locomotion and scratching can be produced without the brain. Moreover, vertebrates without limbs can produce axial locomotion without the brain. Insects can also produce locomotion and scratching without the brain (via the thoracic ganglia). Thus, there is a remarkable conservation of the capacity to produce these rhythmic movements using the central nervous system below the level of the brain. In turtles, at least, the spinal cord is also able to generate blends of two forms of scratching appropriately during stimulation of a transition zone or during simultaneous stimulation of sites in two scratch receptive fields (Mortin et al. 1985; Stein et al. 1986). Blends between swimming and scratching have also been seen (Earhart and Stein 2000). Thus,



Control of Locomotion and Scratching in Turtles, Fig. 1 Schematic illustration of the turtle spinal cord preparation and the forward swimming, scratching, and

limb withdrawal (flexion reflex) motor patterns it generates with different kinds of mechanical or electrical stimulation

coordinated hind limb movement blends can be produced without the brain.

The several forms of swimming and scratching each involve rhythmic contractions of the same hind limb muscles (Lennard and Stein 1977; Robertson et al. 1985). Nonetheless, they can be distinguished from one another based on a set of criteria that involve the amplitudes and timing (i.e., phasing) of muscle contractions. During scratching, knee extension is the major determinant of force generated by the limb against the body surface. A burst of knee-extensor muscle activity occurs during the latter portion of each hip-flexor burst in rostral scratching, during each hip-extensor burst in pocket scratching, and toward the end of the hip-extensor burst and the start of the next flexor burst in caudal scratching. Forward swimming shows a similar knee-hip synergy to rostral scratching, but the knee-extensor and hip-flexor bursts are weaker and briefer, and the hip-extensor bursts are stronger and longer, in

forward swimming as compared to rostral scratching. When forward swim-evoking and rostral scratch-evoking stimuli are delivered simultaneously, the animal produces an adaptive blend of the two (a hybrid), in which the amplitude of hip extension is similar to forward swimming and the amplitudes of knee extension and hip flexion are similar to rostral scratching. The single criterion of the timing of the knee-extensor burst within the hip cycle reliably distinguishes rostral scratching from pocket scratching or caudal scratching, but does not reliably distinguish pocket scratching from caudal scratching or rostral scratching from forward swimming.

The turtle spinal cord can generate the basic patterns of motor neuron activity (i.e., motor patterns) that underlie forward swimming and the three forms of scratching even without movement-related sensory feedback from the limbs (Robertson et al. 1985; Juranek and Currie 2000; Fig. 1). This can be demonstrated by cutting

all of the dorsal roots that carry sensory input from the limbs to the spinal cord, but it is usually demonstrated by chemically blocking acetylcholine receptors at neuromuscular junctions systemically (i.e., the animal is immobilized). The same kind of electrical stimulation in the lateral funiculus that evokes swimming movements in the moving animal evokes forward swimming motor patterns in the immobilized animal. The same kind of mechanical stimulation of the shell or skin that evokes scratching movements in the moving animal evokes each form of scratching motor pattern in the immobilized animal. The patterns of electrical activity in motor nerves that innervate particular hind limb muscles are essentially identical in immobilized animals to the patterns of electrical activity in those muscles during actual swimming and scratching movements. Thus, the spinal cord contains central pattern generators for forward swimming and each form of scratching.

The spinal cord contains sufficient neural circuitry not only to generate the motor patterns for forward swimming and each form of scratching but also to generate adaptive blends of two such motor patterns (Robertson et al. 1985; Stein et al. 1986; Juranek and Currie 2000). Stimulation in a scratch transition zone (rostral pocket or pocket caudal) or two-site stimulation (e.g., rostral + caudal) can evoke appropriate blends of two forms of scratching motor patterns in the immobilized preparation, including both switches and hybrids (Robertson et al. 1985; Stein et al. 1986). Blends between forward swimming and a form of scratching have also been described in the immobilized preparation (Juranek and Currie 2000). Thus, the capacity to produce pure-form locomotion and scratching, as well as coordinated and adaptive blends, is programmed into the spinal cord, in turtles at least.

Several features of scratching motor patterns are consistent with the unit-burst generator hypothesis of Sten Grillner (Grillner 1981) that each joint is controlled by a pair of rhythmogenic modules and inconsistent with the “half-center” hypothesis originally proposed by T. Graham Brown (Brown 1911), at least in its simplest form, which requires mutual inhibition between

flexor and extensor units to generate a rhythm (Stein 2008). A normally occurring variation in rostral scratching (and sometimes other forms of scratching) is missing the hip-extensor phase (i.e., missing both the hip-extensor bursts and the quiescent periods between successive hip-flexor bursts). This is called hip-extensor deletion scratching. Hip-flexor motor neurons continue to burst rhythmically during hip-extensor deletion scratching. This finding suggests that a hip-flexor rhythm can occur in the absence of a hip-extensor rhythm, in contrast to the half-center hypothesis. Knee-extensor bursts can occur normally and can alternate with knee-flexor bursts during hip-extensor deletion rostral scratching, which suggests that the turtle spinal cord contains sufficient neural circuitry to generate rhythmic activity in knee-extensor motor neurons without rhythmic activity in hip-extensor motor neurons (Stein and Daniels-McQueen 2004). This finding is inconsistent with a simple half-center hypothesis in which all limb extensor motor neurons (i.e., both hip and knee) are controlled together. The existence of different knee-hip synergies for the different forms of scratching is also inconsistent with such a simple half-center hypothesis.

The capacity to produce rhythmic, hind limb motor patterns is distributed across several segments of the spinal cord, including all five segments of the hind limb enlargement and the spinal cord segments just rostral to the enlargement (Mortin and Stein 1989). Nonetheless, the more rostral segments of the enlargement and the immediately pre-enlargement segments are more important for generating these rhythms than the caudal enlargement segments are. Spinal cord segments still further caudal are not necessary to generate these rhythmic motor patterns. Similar conclusions have been reached for chick embryo rhythmic activity (Ho and O'Donovan 1993), rodent locomotor-like activity (Cazalets et al. 1995; Kjaerulff and Kiehn 1996; Cowley and Schmidt 1997), and cat scratching motor patterns (Berkinblit et al. 1978; Deliagina et al. 1983). Thus, there appears to be a conserved rostral weighting of spinal cord central pattern generation across limbed vertebrates. The importance of the rostral part of the hind limb enlargement for motor

pattern generation is not directly related to the locations of motor neurons; hip-flexor and knee-extensor motor neurons are located in the rostral segments of the enlargement, but hip-extensor motor neurons are located in caudal segments of the enlargement, in turtles (Ruigrok and Crowe 1984) as in mammals (Romanes 1964).

It is possible to evoke some of these hind limb motor patterns *in vitro*. The turtle spinal cord with a region of the rostral shell still attached to it via peripheral nerves can be used to evoke rostral scratching motor patterns using natural stimulation of the shell *in vitro* (Keifer and Stein 1983; Alaburda and Hounsgaard 2003). Also, the turtle spinal cord with a particular cutaneous nerve (the ventral posterior pocket) attached can be used to evoke pocket scratching motor patterns via nerve electrical stimulation *in vitro* (Currie and Lee 1996).

Neurotransmitters and Ion Channels

Glutamate and glycine have been shown to play important roles in scratching motor patterns. Bath application of glutamate agonists (NMDA and AMPA) to the turtle spinal cord *in vivo* and *in vitro* can evoke rhythmic activity of motor nerves that is similar to scratching motor patterns (Currie 1999). Scratch sensory stimulation can reset these rhythms, indicating interaction, at least, between the networks that produce glutamatergic rhythms and those that produce scratching. Blocking NMDA receptors reduces the rate of the scratching rhythm and the temporal summation of sensory inputs that evoke scratching motor patterns for rostral scratching *in vivo* (Currie and Stein 1992) and for pocket scratching *in vitro* (Currie and Lee 1996). Some individual spinal cord interneurons (i.e., neurons contained entirely within the central nervous system) are similarly active for many seconds following a single scratch stimulus and may contribute to temporal summation during scratching (Currie and Stein 1990). Such interneurons can also have their multisecond activity reduced by blocking NMDA receptors (Currie and Stein 1992). Glycine, on the other hand, slows rostral

scratching motor patterns and blocking glycine receptors speeds them up (Currie and Lee 1997).

Motor Neurons During Locomotion and Scratching

Hind limb motor neurons may contribute actively to the amplitude and perhaps the timing of turtle scratching and swimming rhythms. Motor neurons receive alternating but temporally overlapping excitatory, depolarizing inputs and inhibitory, chloride-dependent, hyperpolarizing inputs during scratching motor patterns *in vivo* (Robertson and Stein 1988; Stein 2010). Intrinsic properties of motor neurons can be studied in more detail in slice preparations, which can be made especially thick for turtle spinal cord, because of its unusual resistance to hypoxia (Hounsgaard and Nicholson 1990). Some motor neuron dendrites can produce calcium-dependent action potentials (Hounsgaard and Mintz 1988). Motor neurons also show bistability or plateau potentials, primarily in the dendrites, meaning that their membrane potentials are stable at two different levels, one of which (the resting potential) is below action potential threshold and the other of which is above it (Hounsgaard and Mintz 1988). This bistability might contribute to the strength and duration of each motor neuron burst during scratching.

The bistability depends on l-type (persistent) voltage-dependent calcium channels, especially CaV1.3 channels (Hounsgaard and Mintz 1988; Alaburda and Hounsgaard 2003; Simon et al. 2003), as well as calcium release from the endoplasmic reticulum via ryanodine receptors (Mejia-Gervacio et al. 2004). There are also calcium-dependent nonspecific cation channels in turtle motor neurons, but they are not required for plateau potentials (Perrier and Hounsgaard 1999). The plateau potentials can be affected by a number of neuromodulators (Delgado-Lezama et al. 1997; Svirskis and Hounsgaard 1998). The plateau potentials are augmented by serotonin (especially via 5-HT₂-type receptors) (Hounsgaard and Kiehn 1989; Perrier and Hounsgaard 2003), group I metabotropic

glutamate receptors, and muscarinic acetylcholine receptors. Plateau potentials are generally increased by neuromodulators that close potassium channels (Hounsgaard and Mintz 1988). A compartmental model of turtle motor neurons also suggests that neuromodulators close potassium channels and that serotonin has multiple effects via different types of ion channels that are differentially distributed in the cell (Booth et al. 1997). In slice preparations, motor neurons can produce oscillations in the presence of the glutamate agonist NMDA even when all action potentials are blocked (by tetrodotoxin) (Guertin and Hounsgaard 1998). These NMDA-dependent motor neuron oscillations disappear if l-type calcium channels are blocked.

Although intrinsic properties of motor neurons may contribute to shaping their bursts during scratching (Alaburda and Hounsgaard 2003), the synaptic input to motor neurons is so strong during rostral scratching motor patterns *in vitro* that it likely overwhelms and suppresses motor neuron intrinsic properties like plateau potentials, which may consequently play a relatively minor role during scratching (Alaburda et al. 2005).

Spinal Interneurons Involved in Locomotion and Scratching

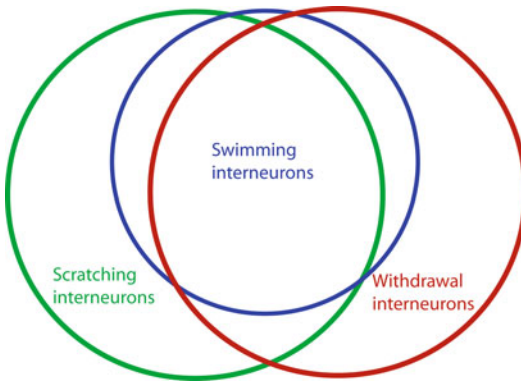
Much is still unknown about the spinal cord interneurons and pathways that mediate locomotion and scratching in turtles and in limbed vertebrates generally. However, some things are known (Berkowitz 2010). Turtles have been particularly useful for studying the extent to which networks of interneurons that generate forward swimming and the three forms of scratching in each hind limb are shared versus separate. It is known that many spinal cord interneurons are rhythmically activated during forward swimming and all three forms of scratching (Berkowitz and Stein 1994a, b; Berkowitz 2001a, b, 2002). These multifunctional interneurons are found throughout the hind limb enlargement spinal cord, as well as in spinal cord segments rostral to the hind limb enlargement (Berkowitz 2001a, b). In the transverse plane, these interneurons are scattered

through the ventral part of the dorsal horn, the intermediate zone, and the dorsal part of the ventral horn. At least some of these interneurons have axon projections that terminate in the ventral horn (Berkowitz 2005, 2008; Berkowitz et al. 2006), consistent with their contributing to motor output during all of these motor patterns, although their synaptic targets are not yet known. Thus, there is a strong likelihood that the networks generating these distinct forms of rhythmic hind limb movement partly overlap in turtles.

Multifunctional and Specialized Spinal Interneurons

Most scratch-activated interneurons are activated during stimulation of the body surface for all three forms of ipsilateral scratching and often contralateral scratching as well (Berkowitz 2001a, b). Nonetheless, most such interneurons are most strongly activated during stimulation of one particular region of the body surface and are progressively less strongly activated during stimulation of sites progressively further away from this preferred region. Thus, the activity of these neurons does not precisely indicate which site has been stimulated. Instead, each is broadly tuned to a region of the body surface. Different scratch-activated interneurons within one animal's spinal cord are broadly tuned to different regions of the body surface. The combination of several such interneurons with different tuning (i.e., population coding) can in principle specify precisely which site has been stimulated and thus which form of scratching should be generated to initiate contact with that site (Berkowitz 2009). If, indeed, the turtle spinal cord uses a large population of broadly tuned interneurons to code stimulus locations and corresponding movement directions, this would be similar to population coding in many animals and for many behaviors, from leech local bending to primate arm reaching (Briggman and Kristan 2008).

Nonetheless, some turtle spinal cord interneurons are behaviorally specialized (Fig. 2; Berkowitz 2010). Some interneurons are rhythmically activated during scratching motor patterns,



Control of Locomotion and Scratching in Turtles, Fig. 2 Schematic Venn diagram illustrating multi-functional and specialized types of spinal interneurons

but are not activated at all or are even inhibited during forward swimming motor patterns (Berkowitz 2002, 2008). In addition, there are interneurons that are strongly activated during limb withdrawal (flexion reflex) motor patterns that are inhibited during forward swimming and each form of scratching motor pattern (Berkowitz 2007). The relative roles and effects of shared versus behaviorally specialized interneurons are not yet understood in turtles. There is also evidence from hatchling tadpoles and larval zebrafish that a combination of shared and behaviorally specialized interneurons contributes to different forms of axial locomotion (Berkowitz et al. 2010). Less is known about the extent to which circuitry is shared in the control of different forms of locomotion and scratching in mammals.

Rhythmic Activity of Spinal Interneurons

Spinal cord interneurons that are activated during swimming and scratching motor patterns tend to be rhythmically active or at least have firing rates that are rhythmically modulated. Most such interneurons tend to fire action potentials (i.e., have a preferred phase) during a particular phase of the hip flexion-extension cycle and tend to maintain this preferred phase across all three forms of scratching and often during forward swimming as well (Berkowitz 2001a, b, 2002). Thus, control of hip movement timing appears to dominate

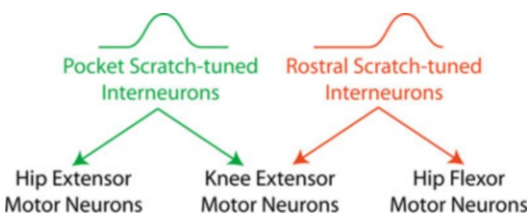
spinal cord interneuron rhythmic activity. Interneurons that are rhythmically active during the hip-extensor phase of scratching motor patterns are generally quiet during hip-extensor deletions, while interneurons that are rhythmically active during the hip-flexor phase are generally active during hip-extensor deletions, suggesting that there is an entire module of interneurons and motor neurons that is inactive during hip-extensor deletions (Stein and Daniels-McQueen 2002; Stein 2008).

In addition to rhythmic, hip-related interneurons, some interneurons do shift their peak firing within the hip activity cycle between scratching and swimming or between one form of scratching and another (Berkowitz 2001a, b, 2002). Such interneurons could be involved directly in control of other joints, such as the knee or ankle, consistent with the unit-burst generator hypothesis. Rhythmic interneurons have been studied that generate bursts of action potentials correlated with knee-extensor or knee-flexor motor neuron activities (Stein and Daniels-McQueen 2003). Some spinal cord ventral horn and dorsal horn interneurons also show the same kind of bistability as seen in motor neurons (Hounsgaard and Kjaerulff 1992; Russo and Hounsgaard 1994, 1996).

Among the spinal cord interneurons that are rhythmically activated during forward swimming and all three forms of scratching is a class of interneurons called transverse interneurons, or T neurons, that can be delineated by their somato-dendritic morphologies (Berkowitz et al. 2006). These interneurons have dendrites that extend far dorsoventrally and mediolaterally (i.e., in the transverse plane) but are short rostrocaudally; they also tend to have a soma that is longer mediolaterally than rostrocaudally. T neurons tend to be very rhythmically active during both swimming and scratching (Berkowitz 2008). They also tend to have higher peak firing rates during scratching, larger membrane potential oscillations during scratching, and briefer afterhyperpolarizations following action potentials than other scratch-activated interneurons (Berkowitz et al. 2006). T neurons are also typically activated during ipsilateral limb

withdrawal. At least some T neurons have axon terminals in the ventral horn in the hind limb enlargement. Thus, T neurons are good candidates to play an important role in motor control for a wide range of limb movements.

A hypothetical architecture has been proposed that could in principle generate the correct knee-hip synergies for rostral scratching and pocket scratching using only broadly tuned interneurons that preferentially fire action potentials in a particular phase of the hip cycle (Fig. 3; Berkowitz 2001a, b). Each such interneuron would project to both a knee motor neuron pool and a hip motor neuron pool. According to this hypothesis, interneurons that are broadly tuned to a rostral scratch region would project to both knee-extensor and hip-flexor interneurons, while interneurons that are broadly tuned to a pocket scratch region would project to both knee-extensor and hip-extensor motor neurons. The knee-hip synergy would then be determined in motor neurons, especially knee-extensor motor neurons, that integrate excitatory and inhibitory inputs with different but overlapping time courses. There is evidence from intracellular recordings of knee-extensor motor neurons that they do receive excitatory and inhibitory postsynaptic potentials that overlap in time during rostral and pocket scratching motor patterns (Robertson and Stein 1988).



Control of Locomotion and Scratching in Turtles, Fig. 3 Hypothetical architecture to account for how broadly tuned spinal interneurons could generate the correct knee-hip synergies for rostral and pocket scratching. Each interneuron would project to two motor neuron pools (directly or indirectly), with differently tuned interneurons having different dual projections. Knee-extensor motor neurons would integrate overlapping excitatory and inhibitory inputs from differently tuned interneurons, thus determining the timing of knee-extensor bursts within the hip cycle. Whichever group of interneurons was more active would determine the knee-hip synergy

Dual Stimulation

The large set of spinal interneurons that are rhythmically activated during both swimming and scratching motor patterns suggests that the central pattern generators for swimming and scratching have common members or at least strong interactions between them. Another way of addressing this question is to deliver two stimuli simultaneously that each individually evokes one of the two motor patterns. If the sets of interneurons that generate the two motor patterns are entirely separate (i.e., the central pattern generators are separate), then simultaneous stimulation should generate a superposition of the two rhythms within motor neurons. If many of the central pattern generator interneurons are shared (or have strong interactions between them, which might be equivalent), however, then one stimulus might modify the motor pattern produced by the other stimulus in a coordinated manner (Berkowitz and Hao 2011).

As noted above, simultaneous stimulation of the body surface in regions that evoke two different forms of scratching can evoke coordinated and adaptive blends of the two (Robertson et al. 1985; Stein et al. 1986). In addition, brief forward swim stimulation can interrupt and reset the rostral scratching rhythm and vice versa (Juranek and Currie 2000). (Also, brief stimulation to evoke a limb withdrawal or flexion reflex motor pattern can reset the scratching rhythm (Currie and Stein 1989).) Finally, prolonged simultaneous forward swim stimulation and scratch stimulation (for all three forms of scratching) can generate swim-scratch blends, generate a swim rhythm when the swim stimulation alone is insufficient, generate a pure-form swim rhythm with a rhythm frequency greater than that evoked by either stimulation alone, and sometimes disrupt one phase of the rhythm or disrupt rhythm generation entirely (Hao et al. 2011). These physiological findings suggest that there are either substantial common elements to the swimming and scratching central pattern generators or strong interactions between the generators.

Computer simulations were also generated of simplified models of caudal scratch and forward

swim networks that were (1) entirely separate, (2) separate but interacting, and (3) shared central pattern generators (Hao et al. 2011). The results of these simulations suggested that shared or strongly interacting central pattern generators can account for the physiological findings but completely separate central pattern generators cannot. The strongly interacting simulated networks and especially the shared simulated network replicated the physiological findings of increased rhythm frequency under dual stimulation and summation of a subthreshold swim stimulus with a suprathreshold scratch stimulus to generate a suprathreshold swim. The success of these models depended on neurons switching their phase in the swim rhythm via escape from inhibition.

Left-Right Hind Limb Coordination

Coordination between the left and right hind limbs also can be generated by the spinal cord. In intact turtles performing forward swimming spontaneously, forward swimming involves alternating (i.e., out-of-phase) coordination between left and right hind limb movements (Field and Stein 1997). Surprisingly, such coordination continues after a cut along the midline of the spinal cord (separating the left and right sides) throughout the hind limb enlargement and the immediately pre-enlargement segments (Samara and Currie 2007). This shows that commissural pathways in more rostral regions (including the forelimb enlargement) are sufficient to produce left-right hind limb alternation.

Scratching, however, is essentially a unilateral behavior; the ipsilateral hind limb rhythmically rubs against the stimulated site, while the contralateral hind limb remains relatively still (Mortin et al. 1985). A close look at the activity of contralateral motor neurons during unilateral scratch stimulation, however, has revealed that they typically are weakly but rhythmically activated in alternation with their ipsilateral counterparts during unilateral scratching (Currie and Stein 1989). It is not clear if this contralateral motor neuron activation is adaptive during scratching; it might

be an epiphenomenon due to activation of networks that are shared between swimming and scratching. In addition, bilateral scratch stimulation and unilateral scratch stimulation near the midline (e.g., near the tail) can evoke bilaterally coordinated scratching movements of the left and right hind limbs (Field and Stein 1997), which might rely on the same spinal cord circuitry that underlies left-right coordination during bilateral swimming. Bilaterally evoked scratching usually involves alternation between the two hind limbs, but can involve synchronized (in-phase) movements, especially for caudal scratch stimulation near the tail. On occasion, the left and right hind limbs display 2:1 coordination, in which one limb moves through two cycles in exactly the time that the other limb moves through one cycle (Stein and McCullough 1998).

Many spinal cord interneurons that are rhythmically activated during ipsilateral scratching motor patterns are also robustly and rhythmically activated during contralateral scratching motor patterns (Berkowitz and Stein 1994a, b; Berkowitz 2001a, b). Such interneurons might be components of networks that produce the coordinated activity in contralateral motor neurons during scratching and potentially during swimming as well. Some such interneurons are rhythmically active in the same phase of the ipsilateral hip-flexor rhythm no matter which side is stimulated, while other such interneurons switch to the opposite phase when the opposite side of the body is stimulated. Collectively, such interneurons could mediate the in-phase and out-of-phase left-right limb coordination that has been observed during scratching and locomotion.

But does the contralateral spinal cord actually play a role in generating unilateral scratching motor patterns? Surprisingly, the answer is yes, as shown by experiments in which the spinal cord on one side was removed, throughout the hind limb enlargement (Stein et al. 1995). Stimulation of the body surface on the intact side evoked a strong rostral scratching rhythm on that side that was consistently missing the hip-extensor phase (i.e., hip-extensor deletion rostral scratching). Stimulation of the body surface on the lesioned side (but rostral to the lesion) evoked a

hip-extensor rhythm alone on the intact side. Both of these findings suggest that the contralateral spinal cord contributes a specific component to the scratching motor pattern, namely, the hip-extensor phase.

In other experiments, a hemisection (i.e., a spinal cord transection limited to one side, e.g., the left) was used to eliminate stimulation of the left hind limb enlargement via ipsilateral descending axons on the left and contralateral descending axons from the right (Stein et al. 1998). In this case, stimulation of the body surface on the intact right side (rostral to the hemisection) evoked hip-extensor deletion rostral scratching. Stimulation of the body surface on the left side (rostral to the hemisection) in combination with the stimulation on the right side evoked a normal rostral scratching rhythm (including the hip-extensor phase), i.e., the rostral scratch motor pattern was “reconstructed” by this two-site stimulation. This finding suggests that descending, crossed axons activate interneurons that produce the hip-extensor phase of scratching and that these interneurons are coordinated with interneurons that are activated through unilateral pathways. In addition, crossed pathways in pre-enlargement segments are sufficient to create the left-right alternation during bilateral rostral scratch stimulation.

All of these findings, in combination with the single-neuron recordings of interneurons that are bilaterally activated during scratching, suggest that there is a bilateral set of interneurons that each contribute to both left and right hind limb scratching (Stein et al. 1995). This set of shared neurons might contribute to bilateral coordination for both scratching and swimming. Surprisingly, though, one side (left or right) of the hind limb enlargement is sufficient to produce rhythmic hip-flexor, hip-extensor, and knee-extensor muscle activities with appropriate phasing during forward swimming movements evoked by electrical stimulation of the contralateral lateral funiculus (in the rostral spinal cord), though cycle frequency and muscle burst amplitude are lower than otherwise. Thus, the contralateral hind limb enlargement spinal cord may actually play a more important role in generating unilateral scratching than in generating unilateral swimming.

Crossed glycinergic inhibition appears to contribute to bilateral coordination during scratching, as coordination is more variable when glycine receptors are blocked (Currie and Lee 1997). Glycinergic inhibition cannot be necessary for coordination during scratching, however, as left-right coordination can continue under glycine receptor blockade.

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Convection-Diffusion Equation

► Fokker-Planck Equation

Coordinate Transformations, Role of Spinal Circuitry in

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Synonyms

[Descending control of spinal circuitry in voluntary movements](#); [Role of descending pathways in extrinsic to intrinsic coordinate transformation](#); [Spinal control of voluntary movements](#)

Definition

The process through which a motor target in the external environment is translated into a body-centered coordinate system is called coordinate

transformation. In the motor system, this translation is often referred to as the transformation of an externally defined (e.g., in a retinotopic coordinate frame) target into a muscle-based (or intrinsically defined) motor command. Multiple cortical areas are known to be involved in this process. Many of these areas, including pre- and post-central sites, project downstream to activate directly and indirectly spinal neurons. The interaction of this extensive system of descending pathways with spinal circuitry may further adjust motor commands before they reach target muscles in a final processing step of coordinate transformation.

Detailed Description

When making a movement directed toward a target in the world around us, the nervous system is faced with a computationally difficult task. The target which is initially defined in a retinotopic coordinate system must be translated into a detailed body-centered motor command that specifies the required spatiotemporal activation profile of all muscles (Shadmehr and Wise 2005). This computation is completed on the fly and in an unconscious manner. It is generally assumed that this process is the outcome of cortical processing in which multimodal sensory information is integrated and converted into appropriate motor commands (Sabes 2011). However, there are several reasons why segmental interneurons (INs) could also contribute to the process of coordinate transformation. First, the segmental network of interneurons is situated between the motor cortical network and corresponding motoneurons (MNs) such that most of the cortical information sent to MNs is relayed via INs (Porter and Lemon 1993). Second, multiple cortical areas transmit information to spinal neurons, including the motor and premotor areas, which could provide INs with diverse information that contains both high- and low-level features of the motor command (Dum and Strick 2002). Some descending output emerges from sensory areas of the parietal lobe, which in itself could provide segmental neurons with sensory-related information (Kuypers 1987;

Toyoshima and Sakai 1982). Other sources of descending input such as the vestibulospinal and rubrospinal pathways may provide further state variables related to posture, balance, etc. that could be relevant to the spinal processing of coordinate transformation (Baldissera et al. 1981). In addition to these sources of processed information, spinal neurons integrate proprioceptive inputs which are relayed via a rich afferent system. Finally, neighboring INs have been shown to engage with local interactions (Jankowska 1992) which can modify converging inputs before finally affecting MNs.

This entry reviews the mounting evidence that spinal neurons provide the final processing step for completing the coordinate transformation in the motor system. It further develops the concept that in addition to the spatial coordinate system, spinal processing also modifies the temporal pattern of descending commands to match it with the required pattern of muscle activation. Finally, the possible implications of this organizational scheme in which motor commands are finalized downstream to M1 are discussed in terms of current research in the field of motor control.

Activity of Spinal Interneurons During Voluntary Movement

There is abundant work on the organization of segmental circuitry in reduced preparations (i.e., cats, rodents, and in some cases monkeys). These studies have mostly concentrated on the input to these neurons from local, peripheral, and/or descending sources. Nonetheless, understanding the functional contribution of spinal neurons to any type of motor behavior requires recording single cell properties and cell-to-cell interactions during task performance, since these characteristics considerably affect the input-to-output transformation of any network. The ability to induce fictive locomotion in reduced preparations (e.g., isolated spinal cord) has led to extensive study of interneuron (IN) activity in these conditions. However, these studies concentrate on spinal network activity rather than its control by descending corticospinal pathways, which

however is the fundamental component of voluntary motor control. Early studies of cervical spinal neurons during normal motor behavior of primates (Fetz et al. 1999) showed that there is both directional and torque tuning of these neurons as well as connectivity with muscles. The connections of INs with muscles were biased toward flexor muscles unlike the generally even corticomuscular connectivity found for motor cortical neurons that have a functional link with flexors and extensors muscles (Fetz 1992). Later studies revealed that spinal neurons are not only active during motor action but modify their rate when preparing for movement during an instructed delay period (Prut and Fetz 1999). This finding demonstrated that spinal INs are not merely related to motor execution but also receive information (which can be excitatory or inhibitory) during motor preparation. Via ascending pathways, this spinal activation can back-modify cortical activity during the pre-movement delay period when coordinate transformation apparently takes place. Further investigation of spinal activity during a two-dimensional wrist task (Harel et al. 2008) revealed that the tuning properties (such as the width and height of tuning curves) were very similar for both motor cortical and spinal neurons but that the distribution of preferred directions (PDs) tended to be more biased across spinal neurons as compared to the uniform distribution of cortical PDs (Georgopoulos et al. 1986). This result provided a first indication that spinal circuitry process arriving input in order to match it to working muscles. Nonetheless, the response properties of spinal neurons have not been found to be dramatically different from those found for motor cortical cells. Thus a general conclusion that can be drawn from studies of the task-related activity of spinal neurons is that these neurons express a rich spectrum of firing properties that are related to different aspects of the task including both motor and non-motor properties.

Some differences have been reported in the firing properties of spinal and cortical neurons. First, spinal neurons generally exhibit higher firing rates than cortical neurons. However, this enhanced firing is more regular (in terms of the

inter-spike interval) and less correlated among neighboring interneurons than that of cortical neurons. Specifically, the spinal noise correlation was found to be independent of the signal correlation recorded for these cells (Averbeck and Lee 2004). Hence neighboring neurons with similar response properties do not express any tendency for rate co-modulation on a trial-to-trial basis. Thus spinal neurons may “amplify” a cortical command and provide a more rigorous drive to working muscles while at the same time spinal circuitry can eliminate any redundancy in the command which may exist at the motor cortical level (Lee et al. 1998).

Integration of Sensorimotor Information in the Primary Motor Cortex

The next step in understanding the contribution of spinal neurons to coordinate transformation is to characterize the properties of the motor command emitted by the motor cortex. The motor cortex integrates multiple sources of information in various modalities as required for performing some form of sensory-to-motor transformation. Information about higher aspects of motor actions and external targets is relayed to the motor cortex via the premotor areas. Neurons in the primary motor cortex may thus express responses to a large set of environmental cues, as long as they are informative about the action to be made. For example, a general visual cue may produce a very weak response in M1, whereas a similar cue that contains directional information may trigger a robust response in the same cell (Asher et al. 2010). Furthermore, even variables which normally are not expected to be coded for in the motor cortex (such as the color of a cue) may induce a distinguishable response as long as they are relevant to the ensuing movement (Zach et al. 2008). In this respect the motor cortex apparently codes the *motor-relevant* information regardless of its specific modality.

Along with information about the environment and targets, the motor cortex receives somatosensory information from the somatosensory cortex which provides it with details about the state of the

plant. It appears that while visual information can be suppressed at the level of motor cortex based on its relevance to the ensuing action, motor cortical response to somatosensory cues (e.g., unexpected perturbation of the arm) is extensive and robust. This is reasonable since any change in the state of the periphery is important for the motor machinery as regards updating and correcting the planned and/or executed movement. Nonetheless, there is evidence that as soon as a movement has been initiated, some sensory information (i.e., cutaneous information) is attenuated in a way which could potentially serve to enhance the feedforward component of motor control. This implies that at least this component of sensory information is important for planning actions, but not for its online guidance.

In addition to the corticocortical information that is integrated by motor cortical neurons, thalamocortical input relays information from the cerebellum and the basal ganglia. This information appears to be more crucial to action selection and action timing (Hikosaka 1998) and thus may not play a dominant role in coordinate transformation. Hence motor cortical neurons appear to integrate different sources of corticocortical information in a weighted manner which is related to the importance of these sources to motor performance. One operative framework that captures this property of motor cortical activity is the Optimal Feedback Control model which posits that motor cortical activity manipulates and optimizes feedback gains in order to minimize some task-specific cost function (Scott 2004; Todorov and Jordan 2002). However, this theory provides no explicit account of the transformation of coordinates by the system.

The Coordinate Frame of Motor Cortical Information

The end result of motor cortical integration is a motor command to the working muscles. The exact coordinate system within which this motor command is specified is a topic of ongoing debate. The classical view suggested a muscle-based coordinate system (Evarts et al. 1984), whereas

later views posited that cortical neurons operate in an extrinsic-based coordinate frame (Georgopoulos et al. 1986). However, the general consensus today is that motor cortical neurons operate in a system that combines both coordinate systems and thus mostly contains a mixed representation of both target-related and muscle-related information, in a fairly heterogeneous manner across the motor cortex (Kalaska 2009).

Early studies used a behavioral paradigm in which monkeys were trained to perform a center-out wrist task with three different hand postures: pronation, mid-position, and supination (Kakei et al. 2003). The use of a single-joint task that relies on the near-isotropic wrist joint allowed for a systematic exploration of the impact of hand posture on spatial tuning properties of motor cortical neurons (compared to a similar approach that was used in a reaching task; Scott and Kalaska 1997). The authors were able to distinguish between three different coordinate systems: external, muscle-based, and joint-based. They found that the majority of neurons exhibited a small shift in their preferred direction (30° shifts on average when the hand rotated from pronation to supination and the muscle rotated $\sim 75^\circ$). Moreover, recordings in the premotor ventral cortex (PMv) revealed that neurons in this high-level motor cortical site do not change their PD during the task; i.e., their tuning is not affected by hand posture. A study that used the same paradigm in primates during spinal recordings revealed that although the majority of spinal neurons express PD shifts that were similar to muscles, cortical neurons recorded at the same time expressed, on average, a much smaller PD shift. The authors concluded that the transformation from external to internal coordinate frame is completed downstream of M1. More generally, the transformation of the coordinate frame does not take place within a single site; rather, there is a gradual and successive transition of the coordinate system via inter-site interactions.

Theoretical studies have argued that it is impossible to deduce the coordinate frame from PD shifts (Shah et al. 2004) because when shifting postures, neurons modify both their PDs and firing rates (often quantified as a dynamic index

which is the difference in firing range in the two postures over the sum of these ranges). This suggests that in practice it is possible to obtain any type of coordinate system irrespective of the extent of PD shift, since there can be a tradeoff between changes in PD and dynamic indices. Nevertheless, spinal neurons and cortical neurons were shown to exhibit similarly symmetric distribution of dynamic indices but different PD shifts. Thus spinal neurons participate in the process of coordinate transformation by providing the final computational step which includes removing any external-based information (which is non-separable at the cortical level) and thus rotating the PD to fit the exclusively muscle-based frame.

Dynamic Properties of Coordinate Transformation

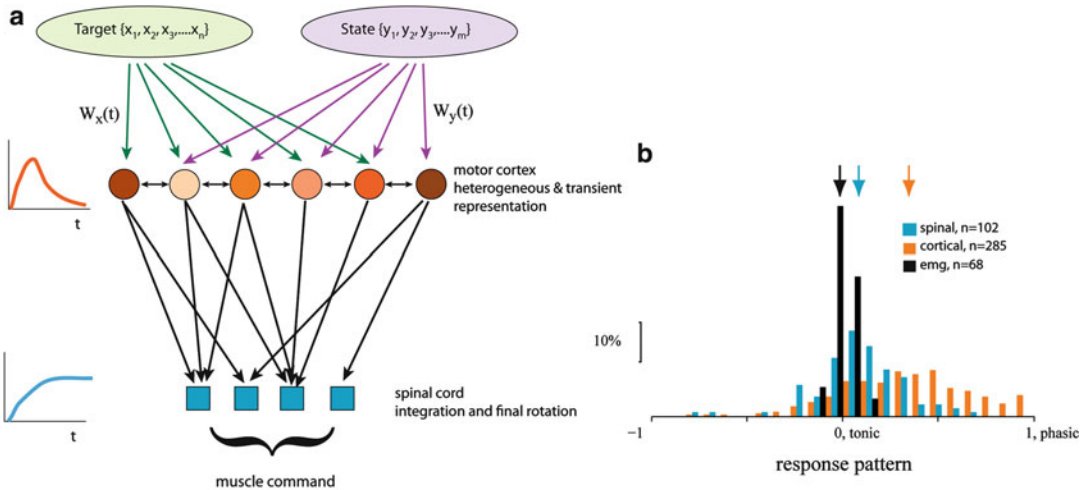
The concept of coordination transformation is often viewed in a “timeless” manner. In other words, the coordinate system of each neuron is considered to be a fixed property that does not change over time. However, this is not necessarily the case. During a behavioral trial the nervous system collects increasingly more information about task-relevant parameters. In addition, the relevance of external cues and the internal state can change along the trial. For example, at cue onset, the spatial information about the cue (which is often given for a short period of time) is critical for correct task performance, whereas the posture of the hand or other muscle-based parameters is less relevant at this stage. By contrast, at the “go” signal, any plan for movement relies on information about posture and muscle states. Indeed it was shown that the coordinate frame of cortical neurons (which unlike spinal neurons have access to information in different modalities) gradually shifts during motor preparation to execution from an external to an internal mode (Harel et al. 2008). This result is similar in spirit but very different in detail from the mental rotation of the population vector reported by Georgopoulos et al. (1989) where the PV shifted from the cued to the actual movement but remained in an externally

based frame of coordinates. Accordingly, integration of different sources of information (e.g., a postural variable and a directional cue) should be modeled using time-dependent weight variables.

Spinal Targets of Descending Pathways

The possibility that the final step in coordinate transformation takes place at the spinal level does not necessarily imply that spinal interneurons are actively or exclusively involved in this processing stage. The termination pattern of corticospinal pathways is rich and extensive in both human and nonhuman primates. These pathways tend to affect interneurons that are located in the intermediate zone, and thus most of the descending cortical command is first processed at this level, though it is possible that some of the command (e.g., a finger-related command) is relayed directly to MNs. The detailed scheme of termination of this pathway could, in itself, provide a processing link for cortical commands. Any organization scheme that respects one descending parameter but ignores another will preserve the information related to the former but not the latter attribute. For example, if all cortical neurons that contain similar PD terminate onto the same spinal target, the PD information will be preserved at the postsynaptic level. However, if the PD distribution of cortical cells that converge upon the same spinal target is uniformly distributed, the directional information will be averaged out. This by no means implies that the spinal target will not be directionally tuned; simply this tuning will not be driven by cortical commands.

Studies stimulating in the motor cortex while recording in the spinal cord uncovered the CS connectivity pattern in awake behaving primates. These studies revealed a very broad CS connectivity pattern with many cortical sites that affect spinal targets. Furthermore, interacting cortical and spinal neurons express aligned directional-torque tuning at movement onset, whereas unconnected sites have inverse tuning directions. This finding further suggests that although information on directional torque is preserved in the CS system, it is organized in a very broad manner; namely, cortical neurons with vaguely



Coordinate Transformations, Role of Spinal Circuitry in, Fig. 1 A Model of the functional organization of the CS system. (a) Motor cortical neurons integrate information about the motor targets ($x_1, \dots, x_n$) and about the peripheral state ($y_1, \dots, y_m$) with time-varying weight constants ($W_x(t)$ and $W_y(t)$), respectively. This integration occurs at random and the resultant response properties of cortical neurons are heterogeneous (depicted as differences in the shading of cortical neurons). Lateral interactions can further modify the response properties and the coordinate frame of the cortical layer. Cortical neurons are characterized by a time-dependent response pattern that appears as a transient signal. Spinal interneurons integrate

similar tuning will tend to affect a single spinal site. In practice this result is consistent with a nonspecific connectivity pattern so that a heterogeneous population of cortical neurons converges upon spinal circuitry (Fig. 1). This differs from the assumption of a unique population of output motor cortical cells that deliver a muscle-based motor command and are specifically connected with premotor spinal targets.

Role of Spinal Interneurons as a “Neural Integrator”

In the process of translating the cortical command into a signal to drive muscles, the spatial coordinate frame as well as the temporal profile of the task-related activity needs to be adjusted. Cortical neurons have often been shown to code time derivatives of motor parameters (e.g., velocity; Schwartz et al. 1988), yet at the pre-muscle

cortical inputs and produce a motor command which is integrated and rotated into a muscle-based command. At this level the response properties are more uniform than at the cortical level. To the left of each layer, a diagram illustrates the mean response profile of cells. (b) Frequencies of different response patterns for cortical neurons (orange), spinal interneurons (blue), and motoneurons (black). Response pattern was quantified using a phasic-tonic index which approached 1 for phasic cells and 0 for tonic cells. Cortical cells had a broader distribution with a significantly higher mean value (a tendency toward phasic firing), whereas spinal interneurons had a narrower distribution with a lower mean value

level, this information needs to be integrated into the required shape of force profile. The alternative that the intrinsic properties of MNs could by themselves integrate a transient motor command for voluntary action seems unlikely given the short time scales available for this operation (Heckman et al. 2009). We found that when sustained torque is required, motor cortical firing is different from spinal firing in two main ways. First, cortical firing is transient, whereas spinal firing is tonic. Second, cortical neuron firing is less informative than spinal neurons about static variables such as hand posture. Similar properties have been reported for the eye movement system where cerebellar receiving neurons fire in relation to eye acceleration, vestibular neurons fire in diverse relations to eye movement parameters, but the abducens MNs fire in relation to eye position (Joshua et al. 2013). In this system it was suggested that a “soft” feedforward hierarchical network can act as an integrator (Joshua et al.

2013; Miri et al. 2011). Similar events may also take place in the corticospinal system where cortical neurons exhibit fairly diverse firing properties and broadly converge upon spinal neurons; here, the needed integration is already present at the spinal interneuronal level.

Modular Organization Versus Coordinate Transformation

A conceptual, data-based model of the functional organization of the motor system suggests that the motor system is characterized by a modular organization principle (Bizzi et al. 2000, 2008). In this scheme, motor actions are constructed by the spatiotemporal superpositioning of basic modules that can be viewed as elementary building blocks of movements (often referred to as motor primitives). Each module provides an activation of a set of muscles (i.e., a muscle synergy). These modules were first extrapolated from work on spinal stimulations of spinalized frogs and appeared to offer an elegant way to mediate coordinate transformations. In this model, a cortical activation signal (presumably expressed in an external frame of coordinates) activates the necessary set of modules which in turn incorporate the descending command into the ongoing motor state. Although considerable data on motor behavior supported the existence of a robust set of motor synergies, their neural substrate remained unclear. More recently, it was shown that electrical activation of the motor cortex in primates produces motor responses which have the characteristics of motor synergies. This result is consistent with earlier studies that showed that prolonged activation of the motor cortex in primates produces a finite repertoire of movements which mimic natural actions (i.e., defensive gestures, self-feeding, etc.; Graziano and Aflalo 2007). Could these results be interpreted as an indication that the motor primitives in fact reside in the motor cortex? In that case, the translation from external to internal coordinate frame appears less intuitive. For example, we would need to assume that motor cortical neurons

that are part of a single module randomly sample the more externally based variable space, since otherwise the resultant motor activation might be biased. More data are needed to understand in what way the modularly organized system deals with coordinate transformation.

Implications for BMI

In recent years many studies have demonstrated that useful signals can be extracted from motor cortical activity to drive prosthetic devices (Hatsopoulos and Donoghue 2009; Schwartz 2007). These devices range from an on-screen cursor to a humanoid robotic limb with multiple degrees of freedom. The most common approach employed in these studies is to assume a fixed coordinate frame (either extrinsic or intrinsic) of these signals. However, findings have shown that the activity of cortical neurons is affected by the operative context. For example, hand posture induces a consistent bias of PDs across motor cortical neurons, which thus cannot be eliminated by population averaging. Furthermore, trial time systematically affects the PDs of cortical neurons. Finally, it is conceivable that the behavioral context may entail other parameters such as mental states which are difficult to control for but may nevertheless affect the PD of cortical neurons in a consistent manner that cannot be eliminated by averaging. In this respect using motor cortical activity as part of a long-term control signal should be consistently updated with an adaptive algorithm that reweighs the activity of different cells to prevent a gradual deviation between the intended and the reconstructed actions.

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Cortical Motor Prosthesis](#)
- [Decision-Making, Motor Planning](#)
- [General Overview of Spinal Anatomy and Physiology Organization](#)

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Coordination Dynamics

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Synonyms

[Haken-Kelso-Bunz model](#)

Definition

Voluntary movements are typically coordinated in the sense that their components form ordered patterns. This includes the coordination of different spatial components of a movement, the coordination of different limbs, and also the coordination of movement with perceived events. More formally, coordination is characterized by stable relative timing of the movement components. Coordination dynamics is a theoretical approach to understanding how coordination arises which postulates that neural oscillators control the timing of each component. The coupling among such neural oscillators leads to stable relative timing. Mathematical models of coordination dynamics have been formulated at the level of the neural oscillators and their coupling, but also at the level of relative phase itself as a macroscopic, phenomenological variable. The observation of instabilities in relative timing has provided support to the notion of coordination dynamics.

Detailed Description

Coordination

That the different limbs are coordinated during locomotion seems obvious, although the phenomenon of relative coordination, in which one limb makes an extra cycle every now and then, shows that coordination requires a quantitative approach (Holst 1973). Rhythmic movements like dancing and making music, but also movements like chewing and speaking that are approximately

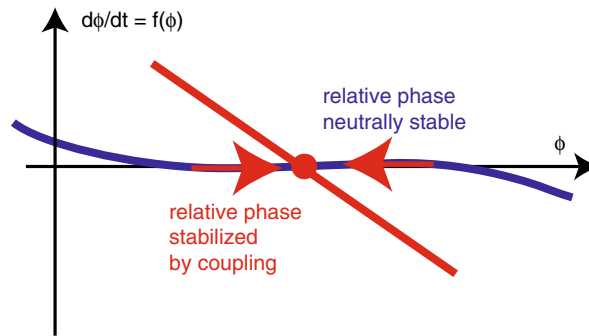
rhythmic, are coordinated in the sense that the relative timing of movement components remains invariant in time and, within limits, across changes of movement parameters such as speed and amplitude (Schöner 2002). Direct evidence for stable relative timing is obtained when a coordination pattern recovers from a perturbation, the lagging component catching up and the leading component falling back to reinstate the pre-perturbation pattern (Schöner and Kelso 1988). Discrete motor acts are also coordinated in the sense that their durations are aligned when the movements are performed concurrently, but not when they are performed separately (Kelso et al. 1979). The coordination of movements with external events, for example, intercepting a moving object may show the same characteristics of relative timing (Warren 2006).

To assess the convergence of coordination patterns that defines their stability, a distance measure among patterns of coordination is needed. The relative phase is such a measure. It is defined as the temporal offset of matching events in two timed movements, measured in percent of the movement time (Schöner 2002).

Neural Oscillators

A key theoretical idea for understanding coordination is that the timing of voluntary motor acts is generated from neural oscillators, whose stable limit cycles drive the effector systems (Schöner 2002). This idea is not limited to rhythmic movement. For discrete motor acts, the limit cycle may be instantiated via a bifurcation at the beginning of the movement and terminated by another bifurcation at the end of a single cycle (Schöner 1990). Perceived events may drive these bifurcations, accounting for the timing of discrete motor acts relative to the environment (Schöner 1994).

Coordination is brought about by coupling multiple such oscillators. Coupling generically induces phase locking (see entry on ► [“Multi-stability of Coupled Neuronal Oscillators”](#)). This can be visualized by looking at the rate of change of relative phase as a function of relative phase (Fig. 1). Limit cycle oscillators always have one



Coordination Dynamics, Fig. 1 The rate of change of relative phase, $d\phi/dt$, plotted against relative phase, ϕ , has a set of marginally stable fixed points when the underlying oscillators are weakly coupled (*blue solid line*) that coalesces into a single-stable fixed point for sufficiently strong coupling (*red solid line*). The *red arrows* illustrate how the

negative slope of the relative phase dynamics leads to convergence to the fixed point which accounts for recovery from perturbations and resistance to noise. The loss of stability for weak coupling leads to predictions of increased variance and relaxation time (Schöner et al. 1986)

Lyapunov exponent that is zero, which reflects that there is no resistance to perturbations that shift the oscillator along the limit cycle. In uncoupled oscillators, the dynamics of the relative phase has a line of fixed points that are marginally stable. Coupling most strongly affects the direction in phase space, in which the vector field is zero, leading generically to a stable fixed-point attractor for relative phase that represents a stable pattern of coordination.

determines the stability of the coordination pattern may be the spatial arrangement of movement components, not necessarily the anatomical nature of the components (Mechsner et al. 2001). If this were true, then perhaps cortical oscillators that control movement in space, rather than spinal oscillators directly linked to the effectors, would be the basis for coordination.

Link to Experiment

The dynamics of relative phase has been used as a direct phenomenological model of the dynamics of coordination (Schöner et al. 1986). In particular, experimental evidence for loss of stability, observed through enhanced fluctuations and slowed relaxation after perturbations, has highlighted that stability is a necessary concept for an understanding of coordination. Loss of stability is typically observed for antiphase patterns of coordination (homologous limbs alternate) when movements become faster (Schöner and Kelso 1988).

The coupled neural oscillators themselves have also been used as a level of description of coordination patterns (Haken et al. 1985; Grossberg et al. 1997) to account for the role of movement amplitude. Behavioral data suggest that what

Cross-References

- [Bifurcations, Neural Population Models and](#)
- [Embodied Cognition, Dynamic Field Theory of](#)
- [Multistability of Coupled Neuronal Oscillators](#)

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Correlation Analysis of Parallel Spike Trains

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Synonyms

Cross-correlogram; Conditional rate function;
Linear system kernel

Definition

Cross-correlation is a measure of the similarity of two signals as a function of the time lag or lead applied to one of the signals. In case the two signals are simultaneously recorded spike trains, the cross-correlation becomes a count of the number of coincidences of firing for the two spike trains as a function of the time delay between them. If one considers one spike train as the

input to a system and the other spike train as the output, then the cross-correlation function between the input and output spike trains normalized on the input autocorrelation function is equal to the impulse response of the linear part of the system. Cross-correlation can also, and in the nervous system more generally, result from common input to the two spike trains, i.e., from providing a sensory stimulus or from rhythmic or other spontaneous activity in the brain.

Detailed Description

I will use the definition of cross-correlation as standard in the field of linear systems analysis as applied to the interaction between two neurons (Marmarelis and Marmarelis 1978). I will (except when noted) assume stationarity of the spike trains. The cross-correlation function reflects the similarity of two spike trains $x(t)$ and $y(t)$, or in sampled form $x(n)$ and $y(n)$, as a function of the delay between them, expressed as a time delay τ or as the number of bins k . T is the duration of the spike trains, and N is the number of bins in the spike train. Note that the time delay can be positive and negative.

$$\begin{aligned}
 R_{xy}(\tau) &= \frac{1}{T} \int_0^T (x(t)y(t+\tau)) \\
 &\times dt \text{ or in sampled form : } R_{xy}(k) \quad (1) \\
 &= \frac{1}{N} \sum_{n=1}^N x(n)y(n+k)
 \end{aligned}$$

The cross-covariance function is obtained by subtracting the means μ_x and μ_y from the two signals (I omit the sampled form here):

$$\begin{aligned}
 C_{xy}(\tau) &= \frac{1}{T} \int_0^T ((x(t) - \mu_x) \\
 &\times (y(t+\tau) - \mu_y)) dt. \quad (2)
 \end{aligned}$$

The cross-correlation coefficient function is obtained by dividing the cross-covariance function

by the time-average variances, σ_x^2 and σ_y^2 , of the two spike trains (again the sampled form is omitted):

$$\rho_{xy}(\tau) = \frac{1}{T} \int_0^T ((x(t) - \mu_x)(y(t + \tau) - \mu_y) \times dt) / \sqrt{\sigma_x^2 \sigma_y^2}. \quad (3)$$

The expressions in the above equations are defined empirical estimates of the underlying statistics. Any deviation from a value of ± 1 for the

correlation coefficient is due to (1) nonlinearity of the system, (2) the presence of noise in the spike generation of the system, and (3) the presence of other spike train inputs to the system that contribute to the output spike train $y(t)$ but are not accounted for by the observed input spike train $x(t)$.

Representation of the Cross-Correlogram in Terms of Coincidences

In case of Poisson spike trains, the cross-correlation coefficient becomes (Eggermont 1992).

$$\rho_{xy}(\tau) = \left[R_{xy}(\tau) - \frac{N_x N_y}{N} \right] / \sqrt{\left(N_x - \frac{N_x^2}{N} \right) \left(N_y - \frac{N_y^2}{N} \right)}. \quad (4)$$

Here, N_x and N_y are the number of spikes in spike trains $x(t)$ and $y(t)$, respectively, and N is the number of bins in the total spike train duration. $\frac{N_x N_y}{N}$ is the expected number of coincidences in case of independence. For small numbers of spikes compared to the number of bins (N) in the record, i.e., low firing rates, this can be approximated by

$$\rho_{xy}(\tau) = \left[R_{xy}(\tau) - \frac{N_x N_y}{N} \right] / \sqrt{N_x N_y}. \quad (5)$$

For statistical purposes this can also be converted (holds for all firing rates) to a z-score, i.e., the number of standard deviations above the mean-corrected R , which is equal to zero:

$$z_{xy}(\tau) = \left[R_{xy}(\tau) - \frac{N_x N_y}{N} \right] / \sqrt{\frac{N_x N_y}{N}}. \quad (6)$$

Statistical significance should be set conservatively, e.g., at $z \geq 4$.

The standard normal distribution that is the basis for the interpretation of z , as the number of standard deviations between a value x and the mean μ of the distribution, is based on the z-score $z = (x - \mu) / \sigma$. For neural cross-correlograms, we generally do not have normal distributions, but we

assume that the bin filling with coincidences follows a Poisson process (the bin size should be so small that the probability of >1 coincidence is vanishingly small). For a Poisson process the standard deviation is the square root of the mean, leading to the standard deviation of the number of coincidences $\sigma_{xy} = \sqrt{\frac{N_x N_y}{N}}$.

If one wants to assess significance based on the cross-correlation coefficient, the standard deviation thereof is equal to $SD(\rho_{xy}) = \sqrt{\frac{1}{N} \left(1 - \frac{N_x N_y}{N^2} \right)}$.

For large numbers of bins in the record and relatively low firing rates, this can be approximated as $SD(\rho_{xy}) = \sqrt{\frac{1}{N}}$. So for a 900 s record length and 2 ms bin width, Δ , the $SD = 0.0015$. So taking 4 SD would make ρ_{xy} values above 0.006 significant, but one can wonder whether values close to 0.006 are relevant. For larger numbers of spikes, the SD decreases compared to this estimate.

Representations of the Cross-Correlogram in Terms of Firing Rate

The cross-correlogram is sometimes defined as a first-order conditional rate function $R_{y|x}(\tau) = R_{xy}(\tau) / \mu_x$ (where μ_x is the mean firing rate for spike

train x) that measures, for one cell y and close to any particular time t , the average instantaneous rate or the likelihood of generating a spike, conditional on an x spike τ time units away (Brillinger et al. 1976). If the trains are independent, then $R_{y|x}(\tau) = \mu_y$, where μ_y is the mean firing rate for spike train y , for all τ . If y spikes are independent of “later” x spikes (causality), then $R_{y|x}(\tau) = \mu_y$ for all $\tau < 0$. This “causality” may apparently be violated if both x and y spikes are caused with some jitter by a third, unobserved, input. Deviation of $R_{y|x}(\tau)$ from μ_y is suggestive of dependency of the y -train on what happened in the x -train τ time units earlier. For all natural spike trains, $R_{y|x}(\tau)$ will be flat and essentially equal to μ_y at large $|\tau|$ values because inevitably (with the exception for oscillatory correlograms) any influence of x on y will have vanished. Assuming a Poisson distribution, one can graph $\sqrt{R_{y|x}(\tau)}$. The variance of $\sqrt{R_{y|x}(\tau)}$ is approximately constant for all τ at a level of $(4\Delta T\mu_x)^{-1}$, so SD lines can be drawn at $\pm (4\Delta T\mu_x)^{-2}$ and become smaller in proportion to $\sqrt{T}$. This provides a good approximation if Δ is not too large and the correlation width of the process is not too large (Voigt and Young 1990).

Time-Dependent Cross-Correlation Functions

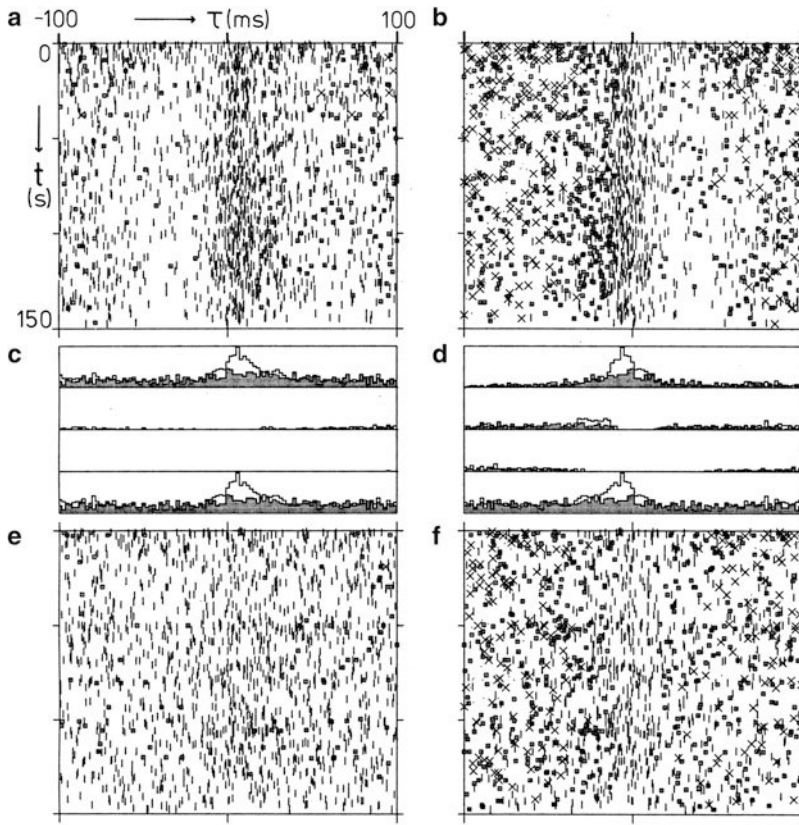
Visual inspection of the time-dependent cross-correlation function, $R_{xy}(t, \tau)$, with t as the running time in the spike trains and τ as the lag-lead time between spikes in trains x and y , shown here in an example (Fig. 1), is often the best first step in judging stationarity. $R_{xy}(t, \tau)$ without any averaging (panels a and b) represents the recurrence times (Van Stokkum et al. 1986) between the two spike trains $x(t)$ and $y(t)$ as a function of τ . Panels c and d represent the time-averaged $R_{xy}(\tau)$. The example reflects simultaneous recordings from two neurons in the auditory midbrain of the European grass frog in response to species-specific vocalizations. The left-hand and right-hand columns refer to the same data, but on the left-hand side, the correlation shown is $R_{xy}(t, \tau)$, whereas the right-hand side shows $R_{yx}(t, \tau)$, i.e., the reference unit has changed.

Vertically, the time over the first 150 s since stimulus onset, t , is shown and horizontally the lag-lead times, τ , between the x and y spikes. Different symbols indicate different order recurrence times. One observes that with the exception of the first 10 s or so, the occurrence of the recurrence times is stationary. The most important events that determine the various order cross-correlograms here (shown in part c, d) are the first-order recurrences, i.e., there are hardly any bursts (indicated by ■ and × symbols) in the y -train (a) but quite a few in the x -train (b), which had the higher firing rate. For calculation of the correlograms, we assume periodic stationarity: this means that for each stimulus presentation at intervals of P sec, the response of the neurons is statistically the same, albeit it is non-stationary in firing rate. By using ensemble averaging, i.e., in Eqs. (1, 2, and 3, the time variable is now t modulo P , and stimulus-dependent cross-correlations can be obtained.

The top correlogram is that based on only first-order recurrence times, the second one on second-order recurrence times, and the third one on third-order recurrence times; the fourth shows the all-order cross-correlogram as commonly used. All correlograms are on the same scale. The shaded correlograms are the shift predictors (see next section), calculated from the time-dependent shift correlograms shown in the bottom row that show only modest stimulus locking to the stimulus. The shape of the cross-correlogram suggests common input as the main source of correlated spike times (see later in this entry).

Pair Correlation Under Stimulus Conditions

A peak in the cross-correlogram can be the result of a neural interaction between units (“noise correlation”) but also the result of a coupling of the firings of the neurons to a stimulus (“signal correlation”) (Gawne and Richmond 1993). As we will see, the interpretation of the cross-correlogram will require both the autocorrelograms of the two units and an estimate of the correlation due to stimulus coupling. Following our earlier approach (Eggermont et al. 1983), we consider two spike



Correlation Analysis of Parallel Spike Trains,

Fig. 1 Time-dependent cross-correlation diagrams of spike trains. The different symbols used indicate the order of the spikes following the reference spike: “I” indicates the first-order recurrence time (defined in Van Stokkum et al. 1986), i.e., the first spike in the y-train following or preceding a spike in the x-train (for the left-hand column); “■” indicates the second-order recurrence time, i.e., the second spike in the y-train following or preceding a spike in the x-train; and finally “x” indicates the third-order recurrence time. (a) Simultaneous time-dependent cross-correlation diagram (no averaging involved), spikes from unit x (2,188 events) are used as triggers; (b) as (a) but now with spikes from unit y (528 events) as triggers; (c) simultaneous and

nonsimultaneous (shaded) recurrence time histograms of orders 1, 2, and 3 and cross-correlation histogram derived from (a) and (e), respectively; (d) as (c) but now derived from (b) and (f); (e) nonsimultaneous time-dependent cross-correlation diagram (defined as the correlation between the 1 s duration spike train x to stimulus presentation at t and spike train y to the next stimulus presentation at time t + 1 s), spikes from unit x are used as triggers; (f) as (e), but now with spikes from unit y as triggers. (With kind permission from Springer Science + Business Media: Biological Cybernetics, Representation of Time-Dependent Correlation and Recurrence Time Functions, volume 55, 1986, page 17–24, I. H. M. van Stokkum, P. I. M. Johannesma, and J. J. Eggermont, Fig. 6)

trains $x(t)$ and $y(t)$ of duration T and represented as a sequence of δ -functions:

$$\begin{aligned} x(t) &= \sum_{i=1}^N \delta(t - t_i) \text{ and } y(t) \\ &= \sum_{j=1}^M \delta(t - t_j). \end{aligned} \quad (7)$$

where t_i and t_j are the spike times. The cross-correlation function is given by

$$R_{xy}(\tau) = \frac{1}{T} \sum_{i=1}^N \sum_{j=1}^M \delta[\tau - (t_i - t_j)]. \quad (8)$$

For a bin width Δ and expectation $E = \mu_x \mu_y$ of $R_{xy}(\tau)$ under independence of firing of the

two spike trains, a cross-covariance histogram is defined:

$$C_{xy}(\tau, \Delta) = \frac{1}{\Delta} \int_{\tau-\Delta/2}^{\tau+\Delta/2} (R_{xy}(\sigma) - E) d\sigma. \quad (9)$$

If one presents the stimulus twice, then the resulting spike trains are $x_1(t)$ and $y_1(t)$ for the first stimulus presentation, respectively, and $x_2(t)$ and $y_2(t)$ for the second one. Presenting the stimulus twice allows us to estimate the correlation between the firing of the two spike trains based on their time locking to the stimulus. In the text I assume a long stimulus consisting of various elements. The predictor for that is to correlate spike train x for stimulus presentation 1 with spike train y for stimulus presentation 2, under the assumption that memory effects have long subsided between the two stimulus presentations. This result is called the shift predictor. For those four spike trains, one can compute ten covariance histograms (or correlograms) as shown in Table 1.

On the main diagonal two estimates, each of the units' autocovariance histograms is found. Under long-term stationary firing conditions, $C_{x_1x_1} = C_{x_2x_2}$, and one commonly uses $C_{xx} = (C_{x_1x_1} + C_{x_2x_2})/2$ as an estimator of the autocovariance function for spike train $x(t)$. For the off-diagonal elements, it is noted that, e.g., $C_{x_1y_1}(\tau) = C_{y_1x_1}(-\tau)$, therefore the table is symmetric provided that the sign of τ is adjusted. We define $C_{x_1y_1}(\tau)$ and $C_{x_2y_2}(\tau)$ as simultaneous cross-covariance histograms, and again we may use their average as an estimate for the cross-covariance function. Following our previously introduced terminology (Eggermont et al. 1983; Epping and Eggermont 1987), cross-correlations obtained under stimulus conditions will be called neural synchrony; they will be a mix of signal and

noise correlations (e.g., Gawne and Richmond 1993). Cross-correlations obtained under spontaneous firing conditions or after appropriate correction for correlation resulting from stimulus locking will be called neural correlation; they exclusively are noise correlations. During stimulation, the "total" neural synchrony consists of a component due to stimulus synchrony and one that is a result of neural connectivity, the neural correlation.

The nonsimultaneous cross-covariance histograms between spike trains $x_1(t)$ and $y_2(t)$, respectively, and $x_2(t)$ and $y_1(t)$ represent correlation between spike trains $x(t)$ and $y(t)$ as a result of stimulus coupling. These stimulus-induced correlations are known as the shift predictors. Another nonsimultaneous cross-covariance histogram is obtained by taking both spike trains for the same unit to obtain $C_{x_1x_2}$ and $C_{y_1y_2}$. These histograms represent the amount of coupling of the units to the stimulus individually and have been called "existence functions" (Aertsen et al. 1979) because any significant peak around $\tau = 0$ indicates a stimulus coupling effect and hence the existence of a stimulus-response relation. This shuffled autocorrelogram technique was rediscovered by Joris et al. (2006).

There is no model-free approach for the separation of correlations produced by direct neural interaction and those caused by stimulus coupling. Under the assumption that the effects of an external stimulus and the effects of neural connectivity to the neural synchrony are additive, Perkel et al. (1967) proposed a correction for the effects of the stimulus. Two formally identical stimulus predictors were suggested, one resulting from a cross-correlation of the two single-unit poststimulus time histograms (PSTHs), which can be used when the stimulus is periodic. One constructs the PSTHs, i.e., the cross-correlograms between stimulus onsets and spikes, $R_{Sx}(\sigma)$ and $R_{Sy}(\sigma)$, and calculates their correlation integral modulo stimulus period P (here σ is the poststimulus time):

$$R_{Scorr}(\tau) = \int_0^T R_{Sx}(\sigma) R_{Sy}(\sigma + \tau) d\sigma. \quad (10)$$

One can also calculate the cross-correlogram between one spike train and a shifted (by 1 stimulus period) version of the second spike train. This latter procedure, resulting in the shift predictor,

Correlation Analysis of Parallel Spike Trains, Table 1 Overview of possible covariance histograms for a double-unit recording with two presentations of the stimulus ensemble

	$x_1(t)$	$y_1(t)$	$x_2(t)$	$y_2(t)$
$x_1(t)$	$C_{x_1x_1}$	$C_{x_1y_1}$	$C_{x_1x_2}$	$C_{x_1y_2}$
$y_1(t)$		$C_{y_1y_1}$	$C_{x_2y_1}$	$C_{y_1y_2}$
$x_2(t)$			$C_{x_2x_2}$	$C_{x_2y_2}$
$y_2(t)$				$C_{y_2y_2}$

has been the most popular and has the advantage that it can be applied to very long stimuli (such as a set of animal vocalizations) that allow only one or a few repetitions; in such a case, calculating the PSTH would be useless. The shift predictor was assumed to represent the amount of correlation that could be attributed to the locking of the neuron's firings to the stimulus. Subtracting the shift predictor from the neural synchrony then would result in the neural correlation.

The assumption of additivity of stimulus-induced correlation and neural correlation may well be the weakest link in the chain of reasoning that leads to an interpretation of stimulus-dependent neural correlations. A strong warning against the use of the shift predictor in estimates of the neural interaction strength came from studies using realistic model neurons (Melssen and Epping 1987). Because stimulus effects and neural connectivity effects on the neural synchrony are generally nonadditive, it was concluded that the use of the shift predictor to separate stimulus and neural effects was of limited value. Yang and Shamma (1990) underlined these objections to the use of correlation methods in identifying neural connectivity and arrived at conclusions similar to those of Melssen and Epping (1987) using simulations with similar model neurons. In case of strong stimulus locking, even all synchrony can be due to stimulus correlation (Eggermont 1994). Under "adequate" stimulus conditions that evoke strongly stimulus-driven and reproducible spike trains, especially for auditory stimuli, the neural synchrony becomes identical to the expected correlation based on the shift predictor, and consequently no inference can be made about possible underlying connectivity (changes). One may avoid this overcorrection effect due to stimulus locking by applying suboptimal stimulation. Thus, a sufficient amount of "neural noise" in the record is required to allow conclusions about changes in functional neural connectivity. Thus, when stimulus-dependent neural correlations are obtained, there are a number of possibilities: the interneuronal coupling itself changes due to application of a stimulus (facilitation, depression, short-term learning), the finding is an artifact due to the selection of the wrong model, or the finding can be explained on the

basis of a pool of neurons affecting the firing behavior of the pair under study in a stimulus-dependent way.

It must be remarked that the additive model (Perkel et al. 1967) is the only one routinely used in stimulus-correction procedures (e.g., Voigt and Young 1990; Eggermont 1994). However, Srinivasan and Bernard (1976) have shown that coincidence-detecting neurons can fire at a rate proportional to the product of the rates of two input neurons, provided that their spike trains are statistically independent. The criteria determining whether the action is additive or multiplicative are the size of the excitatory postsynaptic potential (EPSP) relative to threshold and the time constant of decay for the EPSP. Specifically, EPSP values smaller than the threshold of firing and with a duration less than the average interspike interval of the individual spike trains cause the action to be multiplicative. Larger EPSP values or those with longer duration make the action additive. An alternative formulation from which this effect can be understood is that we consider a spike generator with probability of firing, g , which depends sigmoidally on the EPSP value u (Eggermont et al. 1983).

$$g(z|u) = \exp .\beta u / (1 + \exp .\beta u) \quad (11)$$

Here u is simply considered to be the linear summation of contributions u_i caused by incoming spikes z_i possibly originating from different projecting neurons. Actually $g(z|u)$ describes the well-known S-shaped curve. For relatively small u values, i.e., in the purely exponential region of the curve and temporal overlap of u_1 and u_2 , we have:

$$\begin{aligned} g(z|u_1, u_2) &= \exp .\beta(u_1 + u_2) \times / (1 + \exp .\beta(u_1 + u_2)) \\ &\approx \exp bu_1 \cdot \exp bu_2 \approx g(z|u_1) \times \cdot g(z|u_2) \end{aligned} \quad (12)$$

If the u values are large enough to be in the linear, intermediate, part of the S-curve, then after expansion of the exponential and long division:

$$g(z|u) \approx \frac{1}{2} + 1/4bu \quad (13)$$

and in case u_1 and u_2 are nonoverlapping (low spike rates), averaging over time gives.

$$g(z|u_1, u_2) \approx g(z|u_1) + g(z|u_2). \quad (14)$$

Thus, simply on basis of the size u and duration of the EPSP, the firing probability of the output neuron can be multiplicative (Eq. 13) or additive (Eq. 14) with respect to the input spike trains. In fact $u = u(t)$ and additional conditions regarding the decay time constant may enter the description.

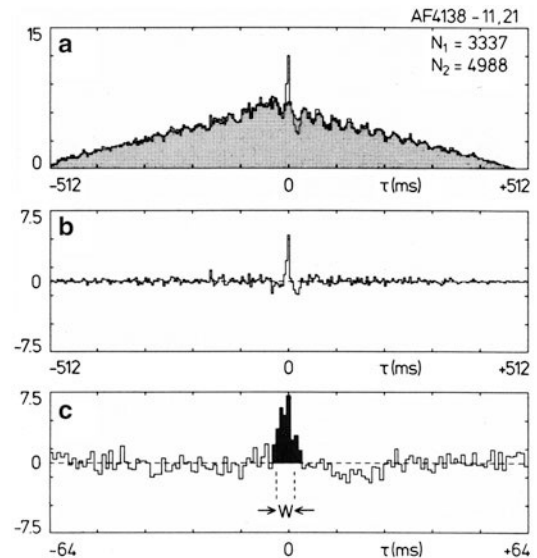
Let us now consider that a multiplicative effect of the stimulus on spike train activity is present, e.g., by two input spike trains both depending on the stimulus and fulfilling the conditions for the EPSP but only one of these input trains is observed together with the output train. In such a case, the degree of multiplicative action is strongly dependent on the type of stimulus. Stimuli such as continuous noise that cause the input spike trains to have a relatively large time jitter, i.e., have a broad existence function, $C_{ii}(z)$, (Aertsen et al. 1979), produce results that better fit a multiplicative model than stimuli that tend to lock the spikes to a considerable degree (e.g., tone pips) as suggested by the Srinivasan and Bernard (1976) model results. Thus, also multiplicative interaction effects may be stimulus dependent. In case they are not, the application of a correction procedure based on an additive model, however, erroneously will indicate a stimulus dependence of the neural correlation (Eggermont 1994). Eggermont (2006) introduced a method to correct for these multiplicative effects, which are substantial when cortical network oscillations are present and will be discussed later on in this entry.

Practical Estimation of Stimulus Correlation

During spontaneous activity, one estimates the expected value of the cross-correlogram under the assumption of independence and subtracts this in order to obtain the neural correlation. During stimulation, the effect of a common input to both spike trains as a result of a correlation of the neuronal firing to the stimulus has to be taken into account if one wants an estimate of the true neural

correlation. If the stimulus is periodic, one can, for instance, use the shift predictor obtained by calculating the cross-correlation between spike trains $x(t)$ and $y(t + P)$, i.e., between the original x -train and the y -train shifted over one stimulus period. This method is the only one that can be used if a long stimulus sequence, e.g., a sequence of vocalizations or other natural sounds, is only repeated once, as discussed above.

As an example of this latter stimulus-correction procedure, we show recordings from the auditory midbrain to 500 ms long 30 Hz amplitude-modulated noise-burst stimulation repeated every 3 s (Fig. 2). The shift predictor is shaded and shows the 30 Hz modulation in the firing rate that obviously is stimulus locked. The triangular shape of



Correlation Analysis of Parallel Spike Trains, Fig. 2 (a) Simultaneous and nonsimultaneous (i.e., the shift predictor; shaded) cross-correlation histograms for two units recorded from the auditory midbrain in the grass frog under amplitude-modulated noise-burst stimulation of 500 ms duration. The triangular shift predictor results from the approximately rectangular stimulus envelope. A 30 Hz stimulus-locked oscillation is visible as well. (b) and (c) difference histogram shown on different time scales; W is the width of the peak at half amplitude. Bin width was 4 ms in (a) and (b) and 1 ms in (c). The number of spikes for each unit is indicated in the top right of panel A. (From Epping and Eggermont 1987)

the predictor is the result of the approximately rectangular envelope for the 500 ms long noise burst. The neural correlation consists of a narrow zero-lag centered peak approximately 5 ms in width (W) at half peak amplitude.

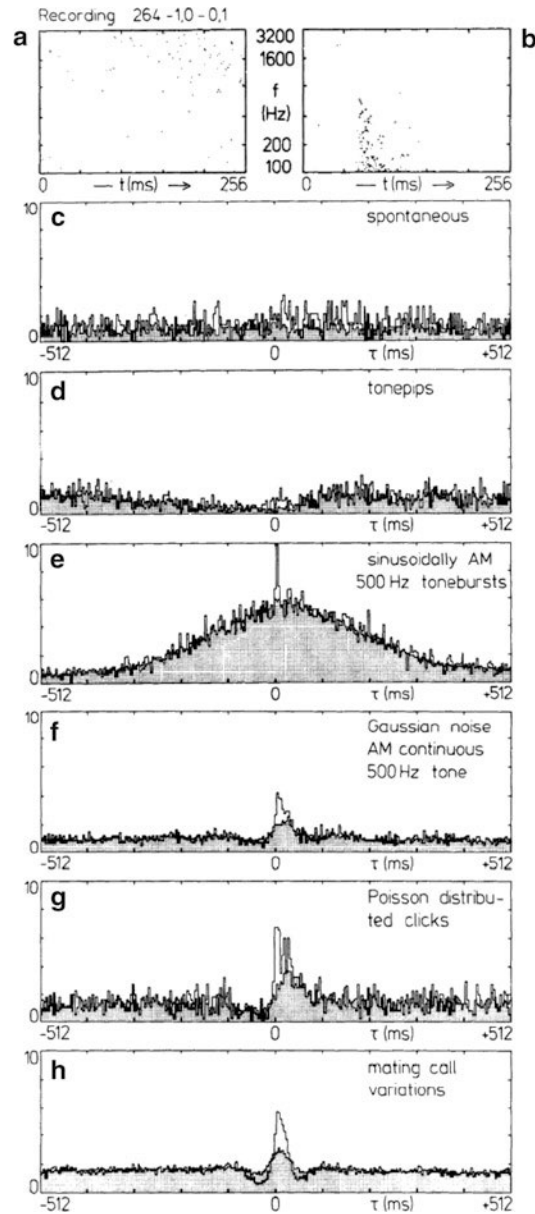
Rate Correlation and Event Correlation

Cross-correlograms frequently show a narrow peak on a broader pedestal (e.g., Fig. 2a) especially when units are recorded on the same electrode (Eggermont 1992; Nowak et al. 1995). The broader pedestal is typically the result of covariance in firing rate between the two spike trains, e.g., caused by the stimulus, whereas the sharp peak indicates event synchrony, i.e., firing coincidences (Neven and Aertsen 1992). The rate covariance under spontaneous conditions can easily be estimated by calculating a cross-correlogram for 50 ms bins that slide in 10 ms steps (Eggermont and Smith 1995). Subtracting the rate covariance from the overall correlogram will result in the event correlation.

This generally assumed model, even if correct, may still result in an inaccurate estimation of the true event correlation. Staude et al. (2008) decomposed the raw cross-correlation as the sum of the modulation rate covariance and spike coordination based on the mean conditional covariance of the processes given the rates. Both, rate covariation and spike coordination alike, contribute to the raw correlation function by triangular peaks. This separation does not always have to result in a broad triangular peak for rate correlation and a narrow one for spike correlation; at least in their procedure, the reverse can be possible as well. Staude et al. (2008) stated “without prior knowledge of the underlying model class, rate estimation will most likely be suboptimal. The resulting predictor leaves a residual central peak in the corrected correlation function, which is likely to be wrongly interpreted as spike coordination.”

Stimulus-Dependent Neural Correlation

An example, exhibiting stimulus-dependent correlation, is provided in Fig. 3. As discussed above,



Correlation Analysis of Parallel Spike Trains, Fig. 3 Unit pair with stimulus-dependent neural correlation. (a) and (b) dot displays of single-unit activity to tone pips with carrier frequencies in the range 100–3200 Hz. The stimulus inhibits the unit shown in (a), whereas it activates the unit shown in (a). (c–f) simultaneous and nonsimultaneous (shift predictor; shaded) cross-correlation histograms for a variety of stimuli. Bin width is 4 ms. (From Epping and Eggermont 1987)

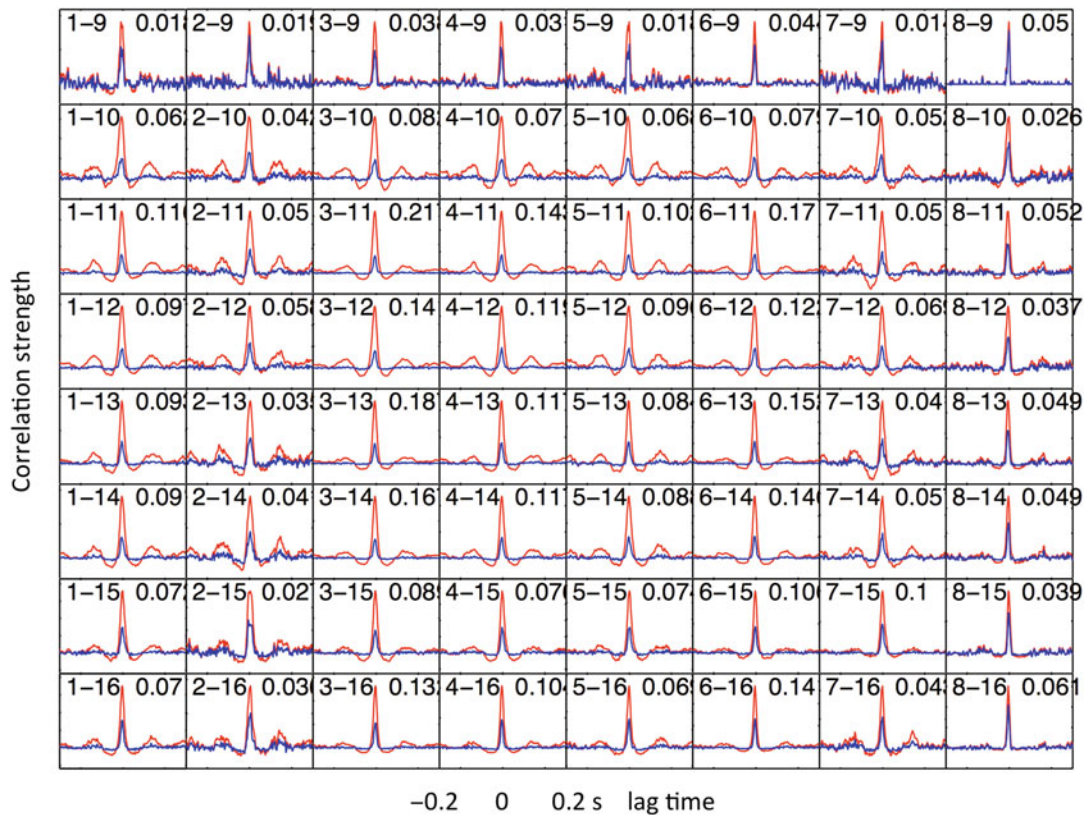
this may potentially result from using the invalid assumption of “neural synchrony equals the sum of stimulus correlation and neural correlation.” The two spontaneously active units shown were recorded in the auditory midbrain of the grass frog on electrodes with an estimated tip separation of 130 μm . The spontaneous rates were 0.34 (A) and 2.5 (B) spikes/s, respectively. Their spectro-temporal sensitivities, represented as dot displays of neural activity, as determined with tone pips presented once per second, are shown in Fig. 3a, b. The spontaneous activity of unit a was suppressed by frequencies below 1000 Hz (Fig. 3a), and the very low spontaneous activity did not result in many spikes in the 256 ms time window, whereas unit b was activated in this frequency range with a latency of 67 ms (Fig. 3b). Neural synchrony histograms and shift predictors (shaded) of spontaneous and stimulus-evoked activity are shown in Fig. 3c–f. For spontaneous firing, the neural synchrony and shift predictor are flat and hardly different (Fig. 3c). For tone-pip stimulation, the shift predictor (Fig. 3d) shows a decrement due to the antagonistic (suppression vs. activation) stimulus influence on the two units. Just visible on top of the shift predictor is a small, rather symmetric peak around the origin, likely indicating shared neural input. The shift predictor to sinusoidally amplitude-modulated (AM) 200 ms tone bursts is broad (Fig. 3e) with a sharp ($W = 6$ ms) peak of the neural synchrony visible on top. Figure 3f shows results for a low-pass noise-modulated tone. One observes an asymmetrical peak with flanking valleys due to the autocorrelation structure of the individual spike trains. The two units responded antagonistically to the tone-pip stimulus, but more alike to the other stimulus ensembles; e.g., when stimulated with sinusoidally AM tone bursts (Fig. 3e) with a carrier frequency of 500 Hz, the units both were excited by a band-limited range of AM rates around 100 Hz. This suggests that the unit pair exhibits stimulus dependencies of both stimulus-induced cross-correlations as revealed by the shift predictor as well as neurally mediated cross-correlations because of changes in form and width of peaks in the neural synchrony as compared with the shift predictor.

Correcting for Common Input Firing Periodicities and Firing Rates

According to de la Rocha et al. (2007), the stimulus-corrected cross-correlation coefficient for common input still depends on the geometric mean of the firing rates of the two neurons, both in cortical slice recordings and in their simulated data. This effect was also visible for *in vivo* recordings from visual cortex (Krüger 1991), and it was used to argue that nearly all of the cortical cell correlations resulted from common retinal input. This suggests that additivity-corrected procedures are inadequate and that multiplicative interactions of stimulus and spontaneous firing activity occur. This can be corrected for by a deconvolution procedure as described below.

The example shown (Fig. 4) was based on spontaneous multielectrode recordings from primary auditory cortex in an anesthetized cat where the EEG showed spindle waves in the frequency range of 8–10 Hz. In anesthetized animals (sleep), spindle oscillations are frequently observed. The oscillations likely reflect common input as the correlograms typically appear symmetric around zero lag, so their effect should disappear in the corrected correlogram using a deconvolution procedure. These periodic oscillations are reflected in the firing times of the spike trains and in the oscillatory character of the cross-correlogram (red curves). This effect was corrected by deconvolving the cross-correlation function by the geometric mean of the autocorrelation functions of the two spike trains (Eggermont and Smith 1996). The corrected result is shown as the blue curves. One notices also the strong contribution (>50%) of these spindle-related correlations on the peak value of the cross-correlogram.

The deconvolution procedure is carried out in the frequency domain by taking the Fourier transform of $C_{xy}(\tau)$, resulting in the cross spectrum $S_{xy}(f)$ and dividing by the square root of the product of the two Fourier-transformed autocorrelation functions, i.e., the power spectra. This gives the complex coherence:



Correlation Analysis of Parallel Spike Trains, Fig. 4 The deconvolution-based correction procedure eliminates the oscillatory aspects resulting from anesthesia-induced spindle oscillations in auditory cortex. Here we show all pair correlations between the spike activity between two eight-electrode arrays; one array with electrodes numbered 1–8 and the other with electrodes numbered 9–16. The red curves show the raw

cross-correlograms for spontaneous activity in cat primary auditory cortex. The blue curves represent the corrected cross-correlograms. All units showed an oscillatory auto-correlation at the same (spindle) frequency, and the effect thereof is eliminated using the deconvolution procedure. All correlograms are scaled to the peak of the raw cross-correlation coefficient value (the red curve), which is shown in each panel. (From Eggermont (unpublished))

$$\gamma_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}} \tag{15}$$

An inverse Fourier transform results in the corrected “correlation coefficient” (Eggermont 2006).

Correlation and Connectivity

In general there is no unique relationship between known connectivity and observed cross-correlation (Meyer and van Vreeswijk 2002). Correlations are in principle determined uniquely by connectivity, including the strengths and delay

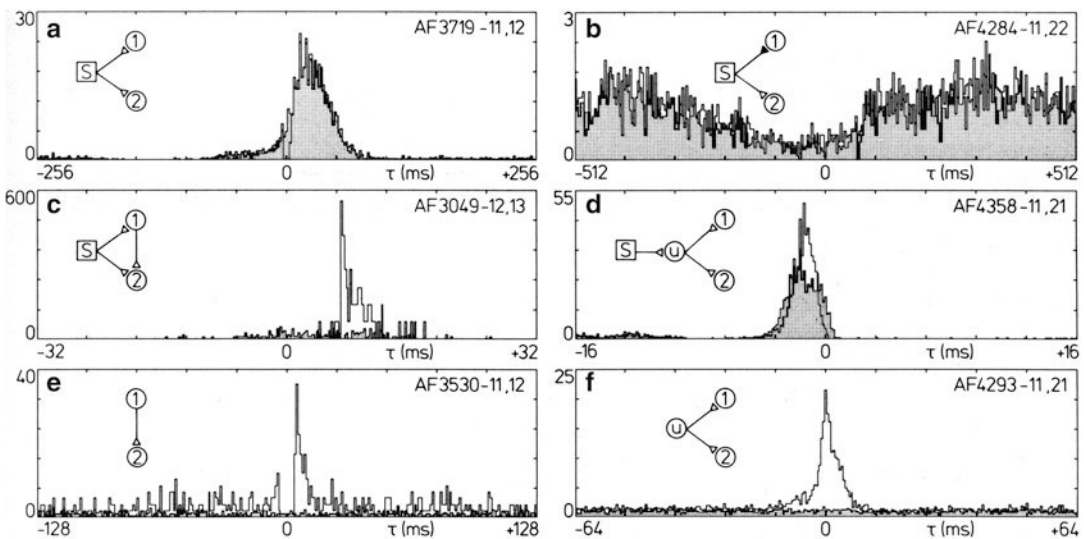
dependence of the connections. From the neural correlation one can, under certain assumptions about the integration of neural input and the shape on the neuron’s response curve, estimate the strength of the neural interaction. Because the estimate of the peak neural correlation is very sensitive about the shape of and working point on the neuron’s response curve (Melsen and Epping 1987), it is generally not permitted to equate the strength of the neural correlation estimated from extracellular recordings with the strength of the neural interaction. When an actual stimulus is applied, one of its effects, especially for cortical neurons, will be to shift the neuron’s working point, and apparent changes in neural

correlation may be found without a concomitant change in the strength of the neural interaction (Aertsen and Gerstein 1985; Melssen and Epping 1987).

The simplest interactions shown by a pair of neurons are that one neuron makes a direct excitatory or inhibitory connection with the other or that both neurons share a common excitatory or inhibitory input. It has been shown in simulation studies that common excitatory input and common inhibitory input result in a peak in the cross-correlogram around zero-lag time. Reciprocal excitatory and inhibitory input to the neurons provided by the same source result in a central dip in the cross-correlogram (Moore et al. 1970). Unilateral excitation shows a peak shifted to positive lag times, and unilateral inhibition shows a dip at positive lag times.

In auditory cortex evidence for direct excitation or inhibition has been scant, unless the neuron pairs were recorded on the same electrode, and nearly all correlograms are of the common input

type (Eggermont 1992, 2000). In visual cortex several interaction types have been shown for recordings with dual electrodes from cells at different depth in the same cortical column (Toyama et al. 1981). However, more variety in correlogram shapes was found in the auditory midbrain (Epping and Eggermont 1987). In the examples shown in Fig. 5, we show (A) stimulus-induced common excitatory effects without neural correlation for two units recorded on the same electrode and (B) stimulus-induced common suppressive effects for a pair recorded on electrodes separated by 130 μm . In both cases the shift predictor is equal to the neural synchrony. Weak stimulus-induced activation combined with a direct excitatory effect from one neuron upon the other recorded on the same electrode (C) is inferred because the shift predictor is hardly visible and the peak of the correlogram is displaced by 6 ms from the origin and highly asymmetrical. This is interpreted as a unidirectional excitatory influence of unit 1 on unit 2. In these three



Correlation Analysis of Parallel Spike Trains, Fig. 5 Potential functional connectivity underlying cross-correlation functions. Simultaneous and non-simultaneous (shift predictor; shaded) cross-correlation histograms are superimposed. (a) Neural synchrony, incremental correlogram. (b) Neural synchrony, decremental correlogram. (c) Unidirectional excitatory input. (d) Neural shared input. (e) Unidirectional excitatory input.

(f) Neural shared input. Stimulus-driven activity in (a–d); spontaneous activity in (e) and (f). Note different time scales. Simple connectivity schemes that can account for the observed phenomena are shown as insets. S, stimulus; 1, neuron 1; 2, neuron 2; u, unobserved neuron. Open and closed triangles indicate excitatory and inhibitory connections, respectively. (From Epping and Eggermont 1987)

examples, the stimulus consisted of random frequency tone pips presented once per second. Part D shows stimulus-induced (Poisson-distributed clicks) common input for a pair recorded with electrodes separated by 290 μm putatively via an unobserved neuron (D), because it has a pronounced shift predictor. For two spontaneous recordings (E, F), reason for the flat shift predictors, unidirectional excitatory input was observed for a single-electrode pair (E) and common input for a dual-electrode pair (separation 160 μm ; F). The highly asymmetrical peak of the neural synchrony displaced from the origin in part E indicates that unit 1 exerts a unidirectional excitatory influence on unit 2. However, there may be a complication due to the dead time of the spike-sorting procedure, and it may well be a common input neural correlation as well. This is a known drawback of using sorted units recorded on the same electrode.

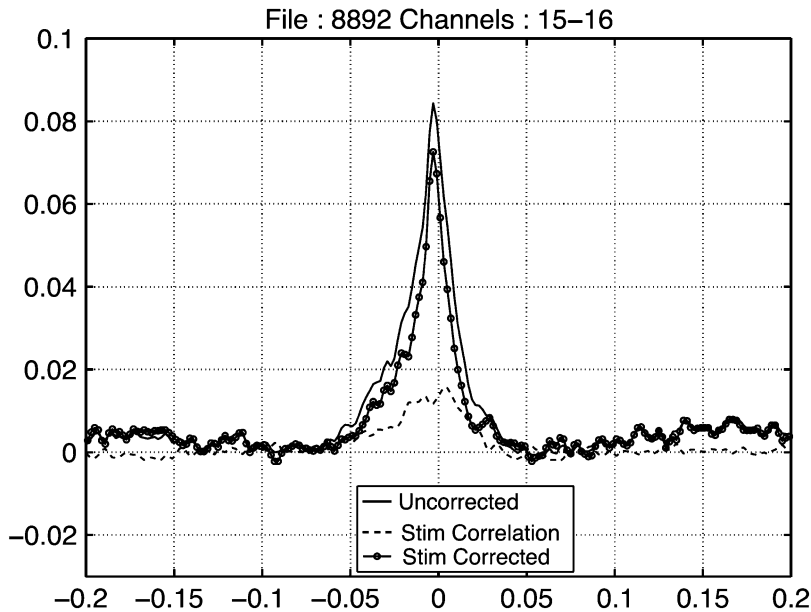
Effects of Spike Sorting on Pair Correlations

Multiunit (MU) recording is common in structures with high cell densities and especially using multielectrode arrays. Spike sorting can result in well-sorted units, but by no means can one be sure that one is dealing with single units (SU), that is, only the case when doing intracellular or patch-clamp recordings. Evidence from neural modeling suggests that interpretation of neural correlations from multiunit recordings may be ambiguous as it is not a linear combination of correlations for the various single-unit pairs (Bedenbauch and Gerstein 1997; Gerstein 2000). However, changes in single-unit correlation strengths will be accompanied by comparable changes in the correlation between multiunit activities as shown in Eggermont (2000). Thus, if a number of single units contribute to each multiple single-unit recording, the changes in the MU values will be positively, but nonlinearly, related to those for the corresponding SU ones. So if SU correlations go up, so will the MU correlation. The only difference is that the R-values are larger for

MU than for the corresponding SU ones but smaller than the sum of all the relevant SU pair R-values. Trying to estimate functional connectivity from sorted multiunit activity is not encouraged.

Correlations and the Brain

Calculating a shift predictor or any other type of stimulus predictor is a way to extract the effects of stimulation on the effective neural connectivity despite the drawbacks that we discussed. However, as we have previously argued (Tomita and Eggermont 2005), it is unlikely that the nervous system performs a correction for stimulus-induced correlation as estimated by the various predictors. It is the actual spike coincidences, i.e., the neural synchrony, that are affecting the potential for firing in a target neuron and not the stimulus-corrected ones. Thus, raw correlations may effectively estimate those coincident firings between neurons that could play a role in neural population coding of sound. The effect of removing common periodicities in spike firing and common bursting activity from the cross-correlation can be justified because these contributions typically do not occur, or occur much less, in awake animals and are often the result of using anesthesia. Nevertheless, in our data for 15-min steady-state stimuli, the effects of a stimulus correction based on the shift predictor are minimal (Fig. 6), so using the stimulus-correction procedure has minimal effect on the interpretation of the data. However, for transient and optimal stimuli, the stimulus correction can be extensive and even remove all correlation (Eggermont 1994), so in this case one has to consider what the correlation estimate needs to support. If one is concerned with estimating connectivity or deciding which wiring scheme is most likely, then both stimulus corrections and corrections for common, network-induced, activity need to be performed. If one is concerned with how the brain performs its task in vivo, then these corrections may obscure the very aspects one wants to understand.



Correlation Analysis of Parallel Spike Trains, Fig. 6 This set of three cross-correlograms illustrates the stimulus-correction procedure applied to spike trains recorded from primary auditory cortex in the cat during a 900 s long random frequency stimulus where the second half was equal to the first. Stimuli were tone pips presented randomly in frequency and time with an overall rate of 28/s across 7 octaves (112 frequencies, so an average rate of 0.25 frequencies/s). The recording comprised 2 arrays of 16 electrodes each. Here we show the pair correlation between two neighboring electrodes separated by

0.5 mm. The uncorrected cross-correlation coefficient function is shown in solid line; the peak cross-correlation is approximately 0.082. The frequency tuning of the two recording sites was nearly identical, yet the stimulus correlation obtained as a shift predictor (dashed line) shows only modest stimulus locking. The stimulus-corrected cross-correlation coefficient function is shown in a connected dot line. (With kind permission from Springer Science + Business Media: Analysis of parallel spike trains, Chap. 5, Pair-correlation in the time and frequency domain, 2010, page 77–102, J. J. Eggermont, Fig. 5.3)

Cross-References

► Spike Train

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Cortical Columns and Neural Population Models

► Mesoscopic Anatomy and Neural Population Models

Cortical Columns, Models of

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Definition

A cortical column is a module in the neocortex, approximately 300–600 μm in diameter, composed of many minicolumns coupled by short-range horizontal connections. Neurons within a column often share dynamic response properties. In general, a column is part of a continuous sheet of neocortex, where the boundaries of individual columns cannot be determined by anatomy alone, although there are exceptions such as the barrel field columns in rodent neocortex. Columns with similar response properties are often connected by long-range horizontal connections. Numerous efforts have been undertaken to develop computational models of the cortical column, which is often equated with the quest to identify the fundamental computational unit of the mammalian brain. These efforts span from highly simplified “mean-field” models that model interactions between homogeneous cell populations to detailed biophysical models with heterogeneous neuron morphologies and diverse electrophysiological behavior. Orientation selectivity in the

primary visual cortex is an example of a computation performed by a cortical column, which has been observed experimentally and modeled computationally. However, a common goal of modeling the cortical column is to identify a more general putative canonical computation occurring throughout the neocortex.

Detailed Description

Background

The neocortex originated in a mammalian ancestor approximately 250 million years ago and its evolution has been critical for the emergence of human cognition and behavior. The types of neurons and their local synaptic connectivity in different parts of the neocortex appear to be variations on a basic stereotypical circuit design. Lorente de Nó (1938) was the first to suggest that “vertical chains” of neurons traversing the six layers of the neocortex formed elementary functional units: “all the elements of the cortex are represented in it, and therefore it may be called an elementary unit, in which theoretically, the whole process of the transmission of impulses from the afferent fibre to the efferent axon may be accomplished.” Vernon Mountcastle and colleagues subsequently showed that neurons separated by a horizontal distance of less than a millimeter share similar response properties (Mountcastle 1957; Mountcastle et al. 1957; Powell and Mountcastle 1959). The term “column” was proposed by Mountcastle who suggested “there is an elementary unit of organization in the somatic cortex made up of a vertical group of cells extending through all the cellular layers” (Mountcastle 1957). The hypothesis is that the column is a functional cortical module, composed of minicolumns, and approximately 300–600 μm in diameter, which is replicated throughout the neocortex as the primary computational unit. The evolutionary expansion of the neocortex is thought to have occurred as a result adding additional cortical columns rather than increasing the size of the cortical column (Rakic 1995). Working in cat visual cortex, Hubel and Wiesel demonstrated functional cortical columns with a

diameter of around 0.5 mm (Hubel and Wiesel 1977). Later studies showed that different patterns of stimuli produced different functional architectures with different spatial fidelity (Mountcastle 1998). In Neuroscience, there has been difficulty adhering to a single definition of a cortical column leading to debate and confusion about both its existence and function (Horton and Adams 2005). However, a common goal of modeling the cortical column is to identify a putative but general canonical computation and the specific neuronal mechanisms that underlie the emergence of diverse functional architectures throughout the neocortex.

Modeling Approaches

An early qualitative model of cortical circuitry was proposed by Hubel and Wiesel (1962) to describe the mechanisms underlying simple and complex cell responses in nonhuman primate cortex based on strongly tuned convergent thalamocortical input.

Douglas and Martin (1991) provided the first canonical microcircuit model from their studies on visual cortex in the cat. This model was based on microanatomical studies and in vivo intracellular recordings. It provided an account of the intracellular responses to pulsed stimulations in terms of an inseparable combination of excitatory and inhibitory responses of three basic populations of neurons. Their model proposed that thalamic input is not the major source of excitatory input to cortical neurons, and instead intracortical input was the dominant source of excitation.

Somers et al. (1995) implemented a large-scale computational model of orientation selectivity in cortical simple cells that demonstrated that sharp orientation tuning could emerge from local recurrent intracortical excitation at the columnar level and be balanced by nonspecific inhibition with only weakly tuned thalamocortical excitation.

Much work has been focused on explaining the function of the cortical column during wakefulness. Hill and Tononi (2005) focused on the observation that the cortical column is multifunctional and can exhibit strikingly different functions in

wakefulness and sleep. Their large-scale model of thalamocortical visual circuitry was based on point neurons organized in repeating columnar structures with patchy long-range connectivity and illustrated how columns transition between spontaneous activity and orientation-selective responses during wakefulness and slow oscillations during sleep.

Traub et al. (2005) has developed a model of a single thalamocortical column (in this case a cortical minicolumn coupled with thalamic and reticular thalamic neurons) based on biophysical models of neurons with schematic morphologies employed to more accurately capture the positioning of synapses on different compartments of neurons. This model exhibited a broad range of oscillatory, epileptic, and sleeplike phenomena.

Launched in 2005, the Blue Brain Project (bluebrain.epfl.ch) proposed a data-driven process to construct highly detailed biophysical models of the cortical microcircuitry that underlies a column (Markram 2006) using extensive measurements of the young rat (P14) somatosensory cortex, including single-cell gene expression, whole-cell patch clamp electrophysiology, morphological reconstructions, synaptic connectivity and plasticity, and more. The models capture the experimentally observed diversity and composition of 55 morphological and 12 electrophysiological classes. The group has since shown that the resulting models can be used to predict synaptic connectivity patterns (Hill et al. 2012) and cellular contributions to the local field potential (Reimann et al. 2013).

A detailed anatomical model of an average barrel column within the somatosensory cortex of the rat has been proposed by Helmstaedter et al. (2007). The barrel cortex provides an example where both the anatomical and functional cortical column is well defined. Work from this group has led to detailed anatomical reconstructions that take into account the numbers and distribution of the somata, dendrites, and thalamocortical synapses of nine cortical cell types, soma location, dendritic morphology, synapse innervation, and predictions of synaptic connectivity for a thalamocortical circuit in the rat vibrissa cortex (Oberlaender et al. 2012).

Summary

A broad diversity of approaches has been taken to modeling the cortical column. In the end, they share a common goal of understanding whether or not there is a canonical computation performed by cortical microcircuitry and what are the mechanisms that govern and generate it.

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Cortical Field Theory

► Neural Field Model, Continuum

Cortical Function, Normative Models of

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Definition

Normative models of cortical function are a class of models that are related to or derived from a well-defined mathematical objective function. They allow to understand the brain's solution to a certain computational problem in relation to an optimal solution that maximizes the chosen objective function, if such a solution can be found.

Detailed Description

Normative models of cortical function are much like other computational models of the cortex.

They try to describe and explain experimental data and make predictions that can be used to falsify them (Dayan and Abbott 2001). But rather than directly asking how the brain solves a particular computational problem, one first asks what the *optimal solution* to this problem is. Then the actual solution embodied in the brain may be understood as a specific implementation of this optimal solution or a reasonable approximation to it. Thus, by using normative models, one approaches the question of how the brain works by first asking how the brain *ought to work*. The great strength of this approach is that it can lead to an understanding of brain function at a deeper level. Rather than only describing *how* something works in the brain, normative models reveal *why* the brain may be operating in this way. Normative modeling approaches are not restricted to *cortical* function, but may be used at essentially all levels of nervous system modeling and beyond.

There is a wide range of existing and conceivable normative models of cortical function due to the vast range of functions in which the cortex is involved. These include perception, cognition, memory, and motor control. In each of these areas, normative models can be used to try to better understand aspects of cortical function. While the cortex is clearly involved in all of the mentioned functions, it is worth noting, however, that all of these functions are also present in animal species without any cortex. In such species, similar computational functions may be implemented in a very different way. In much the same way as different computer algorithms or different implementations of the same algorithm can solve the same problem, different nervous system structures in different species might have evolved to solve the same problem in different ways.

A generic task for a perceptual system that may be implemented in sensory cortical areas is to represent the sensory signals in an efficient way. Sensory stimuli are typically represented by large populations of neurons in sensory cortical areas. Normative models of sensory coding ask how a population of neurons can encode a given class of sensory signals optimally. To this end, certain assumptions about noise in the sensory signals or the processing neurons or a limited energy

budget may be considered. Sparse coding models and predictive coding models are popular examples of normative models of sensory coding.

Another generic computational problem in which the cortex is involved is to make inferences from incomplete and noisy sensory inputs. Examples are recognizing the face of a friend in a poorly lit room or following a conversation in a noisy environment. A popular normative framework for describing how such inferences *ought to be* made is that of Bayesian inference. Correspondingly, much current research aims to understand learning and information processing in the cortex from the perspective of Bayesian inference and attempts to elucidate whether the cortex may implement a specific kind of Bayesian inference and learning algorithm or some approximation to it. Correspondingly, Bayesian inference is a major topic in contemporary computational neuroscience (Doya et al. 2007).

Another generic computational problem in which the cortex is also involved is to make decisions and control our actions. A popular normative framework for describing how decisions *ought to be* made in an optimal way and how an agent *ought to* select actions are those of decision theory and reinforcement learning. Consequently, much research tries to address how the cortex and other brain structures such as the basal ganglia may be implementing approximations to optimal decision making or specific reinforcement learning algorithms.

Overall, normative modeling approaches have already proved to be very fruitful in providing a deeper understanding of brain function in general and cortical function in particular. Beyond merely describing *how* the cortex operates, they reveal *why* this way of operation is appropriate or even optimal.

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Cortex: Overview](#)
- [Predictive Coding](#)
- [Reinforcement Learning in Cortical Networks](#)

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Cortical Maps, Activity-Dependent Development

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Synonyms

[Computational maps](#); [Self-organizing maps](#); [Topographic maps](#)

Definition

The term “cortical map” refers to the existence of a nonrandom relationship between the position of a neuron in the cerebral cortex and the value of some property that can be assigned to it on the basis of physiological or anatomical tests. Typically the property in question is a receptive field parameter of a sensory neuron, e.g., the position in space of the receptive field of a visual sensory neuron, or the color of a stimulus that activates it, but it might also be a projective field, e.g., the position in the body of a muscle or group of muscles activated by neurons in motor cortex, or, more speculatively, some aspect of knowledge or behavior coded for, or produced, by activity in single neurons or groups of neighboring neurons (perhaps as measured by fMRI experiments). A further qualification is that map properties often remain constant in value with depth in the cortex and vary only with lateral (equivalently tangential) position. This property, termed “columnar organization,” (Hubel and Wiesel 1977; Mountcastle 1998) means that the cortex

is normally treated as a two-dimensional array for modeling purposes. “Activity-dependent development” in the context of “cortical maps” refers to a class of computational neuroscience model that seeks to explain the development of cortical maps as the outcome of mathematically specified rules governing axonal growth and synapse formation in which neural activity plays a primary role. All of these models use Hebbian learning rules to achieve a mapping between cells in one or more input layers representing either cell classes in the retina(s) or the lateral geniculate nucleus (LGN) layers and connections with cells in a single output layer that represents the cortex. The interest of the models lies not so much in what can be computed with them, but in the fact that they are often able to replicate, sometimes in a very detailed way, the geometrical properties of different maps and their spatial relationships (Erwin et al. 1995; Swindale 1996, 2003; Goodhill 2007).

Detailed Description

Varieties of Cortical Map

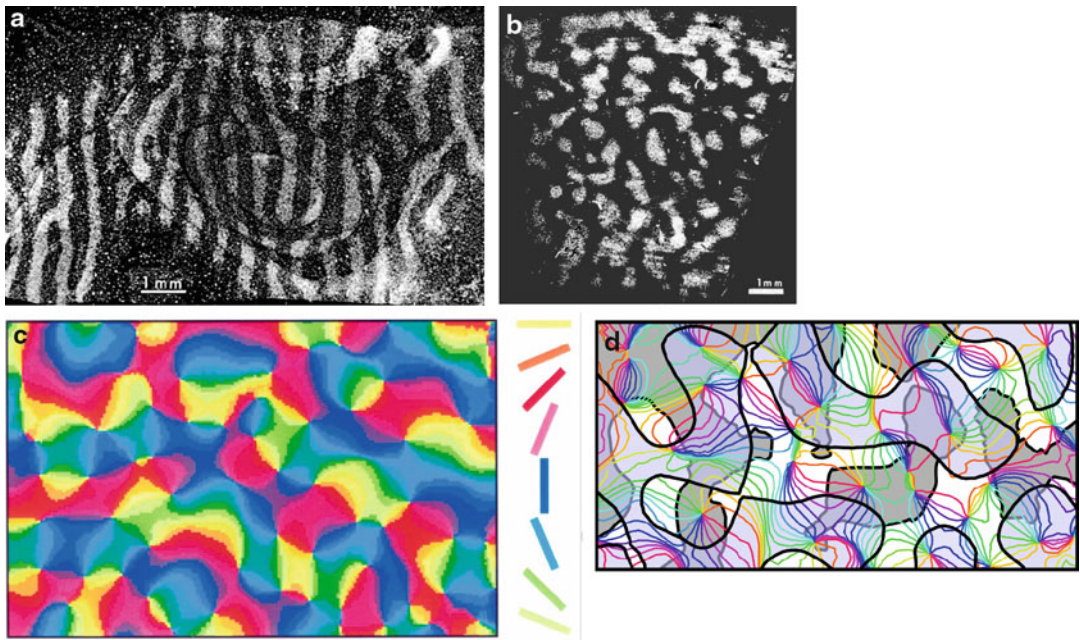
In *retinotopic maps*, there is an orderly mapping of receptive field position in retinotopic coordinates (elevation and azimuth) in a brain region, as a result of topographically ordered connections between retinal ganglion cells and target structures. Such maps possess local order (neighboring retinal neurons tend to project to neighboring regions in the target structure) and global order, i.e., iso-elevation and iso-azimuthal contours have a predictable and consistent layout in the target structure. Retinotopic maps occur in the optic tectum in lower vertebrates such as frogs and fish and in the superior colliculus, LGN, and visual cortical areas of mammals. The rules governing the formation of maps in the optic tectum of frogs and fish, and their responses to experimental manipulations such as removing parts of the retina and/or the tectum, were among the first to be studied experimentally and to be modeled mathematically (Goodhill and Xu 2005; Goodhill 2007; Eglén and Gjorgjieva 2009). Much of this work can be applied to the development of maps in LGN and cortex as well.

Ocular Dominance Maps

When the visual fields of the two eyes overlap substantially, as they do in carnivores and most primates, the retinotopic maps also overlap, i.e., cells in the target structures will have receptive fields that are in approximately the same location in visual space. In such cases, the relative strength of the inputs from the two eyes, a property termed ocular dominance, is often found to vary systematically with position across the map, allowing it to be subdivided into interdigitating regions referred to as ocular dominance columns (Hubel and Wiesel 1977). The layout of the columns is generally periodic with a spacing in the range 0.8–2.0 mm depending on species. In old-world primates (such as macaque monkeys), the morphology is branching stripes (Fig. 1a), whereas in cats and ferrets, there is a less ordered pattern of elongated blobs and patches (Fig. 1b). Ocular dominance columns are not found in all species. They may be variably present in the visual cortex of new-world monkeys (Adams and Horton 2003) and are largely absent in the visual cortices of mice and rats which have only a very small binocular visual field (Hübener et al. 2008).

Orientation Maps

The majority of neurons in the primary visual cortex of all species that have been examined show orientation selectivity, i.e., the neuron will respond selectively to the orientation of a bar or edge flashed in, or moved across, the receptive field. The response is typically a bell-shaped function of stimulus orientation with a width in the range of 20–60° at half height and a peak that defines the cell’s preferred orientation. In carnivores and primates, preferred orientation has a columnar organization and varies smoothly and systematically with tangential position (Fig. 1c). As with ocular dominance columns, the periodicity is generally in the range 0.8–2.0 mm. However, when ocular dominance and orientation maps are simultaneously present in a visual cortical area, which is often the case, the periodicities are usually different. Because orientation is, by definition, a property that is cyclic in the range 0– π , it is often convenient to



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Fig. 1 Ocular dominance column arrangements observed in macaque monkey visual cortex (**a**) and area 17 of cat visual cortex (**b**). *White areas* are regions of cortex labeled by injection of radioactive tracer into one eye. (**c**) Layout of orientation preference in area 17 of cat visual cortex. Singularities (*pinwheels*) are identifiable as points where many *color boundaries* intersect. (**d**) Layout of domains

of ocular dominance (outlined by *upper layer of black lines*), spatial frequency (*lowest layer*), and orientation (*colored lines, middle layer*). Singularities in this panel are identifiable as points where *colored lines* meet (Panel **a** is adapted from Hubel and Wiesel (1977); **b** is adapted from LeVay et al. (1978). **c** is from Hübener et al. (1997). Figure **d** was kindly supplied to the author by M. Hübener)

represent it as an angle-doubled complex number $z = ae^{i2\theta}$, where θ is the orientation and the length a of the vector represents response strength or tuning sharpness, or some combination of the two. Singularities (more commonly referred to as “pinwheels”) occur frequently in orientation maps (Fig. 1c, d). Mathematically these correspond to positions where $z = 0$ which will happen at locations where zero crossings in the real and imaginary components of z intersect (Swindale 1982). For most types of periodic layout of z , this will be a frequent occurrence (Wolf and Geisel 1998). Singularities can be classified by sign, where positive sign means that orientations rotate in a clockwise direction if a circular path enclosing a singularity is traversed in a clockwise direction, while negative sign means that orientations rotate in an anticlockwise direction for clockwise motion around the circuit. Positive and negative singularities are

found in approximately equal numbers in visual cortex maps (Obermayer and Blasdel 1997).

Direction Preference

In addition to selectivity for orientation, many visual cortical neurons give different responses to the two possible directions of motion of a long edge. This can range from the equal responses to both directions to no response at all in the so-called null direction, with the responses of most neurons falling between these two extremes. Direction preference is represented continuously in cat and ferret primary visual cortex with the topological consequence that lines, across which direction preference reverses, extend between and connect pairs of orientation singularities of opposite sign (Swindale et al. 1987). This arrangement has been confirmed experimentally (Swindale et al. 1987; Shmuel and Grinvald 1996; Weliky et al. 1996).

Spatial Frequency Maps

As an alternative to bars and edges, many experimenters have used moving sine wave gratings to study the responses of visual cortex neurons. Since the Fourier transform of an extended sine wave grating is a point in a 2D spatial frequency space (and a moving grating is a point in a 3D spatiotemporal frequency space), such stimuli allow the use of linear systems theory to characterize neuronal responses in space and time. Experimentally, it is found that the majority of primary visual cortex neurons will respond with an elevated, or modulated, firing rate to a moving grating stimulus, with the magnitude of the response varying with the orientation, direction of motion, and spatial frequency of the grating. Cells are also tuned for spatial frequency, with the position of the peak defining the preferred spatial frequency of the cell and the range defining a bandwidth (De Valois and De Valois 1990).

In a 2D space whose coordinates are horizontal frequency on the x -axis and vertical frequency on the y -axis (or equivalently in coordinates, spatial frequency = r and orientation = θ), tuning is typically an approximately Gaussian-shaped region centered on a preferred orientation and spatial frequency (De Valois and De Valois 1990). Transformed back into visual space, such a tuning function corresponds to a Gabor function. This can be explained in the following way: a Gaussian blob in spatial frequency space can be represented as a delta function positioned at the preferred (r , θ) value convolved with a 2D Gaussian. In spatial coordinates, this corresponds to the Fourier transform of a delta function, which equals a sine wave grating, multiplied by the Fourier transform of a 2D Gaussian, which is another Gaussian function. The resulting function turns out to be an excellent description of the spatial receptive field profile of many visual cortex neurons (Ringach 2002). Bandwidths for most visual cortical neurons are about 1–2 octaves, while within a single cortical area (e.g., area 17 of the cat), preferred spatial frequency can vary from cell to cell over a range of about 2–3 (Movshon et al. 1978; Born and Tootell 1991). Experiments in cats, monkeys, and ferrets have shown that preferred spatial frequency varies

periodically with position, with an overall layout that is independent of, but geometrically similar to, that of ocular dominance (Hübener et al. 1997; Issa et al. 2000; Yu et al. 2005; Nauhaus et al. 2012).

Additional Maps

Maps of retinal position, ocular dominance, orientation, direction of motion, and spatial frequency are all simultaneously present in area 17 of the cat (Fig. 1d) and ferret. Area V1 in macaque monkeys also contains a retinotopic map plus maps of ocular dominance, orientation, and spatial frequency. Additional maps are either known or very likely to be present. For example, there is an ordered sensitivity to stereoscopic disparity in cat area 18 (Kara and Boyd 2009), and several investigators have reported maps for color preference in macaque V1 (e.g., Lu and Roe 2008). How many different features may simultaneously be represented in maps in a single cortical area is currently unknown.

Rats, Mice, and Squirrels

It is worth noting specifically that the visual cortices of these animals have retinotopic maps but that the maps for preferred orientation and ocular dominance appear to be random, in both tangential and vertical (columnar) directions (Van Hooser et al. 2005; Ohki et al. 2005; Bonin et al. 2011). This is a violation of the principle of columnar organization and shows that it does not have always to be present. This might suggest that orientation and ocular dominance columns are adaptive features that arose in more recently evolved mammals with larger (and perhaps better) cortices. However, both rats and mice have well-developed visual abilities, and squirrels in particular have good visual abilities so it is hard to avoid the conclusion that columns are not essential features of a working cortex.

Maps in Other Cortical Areas

The bulk of our knowledge of possible forms of cortical map organization comes from studies of visual cortical areas. Maps are present in other

sensory areas (Mountcastle 1998; Inan and Crair 2007), but it is not clear if multiple features are overlaid in them with comparable complexity to visual cortex. Auditory cortex contains an ordered one-dimensional map of frequency, i.e., preferred auditory frequency is constant along one axis but varies, approximately as an exponential function of distance, along the orthogonal axis. There is evidence that other auditory response properties, such as envelope periodicity, may be mapped along the orthogonal dimension (Langner and Ochse 2006). It has long been known that somatosensory cortex has an ordered map of the body surface: early studies of this area showed that in addition to the map of the body surface (analogous to the retinotopic map), there were local subdivisions into regions which received input from different classes of sensory receptor, e.g., superficial and deep. These representations were found to be columnar, and studies showing it, done in the late 1950s, were among the first to demonstrate columnar organization (Mountcastle 1998). Taste has recently been shown to have an ordered representation in mouse gustatory cortex where there are small ($\sim 200\text{--}400\text{ }\mu\text{m}$ diameter) patches of cells, about 1–2 mm apart, that respond selectively to either bitter, salty, sweet, or umami tastants, each of which has a correspondingly specialized receptor in the taste buds (Chen et al. 2011).

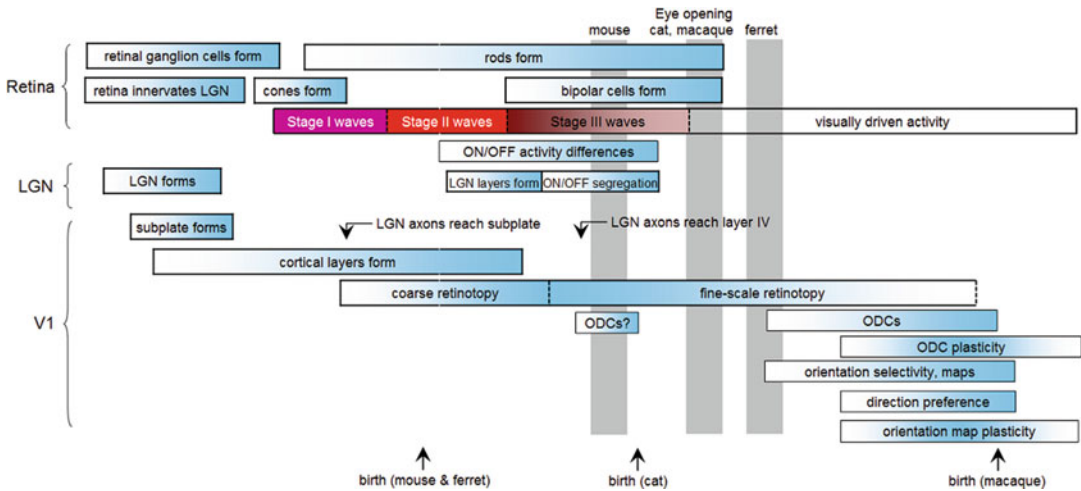
Development of Cortical Maps

There is a long-standing debate about the extent to which human knowledge is innate or acquired through learning. In the narrower context of cortical maps, the debate likewise centers on the extent to which map development is the outcome of molecularly guided (innate, genetic, nature) or neural activity-dependent (environmental, learning based, nurture) cues. Although it is frequently pointed out that there can be complex interactions between genes and the environment, the nature-nurture dimension continues to be a useful one along which to characterize models and research findings. Initial research, begun in the 1960s, showed that cortical maps develop early in life

and that their structure can be altered by exposure, or lack of exposure, to specific stimuli during and after the period of map development. These findings inspired the development of various classes of computational neuroscience model that sought to explain cortical map development as the outcome of a self-organizing, activity-dependent process in which neural activity plays a critical role. However, it is now known that in the superior colliculus and optic tectum of lower vertebrates, retinotopic maps develop under the influence of molecular guidance cues (McLaughlin and O'Leary 2005) and it is highly likely that retinotopic and somatotopic maps in the cerebral cortex do so as well (Rakic et al. 2009; Cang et al. 2005; Inan and Crair 2007). Models based on correlated neural activity and Hebbian learning however remain the best candidates for explaining the refinement of retinotopic maps in the cortex (Huberman et al. 2008) as well as for the development of orientation and direction preference maps (White and Fitzpatrick 2007).

Sequence of Visual Cortex Map Development

While the timing of developmental events measured in days from conception varies considerably in different species, the general order is similar (Fig. 2; Workman et al. 2013). Retinal ganglion cells are generated very early in the sequence, but the retina is unlikely to be responsive to patterned light stimuli until shortly before the time of eye opening, at which point cells in both the LGN and cortex have finished dividing and migrating and LGN axons have already made synaptic connections in layer IV of the cortex. Visual responsiveness is likely to depend not just on the presence of rods and cones but also on the maturation of the bipolar neurons which link rods and cones to ganglion cells, and this happens relatively late in the sequence. Prior to this, and beginning from the time that retinal ganglion cells have reached the LGN, retinal ganglion cells fire coordinated bursts of action potentials that move in a wavelike fashion across the retina, outwards from an originating center (Wong 1999; Warland et al. 2006).



Cortical Maps, Activity-Dependent Development, Fig. 2 Timeline of development of the retina, LGN, and visual cortex maps in mouse, cat, ferret, and macaque monkey. Note that while the actual timing of events differs substantially in the different species, the overall order is similar in all of them. Several qualifications apply to the figure (discussed in the text): there is still debate over the

timing of ocular dominance column development; the mouse does not possess maps of ocular dominance, orientation, or direction preference, nor does the macaque have a direction preference map; the diagram should not be relied upon for exact timing details given that it is a synthesis across several species (Layout taken from Huberman et al. 2008; data from Workman et al. (2013))

(Stages I, II, and III differ in terms of cell type and transmitters and will not be discussed here.) The centers and directions of wavefront motion are seemingly random but with a refractory behavior so that cells that have fired in a burst are unlikely to participate in another one for some time. Such refractory areas often cause propagating waves to die out. The retinal waves continue throughout the period when the LGN layers are segregating and during the period when the LGN axons are innervating layer IV of the cortex. Interference with the waves has been shown to prevent segregation of LGN layers and to reduce the refinement of the retinotopic maps in the cortex (Torborg and Feller 2005; Firth et al. 2005; Huberman et al. 2008). As Fig. 2 shows, the timing of birth relative to development varies greatly in different species. Mice and ferrets are born relatively immature, before the retina is functional and before layers in the LGN and cortex have fully formed. Cats are born shortly before the retina is mature and about a week before the eyes open. Macaque monkeys are born very much later in the sequence with the eyes opening in utero about 6 weeks before birth. As light may well penetrate into the uterus,

the possibility of intrauterine visual stimulation exists, and this might also explain why the eyes would open before birth. However, the extent to which vision can occur in utero remains unknown.

Following birth, the trajectory of visual development is species dependent. In macaque monkeys, born much later relative to developmental milestones than other species, ocular dominance columns are present at birth (Horton and Hocking 1996), while orientation maps have been reported very soon afterwards (Wiesel and Hubel 1974). Ocular dominance and orientation maps begin to develop in cats about a week after eye opening and are adultlike 2–3 weeks later. Orientation maps start to develop in ferrets at the time of eye opening, followed about a week later by direction preference maps. Ocular dominance columns have been reported to be present prenatally in the ferret as well as in ferrets in which both eyes were removed (Katz and Crowley 2002). This observation, plus the recent discovery of a molecular marker for ocular dominance (Tomita et al. 2013), suggests that neural activity might not play a significant role in the formation of ocular dominance columns. However, patterned spontaneous

activity may still be present in the LGN of blinded ferrets, and its role cannot be ruled out. Likewise, a role for retinal waves, or even for intrauterine visual stimulation, cannot be ruled out in the development of ocular dominance columns which are present at birth in monkeys. Although orientation maps normally develop in the presence of visually driven activity in cats and ferrets, the presence of the maps in animals that have been dark-reared, as well as in newborn monkeys, suggests that either neural activity is not involved or that retinal waves, together with patterned spontaneous LGN and cortical activity, are able to cause maps to form in the absence of visually driven input. The observation that blocking activity in ON-center retinal ganglion cells prevents the development of orientation maps (Chapman and Gödecke 2000) suggests that neural activity is involved however.

As noted above, mice do not have maps of ocular dominance or orientation, though individual cells have these properties which hence may arise through activity-dependent interactions.

Although the role played by patterned neural activity, whether spontaneous or visually driven, in the development of orientation and ocular dominance maps remains uncertain, there is no doubt that alterations in the patterns of visual input can cause modification of map structure. Monocular deprivation (closing one eye), if done shortly after birth, causes a loss of inputs from the deprived eye and a gain in the number and strength of inputs from the other eye (Hubel and Wiesel 1977). In cats and monkeys, there is a corresponding change in the widths of the ocular dominance columns with active geniculate inputs taking over cortical territory formerly innervated by the deprived eye. Monocular deprivation has little effect if performed outside of a critical period: in mice, this is within 5 weeks after birth, cats about 3 months and monkeys about 6 months. Manipulation of the distribution of oriented stimuli has been done by either placing young animals in a cylinder on which vertical lines are the only visible contour or by fitting cylindrical lenses to the eyes: these cause orientations not matching the axis of the cylinder to be blurred. Such manipulations have been found to bias the distribution of

orientation preferences and, correspondingly, the structure of orientation maps in cat visual cortex (Sengpiel and Kind 2002). The development of direction preference has also been shown to be prevented by rearing animals in stroboscopic light which abolishes motion cues (White and Fitzpatrick 2007).

Vector Representation of Map Parameters

As outlined above, the receptive fields of neurons in V1 can be parameterized along a variety of dimensions represented in maps (Fig. 1d). For example, in cat visual cortex, we might represent the list as follows: receptive field position (x, y), ocular dominance (d), preferred orientation (itself a vector, $\mathbf{z} = (a, b)$), and preferred spatial frequency (f). We might represent the list of properties measured for cells at a point, i , on the cortical surface, by the vector $\mathbf{v}_i = \{x_i, y_i, d_i, a_i, b_i, f_i\}$. The complete mapping can be conceptualized as the projection of the 2D cortical sheet into a higher-dimensional feature space $\mathbf{S}$. This construction relies on a number of assumptions. Firstly, the representation of the cortex as a 2D sheet is based on the hypothesis of columnar organization. This appears generally to be true although exceptions to it have been claimed. Second, it should be noted that the values of x_i, y_i , etc. are the best values of response functions that are often Gaussian, or approximately Gaussian, in shape; hence, associating a point in the cortex with a single position in $\mathbf{S}$ is an oversimplification. Instead it would be more correct to think of positions in the cortex each populating $\mathbf{S}$ with spikes falling off in density from a central point. Thirdly, the representation of the receptive field as a point assumes that the best values x, y, d , etc. are independent of each other, e.g., that the preferred orientation is independent of the spatial frequency of the stimulus and its precise position. More formally this means (or assumes) that the response to a stimulus, $\mathbf{u}$, $R(\mathbf{u})$, can be expressed as the separable product of receptive field functions for each of the dimensions, i.e., that $R_i(\mathbf{u}) = F_1(x - x_i)F_2(y - y_i) \dots$ where $F()$ is typically a Gaussian. The assumption of

separability (see Yu et al. 2005 for discussion) and the consequent ability to describe cortical receptive fields as positions, or regions, in a feature space underlie many of the models that will be described in the following sections.

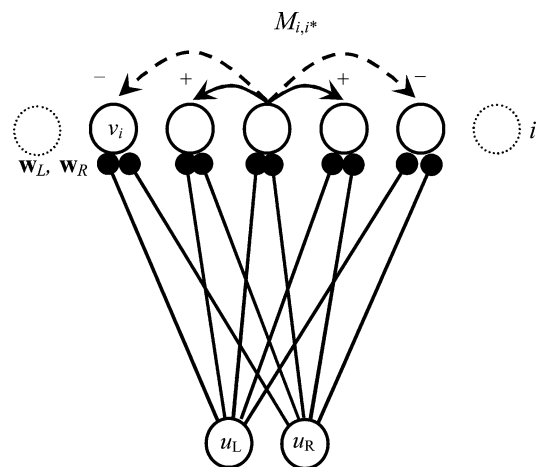
The Models

Linear Correlation-Based Models

All activity-based models of cortical map development assume that maps result from a combination of Hebbian synaptic plasticity, spatially structured activity in the input layer(s), and, necessarily, some form of structured local connectivity in the cortex. (If no local cortical connectivity was present, maps could not arise since the position of a cell in the cortical sheet would have no influence on the type of receptive field that emerged.) The class of correlation-based models discussed in this section further assume (a) that cortical neurons sum their inputs linearly, i.e., that the activity of a cortical unit is given by the dot product of a weight vector $\mathbf{w}$ and an input vector $\mathbf{u}$; (b) that weight changes take place slowly on the timescale of input activity variation, allowing the rate of weight change to be calculated as an average of activity; (c) that local connectivity in the cortex is described by a Mexican Hat function, typically a difference of Gaussians; and finally (d) that the models enforce competition between synapses in the form of normalization rules. These rules can enforce constancy of the sum of the inputs to a neuron; constancy of the sum of the outputs of an input neuron, or sometimes both. Normalization can be done by either multiplicatively scaling all the weights or subtracting from them. If subtractive normalization is done, additional rules have to be implemented to keep weights within realistic biological bounds, i.e., zero and some maximum value. Normalization constraints are usually imposed separately (i.e., following updates of the weight values at each computational step), while the main description of the model will take the form of equations describing the rate of weight change as a function of the weights, distance-dependent correlation functions in the input layers, and the cortical interaction function. However, normalization,

and the way in which it is done, is arguably as important as the rest of the model as this step is often the only one that allows weight values to decrease. This is obviously an essential element in developing response selectivity. Models that use the BCM learning rule, which explicitly includes a mechanism for decreasing weights as part of the learning rule (Dayan and Abbott 2001), are an exception to this.

The use of these assumptions is illustrated in a simplified model of ocular dominance column development presented by Dayan and Abbott (2001). This model is itself based on earlier models. In this setting (Fig. 3), two units with activities u_L and u_R connect, via sets of modifiable feedforward weights $\mathbf{w}_L$ and $\mathbf{w}_R$, to a single layer of cortical units with activities v_i , where i indexes position on the cortical surface. The cortical units are connected by a set of fixed recurrent (i.e., lateral) weights M_{i,i^*} with the property that the strength of the connection varies as a Mexican hat-shaped function of the distance $d = |i - i^*|$ between two positions i and i^* . The vector $\mathbf{u} = (u_L, u_R)$ represents the input activities, the matrix $\mathbf{W} = (\mathbf{w}_L, \mathbf{w}_R)$ represents the feedforward weights, $\mathbf{v}$ represents the activities of the cortical units, and $\mathbf{M}$ represents the connections between cortical units. A simple interpretation of Hebbian learning is that weights change in proportion to the time-



Cortical Maps, Activity-Dependent Development, Fig. 3 The setting for the ocular dominance column model described in the text

averaged product of the activities of the input (pre-) and output (post-) units, i.e., that

$$\tau_w \frac{dW}{dt} = \langle \mathbf{v} \mathbf{u}^T \rangle \quad (1)$$

where τ_w is a learning rate constant. To evaluate this, we first have to calculate the output activities, $\mathbf{v}$, which will depend on recurrent connections as well as the input activities and the connection weights. This can be simplified by finding the steady-state solution of the following recurrent model:

$$\tau_v \frac{dv}{dt} = -\mathbf{v} + \mathbf{W} \mathbf{u} + \mathbf{M} \mathbf{v} \quad (2)$$

which is given by

$$\mathbf{v} = \mathbf{W} \mathbf{u} + \mathbf{M} \mathbf{v}$$

This has the solution

$$\mathbf{v} = \mathbf{K} \mathbf{W} \mathbf{u} \quad (3)$$

where $\mathbf{K} = (\mathbf{I} - \mathbf{M})^{-1}$ and $\mathbf{I}$ is the identity matrix. Note that $\mathbf{K}$ can be regarded as a redefined cortical connection matrix which allows a one-step calculation of the cortical response to a given input vector as

$$v_i = \sum_{i^*=1}^{N_i} K_{i,i^*} (W_{R,i^*} u_R + W_{L,i^*} u_L).$$

Substituting Eq. 3 into Eq. 1 gives

$$\tau_w \frac{dW}{dt} = \mathbf{K} \mathbf{W} \langle \mathbf{u} \mathbf{u}^T \rangle = \mathbf{K} \mathbf{W} \mathbf{Q} \quad (4)$$

where $\mathbf{Q} = \langle \mathbf{u} \mathbf{u}^T \rangle$ is the input correlation matrix. For two inputs, this has the form

$$\begin{pmatrix} q_S & q_D \\ q_D & q_S \end{pmatrix}$$

where q_S is the within-eye correlation (for one unit, this is just the r.m.s firing rate) and q_D is the between-eye correlation. In general, we expect the firing patterns to be different in the two eyes, which guarantees that $q_S > q_D$.

Equation 4 can be solved for sum and difference terms of $\mathbf{w}_R$ and $\mathbf{w}_L$, i.e., by defining $\mathbf{w}_+ = \mathbf{w}_R + \mathbf{w}_L$ and $\mathbf{w}_- = \mathbf{w}_R - \mathbf{w}_L$. We then have

$$\tau_w \frac{d\mathbf{w}_-}{dt} = (q_S - q_D) \mathbf{K} \mathbf{W}_- \quad (5a)$$

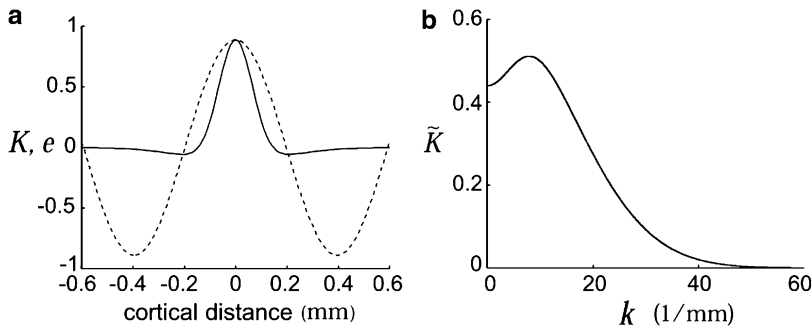
and

$$\tau_w \frac{d\mathbf{w}_+}{dt} = (q_S + q_D) \mathbf{K} \mathbf{W}_+ \quad (5b)$$

Solutions to Eq. 5a for $q_S > q_D$ take the form of a sum of exponentially growing modes determined by the eigenvalues and eigenvectors of $\mathbf{K}$. The eigenvectors are the discrete Fourier components of K and hence are periodic functions of cortical distance $|i - i^*|$. The dominant, most rapidly growing mode will be the one with the largest amplitude (Fig. 4). Solutions to Eq. 5b represent even more rapidly growing modes; however, these represent an increase in the values of the summed weights from both eyes to each cortical cell. Application of normalization rules will ensure that $d\mathbf{w}_+/dt = 0$. Periodic fluctuations in the value of $\mathbf{w}_- = \mathbf{w}_R - \mathbf{w}_L$ can be identified with the reciprocal periodic fluctuations in ocular dominance observed in the real cortex.

A more elaborate version of the above model was presented by Miller et al. (1989). In this model, two input layers (rather than just two units), labeled R and L , project to a sheet of cortical units. Position in the input layers is given by α or β and position in the cortex is given by x or y (note that for 2D arrays these are all 2D position vectors, and not indices). Units in each input layer project to a small area of the output layer as defined by an arbor function $A(x - \alpha)$. $A = 1$ if the distance $|x - \alpha|$ is less than a fixed arbor radius and is zero elsewhere. This formulation enforces a rigid retinotopic mapping with a cortical point x having a receptive field centered at position $\alpha = x$ in the input layer. Connection strengths from the R input layer change according to

$$\begin{aligned} \frac{dw_R(x, \alpha, t)}{dt} = & \varepsilon A(x - \alpha) \sum_{y, \beta} K(x - y) \\ & [Q_{RR}(\alpha - \beta) w_R(y, \beta, t) + Q_{RL}(\alpha - \beta) w_L(y, \beta, t)] \end{aligned} \quad (6)$$



Cortical Maps, Activity-Dependent Development, Fig. 4 (a) A Mexican Hat (difference of Gaussians) lateral interaction function, K , showing the largest eigenvector (e) or (equivalently) the largest of its Fourier components

(dashed line). (b) The Fourier transform of the function, $\tilde{K}$, showing a maximum at a positive wavelength, k (From Dayan and Abbott 2001)

where ε is a constant determining the overall growth rate, K is the cortical interaction function, and the functions Q_{RR} and Q_{RL} describe the dependence of the auto- and cross-correlation functions of LGN activity with distance. Miller et al. assumed that the within-eye correlation functions were positive Gaussians, while the between-eye correlations were either zero or negative Gaussians. The equation for dw_L/dt is obtained by interchanging L and R in Eq. 6.

The behavior of this system is similar to that of Eq. 4 with reciprocal periodic fluctuations in the ocular dominance of the cortical receptive fields developing across the surface of the cortex. As with Eq. 4, the periodicity is predictable from the frequency for which the Fourier power spectrum of K has a maximum amplitude. Less predictably, the model (and others like it) generates spatial patterns of branching stripes and elongated blobs that closely resemble the biological patterns. The production of stripes from circularly symmetric interactions can be regarded as a success of the models although the reasons for it, and possible quantification of the morphology so that model outputs and biological data can be more closely compared, have received relatively little theoretical attention.

Equation 6 can be applied to the development of orientation preference. In this model, the two input layers represent ON- and OFF-center retinal inputs. Model parameters are adjusted so that segregation of inputs occurs on a small scale, within receptive fields, leading to alternating

bands of ON and OFF inputs to each cortical unit and hence resulting in orientation selectivity. Although neighboring cortical cells have similar orientation preferences (the result of the overlap in their receptive fields), the overall layout of orientation in this model is nonperiodic, which is at odds with real orientation maps. A combined model, with ON and OFF layers for each of the two eyes, giving four input layers, has also been presented as a model for the joint development of orientation and ocular dominance maps (Erwin and Miller 1998).

Competitive Hebbian Models

Equation 3 shows that the cortical response to an input vector is the product of the vector and the weight vector for the same point, filtered by the lateral cortical interaction function. The response is proportional to the match (or projection) of the input vector in the space of weights (which has as many dimensions as there are inputs to each cell) and the weights of that cortical unit. This satisfies the intuitive notion that the stimulus that matches the receptive field profile best will be the one that gives the largest response. If the stimulus does not match the weights exactly, Hebbian modification will have the effect of changing the weights so as to make that cortical point more responsive to the stimulus in future presentations. In weight space, this means that the weight vector moves towards the position of the stimulus in the same space. As shown in Eq. 4, the assumption of linear cortical responses allows the calculation of weight

changes to be based on time-averaged correlation functions rather than on a sequential presentation of many different input patterns. This speeds up simulations but does not allow the possible effects of nonlinearities in the cortical response to be taken into account. Kohonen (1997) took an alternative approach to simplifying the calculation of cortical activities by finding the cortical point, i^* , whose weight vector best matched the input vector. Weight values of this point, and, crucially, values of surrounding cortical points in a region defined by a neighborhood function, are then adjusted to make these points more responsive to the stimulus. The fact that only a single cortical point is chosen, no matter what the stimulus, makes the learning competitive and highly nonlinear. The model has been applied in two forms, a high-dimensional version and a low-dimensional version. The setting for the high-dimensional version is similar to the one above where one or more sheets of cells project to a cortical sheet. In this case however, lateral cortical connections are assumed rather than specified explicitly. The winning cortical location is found by calculating $v_i = \mathbf{w}_i \mathbf{u}$ for all cortical locations and finding the point, i^* , for which v_i is a maximum. Weights are then changed according to

$$\mathbf{w}_i(t+1) = \alpha(t)[\mathbf{w}_i(t) + \varepsilon h(i^*, i) \mathbf{u}(t)] \quad (7)$$

where α is a normalization constant chosen to keep the sum of the weight values (or the sum of the squares) constant for each cortical point, ε is a learning rate constant and $h(i^*, i)$ defines the cortical neighborhood function in terms of the distance between points i and i^* , and $\mathbf{u}(t)$ is the input presented at timestep t . The neighborhood function h is normally a Gaussian and for cortical simulations typically is a few hundred microns in width. In simulations employing this rule, static input patterns are presented one at a time and weights are updated at each step. Adaptive weight updating means that cortical units become selectively responsive to those inputs presented during training and lose their responsiveness to stimuli not presented. The cortical neighborhood function, which causes points near the winning one to become more responsive to the same stimulus,

irrespective of their weight values, enforces continuity in the representation of the those points in the stimulus space. Hence, the Kohonen algorithm performs a dimension-reducing, topology-preserving mapping of points in a high-dimensional input space onto a two-dimensional cortex.

In the low-dimensional version, stimuli are represented not as activity distributions in sheets of cells but as points in a reduced feature space whose dimensions are the receptive field parameters represented in the map. Weights in this formulation represent stimulus selectivities of the cortical units rather than single synapses. The learning rule for this version of the model is

$$\mathbf{w}_i(t+1) = \mathbf{w}_i(t) + \varepsilon[\mathbf{u}(t) - \mathbf{w}_i(t)]h(i^*, i) \quad (8)$$

Here, point i^* is defined as the one for which $|\mathbf{u} - \mathbf{w}|$ is a minimum, i.e., it is the cortical point that is closest (most responsive) to $\mathbf{u}$. At each step, learning has the effect of moving $\mathbf{w}_{i^*}$, and its cortical neighbors, closer to $\mathbf{u}$, the currently presented stimulus. For visual cortex maps, the dimensions of the feature space inhabited by $\mathbf{w}$ and $\mathbf{u}$ might be chosen to include retinotopic position (2 dimensions), ocular dominance (1), and orientation (2) to give a five-dimensional space, though other parameters such as spatial frequency or direction of motion might also be added. This rule has a simple geometrical interpretation. Points i index positions in the cortex which may typically be represented on a rectilinear or hexagonal lattice. The function $\mathbf{w}_i$ maps these points into the feature space; hence, one can imagine the cortex as a 2D lattice of points folded into the space. Points $\mathbf{u}$ in the space are chosen one at a time, according to a probability distribution $p(\mathbf{u})$, and for each, the cortical point that is closest is found. This point and its neighbors are moved towards the stimulus. This process is repeated (possibly for many thousands of stimuli) until a map has formed.

Both high- and low-dimensional forms of the Kohonen model have been used to model visual cortex map development (Erwin et al. 1995; Swindale 1996, 2003). The low-dimensional version has the advantage of being simple to

implement and it is relatively fast to compute map layouts for reasonably sized areas of cortex (e.g., a simulation involving five dimensions and 200×200 sized cortex corresponding to an area of about 4×4 mm might take a few hours or less to compute). Unlike the linear correlation-based model discussed above, a fixed retinotopy is not assumed, allowing investigations of possible relations between local magnification of the retinotopic map and the rates of change of other map parameters.

Piepenbrock and Obermayer (2000) introduced a model that bridges the extremes of linear and competitive cortical activation models. In this framework, cortical activation is produced by a softmax function:

$$V_i = \frac{\exp(\beta \mathbf{w}_i \mathbf{u})}{\sum_i \exp(\beta \mathbf{w}_i \mathbf{u})} \quad \left(\text{or} \quad V_i = \frac{(\mathbf{w}_i \mathbf{u})^\beta}{\sum_i (\mathbf{w}_i \mathbf{u})^\beta} \right) \quad (9)$$

In the limit of $\beta \rightarrow \infty$, the output is a delta function positioned at the largest value of v_i leading to the winner-take-all behavior of the Kohonen model. In the limit $\beta \rightarrow 0$, $v_i \rightarrow \mathbf{w}_i \mathbf{u}$ giving the linear noncompetitive learning model.

The Elastic Net Model

The low-dimensional version of the Kohonen mapping algorithm (Eq. 8) causes a 2D cortical sheet to project into a higher-dimensional feature space in such a way that the projection is (a) locally continuous (resulting from the neighborhood function) and (b) the sheet approximates the distribution of stimuli within the space. The elastic net algorithm, devised by Durbin and Willshaw (1987), achieves a similar end, but by different means. The term “elastic net” applies to a lattice of cortical points which can be conceived as an elastic net with adjacent nodes on a square lattice connected by elastic. Under the influence of the elastic forces, the net would collapse to a point. However, stimuli – fixed points in the feature space – exert attractive forces on the net, which get stronger the shorter the distance between the stimulus and the cortical point. The algorithm calculates a stable configuration of the net

(i.e., cortical receptive field values) for a given, fixed set of stimuli distributed in the space in some manner. The learning rule is

$$\mathbf{w}_i(t+1) = \mathbf{w}_i(t) + \alpha \sum_j F_{ij} \cdot (\mathbf{v}_j - \mathbf{w}_i) + \beta \sigma \sum_{k \in N_i} (\mathbf{w}_k - \mathbf{w}_i) \quad (10)$$

where α and β are rate constants, and the summation in the second term is over the nearest neighbors k of point i . The “force” F_{ij} exerted by stimulus j on cortical point i is a Gaussian function of the distance between $\mathbf{w}_i$ and $\mathbf{v}_j$ (i.e., the response, assuming Gaussian receptive fields) normalized by the sum of the responses from all other cortical units, i.e.,

$$F_{ij} = \frac{\exp(-|\mathbf{v}_j - \mathbf{w}_i|^2 / 2\sigma^2)}{\sum_p \exp(-|\mathbf{v}_j - \mathbf{w}_p|^2 / 2\sigma^2)}. \quad (11)$$

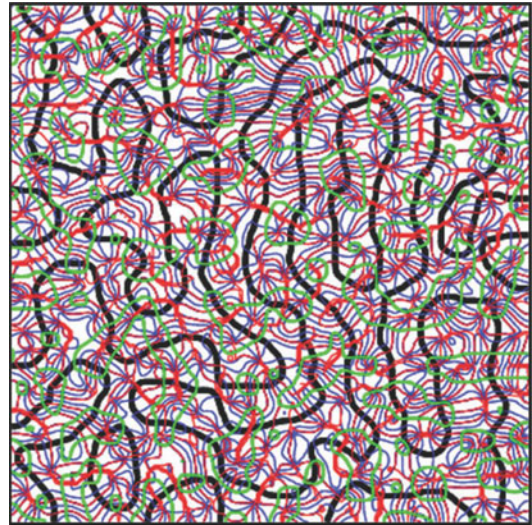
It should be noted that this formulation results in the elastic net algorithm being nonlocal, i.e., it is necessary to sum over every point in the cortex to determine the learning rate of any particular cortical point. This might be criticized as unbiological. However, normalization ensures that stimuli that are far away from any cortical point do not get ignored and exert forces that are as large as those exerted by stimuli that are closer to cortical units. Parameter σ scales the distance over which stimuli exert attractive forces. Initially this distance may be large, and it is typically reduced in size (a process referred to as “simulated annealing”) in order to make individual cortical points approach specific stimuli.

The expression for weight change can be integrated to yield an energy function:

$$E = -\alpha \sigma \sum_i \log \sum_j \exp(-|\mathbf{v}_i - \mathbf{w}_j|^2 / 2\sigma^2) + \frac{1}{2} \beta \sigma \sum_j |\mathbf{w}_j - \mathbf{w}_{j+1}|^2 \quad (12)$$

By definition, this has the property that $\Delta \mathbf{w}_j = -\partial E / \partial \mathbf{w}_j$. At each iteration, $\partial E (= -\Delta \mathbf{w}_j \partial \mathbf{w}_j)$ is guaranteed to be negative provided that $\Delta \mathbf{w}_j$ is

small enough that its sign is always the same as ∂w_j . Hence, the learning rule will always lead to a decrease in the value of E . The expression for E has an interesting interpretation. The term $\exp(-|v_i - w_j|^2/2\sigma^2)$ can be interpreted as the response of cortical point j to a stimulus i , a Gaussian function of the distance between the stimulus v_i , and the receptive field center, w_j . The summation over cortical points indexed by j thus measures the total response of the cortex to a given stimulus (assuming Gaussian tuning functions). The log of this term is then summed over i , that is, over all the stimuli. As in an entropy measure, the magnitude of this sum will be largest, and hence the contribution to E most negative, when the distribution of responses over the stimuli (for a fixed total sum) is flat. Hence, this part of E measures what has elsewhere been termed “coverage uniformity” – the idea being that the cortical maps ought to be organized so that the net response to a stimulus should be invariant with respect to parameters such as retinal location, eye of stimulation, and orientation (Swindale 1996). The second term in Eq. 12 measures the sum of all the distances between the net points as projected into the feature space. Hence, it is a measure of how smooth the map is. It can be minimized by contracting the net to a point, but this will clearly lead to extremely unequal responses to different stimuli. Depending on the ratio between parameters α and β , maps that minimize E will represent a trade-off between coverage uniformity and local smoothness. This fact, plus the finding that maps generated with the elastic net algorithm (Fig. 5) resemble real visual cortex maps (for a range of values of α and β), suggests that cortical maps also represent a compromise between coverage uniformity and local smoothness. Local smoothness is not in itself a functional constraint, but it may be related to axonal connection lengths, if it is assumed that the total number of connections between cell pairs increases with the similarity of their receptive fields. Since axons take up a significant proportion of the volume of cortex, arranging a map so that cells with similar receptive fields are as close to each other as possible (subject to the conflicting constraint of coverage uniformity) will reduce the volume of cortex.



Cortical Maps, Activity-Dependent Development, Fig. 5 Cortical map model produced by the elastic net algorithm. *Black lines (lowest layer)* represent ocular dominance boundaries, *green lines (top layer)* represent spatial frequency domain boundaries, *thin blue- and red-colored lines (middle layer)* show iso-orientation domain boundaries, and *thick red lines* mark lines across which direction preference reverses. These lines begin and end in orientation singularities. Note the frequent orthogonal intersections of all types of boundary. This figure can be compared with the experimental data shown in Fig. 1d (From Carreira-Perpinán et al. 2005)

Models Based on Plasticity of Lateral Intracortical Connections

The LISSOM (Laterally Interconnected Synergetically Self-Organizing Map) model was devised initially by Miikkulainen and has since been extended and explored by him and his colleagues (Miikkulainen et al. 2005). LISSOM differs from most other cortical map models by having modifiable short range excitatory and longer-range inhibitory lateral connections in the cortex. The model exists in various forms but a standard implementation has a single layer of retinal units, representing a visual input, connecting to layers of ON- and OFF-center LGN units via fixed, topographically ordered weights. These units project to a single layer of laterally interconnected cortical units. LGN and cortical units compute their responses as the dot product of the input and weight vectors with a

sigmoidal activation function that constrains activities to lie between 0 and 1. Cortical activities are computed by iterating an activation equation which includes the lateral inputs. Responses are calculated to individual stimulus patterns and then the LGN to cortex weights and the lateral weights are modified according the product of pre- and postsynaptic activities. Following this, weights are normalized divisively.

Much of the interest of the LISSOM model comes from studying its behavior when trained with structured visual inputs (e.g., natural images) which have higher-order correlations that are ignored or absent in standard correlation models. LISSOM incorporates Hebbian strengthening of inhibitory synapses in proportion to the product of pre- and postsynaptic activities. This rule was initially proposed by Barlow and Földiák (1989) and was termed “anti-Hebbian” learning by them. It has the effect of decorrelating cortical responses to correlated input patterns and leads to a more sparse representation of visual images. It is likely that the LISSOM learning rule will lead to the development of receptive fields that are the independent components of the input images which, as shown elsewhere for natural images, are oriented Gabor-like filters closely resembling the receptive fields of simple cells (Olshausen and Field 1996; Hyvärinen and Hoyer 2001).

The assumptions of LISSOM have mixed experimental support: there is evidence for Hebbian plasticity of inhibitory cortical synapses (Gaiarsa and Ben-Ari 2006); however, experimental results show that longer-range (1–5 mm) lateral cortical connections (which are the ones that would seem most likely to be involved in decorrelating images) are excitatory while inhibitory connections travel shorter distances (Gilbert 1992). However, these shorter range connections might still play a role in decorrelating cortical responses. The fact that much cortical map development takes place in the absence of visually driven activity (and hence interesting higher-order structure) suggests that natural images do not play a role in the formation of simple cell receptive fields so that the types of developmental plasticity that LISSOM would seem best at

modeling are perhaps those that occur at relatively late stages of map development.

Overview of “Simple” Models of Map Development

The models outlined above are variably, sometimes highly, simplified abstractions of cortical map development. The advantages of such simplification are many. They make simulations computationally feasible and they allow model behavior to be understood in terms of functional properties, such as wirelength minimization, that are likely to have been important constraints on the evolution of developmental mechanisms. Because the number of parameters is often small, empirical studies of the effects of changing them is much easier. Mathematical simplicity also allows for the possibility of making predictions based on analysis rather than computer simulation and for discovering relationships between different kinds of models. This form of understanding has allowed many of the models to be usefully applied to problems other than simulating cortical map development. For example, the elastic net algorithm can produce solutions to the traveling salesman problem, while the Kohonen algorithm, initially inspired by the problem of cortical map development, has arguably had more applications in areas outside developmental neuroscience than within it (Kohonen 1997). Many forms of connection between Kohonen, elastic net, and correlation-based models have been drawn, the upshot being that all of the models can be shown to perform gradient descent, at least approximately, on a function that represents a trade-off between the conflicting constraints of coverage uniformity and local smoothness (Goodhill and Sejnowski 1997).

“Realistic” Models of Cortical Map Development

These strengths notwithstanding, abstract models can be criticized because of the many details they leave out. These details are likely to play roles in

development that will be best understood in the context of a computational model. Real cortical development is the result of the guided outgrowth, branching, and retraction of axons, together with the reciprocal extension and retraction of dendrites and the coordinated formation and loss of synaptic connections between the two. The field of research studying these processes is large and rapidly progressing and a time should come when the vast majority of the genetic and molecular mechanisms underlying these processes will have been characterized. Arguably, such a reductionist description will not be complete until it can be shown that larger-scale phenomena can be correctly predicted as the outcome of lower-level molecular interactions. This will almost certainly necessitate highly detailed, though also highly constrained, computer modeling of biochemical, cellular, and multicellular interactions and environmental stimulation. A major value of such models may lie in their ability to predict a phenotype given one or more genetic mutations known to play a role in mental illness. Perhaps in anticipation of such a scenario (which may be decades away), several recent models of visual system development have simulated the behaviors of growing axons, incorporating branching and retraction rules, the effect of molecular markers (Ephrin and eph receptor gradients), neuronal growth factors, synaptic plasticity rules, and detailed simulations of retinal input activity patterns (Yates et al. 2004; Godfrey et al. 2009; Grimbert and Cang 2012). While they are capable of correctly replicating known macroscopic developmental features as well as a variety of experimental results, these models currently have the disadvantage that computations are slow to complete and this, plus their complexity, makes it very hard to assess and predict the effects of changes in rules and parameter values on model output. This situation is likely to change as computers get faster and as the models get more tightly constrained by biological findings.

Experimental Tests of Model Predictions

For the class of “simple” model discussed in this article, the interplay between experiment and

theory has been vigorous and interesting. Despite their success however, the assumptions on which most, if not all, of the models are based remain unproved. The most common of these is the postulate of radially symmetric Mexican Hat connectivity in the cortex. Although this exists in the retina, there is no evidence for a greater spread of inhibitory connections relative to the spread of excitatory connections in the cortex. The connections that go furthest in the visual cortex are excitatory and have a patchy, asymmetric spread which is at odds with radial symmetry (Gilbert 1992). It remains possible that there is a second class of lateral excitatory connections which are extremely local ($<250\ \mu\text{m}$), and these, combined with the known inhibitory ones, might provide the desired connectivity. However, this remains a speculation. Neither the Kohonen nor elastic net models explicitly require Mexican Hat connectivity; however, the elastic net model has a normalization term that requires summing over the entire cortex, and since no known intracortical connections span such distances, it is not clear how this might be implemented biologically. The winner-take-all mechanism of Kohonen likewise requires a biologically unfeasible comparison across the entire cortex (as does the related model of Piepenbrock and Obermayer). In these cases, more plausible models might be constructed that avoided global comparisons.

By definition, all the models discussed here rely (implicitly if not explicitly) on the presence of local correlations in the patterns of neural activity in the inputs to the cortex which come primarily from the LGN. Here, the experimental evidence is more supportive. Retinal wave activity has now been fairly thoroughly characterized. The waves introduce correlations between ganglion cell activity that fall off approximately as Gaussian functions with distance (Wong et al. 1993; Stafford et al. 2009). The wave activity is transmitted through the LGN to the cortex (Ackman et al. 2012) and hence is capable of influencing cortical development in the manner proposed by correlation-based models. The cross-eye correlations for spontaneous activity would be expected to be zero although Ackman

et al.'s data suggest the possibility of cross-eye coordination which has so far been assumed not to exist. There is a considerable body of evidence showing that blocking or altering patterns of spontaneous activity in the retina interferes with cortical map development. Examples of this include the finding that blocking spontaneous retinal activity prevents refinement of retinotopic maps in mouse visual cortex and in ferrets disrupts ocular dominance column formation, though it does not completely abolish it (Huberman et al. 2008). This evidence that the initial stages of ocular dominance column formation are activity dependent has to be set against the finding that ocular dominance columns could be observed in ferrets almost simultaneously with the initial innervation of layer IV by LGN afferents, as well as in ferrets whose eyes had been removed (Katz and Crowley 2002). The implication that molecular cues, rather than neural activity, may be involved in segregation is also supported by the recent finding of a molecular marker for ocular dominance columns (Tomita et al. 2013). Whether the molecular markers play a primary or a passive role in segregation, or interact with activity-dependent mechanisms, remains to be determined however.

The role of correlated activity in the development of orientation selectivity is also unclear, mostly because fewer experiments have been done to study the question. Blocking activity in retinal ON-center ganglion cells in ferret retinas prevents the development of orientation selectivity (Chapman and Gödecke 2000). This finding, plus evidence that differences in the spontaneous firing patterns of ON- and OFF-center ganglion cells emerge about halfway during the period of retinal wave activity (Kerschensteiner and Wong 2008), supports the ON-OFF competition-based model of Miller (1994). However, the model has the weakness that it does not produce realistic periodic patterns of orientation preference while the parameter regime required for simultaneous emergence of both ocular dominance and orientation preference is narrow (Erwin and Miller 1998).

In spite of their relative lack of empirical support, many of the models, especially those based

on Kohonen and elastic net algorithms, have been spectacularly successful in reproducing and in several cases correctly predicting experimental observations. Among these successes can be counted the visual resemblance of the layouts of ocular dominance and orientation domains produced by the majority of the models and those observed experimentally. The presence of half-rotation singularities in the orientation maps, their overall density, their tendency to lie in the centers of ocular dominance stripes, and the statistics of the distributions of positive and negative singularities are all correctly reproduced (Erwin et al. 1995; Swindale 1996, 2003; Goodhill 2007). The Kohonen and elastic net models all produce maps in which gradients of change in specific maps (e.g., ocular dominance or spatial frequency) tend to be orthogonal to each other, most likely because of the algorithms' optimization of coverage (Durbin and Mitchison 1990; Swindale 2000; Carreira-Perpinán et al. 2005). Orthogonal gradient relationships have been observed experimentally between orientation and ocular dominance, ocular dominance and spatial frequency, ocular dominance and disparity, and spatial frequency and orientation (Hübener et al. 1997; Yu et al. 2005; Nauhaus et al. 2012). A prediction that reducing the number of feature dimensions present in a map should lead to an increase in the spacing of the remaining features (Swindale 2004; Carreira-Perpinán et al. 2005) was also tested and confirmed (Farley et al. 2007).

Final Words

"Nothing in biology makes sense except in the light of evolution" and the models presented here arguably only make sense because they show how activity-based Hebbian learning rules can optimize a variety of properties likely to have been subject to selection pressure. These include efficiency of information representation as reflected by coverage uniformity and sparseness of coding: good coverage is needed to represent the information in images faithfully, while sparse coding minimizes energy use (Vincent et al. 2005).

Minimizing wirelength leads to a reduction in brain volume and faster processing (Chklovskii and Koulakov 2004). It may be pointed out however that these performance optimizations offer little insight into the kinds of cognitive learning that take place in the cortex after birth. At the other end of the nature-nurture debate, the forms of topographic connectivity that molecular gradients are known to generate seem a long way removed from the kinds of connectivity that would be needed to establish such complex things as universal rules of grammar or neonatal abilities such as speech and face recognition (Marcus 2004). A considerable amount of work remains to be done to show how innate, genetically based mechanisms can lead to the establishment of neural structures on which Hebbian (or other) correlation-based learning rules can operate to produce the behaviors that are critical to the functions of the cortex.

Cross-References

- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [Hierarchical Models of the Visual System](#)
- [Network Theory in Neuroscience](#)
- [Somatosensory Cortex: Organization](#)
- [Topographica](#)
- [Visual Hallucinations and Migraine Auras](#)
- [Wiring Principles, Optimization](#)

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Cortical Maps, Intrinsic Processes

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Definition

A cortical map is a neural representation of an input space (e.g., the two dimensions of visual space and/or features such as orientation preference and ocular dominance) such that similar features in the input space are represented by neurons which are nearby in the cortex.

Detailed Description

A common way in which axonal projections connect areas in the brain is via topographic maps. Although there is no precise mathematical definition of this term, roughly speaking it means that neurons that are physically nearby in the input region, or alternatively neurons that have similar functional properties, map to neurons that are nearby in the target region. The formation of these maps during neural development depends on both intrinsic (molecularly guided) and extrinsic (activity-dependent) cues and has served as a paradigm model for how such cues guide brain development more generally. Activity-dependent effects on map development are the subject of a separate chapter; here we consider the role of intrinsic cues.

The formation of topographic maps has been particularly well studied in the visual system. A paradigmatic example is the projection from the retina to the tectum (frogs, fish, birds)/superior colliculus (mammals). To explain how such maps develop, Sperry (1963) defined the key theoretical idea of chemospecificity: a process of matching of chemically defined labels between the input and target structures. One particularly elegant form of

this idea is that the input structure contains a spatial concentration gradient of a receptor, which is matched to a spatial concentration gradient of a ligand in the target structure. In the 1990s, this prediction was experimentally confirmed via the discovery of gradients of Eph receptors in the retina, and their ligands the ephrins in the tectum/superior colliculus (Fig. 1; McLaughlin and O'Leary 2005).

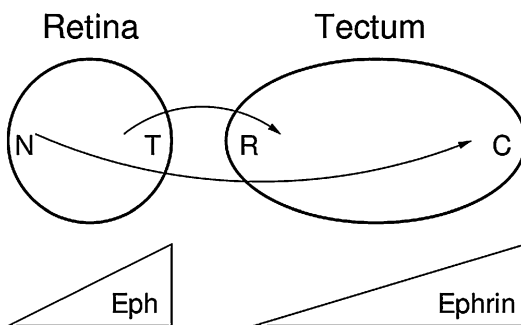
Numerous experimental manipulations to the retinotectal system have provided a rich dataset of mapping outcomes following either molecular disruptions of the gradients (Lemke and Reber 2005; Huberman et al. 2008; Cang and Feldheim 2013) or surgical disruptions of the input or target structures (such as removing or rotating parts of the eye and/or the tectum) (Udin and Fawcett 1988; Goodhill and Richards 1999). Together these experiments provide many constraints for theories of map formation.

Early models in the 1970s and 1980s addressed basic principles for how gradient matching could establish maps in general and how versions of these principles could reproduce many of the surgical manipulation experiments in the retinotectal system (Willshaw and Price 2003; Goodhill and Xu 2005). These principles include competition for target space and other types of fiber-fiber interactions in addition to gradient matching. In the 1990s, models were proposed based closely on the

properties of the newly discovered Eph and ephrin gradients, though often without also considering the surgical manipulation data (Goodhill and Richards 1999). More recent models have been particularly concerned with data from recent gene disruption experiments, where, for instance, Eph levels are changed in only a subset of retinal cells or where a much smaller than normal number of retinal cells send axons to the tectum (Simpson et al. 2009). The mathematical principles underlying all these models are quite diverse, though many are based on the idea of optimizing an energy function for the map. Although no one modeling approach has yet become canonical, together these models have helped to clarify the relative roles and importance of the different biological mechanisms (most notably gradients, competition, and fiber-fiber interactions) involved in map formation.

Intrinsic processes of map development in the cortex have been far less studied than for retinotectal maps; however, there is recent evidence that similar principles of matching between Eph and ephrin gradients also guide their initial formation (Huberman et al. 2008). An intriguing question is whether the formation of functional maps in the cortex, such as ocular dominance and orientation maps in primary visual cortex, could also be partly controlled by intrinsic processes. Recent data has found molecular differences between regions of very young cat visual cortex which are reminiscent of the patterns of ocular dominance columns that subsequently develop, though a causative link has yet to be established. Similarly, clonally related neurons (those arising from a single progenitor cell) in rat visual cortex have been found to have orientation preferences that are more similar than non-clonally related neurons, challenging purely activity-dependent accounts for the development of orientation preference.

In summary, models up to now have played a critical role in demonstrating the effectiveness (or otherwise) of principles for how map development could occur and dissecting how the precise details of particular biological processes affect map structure. However, the constant flow of new data continues to provide new questions and challenges, which will provide inspiration for modeling work in this area for some time to come.



Cortical Maps, Intrinsic Processes, Fig. 1 Gradient matching in the retinotectal system. Eph receptors are expressed in an increasing nasal (N) to temporal (T) gradient in the retina, while ephrin ligands are expressed in an increasing rostral (R) to caudal (C) gradient in the tectum. The Eph-ephrin interaction is repulsive, so that regions of retina with high levels of Eph receptor map to regions of tectum with low levels of ephrin ligand, and vice versa

Cross-References

► Cortical Maps, Activity-Dependent Development

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ECoG	Electrocorticogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-related potential
SCI	Spinal cord injury

Definition

Neuromotor prostheses or, more commonly referred to as brain-machine interfaces (BMIs) or brain-computer interfaces (BCIs), refer to systems controlling prosthetic devices via an interface with ensembles of the neurons often from the cortex. Electrical potentials emanating from neurons in the vicinity of an electrode interface are decoded to extract useful control signals for external devices, typically an artificial limb or a robot. Nonelectric potentials such as the metabolic signals are also being used in some BMIs.

Detailed Description

Cortically controlled BMIs utilize voluntary modulations of cortical neurons in controlling an external prosthetic device. The system-level architecture of a BMI setup is shown in Fig. 1. Individual neural signals, i.e., action potential spikes, local field potentials, ECoGs, and EEGs, or a combination of these signals, can be used to control a motor prosthesis. Temporal and spectral modulations of these signals are typically mapped (or decoded) to generate a resultant control signal, which is then fed to an actuator. The user is normally provided with a feedback signal on the current state of the device. Visual feedback has been the most common type, although, more recently, augmented feedback systems utilize tactile, proprioception, and other sensory substitution modalities.

BMIs have been shown to have great potential in restoring motor function in patients with severe motor dysfunction, to extend the motor capabilities of amputees, and to assist in neural rehabilitation. Several experimental trials on human subjects and nonhuman primates have shown the viability of BMIs. Nevertheless, their clinical applicability is still limited and is a subject of further research.

Cortical Motor Prosthesis

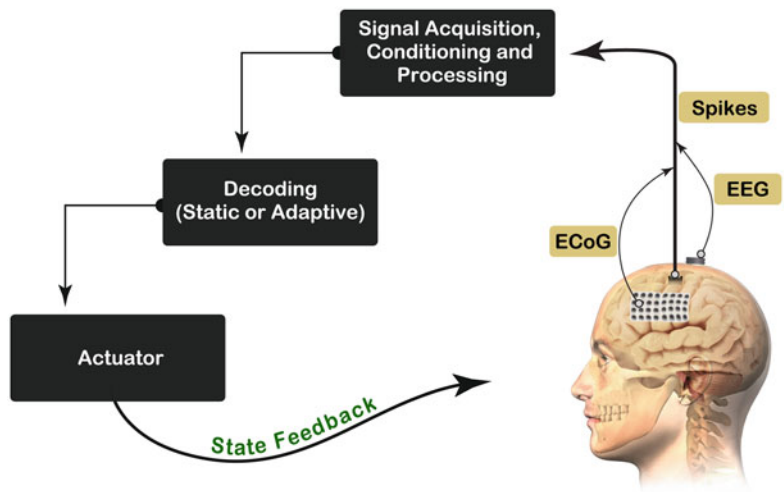
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Abbreviations

ALS	Amyotrophic lateral sclerosis
BCI	Brain-computer interface
BMI	Brain-machine interface
ECG	Electrocardiogram

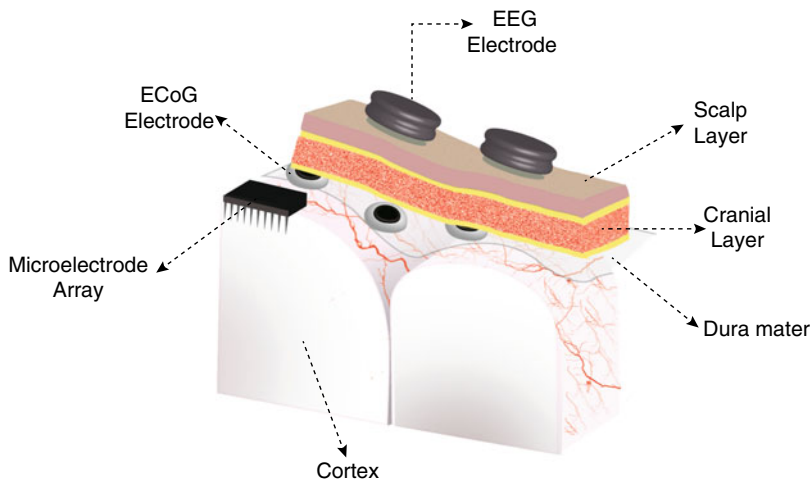
Cortical Motor Prosthesis,

Fig. 1 Schematic diagram of a closed-loop BMI. Neural signals acquired through various electrode technologies are processed to extract information such as spike rate, spectral features, etc. The decoder then maps neural information to a control variable of the actuator. The state of the actuator is provided as feedback to the user



Cortical Motor Prosthesis,

Fig. 2 Schematic representation of various recording modalities. EEG electrodes are placed over the scalp. ECoG arrays collect signals from the surface of the cortex, while microelectrode arrays penetrate the brain parenchyma



A typical BMI is comprised of an electrode interface, a signal processing setup, a decoding algorithm, an actuator, and a sensory feedback system. The following sections discuss the various signals acquired using different electrode systems, some of the potential decoders, actuator control strategies, and feedback modalities. The translational nature and the possible pathways of future BMIs are also discussed briefly.

and also by the degree of invasiveness needed to acquire them (see Fig. 2). Table 1 shows the various classes of neural signals acquired from different electrode interfaces. These signals can be decoded to estimate the neural state and/or motor intentions and subsequently used to control a prosthetic device.

Action Potential Spikes

Neural Signals

Recorded neural signals can be classified according to their temporal and spatial resolution

Neurons exhibit brief 1 ms de- and repolarizations, called action potentials or spikes (Fig. 3a), which are carried forward by other synaptically linked neurons. They can be spontaneously

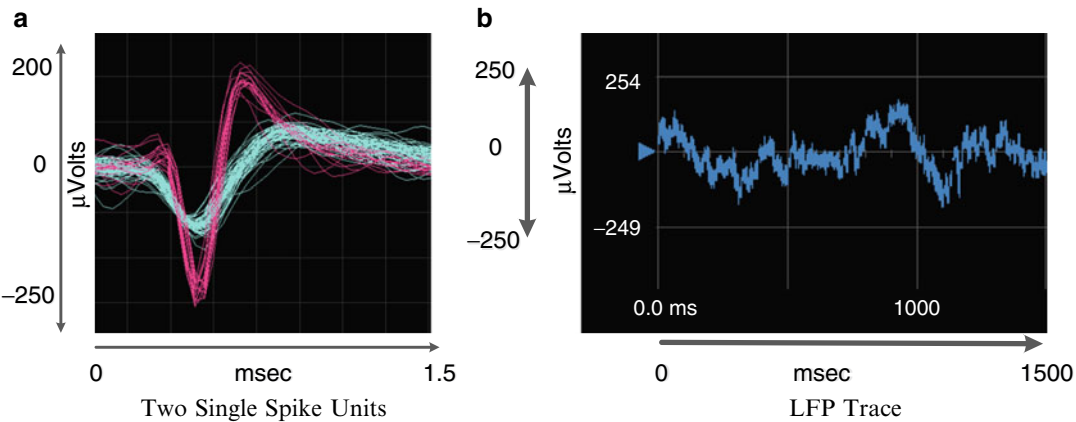
generated or evoked by a stimulus. Volitional intentions or mental imagery of motor actions also elicits neural spikes. These frequency-modulated discrete signal events can be recorded and mapped to an actuator or end effector. Multi-electrode arrays, tetrodes, and microwire arrays are some of the widely used penetrating electrodes used in recording spike activity. Primary motor cortex (M1) has been the *prima facie* location to record neural signals for BMIs, although multiple frontal and parietal cortical areas have also been used by researchers. Over the past 50 years, strong evidence has emerged that M1 neurons encode signals representing limb movement in space. Earlier experiments demonstrated encoding of kinetic variables in M1, while a majority of the present BMIs attempt to decode kinematic variables such as direction, position, and velocity.

Cortical Motor Prosthesis, Table 1 Types of neural signals

Signal type	Temporal resolution (ms)	Spatial resolution (mm)
Action potential spikes	≤ 1	10^{-1}
Local field potentials	~ 10	10^{-1} –1
Electrocorticogram	~ 10	1–10
Electroencephalogram	~ 25	> 10
fMRI	~ 1000	1
fNIRS	~ 1000	> 10

Local Field Potentials

Local field potentials (LFPs) are another class of neurophysiological signaling recorded from penetrating microelectrodes as continuous low-frequency signals (unlike spikes which are discrete events) (see Fig. 3b). The “spatial reach” of these signal sources ranges from < 1 mm (Katzner et al. 2009) to over 1 cm at times depending on the electrode size. Mathematical models and electrophysiological experiments suggest that LFPs represent the aggregate synaptic activity from a group of neurons near the electrode tip. Some experimenters, however, argue that the LFPs are also comprised of “volume-conducted” electrical activity from nonlocal sources. Despite the controversy as to the origin of the LFP, changes in LFP signals have been shown to be linked to motor functions as well as to other important cortical processes such as memory. Its increased spatial resolution compared to noninvasive recording, spectral fidelity, and long-term stability for chronic recording has made this signal modality a viable option for BMI applications. Information from LFPs are extracted from different frequency bands (0–300 Hz) (Andersen et al. 2004; Flint et al. 2012, 2013; Hwang and Andersen 2013). LFPs in certain frequency bands also exhibit widespread synchronous couplings with neurons in motor cortex (Donoghue et al. 1998).



Cortical Motor Prosthesis, Fig. 3 Spike waveforms and local field potential trace

Electrocorticogram

ECoG signals are continuous neural recordings from the surface of the cortex either beneath (subdural) or above (epidural) the dura mater. A strip or grid of electrodes with interelectrode distances of ~ 10 mm (in human implantations) and electrode diameter of ~ 4 mm (with 2.3 mm exposed) is placed on the cortex to record ECoG signals. Computational modeling studies (Slutzky et al. 2010) reported optimal electrode spacing (for maximized information and minimized data redundancy) to be 0.6 mm (subdural) and 0.6–0.9 mm (epidural) for rat cortices and 1.7–1.8 mm (subdural) and 9–13 mm (epidural) for human recordings. ECoGs were originally employed in the domain of clinical studies where human subjects with epileptic seizures or tumors were examined. Recently, ECoGs are shown to have potentials for BMI applications. Higher spatial resolution, bandwidth, signal-to-noise ratio (SNR), immunity to artifacts such as EMG or EOG, and signal stability are some of the advantages of ECoGs over other semi-/noninvasive recording techniques. Similar to LFPs, ECoG activity can be observed at various frequency bands, i.e., theta (4–8 Hz), mu (8–12 Hz), beta (18–25 Hz), and gamma (>40 Hz). The low-frequency bands (mu/beta) are spatially less specific and exhibit amplitude attenuation on movement onset, while the gamma oscillations increase in their amplitude and are spatially specific (Brunner et al. 2009). Schalk et al. (2007) have also observed time-domain features, called the local motor potentials (LMP) that could be used for decoding. Discrete decoding in an online paradigm (Milekovic et al. 2012) has also been reported to establish the viability of ECoG signals for BMI applications.

Electroencephalogram

EEG signals are the least invasive in the hierarchy of neuroelectrophysiological recordings. Differential electrodes placed on the surface of the scalp record the potential difference generated by neuronal sources in and around ~ 10 cm.

Positioning the electrodes is often referred to as the electrode montage and varies between 21, 74, and 142 electrodes located at different scalp landmarks. Events that elicit neural activity would generally be detected as event-related potentials (ERPs) in EEG signals. The averaged ERP component could be *exogenous*, meaning it is recorded within 150 ms of the event, or *endogenous*, a more sustained component. P300 signals are ERPs occurring at an average latency of 300 ms from stimulus event but can vary in latency between 250 and 750 ms and have been a subject of interest in BCI applications (Farwell and Donchin 1988; Li et al. 2010; McFarland et al. 1997, 2010; Nijboer et al. 2008b). EEGs are easily affected by non-brain physiological signals such as EMG, EOG, and ECG, which needs to be detected and eliminated for reliable BMI control.

Metabolic Signals

Apart from the neuroelectrophysiological signals, researchers are also investigating metabolic signals for their suitability in BMI/BCI applications. Sitaram et al. (2009) have used *functional near-infrared spectroscopy* (fNIRS) signals for a BCI discrete classification system. The *fNIRS* technique utilizes *blood-oxygen-level-dependent* (BOLD) responses to detect brain activity. As the neural activity increases, the total hemoglobin and the oxyhemoglobin (oxy-Hb) concentrations in the blood increase, while the deoxyhemoglobin (deoxy-Hb) concentration decreases, in the vicinity of the active brain region. Since oxy-Hb and deoxy-Hb absorb light wavelengths differently, changes in their concentration can be measured using optical diodes serving as light transmitters and receivers. The *fNIRS* has spatial and temporal resolutions in the order of centimeters and seconds, respectively. The most widely studied imaging technique that uses BOLD responses to infer brain activity is *functional magnetic resonance imaging* (fMRI) (Wolpaw and Wolpaw 2012). The oxy-Hb is nonmagnetic, while the deoxy-Hb is slightly magnetic causing a perturbation in the incident magnetic field, thereby changing the strength of the magnetic field. The proportional

changes in the magnetic field due to the presence of deoxy-Hb can then be used in estimating the BOLD response. Since hemodynamic changes are slow, these imaging techniques have temporal resolutions on the order of seconds.

Decoding Systems

Neurons of the motor cortex can encode kinetic variables such as force and torque (Fagg et al. 2009; Cabel et al. 2001; Cheney and Fetz 1980; Sergio et al. 2005; Smith et al. 1975; Taira et al. 1996) or kinematic variables such as position, velocity, and acceleration (Ashe and Georgopoulos 1994; Fu et al. (1993, 1995)). Some neurons encode combinations of these variables (Paninski et al. 2004; Wang et al. 2007; Lawhern et al. 2010). Systems that are used to decipher the encoded values or parameters are termed decoders. However, decoders can map neural data to an output without the need to learn any underlying encoding model. Decoders can be static, adaptive, or stochastic. Linear static decoders, such as the Wiener filters, are widely used due to their simplicity.

Static Decoders

One of the earliest decoding algorithm in systems neuroscience is the so-called “population vector” algorithm that has been used to relate ensemble neural firings to movement parameters, typically direction and velocity. Georgopoulos et al. (1986) observed that neurons tend to fire the most when the actual movement vector is aligned with a direction termed the “preferred direction” and follow a cosine tuning curve in their rate of discharge. The firing rate ($z(D)$) is related to the movement direction as given in Eq. 1:

$$z(D) = \alpha + \gamma \cos \theta_{PD} \quad (1)$$

where θ_{PD} is the angle between the preferred direction P of the neuron and the actual movement direction D . The movement direction can then be decoded by the weighted sum of the neural

firing rate from an ensemble of N neurons, as given by Eq. 2:

$$V(D) = \sum_{i=1}^N f_i(D) \quad (2)$$

where $f_i(D) = (z_i(D) - \alpha_i)P_i$.

Note that each neuron's firing history over multiple time points is not explicitly included in the population decoding.

Wiener filters take into account these time-delayed neural activities and map them to a control variable, either kinetic or kinematic (see Eq. 3):

$$\hat{y} = Z\beta \quad (3)$$

where the neural activity matrix Z (columns corresponding to different time delays of multiple neurons and rows corresponding to different time points) is mapped to the control variable $\hat{y}$ via the system coefficients β (a column vector where each component corresponds to a different time delay). Note that the Wiener filter does not begin with an explicit encoding model like the population vector algorithm. The Wiener filter has the advantage that a closed-form solution for the beta coefficients exists that is optimal by minimizing the error between the predicted and training control variable. With limited training data, regularization terms can be added to the error equation such that large coefficients are penalized resulting in the ridge-regression solution for β . Solving for β in a ridge-regression framework is shown in Eq. 4, with a ridge parameter λ :

$$\beta = (Z^T Z + \lambda I)^{-1} Z^T y \quad (4)$$

Adaptive Decoders

Decoders capable of adapting to the changing input signal statistics are referred to as adaptive decoders. The neural activity matrix is often noisy and the intended motor output can be estimated using optimal linear filters such as the Kalman filter (which adapts the filter gain according to

Cortical Motor Prosthesis, Table 2 Kalman filter algorithm

$x_k = Ax_{k-1}$	State prediction
$\Sigma_k = A\Sigma_{k-1}A^T + R$	Covariance prediction
$K_k = \Sigma_k C^T (C\Sigma_k C^T + Q_k)^{-1}$	Kalman gain
$x_k = \tilde{x}_k + K_k(z_k - C\tilde{x}_k)$	State update
$\Sigma_k = (I - K_k C)\Sigma_k$	Covariance update

the changing covariance estimate of the neural signal). BMIs use a discretized, time-invariant (constant parameters) version of the filter. Kalman filters are linear Gaussian-structured filters and can be easily understood in a state-space framework. It is intended to estimate the state vector, x_k , at each time step taking into account the observed firing rate z_k . In BMIs, the state vector could be the kinematics of a prosthetic limb, $x_k = [\text{position}, \text{velocity}, \text{acceleration}]^T$. The state transition equation for x_k is a linear function given by Eq. 5:

$$x_k = Ax_{k-1} + \epsilon_k \quad (5)$$

where A is the state transition matrix and $\epsilon_k \sim \mathcal{N}(0, R)$ models the transition uncertainty. Similarly, the neural firing rates are again linearly related to the state vector:

$$z_k = Cx_k + \delta_k \quad (6)$$

The firing rate noise is described by $\delta_k \sim \mathcal{N}(0, Q)$. The algorithm for Kalman filtering can be described as a two-step process where the state transition and its covariance are predicted in the first step and subsequently updated using the observed neural firing rates. Table 2 shows the pseudo-code version of the Kalman filter. The matrices A , R , C , Q are chosen such that the joint probability between the kinematic variable X_N and the firing rates Z_N from N training sets, $p(X_N, Z_N)$, is maximized (Black and Donoghue 2007). The closed-form solution yields the matrices as described in Table 3 (Wu et al. 2006). As the state transition progresses with time, it becomes nearly independent of the initial state, and hence, a reasonably chosen random initial condition should suffice for a satisfactory filtering.

Cortical Motor Prosthesis, Table 3 Kalman filter matrices

$A = \left(\sum_{k=2}^N x_k x_{k-1}^T \right) \left(\sum_{k=2}^N x_{k-1} x_{k-1}^T \right)^{-1}$
$R = \frac{1}{N-1} \left(\sum_{k=2}^N x_k x_k^T - A \sum_{k=2}^N x_{k-1} x_{k-1}^T \right)$
$C = \left(\sum_{k=1}^N z_k x_k^T \right) \left(\sum_{k=1}^N x_k x_k^T \right)^{-1}$
$Q = \frac{1}{M} \left(\sum_{k=1}^N z_k z_k^T - C \sum_{k=1}^N x_k x_k^T C^T \right)$

Recently, a modified version of the Kalman filter, referred to as recalibrated feedback intention-trained Kalman filter (ReFIT-KF), was reported that allows users to maintain zero velocity when the target is reached (Gilja et al. 2012). According to this algorithm, in a 2D cursor reaching experiment that decodes both position and velocity, the uncertainty in the estimate of the position p_k was “causally intervened” with a more certain position $\hat{p}_k$ such that the intended movement is always directed towards the minimal path to the target.

Nonparametric Decoders

Under the Bayesian framework, the decoding paradigm can be viewed as estimating the maximum a posteriori value of $p(x_t|Z_t)$, i.e., the movement variable conditioned on the firing rate (Wu et al. 2006). The posterior probability is related to the prior and the likelihood (under Markov assumptions) as

$$p(x_t|z_t) \propto p(z_t|x_t) \times \int p(x_t|x_{t-1})p(x_{t-1}|Z_{t-1})dx_{t-1} \quad (7)$$

Here, the prior and the likelihood can be arbitrary distributions, although Kalman filter assumes them to be Gaussian. In order to decode posterior distributions that are nonlinear and non-Gaussian, nonparametric methods such as particle filters can be used. Particle filters represent the posterior distribution using a set of random samples, or *particles*, (N_p), and their associated state estimate and weights, $\{x_{i,t}, \mathcal{W}_{i,t}\}$, where $i = 1, \dots$,

N_p . There are several flavors of particle filtering available, and one interesting variant, the auxiliary particle filter (APF) (Chen 2003), is discussed here.

The objective is to determine an approximation of the posterior distribution:

$$\hat{p}(x_t|Z_t) \approx \sum_{i=1}^{N_p} \mathcal{W}_{it} \delta(x_t - x_{it}) \quad (8)$$

In order to estimate the weights $\mathcal{W}$, the APF approach uses a two-step process which samples weights from a proposal distribution (q_a) and updates the weight according to some likelihood estimate. Since the actual posterior distribution is unknown and cannot be sampled from, the proposal distribution is used. This could be a simple distribution with Gaussian parameters or a kernel that reflects neural tuning curves from the ensemble. An algorithmic representation of the APF is given in Table 4. These steps are repeated for every time step. Particle filters have been used in decoding the hippocampal place cells (Brown et al. 2001; Mountney et al. 2009) and retinal neurons (Brown et al. 2003), and a real-time implementation is discussed in Mountney et al. (2011).

Cortical Motor Prosthesis, Table 4 Particle filter algorithm

$\hat{x}_{i,t} \sim q_a(x_t x_{i,t-1}, z_t)$	Sample from proposal distribution
$W_{i,0} = 1/N_p, i = 1, \dots, N_p$	Initialize the weights
$\hat{\mathcal{W}}_{i,t} = \mathcal{W}_{i,t-1} \times \frac{p(z_t \hat{x}_{i,t})p(\hat{x}_{i,t} \hat{x}_{i,t-1})}{q_a(x_{i,t} \hat{x}_{i,t-1}, z_t)}$	Calculate the 1st stage weights
$\bar{W}_{i,t} = \frac{\hat{\mathcal{W}}_{i,t}}{\sum_{n=1}^{N_p} \hat{\mathcal{W}}_{n,t}}$	Normalize weights
$\hat{x}_t \sim q_b(\hat{x}_t \hat{x}_{t-1}, z_t)$	Resample from the new proposal distribution
$\mathcal{W}_{i,t} = \mathcal{W}_{i,t-1} \times \frac{p(z_t \hat{x}_{i,t})p(\hat{x}_{i,t} \hat{x}_{i,t-1})}{q_b(\hat{x}_{i,t} \hat{x}_{i,t-1}, z_t)}$	Calculate the 2nd stage weights
$\mathcal{W}_{i,t}^{aux} = \frac{\mathcal{W}_{i,t}}{\sum_{n=1}^{N_p} \mathcal{W}_{n,t}}$	Normalize weights
$p(x_t Z_t) \approx \sum_{i=1}^{N_p} \mathcal{W}_{i,t}^{aux} \delta(x_t - \hat{x}_{i,t})$	Posterior distribution

Decoder Initialization

The process of mapping *a priori* neural signals to any control variables, thereby determining the decoder filter coefficients, is termed decoder initialization. The decoder coefficient matrix to transform neural firing rates into control signals can be estimated by concurrently recording the neural data and the actual kinematic/kinetic variable, as the subject executes the task. This popular mapping approach is often referred to as *biomimetic decoding*. When the subjects have intact nervous systems and limbs, performing the kinematic task is trivial and the biomimetic decoding is preferred. However, the mapping becomes nontrivial when the kinematic variables are not observable, such as in paralyzed or amputee patients. This could be resolved by resorting to either (i) an observation-based initialization or (ii) an unsupervised decoder that does not need the kinematic variable. Subsequent sections below explain briefly the different decoder initialization approaches. Once the decoder is initialized, it could remain static or adaptive.

Observation-Based Initialization

Several regions of the cortex have neurons exhibiting congruent activity during active movement as well as passive observation of the same task (Dushanova and Donoghue 2010; Tkach et al. 2008). Primary motor cortical activity profiles were first reported to be similar when recorded from macaques engaged in a particular task and also while merely observing the same task (Tkach et al. 2008). This idea could be used to initialize a decoder where the subject can imagine a particular movement or observe a relevant task and the neural signals are recorded and mapped to the observed movement. In a BMI experiment reported in Balasubramanian et al. (2013), neural activity collected from the primary motor cortex, as a chronically amputated macaque was observing a robot moving in a desired trajectory, was used to initialize a decoder. Clanton et al. (2013) have used

observation-based decoder initialization in controlling a multiple DOF robot involving translation, rotation, and grasp aperture.

Unsupervised Decoder Initialization

The unsupervised initialization approach ignores the unobservable kinematic variable and shifts the emphasis on the neural signal dynamics to determine the decoder filter coefficients. In one unsupervised approach, decoders are assumed to function as linear correlators and the coefficients are sampled from a multivariate distribution with covariances matching the neural data. Such a decoder is expected to have a matching frequency response to the neural dynamics. A minimum-norm Mahalanobis distance solution was implemented in Badreldin et al. (2013) for initializing a velocity decoder. The coefficients were chosen such that the Gaussian properties of the output are preserved.

At a system level, the decoders and the ensemble of neurons driving them can be viewed as two coupled systems, and either or both can be adaptive. Adaptive decoders (discussed in the previous section) can minimize control errors by adapting the filter coefficients. On the other hand, when a static decoder is initialized using the unsupervised approach, adaptation occurs at the neuronal side of the coupled system.

Operant Conditioning

A proven technique in learning to adapt to a decoder is *operant conditioning*, which relies on providing a reinforcement stimulus whenever a desired behavior occurs (Seel 2012). As learning occurs, the occurrence frequency of the desired behavior increases. In BMI experiments with nonhuman primates, desired behavior can be reinforced using juice reward or fruit bits. Positive reinforcements have been used by Fetz and colleagues in training monkeys to volitionally modulate single-neuron firing activity (Fetz 1969; Fetz and Finocchio 1971). Fetz and Finocchio (1975) also showed that volitional neural modulations can be achieved with complete dissociation from any peripheral muscle

contractions. This degree of flexibility of motor cortex (Wander et al. 2013) has been harnessed in developing BMIs further. Several experiments have successfully used operant conditioning as a mode in BMI training. Recent experiments with a primate model of amputation have used operant conditioning in training macaques to control a multiple DOF robot (Balasubramanian et al. 2013).

Actuator Modalities and Controlled Devices

Experimental BMI studies have reported extensively on cortical control of virtual objects such as computer cursors in 2D or 3D space (Black et al. 2003; Hatsopoulos et al. 2004; Santhanam et al. 2006; Serruya et al. 2002; Shpigelman et al. 2008; Taylor et al. 2002). Tasks include reaching predefined target locations either in sequence or at random, tracking a randomly moving target, free-choice targets with varied reward probability, etc. These experiments were useful in devising a translational pathway to neural motor prosthesis and rehabilitation. Robots, whole-arm manipulators, and virtual avatars allow BMIs to operate many degrees of freedom in a 3D space (Carmena et al. 2003; Lebedev et al. 2005). When controlling a multiple DOF robot using BMIs, decoded signals can (a) operate directly on the joint space controlling the individual joints or (b) define the end-effector position and orientation, while the controllers determine the instantaneous joint configuration. Smooth movement controls can be achieved with a minimum-jerk (Flash and Hogan 1985; Shadmehr 2005) solution, mimicking regularities in biological motion. For nonredundant robots (number of DOFs ≤ 6), a unique inverse kinematic solution is achievable for a given end-effector definition. Redundant robots can have infinite solutions to a given spatial coordination and orientation and hence need numerical controllers or constrained controllers such as null-space controllers (Nemec and Zlajpah 2000; Corke 2011). Finer motor controls such as grasping can be controlled in a reduced dimension

synergistic space rather than the joint space. A large proportion of the variance observed in natural grasp kinematics can be accounted for with few principal components (Ingram et al. 2008; Mason et al. 2001; Santello 2002). For example, the hand has more than 20 DOFs (say, n) and any hand posture belongs to an R^n dimension representation. However, natural grasping behavior resides in a much smaller representational space so that dimensionality reduction techniques such as principal component analysis can be used. The principal components (or *eigengrasps* (Ciocarlie et al. 2007)) of this high-dimension space form a synergistic basis for the complex postures of the hand. A single basis can then be used to represent grasp aperture and is independent of the number of fingers. Similarly, other bases can represent pronation/supination, thumb abduction/adduction, etc. These basis sets offer a direct mapping between a decoded control signal and a control synergy.

Feedback in a BMI

In BMIs, feedback about the state of the prosthesis is essential to compensate for any movement errors. Visual feedback is the predominant feedback modality that uses the natural sensory pathway. Additionally, proprioceptive, tactile (Nicoletis 2003), and, to some extent, auditory feedback (Nijboer et al. 2008a; Schreuder et al. 2010) are being investigated as promising modalities for BMIs. Artificial feedback systems provide tactile and/or proprioceptive feedback in the form of mechanical stimulation of peripheral nerves or electrical stimulation of residual nerves (Hatsopoulos and Donoghue 2009). Extended physiological proprioception (EPP), an approach which uses residual tactile and proprioceptive sensations as feedback pathways, is another important natural form of feedback to augment the visual system. Subjects with spinal cord injury (SCI) and with subsequent motor dysfunction may retain some residual somatosensation (Eide et al. 1996; Finnerup et al. 2004; Grill et al. 2009), which could be taken advantage of for providing EPP feedback.

Multisensory Feedback

Current BMIs are exploring different ways to effectively integrate information from multiple sensory modalities. It is well established that sensory inputs alter motor decisions, when provided as feedback. Experimental evidence has suggested that augmenting feedback with more than one sensory modality provides usable mutual information to the motor cortex (Suminski et al. 2009). Alterations in movement trajectories were observed as early as 70 ms following a proprioceptive cue (Crago et al. 1976). Visual feedback is relatively slow and influences the motor commands around ~150 ms. Macaques performing a target tracking task in a 2D space were able to reach the target faster when the visual feedback was augmented with proprioception. An exoskeleton was used by Suminski et al. (2010) to provide kinesthetic feedback, in addition to vision, about cursor positions in the 2D plane. The exoskeleton is one way of providing EPP to BMI users. Under congruent feedback conditions, BMI performance improved by 40% in terms of the time to target and path length (the ratio between the actual path and the minimal path to target).

Sensory Substitution

In neuromotor prosthesis control, providing biologically plausible sensory feedback (primarily haptic feedback) to the user is a challenging issue and substituted feedback is viable in certain situations. Haptic feedback can be substituted by alternative feedback modalities such as vibrotactile or pneumatic pressure and delivered to a different region of the body (Kaczmarek et al. 1991). Vibrotactile feedback to the tongue has been a successful substitution approach used by visually impaired persons in detecting obstacles (Chebat et al. 2011). Several studies have used vibrotactile stimulation as substituted feedback delivered to the biceps of an intact arm, or residual arm in cases of amputees, to indicate a 1D kinetic variable, such as the output of a pressure sensor (Aniruddha et al. 2007). The Pacinian mechanoreceptors (Mountcastle et al. 1972) are, in general, the target

receptors and determine the applied vibration frequency (~200 Hz). Parameters such as the frequency, intensity, timbre, duration, and body location can be modulated at the receptor level to deliver various forms of feedback information (Cincotti et al. 2007).

Another direct substitution for force feedback is the use of a pneumatic cuff delivering radial pressure to the biceps in proportion to the grasp pressure exerted by the prosthesis (Patterson and Katz 1992). In the BCI context, users with substituted feedback were able to generate relatively more accurate control signals.

Bidirectional Brain-Machine Interfaces

Rich somatosensory feedback can be provided directly to the brain via electrical stimulation of the somatosensory cortex. Intracortical microstimulation (ICMS) is a technique used to deliver small amounts of currents (~25–60 μ A) to neurons via electrodes or microwires (O'Doherty et al. 2011). The delivery rate of stimuli to the neurons is a parameter controlled in delivering discriminable tactile feedback. O'Doherty et al. (2009) has reported using a stimulation frequency of 30 and 60 Hz with pulse widths of 150–200 μ s. Berg et al. (2013) have used ICMS to deliver graded percepts of force stimuli exerted on a prosthetic finger. Amplitude of four graded signals representing the different mechanical stimuli was modulated in proportion to time-varied force output of the prosthetic finger, and equivalent currents were delivered. ICMS to S1 can be used for directional instruction, active tactile sense, or even to represent somatotopic mapping of a body in 3D space (Lebedev and Nicolelis 2011).

BMI Applications in Human Patients

Although currently there do not exist commercially available brain-machine interfaces for human patient use, there have been attempts in research and preclinical settings to examine the capabilities of such systems in tetraplegic patients. Phil Kennedy and colleagues were the first to demonstrate

that severely disabled “locked-in” patients (due to brainstem stroke and ALS) could control switches and cursor movements using spikes and local field potentials from implanted microwires encased in a glass cone (Kennedy and Bakay 1998; Kennedy et al. 2000, 2004). Building on this early work, an FDA clinical trial was initiated on four patients with tetraplegia due to spinal cord injury, ALS, and brainstem stroke using the BrainGate system. This system consisted of a silicon-based 100-microelectrode array implanted in the primary motor cortex. It was shown in two of these patients that effective two-dimensional cursor control was possible using spikes from approximately 27 neurons (Hochberg et al. 2006). More recently, the second-generation BrainGate system (BrainGate 2) has demonstrated that chronic tetraplegics could control three-dimensional reaching and one-dimensional grasping of a multi-articulate robot using motor cortical spiking activity from the implanted silicon-based electrode array (Hochberg et al. 2012). In addition, another group has shown that an individual with tetraplegia could control up to seven independent degrees of freedom of a prosthetic limb including three-dimensional translation, three-dimensional orientation, and grasp using the same implanted array technology (Collinger et al. 2013). A somewhat less invasive approach using field potential oscillations up to 200 Hz recorded from the surface of the cortex via ECoG electrodes has demonstrated effective three-dimensional cursor control in a human tetraplegic (Wang et al. 2013). In contrast to these invasive methods, EEG has been extensively used in human subjects relying primarily on voluntary modulation of slower frequency oscillations below 40 Hz over somatosensory and motor cortices. Despite the weaker information content in EEG-based recordings, it has been possible to control up to three dimensions of cursor movement using voluntary modulation of slow sensorimotor rhythms (McFarland et al. 2010).

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Neural Decoding](#)

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Cortical Representation of Speech Sounds

► Neural Coding of Speech Sounds

Corticothalamic Feedback: Large-Scale Synchrony

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Definition

The thalamus is a pacemaker for several types of brain oscillations, such as sleep spindles. Although these oscillations are generated within thalamic circuits, their triggering and large-scale synchrony depends on cerebral cortex. In particular, it depends on the descending excitatory action of the cortex on the thalamus. Computational models show that the inhibitory-dominant character of this “corticothalamic feedback” can explain the large-scale synchrony of oscillations in cerebral cortex.

Detailed Description

Introduction

The fact that the brain produces oscillations was discovered as soon as electroencephalogram (EEG) recordings of brain activity were available. The first human EEG recordings reported oscillations, which type, frequency, and amplitude highly depend on behavioral state (reviewed in Steriade 2003). In an alert, awake subject, the EEG is dominated by low-amplitude fast activity (“desynchronized EEG”) with high-frequency oscillations (beta, gamma), whereas during slow-wave sleep, the EEG shifts to large-amplitude, slow oscillations. The early stage of slow-wave sleep is associated with EEG spindle waves, which occur at a frequency of 7–14 Hz. As sleep deepens, waves with slower frequencies (0.3–4 Hz), including delta waves and slow oscillations, appear and progressively dominate the EEG. During paradoxical sleep, also called rapid eye movement (REM) sleep, EEG activities resemble those of wakefulness.

The cellular mechanisms of slow-wave sleep oscillations have been investigated since the first extracellular and intracellular recordings in mammals. The major brain regions which have been identified are the thalamus and cerebral cortex, which are densely linked by means of reciprocal projections. The activities of thalamic and cortical neurons during sleep have been largely documented by electrophysiological studies. The cellular mechanisms underlying these oscillations depend on many factors, such as the connectivity and intrinsic properties of the different types of thalamic and cortical neurons. To determine these cellular mechanisms, it is necessary to use computational models, which are based on experimental data, and suggest mechanisms and, if possible, predictions to test them. This type of interaction has been quite successful in the (still ongoing) exploration of the mechanisms of sleep oscillations.

The cellular mechanisms leading to the genesis of spindle oscillations by thalamic circuits were reviewed in another entry (► “[Spindle Oscillations: Models](#)”). Spindle oscillations are generated by interacting thalamic neurons, as illustrated in Fig. 1. Thalamocortical (TC) and

thalamic reticular (RE) cells, endowed with their intrinsic bursting properties and connected via glutamate (AMPA) and GABA_A receptors, can generate spindle oscillations reproducing the typical features observed in intracellular recordings (reviewed in Destexhe and Sejnowski 2001, 2003).

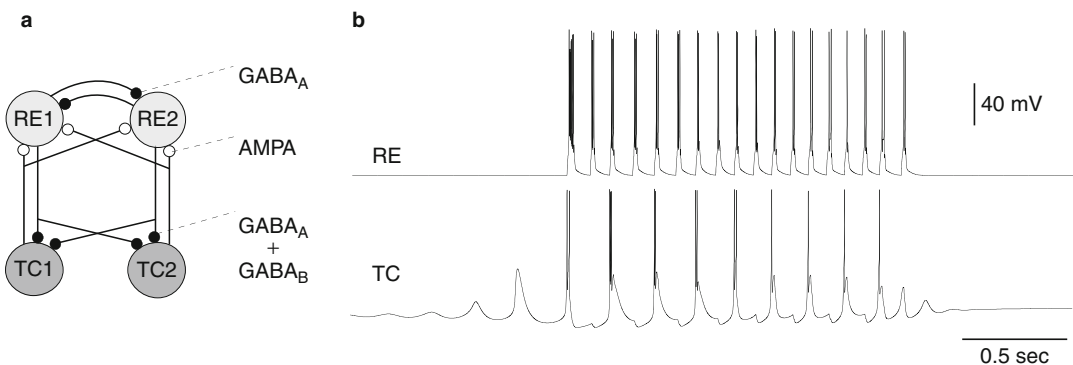
Propagation or Large-Scale Synchrony?

The initiation of spindle oscillations and their distribution in large-scale circuits were investigated using multiple recordings in vivo (Contreras et al. 1996) and in vitro (Kim et al. 1995). Spindle oscillations in vitro showed traveling wave patterns, with the oscillation typically starting on one side of the slice and propagating to the other side, at a constant propagation velocity (Kim et al. 1995). Traveling spindle waves were simulated by computational models of networks of interconnected TC and RE cells (one-dimensional extensions of the circuit shown in Fig. 1), in two independent modeling studies (Destexhe et al. 1996; Golomb et al. 1996). These models were similar in spirit to the circuit shown in Fig. 1a but assumed that there was a topographic connectivity between TC and RE layers, consistent with anatomical data. Under these conditions, the models generated traveling waves consistent with in vitro data.

However, in contrast to thalamic slices, the intact thalamocortical system in vivo showed that spindle oscillations are remarkably synchronized over extended thalamic and cortical regions, with little evidence for propagation (Fig. 2, left). This large-scale synchrony was lost when the cortex was removed (Fig. 2, right). In this case, propagating oscillations were seen, suggesting that although the oscillation is generated by the thalamus, its large-scale synchrony depends on the cortex (Contreras et al. 1996).

Thalamocortical Networks

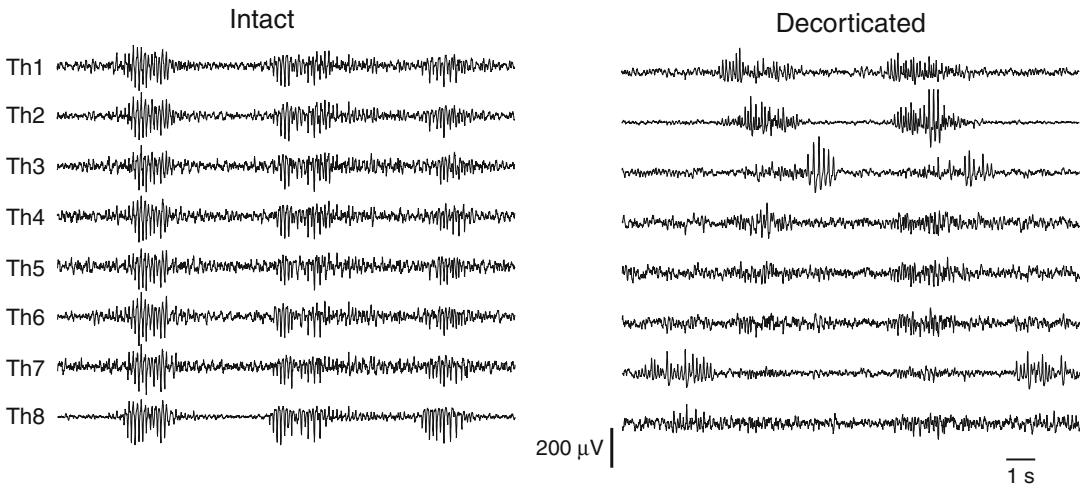
To investigate possible mechanisms underlying large-scale synchrony, a thalamocortical network model was developed by combining a previous model of thalamic slices with a model of deep cortical layers (see details in Destexhe et al. 1998). The principal prediction of this model was that, in order to generate large-scale coherent oscillations, one has to take into account the powerful action of cortex on thalamus (via corticothalamic fibers) and, most importantly, the cortex had to recruit the thalamus primarily through the RE nucleus. Because of the powerful inhibitory action of RE cells, the action of corticothalamic input is “inhibitory dominant” on TC cells, which property is essential to maintain large-scale synchrony by synchronizing the



Corticothalamic Feedback: Large-Scale Synchrony, Fig. 1 Computational model of spindle waves generated by TC-RE interactions. (a) Scheme of a simple circuit consisting of two TC and two RE cells, interconnected

with glutamatergic (AMPA) and GABAergic receptors (GABA_A and GABA_B). (b) Activity of two model neurons during simulated spindle waves. (Modified from Destexhe et al. 1996)

In vivo experiments



Corticothalamic Feedback: Large-Scale Synchrony, Fig. 2 The large-scale synchrony of spindle oscillations. Multiple extracellular field potential recordings (Th1–Th8) in the thalamus of cats *in vivo* are shown in two cases. *Left*: in the intact thalamocortical system (intact), the

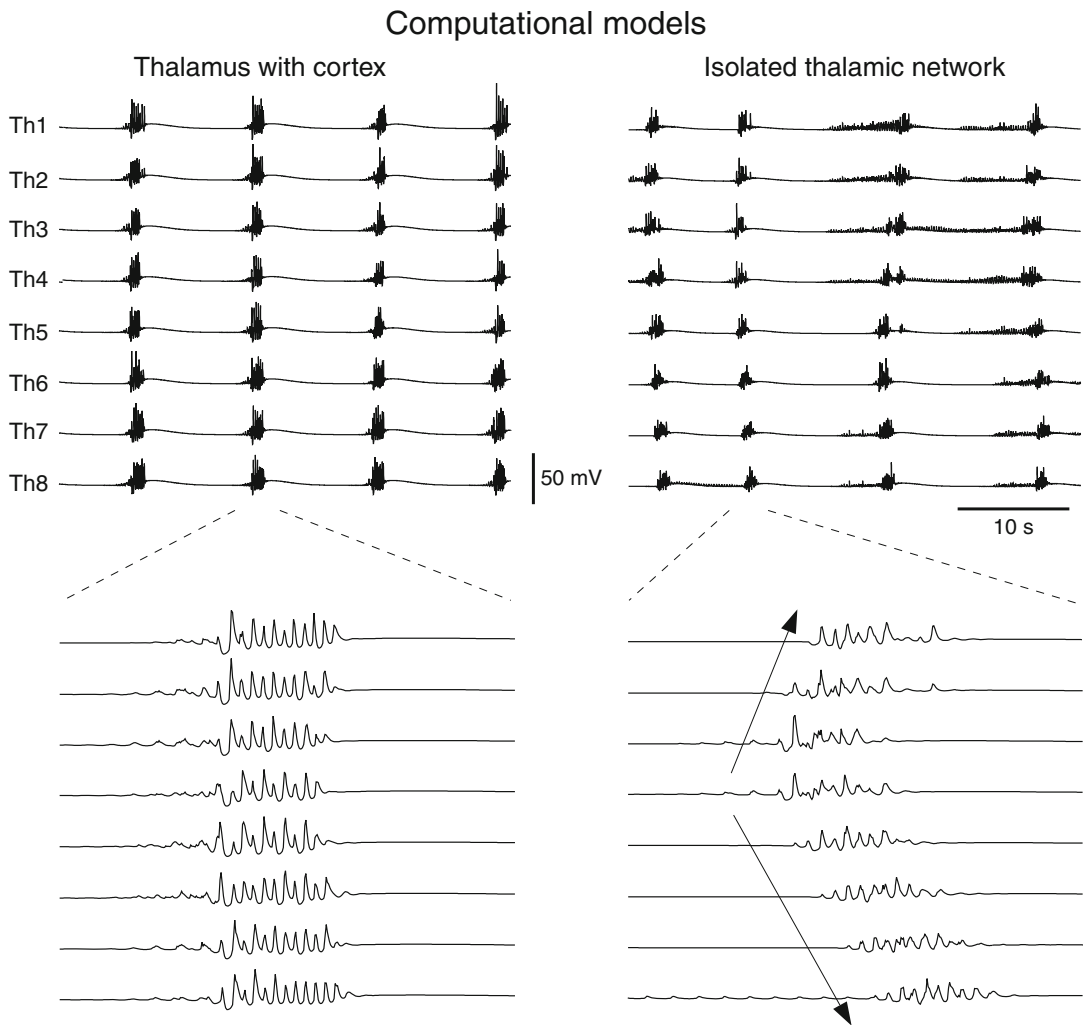
oscillations were synchronized over large distances (7 mm between Th1 and Th8). *Right*: after removal of the cortex (decorticated), the large-scale synchrony was largely abolished. (Modified from Contreras et al. 1996)

rebound bursts of TC cells (Destexhe et al. 1998). This property of inhibitory dominance is generally observed intracellularly in thalamic neurons when stimulating the cortex. In these conditions, the same model was capable of generating large-scale synchrony in the presence of the cortex and traveling wave activity in the isolated thalamus (Fig. 3). Consistent with these models, propagating activity has indeed been observed in the thalamus of decorticated cats *in vivo* (Contreras et al. 1996).

The “inhibitory-dominant” character of corticothalamic feedback on thalamic relay cells has multiple important consequences. Not only it can explain the large-scale synchrony of spindle oscillation, but it can also explain the genesis of some pathological situations such as absence epileptic seizures (Destexhe et al. 1998), as detailed in another entry (► “Slow Oscillations and Epilepsy: Network Models”). As a result of inhibitory dominance, a too strong corticothalamic feedback can over-activate thalamic GABA_B receptors and entrain the *physiologically intact* thalamus into hypersynchronous rhythms at ~3 Hz. This scheme

may explain the genesis of absence seizures, which are hypersynchronous ~3 Hz rhythms that appear suddenly in the thalamocortical system. These seizures can be provoked experimentally by increasing cortical excitability while keeping a physiologically intact thalamus (reviewed in Gloor and Fariello 1988). The thalamocortical model accounts for those experiments and can simulate seizures based on inhibitory-dominant corticothalamic feedback (Destexhe et al. 1998). This model directly predicted that manipulating corticothalamic feedback should entrain intact thalamic circuits to generate hypersynchronous rhythms at ~3 Hz, a prediction which has been verified by two independent studies (Blumenfeld and McCormick 2000; Bal et al. 2000). A similar mechanism, with a different balance between GABA_A and GABA_B receptors, can also generate faster hypersynchronous rhythms (around 5–10 Hz), as observed in rat or mouse experimental models of absence seizures.

In conclusion, in this entry, we have reviewed evidence that the mutual interactions between cortex and thalamus are a very powerful



Corticothalamic Feedback: Large-Scale Synchrony, Fig. 3 Modeling the large-scale synchrony of spindle oscillations. Computational models of thalamocortical networks displaying large-scale synchrony when cortex was

present (*left*) and local synchrony with traveling wave activity in the isolated thalamus (*right*). (Modified from Destexhe et al. 1998)

mechanism to synchronize oscillations over multiple brain areas. This mechanism was revealed by performing recordings in thalamus and cortex, interconnected or isolated from each other, as well as by using computational models. The models revealed that a critical ingredient is that the cortex recruits the thalamus essentially through inhibition. This mechanism can explain all experimental measurements, and it can also explain the genesis of a form of hyper-synchronized pathological oscillations by the thalamocortical system.

Cross-References

- [Slow Oscillations and Epilepsy: Network Models](#)
- [Spindle Oscillations: Models](#)

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Further Reading

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Coupled Oscillations in Neural Control of Breathing

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Synonyms

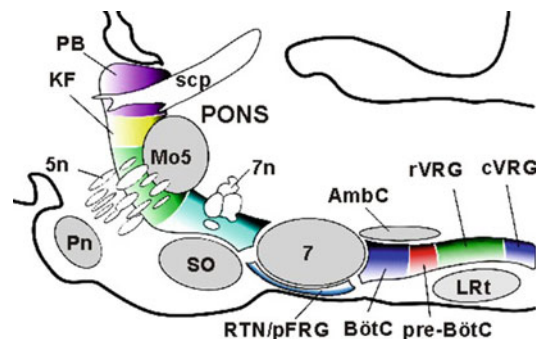
Dual-generator concept

Definition

The respiratory rhythm in mammals is generated by a respiratory central pattern generator (CPG) in

the brainstem and encompasses both pons and medulla (see Fig. 1; Alheid and McCrimmon 2008; Smith et al. 2013). The pre-Bötzinger complex (pre-BötC), located in the ventrolateral region of the medulla, is the putative kernel of rhythmic inspiratory activity. The pre-BötC interacts with the expiratory neurons of Bötzinger complex (BötC) to generate primary respiratory oscillations. These oscillations are defined by both the intrinsic biophysical properties of neurons involved and the network interactions within and between the pre-BötC and BötC. Through the premotor neurons of the rostral ventral respiratory group (rVRG), these oscillations produce rhythmic drive to phrenic motoneurons that through the phrenic nerve (PN) control movements of the diaphragm and lung inflation.

A distinct site of neural oscillations involved with the respiratory function, located more rostral to the pre-BötC, was identified in vitro, in the isolated brainstem-spinal cord preparation. The source of these oscillations, which was termed parafacial respiratory group (pFRG), was found to reside within the retrotrapezoid nucleus (RTN)



Coupled Oscillations in Neural Control of Breathing, Fig. 1 Parasagittal view of brainstem at the level of nucleus ambiguus. **Abbreviations:** 5n trigeminal nerve, 7 facial nucleus, 7n facial nerve, AmbC compact part of nucleus ambiguus, BötC bötzinger complex, cVRG caudal division of ventral respiratory group, KF kölliker-fuse nucleus, Mo5 motor nucleus of the trigeminal nerve, PB parabrachial nucleus, pFRG parafacial respiratory group, Pn basilar pontine nuclei, pre-BötC pre-bötzinger complex, RTN retrotrapezoid nucleus, rVRG rostral division of ventral respiratory group, scp superior cerebellar peduncle, SO superior olive, sol solitary tract, sp5 spinal trigeminal tract, VRG ventral respiratory column of the medulla, VRG ventral respiratory group (Adapted from Alheid and McCrimmon (2008) with permission)

or partially overlaps with it (Onimaru and Homma 2003; Janczewski and Feldman 2006). The pFRG oscillations emerge with increased metabolic demands (e.g., hypercapnia) and via abdominal nerve (AbN) drive abdominal muscles enabling forced lung deflation (active expiration). This rhythmic activity is coupled to the pre-BötC oscillations so that generated bursts represent late-expiratory (late-E) or sometimes biphasic (containing pre-inspiratory, pre-I, and post-inspiratory, post-I, components) discharges (Janczewski and Feldman 2006; Abdala et al. 2009).

Several competing concepts concerning the appearance of RTN/pFRG oscillations and their physiological function have been suggested (Janczewski et al. 2002; Onimaru and Homma 2003; Abdala et al. 2009; Molkov et al. 2010). However, there are still heated debates on the exact physiological role of RTN/pFRG oscillations, the specific conditions for their emergence, and the nature and mechanisms of the interactions between the BötC/pre-BötC and RTN/pFRG oscillators.

Detailed Description

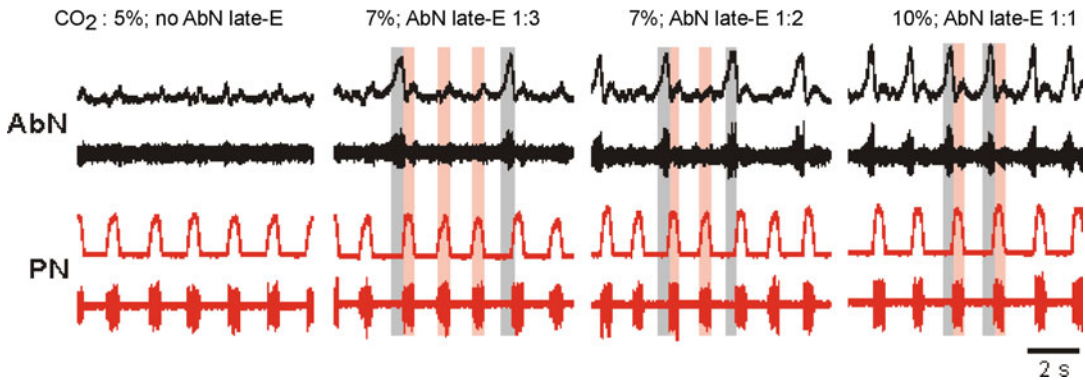
From mathematical viewpoint, the most striking experimental observations that evidence the existence of two distinct oscillators in neural control of breathing are the so-called *quantal slowing* of phrenic rhythm (Janczewski and Feldman 2006; Mellen et al. 2003) and *quantal acceleration* of abdominal discharges (Abdala et al. 2009; Molkov et al. 2010).

The *quantal slowing* of the pre-BötC and/or PN oscillations has been demonstrated with administration of opioid agonists in the in vitro isolated brainstem-spinal cord preparation and in vivo (Mellen et al. 2003; Janczewski and Feldman 2006). This phenomenon consists of a stepwise reduction in the frequency of pre-BötC (and/or PN) oscillations resulting from deletion (missing) of a single or a series of inspiratory bursts in the output activity recorded. Although the exact pharmacological effect of opioids is unknown, the general assumption has been that opioids reduce the excitability of pre-BötC

neurons either directly or indirectly (via the suppression of excitatory synaptic transmission within the pre-BötC).

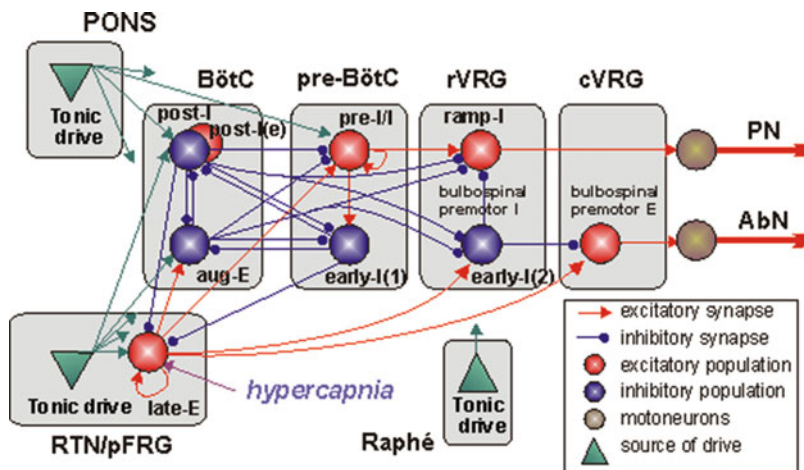
Similarly, *quantal acceleration* of late-E abdominal activity was observed with development of hypercapnia (elevation of CO₂) in the in situ arterially perfused rat brainstem-spinal cord preparation (Fig. 2, see Abdala et al. 2009; Molkov et al. 2010) and in vivo (Iizuka and Fregosi 2007). Experimental studies in the perfused in situ preparation have shown that under baseline normocapnic metabolic conditions (5% CO₂), the abdominal nerve motor output (AbN) typically exhibits a low-amplitude expiratory (post-I) activity. Switching to hypercapnic (7–10% CO₂) conditions evoked large amplitude late-E (also called pre-I) bursts in the AbN. These late-E discharges emerge in AbN at 7% CO₂ followed by a progressive increase in their frequency as the CO₂ concentration in the perfusate is incremented to 10%. Importantly, although the frequency of late-E bursts increases with CO₂, these bursts remained coupled (phase-locked) to the inspiratory bursts in the PN (Fig. 2). With the development of hypercapnia, the ratio of late-E burst frequency to the PN burst frequency showed a stepwise (quantal) increase from 1:5 and 1:4 (not shown) to 1:3, 1:2, and, finally, 1:1 (at 10% CO₂). On returning CO₂ to the control levels, the ratio showed a stepwise reversal.

Several computational models of interacting neural oscillators related to generation of respiratory activity with various levels of complexity have been proposed. The most detailed description of possible interactions between the BötC/pre-BötC and RTN/pFRG circuits (Fig. 3; Molkov et al. 2010) was developed as an extension of the respiratory CPG model proposed earlier by Smith et al. (2007) (see ► “Computational Models of Mammalian Respiratory CPG”). According to that description, the BötC/pre-BötC oscillator controls the emergence of late-E oscillations in RTN/pFRG and their frequency and phase by inhibiting RTN/pFRG oscillator during both expiration (via post-I inhibition) and inspiration (via early-I inhibition). This inhibition prevents late-E activity in RTN/pFRG and AbN to occur under normal metabolic conditions.



Coupled Oscillations in Neural Control of Breathing, Fig. 2 Quantal acceleration of late-E discharges in the in situ brainstem-spinal cord preparation. The phrenic nerve (PN, red) and abdominal nerve (AbN, black) activities are shown by pairs of traces: raw recording (lower trace) and integrated activity (upper trace). PN bursts define

inspiratory phases of respiratory cycles (some highlighted by vertical pink bars), and interburst intervals correspond to expiratory phases. Late-E discharges in AbN occur at the end of expiration, just prior to inspiration (highlighted by gray bars) (Adapted from Molkov et al. (2010) with permission)

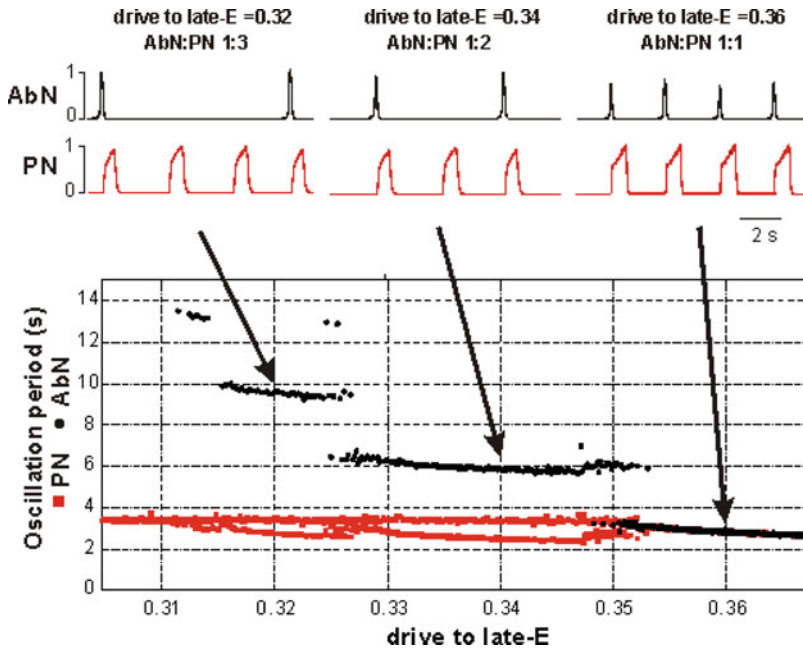


Coupled Oscillations in Neural Control of Breathing, Fig. 3 The schematic of the model. Each population (shown as a *sphere*) consists of 50 single-compartment neurons described in the Hodgkin-Huxley style. The populations are denoted according to their firing pattern: *post-I* post-inspiratory, *aug-E* augmenting expiratory, *pre-I/I* pre-inspiratory/inspiratory, *early-I* early inspiratory, *ramp-I* ramping inspiratory, *late-E* late expiratory. BötC/pre-BötC oscillator (Smith et al. 2007) controls RTN/pFRG oscillator (the intrinsically rhythmic late-E population) by inhibitory inputs from post-I and early-I

(1) neurons. Excitatory late-E neurons send their axons to bulbospinal premotor expiratory (E) neurons in cVRG, representing the source of AbN activity. The model includes three sources of tonic excitatory drive: pons, RTN, and raphé (shown as green triangles) which project to multiple neural populations in the model. The late-E population receives an additional external drive simulating the effect of hypercapnia. All model equations and parameters can be found in Molkov et al. (2010) (Adapted from Molkov et al. (2010) with permission)

The excitability of the late-E population in RTN/pFRG in the model is highly sensitive to hypercapnia which causes their depolarization (see Fig. 3). At some level of CO_2 , this excitation

overcomes the inhibition of late-E population in RTN/pFRG by BötC/pre-BötC circuits and initiates late-E rhythmic activity which translates to AbN. The late-E bursts initially emerge at a very



Coupled Oscillations in Neural Control of Breathing, Fig. 4 Quantal acceleration of AbN activity in the model. The late-E bursts in the AbN are always phase-locked with PN bursts, and the ratio between AbN and PN frequencies quantally increased through 1:3 (at drive to late-E = 0.32) to 1:2 (0.34) and to 1:1 (0.36) as “hypercapnic” drive to the late-E population of RTN/pFRG gradually increases

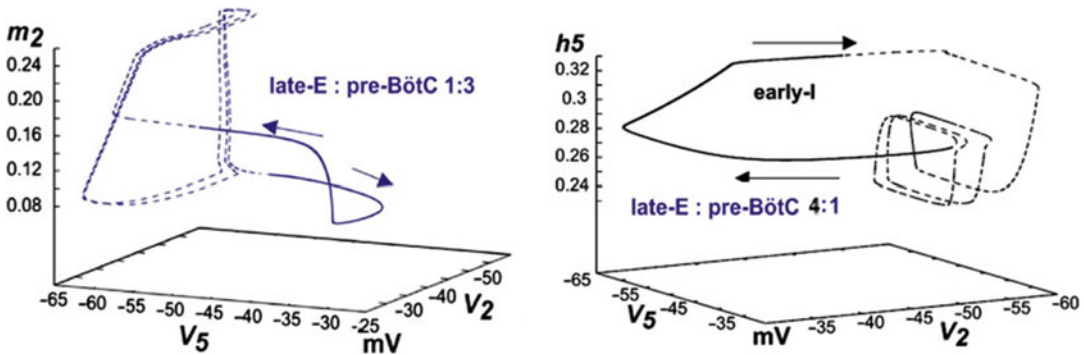
mimicking progressive hypercapnia. The *lower panel* shows the dependence of oscillation periods in AbN (black circles) and PN (red squares) on the hypercapnic drive (*horizontal axis*). The period of AbN late-E discharges sequentially jumps from 4 PN periods to 3, then to 2, and finally to 1 (Adapted from Molkov et al. (2010) with permission)

low frequency, but as CO_2 level progresses (Fig. 4), the frequency of late-E discharges quantally increases, until it reaches 1:1 ratio with the BötC/pre-BötC oscillations that define PN output. In contrast, strong hypoxia or anoxia can evoke the RTN/pFRG oscillations through a reduction of inhibition, specifically the post-I inhibition, and produce an effect similar to hypercapnia by shifting the balance between inhibition and excitation at the level of RTN/pFRG late-E neurons.

Rubin et al. (2011) performed thorough qualitative analysis of the reduced model and explained the regimes of *quantal acceleration* and *quantal slowing* in terms of synchronization of the BötC/pre-BötC and RTN/pFRG oscillators. The dynamics of each oscillator can be represented by a stable limit cycle in some phase space. The phase space of a system of two coupled oscillators is a Cartesian product of the phase spaces of each oscillator. The corresponding limit set is a 2D

invariant torus, and the behavior of this system is represented by a trajectory on this torus. If the ratio of oscillation frequencies of the two oscillators is rational (i.e., equal to N/M , for some integers N and M), then this trajectory is closed, indicating $N:M$ synchronization between oscillators, where N and M represent numbers of rotations around two orthogonal circles that together span the torus.

With changing conditions, the system of coupled oscillators can proceed through regimes characterized by different relations between oscillation frequencies. A progressive increase of RTN/pFRG excitability as defined by the CO_2 level results in an emergence and subsequent increase in the frequency of its oscillations. Due to coupling between RTN/pFRG and BötC/pre-BötC oscillators, the system proceeds through a series of phase-locked resonances with 1: N ratios between the RTN/pFRG and BötC/pre-BötC frequencies, with N decreasing from an initial higher



Coupled Oscillations in Neural Control of Breathing, Fig. 5 The phase trajectories in the reduced model illustrating two synchronized late-E: pre-BötC states during hypercapnia (1:3 regime, *left panel*) and after suppression of pre-BötC (4:1 regime, *right panel*). The reduced model by Rubin et al. (2011) describes neural populations as two-dimensional relaxation oscillators with one fast and one slow variable. Fast variables V_2 and V_5 represent membrane potentials of early-I neuron in pre-BötC and late-E neuron in RTN/pFRG, respectively; m_2 and h_5 are slow

variables of these oscillators. Subthreshold activities of late-E neuron (*left*) and early-I neuron (*right*) are shown by *dashed lines*. Suprathreshold parts of trajectories (*solid lines*) correspond to bursts of the late-E (*left*) and pre-BötC (*right*) neurons. Cyclical subthreshold movement on the *left panel* indicates two periods of early-I activity during which the late-E neuron fails to burst. Similar movement on the *right* shows four late-E oscillations during which pre-BötC neurons fail to activate (Adapted from Rubin et al. (2011) with permission)

value to 1 ($N = 3$ on Fig. 5). The specifics of this coupling define a phase (late-E) of RTN/pFRG oscillations in all synchronized states.

In contrast, progressive suppression of pre-BötC excitability (e.g., by opioid agonists) results in a decrease in frequency of BötC/pre-BötC rhythm generator and ultimately in cessation of its oscillations. In this regime, the pre-BötC neurons depend on recruitment by the late-E neuron to activate. Because of this coupling, the pre-BötC frequency is quantally reduced through a series of resonances with M:1 ratios between the RTN/pFRG and BötC/pre-BötC frequencies with M increasing from 1 to higher values (see $M = 4$ on Fig. 5).

Cross-References

- [Computational Models of Mammalian Respiratory CPG](#)

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Coupling of Local Field Potentials

- [Local Field Potential, Synchrony of](#)

CPG

- [Locomotor Pattern Generation in the Rodent Spinal Cord](#)

Critical Branching Process

- [Neuronal Avalanches](#)

Cross-Correlation of Local Field Potentials

- [Local Field Potential, Synchrony of](#)

Cross-Correlogram

- [Correlation Analysis of Parallel Spike Trains](#)

Crowding Models

- [Peripheral Vision, Models of](#)

CSD

- [Current Source Density \(CSD\) Analysis](#)

CSD Method

- [Current Source Density \(CSD\) Analysis](#)

Current Source Density (CSD) Analysis

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Synonyms

[CSD](#); [CSD method](#); [Reconstruction of current sources](#)

Definition

Current source density analysis (CSD) is a class of methods of analysis of extracellular electric potentials recorded at multiple sites leading to estimates of current sources generating the measured potentials. It is usually applied to low-frequency part of the potential (called the local field potential, LFP) and to simultaneous recordings or to recordings taken with fixed time reference to the onset of specific stimulus (evoked potentials, EP).

Detailed Description

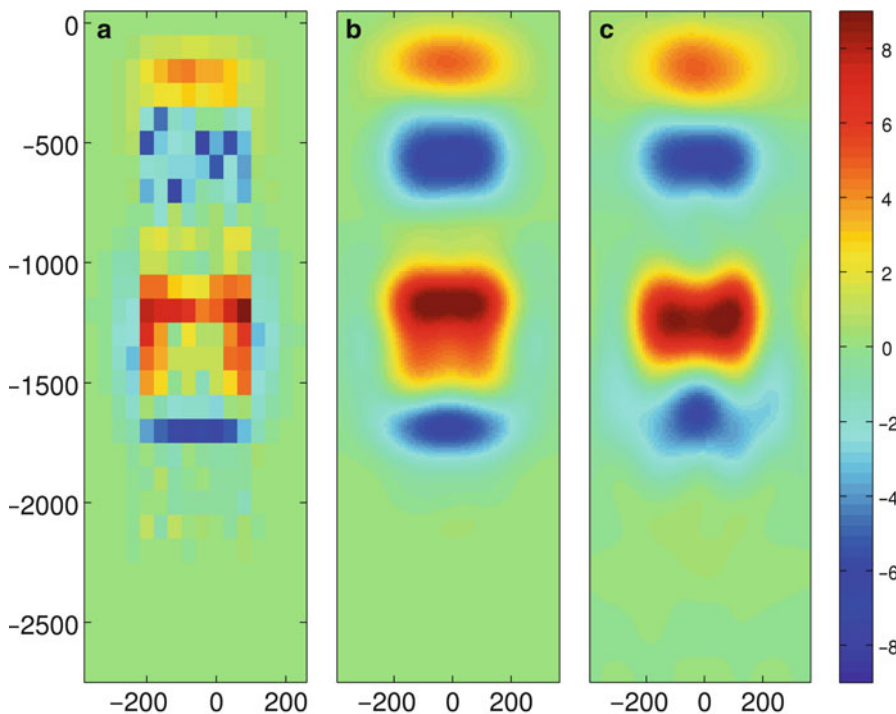
Among the different mechanisms contributing to extracellular electric potential in the tissue (Buzsáki et al. 2012; Einevoll et al. 2012), trans-membrane currents in neurons are believed to

dominate. These are ionic currents passing through all the different membrane channels (passive, voltage dependent, calcium dependent, synaptic, etc.) as well as the capacitive currents which, while charging the membrane, also contribute to the motion of ions in the extracellular space, influencing the extracellular potential and seen by the extracellular electrode. The places where net current is entering or leaving the cell are called *current sources or sinks*. While these sources are localized along the membrane of the neuron, in practice, with a finite resolution afforded by available electrode setups and limited by typical densities, we may only recover coarse-grained density. This is what we have in mind when discussing estimation of current source density. Figure 1 shows the relation between the “microscopic” currents (a), coarse-grained field we usually have in mind (b), and a

reconstruction of the CSD from measured potentials (c).

CSD analysis can be performed for signals in full spectrum or in any selected band, although it is usually applied to the low-frequency part (<500 Hz) of the extracellular potential (LFP). We propose here such an expansion of LFP as the commonly used term local field potential is actually a misnomer, since due to the long-range nature of the electric field, LFP can be observed millimeters away from sources (e.g., Kajikawa and Schroeder 2011; Lindén et al. 2011; Hunt et al. 2011; Łęski et al. 2013). Despite that filtering in frequencies, it is known that fast processes, such as spikes, may still contribute to the LFP (Buzsáki et al. 2012; Einevoll et al. 2012; Reimann et al. 2013).

When net positive current enters the cell, we speak of current sink, and it corresponds to



Current Source Density (CSD) Analysis, Fig. 1 Comparison of the current sources obtained in a simulation (a) with coarse-grained CSD (smoothed with a Gaussian kernel of $\sigma = 75 \mu\text{m}$) (b) and a reconstruction with kernel CSD method (c) from LFP computed at a grid of 8×14 electrodes from the data in (a). Data were taken from the cortical part of a simulation of 3500 cells in the

model of thalamocortical loop based on Traub et al. (2005), 10 ms after simulated thalamocortical stimulus. Dominating contributions to CSD come from infra- and supragranular pyramidal cells. Vertical distance given in μm from cortical surface, horizontal from the center of the simulated column (H. Głabka)

negative CSD. When net negative current enters the cell, we speak of current source, and it corresponds to positive CSD. Since negative CSD is observed for excitatory synaptic stimulation (positive current entering the cell/negative CSD), many researchers prefer to denote current sinks by red (“hot spot”) and current sources by blue. There are a comparable number of researchers who prefer to do the opposite, according to the sign of CSD (red for positive, blue for negative). This situation has led to two opposite conventions being in wide use. A reader is advised to always check carefully what is the convention used in a given work.

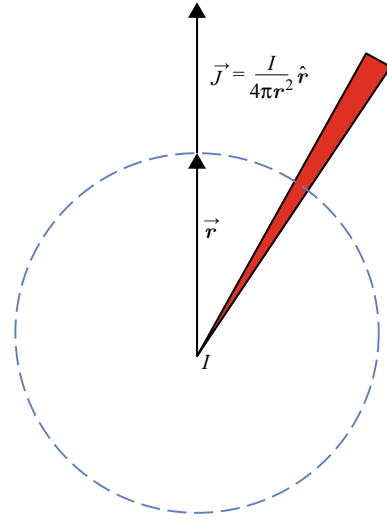
Physics Behind the Relation Between the CSD and LFP

To get intuitive understanding of the basic relation between current sources and extracellular potential, consider infinite, homogeneous, and isotropic conductive medium of conductivity σ (Tranquillo 2008). If we place a stimulating electrode and inject current I , it will induce current flow in the tissue with current density $\vec{J} = I\hat{r}/(4\pi r^2)$ radially at a distance r away from the stimulation point (Fig. 2).

In a purely conductive medium, Ohm’s law holds $\vec{J} = \sigma\vec{E} = -\sigma\nabla V$, which gives us the potential in space $V(r) = I/(4\pi\sigma r)$. A multitude of currents I_j located at $\vec{r}_j$ induce potential $V(\vec{r}) = \sum_j I_j / (4\pi\sigma |\vec{r} - \vec{r}_j|)$. It is natural to introduce *current source density (CSD)*, $c(\vec{r}) = \sum_j I_j \delta(\vec{r} - \vec{r}_j)$, a scalar density field which is usually coarse grained to a smooth quantity (see Fig. 1). With this definition we get the relation between the CSD and the potential as

$$V(\vec{r}) = \frac{1}{4\pi\sigma} \int d^3\vec{r}' \frac{c(\vec{r}')}{|\vec{r} - \vec{r}'|} \quad (1)$$

or inverting this relation, we obtain the Poisson equation



Current Source Density (CSD) Analysis, Fig. 2 Current I injected at the origin of the system spreads uniformly in all directions in infinite, homogeneous, and isotropic medium

$$C(\vec{r}) = -\sigma\Delta V \quad (2)$$

Equations (1) and (2) are valid only in our restricted setting. Equation (2) can be generalized for arbitrary conductivity tensor fields σ :

$$C(\vec{r}) = -\nabla \cdot [\sigma \nabla V] \quad (3)$$

Solving Eq. (3) usually requires numerical methods. Careful derivations of Eq. (3) can be found in (Nicholson 1973; Stevens 1966; Nunez and Srinivasan 2005).

Methods of CSD Estimation

The simplest numerical approximation to the Laplacian is the three-point formula

$$\begin{aligned} C(x_k, y_l, z_m) \approx & -\sigma [V(x_{k+1}, y_l, z_m) \\ & - 2V(x_k, y_l, z_m) + V(x_{k-1}, y_l, z_m) + V(x_k, y_{l+1}, z_m) \\ & - 2V(x_k, y_l, z_m) + (x_k, y_{l-1}, z_m) \\ & + V(x_k, y_l, z_{m+1}) - 2V(x_k, y_l, z_m) \\ & + V(x_k, y_l, z_{m-1})] / \delta^2 \end{aligned}$$

which was introduced by Pitts (1952). While in the original application two-dimensional case was considered, by far the most common use of this approach has been in the study of one-dimensional cortical recordings with linear multi-electrodes. One then considers lateral invariance of the potential as a consequence of laminar structure of the cortex keeping a single term in the above formula. This approach has been made popular in the early 1970s by work of Haberly and Shepherd (1973) and especially Nicholson and Freeman (1975). Much of the work in this area till 1985 has been summarized by Ulla Mitzdorf in her still very useful review (1985).

We refer to this approach as the *traditional CSD (tCSD) method*.

Methodologically, there have been few advances in the estimation of CSD from the measurements since Pitts work till 2006. The main deficiencies of the traditional approach are lack of control over the assumptions made, such as extent of the sources in the dimensions which are not probed and between the contacts, spatial and measurement noise, and the necessity of exclusion of contacts at the border. To reduce the noise, Rappelsberger et al. (1981) proposed to smooth the measurements with a Hamming window obtaining a five-point formula in 1D

$$C(z) = -\sigma[0.23V(z - 2\delta) + 0.08V(z - \delta) + 0.08V(z + \delta) + 0.23(z + 2\delta)]/\delta^2$$

which gained some popularity. In 1988, Vaknin et al. proposed to extend the grid of electrodes beyond the actual set of contacts copying the outmost recordings to the added contacts. While in general physically questionable, this numerical trick allowed computation of CSD values for all contact positions and was used in cortical studies.

Rapid development of new multielectrodes at the beginning of the twenty-first century (Egert et al. 1998; Csicsvari et al. 2003; Buzsáki 2004; Berdondini et al. 2005; Kipke et al. 2008; Frey et al. 2009) stimulated renewed interest in LFP recordings and analysis, including CSD analysis. In 2006, Pettersen et al. proposed a new, model-based approach to CSD estimation, which they termed *inverse CSD (iCSD) method*. The method was later generalized to three- and two-dimensional regular recording setups (Łeński et al. 2007, 2011).

The idea behind iCSD is to assume a parametric model of the sources of as many parameters as the number of measurements. For example, for measurements of potential $V_1, \dots, V_N$ at points $\vec{x}_1, \dots, \vec{x}_N$, we may take the values of CSD at measurement points $C_1, \dots, C_N$ as parameters and spline interpolate in between (*spline iCSD*). Then

$$C(\vec{x}) = \sum_{k=1}^N C_k f_k(\vec{x}), \text{ where } f_k(\vec{x}) \text{ is a}$$

function taking 1 at $\vec{x}_k$, 0 at $\vec{x}_{l \neq k}$, and spline interpolated in between. From such a model, one can compute potential at the measurement points using forward modeling formula, Eq. 1. This leads to a matrix relation between the potential and the CSD given by $V_j = \sum_k M_{jk} C_k$, where

$$M_{jk} = \frac{1}{4\pi\sigma} \int d^3\vec{x}' \frac{f_k(\vec{x}')}{|\vec{x}'_j - \vec{x}'|}$$

In lower dimensionality (1D, 2D), where one does not probe all directions, it is necessary to make assumptions about source behavior there. For example, in 1D one may assume invariance of CSD on disks of some radius R (e.g., of the size of cortical column) orthogonal to the shaft, and in 2D one may assume constancy or Gaussian decay of the source on an interval orthogonal to the MEA plane. These assumptions lead to other forms of matrix elements which incorporate the specific form of the model (Pettersen et al. 2006; Łeński et al. 2011).

For typical recordings the matrix relation between the LFP and CSD can be inverted leading to a formula for C_k as a function of measured potential, $\vec{C} = M^{-1}\vec{V}$, and in consequence to an estimate of current sources in the whole probed

region. A convenient feature of iCSD method is that the matrix M^{-1} is estimated once for a given setup and model of sources. Also, one can easily incorporate different boundary conditions overcoming naturally this limitation of the traditional approach (Łęski et al. 2007).

Inverse CSD is a framework which allows one to incorporate different assumptions about the structure of the sources or the properties of the tissue, e.g., its conductivity (Goto et al. 2010). An interesting variant was developed for localization of single-cell current sources during action potential generation (*spike CSD*, **sCSD**, Somogyvári et al. 2005, 2012). The flexibility of the framework is in the construction of the function space used for estimation. However, iCSD was developed for regular recording grids and under the assumption of negligible recording and position noise, which could not be easily overcome within this framework.

A general solution to these problems was provided with *kernel current source density (kCSD) method* (Potworowski et al. 2012). While in iCSD the dimension of the function space in which one does estimation is equal to the number of measurements, in kCSD one constructs spaces of much larger dimensionality. The flexibility in tackling arbitrary electrode setups comes from separation of the construction of estimation space from the definition of the setup. The use of

kernel methods allows us to use standard techniques for dealing with noise (e.g., ridge regression, etc.) as described below.

Assume potentials $V_1, \dots, V_N$ measured at points $\mathbf{x}_1, \dots, \mathbf{x}_N$. To construct the framework of kCSD, we start with two linear spaces: the space of sources

$$\tilde{\mathcal{F}} = \left\{ C(\mathbf{x}) = \alpha_1 \tilde{b}_1(\mathbf{x}) + \dots + \alpha_M \tilde{b}_M(\mathbf{x}) : \tilde{b}_i : \mathbb{R}^d \rightarrow \mathbb{R} \right\},$$

and the space of potentials

$$\tilde{\mathcal{F}} = \left\{ V(\mathbf{x}) = \alpha_1 b_1(\mathbf{x}) + \dots + \alpha_M b_M(\mathbf{x}) : b_i : \mathbb{R}^d \rightarrow \mathbb{R} \right\},$$

with the dimension of the spaces, M , much greater than the number of measurements, N . The basis functions are related by a linear operator $\mathcal{A} : \tilde{\mathcal{F}} \mapsto \mathcal{F}$ so that $b_i = \mathcal{A} \tilde{b}_i$, and $V(\mathbf{x}) = \mathcal{A} C(\mathbf{x}) =$

$\sum_{i=1}^M \alpha_i b_i(\mathbf{x})$. In three dimensions (isotropic, homogeneous) $\mathcal{A} = -\sigma \Delta$, in lower dimensionality, we must assume properties of the sources in the directions not probed for the same reasons as in iCSD. For instance, if in 2D we assume that the sources are invariant in the direction z orthogonal to the electrode plane (x, y) within a layer of $2h$, then the physical $CSD(x, y, z)$ is $C(x, y)$ for $|z| < h$ and 0 otherwise, and

$$b_i(x, y) = \mathcal{A} \tilde{b}_i := \frac{1}{2\pi\sigma} \int dx' \int dy' \arcsinh \left(\frac{h}{\sqrt{(x-x')^2 + (y-y')^2}} \right) \tilde{b}_i(x', y')$$

We require that b_i ($\tilde{b}_i$) are linearly independent and so they constitute bases of the linear spaces $\tilde{\mathcal{F}}$ and $\mathcal{F}$. To efficiently estimate in such a large space, we construct a kernel function

$$K(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^M b_i(\mathbf{x}) b_i(\mathbf{x}'),$$

which introduces the structure of reproducible kernel Hilbert space (RKHS) on $\mathcal{F}$ (Aronszajn

1950). Using representer theorem from RKHS theory (Schoelkopf and Smola 2002), one can show that minimum estimation error

$$err(V(\cdot)) = \sum_{i=1}^N (V(x_i) - V_i)^2 + \lambda \|\beta\|^2$$

is obtained for potential function of the form

$$V(\mathbf{x}) = \sum_{k=1}^N \beta_k K(\mathbf{x}_k, \mathbf{x}) \in \mathcal{F},$$

where

$$\begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} = \begin{bmatrix} K(\mathbf{x}_1, \mathbf{x}_1) + \lambda & \cdots & K(\mathbf{x}_1, \mathbf{x}_N) \\ \vdots & \ddots & \vdots \\ K(\mathbf{x}_N, \mathbf{x}_1) & \cdots & K(\mathbf{x}_N, \mathbf{x}_N) + \lambda \end{bmatrix}^{-1} \begin{bmatrix} V_1 \\ \vdots \\ V_N \end{bmatrix},$$

which can be written in more compact notation as

$$\boldsymbol{\beta} = (\mathbf{K} + \lambda \mathbf{I})^{-1} \cdot \mathbf{V}$$

with an obvious definition of terms. Having estimated the potential, we use the relation between the basis functions to construct a cross-kernel function:

$$\tilde{K}(\mathbf{x}, \mathbf{x}) = \sum_{j=1}^M b_j(\mathbf{x}) \tilde{b}_j(\mathbf{x})$$

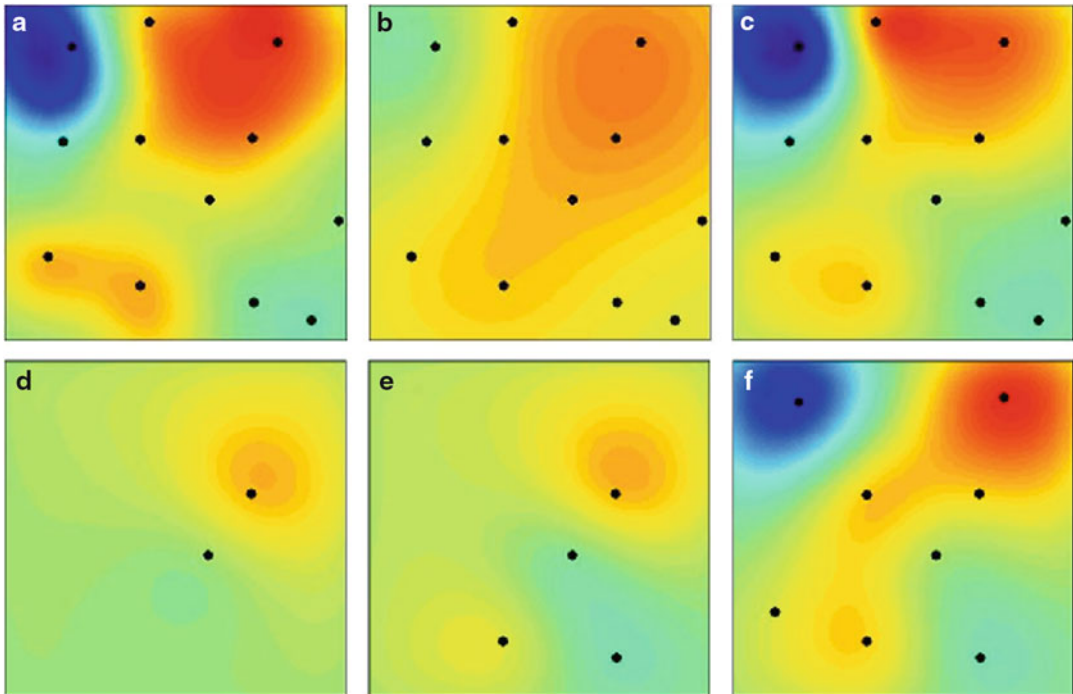
with which the current sources estimated in the measurement space are given

$$\text{by } C * (\mathbf{x}) = \tilde{\mathbf{K}}^T(\mathbf{x}) \cdot (\mathbf{K} + \lambda \mathbf{I})^{-1} \cdot \mathbf{V} \quad \text{with} \\ \tilde{\mathbf{K}}^T(\mathbf{x}) := [\tilde{K}(\mathbf{x}_1, \mathbf{x}), \dots, \tilde{K}(\mathbf{x}_n, \mathbf{x})].$$

Parameter λ can be selected from data using, for instance, cross-validation. For further details on kCSD, see Potworowski et al. (2012). Figure 3 shows an example of CSD estimation with kCSD method.

Limitations of CSD Analysis

The main difficulty in the interpretation of CSD profiles is that it is not possible to tell without extra knowledge what is the nature of a given observed feature, for example, if a spot of negative CSD is due to excitatory synaptic stimulation or a passive return current matching inhibitory current elsewhere. Thus, one usually has to build on extra a priori knowledge of system's anatomy



Current Source Density (CSD) Analysis, Fig. 3 Example of source reconstruction with kCSD method. (a) Model sources shown were used to generate potentials at randomly selected electrode locations marked with black dots. (b) Potential interpolated from the

potential measured at the electrode locations. (c) CSD reconstructed from the random 16 measurements. (d–f) Sources reconstructed from 2, 4, and 8 measurements, respectively

and physiology (Gratiy et al. 2011) or use computational models of the studied systems (Makarov et al. 2010; Potworowski et al. 2011). If possible, do both.

CSD analysis allows one to better localize neural activity by deconvolution of the inverse distance kernel. However, since usually multiple cell populations overlap, observed profile of the current sources will reflect summary activity of all of them. One way to overcome this problem is to use a method of source decomposition (see Einevoll et al. 2013, for a discussion). It seems that independent component analysis (ICA) following CSD gives functionally meaningful results (Łęski et al. 2010; Makarov et al. 2010; Potworowski et al. 2011).

To tackle both the problem of overlapping populations and unknown origin of the given source, it is particularly useful to generate ground truth data as close to the system studied as possible, for instance, from large-scale models (Potworowski et al. 2011; Reimann et al. 2013).

Finally, let us observe that all the CSD methods mentioned so far rely on Eq. (3) which has recently been challenged (see chapter Local Field Potentials: Interaction with the Extracellular Medium for a review). In that case the physical part of the CSD model must be modified (Bedard and Destexhe, Physical Review E 2011).

Cross-References

- [Independent Component Analysis of Images](#)
- [Local Field Potentials: Interaction with the Extracellular Medium](#)
- [Local Field Potentials: LFP](#)

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Further Reading

Scholarpedia
Local field potential

Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture

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Definition

We can identify objects by the way they feel. As we move our fingers over objects in our pocket or purse, we can easily distinguish between our keys and our phone or between two different fabrics in our dresser drawer. The tactile perception of the surface texture of objects, i.e., of their microstructure and material properties, contributes to our ability to identify them by touch. Signals in the nerve convey information that allows us to identify different textures, as well as attribute different

perceptual properties (e.g., roughness or hardness) to them.

Detailed Description

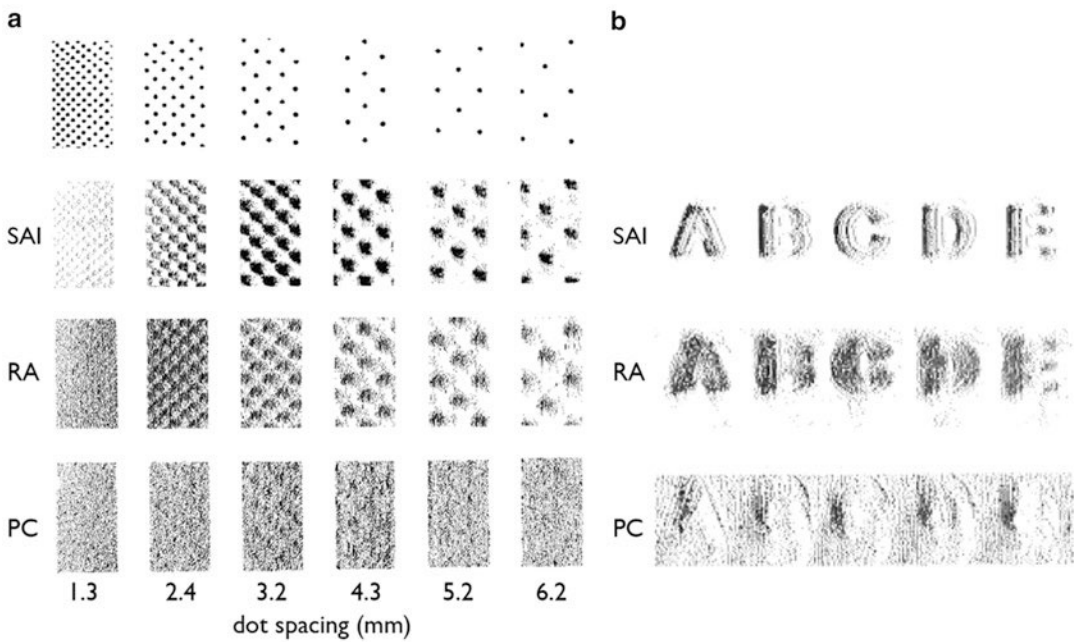
Spatial and Temporal Mechanisms

When we run our fingers across a textured surface, a characteristic pattern of deformations is produced in the skin (Sripati et al. 2006), and the resulting stresses and strains are transduced by multiple populations of mechanoreceptors embedded in the skin. The spatial layout and timing of the consequent spatiotemporal patterns of afferent activation convey information about surface texture (Weber et al. 2013).

As coarse textural features indent the skin, their spatial layout is reflected in the spatial pattern of activation evoked across the population of Merkel disks, which are relatively dense in the fingertip skin and are innervated by slowly adapting type 1 (SA1) afferents (Johansson and

Vallbo 1979) (Fig. 1). SA1 afferents thus encode spatial patterns in a manner analogous to photoreceptors in the retina. SA1 responses are uniquely suited to transduce spatial features as they have small receptive fields; that is, they only respond to small and sharply defined patches of skin. SA1 responses are strongly modulated by spatial features like edges, corners, and indentation depth (Johnson 2001). The spatial image carried by SA1 afferents is further elaborated in the somatosensory cortex, where neural responses exhibit a sensitivity to spatial features like edges (Bensmaia et al. 2008; Phillips et al. 1988), curvature (Yau et al. 2013), and motion (Pei et al. 2010) in ways that draw strong analogies to their visual cortical counterparts.

Although the SA1 spatial image effectively relays information about coarse textural features, many tangible surface features are too fine to be resolved spatially, given that the skin filters out very fine features (Sripati et al. 2006; Weber et al. 2013). In fact, information about fine textural



Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture, Fig. 1 SA1 spatial image. SA1 receptors carry a spatial pattern of information. (a) When *dot* patterns (*top*) are serially scanned over the finger, they elicit a spatial pattern of activation in example *SAI*, *RA*, and *PC*

receptors (Connor et al. 1990). (b) Examples of the *SAI*, *RA*, and *PC* response to letters serially scanned over the finger (Phillips et al. 1988). Note that the SA1 spatial image is characterized by well-resolved edges and corners (when compared to the RA and PC spatial images)

features is not perceptually accessible until the skin is actively scanned over a surface (Hollins and Risner 2000). Movement between a textured surface and the skin results in vibrations (Manfredi et al. 2014; Bensmaia and Hollins 2003, 2005) that reflect both spatially resolvable features as well as fine surface microgeometry. These vibrations elicit highly precise and repeatable temporal spiking patterns in rapidly adapting Meissner corpuscles (innervated by rapidly adapting or RA afferents) and Pacinian corpuscles (innervated by PC afferents). These patterns carry information about the skin vibrations (Talbot et al. 1968; Mackevicius et al. 2012) and thus about the texture itself (Weber et al. 2013; Fig. 2).

In summary, then, coarse textural features are encoded in the spatial pattern of activity evoked in one population of afferents – SA1 fibers – while

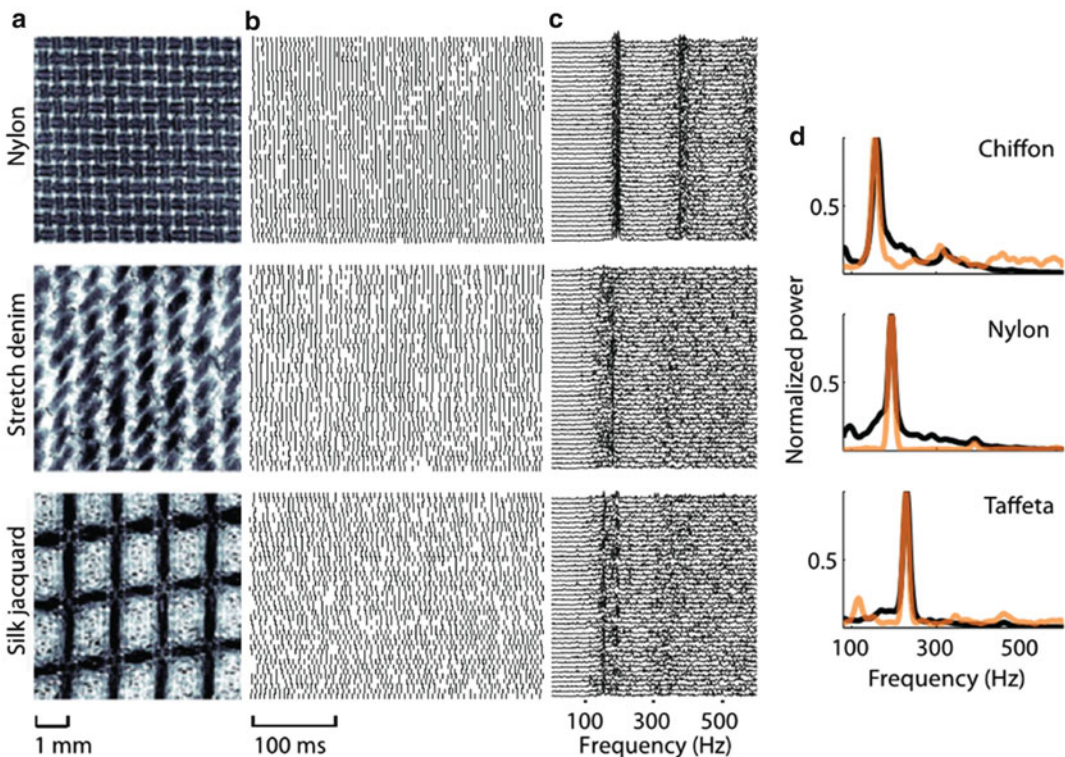
fine textural features are encoded in the temporal patterns of activity evoked in the other two, RA and PC fibers.

Multidimensionality of Texture Perception

The sensation of exploring a surface can be described along a number of perceptual dimensions: things may feel rough or smooth, hard or soft, sticky or slippery, and warm or cool (Hollins et al. 2000). The dominant dimension, and the most studied one, is roughness.

Roughness

Perceived roughness is determined by how variable the neural responses to textures are over time



Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture, Fig. 2 The timing of PC responses encodes information about skin vibrations. (a) High-resolution surface profiles of natural texture stimuli. (b) Texture-specific responses by an example PC receptor. PC responses are precisely timed and repeatable. (c) Trial-by-

trial power spectra of PC responses. Textures may elicit sharply periodic responses from PC receptors. (d) The periodicity in PC responses (average power spectra, orange) matches the frequency of skin vibrations (black) (Weber et al. 2013)

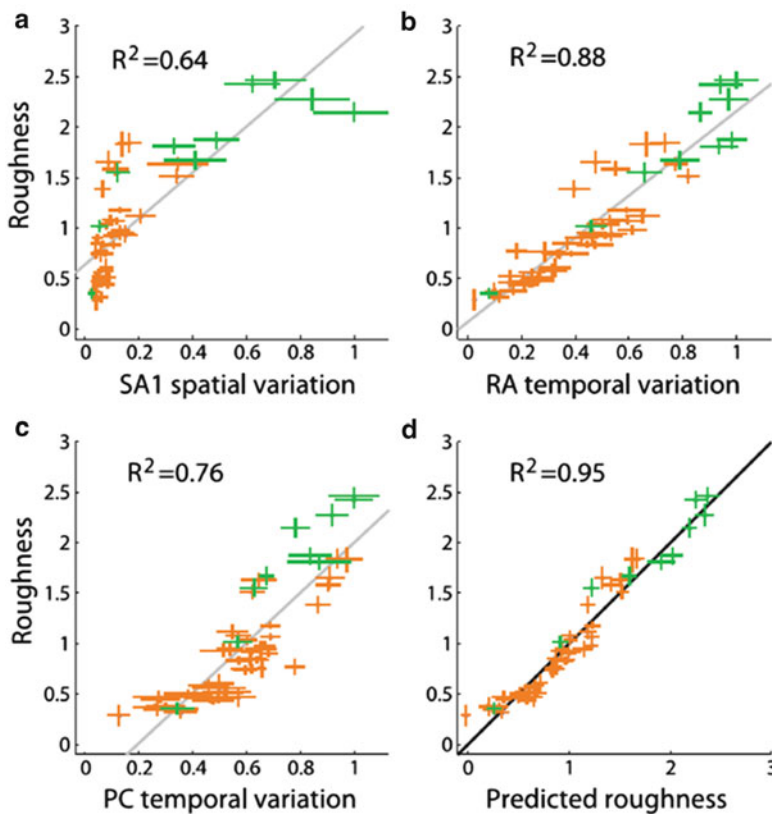
and space. Specifically, the spatial variability across the SA1 population response (Fig. 3a; Connor et al. 1990; Connor and Johnson 1992; Blake et al. 1997) is integrated with the temporal variability in the response of RA and PC afferents (Fig. 3b, c; Weber et al. 2013) to culminate in a percept of roughness (Fig. 3d). In other words, a texture is perceived as rough to the extent that different SA1 afferents produce different responses and individual RA and PC afferents produce responses that change over time.

Sensitivity to peripheral variability is a common feature of sensory processing. Indeed, when stimuli do not change in time, central sensory neurons across all modalities adapt toward their

baseline level of activity (Wark et al. 2007). In this way, adaptation serves to increase neural sensitivity to variations in the sensory input. Furthermore, sensory neurons in both visual and somatosensory cortex exhibit both excitatory and inhibitory components and thus show sensitivity to spatial differences in activation across the sensory sheet.

Hardness

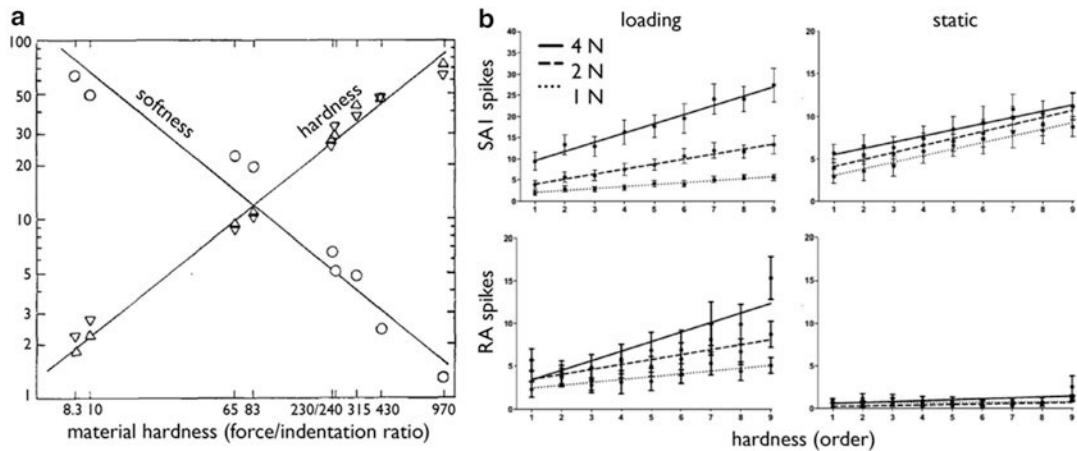
Judgments of surface hardness lie on a subjective continuum that closely covaries with measurements of surface compliance (Fig. 4a; Harper and Stevens 1964). Information from spatial patterns of afferent activation, response timing, kinesthesia, and even audition may be combined to culminate in a percept



Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture, Fig. 3

Signals from multiple receptors types are necessary to explain roughness. (a) SA1 spatial variation is plotted against judgments of roughness for natural textures, including both coarse (plastic dots and gratings, green) and fine (fabrics and sandpapers, orange) textures. Error bars represent SEMs across subjects

(roughness) and neurons (variation). The gray line denotes the line of best fit. SA1 spatial variation barely changes across a fourfold scale in roughness for fine textures. (b and c) Temporal variation for RA and PC afferents, respectively, plotted against perceived roughness. (d) A combined model of all three predictors almost perfectly predicts texture roughness (Weber et al. 2013)



Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture, Fig. 4 Hardness perception. (a) Judgments of hardness and softness covary closely with a measure of surface compliance (Harper and Stevens 1964). (b) Afferent activity in response to compliant stimuli indented into the skin. SA1 (*top*) and RA (*bottom*) responses are plotted against surface compliance

(numbered from the softest (1) to hardest (9) surface) for three different application forces. Both SA1 and RA afferents fire, while surfaces are actively loaded onto the skin (*left*), but only SA1 afferents fire when the surfaces are static (*right*). For a given force, firing rates increase with surface hardness

of hardness (Srinivasan and Lamotte 1995; LaMotte 2000). Thus, hardness perception involves a complex reconstruction of a measurable surface property but does not seem to be based on a simple readout of a singular neural quantity.

Information from both spatial and temporal mechanisms is combined to reconstruct judgments of hardness. Surfaces with different compliance lead to different spatial patterns of deformation of the skin: soft surfaces deform around the skin, while hard surfaces change the shape of the skin. These spatial patterns of skin deformations are reflected in the spatial patterns of activation elicited in populations of SA1 afferents (Franzén et al. 1996).

Precisely timed information can also be used to determine hardness. When judged through a probe, hardness is most effectively perceived using rapid tapping motions (LaMotte 2000), which elicit dynamic force profiles that most effectively recruit RA and PC afferents. Indeed, while SA1 responses to statically indented stimuli are informative about surface compliance, RA responses only convey hardness information during the dynamic loading phase (Fig. 4b; Condon et al. 2013).

Stickiness

Perceptual judgments of stickiness are often closely correlated with perceptual judgments of roughness (Hollins et al. 2000). When exploring the stickiness of a surface, subjects tend to apply a set amount of force normal to the surface. The resulting range of force tangential to the surface covaries closely with measurements of perceived stickiness (Smith and Scott 1996). Tangential forces stretch the skin, which excites Ruffini cylinders (innervated by slowly adapting type II (SAII) afferents) (Knibestol 1975) as well as SA1 and RA afferents (Birznieks et al. 2001, 2010).

Thermal Conductivity

Perception of a surface's temperature is clearly used for object identification (Katz and Krueger 1989) and is incorporated into the multidimensional percept of texture (Bensmaia and Hollins 2005; Hollins et al. 2000). Because everyday objects tend to be colder than skin temperature, surface temperature is determined by the rate of heat flow out of the skin (Ho and Jones 2006). This heat flow is almost certainly transduced by thermoreceptive afferents in the skin (Darian-Smith et al. 1973, 1979; Johnson et al. 1973, 1979).

Conclusion

Spatiotemporal patterns of activation across the four main populations of afferents that innervate the glabrous skin of the hand – SA1, RA, PC, and SAI – as well as thermoreceptors, convey exquisite and multidimensional information about surface texture. Different information about surface texture is conveyed in different aspects of afferent responses, with spatial patterns mediating the perception of coarse features and compliance and temporal patterns mediating the perception of fine features. Importantly, the perception of texture reflects the integration of different types of signals from multiple different tactile submodalities.

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Cx3D: Cortex Simulation in 3D

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Definition

Cx3D (pronounced Cortex 3D) is a simulation tool for simulating the growth primarily of neural tissue but is also capable of simulating other tissue growth. Cx3D allows a modeler to simulate the behavior of cells and their axonal and dendritic extensions in an artificial environment. Each cell can interact locally with its environment that consists of other cells and a chemical environment. The emphasis in Cx3D is on the local behavior of cells and the emergence of a global structure through the local behavior of the cells. It is not concerned with the simulation of an individual cell's internal environment but how multiple cells can organize themselves.

Detailed Description

In order to understand how tissue forms, and therefore how parts of the body of a multicellular organism form, we must study how cells organize themselves into these composites. Each cell is an individual; it has an internal environment of chemicals that is separated by a membrane from the external environment. The cell is the basic operational unit of an organism. In the development of an animal, each body starts with the

fertilized egg. The fertilized egg, a single cell, starts to divide and create more cells. With each cell cycle the number of cells potentially doubles, and thus, exponentially more cells are created over time. These cells form all the body parts, but how do they do this? There is no global controlling unit that tells each cell what to do. Each cell individually has to figure out what it has to do in this vast sea of potentially billions of other cells.

Cx3D is a simulation program that allows modelers to try out their theories of how the developmental process happens. Even though Cx3D was written with the intention of studying the development of neural tissue, it is not limited to that. Cx3D allows cells to divide, grow out axons and dendrites, secrete external and internal chemicals, read internal and external chemicals, and move around in the environment (the extracellular matrix which forms the biological environment of cells). The modeler has full control over these actions and can write small modules called *BiologicalModules* that are essentially programs running in the cells to define their behavior. *BiologicalModules* can be seen as an epiphenomenological model of proteins working together that define one behavior of a cell, e.g., to move the cell in a direction defined by an extracellular chemical gradient.

Cx3D provides a basic physics engine that prevents cells and cell parts from overlapping. The user of the simulation tool does not have to worry about the detailed implementation of the physical processes if he does not want to do so and can focus on the biological aspects of the model. In order to support the modeler even further, a language has been developed that supports the modeler in only allowing biologically plausible commands for the cells. This language, named *GCode*, is not directly part of Cx3D and therefore does not have to be used, but it proves to be very helpful in developing correctly behaving models.

In Cx3D, the cells are compartmentalized. The soma is approximated with a sphere, and the axons, dendrites, and other processes are approximated with cylinders. Each of these compartments can potentially run a different *BiologicalModule* and therefore have a biologically active behavior.

They are all passively subject to the force scheme of the simulation tool.

Cx3D operates on three levels of simulation: a biological, a physical, and a spatial level. The spatial level provides the neighborhood relations between the different compartments of the cells. The physical level uses the spatial information to calculate forces between the cellular compartments and takes care of intracellular and extracellular chemical diffusion processes. The biological level makes use of the physical level and organizes the compartments into cells that can run BiologicalModules. The simulation is round based and approximates development in small time steps.

Since tissue is built of thousands and potentially millions of cells, Cx3D has been extended into Cx3Dp (p for parallel) that runs in a multi-core/multi-computer environment to allow for these big simulations.

More information on Cx3D, along with links to publications and the latest version of the source code, can be found at <http://www.ini.uzh.ch/~amw/seco/cx3d>.

Cytoplasmic Resistivity

► [Resistivity, Axial](#)

D

Decision Making, Countermanding Oculomotor Models

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Definition

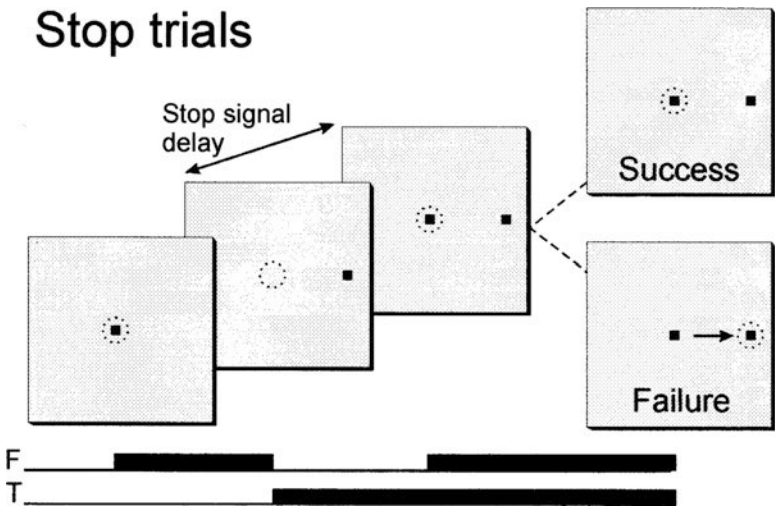
The countermanding oculomotor task or stop-signal task (see Fig. 1) requires participants to make a saccade to a GO stimulus (*no-stop-signal* trial) but stop the saccade when a STOP signal is presented (*stop-signal* trial). Participants' ability to inhibit the response depends on the interval between the GO and STOP signals, often referred to as the *stop-signal delay* (SSD). When the GO signal has a small head start relative to the STOP signal, then subjects succeed at inhibiting their responses. As the head start grows, subjects often fail to inhibit the response.

Detailed Description

The Countermanding Oculomotor Task

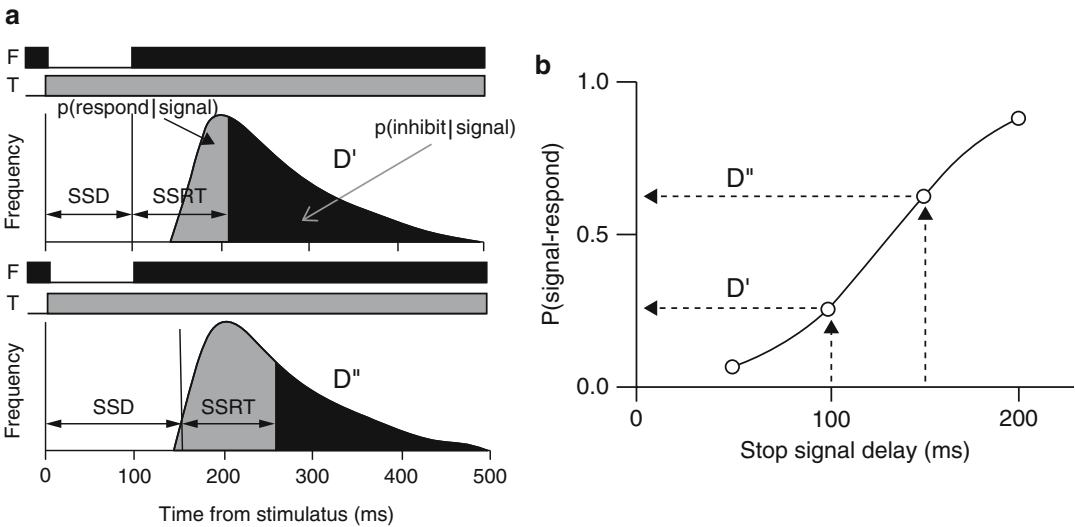
The countermanding saccade task (Fig. 1) is a response inhibition paradigm, in which participants are required to make a saccade as quickly

as possible to a GO signal (*no-stop-signal* trial). In few trials a STOP signal is presented, and the response must be stopped (*stop-signal* trial). There are two possible behavioral outcomes in this paradigm: (1) Participants fail to inhibit their response producing a *signal-respond* trial with a signal-respond reaction time (RT) and (2) participants inhibit their response producing a *signal-inhibit* or cancelled trial. Participants' ability to inhibit their response depends on the interval between the GO and STOP signal presentation, often referred as the *stop-signal delay* (SSD) (see Fig. 2a). When SSD is short, subjects often succeed at inhibiting; as SSD grows, subjects often fail to inhibit the response. When subjects fail to stop on stop-signal trials, their responses tend to be faster than on trials without a stop signal. An important aspect of the countermanding task is to determine the *stop-signal reaction time* (SSRT), the length of time required to cancel the saccade being programmed and maintain fixation on the central fixation spot. Because the duration of this inhibitory process is not explicit in the behavioral data, then an estimate of SSRT is calculated as the mean reaction time when no-stop signal is given minus the delay for which inhibition occurs on 50% number of trials (Hanes and Carpenter 1999). The probability of inhibiting/probability of responding as a function of SSD is referred as the inhibition function (see Fig. 2b for the probability of responding as a function of SSD).



Decision Making, Countermanding Oculomotor Models, Fig. 1 Basic design of the countermanding task. (Reproduced with permission from Hanes and Carpenter (1999), Fig. 1, p. 2778, Copyright © 1999, Elsevier). Typically a participant fixates on a central fixation spot (F) for a variable interval. Once it disappears, a visual target (T) simultaneously appears in the periphery.

After a delay in some trials, the fixation spot may reappear (stop-signal delay (SSD)) during which subjects are instructed to withhold the movement. Subjects sometimes successfully countermand the saccades, and sometimes they do not. The dotted circle indicates the focus of gaze at each interval, and the arrow indicates the saccade



Decision Making, Countermanding Oculomotor Models, Fig. 2 (a) Schematic indicating how the probability of responding [$p(\text{respond}|\text{signal})$] and the probability of inhibiting [$p(\text{inhibit}|\text{signal})$] depend on GO- RT, SSD, and SSRT distributions. (Reproduced with minor changes from Boucher et al. (2007), Fig. 1D, p. 377, Copyright ©

2007 American Psychological Association). (b) Plot of inhibition function as function of SSD. D' and D'' indicate the proportion of signal-respond trials at SSDs of 100 ms and 150 ms, respectively. (Reproduced with from Boucher et al. (2007), Fig. 1C, p. 377, Copyright © 2007 American Psychological Association)

Human Performance in the Countermanding Oculomotor Task

Early countermanding or stop-signal experiments involved manual responses to visual GO signals and visual/auditory STOP signals (Logan and Cowan 1984). The first countermanding oculomotor task was introduced by Hanes and Carpenter (1999). In this task, participants were asked initially to fixate on a central stimulus. As soon as the central (fixation) stimulus disappeared, a peripheral (target) stimulus appeared either to the left or right peripheral visual field, and the participants had to make a saccadic eye movement toward it. On some trials, the fixation stimulus reappeared, acting as a STOP signal, instructing the participant that the saccade should be inhibited and instead to hold his/her gaze on the fixation stimulus. Mean saccade latencies on the GO trials were reported to be 200–300 ms and were faster with a higher luminance contrast visual stimulus. On the other hand, SSRTs ranged from 125 to 145 ms but did not vary with target luminance. Schall and Thompson (1999) suggested that the short STOP signal latency may be due to the STOP signal being presented centrally to the fovea. Asrress and Carpenter (2001) tested the effectiveness of central and peripheral visual stimuli in the stop-signal response. They reported that central and peripheral visual stop cues produced the same SSRTs. However, when both cues were used, then the SSRTs were shortened, suggesting that the central and peripheral stop signals have independent inputs to the stopping process.

Other experiments examined the effects of other sensory modalities in response inhibition and reported that the SSRTs were slightly longer when an auditory or a tactile instead of a visual stimulus was used as a STOP signal (Armstrong and Munoz 2003; Morein-Zamir and Kingstone 2006; Akerfelt et al. 2006; Cabel et al. 2000). Subsequent experiments have reported that human subjects respond faster and with greater accuracy to stimuli that are brighter, louder, and associated with larger reward or have larger

probability of appearance, than to neutral stimuli (Wattiez et al. 2016).

Recent experiments investigated how saccade cancellation is influenced by the fixation disengagement (Stevenson et al. 2009). Human participants performed countermanding experiments that required them to try to cancel an impending saccade in the presence of an imperative visual STOP signal, across different fixation conditions. Stop signal reaction times were ~40 ms shorter on trials with a 200 ms gap between fixation point removal and target presentation compared with when the fixation point remained illuminated. Investigators concluded that the reduction in SSRTs were primarily due to removal of a foveal fixation point (as opposed to a generalized warning effect) and persisted with an auditory stop signal that controlled for potential differences in stop signal saliency across different fixation conditions.

Countermanding Oculomotor Performance in Disorders

Countermanding performance has also been investigated in many neurological and psychiatric disorders including attention deficit hyperactivity disorder (ADHD; Armstrong and Munoz 2003; Hanisch et al. 2006), schizophrenia (Thakkar et al. 2011, 2015), bipolar disorder (Thakkar et al. 2015), and Parkinson's disease (Farooqui et al. 2011).

In particular, patients with ADHD involved in a countermanding saccade task (Armstrong and Munoz 2003) made more impulsive eye movements than age-matched controls. Furthermore, ADHD participants were faster to respond to a target, but they were more likely to fail to countermand an eye movement on STOP trials (Armstrong and Munoz 2003). SSRTs of adult ADHD patients were reported to be longer in a saccadic countermanding task, particularly with an auditory or peripheral visual stop signal (Armstrong and Munoz 2003). Slower SSRTs were also observed in children diagnosed with ADHD (Hanisch et al. 2006).

Similarly, patients suffering with schizophrenia (Thakkar et al. 2011) were associated with increased latency to inhibit a planned saccade. Longer SSRTs were found in patients, despite patients having equal sensitivity to the stop signal and similar latencies to initiate a saccade. Their SSRTs were correlated with increased negative symptoms and poorer occupational functioning, indicating the clinical relevance of these findings. Patients made appropriate RT adjustments after errors but slowed down significantly more than control subjects after correctly inhibited saccades. Subsequent experiments from the same group tested the countermanding performance of schizophrenia patients in a double-step task (Thakkar et al. 2015). In this task, participants were required to make a saccade to a visual target. Infrequently, the target jumped to a new location, and participants were instructed to rapidly inhibit and change their response. Patients had poorer efficiency of inhibition, indexed by longer TSRT (target step reaction time). An impairment in response execution was also observed when patients were required to redirect gaze to a new location.

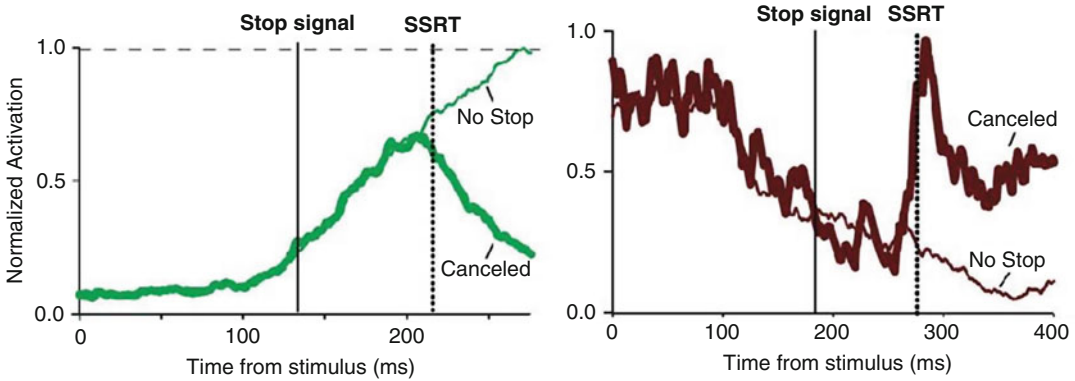
Non-human Primate Performance in the Countermanding Oculomotor Task

The primate brain circuits involved in the countermanding oculomotor task are complex, involving many brain areas (for reviews see Schall and Godlove (2012)). Neurons in the frontal eye field (FEF), supplementary eye field (SEF), lateral intraparietal area (LIP), pre-supplementary motor area (preSMA), and subthalamic nucleus (STN), and superior colliculus have been described as movement-related in the saccade countermanding task. However, neuronal recordings from SEF, LIP, preSMA, and STN have produced conflicting results (for more details see Stuphorn et al. 2000; Scangos and Stuphorn 2010; Isoda and Hikosaka 2007, 2008). The two brain areas that are the most studied and have produced the most consistent results in response inhibition in the countermanding task are the FEF and SC.

FEF is an area in the dorsolateral prefrontal cortex of macaque monkeys where neurons respond to visual stimuli but also are involved

in the production of saccadic eye movements (Bruce et al. 1985; Hanes and Schall 1996; Sommer and Wurtz 2000; Segraves and Goldberg 1987). The FEF movement-related neurons have been shown to discharge before and during saccades (Bruce and Goldberg 1985; Hanes and Schall 1996) and innervate other movement-related neurons in SC and the brainstem (Segraves and Goldberg 1987; Sommer and Wurtz 2000; Segraves 1992). Other FEF and SC neurons have been shown to discharge during fixation but suppress their activities during saccades. These fixation cells are critical for controlling saccade initiation. Electrical stimulation of SC fixation cells can interrupt saccades in monkeys (Gandhi and Keller 1999), and their deactivation results in excessive saccade initiation (Munoz and Wurtz 1993). Two experimental studies have described the activities of movement-related and fixation neurons in FEF and SC in macaque monkeys performing a saccade stop signal task (Hanes et al. 1998; Pare and Hanes 2003). Once the GO signal was given (target appeared), then movement-related neuronal activity in both areas grew toward a threshold. In trials where no STOP signal was presented, these activities continued to grow (see Fig. 3a left). The activities of corresponding fixation neurons were decreased (see Fig. 3a right). If a STOP signal was presented (*cancelled trial*), then the movement-related activities were inhibited (see Fig. 3a left) and the fixation cells generated rapid bursts (see Fig. 3a right). This activation reciprocity of movement-related and fixation cells naturally reinforces the idea that they share a mutually inhibitory relationship.

A similar inhibitory relationship exists between fixation and saccade neurons in macaque monkeys performing the antisaccade task (Everling et al. 1999; Everling and Munoz 2000). Fixation cells are tonically active when subjects are fixating, and they pause their activities when a saccade is executed. Saccade neurons, on the other hand, discharge when a saccade is initiated but remain silent during fixation. Two populations of saccade neurons have been recorded in SC: buildup and burst cells (Munoz and Wurtz 1993, 1995a, b).



Decision Making, Countermanding Oculomotor Models, Fig. 3 Normalized activity of FEF gaze-shifting (left) and gaze-holding (right) neurons. (Reproduced with permission from Schall and Godlove (2012), Fig. 2, p. 1014, Copyright ©, Elsevier). Thick green and red lines represent the activities of cancelled FEF gaze-shifting and gaze-holding neurons, respectively. Thin green and red

lines represent the activities of non-cancelled FEF gaze-shifting and gaze-holding neurons, respectively. Presentation of the stop signal is indicated by the solid vertical line. The time needed to cancel the planned movement – stop signal reaction time (SSRT) – is indicated by the dashed vertical line

Computational Models of Countermanding Oculomotor Performance

Over the years many mathematical and computational models of countermanding oculomotor performance have been proposed. Some of these models provide explicit descriptions of the mental processes that are tightly linked to countermanding behavior, and others focus on the neurons, networks, or brain regions involved in the countermanding task. A direct comparison of the performance of these various computational models in the countermanding task can be found in Table 1.

Independent Horse-Race Model

The oldest and most successful model of the countermanding task is the “independent horse-race model” (Fig. 4; Logan and Cowan 1984). The model is intuitively simple consisting of two *independent* accumulators, a GO process and a STOP process, which race each other till a predefined threshold is reached by one process. If the GO process, initiated at GO stimulus onset, reaches the threshold first, then stimulus response is generated, and the trial ends; if the STOP process, initiated at the STOP stimulus onset,

reaches the threshold first, then the subject stops, and the trial ends. The STOP process wins the race if $SSRT + SSD$ is less than the GO-RT. Then, the response is inhibited and a signal-inhibit trial takes place. If the $SSRT + SSD$ is greater than the GO-RT, then the GO process wins, the response is executed, and a signal-respond trial occurs. Because the GO-RT and SSRT are assumed in the model to be independent random variables drawn from their response time distribution, then the outcome of the race includes a random component. Increases in SSD favor the GO process and so the STOP process wins less often. Thus, the probability of inhibiting the response decreases, and the probability of responding increases. Such a relationship reproduces the experimentally observed inhibition function. The “independent race model” explains further why the responses in the stop-signal trials are faster than the no-stop-signal ones and how they change in relation to the SSD. When the SSD is short, only the fastest GO-RTs are faster than $SSRT + SSD$, so signal-respond RT is very short, reflecting the lower tail of the GO-RT distribution. As the SSD increases, more GO-RTs are fast enough to win the race, so signal-respond RT increases. If the SSD is long enough, all GO-RTs will win the race, and signal-respond RT will

Decision Making, Countermanding Oculomotor Models, Table 1 Comparison of performance of computational models in the countermanding paradigm.

(Reproduced with permission from Cutsuridis (2017), Table 1, p. 9, Copyright ©, Royal Society Publishing)

Modelling study	Behavioral data		Neurophysiology data			
	Inhibition function	Cumulative reaction time distributions	Movement neuron profile		Fixation neuron profile	
			No-stop	Cancelled	No-stop	Cancelled
Independent race model (Logan and Cowan 1984)	√	√				
Countermanding LATER model (Hanes and Carpenter 1999)	√	√				
Interactive race model (Boucher et al. 2007)	√	√	√	√	√	
Augmented interactive race with pre-target model (Wong-Lin et al. 2010)	√	√	√	√	√	
Spiking neural model with top-down control (Lo et al. 2009)	√	√	√	√	√	
Cancellable rise-to- threshold model (Salinas and Stanford 2013)	√	√				
Blocked-input 1.0 model (Logan et al. 2015)	√	√	√	√	√	
Blocked-input 2.0 model (Logan et al. 2015)	√	√	√	√	√	
Boosted-fixation 1.0 model (Logan et al. 2015)	√	√	√	√	√	

approach no-stop-signal RT. The model has been successfully able to quantitatively simulate the inhibition function as a function of SSD and the SSRT distributions across age, patient groups, and experimental conditions. The model did not though consider the underlying neural processes. Furthermore, recent experimental evidence has ruled against the independent race of the GO and STOP processes (Montagnini and Chelazzi 2009).

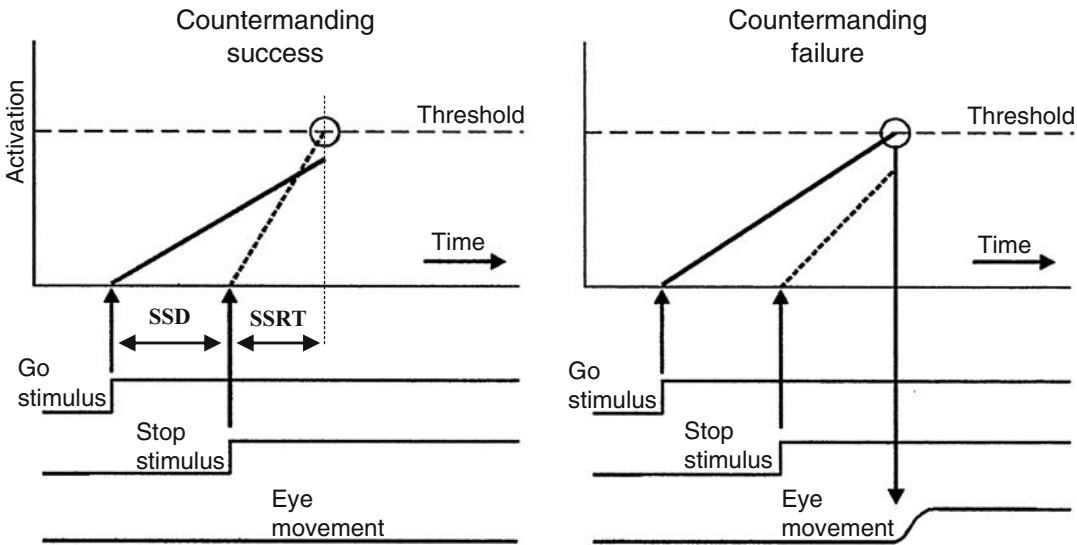
Countermanding LATER Model

A model similar to Logan and Cowan’s (1984) “independent horse-race model” is the countermanding LATER model of Hanes and Carpenter (1999) (see Fig. 5). The countermanding LATER model consists of two independent LATER units, a GO unit and a STOP unit, racing each other to a threshold. The rate of rise of each LATER unit’s activity takes values from two normal distributions with different means and standard deviations. In the model, as in the experiment, the GO

unit is activated first, followed by activation of the STOP unit, which in turn inhibits the GO unit. If the GO unit reaches the threshold before the STOP unit, then a GO response is generated. If the STOP unit reaches the threshold before the GO unit, then a No-GO response is generated. If the GO unit activity reaches threshold first, then a GO response is generated. The model is able to simulate accurately the RT distribution and inhibition function as a function of SSD. However, it does not attempt to provide any insights to the neural mechanisms of stopping.

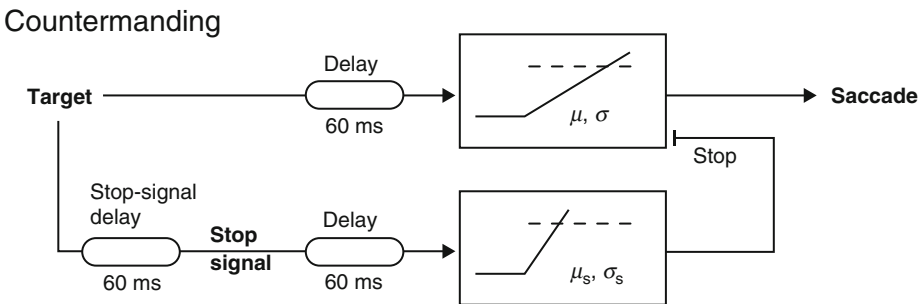
Interactive Race Model

The “interactive race model” (see Fig. 6) was introduced (Boucher et al. 2007) as an alternative to the previous race models in order to suggest how neural circuitry could give rise to the observed behaviors. To this end, the authors (Boucher et al. 2007) quantitatively simulated the behavior of the countermanding task and



Decision Making, Countermanding Oculomotor Models, Fig. 4 Basic schematic of the independent horse-race model of countermanding performance. Two independent processes race toward a threshold, where one process is initiated by a GO signal, while the other process by a STOP signal after a variable stop signal delay (SSD). If the GO process crosses the threshold first, it wins the race and a non-cancelled response is made. If the STOP

process crosses the threshold first, it wins the race, and the response is inhibited. The STOP signal response time (SSRT) is the time between STOP signal onset and the point where the STOP process crosses the threshold to countermand the response. (Reproduced with permission from Hanes and Carpenter (1999), Fig. 4, p. 2782, Copyright ©, 1999, Elsevier)

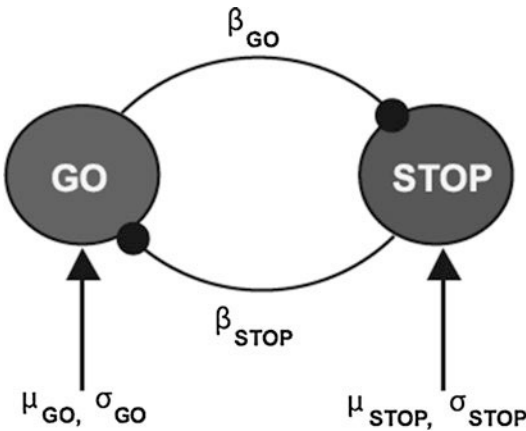


Decision Making, Countermanding Oculomotor Models, Fig. 5 Countermanding LATER model. (Reproduced with permission from Noorani (2014), Fig. 4, p. 3, Copyright ©, Frontiers publishing company). A GO unit competes with a STOP unit, and the winner of

the competition determines the outcome. In some trials, the GO unit reaches threshold even in the presence of the STOP unit, which failed to stop it (non-cancelled trials). In other trials, the STOP unit is faster than the GO unit, so no response (saccade) is generated (cancelled trials)

specified the neural underpinnings of stopping. They proposed that lateral inhibition between competing neural accumulators is the mechanism for stopping. This model assumption was in line with the experimentally observed modulation of neural activity from recurrently inhibited neurons in SC and FEF, two brain areas directly

involved in saccadic eye movements (discussed in the previous section; Hanes et al. 1998; Pare and Hanes 2003). As in the previous models, the interactive model consisted of two accumulators, the GO process and the STOP process. The GO process was modelled as a stochastic accumulator that integrated neural activity over time until it



Decision Making, Countermanding Oculomotor Models, Fig. 6 Interactive race model. (Reproduced with permission from Logan et al. (2015), Fig. 9b, p. 49, Copyright © 2015 American Psychological Association)

reached a threshold, after which a response was made. Similarly, the STOP process was modelled as a stochastic accumulator that stopped the response by inhibiting the GO activation and preventing it from reaching the threshold. The STOP and GO processes were mutually inhibiting each other, but their strengths were asymmetric with the STOP process inhibiting the GO process more than the GO process inhibited the STOP process. Because in the model the GO and STOP processes proceed independently for most of their duration, the STOP unit inhibited the GO unit strongly only very late in the trial. This produces finishing times that appear independent, as in the independent model. The model has been successful at simulating accurately both behavioral and neurophysiological data including the activation profiles of gaze-responding neurons (movement and fixation cells) in the signal-inhibit and no-stop-signal trials.

Cancellable Rise-to-Threshold Model

Salinas' and Stanford's (2013) "cancellable rise-to-threshold model" is built on the foundation of the compelled saccade task (Shankar et al. 2011), which attempts to separate the contribution of perceptual and motor processing in the countermanding task. As in the interactive race model, programming a saccade involves a process

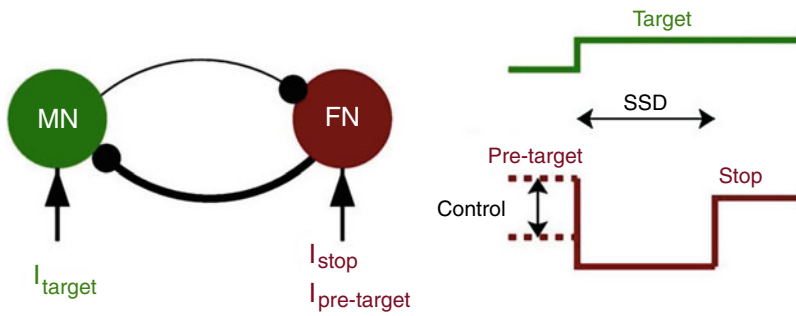
building activity to a threshold. The model assumes that once a stop-stimulus is presented, a perceptual mechanism detects it with a particular speed and reliability. Once the signal is detected, then the movement plan decelerates, and the movement is stopped. The model successfully replicates the experimentally observed countermanding behavior, but it does not attempt to reproduce the recorded neural activity. However, it has been suggested to be profoundly similar to the "interactive race model" and hence matches the earlier model in its predictions (see Bissett (2013) for a critique of the "cancellable rise-to-threshold model").

Augmented Interactive Race with Pre-target Input Model

Wong-Lin and colleagues (2010) advanced an extension (see Fig. 7) of the "interactive race model" by including an additional pre-target input to account for the experimentally reported high firing rates of fixation neurons (Hanes et al. 1998). They demonstrate that such simulated pre-target fixation neuronal activity reproduces countermanding behavior that maximizes reward rate as a function of SSD, fraction of stop-signal trials, intertrial interval, duration of timeout, and relative reward value. Further, it simulated accurately the neural traces of movement and fixation cells in no-stop and cancelled trials.

Spiking Interactive Race with Top-Down Inhibition Control Model

Lo and colleagues (2009) introduced an attractor-based model of neural spiking dynamics. The neural network model was multi-modular consisting of a premovement module that controlled inhibition of movements and a control module that provided a top-down inhibitory control over the premovement module. The model replicated the probability of responding and RTs on correct and error trials as well as the patterns of activity observed in SC and FEF (Hanes et al. 1998; Pare and Hanes 2003). The model made new predictions and suggested new experiments. Particularly, their model predicted that the neural activities of movement and fixation neurons are negatively correlated earlier in



Decision Making, Countermanding Oculomotor Models, Fig. 7 (Left) Augmented interactive race with pre-target input model. (Reproduced with permission from Wong-Lin et al. (2010), Fig. 1A, p. 12, Copyright © 2010 Elsevier Science Ltd). Asymmetrical mutual inhibition

between movement (MN) and fixation (FN) neural units is observed. (Right) Inputs trace to MN (green) and FN (red). SSD = stop signal delay. Cognitive control is assumed to vary pre-target FN input

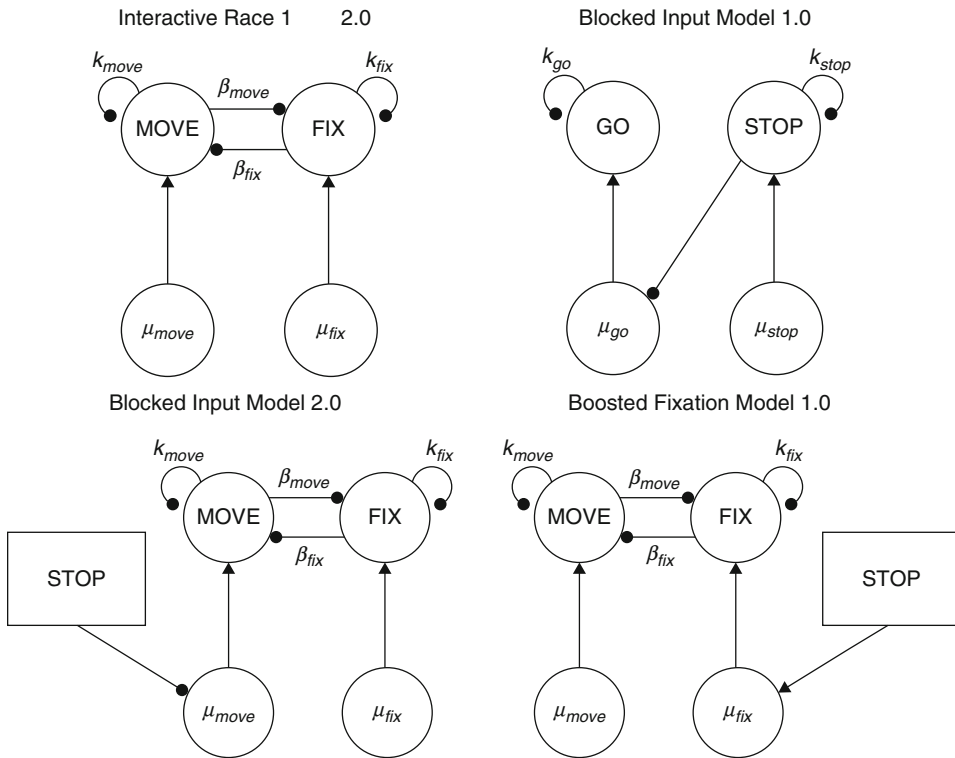
non-cancelled trials than in cancelled trials. It demonstrated that inhibitory control in the countermanding task is due to modulation of the strength of the top-down drive to the movement module. Weaker simulated top-down control resulted in shorter reaction times, more errors, but unchanged SSRTs.

Despite its successes, the model did not incorporate all of the brain circuits involved in control of saccades, omitting areas such as the supplementary frontal eye field (SEF), and anterior cingulate cortex (ACC). Furthermore, the model did not separate the stimulus-driven input and the top-down input to fixation neurons in order to assess their effects on inhibitory control (Asrress and Carpenter 2001).

Other Race Models

Recently, Logan et al. (2015) introduced new variations of the original interactive race model (Boucher et al. 2007), namely, the “blocked-input 1.0 race model,” the “blocked-input 2.0 race model,” and the “boosted-fix 1.0 race model” (see Fig. 8). The “blocked-input 1.0 race model” assumed that the STOP unit did not directly inhibit the GO activation, but instead it activated a top-down process that turned off the GO activation and set the mean neural GO activity to zero once it reached the threshold. If the input is blocked early enough, then the GO neural activation did not reach the threshold and the response was inhibited. If the GO activation reached the

threshold before its input was blocked, then inhibition failed and the GO response was executed. The “blocked-input 1.0 race model” fits the behavioral data as well as the original interactive model indicating that direct inhibition from the STOP process on the GO process is not needed to account for the countermanding behavior. The “blocked-input 1.0 race model” fitted monkey neurophysiological data better than the original interactive model by predicting growth rates, decay rates, and cancel times that fell within the 95% confidence intervals of the observed monkey data. The “blocked-input 2.0 race model” was the same as the original interactive model with mutual inhibition between the GO and STOP processes except that it also includes a third independent top-down process that also inhibits the GO signal. Version 2.0 of the “blocked-input race model” produced as good a fit to the behavioral and neurophysiological data as version 1.0 but a better one than the original interactive model. The “boosted-fix 1.0 race model” assumed the presence of a similar top-down process, but which boosted the STOP activation instead of blocking the GO activation. It produced as good a fit to the data as the “blocked input 2.0 race model.” Further neurophysiological experimentation will show if such a hypothesized top-down signal that blocks the GO activation and/or boosts the STOP activation really exists and what mechanisms allow it to switch modes of operation.



Decision Making, Countermanding Oculomotor Models, Fig. 8 Architecture of Interactive Race Model 2.0 (*top left*), Blocked Input Model 1.0 (*top right*), Blocked Input Model 2.0 (*bottom left*), Boosted Fixation Model 1.0

(*bottom right*). (Reproduced with permission from Logan et al. (2015), Figs. 8 and 9, Copyright ©, American Psychological Association)

Cross-References

- [Accumulation of Evidence in Decision-Making](#)
- [Choice Behavior](#)
- [Decision-Making, Antisaccade Models of](#)
- [Decision-Making, Bias](#)
- [Decision-Making, Models](#)
- [Decision-Making, Threshold](#)
- [Decision-Making: Overview](#)
- [Perceptual Decision-Making](#)
- [Speed-Accuracy Tradeoff](#)

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Further Reading

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- Frontal eye fields. http://www.scholarpedia.org/article/Frontal_eye_field

Wikipedia

- Antisaccade task. https://en.wikipedia.org/wiki/Antisaccade_task
- Two alternative forced choice. https://en.wikipedia.org/wiki/Two-alternative_forced_choice

Decision Space Boundary

- [Decision-Making, Threshold](#)

Decision-Making

- [Choice Behavior](#)

Decision-Making Tasks

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Definition

A diverse repertoire of behavioral tasks has been employed to examine the cognitive processes and neural basis underlying decision-making in humans and animals. Some of these have their origins in psychology, others in cognitive

neuroscience, yet others in economics. There is also a continual invention of novel or hybrid paradigms, sometimes motivated by deep conceptual questions stimulated by computational modeling of decision-making and sometimes motivated by specific hypotheses related to functions of neuronal systems and brain regions that are suspected of playing an important role in decision-making.

Detailed Description

The area of decision-making is a dynamically evolving, multifaceted area of active research that sits at the interfaces of many areas, among them psychology, neuroscience, economics, finance, political science, engineering, and mathematics. The range of decision-making tasks seen in the literature is extremely diverse, reflecting the interdisciplinary nature of the area and the diverse background of the researchers engaged in it. This entry attempts to summarize and categorize the major classes of decision-making tasks with respect to the formal, mathematically quantifiable properties of the tasks and the cognitive processes that may consequently be entailed. Broadly, decision-making tasks can be grouped into the following categories and subcategories:

- Decision-making under uncertainty
 - Sensory uncertainty
 - Outcome uncertainty
- Multidimensional decision-making
 - Target-distractor differentiation
 - Multisensory integration
- Preference-based decision-making

Decision-Making Under Uncertainty

Many decision-making tasks require the subjects to make choices among alternatives under conditions of uncertainty. Uncertainty can arise from noise related to sensory inputs, ignorance about stimulus or action outcomes, stochasticity or imprecise representation related to (relative) temporal onset of events, or some hybrid combinations of two or more of these factors. The

difficulty of the tasks can often be controlled parametrically via the level of uncertainty induced experimentally, and the tasks can therefore be used to probe fundamental limitations and properties of human and animal cognition, as well as characterize individual and group differences.

Sensory Uncertainty

Decision-making under sensory uncertainty, or *perceptual decision-making*, involves tasks in which the subject views a noisy stimulus and chooses a response consistent with the perceived response. One such widely used task is the random-dot coherent motion task (Newsome and Paré 1988), in which a field of flickering dots is displayed to the subject, a fraction (usually a minority) of which has simulated motion in a coherent direction, and the remainder either move in random directions (Newsome and Paré 1988) or have no discernible direction of motion (Shadlen and Newsome 2001). Based on the stimulus, the subject then chooses the appropriate response to indicate the perceived direction of coherent motion in the stimulus. This is usually done by eye movements in monkeys and either eye movements or key presses in humans. Typically, there are two possible directions of motion, out of which the subject must choose, making this a 2-alternative forced choice (2AFC) task; occasionally, it has been done with more than two alternatives or in a multiple-alternative forced choice (mAFC) format (Churchland et al. 2008). When the 2AFC version is done in conjunction with recordings of neurons that are sensitive to the direction of motion of the stimulus, the two possible directions of motion are chosen to be aligned with the preferred and anti-preferred directions of the neuron being recorded (Shadlen and Newsome 2001); in the mAFC version, one of the possible motion directions is aligned with the preferred direction of the neuron (Churchland et al. 2008).

There are two major variants of the random-dot coherent motion task, one in which the stimulus is present for a fixed duration (Newsome and Paré 1988) and one in which the stimulus is present until the subject makes a perceptual response (Roitman and Shadlen 2002). The latter, known

as the reaction time (RT) variant, is the behaviorally more interesting case, as it allows the subject to decide not only which stimulus was seen but how much sensory data to accumulate about the stimulus before responding. This has made this task a simple yet effective means for probing the speed-accuracy trade-off in perception (Gold and Shadlen 2002). Another property of the task that makes it ideal for examining the speed-accuracy trade-off is that it corrupts the sensory stimulus with a significant amount of noise that is identical and independent over time, making the informational value of the sensory stimulus constant over time (Bogacz et al. 2006). This property also gives the experimenter an accessible experimental parameter for controlling the information rate (signal-to-noise ratio) of the stimulus, through the coherence of the stimulus, or the percentage of coherently moving dots.

The mathematically optimal decision policy for choosing among two hypotheses based on independent, identically distributed data, where the observer can choose how much data to observe, is known as the sequential hypothesis ratio test (SPRT). It is the optimal policy for minimizing any cost function that is monotonically related to average reaction time and probability of error (Wald 1947; Wald and Wolfowitz 1948). It states that the observer should accumulate evidence, in the form of Bayesian posterior probability using Bayes rule or, equivalently, by summing up log odds ratios, until the total evidence exceeds a confidence bound that favors one or the other stimulus; then, at that point, the observer should terminate the observation process and choose the more probable alternative. The height of the decision boundary is determined by the relative importance of speed and accuracy in the objective function, with greater importance of speed relative to accuracy leading to lower decision boundaries, and vice versa for decreasing importance of speed relative to accuracy. In the limit when many data samples are observed before the decision is made, SPRT converges to the drift-diffusion process first studied in connection with statistical mechanics; it is essentially a bounded linear dynamical system with additive Wiener noise and absorbing boundaries (Laming

1968; Ratcliff and Rouder 1998; Bogacz et al. 2006). Many mathematical properties of the drift-diffusion process are well known, such as the average sample size before termination, and the probability of exceeding the correct boundary, for different problem parameters and task conditions. It therefore provides a convenient mathematical framework for analyzing SPRT and thus experimental behavior in different task settings.

A popular alternative to the 2AFC paradigm is the Go/NoGo (GNG) task, in which one stimulus requires a response (Go) and the other requires the response to be withheld (NoGo). One apparent advantage of the GNG paradigm is that it obviates the need for response selection (Donders 1969), thus helping to minimize any confounding influences of motor planning and execution when the experimental focus is on perceptual and cognitive processing. However, within-subject comparison of reaction time (RT) and error rates (ER) in 2AFC and Go/NoGo variants of the same perceptual decision-making task has found systematic biases between the two (Gomez et al. 2007). Specifically, the go stimulus in the Go/NoGo task elicits shorter RT and more false-alarm responses than in the 2AFC task, when paired with the same opposing stimulus in both paradigms, resulting in a Go bias. This raises the question of whether the two paradigms really probe the same underlying processes.

Existing mechanistic models of these choice tasks, mostly variants of the drift-diffusion model (DDM; Ratcliff and Smith 2004; Gomez et al. 2007) and the related leaky competing accumulator models (Usher and McClelland 2001; Bogacz et al. 2006), capture various aspects of behavioral performance, but do not clarify the provenance of the Go bias in GNG. Recently, it has been shown that the Go bias may arise as a strategic adjustment in response to the implicit asymmetry in the cost structure of the 2AFC and GNG tasks and need not imply any fundamental differences in the sensory and cognitive processes engaged in the two tasks. Specifically, the NoGo response requires waiting until the response deadline, while a Go response immediately terminates the current trial (Shenoy and Yu 2012). Using a Bayes-risk minimizing decision policy that minimizes not only error rate but also average decision

delay naturally exhibits the experimentally observed Go bias. The optimal decision policy is formally equivalent to a DDM with a *time-varying threshold* that initially rises after stimulus onset and collapses again just before the response deadline. The initial rise in the threshold is due to the diminishing temporal advantage of choosing the fast Go response compared to the fixed-delay NoGo response.

Outcome Uncertainty

This class of decision-making tasks is designed such that subjects have no uncertainty about the stimulus identity, but rather about the consequences of choosing one alternative over another. To induce such uncertainty, the subjects are not explicitly told about the reinforcement consequences of the different alternatives, but instead they have to learn them over time. The reinforcements are typically in the form of a reward, such as money for human subjects, juice for monkeys, or seeds for birds; but occasionally they can also be in the form of a penalty, such as money taken away for human subjects, a foot shock for rats, or air puff for rabbits. This class of task originated in the study of associative learning, which showed that subjects' asymptotic choice performance after substantial learning exhibited interesting features. For example, Herrnstein (Herrnstein 1961) found that pigeons, when faced with a choice between pecking two different buttons in a Skinner box, did not always choose the one with the higher reward rate, which is mathematically optimal, but rather alternated among the choices stochastically so as to "match" their underlying reward rates. Based on these results, Herrnstein formulated the "matching law" and the related "melioration theory" (Herrnstein 1970), which gave a procedural account of how matching-like behavior can arise from limited working memory. A more recent account, using Bayesian learning theory, shows that matching-like behavior is, at a finer timescale, the consequence of a maximizing choice strategy (always choosing the best options), coupled with a learning procedure that assumes the world to be nonstationary and thus

results in internal beliefs that fluctuate with empirical experiences, even those driven by noise in a truly stationary environment (Yu and Cohen 2009; Yu and Huang 2014).

In order to induce continual outcome uncertainty, many implementations of this task incorporate unpredictable, unannounced changes in the stimulus-outcome contingencies during the experimental session. A classical example of such a manipulation is reversal learning, in which the choice with the better outcome suddenly becomes the worse choice, while the previously bad choice now becomes the better choice. This type of tasks has been used to study, among other things, how perseverative tendencies might change as a function of experimental condition or manipulations of the neural circuitry in the brain. Such tasks are rich for theoretical modeling of the neural representation, computation, and utilization of different forms of uncertainty that arise during learning and decision-making (Yu and Dayan 2005; Nassar et al. 2010). For example, there is thought to be a differentiation of at least two kinds of uncertainties, “expected uncertainty,” dealing with known uncertainties and variabilities in the environment, and “unexpected uncertainty,” arising from dramatic, unexpected changes in the statistical contingencies in the environment. Experimentally, human subjects have been shown to be more ready to alter choice strategy under conditions of more frequent choice-outcome contingencies compared to when these changes are less frequent (Behrens et al. 2007); the upregulation of the neuromodulator norepinephrine has been shown to increase the rates for learning such changes (Devauges and Sara 1990); pupil diameter in human subjects, under the control of noradrenergic and cholinergic neuromodulatory systems, has also been shown to correspond to specific model-derived uncertainty signals (Nassar et al. 2012).

Multidimensional Decision-Making

There are two main types of multidimensional decision-making: (1) target-distractor differentiation, in which subjects must exclude the interfering influence of a distractor stimulus or attribute, in

order to focus on the target stimulus or attribute, and (2) multisensory integration, in which subjects must integrate multiple stimuli, often differing in sensory modalities, to reach a combined choice response.

Target-Distractor Differentiation

One classical task of this type is the Stroop task (Stroop 1935), in which subjects must ignore the meaning of a color word and report the physical color in which the text is written. Subjects consistently respond faster and more accurately when the meaning and physical attribute of the color word are congruent than when they are not. A related task is the Simon task, in which a stimulus present on one side (e.g., visual stimulus on the left side of the screen or auditory stimulus to the left ear) may instruct the subjects to respond with the other, less direct response (e.g., right button press), and again, performance is better when the two dimensions are congruent than when they are not (Simon 1967). Yet another similar task is the Eriksen task (Eriksen and Eriksen 1974), which requires the subject to identify a central stimulus (e.g., the letter “H” or “S”) when flanked on both sides by letters that are either congruent or incongruent with the central stimulus; again, subjects are significantly better in the congruent condition. These tasks have been used to discern how the brain identifies and filters out (or fails to do so) irrelevant distractors. Careful behavioral analysis of choice accuracy as a function of reaction time (Cho et al. 2002) has given clues as to the role of cognitive processes such as attentional control and stimulated theoretical modeling of the neural computations giving rise to specific features of the behavioral dynamics in such tasks (Yu et al. 2009).

A related but distinct class of tasks involves a prepotent “go” signal present on each trial and an occasional “stop” signal on a small fraction of trials, whereby the subject must execute the “go” response only on “go” trials and not on “stop” trials. In the stop-signal task (Logan and Cowan 1984), the “stop” signal appears, if at all, at an unpredictable time after the “go” stimulus, and the

greater the onset asynchrony, the more unlikely that the subject is able to withhold the “go” response. A related task is what has been called a “compelled-response task,” in which the subject is instructed to go *before* being shown the cue that indicates which of the two responses is correct (Salinas et al. 2010). These tasks have given rise to competing theoretical models that postulate either the existence (Logan and Cowan 1984) or absence (Shenoy and Yu 2011; Salinas and Stanford 2013) of a specific stopping process or pathway and, in the latter class, the precise capacity to stop depending on either a normative, sequential consideration of the pros and cons of responding (Shenoy and Yu 2011) or the efficiency of the perceptual process itself (Salinas and Stanford 2013). However, recent experimental results indicate systematic and rational changes in subjects’ stopping capacity as a function of the reward structure of the task (Leotti and Wager 2009), suggesting not only that the “go” response is context sensitive and strategically malleable but also that it takes into account perceptual uncertainty and decision-theoretical factors such as reward contingencies (Shenoy and Yu 2011).

Multisensory Integration

Instead of investigating how the brain selectively processes certain aspects of the environment and excludes others, simultaneously present stimuli have also been employed in experimental tasks to examine how the brain combines multiple sources of sensory information, in particular across sensory modalities. For instance, several studies in recent years have shown that human subjects combine differentially reliable sensory inputs from different modalities in a computationally optimal (Bayesian) way, such that greater weight is assigned to sensory inputs with less noise (and greater reliability) in the combined percept (Jacobs 1999; Ernst and Banks 2002; Battaglia et al. 2003; Dayan et al. 2000; Shams et al. 2005). This explains, for instance, why vision typically dominates over auditory modality in spatial localization in a phenomenon known as

“visual capture” – this follows directly from the Bayesian formulation, since vision has greater spatial acuity and reliability than audition (Battaglia et al. 2003). Conversely, when the localization task is in the temporal domain instead of spatial, where audition has greater temporal acuity and reliability, auditory stimuli can induce an illusory visual percept. For example, when a single visual flash is accompanied by several auditory beeps, the visual percept is that of several flashes (Shams et al. 2000). Again this phenomenon can be explained by a statistically optimal ideal observer model (Shams et al. 2005; Kording et al. 2007). Recent neurophysiological studies have also begun to elucidate the neural basis of multisensory integration [see, e.g., Driver and Noesselt (2008) for a review].

Preference-Based Decision-Making

One area of decision-making is devoted to the study of how humans make their choices based on their own internal preferences, such as in consumer decision-making, instead of based on sensory features or behavioral outcomes associated with the options. When choosing among options that differ along multiple attribute dimensions, humans consistently exhibit certain puzzling preference shifts, or even reversals, depending on the context. Three broad categories of contextual effects are studied in the psychology literature. In the *attraction effect*, given two similarly preferred options, A and B , the introduction of a third option Z that is similar to B , but also clearly less attractive than B , results in an increase in preference for B over A (Huber and Payne 1982; Heath and Chatterjee 1995). In the *compromise effect*, when $B > A$ in one attribute and $B < A$ in another attribute and Z has the same trade-off but is even more extreme than B , then B becomes the “compromise” option and becomes preferred relative to A (Simonson 1989). In the *similarity effect*, the introduction of a third option Z that is very similar to B in both attribute dimensions shifts the relative preference away from B to A (Tversky n.d.).

Traditionally, there have been two lines of explanations for such effects, the first attributing them to biases or suboptimalities in human decision-making (Kahneman and Tversky 1979; Kahneman et al. 1982) and the other suggesting that they are by-products of specific architectural or dynamical constraints on neural processing (Busemeyer and Townsend 1993; Usher and McClelland 2004; Trueblood 2012). A more recent, normative account (Shenoy and Yu 2013) uses a Bayesian model to demonstrate that these contextual effects can arise as rational consequences of three basic assumptions: (1) humans make preferential choices based on relative values anchored with respect to “fair market value,” which is inferred from both prior experience and the current set of available options; (2) different attributes are imperfect substitutes for one another, so that one unit of a scarce attribute is more valuable than one unit of an abundant one; and (3) uncertainty in beliefs about “market conditions” induces stochasticity in relative preference on repeated encounters with the same set of options. This model not only provides a principled explanation for *why* specific types of contextual modulation of preference choice exist, but a means to *infer* individual and group preferences in novel contexts given observed choices.

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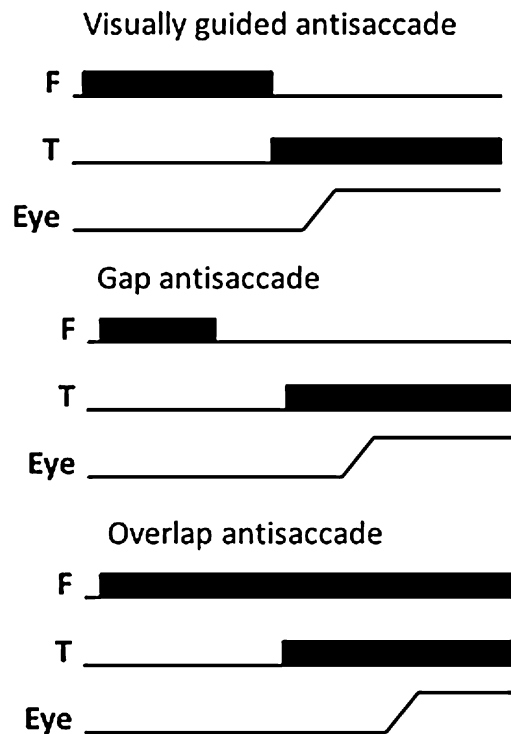
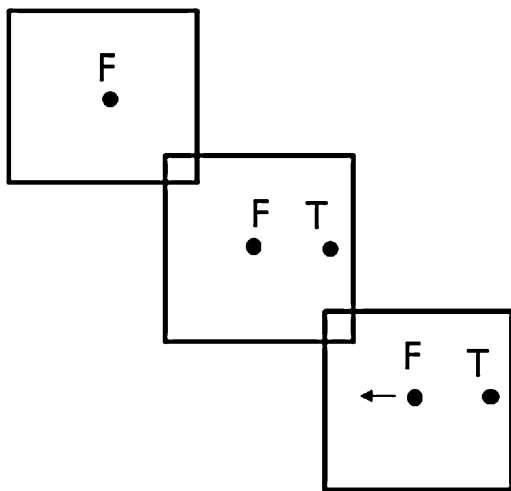
Decision-Making, Antisaccade Models of

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Definition

The antisaccade task in its most typical form (the visually guided antisaccade; Fig. 1) is a reaction time task in which subjects are instructed to perform an immediate eye movement in the opposite direction to a peripheral stimulus, which is presented in their right or left visual field, while they are fixating on a central stimulus (Hallett 1978). Variations of the typical antisaccade (gap antisaccade and overlap antisaccade; Fig. 1) in the horizontal or vertical plane were designed over the years to investigate the effect of the fixation stimulus on the decision to move (Goldring and Fischer 1997; Forbes and Klein 1996; Fischer et al. 1997).



Decision-Making, Antisaccade Models of, Fig. 1 Basic design of the antisaccade task. Typically a participant starts each trial fixating on a stimulus. When a target stimulus appears, the participant must make an eye movement in the opposite direction (antisaccade) of the target stimulus. *Visually guided antisaccade*: the antisaccade is performed immediately after fixation stimulus (F) is extinguished and target stimulus (T) appears. *Gap antisaccade*: a gap period exists between disappearance of

Detailed Description

Basic Antisaccade Behavior

The antisaccade task was first developed to dissociate the stimulus location from the goal of the saccade. During a single trial of the antisaccade task two processes take place: (1) suppression of an erroneous prosaccade toward the peripheral stimulus and (2) generation of a volitional saccade to a position in the opposite direction (antisaccade) (Munoz and Everling 2004). In a single trial, a participant may express any of the following three oculomotor behaviors: (1) the subject makes an antisaccade (an eye movement in the opposite direction of the peripheral stimulus), or (2) the subject makes an erroneous prosaccade (an eye movement in the direction of the peripheral stimulus), or (3) the subject makes an erroneous prosaccade followed by a corrected antisaccade. An error is an eye movement toward the peripheral stimulus instead of the opposite direction. Antisaccade performance involves different metrics such as the mean and standard deviation of the saccade reaction time (SRT) of each eye movement as well as the error rate (Ettinger et al. 2003). Healthy participants typically fail to suppress erroneous prosaccades toward the target on about 20–25% of trials, before correctly saccading toward a location in the opposite direction (Fischer and Weber 1992; Everling and Fischer 1998; Smyrnis et al. 2002; Ettinger et al. 2003; Tatler and Hutton 2007). Unimodal skewed to the right distributions of antisaccades, erroneous prosaccades, and corrected antisaccades are observed. The mean and standard deviation of the antisaccade reaction time from a large cohort of 2006 healthy subjects is reported to be 270 ms and 56 ms, respectively (Evdokimidis et al. 2002). In the same group, the mean and standard deviation of the erroneous prosaccade reaction time is 208 ms and 46 ms, respectively, whereas the mean and standard

← **Decision-Making, Antisaccade Models of, Fig. 1** (continued) fixation stimulus and target stimulus appearance. *Overlap antisaccade*: fixation stimulus remains on during target stimulus presentation

deviation of the corrected antisaccade reaction time is 146 ms and 85 ms, respectively (Evdokimidis et al. 2002).

Antisaccade Oculomotor Circuit

The antisaccade oculomotor circuit consists of several cortical and subcortical areas including the frontal eye fields (FEF), supplementary eye fields (SEF), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), lateral intraparietal area (LIP) (parietal eye field (PEF) in the human), basal ganglia, thalamus, superior colliculus (SC), brainstem reticular formation, and cerebellum (Munoz and Everling 2004). Visual information is processed via the retinogeniculo-cortical pathway to primary visual cortex and from there to LIP/PEF and via the retinotectal pathway to the superficial layers of the SC (SCs). LIP is an area in the parietal cortex coding for space. LIP/PEF then projects to both the intermediate layers of the SC (SCi) and frontal cortical oculomotor areas including FEF, SEF, ACC, and DLPFC. FEF is critical for voluntary saccade execution. SEF is implicated in internally guided decision-making and sequencing of saccades. AAC plays a role in conflict resolution and error monitoring. DLPFC is critical in executive function, spatial working memory, and suppressing automated or reflexive responses. These frontal oculomotor areas project to SCi, an area important for decision-making, which then projects to the reticular formation of the brainstem to provide the necessary input to guide saccades.

Another pathway to SCi from the frontal oculomotor areas is through the basal ganglia structures via the direct, indirect, and hyperdirect pathways (Munoz and Everling 2004). Via the direct pathway, frontal areas project to the caudate nucleus (CD), which in turn inhibits the substantia nigra pars reticulata (SNr). SNr disinhibits the SCi and motor nuclei of thalamus, which project back to frontal cortex. Via the indirect pathway, CD projects to the external segment of the globus pallidus (GPe), which in turn projects to the subthalamic nucleus (STN). STN sends excitatory projections to SNr and GPe, which projects via GABAergic connections back to SNr. Via the hyperdirect pathway, cortical regions excite

STN, which in turn excite SNr. These complex sets of excitatory and inhibitory projections within the basal ganglia provide a rich set of control mechanisms to help guide voluntary behavior (Coe and Munoz 2017).

Primate Neurophysiology Overview

A number of brain areas in monkeys are involved in the antisaccade task, including the DLPFC (Funahashi et al. 1993), the ACC (Phillips et al. 2010), the LIP (Gottlieb and Goldberg 1999), the SEF (Schlag-Rey et al. 1997; Amador et al. 2004), the FEF (Everling and Munoz 2000), and the SC (Everling et al. 1999). Understanding how neurons in these brain areas participate in the suppression of automatic responses and the generation of antisaccades is crucial for explaining the antisaccade behavior.

Single neuron recordings in FEF and SC have revealed the existence of two distinct and reciprocally activated populations of neurons: the fixation cells and the saccade cells. Fixation cells are tonically active during visual fixation, and their activity ceases when a saccade is executed. On the other hand, saccade cells are silent during fixation but discharge when the animal is making a saccade. In SC, two distinct types of saccade neurons have been recorded: buildup and burst cells (Munoz and Wurtz 1995a, b). A network of inhibitory interneurons is thought to control the reciprocal activation of fixation and saccade neurons (Munoz and Istvan 1998). During fixation in the gap condition (gap prosaccade versus gap antisaccade), fixation activity is greater in the antisaccade trials than in the prosaccade trials in both FEF and SC. This pattern of enhanced fixation activity explains the so-called anti-effect (Munoz and Everling 2004): longer reaction times on antisaccade trials than on prosaccade trials. A few milliseconds into the gap period, there is a drop in activity of fixation neurons and a slow buildup of low-frequency activity of a subset of saccade neurons in both SC (Everling et al. 1999) and FEF (Everling and Munoz 2000). The appearance of the visual stimulus in the right visual field leads to phasic activation of visually responsive saccade neurons in FEF and SC on the contralateral (left) side of the brain, and to phasic inhibition of

saccade neurons on the ipsilateral (right) side of the brain. On the prosaccade trials, saccade neurons on the left side discharge a saccadic burst for the rightward prosaccade immediately after the visual phasic response. On antisaccade trials, the saccade neurons in the left FEF and SC are inhibited compared to saccade neurons in the right FEF and SC, which are active to drive the leftward antisaccade.

Recordings from neurons in PFC in rhesus monkeys trained to perform a delayed antisaccade task (Funahashi et al. 1993) revealed that most PFC neurons code the location of the visual stimulus in working memory, and this memory can be engaged to suppress and prescribe a response. Response-coding neurons in smaller percentages were also found, some of which increased their firing rate for the direction of the saccade (e.g., rightward saccade) irrespective of the stimulus location, and others coding for both stimulus location and saccade direction. Similarly, recordings in LIP (Gottlieb and Goldberg 1999) also revealed the majority of LIP neurons reliably coding for the encoded cue location, with only a very small minority encoding for the direction of the upcoming saccade.

Electrical microstimulation in dorsal AAC in monkeys performing alternating blocks of prosaccade and antisaccade trials (Philips et al. 2010) suggested a direct role of AAC in antisaccade performance. On antisaccade trials, microstimulation decreased SRTs for both ipsilateral- and contralateral-directed antisaccades. On the other hand on prosaccade trials, SRTs were increased for saccades contralateral to and decreased for saccades ipsilateral to the stimulated hemisphere.

Finally, recordings from SEF in monkeys (Amador et al. 2004; Schlag-Rey et al. 1997) showed that the vast majority of SEF movement neurons fired significantly more before antisaccades than before prosaccades. The level of their firing was predictive of the correct performance on antisaccades on individual trials.

Antisaccade Performance Across Lifespan

Antisaccade performance varies systematically with age (Munoz et al. 1998; Klein and Foerster

2001; Peltsch et al. 2011). Young children (5–8 years old) have slow SRTs, large intra-subject SRT variance, and the largest error rate in the anti-saccade task. Young adults (20–30 years of age) typically have the fastest SRTs, the lowest intra-subject variance in SRT, and the fewest direction errors. Elderly subjects (60–85 years of age) have slower SRTs than other subject groups. These results demonstrate very strong positive correlation of age and subject antisaccade performance, which may reflect different stages of normal development and degeneration in the nervous system. The dramatic improvement in antisaccade performance observed from the ages of 5 to 15 years is attributed to delayed maturation of the frontal lobes.

Antisaccade Performance in Disorders

Antisaccade performance has been investigated in many neurological and psychiatric disorders including attention deficit hyperactivity disorder (Munoz et al. 2003; Hakvoort Schwerdtfeger et al. 2013), fetal alcohol spectrum disorders (Green et al. 2007; Paolozza et al. 2013), Huntington disease (Peltsch et al. 2008), Parkinson's disease (Chan et al. 2005; Cameron et al. 2012; Cameron et al. 2010; Amador et al. 2006; Antoniadis et al. 2015), Alzheimer's disease (Peltsch et al. 2014; Kaufman et al. 2012), mild cognitive impairment (Peltsch et al. 2014; Heuer et al. 2013), amyotrophic lateral sclerosis (Witiuk et al. 2014), bipolar disease (Soncin et al. 2016), schizophrenia (Levy et al. 2004; Zanelli et al. 2005; Theleritis et al. 2014), obsessive-compulsive disorder (Lennertz et al. 2012; Jahanshahi and Rothwell 2017), Tourette syndrome (Jahanshahi and Rothwell 2017), multiple sclerosis (Clough et al. 2015), depression (Carvalho et al. 2014; Malsert et al. 2012), epilepsy (Lunn et al. 2016), ventrolateral prefrontal damage (Hodgson et al. 2007), and frontotemporal dementia (Burrell et al. 2012; Boxer et al. 2012).

In particular, patients with frontal lobe lesions (Guitton et al. 1985; Pierrot-Deseilligny et al. 2002) and patients suffering from schizophrenia (Fukushima et al. 1988) make more antisaccade errors and their antisaccade latencies are more variable within and across subjects (Fukushima

et al. 1988; Hutton et al. 1998; Karoumi et al. 1998; Brownstein et al. 2003). An increase in correct antisaccade mean latency in schizophrenia patients was recently reported (Damilou et al. 2016). Impaired antisaccade task performance has also been reported in patients with recent onset schizophrenia and first-episode schizophrenia (deWilde et al. 2008; Ettinger et al. 2004; Grootens et al. 2008; Hutton et al. 2002, 1998; Kirenskaya et al. 2013), chronic schizophrenia (Boudet et al. 2005; Curtis et al. 2001a; Fukushima et al. 1988; Behrwind et al. 2011), and remitted schizophrenia (Curtis et al. 2001b). Aberrant antisaccade performance has also been reported by first degree unaffected biological relatives of schizophrenia patients (Kang et al. 2011; Radant et al. 2010; Zanelli et al. 2009). The antisaccade performance deficit in schizophrenia patients is reported to be due to: (1) a deficit in top-down inhibition control of the erroneous response (Everling and Fischer 1998; Broerse et al. 2001; Brownstein et al. 2003; Curtis et al. 2001), (2) a deficit in response generation of the antisaccade (Everling and Fischer 1998; Broerse et al. 2001; Brownstein et al. 2003; Curtis et al. 2001), or (3) an emergent property of competing noisy decision accumulating processes (the erroneous prosaccade and the antisaccade) (Cutsuridis et al. 2014; Cutsuridis 2010).

Various psychopharmacological manipulations including administration of lorazepam (Green and King 1998; Green et al. 2000), risperidone (Burke and Reveley 2002; Hutton 2002), nicotine (Petrovsky et al. 2012; Rycroft et al. 2007; Depatie et al. 2002; Larrison-Faucher et al. 2004), amphetamine (Dursun et al. 1999), and modafinil (Rycroft et al. 2007) led to changes in the antisaccade performance of cohorts of patients. Risperidone has been observed to improve error rates in some schizophrenia patients (Burke and Reveley 2002; Hutton 2002). Nicotine administration in schizophrenia patients improves their antisaccade performance (Petrovsky et al. 2013; Depatie et al. 2002; Larrison-Faucher et al. 2004).

Antisaccade performance, on the other hand, of obsessive compulsive (OCD) patients has been variable and contradictory. Initial studies reported

increased error rates in OCD patients compared to healthy controls, but no difference in their latencies of antisaccades (Tien et al. 1992). Other studies reported higher antisaccade latencies in OCD patients compared to healthy controls, while their error rate did not differ significantly (Maruff et al. 1999; van der Wee et al. 2006). Another study observed no differences in error rates and latencies of antisaccades between OCD patients and healthy subjects (Kloft et al. 2011). An increase in error rates and in latency of corrected antisaccades was recently reported (Damilou et al. 2016). It is speculated that the OCD antisaccade performance is due to a deficit in erroneous response inhibition control in the oculomotor circuit (Chamberlain et al. 2005; Everling and Fischer 1998; Broerse et al. 2001; Brownstein et al. 2003; Curtis et al. 2001).

Types of Theoretical Models of Antisaccade Performance

Theoretical models of antisaccade performance fall under two categories:

- Accumulator models:** In these models, the process of decision-making often involves a *linear* gradual accumulation of information concerning the various potential responses starting at some baseline level S_0 , which represents the prior expectation, at a constant rate r until it reaches a threshold S_T , which represents the confidence level required before the commitment to a particular course of action. Once the decision signal crosses S_T , then a response toward the target is initiated. Response time (RT) is measured as the time from the onset of the decision process till when the decision signal crosses S_T . Often the rate of accumulation is assumed to vary randomly from trial to trial, with a mean μ and variance σ^2 (Reddi and Carpenter 2000). Changes in the baseline level of activity, the rate of accumulation, or the threshold often result in changes in response latency. Prior expectation and level of activation of intention influence the baseline levels of activation.

- **Neural accumulator models:** In these models, the accumulation process is represented by the firing rate of usually a population of neurons. Changes in the rate (slow or fast) of neural firing are usually *nonlinear*, often competing, and reflect the changes in the rate of accumulation in the linear accumulator.

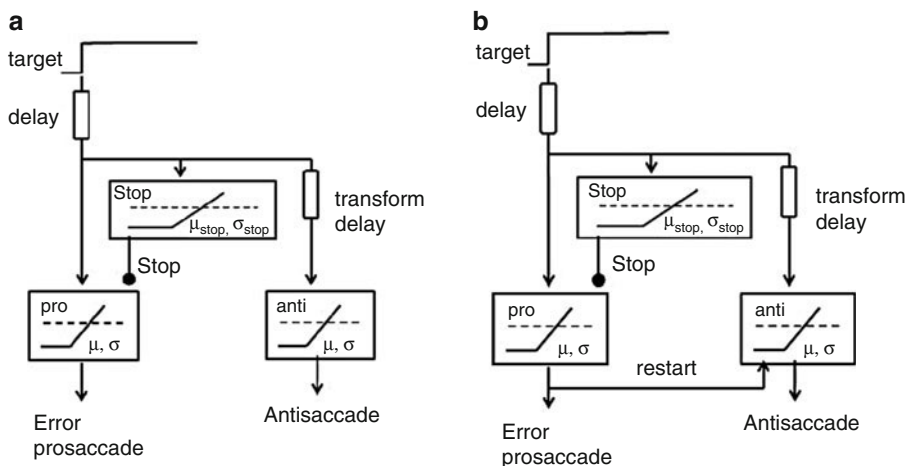
Below I will review models of various degrees of antisaccade performance from both categories.

Accumulator Models

A notable modeling attempt of the antisaccade paradigm was Noorani's and Carpenter's (2013) three-unit model (see Fig. 2a). The model consisted of three LATER units racing to threshold: an ANTI unit, a PRO unit, and a STOP unit. An important model feature was that the ANTI unit was identical (μ and σ) to the PRO unit. In the model, the STOP unit prevented the PRO unit from reaching threshold, thus allowing the ANTI unit to reach a different threshold a little later. The authors hypothesized that the threshold level of the PRO unit was higher than the ANTI unit's threshold, reflecting the advice given by the experimenters to every subject to avoid errors. How often the STOP unit cancelled the PRO unit depended on its rate of accumulation (μ) and its variance (σ^2). The model's performance

was contrasted against the performance of five healthy subjects performing the antisaccade task. The model captured *most* of the response repertoire observed in the antisaccade task, namely the antisaccades and the erroneous prosaccades, their corresponding latency distributions, and the error response rate. Despite the model's successes, the model had several shortcomings. The model failed to produce "the erroneous prosaccade followed by the corrected antisaccade" behavior. Moreover, the model postulated the existence of a third inhibitory signal (the STOP signal), which occasionally stopped the erroneous prosaccade response and indirectly allowed just the anti-saccade response to be expressed. Recent experimental evidence has challenged the existence of such a third signal (Everling and Johnston 2013).

To address some of these shortcomings, Noorani and Carpenter (2014) extended their previous model (Noorani and Carpenter 2013) by including a RESTART mechanism (see Fig. 2b). In this case, when the PRO unit reached the threshold first, it restarted the ANTI unit allowing it to reach the threshold and generate the anti-saccade response. Their new model successfully reproduced the "erroneous prosaccade followed by the corrected antisaccade" behavior, but failed now to reproduce the *just* erroneous prosaccades. This shortcoming was inherent in their model.



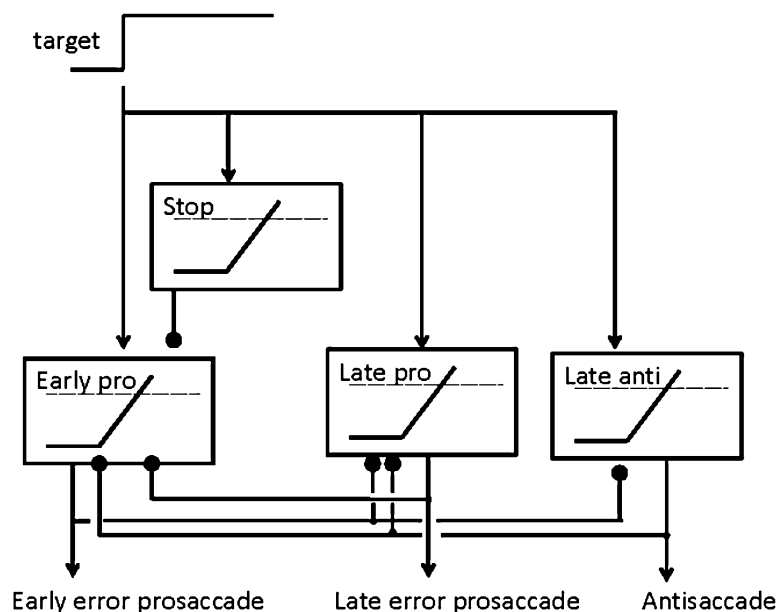
Decision-Making, Antisaccade Models of, Fig. 2 (a) Three-unit antisaccade model. (b) Three-unit antisaccade model with RESTART mechanism

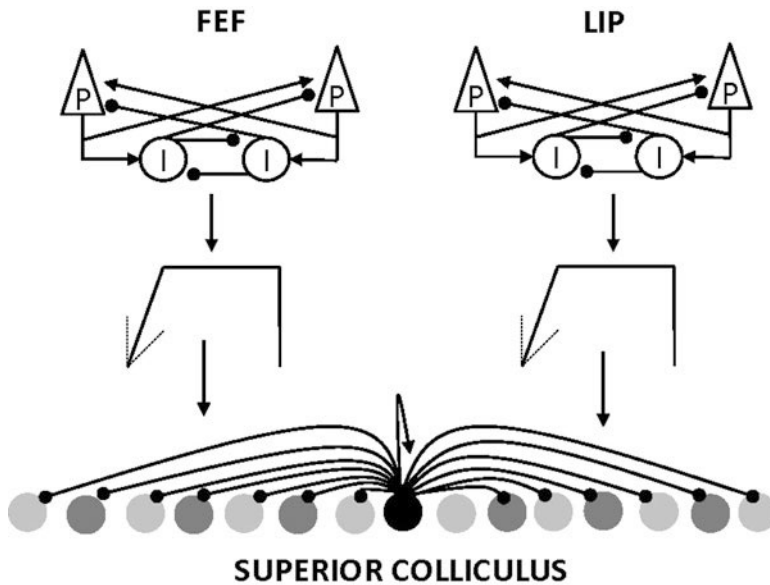
The authors postulated that if the STOP signal did not prevent the erroneous prosaccade response, then the PRO unit will *always* restart the ANTI unit (Noorani and Carpenter 2014). This meant the erroneous prosaccades followed by corrected antisaccades will always be produced. If the STOP unit did prevent the PRO unit, then the ANTI unit would not restart (the corrected antisaccade will not be produced), and an antisaccade response would be generated (Noorani and Carpenter 2014). In either scenario, *just* an erroneous prosaccade response cannot be generated. The authors claimed in their studies participants never made any *just* erroneous prosaccades (private communication of the author with Roger Carpenter). However, psychophysical studies of a large group of 2006 participants performing the antisaccade task (Evdokimidis et al. 2002) reported that subjects do make the *just* erroneous prosaccades, but their response frequency is low. Another limitation of their new model was their consideration that the simulated latency of the corrected antisaccade is the result of the linear sum of latencies of the erroneous prosaccade and the antisaccade minus the latency of the STOP activity. This shortcoming was inherent in the model, because its units are considered linear encoders of the input information.

The three-unit antisaccade model was recently applied to a large sample of Huntington’s disease (HD) patients against healthy controls in an effort to quantitatively predict HD before symptom onset (Wiecki et al. 2016). Experimental RT distributions and error rates of pre-manifest individuals carrying the HD mutation (pre-HD), early symptomatic, and healthy controls performing the antisaccade conflict task were fit using the three-unit antisaccade model. Further machine learning analysis based on fitted model parameters revealed a key executive control parameter was predictive of HD prior to symptom onset, whereas response inhibition processes are impaired only after the motor symptoms are observed.

Extensions of the three-unit antisaccade model were very recently introduced by Aponte et al. (2017) in the form of three probabilistic models, PROSA, SERIA, and SERIA_{lr}. SERIA_{lr} (see Fig. 3) predicted that two decision processes (one early race between a prepotent response toward a target and an endogenously generated signal to cancel this action, and a secondary late race between two units encoding two cue-action mappings) are necessary to properly model the antisaccade task. The two decision processes in SERIA_{lr} were considered to be the sources of early errors, fast erroneous prosaccades in

Decision-Making, Antisaccade Models of, Fig. 3 SERIA_{lr} model. The presentation of a visual cue (target) triggers the race of four independent units.. The Stop unit can stop an early response. The late decision process is triggered by the competition between two further units





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Decision-Making, Antisaccade Models of, Fig. 4 Three module neural accumulator model of antisaccade performance of healthy controls (Cutsuridis et al. 2007a, b). A reactive input (LIP population output) and a planned input (FEF population output) activate the superior colliculus module. Both inputs have a linearly rising phase, whose slope varies from a normal distribution, a

plateau phase, and an offset phase. Lateral inhibitory interactions between cells mediate the inhibitory effects of inhibitory interneurons in the superior colliculus. P: cortical pyramidal cell; I: cortical inhibitory interneuron; Black node: SC fixation cell; Dark gray node: SC buildup cell; Light gray node: SC burst cell

antisaccade trials, and late errors, late actions incongruent with the cue presented. Bayesian model comparison showed that the SERIA_{lr} model explains the data better than other competing models that did not incorporate a late decision process. Early decision processes were predicted to be insensitive to cue presented in every trial. Changes in reaction time and error rate due to probability of trial type were best explained by faster or slower inhibition in the model.

Neural Accumulator Models

Rate-Based Models

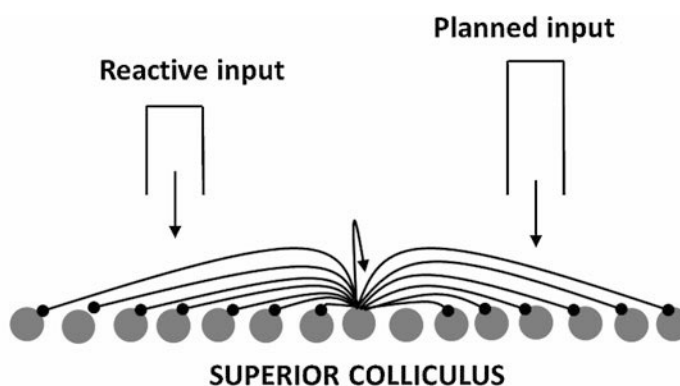
The first ever attempt to simulate the antisaccade task and uncover its neural mechanisms was made by Cutsuridis et al. (2007a) when they introduced a neural nonlinear accumulator model with competition via lateral inhibition between its components. The model was a 1D layer neuronal arrangement of the intermediate layer of SC with three different types of cells, namely the fixation,

buildup, and burst neurons (Trappenberg et al. 2001) (see Fig. 4). In the model, the fixation cells were activated by the fixation stimulus, and the buildup and burst cells by two inputs, a reactive input that represented the erroneous prosaccade motor plan and originated from the lateral intraparietal (LIP) area (Gottlieb and Goldberg 1999) and a planned input which represented the antisaccade motor plan and originated from FEF (Everling and Munoz 2000). The inputs were linear ramping processes till a maximum value after which they were either abruptly brought or smoothly decayed to zero. The slopes values of these linearly ramping processes took values from Gaussian distributions with different means and standard deviations for each input. Both inputs were integrated by spatially distant buildup and burst cells, which competed one another via lateral inhibition (Munoz and Istvan 1998). Each simulation trial started with the model fixation cells firing maximally for as much time as the subjects were fixating to the

central stimulus and buildup and burst cells being silent. As soon as the peripheral stimulus appeared and the subjects had to make an antisaccade, then the model fixation activity started to decay to zero and the buildup cell activity started to rise. In the model, the buildup cells had the role of accumulator cells that integrated evidence till some user pre-set threshold. Once the threshold was crossed, then the cue was given to the model burst cells to fire maximally, but for a short period of time (phasic activation). In the model, the burst activity represented the final motor command given to the eyes to move. Occasionally, in some simulated trials both erroneous prosaccade and antisaccade buildup cells crossed the threshold, which then cued their corresponding burst cells to fire. Behaviorally that meant that the virtual subject made an erroneous prosaccade first and corrected with an antisaccade. The model was able to produce all three oculomotor behaviors of the antisaccade task, namely the erroneous prosaccade, the antisaccade, and the corrected antisaccade. The model was also able to simulate accurately the antisaccade performance (latency distributions of the erroneous prosaccades and antisaccades as well as the error rates) of 10 virtual groups of participants with only five free parameters. The model predicted that competition via lateral inhibition and

not a third inhibitory signal accounts for the antisaccade performance of a large cohort of healthy participants. Despite its successes the model suffered from shortcomings. The simulated discharged rates of the fixation and buildup cells were unrealistically high (roughly 600 Hz) (Munoz and Wurz 1993, 1995a, b). For lower discharged rates the model can still accurately simulate the behavioral and neurophysiological properties of the antisaccade task, but for different parameter values (unpublished observations). Furthermore, the model failed to uncover the ionic and synaptic mechanisms that may produce the range of values of input slopes needed to produce the latency distributions of the erroneous prosaccades and antisaccades.

Recently, Cutsuridis extended his neural non-linear accumulator with competition model of antisaccade performance (Cutsuridis et al. 2007a) into the disorder domains of schizophrenia and obsessive-compulsive disorder (OCD) (Cutsuridis et al. 2014; Cutsuridis 2017a, b). In the new model (see Fig. 5), variations in the integration constants of buildup cell activities in the model SC and not in the slopes of the ramping phases of the cortical inputs produced the error rates and latency distributions of the erroneous prosaccades, antisaccades, and corrected antisaccades of healthy controls



Decision-Making, Antisaccade Models of,
Fig. 5 Neural accumulator model of antisaccade performance of schizophrenia and OCD patients (Cutsuridis et al. 2014; Cutsuridis 2017b). Two inputs activate opposite sides of the superior colliculus: a reactive input originating from LIP and a planned input originating from FEF. Each

node in SC excites itself and inhibits its neighbors (on-center, off-surround connectivity). Lateral inhibitory interactions between cells mediate the inhibitory effects of inhibitory interneurons in the superior colliculus. Gray node: SC buildup cell

(Ettinger et al. 2003), schizophrenia, and OCD (Damilou et al. 2016) suffering subjects. The model showed that the poor antisaccade performance in schizophrenia is due to a more noisy accumulation of information, but the schizophrenia patients are as confident (threshold level is unchanged) as their healthy counterparts (Cutsuridis et al. 2014). In contrast, in OCD, the accumulation of information is also noisy, but the OCD subjects are less confident (threshold level is changed) than the healthy participants (Cutsuridis 2017b). In both disorders, the model predicted the antisaccade performance is *not* due to a deficit in the top-down inhibitory control of the erroneous response as many speculated, but instead it is due to a local inhibitory mechanism in the form of a competitive race to a threshold between the buildup cell representations of the erroneous prosaccade and antisaccade in SC. In favor of this competitive race to a threshold between competing prosaccade and antisaccade signals is the Massen (2004) study, which selectively manipulated the exogenous and endogenous processes in the antisaccade task (e.g., slowing down or speeding up one of these or both processes) and observed the effects of this manipulation on error rate. Massen (2004) observed that if a manipulation slowed the generation of antisaccades, while having no effect on prosaccade generation, then the error rate was increased. If, however, manipulation influenced both pro- and antisaccade generation to the same degree, then the error rate remained unchanged. Massen (2004) argued that antisaccade performance is explained in terms of a competition between two parallel programs for saccade execution: if the volitional antisaccade is programmed fast enough (e.g., reaches some threshold for activation), then it will win the competition, and the reflexive prosaccade will be cancelled. Alternatively, if the prosaccade is programmed fast enough or the computation for the antisaccade is too slow, an erroneous prosaccade will be made first followed by the correct antisaccade. This account is in line with Cutsuridis et al.'s (2007a, 2014, 2017b) computational studies favored the concept of an active inhibitory mechanism in the form of competition between competing decision signals as being critical to antisaccade performance.

Spiking Neuron Models

To uncover the ionic and synaptic mechanisms that produced the range of values of accumulation rates needed to produce the latency distributions of the erroneous prosaccades and antisaccades in Cutsuridis et al.'s (2007a) model, the same group (Cutsuridis et al. 2007b) introduced a multi-modular neural network model consisting of two cortical modules (FEF and LIP) that drove the SC module to decide the winning motor command to move the eyes (Fig. 4). Each cortical module was a network of Hodgkin-Huxley type excitatory and inhibitory neurons connected together. The SC module was the same as in Cutsuridis et al.'s (2007a) study. No connectivity was assumed between the cortical modules, although it has been experimentally observed (Schall 1997). Symmetric and asymmetric connection types were tried. Background noise and synaptic noise were also included in the cortical model neurons and in their connections to simulate homogeneous and heterogeneous neuronal firings. The population activity from each cortical network was extracted and a line was fitted to its ramping activity to estimate its slope. Variations in all model ionic and synaptic conductances were attempted to uncover which current(s) and what range of their conductance values reproduced the full range of slope values of the planned and reactive inputs to the SC model needed to reproduce the latency distributions and error rates of the virtual groups of participants in the Cutsuridis et al.'s (2007a) study. The model predicted that only conductance variations of the persistent Na^+ , NMDA and AMPA currents could produce the necessary slope variability in the cortical decision signals to reproduce the latency distributions and response probabilities of the virtual subjects.

Recently, a two-module spiking with competition network model of antisaccade performance was advanced by Lo and Wang (2016). The model consisting of sensorimotor remapping and action selection modules, the latter endowed by a "Stop" process through tonic inhibition, both under the modulation of rule-dependent control revealed the circuit mechanisms for the experimentally observed distributions of erroneous responses in the antisaccade task. In the model, fast errors

resulted from failing to inhibit the quick automatic responses and therefore exhibited very short response times. Slow errors, on the other hand, were due to an incorrect decision in the remapping process and exhibited long response times comparable to those of correct antisaccade responses.

Cross-References

- [Accumulation of Evidence in Decision-Making](#)
- [Choice Behavior](#)
- [Decision-Making, Bias](#)
- [Decision-Making, Models](#)
- [Decision-Making, Threshold](#)
- [Decision-Making: Overview](#)
- [Perceptual Decision-Making](#)
- [Speed-Accuracy Tradeoff](#)

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Further Reading

Scholarpedia

Frontal eye fields. http://www.scholarpedia.org/article/Frontal_eye_field

Human saccadic eye movements. http://www.scholarpedia.org/article/Human_saccadic_eye_movements

Wikipedia

Antisaccade task. https://en.wikipedia.org/wiki/Antisaccade_task

Two alternative forced choice. https://en.wikipedia.org/wiki/Two-alternative_forced_choice

Decision-Making, Bias

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Definition

Biases in decision making are identified as patterns of choice behavior that violate normative theory of choice allocation.

Detailed Description

According to the axioms frequently used in economic theory, a *rational decision maker* is an agent who makes consistent choices over time, and therefore exhibits stable *preferences* (Samuelson 1938; Friedman and Savage 1948, 1952). Importantly, the rationality assumption does not prescribe that the decision maker should always optimize her objective outcome, e.g., her monetary payoff, but it does prescribe that an individual should behave consistently, given the assumption of stable preferences. This rationality assumption has been applied to both human and animal behavior (Kacelnik 2006). However, both in the human and animal literature, numerous examples of violations of economic rationality, i.e., biases in decision making, can be found (Kalenscher and Van Wingerden 2011).

Present Bias and Time-Inconsistent Preferences

A ubiquitous finding in decision making studies is that decision makers prefer immediate or briefly

delayed outcomes over longer delayed outcomes (e.g., Ainslie 1974; Green et al. 1994; see Kalenscher and Pennartz 2008 for a review), even if the delayed outcomes clearly constitute the better long-term choice (e.g., saving for a pension plan vs. drinking away your money today). This myopic choice behavior is usually termed ‘impulsivity’. Impulsive, shortsighted intertemporal decision making violates several assumptions made in rational choice theories, such as Discounted Utility Theory (DUT). DUT is a normative account of decision-making over time, which predicts a rational decision maker’s preference for immediate over delayed reward (see ► “Choice Behavior”). DUT states that agents should maximize discounted utility when making intertemporal decision, where discounted utility reflects the reduced current value incurred by options that are deferred into the future. For example, when choosing between a smaller, sooner (SS) or a larger, later (LL) outcome, an agent’s discount function combined with the duration of the delays could lead a decision maker to prefer SS over LL or vice versa, depending on the delays and magnitudes involved. Importantly, for a rational decision maker, such preferences are assumed to be stable. Specifically, one of the predictions of DUT is that decision makers discount future rewards at a constant rate. This means that, if a decision maker reveals a preference for, say, an SS outcome delivered after delay t_1 over an LL outcome delivered after delay t_2 , with $t_1 < t_2$, she should still prefer the SS outcome if both outcomes are deferred into the future by the same time interval Δt , because both outcomes would be discounted at the same rate. However, in contrast to the assumption of stable intertemporal preferences, in practice, most human as well as animal decision makers exhibit *preference reversals*, typically changing their choice behavior from preferring the SS to preferring the LL outcome when a common front-end delay (Δt) is added (Rachlin and Green 1972; Ainslie 1974; Bateson and Kacelnik 1996; Isles et al. 2003; Kalenscher et al. 2005; Kalenscher and Pennartz 2008; Louie and Glimcher 2010; Kalenscher and van Wingerden 2011). Assuming that the overt choice behavior reflects an internal ranking of discounted

utility, this implies that the time-discounted utility attached to the SS option has sunk below that of the LL, invalidating constant discounting.

DUT is agnostic about whether a given SS should be preferred over an LL alternative. In the context of animal foraging, however, optimal foraging theory (Charnov 1976; Stephens and Krebs 1986) prescribes *long-term rate maximization* to increase Darwinian fitness (see ► “Choice Behavior”). In self-control paradigms, paradoxically, animals typically fail to optimize their long-term rates. Imagine an SS option yields reward G_1 after some time t_1 while an LL option yields G_2 after t_2 . The choice is presented to the animals after some inter-trial interval τ . A long-term rate maximizing decision rule (Stephens and Krebs 1986) would predict that animals should always choose the LL alternative G_2 if its long-term rate exceeds that of the SS option G_1 . Animals typically exhibit present-bias, a failure to maximize long-term rates, by choosing the SS option even when a post-feeding delay (p) is added to it, making the trial durations equivalent (Mazur and Logue 1978; Green et al. 1981).

$$\frac{G_2}{\tau + t_2} > \frac{G_1}{\tau + t_1 + p} \quad (1)$$

How can such time-inconsistent behavior be explained? Two-system models of decision making posit that the utility premium put on immediate over delayed outcomes can be traced to different (competing) neural systems that process immediate vs. delayed outcomes. McClure et al. (2004, 2007) and others have shown that ‘limbic’ regions such as the ventromedial prefrontal cortex and ventral striatum (Hariri et al. 2006) are preferentially activated by immediate outcomes, while other prefrontal structures such as lateral prefrontal cortex are engaged by both immediate and delayed outcomes. The inverse of impulsivity, self-control, can be invoked to combat present-bias in decision making. Hare et al. (2009, 2011) have shown that activity in dorsolateral prefrontal cortex is associated with self control, and that this activity can modulate value signals in ventromedial prefrontal cortex, downregulating the value of

liked, but unwanted outcomes when self control succeeds.

Certainty Effect in Decision Making

In decision making under risk, the normatively flavored Expected Utility Theory framework (EUT, see Choice Behavior) posits that monetary outcomes are nonlinearly transformed to subjective value or *utility*. This transformation can explain the commonly found risk-aversion when choosing between a certain and a probabilistic outcome. EUT assumes that, while gains are non-linearly transformed, probabilities are not, so that each outcome’s expected utility is the linearly weighted sum of the probability-weighted utilities of the possible outcomes. However, behavioral data show that decision makers over-value certain outcomes. The Allais paradox supports this notion by showing that adding a probabilistic outcome to two gambles in a choice set, so that one of the options now becomes certain instead of probabilistic, induces decision makers to reverse their preferences (Allais 1953; Kahneman and Tversky 1979; Hsu et al. 2009). So, suppose that the choices are a large gain G_1 with a low probability P_1 or a small gain G_2 with high probability P_2 , and the subject prefers the first, riskier option. According to the independence axiom of EUT, the preference should be the same when the same probabilistic outcome is added to both options. So, if a gain G_2 with probability $(1 - P_2)$ is now added to *both* choices, both expected outcomes increase by the same amount, but the second one becomes certain, i.e., G_2 with a probability of 1, and in this case decision makers typically prefer the second option, reversing their original preference. In other words, decision makers have a strong preference for outcomes that are certain over outcomes that are probabilistic, even if the expected utility ranking is maintained. A recent brain imaging study (Hsu et al. 2009) building on *prospect theory* (Kahneman and Tversky 1979; Tversky and Kahneman 1992) indicates that neural activity in the striatum when evaluating probabilistic outcomes is better explained by a non-linear

(reverse-S shaped) function than a strictly linear function. In animals studies, results that resemble Allais-like certainty effects are observed in rats (MacDonald et al. 1991) and honeybees (Shafir et al. 2008).

Sign/Reflection Effects in Decision Making

Economic theory usually assumes a monotonically increasing utility function linking objective quantities of a good to a subjective valuation as the basis for preference judgments (Samuelson 1937, 1938; von Neumann and Morgenstern 1944). When outcomes are not certain, EUT prescribes that the expected utility of a choice can be calculated simply by weighing the utilities of the possible outcomes of a decision by their probabilities and summing across these outcomes (see ► “Choice Behavior”). According to EUT, a decision maker should base her choice on the final state of wealth, taking into account all (discounted) utilities of all outcomes, and it should not matter whether changes in good quantities are accounted as gains or losses. However, humans seem to treat gains differently to losses. Because of the concave, decelerating nature of the utility function, humans tend to be risk-averse when choosing between gambles with gains. However, when the gambles are presented as potential losses rather than gains, risk attitudes often change from risk-averse to risk-seeking (Kahneman and Tversky 1979, 1984). This is called the *reflection effect*, the finding that risk attitudes change when the prospects flip around 0.

Further indications that losses are treated differently from gains come from research on *loss aversion* (Kahneman and Tversky 1984; Tversky and Kahneman 1992). The idea that losses loom larger than gains is illustrated by the fact that most participants reject a 50/50 gamble on a coin toss or fair die. In fact, the gains need to be about twice as big to offset the potential loss. In the brain, several areas including the VStr and ventromedial prefrontal cortex (vmPFC) show a pattern of ‘neural’ loss aversion – that is, the slope of BOLD deactivations to losses is steeper than activations to

gains, when mixed gambles of potential losses and gains are evaluated (Tom et al. 2007). In animals, loss aversion is also observed (Chen et al. 2006; but see Silberberg et al. 2008).

Framing Effect in Decision Making

The differential treatment of losses and gains is even more strikingly evident in the *framing effect*. Kahneman and Tversky (1984) showed that when a decision has to be made between a certain and a probabilistic outcome on human lives saved (gain frame) versus lost (loss frame), with the exact same numerical outcomes, the gain frame induces risk aversion whereas the loss frame induces risk seeking choice behavior in participants. This shows that the wording used to present a decision problem is sufficient to bias a subject between treating identical outcomes as gains or losses, and affecting risk attitude accordingly. There is some evidence that decisions in the direction of the framing effect, as opposed to those decisions in opposition to the choice biases, elicit more activity in the amygdala (De Martino et al. 2006; but see Talmi et al. 2010), and that resilience against the framing bias is associated with activity in OFC. In animals, starlings show behavior in line with a framing effect. When the baseline expectation of a food outcome is either low (gain frame) or high (loss frame), the birds are more prone towards risk-averse behavior (selecting the fixed outcome) or risk-seeking behavior (selecting the probabilistic outcome), respectively (Marsh and Kacelnik 2002).

Non-stationary Preferences: Intransitivity

A rational decision maker should exhibit stable preferences. Formally, if a decision maker prefers A over B and B over C, she should also prefer A over C (transitivity of preferences). However, human subjects often show *context-dependent* or *intransitive choices* (Tversky 1969; Kalenscher and Pennartz 2010; Kalenscher et al. 2010). Intransitive preferences seem to occur readily

when choice options differ on several value-related attributes, such as probability and reward magnitude, and could stem from an attribute-wise comparison instead of an alternative-wise integration of choice attributes. For instance, consistent with the *additive difference model* put forward by Tversky (1969), Kalenscher et al. (2010) showed that participants choosing between two gambles tend to weigh differences in probabilities and reward magnitudes differentially. So, a large difference in probabilities (with a moderate difference in reward magnitude) resulted in a strong weighting of this attribute, and correspondingly risk-averse choices, whereas a large difference in reward magnitude (with a moderate difference in probability) resulted in a strong weighting of magnitude, together with risk-seeking choices. This context-dependent shift from risk-aversion to risk-seeking, depending on the difference in the gambles' attributes, rendered the potential for circular, intransitive preference structures. The neural data by Kalenscher et al. support separate tracking of the context-dependent weight of outcome probabilities (posterior cingulate cortex) and magnitudes (posterior insula).

Sunk Cost Effect in Decision Making

The sunk cost effect is the tendency to persist in an endeavor once an investment of effort, time, or money has been made (Thaler 1980). A famous example entails the continuation of the *Concorde* supersonic airplane project, even when profitability analyses indicated that the project would never make money (Arkes and Ayton 1999). Besides policy makers, participants in the lab also exhibit the sunk cost effect. Navarro and Fantino (2005) and others have shown that human participants persist in a choice option searching for payout beyond the moment when switching, abandoning or resetting would be optimal (Kogut 1990). In animals, sunk costs have been studied in pigeons. Like humans, pigeons generally persisted longer on a probabilistic choice than prescribed by optimal choice, and this persistence was modulated by the size of the sunk costs (Navarro and Fantino 2005; Pattison et al. 2012).

Prosocial Biases in Decision Making

One of the tenets of microeconomic theory is that decisions should be made from a purely self-interested perspective, and that other people's outcomes should be disregarded. Obviously, this notion does not conform to reality. Human decision makers experience consistent prosocial biases that become manifest in costly helping behavior, e.g., when an agent reduces her own outcome in favor of another's. The most straightforward example of this is the Dictator Game (DG; Fehr and Fischbacher 2003; Engel 2011), where a participant can split a sum of money between herself and a powerless partner. The partner has to accept, and cannot retaliate. From a game theoretical perspective, the dictator should keep all the money for herself. This is not the case, people across all cultures and socio-economic groups consistently give sums larger than 0, even in anonymous, one-shot games where reputation building or other strategic motives can be ruled out (Fehr and Fischbacher 2003; Engel 2011). This suggests that decision makers are presumably not the selfish, own-payoff maximizers postulated by economic theory, but do take the well-being of others into consideration.

Cross-References

► [Choice Behavior](#)

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Decision-Making, Models

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Definition

Models of decision making attempt to describe, using stochastic differential equations which represent either neural activity or more abstract psychological variables, the dynamical process that produces a commitment to a single action/outcome as a result of incoming evidence that can be ambiguous as to the action it supports.

Detailed Description

Background

Decision making can be separated into four processes (Doya 2008):

1. Acquisition of sensory information to determine the **state** of the environment and the organism within it.
2. Evaluation of potential actions (options) in terms of the cost and benefit to the organism given its belief about the current state.
3. Selection of an **action** based on, ideally, an optimal trade-off between the costs and benefits.
4. Use of the outcome of the action to update the costs and benefits associated with it.

Models of the dynamics of decision making have focused on perceptual decisions with only two possible responses available. The term two-alternative forced choice (TAFC) applies to such tasks when two stimuli are provided, but the term is now generally used for any binary choice discrimination task.

In a perceptual decision, the response, or action, is directly determined by the current percept. Thus, the decision in these tasks is essentially one of perceptual categorization, namely, process (1) above, though the same models can be used for action selection given ambiguous information of the current state (process 3).

Evaluation of the possible responses in terms of their value or the resulting state's utility (process 2) (Sugrue et al. 2005) given both uncertainty in the current state, and uncertainty in the outcomes of an action given the state, is the subject of expected utility theory and prospect theory.

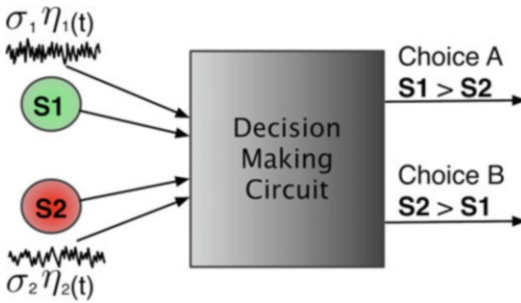
The necessary learning and updating of the values of different actions given the actual outcomes they produce (process 4) are the subject of instrumental conditioning and reinforcement learning, for example, via temporal difference learning (Seymour et al. 2004) and actor-critic models (Joel et al. 2002).

This entry is primarily concerned with the dynamics of the production of either a single percept given unreliable sensory evidence (1) or a single action given uncertainty in the outcomes (3).

General Features of Discrimination Tasks or TAFC Tasks

In a TAFC task, a single decision variable can be defined representing the likelihood ratio – the probability that evidence to date favors one alternative over the other. While TAFC tasks (Fig. 1) have provided the dominant paradigm for analysis of choice behavior, the restriction to only two choices is lifted in many of the more recent models of decision making based on multiple variables, allowing for the fitting of a wider range of data sets.

The tasks can be based on either a free-response paradigm, in which a subject responds after as much or little time as she wants, or an



Decision-Making, Models, Fig. 1 Scheme of the two-alternative forced-choice (TAFC) task. Two streams of sensory input, each containing stimulus information, or a signal ($S1$ and $S2$) combined with noise ($\sigma_1 \eta_1(t)$ and $\sigma_2 \eta_2(t)$), are compared in a decision-making circuit. The circuit must produce one of two responses (A or B) indicating which of the two signals is stronger. The optimal method for achieving this discrimination is via the sequential probability ratio test (SPRT) which requires the decision-making circuit to integrate inputs over time

interrogation (forced response) paradigm, in which the stimulus duration is limited and the subject must make a response within a given time interval. The free-response paradigm is perhaps more powerful, since each trial produces two types of information: accuracy (correct or incorrect) and response time. However, by variation of the time allowed when responses are forced, both paradigms are valuable for constraining models, since they can provide a distribution of response times for both correct and incorrect trials, as well as the proportion of trials that are correct or incorrect with a given stimulus. These behavioral data can be modified by task difficulty, task instructions (such as “respond rapidly” versus “respond accurately”), or reward schedules and intertrial intervals.

Most models of the dynamics of decision making focus on tasks where the time from stimulus onset to response is no more than one to two seconds, a timescale over which neural spiking can be maintained. Choices requiring much more time than this are likely to depend upon multiple memory stores, neural circuits, and strategies, which become difficult to identify, extract, and model in a dynamical systems framework (a state-based framework is more appropriate).

In the standard setup of the models, two parallel streams of noisy sensory input are available,

with each stream supplying evidence in support of one of the two allowed actions (see Fig. 1). The sensory inputs can be of either discrete or continuous quantities and can arrive discretely or continuously in time. The majority of models focus on continuous update in continuous time so they can be formulated as stochastic differential equations (Gillespie 1992; Lawler 2006). The sensory evidence, which is momentary, produces a decision variable, which indicates the likelihood of choosing one of the two alternatives given current evidence and all prior evidence. The primary difference between models is in how sensory evidence determines the decision variable. While most models incorporate a form of temporal integration of evidence (Cain and Shea-Brown 2012) and include a negative interaction between the two sources of evidence, differences arise in the stability of initial states which determines whether integration is perfect and in the nature of the interaction: feedforward between the inputs, feedforward between outputs, or feedback from outputs to decision variables (Bogacz et al. 2006). Models can also differ in their choice of *decision threshold* – the value of the decision variable at which a response is produced – in the free-response paradigm (Simen et al. 2009; Deneve 2012; Drugowitsch et al. 2012) and in particular whether this parameter or other model parameters, such as input gain, which also affect the response time distribution, are static or dynamical across a trial (Shea-Brown et al. 2008; Thura et al. 2012).

As the time available for acquisition of sensory information increases, so does the accuracy of responses in a perceptual discrimination task. Accuracy is measured as probability of choosing the response leading to more reward, which is equivalent to obtaining a veridical percept in these tasks. All of the models to be discussed below can produce such a speed-accuracy trade-off by parameter adjustment. If parameters are adjusted so as to increase the mean response time, then accuracy increases. Such a trade-off is observed in behavioral tasks under two regimes: one, when either instructions or the schedule of reward and punishment encourages participants to respond as quickly as possible while being less concerned about making errors or two, when

subjects respond as accurately as possible while being less concerned about the time it takes to decide. The simplest way to effect such a trade-off is to adjust the intertrial interval, which if long compared to the decision time means that accuracy of responses impacts reward rate much more so than the time for the decision itself. Models can replicate such behavior when optimal performance is based on the maximal reward rate. Typical parameter adjustments to increase accuracy while slowing responses would be a multiplicative scaling down of inputs (and the concurrent input noise) or a scaling up of the range across which the decision variable can vary by raising a decision threshold (Figs. 2 and 3) (Ratcliff 2002; Simen et al. 2009; Balci et al. 2011). A similar effect can be achieved in alternative, attractor-based models through the level of a global applied current, which affects the stability of the initial “undecided” state (Figs. 6–9) (Miller and Katz 2013).

From a neuroscience perspective, the decision variable is typically interpreted as either the mean firing rate of a group of neurons or a linear combination of rates of many neurons (Beck et al. 2008), the difference between two groups being the simplest such combination. There has been remarkable progress in matching the observed firing patterns of neurons (Newsome et al. 1989; Shadlen and Newsome 2001; Huk and Shadlen 2005) with the dynamics of a decision variable in more mathematical models of decision making (Glimcher 2001, 2003; Gold and Shadlen 2001, 2007; Smith and Ratcliff 2004; Ratcliff et al.

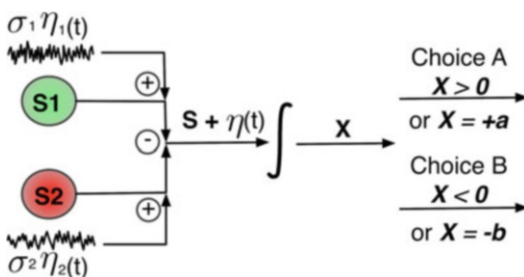
2007). This has led to the introduction of biophysically based models of neural circuits (Wang 2008), which have accounted for much of the concordance between simple mathematical models, neural activity, and behavior.

Optimal Decision Making

An optimal decision-making strategy either maximizes expected reward over a given time or minimizes risk. In TAFC perceptual tasks, a response is either correct or an error. In the interrogation paradigm, with fixed time per decision, the optimal strategy is the one leading to greatest accuracy, that is, the lowest expected error rate. In the free-response paradigm, the optimal strategy either delivers the greatest accuracy for a given mean response time or produces the fastest mean response time for a given accuracy. In these tasks, the sequential probability ratio test (SPRT), introduced by Wald and Wolfowitz (Wald 1947; Wald and Wolfowitz 1948), and, in its continuous form, the drift-diffusion model (DDM) (Ratcliff and Smith 2004; Ratcliff and McKoon; 2008) lead to optimal choice behavior by any of these measures of optimality (see (Bogacz et al. 2006) for a thorough review).

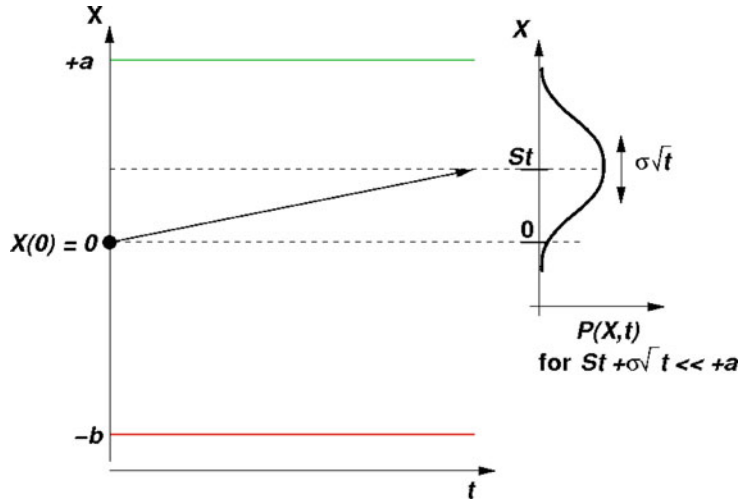
Using SPRT in the interrogation paradigm, one simply accumulates over time the log-likelihood ratio of the probabilities of each alternative given the stream of evidence, where the observed sensory input per unit time has a certain probability given alternative A and another probability given alternative B. Integrating the log-likelihood over time, after setting the initial condition as the log-likelihood ratio of the prior probabilities, $\log[P(A)/P(B)]$, leads to a quantity $\log[P(A|S)/P(B|S)]$ which is greater than zero if A is more likely than B given the stimulus and less than zero otherwise. Thus, from standard Bayesian theory, the optimal procedure is to choose A or B depending on the sign of the summed, or in the continuous limit, integrated, log-likelihood ratio.

In the free-response paradigm, a stopping criterion must be included. This is achieved by setting two thresholds for the integrated log-likelihood ratio, a positive one ($+a$) for choice A and a negative one ($-b$) for choice B. The further the thresholds are from the origin, the



Decision-Making, Models, Fig. 2 The drift-diffusion model (DDM). The DDM is a one-dimensional model, so the two competing inputs and their noise terms are first combined: in this case $S = S_1 - S_2$ and $\sigma^2 = \sigma_1^2 + \sigma_2^2$

Decision-Making, Models, Fig. 3 The drift-diffusion model is a Wiener process (one-dimensional Brownian motion) with absorbing boundaries. In the absence of the boundaries, the probability distribution is Gaussian, centered at a distance St from its starting point with variance increasing as $\sigma^2 t$



lower the chance of error, but the longer the integration time before reaching a decision. Thus, the thresholds reflect the fraction of errors that can be tolerated, with $a = \log \frac{\beta}{1-\alpha}$ and $b = \log \frac{\alpha}{1-\beta}$ where α is the probability of choosing A when B is correct and β is the probability of choosing B when A is correct.

The Models

Accumulator Models

The first models of decision making in humans or animals were accumulator models, sometimes called counter models or race models. In these models, evidence accumulates separately for each possible outcome. This has the advantage that if many outcomes are possible, the models are simply extended by addition of one more variable for each additional alternative, with evidence for each alternative accumulating within its allotted variable. In the interrogation paradigm, one simply reads out the highest variable, so the choice depends on the sign of the difference of the two variables in the TAFC paradigm. Thus, if the difference in accumulated quantities matched the difference in integrated log probabilities of the two types of evidence, such readout from an accumulator model would be equivalent to an SPRT, so would be optimal.

In the free-response paradigm, accumulator models produce a choice when any one of the

accumulated variables reaches a threshold, so these models can be called “race to threshold models” or simply “race models.” The original accumulator models included neither interaction between accumulators nor ability for variables to decrease. However, for decisions in nature or in laboratory protocols, evidence in favor of one alternative is typically evidence against the other alternative. This is particularly problematic in the free-response paradigm, because the time at which one variable reaches threshold and produces the corresponding choice is independent of evidence accumulated for other choices. Thus, the behavior of simple accumulator models is not optimal. Comparisons of response time distributions of these models with behavioral responses showed the models to be inaccurate in this regard – observed response time distributions are skewed with a long tail, whereas the response times of accumulator models were much more symmetric about the mean. These discrepancies led to the ascendance of Ratcliff’s drift-diffusion model (Ratcliff 1978).

The Drift-Diffusion Model

The drift-diffusion model (DDM) is an integrator with thresholds (Fig. 2), or more precisely, the decision variable, x , follows a Wiener process with two absorbing boundaries (Fig. 3). It includes a deterministic (drift) term, S , proportional to the rate of incoming evidence and a

diffusive noise term of variance σ^2 , which produces variability in response times and can lead to errors:

$$\frac{dx}{dt} = S + \sigma\eta(t)$$

where $\eta(t)$ is a white noise term defined by $\langle\eta(t)\eta(t')\rangle = \delta(t - t')$.

If the model is scaled to a given level of noise, then its three independent parameters are drift rate (S) and positions of each of the two **thresholds** (a , $-b$) with respect to the starting point. When the model was introduced, these parameters were assumed fixed for a given subject in a specific task. The threshold spacing determines where one operates in the speed-accuracy trade-off, so it can be optimized as a function of the relative cost for making an incorrect response and the time between trials. Any starting point away from the midpoint represents bias or prior information. The drift rate is proportional to stimulus strength.

With fixed parameters, which could be fitted to any subject's responses, the DDM reproduces key features of the behavioral data: notably the skewed shape of response time distributions and the covariation of mean response times and response accuracy with task difficulty. Skewed response time distributions arise because the variance of a Wiener process increases linearly with time – responses much earlier than the mean response time, when the variance in the decision variable is low, are less likely than responses much later, when the variance in the decision variable is high. A more difficult perceptual choice is represented by a drift rate closer to zero, which increases response times and increases the probability of error. Such covariation of response times with accuracy matches behavioral data well, so long as an additional processing time is added to the model – the additional time representing a variable sensory transduction delay on the input side and a motor delay on the output side, both of which contribute to response times in addition to the processing within any decision circuit.

While the original DDM included trial-to-trial variability through the diffusive noise term,

additional trial-to-trial variability in the parameters was needed to account for differences between the response time distributions of correct trials from those of incorrect trials. With fixed parameters and no initial bias, the DDM produces identical distributions (though with different magnitudes) for the timing of correct responses and errors. However, response times of human subjects are typically slower when they produce errors, unless they are instructed to respond as quickly as possible, in which case the reverse is true. These behaviors are accounted for in the DDM by including trial-to-trial variability in the drift rate and/or the starting point. Trial-to-trial variability in drift rate leads to slower errors, as errors become more likely on those trials when the drift rate is altered from its mean toward zero and mean responses are longer. Trial-to-trial variability in the starting point leads to faster errors, as errors become more likely on those trials in which the starting point is closer to the error boundary, in which case the response is faster. Error response times are reduced more by such variability than are correct response times since the correct responses include more of the trials started at the midpoint where mean times are longer.

Prior information or bias can be incorporated in the drift-diffusion model, either through a shift in the starting point of integration or an additional bias current to the inputs to be integrated. A shift in starting point is more optimal and has led to two-stage models, where the first stage sets the starting point from the values of the two choices, before a second stage of integration toward threshold commences. Such a model is supported by electrophysiological data (Rorie et al. 2010).

The Leaky Competing Accumulator Model

The leaky competing accumulator (LCA), introduced by Usher and McClelland (2001), was suggested to be in better accord with neural data and to better fit some behavioral data than the DDM. The LCA is a two-variable model, with each variable integrating evidence in support of one of the two alternatives in a TAFC task. The model includes a “leak” term, as decay back to baseline for each individual variable in the absence of incoming evidence. The “competition”

in LCA is a cross-inhibition between the two variables, thus improving upon original accumulator models in allowing evidence for one variable contributing to a reduction in the other variable (Fig. 4).

$$\tau \frac{dX_1}{dt} = S_1 - kX_1 - \beta X_2 + \sigma_1 \sqrt{\tau} \eta_1(t)$$

$$\tau \frac{dX_2}{dt} = S_2 - kX_2 - \beta X_1 + \sigma_2 \sqrt{\tau} \eta_2(t)$$

The difference in the two LCA variables, $X_d = X_1 - X_2$, follows an Ornstein-Uhlenbeck process:

$$\tau \frac{dX_d}{dt} = S_d - kX_d + \beta X_d + \sigma_d \sqrt{\tau} \eta(t)$$

where $S_d = S_1 - S_2$ and $\sigma_d = \sqrt{\sigma_1^2 + \sigma_2^2}$. It should be noted that the DDM is retrieved as a special case of the LCA, if the coefficient of the term linear in X_d , that is, $\beta - k$, is set to zero.

If the only criterion for choosing the best model were its match to behavioral data, one could use Akaike information criterion or Bayesian information criterion to assess whether inclusion of a nonzero term in the LCA is justified by the better fit to data so produced. As well as ability to fit human response times, the ability for a model

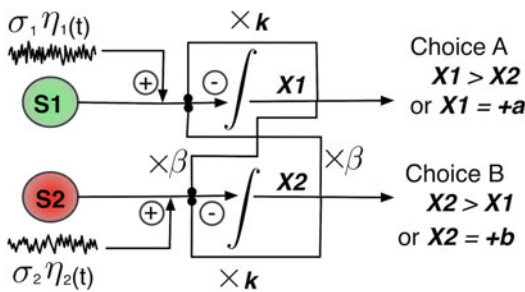
to match neural activity and to be generated robustly in a neural circuit should be considered when assessing its value and relevance. One achievement of the LCA is to reproduce an initial increase in both variables, before the competition between variables causes one variable to be suppressed, while the other variable accelerates its rise. Such behavior matches electrophysiological data recorded in monkeys during perceptual choices – in particular, firing rates of neurons representing the response not chosen increase upon stimulus onset before they are suppressed (cf. trajectories in Fig. 6).

Neural Network Models and Attractor States

Some of the first models of perceptual categorization, which have had significant impact on neuroscience, were Hopfield networks, Cohen-Grossberg neural networks, and Willshaw networks. While these models are primarily aimed at formation and storage of memories, the retrieval of a memory via corrupted information is identical to a perceptual decision.

A correspondence between memory retrieval and decision making should not be surprising, since Ratcliff's introduction of the DDM – the archetype of decision-making models – was within a paper entitled “A theory of memory retrieval.” Ratcliff was focused on fitting response times and thus produced an inherently dynamical model; memory retrieval was treated as a set of parallel DDMs, each representing an individual item with a “match” and “non-match” threshold to indicate its recognition or not. The rate of evidence accumulation in each individual DDM was set in terms of the similarity between a current item and one in memory.

Models such as those of Hopfield respond to the match between a current item and memories of previously encoded items, which are contained within the network as attractor states. The network's activity reaches a stable attractor state more rapidly if the match is close. The temporal dynamics of memory retrieval or pattern completion, which comprises the decision process, is not addressed carefully in neural network models, in which neural units can be binary and time can be discretized, since this is not their goal. However,



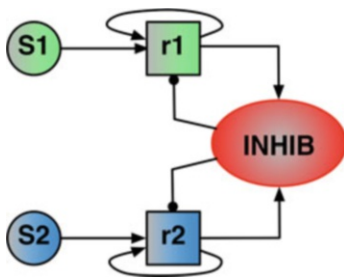
Decision-Making, Models, Fig. 4 The leaky competing accumulator (LCA) model. Two separate integration processes for the two separate stimuli produce two decision variables, X_1 and X_2 . A “leak” term proportional to k causes a decay of the decision variable through self-inhibition, while a cross-inhibition term proportional to β produces competition. In the interrogation paradigm, a decision is made according to the greater of X_1 or X_2 at the response time, while in the free-response paradigm, a choice is made when one decision variable first reaches its threshold (given as $+a$ and $+b$, respectively)

the use of attractor states to represent the outcome of a decision or a perceptual categorization has achieved success in biophysical models based on spiking neurons (Wang 2008), albeit with far simpler attractor states than those of neural networks.

Biophysical Models

The LCA model (Usher and McClelland 2001), being motivated by neurophysiology, is similar in spirit to the more detailed biophysical models that followed it. In particular, the first model of decision making based on spiking neurons assumes two competing integrators, where integration is produced through tuned recurrent excitation and competition is the result of cross-inhibition between the pools of neurons (see Fig. 5). However, when even the most elementary properties of spiking neurons are taken into account, a few additional complications arise (Wong and Wang 2006).

First, neurons emit spikes as a point process in time, so that even at a constant firing rate they supply a variable current to other cells. The variability in the current can be reduced with an increase in the number of cells in a group, so long as the spike times are uncorrelated – that is, cells are firing asynchronously. Asynchrony is most easily achieved when neurons spike irregularly, a feature produced by adding additional noise to each neuron in the decision-making circuit. So, in accord with most likely realizations of



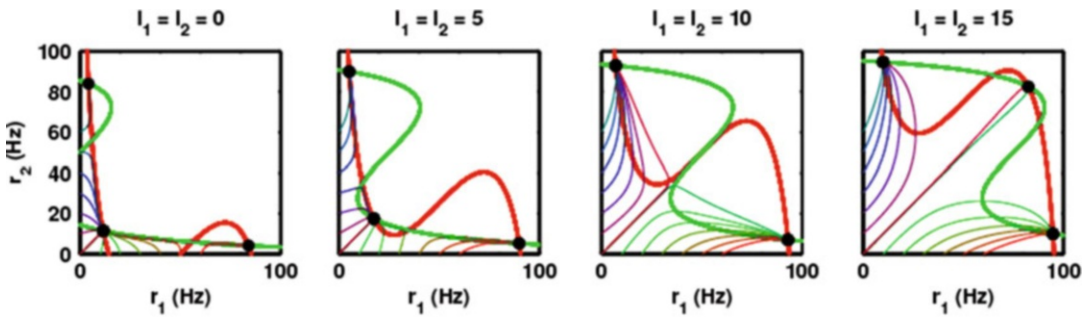
Decision-Making, Models, Fig. 5 A neural circuit model of decision making. Integration of stimuli ($S1$, $S2$) by groups of neurons with rates $r1$ and $r2$ can be achieved through strong excitatory recurrent connections within groups (looped connections with arrows). The mean firing rate of cells in the inhibitory pool (“INHIB”) increases with both $r1$ and $r2$, producing competition through inhibitory input to both cell groups (solid circles) (Wang 2002)

a decision-making circuit in vivo, biophysical models introduce additional noise into the decision-making model itself, which inevitably adds to any already-present stimulus noise (Wang 2002).

Second, neurons are either excitatory or inhibitory, so in order for two groups of cells with self-excitation to inhibit each other, at a minimum, a third group of inhibitory cells must be added. The need for an extra cell group to mediate the inhibition adds a small delay to the cross-inhibition compared to self-excitation, though this effect can be counteracted with fast responses in the synaptic connections to and from inhibitory cells versus slower synaptic responses in excitatory connections. The second effect of an intermediate cell group is to add the nonlinearity of the inhibitory interneuron’s response function into the cross-inhibition. Thus, the inhibitory input to one excitatory cell group is not a linear function of the firing rate of the other cell group. The consequences of this and other nonlinearities are discussed further below.

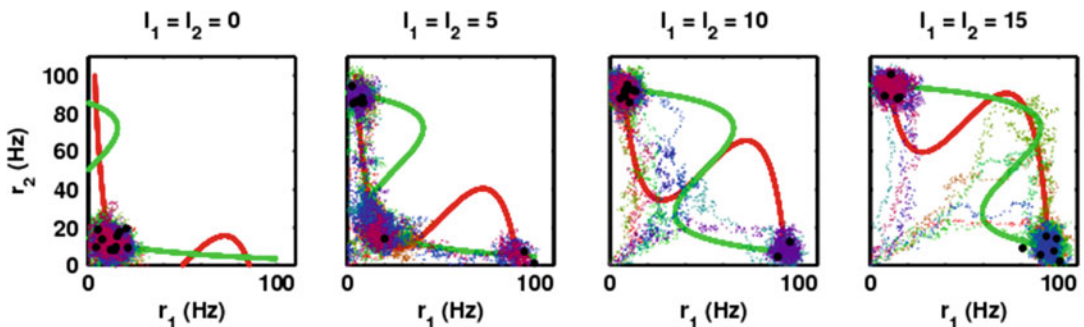
Third, biophysical models of neurons, just like neurons in vivo, respond nonlinearly to increased inputs. Similarly, synaptic inputs to a cell saturate, so are a nonlinear function of presynaptic firing rates. In the LCA model (Usher and McClelland 2001), both the neural response and the feedback are linear functions passing through the origin, so via the tuning of one variable, the two curves can match each other and produce an integrator. Integrators require such a matching of synaptic feedback to neural response so they can retain a stable firing rate in the absence of input – the firing rate produced by a given synaptic input must be exactly that needed to generate the same synaptic input – and this must be true for a wide range of firing rates. Such matching of synaptic feedback to neural response produces a state of marginal stability, typically called a line attractor or continuous attractor.

However, in the absence of symmetry or a remarkable similarity in the shape of neural response curves and synaptic feedback curves, the nonlinear curves of biophysical neurons intersect at no more than three points (Fig. 6), leading to the possibility of two discrete stable attractor



Decision-Making, Models, Fig. 6 Nonlinearity of neural response functions produces stable fixed points, toward which neural activity evolves. Nullclines are represented by the *solid thick red/green lines*, the green line where $dr_2/dt = 0$ at fixed r_1 and the red line where $dr_1/dt = 0$ at fixed r_2 . Crossings of the lines are fixed points of the system, with stable fixed points denoted by *solid black circles*. Decision states are stable fixed points with $r_2 > r_1$ or $r_1 > r_2$. As a symmetric input current is added to the network, the spontaneous “undecided” state, that is, the fixed point of low rates with $r_1 = r_2$, becomes

unstable, so that by $I_1 = I_2 = 10$, the only stable fixed points correspond to one choice or the other and a decision is forced. With high enough applied input current, $I_1 = I_2 = 15$, a new symmetric stable state appears at high firing rates, but this plays no role in the decision-making process. Deterministic trajectories from a range of starting points are indicated by the *thin colored lines* that terminate at a fixed point. See Table 1 for an *xppaut* code that produces the nullclines and Table 2 for the Matlab code that produces the trajectories

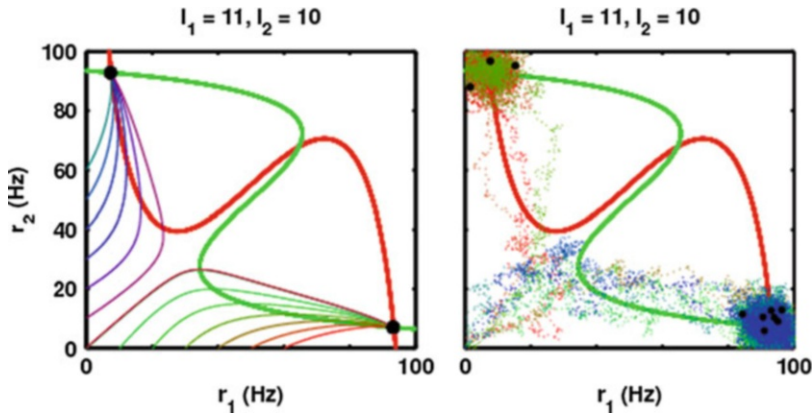


Decision-Making, Models, Fig. 7 Stochastic noise in the simulation produces trial-to-trial variability in the neural responses. With the same neural circuit of Fig. 6, addition of noise can cause neural activity to end up in different states, even with the same starting points. *Small colored dots* indicate trajectories, with *black solid circles* denoting end points after 5 s. All simulations begin with $r_1 = r_2 = 0.1$ Hz. *Far left*: with no applied current, neural activity is maintained near the low-rate spontaneous state. *Center left*:

with moderate applied current, noise can induce transitions to one of the two “decision states.” *Center and far right*: with increased applied current, trajectories always end up at a decision state – even with $I_1 = I_2 = 15$, the two decision states are more stable than the symmetric high-rate state (*far right*). See Table 1 for an *xppaut* code that produces the nullclines and Table 2 for the Matlab code that produces the trajectories

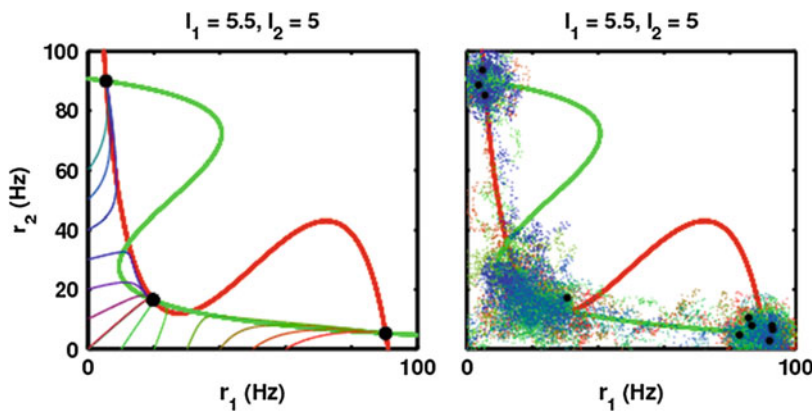
states for a group of cells (with an unstable fixed point in between). When two such groups are coupled, such as by cross-inhibition, the network can have at most four stable states, given by the combinations of low and high firing rates for the two groups. In the winner-takes-all model of decision making, three of these states can be stable in the absence of input: the state when both cell

groups have low or spontaneous activity and the two states with just one of the cell groups possessing high activity. The fixed point with both groups possessing high activity is unstable. In the presence of input, the symmetric low-activity state becomes unstable, and only two stable states remain: the decision states with one group active (“the winner”) and the other group



Decision-Making, Models, Fig. 8 A bias in the inputs causes neural activity to favor one decision state over the other, though noise means that “errors” can arise. *Left*: in the deterministic system, more trajectories terminate at the attractor point of high r_1 , because group 1 receives higher input current. In particular, a symmetric initial condition ($r_1 = r_2$) results in termination with high r_1 and low r_2 . That

is, the basin of attraction for the state with $r_1 > r_2$ includes the line $r_1 = r_2$. *Right*: with added noise, some trials with a symmetric starting point terminate in the state with high r_2 – these correspond to “errors” in the standard terminology of decision making. See Table 1 for an *xppaut* code that produces the nullclines and Table 2 for the Matlab code that produces the trajectories



Decision-Making, Models, Fig. 9 In a noisy system, the initial state can remain deterministically stable, but responses terminate in one of the decision states, with the bias favoring one final state over the other. *Left*: in the absence of noise and a bias in the inputs, more trajectories evolve to the fixed point favored by the input, but many terminate at the “undecided” state. *Right*: with added noise and symmetric initial conditions, most otherwise

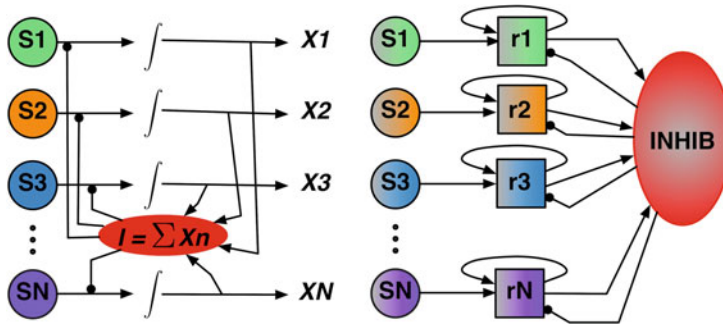
“undecided” responses switch to the decision state favored by the input bias (corresponding to “correct” responses), while a few terminate in the other decision state (“incorrect” responses) and one remains in the symmetric low-rate state (an “undecided” response). See Table 1 for an *xppaut* code that produces the nullclines and Table 2 for the Matlab code that produces the trajectories

inactive (“the loser”). Importantly, with a combination of slow synaptic time constants (NMDA receptors with a time constant of 50–100 ms are an essential ingredient of the model) and sufficient fine-tuning of parameters of the network, the time course for the network’s activity to shift from the unstable initial state to one of the two remaining

stable attractor states is slow enough to match neural and behavioral response times.

Extension of Models to Multiple Choices

Many decision-making models for TAFC are simply extended to the case of multiple alternatives (Bogacz et al. 2007b; Furman and Wang 2008;



Decision-Making, Models, Fig. 10 Models for decision making with multiple alternatives. *Left:* extension of the leaky competing accumulator model to multiple alternatives, such that the negative feedback is proportional to the

sum of multiple decision variables. *Right:* extension of the biophysical model, in which cells providing inhibitory feedback are activated by the summed activity of multiple groups of excitatory cells

Niwa and Ditterich 2008; Ditterich 2010). Electrophysiological data suggests that neural firing rates reach a threshold independent of number of alternatives, but neurons receive greater inhibition, as revealed by reduced firing rates in their initial, spontaneous activity state (Churchland et al. 2008; Churchland and Ditterich 2012). This is akin to a reduction in the prior probability of each individual choice alternative before stimulus onset, if prior probability impacts the starting point of integration. Models in which the total amount of inhibition depends on the total number of alternative choices (see Fig. 10) reproduce such behavior. One consequence of the increased inhibition is a slowing of decision times as the number of alternatives increases.

Sequential Discrimination, Context-Dependent Decisions, and Prior Information

The most developed dynamical models of decision making pertain to the identification of an incoming sensory stimulus or the comparison of two or more concurrent stimuli. However, many decisions require a comparison of successive stimuli, and even when two stimuli are concurrent, our attention typically switches from one to the other when making a perceptual choice. Thus, models of decision making have been developed in which the stimuli are separated in time, so a form of short-term memory is required, with the contents of short-term memory and a later sensory input both affecting the choice of action (Romo

and Salinas 2003; Machens et al. 2005; Miller and Wang 2006). The process of making a decision by combining short-term memory, which can represent the current “context” (Salinas 2004), with sensory input provides the essential ingredient for working memory tasks and for model-based strategies of action selection (Deco and Rolls 2005).

Prior information can make one response either a more likely alternative or a more rewarding alternative given ambiguous sensory information and can lead to across-trial dependences in decision-making behavior. Consideration of how much to weigh prior information compared to the current stimulus requires a separate choice (Hanks et al. 2011), which establishes how long one should continue to acquire sensory input. Such a choice is akin to setting a decision-making threshold. Factors affecting the optimal period for obtaining sensory input include the relative clarity of incoming information compared to the strength of the prior (Deneve 2012), as well as the intrinsic cost of a reduced reward rate when taking more time to decide (Drugowitsch et al. 2012). At some point in time, awaiting further sensory evidence does not improve one’s probability of a correct choice sufficiently to warrant any extra delay of a potential reward. Solution by dynamical programming (Bellman 1957) of a model that takes into account these factors suggests that monkeys respond according to an optimal, time-varying cost function (Drugowitsch et al. 2012).

Decision-Making, Models, Table 1 A code base on xppaut to produce nullclines and fixed points for two interacting groups of neurons, connected in a decision-making circuit, as used to produce Figs. 6, 7, 8, and 9.

```
# Rate-based model of two coupled neuron populations.

# I1 and I2 are the inputs to each population, which should be varied.
par I1=5
par I2=5.5

# Strength of self-excitation
par wself=1
# Cross connections are net inhibitory
par wcross=-0.2

# tau is the time constant -- the slowest synaptic time constant, of NMDA is
used.
# tau has no effect on steady state solutions.
par tau=0.075

# Sigmoidal f-I curves require three parameters, these are:
# rmax, the maximum rate
par rmax=100
# Ithresh, current to produce half-maximum rate
par Ithresh=50
# delta, determines the width of the sigmoid (sensitivity near Ithresh).
par delta=20

# Initial firing rates can be varied.
init r1=0
init r2=0

dr1/dt=-r1/tau+rmax/(1+exp(-(I1+wself*r1+wcross*r2-Ithresh)/delta))/tau
dr2/dt=-r2/tau+rmax/(1+exp(-(I2+wself*r2+wcross*r1-Ithresh)/delta))/tau

# The following are default values for the start-up of xpp.

@method=rk,total=2,bound=500,dt=.005,dtmin=1e-12,atoler=1e-7
@toler=1e-5,xhi=2,yhi=100,ylo=0 njmp=5
@ bell=off,nout=50

done
```

D

Testing Decision-Making Models

Decision-making models can be tested more stringently using tasks in which the stimulus is not held constant across the time allotted for producing a response (Zhou et al. 2009; Stanford et al. 2010; Shankar et al. 2011; Rüter et al. 2012). For example, in models such as the DDM based on perfect integration, if a stimulus is altered or even reversed for a short amount of time, so long as the stimulus alteration is in the period of its integration, it has the same effect on

response time and choice probability whether it is early or late. However, in models where the initial state is unstable, a late altered stimulus has weaker impact on the decision-making dynamics than an early one. Conversely, in models where the initial state is stable, such as the LCA with a positive leak term, only stimuli presented shortly before the final response contribute to it; the time constant of the drift term that draws the decision variables back to the initial state corresponds to a time constant for the forgetting of earlier evidence.

Decision-Making, Models, Table 2 The Matlab function used to simulate multiple decision-making trials as plotted in each panel of Figs. 6, 7, 8, and 9.

```
function[ r1 r2 ] = WTAtrials( Iapp1,Iapp2,sigma );
% WTAtrials produces multiple trials of a winner-takes-all network produced
% by coupling two sigmoidal firing rate models, each representing a neural
% population.
% Iapp1 and Iapp2 are the respective current inputs to the 2 populations.
% sigma is the level of noise (added independently to each population).
% The function returns the firing rate as a function of time for each
% trial for each population.
% Number of trials is defined within the function as Ntrials = 10.

dt = 0.001;           % timestep for simulation
tmax = 5.0;           % max time for integration
tvec = 0:dt:tmax;     % time vector

Ntrials = 10;

r1 = zeros(Ntrials, length(tvec)); % records rate of one cell group
r2 = zeros(Ntrials, length(tvec)); % records rate of other cell group

tau = 0.05;           % time constant (cf NMDA receptors)

rmax = 100;           % max rate of cells
Ithresh = 50;         % input needed for 1/2-max firing
Idelta = 20;          % determines steepness of sigmoidal f-I curve

wself = 1;            % recurrent excitatory feedback
wcross = -0.2;        % strength of cross-inhibition

trial = 0;
rhighstart = 0*rmax;  % If nonzero, provides a range of starting points.
for trial = 1:Ntrials
    if( trial <= Ntrials/2 )
        r1init = 0.1+rhighstart*(Ntrials/2-trial)/(Ntrials/2-1);
        r2init = 0.1;
    else
        r2init = 0.1+rhighstart*(Ntrials-trial)/(Ntrials/2-1);
        r1init = 0.1;
    end

    % Implement initial conditions
    r1(trial,1) = r1init;
    r2(trial,1) = r2init;

    % Produce independent random noise for each population
    noise1 = sigma*sqrt(dt/tau)*randn(size(tvec));
    noise2 = sigma*sqrt(dt/tau)*randn(size(tvec));

    % Now integrate with basic Euler-Maruyama method using sigmoid f-I
    % curves and current, I, linear in rate.
    for i = 2:length(tvec)
        r1(trial,i) = r1(trial,i-1) + ...
            dt/tau*( rmax/(1+exp(-(Iapp1+wself*r1(trial,i-1)+ ...
            wcross*r2(trial,i-1)-Ithresh)/Idelta))-r1(trial,i-1) )+ ...
            noise1(i);
        r2(trial,i) = r2(trial,i-1) + ...
            dt/tau*(rmax/(1+exp(-(Iapp2+wself*r2(trial,i-1)+ ...
            wcross*r1(trial,i-1)-Ithresh)/Idelta))-r2(trial,i-1) )+ ...
            noise2(i);
    end
end
end
```


Alternatively, if one sets up a task in which noise in the stimulus, controlled by the experimenter, is the dominant noise source in the decision-making process, one can analyze separately correct trials and error trials and align them by either time of stimulus onset or time of response to assess the impact of noise fluctuations on choice probability or response times. Care must be taken when aligning by response times, since threshold crossings are inevitably produced by noise fluctuations in the direction of the threshold crossed. However, in all cases, model predictions can be tested with experimental measurements. Current results appear to be task dependent, as some data sets suggest all evidence is equally impactful (supporting a perfect integrator) (Huk and Shadlen 2005; Brunton et al. 2013), while others suggest the weighing of sensory evidence is higher early (Ludwig and Davies 2011) or higher late (Cisek et al. 2009; Thura et al. 2012) or oscillatory (Wyart et al. 2012) across stimulus duration.

Beyond Discrimination: Action Selection

In the models considered heretofore, the decision of what action to take has been equivalent to the question of what is perceived. This is because in the relevant tasks, the difficulty is in unraveling the cause of a sensory input, which has been degraded either at source, or through sensory processing, or as a result of imperfections of memory encoding and recall. The requisite action given a sensory percept is either via a straightforward instruction for human subjects or produced by weeks to months of training in nonhuman animal subjects. Thus, in the post-training stage used to acquire data, the step from percept to action can be considered very fast and independent of the parameters varied by the experimenter to modify task difficulty.

However, most decisions require us to select a course of action given a percept or given a combination of percepts. Two general strategies, termed model based or model-free (Dayan and Daw 2008; Dayan and Niv 2008), are possible for action selection. Model-based strategies require an evaluation of all possible consequences, with their likelihood, similar in a chess

game to calculating all the combinations of moves in response to one move, or, conversely, all the possible causes of an observation. A model-free system simply learns the value of a given state and selects an action based on the immediately reachable state with highest value. For example, one could move a chess piece to produce the pattern of pieces that has led to most games won in the past.

A wide literature in the field of reinforcement learning (Barto 1994; Redish et al. 2007) and its possible neural underpinnings (Daw and Doya 2006; Johnson et al. 2007; Lee and Seo 2007) addresses how one can learn the value of states over multiple trials. This literature has influenced model-free biophysical models of decision making (Soltani and Wang 2008, 2010), with the principal requirement being a need for enhanced Hebbian learning when the resulting action leads to positive reinforcement, but not otherwise. The neural activity underlying the decision precedes the reinforcement signal, so in order for the appropriate synapses to be potentiated when positive reinforcement arrives, authors have suggested the activity itself remains in a persistent state of high firing rate (Soltani and Wang 2006) or a molecular “eligibility trace” of earlier activity persists through the time of the reinforcement signal (Bogacz et al. 2007a; Izhikevich 2007).

A model-based method for making a decision is more flexible and can be more accurate, but in all but the simplest cases, the combinatorial explosion of alternatives becomes unwieldy and time-consuming to calculate. Hierarchical reinforcement learning renders such models more manageable (Barto and Mahadevan 2003; Ito and Doya 2011; Botvinick 2012).

Cross-References

- [Decision-Making Tasks](#)
- [Decision-Making, Bias](#)
- [Decision-Making, Motor Planning](#)
- [Decision-Making, Threshold](#)
- [Decision-Making: Overview](#)
- [Perceptual Decision-Making](#)
- [Reinforcement Learning in Cortical Networks](#)
- [Speed-Accuracy Tradeoff](#)

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Decision-Making, Motor Planning

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Synonyms

Action planning; Action selection; Motor intention; Motor preparation; Motor set; Preparatory set; Response planning; Response selection

Definition

“Motor planning” refers to the cognitive operations that are antecedent to the execution of a voluntary, goal-directed motor act or sequence.

Detailed Description

As the term implies, *motorplanning* refers to the mental operations that precede the initiation of a voluntary motor act. Imagine, for example, the simple act of reaching to pick up a glass of wine while dining at a restaurant. If you are like most people, you have just envisioned yourself making a deliberate reach to pick up the glass, presumably for the eventual purpose of taking a sip. Now, instead imagine that this same glass of wine is teetering due to an inadvertent bump of the table by a passing waiter. It is readily apparent that your reaching movement in this circumstance, though requiring the same basic excursion, would be substantively different in both its intended purpose and, accordingly, in the manner in which it is executed. Intuitively, the most likely distinction between a reach intended to take a sip of wine and one designed to prevent it from spilling is that the latter would need to be executed much more rapidly if it is to have any chance of producing a successful outcome. From the perspective of neural computation, the difference between the two

movements would at first glance seem rather trivial – reaching faster simply requires that a “stronger” neural command be provided to the relevant musculature – but, in fact, deeper consideration of what would constitute an effective motor plan in each case reveals that the problem is not at all simple from a neural coding perspective.

As is generically true for any “plan,” a motor plan is a prescription for action that is informed by current circumstances and with an eye toward an expected, future outcome. If considered as a series of mental events, the “plan” then is what occurs *after* one has decided what to do (e.g., take a sip of wine) but *before* one actually does it; by definition, a plan can be canceled, thus resulting in no action. As detailed in another entry in this section (see ► “Perceptual Decision-Making”), this depiction of mental events as discrete and serial is unlikely to have a direct correspondence in neural processing stages (see also Requin et al. 1988; Cisek and Kalaska 2010), but it is of heuristic value for considering the formulation of a motor plan as a problem of neural computation. With this in mind, it is a simple matter to consider how the motor plans for the aforementioned hypothetical scenarios must differ on the basis of presumed input and desired output. Clearly, a motor plan developed to take a taste of wine is guided by very different sources of information than that for stabilizing the unsteady glass. In the former case, the decision, and consequently the plan, to reach for the glass is informed primarily by a host of appetitive and social cues, while in the latter, visual (swaying motion of the glass) and tactile (vibration of the table) motion cues would likely predominate. In addition to receiving input from vastly disparate sources, the ensuing motor plans must evolve to produce outputs that optimize different movement parameters. Ideally, a reach to drink the wine would be graceful, or at least sufficiently precise, so as to avoid knocking over the salt shaker or dipping one’s sleeve in the olive oil intended for dipping bread. In contrast, grace may be sacrificed in the name of urgency when attempting to prevent a spill. Here, in addition to moving with greater speed, a more direct hand path to the glass (salt shaker be damned!) might be more effective. It goes without saying that if the

respective motor plans are to specify movements having different speeds and trajectories, their corresponding neural correlates must carry information that can be translated into the appropriately distinct dynamical signals at the effector level (e.g., force, joint torque).

Along with providing a general sense for what a motor plan is, the juxtaposition of these real-world reaching scenarios makes a crucial point: motor planning, and the neural that implements it, represents a flexible interface that ties internal and external cues to motor effectors in a way that ensures that actions are appropriate to context. Once again, if motor planning could be thought of as a discrete computational stage, it is one that must be receptive to all manner of possible input and capable of producing a widely varied range of output – a formidable computational problem to be sure.

Experimental Investigation

The preceding section provides a highly descriptive account of motor planning, making use of a concrete example to generate some intuition about its implications for behavior and the neural activity that underlies behavior. In the laboratory, neurophysiological studies of motor planning have a long history, and our understanding has relied extensively on behavioral tasks that incorporate what is known as an “instructed delay period,” sometimes simply referred to as the “delay period” or “instructed delay.” (The term “delay period” in this context should not be confused with its use to refer to a memory retention interval (e.g., see Funahashi et al. 1989). The delay period is the interval of time that elapses between two task instructions. The first instruction comes in the form of a sensory cue informing the subject about *what* to do and the second (the “go signal”) instructs the subject *when* to do it. In principle, the delay period is a window of time during which the subject can perform the necessary perceptual evaluation of the instruction and subsequently formulate aspects of the motor plan (e.g., select the appropriate response, specify metrics), all in advance of receiving the instruction to execute the

action. Crucially, the time allowed for advance preparation contrasts with standard reaction time tasks, in which the go signal and the informative sensory cue are simultaneous, so perceptual judgment and motor planning processes are all completed within the reaction time interval. The temporal expansion of processing time that is afforded by the delay period has been oft exploited in neurophysiological studies of the covert cognitive processes that lead to an overt motor response.

Traditionally, single-neuron electrophysiological studies of motor planning have concentrated on the activity associated with either saccadic eye movements or reaching movements of monkeys trained to direct movements toward visual goals. Superficially at least, the neural activity recorded in association with performance of a “delayed saccade” or “delayed reaching” task is strikingly similar. Whether recorded in saccade-specific or reach-specific brain regions, a substantial fraction of neurons display two temporally discrete periods of activation, one linked to the initial stimulus indicating the movement goal (sensory event) and another to the motor response (saccade or reach). Interposed between these event-linked bursts of activity is the so-called delay period activity, a major focus of neurophysiologists’ attempts to understand how motor planning is represented in the activity of single neurons. Consistent with the logic of the instructed delay task, activity during this period demonstrates the hallmark features of that which would constitute a plan for action. First, such activity reflects the vector of the upcoming movement well in advance of the imperative signal to actually produce it (i.e., the go signal). And second, as mentioned earlier, such delay period representations of future movement need not lead to execution – plans can be canceled – as has been convincingly demonstrated with behavioral tasks that later “countermand” the initial instruction of “what to do.” That the specification of movement parameters in neural activity does not inevitably lead to the initiation of movement firmly supports the interpretation of such pre-movement activity as a motor *plan* and not a motor *command*.

Specificity of Motor Plans

The question of precisely what information is being represented in motor planning activity can be a difficult one, particularly so for the skeletomotor system where it is not entirely clear what movement parameters are being optimized upon execution (e.g., see Shenoy et al. 2013). For example, returning to the example of how to plan movements of different speed, one would not be particularly surprised if *during* movement execution, the concurrent activity of motor-related neurons displayed different firing rates in association with movements of different speed. But is there a neural correlate of the *intention* to move at a certain speed? More specifically, could one predict from *delay period* activity whether an impending movement will be fast or slow? Indeed one can, as shown in an elegant study by Churchland and colleagues (2006; see also Cisek 2006) that exemplifies the way in which different intentions may manifest as differences in neural activity. In this experiment, monkeys were trained on an instructed delay task to make either a high- or low-velocity reach depending on the color of the target to be acquired. Single-neuron recordings from dorsal premotor and primary motor cortex revealed that, along with representing the vector of the upcoming movement, the delay period activity of individual motor cortical neurons was strongly modulated by the instructed speed of the reach. Though clearly demonstrating a neural correlate of planned speed, the relationship was not a simple one; the activity of individual neurons could be positively *or* negatively modulated by the intention to make a faster movement, and furthermore, this representation of intended speed was shown to interact with those of ostensibly orthogonal spatial dimensions like movement distance and direction.

The Churchland et al. study is but one example taken from more than three decades of work demonstrating how movement parameters ranging from low (e.g., force) to high (e.g., trajectory) level can be observed in the preparatory activity associated with limb movements (e.g., Tanji and Evarts 1976; Wise 1985; Kalaska et al. 1989; Riehle and Requin 1989; Fu et al. 1995; Crammond and Kalaska 2000). As is the case for

movement speed, it is not fully clear how the varied and sometimes redundant information concurrently present within motor preparatory activity is read out to yield the eventual motor commands. This is a rich topic and well beyond the scope of this short entry; nevertheless, it should be appreciated that current models of how plans become action are necessarily constrained by assumptions about how such signals would need to be transformed to yield the requisite downstream signals.

Planning of Eye Movements

Relative to the skeletomotor system, the oculomotor system is considerably less complex biomechanically, and as such, its study has been instrumental to deciphering how cognitive processes influence the neural activity that leads to movement. However, in contrast to reaching, introspection is not quite so valuable for considering how motor plans might differ when it comes to making saccades. Indeed, while making approximately three saccades every second, the complex decision and motor planning processes that inform one's choices of where and when to look go largely unnoticed. Yet such decisions and the plans that embody them are essential to effective interaction with the environment, whether that entails watching a movie, hitting a baseball, or just searching for one's keys on a cluttered countertop.

While it may be difficult to deduce from one's own eye movements, there is no argument that cognitive strategy, or planning, plays a major role in guiding saccade choices. In his pioneering studies of nearly a half century ago, Russian psychologist Alfred Yarbus showed (Yarbus 1967) that subjects who were viewing static images could be induced to alter their patterns of saccadic landing points simply by changing task instructions (and not the image itself). Thus, the way in which saccades interrogate a visual scene depends heavily on prior knowledge of what information needs to be gleaned from it. While many subsequent insights have come from psychophysical studies of natural visual scanning, studies attempting to expose the neural correlates of visual decision making and saccadic motor

planning have typically relied on more controlled task settings. As is the case for limb movements, the neural signature of oculomotor planning in its most fundamental form is that of a representation of impending saccade vector. Such is readily observed in single-neuron recordings from monkeys trained to perform variants of a delayed saccade task, and at least qualitatively similar spatial representations have been observed in visuo-oculomotor territories in frontal cortex, parietal cortex, midbrain, thalamus, and basal ganglia (e.g., Thompson et al. 1996; Snyder et al. 1997; Glimcher and Sparks 1992; Schlag and Schlag-Rey 1984; Schlag-Rey and Schlag 1984; Hikosaka et al. 1989). But more than simply predicting *where* the eyes will go, a correlate of *when* the eyes will move, or saccadic reaction time can also be observed in the preparatory activity of visuo-oculomotor neurons, specifically those with ties to brainstem circuits that are proximal to the extraocular muscles (e.g., Hanes and Schall 1996; Dorris et al. 1997).

Planning Versus Executing

At what point does an oculomotor plan become a commitment to action and what is the neural basis of this transition from the merely possible to the inevitable? In a compelling demonstration, Hanes and Schall (1996) tested the hypothesis that commitment to a particular saccadic choice occurs only when the preparatory activity of oculomotor neurons representing that choice (i.e., a given saccade vector) exceeds a specific or fixed threshold. They recorded from saccade-related neurons in the primate frontal eye field while monkeys performed the simple task of looking toward a single visual target presented at an eccentric location. Importantly, even when looking toward a highly salient and unambiguous goal, saccadic reaction times are known to display considerable variance. Hanes and Schall demonstrated that the fixed-threshold mechanism could account for this variance by verifying two predictions about frontal eye field saccade-related activity. First, they observed that the activity of individual neurons increased monotonically leading up to saccade onset, and just prior to saccade onset, activity

consistently attained the same level. The second prediction is a necessary consequence of the first one. If the commitment to move occurs when the increasing motor planning activity crosses a fixed threshold, then the reaction time should be inversely related to the rate at which the plan rises: shorter reaction times should correspond to motor plans that build up quickly and longer reaction times should occur when the accumulation is more gradual. Indeed, this is precisely what they observed. In an interesting variation on this experiment, Hanes and Schall also employed a countermanding version of the task wherein, on some trials, monkeys were cued to withhold the already instructed saccade. They found that trials in which the monkey was successful in withholding the eye movement corresponded to those in which the accumulating activity of frontal eye field neurons failed to achieve the putative threshold criterion – i.e., the neural correlate of a canceled motor plan.

Motor Planning Dynamics

The above-described examples from the skeletomotor and oculomotor systems convey the essence of what a motor plan is and how it is manifested in the neural activity that precedes an action. Such an account, however, fails to capture the dynamism of how motor plans are informed by perceptual events and changing internal states in the milliseconds leading up to a motor choice. As noted above, the perception-action cycle has been conceptualized as consisting of a series of discrete computational stages, a characterization that is reinforced by the way in which its neural basis has been studied. For the most part, the neural activity associated with performing a perceptually guided motor response has been examined with tasks, like the instructed delay task, that promote or even mandate serial completion of perceptual evaluation and motor planning processes. But, unlike for many laboratory tasks, perceptual information and behavioral goals are fluid in real life, and accordingly, plans may evolve in ways that reflect this ever-changing reality. As discussed at length in another entry (see ► [“Perceptual Decision-Making”](#)), the notion

that accumulating sensory evidence is manifested directly in developing motor plans (e.g., Gold and Shadlen 2000) blurs the distinction between perceptual and motor processes and hints at a more continuous interplay between perceptual evaluation and response selection. In fact, studies of perceptual decision making have consistently demonstrated that the neurons that accumulate sensory evidence in favor of a particular choice are very often the same ones that plan the action that serves as the ultimate expression of the decision/choice process (e.g., Requin et al. 1988; Gold and Shadlen 2000; de Lafuente and Romo 2006; Hernández et al. 2010). Clearly, a direct and intimate relationship between perceptual decision and motor planning makes good sense if the objective is to base actions on the most currently available information. In fact, the immediacy of this relationship is emphasized by recent studies of urgent decision making with tasks that prioritize the incorporation of incoming sensory information to guide ongoing motor plans. Remarkably, these studies suggest that motor systems may simultaneously harbor multiple and sometimes mutually exclusive motor plans until just milliseconds before a single alternative is committed to action – a conflict resolved on the basis of a timely perceptual cue (Cisek et al. 2009; Cisek and Kalaska 2010; Stanford et al. 2010). Ultimately, understanding the neural basis of motor planning will require a more complete framework for describing how perceptual and motor systems interact to affect the right action at the right time.

Cross-References

► Perceptual Decision-Making

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Decision-Making, Threshold

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Synonyms

Absorbing boundary; Decision space boundary

Definition

A decision-making threshold is the value of the decision-making variable at which the decision is made, such that an action is selected or a commitment to one alternative is made, marking the end of accumulation of information.

Detailed Description

A decision-making threshold determines when a decision-making process is completed. It

represents a value of the decision variable, which in practice could be a linear combination of a set of neural firing rates, at which the accumulation of sensory evidence terminates and a response or action is chosen. In two-alternative forced-choice tasks, two thresholds exist, one for each of the two alternatives.

In models of decision making, the threshold can be either static or dynamic during an individual trial. Mathematically, a threshold is an absorbing boundary of the diffusion process for the decision variable. The time for the decision variable to reach such an absorbing boundary is the decision-making time (Fig. 1).

Static Thresholds

If the threshold is static, it determines where one is operating in the speed-accuracy trade-off. Low thresholds produce speedier responses, whereas higher thresholds increase accuracy. In particular, for the drift diffusion model, which is based on a perfect integrator, noise accumulates as the square root of time, whereas the signal accumulates linearly in time. Therefore, with large enough



Decision-Making, Threshold, Fig. 1 Two static thresholds act as absorbing boundaries for the 1D Brownian motion of the decision variable, X . The boundary reached in any particular trial determines the choice (or percept in a perceptual categorization task) with the time for the decision variable to reach the boundary making the dominant contribution to response time

thresholds resulting in long enough decision-making time, accuracy of decisions can approach 100%. Specifically, if the decision variable has an initial value of zero and thresholds are set at a and b , the two types of error rate, α (probability of choosing + when the signal, S , is $-$) and β (probability of choosing $-$ when the signal, S , is $+$), are given by (Ratcliff 1978):

$$\alpha = \frac{\exp\left(-\frac{2|S|a}{\sigma^2}\right) - 1}{\exp\left(-\frac{2|S|a}{\sigma^2}\right) - \exp\left(-\frac{2|S|b}{\sigma^2}\right)} \text{ and}$$

$$\beta = \frac{1 - \exp\left(-\frac{2|S|a}{\sigma^2}\right)}{\exp\left(-\frac{2|S|a}{\sigma^2}\right) - \exp\left(-\frac{2|S|b}{\sigma^2}\right)}$$

Notably, if thresholds are symmetric ($a = b$) with a starting point at the origin, then

$$\alpha = \beta = \frac{1}{1 + \exp\left(\frac{2|S|a}{\sigma^2}\right)}$$

which decreases exponentially with increasing threshold, a .

Prior belief can be incorporated by setting the two thresholds to be different, reducing a or b , respectively, if a positive or negative response is preferable or, more likely, according to information acquired before stimulus onset.

Response Times

Assuming a positive stimulus ($S > 0$), the distribution of response times for correct trials, $P(T^+)$, is given by

$$(1 - \beta)P(T^+) = \frac{\pi\sigma^2}{(a + b)^2} e^{-\frac{Sb}{\sigma^2}}$$

$$\sum_{k=1}^{\infty} k \sin\left(\frac{\pi ka}{a + b}\right) e^{-\frac{1}{2}\left(\frac{S^2}{\sigma^2} + \frac{\pi^2 k^2 \sigma^2}{(a+b)^2}\right)t}$$

and the distribution of response times for incorrect trials, $P(T^-)$, is given by

$$\beta P(T^-) = \frac{\pi\sigma^2}{(a + b)^2} e^{-\frac{Sa}{\sigma^2}}$$

$$\sum_{k=1}^{\infty} k \sin\left(\frac{\pi ka}{a + b}\right) e^{-\frac{1}{2}\left(\frac{S^2}{\sigma^2} + \frac{\pi^2 k^2 \sigma^2}{(a+b)^2}\right)t}$$

This leads to a mean response time of (Bogacz et al. 2006).

$$\langle T \rangle = (1 - \beta)\langle T^+ \rangle + \beta\langle T^- \rangle = \frac{a + b}{2S} \tanh\left[\frac{S(a + b)}{2\sigma^2}\right]$$

$$+ \frac{(a + b)\left[1 - e^{-\frac{S(a-b)}{\sigma^2}}\right]}{S\left[e^{\frac{S(a+b)}{\sigma^2}} - e^{-\frac{S(a+b)}{\sigma^2}}\right]} + \frac{a - b}{2S}.$$

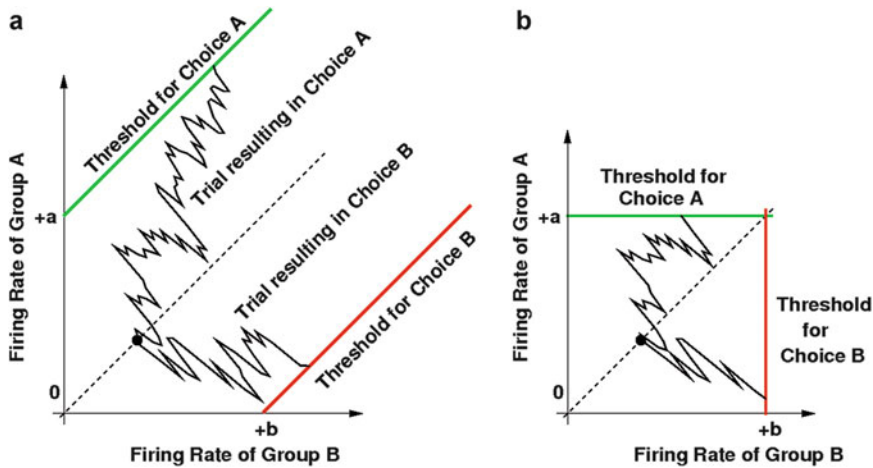
In the symmetric condition, with $a = b$, then $P(T^+) = P(T^-)$ and the mean response times are given by

$$\langle T \rangle = \langle T^+ \rangle = \langle T^- \rangle = \frac{a}{S} \tanh\left(\frac{Sa}{\sigma^2}\right)$$

If thresholds are static, they can be set at an optimal level, by making use of the above formulae, if the statistics of the task and the relative costs of different types of error are known. In particular, if errors are costly, such as in lost time due to a long intertrial interval, it pays to use thresholds far from the decision variable's initial value.

Multidimensional Models

In models with two decision variables, a static threshold can depend either on each variable separately, independent of the value of the other variable, or on the difference between the two variables (see Fig. 2). In terms of neural circuits, the former corresponds to independent outputs from the competing groups of neurons, whereas the latter corresponds to a push-pull arrangement, such that each group excites one response while inhibiting the other. It is notable that for a two-variable integrator model with static independent thresholds (Fig. 2b), the difference in decision variables follows a single-variable integrator model, but with thresholds which collapse toward zero as the sum of the two variables increases.



Decision-Making, Threshold, Fig. 2 In models of decision making with two variables, each variable represents a simple function (like the mean) of neural firing rates. (a) If the thresholds correspond to a constant difference in firing rate, the model can map to a 1D model (Fig. 1) with static

thresholds. (b) If thresholds correspond to a constant absolute firing rate for each cell group, then a decision is made with smaller difference in rates as the sum of rates increases. This can be equivalent to a 1D model with collapsing thresholds

Dynamic Thresholds

In models of decision making with a single decision variable, dynamic thresholds can improve accuracy in tasks with fixed stimulus duration and can optimize reward accumulation in other situations where the cost for acquiring information is not constant in time (Drugowitsch et al. 2012). If thresholds are initially high, they can ensure the decision process is not terminated too quickly and evidence has time to accumulate and outweigh the noise. However, if thresholds collapse to zero by the end of the stimulus duration, they ensure a response is made and any evidence accumulated up until then contributes to the determination of that response.

Implicit in the calculation of performance of models with collapsing threshold is an assumption that the system can distinguish very small differences in the decision variable as the two thresholds converge on each other. An equivalent assumption is the system's ability to respond to very small differences in the times when the decision variable reaches one threshold versus the other, since the two thresholds reach zero simultaneously.

When the statistics of the inputs are unknown, one can optimally adjust the thresholds over the course of the decision, according to whether the inputs are strongly informative or not. Perhaps surprisingly, when the inputs are more ambiguous in their evidence for one response or another, it is optimal for thresholds to collapse quickly, enforcing a rapid response that depends little on information in the stimulus but more closely follows one's prior beliefs (Deneve 2012).

Cross-References

- [Accumulation of Evidence in Decision-Making](#)
- [Decision-Making Tasks](#)
- [Decision-Making, Bias](#)
- [Decision-Making, Models](#)
- [Diffusion Equation](#)
- [Speed-Accuracy Tradeoff](#)

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Decoding Field Potentials

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Synonyms

[Local field potential decoding](#)

Definition

The local field potential (LFP) is believed to represent the aggregated neuronal activity of populations of neurons. LFP activity encodes information related to the control of movements as well as information about sensory and other cognitive processes. LFP decoding refers to the process of extracting features of these processes from the measured LFP signals. LFP decoding is typically performed for a brain-machine interface application to allow control of an external device such as a prosthetic limb or a cursor on a screen.

Detailed Description

Overview

Neuromotor prosthesis is a class of brain-machine interfaces (BMIs) that aims to restore lost motor function by decoding control information from neural signals. The local field potential (LFP) is one such neural signal that can be utilized. The LFP is operationally defined as the low-frequency components ($< \sim 300$ Hz) of neural activity recorded extracellularly using microelectrodes

and is generated via the summation of transmembrane currents (Buzsáki et al. 2012). There is great interest in decoding LFP activity due to the relative ease of recording and long-term stability of the signal in comparison with the spiking activity of individual neurons (Andersen et al. 2004; Hwang and Andersen 2013). Further, the LFP has been shown to be information rich and contains temporally structured information that reflects behavioral processes, such as movement planning and execution (Pesaran et al. 2002; Scherberger et al. 2005). There is mounting evidence that specific frequency bands of the LFP may reflect neuronal processes at different spatial scales (Siegel et al. 2012). Gamma band (30–90 Hz) and high gamma band (90–300 Hz) activity is hypothesized to reflect local encoding due to firing of neurons near the recording electrode (Schomburg et al. 2012). Activity in lower-frequency bands, < 30 Hz, is believed to reflect distributed processing across larger-scale circuits (Donner and Siegel 2011; Fries 2005; Pesaran et al. 2008).

Previous work has shown that the LFP can be decoded off-line to reconstruct high-dimensional upper limb kinematics (Bansal et al. 2011; Zhuang et al. 2010), 2-dimensional movement trajectories (Mehring et al. 2003), and the end goal of movements (Hwang and Andersen 2013; Markowitz et al. 2011). The LFP can also be used in conjunction with spiking activity to decode behavioral states (Aggarwal et al. 2013); however, the information content of the LFP is not necessarily dependent on spiking activity being present in the vicinity of the electrode (Flint et al. 2012a). In fact, the information conveyed via spiking and LFPs can differ in how they vary with cortical depth (Markowitz et al. 2011).

Work is now being undertaken to move LFP decoding online, with subjects controlling a cursor on a screen (Flint et al. 2012b).

Applications

Applications of LFP decoding include extracting information regarding skeletal joint angles, bone segment kinematics, and movement end goal

states. This information can then be used to control external actuators such as an upper limb prosthetic, motorized wheelchairs, speech decoders, a computer cursor on a screen, or function electrical stimulators to restore movements or paralyzed muscles.

Methods of Decoding

The LFP is a continuous time varying voltage signal and comprises a multivariate set of observations when many electrodes are recorded simultaneously. Decoding can be performed by using the amplitude of the time varying signal or by transforming the signal into a set of features. Commonly used features involve applying time frequency spectral techniques and decoding in the frequency domain (Mitra and Pesaran 1999), but other features include those based on wavelet transformations and other sparse, over-complete basis sets. To estimate the frequency spectrum, the LFP is generally assumed to be stationary over a short time window, typically 100–500 ms in duration. The window is then stepped in time allowing decoding across time. To minimize bias in the spectral estimates, the LFP can be first multiplied by one or many orthogonal data tapers before being Fourier transformed.

Decoding in the frequency domain allows for extraction of information carried at each frequency band; however, this greatly increases the number of inputs to the decoder. When decomposing N channels into M frequency bands, the number of potential inputs to the decoder increases to $N \times M$. Due to the challenge of fitting decoding algorithms in many dimensional feature spaces, the real-time demands of applications, and limitations in computing power, dimensionality reduction such as principal component analysis can be applied to the frequency transformed LFP to extract a set of modes (Markowitz et al. 2011). Feature selection can then be performed on these modes to obtain a smaller number of features that are then used for decoding.

Once the LFP has been preprocessed to give features, the features are decoded to obtain control

signals. Discrete control signals, such as selecting letters on a keyboard, can be decoded using classification algorithms such as linear discriminant analysis (Pesaran et al. 2002), the naïve Bayes classifier (Bai et al. 2007), and support vector classifiers. Continuous control signals, such as the trajectory of an arm movement, can be decoded using regression algorithms, such as linear regression (Wessberg et al. 2000), penalized linear regression (Mulliken et al. 2008), Kalman filters (Wu et al. 2006), and support vector regression (Shpigelman et al. 2009).

Advantages of the Approach

Local field potential decoding offers the advantage of improved long-term stability and ease of recording compared to decoding of action potentials generated by individual neurons. Recordings of action potentials can be difficult to acquire as neurons need to be within ~100 μm from the tip of the recording electrode (Buzsáki and Draguhn 2004). Further, action potential recordings are highly susceptible to changes in electrode characteristics due to local inflammatory responses such as the buildup of scar tissue (Polikov et al. 2005). In comparison, the LFP has proven to be easier to acquire and the information content more stable to tissue responses (Andersen et al. 2004). The low-frequency, $< \sim 300$ Hz, nature of the LFP also minimizes the sampling frequency required to acquire the signal compared to spiking activity. This greatly reduces the power consumption and data transfer requirements of the end application BMI wireless recording systems.

Limitations

The main limitation of decoding the LFP is that the integrative nature of the signal results in reduced spatial and temporal information. Currently, it is unclear whether enough information can be decoded from the LFP to control higher-dimensional devices such as an upper limb prosthetic. Finally, challenges presented by

performing spectral analysis in real time via a fully implanted device also remain to be resolved.

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Local Field Potentials: LFP](#)
- [Spectral Methods in Neural Data Analysis: Overview](#)

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Deep Brain Stimulation

- [Parkinson's Disease: Deep Brain Stimulation](#)

Deep Cerebellar Nuclei

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Definition

The deep cerebellar nuclei (DCN) consist of three nuclei: the fastigial (medial) nucleus, the interposed nucleus, and the dentate (lateral) nucleus. Together they form the primary output from the cerebellum. DCN excitatory neurons project to a variety of extra-cerebellar targets, whereas the inhibitory neurons project exclusively to the inferior olive. The activity of DCN neurons is shaped by massive inhibitory input from Purkinje cells in the cerebellar cortex and excitatory input arriving via the inferior olive axons – the climbing fibers – and mossy fiber collaterals carrying information from the spinal cord, the cerebral cortex, and several brainstem structures. Hyperpolarization induced by the inhibitory input actively controls plasticity in the excitatory synapses in the cerebellar nuclei. Overall, DCN neurons participate in local and global feedback and feedforward networks thus generating complex dynamics.

Detailed Description

DCN neurons can be divided into three main subcategories: excitatory projection neurons targeting a variety of extra-cerebellar structures, including the cerebral cortex via the thalamus; inhibitory projection neurons targeting exclusively the inferior olive; and local inhibitory interneurons. All types of neurons receive similar ratios of converging afferents; however, the information can differentially be processed due to cell-type-specific biophysical mechanisms. The main synaptic input to the DCN arrives from the Purkinje cells which provide 60–80% of the total number of synapses formed on DCN neurons. Recent estimates suggest a convergence ratio of about 20–50 Purkinje cells per nuclear cell which is by an order

of magnitude smaller than previously estimated (600–800 Purkinje cells per one DCN neuron). The climbing fiber collaterals constitute about 5% of DCN input, and the number of interneuron and mf synapsing on the projection neurons remains unclear. In addition to their glutamatergic and GABAergic synaptic inputs, the DCN receive a less studied serotonergic and cholinergic neuromodulatory input. Neurons in the DCN tend to fire spontaneously at rates >10 spikes/s and can modulate their firing rates in complex ways in response to either sensory or motor activation.

The DCN are classically considered relay stations that linearly integrate incoming information; however, recent advancement in cerebellar research suggests otherwise. Neuronal mechanisms such as short-term depression at the Purkinje cell–DCN neuron synapse, the occurrence of rebound response, and diversity in the convergence–divergence ratios of DCN afferents enhance the capacity of DCN neurons to perform complex computation.

DCN Networks

The Olivocerebellar Pathway: The DCN form a local closed-loop network with the inferior olive (IO) and the cerebellar cortex. The climbing fibers which are the axons of the inferior olive induce complex spikes in Purkinje cells which in turn inhibit the DCN. Then via their inhibitory projection neurons, the DCN regulate the coupling strength within IO neurons by activating GABAergic receptors near the IO dendritic gap junctions. The strength of the IO coupling influences the probability of the IO to generate an action potential in the climbing fibers. Climbing fiber collaterals innervate DCN regions in a closed-loop manner with the Purkinje cells activated by them. The one-to-one relation between the climbing fiber activity and complex spike occurrence in Purkinje cells and the strong synaptic connection formed by the climbing fiber collateral in the DCN generate a unique excitation–followed-by-inhibition activation sequence in the DCN.

The Mossy Fiber-Cerebellar Pathway: Information arriving via the mossy fibers is processed by the granule cells and then distributed by the parallel fiber system to the Purkinje cells from which it is projected to the DCN. The mossy fiber collaterals show considerable ramification and a bilateral projection pattern in the DCN thus generating complex convergence–divergence relation with the mf pathway propagating through the cerebellar cortex. Thus far, information processing rules governing the mossy fiber-cerebellar pathway remain to a large extent an enigma.

The Shaping of DCN Activation

DCN activation is shaped primarily by massive inhibitory input arriving from the Purkinje cells. Two neuronal mechanisms are responsible for regulating the effectiveness of Purkinje cell inhibition: the Purkinje cell–DCN synaptic characteristics and DCN rebound response.

The Characteristics of the Purkinje Cell–DCN Synapse: Two unique features characterize the dynamics of the Purkinje cell–DCN synapse – the short duration of its inhibitory postsynaptic current (IPSC) and short-term depression (STD).

The synapse between the Purkinje cells and the DCN has extremely fast inhibitory postsynaptic current kinetics ($\tau_{\text{decay}} = 2.5$ ms) which prevents accumulative effect of residual currents. Consequently, DCN neurons are inhibited by asynchronous Purkinje cell activity and are entrained to a synchronized subset of Purkinje cells displaying similar firing rates.

The Purkinje cell–DCN synapse displays strong STD which ranges from 30% for a 20 spikes/s input to 90% for rates >140 spikes/s. As a result, the massive Purkinje cell–DCN projection is counteracted by a nonlinear physiological mechanism which controls the dominant influence of Purkinje cells as indicated by anatomy. The STD mechanism enhances the Purkinje cell–DCN synapse sensitivity to dynamic than to steady Purkinje cell activation. The DCN remain within their active zone despite the significant depression at this synapse by intrinsically firing at high rates. The STD together with the short-

duration IPSCs generates a neuronal mechanism that enables the DCN to preferentially respond to low-rate, synchronized Purkinje cell inputs within a high-rate, stochastic background activity.

After-Hyperpolarization Rebound Response: DCN neurons respond to a hyperpolarizing current with a after-hyperpolarization rebound response, which plays a major part in most cerebellar theories; following hyperpolarization, the membrane rapidly depolarizes and is capable of producing spikes at membrane potentials lower than prior to hyperpolarization. The strength of the rebound response increases with the hyperpolarization amplitude and duration. Rebound firing endows DCN neurons with the ability to respond to inhibitory inputs with a spiking output and also to respond differently to the same input depending on the history of synaptic input. The occurrence of rebound response in normal in vivo conditions is still controversial.

Oscillations in the DCN

Occasionally, a subset of DCN neurons display highly synchronized transient epochs of coherent oscillations at a dominant frequency of 6–9 Hz during nonrhythmic movement. The source and computational relevance of these transient oscillations remains to be unraveled; however, recent findings suggest that together with the spinal cord and multiple cortical and subcortical brain regions, DCN oscillations may underlie the 6–9 Hz discontinuities detected in muscle activity during smooth slow finger movements. By generating coherent oscillations at different phase lags, this global network may limit drive to muscle at the oscillation dominant frequency, thereby reducing tremor and improving movement precision. The concept of neuronal oscillations as a biological controller is intriguing and should be further examined experimentally, computationally, and theoretically.

Summary

Over the years the DCN have received little attention in comparison to the plethora of studies which

focused on the olivocerebellar cortex system. The discovery of several complementary nonlinear neuronal mechanisms for controlling DCN neuronal activity makes it attractive to computational and experimental neuroscientists who are interested in adding the DCN to the cerebellar loop and thus develop a broader view of its function (Beitz and Chan-Palay 1979; Teune et al. 1998; Shinoda et al. 2000; Telgkamp and Raman 2002; Pedroarena and Schwarz 2003; Baumel et al. 2009; Steuber et al. 2010; Williams et al. 2010; De Zeeuw et al. 2011; Jaeger 2011; Person and Raman 2012; Uusisaari and Knopfel 2012).

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Delayed Rectifier and A-Type Potassium Channels

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Synonyms

[Non-inactivating potassium current/conductances](#); [Transient potassium currents](#)

Definition

Voltage-gated potassium channels can be grouped into two broad categories: the delayed rectifiers and the “A-type” channels. Delayed rectifiers are named after their delay before activation commences following a voltage change and their contribution to rectification of the current-voltage relationship of cells once they are activated. Delayed rectifiers show little time-dependent inactivation. Inactivation is a process whereby the channels close without a change in the driving force. A-type potassium channels, in contrast, show prominent time and voltage-dependent inactivation. A-type channels may also activate with a delay. There are several approaches to modeling these channels. The roles that the different classes of channels may play in neuronal excitability depend on their interactions with other channels, the time course of voltage fluctuations in the cells, and their localization in the membrane. A-type potassium channels in particular can impart interesting time and voltage-dependent regulation of spike timing that can significantly affect the temporal representation of information in the nervous system.

Detailed Description

Background

Voltage-gated potassium channels are a highly heterogeneous family. Voltage-gated potassium channels appeared early in cellular evolution, and homologous channels can be even found in plants (Cherel 2004). Early voltage clamp studies in invertebrate preparations first identified the delayed rectifier conductances (Hodgkin and Huxley 1952). Subsequent studies identified potassium conductances that inactivated rapidly (Nakajima 1966; Connor and Stevens 1971), which were then termed A-type currents.

The discharge patterns of neurons result from the interplay between the membrane voltage and all of the space, time, and voltage dependence of their ion conductances. The expression of potassium conductances varies widely among neurons and is one of the main determinants of excitability and discharge patterns. However, potassium conductances, even from a single class, play multiple

roles that depend on where they are located in the cell membrane (Jensen et al. 2011). Those conductances located in the soma and axon hillock region are important for discharge pattern and spike rates. Conductances located in dendritic trees help to shape synaptic integration (Johnston and Narayanan 2008) and can contribute to bursting behavior of cells. Conductances located in the presynaptic membrane can regulate transmitter release. Thus, both delayed rectifier and A-type potassium channels can confer very different spiking patterns, subthreshold dynamics, and shaping of synaptic integration and thus are versatile tools for neural information processing.

In mammals, versatility in part results from the production of voltage-gated potassium channels by multiple gene families. Each gene family directs the production of proteins corresponding to primary subunits, auxiliary subunits, and channel-associated proteins, and each of these can have quite distinct physiological functions (reviewed in Coetzee et al. 1999; Jan and Jan 2012; Rudy et al. 2009). The delayed rectifier and A-type channels arise from that is known as the Kv family of channels. There are four broad Kv families, which in the literature are addressed by multiple nomenclatures. Kv1 (KCNA), Kv2 (KCNB), Kv3 (KCNC), and Kv4 (KCND) are the primary α -forming families. Each of the α -subunits, which have six trans-membrane domains, forms the pore-conducting portion of the channels and assembles as tetrameric protein complexes. The channel pore loop (the permeation pathway through which potassium flows) is located between the fifth and sixth trans-membrane spans of each α -subunit, and the assembly together forms a single pore. The β -subunits, which can modify channel function, associate with the α -subunits with a 1:1 stoichiometry.

Diversity in Kv channel structure arises from two principal sources. One is the existence of splice variants (in Kv1.5, Kv3.1, Kv3.2, Kv3.3, Kv3.4, and Kv4.3). The other is the way in which the tetrameric structure is assembled. The specific assembly of the channel subunits is thought to be governed by C-terminal protein interactions such that all of the subunits of a given channel must belong to a single family. Although there is some evidence for specific rules regarding assembly, the combinatorial possibilities of various α and

auxiliary subunits, as well as splice variants, can create channels with a wide diversity of voltage-dependent behavior and with the potential for specific targeting by intracellular messengers. There seems to be no evidence for posttranslational editing of these channels in mammals. However, posttranslational modifications of the channels, including glycosylation (Watanabe et al. 2003) and phosphorylation (Jones and Kaczmarek 1996; Song and Kaczmarek 2006), can significantly alter channel function.

Although the details of channel assembly are not well understood, there is evidence that assembly depends on targeting motifs in the protein that regulate channel trafficking to the membrane (Jensen et al. 2011), as well as specific interactions among subunits during trafficking through the endoplasmic reticulum (Heusser and Schwappach 2005). In addition, auxiliary subunits (beta subunits) have been shown to act as chaperones and influence the targeting and assembly of the channels, as well as gating in assembled channels. Furthermore, the localization of Kv channels can be regulated by motifs that can target the channels to postsynaptic densities. Channel localization in the membrane is not random, but is, at least for some channels, quite focal. This allows the channels to interact with other proteins and may also facilitate local modulation by short-range messengers, including calcium (An et al. 2000; Anderson et al. 2010).

The classification of ion channels is complex, much as the classification of cell types in a given brain region. A variety of factors must be considered, including the voltage dependence of activation, the kinetics of activation, the presence and speed of inactivation, and the voltage dependence of inactivation. As each of these parameters usually is represented as a continuum, the categorization is necessarily fuzzy. Furthermore, the categorization of delayed rectifiers and A-type channels does not map cleanly onto particular Kv families. For example, Kv1.4 is often considered an “A-type” channel, while Kv1.1 and Kv1.2 are delayed rectifiers. It could be argued however that the entire Kv1 family is best described as delayed rectifiers, with varying amounts of slow inactivation. Similarly, Kv3.4 is often considered “A-type,” while Kv3.1 is another kind of delayed

rectifier; however the same argument as for Kv1 might be used here, in that Kv3.4 inactivation is slow and incomplete. The three members of the Kv4 family all create channels that show rapidly inactivating currents and thus are “classical” A-type channels in this respect. The two members of the Kv2 family are delayed rectifiers and do not show inactivation.

Basis of Models

The classical models of Hodgkin and Huxley are the most commonly used formulations to represent the responses of delayed rectifier ion channels. These models provide macroscopic descriptions of conductances and have the advantage that they have been well studied and are readily implemented.

Measurements Needed to Constrain Models

In order to construct a model for a particular conductance, a number of parameters must be measured. The measurements are usually re-represented, through curve fitting, by convenient analytic functions that capture the voltage and time dependence of channel function. In many cases, these functions represent an approximation of the underlying biophysical basis for channel gating. Thus, the voltage dependence of the channel activation (and inactivation), as well as the rates that the channels open, close, and inactivate at different voltages, needs to be measured. Such measurements can only be made using voltage clamp methods and are best made on cells with few processes to improve space clamp, or using membrane patches, such as outside-out patches. The voltage dependence and rate of *activation* (channel opening) are measured by holding the cell at a negative voltage and then stepping to different voltage levels, while recording the time course of the current. The voltage-dependent rate of *deactivation* (channels returning to a closed state following a step that reduces activation) that can be used is measured at voltages where activation is weak or nonexistent by

stepping the cell (or patch) to a voltage where the channels are substantially opened and then stepping the membrane potential to a new level. The voltage dependence of *inactivation* (channels closing while the voltage is maintained at a level that would otherwise keep the channels open) is usually measured by activating the conductance and then measuring the time course of inactivation directly from the decrease in current over time with a constant driving force. An additional set of measurements of the recovery from inactivation also need to be made. Recovery can be measured by stepping the patch to a voltage that nearly fully activates the channels, holding long enough to allow them to inactivate, and then using a test pulse to measure the return of the current at various times after the end of the inactivation step, for a variety of voltages during the intermediate period (Fig. 8).

The kinetics of the channel opening are measured by direct fits of equations to the activation phase. Typically, the goal is to extract the time constants as a function of voltage, and the rising phase is sigmoidal. Thus, the activation function will be

$$A(V, t) = A_0 * \left(1 - e^{-t/\tau}\right)^+$$

where $A(V, t)$ is the current at voltage V , as a function of time following the onset of a step voltage change; A_0 is the amplitude of the current change; τ is the time constant for activation at voltage V ; and n determines the shape of the sigmoidal rise of the current and is usually an integer value between 1 and 4.

In some cases, multiple terms are needed, for example, when the activation has both a sigmoidal rise and a slow component.

Deactivation rates are determined from

$$A(V, t) = b * e^{-t/\tau}$$

Usually this single-exponential function is sufficient. However, there are some conditions where the current decay associated with the channels turning off at a new voltage may have multiple components. For example, a cell might express two populations of channels that cannot be pharmacologically isolated. Alternatively, there might

only one set of channels that have multiple energetically distinct open states or closed states. In this case, the closing rate will depend on which state a population of channels might be in at the time of the step. In intact neurons with extensive dendritic trees, multiple decay time constants may also appear, but will have an ambiguous interpretation. While such decays may represent multiple channels or states within channels, they can also result from channels located at different places in the cell that are not adequately controlled by the voltage clamp and so are not at the same voltages or state when the step is terminated.

These rates are, in all cases, aggregate rates resulting from the equilibrium rates, which are usually analyzed in terms of a two-state model:



The τ values are related to α and β as follows:

$$\tau = \frac{1}{\alpha + \beta}$$

To isolate alpha and beta, the voltage dependence of steady-state or peak activation can be measured and fit to a Boltzmann function:

$$n(V) = \frac{1}{1 + e^{-(V-V_o)/k}}$$

where $n(V)$ represents the fraction of channels open at any given time, which is also $\alpha/(\alpha + \beta)$. Following some algebraic manipulations, α and β can then be computed from the τ and $n(V)$ curves as

$$\alpha = n(V)/\tau \quad \beta = (1 - \tau * \alpha)/\tau$$

These calculations can be done for the individual voltage points. The resulting $\alpha(V)$ and $\beta(V)$ are then typically fit to exponential functions of voltage. Alternatively, the $\tau(V)$ can be fit, combining activation and deactivation kinetic measurements to a more complex function, usually of the form

$$\tau(V) = \frac{1}{a * e^{-(V-V_1)/k_1} + b * e^{-(V-V_2)/k_2}} + O$$

although any equation that adequately describes the data can be used.

Measuring Inactivation

The voltage dependence of inactivation is measured by using a series of voltage steps, usually of fairly long duration, prior to a depolarizing step that activates the channels. The peak current is then fit to a Boltzmann function to describe the steady-state inactivation. In practice, it may be necessary to also measure the voltage-independent conductances (such as residual delayed rectifiers) using a depolarizing conditioning voltage step and subtracting the two sets of traces to isolate the transient component of the current. Inactivation may be incomplete, so the function needs to include an offset parameter to account for the minimum level of inactivation. The voltage dependence of the rate of inactivation is measured by first holding at a negative potential to remove all inactivation and then stepping to various positive potentials. The decay phase of the current is then fit to a single or double exponential function, and these rates are used for the τ curves.

Problems Encountered in Making These Measurements

Technical

As already indicated, having adequate space clamp is absolutely necessary. This can be achieved by using expression systems in small cells without processes, performing acute isolations of cells, which shears off most of the processes, or by using outside out, inside out, or enucleated patches. In addition it is important to properly compensate the amplifiers so that the current measurements and time course are as accurate as possible. The best measurements are made by minimizing series resistance and electrode capacitance and using a wide-band amplifier with minimum lag settings.

Heterogeneity

When working with native channels, it is quite common to encounter heterogeneity in the responses to voltage steps. There are two sources

of heterogeneity in such measurements. The first is measurement error that arises from incorrect voltage clamp due to space clamp problems, or inadequate compensation for series resistance. The second is true biological variability, such as modifications of voltage dependence or open probability by phosphorylation. This increases the scatter in the data. This can be addressed either by averaging results from many cells (or fitting to the population data) or by identifying an underlying mechanism that causes the scatter, such as phosphorylation, and attempting to control that factor. Another approach is to fit the data from individual cells and to use the variability in subsequent modeling.

Alternative Approaches

While measurements of the macroscopic behavior of neuronal conductances are frequently sufficient to model the excitability of cells, more detailed kinetic information may be obtained from single-channel measurements.

Additional Kinetic Components

In some cases, the kinetic behavior of the channels appears to be more complex than a simple model may predict. For example, some channels show additional state-dependent transitions that appear as slow changes in open probability or multiple stages in recovery from inactivation. In this case more insight can be gained by examining single-channel currents using the same protocols described above. The incorporation of additional kinetic components requires some care and can be done either as an adjustment to an existing model or by treating the kinetic components as if they arose from a separate population of independent channels.

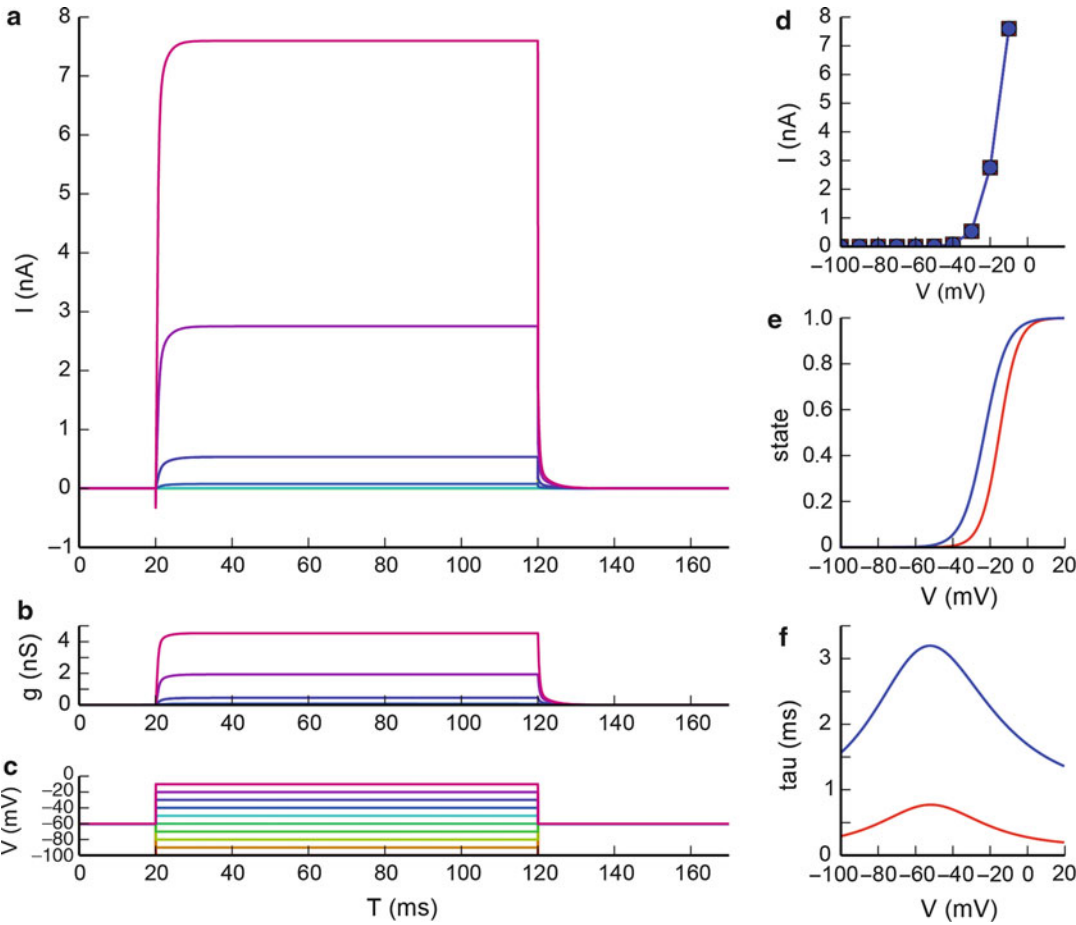
Computation of Models

There are several approaches that can be used for the computation of the models. The first, and most common, is to express the channel kinetics as a set of coupled differential equations and to solve those equations numerically for forcing functions that change the voltage. This is the approach used

in the examples that are shown below. A second, which can give insight into the structure of the model, is to use the Q-matrix formulation (Colquhoun and Hawkes 1995). Q matrices are useful for examining state changes in response to step perturbations. The simulations shown in Figs. 1–10 were computed using NEURON (www.neuron.yale.edu), with Python. The equations for the channels are from Rothman and Manis (2003b). For simulations with action potentials, a model of the NaV1.1 sodium channel (Barela et al. 2006) was incorporated into the model.

Examples of Delayed Rectifier Models

Example 1 Figure 1 shows an example of a voltage clamp simulation of a delayed rectifier potassium conductance, using the description of Rothman and Manis (2003a, 2003b). This is a “high-voltage” activated delayed rectifier. The voltage clamp command voltages are shown in Fig. 1c, and the resulting currents are shown in Fig. 1a, for steps up to 0 mV. The current grows nonlinearly with voltage. The channels activate rapidly, and current through the channels is sustained during the 100 msec voltage step.



Delayed Rectifier and A-Type Potassium Channels, Fig. 1 Currents and conductances for delayed rectifier potassium conductance

A tail current is visible at the end of the step (at 120 ms). Figure 1b shows the conductance of the potassium channels during the voltage step. Figure 1d shows the steady-state current-voltage relationship of the currents in Fig. 1a. The channels begin to open near -40 mV, and once activated, the currents become large with increasing voltage. Figure 1e shows the gating variables, which range from 0 to 1. There are two activation gating variables in this model, corresponding to a rapid activation (in red), and a small component with slower activation (in blue). The activation rates, as a function of voltage, are plotted in Fig. 1f for this model.

This delayed rectifier is typical of the channels that help repolarize action potentials in cortical interneurons and neurons of the auditory pathway and is associated primarily with the Kv3 (Kv3.1, Kv3.2) family of potassium channels. Note that the conductances do not activate until nearly -40 mV.

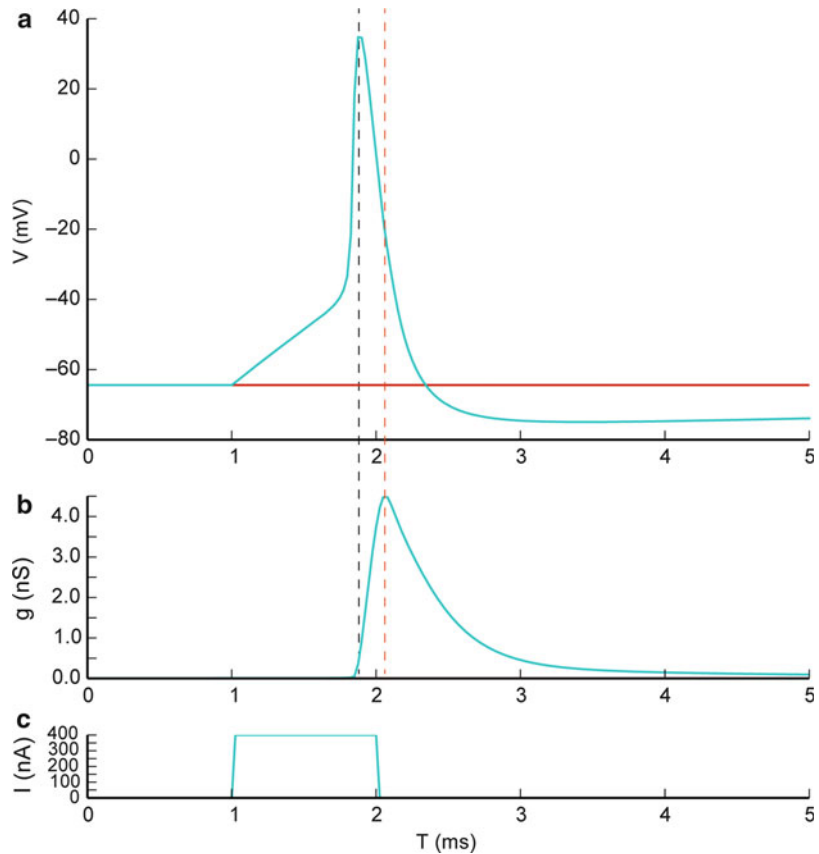
This high activation voltage suggests that the conductances will not play a role in the integration of synaptic events, but are only triggered when action potentials occur.

Figure 2 shows the time course of the delayed rectifier channel activation during an action potential, in current clamp. The current begins to activate near the peak of the action potential (indicated by the black dashed line) and reaches its peak (indicated by the red dashed line) about halfway down the falling phase of the action potential. Thus, the delayed rectifier can help repolarize action potentials.

This conductance does not show inactivation and deactivates very rapidly. Therefore, it should be available to repolarize action potentials with nearly the same conductance every time. This ability is illustrated in Fig. 3, where a high-frequency train of action potentials is elicited by

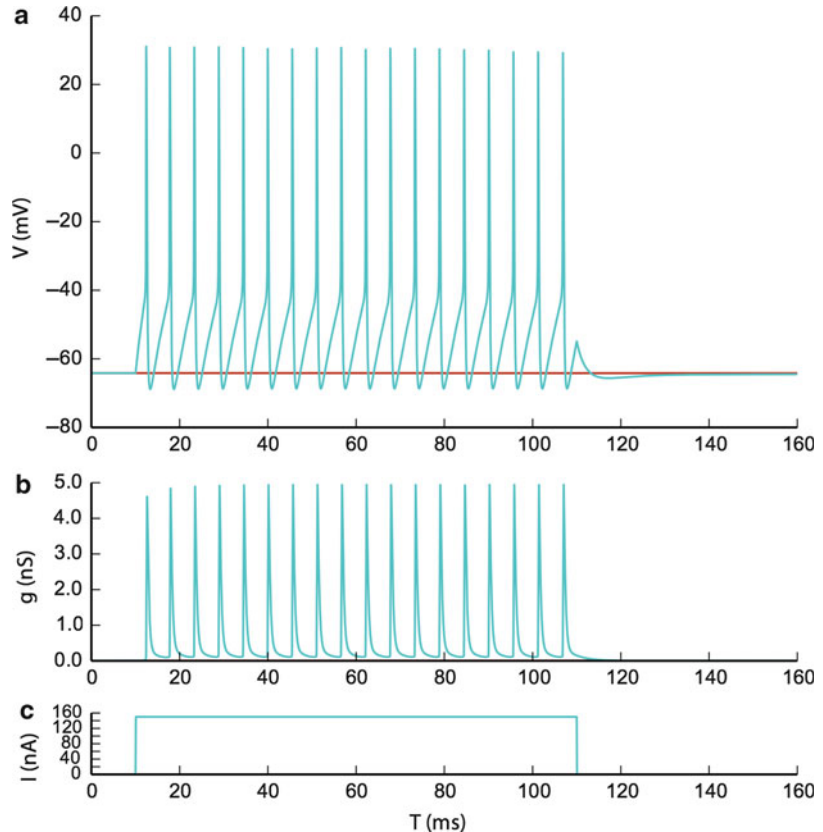
Delayed Rectifier and A-Type Potassium Channels,

Fig. 2 Activation time course of delayed rectifier channels during an action potential



Delayed Rectifier and A-Type Potassium Channels, Fig. 3

Delayed rectifier that activates in nearly the same way for every action potential in a high-frequency train

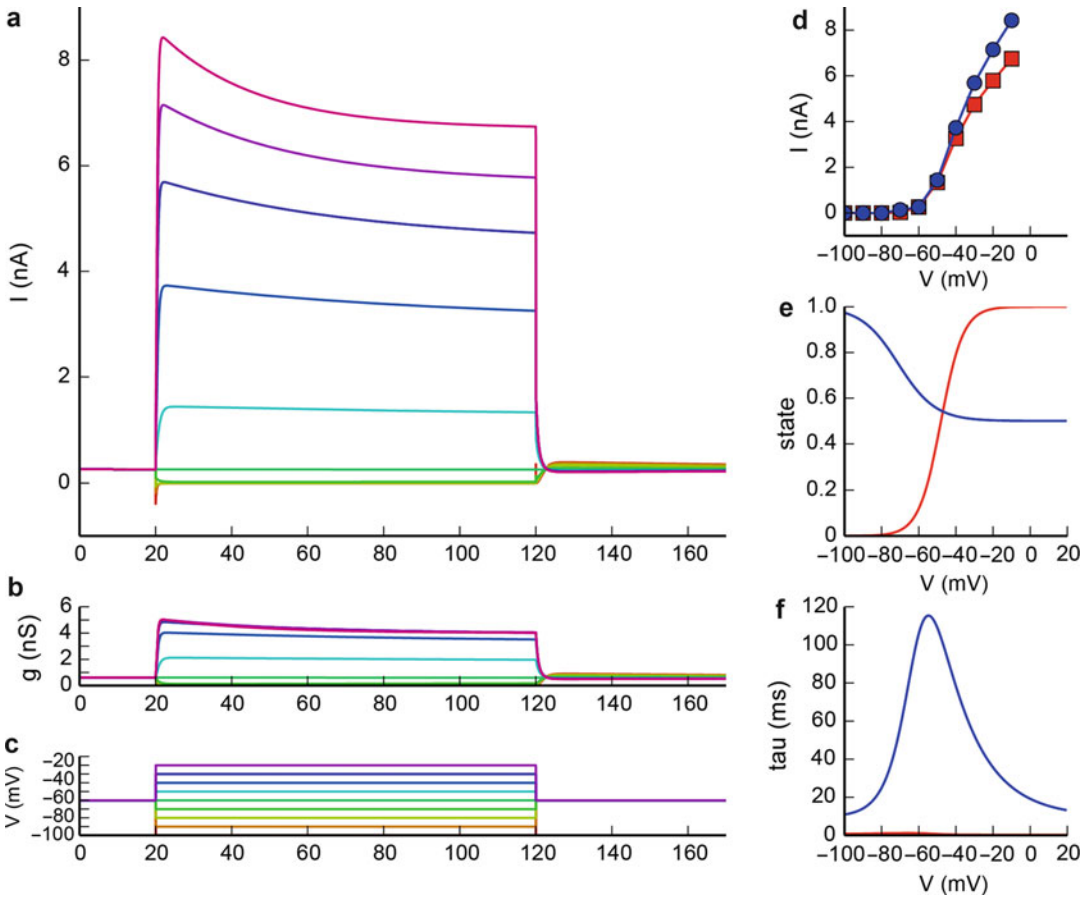


a depolarizing current pulse. The potassium conductance, plotted in Fig. 3b, is nearly the same for each action potential. The slightly smaller current associated with the first action potential is related to initial conditions and the presence of other channels in the model that affected the action potential width very slightly.

Example 2 The delayed rectifier class of channels shows variability in the activation voltage range and in the amount of inactivation that can occur. The channels in Example 1 represent one part of the spectrum and have a relatively high-voltage threshold and no inactivation. However other channels have a much lower activation-voltage range and show some inactivation. For example, the channels that help repolarize action potentials at the nodes of Ranvier in axons are largely composed of Kv1 family channels (Rasband 2010). These channels are also found in the cell bodies of some neurons, where they

play a role in the integration of synaptic events and regulate discharge patterns. As an example of these channels from this group, simulations are shown in Fig. 4 for voltage clamp of the low-voltage activated potassium conductance found in neurons of the auditory brainstem, which are composed of various mixtures of Kv1 subunits.

There are several features of the voltage clamp currents in Fig. 4a that are important to identify. First, with the model cell held at -60 mV, there is a slight outward current (visible from 0 to 20 ms). This current arises because these channels have a significant open probability at this voltage, which is close to the resting potential of typical neurons. Second, with depolarization, the current activates rapidly, but then begins to inactivate. However, the inactivation is slow and incomplete. Third, hyperpolarizing pulses turn the conductance off. At the end of a hyperpolarizing pulse, the conductance activates again, and because some of the inactivation has



Delayed Rectifier and A-Type Potassium Channels, Fig. 4 Delayed rectifier with incomplete inactivation and low activation-voltage range

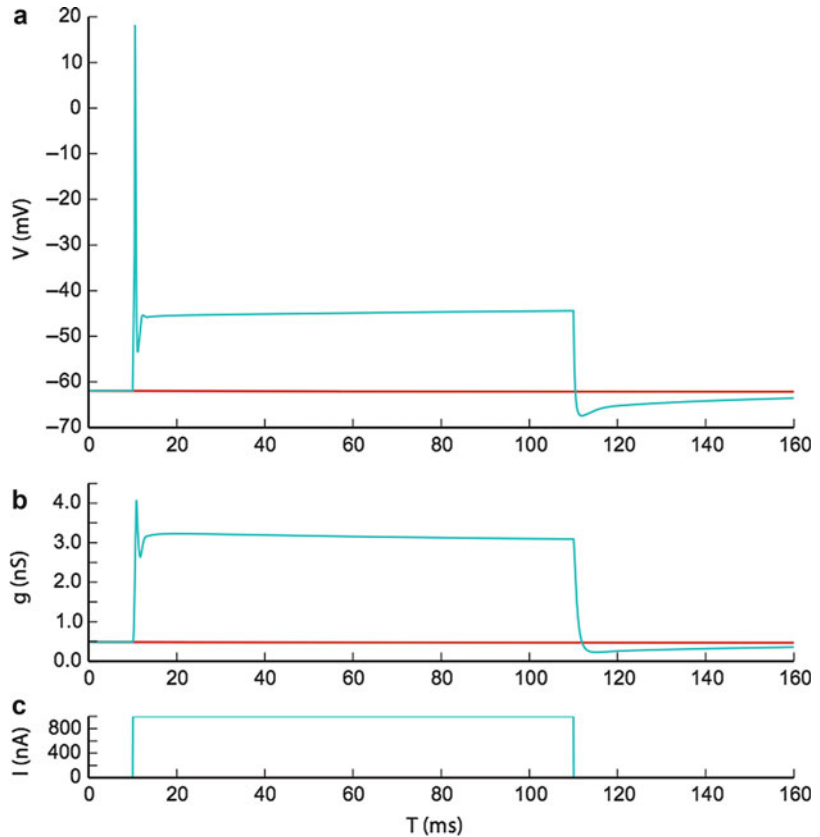
been removed by the hyperpolarization, the current shows a slight peak before settling to a new equilibrium. This rebound is visible in the slight outward current between 125 and 150 ms. These features are also all visible in the conductance traces in Fig. 4b. Figure 4d shows the peak (blue) and steady-state (red) currents as a function of voltage, showing how the inactivation increases with more depolarized steps. The activation and inactivation state variables are plotted in Fig. 4e. Note that near the resting potential (-60 mV), the activation curve is already at 5–10% of the channels “open,” while the conductance is fully activated by -20 mV. Figure 4f shows the activation rate (in red), which is very fast, and the slower inactivation rate in blue. These curves have the typical voltage dependence, where the time

constants are slowest near the resting potential of the cells.

These low-voltage activated conductances often prevent cells (and axons) from firing repetitively during depolarization. This feature is illustrated in Fig. 5a. A large depolarization can initiate a single spike, and the rapid activation of this conductance (Fig. 5b) contributes to the repolarization of the action potential. In addition, the activation of the conductance generates a sustained shunting current that prevents subsequent action potentials. The voltage during the current pulse in Fig. 5a represents an equilibrium between the depolarization caused by the current step (Fig. 5c) and the outward, hyperpolarizing current generated by the conductance (Fig. 5b). This single-spike firing pattern is also typical of models using the standard

Delayed Rectifier and A-Type Potassium Channels, Fig. 5

Low-voltage activation range of some delayed rectifier channels that can suppress repetitive firing



Hodgkin-Huxley delayed rectifier, which has a similar activation voltage close to the resting potential. Note that the membrane depolarizes slightly during the current pulse, as the slow inactivation of the conductance proceeds. Cells that express high levels of this conductance are sensitive to the slope, not just the amplitude, of synaptic potentials, and the conductance can prevent action potentials from being elicited by slow depolarizations. In addition, because the conductance is active at the resting potential, cells tend to have short time constants.

Finally, we can consider the states of the channels, as a useful reminder that the total conductance is an equilibrium condition across a population of channels and that the channels exist in more than just two states (open and closed). In the Hodgkin-Huxley formulation, the activation of a channel requires a series of energetic transitions across a set of four closed states, culminating in the open state. At any given voltage, the channels are distributed across these states, in different proportions. Using the Q-matrix formulation

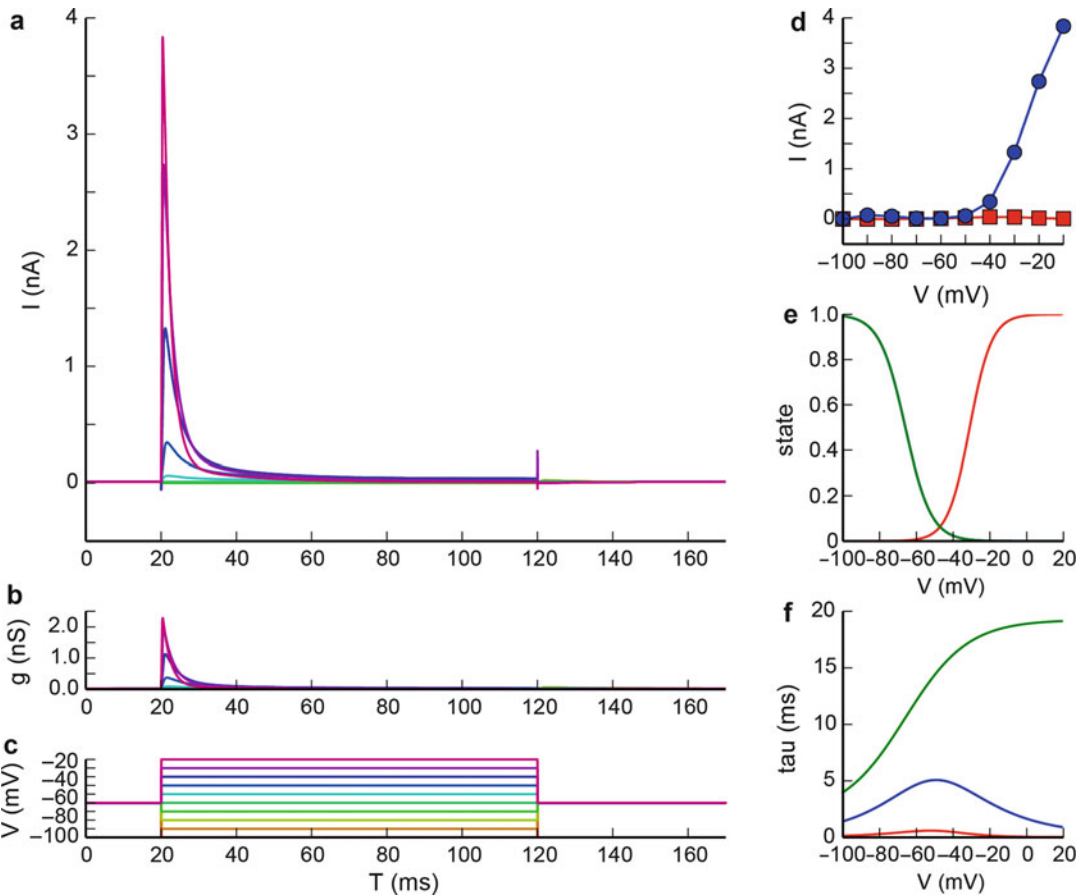
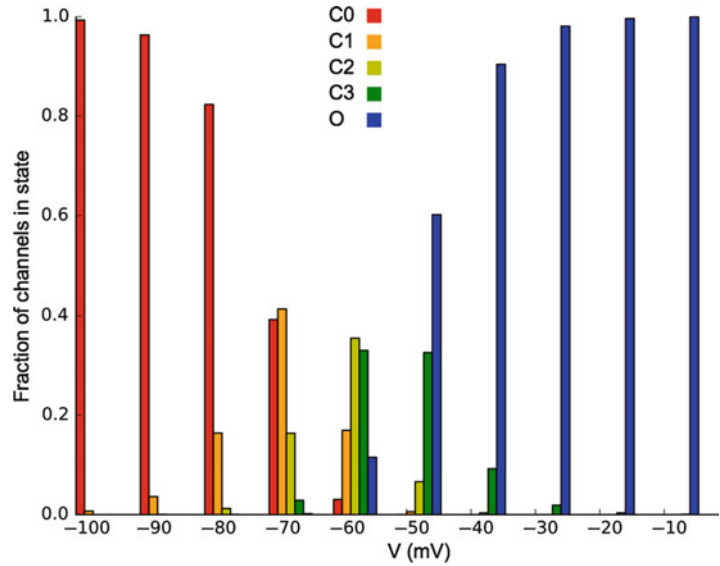
(Colquhoun and Hawkes 1995), we can easily see at equilibrium what this distribution is like for any given state, as shown in Fig. 6. This figure shows the distribution of channel subunit states for the model:

$$C_0 \rightleftharpoons C_1 \rightleftharpoons C_2 \rightleftharpoons C_3 \rightleftharpoons O$$

where each of the C_n refers to a population of subunits (e.g., four subunits in the “closed” state at C_0 , three at C_1 , etc.) and O refers to the open (conducting) state. Thus, at -100 mV, nearly all of the subunits are in the C_0 state, while at -20 mV, nearly all are in the O state. The voltages near rest (-70 to -50) are interesting. Here, we see that the channel subunits are in a different equilibrium, with a high probability of subunits being in the C_2 or C_3 state. Channels with subunit state distributions like this will activate very rapidly, and the activation may appear to be first order, rather than sigmoidal as might be expected. This is particularly true at -60 mV, where about 10% of the channels are

Delayed Rectifier and A-Type Potassium Channels,

Fig. 6 Residence of channel states in a multistate model that is voltage dependent



Delayed Rectifier and A-Type Potassium Channels, Fig. 7 Voltage clamp model of A-type (transient potassium) currents, based on channels from Rothman and

Manis (2003b). This channel has two different voltage-dependent inactivation rates (visible in F with different colors)

open, while just over 30% are in the C_3 state. The channels in the C_3 state only have to go through a single energetic transition to reach the open state, and thus the activation will be immediate and take on a single-exponential shape. The channels in the C_2 state (~35%) will also transit into the C_3 and O states, with those reaching the O state doing so with a second-order exponential activation (sigmoidal) function. This state-based approach is conceptual but also very useful in thinking about how channels activate or deactivate and in understanding channel behavior in the important voltage range at the cusp of activation.

Examples of A-type Potassium Channel Models

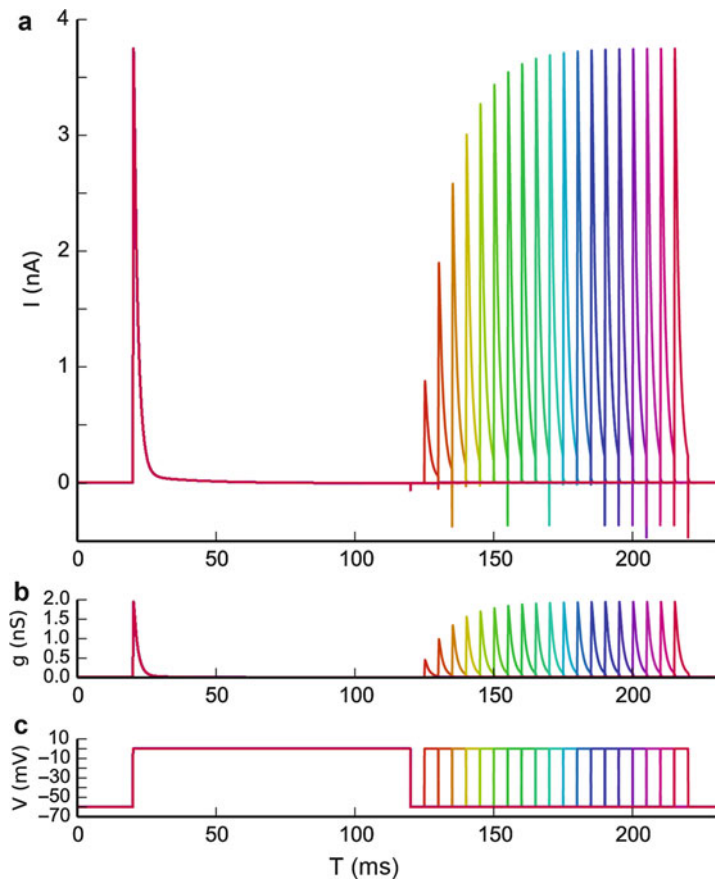
The transient potassium conductances can be modeled in the same way as the delayed rectifiers,

but with the addition of a term that describes the rate at which the channels inactivate. Inactivation was discussed briefly above with respect to low-voltage activated channels. Modeling inactivation requires the addition of a state variable and its rate constants as a function of voltage. Typically, an inactivating conductance is represented as

$$g(t, V) = g_{\max} * a(t, V)^n * b(t, V)$$

where $g_{\max}$ is the maximal conductance, a represents the activation state variable, and b is the inactivation state variable. The time evolution of a and b is computed in the same way as described for delayed rectifiers (or the Hodgkin-Huxley sodium channel), taking into account the instantaneous rates as a function of voltage. This formulation is equivalent to adding an inactivating state, but does not ascribe a particular mechanism to inactivation. Nonetheless, it often

Delayed Rectifier and A-Type Potassium Channels, Fig. 8 Time course of recovery from inactivation of A-type potassium channel model using a two-pulse paradigm



provides an acceptable description of channel behavior under a variety of conditions.

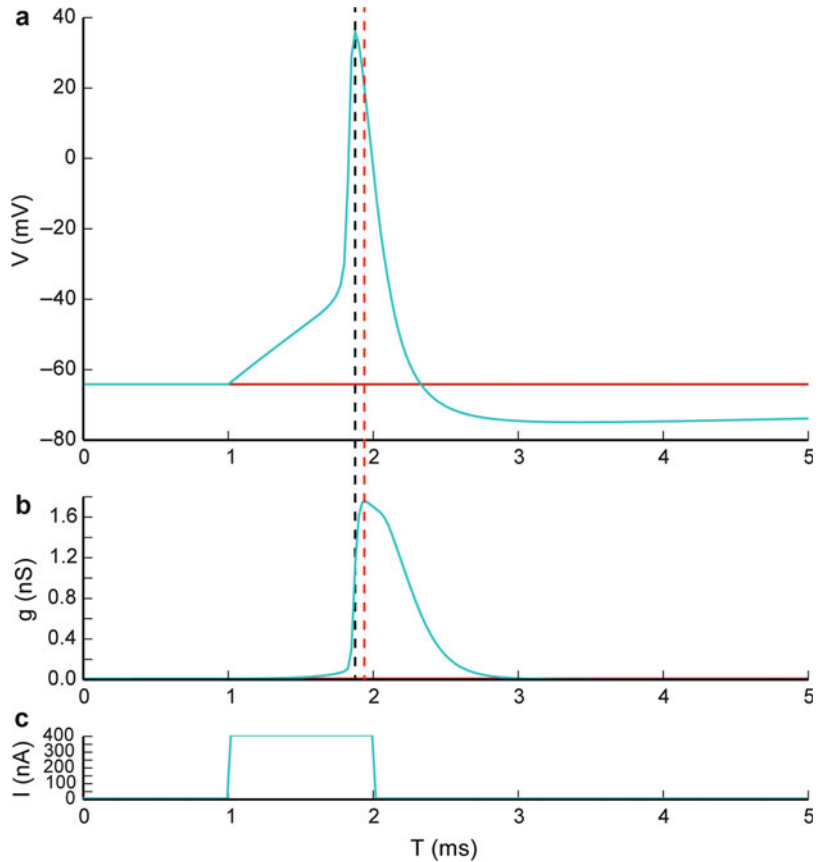
The response of a voltage-clamped cell with a rapidly inactivating potassium current (from Rothman and Manis 2003a, b) is shown in Fig. 7. Activation with depolarization is fast (Fig. 7a), but inactivation begins immediately, shutting off the conductance (Fig. 7b) and decreasing the current until the channels are nearly completely off. The peak activation is similar to that of the delayed rectifier (Fig. 7b), but the steady-state current shows only a small hump in the middle of the voltage range. The steady-state activation and inactivation curves are shown in Fig. 7e. Note that there is overlap of the curves in the -60 to -40 mV range. This overlap creates a “window” current, which causes the hump in the steady-state relationship in Fig. 7d. In this range, the channels both activate and inactivate, but there is a finite probability that some channels will be in

the open state at any time. The rate constants are shown in Fig. 7f. This particular version of the A-current had a second slow inactivation component, whose unusual voltage dependence is shown by the green curve.

After inactivation, the channels require some time at a hyperpolarized voltage to recover and become available for activation again. This is illustrated in Fig. 8a. A 100 ms voltage clamp step to -10 mV is followed at a variable delay by 10 ms steps to 0 mV. As the delay increases, the channels recover from the inactivated state, eventually reaching the same conductance that they did when activated from -60 mV. The recovery is quite fast and essentially proceeds with a single-exponential time course, beginning at the instant of repolarization. Recovery proceeds more quickly with deeper hyperpolarization between the conditioning 100 ms step and the test step.

Delayed Rectifier and A-Type Potassium Channels, Fig. 9

Time courses of A-type potassium conductance during an action potential. The activation is similar to the delayed rectifier in Fig. 2. Note that the action potential is also being repolarized by the delayed rectifier in this model



Like the delayed rectifier, the activation of the transient currents begins near the peak (Fig. 9a) of the action potential, after which the channels close quickly (Fig. 9b). During trains of action potentials, recovery from inactivation depends on the depth of the spike after hyperpolarization and the interspike interval. Thus, the contribution of transient potassium currents is highly dependent on multiple factors. In Fig. 10, a train of action potentials (Fig. 10a) is associated with variable activation of the transient current. The transient conductance decreases during the train, as channels are inactivated and there is not sufficient time for full recovery from inactivation between successive action potentials.

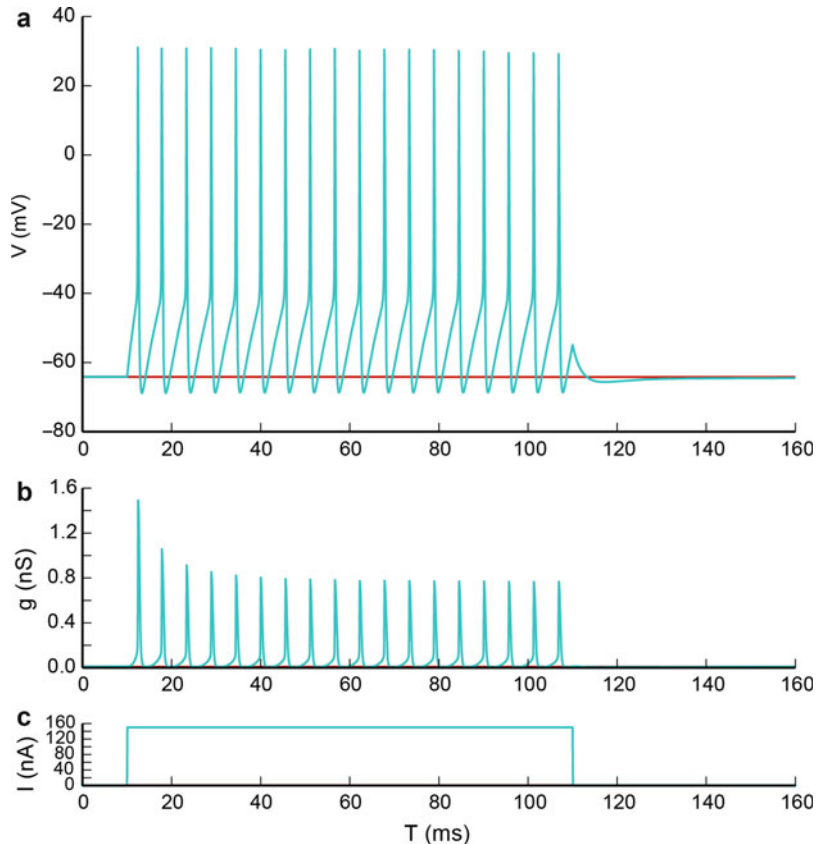
Biological Significance

The variety of potassium conductances contributes to a rich repertoire of firing patterns among

neurons. The details of the voltage dependence of activation and inactivation, as well as the voltage dependence of rates, all play into the functional contributions of the channels. While the repolarization of action potentials is one important function, the A-type channels in particular can have a complex effect on spike latency in many cells. Channels with a relatively negative activation and inactivation that are significantly modulated by small changes in membrane potential near and below rest are especially poised to interact with synaptic potentials and to regulate spike discharge patterns and spike latency (Kanold and Manis 1999). Indeed, interesting nonlinearities and bifurcation behavior of the spike patterns have been seen and analyzed (Meng et al. 2011). As the relative timing of spikes in neurons, even on a millisecond scale, is thought to be important in the representation of information, mechanisms that can modulate that timing are likely to play

Delayed Rectifier and A-Type Potassium Channels,

Fig. 10 Activation of A-type potassium conductance during a train of action potentials. Note that the conductance decreases during the train because of inactivation



important roles in how information is integrated in downstream neurons.

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Delay-Induced Transient Oscillation (DITO) and Metastable Behavior

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Definition

Delay-induced transient oscillations (DITOs) are oscillations that occur in bi- or multi-stable system of delayed differential equations as it

converges to one of its stable equilibria, oscillations that do not exist when the delay vanishes.

Metastable oscillations are transient oscillatory patterns (or states) that attract neighboring initial conditions and last for a “long time” almost without change. These oscillatory patterns seem to be stable: to detect their instability, it is necessary to observe the system over a seemingly endless time window. Such long-lasting transients would be undistinguishable from (nearly) periodic solutions. A mathematical definition of metastability needs a quantification of “long time”. The most common approach is to consider a one-parameter family of systems and to compare the transient time duration for different values of the parameter. For instance, if $\varepsilon > 0$ is a real parameter, then an oscillatory pattern is said to be metastable if the time duration of the transient oscillations grows exponentially as $\varepsilon \rightarrow 0$.

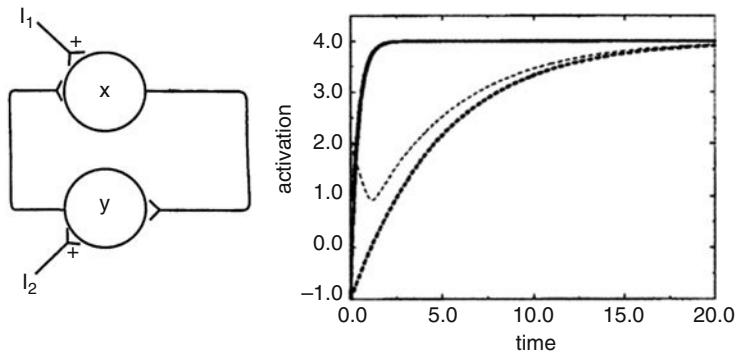
Long-lasting DITOs could be very important in understanding the dynamics of the system.

Detailed Description

Delays are ubiquitous and have many different sources. In neurons the delay corresponds to the time it takes for a signal to be transmitted (see entry ► “[Time-Delayed Neural Networks: Stability and Oscillations](#)”). Experimental studies of the behavior of self-connected single neurons have shown that the discharge pattern of biological neurons (Vibert et al. 1979; Diez-Martínez and Segundo 1983) can be influenced by the delay. Different ranges of delay correspond to different patterns of neural activities (an der Heiden 1981; Plant 1981; Chapeau-Blondeau and Chauvet 1992; Lourenço and Babloyantz 1994; Vibert et al. 1994; Menon 1995; Hangartner and Cull 1995; Pakdaman et al. 1996).

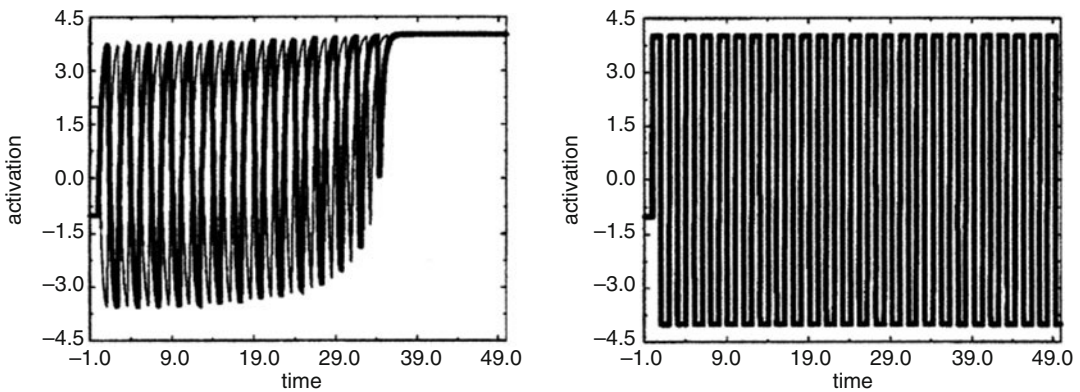
In some artificial neural network (ANN) applications, such as content addressable memories, information is stored as stable equilibrium points of the system. Retrieval occurs when the system is initialized within the basin of attraction of one of the equilibria and the network is allowed to stabilize in its steady state (Hopfield 1984; Hirsch 1989; Foss et al. 1996). Delayed interunit

transmissions may render some equilibria unstable, thus deteriorating information retrieval. Many studies have derived conditions that ensure that the asymptotic behavior of networks with and without delay is similar. (i) The system with delay and the system without delay should have exactly the same stable equilibria (the delay does not alter local stability). (ii) The system without delay and the system with delay are both almost convergent, so that the delay does not induce spurious stable undamped oscillations. Constraints (i) and (ii) avoid delay-induced changes in the asymptotic behavior of the system. Yet, even under such constraints, the delay may still influence important features in the system’s dynamics. For instance, the delay can alter the boundary of the basins of attraction of the stable equilibrium points of the network as shown in Pakdaman et al. (1998a). Moreover, the delay can also produce transient oscillations that end up vanishing with time. In Pakdaman et al. (1997a, 1998a), it was studied the influence of the delay on the behavior of a network composed of graded-response neurons (GRNs) forming a ring where each unit is connected unidirectionally to the next one. The GRN has constant decay rate, and its output is a sigmoidal function (for instance, tanh function) that depends on its activation. The connection is said to be *excitatory*, when the sigmoidal function is increasing, and it is said to be *inhibitory* when it is decreasing. The GRN ring network satisfies the constraints (i) and (ii), so the system will converge to one of its equilibrium points if the interunit connections are instantaneous or delayed. However, the transient regime of the system with instantaneous interunit transmission greatly differs from that of the system with delayed interunit transmission. In the case of a pair of interconnected GRNs sketched in Fig. 1, when the connections are instantaneous, the system evolves rapidly (without oscillations) to the equilibrium which basin of attraction contains the initial condition. The smaller the decay rate (charge-discharge time) of the neurons, the faster it will reach the equilibrium: the time evolution of the neuron activation x , y , represented by the solid line in Fig. 1 (graph on the right), corresponds to a pair



Delay-Induced Transient Oscillation (DITO) and Metastable Behavior, Fig. 1 Left: sketch of the system formed by two interconnected GRN (I_1 and I_2 are external inputs). Right: temporal evolution of the neuron activation

x, y in the case of identical neurons ($I_1 = I_2$) with instantaneous connections. The smaller the decay rate (charge-discharge time) of the neurons (solid line), the faster it will reach the equilibrium



Delay-Induced Transient Oscillation (DITO) and Metastable Behavior, Fig. 2 Transient oscillations when the interunit connections are delayed. The larger the delay, the longer the duration of the transient. Time is

measured in units of delay. Left: thick and thin lines represent the activations x and y , respectively. Right: larger delay, only the activation x is displayed

of neurons with decay rate smaller than the decay rate of the pair of neurons corresponding to the dashed lines in Fig. 1 (thick dashed line represents activation x ; thin dashed line represents activation y).

When the connections are delayed, the GRN activation will oscillate before converging to the equilibrium point as shown in Fig. 2 for two values of the delay. As the delay increases, the longer is the duration of the oscillations of the activations x and y . Also, as displayed in Fig. 2, the shape of the transient oscillations assumes a square-wave-like shape for large delays, the square-wave-like oscillations outlasting the

observation window. Only the a priori knowledge that the point is in the basin of attraction of one of the equilibria allows us to state that these oscillations are transient. In Pakdaman et al. (1998b), the term DITO was coined for this phenomenon both as an acronym for “delay-induced transient oscillation” and as a means to emphasize its repetitive nature.

A ring network of GRN is inhibitory only if it has an odd number of inhibitory connections. Therefore, a pair of two interconnected GRNs is excitatory when both connections are excitatory (like in Pakdaman et al. 1997a, 1998b) or both inhibitory (like in Milton et al. 2010). So the time

evolution of the activations x and y , displayed in Figs. 1 and 2, describe the behavior of a pair of reciprocally excitatory neurons or a pair of reciprocally inhibitory neurons.

Experimentalists have long recognized the importance of transients in neural behavior as a means to convey information about environmental as well as internal changes (e.g., Segundo et al. 1994). Long-lasting DITOs could strongly alter the dynamics of the system and, for instance, interfere with information retrieval in neural networks. The information contained in the transient regime is all the more important when the system evolves in rapidly changing environments where the neural networks involved in information processing do not dispose of the time lapse necessary to reach a stationary regime. Overall oscillatory patterns are frequently observed in the activity of nervous systems. Their roles are either clear as in respiration, where they control motor activity, or unexplained as in the electroencephalogram where they are apparently related to the brain information processing in a still obscure way. Oscillatory patterns are observed when units discharge periodically and synchronously. In living nervous systems, delays are ubiquitous, ranging from a few to several hundreds of milliseconds. They are due to action potential propagation along axons, synaptic delay, etc. Delay-induced long-lasting transient oscillations could thus take part in various nervous system operations: epileptic seizure, for instance, could be due to a DITO (see Milton et al. 2017 and entry ► “Dynamics of Disease States: Overview”). In ANN applications relying on the convergence of the network to a steady state, control over the transient regime is also an important issue. Large increase in the transient regime duration can seriously deteriorate the network performance by slowing down the system.

Example 1

Consider the following system of a single delayed differential equation

$$\frac{da}{dt}(t) = -a(t) + \tanh[2a(t - \tau)], \quad (1)$$

where the delay $\tau \geq 0$ is constant. This equation is used to describe a single neuron with delayed self-

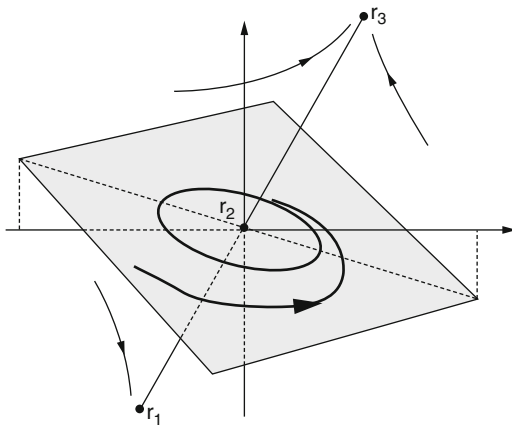
excitatory positive-feedback connection. This equation has three equilibria: $a = a_- < 0$, $a = 0$, and $a = a_+ > 0$. If $\tau = 0$ then the equation is an ordinary differential equation without delay. In this case, if the initial condition $a(0) = a_0$ is strictly negative (positive), then the solution converges to a_- (a_+). So, all solutions but $a = 0$ converge to either a_- or a_+ , and the system is said to be bistable. The equilibrium point $a = 0$ is the boundary of the basin of attraction of a_- and a_+ . If $\tau > 0$, the initial condition is a continuous function $a_0: [-\tau, 0] \rightarrow \mathbb{R}$ that gives the history of the variable a up to time $-\tau$ (beyond $-\tau$ past cannot affect future). In this case the equation has a delay, and the space of initial conditions is infinite dimensional. It is possible to show (see Pakdaman et al. 1997b and references therein) that the system with delay is still bistable and most solutions converge to either equilibrium a_- or equilibrium a_+ . The difference to the case $\tau = 0$ is that the boundary of the basins of attraction of a_- and a_+ is an infinite dimensional set in the space of initial conditions. Any solution that starts at the basin boundary must oscillate forever either with a vanishing amplitude, as the solution tends to the unstable equilibrium $a = 0$, or with a finite amplitude, as the solution tends to an unstable periodic orbit which is in the basin boundary (see illustration in the Fig. 3). DITOs appear whenever the initial condition a_0 changes sign within the interval $[-\tau, 0]$ in a way that a_0 is close to but not in the basin boundary. These are the delay-induced transient oscillations (DITOs).

Example 2

The space of initial conditions of Eq. (1), $a_0: [-\tau, 0] \rightarrow \mathbb{R}$, changes with the delay parameter τ . When the goal is to analyze the dependence of the solution on the delay, it is convenient to fix the space of initial conditions to $a_0: [-1, 0] \rightarrow \mathbb{R}$ by rescaling time as $t = \tau s$. Eq. (1) becomes

$$\varepsilon \frac{da}{ds}(s) = -a(s) + \tanh[2a(s - 1)], \quad (2)$$

where $\varepsilon = 1/\tau > 0$. The time duration of the transient oscillations of Eq. (2) increases as ε decreases (τ increases). These oscillations last



Delay-Induced Transient Oscillation (DITO) and Metastable Behavior, Fig. 3 Schematic phase portrait representation of the boundary of the basins of attraction of the delayed self-excited neuron (Eq. 1). The gray surface represents the boundary separating the basins of attraction of the two stable equilibria $r_1 = a_-$ and $r_3 = a_+$. The boundary contains the unstable equilibrium $r_2 = 0$, together with an unstable closed orbit. Some solutions are transiently attracted to the oscillatory solutions on the boundary before approaching one of the stable equilibria $r_1 = a_-$, $r_3 = a_+$.

for times of order $\exp(c/\varepsilon)$, for some $c > 0$, as $\varepsilon \rightarrow 0$ (see Pakdaman et al. 1997b; Grotta-Ragazzo et al. 2010), so they are said to be *metastable*. In terms of the original time t , the metastable oscillatory pattern persists for a time of the order $\exp(c\tau)$. When ε is small enough, the metastable oscillatory pattern is close to a square-wave function (see Fig. 2, right panel).

DITO and the Boundary of the Basins of Attraction: Mathematical Tools

DITOs appear in various systems of delayed differential equations: one equation (Pakdaman et al. 1997b; Pakdaman and Malta 1998), two equations (Pakdaman et al. 1998b), and many equations (see Pakdaman et al. 1997a and entry ► “Time-Delayed Neural Networks: Stability and Oscillations”). In all these systems, almost all initial condition leads to a solution that converges to a stable equilibrium point. DITOs are generated by initial conditions close to the boundary of the basins of attraction, as in the

case of Eq. (1). So, the geometric understanding of DITO is related to the geometric understanding of the boundaries of the basins of attraction of the equilibria. The boundary of the basins of attraction of simple systems with a few stable equilibria may be very complicated. (For instance, for almost all initial condition, Newton’s method converges to one of the three roots of the complex polynomial $z^3 - 1 = 0$. The boundary of the basin of attraction of each attracting fixed point has the “Wada property,” namely, a point is in the boundary of one of the basins of attraction if, and only if, it is simultaneously in the other two basin boundaries.) So it is remarkable that it is possible to geometrically describe the boundary of the basin of attraction of delay differential equations (Pakdaman et al. 1997b, c, 1998a, 1999).

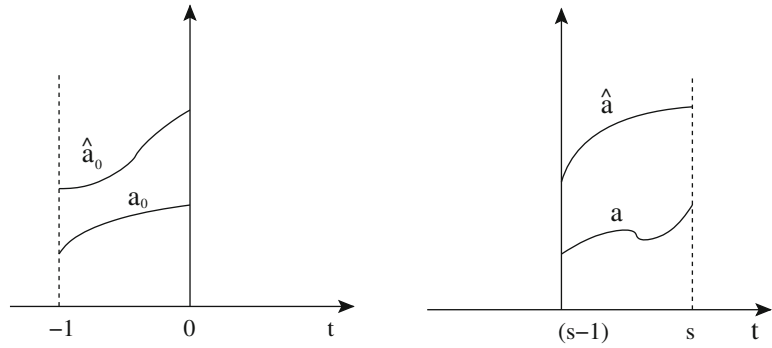
The mathematical property that allows for this description is the monotonicity of the semiflows generated by the equation. This property means that Eq. (2) (see Pakdaman et al. 1997b) is order preserving: if $a_0: [-1, 0] \rightarrow \mathbb{R}$ and $\hat{a}_0: [-1, 0] \rightarrow \mathbb{R}$ are two different continuous initial conditions such that $\hat{a}_0(\eta) \geq a_0(\eta)$ for $\eta \in [-1, 0]$, then for $s > 2$ the solutions $\hat{a}$ and a satisfy $\hat{a}_0(s + \eta) > a(s + \eta)$ for all $\eta \in [-1, 0]$. This is illustrated in Fig. 4. This order-preserving property implies that for a given continuous function $a_0: [-1, 0] \rightarrow \mathbb{R}$, the initial condition $a_0 + c$, where c is a real constant, generates a solution to Eq. (2) that converges to the equilibrium a_+ , if c is sufficiently large, or converges to a_- , if c is sufficiently small. Moreover, for a unique value of c , it converges neither to a_- nor to a_+ but remains oscillating in the boundary of the basin of attraction of a_+ and a_- . So the basin boundary is a subset of the set of initial conditions that is transversal to the one-dimensional subspace of constant functions in $[-1, 0]$. Similar ideas are used to describe the boundary of the basins of attraction for systems with two or more equations.

Are DITOs Always Metastable?

The answer is no. DITOs seem to appear very often in multi-stable delay equations, but the

Delay-Induced Transient Oscillation (DITO) and Metastable Behavior,

Fig. 4 Illustration of the order-preserving property



oscillations do not necessarily persist for a time t of the order of $\exp(c\tau^\beta)$, for some constants $c > 0$ and $\beta > 0$, as $\tau \rightarrow \infty$. The mathematical question of existence of metastable solutions is delicate as the following examples show. Consider a scalar equation of the form

$$\varepsilon \frac{da}{ds}(s) = -a(s) + f(a(s-1)). \quad (3)$$

Let us assume that

$f(a) = l$ if $a < 0$ (left value), $f(0) = 0$, $f(a) = r$ if $a > 0$, (right value).

If $l < 0$ and $r > 0$ (positive feedback), then the equation is bistable with two attracting equilibria $a = l$ and $a = r$. Since f is a piecewise constant, function an explicit computation (Grotta-Ragazzo et al. 1999) shows that DITOs are metastable if, and only if, $-l = r$. If $l > 0$ and $r < 0$ (negative feedback), then the equation has a single attracting periodic orbit, which attracts most initial conditions, with period $p(\varepsilon) > 2$ and exactly two sign changes within a period (a “slowly oscillating periodic orbit”). In this case, DITOs are transient oscillatory solutions with more than two sign changes in a time interval of length 2. In contrast to the positive-feedback case, in the negative-feedback case, metastable DITOs always exist regardless of the values of l and r . When f is a smooth function, the mathematical analysis of the existence of metastable oscillations for Eq. (3) is difficult. In Grotta-Ragazzo et al. (2010), using “transition layer equations” (Chow and Mallet-Paret 1983), in the positive-feedback case ($\frac{df}{da} > 0$), it was possible to show that odd symmetry of the positive-feedback f is a sufficient

condition for the existence of metastable oscillations. However, the oddness of positive-feedback f is not a necessary condition for metastability as there are positive-feedback functions f that are not odd but satisfy instead a condition formulated in terms of transition layer solutions, for which metastable oscillations occur. In the negative-feedback case ($\frac{df}{da} < 0$), metastable oscillations always exist (see Grotta-Ragazzo et al. 2010 for details), provided a “slowly oscillating periodic orbit” exists.

Metastable oscillations were detected not only in scalar equations but also in systems (Pakdaman et al. 1997a, b, 1998b). In all these works, the existence of metastable oscillations was shown by both numerical investigation and theoretical analysis using symmetries of the equations. For scalar equations or systems, if f is smooth or not, the short-time stability of metastable oscillatory patterns is a consequence of the behavior of the system in the singular limit $\varepsilon = 0$ (the analysis of the singular limit is a classical idea present in several previous results, for instance, Chow and Mallet-Paret 1983; Ikeda and Matsumoto 1987; Sharkovsky et al. 1993).

In physics, metastable behavior is mostly related to phase transitions as some parameter (for instance, temperature) crosses some threshold value (Fusco and Hale 1989). In a bistable system, the phase transition value separates parameter regions where either one of the stable states dominates. In multi-stable complex networks modeled by differential equations with delay, the analysis of transient time duration may be an important and practical tool to detect important global changes in the system due to variation of a parameter that is not the delay. For instance, for the piecewise

constant f with fixed $l < 0$ and varying $r > 0$, metastable oscillations occur at $r = -l$, where the system has a reflection symmetry that interchanges the two equilibria. As the analysis in the positive feedback shows (Grotta-Ragazzo et al. 2010), at a phase transition threshold, the system does not have to exhibit an explicit symmetry like the oddness of the function f .

Conclusion

DITOs seem to appear quite often in multi-stable systems of delayed differential equations, for constant delay, and also for state-dependent delay (Pellegrin et al. 2014). The transient oscillations occur for initial conditions close to the boundary of the basins of attraction. The time duration of transient oscillations may be very long and, depending on the system, may increase exponentially with increasing delay. In this case DITOs could be misidentified as stable oscillations. Metastable patterns may appear at a particular value of a parameter of the system, and this can be an indication of a dynamical “phase transition” at that value.

Cross-References

- [Dynamical Systems: Overview](#)
- [Dynamics of Disease States: Overview](#)
- [Fitzhugh–Nagumo Model](#)
- [Multistability in Neurodynamics: Overview](#)
- [Multistability in Seizure Dynamics](#)
- [Multistability of Coupled Neuronal Oscillators](#)
- [Neural Decoding](#)
- [Slow Oscillations and Epilepsy: Network Models](#)
- [Time-Delayed Neural Networks: Stability and Oscillations](#)

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Delta Rhythms: Models and Physiology

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Synonyms

Slow oscillation; Slow-wave oscillation (SWO)

Definition

A high amplitude brain rhythm with frequency between 1 and 4 Hz.

Detailed Description

History

The term “delta” was first introduced by Walter in 1936 to describe frequencies below the alpha (9–11 Hz) band while attempting to diagnose tumors using EEG signatures (Walter 1936). He subsequently, with Berger, subdivided this band to include theta rhythms (between 4 and 8 Hz). Since then the presentation of delta rhythms has been shown to be variable in frequency and amplitude during sleep (Church 1975), and some observers subdivide delta further into delta1 (1–2 Hz) and delta2 (3–4 Hz); this may have some mechanistic validity given the different potential origins of the rhythm (see below, Weiss and Rappelsberger 2000).

Association with Brain State

Delta rhythms (1–4 Hz) are predominantly associated with deep sleep (stage N3). These sleep stages are manifest most strongly during the first few hours of sleep in humans, occurring iteratively in epochs of ca. 0.5–1.0 h, with decreasing power as sleep progresses (Campbell 2009). They have been linked to the consolidation of memories of consciously experienced events (Huber et al. 2004). However, it currently remains unclear how such memory consolidation may take place. The correlation with deep sleep is reinforced with observations of very large increases in delta rhythms following sleep deprivation and an association with narcolepsy.

Delta rhythms are also associated with certain forms of cognition during wakefulness. They are manifest during the processing of repetitive auditory sensory information (Lakatos et al. 2008), being precisely phase reset by entrainment to such inputs. This results in response gain enhancement and reaction time improves (Lakatos et al. 2008). Such a process is seen predominantly when there is a pattern of sensory input to entrain to. Without such predictable input, the lower frequency delta “carrier wave” becomes detrimental to cortical function and is actively suppressed in favor of a state of near-continuous

vigilance manifest as continuous high-frequency rhythms (Schroeder and Lakatos 2009).

Function

Little is known with certainty about what delta rhythms do in the brain. In general, slow-wave sleep is associated with consolidation of declarative memory – suggesting a role in modifying synaptic plastic changes induced during wakefulness by sensory input. This has led to the “synaptic rescaling” hypothesis – the restoration of a mean baseline of synaptic weights in the cortex (Tononi and Cirelli 2003, 2006). The type of plasticity seen during deep sleep appears to be dominated by long-term depression. Dopaminergic neuromodulation is very low during deep sleep, and, specifically, D1 receptor activation impairs long-term depression and enhances spike timing-dependent long-term potentiation (Xu and Yao 2010). Computational models predict that as delta rhythms decline during sleep, so does overall cortical synaptic strength (Riedner et al. 2007), and, experimentally, GluR1 receptor phosphorylation levels are potentiated during wakefulness and depressed after sleep (Vyazovskiy et al. 2008). From a synaptic dynamic point of view, activity in the delta frequency band in general facilitates depression (Staubli and Lynch 1990).

If delta rhythms do chaperone a synaptic depression process, which exact cortical representations are being attenuated? Sleep-associated slow rhythms in general have been proposed to be temporally discrete (hundreds of ms) fragments of wakefulness (Destexhe et al. 2007). Thus it is perhaps not surprising that brief, iterative epochs of sensory-/memory-associated cortical representations are somehow operated upon during delta (Peyrache et al. 2009; Riedner et al. 2007). By “cortical representation,” we mean here “defined sets of synapses and the neurons they interconnect.” Studies on delta rhythms generated experimentally in local circuits of association cortex have shown an iterative cycle of reciprocal interactions between superficial and deep cortical laminae (Carracedo et al. 2013). This type of switching between descending and ascending interlaminar interactions has been seen during

wake states on a slower timescale and more persistently during memory tasks: Coding of sensory inputs is associated with descending interlaminar communication, whereas the subsequent memory component of the task involves a switch to ascending interactions (Takeuchi et al. 2011). In addition, this pattern of activity closely matches the “Helmholtz machine” proposed by Hinton and colleagues as a general format for unsupervised learning (Hinton and Zemel 1994; Hinton et al. 1995). The mechanistic key to any selectivity in changing synaptic weights comes from the interaction of delta rhythms with theta oscillations. *More active neurons* generate outputs at the delta-nested theta frequency, which promotes or preserves synaptic weights (Larson et al. 1986), whereas *weaker activated* neurons fire only at the synaptic depression inducing delta frequency.

Mechanism

When considering experimental evidence for mechanisms underlying delta rhythms, it is important to clearly define the frequency band. Oscillations faster than 4 Hz in the neocortex are mechanistically distinct (from delta) when they coexist with such delta rhythms – the faster oscillations involve a different population of layer 5 pyramidal neurons from those generating the delta rhythm (Carracedo et al. 2013). Frequencies lower than 1 Hz are also seen with delta rhythms during very deep sleep but, again, appear to have different mechanisms (Steriade et al. 1990). In particular the dependence of very slow “up-/down-state” oscillations has been shown to be exquisitely sensitive to balance between fast synaptic excitation and inhibition, while delta rhythms are more robust in this respect (cf Carracedo et al. 2013 with Haider et al. 2006). This entry will consider delta rhythm mechanisms only. It will focus on a brief description of what is known about the thalamic and neocortical generators separately, though both clearly interact to produce the rich dynamic signatures associated with noninvasive recordings of in vivo brain function during slow-wave oscillations (Crunelli and Hughes 2010).

Thalamic Generator

A thalamic generator of delta (1–4 Hz), modified by sensory input, is seen in the thalamus (Amzica et al. 1992). This delta activity persists after disconnection of the thalamus from the cortex (Steriade et al. 1987) and can be seen in individual thalamocortical cells in a manner dependent on membrane potential (McCormick and Pape 1990). These authors showed a mechanism involving behavior of intrinsic membrane conductances (I_h and I_T , respectively, the anomalous rectifier and low-threshold, T-type, calcium conductance). Specifically, a window current generated by T-type calcium channels, formed by the overlap at around -60 mV between their steady-state activation and inactivation behaviors, has been well characterized (Pirchio et al. 1997; Hughes et al. 1999, 2002). Small perturbations in membrane potential around this window generate large signal amplifications and the rhythmic behavior typical of thalamic delta rhythms (Williams et al. 1994). The conditions in which expression of this intrinsic delta behavior is favored in vitro match the neuromodulatory state of the in vivo brain during deep sleep. Cholinergic and monoaminergic tone are very low during deep sleep, abolishing a tonic depolarized state in thalamocortical neurons (McCormick and Pape 1990) and facilitating activation of the window current.

Neocortical Generator

Some forms of delta rhythm have characteristics, suggesting a purely cortical origin (Amzica and Steriade 1998; Fell et al. 2002). During deep sleep, cortical delta rhythms can be generated locally (Vassalli and Dijk 2009), sometimes having dynamic properties consistent with discrete cortical region specificity (Vyazovskiy et al. 2011). In general the expression of delta in cortex shows strong nonuniformity – favoring the frontal-parietal axis (Ioannides et al. 2009).

Current source density measurements during sleep in experimental animals and humans reveal a strong source in superficial layers, suggesting that any synaptic drive underlying delta rhythms was located in these layers (Csercsa et al. 2010).

In contrast, targeted activation of deep layer pyramids strongly modulated slow-wave sleep rhythms, whereas targeted activation of superficial neurons did not (Beltramo et al. 2013). A potential resolution to this dichotomy came from in vitro models of local delta rhythms that showed a critical role for intrinsically bursting neurons in layer 5 of the parietal cortex (Carracedo et al. 2013). These neurons have cell bodies in upper layer 5 but also have tufted distal apical dendrites extending up through layers 1–3. Pharmacological manipulation of this model demonstrated a mechanism whereby interplay between slow GABA_B receptor-mediated inhibition and NMDA receptor-dependent synaptic excitation, and gap junctional excitation, was vital to delta generation. Intrinsically bursting neurons have high concentrations of these synaptic receptor subtypes out on their distal dendrites suggesting that whereas the synaptic connections that underlie the rhythm as an emergent property of local networks are located mainly in dendrites in superficial layers, the intense burst outputs of these neurons during delta arise from the somata of these cells in deep layers.

This experimental prediction for the core delta mechanism model is supported by observations showing that reduced gap junction conductance, or blockade of NMDA receptors, reduces slow-wave sleep and layer 5 neuron bursting (Armstrong-James and Fox 1988; Franco-Pérez and Paz 2009). In addition, generation of intense bursts from interneurons appeared to underlie the slow GABA_B receptor-mediated IPSP separating the active phase of each delta period, perhaps through volume conduction of GABA overspill from intensely active synapses and/or neurogliaform neuronal output (Oláh et al. 2009). However, a remarkable division of labor appears to exist in layer 5. While *intrinsically bursting* neurons participate in circuits generating delta, their outputs nest a theta generator centered around layer 5 *regular spiking* neurons. It is this nested theta output that provides the substrate for at least one set of “weights” in the Helmholtz analogy – those dictating the degree of reciprocal interlaminar interaction seen on each delta period.

Models

Thalamic Models

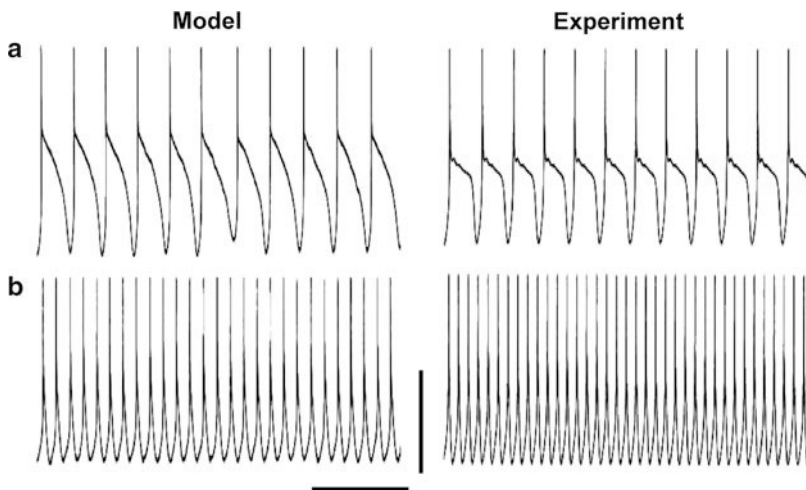
The intrinsic delta generator in thalamocortical neurons has been modeled extensively based on the interplay between a hyperpolarization-activated nonspecific cation current (I_h) and the transient low-threshold calcium current (I_T) (see Tóth and Crunelli 1992). In addition most model neurons possess a leak conductance and fast currents underlying sodium spikes (I_{Na} and $I_{K(DR)}$, Traub et al. 1991). In single-compartment models the steady-state values for activation and inactivation of I_T and I_h were critical in generating both the occurrence and frequency of delta rhythms and the transition from slow delta bursting to fast, continuous firing (Williams et al. 1997, Fig. 1). Using multicompartment models capturing the dendritic structure of thalamocortical cells, it has been shown that a distal dendritic location of these two currents was optimal for delta generation (Lytton et al. 1996) – a prediction with interesting consequences when considering the proximal vs. distal location of inputs to these neurons from ascending sensory streams and feedback corticothalamic neurons.

Further development of these thalamocortical models included interaction with GABAergic

neurons in thalamic reticular neurons. Neurons in the nucleus reticularis also show burst behavior at hyperpolarized membrane potentials with dependence on I_T . Coupling such neurons with model GABAergic synapses generated robust oscillations in the spindle frequency range (7–14 Hz) (Destexhe et al. 1998) and provides a compelling basic structure, when coupled to thalamocortical neurons, for interaction between spindling and delta rhythms seen in vivo.

Neocortical Models

In contrast to the dominance of intrinsic single-cell conductance interactions for the thalamic generator, a combination of (a) compartment-specific conductance expression and (b) the manifestation of the neocortical delta rhythm as an emergent property of local networks requires a more complex model structure to capture biological realism. The cortical column model of Traub et al. (2005) was modified to generate the delta computational model in Carracedo et al. 2013. The model predicted the experimental derivation of the core delta rhythm circuit with high fidelity in a circuit consisting of 2000 layer 5 intrinsically bursting neurons, coupled via NMDA receptors and gap junctions, driving GABA_B receptor-mediated feedback dendritic



Delta Rhythms: Models and Physiology, Fig. 1 Comparison of single-cell electrophysiology with computational model of thalamic delta oscillations. (a) and (b) show the upper and lower limits of existence of the

window current-generated delta rhythm in thalamocortical cells (experiment) and computational model. Frequency ranged from ca. 0.6–1.6 Hz. Scale bars 20 mV, 4 s. (Adapted from Williams et al. 1997, Fig. 7)

inhibition through mixed glutamatergic excitation of “neurogliaform” interneurons (fast spiking interneurons modified to be delayed spiking via somatodendritic “A”-type potassium conductance).

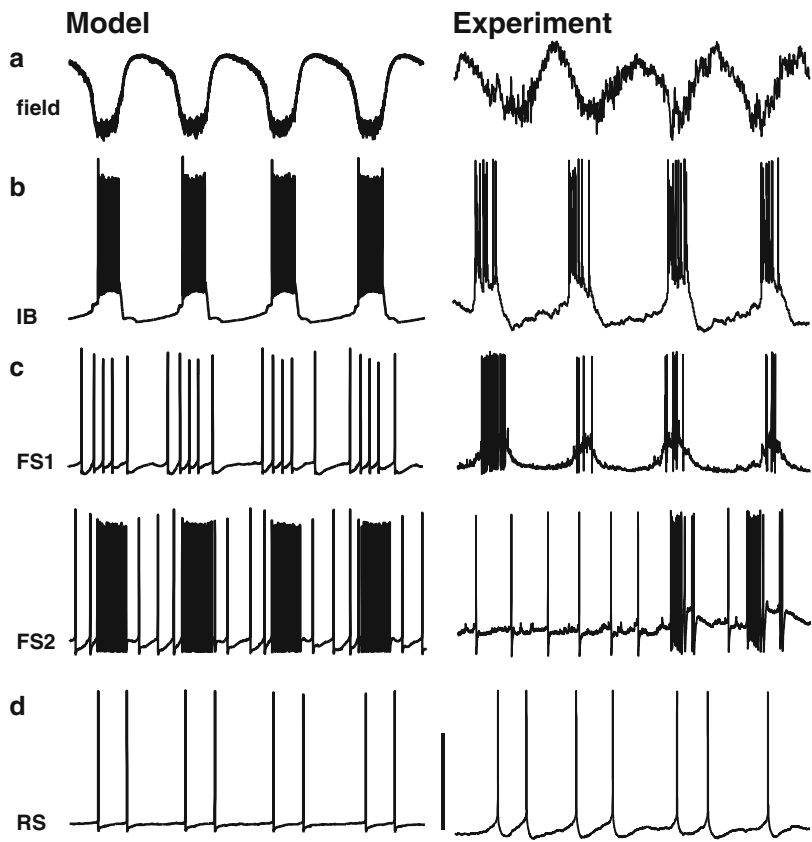
In this manner, the model reproduced dominant, delta-locked spike outputs in intrinsically bursting and neurogliaform cells. The behavior was initiated by predominantly NMDA receptor-mediated recurrent excitatory connections between intrinsically bursting cells and terminated by a combination of the strong intrinsic afterhyperpolarization (SK-type potassium channel-mediated) in this neuron subtype and a phasic GABA_B receptor-mediated slow inhibitory postsynaptic potential. It also suggested the layer 5 nested theta generator was mediated by a combination of regular spiking layer 5 neuron intrinsic properties and their appropriately weighted synaptic inputs (Fig. 2).

Combined Models

Currently no model has been published combining the biophysical detail of both the cortical and thalamic delta generators highlighted above. However, higher-level simulations using integrate and fire neurons have been generated and used to understand the emergence of behavior typical of slow-wave sleep, again implicating low-threshold bursting neuron in controlling the global thalamocortical network state (Destexhe 2009). In general such models reveal much reciprocity in thalamocortical interaction: Cortical projections to thalamus play a vital role in stabilizing thalamic output, as seen in experiment (Contreras et al. 1996), and conversely thalamic projections to the cortex are vital in controlling neuronal response state (Bazhenov et al. 2002). While increasingly biophysically accurate models are being generated, similar basic principles become apparent:

Delta Rhythms: Models and Physiology,

Fig. 2 Comparison of electrophysiology with network computational model of neocortical delta oscillations. Extracts of field (a) and single neuron subtype behavior in a columnar model of local circuit interactions. The ca. 2 Hz rhythm in layer 5 field recordings was accompanied by intense spike bursting in intrinsically bursting (IB, layer 5 pyramids (b)) cells, fast spike bursts in basket cells (FS1), and intense spike bursts and theta-frequency single spiking in model neurogliaform cells (FS2, c). In contrast layer 5 regular spiking cells (RS) generated packets of theta-frequency single spike outputs phase locked to the delta rhythm (d). Scale bars 30 mV, 600 ms. (Adapted for Carracedo et al. 2013)



The detailed biophysical thalamocortical model of Hill and Tononi (2005) reiterated the importance of hyperpolarization of neurons (in their case via an increase in potassium leak conductance) in stabilizing a c.2 Hz delta rhythm. In addition, in the cortex and thalamus, a vital role for I_h was also evident.

Cross-References

- [Low Frequency Oscillations \(Anesthesia and Sleep\): Overview](#)
- [Sleep, Neural Population Models of](#)

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Dendritic Arithmetic

► Dendritic Computation

Dendritic Computation

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Synonyms

[Dendritic arithmetic](#); [Dendritic operations](#); [Linear/nonlinear dendritic integration](#)

Definition

Dendritic computations refer to the ability of individual dendritic branches to perform elementary computations on incoming signals. These computations include addition, subtraction, multiplication, and division and can also take the form of logical operations (e.g., AND, OR, XOR). In this

chapter, we discuss evidence regarding the type of computations that have been observed in dendritic branches of multiple neuron types as well as the impact of these computations on the function of neural cells and circuits.

Detailed Description

Dendrites are elaborate processes that extend from the cell body of neurons and form the locus of synaptic communication between cells. The biophysical mechanisms that reside in dendrites allow them to locally integrate synaptic inputs in a linear and/or nonlinear manner enabling them to perform different types of computations (London and Häusser 2005; Silver 2010). In the following paragraphs, we discuss several examples of dendritic integration focusing primarily on pyramidal neurons, as these cells comprise the main processing class in the brain (Spruston 2008).

Factors That Influence Dendritic Integration

The ways in which incoming inputs are combined within dendritic branches depend mainly on two factors: (a) the morphology of the dendritic tree and (b) the repertoire of local ionic conductances. Dendritic morphology together with ionic mechanisms whose conductance does not depend on membrane voltage shapes the “passive” properties of neurons, while voltage-dependent mechanisms contribute to the “active” properties of neurons. The following sections discuss examples of how *passive* and *active* mechanisms shape dendritic properties and in turn the output of the neuron.

Passive Properties

The traditional view of dendritic processing considered dendrites as passive devices whose primary function is to transmit signals towards the soma. The extended morphology of the dendritic tree often seen in multiple neuron types was

simply considered as a means of increasing the surface area for receiving synaptic inputs. This simplified view of dendrites resulted in their omission from early neuronal models, whereby all processing was done at the cell body. Specifically, single neurons were treated as thresholded summation devices that generated an axon potential when the additive combination of incoming signals reached a certain threshold (McCulloch and Pitts 1943), completely disregarding the function of dendrites.

This notion of dendrites as conduction wires led to the formulation of “passive cable theory” which describes how electrical signals travel from their point of origin in a particular dendrite towards other parts of the neuron. A few years later, applications of the cable theory revealed that the complex geometry of dendrites in combination with their passive properties enables neurons to integrate their inputs in highly nonlinear ways. For example, when a postsynaptic potential propagates through a passive dendrite towards its integration site (soma or axon), its amplitude is attenuated in a distance-dependent manner. This effect was first described theoretically by Wilfrid Rall back in 1967 (Rall 1967), whose work revealed that passive dendrites act as low-pass filters. The diameter of dendritic branches affects the filtering of synaptic inputs for two reasons: (a) Distal dendrites are usually thinner compared to proximal ones, and as a result, synaptic potentials that travel towards the soma are reduced in amplitude (Rinzel and Rall 1974; Zador et al. 1995). This attenuation can be more than 100-fold, in pyramidal neurons (Stuart and Spruston 1998) or in cerebellar Purkinje cells (Vetter et al. 2001), and it appears to be similar for the apical and basal trees, at least in layer V pyramidal neurons (Williams and Stuart 2002; Nevian et al. 2007). (b) A smaller dendritic diameter results in larger input resistance which in turn leads to larger local EPSPs. Membrane capacitance is also smaller due the reduced membrane area, inducing faster local depolarizations in distal dendrites (Rinzel and Rall 1974; Agmon-Snir and Segev 1993).

Due to the abovementioned anatomical properties, summation of multiple excitatory synaptic

inputs within passive dendrites depends on the degree of their spatial and temporal isolation: When inputs are spatially clustered or synchronously activated, they summate sublinearly, as a consequence of the reduction in the ionic driving force. However, this conclusion is reversed when taking into account the presence of voltage-dependent (active) conductances that greatly influence local responses and counteract attenuating effects.

Active Properties

Over the last decade, advances in technology led to the discovery of an array of voltage-dependent ion channels with different densities and biophysical properties that lie along the axo-somato-dendritic axis (Spruston 2008). These findings revealed the key role of dendritic branches in shaping synaptic integration locally and in turn the response of the neuron. Dendrites are enriched with a variety of voltage-dependent channels, whose conductance and distribution differ among neuronal types, dendritic layers (e.g., apical vs. basal dendrites), as well as with distance from the cell body. Therefore, the integration of synaptic inputs does not only depend on the specific morphological features and passive properties of the dendritic tree but also on the expression profile and kinetics of the various active conductances.

The toolkit of active dendritic mechanisms includes a variety of channel types, such as Na^+ , Ca^{2+} , K^+ , and h channels and NMDA receptors. In general, Na^+ and Ca^{2+} channels are considered as boosters of postsynaptic potentials, whereas both K^+ and h channels are more likely to dampen dendritic excitability and contribute to the control of action potential frequency or act as pacemaker currents, respectively (Migliore and Shepherd 2002; Larkum and Nevian 2008; Spruston 2008). Importantly, various ionic conductances in the dendrites, such as sodium (Stuart and Sakmann 1994), calcium (Yuste et al. 1994), NMDA (Schiller et al. 2000), or a combination of the above (Wei et al. 2001; Ariav et al. 2003), have been shown to facilitate the back- or forward-propagation of dendritic spikes, allow the supralinear summation of synaptic inputs as

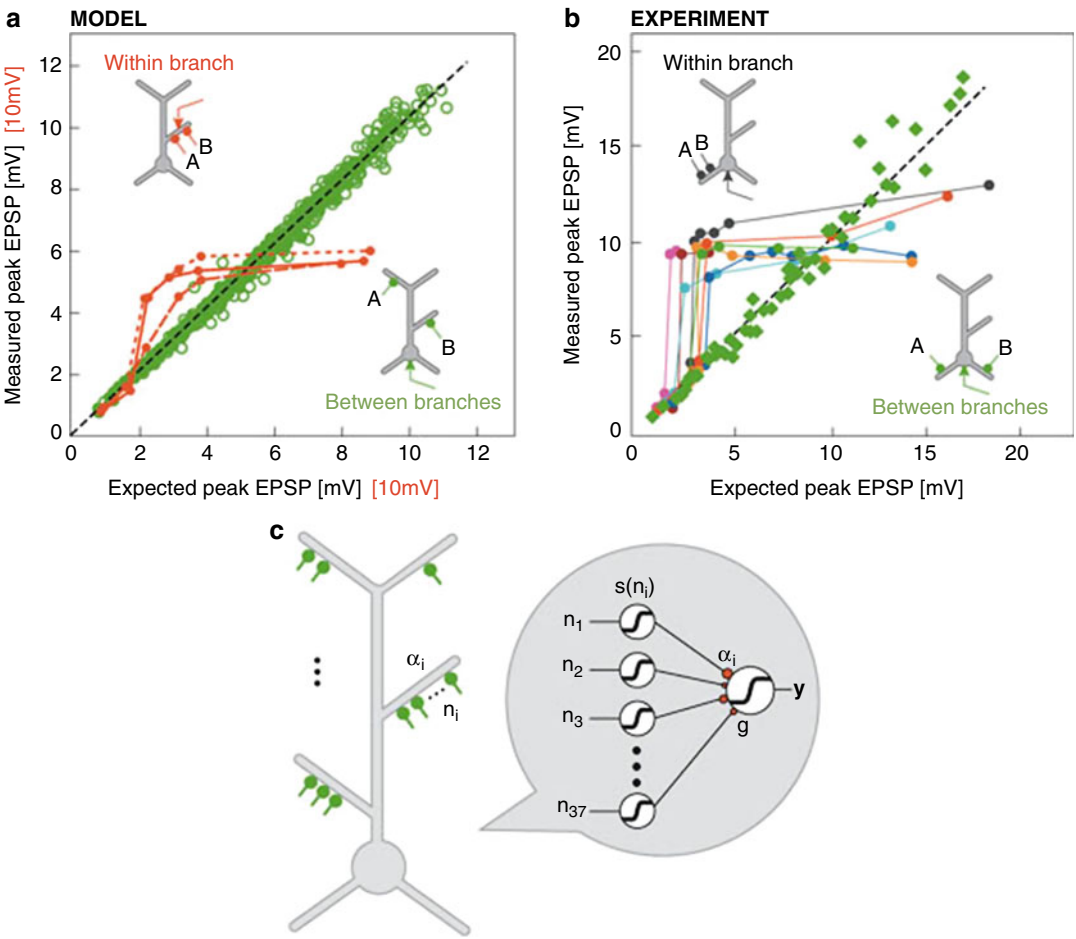
shown in Fig. 1a, b (Poirazi et al. 2003a, b; Polsky et al. 2004; Losonczy and Magee 2006), and enhance LTP induction (Magee and Johnston 1997; Remy and Spruston 2007). In particular, NMDA receptors when sufficiently activated can lead to the generation of dendritic regenerative events termed NMDA spikes.

Those spikes are characterized by larger local amplitude and duration, compared to the briefer Na^+ spikes, but smaller amplitude compared to Ca^{2+} spikes. NMDA spikes are highly localized events, confined to thin dendritic branches. For these reasons, NMDA spikes are considered an attractive dendritic mechanism for the detection of incoming signals that arrive at close temporal and/or spatial proximity (Ariav et al. 2003; Losonczy and Magee 2006). Interestingly, recent work has assigned new roles to NMDA spike generation: (a) to extend the temporal window for supralinear integration in CA1 pyramidal neuron dendrites in response to bursty signals (Gomez et al. 2011) and (b) to serve as a mechanism for the detection of “preferred” sensory signals, namely, signals that will induce persistent activity in a single-layer V PFC pyramidal neuron (Sidiropoulou and Poirazi 2012). Importantly, the majority of the excitatory glutamatergic inputs in layer V pyramidal neurons is received by their basal, oblique, and apical tuft dendrites that can give rise to regenerative NMDA events (Antic et al. 2010).

Although such regenerative events can be confined to their dendritic site of origin (Schiller et al. 2000; Wei et al. 2001), physiologically relevant situations such as large, suprathreshold synaptic stimuli in the distal dendrites or the co-activation of several branches allow these spikes to act globally and modulate neuronal output (Larkum et al. 2001). Thus, dendritic events emerge as key players in shaping neuronal responses.

Dendritic Morphology

While extensive experimental and theoretical work has characterized the arithmetic of synaptic summation in pyramidal neurons, the role of dendritic morphology in this process remains poorly understood. Electrophysiological characterization with current injection has shown that neurons with



Dendritic Computation, Fig. 1 Nonlinear dendritic computations. **(a)** Summation of paired, single-pulse inputs in the apical dendrites of a CA1 pyramidal model cell. Simulations predict a sigmoidal modulation of combined excitatory postsynaptic potentials (EPSPs) within a branch (red symbols) and a linear summation of EPSPs between branches (green symbols). Red curves correspond to within-branch data for dendrites at 92 μm (short dashes), 232 μm (solid), and 301 μm (long dashes) from the soma. Due to differences in local compared with somatic responses, axis values for the red curves are scaled up by a factor of 10. **(b)** Experimental verification of predicted summation rules in basal dendrites of a layer V pyramidal

neuron as reported in Polsky et al. (2004). Single-pulse stimulation of synapses in different branches results in linear summation at the cell body (green squares). When γ -aminobutyric acid (GABA)ergic inhibition is blocked, the summation of within-branch EPSPs is modulated by a sigmoidal nonlinearity (all other symbols). **(c)** Schematic representation of a pyramidal neuron as a two-layer neural network. Radial oblique dendrites provide the first layer of the network, each performing individually thresholded computations as shown in **(a)** and **(b)**. The outputs of this layer feed into the cell body, which constitutes the second layer of the network model (Reproduced with permission from Sidiropoulou et al. (2006))

a more complicated morphology (in terms of larger and more elaborate dendritic trees, more branches, extensive bifurcations, and more spines) display bursting firing patterns, whereas neurons with simpler morphologies tend to fire tonic spikes (Bilkey and Schwartzkroin 1990; Chagnac-Amitai et al. 1990; Yang et al. 1996).

Simulations of reconstructed neurons are in accordance with the *in vitro* studies (Mainen and Sejnowski 1996; Sheasby and Fohlmeister 1999; Krichmar et al. 2002) and further propose that dendritic trees with asymmetric branch connections are associated with bursting (van Elburg and van Ooyen 2010).

The branching pattern of the dendritic tree also influences both the forward and the back-propagation of signals (Vetter et al. 2001) while at the same time shaping coincidence detection (Schaefer et al. 2003). Even the area of the bifurcation tapering membrane surrounding a branch point can determine neuronal excitability, through its effects on the generation, propagation, and timing of dendritic spikes (Ferrante et al. 2013). Taken together, the elaborate morphology of the dendritic tree seems to play a critical role in shaping dendritic as well as neuronal responses.

Importance and Functional Implications of Dendritic Computations

The various active properties of dendrites expand the computational capabilities of various neuron types and add spatiotemporal specificity to their functional output (Stuart et al. 2008, 2010; Silver 2010). In pyramidal neurons, synaptic inputs are integrated linearly when they are located on different dendritic branches and sigmoidally when located within the same dendrite (Poirazi et al. 2003a; Poirazi et al. 2003b; Polsky et al. 2004; Losonczy and Magee 2006), but they could also be integrated sublinearly, depending on the spatial distribution of incoming signals (Oviedo and Reyes 2012). In CA1 pyramidal neurons, dendrites produce two distinct modes of integration: Asynchronous or spatially distributed synaptic inputs are integrated linearly, while synchronous and/or clustered inputs are integrated in a sigmoidal manner (Cash and Yuste 1999; Gasparini and Magee 2006). These phenomena are mediated by the generation of dendritic spikes that are locally confined.

The combination of a complex dendritic morphology with a location-specific distribution of ionic mechanisms results in the formation of distinct dendritic subunits which can integrate inputs in a quasi-independent manner (Poirazi et al. 2003a, b; Polsky et al. 2004; Losonczy and Magee 2006), thus enabling the cell to integrate inputs like a two-layer neural network. This ability to integrate inputs like a two-layer neural

network, graphically illustrated in Fig. 1c, boosts the computational capacity of the neuron by at least an order of magnitude compared to that of a thresholding point neuron (Poirazi and Mel 2001). Recent experimental evidence shows that the distribution of synapses both along the somatodendritic axis and along the oblique branches in CA1 pyramidal neurons favors a two-stage integration model (Katz et al. 2009).

At a smaller scale, single dendrites of layer II/III and layer V pyramidal neurons exhibit non-uniform synaptic integration modes along their length. Synaptic inputs in the distal end of the dendrite summate sigmoidally with a low threshold for dendritic spike generation, while inputs to the proximal end of the same dendrite summate linearly and exhibit a higher threshold for dendritic spikes (Major et al. 2008; Branco and Häusser 2011). These and previous data indicate that the spatial arrangement of synaptic inputs within dendritic branches greatly influences local responses by differentially engaging local conductances (Larkum and Nevian 2008). For example, the co-activation of nearby synapses, also termed “synaptic clustering,” leads to signal amplification via the induction of dendritic spikes, resulting in a much larger somatic response than the one obtained when the same number of synapses is stimulated in a distributed manner. As dendritic depolarization and dendritic spikes can have a strong effect on LTP induction, clustered synapses are also more likely to undergo stronger potentiation than diffusely activated inputs (Hardie and Spruston 2009).

Overall, these findings show that dendritic arithmetic obeys complex rules that are often not only brain region but also branch-type specific. This ability of dendrites to perform complex local computations has led to the proposal that dendritic branches (as opposed to single synapses or whole neurons) should be considered as the lowest-level processing unit of the nervous system (Branco and Häusser 2010). If proven, this hypothesis will change our current view of information processing and storage in the brain and will open new avenues for experimental investigations regarding the cellular substrate of learning and memory.

Cross-References

► Cable Theory: Overview

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Dendritic Spines

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Definition

Many types of neurons receive synaptic inputs on dendritic spines which are short protrusions of membrane composed of a bulbous “head” connected to the dendrite by a thin “stem” or “neck” (Yuste 2010). Although spines are typically small in size, they occur in high densities along dendrites and may compose 40–60% of the total dendritic surface area. There are two straightforward methods for including spines in computational models of neurons without representing every spine explicitly.

Detailed Description

Spines are widely regarded to serve a biochemical function by providing an isolated compartment where highly localized calcium signals and subsequent reactions can occur. An electrical function was initially proposed by Rall who showed that the steady-state attenuation of a signal from the spine head to the dendrite could be expressed as $V_{SH}/V_{BI} = 1 + R_{SS}/R_{BI}$, where V_{SH} and V_{BI} are the voltages at the spine head and dendrite, respectively; R_{SS} is the spine stem resistance; and R_{BI} is the input resistance at the dendrite. Rall suggested that changes in spine stem diameter might be important for plasticity because of its effect on R_{SS} , but studies searching for such changes produced mixed results. Others have suggested that if voltage-dependent conductances are present on spines, then spines might amplify inputs and could otherwise increase the computational possibilities of the cell. Many of the more interesting possibilities suggested by theoretical studies require a large R_{SS} , but whether or not R_{SS} is sufficiently large has been controversial.

Dendritic Operations

► Dendritic Computation

Because the proportion of membrane area occupied by spines can be large, single-neuron models that ignore spines are bound to produce erroneous results. There are two straightforward methods for including spines in models without coding each and every spine, as long as these implicitly included spines do not receive synaptic input. First, if dendritic and spine membranes are assumed to have the same specific membrane resistance and capacitance, R_m and C_m , spines can be implicitly included in a model by increasing C_m and reducing R_m according to the proportion of total membrane area contributed by spines. We call this the R_m - C_m method. For example, if spines increase the membrane area of a dendrite by 33%, then spines can be implicitly modeled by multiplying the dendrite C_m by 1.33 and dividing dendritic R_m by 1.33. Alternatively, one can keep R_m and C_m constant but increase length and diameter in such a way as to keep intracellular resistance constant (i.e., keep length/diameter² constant). We call this the l-d method. For example, if spines increase membrane area by 33%, let $F = 1.33$ and multiply length by $F^{2/3}$ and diameter by $F^{1/3}$.

These two methods for including spines in models implicitly provide identical results with passive models, but they make very different assumptions when voltage-dependent conductances are present. The first method, where R_m and C_m are changed, assumes that spines have passive membrane, while the second method, where length and diameter are changed, assumes that the spines have the same densities of voltage-dependent conductances as the dendrite. The cell should have a lower input resistance with the second method but should also respond more nonlinearly with voltage perturbations. Needless to say, results may be very different.

Nevertheless, it is straightforward to modify either method to include spines possessing different densities of voltage-dependent conductances than present on the dendrite. With the first method, one should change dendritic R_m and C_m as described above but also modify the maximum conductance density (g-bar) for each conductance

by $\bar{g}_{d-new} = (\bar{g}_{d-old}A_d + \bar{g}_{spine}A_s)/A_d$ where A_d is the membrane area of the dendritic segment and A_s is the membrane area of all spines on that segment. With the second method, one should modify the maximum conductance density for every conductance on each dendrite by $\bar{g}_{d-new} = (\bar{g}_{d-old}A_d + \bar{g}_{spine}A_s)/(A_d + A_s)$ and then change length and diameter of the dendrite as described above. These expressions assume spine head and neck have the same channel densities. If this is not true, one could calculate an equivalent $\bar{g}_{spine}$ to use.

These methods are easily incorporated into single-neuron simulators such as NEURON or GENESIS and work well for voltage-dependent conductances with fixed reversal potentials. However, these methods are subject to error when calcium and calcium-dependent conductances are present and particularly so if these conductances have different densities in spines and dendrites. Calcium accumulation and removal can be different in spines and dendrites, and different intracellular calcium concentrations will affect the calcium Nernst potential and activation of calcium-dependent conductances differently. The R_m - C_m method is preferred if dendrites have calcium conductances and spines do not. The l-d method is preferred if calcium conductances are on both dendrites and spines, but activation of calcium-dependent potassium conductances in spines remains problematic. It is possible to compensate for these types of errors by adjusting calcium pool parameters or by considering spine calcium and calcium-dependent conductances as separate conductances with their own parameters when conductances are merged into dendrites. These errors are not likely to be significant in short-time simulations but can be seen to accumulate over longer time periods.

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Dendritic Spines: Continuum Theory

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Synonyms

Baer-Rinzel (BR) continuum model; Continuum spine model; Continuum spine theory; Continuum theory for active spines

Definition

The continuum theory for dendritic spines, developed by Baer and Rinzel (1991), is an extension of classical cable theory for which the distribution of spines is treated as a continuum. The theory applies when the interspine distance is much less than the length scale of the dendrite, for example, when the dendrite is populated by a large number of spines. The formulation maintains the basic feature that there is no direct coupling between neighboring spines; voltage spread along dendrites is the only way for spines to interact. With the continuum theory, different spine morphologies, multiple populations of spines, and distributed physiological properties are represented explicitly and compactly by relatively few differential equations. The theory is general so that idealized or realistic kinetic models may be adapted.

Detailed Description

Classical cable theory has provided valuable insights into structure-function relationships and guidance in the design of experiments. Perhaps the best example is Rall and Shepherd's electrotonic model of the olfactory bulb, which predicted the existence of functional dendrodendritic synapses (Rall and Shepherd 1968). Cable equations have been used successfully to study tapered nerves and extensively branched dendritic trees

(Jack et al. 1975; Rall 1977), as well as cables with nonuniform electrical parameters such as specific membrane resistivity (Holmes and Woody 1989).

In the 1970s and 1980s, Rall, Rinzel, Miller, and Segev spearheaded efforts that accelerated the theoretical investigation into the function of dendritic spines (Rall and Rinzel 1971a, b; Miller et al. 1985; Shepherd et al. 1985; Rall and Segev 1987; Segev and Rall 1988). Dendritic spines are small knoblike evaginations of the dendritic surface (see Fig. 1a, b), and a single neuron may have 10^5 spines. These large numbers of spines present a challenge for computational studies, particularly when using compartmental modeling. To address this, Baer and Rinzel (1991) formulated an extension of classical cable theory to model cables with large spine densities. They treated the distribution of spines as a continuum (see Fig. 1). This allowed a single cable with hundreds or thousands of spines to be modeled with just a few differential equations. Baer and Rinzel's model is

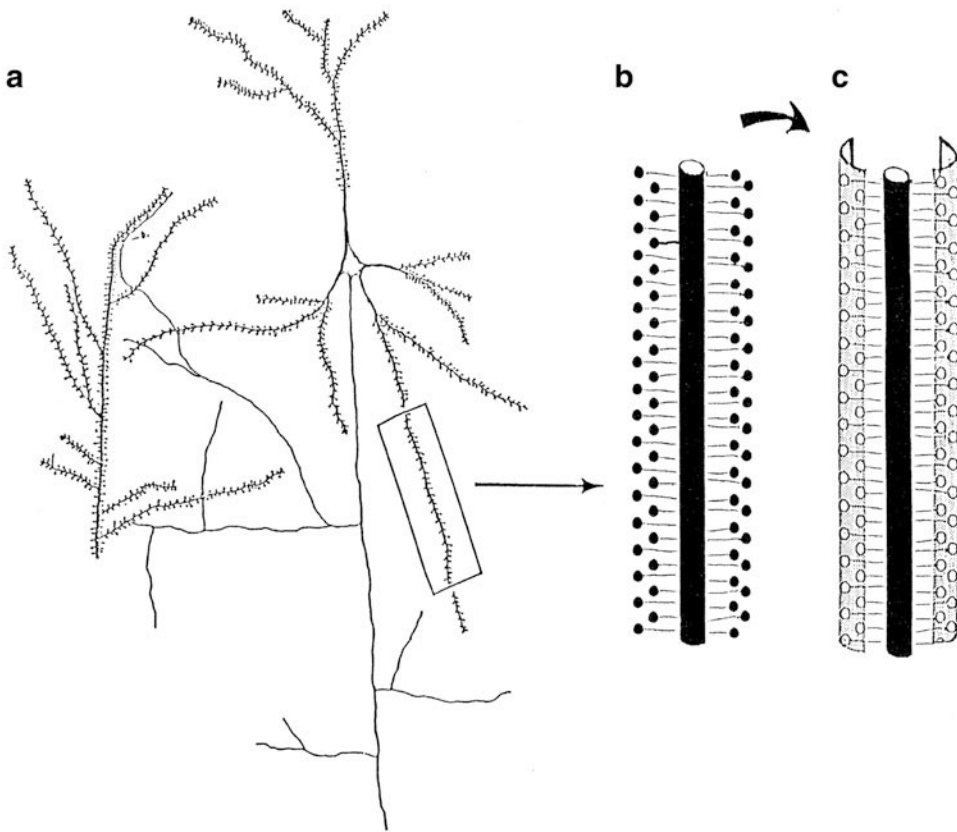
$$\tau_m \frac{\partial V_d}{\partial t} = \frac{\partial^2 V_d}{\partial X^2} - V_d + R_\infty \bar{n}_i I_{ss} \quad (1)$$

$$C_{sh} \frac{\partial V_{sh}}{\partial t} = -I_{ion} - I_{syn} - I_{ss}, \quad (2)$$

where

$$I_{ss} = \frac{V_{sh} - V_d}{R_{ss}}. \quad (3)$$

Here, V_{sh} and V_d are, respectively, the membrane potential in the spine head and the dendritic base (or shaft). Equation 1 is the cable equation in terms of dimensionless (electrotonic) length X (computed for the passive cable without spines), τ_m is the membrane time constant, and R_∞ is the input resistance for a semi-infinite passive cable with circular cross section. The spine density $\bar{n}$ expresses the number of spines per unit electrotonic length. The spine stem current is denoted by I_{ss} and represents the $I \cdot R$ voltage drop across the spine stem resistance R_{ss} , as expressed in Eq. 3. The spine head is modeled in Eq. 2 as an



Dendritic Spines: Continuum Theory, Fig. 1 Continuum of dendritic spines. (a) Cortical pyramidal cells (Modified from Berkley 1897). (b) A schematic magnification from (a) shows the dendrite (cylinder) studded with spines. (c) If there are many spines, the dendritic electrical response can be approximated by

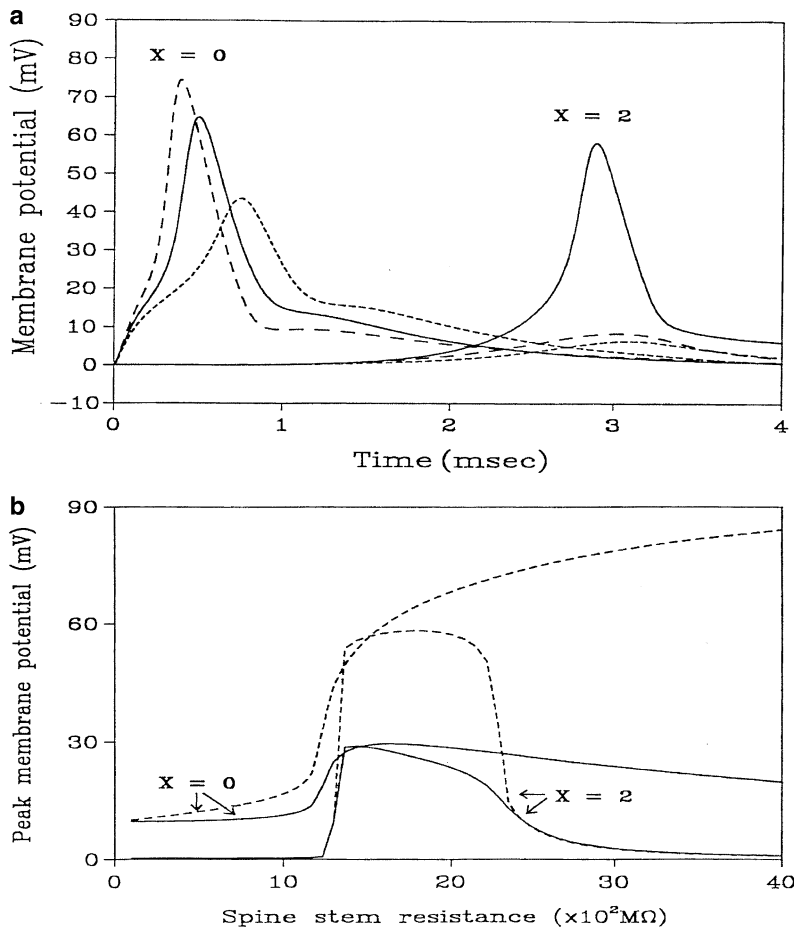
considering a continuum of spines (stippled envelope). Although spines are treated mathematically as a continuum, the model is constructed so that spines interact only through spread of dendritic potential. (From Baer and Rinzel 1991; Fig. 1)

isopotential compartment with surface area A_{sh} (μm^2) and specific membrane capacitance C_m ($\mu\text{F}/\text{cm}^2$); individual spines have a capacitance of $C_{sh} = A_{sh} C_m$ (μF). Equation 2 describes the membrane potential in a single spine obtained from a current balance relation for the capacitive, ionic, spine stem, and synaptic currents.

The primary focus of Baer and Rinzel's study was on threshold properties, e.g., minimum number of synaptically activated spines, or minimal density of spines, for the initiation and spread of activity. They found that propagation was precluded for spine stem resistance (R_{ss}) either too large or too small (Fig. 2). Moreover, even if R_{ss} was in a suitable range for the local generation of an action potential (resulting from local synaptic

excitatory input), the range was shown to be not suitable to initiate a chain reaction of spine firings along the dendrite; success or failure of impulse propagation depends on an even narrower range of R_{ss} values. Also demonstrated was that appropriate clustering of spines can enhance synaptic amplification and spread of activity (Fig. 3).

The Baer-Rinzel model led to some new and important insights into the electrical interplay between passive and excitable membranes. For example, regions of decreased conduction load (e.g., near sealed ends of nerves) have a higher safety factor and therefore facilitate attenuating waves and further enhance waves that are successfully propagating. In regions of increased



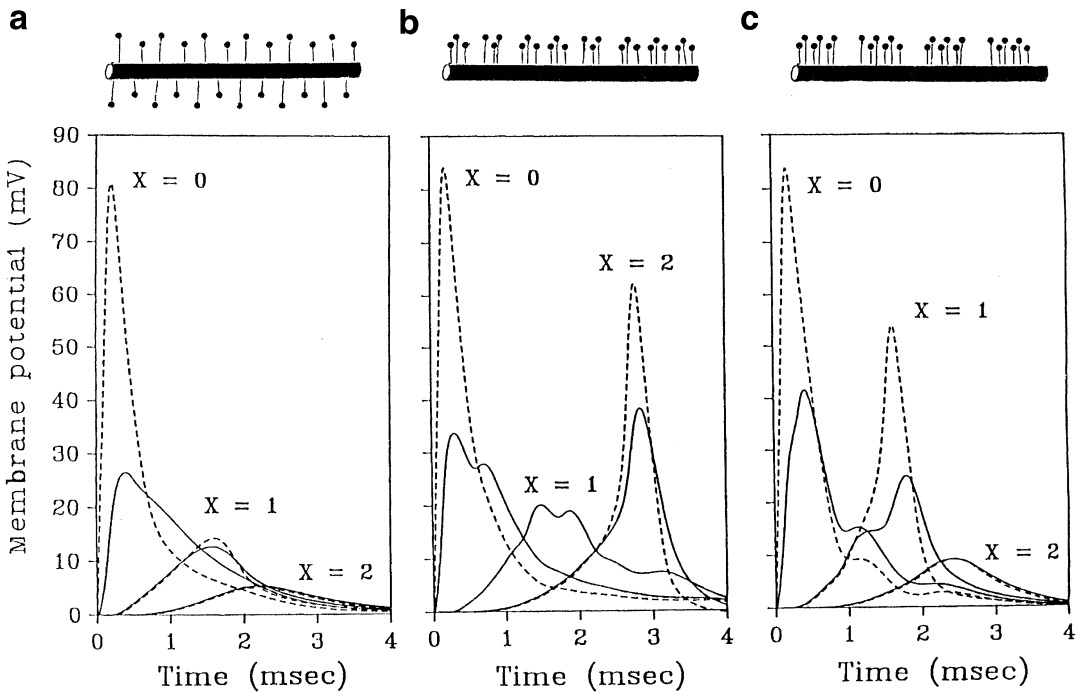
Dendritic Spines: Continuum Theory, Fig. 2 Propagation failure for spine stem resistance too large or too small. A dendrite of electrotonic length 3 has 60 uniformly distributed excitable spines. Four spines are synaptically activated near $X = 0$ using an alpha function stimulation. Electrode recordings in the spine head and dendrite are simulated at $X = 0$ and $X = 2$. (a) Voltage transients in the head indicate propagation failure when the spine stem resistance is too low (short-dashed curves) because dendritic loading effectively raises the threshold for a local action potential out of range for the given input.

Propagation also fails when the stem resistance is too high (long-dashed curves) because large stem resistance results in a decreased shaft potential; the spreading dendritic depolarization becomes too weak to bring the spine heads in front of the wave to threshold. However, for intermediate values of spine stem resistance (solid curves), a “spike-diffuse-spike” chain reaction occurs, and the wave propagates. (b) Peak voltage versus stem resistance in spine head (dashed) and dendritic shaft (solid). (From Baer and Rinzel 1991; Fig. 3, with figure caption modified)

conductance load such as common branch points, attenuation of the potential and propagation failure is more likely. Spine densities (passive or excitable) also affect conductive loading and safety factor. A suitable spine density could ensure propagation through regions where the safety factor is low. More generally, propagation in regions of nonuniform loading may be complemented or counteracted by variations in

spine density; the dynamics of electrical current flow in cables with spines are dependent on spine distribution and spine morphology.

The continuum model has been applied to a variety of problems, for example, the dynamics of receptor potentials in mechanoreceptors (Bell and Holmes 1992) and the effect of noise on spiny dendrites (Coutts and Lord 2013), and more recently, the model was used to demonstrate



Dendritic Spines: Continuum Theory, Fig. 3 Spine clusters. Impulse propagation is contingent on the spatial distribution of spines. Effects of 3 spatial distributions of 24 excitable spines are compared in a cable of electrotonic length 2. Simulated electrode recording positions are $X = 0, 1$, and 2. Solid curves denote dendritic potentials, and dashed curves denote spine head potentials. Three spines near $X = 0$ are activated synaptically. (a) With a uniform but low density of spines ($\bar{n} = 12$ spines per e.l.), an impulse fails to propagate. (b) The same 24 spines are grouped into 8 clusters spaced 0.34 apart. Each cluster has

3 spines and width 0.04 ($\bar{n} = 75$ within a cluster). Impulse propagation is successful for this case. At $X = 1$ the simulated electrode recording is between spine clusters; hence, membrane potential is shown for the dendrite only. (c) The 24 spines are grouped into 4 clusters spaced 0.42 apart. Each cluster has 6 spines and width 0.08 (again, $\bar{n} = 75$ within a cluster). Here the impulse propagates to $X = 1$ but fails before reaching $X = 2$. Although the clusters have the same density as in (b), they are too far apart for successful propagation. (From Baer and Rinzel 1991; Fig. 4)

spatial delays and spatial memory effects in response to slow current ramps in a dendrite with excitable spines (Bilinsky and Baer 2018). The continuum theory of dendritic spines has been extended to study spine plasticity (Verzi et al. 2004), and it has spawned other computational approaches, including the spike-diffuse-spike model (Coombes and Bressloff 2003), originally intended as a computationally simple version of the Baer-Rinzel model.

Cross-References

- [Cable Equation](#)
- [Cable Theory: Overview](#)

- [Dendritic Computation](#)
- [Dendritic Spines](#)
- [Quasi-active Approximation of Nonlinear Dendritic Cables](#)

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Determining Network Structure from Data: Nonlinear Modeling Methods

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Definition

In this entry we focus on inference of network structures from data. One possible approach to studying networks is to model the nodes, such as neurons, and generate networks and run simulations and observe the network behavior. This approach requires on a priori assumptions about the constituent parts; for instance, Hodgkin-Huxley neurons may be coupled and the resulting network behavior is investigated. The model behaviors can be compared to the measured neuronal signals through statistical analysis. However, this approach only provides indirect information about the network structure. An alternative approach to studying network structure is to use parametric, semiparametric, and nonparametric analyses of the observed signals and reconstruct the network connections. Such analyses are essential tools for systems in which network structure is not known, such as when anatomical connections are not known or information is not sufficient.

A particular challenge when inferring the network structure from data lies in the fact that analysis techniques to investigate interactions are often bivariate, investigating pairwise connections. Often, analyses cannot distinguish between direct and indirect interactions. A good measure of coupling between nodes should be able to distinguish direct and indirect interactions. To achieve this, a multivariate data analysis approach needs to be used. For linear systems multivariate data analysis approaches have been developed over the past decades. However, for nonlinear

systems, the development of multivariate analysis techniques is in its infancy. Nonlinear approaches typically require computationally intensive algorithms and large data sets which have limited their application.

In this entry, we provide a survey of approaches for inferring the network structure from nonlinear systems using nonlinear data-based modeling.

Detailed Description

Introduction

Mathematicians and physicists often generate models of complex networks starting with first principles. However, for complex biological systems found in neuroscience, the dynamics of neuronal behavior underlying the measured signals is poorly understood, leaving an approach based on first principles ideal. Therefore, an understanding of the behavior can only be based upon the analysis of measured data of the dynamics, i.e., time series from EEG or other population level signals, and point processes, from action potential timing. This approach is called data-based modeling.

Time series and point process analysis have different roots originating in mathematics, physics, and engineering. The underlying assumptions of the sources of the signals are different resulting in different approaches to the analysis. In mathematical statistics, the model has been based on linear stochastic systems; in physics the models have been of nonlinear deterministic systems. While methodological developments evolved independently across disciplines, over the past decade cross-fertilization has resulted in novel approaches to data-based modeling of nonlinear stochastic systems (Schelter et al. 2006b).

Reconstruction of networks depends on the detection of coupling between areas, particularly *causal influences* between two different processes, for instance, between brain areas or between brain areas and the periphery. The goal is to detect changes in coupling that may be caused by the underlying diseases. Detection of changes in coupling may lead to improved diagnosis and treatment strategies especially for neurological diseases.

The approach proposed here considers the brain as a dynamic system from which we measure the activity through the electroencephalogram (EEG), magnetoencephalogram (MEG), or another representation of the underlying neuronal activity. By applying the network analysis to the data sets recorded from normal patients and those suffering from neurological diseases, we hope to gain an understanding of the underlying mechanisms generating these dysfunctions (Volkman et al. 1996; Tass et al. 1998; Hellwig et al. 2001). However, there is a wide variety of applications beyond neurosciences to which the linear as well as nonlinear data analysis techniques presented here can be applied successfully.

Various linear analysis techniques have been proposed to determine interdependency between dynamic processes and to determine causal influences in multivariate systems (Schelter et al. 2006a). Using the Fourier transform, a signal can be converted to the frequency domain and the interdependencies analyzed using the cross-spectrum and coherence. But these tools are not sufficient to adequately describe interdependence within a multivariate system where correlation arises not because the two are directly coupled but because they receive common inputs. To enable a differentiation between direct and indirect influences in multivariate systems, multivariate linear approaches have been developed (Dahlhaus 2000; Baccala and Sameshima 2001; Ding et al. 2006).

Furthermore, multivariate network analysis can uncover directed interactions, which enables deeper insight into the basic mechanisms underlying such networks. These tools can determine not only if nodes are connected but the direction of the connection. In some cases in which communication is present in both directions, it is possible that they can communicate in distinct frequency bands. To detect directed nonlinear connections, appropriate analysis techniques are needed. Granger causality (Granger 1969) is utilized to determine causal influences when the coupling is linear. This probabilistic approach to determining causality is based on the principle that a cause precedes the effect in time and this is formulated in terms of predictability. Granger

causality is done by fitting autoregressive models to the signals and determining if the error in prediction of the next time point of one signal can be improved by the knowledge of the other. A graphical approach for modeling Granger-causal relationships in multivariate processes has been discussed (Eichler 2007). More generally, networks may be determined by the use of Granger causality between the nodes, but unlike linear cross-correlation, this approach tries to address spurious causalities caused by confounding by unobserved processes (Eichler 2005).

Nonlinear systems can show behaviors that are impossible in linear systems (Pikovsky et al. 2001); for example, nonlinear systems can synchronize. In the seventeenth century, Huygens observed synchronization between two pendulum clocks on the same wall. These clocks are coupled self-sustained oscillators. The process of synchronization is an adaptation of certain characteristics of the two processes. The oscillations between the clocks were always antiphase and restored synchronization after being perturbed (Pikovsky et al. 2000); for general systems, different phase relations are conceivable. A weaker form of synchronization has been observed between two coupled chaotic oscillators. These oscillators can synchronize their phases while their amplitudes stay almost uncorrelated (Pikovsky et al. 2001; Boccaletti et al. 2002; Wiesenfeldt et al. 2001). Several forms of synchronization have been described, ranging from phase synchronization via lag synchronization to almost complete synchronization (Boccaletti et al. 2002). Generalized synchronization is the most general case where one signal is related to the other through any arbitrary function.

While a battery of various analysis techniques is available for linear stochastic systems, for nonlinear systems techniques are still in their infancy. This entry is dedicated to the inference of the network structure based on the observation of nonlinear processes utilizing nonlinear data-based modeling approaches. The entry is subdivided into Phase-Based Approaches, Recurrence-Based Approaches, Information Theoretic Approaches, and Linear Approaches. We should note that it is

impossible to provide a complete survey of all approaches.

We begin this entry by introducing the general concept underlying most of the approaches to provide a quick introduction into the topic.

General Concept

One challenge when inferring the network structure from data lies in distinguishing direct and indirect interactions. Given a network with direct and indirect interactions, a bivariate analysis can be applied to every pairwise combination of nodes of the network to detect all connections. The resulting network could be fully connected. But the indirect connections are often weaker than direct ones. By setting some finite statistical power, we can hope to distinguish the direct ones from the indirect ones. But such an approach indeed relies on the assumption that indirect connections are the weakest in the network and that the statistical power is actually too low to detect the interaction. In general, both assumptions are not valid and bear the risk that erroneous conclusions are drawn; this leads to several *false-positive* conclusions.

Multivariate approaches attempt to correct for these problems with bivariate approaches. The theory behind multivariate approach is that if all contributing processes have been observed, it should be possible to infer whether or not a connection is indirect. This is done by partializing the information of the third processes. Practically, there are several approaches to do this. Here, we just provide an outline for how this is done. To test if two systems are direct or indirect, we will first assume for simplicity that there are only the two systems in question and one other system that could potentially influence them. Because we have observed all the systems, it is possible to determine the amount of information transfer from the third system onto the two systems of interest. If this extra information from the third process suffices to fully explain the information transfer between the first two systems, then we can conclude that the connection is indirect. If the third cannot explain all the information transfer, then we conclude that they are directly connected.

Whether the connection between the two systems of interest is causal can be determined by only using past points of each process to predict the future behaviors of the other processes.

In the following, we present some concepts how the partialization is performed in practice. A complete coverage of all possible approaches is beyond the scope of this entry.

Phase-Based Approaches

Synchronization analysis is a common approach to detect interactions between nonlinear self-sustained oscillators (Pikovsky et al. 2001). Following the observations and pioneering work of Huygens, the synchrony has been observed in many different systems including systems with a limit cycle or a chaotic attractor. Several different types of synchronization have been observed for these systems, ranging from phase synchronization, as the weakest form of synchronization via lag synchronization, to generalized or complete synchrony (Rosenblum et al. 1996; Rosenblum et al. 1997; Kocarev and Parlitz 1996; Pecora and Carroll 1990).

Phase synchronization analysis is a powerful tool because it detects even weak coupling between oscillators. For example, in some chaotic oscillators, very weak coupling between oscillators can synchronize their phases but not their amplitudes (Rosenblum et al. 1996). To quantify the process of synchronization, different measures have been proposed (Tass et al. 1998; Mormann et al. 2000; Rosenblum et al. 2001). The first approach presented here is a measure based on circular statistics, which is the so-called mean phase coherence (Mormann et al. 2000). We will introduce it by first reviewing phase synchronization that in weakly coupled self-sustained oscillators. For a more detailed introduction to synchronization including phase synchronization, we refer to the literature, e.g., Pikovsky et al. (2001).

Self-Sustained Oscillators

To discuss synchronization, we must start with a simple model of each node. One of the simplest

behaviors with nonlinear dynamics is a self-sustained oscillator. In general these oscillators can be described using the very general differential equation:

$$\dot{\mathbf{X}}(t) = f(\mathbf{X}(t), \alpha(t), U(t)),$$

where $\mathbf{X}(t)$ is a multidimensional variable to ensure an oscillatory behavior. The external influence $U(t)$ as well as the parameters $\alpha(t)$ are vectors. In this case, external driving is neglected in the following and the parameters α_i are assumed to be constant in time.

Two coupled oscillators can be written as follows:

$$\begin{aligned}\dot{\mathbf{X}}_1(t) &= f_1(\mathbf{X}_1(t), \alpha_1) + \epsilon_{1,2} \mathbf{h}_1(\mathbf{X}_1(t), \mathbf{X}_2(t)) \\ \dot{\mathbf{X}}_2(t) &= f_2(\mathbf{X}_2(t), \alpha_2) + \epsilon_{2,1} \mathbf{h}_2(\mathbf{X}_2(t), \mathbf{X}_1(t))\end{aligned}$$

where the coupling from oscillator j onto oscillator i is the coefficient. If $\epsilon_{i,j}$ is nonzero, then the system is considered coupled. $\mathbf{h}_1(\cdot)$ and $\mathbf{h}_2(\cdot)$ are the coupling functions and can be any arbitrary function. Usually, diffusive coupling is assumed, i.e.,

$\mathbf{h}_1(\mathbf{X}_1(t), \mathbf{X}_2(t)) = (\mathbf{X}_2(t) - \mathbf{X}_1(t))$ and for $\mathbf{h}_2$ accordingly.

Phase Synchronization

The phase of a limit cycle oscillator is a monotonically increasing function with $\Phi(t)|_{t=pT} = p2\pi = p\omega T$, where p denotes the number of completed cycles, T is the time needed for one complete cycle, and ω is the eigenfrequency of the oscillator. But, more generally, we can consider the phase of any oscillation from a differential equation

$\dot{\Phi}_i(t) = \omega_i, i = 1, \dots, N$ where the ω_i are the frequencies of the uncoupled oscillators with i denoting the i -th oscillator.

Differential equations describing the phase in a coupled two-oscillator system with different frequencies n and m can be written as follows:

$$\begin{aligned}n\dot{\Phi}_1(t) &= n\omega_1 + \epsilon_{1,2}nH_1(\Phi_1, \Phi_2) \\ m\dot{\Phi}_2(t) &= m\omega_2 + \epsilon_{2,1}mH_2(\Phi_2, \Phi_1),\end{aligned}$$

which can be written as the phase difference between the two oscillators

$$\begin{aligned} n\dot{\Phi}_1(t) - m\dot{\Phi}_2(t) &= n\omega_1 - m\omega_2 \\ &+ \epsilon_{1,2}nH_1(\Phi_1, \Phi_2) \\ &- \epsilon_{2,1}mH_2(\Phi_2, \Phi_1) \end{aligned}$$

This equation represents the generalized phase difference (Pikovsky et al. 2001).

In the case of $\epsilon_{2,1} = \epsilon_{1,2}$ then $\Phi_{1,2}^{n,m} = n\Phi_1 - m\Phi_2$ and $\Delta\omega = n\omega_1 - m\omega_2$; the above differential equation can be rewritten as

$$\dot{\Phi}_{1,2}^{n,m}(t) = \Delta\omega + \epsilon_{1,2}H(\Phi_{1,2}^{n,m})$$

with a new periodic function $H(\cdot)$.

This differential equation has a fixed point characterized by the following equation:

$$\Delta\omega + \epsilon_{1,2}H(\Phi_{1,2}^{n,m}) = 0$$

In this case, the phase difference is constant with time. Thus, both phases maintain a fixed relationship and the system is considered to be $n:m$ phase synchronized.

If some stochastic influence is present in the oscillators, which in turn alters the phase difference dynamics, certain fluctuations are possible but these are restricted by an appropriately chosen constant, i.e.,

$$|\Phi_{1,2}^{n,m} \bmod 2\pi| \leq \text{const}$$

In this case there will be variability between the phases, but the phase synchronization will still be preserved.

The Mean Phase Coherence

If the weakly coupled self-sustained oscillators are phase synchronized, the above equation can be reformulated to yield a single number to quantify the phase synchrony.

If there is a sharp peak in the phase difference distribution of $\Phi_{1,2}^{n,m} \bmod 2\pi$, it indicates that two phases have a coherent motion; if the distribution is flat, then it indicates that the two have independently evolving phases. Based on circular statistics, the phase difference distribution can be quantified as follows:

$$|R_{12}^{n,m}| = \left| \frac{1}{T} \sum_{t=1}^T e^{i\Phi_{1,2}^{n,m}(t)} \right|$$

This quantity is normalized between 0 and 1 and will be one for perfectly synchronized phases and zero for independent signals (Tass et al. 1998; Mardia and Jupp 2000; Mormann et al. 2000).

Often the phase of a signal cannot be directly measured. In which case, we can use the Hilbert transform to calculate a 90° phase shifted version of the time series measured, with which we can use to calculate the instantaneous phase

$$X_h(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{\infty} \frac{X(\tau)}{t - \tau} d\tau$$

where P.V. refers to Cauchy's principal value. This leads to

$$V(t) = X(t) + iX_h(t) = A(t)e^{i\Phi(t)}$$

where i is the imaginary number and through Euler's formula can be written as a complex exponent where $\Phi(t)$ is the phase. Alternative approaches to obtain the phases are conceivable based on, e.g., wavelet transformations (Le van Quyen et al. 2001; Bandrivskyy et al. 2004). Note that this transformation is applicable for signals in which a frequency is well defined; different approaches are needed for broad band signals (see below) or point processes (Smirnov et al. 2007).

Multivariate Phase Synchronization

If multiple signals are being analyzed, a multivariate phase synchronization, also referred to as partial phase synchronization, can be used. For an N -dimensional process, the following matrix of pairwise interactions can be generated:

$$R = \left(R_{ij}^{n,m} \right)_{i=1, \dots, N, j=1, \dots, N}$$

This is called the *synchronization matrix* containing all pairwise phase synchronization measures. The inverse $\mathbf{PR} = \mathbf{R}^{-1}$ of this matrix

leads to the definition of the $n:m$ partial phase synchronization index

$$R_{kl|Y} = \frac{|PR_{kl}|}{PR_{kk} PR_{ll}}$$

between oscillators k and l . It is conditioned on the remaining processes which are summarized as Y . It can be analytically shown (Dahlhaus 2000; Schelter et al. 2006b) that this matrix inversion partializes the information of the third processes, as introduced in the “General Concept” section. Indirect interactions are characterized by a vanishing partial phase synchronization. If the bivariate phase synchronization index R_{kl} is considerably different from zero while the corresponding multivariate partial phase synchronization index $R_{kl|Y}$ is approximately zero, then the connection is most likely due to indirect coupling between the processes k and l (Schelter et al. 2006b). A rigorous statistical test using natural surrogates or twin surrogates (Nawrath et al. 2010) can be used to determine significance.

Example

Three coupled stochastic Roessler oscillators (Roessler 1976) are an example of a system of weakly coupled self-sustained phase-coherent stochastic oscillators:

$$\begin{aligned}\dot{X}_j &= -\omega_j Y_j - Z_j + \left[\sum_{i, i \neq j} \varepsilon_{j,i} (X_i - X_j) \right] \\ &\quad + \sigma_j \eta_j \\ \dot{Y}_j &= \omega_j X_j + a Y_j \\ \dot{Z}_j &= b + (X_j - c) Z_j\end{aligned}$$

with $i, j = 1, \dots, 3$ and parameters are set to $a = 0.15$, $b = 0.2$, $c = 10$, $\omega_1 = 1.03$, $\omega_2 = 1.01$, and $\omega_3 = 0.99$ yielding chaotic behavior in the deterministic case. The noise term, η_j , is Gaussian distributed with mean of zero and standard deviation $\sigma_j = 1.5$. Both the bidirectional couplings between oscillators 1 and 3 and 1 and 2 are varied

between 0 and 0.3. The oscillators 2 and 3 are not directly coupled.

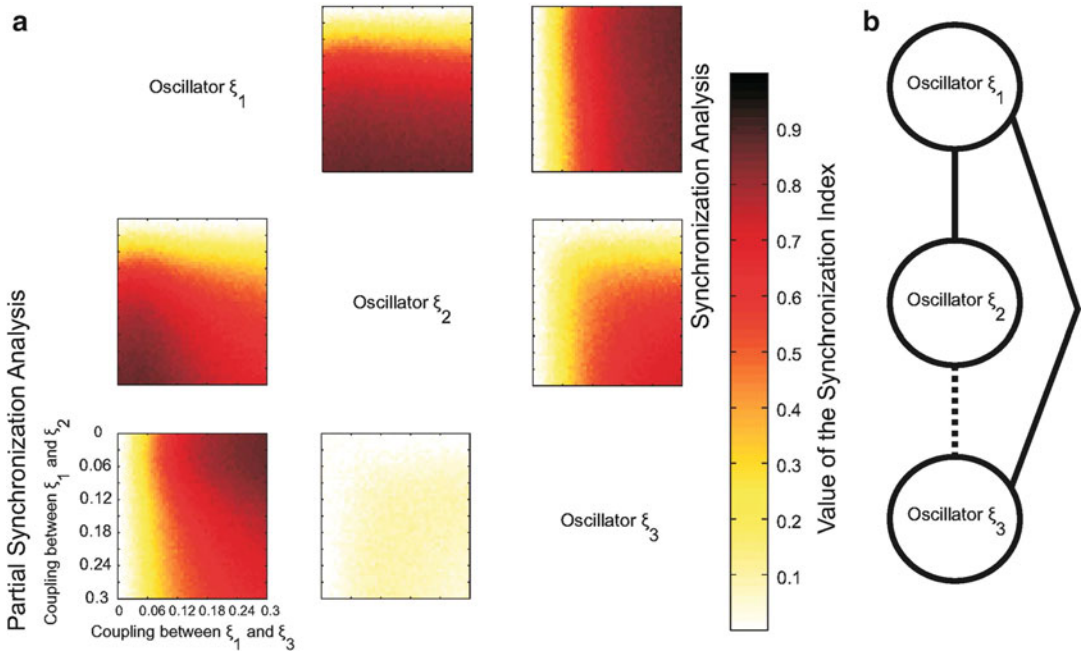
The 1:1 mean phase coherence and the partial phase synchronization indices are depicted in Fig. 1. The bivariate synchronization index mean phase coherence R_{12} , as well as R_{13} , increases for increasing coupling strength, indicating phase synchronization (Fig. 1a upper triangular). Once there is a sufficiently strong coupling between oscillators 1 and 2 as well as 1 and 3, indirect coupling is seen between 2 and 3 with a nonvanishing bivariate synchronization index R_{23} (Fig. 1a upper triangular). This high but spurious phase synchronization is caused by the common influence from oscillator 1. In the same figure (Fig. 1a below the diagonal), the results of partial phase synchronization analysis are shown. While $R_{12|3}$ and $R_{13|2}$ are essentially unchanged compared to the bivariate synchronization indices, $R_{23|1}$ stays almost always below 0.1 and therefore indicates this measure is due to spurious synchronization, indicating that there is an absence of a direct coupling between oscillators 2 and 3. Hence, the true underlying (multivariate) network structure is correctly revealed by the analysis (Fig. 1b).

Phase Dynamics Modeling

Another approach in reconstructing networks is to estimate the coupling functions $H_1(\Phi_1, \Phi_2)$ and $H_2(\Phi_2, \Phi_1)$ from observations of the dynamics. These reconstructions can, for instance, be based on approximating the functions H_1 and H_2 with trigonometric functions. With this approach, it has been shown that a reliable detection of interactions (Smirnov et al. 2007 and references therein) and therefore the reconstruction of the network topology are possible (Kralemann et al. 2011).

Recurrence-Based Approaches

If the processes are not phase-coherent, which is typically the case for many observed systems, the approach based on the direct calculation of the phases is not feasible because neither the phase nor the onset of phase



Determining Network Structure from Data: Nonlinear Modeling Methods, Fig. 1 (a) Phase synchronization as well as partial phase synchronization analysis. (b) Corresponding network as inferred from the observations

synchronization can be explicitly defined. Bivariate analysis of noncoherent systems has been approached by testing synchronization using alternate notion of the phase, i.e., a phase that builds on the general idea of curvature (Osipov et al. 2003). However, such a definition of the phase restricts the analysis to systems where the phase trajectory corresponds to a curve with a positive curvature on some projection plane. An alternative approach is based on recurrence analysis.

Recurrence Analysis

A synchronization measure based on the recurrences of a trajectory can also be used. This approach considers phase synchronization in a statistical sense. The notion of recurrences in phase space was originally introduced by Poincare (1890). A representation of these recurrences is given by the recurrence matrix (Eckmann et al. 1987; Marwan et al. 2007):

$$RP(\varepsilon)_{i,j} = \Theta(\varepsilon - \|\mathbf{X}(i) - \mathbf{X}(j)\|), i, j = 1, \dots, nn$$

where $\mathbf{X}(i)$ and $\mathbf{X}(j)$ denote trajectories of length n in phase space, $\Theta(\cdot)$ is the Heaviside function, $\|\cdot\|$ is an appropriate norm, and ε is a predefined threshold. If only a scalar time series has been observed, the state of the system, i.e., the vector $\mathbf{X}(i)$, can typically be reconstructed by delay embedding (Packard et al. 1980; Takens 1981; Sauer et al. 1991), where each dimension represents the data at some time lag τ in the past:

$$\mathbf{X}(i) = [\mathbf{X}(i), \mathbf{X}(i - \tau), \dots, \mathbf{x}(i - k\tau)]$$

When a series of points stays within a small distance apart, say within a small tube of radius ε around the other, that section of the trajectory corresponds to a diagonal of 1's in the recurrence matrix. Thus, an estimate of the probability

$$\hat{p}(\varepsilon, \tau) = RR_\tau(\varepsilon) = \frac{1}{L - \tau} \sum_{j=1}^{L-\tau} RP(\varepsilon)_{i,i+\tau}$$

that a system recurs to the ε -neighborhood of a former point of the trajectory after τ time steps is given by the diagonal-wise calculated recurrence rate $RR_\tau(\varepsilon)$.

This measure can be considered as a generalized autocorrelation function (Romano et al. 2005), since it also describes higher-order correlations among the points of the trajectory. It measures the adaptation of the time scales of two interacting systems by comparing their corresponding recurrence matrices; if the distances between diagonal lines in their recurrence matrices coincide, the time scales of the systems adapt to each other. To quantify this, the cross-correlation coefficient of the probabilities of recurrence can be calculated as follows:

$$CPR_{kl} = \langle \hat{p}_k(\varepsilon, \tau) \hat{p}_l(\varepsilon, \tau) \rangle, CPR_{kl} \in [0, 1]$$

In the case when the two systems have locked phase dynamics, the probability of recurrence is simultaneously high for both systems and the CPR_{kl} will differ from zero significantly. This synchronization measure has been demonstrated to be effective for detecting coupling in a general class of non-phase-coherent and nonstationary systems and even for time series corrupted by strong noise (Romano et al. 2005).

Multivariate Recurrence Analysis

Recurrence analysis can also be applied to a multivariate system with N interdependent and non-phase-coherent processes. To treat the multivariate case can be generated as a matrix of the bivariate CPR synchronization indices:

$$CPR = (CPR_{ij})_{i,j=1,\dots,N}$$

is used. This matrix has the same symmetry properties as the synchronization matrix for phasecoherent systems. Using the inverse

CPR^{-1} , the generalized partial synchronization index can be calculated:

$$CPR_{kl|Y} = \frac{|CPR_{kl}^{-1}|}{\sqrt{CPR_{kk}^{-1} CPR_{ll}^{-1}}}$$

This measure quantifies phase synchronization between two oscillators k and l , conditioned on third processes Y of a multivariate possibly non-phase-coherent and noisy oscillatory process (Nawrath et al. 2010).

Information Theoretic Approaches

Information theory-based approaches complement the nonlinear approaches presented above. The mutual information between time series X and Y can be calculated as follows:

$$I(X; Y) = \sum_{y \in Y} \sum_{x \in X} p(x, y) \log \frac{p(x, y)}{p(x)p(y)}$$

where $p(x)$ represents the probability that the signal X will have the amplitude x and $p(x, y)$ is the joint probability that the time series X will have the value x while simultaneously the time series Y will have the value y . Transfer entropy calculates the direction of information flow between two systems by testing how the information from the past of the two systems predicts the future of one of the signals:

$$T_{X \rightarrow Y}(k, l) = \sum p(y_{t+1}, y_t^{(k)}, x_t^{(l)}) \log \frac{p(y_{t+1} | y_t^{(k)}, x_t^{(l)})}{p(y_{t+1} | y_t^{(k)})}$$

This approach utilizes the fundamental concepts of the information theoretic approaches (Kantz and Schreiber 1997). The $p(y_{t+1} | y_t^{(k)}, x_t^{(l)})$ are the conditional probability density functions where the probability of y_{t+1} given the previous k points of the times series $y_t^{(k)}, x_t^{(l)}$.

The information and the transfer information as presented are bivariate; however multivariate extensions are straightforward as the (conditional) probability density functions can include more processes. The challenge in calculating these measures in higher dimensional densities is that they quickly become computationally intensive to find all the conditional probabilities. Solutions are possible and can, for instance, be found in Palus and Stefanovska (2003), Runge et al. (2012), or Wibral et al. (2012) and references therein.

Linear Approaches

Although linear approaches are strictly speaking not part of the nonlinear data-based modeling approaches, we include them here. They are indeed very powerful in revealing the true underlying network structure despite the fact that they are technically speaking not applicable. Due to space limitations, we can only discuss one of the linear approaches, although many more exist in the literature. We refer the reader, for instance, to Schelter et al. (2006a) and references therein.

The concept of Granger causality (Granger 1969) is based on the commonsense conception that causes precede their effects in time. Partial directed coherence

$$|\pi_{i \leftarrow j}(\omega)| = \frac{|A_{ij}(\omega)|}{\sqrt{\sum_m |A_{mj}(\omega)|^2}}$$

with

$$\mathbf{A}(\omega) = \mathbf{I} - \sum_{r=1}^p \mathbf{a}(r) e^{-i\omega r}$$

for an N -dimensional vector autoregressive process of order p (VAR[p] process)

$$\mathbf{X}(t) = \sum_{r=1}^p \mathbf{a}(r) \mathbf{X}(t-r) + \varepsilon(t),$$

where $\varepsilon(t)$ is a multivariate Gaussian white noise process with covariance matrix Σ . This measure

was introduced by Baccala and Sameshima (2001) as a measure of Granger causality.

Partial directed coherence $|\pi_{i \leftarrow j}(\omega)|$ provides a measure for the directed, linear influences from $X_j(t)$ onto $X_i(t)$ at frequency ω . It is estimated by fitting an N -dimensional VAR[p] model to the data and directly using the above equations with the parameter estimates substituted for the true parameters.

Particularly important for nonlinear systems is the corresponding pointwise α -significance level for the partial directed coherence (Schelter et al. 2006c)

$$\left(\frac{\hat{C}_{ij}(\omega) \chi_{1,1-\alpha}^2}{n \sum_m |\hat{A}_{mj}(\omega)|^2} \right)^{1/2}$$

where $\chi_{1,1-\alpha}^2$ is the $1-\alpha$ quantile of the χ^2 -distribution with one degree of freedom. The values

$$C_{ij}(\omega) = \sum_{ii} \left[\sum_{l,m=1}^p H_{ij}(l,m) \right.$$

$\left. (\cos(l\omega) \cos(m\omega) + \sin(l\omega) \sin(m\omega)) \right]$ can be calculated based on the inverse $\mathbf{H} = \mathbf{V}^{-1}$ of the covariance matrix $\mathbf{V}$ of the VAR[p] process $\mathbf{X}(t)$, which is composed of the entries

$\mathbf{V}_{ij}(l, m) = \text{cov}(X_i(t-l), X_j(t-m))$ for $i, j = 1, \dots, N$ and $l, m = 1, \dots, p$ (Luetkepohl 1993).

We emphasize that the significance level depends on the order of the vector autoregressive process; higher model orders lead to higher significance levels which in turn indicates that for higher models the ability to detect weak couplings decreases.

Partial directed coherence by construction is a multivariate analysis technique. It has been developed for linear stochastic processes. However, in neurophysiology, nonlinear stochastic processes are generating the time series. In most of these cases, the dependence structure is reflected in the linear second-order structure; for this reason the partial directed coherence discloses the network structure also for nonlinear processes.

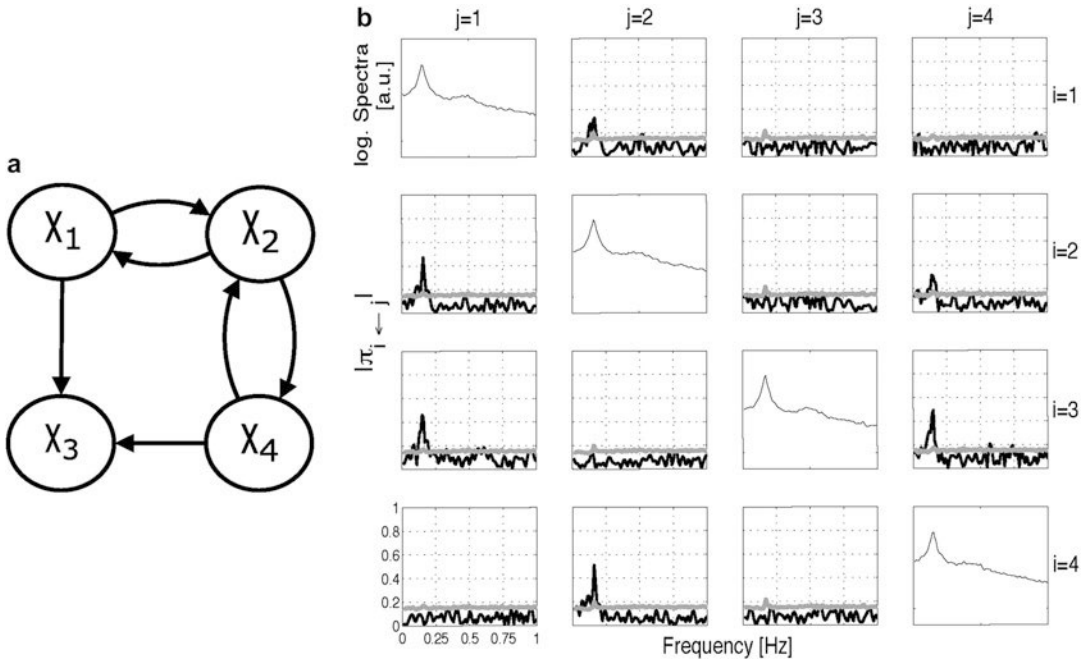
As an example system for which to test these tools, we will introduce a system of coupled stochastic van der Pol oscillators (van der Pol 1922):

$$\begin{aligned}
\ddot{X}_1 &= \mu(1 - X_1^2)\dot{x}_1 - \omega_1^2 X_1 + \sigma\eta_1 + \varepsilon_{12}(X_2 - X_1) + \varepsilon_{13}(X_3 - X_1) + \varepsilon_{14}(X_4 - X_1) \\
\ddot{X}_2 &= \mu(1 - X_2^2)\dot{x}_2 - \omega_2^2 X_2 + \sigma\eta_2 + \varepsilon_{23}(X_3 - X_2) + \varepsilon_{24}(X_4 - X_2) + \varepsilon_{21}(X_1 - X_2) \\
\ddot{X}_3 &= \mu(1 - X_3^2)\dot{x}_3 - \omega_3^2 X_3 + \sigma\eta_3 + \varepsilon_{34}(X_4 - X_3) + \varepsilon_{31}(X_1 - X_3) + \varepsilon_{32}(X_2 - X_3) \\
\ddot{X}_4 &= \mu(1 - X_4^2)\dot{x}_4 - \omega_4^2 X_4 + \sigma\eta_4 + \varepsilon_{41}(X_1 - X_4) + \varepsilon_{42}(X_2 - X_4) + \varepsilon_{43}(X_3 - X_4)
\end{aligned}$$

where the oscillators are given coefficients $\omega_1 = 1.5$, $\omega_2 = 1.48$, $\omega_3 = 1.53$, $\omega_4 = 1.44$, $\sigma = 1.5$, and Gaussian distributed white noise η_i . This system is simulated for $n = 50,000$ data points for each process to generate signals to apply the tools for reconstructing the network topology. Note that although the four oscillators are diffusively coupled and therefore their interactions are still linear, the system is nonlinear. The nonlinearity parameter μ is fixed to $\mu = 5$, leading to a highly nonlinear behavior of the van der Pol oscillators. The unidirectional and bidirectional couplings between these four nonidentical oscillators are

set to $\varepsilon_{12} = \varepsilon_{21} = 0.2$, $\varepsilon_{24} = \varepsilon_{42} = 0.2$, $\varepsilon_{31} = 0.2$, and $\varepsilon_{34} = 0.2$.

The causal influences are summarized in the graph in Fig. 2a. Estimated partial directed coherences as well as the spectra are given in Fig. 2b. The order of the vector autoregressive process is chosen to be $p = 200$. This high model order is required to reproduce the spectra with sufficient accuracy, as opposed to nonparametric spectral estimates. The corresponding 5% significance levels are indicated by gray lines. Partial directed coherence correctly detects the causal influences in the van der Pol system. Note that the significance level depends on the



Determining Network Structure from Data: Nonlinear Modeling Methods, Fig. 2 Causal influences for the example of four coupled stochastic van der Pol oscillators (a). Corresponding spectra (diagonal) and partial directed coherence (off-diagonal) (b). The

corresponding 5% significance levels are indicated by gray lines. The simulated causal influences are reproduced correctly since only those partial directed coherences that correspond to direct interactions are statistically significant at the oscillation frequencies

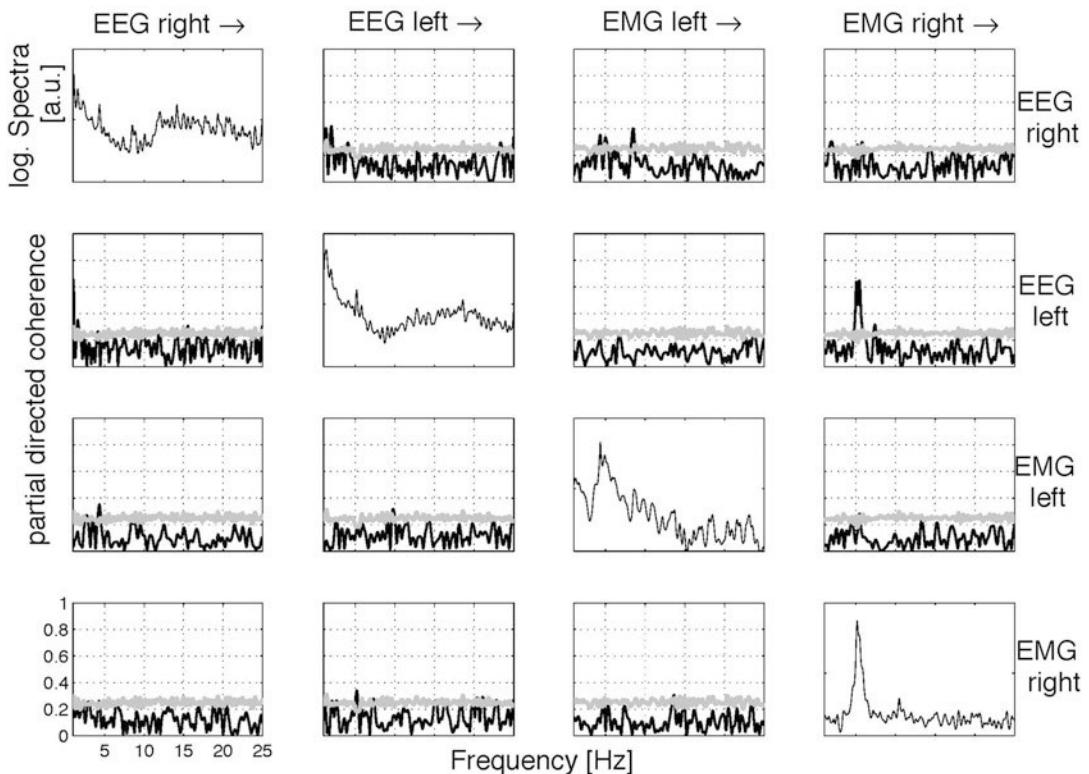
investigated frequency. At the peaks in the spectra of the van der Pol oscillators, the significance level is slightly higher than at the remaining frequencies. Thus, only those partial directed coherencies are statistically significant that correspond to a direct causal influences between the oscillators.

Application

So far, the multivariate analysis techniques presented here have been applied to simulated time series. To illustrate their performance in physiological applications, examples of patients suffering from essential tremor are presented.

The pathophysiological basis of essential tremor, a common neurological disease with a prevalence of 0.4–4% (Louis et al. 1998), is not precisely known. Essential tremor manifests

itself mainly in the upper limbs, when the hands are in a postural outstretched position. Usually the trembling frequency of the hands is 4–10 Hz. To elucidate the tremor generating mechanisms in essential tremor, relationships between the brain and trembling muscles are of particular interest. For unilaterally activated tremor, tremor-correlated cortical activity to the contralateral tremor side has been revealed by magnetoencephalography (MEG) and electroencephalography (EEG) for Parkinsonian tremor (Volkmann et al. 1996; Hellwig et al. 2001) and by electroencephalography for essential tremor (Hellwig et al. 2001). In bilaterally activated essential tremor, however, a more complex interrelation structure has been observed by simultaneous electroencephalographic recordings from the scalp and electromyographic (EMG) recordings from the extensor muscles (Hellwig et al. 2003). In addition to contralateral coherences,



Determining Network Structure from Data: Nonlinear Modeling Methods, Fig. 3 Partial directed coherence analysis for a patient suffering from essential tremor. A significant influence from the *right EEG* onto the

left EMG (3rd row/1st column), from the *left EMG* onto the *right EEG* (1st row/3rd column), from the *left EEG* onto the *right EMG* (4th row/2nd column), and from the *right EMG* onto the *left EEG* (2nd row/4th column) is detected

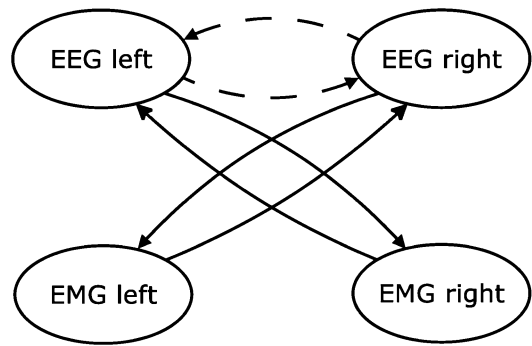
also ipsilateral coherences between the sensorimotor cortex and the muscles have been detected.

In this study, patients were seated in a comfortable chair having their forearms supported while their hands were outstretched to activate tremor. Data were sampled at 1,000 Hz. The EEG data as well as the EMG data were preprocessed applying a band-pass filter between 30 and 200 Hz to avoid aliasing and movement artifacts; the EMG was rectified afterward. The EEG was then high-pass filtered above 0.5 Hz to avoid baseline fluctuations and also anti-aliasing filtered. Scalp electrodes over the left and right sensorimotor cortex and the EMG of the left and right wrist extensor are analyzed.

It is of importance to investigate whether the cortex imposes its oscillatory activity on the muscles via the corticospinal tract or whether the muscle activity is just reflected in the cortex via proprioceptive afferences. To get these deeper insights into the tremor generating mechanisms, partial directed coherence is applied to data recorded from these patients.

In Fig. 3, the results of the partial directed coherence analysis for the two EMG and the two EEG channels are shown for an exemplary patient. Both directions from the cortex to the muscles and vice versa are observed. A significant influence from the right EEG onto the left EMG, from the left EMG onto the right EEG, from the left EEG onto the right EMG, and from the right EMG onto the left EEG is detected. Especially, the partial directed coherence from the right EMG to the left EEG is rather large.

The graph summarizing the results of partial directed coherence analysis for the essential tremor patient is presented in Fig. 4. The influences between both EEGs are marked by dashed arrows. This is due to the fact that partial directed coherence is not significant exactly at the tremor frequency but over a range of frequencies close to the tremor frequency. Since causal influences from both EEGs to the corresponding contralateral EMGs are present, participation of the motor cortex in tremor generation is strongly indicated. Moreover, there is also a significant partial directed coherence from the EMG to the contralateral EEG at the tremor



Determining Network Structure from Data: Nonlinear Modeling Methods, Fig. 4 Graph for partial directed coherence analysis of the tremor application of Fig. 3. The arrows indicate a direct and directed interrelation at the tremor frequency. The dashed arrows indicate possible interactions between the EEGs that could not be unambiguously shown

frequency. This corresponds to a feedback from the muscles to the somatosensory cortex. For both patients, unexpected ipsilateral interrelations are not detected by partial directed coherence analysis.

Summary

Several approaches to data-based modeling are conceivable. In this entry, we focused on a few multivariate approaches that enable to distinguish direct from indirect interactions. Some even provide directions for the interactions, for instance, Granger-causality-based concepts. In applications to observed nonlinear systems, the type of data, its dimension, noise contamination, and stationarity typically decides which technique can be applied and what conclusions can be drawn. Typically, simulation studies tailored to the problem at hand should be performed prior to any analysis.

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Deterministic Reaction-Diffusion Simulators

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Definition

A deterministic reaction-diffusion simulator is a software designed to approximate the dynamics of a system governed by the diffusion and interaction

of species within or across domains in a deterministic fashion.

Detailed Description

In a neural tissue, much physiological activity is governed or moderated by diffusion and interaction of many types of molecules and ions. Intracellularly, signaling molecules and ions such as cAMP, G-proteins, and calcium diffuse and moderate the activity of ion channels and other proteins. They also interact with receptors on organelles, as seen with calcium-induced calcium release. Extracellularly, bulk diffusion of glutamate, calcium, sodium, and potassium has both pathological and physiological effects. In addition to diffusion through the aqueous media of intracellular and extracellular space, there is also diffusion of signaling molecules and of ion-channel-forming proteins within the membrane. Modeling and simulating such complex reaction-diffusion systems accurately is needed for the mechanistic understanding of these processes.

Historically, reaction-diffusion simulators were developed to dissect the role of different molecules in signaling pathways and have been used by the systems biology community. In the past, most neural electrophysiology models were either kept completely separate from reaction-diffusion systems or used only simple approximations to implement phenomenological effects. Realizing the importance of coupling reaction-diffusion with excitability models, several tools have now been developed to handle it at various levels of detail. Most of these simulators provide options of running the simulations in a deterministic, stochastic, or hybrid manner. However, each of those simulations requires users to choose specific options which best describe the system. For example, stochastic simulations are more suitable when a small number of molecules are involved and high-resolution dynamics are required, whereas deterministic simulations suffice when a large number of molecules are involved and low-resolution dynamics are expected to give good approximation. Hybrid simulations allow to speed up the computations by using deterministic steps for the molecules

that are large in numbers and stochastic steps for molecules that are small in numbers.

Theory

Deterministic simulators are most appropriate when each compartment has a large number of molecules, either because the concentration is sufficiently high (e.g., sodium ions in a neuron) or because the compartment is sufficiently large. Either way, the law of large numbers (Kotelenez 1986) applies when many ions or molecules are present so that the dynamics of the population can be well approximated by the mean dynamics.

This assumption of large numbers underlies the key trade-off between deterministic and stochastic simulators. Deterministic simulations allow the use of a single number to represent the concentration in a given volume over a relatively large time step in the setting of large numbers of particles. Stochastic simulations are needed when the number of molecules is small, but exact stochastic methods generally require either a state variable for each molecule (which is computationally expensive) or small time steps (Kerr et al. 2008; Rathinam et al. 2003).

Fick's second law of diffusion states that the diffusion of a species with concentration u at position x (in one, two, or three dimensions) and time t within a domain is governed by

$$u_t = D\nabla^2 u \quad (1)$$

which states that the rate of change of concentration at a given point and time is proportional (with proportionality constant D , the diffusion constant) to the Laplacian of the concentration u , a measure of its unevenness. A reaction-diffusion equation for a single species is the diffusion equation except with an additional term $f(u, t)$ added to the right-hand side to describe reactions:

$$u_t = D\nabla^2 u + f(u, t) \quad (2)$$

When multiple species are present, the system of partial differential equations (PDEs) consists of many equations of this form, where the reaction

term may depend on all species present. Initial and boundary conditions complete the mathematical description (Fife 1979). In neuroscience, Neumann boundary conditions are common, as they describe the flux across the boundary, such as occurs through ion channels.

Practice

A reaction-diffusion simulator must specify the following: (1) **domains**, discretized volumes, areas (membranes), or lines (for 1D diffusion down a neurite); (2) **species**, molecules or ions that can be assigned to different domains; (3) **reactions**, among diffusion species or with fixed sites; and (4) **rates** of reactions and of diffusion (diffusion rates will differ among species).

Although diffusion is defined by a PDE (Eq. 1), most simulators internally convert all the PDEs into ordinary differential equations (ODEs) and from there to difference equations. The equations are typically solved using one of the three strategies: finite difference, finite elements, or finite volumes. Finite difference is the most mathematically straightforward, but unlike the other two strategies, it requires a uniform grid. Finite element methods assume concentration varies in a piecewise linear or nonlinear (based on spatial pattern) fashion within each element. Finite volume methods assume each volume is well-mixed which helps ensure conservation of mass.

A few commonly used deterministic reaction-diffusion simulators within the broader computational biology community are COMSOL (COMSOL Inc. www.comsol.com), COPASI (Hoops et al. 2006), FEniCS (Langtangen and Logg 2016), Morpheus (Starruß et al. 2014), and Virtual Cell (Loew and Schaff 2001). Both COMSOL and FEniCS are general-purpose PDE simulators, which provide a variety of functions to create different types of meshes and to simulate reaction-diffusion dynamics with discretized elements. COMSOL provides implicit and explicit methods for solving ODEs to tackle stiff and nonstiff problem. Additionally, it also includes

an advanced library of solvers (LAPACK, MUMPS, PARDISO, SPOOLES, Damped Newton methods, Double Dogleg, etc.) to tackle linear and nonlinear algebraic systems. FEniCS supports the creation of complex meshes using a technique called *constructive solid geometry*, which allows defining geometry in terms of simple shapes and set operations: union, intersection, and set difference. By default, FEniCS uses sparse LU decomposition (Gaussian elimination) to solve linear systems of differential equations. The interface with *linear algebra backends* allows using a variety of preconditioned Krylov solvers (iterative methods) for solving larger systems. A few of the methods are biconjugate gradient, conjugate gradient, generalized minimal residual, minimal residual, Richardson, parallel sparse LU, transport-free quasi-minimal residual, and UMFPACK. COPASI allows arbitrary discrete events for convenient interaction with the model. It also uses variably sized compartments to specify domains. Though COPASI is mainly a stochastic simulator, it allows deterministic simulations via LSODAR algorithm (Hindmarsh and Petzold 2005). Morpheus is a modeling and simulation environment for the study of multi-scale and multicellular systems. It allows coupling ODEs, PDEs, and cellular Potts models in 2D or 3D. It implements finite difference methods, Euler, Heun, and Runge-Kutta (RK4), all with fixed time step. Virtual Cell has been used to develop signaling pathway models in a large variety of cell types. It simulates on one-, two-, or three-dimensional domains specified either analytically or via segmented images discretized using a regular Cartesian mesh. It supports a variety of explicit, implicit, and semi-implicit finite volume methods. Although these simulators provide great functionality to study molecular pathways and related neurological phenomenon, they are not primarily designed to simulate electrophysiology models.

GENESIS (Bower et al. 2013), MOOSE (Ray and Bhalla 2008), NEURON (Carnevale and Hines 2006), and STEPS (Hepburn et al. 2012) allow coupling between reaction-diffusion system and electrophysiology models. Historically, general neural modeling software like GENESIS,

MOOSE, and NEURON allowed 1D longitudinal diffusion between compartments, which could be extended to 2D diffusion by specifying concentric shells within a compartment and writing equations for diffusion between adjacent shells.

These simulators have all now been extended to permit more general reaction-diffusion solutions: Chemesis (Blackwell and Kotaleski 2003) for GENESIS, Kinetikit (Vayttaden and Bhalla 2004) for MOOSE, and RxD (McDougal et al. 2013) for NEURON. In Chemesis, numerical methods for both reactions and diffusion use the GENESIS solvers and thus typically employ the exponential Euler method. Earlier version of Kinetikit used exponential Euler; however, Kinetikit 12 uses adaptive time-step fifth-order Runge-Kutta-Fehlberg from the GNU Scientific Library. NEURON RxD supports first- and second-order implicit fixed-step integration via implicit Euler and Crank-Nicolson (Crank and Nicolson 1996), respectively. NEURON also supports variable-step variable-order implicit methods from the SUNDIALS library (Hindmarsh et al. 2005). In addition to providing a user-friendly interface for modeling reaction-diffusion in NEURON, RxD also allows the specification of arbitrary spatial and volumetric domains. Three-dimensional extracellular simulations (Newton et al. 2018), solved using a parallelized Douglas-Gunn Alternating Direction Implicit method (DG-ADI) (Douglas and Gunn 1964), incorporate the effects of extracellular structures as local changes to the free volume fraction and tortuosity.

STEPS is primarily a stochastic simulator, but it also allows both deterministic and hybrid simulations. Reaction-diffusion in STEPS requires well-mixed volumes in the form of tetrahedrons. Any reconstructed 3D neuronal morphology can be used to specify arbitrary domains and then can be discretized into tetrahedrons using external software. STEPS supports deterministic spatial reaction-diffusion solutions by solver “TetODE,” which is based on the CVODE library.

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Diaphragm Pacing

- [Peripheral Nerve Interface Applications, Respiratory Pacing](#)

Diffusion Equation

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Synonyms

[Fick's second law](#); [Heat equation](#)

Definition

The diffusion equation (DE) is a second-order parabolic partial differential equation describing mass transport phenomena due to thermal motion of particles (Crank 1975).

Detailed Description

Diffusion is an important transport mechanism in neurons (Bloodgood and Sabatini 2005; Ehlers et al. 2007; Korkotian and Segal 2006; Makino and Malinow 2009; Qian and Sejnowski 1988; Renner et al. 2009; Sabatini et al. 2002; Santamaria et al. 2006; Schmidt et al. 2007a. Smith et al. 1993; Soler-Llavina and Sabatini 2006). It takes place in the cytosol, the cell membrane and the endoplasmic reticulum. Subject to diffusion are both ions (Ca^+ , Na^+ , K^+ , Cl^- , etc) and large complex molecules (lipids, proteins, DNA, RNA, etc.). The physical process of diffusion in absence of any chemical reactions is described by the diffusion equation:

$$\frac{\partial C(\mathbf{x}, t)}{\partial t} = \nabla \cdot (D(\mathbf{x}, t) \nabla C(\mathbf{x}, t))$$

where D is the diffusion coefficient (diffusivity) and C is the concentration.

In the case of constant isotropic diffusion coefficient, the DE,

$$\frac{\partial C}{\partial t} = D \nabla^2 C = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$$

is separable.

In the one-dimensional case, the DE becomes

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}$$

For an initial amount of substance M released at $t = 0$ and $x = 0$, assuming that $C \rightarrow 0$ as $x \rightarrow \pm \infty$, the solution to the one-dimensional DE is given by

$$C(x, t) = \frac{M}{\sqrt{4\pi Dt}} e^{((-x^2)/4Dt)}$$

and the mean square displacement (MSD) of the diffusing particles is a linear function in time $MSD \sim t$.

There are two approaches to deriving the DE: the phenomenological and the atomistic (Philibert 2005). The phenomenological

approach employs Fick's first law, stating that the flux of particles J is proportional to the gradient of the concentration

$$J = -D \frac{\partial C}{\partial x}$$

Since particles cannot be created or destroyed in the process, the flux of particles into a region must be equal to the particle flux out of the region, i.e., particles must satisfy the continuity equation:

$$\frac{\partial C}{\partial t} + \nabla \cdot J = 0$$

Combining Fick's first law with the continuity equation yields $\partial C / \partial t = \nabla \cdot (D \nabla C)$

Another way of deriving the diffusion equation is by introducing the concept of the random walk. Consider a particle moving along the real line starting at $t = 0$ and $x = x_0$. At each time step Δt , the particle can make a jump left or right at a distance Δx with equal probability.

Then the probability for the particle to be at position x at time $t + \Delta t$ will be

$$p(x, t + \Delta t) = \frac{1}{2} p(x - \Delta x, t) + \frac{1}{2} p(x + \Delta x, t)$$

Combining the Taylor expansions of the left and the right hand sides

$$p(x, t + \Delta t) = p(x, t) + p_t(x, t) \Delta t + O(\Delta t^2)$$

$$p(x \pm \Delta x, t) = p(x, t) \pm p_x(x, t) \Delta x + \frac{1}{2} p_{xx}(x, t) \Delta x^2 + O(\Delta x^3)$$

in the limit $\Delta t \rightarrow 0$ and $\Delta x \rightarrow 0$ leads to where

$$D = \lim_{\Delta t \rightarrow 0, \Delta x \rightarrow 0} \frac{\Delta x^2}{\Delta t}$$

Reaction-Diffusion Equation

In the presence of chemical reactions, additional terms (usually nonlinear) reflecting the various chemical reactions in the system can be added to the diffusion equation. Such a generalized

variation of the diffusion equation is known as the reaction-diffusion equation:

$$\frac{\partial C_A(x, t)}{\partial t} = \nabla \cdot (D_A(x, t) \nabla C_A(x, t)) + \sum_{i=1}^N f_i(C_A, R_i)$$

where R_i are the reactants interacting chemically with substance A.

Anomalous Diffusion

Random walks with biased jump probabilities give rise to the so-called anomalous diffusion. In that case, the MSD of the diffusing particles is a power law, i.e., $MSD \sim t^\alpha$. The regime with $0 \leq \alpha \leq 1$ is called subdiffusion, and the regime with $\alpha > 1$ is called superdiffusion (Metzler and Klafter 2000).

Anomalous diffusion can be described in terms of fractional calculus, i.e., the anomalous diffusion equation can be written as

$$\frac{\partial^\alpha C}{\partial t^\alpha} = D \frac{\partial^2 C}{\partial x^2}$$

where the fractional derivative of the Riemann-Liouville type for is given by

$$D_t^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \frac{d}{dt} \int_0^t \frac{f(\tau)}{(t-\tau)} d\tau$$

Applications

Diffusion in neurons has been modeled using 1D to 3D approximations with stochastic and differential equation models (Santamaria et al. 2006; Santamaria et al. 2010; Santamaria et al. 2011; Bressloff and Earnshaw 2009; Brown et al. 2008; Jedlicka et al. 2011; Schmidt et al. 2007b; Holcman and Triller 2006). A large number of studies have concentrated in the diffusion of intracellular calcium ions. Calcium ions can activate potassium channels or act as second messengers in biochemical cascades activated by synaptic activity.

Differential Versus Stochastic Simulation

It could be confusing that the same physical process can be modeled with two frameworks. Choosing between modeling using differential equations or a stochastic process depends on the nature of the problem. The differential equation diffusion model is amenable to be applied to compartments as those used in modeling the electrical activity of neurons. The fundamental properties of the equation are identical to those of the cable equation. When using more complex dendritic structures, solving the diffusion equation becomes computationally expensive. A reality check has to be performed when using differential equation since the volumes being investigated could be very small and the concentrations could be in the nanomolar range. If the concentrations being modeled are equivalent to fractions of molecules that would call into question the results of the simulations, especially if there are biochemical reactions involved.

The stochastic simulation strategy is used when the model is tracking the position of individual molecules or small groups of molecules. In this case boundary conditions are solved by assuming that particles collide and are reflected. Although highly accurate, this process could become computationally intractable for large sections of dendritic tree being modeled and is not easily integrated into compartmental models of electrical activity.

Shell Approximation

In compartmental modeling the electrical variables (conductances, voltages, and currents) are homogeneous through the compartment (Jedlicka et al. 2011). However, if calcium ions flow into the cell, they could diffuse to the center of the dendrite or along the dendrite. To simulate this mechanism, the problem is simplified to a 2D diffusion process. Within a single compartment, it is assumed that the concentration of a molecule will be homogenous along the radial axis of the compartment; thus, the volume is divided into concentric shells. Diffusion takes place between contiguous shells with each shell potentially having immobile buffers. Diffusion from one compartment to its neighbors has been implemented on shells of the

same level across compartments. Thus, each compartment has the same number of shells, but not all shells have the same thickness due to variations in the diameter of each compartment.

Stochastic Approximation

The diffusion of molecules inside a dendrite can be modeled with a random walk. Each molecule is characterized by a diffusion coefficient. From this diffusion coefficient, a random number generator chooses distances to move along a random direction. The average movement of the particle can be described with the stochastic version of the diffusion coefficient ($\text{MSD} \sim t$). If a particle collides with a membrane, then the molecule is reflected and continues its movement. This type of modeling can be used to study the diffusion of ions and proteins in dendrites and spines. The shapes of dendrites can be modeled or obtained from serial electron microscope reconstruction. The same strategy has been used to study the lateral mobility of glutamate receptors in and out of a synapse.

Modeling Anomalous Diffusion

The fundamental assumption to use the stochastic or differential equation models of diffusion is that molecules are moving without any memory of their past. This is called a Markovian process. However, the complex structure of dendrites can impose correlations in the diffusing molecules. For example, when molecules move along dendrites, they can enter a spine. Due to the spine bottle-neck produced by the spine head to neck diameter ratio, the molecule remains trapped in the spine for a random period of time. Once the molecule escapes one spine, it can then be trapped by another spine. If the dwell time in each spine varies widely, then the position of the molecule along the dendrite can no longer be assumed to be Markovian. Instead, the diffusion of the molecules becomes correlated due to the density of spines and their shape. It has been experimentally shown that this process causes anomalous diffusion in Purkinje and hippocampal pyramidal cells (Santamaria et al. 2006, 2011).

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Digital Filtering

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Definition

Digital filtering is the process of transforming a discretely sampled input signal into an output signal, such that certain spectral characteristics of the input signal are lost, while others are retained. In neuroscience, it is performed on time series that represent electrophysiological or hemodynamic signals measured over time. Whereas analog filters are applied online and implemented as electronic circuits, digital filters are applied off-line and implemented in software.

Detailed Description

Introduction

A digital filter is an important signal processing tool for the analysis of neuroscientific data. It is used to increase sensitivity to aspects of the signals that are of interest while suppressing noise. For the purpose of simplicity, we will focus on electrophysiological time series, e.g., temporal fluctuations of the electric potential measured at the scalp (for an extensive treatment of digital

filters see Smith 2003). Yet, a digital filter can be applied to any discrete signal sampled as a function of time, e.g., hemodynamic time series, but also to signals sampled across space such as an anatomical image obtained with magnetic resonance imaging (MRI). Typical applications of digital filters in computational neuroscience include the removal of (power-)line noise, high-pass filtering prior to rectification for the analysis of multiunit activity, and low-pass filtering for the reduction of high-frequency noise prior to event-related potential averaging.

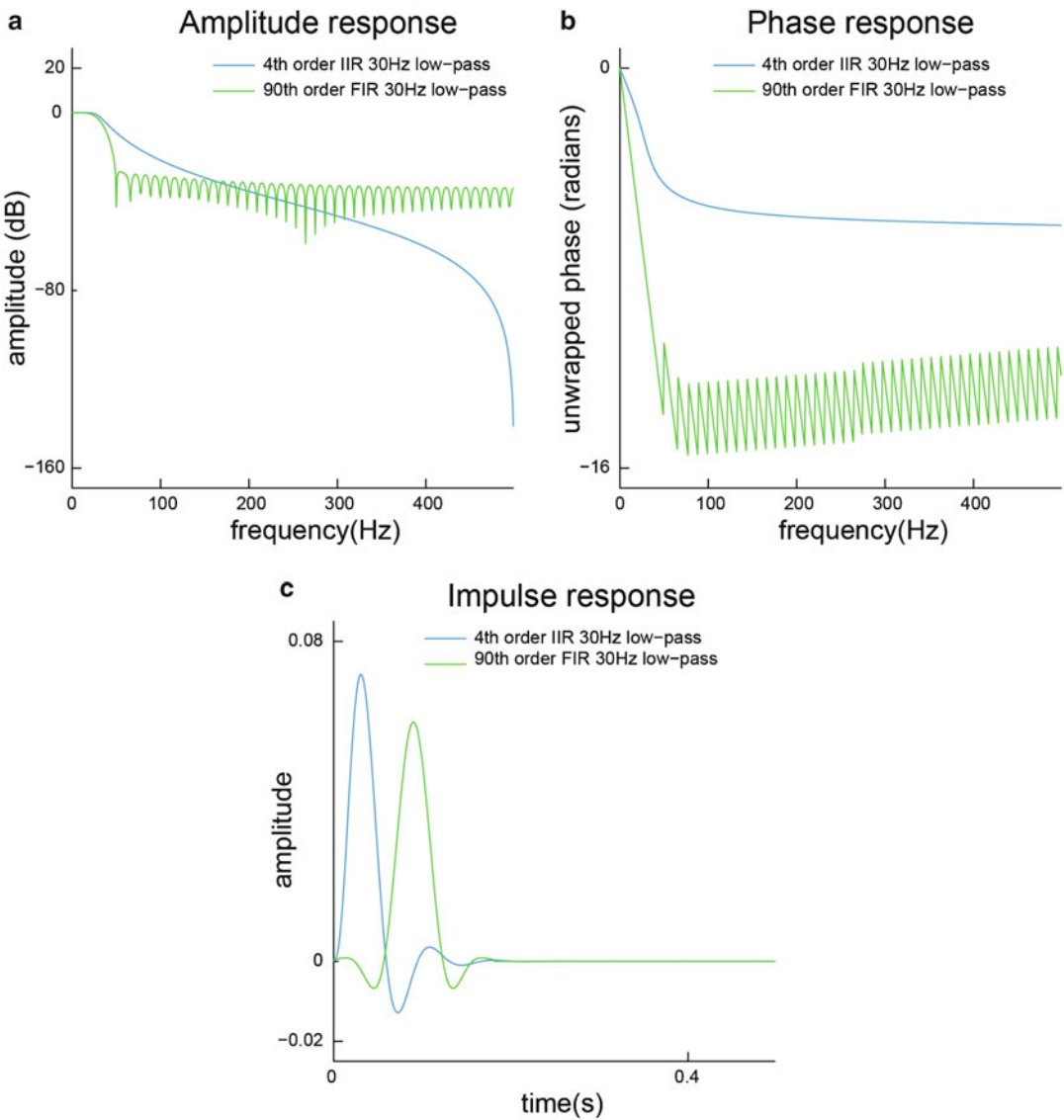
A digital filter changes the shape of the input signal in a way that can be fully characterized by means of its impulse response. For practical purposes, however, it is more convenient to describe filter performance in terms of its frequency domain response.

Frequency Domain Performance

A filter is designed to keep certain spectral content and remove others. For example, a high-pass filter only passes spectral content from the input signal above a certain cutoff frequency, and a band-stop filter suppresses spectral content in a certain frequency band. A more detailed account of filter performance is given by the filter's amplitude and phase response as a function of frequency (Fig. 1a, b). This can be obtained by taking the discrete Fourier transform of the impulse response (Fig. 1c).

The ideal amplitude response would be a box-car function, indicating that the amplitude of the “pass” frequencies is unaffected and the amplitude of the “stop” frequencies is fully suppressed. In reality, however, the transition from passband to stopband is in general much more gradual, and the amount of attenuation in the stopband is variable. Figure 1a (blue) shows as an example the amplitude response of a 30 Hz low-pass filter, with a slow but deep roll-off. The filter in Fig. 1a (green) has a steep but oscillating roll-off. A filter can also have unwanted effects on the “pass” frequencies.

The phase response shows to what extent the phase of the oscillatory components in the input



Digital Filtering, Fig. 1 Example of two 30 Hz low-pass (forward) filters. (a–c) *blue lines* are the fourth-order IIR forward filter (Butterworth), and *green lines* are the 90th-order FIR forward filter (window method). (a) Amplitude response. Note the fast but oscillating roll-off of the FIR

filter (*green*) and the slow but deep roll-off of the IIR filter (*blue*). (b) Phase response. The FIR filter has a linear phase for the first part of the stopband. The IIR filter has a nonlinear phase throughout the stopband. (c) Impulse response

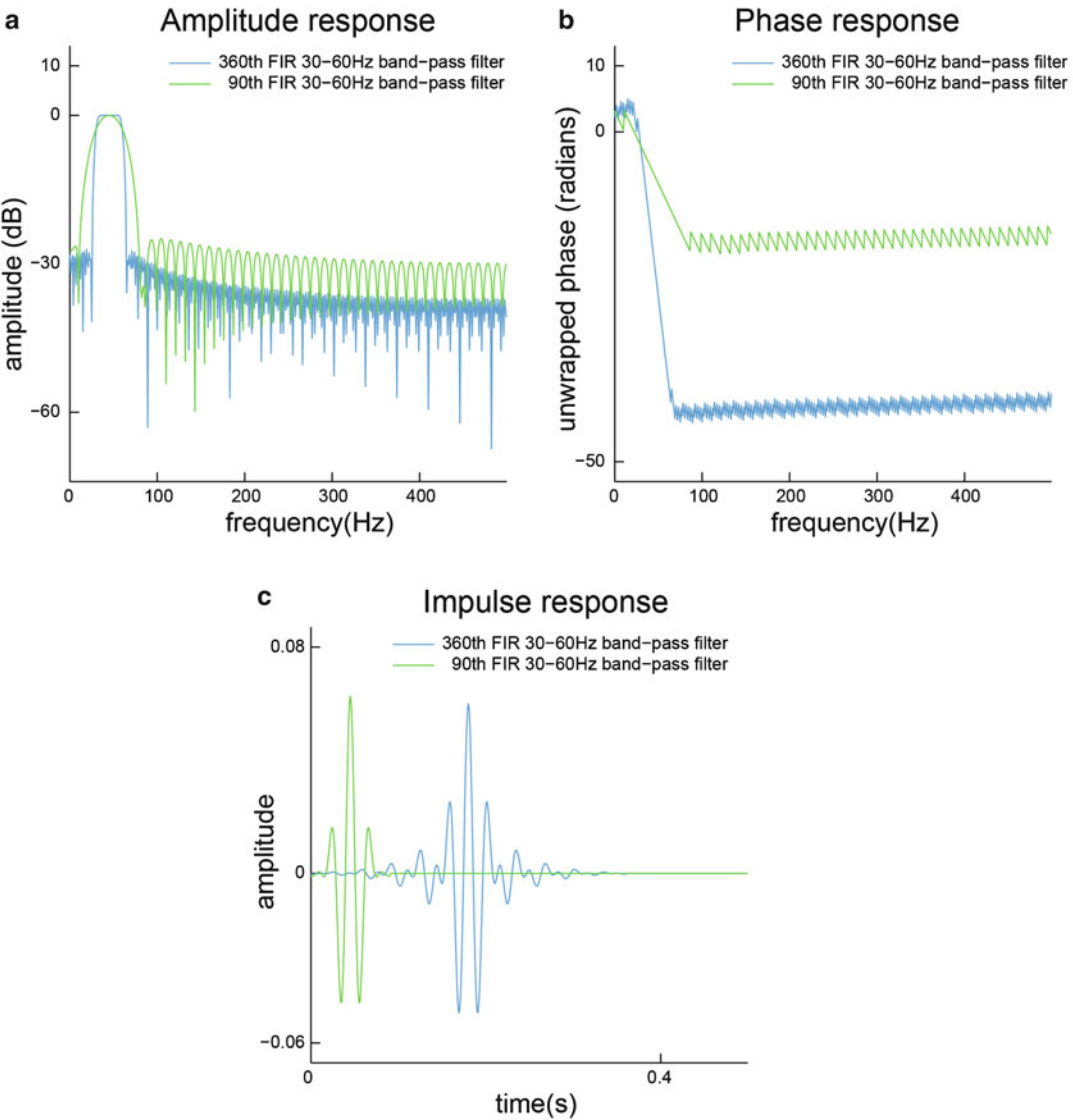
signal is affected by the filter. Filters that do not introduce a phase shift, i.e., the peaks of the oscillations in the output signal occur at the same time points as the peaks of the oscillations in the input signal, are called zero phase, or acausal filters. In contrast, nonzero phase or

causal filters introduce a phase shift, which can be either linear as a function of frequency (Fig. 1b, green) or nonlinear (Fig. 1b, blue). The desired phase response depends on the aim of the analysis step. In most cases a zero phase or acausal filter is desired.

Affecting the Amplitude Response

The amplitude response of a filter is determined mainly by the filter order. Filter order can be thought of as the “length” of the filter. It specifies how much time-domain information from the input signal is used to construct each sample of the output signal. The higher the filter order, the

better individual frequencies can be distinguished, thus leading to “faster” transitions in the amplitude response (also termed fast roll-off) (Fig. 2a, blue). In contrast, a low filter order results in a “slow” amplitude response (slow roll-off) (Fig. 2a, green). Additionally, the longer the impulse response, the further oscillatory components are time shifted in the output signal, i.e., the



Digital Filtering, Fig. 2 Example of a high and low order 30–60 Hz band-pass (forward) FIR filter. (a–c) *blue lines* are the 360th-order FIR forward filter (window method), and *green lines* are the 90th-order FIR forward filter (window method). (a) Amplitude response. The higher-

order filter shows a considerably quicker passband to stopband transition. Higher-order filters use more time-domain information and can thus more easily distinguish neighboring frequencies. (b) Phase response. (c) Impulse response

bigger the phase shift in the phase response (Fig. 2b). Note that there is always a trade-off between frequency and time resolution (Fig. 2c). A higher filter order trades time resolution for a sharper amplitude response.

Affecting the Phase Response

Typically the phase response is considered to be of less importance than the amplitude response. In applications where the phase of the oscillations is relevant, it should always be taken into account. Practically, any causal filter can be made acausal. This is achieved by filtering the input signal twice, in opposite directions. The phase shift introduced in the first filter step is “undone” by the filter applied to the signal in reverse (Fig. 3). These two steps are also called forward and backward filtering. Note that this bidirectional filtering attenuates all amplitudes twice as compared to unidirectional filtering.

Two Classes of Filters

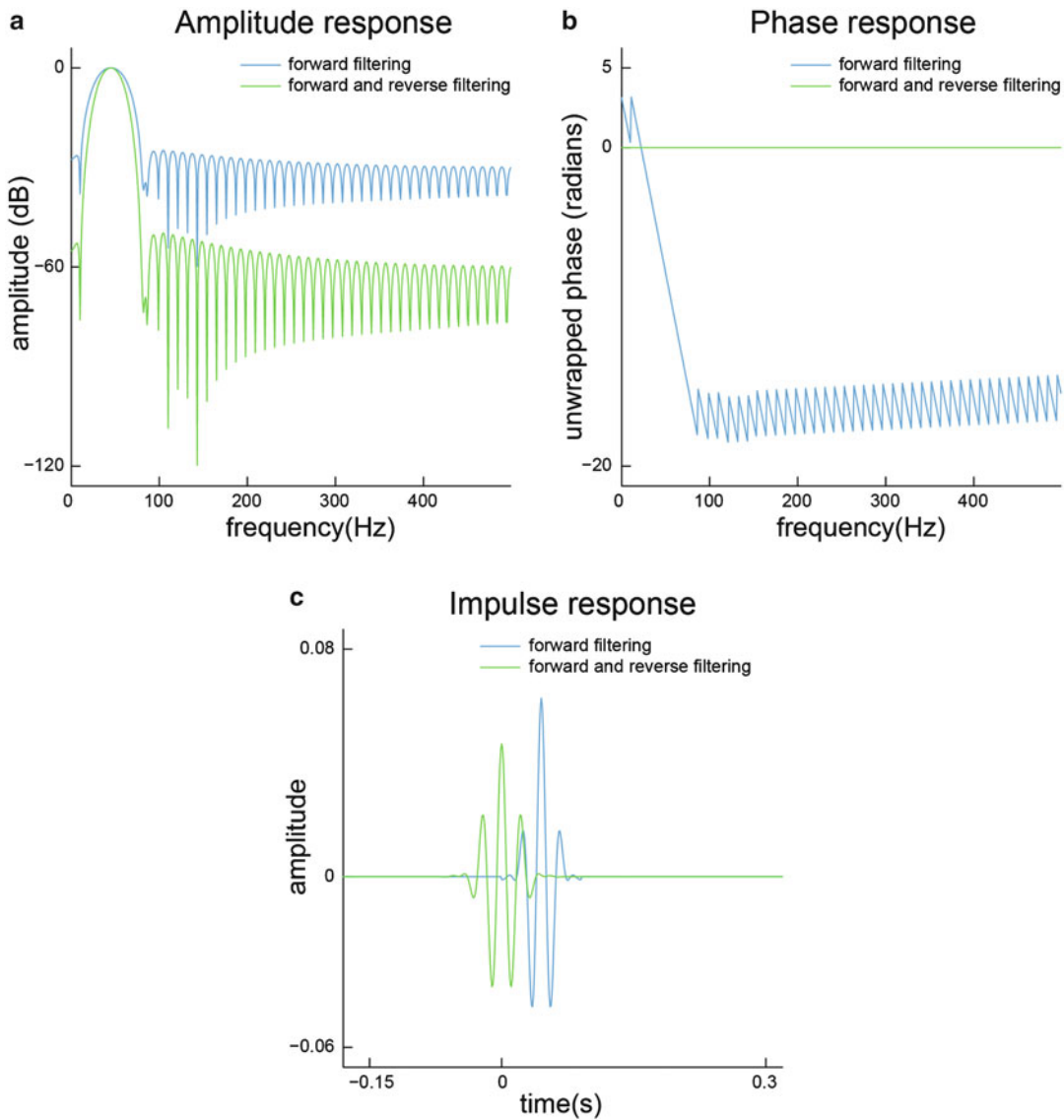
Of the many types of filters that exist, two broad classes can be distinguished: (1) convolution, or finite impulse response (FIR) filters, and (2) recursive, or infinite impulse response (IIR) filters. FIR filters operate by convolution of the input signal with the filter coefficients. In short, the result of the convolution operation is that each sample in the output signal is constructed as a weighted sum of N samples of the input signal, where N represents the filter order and the weights are given by the filter coefficients. As a consequence the length of the impulse response is equal to the filter order, which gives the FIR filter its name. The filter coefficients can be constructed in various ways. A common approach is the “window method,” in which an ideal IIR filter is constructed and then truncated by a particular window function (such as a Hamming window) of N samples. Another approach is the “least squares method,” in which a filter of order N is found whose amplitude response is the least squares approximation of the desired amplitude response.

IIR filters operate in a different way. In this case each sample of the output signal is constructed from a weighted combination of N samples of the input signal and of $N-1$ previously obtained samples of the output signal. Because of this recursion, all previous samples in the input signal contribute to the output signal. The impulse response thus is infinitely long, which gives the IIR filter its name. Still, most of the energy of the impulse response is concentrated in a limited number of samples, the length of which depends on the filter order, the pass/stop frequencies, and their range. Commonly used IIR filters are Butterworth and Chebyshev filters.

Which class of filter is most optimal depends on the situation. In general FIR filters are preferred when temporal spread of the impulse response is undesired. An example would be band-pass filtering followed by a Hilbert transform to estimate temporal fluctuations in the amplitude and phase of band-limited signal components. In this case it is desired to have full control over the temporal information that is used to construct the filtered signal, because one would like to relate more or less precisely the “instantaneous” amplitude to the time point at which that amplitude occurred. The FIR filter order directly specifies the temporal information that is used. An IIR filter will only provide very indirect control of temporal spread and is therefore less ideal to use in this scenario. Note that FIR filter bandwidth must be sufficiently large for a well-behaved amplitude response. When the length of the impulse response is unimportant, IIR filters are often the preferred choice, as they are more computationally efficient than FIR filters. An example would be the suppression (power-)line noise. In this case it is irrelevant how much temporal information is used, as long as the noise is maximally suppressed. Temporal spread of the impulse response is important to keep in mind for other practical considerations such as edge artifacts (described in the next section).

Edge Artifacts

Apart from desired effects, a filter can also have undesired effects. A common one is an

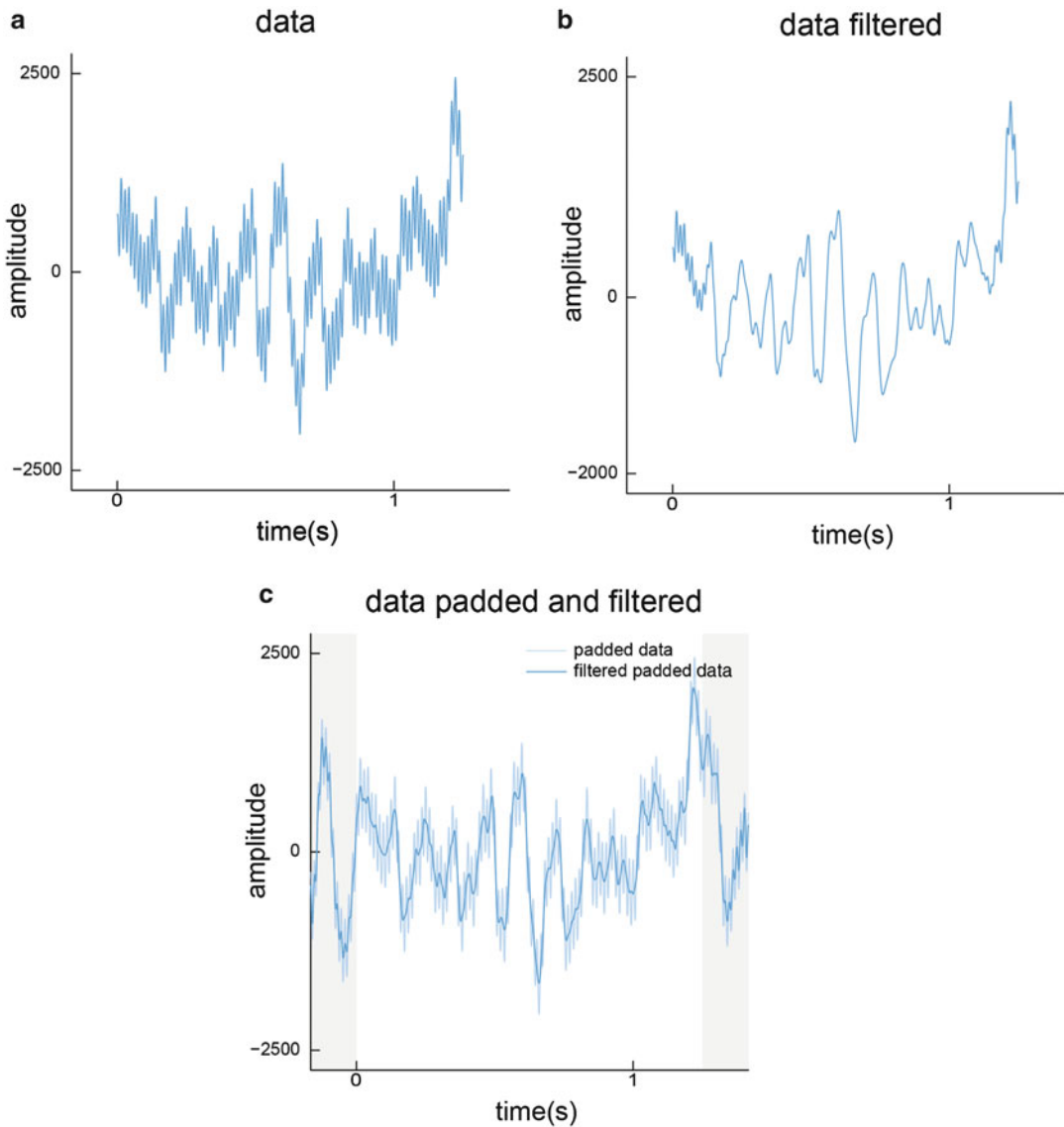


Digital Filtering, Fig. 3 The effect of bidirectional filtering with a 30–60 Hz band-pass 90th-order FIR filter (window method). (a–c) *blue lines* represent filtering only in the forward direction, and *green lines* represent forward *and* reverse filtering. (a) Amplitude response. The bidirectional filter (*green*) has a much stronger amplitude attenuation of the stopband but also has a faster roll-off. (b) Phase response. The original forward filter shows a

considerable linear and nonlinear phase shift. The bidirectional filter, however, has zero phase, indicating that all of the phase shifting of the forward filter is reversed. (c) Impulse response. In this example, the impulse was centered at $t = 0$. Because the forward filter was causal, the impulse response occurs *after* $t = 0$. The bidirectional filter is acausal; however, the impulse response is centered *around* $t = 0$

edge artifact, from which all filters suffer. When filtering the beginning of a signal, the filter is not fully immersed in the data. Because only a part of the filter is used, the performance is very poor, resulting in “filter

ringing” at the edges (Fig. 4a, b). It takes an FIR filter at least N samples of the input signal to stabilize, where N is the filter order. For an IIR filter it is more complicated, as the other parameters play an equally important role. The



Digital Filtering, Fig. 4 Example of edge artifacts and their prevention. *Panel A* shows 1.5 s of example data with a strong 60 Hz line noise component on top of it. In order to remove this, a 59–61 Hz band-stop fourth-order bidirectional IIR filter (Butterworth) is used (*panel B*). However, at the edges of the signal, the filter is not fully immersed in

the data, causing residual 60 Hz noise to present. In order to remedy this, a larger data segment is filtered (200 ms data padding on each side; *panel C*; gray boxes). The edge artifacts now occur in the padded segments. After removal of the padded segments, the original 1.5 s of data is artifact-free

easiest solution to edge artifacts is data padding. By filtering a longer signal than required, the artifacts end up in the uninteresting parts of the signal, which can be cut off afterward (Fig. 4c). Other padding methods, like mirror/zero/mean padding, are less optimal, because these may introduce sharp transitions in the signal.

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Further Reading

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Direct Current Nerve Block (DC Block)

► [Peripheral Nerve Stimulation Technique, Nerve Block](#)

Directed Information Flow and Causality in Neural Systems

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Definition

In the human experience, information typically flows from one place to another. By contrast, the notion of mutual information introduced by Shannon (1948) is perfectly symmetric in its arguments and does not distinguish between “input” and “output.” In this sense, it is perhaps surprising that this very measure of information indeed captures the capacity of any communication channel – though we should recall that the proof of this fundamental fact is not merely a simple consequence of Shannon’s definition.

In spite of Shannon’s strong and fundamental results, it has been tempting to define a notion of *directed* information. This was first proposed in (Marko 1973) for stationary processes. The more general and useful definition was given in the brief and beautiful note by Massey (1990). Moreover, Massey (1990), Kramer (1998) and subsequent work revealed that directed information has a natural place in the study of information transmission with feedback from the output to the input.

In the present note, a different aspect of directed information is illuminated: that of identifying causal relationships. The basic idea is that if there is a causal relationship from one process to another, the directed information in the forward direction should be large. Additionally, one may also require the directed information in the reverse direction to be small.

It is important, however, to observe that inferring causality from observations is an ill-posed question. This has been discussed in depth in the context of Granger causality (Granger 1969), where a rich literature exposes several fundamental issues. The same qualitative issues apply to any causality argument based on directed information measures. The difference is that Granger causality uses correlation measures, whereas here, we consider directed information.

Detailed Description

Directed Information

The usual mutual information can be defined between any two random variables. For directed information, however, we need to consider *ordered sequences* of random variables.

Specifically, for two random sequences $X = (X_1, X_2, \dots, X_N)$ and $Y = (Y_1, Y_2, \dots, Y_N)$ of equal length N , the directed information is defined as

$$I(X \rightarrow Y) = \sum_{n=1}^N \{I(X_1, \dots, X_n; Y_1, \dots, Y_n) - I(X_1, \dots, X_n; Y_1, \dots, Y_{n-1})\},$$

where $I(\cdot;\cdot)$ denotes the regular Shannon mutual information. Let us first record that this is always nonnegative: $I(X \rightarrow Y) \geq 0$, which follows directly from the definition and the fact that Shannon mutual information is always nonnegative. Second, we note that the directed information is never larger than the regular Shannon mutual information between the two sequences.

Moreover, it is tempting to ask about the relationship between the forward directed information $I(X \rightarrow Y)$ and the reverse directed information $I(Y \rightarrow X)$. For general probabilistic models, there does not appear to be an intuitively pleasing connection between these two. However, if one considers instead the following new random sequence $\tilde{Y} = (0, Y_1, Y_2, \dots, Y_{N-1})$, then the following conservation law applies (Massey and Massey 2005):

$$I(X \rightarrow Y) + I(\tilde{Y} \rightarrow X) = I(X; Y), \quad (1)$$

where the latter denotes the regular Shannon mutual information between the two sequences X and Y .

To have a brief and simple example, let us consider the situation where $(X_1, X_2, \dots, X_N)$ are independent normal (Gaussian) random variables of mean zero and variance 1. Let Y_1 also be a mean-zero unit-variance normal. For $n \geq 2$, we set $Y_n = \alpha X_{n-1} + W_n$, where W_n are independent normal random variables of mean zero and variance $1 - \alpha^2$ and $0 \leq \alpha \leq 1$. Then, the directed information evaluates to

$$I(X \rightarrow Y) = \frac{N-1}{2} \log_2 \left(1 + \frac{\alpha^2}{1 - \alpha^2} \right). \quad (2)$$

In this example, the reverse directed information vanishes: $I(Y \rightarrow X) = 0$.

Finally, we also note that another 10 years later, directed information was again discovered (interestingly again with a stationarity assumption) under the name of transfer entropy (Schreiber 2000).

Directed Information in Networks

The concept of information flow requires that information cannot be created simply by processing a signal in a particular way. For mutual information, this is ensured by the data processing inequality, stating that the mutual information cannot be increased by further processing of the output signal. For directed information, the situation is a little more complex. Namely, a data processing inequality still applies but only to *causal* processing of the output signal. That is, if Z is a sequence obtained by processing the sequence Y in a causal fashion, possibly involving additional independent randomness, then we have that

$$I(X \rightarrow Z) \leq \min \{I(X \rightarrow Y), I(Y \rightarrow Z)\}. \quad (3)$$

As with all information measures, the reverse is not true. More precisely, let us reconsider the scenario just discussed involving the sequences X , Y , and Z . Then, even if both $I(X \rightarrow Y)$ and $I(Y \rightarrow Z)$ are large, this *does not* imply any lower bound on $I(X \rightarrow Z)$; in fact, the latter might even be zero.

Information Measure of Causality

Directed information can be postulated to be a measure of causality in the following sense: One claims a causal relationship from X to Y if the directed information $I(X \rightarrow Y)$ is large. In the explicit example involving normal random variables discussed above, this is easy to see: The directed information from X to Y is large, and indeed, for this example, we would expect any rationale to conclude that the sequence X drives the sequence Y in a causal fashion (at least as long as α is close to one). Moreover, in this example, $I(Y \rightarrow X) = 0$, ruling out any causal relationship in the reverse direction.

The remaining issue is to define a threshold on the directed information above which the relationship is claimed to be causal. There is no

intuitive a priori rule, and in most cases, the threshold must be selected arbitrarily or using additional knowledge of existing causal connections, e.g., from physiological insight into the considered connection. To make matters more complicated, it is also important to notice that due to the nonnegativity of directed information, most classical estimators must be expected to have a positive bias.

It should also be noted that this is closely related in spirit to the notion of Granger causality (Granger 1969). In the latter, *correlation* (i.e., second-order statistics) is exploited to claim causality. Directed information, by contrast, is sensitive to the full probability distribution in the usual entropy sense. Note that when directed information is considered with normal distributions, it is closely related to Granger causality.

Experimental Studies

Directed information measures have been recently applied to simultaneous recordings in the primary motor cortex of rodents and macaque monkeys (Quinn et al. 2011; So et al. 2012), leading to conjectured causality maps (directed graphs) between the observed neurons. An additional rich literature concerns the transfer entropy mentioned above, but is discussed elsewhere.

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Directed Spectral Methods

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Definition

Directed spectral measures quantify, in the frequency domain, directed statistical interactions between time-series variables. Most commonly, the various measures are computed based on a (linear) multivariate autoregressive (MVAR) model of the data. The various methods quantify in different ways the strength of interaction terms in the Fourier transform of the MVAR model. While these methods are sometimes referred to as capturing “causal” or “effective” connectivity, they are most properly described as reflecting “directed functional connectivity” (Friston et al. 2013).

Detailed Description

For a multivariate n -channel process $X(t) = [X_1(t), X_2(t), \dots, X_n(t)]^T$ (with zero mean), the MVAR model is given by:

$$\mathbf{X}(t) = \sum_{k=1}^p \mathbf{A}_k \cdot \mathbf{X}(t-k) + \epsilon(t), \quad (1)$$

where the $\mathbf{A}_k$ are matrices of regression coefficients, p is the model order, and $\epsilon(t)$ are the residuals (Lütkepohl 2007). The coefficients of this model are uniquely specified by imposing zero correlation between the residuals and the regressors $\mathbf{X}(t-k)$, $k = 1, \dots, p$, and can be derived from the Yule-Walker procedure (Ding et al. 2006). Ideally, the model order should be sufficiently high to obtain a good representation of the data, but not so high that overfitting and poor parameter estimation occur. Commonly the model order is selected based on minimizing either the Akaike Information Criterion or the Bayes Information Criterion, both of which balance the residual variance against the number of coefficients to be estimated (Ding et al. 2006).

Directed spectral measures are computed from the frequency domain representation of the MVAR model:

$$\mathbf{A}(\omega) \cdot \tilde{\mathbf{X}}(\omega) = \tilde{\epsilon}(\omega), \quad (2)$$

where explicitly in terms of the regression coefficients:

$$\mathbf{A}(\omega) = \mathbf{I} - \sum_{k=1}^p z^k \mathbf{A}_k, \quad (3)$$

$z = e^{-2i\pi\omega\Delta t}$ and Δt is the time between observations. (Let tildes denote Fourier transform and dagger the Hermitian conjugate.) The measures are written in terms of $\mathbf{A}(\omega)$, the spectral density (or power) $S(\omega) = \tilde{\mathbf{X}}(\omega) \cdot \tilde{\mathbf{X}}^\dagger(\omega)$, the covariance matrix of the residuals Σ , and also the transfer matrix $\mathbf{H}(\omega) =: \mathbf{A}^{-1}(\omega)$, which yields $\tilde{\mathbf{X}}(\omega)$ when it acts on the Fourier transformed residuals:

$$\tilde{\mathbf{X}}(\omega) = \mathbf{H}(\omega) \cdot \tilde{\epsilon}(\omega). \quad (4)$$

Nonparametric estimation. An alternative method for computing directed spectral measures involves obtaining the transfer matrix directly from

Fourier and wavelet transforms of the data, obviating the need to explicitly fit an MVAR model (Dhamala et al. 2008; Percival and Walden 2000). An advantage of this approach is that it bypasses the need for model order estimation; however, this is replaced with the task of choosing the wavelet prototype and number of tapers appropriately.

Granger-Geweke Causality (GGC)

For a pair of variables $\mathbf{X}(t) = [X_1(t), X_2(t)]^T$, the Granger-Geweke causality $\text{GGC}_{2 \rightarrow 1}(\omega)$ from X_2 to X_1 at frequency ω quantifies the directed contribution of X_2 to the power of X_1 at frequency ω (Ding et al. 2006; Geweke 1982). It does this by expressing the total power of X_1 as the sum of an “intrinsic” term and a “causal” term, and comparing the logarithms of the total power and the intrinsic power. From an MVAR model of the two variables, the power can be expressed via (4) as:

$$S(\omega) = \mathbf{H}(\omega) \cdot \Sigma \cdot \mathbf{H}^\dagger(\omega). \quad (5)$$

The decomposition of this into an intrinsic term and a causal term is obtained via the transformation of variables $X_2 \rightarrow X_2 - (\sigma_{21}/\sigma_{11})X_1$, which diagonalizes Σ and hence removes the cross-terms from the RHS. (Since GGC is interested in the independent causal contribution from X_2 to X_1 , it should by definition be invariant under the addition of a multiple of X_1 to X_2 .) After this transformation, we have:

$$S_{11}(\omega) = H_{11}(\omega)\sigma_{11}H_{11}^*(\omega) + H_{12}(\omega)\sigma_{22}H_{12}^*(\omega). \quad (6)$$

GGC is given (after the transformation) by:

$$\text{GGC}_{2 \rightarrow 1}(\omega) = \ln \left\{ \frac{S_{11}(\omega)}{H_{11}(\omega)\sigma_{11}H_{11}^*(\omega)} \right\}. \quad (7)$$

To analyze a system of n variables, one can compute the above pairwise GGC between each pair of variables by fitting MVAR models successively to each pair of variables. There also exists: (i) the more complicated $\text{GGC}_{j \rightarrow i | k_1, \dots, k_\ell}$, i.e., the conditional GGC from X_j to X_i conditional on

$X_{k_1}, \dots, X_{k_\ell}$ (Ding et al. 2006; Geweke 1984), which computes in the same fashion the causal contribution of X_j to the power of X_i that is independent of the causal contributions of $X_{k_1}, \dots, X_{k_\ell}$ to the power of X_i and the intrinsic power of X_i ; (ii) “multivariate GGC” from one group of variables to another group of variables (Barrett et al. 2010; Geweke 1982).

The spectral GGC is related to its time-domain formulation (Ding et al. 2006; Geweke 1982; Granger 1969). The time-domain GGC from X_2 to X_1 quantifies the extent to which the past of X_2 helps predict the future of X_1 over and above the extent to which the past of X_1 predicts its own future. Specifically, it is given by the logarithm of the ratio of the residual variance in a restricted regression of X_1 on its past to the residual variance σ_{11} in the (unrestricted) MVAR model of $[X_1, X_2]^T$. The mean spectral GGC over all frequencies up to the Nyquist frequency is equal to the corresponding time-domain GGC.

Partial Directed Coherence (PDC)

The partial directed coherence $PDC_{j \rightarrow i}(\omega)$ is defined as (Baccalá and Sameshima 2001):

$$PDC_{j \rightarrow i}(\omega) = \frac{A_{ij}(\omega)}{\sqrt{\sum_{k=1}^n |A_{kj}(\omega)|^2}}. \quad (8)$$

This measure represents the relative coupling strength of the interaction from X_j to X_i , as compared to all of X_j 's interactions as a source with other structures. The PDC ranks the relative interaction strengths with respect to a given signal source, and the normalization is such that:

$$0 \leq |PDC_{j \rightarrow i}(\omega)|^2 \leq 1, \quad (9)$$

$$\sum_{i=1}^n |PDC_{j \rightarrow i}(\omega)|^2 = 1. \quad (10)$$

Directed Transfer Function (DTF)

The directed transfer function $DTF_{j \rightarrow i}(\omega)$ is defined as (Kaminski and Blinowska 1991):

$$DTF_{j \rightarrow i}(\omega) = \frac{H_{ij}(\omega)}{\sqrt{\sum_{k=1}^n |H_{ik}(\omega)|^2}}. \quad (11)$$

This measure represents the coupling strength of the interaction from X_j to X_i , as compared to the sum of those from all variables to X_i . Similar to PDC, the normalization is such that:

$$0 \leq |DTF_{j \rightarrow i}(\omega)|^2 \leq 1, \quad (12)$$

$$\sum_{j=1}^n |DTF_{j \rightarrow i}(\omega)|^2 = 1. \quad (13)$$

Since it makes use of the inverse of the regression matrix, the DTF measure is a linear combination of direct and indirect couplings. The “direct DTF” (dDTF) variant is an alternative that emphasizes direct connections (Korzeniewska et al. 2003). Note that, unlike for GGC, there is no corresponding time-domain connectivity map for PDC or DTF.

Limitations and Extensions

Stationarity. These measures assume that the time-series are covariance stationary. Non-stationary data should be divided into windows that by themselves are approximately stationary (Seth et al. 2015). Moving average components can be dealt with by computing these measures on stationary hidden variables in a “state-space” model (Barnett and Seth 2015).

Dependence on variables. The measures reflect directed statistical dependencies among the particular set of variables chosen and should not be interpreted as directly reflecting physical causal chains.

Linearity. The linear formulation of these measures can obviously only give information about linear features of signals. Extension to non-linear cases can however present further problems. Marinazzo et al. (2011) review some nonlinear approaches to GGC. Note that for (stationary) Gaussian variables, interactions are necessarily linear, and time-domain GGC is equivalent to transfer entropy, enabling an interpretation of GGC in terms of Shannon information flow (Barnett et al. 2009; Barrett et al. 2010).

Neurobiological Application

The above limitations should always be kept in mind when applying these measures to neurobiological data. A general principle is that shorter data segments are more stationary than longer data segments but yield poorer parameter estimates. Thus a trade-off must be made in choosing the segment length; the most appropriate choice will depend on whether the data are “event-related” or “steady-state,” and on the estimated model order (Cohen 2014; Seth et al. 2015). Typically, segment lengths range from 500 to 2000 ms (Cohen 2014). These measures are applicable to continuous variables, and therefore to M/EEG or local field potential data, as opposed to spiking data. The sampling rate should be sufficiently high for the Nyquist frequency to be substantially greater than the highest frequency of interest, but not so high that the model order becomes too large (Barnett and Seth 2017); 200–250 Hz is typical (Cohen 2014). For M/EEG, preprocessing should include some form of spatial filtering or source localization in order to minimize volume conduction artifacts (Seth et al. 2015). Bandpass temporal filtering should be avoided as this smears the data in time and can increase model orders, thus leading to poorer estimates of the measures (although notch filtering to remove line-noise will not contaminate frequencies that are far away from the stop-band (Barnett and Seth 2011)). Application to fMRI is problematic due to the combination of slow sampling rate and the measuring of smeared neurodynamics, in the form of hemodynamics, although research into this is ongoing (Barnett and Seth 2017). The freely available “Multivariate Granger causality toolbox” (Barnett and Seth 2014) can facilitate application of GGC.

Summary and Comparison of Measures

$\text{GGC}_j \rightarrow i$ is a measure of the directed functional effect that X_j has on X_i and compares “intrinsic” and “causal” contributions to the power in a bivariate autoregressive model (conditional versions of GGC are used if one wants to separate out direct and indirect causal effects). $\text{PDC}_j \rightarrow i$

captures the relative strength of the direct pairwise coupling from X_j to X_i , compared to the total coupling from X_j to other variables in the frequency domain MVAR model for the set of variables. $\text{DTF}_j \rightarrow i$ compares the coupling from X_j to X_i with the total coupling from all variables to X_i in the transfer matrix for the set of variables; as such it is a measure of the combined strength of direct and indirect couplings from X_j to X_i . These measures, of which GGC is the most common and perhaps best founded, hold great promise in moving beyond functional localization towards the important problem of dissecting the functional circuits underlying cognition, perception, and behavior.

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Directional Motion

- [Optic Flow Processing](#)

Disparity Energy Model

- [Spatiotemporal Energy Models](#)

Distributed Robustness

- [Neuronal Parameter Non-uniqueness](#)

Distributed Speech Processing

- [Neural Coding of Speech Sounds](#)

Dorsal Column Stimulation

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Dorsal Root Stimulation

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)

Dose-Response Functions

- [Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response](#)

Down Under Neural Population Models

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Synonyms

[Liley model](#); [Robinson model](#); [Steyn-Ross model](#)

Definition

Australia and New Zealand, despite their relatively small academic communities, have been vibrant sites for the development and application of a number of important approaches to the mesoscopic modeling of neural populations, developed initially to account for the physiological genesis of rhythmic activity in the mammalian electroencephalogram. These models are collectively referred to as “down under” neural population models.

Detailed Description

History

The work of Wright (Wright and Kydd 1984), which aimed theoretically to account for the regulatory effects of lateral hypothalamic activity on electrocortical activity, can be seen as the progenitor of the later “down under” models that were developed to account for electrocortical rhythmogenesis. In this approach telencephalon was functionally modeled as a mass of coupled linear oscillators. While largely phenomenological and not formulated in terms of the structure and composition of cortical tissue, this theory nevertheless gave mathematical form to the role that a specific anatomical pathway played in modulating electroencephalographic activity. The ambitions of Wright’s approach significantly influenced the subsequent development of a number of neural population models.

Primary Models

Three principal neural population models form the core of “down under” approaches. The population model of Robinson et al. (1997) considered the propagation of axonal pulse activity in continuously distributed planar cortical populations of excitatory and inhibitory neurons and was later extended to include thalamocortical feedback (Robinson et al. 2002). The model of Liley et al. (1999, 2002), which also theoretically incorporated spatially continuous axonal pulse propagation, focused on the topology of intracortical and cortico-cortical connectivity and differentiating the kinetics of excitatory and inhibitory neurotransmission. Finally Steyn-Ross et al. (2007) developed an approach based on Liley et al. (1999, 2002) that included the effects of electrical gap junction synapses. All models represent examples of continuum neural field models (see entries ► “Neural Field Model, Continuum”; ► “Neural Population Model”).

Robinson et al.: Thalamocortical Feedback

The model of Robinson et al. (2002) originally described cortical activity in terms of a spatially

homogeneous field quantity ϕ_e (propagated excitatory neuronal pulse rate) evolving according to the following set of *delay ordinary differential* equations:

$$\left. \begin{aligned} L_{ax} \phi_e(t) &= S[V_e(t)], \\ L_{dend} V_e(t) &= a_{ee} \phi_e(t) + a_{ei} S[V_e(t)] + a_{es} S[V_s(t - T/2)], \end{aligned} \right\} \text{cortex} \quad (1)$$

$$\left. \begin{aligned} L_{dend} V_r(t) &= a_{re} \phi_e(t - T/2) + a_{rs} S[V_s(t)], \\ L_{dend} V_s(t) &= a_{se} \phi_e(t - T/2) + a_{sr} S[V_r(t)] + a_{sn} \phi_n(t), \end{aligned} \right\} \text{thalamus} \quad (2)$$

where e, i, r, s index, respectively, cortical excitatory, cortical inhibitory, thalamic reticular, and thalamic relay neuronal populations, a_{jk} nominally represent population synaptic weights, V_l represents a mean population membrane potential, S a sigmoidal firing rate function, τ a fixed delay, and ϕ_n an external pulse input. The fixed delay τ represents the return corticothalamic conduction time. L_{ax}, L_{dend} define *second-order* linear ordinary differential operators that account for passive neuronal population cable delays and pulse propagation via cortico-cortical fibers, respectively:

$$\begin{aligned} L_{ax} &= \frac{l^2}{v^2} \frac{d^2}{dt^2} + 2 \frac{1}{v} \frac{d}{dt} + 1; L_{dend} \\ &= \frac{1}{\alpha\beta} \frac{d^2}{dt^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta} \right) \frac{d}{dt} + 1, \end{aligned} \quad (3)$$

where l is the mean range of excitatory axons of velocity v . This model was subsequently generalized to the spatially inhomogeneous case (Robinson et al. 2004). This model has been used to investigate the genesis of the resting alpha rhythm, the dynamical instability of epilepsy, and the oscillatory architecture of sleep.

Liley et al.: Kinetics of Excitatory and Inhibitory Neurotransmission

The neuronal population formulation of Liley et al. (2002) is an example of a conductance-based model. The defining equations distinguish between the kinetics of excitatory and inhibitory neurotransmission and the topology and properties of intracortical and cortico-cortical

connectivity. It describes cortical activity in terms of the mean soma membrane potential $h_k(r, t)$ of spatially continuously distributed cortical populations of excitatory ($k = e$) and inhibitory ($k = i$) neurons:

$$T_k \partial_t h_k(r, t) = h_k^{\text{rest}} - h_k(r, t) + \sum_l \psi_l [h_k(r, t)] I_{lk}(r, t), \quad (4)$$

$$(\partial_t + \gamma_{lk})^2 I_{lk}(r, t) = \exp(1) \gamma_{lk} \Gamma_{lk} \left\{ N_{lk}^\beta S_l [h_l(r, t)] + \phi_{lk} + p_{lk}(t) \right\}, \quad (5)$$

$$(\partial_t + v_{ek} A_{ek})^2 \phi_{ek}(r, t) + \frac{3}{2} v_{ek}^2 \nabla^2 \phi_{ek}(r, t) = N_{ek}^\alpha v_{ek}^2 A_{ek}^2 S_e [h_e(r, t)], \quad (6)$$

$$\phi_{ik}(r, t) = 0, \quad (7)$$

where $r \equiv (x, y)$, τ_k is a membrane time constant and $\psi_l [h_k(r, t)]$ incorporates the effect of the reversal potential on the respective postsynaptic potential of type l . ∂_t and ∇^2 are the temporal derivative and 2D Laplacian operator, respectively. The amplitude and characteristic timescale of the unitary postsynaptic potential of type l are given by Γ_{lk} and γ_{lk} , respectively. The topology of neuronal population connectivity is defined in terms of the intracortical (N_{lk}^β) and cortico-cortical (N_{lk}^α) connectivity between a presynaptic population l and a postsynaptic population k . Cortico-cortical connectivity is assumed to exclusively propagate pulses via axons of excitatory neurons having a conduction velocity v_{lk} and a characteristic length l/A_{lk} . This model has been utilized to account for the emergence of the resting EEG spectrum and its perturbation during anesthesia.

Steyn-Ross et al.: Electrical Gap Junctions

In a novel departure from the usual axo-synaptic connectivity of most neural population models,

Steyn-Ross et al. (2007), on the basis of substantial empirical evidence, added the bulk effects of gap junction currents. Gap junctions are intercellular protein channels that can form spontaneously at the point of contact between the dendritic trees of two adjacent neurons and enable the free diffusion of ions (current) along intercellular electrochemical gradients. By assuming homogeneous cellular ionic environments, such free diffusion will be determined by intercellular potential differences. On this basis Steyn-Ross et al. (2007) defined the mean soma membrane potential $h_k(r, t)$ of a spatially continuously distributed cortical neuronal population of type k in terms of a modified conductance-based neuron:

$$T_k \partial_t h_k(r, t) = h_k^{\text{rest}} - h_k(r, t) + \sum_l \psi_l [h_k(r, t)] I_{lk}(r, t) + D_{kk} \nabla^2 h_k(r, t) \quad (8)$$

where D_{kk} is a diffusive coupling strength between adjacent neurons of type k . The remaining equations defining the model are similar to that of Liley (see above). In general, because the density of gap junction coupling between inhibitory neurons is much greater than excitatory neurons, $D_{ii} \gg D_{ee}$. All other symbols are defined as before. This model has been invoked to account for the low-frequency oscillations seen in resting-state functional MRI.

Cross-References

- [Anesthesia, Neural Population Models of](#)
- [Gap Junctions in Small Networks](#)
- [Mesoscopic Anatomy and Neural Population Models](#)
- [Neural Field Model, Continuum](#)
- [Neural Mass Action](#)
- [Neural Population Model](#)
- [Sleep, Neural Population Models of](#)
- [Synaptic Connectivity in Neural Population Models](#)

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Drift-Diffusion Equation

- [Fokker-Planck Equation](#)
- [Nernst-Planck Equation](#)

Drug effect

- [Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation](#)

Dual-Generator Concept

- [Coupled Oscillations in Neural Control of Breathing](#)

Dynamic Attending

- [Rhythm Perception: Pulse and Meter](#)

Dynamic Causal Modelling with Neural Population Models

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Definition

Dynamic causal models with neural populations are state-space models that impose a specified dynamical systems form to the generation of neuroimaging and electrophysiological data. The forms of these models constitute neurobiologically motivated and identifiable parameterizations, where empirical observations offer conditional descriptions of parameter space following application of a Bayesian inversion scheme. They comprise separate generative processes at the neuronal level and at the observation level through a set of deterministic or stochastic differential equations and an observer functional, respectively.

Detailed Description

Dynamic causal models were first invented in 2003 for the purpose of estimating human brain connectivity and task-dependent functional integration using functional magnetic resonance imaging (fMRI) (Friston et al. 2003). The framework was extended for electrophysiological domains including non-invasive electroencephalography (EEG) and magnetoencephalography (MEG) and later for invasive local field potential recordings. Application domains share a common generative and inversion framework (Stephan et al. 2010). At the neuronal level, a network of “nodes” are connected with intrinsic (within-region) and extrinsic (region-to-region) connections.

These effective or model-based connections constrain the output of a set of differential equations and can be modulated by experimental perturbation. These are modality-dependent, mesoscale descriptions of neuronal ensemble activity and are summarized through mean-field reductions. Different connectivity architectures can be considered as different models, embodying competing hypotheses to be formally tested. At the observation level, contributing neuronal states form inputs to a second dynamic process or static function (lead field), transforming neuronal activity to the required measurement space, e.g., blood oxygen level dependent – BOLD fMRI responses. Together, these form a complete forward model that is inverted, given real data, using Bayesian approaches.

Modality-Dependent Population Models

The neural population model describes the time evolution of unobservable neuronal states. For fMRI, $\mathbf{x}$ is an $n \times 1$ column vector representing neuronal activity at n brain regions. This activity is under the control of inhibitory rate parameters, $a_{ij} \forall j = i$, describing the influence of regional activation on its own output activity and the excitatory or inhibitory influence, $a_{ij} \forall j \neq i$, from other brain regions. This $n \times n$ matrix A is referred to as the endogenous or intrinsic connectivity matrix. A bilinear approximation $B^{(j)}$ is an $n \times n$ matrix used to capture effects from m , experimental input modulations, and C , an $n \times k$ matrix, represents the direct perturbation from k experimental inputs, giving

$$\dot{\mathbf{x}} = \left(A + \sum_{j=1}^m u_j B^{(j)} \right) \mathbf{x} + C \mathbf{u} \quad (1)$$

Here, each state is a one-dimensional neural mass model representing the mean neuronal activity within a region encompassing approximately 10–100 voxels. Such a mean-field reduction is also applied to electrophysiological modalities where multiple-state models are used to represent several dimensions of unobservable dynamics within a single brain region (e.g., membrane depolarization changes at different inhibitory and

excitatory cell ensembles), owing to their higher temporal resolution. For example, DCM for EEG employs (among other models) the Jansen and Rit formulation (Jansen and Rit 1995) to describe layer-specific synaptic responses, where inputs, u , are convolved with postsynaptic kernels, h , which can depolarize (e) or hyperpolarize (i) the postsynaptic neuronal ensemble to produce an average membrane potential, v :

$$\begin{aligned} v &= h_{e/i} \otimes u \\ h_{e/i} &= H_{e/i} \kappa_{e/i} t \exp(-t \kappa_{e/i}) \end{aligned} \quad (2)$$

The parameter H tunes the maximum amplitude of PSPs and κ is a lumped representation of the sum of the rate constants of passive membrane and other spatially distributed delays in the dendritic tree. The convolution leads to a second-order differential equation (David and Friston 2003) that can be decomposed into normal form as

$$\begin{aligned} v(t) &= i(t) \\ i(t) &= H_{e/i} \kappa_{e/i} u(t) - 2\kappa_{e/i} x(t) - \kappa_{e/i}^2 v(t) \end{aligned} \quad (3)$$

A sigmoidal operator, S , then transforms the average membrane potential into a population firing rate and allows us to substitute direct (thalamic) input, u , with afferent input from other cell populations. These inputs are parameterized with a connectivity parameter γ and can arise from within the local layered neural mass or from pyramidal cells of other connected brain regions (both having identical mathematical form), giving, for example,

$$\begin{aligned} v &= i \\ i &= \kappa_e H_e (\gamma S(v_{\text{aff}}) + u) - 2\kappa_e i - \kappa_e^2 v \end{aligned} \quad (4)$$

Modality-Dependent Observers

Feature extraction from these neural population models is specified through an appropriate transform from the neural state space to measurement space. In the case of fMRI, this transform can be parameterized by a nonlinear “balloon model” (Buxton et al. 1998) describing the neuronal activity-induced dynamic alterations in vasodilation, blood flow, and subsequent volume and

deoxyhemoglobin content – to predict the observed BOLD time series. For electrophysiological modalities, a static lead field transforms a mixture of cell membrane potentials from each source to scalp-level-evoked, scalp-level-induced, or correlational data features (Kiebel et al. 2006):

$$h = L.Kx \quad (5)$$

where K describes the contribution from different cell ensemble potentials x , which is used to weigh, primarily, pyramidal cell contributions, and L is a lead-field matrix that accounts for passive conduction of their electromagnetic field and can be constrained along three orthogonal dimensions, when dipole orientations are not known.

Together with the neuronal state space, these transforms produce a full generative model with which mechanistic hypotheses regarding the physiological processes underlying empirical data observations can be performed.

Bayesian Inversion, Parameter Estimation, and Model Selection

The models described above produce the data likelihood and when combined with a set of priors on parameter space allow for a full Bayesian inversion. The inversions employed in DCM mostly use a variational expectation maximization routine (Šmídl and Quinn 2006) (stochastic routines employ generalized filtering). Here, a partition between the multivariate Gaussian model parameter space and the observation noise parameter (known as the hyperparameter) provides a scheme over which gradient ascent on a free energy objective function is amenable:

$$\begin{aligned} F &= \ln .25 \text{emp}(y|m) \\ &= KL(q(\theta) \parallel p(\theta|y, m)) \end{aligned} \quad (6)$$

This quantity F thence returns an approximation to the model evidence, which is exact for linear models as well as an approximate conditional parameter density q . These two quantities can then be used to assess competing model architectures

and the particular conditional (data: y , dependent) distributions on parameters, respectively.

Applications of DCM

The DCM approach has been applied to many experimental preparations and imaging modalities (a PubMed search reveals ~400 articles associated with dynamic causal modeling). As well as offering insights into the fundamental role of effective brain connections, e.g., how callosal connections support interhemispheric integration in a task-dependent manner (Stephan et al. 2005) or how feedback loops are necessary to support prototypical event-related potentials (Garrido et al. 2007), specific network topologies have been elucidated for cognitive and motor phenomena in health and disease. DCM for fMRI was used in one study to ascertain which regions in a prefrontal-subcortical network drive the so-called “status quo” motor-bias behavior (Fleming et al. 2010), finding a prefrontal-causality the most likely. During learning, similar networks have been shown to adapt along bottom-up axes, with changes in connections that support motor responsivity driven by modulation from subcortical structures (den Ouden et al. 2010). In disease, support for disconnection-related mechanisms has been observed in patients with schizophrenia (Dima et al. 2009) but also in neurological disorders more traditionally associated with focal lesions, such as Parkinson’s disease (Marreiros et al. 2012). As a “mathematical microscope,” electrophysiological DCMs have been applied to small, one-node networks to uncover particular synapses and receptors subtending memory performance (Moran et al. 2011). Overall, the methodology provides a principled Bayesian framework to address the mechanisms of functional brain architectures that support our mental repertoire.

Cross-References

- [Determining Network Structure from Data: Nonlinear Modeling Methods](#)
- [Forward and Inverse Problems of MEG/EEG](#)
- [Imaging Analysis, Bayesian](#)

- Jansen-Rit Model
- Neural Mass Action
- Neural Population Model
- Neuroimaging, Neural Population Models for
- Pattern Formation in Neural Population Models
- Population Density Model
- Stochastic Neural Field Theory
- Synaptic Connectivity in Neural Population Models

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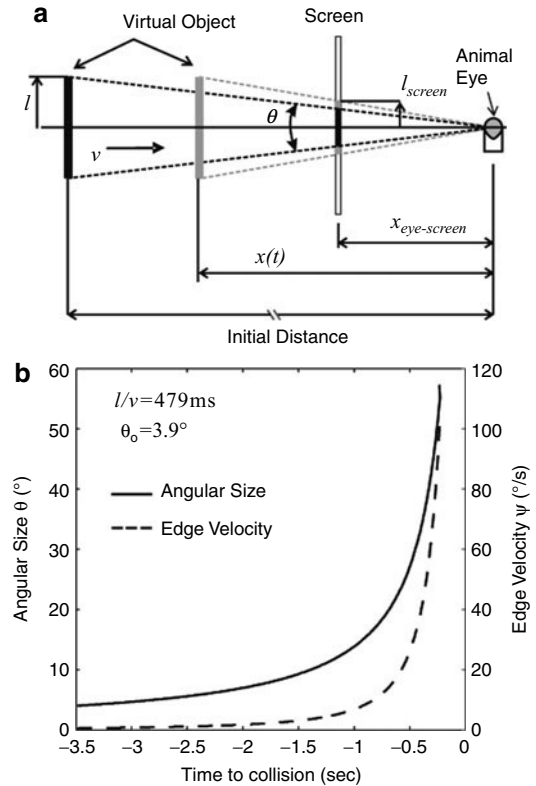
Dynamic Clamp Technique

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Definition



Dynamic clamp is an electrophysiological technique for introducing simulated electrical components into biological cells using a real-time closed loop between the cell and a computer or another electronic device. Classic dynamic clamp protocols build a voltage-dependent current injection cycle to implement artificial membrane or synaptic conductances in the cell membrane of biological neurons. These protocols are employed to assess a large variety of neuronal computational

properties and are widely applied for studying the physiology of neural systems at the cellular and circuit levels.

Detailed Description

History

The use of closed-loop feedback interactions with living neurons for observation and control purposes goes back to the beginnings of electrophysiology when the voltage clamp technique was developed (Marmont 1949; Cole 1955). The voltage clamp technique measures currents across the membrane of excitable cells while holding the membrane potential at a constant level. In current clamp, on the other hand, the current passing into and out of the neuron is tightly controlled, while the membrane potential is being recorded. Both voltage and current clamp protocols are routinely used to study the electrical properties of neuronal membranes and contribute to the design of conductance-based neuron models. In the early 1990s, the first hybrid circuit experiments coupling living and artificial cells through synthetic electrical connections were carried out in heart cells (Tan and Joyner 1990) and neurons (Yarom 1991).

In 1992, Sharp et al. and Robinson and Kawai independently developed the dynamic clamp concept (Sharp et al. 1993; Robinson and Kawai 1993). The dynamic clamp technique operates in a real-time closed-loop manner: an intracellular electrode measures the membrane potential of a neuron, which is fed into a computer or an electronic device that calculates a current to inject into a postsynaptic neuron. The injected current is computed after solving a model that represents ionic or synaptic conductances or simulates the dynamics of individual neurons or neural networks. The postsynaptic cell can be identical to or different from the one from which the membrane potential is being recorded. This activity-dependent closed loop is repeated indefinitely and has to be implemented at a high enough frequency to achieve a realistic effect. Figure 1 illustrates a typical dynamic clamp configuration.

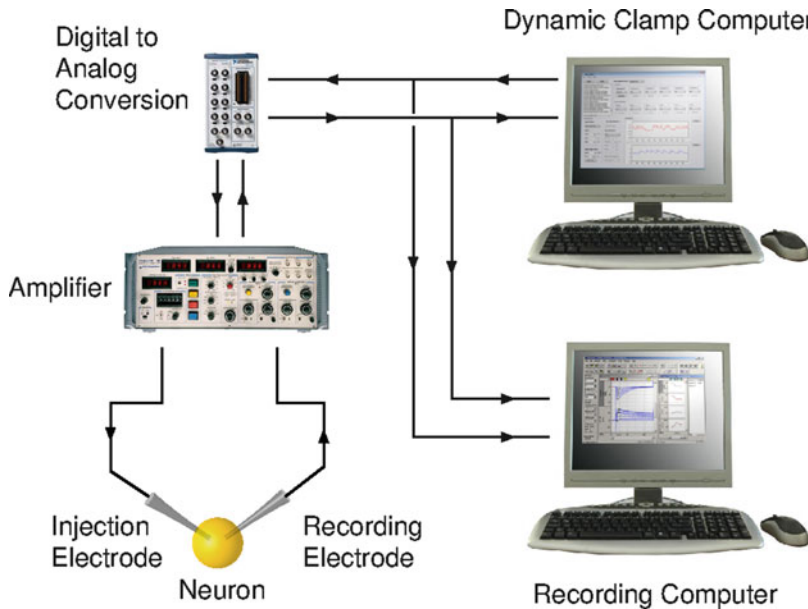
Applications and Implementations

The dynamic clamp technology for in vitro and in vivo electrophysiology has produced many examples of successful closed-loop interactions with neural systems, which include adding or cancelling ionic channels, adding or cancelling electrical or chemical synapses (including learning and plasticity protocols), and implementing hybrid circuits of real and artificial neurons and networks (for reviews see Prinz et al. (2004), Goaillard and Marder (2006), Destexhe and Bal (2009), and Economo et al. (2010)).

Different dynamic clamp software implementations have increasingly become available under both Windows (Pinto et al. 2001; Kullmann et al. 2004; Nowotny et al. 2006; Kemenes et al. 2011) and real-time Linux operating systems (Butera et al. 2001; Dorval et al. 2001; Muniz et al. 2009; Lin et al. 2010) and contribute to expand the use of dynamic clamp protocols by implementing a realistic cycle update in soft or hard real-time approaches. Novel active electrode compensation techniques also allow experimenters to conduct dynamic clamp experiments with a single high-resistance electrode (Brette et al. 2008; Samu et al. 2012).

Modern Developments

The dynamic clamp technique has been generalized in the context of activity-dependent stimulation protocols beyond electrophysiological input/output by using chemical and mechanical stimulation and optical recording methods (Chamorro et al. 2012). Dynamic clamp-inspired closed loops can also be used in novel assisted neurofeedback techniques by implementing goal-driven stimuli that not only depend on instantaneous measurements but also on an adequately long history of the recordings (Wallach et al. 2011; Chamorro et al. 2012; Fernandez-Vargas et al. 2013). Dynamic clamp and novel activity-dependent stimulation techniques reveal neural dynamics otherwise hidden under traditional stimulus–response protocols, provide control of regular and pathological states, induce learning processes, bridge between distinct



Dynamic Clamp Technique, Fig. 1 Typical dynamic clamp configuration. A cell is impaled by two electrodes, one for monitoring the membrane potential and one for injecting currents. The signal from the recording electrode is amplified, converted to a digital signal, and fed into the dynamic clamp software. The software calculates the appropriate current according to the model that is

simulated and issues a current command that is converted to an analog command and injected as a current through the current injection electrode. This cycle is repeated at a high frequency on the order of kHz. A second recording computer is often used to obtain an unbiased record of the experiment

levels of analysis, and lead to a further automation of experiments in neuroscience research.

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Dynamic Diseases of the Brain

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Synonyms

[Dynamical diseases](#); [Periodic diseases](#)

Definition

A *dynamic disease* of the nervous system is a disease that arises from abnormalities in neural control mechanisms. Whereas traditional approaches for classifying neurological diseases are based on (static) anatomical, cellular, and molecular abnormalities, the focus here is on

dynamics, namely the variation of signs and symptoms of disease as a function of time. The hallmarks of dynamic diseases are sudden, qualitative changes in the temporal pattern of clinical signs. Identifying a neurological disorder as a dynamic disease has two major implications: (1) the observed dynamics and their responses to various manipulations provide important insights into the nature and abnormality of neural control and (2) based on computational models of the abnormalities, it may be possible to devise novel treatment strategies for dynamic diseases of the brain.

Detailed Description

Historical Perspectives

The concept of a dynamic disease arises out of the concept of a *dynamical disease* introduced by Uwe an der Heiden, Leon Glass, Michael C Mackey, and their coworkers (Mackey and Glass 1977; Glass and Mackey 1979, 1988; Mackey and Heiden 1984; Bélair et al. 1995). A dynamical disease was defined as a disease that occurs in a normal feedback control mechanism operating in a range of parameters that produced qualitatively altered and presumably unhealthy, dynamical behaviors. The concept was illustrated by applications to the respiratory and hematopoietic systems where the onset of disease was marked by a change involving an oscillatory physiological pattern: in Cheyne–Stokes respiration, a regular breathing transforms to a periodically modulated breathing pattern; and in periodic chronic myelogenous leukemia, a normally constant level of leukocytes switched first to a periodically and then to a chaotically varying level. In each case, the qualitative changes associated with the onset of disease were explained via an analogous transition in the dynamics of a mathematical model of an underlying feedback control mechanism. Since time delays are essential components of feedback controllers, the models took the form of delay differential equations (see chapter ► [“Time-Delayed Neural Networks: Stability and Oscillations”](#)). To induce the transition in the models, only quantitative changes of parameters

were required. The changes in dynamics arose when the parameter values crossed so-called stability boundaries, corresponding mathematically to *bifurcations*. It was hypothesized that pathological oscillations in the selected diseases arose because normal physiological control mechanisms were operating in an abnormal parameter range. A consequence of the computational studies is that the understanding of the mechanism can lead to the prediction of novel treatments: in the case of a rare hematological disease, cyclic neutropenia, the oscillations in neutrophils can be stopped by the administration of granulocyte colony stimulating factor (G-CSF) (Foley and Mackey 2009), an intervention resulting in a bifurcation (specifically, a reverse Hopf bifurcation).

However, changes in dynamics can have various origins and are not necessarily associated with bifurcations. This is especially true in the nervous system in which sudden changes in neural dynamics can arise because of the responses of multistable neural networks to perturbations, the transient synchronization of neural population activity, the formation of traveling waves of electrical potential, and the response to random fluctuations in the vicinity of critical phenomena such as phase transitions. The more inclusive term dynamic disease includes all disorders characterized by abnormal dynamical behaviors. Thus, for example, epileptic seizures are the manifestations of a dynamic disease (Milton and Black 1995; Milton and Jung 2003) where features other than bifurcations have been proposed as underlying mechanisms.

In retrospect, it is surprising that diseases of the nervous system received only scant mention in early discussions of the dynamics of diseases (Glass and Mackey 1979, 1988; Mackey and an der Heiden 1984; Mackey and Milton 1987). Abnormal dynamical behaviors are frequently associated with diseases of the nervous system (Milton and Black 1995; Erdi et al. 2017) and characterize, for example, disorders of movement (e.g., tremors, Parkinsonism), mood (e.g., affective and psychotic disorders), and

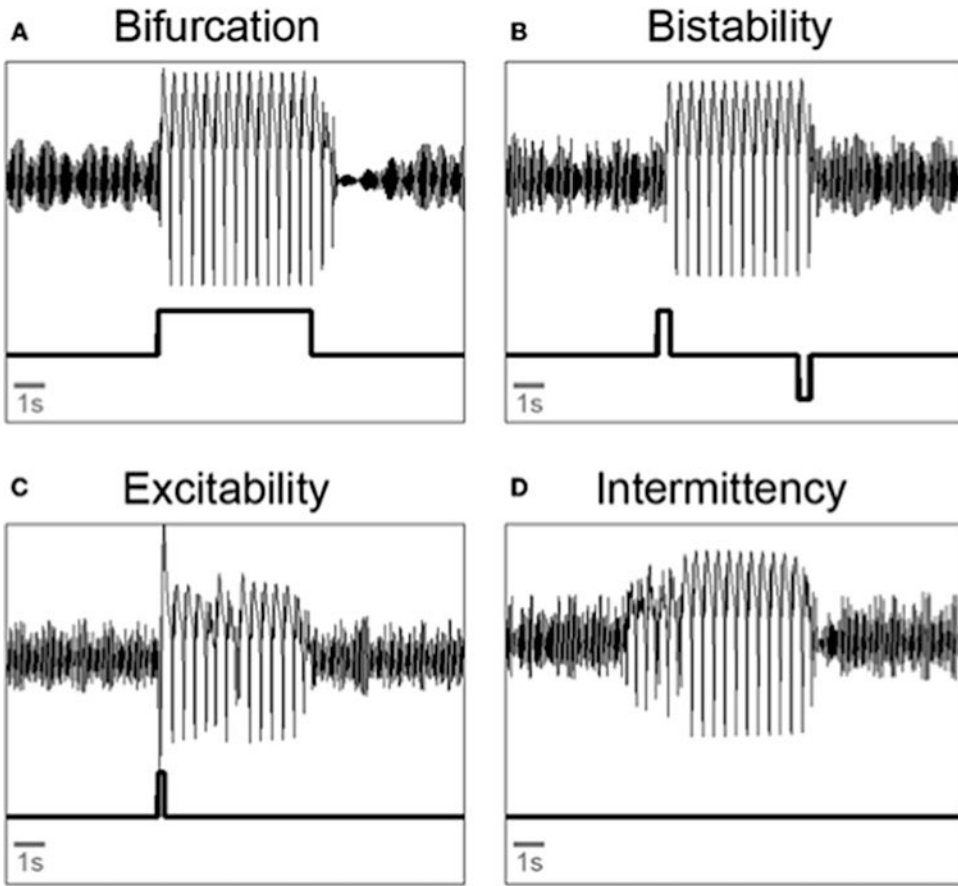
consciousness (e.g., epilepsy, migraines, sleep-wake cycles). The large number of articles in this encyclopedia that address the computational aspects of disease attest to the importance of adopting a dynamical perspective in order to understand and treat dynamic diseases of the nervous system. Here we focus on a number of challenges and unsettled issues that concern the application of computational modeling to clinical practice. Our discussion of dynamical disease states is along a similar vein that Izhikevich has made for the mathematical classification of neuronal bursting patterns (Izhikevich 2007). Namely, an understanding of the basic mathematical mechanisms is mandatory to properly analyze the computational studies and to use these studies for the interpretation of clinical recordings of human brain activity. We therefore introduce a basic mathematical classification of transition between dynamic states and give examples where these concepts have been applied to disease states of the human brain. Finally, we discuss the unresolved computational challenges for the modeling of dynamic diseases of the nervous system and the development of novel, dynamically inspired treatment strategies.

Dynamical Transitions

We first restrict the discussion to qualitative changes in the temporal dynamics of some physiological variable. Taking the simplest case where there is the sudden appearance or disappearance of an oscillatory state, there are four major mathematical concepts that can explain this observation (Baier et al. 2012) (Fig. 1): (1) bifurcation; (2) bistability; (3) excitability; and (4) spontaneous bursting behavior (intermittency). These are illustrated in Fig. 1.

Bifurcation (Fig. 1a): A quantitative parameter change results in transition from one dynamic state to a qualitatively new state. The new state persists as long as the parameter value remains altered. Both states are robust to noise perturbations.

Bistability (Fig. 1b): Two qualitatively different states coexist under the same conditions (same



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Dynamic Diseases of the Brain, Fig. 1 State transitions in dynamical systems as a function of control parameter. (a) In a monostable system, a transition is induced when a parameter crosses a bifurcation point. (b) In a bistable system, a suprathreshold stimulus (e.g., a short change of parameter) is required for each state transition. (c) In an

excitable system, a suprathreshold stimulus is required only to induce the first transition. The return to the original state is spontaneous. (d) In a system which exhibits spontaneous bursting behavior (deterministic intermittency), the transitions do not require change of parameter or external input to occur. (Reproduced from Baier et al. 2012)

parameter values). Transitions into and out of the abnormal state are realized via perturbations that are strong enough to cross the boundary separating the two states (the separatrix). Both states are vulnerable to noise perturbations.

Excitability (Fig. 1c): A stable state is interrupted temporarily by a qualitatively different abnormal state due to a suprathreshold perturbation. Both states are vulnerable to noise perturbations, but the return to the original state is spontaneous (i.e., does not require perturbation). Therefore, the abnormal state is only a transient.

Note that in principle, the transient can be arbitrarily complex.

Spontaneous bursting behavior (Fig. 1d): This globally stable state consists of two qualitatively different substates that alternate spontaneously, irregularly, and last for irregular periods of time. Consequently, both normal and abnormal dynamics are part of the overall state. Mathematically, this is equivalent to the type of dynamics called intermittency. However, whereas most of the mathematical literature on intermittency deals with low-dimensional models, actual brain

dynamics will more generally display spatiotemporal intermittency which at present is only incompletely understood.

This is the basic classification assuming that there is only one well-defined normal state. However, an organism can also transit from one state to another normal state, both characterized by different dynamics (e.g., during development or when transiting from sleep to the awake state). Pathological dynamics can then also occur (transiently) during the transition between two normal states (Milton et al. 2017) and see chapter ► “[Delay-Induced Transient Oscillation \(DITO\) and Metastable Behavior](#)”). The classification of such transitions is presently incomplete, but we will discuss an example below. We assume that such classification will necessarily involve advanced multivariate data analysis and will benefit from machine learning techniques as in the case of abnormally intermittent activity related to newborn and early childhood epileptic encephalopathies (Rosch et al. 2017).

Finally, the basic classification looks exclusively at temporal changes, whereas brain dynamics involves spatiotemporal changes of (neuro-) physiological variables. The theory of spatiotemporal systems again allows for more complex pathodynamics but is presently incomplete and will be illustrated only via example below.

Pathodynamics in the Human Brain

In order to illustrate dynamic disease approaches to neurological disease, we focus our discussion on epileptic seizures (see chapters ► “[Epilepsy: Computational Models](#),” ► “[Epilepsy: Abnormal Ion Channels](#),” ► “[Epilepsy, Neural Population Models of](#),” and ► “[Slow Oscillations and Epilepsy: Network Models](#)”). Topologically, seizures are characterized by their mode of onset. The term *focal* or *focal onset* is used to indicate a seizure which begins in a localized area of the brain. Focal or focal onset seizures are termed *simple* if there is no alteration in consciousness and *complex* if there is an alteration in consciousness. Traditionally, generalized seizures were distinguished between those that were generalized from the onset (primary generalized) and those that were the result of spread from an epileptic focus

(secondarily generalized). However, it is now clear that even in the primary generalized epilepsies, such as childhood absence epilepsy, there is a focal onset to the seizure (Gupta et al. 2011; Tenney et al. 2013; Westmijne et al. 2009). Thus the distinctions between primary and secondary generalization refer to the mechanism and pathways by which the seizure generalizes (Milton and Jung 2003). Dynamically, seizures are characterized by the sudden onset of an uncontrolled discharge pattern in very large populations of neurons and the diagnosis of epilepsy depends (in addition to the clinical history and description of the seizures) on the qualitative electroencephalographic (EEG) changes associated with seizures. Epilepsy, with its recurrent seizures, can therefore serve as the epitome of a dynamic disease.

Bifurcations

It is well established at the benchtop that dynamical transitions occur in neurons and simple neural circuits in which identified parameters have been changed systematically (Izhikevich 2007; Gerstner and Kistler 2002; Wilson 1999; Jirsa et al. 2014). The changes of neural activity here correspond to bifurcations in the appropriate mathematical models. In the context of brain disease, it has been difficult to demonstrate this phenomenon convincingly (Milanowski and Suffczynski 2016). There are two problems: (1) the relevant control parameter(s) cannot be directly identified from the observation of a dynamic transition and (2) the bifurcations exhibited in neural networks may be more complex (Jirsa et al. 2014; El Houssaini et al. 2015; Yang and Robinson 2017), a reflection of the possibility that seizures are generated by spatially extended epileptic systems (Milton et al. 2009; Eissa et al. 2017; Jirsa et al. 2017). Indirect evidence can be used in computational studies to argue for certain parameter changes and corresponding bifurcation patterns with some plausibility. The indirect evidence comes in various forms, for instance, by studying the phenomenology of waveforms (Ebersole and Milton 2003); by doing systematic parameter scan and sensitivity analysis; and by comparison with

experimental results from animal models of a specific disease.

The evolution of complex focal epileptic seizures has been considered to be an example where different states arise through transitions via bifurcations (Lopes da Silva et al. 2002). Analysis of clinical data from subdural and depth electrode recordings identifies a number of abnormal states characterized by distinct rhythmic properties: frequency, amplitude, and waveform. One model of focal seizures proposed by Wendling et al. is based on the mean behavior of large neural populations of principal and inhibitory neurons in the cortex (Wendling et al. 2002). A study of the generic bifurcation structure of this model identifies potential transition points where the dynamics change from background to pre-seizure, seizure, and post-seizure activity in accordance with the clinical data. Interestingly, the exploration of the model leads the authors to identify dynamics corresponding to a significant proportion of the highly heterogeneous rhythms during focal complex seizures with hippocampal origin. The computational study thus supports the hypothesis that patients with focal seizures share the basic neural circuitry but vary in the settings of their individual parameters. The model also explains how abnormal epileptic activity results from the unbalanced cooperation between excitatory and inhibitory neural populations. The major insight from the computational study is that focal-onset seizures tend to follow a certain route in parameter space during the course of the seizure (Wendling et al. 2005).

Bistability

As is the case for bifurcations, it is well established that neurons (Tasaki 1959; Guttman et al. 1980) and simple neural circuits (Foss et al. 1997; Foss and Milton 2000; Kleinfeld et al. 1990; Ma and Wu 2007) can exhibit bistability. It is to be expected that similar phenomena also occur on the level of the brain in vivo. Physicians have known for a long time that it is sometimes possible to abort pathological dynamics like cardiac arrhythmia or an epileptic seizure using a brief mechanical, electrical, or sensory stimulus (Lopes da Silva et al. 1994, 2002; Milton 2000;

Milton and Foss 1997; Rajna and Lona 1989). This points to the possibility that a seizure state coexists with a normal brain state and can be reached and left via specific perturbations (c.f. Fig. 1b). The likelihood of causing a switch between coexisting attractors by choosing the magnitude and timing of the stimulus randomly is very low (see chapter ► “Multistability: Stopping Events with Single Pulses”). Thus a great deal of attention has been focused on determining the basin of attraction of the normal state (Lopes da Silva et al. 2003; Zakyntinaki et al. 2010), that is, the set of state variables that will result in normal behavior. Noise-induced transitions across the separatrix (additive noise) provide another possible mechanism for epilepsy in the setting of bistability since they can be accompanied by the occurrence of delay-induced transient oscillations (see chapter ► “Delay-Induced Transient Oscillation (DITO) and Metastable Behavior”). Delay-induced transient oscillations may be related to the tendency of seizures in patients with nocturnal frontal lobe epilepsy to occur at transitions between sleep stages (Quan et al. 2011). A similar mechanism may account for the transient Notch-pathway oscillations observed during fate assignment in vertebrate neurogenesis (Momiji and Monk 2009).

In the case of primary generalized epileptic seizures, analysis of the clinical data has supported the hypothesis that the epileptic state coexists with the normal brain dynamics (Milton et al. 2017; Lopes da Silva et al. 1994; Milton 2000). From this point of view, the main difference between a person who does not experience seizures and one who does is the distance of the separatrix from the normal behavior in phase space. The smaller the distance, the more likely it is to spontaneously switch from one state to another. A biophysical computational model of this dynamics was proposed by Suffczynski et al. (2004). The model was validated using animal experimental and clinical data and a numerical bifurcation analysis. The model could specifically explain how the interaction between cortical neural populations and populations in the thalamus interact to produce the noise-induced transition to large-amplitude, slow frequency

rhythms. In addition, an analysis of simulations of external stimulation suggested that the termination of the epileptic state might be favorable at certain phases of the epileptic rhythm only whereas the desired result might be missed for stimulations at other phases.

In the case of focal and focal-onset seizures, an extensive study of the spatiotemporal dynamics of a model representing a piece of neocortical tissue pointed to a large number of potential dynamic mechanisms (Wang et al. 2014). It was proposed that detailed dynamic analysis of EEG or ECoG data might yield markers pointing to either the bifurcation or the bistability mechanism or a combination of both. For each subtype, specific treatment recommendations are indicated.

The concept of bistability also arises in studies concerning other neurological diseases, including migraine (see chapter ► “[Migraines and Cortical Spreading Depression](#)”) and bipolar affective disorders (see chapter ► “[Computational Psychiatry](#)”). Analysis of data of the spreading depression in migraine suggests a switch from the normal polarized state of the cortex to a totally depolarized state (Dahlem et al. 2008). This transition is supported by computational models of the cortical polarization state. However, the full dynamics of spreading depression is only given if the depolarization can propagate in space (see below). In the context of psychiatric disorders, high-level considerations have led to the proposal of a bistable mechanism for the occurrence of disorders of the bipolar spectrum. The interaction of a manic and a depressed state can lead to a bistable situation which exhibits both the possibility for regular transitions between the states (manic-depressive illness) and the possibility for perturbation-induced transition (e.g., the known phenomenon that antidepressants are able to induce the transition to the manic state (Goldbeter 2011)).

Excitability

Neurons are excitable and excitability can also be observed in large neural populations, e.g., in the human cortex. In an individual neuron, a well-defined depolarization threshold is found beyond

which an action potential can be induced. In neural populations within the living brain, it is difficult to do quantitative experiments but clinical observations point to similar mechanisms in some pathological cases. Notably, in patients with epilepsy, the so-called interictal spike is a candidate for suprathreshold response to stimuli from the surrounding brain tissue. Model studies support the idea that in some location on the cortex or within the hippocampus, the excitability threshold is lowered such that the surrounding activity occasionally reaches the excitation threshold and induces an abnormal response in the form of a single spike or sharp wave. In contrast to action potentials (which last on the order of a few milliseconds), the epileptic spike or sharp wave last on the order of 60–200 milliseconds. Cortical excitability has been proposed to be of clinical relevance to distinguish normal from abnormal tissue response. Valentin et al. (2005) studied the response of different cortical locations to single-pulse stimulations and concluded that simple excitability, a single population spike, indicated normal tissue. In the case of abnormally altered tissue, they frequently saw rhythmic responses that consisted of several oscillations before they disappeared. In addition, the epileptiform responses appeared to recruit wider cortical areas, i.e., they had a tendency to spread. A computational modeling study confirmed that spatially extended neural population models of human cortex gave single spike responses when the balance between excitation and inhibition was intact (Goodfellow et al. 2012a). In cases where locally diminished inhibition was assumed, the response to simulated perturbations was prolonged and rhythmic as in the clinical data. A modeling study of stimulation-induced afterdischarges showed that prolonged rhythmic transients are even possible in low-dimensional models when operating near the bifurcation to a bistable state (Baier et al. 2017). The predicted responses included rhythmic slow waves, spike waves, and poly-spike waves.

In an excitable neural medium like the neocortex, propagation of a disturbance can take the form of synchronized waves of neural activity.

Synchronization of neural population activity is involved in binding of sensory stimuli and organization of large numbers of neurons into synchronized waves lies at the basis of phenomena such as consciousness, cognition, and sleep and thought to underlie the generation of the EEG. Abnormal wave propagation arises in a number of neural conditions including flicker phosphenes (see chapter ► [“Flicker-Induced Phosphenes”](#)), drug-induced visual hallucinations (see chapter ► [“Visual Hallucinations and Migraine Auras”](#)), migraine (see chapter ► [“Migraines and Cortical Spreading Depression”](#)), stroke and the propagation of epileptic seizures (see (Milton and Jung 2003; Baier et al. 2012) and chapter ► [“Epilepsy: Computational Models”](#)). However, seizure propagation from an epileptic focus is exceedingly complex (Milton et al. 2009).

Moreover, it is difficult to obtain data on seizure propagation in humans since pathways involving subcortical and brainstem nuclei, for example, thalamo-cortical circuits, play major roles. The subject of seizure propagation represents an opportunity for computational neuroscience and may potentially point to treatment strategies designed to prevent or limit seizure propagation.

Spontaneous Bursting Behaviors

In dynamical systems, the subject of bursting behaviors falls under the broad subject heading of intermittency. There are several mechanisms that can generate intermittent (bursting) behaviors. In contrast to the bursting behaviors exhibited by single neurons (Izhikevich 2007), intermittency refers to patterns of burstiness in which both the size and timing of the bursts vary unpredictably. First, intermittency can be generated by purely deterministic mathematical models (Pomeau and Manneville 1980). This type of intermittency belongs to the class of chaotic systems and in low-dimensional systems is associated with inverse tangent, subharmonic, or secondary Hopf bifurcations. Despite the deterministic nature of the model, the timing (and size) of the laminar phases cannot be predicted. However, the probability distribution of the

duration of laminar phases is often associated with a power law (as is observed for the other mechanisms discussed below). Following some evidence from animal model data (Hramov et al. 2006), it has been shown that the occurrence of seizures in primary generalized epilepsy may be related to deterministic intermittency (Goodfellow et al. 2012b). Interestingly, the model resulted from the coupling of bistable local elements (cortical compartments) and introducing a certain degree of heterogeneity in the parameter for different cortical locations. The model predicts the spontaneous transition to the seizure and spontaneous termination and the essentially unpredictable nature of typical absence seizures.

A second mechanism that generates intermittency arises in slowly driven dissipative systems that self-organize themselves, without an external finetuning of control parameters, into a critical state near a state transitions. The critical state is characterized by a propensity to generate transient phenomena which occur on all length scales (Bak 1996; Sornette 2006). In this situation, abnormal discharges in the form of transient oscillations continue to appear and abort spontaneously even though the parameters are fixed and there are no external inputs. The transients are induced by internal (e.g., thermal) fluctuations. The key point is that the length of time between successive oscillatory bursts, or *laminar phases*, obeys a power law distribution. This means that laminar phases of all length scales are possible (Stead et al. 2010). Evidence for such power law behaviors has been obtained in the case of epileptic seizure recurrences (Osorio et al. 2011) and neuronal avalanches (see (Milton 2012; Beggs and Plenz 2003)). Although no general method is known that can prevent these recurrences, it is currently thought that some degree of predictability may be possible (Sornette and Ouillon 2012).

Finally, noise-induced type of intermittency referred to as *on-off intermittency* can arise in dynamical systems that are tuned close enough to a stability boundary (“edge of stability”) so that noisy perturbations causes transient switches

between two states (see chapter ► “[Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)”). In the case that the noise enters through a parameter (multiplicative noise), power law behaviors arise (Cabrera and Milton 2002). This phenomena would be anticipated to arise generically in situations in which instability, such as manifested by epileptic cortex, is controlled by cortical and subcortical represented by delayed antagonistic dynamics (Cabrera 2005).

Computational Challenges

Dynamical behaviors can be combined with molecular and structural information to make a complete classification of neural disease. The modern day’s reductionist approach of associating with each disease a molecular defect is often not sufficient to base the development of therapeutic approaches. While temporal structure is obviously important for clinicians to diagnose and treat pathological states such as ventricular tachycardia, its role in diseases for which measurements with appropriate temporal resolution are not routinely available as, e.g., in pulsatile hormone release, is less obvious to the practicing physician. On the other hand, current dynamic disease approaches shed little light on the genesis of diseases such as epilepsy. In other words, what is the dynamic basis of epileptogenesis, namely, the process which describes why an initially seizure free individual, such as a child, develops over the course of many years, medically intractable epilepsy. Presumably the missing link is related to the self-organization of complex dynamical systems. The nonlinear dynamics of physiological processes assumes that macroscopic behavior is in the form of dissipative structures, namely structures which are maintained by a supply of energy. This implies that although the generating anatomical-physiological mechanisms may be rather complex, structural features can be studied properly in simplified models that omit certain details of the biological mechanisms. We stress that only in rather simple and abstract, nonlinear models, can current mathematical tools allow a thorough explanation of the basic mechanism of change between patterns that are associated with a transition to disease.

Questions of scale are central to dynamical approaches to disease. In other words, “How are dynamics at the length scale of molecules translated into behaviors that are observable at the bedside?” Our emphasis on simple models to investigate complex phenomena is based on the observation that complex dynamical systems can exhibit phenomena which are largely independent of scale. For example, limit cycle oscillations can be generated at the level of molecules, single neurons, small neural circuits, large neural populations, the human nervous systems, and human populations. Despite differences in the details and scales of the underlying mathematical models, limit cycles at all levels of organization share common properties with respect to the response to external perturbations including stability, similar responses to perturbations, and the capacity to synchronize with other oscillations.

Most nonlinear dynamical systems when tuned at the edge of stability exhibit low-dimensional dynamics (Guckenheimer and Holmes 1983). In particular, the center manifold theorem states that the dynamics at the edge of stability reduce to a low-dimensional normal form on a center manifold that can be written in terms of a first- or second-order differential equations referred to as the *normal forms*. Hence one would anticipate that one might be able to capture the dynamics for complex neural systems by using models based on the normal forms. An example occurs in the spring–thumb compression task in which a subject tries to compress a spring held between their thumb and index finger without causing the spring to buckle (Venkadesan et al. 2007). Mechanical considerations suggest that the likely normal form is the one that describes a pitchfork bifurcation, i.e.,

$$\frac{dx}{dt} = \mu x + x^3 - x^5, \quad (1)$$

where μ is a bifurcation parameter. This simple model is sufficient to capture the dynamics of this task observed in the laboratory.

A disadvantage of the normal form approach is that it does not necessarily capture the responsible

mechanism(s). Two approaches have been developed to try to close this gap. The first approach makes use of the phase resetting curve (PRC) for periodically spiking and bursting neurons (see chapter ► [“Phase Response Curves: Overview”](#)). The advantage is that the PRC can be measured experimentally. Models which incorporate the PRC have been quite successful in describing, for example, bistability in simple neural circuits (Foss and Milton 2000). Population models using the PRC approach exhibit many complex and counterintuitive dynamical properties (Timme and Wolf 2008).

The second approach uses neural mass models, such as that developed by Wilson and Cowan (see chapters ► [“Epilepsy: Computational Models”](#), ► [“Large-Scale Neural Networks: Vision”](#), ► [“Stochastic Neural Field Theory”](#), and ► [“Visual Hallucinations and Migraine Auras”](#)), to make a compromise between an abstract mathematical construct and a mechanistic biophysical model. In particular, it is possible to develop a statistical mechanics for neurodynamics (Buice and Cowan 2009) and then analytically derive the nature of the emergent properties that arise as a function of scale. However, the development of these statistical approaches requires that the effects of neuronal heterogeneity and connectivity pathways be suitably averaged. Thus it can become difficult to translate predicted dynamical behaviors into treatment strategies based on known molecular and neurophysiological mechanisms. Instead these models are more suited to capture the mean or population output of large numbers of neurons. They can also be used to investigate the nature of the underlying bifurcations and complex dynamical properties (Wang et al. 2012). By combining mathematical insight with mechanistic predictions, it is possible to explore, for example, the impact of inhibitory processes on a given pathophysiological phenomenon.

A further computational question concerns the role of time delays. Time delays are intrinsic components of the nervous system and arise because neural processing times and axonal conduction velocities are finite. The inclusion of time delays in computational models may become

increasingly important as the spatially extended nature of neural control mechanism is taken into account. There is a 10–20-fold difference in the conduction velocity between unmyelinated thin and larger diameter, myelinated axons of cortical neurons. Thus fast transfer of neural activity occurs initially in the direction perpendicular to the gray matter via corticothalamic, and intracortical and interhemispheric commissural fibers, whereas slow activity transmission occurs in parallel directions within the gray matter. These observations point to computational models of cortical dynamics which take the form of delay, or partial delay, differential equations (see chapter ► [“Time-Delayed Neural Networks: Stability and Oscillations”](#)) that include either multiple discrete delays or a distribution of delays.

The Future

The identification of the dynamical aspects of neurological disease motivates the development of dynamic treatment strategies. It is quite likely that proposed therapeutic strategies will be based on the use of external stimuli to control dynamics. The stimuli could be chemical, electrical, or mechanical (e.g., vibrations) and take the form of brief pulses or pulse trains. Even noisy signals can be of benefit (see chapter ► [“Stochastic Resonance: Balance Control and Cochlear Implants”](#)). Most present day implantable devices operate in an open loop mode, namely, the same stimulus or stimulus protocol is delivered regardless of the state of the patient’s nervous system. Examples include the vagal nerve stimulator for epilepsy, deep brain stimulators for Parkinson’s disease (see chapters ► [“Parkinson’s Disease: Deep Brain Stimulation”](#) and ► [“Computational Models of Deep Brain Stimulation \(DBS\)”](#)), and spinal cord stimulation for pain control and spasticity. An important observation is that all of these implementations do not benefit from insights potentially available from modeling efforts. Thus from the computational neuroscience point of view, the good news is that there is a lot of room for improvement.

Closed-loop treatment strategies have the advantage that the therapy is delivered based on

the state of the patient's nervous system (Milton and Jung 2003; Milton and Foss 1997). Such devices would likely take the form of implantable electronic computer devices which both monitor the important variables and then deliver the appropriate stimulus. Devices of this type have already been developed for treating epilepsy (Heck et al. 2014). An exciting development is the increasing availability of noninvasive, EEG sensors suitable for long-term uses (e.g., weeks, months) (Chi et al. 2012). Such data sets will likely prove invaluable since they will provide the first detailed insights into the nature of neurodynamics during a patient's daily life, as distinct from the behaviors observed in the physician's office and in the hospital bed. The availability of such information will impact the goals of computational neuroscience: (1) should more efforts be directed towards the prediction of rare events and (2) can computational neuroscience techniques be used to develop more efficient implementations of a control strategy, e.g., strategies that maximize battery life (changing a battery requires an operation). As an example, predictions of state-dependent responses to single-pulse perturbations were obtained from a model of primary generalized spike-wave seizure activity (Taylor et al. 2014). A closed-loop implementation was proposed which allowed to empirically test the success of stimulation in cases where real-time feedback is possible.

A further possibility for treating neurological disease is to simply replace the broken part with a new one. It may be eventually be possible to use stem cell techniques to produce the replacement part. However, it is more likely to be the case in diseases of the nervous system that the replacement part will take the form of an electronic circuit that can directly interface with the patient's nervous system. Existing examples include brain-motor prosthesis (see chapters ► "Functional Neuroscience: Cortical Control of Limb Prostheses" and ► "Cortical Motor Prosthesis"), exoskeletons, and insect robots. In some sense, computational neuroscience may be well suited for the design of such replacement neural circuits. After all the nervous system appears to be plastic

enough to adapt to whatever errors the circuits may have introduced. Thus we anticipate that computational approaches may play an important role in this area. And finally, there exist studies looking into the possibility of training patients to self-suppress epileptic seizures making use of brain-computer interfaces, e.g., by learning to control slow cortical potentials (Kotchoubey et al. 2001). However, regulation of slow cortical potentials in such settings is rather unspecific and the placebo effect may play a role. Recent applications of dynamic network analysis have led to the possibility to identify brain states with different susceptibility to more specific interventions, e.g., mental arithmetics (Muldoon et al. 2018). This raises the possibility that state-dependent cognitive activity might be employed to interfere with the evolution of an epileptiform brain activity.

Cross-References

- [Computational Models of Deep Brain Stimulation \(DBS\)](#)
- [Computational Psychiatry](#)
- [Cortical Motor Prosthesis](#)
- [Delay-Induced Transient Oscillation \(DITO\) and Metastable Behavior](#)
- [Epilepsy: Computational Models](#)
- [Flicker-Induced Phosphenes](#)
- [Functional Neuroscience: Cortical Control of Limb Prostheses](#)
- [Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)
- [Large-Scale Neural Networks: Vision](#)
- [Migraines and Cortical Spreading Depression](#)
- [Multistability: Stopping Events with Single Pulses](#)
- [Parkinson's Disease: Deep Brain Stimulation](#)
- [Phase Response Curves: Overview](#)
- [Stochastic Neural Field Theory](#)
- [Stochastic Resonance: Balance Control and Cochlear Implants](#)
- [Time-Delayed Neural Networks: Stability and Oscillations](#)
- [Visual Hallucinations and Migraine Auras](#)

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Dynamic Models

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Dynamical Diseases

- [Dynamic Diseases of the Brain](#)

E

Echo State Networks

► [Recurrent Network Models, Reservoir Computing](#)

Echoic Memory

► [Auditory Memory](#)

ECoG

► [Local Field Potentials in Olfaction](#)

EEG

► [Local Field Potentials in Olfaction](#)

EEG, Neural Population Models of

► [Neuroimaging, Neural Population Models for](#)

Efficient Population Coding

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Synonyms

[Coding accuracy of neural populations](#); [Coding efficiency of neural populations](#); [Information transmission by neural populations](#)

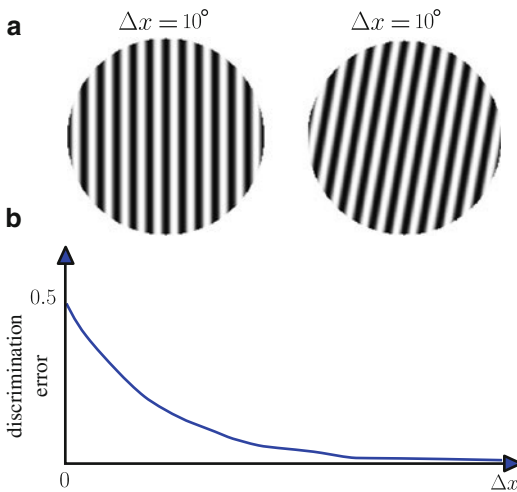
Definition

Natural stimulations caused by objects in the surrounding world do not stimulate single sensory receptors in isolation but lead to the activation of large numbers of neurons simultaneously. Thus, typical stimulus variables of interest are represented only implicitly in activation patterns across large neural populations. These patterns are statistical in nature since repeated presentation of the same stimulus usually leads to highly variable responses. The large dimensionality and randomness of the neural responses make it difficult to assess how well different stimuli can be discriminated. Depending on how effectively neurons share the labor of encoding, the accuracy with which stimuli are represented can change

dramatically. Thus, studying the efficiency of population codes is important for our understanding of both which information is encoded in neural populations and how it is encoded.

Detailed Description

The question for the efficiency of population codes naturally arises if one seeks to relate the psychometric performance in a sensory discrimination task to the amount of information available from the activation of neural populations. For illustration, we consider an orientation discrimination task (Fig. 1a) for which the behavioral performance can be summarized by the *psychometric function* (Fig. 1b). The latter quantifies the discrimination error as a function of the stimulus parameter of interest. If one records from a neural population, one can use decoders to solve the same task on the basis of the neural responses and compare the resulting *neurometric performance* to the psychometric one. In addition, one can try to predict the behavioral choice from the neural responses which is quantified using the so-called choice probabilities.



Efficient Population Coding, Fig. 1 In each trial of an orientation discrimination task two gratings are presented as depicted in (a) where one of the two gratings is tilted to the right and the task is to say which of the two gratings is tilted. The task performance can be quantified by measuring the error frequency as a function of the tilt angle. The resulting *neurometric function* is sketched in (b)

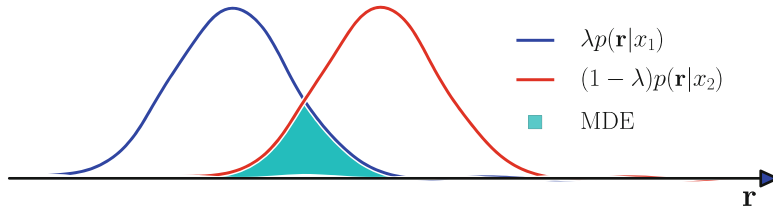
For several tasks it has been observed that the neurometric function obtained for a single neuron or few is sufficient to explain the behavioral, psychometric performance. Given that the population of sensory neurons encoding for the stimulus contains many more neurons than just the recorded ones, this observation indicates that the *encoding* or the *decoding* of the task-relevant information from this sensory population is highly suboptimal: In case of *suboptimal encoding*, the information conveyed by each of these neurons is extremely redundant such that the entire population does not convey more information about the task than small subsets of neurons in this population (Zohary et al. 1994). In case of *suboptimal decoding*, the sensory population carries more information about the task than its individual neurons, but the readout of downstream neurons is unable to extract this distributed information (Beck et al. 2012).

The relationship between neural representation and behavioral performance can be studied using probabilistic modeling. In the beginning we will assume that the stimulus entity of interest is parameterized by a one-dimensional variable x (e.g., contrast, orientation, etc.). Later, we will also discuss the encoding of high-dimensional stimuli such as natural images in the context of normative approaches to population coding that investigate optimal encoding strategies from an engineering perspective.

Throughout this entry neural responses will be denoted by a vector $\mathbf{r}$ which oftentimes describes the spike counts of the different neurons but could similarly describe other properties such as response latencies, interspike intervals, or alike as well. Since the same stimulus usually leads to variable responses, the relationship between stimulus and population response is determined by the conditional probability distribution $p(\mathbf{r}|x)$. This conditional probability function specifies the encoding of the task-relevant stimulus variable.

Ideal Observer Analysis (Minimum Discrimination Error)

In order to assess how much information in principle can be extracted from a neuron or a population, it is necessary to determine the performance



Efficient Population Coding, Fig. 2 The decision boundary of the MAP estimator is located at the intersection of the two curves. Correspondingly, the minimum discrimination error is given by the shaded area

E

of an ideal observer. In a binary discrimination task with prior probabilities $p(x = x_1) = \lambda$ and $p(x = x_2) = 1 - \lambda$ for the two possible stimuli x_1, x_2 , the discrimination error is minimized by the maximum a posteriori (MAP) estimator $\hat{x}_{MAP} = x_1$ if $p(x_1 | \mathbf{r}) > p(x_2 | \mathbf{r})$ and $\hat{x}_{MAP} = x_2$ if $p(x_2 | \mathbf{r}) > p(x_1 | \mathbf{r})$. Correspondingly, the minimum discrimination error (MDE) is given by (see Fig. 2)

$$\text{MDE} = \int \min \{ \lambda p(\mathbf{r} | x_1), (1 - \lambda) p(\mathbf{r} | x_2) \} d\mathbf{r}$$

In case of Gaussian distributions $p(\mathbf{r} | x) = \mathcal{N}(\mathbf{r} | \mathbf{f}(x), C)$ with fixed noise covariance matrix C , one can show that the optimal classifier is linear and takes the following form:

$$\begin{aligned} \hat{x}_{MAP} = x_1 & \text{ if } \left(\vec{\mu}_1 - \vec{\mu}_2 \right)^T C^{-1} \left(\vec{x} - \langle \vec{\mu} \rangle \right) \\ & > \log \frac{\lambda}{1 - \lambda}, \quad \hat{x}_{MAP} = x_2 \quad \text{otherwise} \end{aligned}$$

$$\text{with } \mu_1 = \mathbf{f}(x_1), \mu_2$$

$$= \mathbf{f}(x_2), \text{ and } \langle \vec{\mu} \rangle = \frac{1}{2} \left(\vec{\mu}_1 + \vec{\mu}_2 \right)$$

Furthermore, if $\lambda = 1 - \lambda = 0.5$, the MDE is given by

$$\begin{aligned} \mathcal{F} \left(-\frac{d'}{2} \right) &= \int_{-\infty}^{-\frac{d'}{2}} \mathcal{N}(z | 0, 1) dz, \\ \text{where } d' &:= \sqrt{\left(\vec{\mu}_1 - \vec{\mu}_0 \right)^T C^{-1} \left(\vec{\mu}_1 - \vec{\mu}_0 \right)} \end{aligned}$$

In the absence of noise correlations, the noise covariance matrix C is diagonal. Its

dimensionality equals the number of neurons N and d' is of the order of $\sqrt{N}$. Thus, for uncorrelated noise the minimum discrimination error converges to zero in the limit of large N . In the presence of certain types of noise correlations, however, the error may saturate at a nonzero level. For example, this can happen in case of input noise which obviously cannot be removed by subsequent signal transmission (unless by the use of contextual side information).

As an illustration, consider the following linear encoding $\mathbf{r} = \mathbf{f}(x + n_x) + \mathbf{n}_r$ with $\mathbf{f}(x) = \mathbf{w}x$ where $n_x \sim \mathcal{N}(0, \sigma_x^2)$ denotes the input noise and $\mathbf{n}_r \sim \mathcal{N}(0, \sigma_r^2 I)$ constant additive output noise. In this case, the total noise covariance matrix reads $\mathbf{w} \sigma_x^2 \mathbf{W} + \sigma_r^2 I$, and its largest eigenvalue is given by $\sigma_x^2 + \sigma_r^2$ with eigenvector $\mathbf{w}$. The remaining $(n-1)$ dimensions belong to the same degenerated eigenvalue σ_r^2 . Using the Sherman-Morrison formula, it is possible to determine the inverse of this covariance matrix

$$C^{-1} = \frac{1}{\sigma_r^2} \left(I - \frac{\sigma_x^2 \mathbf{w} \mathbf{w}^T}{\sigma_r^2 + \sigma_x^2 \mathbf{w}^T \mathbf{w}} \right)$$

and

$$d' = \Delta x \cdot \sqrt{\frac{A}{1 + \sigma_x^2 A}} \quad \text{with } A := \frac{\mathbf{w}^T \mathbf{w}}{\sigma_r^2},$$

where A is of the order of N . Accordingly, for finite input noise $\sigma_x > 0$, the population sensitivity d' converges to $\Delta x / \sigma_x$ in the limit $N \rightarrow \infty$. This can be one reason why behavioral performance may be not much better than one would predict on the basis of the neurometric performance of very few neurons. By estimating

$(\Delta x/d')^2$ as a function of N for empirical data, one can use the following relationship

$$\left(\frac{\Delta x}{d'}\right)^2 = \sigma_x^2 + \frac{1}{A} \xrightarrow{N \rightarrow \infty} \sigma_x^2$$

for estimating the effective amount of input noise (see also Fig. 3).

Further reading: (Dayan and Abbott 2001; Salinas and Abbott 1994; Abbott and Dayan 1999; Shamir and Sompolinsky 2004, 2006; Ecker et al. 2011; Haefner et al. 2013; Shamir 2014).

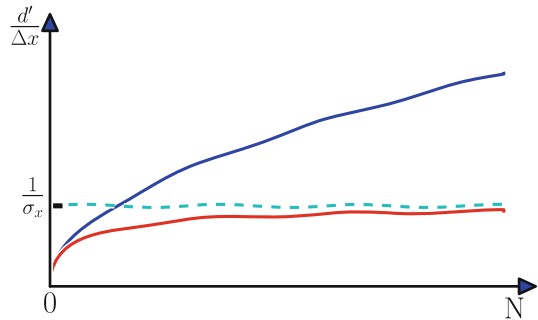
Discrimination, Mutual Information, and Minimum Mean Square Estimation

The minimum discrimination error is only one way to evaluate the coding accuracy of a neural population. Other popular measures are based on the

mutual information between stimulus and response or minimum mean square estimation. In contrast to the discrimination approach, these other measures make assumptions about the stimulus distribution in order to obtain an average performance. If one assumes a binary stimulus distribution, the mutual information between stimulus and response is also called the Jensen-Shannon divergence which provides an upper and lower bound on the minimum discrimination error (see Fig. 4) but is not related to it in a one-to-one fashion (Berens et al. 2009). For Gaussian stimulus distributions, if we still assume a linear encoding and a Gaussian noise model, the joint distribution of stimulus and response is Gaussian, and mutual information as well as the minimum mean square error can be computed analytically. For nonlinear encodings and non-Gaussian noise models, these quantities are much more difficult to assess and approximation approaches are important.

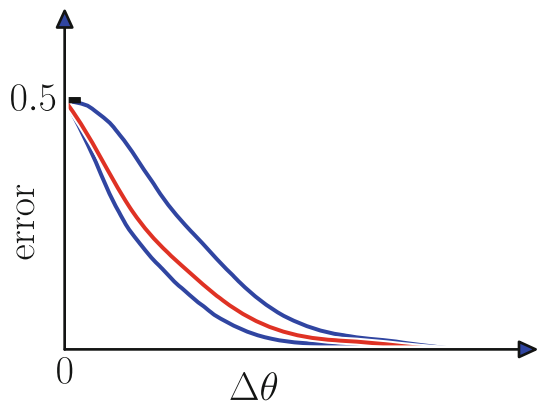
Efficient Population

Coding, Fig. 3 The sensitivity index d' as a function of the number of neurons N in the presence (red) or absence (blue) of input noise



Efficient Population

Coding, Fig. 4 The minimum discrimination error can be bound from above and below (Berens et al. 2009) by the Jensen-Shannon information $H_B^1(1 - I_{JS}) \leq MDE \leq \frac{1}{2}(1 - I_{JS})$ where $H_B(u) = -u \log u - (1 - u) \log(1 - u)$ and the Jensen-Shannon information is equal to the mutual information $I_{JS} = I[x:r]$ between the stimulus x and the responses r



Fine Discrimination and Fisher Information

We cannot expect that neural encoding is accurately captured by a linear Gaussian model. Nevertheless, in the case of fine discrimination, when $|x_2 - x_1|$ is sufficiently small, d' can often be used to quantify approximately how well the two stimulus alternatives can be discriminated.

In a fine discrimination task, we study how well a stimulus at any location $x_1 = x$ can be discriminated from a stimulus with a slightly changed parameter value $x_2 = x + \Delta x$. Assuming that the tuning functions are smooth and the noise variance is finite, the discrimination performance approaches chance level $MDE \rightarrow 0.5$ in the limit of small differences in the stimulus parameter $\Delta x \rightarrow 0$. The asymptotic behavior in the limit of fine discrimination is more amenable to an analytical derivation of coding efficiency. Specifically, we can bound the minimum discrimination by the Jensen-Shannon information (see Fig. 2) which for small Δx can be approximated by the Fisher information:

$$I_{JS}(\Delta x) \approx \frac{f(x)}{8} \Delta x^2$$

Fisher information is defined as the variance of the score $V = \partial_x \log p(\mathbf{r} | x)$ conditioned on the stimulus x :

$$J(x) := \text{Var}[V | x] = E[V^2 | x]$$

where the second equality holds because it generally holds $E[V|x] = 0$. Many papers on neural coding refer to the Cramer-Rao bound to motivate the evaluation of Fisher information which gives a lower bound on the mean squared error of any unbiased estimator:

$$E[(\hat{x}_{\text{unbiased}}(\mathbf{r}) - x)^2 | x] \geq \frac{1}{J(x)}$$

This bound, however, is only of intuitive use for the evaluation of encodings as it does not account for the fact that the signal x must be a random variable and the precision with which

x can be decoded strongly depends on the stimulus distribution $p(x)$. Similarly, the local expansion of the Jensen-Shannon divergence must be wrong whenever I_{JS} exceeds 1 bit since it generally holds $I_{JS} \leq 1$ bit. Thus the approximation for fine discrimination only holds if

$$\Delta x^2 \ll \Delta x_c^2 \equiv \frac{8}{J(x)}$$

In the next section, we will discuss the evaluation of population codes if the stimulus distribution $p(x)$ is given.

Coding Efficiency and Optimal Encodings

The question of coding efficiency critically depends on the stimulus distribution $p(x)$ which often requires additional considerations that go beyond the framework of discrimination. While for each pair of stimuli tested for in a discrimination task the prior distribution is reduced to two discrete alternatives, for continuous stimulus parameters in principle, any pair of stimuli could be picked. Therefore, one often rather wants to assess the coding efficiency for a prior distribution that describes how the stimulus parameter is distributed under natural conditions. For example, if the stimulus parameter is contrast or speed, one would assume that the natural distribution has a unimodal density over the positive real axis which takes its maximum at zero and is monotonically decreasing.

To be able to compare the performance of two coding schemes, it is necessary to use a measure that provides a unique ordering relation. A direct ranking of neurometric functions, for example, is not possible unless in the special case if one function lies uniformly above or below the other one. If one was interested exclusively in fine discrimination, one could compare just the slope of the neurometric function at chance level describing how fast the MDE drops from chance level and ignore the discrimination performance for larger differences in the stimulus parameter. In most cases however, one would rather be interested in

the average performance when the stimuli are drawn from the natural distribution. The corresponding notions and assessments of coding efficiency can be very different. The optimization for fine discrimination is tightly related to optimizing Fisher information, whereas an optimization of the average discrimination error (Berens et al. 2011) is more similar (but not equivalent) to optimizing mutual information (Yarrow et al. 2012) or the minimum mean squared error.

There is a special condition for which the minimum mean squared error is determined by Fisher information. If the responses of the different neurons can be described as independent, identically distributed (i.i.d.) observations or more generally if the conditions of the central limit theorem are fulfilled, then Fisher information can be used to determine an asymptotic approximation of the decoding error (Bethge et al. 2002). Optimal codes, however, generically exhibit highly heterogeneous encodings which preclude the use of the central limit theorem. In particular, one should note that the linear increase of Fisher information in case of i.i.d. observations corresponds to a very slow logarithmic growth in mutual information. In contrast, encodings that are optimized for mutual information usually achieve a much faster, linear growth of the mutual information. The two situations can be illustrated with the following two prototypical examples:

$$\begin{aligned} \text{iidcoding} : p_{iid}(\mathbf{r}, \mathbf{x}) &= p(\mathbf{x}) \prod_{k=1}^N p(r_k | f(\mathbf{x})) \quad \text{vs} \\ \text{factorial} \\ \text{mathrmcoding} : p_{fac}(\mathbf{r}, \mathbf{x}) &= p(\mathbf{x}) \prod_{k=1}^N p(r_k, f_k(\mathbf{x})) \end{aligned}$$

It is easy to derive (Brunel and Nadal 1998) that for the left example of i.i.d. coding mutual information grows only logarithmically, $I[\mathbf{r}, \mathbf{x}] \propto \log(N)$, whereas for the right example of a factorial code (Nadal and Parga 1994), mutual information grows linearly, $I[\mathbf{r}, \mathbf{x}] \propto N$. Thus, for large populations of neurons, i.i.d. coding is highly inefficient compared to factorial coding.

In cases other than i.i.d. coding (or, more generally, whenever the conditions for the central limit theorem are not fulfilled), the behavior of Fisher information can be very different from that of mutual information. For example, it is possible to build factorial codes for which Fisher information grows only linearly in N just like in the case of i.i.d. coding, but an exponential or super-exponential growth of Fisher information is possible as well. Conversely, it is easy to construct encodings for which Fisher information grows arbitrarily fast with N , but this does not imply that mutual information grows linearly (Bethge et al. 2002). Fisher-optimal codes are exclusively optimized for fine discrimination and may exhibit extremely poor performance for any discrimination for which $\Delta x^2 \geq \Delta x_c^2$.

Task Dependence of Coding Efficiency

While it is obvious that coding efficiency is highly task dependent, it is important to understand the implications of this task-dependency for the interpretation of the available experimental data. As mentioned in the beginning of this entry, it is typically observed that the neurometric function obtained for a single neuron or few is sufficient to explain the behavioral, psychometric performance and that this may hint to highly inefficient encoding or decoding. If the encoding is fixed (i.e., independent of the task), it is straightforward to show that the efficiency of the encoding will depend on the task. For illustration, let us assume we have the same number of neurons as stimulus dimensions and the following encoding with independent noise model:

$$p_{enc}(\mathbf{r} | \mathbf{x}) = \prod_{k=1}^N p(r_k | x_k)$$

Depending on which stimulus distribution $p(\mathbf{x})$ we use, one can obtain either a highly redundant i.i.d. coding scheme or a maximally efficient factorial code. Specifically, if we set $p(\mathbf{x}) = \prod_{k=1}^N p(x_k)$ we obtain the maximally efficient factorial code

$$p_{enc}(\mathbf{r} | \mathbf{x})p(\mathbf{x}) = \prod_{k=1}^N p_{enc}(r_k | x_k)p(x_k) \\ = \prod_{k=1}^N p(r_k, x_k),$$

whereas if we choose a stimulus distribution $p(\mathbf{x}) = p(x_1)\prod_{k=2}^N \delta(x_k - x_1)$, for which it always holds $x_1 = x_2 = \dots = x_N$, we then obtain the highly redundant i.i.d. coding scheme. The first example roughly corresponds to a task where any two images are to be discriminated, while in the second case only full-field uniform gray images need to be discriminated.

The mutual information between stimulus $\mathbf{x}$ and population response $\mathbf{r}$ cannot be larger than the entropy of the stimulus distribution. For good reasons, typical laboratory tasks are inherently biased toward low entropy stimuli. More specifically, most experiments are designed such that it is not critical which neurons exactly are recorded. In vision, this is achieved by using global homogeneous stimuli such as global motion patterns or gratings. By varying only one parameter of these stimuli like the net velocity or orientation, it is achieved that all neurons encode the same parameter in an i.i.d. fashion. Correspondingly, mutual information cannot grow faster than logarithmically with the number of neurons yielding a highly suboptimal population coding strategy.

For many tasks, however, it is likely that this type of suboptimality is not sufficient to explain why behavioral performance does not utilize more information than provided by a single or few neurons. For spatially homogeneous stimuli, the information of neurons with different receptive field locations should still accumulate such that doubling the number of neurons should reduce the squared error by a factor of two as predicted by an i.i.d. coding scheme. This fact, however, is not consistent with the observation that the information of a local population of neurons reaches behavioral performance. Thus, it seems that for typical low-level tasks, the readout cannot integrate information from different local regions.

In conclusion, both encoding and decoding are likely to render behavioral performance highly suboptimal in case of common laboratory tasks for which the decision space has low entropy and for which the stimulus size is rather large. In the future, important new insights about principles of neural coding and sensory decision making may be obtained by choosing more ecologically relevant tasks such as natural scene classification. The importance of studying natural tasks may be corroborated by the example of grid cell encoding in hippocampus. Despite the fact that the stimulus parameter is only two dimensional – namely, the x-y position of the animal – the mutual information between this stimulus parameter and the grid cells scales proportional to the number of neurons (Sreenivasan and Fiete 2011; Mathis et al. 2012). Similarly, one would expect a linear growth of mutual information for the encoding of natural images in the visual system.

Further reading: (Brunel and Nadal 1998; Bethge et al. 2003a, b, Huys et al. 2007; McDonnell and Stocks 2008; Klam et al. 2008; Haefner and Bethge 2010).

Cross-References

- [Bayesian Inference with Spiking Neurons](#)
- [Choice Behavior](#)
- [Cortical Function, Normative Models of](#)
- [Decision-Making, Threshold](#)
- [Estimating Information-Theoretic Quantities](#)

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Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits

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Synonyms

[Hebb's postulate of learning](#); [Hebbian conditioning paradigms](#); [Hebbian learning](#); [Hebbian plasticity](#)

Definition

Spike-timing-dependent plasticity refers to correlated activity of neurons that leads to long-term strengthening or weakening of connections, depending on the order of firing of pre- and postsynaptic neurons. The relative timing of pre- and postsynaptic spiking determines the extent and direction of synaptic changes but should not exceed 50 ms. Repetitive postsynaptic spiking, within this time window, after presynaptic activation results in strengthening of connections. Conversely, presynaptic spiking that follows postsynaptic activation produces long-term weakening of connections. Hebbian electrical-conditioning paradigms seek to modulate synaptic connectivity by promoting synchronous neuronal activity based on these rules and

have important implications for augmenting spared pathways that may be weakened by injury or disease.

Detailed Description

Spike-Timing-Dependent Plasticity

In 1949, Donald Hebb stated “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.” This is known as Hebb’s postulate of learning (Hebb 1949). Manipulations of neuronal activity based on this mechanism have been used extensively to modify the strength of connections.

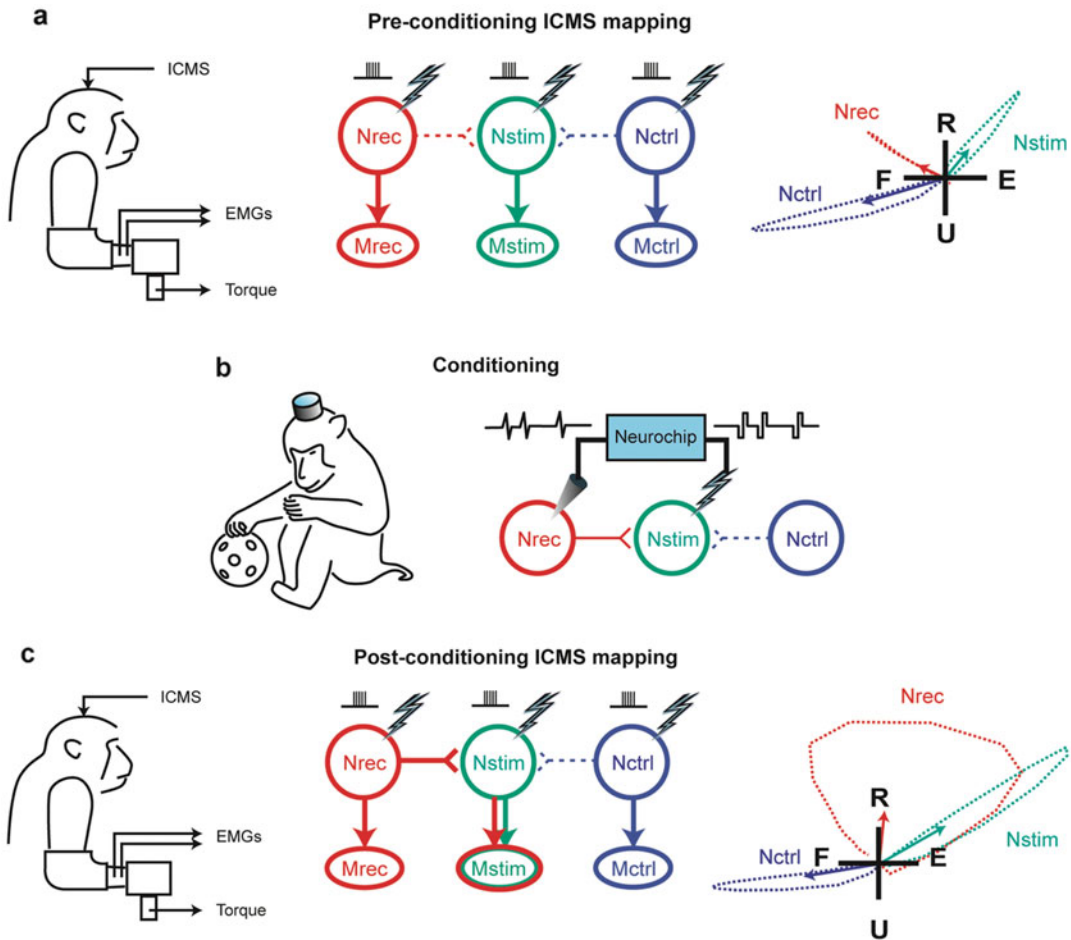
Seminal studies in the late 1990s built on Hebb’s postulate (Hebb 1949) to define the temporal relationship between spiking in pre- and postsynaptic neurons, which dictates the polarity of plastic changes (i.e., potentiation vs. depression). In different neuronal preparations, ranging from neocortical slices (Markram et al. 1997), hippocampal slices (Debanne et al. 1998), and hippocampal cell cultures (Bi and Poo 1998), long-term strengthening of connections was observed if presynaptic action potentials consistently preceded postsynaptic firing by no more than 50 ms. Conversely, presynaptic action potentials that followed postsynaptic spikes produced long-term weakening of connections. Furthermore, the largest changes in synaptic efficacy occurred when the latency between the firing of the pre- and postsynaptic cells was small, and there was a sharp reversal from strengthening to weakening as this latency passed through zero. This form of synaptic modification has been referred to as spike-timing-dependent plasticity (STDP).

STDP-Based Approaches for Strengthening Neural Pathways and Promoting Recovery After Injury

STDP rules (Bi and Poo 1998) have been employed *in vivo* in rats and monkeys to regulate the timing of activity across synapses in an effort to induce Hebbian plasticity. Jackson et al.

employed an autonomous head-fixed recurrent brain-computer interface, called the neurochip (Jackson et al. 2006a; Mavoori et al. 2005), in the primary motor cortex of behaving macaque monkeys to strengthen cortico-cortical connections (Jackson et al. 2006b). Action potentials recorded from a presynaptic neuron were used to trigger delivery of single stimulus pulses to neighboring cortical cells. The stimulation was timed to activate postsynaptic neurons, to which the triggering cell projected, with a specific delay. Electrical conditioning was delivered for 2 days using the neurochip while animals engaged in free behavior in their home cages. After conditioning with a 5-ms spike-stimulus delay, the movement representation of the presynaptic recording site shifted toward that of the postsynaptic stimulated site, presumably due to strengthening of the connection from the pre- to the postsynaptic site, while the output from nearby (unstimulated) control sites remained unchanged (Fig. 1). The extent of the change was dependent on the spike-stimulus delay, consistent with the STDP rule (Bi and Poo 1998). Importantly, the induced Hebbian plasticity persisted for more than a week in some cases.

In a second example, Nishimura and coworkers modified the strength of connections between the motor cortex and the spinal cord with the neurochip (Jackson et al. 2006a; Mavoori et al. 2005) in monkeys (Nishimura et al. 2013). Electrical stimuli, triggered by action potentials of single corticomotoneuronal cells, were delivered in the spinal cord during free behavior. The activity-dependent stimulation modified the strength of corticomotoneuronal connections to motoneurons, which was documented with spike-triggered averages of electromyographic activity (EMG) in target muscles. In this study, both strengthening and weakening of connections was observed, using different spike-stimulus delays. In some cases, the effects lasted for days after the end of conditioning. Notably, delays of 50 ms and longer didn’t produce significant changes despite involving the same amount and pattern of spinal stimulation, thus emphasizing the importance of the relative timing of stimulation on the induced plasticity.



Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits, Fig. 1 Reorganization of motor output using a closed-loop electronic neural interface. **(a)** Intracortical microstimulation (ICMS) at three neuronal sites in the motor cortex, designated as Nrec, Nstim, and Nctrl, with the monkey at rest, evoked distinct muscle responses (Mrec, Mstim, and Mctrl, respectively), which were measured using EMG and two-dimensional isometric wrist torques (left and middle panels). Right panel shows the average wrist-torque responses to ICMS, superimposed on the flexion-extension (F-E) and radial-ulnar (R-U) axes. **(b)** Cortical conditioning with the neurochip (Jackson et al. 2006a; Mavoori et al. 2005)

involved 2 days of triggered microstimuli at Nstim for every spike recorded at Nrec during free behavior and sleep. **(c)** Post-conditioning ICMS of Nrec activated Mstim, presumably through strengthening of horizontal projections to Nstim, and Mrec through the direct projection, while the outputs from Nctrl and Nstim remained unchanged. The mean torque generated by ICMS at Nrec also shifted toward the output produced by Nstim. For **(a)** and **(c)**, arrows in the right panels indicate means of 200-ms torque trajectories, denoted by the dashed lines. (Image adapted, with permission, from Jackson et al. 2006b)

Proxies for neuronal activity have also been used to induce Hebbian-like plasticity. In monkeys, Lucas and Fetzi used EMG signals from contralateral forelimb muscles to trigger stimulation of sites in the primary motor cortex associated with different (forelimb) muscles (Lucas and Fetzi 2013). The neurochip (Jackson et al. 2006a;

Mavoori et al. 2005), in this case, was used to transform forelimb EMG into subthreshold intracortical stimuli, which were delivered during hours of unrestrained behavior. As observed by Jackson et al. (2006b), EMG-triggered conditioning promoted a shift in the movement representation of the presynaptic recording site toward that

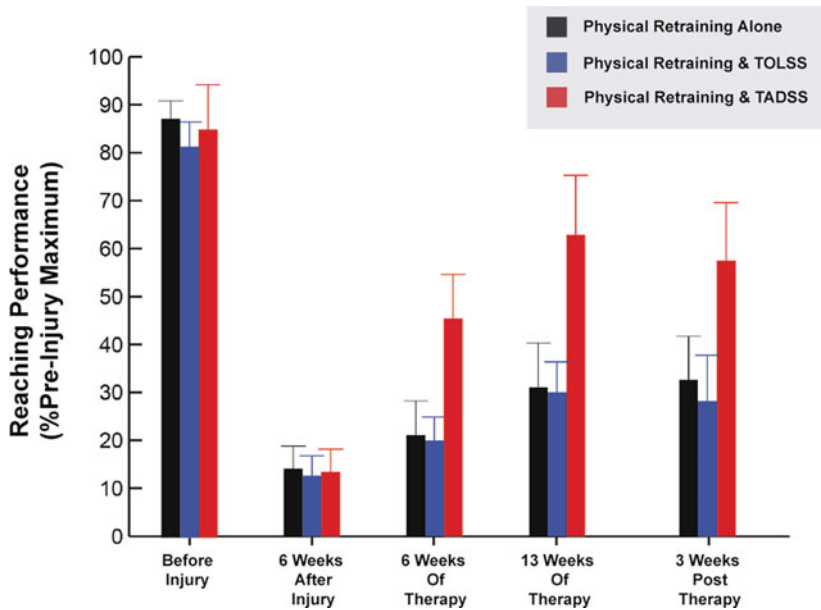
of the postsynaptic stimulated site, presumably due to strengthening of the connection from the pre- to the postsynaptic site. Importantly, the output from nearby control sites that received pseudoconditioning remained unchanged. Reorganization was observed within 25 min and could be maintained with intermittent conditioning for up to 5 days. Moreover, reorganization was site specific (occurring only at the presynaptic site) and input specific (occurring only with EMG-triggered stimulation). Control stimulation that was independent of muscle activity failed to produce reorganization, yet again underscoring the importance of timing over open-loop stimulation approaches. Lastly, this investigation provided evidence for muscle activity being an effective surrogate of associated cortical activity for producing targeted reorganization of the motor cortex, implying that the timing of activity in the motor output of cortical sites is sufficiently correlated to its neuronal activity for mediating conditioning.

The studies highlighted above provided important insights into the capability of activity-dependent electrical stimulation for remodeling neural connections during behavior. Corresponding to these fundamental research opportunities are prospects for translating circuit-retraining investigations into clinical therapies. By delivering stimuli synchronized with cell activity, continuous operation of recurrent brain-computer interfaces can strengthen neural connections weakened by disease or trauma. This paradigm was explored by McPherson et al. to promote forelimb-motor recovery after chronic cervical spinal cord injury (SCI) in rats (McPherson et al. 2015). Delivery of intraspinal microstimulation below the injury was synchronized with arrival of functionally related volitional motor commands, signaled by EMG in the impaired forelimb, a paradigm similar to that developed by Lucas and Fetz (2013). Stimulation was delivered for 5–8 h/weekday for 3 months during which the rats also received physical retraining on a reach-and-grasp behavior that encouraged use of the impaired forelimb. Rats that received the targeted activity-dependent spinal stimulation (TADSS) exhibited markedly

enhanced recovery compared to the two control groups that received targeted open-loop spinal stimulation (TOLSS) or physical retraining alone. Moreover, the therapeutic benefits of TADSS persisted for at least 3 weeks after the stimulation had ended (Fig. 2).

The maintenance of TADSS-driven recovery for 3 weeks beyond the intervention is both a novel and clinically significant finding (McPherson et al. 2015). It distinguishes TADSS from most open-loop electrical-stimulation therapies, whose benefits are often contingent on the continued delivery of stimulation. Additionally, this finding strongly suggests that the enhanced and lasting recovery afforded by TADSS is an effect unique to activity-dependent conditioning of specific neural circuits. Consistent with this notion, spike-triggered intracortical stimulation delivered for 3 weeks restored communication between motor and somatosensory areas in the cerebral cortex after focal traumatic-brain injury in adult rats, leading to accelerated forelimb-motor recovery compared to open-loop intracortical stimulation (Guggenmos et al. 2013). Cortico-pallidal stimulation, contingent on the occurrence of action potentials in the globus pallidus or the primary motor cortex, was also more successful in ameliorating parkinsonian akinesia and pathological neuronal discharges in monkeys compared to continuous high-frequency deep-brain stimulation (Rosin et al. 2011; Santos et al. 2011). Lastly, transcranial electrical stimulation triggered by local-field-potential activity during a spike-and-wave episode, a common signature of an epileptic seizure, reduced seizure duration by 60% on average in a rat model of generalized epilepsy (Berényi et al. 2012).

Paired-associative stimulation has also been used for inducing Hebbian plasticity. Taylor and Martin altered the strength of corticomotoneuronal synapses by repeatedly pairing transcranial-magnetic and peripheral-nerve stimuli at different interstimulus intervals to produce bidirectional plasticity in human subjects (Taylor and Martin 2009). The induced plasticity influenced the voluntary motor output, producing a bidirectional modulation in both the EMG and force output. Thus, a protocol designed



Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits, Fig. 2 EMG-triggered intraspinal stimulation promotes motor recovery after chronic SCI. Rats were trained on a forelimb reach-and-grasp pellet-retrieval task before injury. Starting 6 weeks post injury, animals received 13 weeks of one of three different types of treatments. Over 13 weeks of treatment, animals receiving physical retraining and TADSS (red) recovered to a significantly greater extent than animals that received either physical retraining and TOLSS (blue) or physical retraining alone (black). After 13 weeks of intervention, the TADSS animals had recovered to 63%

of their pre-SCI skilled-reaching performance, whereas the TOLSS and physical-retraining-only cohorts averaged 30% and 31%, respectively. Importantly, the therapeutic benefits of TADSS persisted for at least 3 weeks after the stimulation had ended. Note that the performance of TOLSS and physical-retraining-only cohorts was statistically indistinguishable from each other. Y-axis shows the average weekly reaching scores across all rats in each cohort expressed as a percentage of each rat's pre-SCI maximum. Error bars represent standard error of the mean. (Data replotted from McPherson et al. 2015)

to induce synaptic STDP produced concurrent changes in corticospinal transmission and altered normal physiological motor output. This strategy was used by Bunday and Perez to strengthen pathways weakened by injury in humans with chronic incomplete cervical SCI (Bunday and Perez 2012). Using noninvasive techniques, they precisely timed the arrival of descending and peripheral volleys at corticomotoneuronal synapses of an intrinsic finger muscle. Corticospinal neurons were activated via transcranial magnetic stimulation delivered over the hand representation of the motor cortex, and spinal motoneurons were activated antidromically through peripheral-nerve stimulation delivered to the wrist. Consistent with STDP-learning rules (Bi and Poo 1998), they found that arrival of presynaptic volleys prior to motoneuron discharge enhanced corticospinal

transmission and voluntary motor output. The reverse order of volley arrival decreased voluntary motor output and electrophysiological outcomes. The induced plastic changes lasted for up to 80 min after 17 min of paired stimulation. Cortical and peripheral-nerve stimulation have also been paired by Perez and coworkers to change transmission at spinal synapses of lower-limb motoneurons in humans with chronic incomplete SCI (Urbin et al. 2017). Thus, STDP of residual corticomotoneuronal synapses holds considerable promise for improving motor function after SCI.

Finally, a recent study by Bunday et al. found that volitional activity during a paired corticomotoneuronal stimulation protocol enhanced corticospinal transmission in humans with SCI (Bunday et al. 2018). Transmission was significantly improved when the paired

stimulation was combined with relevant muscle activity compared to delivery of stimulation at rest, underscoring the role of volitional activity, which occurs at a very different timescale from STDP (Drew and Abbott 2006), in boosting synaptic plasticity. A similar observation was made almost three decades ago by Ahissar et al., who found that strengthening of cortical connections was strongly dependent on the behavioral context of the stimuli that induced such modifications (Ahissar et al. 1992). Correlated activity of neurons was often necessary, but not sufficient, for induction of plasticity.

STDP: Complexities and Challenges

In some studies, STDP-based stimulation protocols produced global modifications of synaptic strength, affecting connections beyond the site of induction. Poo and coworkers found presynaptic propagation of long-term potentiation (LTP) from the site of induction (Hui-zhong et al. 2000). LTP propagated retrogradely to glutamatergic synapses on the dendrites of the presynaptic neuron and laterally to those made by its axonal collaterals onto other glutamatergic cells. No postsynaptic lateral or forward propagation or secondary propagation of LTP to synapses not directly associated with the presynaptic neuron were observed. Such selective propagation would require the existence of long-range cytoplasmic signaling within the presynaptic neuron, triggered, in turn, by a retrograde messenger. The researchers also found that the spread of long-term depression (LTD) followed a similar pattern of presynaptic propagation (Fitzsimonds et al. 1997). Brain-derived neurotrophic factor (BDNF) and nitric oxide, secreted as a result of LTP and LTD induction, were implicated in triggering retrograde potentiation and depression, respectively (Du et al. 2009).

Other studies have also reported the spread of LTP to nearby connections from the activated synapse but have not found such a selective pattern of propagation (Bonhoeffer et al. 1989; Engert and Bonhoeffer 1997; Schuman and Madison 1994). Engert and Bonhoeffer, for example, found that there was no input specificity at a distance less than 70 μm from the activated synapse (Engert and Bonhoeffer 1997). Synapses in

close proximity to the site of LTP induction were potentiated, regardless of their own history of activation, whereas synapses far away showed no potentiation, a stark contrast to the LTP-propagation pattern observed by Poo and coworkers (Hui-zhong et al. 2000). Nevertheless, these studies all highlight the lack of target specificity associated with STDP protocols.

The patterns of activity that induce changes in strength of synapses that involve inhibitory neurons are quite diverse and differ markedly from synapses that involve excitatory cells alone. Involvement of γ -aminobutyric acid-ergic (GABAergic) neurons leads to a variety of STDP-timing dependencies (Bi and Poo 1998; Holmgren and Zilberter 2001; Woodin et al. 2003). Woodin et al., for example, showed that repetitive postsynaptic spiking within 20 ms both before and after the activation of GABAergic synapses led to persistent increases in synaptic strength in rat hippocampal cultures and slices (Woodin et al. 2003). Changes in synaptic strength could also be induced by postsynaptic activity alone (Kurotani et al. 2008; Sieber et al. 2013). Furthermore, LTP- and LTD-propagation patterns in networks containing GABAergic neurons deviated from those observed within excitatory pathways (Fitzsimonds et al. 1997; Hui-zhong et al. 2000).

Implementation of STDP-based approaches in vivo poses other complexities. Several studies have noted a variability in both the extent and duration of plasticity across conditioned sites (Jackson et al. 2006b; Lucas and Fetz 2013; Nishimura et al. 2013), making it difficult to predict the effects of conditioning for a given site pair. In a recent study by Seeman et al., paired stimulation delivered to the sensorimotor cortex of awake behaving monkeys, at fixed intervals consistent with the STDP window (Bi and Poo 1998), failed to induce changes at 13/15 tested site pairs (Seeman et al. 2017). Moreover, the stimulation protocol often produced increases in global excitability or depression of the conditioned pair. Secondly, the use of proxies, such as EMG (Lucas and Fetz 2013; McPherson et al. 2015) or movement, for inducing STDP undoubtedly produces a range of firing latencies between pre- and

postsynaptic neurons in the conditioned pathways. The most parsimonious explanation for how such protocols lead to STDP, despite only loosely controlling spike timing, is that activity-dependent stimulation generates a statistical preponderance of spike pairs with the appropriate intervals. Nonetheless, additional work is needed to reconcile the large discrepancy in timescales: protocols relying on proxies of neuron spiking involve temporal associations on the order of one or more seconds, while STDP occurs over timescales of tens of milliseconds (Drew and Abbott 2006). Thirdly, the mechanisms by which behavior enhances the effects of conditioning, as seen in experiments by Ahissar et al. (1992) and Bunday et al. (2018), are also unclear. In unpublished work by Moorjani et al., movement-triggered stimulation produced significant and lasting strengthening of cortico-cortical connections in monkeys only when paired with relevant muscle activity. Neither movement alone nor stimulation alone produced similar effects, yet again emphasizing the importance of behavioral context on the resultant plasticity.

Complexities and challenges abound, but it has been demonstrated unequivocally that STDP-based electrical-stimulation protocols can modulate synaptic connections during normal behavior. These approaches drive endogenous-plasticity mechanisms rather than producing a generalized increase in excitability alone. Consequently, they offer promise for functional and lasting reorganization of neural circuitry impaired by injury. Combination with other strategies, such as targeted delivery of plasticity-enhancing neuromodulators, may further enhance and prolong the duration of effects achieved using activity-dependent or paired-associative stimulation (Moorjani 2016; Silver and Miller 2004). For example, a large body of work has shown that BDNF (Cotman and Berchtold 2002; Kohara et al. 2001), much like a neurotransmitter and unlike a neurotrophin, and its high-affinity receptor, tropomyosin-related kinase B (TrkB; Meyer-Franke et al. 1998), are transported retrogradely and anterogradely to synapses in an activity-dependent manner. Once at the synapses, BDNF binds to presynaptic TrkB receptors to modify

neurotransmitter release (Cotman and Berchtold 2002). Postsynaptically, BDNF modifies sensitivity (Cotman and Berchtold 2002), e.g., through its interactions with N-methyl-D-aspartate receptors (which are necessary for induction of LTP; Bi and Poo 1998). This activity-dependent signaling ultimately results in changes in neuronal morphology (Horch and Katz 2002; Ji et al. 2010) and potentiation of synaptic transmission (Cotman and Berchtold 2002; Ji et al. 2010; Kovalchuk et al. 2002). These studies suggest that targeted delivery of BDNF can potentially strengthen and prolong the duration of plasticity achieved using STDP-based stimulation approaches and exploration of such combinatorial interventions may represent important future directions.

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Electrical Nerve Block

- [Peripheral Nerve Stimulation Technique, Nerve Block](#)

Electrocorticogram

- [Local Field Potentials in Olfaction](#)

Electrocorticogram (ECoG)

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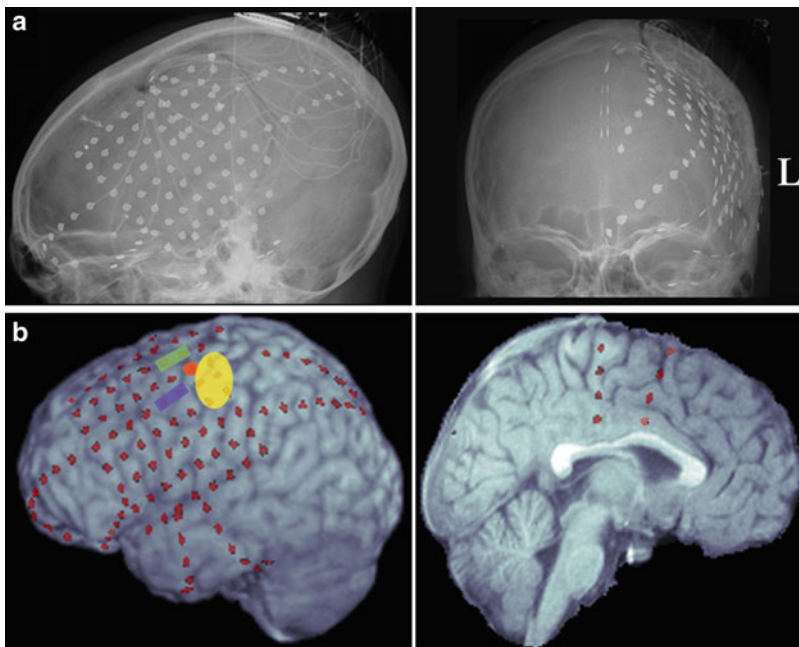
Synonyms

Modeling intracranial electroencephalography (iEEG) signals; Modeling the electrocorticogram

Definition

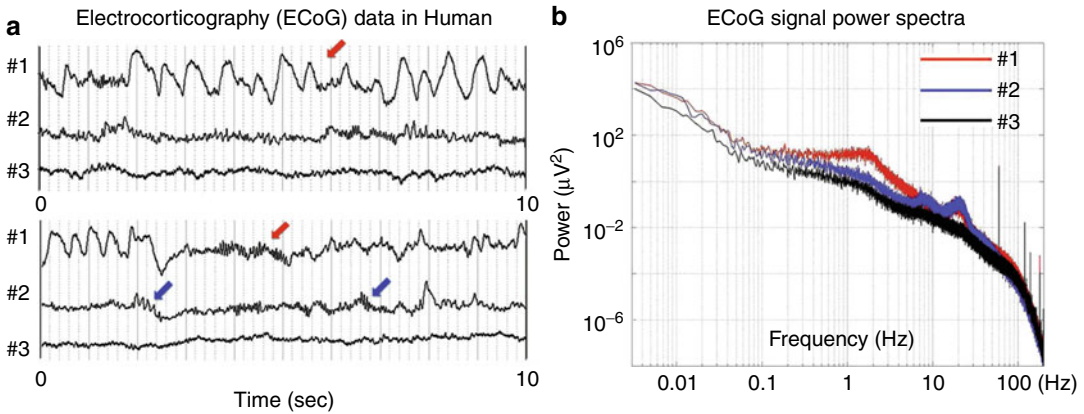
ECoG refers to the invasive technique of recording brain electrical field potentials with electrodes placed directly on the cortical surface. ECoG electrodes are typically placed subdurally, above the

pia mater. In humans, ECoG is often conducted in patients with medically intractable epilepsy in order to monitor their seizures. Because a craniotomy (a surgical incision into the skull) is required to implant the electrode grid, ECoG is an invasive procedure. Clinical ECoG offers a rare and invaluable research opportunity for obtaining invasive electrophysiological signals in awake, behaving humans. Another avenue of research that is beginning to be explored is cortical stimulation using ECoG electrodes (e.g., Parvizi et al. (2013)). The electrode grids often cover much wider areas than the epileptogenic zone, allowing recordings from healthy brain tissue. A postoperative CT scan allows visualization of the electrodes and documentation of their positions in relation to skull geometry (Fig. 1a). By co-registering the CT scan with a preoperative MRI scan, the precise locations of the electrodes on the cortical surface can be determined (Fig. 1b). Such co-registration allows the comparison between ECoG signals and



Electrocorticogram (ECoG), Fig. 1 Spatial topography of electrode coverage in an example patient. (a) X-ray showing electrode placements. **(b)** 3D rendering of anatomical MRI and projection of electrode locations onto the 3D surface. Clinical mapping of the sensorimotor cortex is indicated by color patches. *Red*, hand motor area

based on median nerve somatosensory evoked potential (SSEP); *yellow*, hand sensory area based on SSEP; *blue*, facial twitching in response to cortical stimulation; *green*, hand grasp in response to cortical stimulation. *L* left hemisphere. (Adapted from He et al. (2008))



Electrocorticogram (ECoG), Fig. 2 Sample human ECoG recordings and power spectra. (a) Raw activity traces from three ECoG electrodes in a neurosurgical patient. Electrodes #1 and #2 were over the left frontal cortex, electrode #3 over left temporal cortex. Data were recorded using DC-coupled amplifier with a 500-Hz sampling rate. Two 10-s-long segments are shown. Arrows

point to examples of oscillations. (b) Power spectra for the three electrodes shown in a, averaged over 83-min recording during the awake state. The spectra are presented in log-log scale, under which a power-law distribution manifests as a roughly straight line ($\log(P) \propto -\beta \log(f)$). (Adapted from He et al. (2010))

functional magnetic resonance imaging (fMRI) data obtained in the same subject. As with other types of brain field potentials, such as local field potentials (LFPs), ECoG signals are a mixture of arrhythmic activity and brain oscillations (Fig. 2a). In this entry, we will specifically address computational modeling of arrhythmic ECoG activity.

Detailed Description

Brain Oscillations Versus Arrhythmic Brain Activity

Brain oscillations are recurring patterns of brain activity that follow a particular temporal beat. For example, the first discovered EEG rhythm, the occipital alpha wave, proceeds at roughly 10 cycles per second (Berger 1929). Thus, brain oscillations (arrows in Fig. 2a) are most easily identified in the frequency domain, as their power spectra contain a peak at the corresponding frequency (Fig. 2b). There are a number of brain oscillations at different frequencies, each with their own underlying mechanisms and cognitive functions (Buzsaki et al. 2013).

At the same time, the power spectrum of brain field potentials contains a predominant “ $1/f$ ” component; that is, power tends to fall off with increasing frequency following a power-law function: $P \propto 1/f^\beta$, where P is power, f is frequency, and β is a parameter (typically in the region of 0–3) named the “power-law exponent” (Fig. 2b). A power-law function is indicative of scale invariance, suggesting that no particular time scale or frequency dominates the dynamics. Hence, the brain activity contributing to this $1/f$ slope in the power spectrum is devoid of periodicity (i.e., being arrhythmic or “scale-free”). Note that white noise (including Poisson firing patterns) is a special case of arrhythmic activity, in which case β equals 0. A power-law distribution of the power spectrum is characteristic of the temporal dynamics of brain activity at many different observational levels: It has been described in the fluctuations of neuronal membrane potentials, LFP, ECoG, EEG and magnetoencephalography (MEG) recordings, and fMRI signals. In addition, the amplitude fluctuations of narrowband brain oscillations in EEG/MEG recordings exhibit prevalent scale-free dynamics (Linkenkaer-Hansen et al. 2001). A power-law distribution has also been reported in the statistics of neurotransmitter

release (Lowen et al. 1997) and neuronal firing (Lowen et al. 2001), where it has been more controversial. Lastly, fluctuations of human behavioral output such as reaction times, hit rate, and force have often been found to exhibit a $1/f$ -like power spectrum as well (Gilden 2001; Kello et al. 2010).

Modeling the Arrhythmic ECoG Signals

Studies investigating the power spectrum of ECoG and LFP signals have reported very similar values for the power-law exponent, which is typically in the range of 2–3 (Freeman and Zhai 2009; He et al. 2010; Miller et al. 2009; Milstein et al. 2009). Similar power-law exponents were found in the power spectrum of neuronal membrane potential fluctuations (Destexhe et al. 2003; El Boustani et al. 2009). In particular, two studies using human ECoG, focusing on the relatively low-frequency (from <0.01 to 100 Hz) (He et al. 2010) and relatively high-frequency (10–500 Hz) (Miller et al. 2009) ranges, respectively, have reported strikingly similar exponents in the middle-frequency range: $\beta = 2.44$ in the range of 1–100 Hz in the first study, and $\beta = 2.46$ in the range of 15–80 Hz in the second study. The close alignment of these numbers exemplifies the robustness of the scale-free distribution.

In addition to this middle-frequency range, Miller et al. (2009) found a transition to $\beta \approx 4$ in the high-frequency range above 75 Hz. They proposed a simple model that can explain the power spectral shape, which utilizes the convolution of two exponentially decaying functions representing, respectively, the postsynaptic current and the membrane leak. An exponentially decaying function in the time domain is characterized by a “Lorentzian” function in the frequency domain of the form $P \approx \text{constant}$ for $f < \ll f_0$ and $P \propto 1/f^2$ for $f \gg f_0$, where f_0 is the “knee” frequency. The “knee” frequency is directly related to the time constant τ of the exponential decay such that $f_0 = 1/(2\pi\tau)$. Recalling that convolution in the time domain is equivalent to multiplication in the frequency domain, the

resulted power spectrum from this model is thus the multiplication of two Lorentzians, following the form $P \approx \text{constant}$ for $f < \ll f_1$, $P \propto 1/f^2$ for $f_1 < \ll f < \ll f_2$, and $P \propto 1/f^4$ for $f \gg f_2$, where f_1 and f_2 are two “knee” frequencies determined by the time constants.

The locations of f_1 and f_2 can be determined empirically. While Miller et al. found f_2 to be around 75 Hz, their data do not reveal the location of f_1 in the lower-frequency range. This information is provided in He et al. (2010), which found f_1 to be around 1–2 Hz. Together, these results suggest the existence of two time constants: one around 2–3 ms and another around 100 ms. At present, the origins of these time constants remain a speculation. One possibility is that the 2–3 ms time constant originates from synaptic current and the ~ 100 ms time constant from membrane leak (Miller et al. 2009). An alternative possibility is that the ~ 100 ms time constant comes from the slow NMDA synaptic current (Gibb and Colquhoun 1991; Wong and Wang 2006) and the membrane time constant can be as short as 2–3 ms during active synaptic activity (Koch et al. 1996). Adjudication between these two scenarios will require future experiments, such as blocking NMDA signaling and examining the resulting change in the power spectrum of field potentials. In addition, the contribution of dendritic filtering to the ECoG power spectrum should be further explored (Dehghani et al. 2010; Einevoll et al. 2013).

At the very low-frequency range, below a “shoulder” of 0.1–1 Hz where power is relatively flat, the power spectrum again follows a form close to $P \propto 1/f^2$ (He et al. 2010). Potential generative mechanisms for this low-frequency behavior have recently been explored in a recurrent network model (Chaudhuri et al. 2014). It was found that a recurrent network of rate-based nodes with linear couplings and random connectivity, when poised near criticality (i.e., with balanced excitation and inhibition), could reproduce the low-frequency behavior of the ECoG power spectrum. In such a network, the network recurrent activity produces one or more very slow time constants, whose corresponding “knee” frequencies are below that so far investigated empirically

(0.003 Hz). Moreover, reducing the spatial correlation of the inputs to different nodes resulted in a flattening of the power spectrum, similar to that observed in ECoG and fMRI data during task performance (He 2011; He et al. 2010). Thus, this network naturally converts spatial correlation into temporal correlation, providing support for a previous proposal that decoupling among neuronal groups might underlie the reduction of power-law exponent during task (He 2011).

This low-frequency range of the ECoG activity bears significant resemblance to persistent neural activity (Brody et al. 2003; Major and Tank 2004). As with persistent neural activity, both network and cellular mechanisms may be at play in generating the low-frequency ECoG signals. The effect of different network topology on the power spectrum is an active topic of current investigation. Two recent modeling studies found that network multistability caused by clustered connections or inhibitory neurons is conducive to producing slow fluctuations in population activity (Ho et al. 2012; Litwin-Kumar and Doiron 2012). Potential slow cellular mechanisms include metabotropic glutamate receptors (Zhang and Seguela 2010), endocannabinoid signaling (Carter and Wang 2007), and the cholinergic pathway (Letzkus et al. 2011). The contributions of these different mechanisms to low-frequency ECoG signals should be investigated by future experimental studies.

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Electroencephalogram

- [Local Field Potential, Relationship to Unit Activity](#)
- [Local Field Potentials in Olfaction](#)

Electron Microscopic Imaging

- [Imaging, Electron Microscopy](#)

Electron Microscopy

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Electronic Retinal Implants

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Electrophysiological Indices of Speech Processing

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Some Core Facts About Event-Related Brain Potentials (ERPs)

Speech and its acoustic and linguistic properties essentially evolve in time (Kotz and Schwartz 2010). Therefore, high-temporal-resolution methods such as the electroencephalography (EEG) or magnetoencephalography (MEG) are well suited to trace the temporal unfolding of the speech signal. In particular, ERPs embedded in the EEG permit speech to be monitored with millisecond resolution. By time-locking and averaging ERPs to a large number of specific and similar speech events, responses to acoustic and linguistic properties of these events can tell us how an event is perceived and understood as it occurs. The resulting wavelike pattern consists of an alteration of positive and negative peaks that, when compared to a control condition, leads to the emergence of components that are defined by their polarity (*positive or negative*), by the delay after the onset of an event of interest (*latency*), and by their distribution across the scalp (*topography*). For example, the N400 component is a negative deflection (hence “N”) that peaks around 400 ms post-stimulus onset. Note that while the N400 has a relatively global scalp distribution in the auditory modality, we cannot relate cognitive processes tied to the N400 scalp topography to specific underlying neural sources in the brain. The reason is that EEG activity is oriented orthogonally to the sulcated cortex surface and not to the skull surface. Consequently, ERP patterns recorded at the surface of the skull likely reflect the summation of infinite large numbers of differently oriented sources (*generators*).

What Can ERPs Tell Us About Successful Speech Comprehension?

When listening to speech, our primary goal is to understand what is said. This necessitates the integration of sensory, perceptual, and cognitive processes to ensure successful speech comprehension (Obleser and Kotz 2011). While there has been ample research identifying the neural sources of such integration in neutral (for a review, see Scott and Johnsrude 2003) and emotional speech (for a review, see Schirmer and Kotz 2006), there is less evidence from ERP studies. This is surprising in light of the fact that ERPs monitor the unfolding speech signal from the sensory to the cognitive stage at millisecond resolution and may thus give more precise insight into not only how these processes unfold but also how they are integrated with high temporal precision. Therefore, a number of exemplar ERP studies that have explored the sensory-cognitive interface in speech processing will be reviewed in the following.

A good way to test how early sensory and later cognitive processes in speech processing interact is to study speech in noise. In principle there are at least three sources of noise that can impact successful speech comprehension: noise (i) in the environment, (ii) in the hearing system, and (iii) in the speech signal itself. All three types of noise are considered to disrupt the acoustic/phonetic interface and consequently successful lexico-semantic integration (e.g., Boulenger et al. 2011). A number of ERP investigations have therefore systematically manipulated speech signal quality to look at its consequences on lexico-semantic integration and its impact on successful speech comprehension. In this research two ERP components feature prominently: the N100 and the N400.

Two Components of Interest: N100 and N400

Early ERP components such as the *N100* have been linked to the physical properties of a stimulus and are considered to reflect early obligatory sensory processing (e.g., Luck 2005;

Steinschneider and Dunn 2002). In audition the N100 is considered to encode a sound's onset (e.g., Martin et al. 2008) and to index early perception formation (e.g., Näätänen 2001). It is also attuned to task demands in speech processing (e.g., Bonte et al. 2009; Obleser et al. 2004; Poeppel et al. 1996 for N100m magnetoencephalographic evidence) and the degradation of the sound signal (Miettinen et al. 2010).

N400 research looks back onto a long tradition and has tested semantic anomalies (whether a word fits into a sentence context or not; e.g., Kutas and Hillyard 1980), semantic cloze probability (how likely a word fits a sentence context; e.g., Kutas and Hillyard 1984), context manipulation (how expected a word is in a sentence context; e.g., Van Petten and Kutas 1990), and semantic priming (does a preceding word facilitate the processing of a following word; e.g., Holcomb 1988) in word lists and sentence paradigms in both the auditory and visual modalities. A common viewpoint is that a rise in N400 amplitude reflects the effort of how successfully lexico-semantic integration has taken place (Chwilla et al. 1995; Van Berkum et al. 1999; Friederici 2002; for recent comprehensive reviews, see Lau et al. 2008; Kutas and Federmeier 2011). As such, any modulation of the N400 amplitude, latency, or topography as a function of speech quality is an excellent marker of how alterations of acoustic/phonetic speech properties affect the outcome of lexico-semantic integration and, consequently, successful speech comprehension.

Some Exemplar ERP Investigations of Speech Comprehension

Aydelott et al. (2006) acoustically degraded the speech signal by utilizing a 1-kHz low-pass filter, thereby perceptually changing it. Further, the effect of degradation on lexico-semantic integration was tested on target words that either semantically matched or mismatched a given sentence context. Thus, the ease of lexico-semantic integration was tested by (i) contextually driving semantic expectancy and (ii) manipulating the signal quality of the sentence context. Results revealed

that the N100 response to target words in degraded speech context was enhanced. In addition, the N400 effect (e.g., the difference in amplitude rise to matching and mismatching target words in a sentence context) was reduced in degraded speech when compared to non-degraded speech. The authors concluded that acoustic degradation of the speech signal affects both early perceptual (N100) and later lexico-semantic integration processes (N400). However, the authors did not further address how early and late degradation effects relate to each other. In an attempt to mimic real-life noise situations, *Sivonen et al. (2006)* altered the beginning of sentence final high- and low-cloze probability words by overlaying half of the sentence final words with a cough (short or long) that reduced the phonetic information of the word. Long but not short coughs elicited a larger N100 response to high-cloze probability words in continuous speech. Even though coughs disrupted early phoneme detection, target words were recognized. While there was no N400 amplitude difference for low-cloze compared to high-cloze probability words when words were presented in a noise condition, the onset of the N400 was delayed indicating some difficulties in lexico-semantic integration. The authors suggested that when semantic context is strong enough, incomplete phonemic information can be compensated (e.g., a cough overlaying phonemes).

Obleser and Kotz (2011) used spectrally degraded speech (*Obleser and Kotz 2010*) by applying a noise-band vocoding algorithm that alters the degree of speech intelligibility (*Shannon et al. 1995*). By varying the cloze probability of sentence final words, they tested how small semantic changes in a sentence context affect speech comprehension when the speech signal is compromised. Next to the expected modulation of the N400, the authors reported an early sensory-driven N100 response to speech signal quality at sentence onset. Both the N100 amplitude and latency responded to the degradation strength of the speech signal (strong speech signal degradation led to largest N100 rise and peak). Most importantly, the degree of speech intelligibility significantly impacted the degree

of lexico-semantic integration in the case of low-cloze probability final words. The more intelligible the speech signal, the better the response to unexpected target words in a given sentence context. Therefore, these results clearly show that early sensory-driven effects interact with lexico-semantic integration (for more information on induced oscillatory brain activity, see *Obleser and Kotz 2011*).

A further study by *Boulenger et al. (2011)* tested whether temporally reversing (altering the temporal properties of speech while keeping spectral properties intact) the signal quality of a sentence final word affects how a high-cloze or a low-cloze probability word is integrated into a sentence context. Again, the core of the investigation was to find out how alterations of the speech signal affect lexico-semantic integration. The authors reported early fronto-central negativity in response to target words independent of the degree of temporal reversal (e.g., how much of the speech signal was temporally altered) and cloze probability. This early negativity was spatiotemporally comparable to a mismatch negativity (MMN) recorded in the same participants in an auditory oddball (detection of syllable deviance in temporally reversed speech) in a stream of standard syllables (temporally non-reversed speech). In line with an MMN interpretation that links this component to an automatic and fine-tuned discrimination auditory response mechanism (e.g., *Näätänen 2001*), the authors consider this interpretation also valid in auditory speech comprehension, that is, the MMN response is similar to sinusoidal sound or speech sounds. When looking at the effects of time reversal on lexico-semantic integration, the authors observed an interaction. The degree of temporal reversal (low rather than high reversal) reduced the N400 amplitude response to low-cloze probability words at fronto-central electrode sites. The authors conclude similar to previous accounts that early acoustic/phonetic information interacts with lexico-semantic integration to ensure successful speech comprehension.

Strauß and colleagues (Strauß et al. 2013) pushed forward the investigation of speech intelligibility (three levels of degradation) and

lexico-semantic expectancy. The authors asked the critical question which one of the two factors supporting successful speech comprehension drives the interaction. In other words, is it the bottom-up sensory information or the top-down lexico-semantic information that drives the interaction? The extent of lexico-semantic expectancy in sentence context was varied by manipulating the context strength as well as the cloze probability of the critical word. The results showed that the N400 response to both high- and cloze probability words in a strong sentence context did not differ when speech was intelligible. However, when speech was moderately degraded, only high-cloze probability words in a strong sentence context revealed a decrease in N400 amplitude. This indicates that perceptual constraints may critically impact how context can influence lexico-semantic integration.

In summary, the current evidence on how early sensory and late cognitive processes interact to ensure successful speech comprehension appears to depend upon two processing streams, that is, a bottom-up sensory one and a top-down contextual one. Clearly future research will have to show how task- and/or stimulus-driven demands engage bottom-up or top-down processing streams during successful lexico-semantic integration in speech comprehension.

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Electrophysiology Analysis, Bayesian

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Synonyms

[Bayesian modeling of neural recordings](#); [Bayesian neural data analysis](#)

Definition

Bayesian analysis of electrophysiological data refers to the statistical processing of data obtained in electrophysiological experiments (i.e., recordings of action potentials or voltage measurements with electrodes or imaging devices) which utilizes methods from Bayesian statistics. Bayesian statistics is a framework for describing and modeling empirical data using the mathematical language of probability to model uncertainty. Bayesian statistics provides a principled and exible framework for combining empirical observations with prior knowledge and for quantifying uncertainty. These features are especially useful for analysis questions in which the dataset sizes are small in

comparison to the complexity of the model, which is often the case in neurophysiological data analysis.

Detailed Description

Overview

The Bayesian approach to statistics has become an established framework for analysis of empirical data (Gelman et al. 2003; Spiegelhalter and Rice 2009). While originating as a subdiscipline of statistics, Bayesian techniques have also become associated with the field of *machine learning* (Bishop 2006; Barber 2012). Bayesian statistics is well suited for the analysis of neurophysiological data (Brown et al. 2004; Kass et al. 2005; Chen 2013; Linderman and Gershman 2017): It provides a principled framework for incorporating a priori knowledge about the system by using *prior distributions*, as well as for quantifying the residual (or *posterior*) uncertainty about the parameters after observing the data. For many analysis questions in neurophysiology, one needs to make inferences based on datasets which are small in comparison to the dimensionality or complexity of the model of interest. First, this makes it important to *regularize* the parameter estimates such that they favor explanations of the data which are consistent with prior knowledge. The use of priors also makes it possible to automatically control the complexity of the model inferred from data. Second, the fact that data sizes are small also implies the need to quantify and visualize to what extent model parameters are well constrained by the data. Third, in Bayesian statistics model, parameters are themselves treated as stochastic variables. This provides means of defining richer models by using simple models as building blocks of hierarchically defined models. Fourth, Bayesian statistics provides powerful machinery for dealing with the presence of unobserved processes in the model (so-called latent variables), which are ubiquitous in neurophysiological applications, e.g., arising from internal states or inputs that cannot be measured directly.

In Bayesian statistics, one starts by writing down a probabilistic model $P(Y|\theta)$ of how data Y collected in an experiment are related to an underlying parameter θ . Regarded as a function of θ , $P(Y|\theta)$ is sometimes referred to as the *likelihood*. Prior knowledge about the possible values of θ is encoded by a *prior distribution* $P(\theta)$. Taken together, the prior and the model $P(Y|\theta)$ define a *generative model* of the data – one models the process of data generation as first picking a set of parameters from $P(\theta)$ and then data as being generated from the likelihood model $P(Y|\theta)$. In *Bayesian inference*, one then tries to invert this process: Given empirical data Y , which values of θ are consistent *both* with Y and with the prior assumptions encoded in $P(\theta)$? The trade-off between prior and likelihood will be determined by the amount of available data: For small dataset sizes, the prior will have a strong influence, but for large datasets, the likelihood term which depends on the observed data will dominate. Thus, use of prior distributions can be seen as a form of *regularization* which protects the model against *over fitting* to the observed data.

The *posterior distribution* $P(\theta|Y)$ is calculated via Bayes rule:

$$P(\theta|Y) = \frac{P(Y|\theta)P(\theta)}{P(Y)}. \quad (1)$$

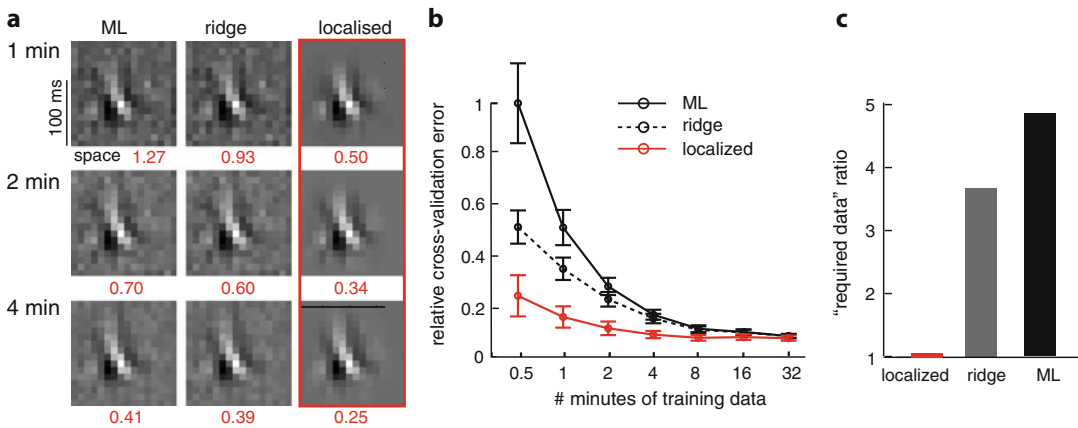
The posterior distribution $P(\theta|Y)$ can then be used to make statements about the parameter values θ . For example, the *posterior mean* $E(\theta|Y) = \int \theta P(\theta|Y) d\theta$ is often reported and visualized in analyses of neurophysiological data as a *point-estimate* of the parameters. In addition, the posterior distribution also gives insight into which properties of θ are well or less well constrained by the data. If, for example, the posterior variance $\text{Var}(\theta|Y)$ is small, this implies that the posterior distribution is concentrated around the posterior mean and thus that θ is well constrained by the data. In general, Bayesian estimators are derived from the posterior distribution, and the focus of Bayesian approaches is always to characterize the distribution of parameters θ *given a particular dataset*. This is in contrast to classical

(or frequentist) statistical approaches, which generally focus on making statements about what will happen – or what is unlikely to happen – if one repeatedly sampled datasets *given a particular parameter setting*.

The denominator $P(Y)$ in Eq. (1) has to be such that the posterior distribution is normalized, i.e., $P(Y) = \int P(Y|\theta') P(\theta') d\theta'$. As $P(Y)$ is the likelihood of the data after marginalizing out (i.e., integrating) the parameters θ , $P(Y)$ is sometimes referred to as the *marginal likelihood* or *evidence*. The evidence provides an estimate of how likely the observed data are for a given model and prior. It is a useful quantity for setting so-called hyper parameters as well as for calculating *Bayes factors*. A Bayes factor is the ratio of the marginal likelihoods of two models and can be used for hypothesis testing and model selection, i.e., for deciding which of two possible models provides a better explanation of some observed data Y (Gelman et al. 2003; Spiegelhalter and Rice 2009). While the use of Bayes factors is gaining popularity in the field of neuroscience, publishing conventions imply that the majority of statistical reporting of results in neurophysiological studies is based on classical, frequentist tests and definitions of p-values.

Example: Receptive Field Estimation

We illustrate the utility of Bayesian approaches for neural data analysis using the example of receptive field estimation for stochastic stimuli using linear models. In a linear encoding model (Paninski et al. 2007), it is assumed that mean firing rate $\mu(s)$ of a neuron in response to a given D -dimensional stimulus can be modeled as being a linear function of the stimulus, $\mu(\mathbf{s}) = \sum_{i=1}^D \theta_i s_i$. In the simplest case, the variability around the mean response is then assumed to be given by a Gaussian distribution, $Y = y|s \sim \mathcal{N}(\mu(\mathbf{s}), \sigma^2)$ with variance σ^2 . The parameter vector θ is called the receptive field, and one tries to estimate θ from the responses $y_1 \dots y_n$ of the neuron to multiple stimuli $\mathbf{s}_1 \dots \mathbf{s}_n$. In classical approaches, one would not place any prior distribution on the values of the parameters θ , and this approach would yield receptive field estimates which *over*



Electrophysiology Analysis, Bayesian, Fig. 1 Illustration of a Bayesian approach for estimating receptive fields (RFs). (Modified, with permission, from Park & Pillow, Plos Computational Biology, 2012 (Park and Pillow 2011)). (a) Spatiotemporal RFs of neurons in primary visual cortex. A light pixel indicates that the neuron is excited by a dark stimulus at a given spatiotemporal position, a dark pixel that its firing is suppressed, gray that its firing rate is not modulated. **ML**, RFs estimated using maximum likelihood (i.e., with a “non-Bayesian” approach) using 1, 2, or 4 min of data; **ridge**, RF estimated

with a simple prior that favors solutions with small weights; **localized**, RFs estimated with Bayesian method developed by Park and Pillow which incorporates the prior knowledge that receptive fields are localized and smooth. Localized estimator achieves better receptive field estimates (as indicated by a cross-validation error metric, red numbers). (b) Advantage of localized estimator persists across different dataset sizes. (c) On average, the non-Bayesian method (ML) requires five times more data than localized estimator to achieve a similar cross-validation error

fit and therefore give noisy estimates, especially for small datasets (see Fig. 1a, left column).

In Bayesian approaches one places a prior distribution $P(\theta)$ on θ . A popular choice for $P(\theta)$ is to choose multivariate normal distribution $P(\theta) \sim \exp\left(-\frac{1}{2}\sum_{i,j}\theta_i\theta_jQ_{ij}\right)$ on θ , where Q is the inverse-covariance matrix of the distribution and different choices of Q correspond to different priors. Q is sometimes chosen to be proportional to an identity matrix. In this case, the Bayesian estimate of θ penalizes solutions for which the square deviations $\sum_j\theta_i^2$ are big. However, as this simple prior does not capture well the structure of receptive fields, it only yields slightly improved estimates (Fig. 1a, middle column). It has generally been assumed that receptive fields are smooth and localized, and covariance matrices which reflect these properties have been developed (Sahani and Linden 2003; Park and Pillow 2011). Figure 1b, c shows that using the Bayesian approach developed by Park and Pillow (which

favors solutions that are localized and smooth) yields receptive field estimates which have superior quality to those obtained using maximum likelihood and which are identifiable on smaller dataset sizes. It is worth noting this prior (and any appropriately constructed Bayesian prior) only *favors* but does not *enforce* receptive fields which are consistent with its assumptions and therefore would still leave open the possibility of being “overruled” if the data provide strong evidence for a solution violating the assumptions.

Algorithmic Challenges

One of the key challenges and practical drawbacks of Bayesian statistics is the fact that computation of the posterior distribution $P(\theta|Y)$ is often hard. Exact solutions are only available in a small number of cases (e.g., when the likelihood of the model is in the exponential family and the prior distribution is *conjugate* to the likelihood (Gelman et al. 2003)), but not for most models

of interest in neurophysiological data analysis. Therefore, in general, approximate methods have to be used to characterize the posterior distribution and its properties (Chen 2013).

Approximate methods can be broadly characterized as being either *deterministic* or *stochastic*. In deterministic approximations, the posterior distribution is approximated by a distribution which has a simpler functional form. In general, numerical optimization is used to find an approximating distribution which is similar to the true posterior. Various approaches exist for finding a “good” approximation, such as the Laplace approximation, expectation propagation, variational inference, and stochastic variational inference, which make it possible to apply these techniques in big data scenarios (Bishop 2006; Hoffman et al. 2013; Blei et al. 2017).

In stochastic (or *Monte Carlo*) methods, the posterior distribution over model parameters is approximated by a set of samples drawn from the posterior. Sampling algorithms are used to generate samples from the posterior distribution $P(\theta|Y)$, and these samples can then be used to perform analyses such as calculating the mean and other moments of the distribution or computing its marginals. While Monte Carlo methods are typically more flexible than deterministic approximations, sampling algorithms such as *Markov Chain Monte Carlo* methods can be computationally intensive (Kass et al. 1998; Gelman et al. 2003; Cronin et al. 2010).

Example Applications

Bayesian statistical methods have been used extensively on a wide range of analysis questions within neurophysiology, including the following examples:

Neural characterization: To describe how neural spiking activity depends on external stimuli, on its own spiking history, as well as on the activity of other neurons, Bayesian methods can be used to estimate receptive fields (Sahani and Linden 2003; Gerwinn et al. 2010; Park and Pillow 2011), tuning curves (Cronin et al.

2010), and spike-history filters (Paninski et al. 2007).

Spike sorting and detection: Inference in hierarchical Bayesian models has been used to extract putative spikes of single neurons from extracellular recordings (Wood et al. 2006) or calcium measurements (Vogelstein et al. 2009; Speiser et al. 2017).

Stimulus reconstruction and decoding: Bayesian time series models have been developed, to reconstruct external stimuli and behavior from population activity or to decode intended movements for brain-machine interface applications (Wu et al. 2006; Gerwinn et al. 2009).

Estimation of information-theoretic quantities: Priors over histograms have been proposed in order to reduce the bias in estimating information-theoretic quantities such as entropy or mutual information (Nemenman et al. 2004; Archer et al. 2012).

Functional connectivity across brain areas: Functional connections across brain areas have been estimated with a range of different Bayesian approaches. In particular, *dynamic causal models* have enjoyed popularity especially for modeling fMRI and EEG data (Marreiros et al. 2010).

Cross-References

► [Imaging Analysis, Bayesian](#)

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Electrotonic Length, Formulas and Estimates

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Definition

The electrotonic length of a cylindrical neurite is its physical length divided by its space constant. The electrotonic length of a dendritic tree is estimated with formulas that assume the dendritic tree can be approximated as an equivalent cylinder.

Detailed Description

Rall showed that the complex branched morphology of a dendritic tree can be reduced to an equivalent cylinder given a certain set of assumptions (see entry ► [“Equivalent Cylinder Model \(Rall\)”](#)). An important property of the equivalent cylinder is its electrotonic length, L , which equals the physical length of the cylinder, ℓ , divided by λ , the space constant. An estimate of L will tell us how far distal synapses are electrotonically from the soma, and this will tell us whether these synapses can be effective in driving the cell to threshold.

For a cell represented as an equivalent cylinder, Rall (1969) used separation of variables to derive the transient solution for voltage in the cylinder as

$$V(X, T) = \sum_{n=0}^{\infty} B_n \cos\left(\frac{n\pi X}{L}\right) \exp\left[-\left(1 + (n\pi/L)^2\right)T\right]$$

where X is normalized distance along the cylinder, defined by $X = x/\lambda$ (x is physical distance), and T is normalized time, defined by $T = t/\tau_m$ where τ_m is the membrane time constant. The B_n are determined from the initial conditions $V(X, 0)$. For $n = 0$, the exponential part of the solution is just

$\exp(-t/\tau_0)$ where $\tau_0 = \tau_m = R_m C_m$, the membrane time constant. For $n > 0$, the coefficient of t in the exponential term is $[1 + (n\pi/L)^2]/\tau_0$ where again $\tau_0 = \tau_m$. Rall defined the “equalizing” time constants as $\tau_n = \tau_0/[1 + (n\pi/L)^2]$ and let $C_n = B_n \cos(n\pi X/L)$ to simplify the solution to

$$V(x, t) = \sum_{n=0}^{\infty} C_n e^{-t/\tau_n}$$

where we have also changed back from dimensionless variables X and T to the actual variables x and t . The C_n will depend on the initial conditions. If one applies a current pulse or step and then records the voltage decay once this current is turned off, then this voltage decay is described by

$$V(x, t) = C_0 \exp(-t/\tau_0) + C_1 \exp(-t/\tau_1) + \dots$$

The coefficients and time constants can be estimated from the experimental voltage trace by standard curve fitting procedures. In cells that have significant electrical extent, two time constants are usually obtained, although three are sometimes possible. We are particularly interested in the time constants, because we can rearrange the expression for the equalizing time constants above to get the formula

$$L = \frac{\pi}{\sqrt{\tau_0/\tau_1 - 1}}$$

Thus, if we have τ_0 and τ_1 , we can get an estimate of the cell’s electrotonic length $L = \ell/\lambda$. One must be careful to fit as many terms as possible and then determine if adding a term results in a statistically significant improvement in the fit. Also one must make sure that the values of the coefficients, C_i , are all significantly different from 0.

Rall (1969, 1977) noted that many formulas were possible:

$$L_{\tau_0/\tau_1} = \pi/(\tau_0/\tau_1 - 1)^{1/2}$$

$$C_0/V_0 = \tanh(L_{C_0})/L_{C_0}$$

$$L_{C_0/C_1} = \pi/(2C_0/C_1 - 1)^{1/2}$$

$$L_{vc} = \pi/[2(\tau_0/\tau_{vc1} - 1)^{1/2}]$$

$$L_{vc2} = \pi(9\tau_{vc2} - \tau_{vc1})^{1/2}/[2(\tau_{vc1} - \tau_{vc2})^{1/2}]$$

In these formulas, the subscript of L merely distinguishes the different L estimates. C_0 , C_1 , τ_0 , and τ_1 are the first two coefficients and time constants from the general solution given above estimated from the voltage transient at the soma for a current step applied to the soma. The τ_{vc1} and τ_{vc2} represent time constants estimated from the voltage clamp current transient for voltage clamp at the soma. The V_0 in the second formula equals IR_N the product of the applied current and the input resistance.

The first formula is the one recommended by Rall and is the one used most often; it works well for both brief and long current steps. The second and third formulas rely on coefficient estimates that are prone to error because of floating baseline problems caused by voltage-dependent conductances. The fourth formula requires time constants from both current clamp and voltage clamp experiments, but it may be difficult to get both, particularly in small cells. The last formula requires two voltage clamp time constants, but the second is usually too small to be measured accurately.

These formulas have been applied to data in hundreds of studies, and in most cases L estimates have been 1.0 or less. However, problems can arise with these L estimates if cells cannot be approximated well as an equivalent cylinder. In an equivalent cylinder, the τ_1 (and subsequent τ_n) can be interpreted as equalizing time constants over the length of the cylinder, but if the cell has dendrites that end at different electrotonic distances, the actual τ_1 represents equalization along the longest tip-to-tip path in the cell. The hope is that the estimated τ_1 will reflect equalization between

the soma and dendritic tips, but whether or not this happens depends on the values of the coefficients, many of which have very small values. A second problem is soma shunt with electrode penetration. In this case, the formulas will tend to overestimate L . These issues are discussed in length in series of papers by Holmes et al. (1992), Holmes and Rall (1992), and Major et al. (1993a, b).

Cross-References

► [Equivalent Cylinder Model \(Rall\)](#)

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Embodied Cognition, Dynamic Field Theory of

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Synonyms

[Cognition and control](#); [Neural population models for](#)

Definition

The insight that cognition is grounded in sensorimotor processing and shares many properties with motor control, captured by the notion of “embodied cognition,” has been a starting point for neural process models of cognition. Neural Field models represent spaces relevant to cognition, including physical space, perceptual feature spaces, or movement parameters in activation fields that may receive input from the sensory surfaces and may project onto motor systems. Peaks of activation are units of representation. Their positive levels of activation indicate the instantiation of a representation, while their location specifies metric values along the feature dimensions. By ensuring that peaks are stable states (attractors) of a neural activation dynamics, cognitive processes are endowed with the stability properties required when cognition is linked to sensory and motor processes. Instantiations of cognitive processes arise from instabilities that may induce peaks and suppress. Such events may represent detection, selection, or classification decisions. Neural Field models account for classical behavioral signatures of cognition including response times, error rates, and metric estimation biases but also link to neurophysiological correlates of behavior like patterns of population activation and their temporal evolution. Robotic demonstrations of Neural Field models are used to establish the capacity of these models to provide process accounts of cognition that may link to real sensory

Elementary Motion Detection

► [Visual Motion Detection in *Drosophila*](#)

information and generate real movement in the physical environments.

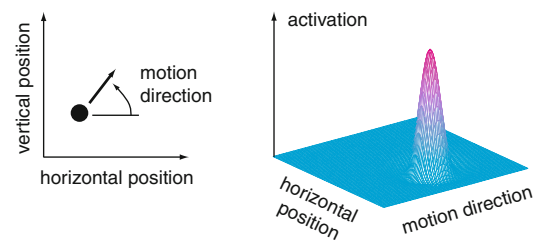
Detailed Description

Elementary forms of cognition are the detection and selection decisions that control attention and eye movements but are also the basis for object perception. Committing detected perceptual states into working memory and then long-term memory is a key element of cognition. Serially organized sequences of cognitive states are the basis for cognitive processes. Motor actions require that the initiation, termination, and potentially the online update of planned movements be autonomously generated. Neural Field models of cognition and control provide a neural account for such elementary cognition based on four elements: the spaces that such cognitive processes are about, the activation fields defined over these spaces within which neural representations can be created, the neural activation dynamics that drive neural representations forward in time, and the instabilities that give rise to the elementary forms of cognition. This use of Neural Field models to account for cognition and its sensorimotor grounding has been called Dynamic Field Theory (DFT). DFT is a mathematically formalized conceptual framework for understanding embodied cognition that is linked to neural process modeling but abstracts from some of the specific anatomical and biophysical details of neurophysiology to enable a close link to behavior (Schneegans and Schöner 2008).

Spaces

That cognition is grounded in sensorimotor processes is a central insight that the embodiment perspective on cognition emphasizes (Riegler 2002). In this view, cognition is *about* states of the world that may become linked to cognition through perception or action, but are not dictated by perception and action alone. Even mental imagery, for instance, shares the sensorimotor grounding, though it is decoupled in the moment from actual sensorimotor processes. Neural

accounts for cognition must, therefore, take into account how sensory information may potentially drive cognition, primarily through the sensory cortical and subcortical neural structures. Such accounts must also take into account how motor states are driven from cortical and subcortical structures. Common to both domains of sensation and movement is the observation that they are characterized by continuous dimensions: there are continua of possible percepts and continua of possible motor actions. For instance, the possible percepts of a single moving object form a continuum that may be spanned by the retinal location of the object, the direction of motion, perhaps its speed, or motion in depth. The object may have a color that may vary continuously in hue space, have characteristic texture that may vary along a spatial frequency dimension, and may have a surface curvature that varies continuously. Figure 1 illustrates three of these dimensions. Movements similarly form continua, spanned by movement parameters such as the movement direction, extent, and peak velocity of the end effector in a body-centered reference frame. Much of cognition is embedded in the physical space that surrounds our body, even when it takes such flexible form as positioning a thought at a location in space through a hand gesture. Categories are embedded in feature spaces. While a dog is categorically different from a car, both may be morphed into their many different instantiations.



Embodied Cognition, Dynamic Field Theory of, Fig. 1 *Left:* The possible percepts of a single moving object (filled circle moving as indicated by the arrow) may be spanned by continuous dimensions such as the location of the moving object in the visual array and the direction of motion. *Right:* A neural activation field defined over these dimensions (only two shown here) represents a motion percept as a peak of activation positioned over the location that specifies the seen motion

Even superordinate categories may be embedded in feature spaces by combining the feature dimensions of hierarchically organized attributes (McClelland and Rogers 2003).

Neural Fields

Neural Field models of embodied cognition represent the state outside the nervous system by neural activation patterns that are inside the nervous system. Neural activation, as used in Dynamic Field Theory, is a real number, u , that may both be positive or negative. The link to biophysically detailed accounts of neural activity can be established in multiple different ways (see entries ► “Neural Field Model, Continuum”; ► “Neural Population Models and Cortical Field Theory: Overview”). Critical for the link to behavior is the assumption that only sufficiently positive levels of activation impact on downstream structures and ultimately on motor systems. This is expressed mathematically through a sigmoidal function, $g(u)$, often chosen as $1/(1 + \exp(-\beta u))$, where β is the steepness of this nonlinearity.

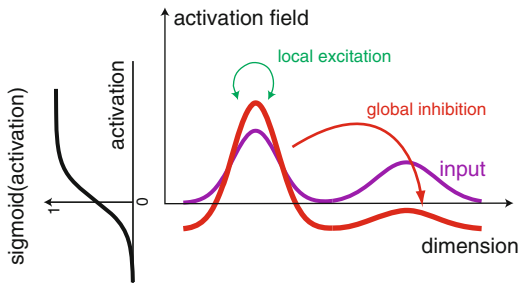
A Neural Field is a continuum of such activation variables, one for each location of the represented space. For instance, in Fig. 1, a level of activation represents each possible horizontal position and motion direction of a moving object. The field notion is thus analogous to how fields are used in physics. Peaks of activation are units of representation. Their positive levels of activation imply that they impact on downstream processes. Their location specifies the represented state.

How does a location in a Neural Field acquire the meaning ascribed to it in this interpretation? It is ultimately the connectivity to the sensory or the motor surfaces that determines what a field location “stands for.” In perceptual representations such as the one illustrated in Fig. 1, this would be, for instance, the connectivity from the retina, through simple and complex cells, to motion detectors, anatomically probably located in area MT of the cortex. Field locations thus have a “tuning curve.” Similarly, the forward projection onto the motor system implies a specificity that

could be interpreted as a tuning curve for movement parameters. We know that in the cortex as well as in such subcortical structures as the colliculus and thalamus, tuning curves tend to be broad and overlapping, an indication that broad populations of neurons are activated for any individual perceptual or motor state represented. This fact together with detailed analysis of how strongly all activated neurons contribute to a percept or motor action has given rise to the hypothesis that the activity of small populations of neurons is the best neural correlate of behavior (Cohen and Newsome 2009). DFT is based on the further hypothesis that Neural Fields represent the activity of such small populations of neurons in the higher nervous system that are tuned to particular sensory or motor states. In fact, it is possible to estimate Neural Fields from recorded population activity (Erlhagen et al. 1999). This link to population activity frees Neural Fields from the more literal interpretation prevalent in some neural modeling, in which the activation fields are directly defined over the cortical surface. Instead, the Neural Fields on which DFT is based are organized in terms of the topology of the outer space that is being represented. The two interpretations are aligned where cortical maps are topographic. In other cases, however, topography is violated, such as for the tuning of neurons in motor cortex to the direction of a planned hand movement. The Neural Fields of DFT effectively rearrange neurons so that neighboring sites always represent neighboring states. In fact, strictly speaking, neurons are smeared out across the field dimensions by contributing their entire tuning curve to the representation (Erlhagen et al. 1999).

Neural Dynamics

Neural Field models construe time as continuous to approximate at the population level the discrete, but asynchronous spiking events that individual neurons contribute. Mathematically, the evolution in time of the activation state of a Neural Field is described, therefore, by a differential equation (an integrodifferential equation in the specific



Embodied Cognition, Dynamic Field Theory of, Fig. 2 *Left:* A sigmoidal function, $g(u)$, approaches zero for sufficiently negative values, and a positive constant for sufficiently positive values of activation, u . *Right:* Sufficiently activated sites interact excitatorily with nearby locations (green arrow), stabilizing peaks against decay, and inhibitorily with locations that are further removed (red arrow), stabilizing peaks against unlimited growth

formulation reviewed here). DFT postulates that peaks of activation, the meaningful macro-states of Neural Fields, are stable states and fixed-point attractors of the neural dynamics. This constrains the class of admissible dynamical models. Qualitatively, the neural interactions illustrated in Fig. 2 express these constraints. Excitatory neural coupling among neighboring field sites stabilizes peaks against decay; inhibitory coupling among field sites at longer ranges stabilizes peaks against unlimited growth. In the cortex, similarly tuned neurons are typically excitatorily coupled. Inhibitory coupling, mediated by interneurons, is also prevalent (Jancke et al. 1999).

Amari (1977) analyzed a generic Neural Field model in the limit case in which these neural interactions are dominant and showed that peaks of activation may be attractor solutions under appropriate conditions. This is why that particular model has been used in many Neural Field models of embodied cognition, becoming the workhorse of DFT. For a one-dimensional field, $u(x, t)$, defined over a space, x , the dynamics reads

$$\tau u(x, t) = -u(x, t) + h + s(x, t) + \int c(x - x')g(u(x'), t)dx'.$$

The parameter, τ , determines the overall time-scale of the evolution of $u(x, t)$. The “ $-u$ ” term

provides stability to the dynamics and is a reflection of the intrinsic dynamics of neural populations. The parameter $h < 0$ is the resting level of the field, stable in the absence of input, $s(x, t)$. Interaction integrates over all field sites, x' . Each site contributes to the extent to which activation exceeds the threshold of the sigmoidal function $g(u(x', t))$ with a coupling strength, $c(x - x')$ that is a function of the distance between interacting field sites. For close distances, coupling is excitatory ($c(\text{small}) > 0$), for larger distances, inhibitory ($c(\text{large}) < 0$). The Amari model is a simplification over biophysically more detailed models that, among other approximations, neglects the time delays involved in synaptic transmission and lumps together excitatory and inhibitory neural populations (see entry ▶ “Neural Field Model, Continuum”).

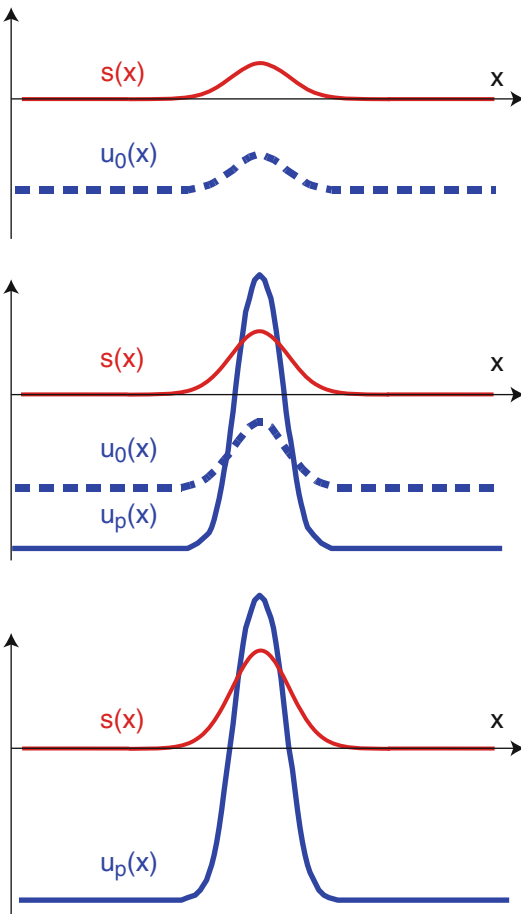
Instabilities

There are two qualitatively different attractor solutions of this equation, which are separated by instabilities. In the subthreshold state, the field activation is below zero everywhere, so that interaction is not engaged. If we neglect small values of the sigmoid and assume that inputs vary only very slowly in time, this attractor solution is given by

$$u_0(x, t) = h + s(x, t) < 0,$$

which tracks slowly varying input, $s(x, t)$, apart from a downward shift by h . When input is zero, $s(x, t) = 0$, this is the resting state of the field.

The other solution is a self-stabilized peak of activation, $u_p(x)$, whose activation level is lifted above the level specified by input, $h + s(x, t)$, through excitatory neural interaction, while outside the peak the field is suppressed below the resting level, h , through inhibitory interaction (Fig. 3). For small levels of input, $s(x, t)$, the subthreshold solution is monostable (top panel of Fig. 3), and for sufficiently large levels of input, the self-excited peak solution is monostable (bottom panel of Fig. 3). When input levels are



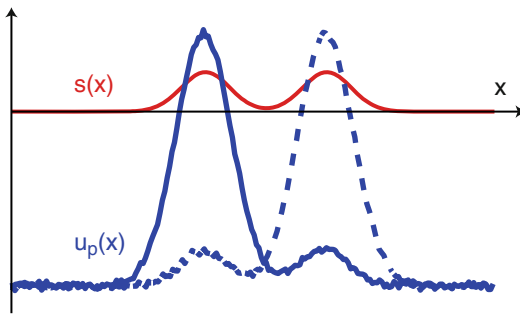
Embodied Cognition, Dynamic Field Theory of, Fig. 3 A Neural Field, $u(x)$, over dimension, x , illustrated for three levels of input, $s(x)$ (dashed green line) that increase from the *top* to the *bottom* panel. The subthreshold solution, $u_0(x)$ (dashed blue line), is stable for the two lowest levels of input, and the self-excited peak solution, $u_p(x)$ (blue solid line), is stable for the two highest levels of input. The bistable regime is delimited at high levels of input by the detection instability and at low levels of input by the reverse detection instability

increased, the subthreshold solutions become unstable in the detection instability. When input levels are again lowered, the self-stabilized solutions become unstable in the reverse detection instability. Because the reverse detection instability occurs at lower levels of input than the detection instability, the subthreshold and the self-excitatory solutions coexist bistably in a regime of intermediate levels of input strength. This bistable regime stabilizes detection decisions

hysterically. This is critical, when perceptual states represented by peaks are continuously linked to sensory inputs. In the presence of noise, detection decisions must be stabilized against varying input levels to create coherent perceptual experience. Analogously, movement plans must persist when the input from perceptual or cognitive processes, which induces motor intentions, fluctuates.

Both subthreshold and self-stabilized peak solutions are continuously linked to sensory input. The peak may track, for instance, continuously shifting local input patterns. Moreover, if input strength increases in a graded, time-continuous way, the Neural Field autonomously creates a discrete detection event when it goes through the detection instability. Similarly, if input that supports a self-stabilized peak is gradually reduced in strength, the peak collapses at a critical point through the reverse detection instability. Such discrete events emerge from continuous-time neural dynamics through the dynamic instabilities. This provides a mechanism that is critical for understanding how sequential processes may arise in neural dynamics (Sandamirskaya and Schöner 2010).

With sufficiently strong interaction or when broad inputs or a high resting level pushes activation close enough to threshold, the reverse detection instability may not be reached when the strength of a local input is reduced. In this case, a self-stabilized peak induced by local input remains stable and is sustained, even after any trace of the local input has disappeared. Such self-sustained activation peaks are the standard model of working memory (Fuster 2005). Mathematically, self-sustained peaks are marginally stable. They resist change in their shape but are not stable against shifts of the peak along the field dimensions. This leads to drift under the influence of noise or broad inputs. Such drift is psychophysically real: memory for metric information develops metric bias and increases variance over the timescale of tens of seconds (Spencer et al. 2009). Moreover, sustained peaks may be destabilized by competing inputs at other field locations. Again, this limitation of the stability of sustained peaks matches properties of working



Embodied Cognition, Dynamic Field Theory of, Fig. 4 The attractor states, $u_p(x)$, of an activation field are shown in blue; a bimodal input, $s(x)$, is shown in red. There are two attractor states (solid vs. dashed line), which coexist bistably. Each has a single self-stabilized peak positioned over one of the maxima of input, while activation at the other stimulated site is strongly suppressed by inhibitory interaction. The field states were obtained from simulations of the neural dynamics in which independent Gaussian white noise was added at each field location to probe the stability of the stationary states

memory, which is subject to interference from new items entered into working memory.

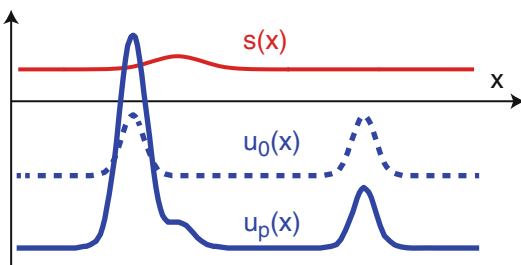
If the inhibitory component of neural interaction is sufficiently strong and broad, the Neural Field may enact selection decisions as illustrated in Fig. 4. A self-stabilized activation peak may effectively select one of a number of locations in the underlying space that receive localized input. Typically, the most strongly stimulated site will be selected, because after input is provided, activation at that site will reach threshold earliest and begins to suppress activation at other locations before these may reach threshold and, in turn, suppress other locations. Inhibitory interaction thus translates a temporal advantage into a competitive advantage. This is the general feature of decision making in Neural Field models (Trappenberg 2008). In the limit case illustrated in Fig. 4, in which two local inputs have the exact same strength, stochastic fluctuations may bias the competition one way or the other by chance. Once a decision has been made, it is stabilized by the neural interaction within the field. As for detection decisions, this is critical when selection decisions are made, while a system is continuously linked to the sensory surface. Which site receives maximal stimulation may fluctuate in time and a simple

“winner-takes-all” rule would lead to random switching among the selection choices.

The resistance to change is also a reason, while selection decisions are typically made in response to a transient in the input stream. Once locked into a decision, a Neural Field is not open to change, unless the differences in input strength become very large and the selection instability moves the system from a bistable or multi-stable regime to a monostable regime in which only one selection decision is stable. Such resistance to change can be observed as change blindness in which observers fail to detect a change in an image (Simons and Levin 1997). Normally, when an image changes in some location, the visual transients in the sensory input attract visual attention and help detect the change. That transient signal may be masked by turning the entire image off and then turning the locally changed image back on. Observers are blind to change when transients are masked this way, unless they happen to attend to the changed location. Because sensory inputs in the nervous system are typically transient in nature, the mechanism for making selection decisions in DFT is normally engaged by change, so that change detection in the absence of a masking stimulus may also be understood within DFT (Johnson et al. 2009).

The interplay between detection and selection instabilities brings to light a further facet of Neural Fields that provides a bridge to the emergence of categories from the underlying continuous representations. The limit case of a completely homogeneous field, in which all sites have the same dynamic properties, is an idealization, of course. It is easy to break such homogeneity, for instance, by learning processes. In the simplest case, locations at which activation peaks have frequently been induced may acquire higher resting levels, a learning mechanism sometimes used in connectionist models that invoke a bias term and termed the “memory trace” in DFT (Schneegans and Schöner 2008). Hebbian learning may similarly reshape the connections from a cortical surface and induce inhomogeneous levels of activation (Sandamirskaya 2014). Such inhomogeneities may be amplified in Neural Fields by the detection

instability into macroscopic decisions! In the extreme case, an inhomogeneous subthreshold solution may be made unstable by a perfectly homogeneous input, which may be construed as an increase of the resting level, h , that pushes the field over the threshold. The location that first reaches threshold self-excites while at the same time suppressing activation everywhere else. As a result, a self-stabilized peak will arise at that location, in a sense, out of nowhere, because there was no localized input that specified the state that the Neural Field should instantiate. The input that induces a detection instability will not typically be completely homogeneous. It may favor particular locations in the field. Figure 5 illustrates a field that has a pre-shaped subthreshold state, $u_0(x)$. The pre-shape may have arisen from a learning process in which two field locations were frequently activated. An input, $s(x)$, that drives the field through the detection instability provides a broad boost but also contains a small localized component. The self-stabilized peak that emerges is positioned over the pre-activated location that is closest to the localized input. If the location that receives local input was varied continuously, the self-stabilized peak would continue to be positioned close to one of the two pre-activated locations. In this sense, the field responds categorically to spatially continuous input.



Embodied Cognition, Dynamic Field Theory of, Fig. 5 A Neural Field with a pre-shaped subthreshold solution, $u_0(x)$ (blue dashed line), is driven through the detection instability by an input, $s(x)$ (red solid line), that contains a homogenous boost across the entire field and a small localized contribution. A self-stabilized peak solution, $u_p(x)$ (blue solid line), is induced. Its peak is positioned at the closest location that has prior activation, not the stimulated location

Neural Field Models of Embodied Cognition

Neural Field models have been used within the framework of DFT to account for a large and broad set of experimental signatures of the neural mechanisms underlying embodied cognition. Sensorimotor selection decisions were modeled for saccadic eye movements (Kopeck and Schöner 1995) and infant perseverative reaching (Thelen et al. 2001). Influences of non-stimulus factors were accounted for both for saccades (Trappenberg et al. 2001) and in the infant model. The capacity of Neural Field models to account for the confluence of multiple factors is, in fact, a major strength of the approach. An exhaustive account of the influence of many different task and intrinsic factors on motor response times was foundational for DFT (Erlhagen and Schöner 2002). That model also accounted for the time course of movement preparation as observed in the timed movement initiation paradigm. The same model was linked to neural population data from motor and premotor cortex (Bastian et al. 1998), and related ideas were used to account at a much more neurally detailed level for spatial decision making (Cisek 2006). The temporal evaluation of population activity in the visual cortex has been modeled using Neural Fields (Jancke et al. 1999), including recent data that assessed cortical activity through voltage-sensitive dye imaging (Markounikau et al. 2010).

DFT has been the basis of a neural processing approach to the development of cognition (Spencer and Schöner 2003) that emphasizes the sensorimotor basis of cognitive development but has reached to an understanding of how spatial and metric memory develops (Spencer et al. 2006) and how infants build memories through their looking behavior (Schöner and Thelen 2006; Perone and Spencer 2013). A Neural Field model of metric working memory has led to predictions that have been confirmed experimentally (Johnson et al. 2009) and included an account for change detection (Johnson et al. 2008). Neural Field models of motion pattern perception (Hock et al. 2003), attention (Fix et al. 2011), imitation (Erlhagen et al. 2006), and the perceptual

grounding of spatial language (Lipinski et al. 2012) illustrate the breadth of phenomena accessible to Neural Field modeling.

Neural Fields can also be used to endow autonomous robots with simple forms of cognition (Bicho et al. 2000). This work has shown how peaks of activation may couple into motor control systems, an issue first addressed in Kopecz and Schöner (1995). Robotic implementations of the concepts of DFT have generally been useful demonstrations of the capacity of Neural Fields to work directly with realistic online sensory inputs and to control motor behavior in closed loop. Robotic settings have also been useful to develop new theoretical methods that solve conceptual problems. A notable example is the generation of serially ordered sequences of actions (Sandamirskaya and Schöner 2010). Because the inner states of Neural Fields are stable, they resist change. Advancing from one step in a sequence to a next requires, therefore, the controlled generation of instabilities, the release a previous state from stability, and enabling the activation of the subsequent state. The innovative step in (Sandamirskaya and Schöner 2010) was to use a representation of a “condition of satisfaction” that compares current sensory input to the sensory input predicted at the conclusion of an action. This concept has since been used in a variety of models that generate autonomously sequences of mental events. A robotic example is the autonomous acquisition of a scene representation from sequences of covert shifts of attention (Zibner et al. 2011).

Ongoing work in Neural Field modeling of embodied cognition advances on three fronts. On the one hand, the elementary forms of cognition must be integrated into the more complex dynamics of movement generation, coordination, and motor control (Martin et al. 2009). This entails dynamically more complex attractor states including limit cycles, as well as understanding how motor control in closed loop may interface with the population representations modeled by Neural Fields. On the other hand, a systematic push from embodied toward higher cognition (Sandamirskaya et al. 2013) ultimately aims at an understanding of all cognition in neural

processing terms. Such an account faces the challenge of how to reach the power of symbol manipulation while maintaining the grounding in sensory and motor processes. Finally, Neural Field modeling needs to interface more closely with neural mechanisms of learning (Sandamirskaya 2014).

Cross-References

- [Amari Model](#)
- [Bifurcations, Neural Population Models and Cognition, Bayesian Models of](#)
- [Cortical Maps, Activity-Dependent Development](#)
- [Decision-Making, Models](#)
- [Decision-Making, Motor Planning](#)
- [Dynamical Systems: Overview](#)
- [Multistability in Neurodynamics: Overview](#)
- [Multistability in Perception Dynamics](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Models and Cortical Field Theory: Overview](#)
- [Perception, Bayesian Models of](#)
- [Perceptual Decision-Making](#)

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Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling

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Definition

Orientation tuning is a characteristic response property of neurons in primary visual cortex.

Models of orientation tuning describe the transformation of response selectivity from lateral geniculate relay cells, which are not orientation selective, to neurons in layer 4 of the primary visual cortex. These models aim to constrain and identify the neural circuitry underlying this canonical transformation in the representation of the visual world.

Detailed Description

Introduction

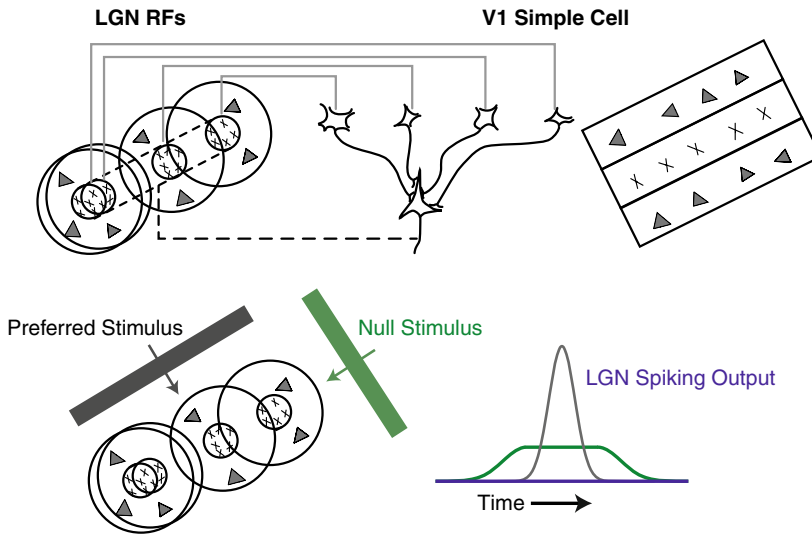
The overarching goal of systems neuroscience is to explain how the sensory inputs we receive are integrated to generate appropriate behaviors. One method of achieving this goal is to study the mechanisms underlying a single computation and build models which may be applied more generally. Computations performed by the cerebral cortex are amenable to this approach due to the relative uniformity of cortical circuitry. Not only does mammalian cerebral cortex contain a common set of neuron cell types with a similar lamination pattern, but it contains a common pattern of neuronal circuitry that processes sensory, motor, and planning-related information. We focus here on a specific computation performed in the visual cortex, orientation selectivity, because this response property is found in primary visual cortex of all mammals in which it has been studied and also because its emergence does not depend on a specific circuitry in visual cortex, as rewiring visual inputs to other portions of the cerebral cortex also yields orientation-selective responses (Sharma et al. 2000). By studying this single property, we therefore hope to gain access to the general computation performed by the cerebral cortex.

In the visual system, sensory information is initially transduced from photons to electrical potentials by retinal photoreceptors. From the photoreceptors, incoming visual information undergoes a number of transformations within the laminar series of neurons in retina, ultimately progressing to retinal ganglion cells, which constitute the retinal output. Retinal ganglion cells have circularly symmetric receptive fields with an antagonistic center/surround organization, meaning they are

unselective for the orientation of objects in visual space (Kuffler 1953). In mammals, retinal ganglion cells project to the lateral geniculate nucleus (LGN) of the thalamus, where relay cells in turn send visual information to the first cortical station: the primary visual cortex (V1). While the receptive field profiles of both retinal ganglion cells and their target LGN relay cells are circularly symmetric, V1 neurons are sensitive to several complex visual stimulus attributes, including stimulus orientation, direction, and binocular disparity (Hubel and Wiesel 1962; Pettigrew et al. 1968; Ohzawa and Freeman 1986). In many cases this selectivity is exquisite: V1 neurons may not respond to visual stimulation at all unless the stimulus features specifically match the neuron's preference. A prime example of this selectivity is the orientation selectivity of V1 neurons: a bar of light oriented along one spatial axis might evoke a robust spiking response in a visual cortical neuron, but the same bar oriented along the orthogonal spatial axis would evoke no response. Following the discovery of orientation tuning in V1 neurons, numerous models have been developed to explain its emergence. We begin by describing the initial proposal to describe orientation tuning, the Hubel and Wiesel feedforward model, as well as the successes and failures of this model in describing orientation tuning in V1.

The Feedforward Model of Orientation Tuning

When Hubel and Wiesel first described cortical orientation selectivity (1962), they proposed a simple and elegant model to explain its emergence, a model which continues to be a reference point for computational models of cortical processing. In their model, neurons in layer IV of the cortex, which receive the bulk of the direct input from thalamic relay cells (Hubel and Wiesel 1962; Gilbert 1977; Bullier and Henry 1979), become orientation selective through the convergence of multiple LGN relay cells (Fig. 1). Thalamic relay cells are themselves generally unselective for orientation since they have circularly symmetric receptive fields. Hubel and Wiesel hypothesized that multiple LGN relay cells



Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling, Fig. 1 Hubel and Wiesel feedforward model. LGN relay cell receptive fields spatially aligned along one axis form the basis of the receptive field of a single V1 simple cell (Adapted from Hubel and

Wiesel (1962)). A stimulus oriented along this axis activates all LGN cells simultaneously, generating a large synchronous spiking response. The orthogonal stimulus activates the LGN cells asynchronously, producing a temporally uncorrelated spiking response

with spatially offset receptive fields along a single axis in visual space could converge onto a target cortical cell (Fig. 1). In this way, a visual stimulus oriented along the axis of the spatial offset activates the afferent LGN relay cells simultaneously and produces a large synaptic input onto the recipient simple cell (Fig. 1).

This simple model for cortical orientation selectivity predicts that the relative timing of LGN relay cells is an essential component for the generation of orientation selectivity. Because LGN neurons have circular receptive fields, they respond equally well to all orientations, but their relative timing will vary with stimulus orientation: the spiking responses of LGN relay cells will be nearly simultaneous when an oriented stimulus is presented at the target V1 neuron's preferred orientation but will be spread out in time, or asynchronous, for the orthogonal orientation (Fig. 1).

The elegance of this model lies in the feedforward nature of the systematic transformation of visual information from LGN relay cells to V1: the only requirement being spatial organization of converging excitatory thalamocortical afferents. There is substantial evidence supporting this simple feedforward model. Layer 4 of the

primary visual cortex is composed of neurons which receive direct thalamocortical input (Hubel and Wiesel 1962; Gilbert 1977; Bullier and Henry 1979; Hirsch and Martinez 2006; Martinez et al. 2006; Ferster et al. 1996; Ferster and Lindström 1983). These neurons, called simple cells, have receptive fields composed of oriented and segregated subregions, each giving exclusively ON or OFF responses (response to light onset/dark offset or light offset/dark onset). The LGN relay cells that provide direct input to target simple cells have receptive fields that overlap in spatial position and polarity (Reid and Alonso 1995; Tanaka 1983). Further, inactivation of the cerebral cortex does not disrupt orientation tuning of synaptic input onto simple cells (Ferster et al. 1996; Chung and Ferster 1998; Jagadeesh et al. 1997). These results support, at least in part, the original proposal by Hubel and Wiesel for the generation of cortical orientation selectivity.

Failures of a Simple Feedforward Model

Despite success in describing V1 orientation selectivity, the feedforward model fails to capture

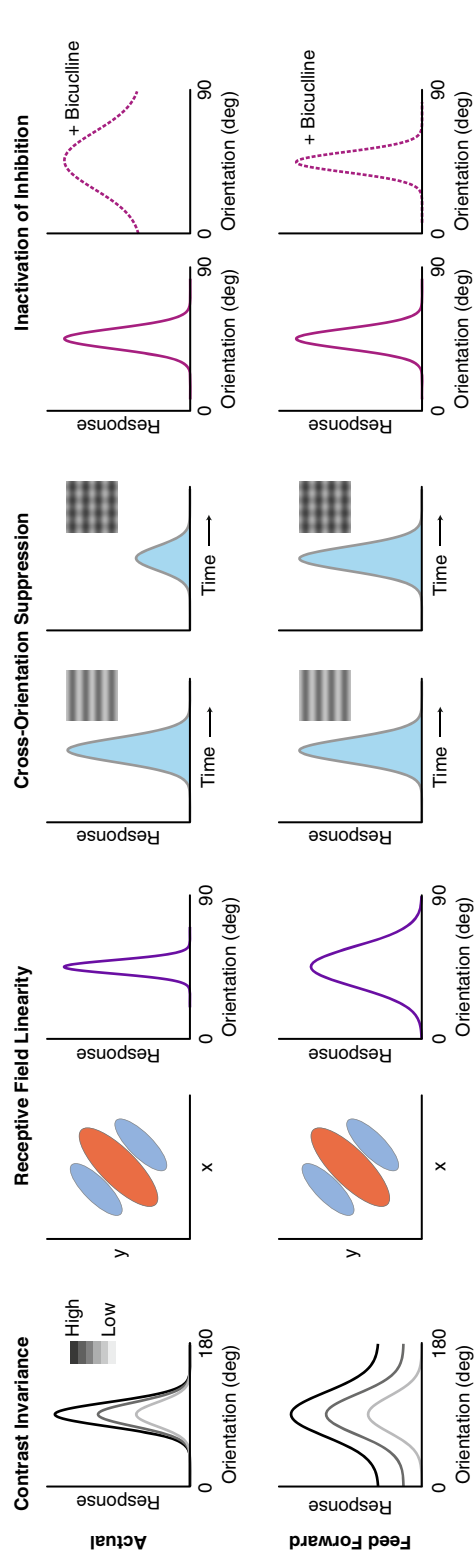
a number of key response properties of cortical neurons. These failures have driven the field to propose a number of alternative hypotheses for the generation of orientation selectivity. The first response property challenging the feedforward model is contrast-invariant orientation tuning (CIOT) (Alitto and Usrey 2004; Sclar and Freeman 1982; Skottun et al. 1987; Troyer et al. 1998; Finn et al. 2007). Despite large changes in stimulus contrast, the orientation tuning width of cortical neurons is largely invariant (Fig. 2). CIOT poses a challenge to the feedforward model because as stimulus contrast increases, the overall activity of relay cell afferents also increases. Because the overall synaptic input to V1 neurons increases with stimulus contrast, the range of orientations evoking a response, and thus the tuning width, should also increase (Fig. 2). A second challenge to the feedforward model is the significant discrepancy between the orientation tuning of individual simple cells based on the response to bars or grating stimuli and the predictions of orientation selectivity based on receptive field maps (Volgushev et al. 1996; Gardner et al. 1999). Receptive field maps, which form the feedforward model basis for how orientation selectivity emerges, systematically underestimate the tuning width of neurons to bars and gratings (Fig. 2). The third challenge to the feedforward model lies in the observed suppression between orientations, known as cross-orientation suppression. Two stimuli of orthogonal orientations (i.e., preferred and orthogonal) induce a suppression of spiking responses in cortical neurons (Allison et al. 2001; Bishop et al. 1973; DeAngelis et al. 1992; Morrone et al. 1982) (Fig. 2). The feedforward model does not include any interaction between neurons tuned to different orientations, so it has been unclear how this suppression would emerge (Fig. 2). A final challenge to the feedforward model is the observed effects of blocking cortical inhibition. Blocking cortical inhibition using bicuculline decreases orientation selectivity, even at concentrations that do not dramatically increase excitatory responses (Sillito 1975; Crook et al. 1997; Hata et al. 1988) (Fig. 2). The feedforward model, however, does not include any role for inhibition, predicting little change in

orientation selectivity following the blockade of the inhibition (Fig. 2).

To account for these response properties that do not necessarily emerge from Hubel and Wiesel's original feedforward model, four primary classes of models have been proposed. It has been argued that orientation tuning arises primarily from intracortical networks, arises from a combination of feedforward mechanisms and cortical inhibitory components, arises from feedforward mechanisms that include known nonlinearities from biophysical properties of individual cortical neurons, and, finally, arises from a feedforward model incorporating LGN relay cell nonlinearities. We will discuss each of these model classes following a top-down approach, starting with a strong emphasis on cortical circuitry and ending with a focus on LGN relay cells.

Models Orientation Tuning Arising from Cortical Circuitry

While the feedforward model does not describe a role for cortical circuitry in the generation of orientation selectivity, the excitatory and inhibitory cortical network may play an important role in the generation of orientation selectivity. One suggestion for how cortical circuitry might contribute to orientation selectivity is that it acts as a ring-attractor network (Ben-Yishai et al. 1995; Goldberg et al. 2004) (Fig. 3a). In ring-attractor networks, orientation selectivity results from the circuitry within cortex, requiring little feedforward selectivity from the convergence of LGN relay cells. Ben-Yishai's model includes all possible cortical interactions (e.g., excitatory-excitatory, excitatory-inhibitory), where the strength of the interactions are related to the differences in the orientation preference of each neuronal pair. Both excitatory and inhibitory inputs share orientation preference, but excitatory inputs dominate between cell pairs with similar tuning, whereas inhibitory inputs dominate between cell pairs with orthogonal tuning. The cortical circuitry generates a ring stable states where all orientations are represented. Only a small bias in external input for orientation pushes the network to converge onto a stable state (Fig. 3a).



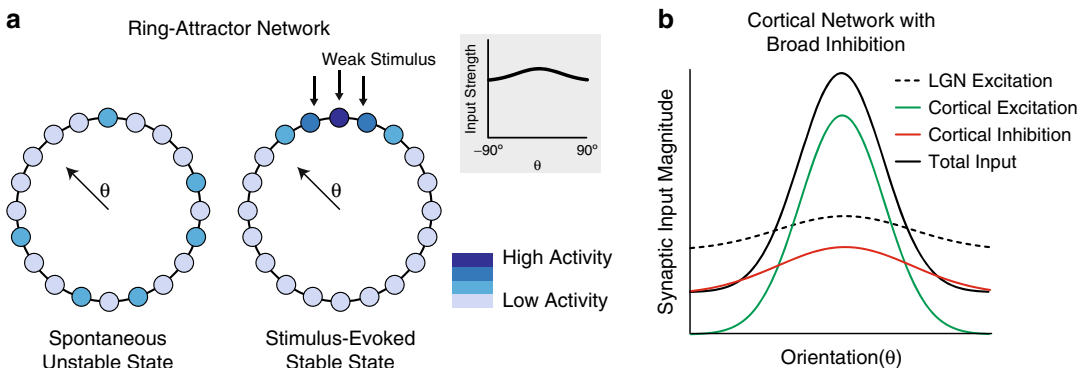
Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling,
Fig. 2 Failures of the feedforward model. The Hubel and Wiesel feedforward model (*bottom row*) fails to capture characteristics of orientation tuning in actual V1 cortical neurons (*top row*): (1) orientation tuning width varies with contrast (*left*) and

An interesting feature of this model architecture is that it predicts that orientation tuning does not depend on other stimulus features, including the spatial frequency and the contrast of the stimulus, since selectivity is determined by the cortical architecture. In this way, the cortical network represents all orientations, invariant to the contrast of the stimulus.

A similar model of orientation selectivity relying on the cortical network has also been proposed by Somers et al. (1995). As with the Ben-Yishai model, weak orientation preference is provided by the convergence of LGN relay cells, but the cortical circuitry amplifies and sculpts that weak bias into strong orientation tuning (Carandini and Ringach 1997). Intracortical excitation provides the dominant source of excitatory drive, with neurons that share orientation preference strongly interconnected. To maintain sharp orientation tuning and contrast invariance, model simple cells receive a significant inhibitory input. This inhibition comes from inhibitory neurons sharing orientation preference and is required for canceling the weakly tuned excitatory relay cell input. To assure that nonpreferred orientations are quenched by inhibition, the model proposes that inhibitory input onto simple cells is more broadly tuned than excitatory input (Fig. 3b). A nonpreferred

orientation will drive afferent LGN neurons to a cortical excitatory cell, but that weak input is suppressed by inhibition, either from inhibitory neurons that are more broadly tuned than excitatory neurons or from inhibitory neurons with different orientation preferences. In contrast, the preferred orientation drives a weak LGN input amplified by intracortical excitatory circuitry. A related model architecture has also been proposed by McLaughlin et al. (2000), relying on intracortical connectivity to shape orientation selectivity. The McLaughlin model architecture is characterized by an isotropic connectivity pattern for excitation and inhibition instead of the Somers's proposed architecture with broad inhibition. To account for contrast-invariant orientation tuning, this model incorporates large intrinsic fluctuations emerging from sparse connectivity. These fluctuations push the model into a critical state such that contrast-invariant orientation tuning may emerge (Tao et al. 2006).

The proposals by Ben-Yishai et al., Somers et al., and McLaughlin et al. all rely on cortical interactions to generate the shape of the orientation selectivity but still require a weak orientation bias in the input, which could come from the convergence of spatially offset neurons, as originally proposed by Hubel and Wiesel. In contrast,



Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling, Fig. 3 Cortical mechanisms of orientation tuning. (a) A ring-attractor network produces cortical orientation tuning independent of stimulus parameters. An attractor network representing all orientations (theta) explores unstable states of activity without external input. A small external input, such as weak orientation selectivity from the LGN (*inset*), pushes the ring into a

stable configuration with neural activity centered around the orientation bias of the input. (b) Orientation tuning curves of different input onto a single cortical neuron in the Somers et al. (1995) model. Weakly tuned LGN excitation is combined with sharply tuned cortical excitation and more broadly tuned inhibition to generate orientation-selective input

Adorján et al. (1999) have proposed a model based purely on an “intracortical hypothesis,” wherein lateral intracortical connections drive *both* initial orientation bias and subsequent amplification without selectivity of thalamocortical inputs. To generate orientation selectivity from cortical mechanisms alone, the authors propose cortical RFs lie along one axis in visual space. Neurons whose RFs fall onto one axis belong to an orientation column and laterally connected by strong excitatory interactions. Such a connectivity anisotropy forms the basis for orientation specificity from incoming retinotopic inputs. Using this initial anisotropy to generate a bias in orientation selectivity, the shape of the orientation tuning curve is sculpted by a convergence of excitatory input amplifying the initial bias and inhibitory input, which is more broadly selective than excitatory inputs, as in the proposal by Somers et al. (1995). This proposal is particularly relevant to the emergence of orientation selectivity in the primate V1. In contrast to cat V1, where orientation selectivity is apparent in layer 4, strong orientation selectivity in primate V1 is only observed in layers that do not receive direct input from relay cell afferents (Hubel and Wiesel 1968; Blasdel and Fitzpatrick 1984; Ringach et al. 2002). In the primate, therefore, it appears that a strong role for cortical circuitry is required to generate orientation selectivity.

Models of Inhibition Sculpting Orientation-Tuned LGN Synaptic Input

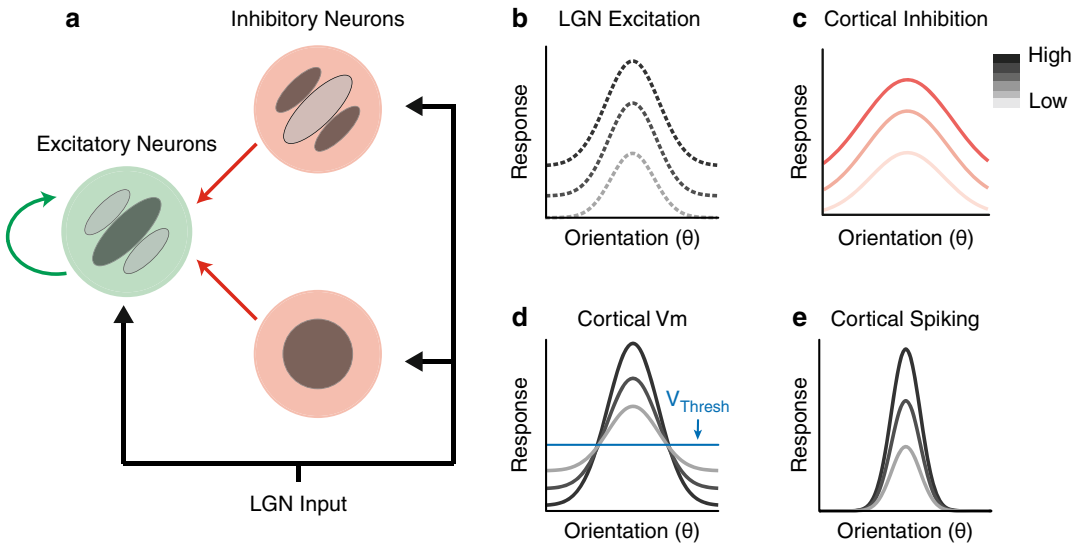
A second class of models asks how cortical circuitry, inhibition in particular, might enhance or sharpen feedforward input into V1, but these models rely primarily on the feedforward input to determine selectivity. Importantly, the inclusion of cortical excitation and inhibition allows for these models to express many of the behaviors that are missing the simple feedforward model (Fig. 2).

To account for contrast-invariant orientation selectivity, Troyer et al. (1998) developed a model using both a well-defined and physiologically realistic LGN firing pattern as input to a

cortical network and correlation-based connections between cortical layer 4 neurons. Correlation-based input is defined as the connection probability between neuronal pairs as a function of the degree of correlation (excitatory-excitatory) or anticorrelation (inhibitory-excitatory) between RFs. Receptive fields that are highly correlated are those from neurons sharing both orientation selectivity and a similar pattern of ON and OFF subfields, while anticorrelated receptive fields are from neurons that share orientation selectivity but have the opposite pattern of ON and OFF subfields (Fig. 4a). In this pattern of connectivity, the orientation selectivity for inhibition and excitation share orientation preference but are evoked by the opposite polarity stimulus conditions (Fig. 4a). This relationship between excitation and inhibition is called push-pull.

To solve the problem of contrast invariance, it is important to note that the aggregate LGN input contains two components: (1) an orientation-tuned component and (2) an untuned, contrast-dependent component (Fig. 4b). As contrast increases, the untuned contrast-dependent component of the LGN increases and must be suppressed to preserve invariance. In the Troyer et al. model, inhibitory neurons suppress this untuned component by having different orientation tuning than excitatory neurons. Specifically, these inhibitory neurons respond to all stimulus orientations, providing a suppressive signal related to stimulus contrast. This contrast-dependent inhibition removes the untuned component of the LGN input and preserves orientation selectivity (Fig. 4b and c). LGN excitation and cortical inhibition are combined to generate cortical membrane potential (Fig. 4d), which is then passed through threshold non-linearity to produce cortical spiking responses and CIOT (Fig. 4e).

This model makes several predictions about inhibitory input onto layer 4 V1 neurons. First, inhibitory neurons should have similar RF structure as excitatory neurons in cat layer 4 in order to create the tuned inhibitory component. In fact, several studies have shown this to be the case (Gilbert and Wiesel 1979; Toyama et al. 1981; Martin 1988; Hirsch et al. 1998, 2003). Second, there must exist inhibitory neurons in layer



Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling, Fig. 4 Feedforward model with cortical inhibition. (a) Schematic of layer 4 cortical circuit. LGN relay cells innervate both cortical excitatory and inhibitory neurons. Inhibitory neurons provide suppressive input onto excitatory neurons. There are two inhibitory components: an orientation-selective with opposite receptive field phase component generating push-pull and an unselective contrast-sensitive component providing DC

suppression. These are hypothesized to be due to separate neuron populations (Hirsch et al. 2003). (b) LGN excitation exhibits broad orientation tuning and the untuned (mean) component increases with contrast. (c) Cortical inhibition exhibits broad tuning and increases with contrast for all orientations to suppress untuned LGN component. (d–e) Cortical membrane potential generated from LGN excitation and cortical inhibition is passed through a threshold nonlinearity (blue) to generate spiking responses

4 which provide untuned (unmodulating, phase nonspecific), contrast-dependent responses. Identified inhibitory neurons in layer 4 are generally orientation selective, like their excitatory counterparts, which is contrary to the suggestion in the Troyer model (Cardin et al. 2007). A small proportion of inhibitory neurons have been recorded from that are completely untuned for orientation, and these neurons could provide the required suppression to remove the untuned component of the feedforward input (Hirsch et al. 2003) (Fig. 4a). Following the study by Hirsch et al., a modified version of the original Troyer model was proposed to that included a combination of orientation-tuned and untuned inhibitory neurons. This model also accounts for CIOT (Lauritzen and Miller 2003) (Fig. 4d and e). An additional prediction of Troyer and Lauritzen models is that V1 neurons with direct thalamocortical innervation should have excitatory and inhibitory conductances which are antagonistic in nature. Evidence for this final prediction has been reported in the

synaptic integration of simple cells (Hirsch et al. 1998), direction selectivity of simple cells (Priebe and Ferster 2005), and measurements of conductances underlying orientation tuning (Anderson et al. 2000).

An additional model that has been proposed which relies on the LGN input for orientation selectivity is the proposal by Wörgötter and Koch (1991). They explore a recurrent cortical network composed solely of intracortical inhibition. Although there were no intracortical excitatory connections, both inhibitory and excitatory neurons received the same thalamocortical input. Using this model they test the effects of many different inhibitory connection regimes to supplement the basic Hubel and Wiesel framework: random, sparse, local, circular broad, and cross-orientation input. They found that cross-orientation inhibition was not effective in producing a realistic population of cortical orientation tuning, as an emergent property of the network was an overrepresentation of vertical and horizontal orientations.

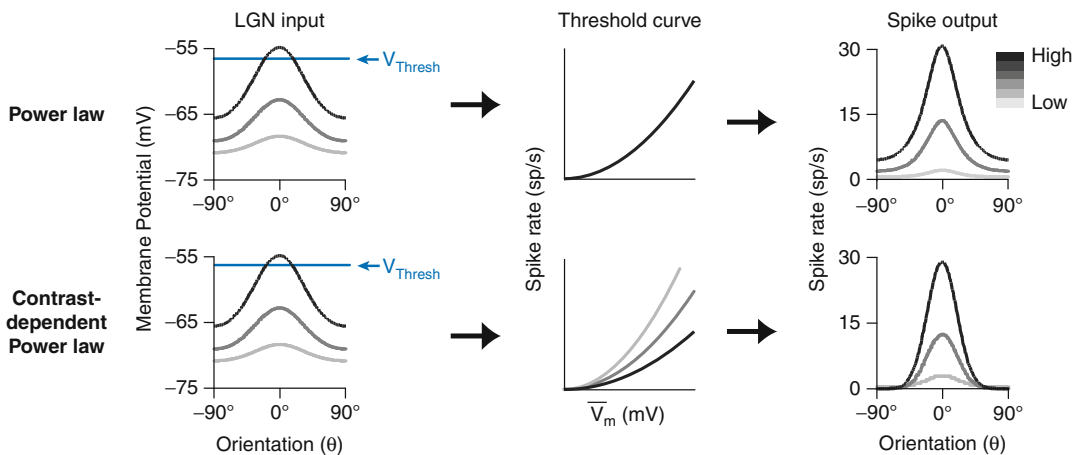
A combination of circular broad inhibition (500 μm range) and local, iso-orientation (within column) inhibitory input was able to produce orientation tuning in layer 4. In this way, a weak LGN input was sculpted away leaving highly selectivity orientation tuning. This model is very similar to the framework of Somers et al. (1995) (Fig. 3b), but without contribution of any intracortical excitation. The use of circularly broad and local inhibitory inputs is conceptually similar to models of contrast-set gain control whereby a divisive mechanism integrates over a “normalization pool” to compress responses at high contrasts (Heeger 1992; Geisler and Albrecht 1992).

Models of Biophysical Properties in Cortical Neurons

A third class of models examines how the nonlinear properties of cortical neurons receiving direction thalamocortical input would add onto the original Hubel and Wiesel framework to generate orientation tuning. Unlike the last two model classes, which rely on intracortical interactions to shape tuning, these models compliment the feedforward model with the nonlinear biophysical properties of cortical neurons and the LGN input.

Surprisingly the inclusion of simple, known biophysical properties of neurons along the visual pathway can contribute to the emergence of contrast invariance, tuning profile sharpness, and cross-orientation suppression (Carandini and Ferster 2000; Finn et al. 2007; Priebe and Ferster 2008).

A detailed examination of a purely feedforward Hubel and Wiesel model reveals a problematic mismatch between orientation tuning predictions from an RF map and the actual responses of a given neuron (Gardner et al. 1999; Jones and Palmer 1987) (Fig. 2). One resolution to this issue is that this mismatch is a by-product of the nonlinear transformation of subthreshold membrane potential to action potentials (Priebe and Ferster 2008). To incorporate this nonlinearity models, retain the simple elements of a feedforward mechanism, but pass the aggregate LGN input through a nonlinearity composed of either a threshold followed by a linear function or a power law (Fig. 5, *top*). Measurements of both subthreshold and suprathreshold responses, incorporating this nonlinearity, generate more accurate predictions of spike tuning in V1 simple cells (Bringuier et al. 1999; Carandini and Ferster 2000; Finn et al. 2007; Priebe and Ferster 2008). As predicted from this simple nonlinearity



Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling, Fig. 5 Feedforward model with biophysical cortical nonlinearities. Subthreshold membrane potential (V_m) orientation tuning is passed through a static nonlinearity (power law) to generate spiking

responses (*top*). Orientation tuning of spiking output is narrower than LGN input or V_m but still contains untuned component (compare spiking at high and low contrasts at 90°). A contrast-dependent power law (*bottom*) generates contrast-invariant orientation tuning of spiking responses

subthreshold membrane, potential responses are consistently more broadly tuned than spiking responses (Fig. 5) (Carandini and Ferster 2000; Finn et al. 2007; Nowak et al. 2010). Although in some cases, the difference between subthreshold and suprathreshold spatial-temporal RF maps can be entirely explained by a static nonlinearity (Mohanty et al. 2012), simply incorporating this nonlinearity to the output of simple cells falls short of explaining contrast invariance, because as contrast increases, more and more inputs should cross spike threshold, therein increasing tuning width (Figs. 2 and 5).

How could contrast invariance be attained utilizing only nonlinear properties of cortical neurons? Finn et al. (2007) proposed an elegant solution: the relationship between membrane potential and spiking activity depends on contrast. Specifically, they proposed that the threshold nonlinearity is dependent on response variability and this variability is affected by stimulus contrast (Fig. 5, *bottom*). As contrast decreases, variability increases, which increases steepness of the expansive component (Fig. 5, *bottom*). Increased steepness in the expansive component equates to membrane potential fluctuations generating larger spiking responses. A contrast-dependent threshold nonlinearity provides a simple method to scale the transformation of membrane potential inputs into spiking responses. At low contrasts, only membrane potential fluctuations at or near the preferred orientation can elicit spikes. At high contrasts, membrane potential depolarizations are much larger, but since the threshold nonlinearity greatly decreases a neuron's sensitivity to these inputs, only sufficiently large inputs at or near the preferred orientation elicit spikes. In this way, contrast invariance can appear in simple cells without inhibitory input or contribution of intracortical excitation.

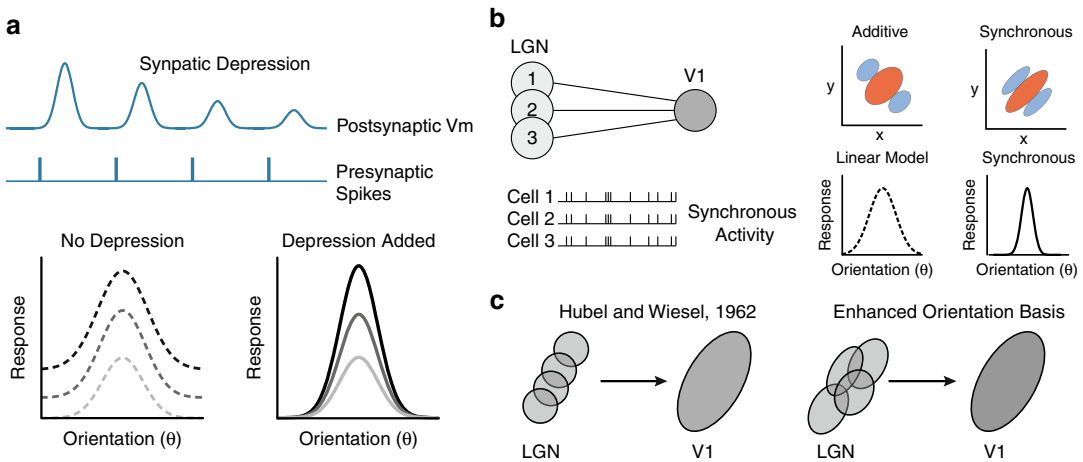
Models of LGN Response Properties and Orientation Bias

Thus far, the models examined focus on the cortex, the target of thalamocortical axons, and the site of the emergence of orientation selectivity.

This final class of models proposes alternate solutions for the emergence of orientation selectivity that include the properties of the thalamic relay cells. Here we discuss several models which utilize different aspects of the relay cells to generate orientation-tuned synaptic input onto V1 simple cells. These include synaptic depression of geniculate relay cell axons, trial-to-trial variability in LGN synaptic input, synchronicity of geniculate cell spiking activity, and a radial bias in the selectivity of LGN cells.

Synaptic depression is attributed to the depletion of readily releasable synaptic vesicles in the presynaptic axon terminal. Repeated activation of a single terminal over short timescales can decrease the number of vesicles released, reducing the efficacy of the synapse. As presynaptic LGN spiking activity increases with contrast, so does the effect of synaptic depression on a postsynaptic targets (Markram and Tsodyks 1996; Abbott et al. 1997). As a presynaptic cell fires more action potentials, the efficacy of individual action potentials on the postsynaptic cell decreases (Fig. 6a, *top*). Banitt et al. (2007) measured the effects that synaptic depression would have on a biophysically realistic layer 4 model cortical cell receiving a large number LGN inputs, largely following the Hubel and Wiesel framework. Strong feedforward synaptic depression compressed responses to all different contrasts. In particular, high contrast stimuli were larger and showed broader tuning without synaptic depression of thalamocortical synapses (Fig. 6a, *bottom*). Incorporating the synaptic depression sharpened tuning (Fig. 6a, *bottom*), produced CIOT (Banitt et al. 2007; Carandini et al. 2002). For nonpreferred stimuli, membrane potential depolarizations were too small to evoke spiking responses with synaptic depression, while co-activation of LGN relay cells for preferred stimuli were large enough to evoke spiking activity. Thus, a biophysical feedforward model including synaptic depression generated invariant orientation tuning.

A primary component of the Hubel and Wiesel model is that preferred orientation visual stimuli evoke a synchronous activation of LGN relay cells. Individual layer 4 V1 neurons integrate



Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling, Fig. 6 Feedforward model with biophysical LGN nonlinearities. (a) Synaptic depression of thalamocortical synapses (top) onto layer 4 cortical neurons compresses LGN input and can generate contrast-invariant orientation tuning. (b) Synchronicity of multiple LGN relay cells onto a single cortical neuron can increase orientation selectivity. Synchronous spiking activity, compared to additive activity, generates narrower receptive

fields in cortical neurons. Synchronous spiking activity also creates narrow orientation tuning compared to a simple linear model of LGN spiking input. (c) Circularly symmetric LGN receptive fields are aligned to one axis to generate oriented receptive fields in V1. Incorporating oriented LGN receptive fields to the original Hubel and Wiesel model can generate oriented receptive fields and orientation tuning without a strict arrangement

over 10–100 different LGN relay cells. Any synchrony between the LGN relay cells could play an important role in the generation of V1 orientation selectivity (Fig. 6b, left). Stanley et al. (2012) envisioned two extreme ways in which incoming thalamic spikes might combine to generate spikes in cortical simple cells: through either additive or multiplicative nature. Addition of presynaptic spikes to generate cortical spikes is a linear process, meaning that 1 spike from two relay cells arriving simultaneously would generate 2 spikes in a cortical neuron. Multiplication of incoming spikes would imply that 1 spike arriving simultaneously from 2 relay cells would only generate 1 spike in the postsynaptic cortical neuron. In this way, synchronous activity is represented by multiplicative nature of LGN pairs. Models demonstrate synchronicity could enhance RF elongation and sharpen orientation tuning (Stanley et al. 2012; Wang et al. 2010) (Fig. 6b, right). Varying the “jitter” in relay cell spike arrival times onto the cortical neuron causes significance changes in the membrane potential and spike rate transformation and therefore alters the tuning of downstream

targets. If the degree of relay cell synchrony is linked to contrast, this synchrony could play an important role in the emergence of contrast-invariant orientation tuning (Finn et al. 2007; also see above) (Fig. 6b, right).

Geniculate relay cells, like many sensory neurons in the central nervous system, have variability in their responses to a stimulus. How might this variability play a role in the generation of orientation tuning? Sadogopan and Ferster (2012) measured the contrast dependence of relay cell variability and found that it shares the known contrast dependence of variability of target cortical neurons. They use a biophysical feedforward model of geniculate relay cells innervating a layer 4 simple cell (Fig. 5) to demonstrate that cortical variability could be inherited from the thalamus. Their model contained many linear and nonlinear components, including LGN RF convergence and spatial organization, pairwise correlations in relay cells, variability in LGN spiking responses, thalamocortical synaptic depression, a conductance-based synaptic input onto cortical neurons,

and the nonlinear transformation from conductance to membrane potential. This model was able to capture subthreshold membrane potential responses of cortical simple cells but also demonstrated sharp, contrast-invariant orientation tuning. It should be noted, however, that this model does incorporate several nonlinear properties of geniculate and cortical neurons. Although variability in LGN inputs might be an important factor for generating realistic orientation tuning, this response property most likely arises from a multitude of nonlinear mechanisms.

A final model orientation tuning centers around orientation selectivity of LGN relay cells themselves. Evidence for subcortical orientation selectivity has been observed in carnivores, where orientation biases have been associated with systematic asymmetries of retinal ganglion cell arbors (Boycott and Wässle 1974; Cleland and Levick 1974; Hammond 1974; Levick and Thibos 1980; Leventhal and Schall 1983; Shou et al. 1995). Volgushev et al. (1996) and Vidyasagar et al. (1996) proposed a simple model in which these asymmetries add to the original Hubel and Wiesel framework to generate orientation tuning. In their model, weak selectivity in thalamocortical inputs is combined LGN RF spatial overlap (Fig. 6c). As long as radial biases are parallel to the spatial organization of LGN RFs, then stimuli oriented along that axis should generate a larger synaptic input onto cortical neurons. This selectivity could be further enhanced either by dendritic nonlinearities such as voltage-gated ion channels (Pei et al. 1994; Vidyasagar et al. 1996) or simply through the transformation of membrane potential to action potentials in cortical simple cells.

Concluding Remarks

We have discussed four major classes of models of describing orientation tuning in V1. These include hypotheses that cortical circuitry determines orientation selectivity, inhibition sculpting feedforward excitation generates invariance and other properties, biophysical nonlinearities of cortical neurons are sufficient to generate

orientation tuning, and feedforward LGN input already poses nonlinearities which culminate to generate properties of cortical tuning. It is important to note that many mechanisms of these models are not exclusive, but rather inclusive and communal. For example, network models are not capable of producing invariant orientation tuning with inhibitory contributions. Additionally, biophysical models often contain many overlapping features like synaptic depression. All these biophysical mechanisms are known to exist: synaptic depression is basic property of chemical synapses (Stratford et al. 1996), as is the transformation of membrane potential to spiking activity in cortical neurons (Hodgkin and Huxley 1952). A similar argument can be applied to cortical networks; despite strong focus on strictly feedforward models, it is well known that cortical circuitry is complex and there exist a number of synaptic connections between excitatory and inhibitory neurons. These facts suggest that perhaps all models of orientation tuning reflect the true sensory computation. That is, the mammalian early visual system may have adopted a number of mechanisms which work in tandem to generate orientation tuning (Monier et al. 2003).

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Endocrine Cell Function and Dysfunction

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Definition

The endocrine system refers to the cells and tissue that release hormones into the blood. Unlike synaptic chemical communication, which is localized to the target cell, endocrine communication is global. The hormones act on other endocrine glands such as the adrenal gland, ovaries, testes, and others, as well as on the heart, kidneys, muscle, and the brain. Mathematical modeling has been used to understand network interactions mediated by the endocrine system, as well as the effects of hormones on single cells.

Detailed Description

Background

Like neurons, many endocrine cells are electrically excitable and release hormones through Ca^{2+} -mediated exocytosis (Stojilkovic et al. 2010). These have been the focus of mathematical modeling and computer simulation to better understand the mechanisms through which the cells operate. Several endocrine cell types are involved in diseases with substantial morbidity and mortality, making them an important target for model-assisted investigation.

The most computational work to date has focused on the endocrine cells located within the pancreas in micro-organs called **islets of Langerhans** and cells in the anterior region of the pituitary gland. There has also been modeling work done on the interaction between endocrine cells of different glands and between an endocrine gland and the brain. However, modeling of the endocrine system is still in its infancy, so there is much potential for future work. Here, we consider two examples. The first illustrates cellular-level

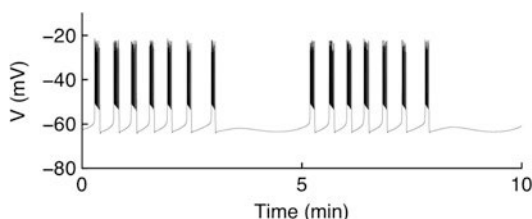
modeling of endocrine cells, and the second illustrates mean-field modeling of interactions between two endocrine glands.

Models of Pancreatic Islets

Islets are clusters of endocrine cells coupled together by gap junctions. They serve as endocrine micro-organs, and the pancreas contains hundreds of thousands of them. An islet consists of glucagon-secreting α -cells, insulin-secreting β -cells, somatostatin-secreting δ -cells, and cells that secrete pancreatic polypeptide. The gap junctions that connect neighboring cells provide electrical coupling among cells of the same type, which has the effect of synchronizing their activity.

Almost all of the computational modeling that has been done on islets has focused on the β -cells. These cells sense the blood glucose concentration, and when the concentration is sufficiently high, they produce a rhythmic pattern of electrical activity called **bursting**, cycles of electrical impulses separated by quiescent periods. Insulin is secreted during the active phase of the burst, which acts on target tissue such as muscle and the liver to take up glucose from the blood and metabolize it. The physiological importance of insulin secretion from β -cells, and the interesting question of how this periodic electrical activity could be produced, prompted Teresa Chay and Joel Keizer to develop the first mathematical model of β -cell electrical activity in 1983 (Chay and Keizer 1983). This model provided key insights into biophysical mechanisms for burst generation and initiated a several-decade-long series of models by them and others for pancreatic β -cells, each differing primarily in the mechanism for burst generation.

A key prediction of the **Chay-Keizer model** is that the intracellular Ca^{2+} concentration should have a sawtooth shape. This prediction was falsified when fura-2 fluorescent dye was used to measure the intracellular Ca^{2+} concentration and it was demonstrated that it has more of a square-wave shape. Other data has continued to drive revisions in the β -cell models. As the models

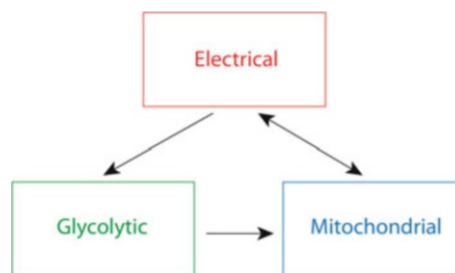


Endocrine Cell Function and Dysfunction, Fig. 1 Compound bursting oscillations in electrical activity generated by the Dual Oscillator Model

have grown in complexity, they have grown in explanatory capacity.

A good model of islet β -cells should be capable of explaining the 5-min oscillations in the blood insulin concentration that is typical in nondiabetic humans, mice, rats, and dogs. These oscillations correspond to either **slow bursting** or **compound bursting** activity in islets. The latter consists of bursts of electrical bursts (Fig. 1). Both slow and compound bursting oscillations have been observed frequently in isolated islets when the patch clamp technique is used to measure β -cell voltage (rather than a sharp electrode, as was used earlier). A model capable of producing slow and compound bursting oscillations, as well as the faster bursting oscillations often seen in islets, is the **Dual Oscillator Model** (Fig. 2) (Bertram et al. 2004, 2007a).

The first element of this model is an electrical component that also takes care of Ca^{2+} handling. This is a descendent of the Chay-Keizer model, with significant modification, and can account for the fast bursting oscillations often seen in islets. The second element describes a portion of the glycolytic pathway containing the allosteric enzyme phosphofructokinase. The product of this enzyme stimulates the enzyme's own catalytic activity and can produce slow oscillations in glycolytic activity. The third element describes portions of the citric acid cycle and oxidative phosphorylation, both of which occur in mitochondria. In the model, either slow or compound bursting oscillations are produced when the glycolytic subsystem is in an oscillatory state, which results in packaging of electrical activity into episodes. The effect of glycolytic oscillations on the electrical activity is mediated via the

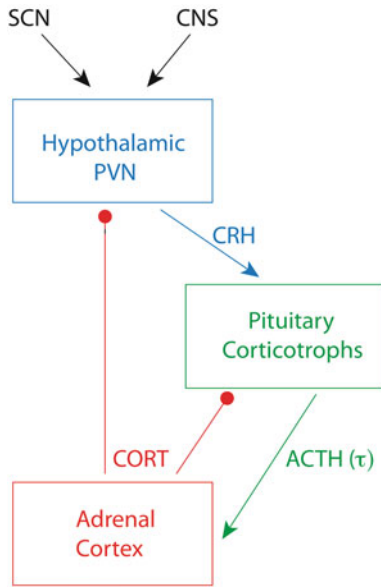


Endocrine Cell Function and Dysfunction, Fig. 2 The three main components of the Dual Oscillator Model and the interaction flow

mitochondrial production of adenosine triphosphate (ATP), which acts on ATP-sensitive potassium ion channels in the plasma membrane. This model is able to account for the different types of bursting observed in islets, the ability of changes in glucose to convert the islet from one type of bursting pattern to another, and the effects of several pharmacological manipulations. Importantly, the model has been used to design experiments and to interpret experimental results in unintuitive ways. See Sherman (2010) and Bertram et al. (2007b) for details.

A Model for Glucocorticoid Pulsatility

Glucocorticoids (cortisol in humans and corticosterone in rats and mice) are released from the adrenal cortex and are key stress hormones that regulate the cardiovascular, cognitive, metabolic, and immunological states of the animal. Like many hormones, glucocorticoids are released in a pulsatile manner. This **ultradian rhythm**, with period of about 1 h, is superimposed on a **circadian rhythm** of glucocorticoid release so that the ultradian pulse amplitude is high during the active period of the animal and low during sleep. It has been demonstrated that the physiological response to a stressor is determined in part by the time of onset of the stressor in relation to the phase of the rhythm (Windle et al. 1998). It has also been demonstrated that glucocorticoid-responsive genes respond differently to pulses of glucocorticoids versus constant application of the hormone (Stravreva et al. 2009).



Endocrine Cell Function and Dysfunction, Fig. 3 Diagram of the stimulatory (arrows) and inhibitory (ball and stick) interactions responsible for the control of glucocorticoid (CORT) release. The effect of corticotrophin (ACTH) has a delay time τ reflecting the time required to synthesize CORT

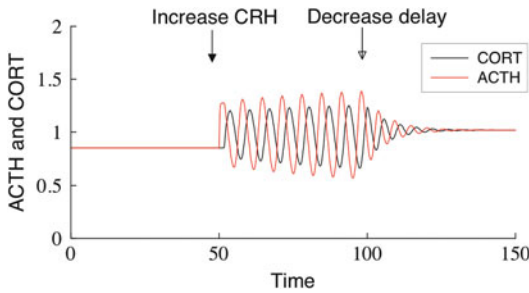
The network of interactions controlling the release of glucocorticoids is illustrated in Fig. 3. Time of day information is provided by the supra-chiasmatic nucleus (SCN) of the hypothalamus, and information on cognitive and physical stressors is provided by the central nervous system (CNS). A set of neurons in the paraventricular nucleus (PVN) of the hypothalamus receives and integrates this information and then releases the neurohormone corticotropin-releasing hormone (CRH) into portal blood vessels that project to cells of the anterior pituitary gland. Corticotroph cells are stimulated by CRH and in response release corticotropin (ACTH) into the general circulation. This hormone acts on cells of the adrenal cortex to produce and release glucocorticoids (CORT). Because CORT is not stored, but is synthesized only in response to ACTH, there is a time delay between ACTH stimulation and CORT release. Once released, the CORT feeds back onto and inhibits both the CRH-releasing neurons in the hypothalamus and the ACTH-releasing corticotrophs in the pituitary gland.

Computer simulations with a mathematical model demonstrated that the ultradian rhythm in CORT can be produced by the mutual interactions of corticotrophs with adrenal cells (Walker et al. 2010). That is, the rhythm can be generated even with a constant input from the hypothalamus, as long as the strength of that input is in the right range and the time delay is long enough. To demonstrate this, they used a mean-field model with three variables: a = ACTH concentration, r = glucocorticoid receptor availability in the corticotrophs, and c = corticosterone. The variables change in time according to the differential equations

$$\begin{aligned}\frac{da}{dt} &= \frac{p_1}{1 + p_2rc} - p_3a \\ \frac{dr}{dt} &= \frac{(cr)^2}{p_4 + (cr)^2} + p_5 - p_6r \\ \frac{dc}{dt} &= a(t - \tau) - c\end{aligned}$$

where the p_j are parameters. The first equation includes the negative feedback of CORT onto ACTH release (c in the denominator of the first term). The second equation includes the positive influence of CORT on glucocorticoid receptors; the receptor number increases when CORT levels increase. The third equation includes the positive influence of ACTH on CORT synthesis and release. This has an explicit time delay of τ time units, representing the time required for the synthesis of CORT following the receipt of ACTH by the adrenal gland. These equations were constructed in dimensionless form.

Figure 4 shows the results of computer simulations with this model, with parameters chosen as in Walker et al. (2010). In these simulations the CRH level is fixed and is represented by the parameter p_1 . This is initially set at a low value of 10 and no oscillations are produced. Then, at the closed arrow, the CRH drive is increased to 15. This initiates oscillations in CORT (black), as well as oscillations in ACTH (red) that are phase shifted with the CORT oscillations. When the time delay is later decreased from 1.5 to 1 time units (open arrow), the oscillations die out and the system



Endocrine Cell Function and Dysfunction,

Fig. 4 Oscillations in CORT and ACTH due to the delayed positive feedback of ACTH onto CORT production. These oscillations require sufficient drive from the hypothalamus (*closed arrow*) and they die away if the time delay is too short (*open arrow*). All variables are dimensionless

approaches a steady state. Thus, this simple model elegantly demonstrates several important predictions: (1) ultradian oscillations can be generated even if the output from the hypothalamus is held constant at a sufficiently high level, (2) the ACTH oscillations will be phase shifted relative to the CORT oscillations, and (3) oscillations only occur if the time lag between ACTH release and CORT synthesis and release is sufficiently large.

The essential ingredient for rhythm generation in this model is the delayed positive feedback of one component onto its inhibitor. Another model in which this occurs describes a semicircadian rhythm in the secretion of prolactin from pituitary lactotrophs (Bertram et al. 2006). This rhythm occurs during the first half of pregnancy in the rat and, according to the mathematical model, is produced by the delayed positive feedback of prolactin onto the dopamine-secreting neurons of the hypothalamic arcuate nucleus. The dopamine is synthesized in response to prolactin activation with a time delay. Once released into the portal blood vessels connecting the hypothalamus to the pituitary, dopamine acts on lactotrophs and inhibits prolactin secretion, just as CORT inhibits ACTH secretion from corticotrophs.

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Enhancement

► [Short-Term Synaptic Plasticity in Central Pattern Generators](#)

Ensemble Density Model

► Population Density Model

Entrainment

► Somatosensory Neurons: Spike-Timing

Envelope-Following Response (EFR)

► Auditory Frequency-Following Responses

Environmental Sound Perception: Effects of Aging and Hearing Loss

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Definition

Environmental sounds comprise a broad and heterogeneous class of acoustic signals which convey meaningful information about objects and events in the listener's surroundings. Environmental sounds are usually distinguished from speech, music, and parametrically generated sounds used in psychoacoustic experiments or clinical tests. Research interest in environmental sound perception in the context of aging and hearing loss is motivated by their importance for individual safety and quality of life as well as their relevance to fundamental questions in perception, cognition, and neurophysiological processing of objects and events in everyday environments. Although environmental sound perception generally remains robust as people age, it is negatively

affected by hearing loss, masking, and complexity of perceptual tasks. Deficits in environmental sound perception may negatively impact listeners' well-being and exacerbate a decline in cognitive abilities and social interactions, potentially leading to further cognitive and neurological deterioration. A better understanding of mechanisms and processes involved in environmental sound perception can inform the development of rehabilitative strategies for older adults with hearing loss, which may also delay age-related cognitive decline.

Detailed Description

Environmental Sound Perception

Environmental sounds are an integral part of most acoustically rich everyday environments, often referred to as auditory scenes (Bregman 1990) or soundscapes (Truax 2001). They provide the listener with information about objects and events in their surroundings. In the course of everyday life, environmental sound perception mostly occurs below the threshold of awareness. However, specific sounds can quickly become the focus of one's attention, alerting listeners to important changes in one's surroundings (Truax 2001; Jenkins 1985). Accurate identification of environmental sounds plays an important role in the listener's safety. Furthermore, environmental sounds can elicit emotional responses (Picou 2016; Husain et al. 2014) and are known to contribute to the overall sense of well-being and connection with one's surroundings (Ramsdell 1978; McRackan et al. 2019; Dixon et al. 2020). Successful environmental sound perception, however, involves two inter-related fundamental problems: (a) parsing complex acoustic signals from auditory scenes into spectral and temporal components which reflect the behavior of multiple distinct sound sources and (b) identifying discrete sound sources with their semantic characteristics and physical properties.

Despite their ubiquity, much less is known about perception and cognition of environmental sounds than about other classes of meaningful sound such as speech and music, or acoustic

stimuli used in psychoacoustic research, which tend to focus on narrowly defined stimulus characteristics. Whereas parametrically generated stimuli used in psychoacoustic research rarely reference specific real world sound sources, environmental sounds tend to convey meaningful information about distal objects and events. Acoustic signals of environmental sounds are acoustic byproducts of mechanical interactions of sound-producing objects (e.g., moving vehicles, tools, animal or human vocalizations, and bodily sounds), or learned arbitrary associations between a particular sound and its meaning (e.g., computer auditory icons, signaling sounds and alarms). In everyday listening environments, individual environmental sounds are typically embedded within auditory scenes, with multiple sequential or simultaneously occurring sound sources. Such arrangements in turn tend to reflect probabilistic contingencies among objects and events that characterize specific environments (e.g., construction sites, intersections, hospitals, schools).

Phylogenetically, environmental sound perception precedes that of speech and music, and differs from these two major sound classes in several important respects. Unlike speech, environmental sounds do not transmit linguistic information following a set of language-specific rules. They are also distinct from traditional music compositions that are primarily structured to convey affective and aesthetic intent. In contrast, when listeners are presented with naturally occurring sounds, they tend to perceive them in terms of underlying sound sources and refer to more abstract auditory qualities only when sound sources cannot be readily identified (Gaver 1993; Ballas 1993; Gregg and Samuel 2009; Marcell et al. 2007; Gygi et al. 2007; Guastavino 2007).

Previous research indicates that healthy adults with normal hearing are able to accurately identify a vast variety of common environmental sounds, often revealing remarkably accurate perception of intricate sound source properties based on sound alone. These include judgments of object size (Carello et al. 1998), and behavior over time, such as anticipating the timing of the next bounce

of a ball after hearing preceding bounces (Gygi et al. 2015). Listeners can similarly identify sex and posture of a walker by the sound of his/her footsteps (Li et al. 1991; Pastore et al. 2008), estimate the fullness of a vessel from the sound of water pouring into it (Cabe and Pittenger 2000), or judge the configuration of two hands from the sounds of clapping (Repp 1987).

In addition to providing instantaneous detailed information about sound sources around the listener, including those outside one's field of vision, environmental sounds can also contribute to non-auditory aspects of perceptual experience and actions. For example, listener's judgments of the crunchiness of potato chips appear to be affected by the chewing sounds, while the enjoyment of a beverage can be affected by the sound of opening its container (Spence and Wang 2015). Environmental sounds also play a role in guiding human actions by providing information about distance and reachability of unseen moving objects through sound alone (Rosenblum et al. 1996; Neuhoﬀ 2004) or through interactions of hearing with other sensory modalities (Ecker and Heller 2005; Castiello et al. 2010; Hauck and Hecht 2019; Roudaia et al. 2013). The walking patterns of healthy adults and Parkinson's patients are affected by the sounds of footsteps they hear (Turchet et al. 2015; Young et al. 2014).

Perceptual organization of environmental sounds appears to be based on the characteristics of their underlying sources or learned arbitrary referents. Multidimensional scaling solutions derived from similarity comparisons of the names of environmental sounds, and separately, from corresponding sounds revealed a similar grouping (Gygi et al. 2007; Lemaitre et al. 2018a). Importantly, the neurophysiological processing of environmental sounds' semantic characteristics appears to be an automatic process, which is engaged even when listeners are not explicitly instructed to attend to environmental sounds' meanings (Orgs et al. 2008).

Existing evidence indicates considerable overlap in the topology of neurophysiological processing involved in the perception of speech and environmental sounds, as well as some degree of dissociation (Dick et al. 2016; Noppeney et al.

2008; Thierry et al. 2003; Humphries et al. 2001; Van Petten and Rheinfielder 1995; Saygin et al. 2010; Tomasino et al. 2015). For instance, activation elicited by hand-manipulated tool sounds differed topographically from activation elicited by animal vocalization (Lewis et al. 2005). The encoding of abstract category properties of sounds of living and human-action sounds appear to be distinct from the neural processing of other non-speech sounds (Giordano et al. 2013). Although some findings support the notion of a dual processing route for the processing of speech and meaningful nonspeech sounds (Thierry et al. 2003; Norman-Haignere et al. 2015), similarities in the neural processing of higher-order conceptual information have also been reported (Schirmer et al. 2011).

Several attempts have been made to construct a comprehensive ecologically based taxonomy of environmental sounds (Gaver 1993; Jenkins 1985) and place environmental sound listening within a larger acoustic communication framework (Truax 2001). To date, however, no single taxonomy has been able to fully capture the complexity of environmental sounds as a class, largely due to their extreme physical heterogeneity and perceptual multidimensionality. Nevertheless, some valuable classifications have emerged. Specifically, a productive distinction has been made between perception of actions and events, on the one hand, and objects and materials, on the other (Warren and Verbrugge 1984; Gaver 1993; Lemaitre and Heller 2012). This basic distinction appears to be supported by both behavioral and neurophysiological findings indicating that perception of actions (e.g., knocking) is more immediate and involves more localized neurophysiological processing, than perception of materials (Lemaitre and Heller 2013; Lemaitre et al. 2018b).

Effects of Aging and Hearing Loss

Aging is a complex systemic process associated with multiple anatomic-physiological, behavioral, psychological, and social changes. In the auditory system, aging affects both peripheral encoding of sensory input and more central information processing (Cardin 2016; Sheft et al. 2015; Humes

et al. 2012; Lin et al. 2011; Bao et al. 2020). One of the better known and extensively documented consequences of aging in the auditory system is presbycusis or age-related hearing loss. Presbycusis is typically associated with a progressive bilateral rise in audibility thresholds, especially in high frequencies, which sometimes precedes more severe sensorineural hearing loss or combines with other types of hearing impairments. In addition to reduced audibility, central effects of presbycusis include deficits in perception of spectral and temporal characteristics of acoustic signals at suprathreshold audibility levels (Humes et al. 2010; Sheft et al. 2012; Füllgrabe et al. 2015).

Changes in sensory processing associated with aging are further accompanied by a decline in auditory-specific and domain-general cognitive abilities involved in higher-level information processing (Lin et al. 2013). However, the rates of decline vary considerably across individuals and also across specific cognitive abilities (Park et al. 2001; Hartshorne and Germine 2015). A subset of cognitive abilities, referred to as fluid intelligence (e.g., working memory, problem-solving), tend to reach performance peak earlier in life and decline sooner than a subset of cognitive abilities, referred to as crystallized intelligence, relating to general world knowledge (e.g., vocabulary size). Although currently specific mechanisms responsible for age-related changes in auditory information processing are not fully understood, a number of contributing factors have been identified (Humes et al. 2010; Pronk et al. 2019; Humes and Young 2016; Pichora-Fuller et al. 2016).

Given the pervasiveness of aging-related changes, a number of effects have been observed for all categories of complex meaningful sounds, including environmental sounds (Aydelott et al. 2010). Generally, identification of isolated everyday familiar sounds presented in quiet appears to be well preserved in healthy older adults with normal hearing or mild hearing losses (Ballas and Barnes 1988; Harris et al. 2017; Shafiro et al. 2020). Differences in environmental sound perception between older and younger listeners become more pronounced when stimulus quality is degraded due to reverberation, signal

processing distortions, or masking by extraneous sounds (Dick et al. 2016; Gygi and Shafiro 2013). Similarly, performance of older listeners is also more negatively affected than that of young adults when task complexity is increased, resulting in a greater cognitive load and leading to more effortful listening (e.g., attending to several sounds or performing more than one task).

When identifying environmental sounds in naturalistic auditory scenes, some of the acoustic cues used to identify individual sounds may become inaccessible due to energetic masking by other sounds in the scene. In addition, semantic characteristics of other sounds in the scene may also influence identification of target sounds (Ballas and Mullins 1991; Leech et al. 2009). The effect of scene context was investigated by Gygi and Shafiro (2013) who asked listeners to identify individual environmental sounds embedded in naturalistic auditory scenes which were either semantically congruent with the target sound or semantically incongruent with it (e.g., a horse galloping at a race track scene vs. in a restaurant scene). An effect of semantic congruence was observed for both younger and older adults. For both listener groups, the direction of the context effect, facilitatory or inhibitory, was mediated by the signal-to-noise (SNR) ratio. At high SNR ratios identification was higher for sounds incongruent with the scene, while the reverse was observed for lower SNRs where greater overall accuracy was observed for sounds which were semantically congruent with the scene. However, younger and older adults differed in overall performance accuracy. Older adults demonstrated significantly lower overall identification accuracy regardless of semantic congruency. This difference in performance appeared to be largely due to reduced audibility of high frequencies, which is typical of presbycusis. When a new group of young adults was presented with the same stimuli lowpass filtered at 4 kHz, the performance of young adults was similar to that of older listeners.

Limitations in the quality and quantity of sensory input in older adults with hearing loss can further exacerbate difficulties in environmental sound perception. Shafiro and colleagues

(2016) presented listeners of different age and hearing status with sequences of five familiar environmental sounds and asked to identify each sound and arrange the sounds in the order they were presented. In half of the sequences, the sounds were semantically coherent (e.g., snoring, rooster, alarm clock, yawn, bird chirping), while in the other half of the sequences individual sounds lacked any apparent semantic coherence. The overall benefit of coherent semantic context was observed regardless of age and hearing status, with no differences in the ability to identify individual sounds which were part of the sequences. Performance differences emerged, however, when correct presentation order was taken into account, possibly because this component of the task requires greater working memory involvement. Young adults outperformed both older normal hearing listeners and listeners with mild-to-moderate hearing loss, with the latter two groups performing at a similar accuracy levels. When the test was given to listeners with cochlear implants (CIs), devices that provide direct electrical stimulation of the auditory nerve bypassing typical peripheral auditory processing, further differences were observed. Although CI listeners' performance on coherent sequences was comparable to that of older normal hearing and hearing impaired groups, they demonstrated particular difficulties with incoherent semantic sequences, suggesting that CI listeners may be even more reliant on contextual cues when identifying environmental sounds.

Indeed, previous research has consistently demonstrated that for CI listeners environmental sound identification accuracy is substantially reduced, even when sounds are presented one at a time in quiet under the ideal listening conditions (Reed and Delhorne 2005; Inverso and Limb 2010; Looi and Arnephy 2010; Shafiro et al. 2011; Lee and Kim 2011). This has been found in children who were implanted early in life (Liu et al. 2013) and also in postlingually implanted adults who have received their implants postlingually, after developing aural language communication abilities (Harris et al. 2017). Recent research further indicates that in postlingually implanted adults, environmental sound

identification, on average, does not appear to exceed that of hearing impaired adults who are cochlear implant candidates, even as the average speech perception accuracy improves following implantation (McMahon et al. 2018; Harris et al. 2019). Possibly, unlike speech perception which can remain robust with primarily envelope cues (Shannon et al. 1995), accurate identification of many environmental sounds relies to a much greater extent on dynamic spectral changes and temporal fine structure of the corresponding acoustic signals. Nevertheless, positive changes in environmental sound identification could still be achieved following training (Shafiro et al. 2015).

Recent findings with a free sorting task in which CI listeners were asked to group a number of sounds based on any criteria they choose, revealed gradual changes in perceptual organization of environmental sounds following implantation (Strelnikov et al. 2018). Whereas the initial post-implantation grouping reflected CI listeners' reliance on sounds' acoustic characteristics, over time, their grouping of sounds began to reflect sounds' semantic categories, suggesting more general reorganization in mapping sounds to their meanings.

Reduced hearing abilities in older adults can also exacerbate existing cognitive deficits. Coebergh et al. (2020) tested environmental sound perception in older adults with mild Alzheimer's disease. Participants with greater agnosia for environmental sounds had higher pure-tone thresholds, even though their average audibility threshold remained within normal limits. Furthermore, mild-to-moderate hearing loss has been shown to be a significant factor in reducing listener ratings of emotional valence of environmental sounds (Picou 2016). This finding corroborated earlier reports of systematic differences in the distribution of brain activity patterns in normal hearing and hearing impaired listeners, following exposure to environmental sounds with varying emotional valence (Husain et al. 2014). It is conceivable that reduction in the range of emotional responses to objects and events in one's surroundings, mediated by hearing loss, can have a negative effect on individual sense wellbeing.

As research interest in environmental sound perception has continuously grown over the last several decades, there is an increased awareness of the practical and theoretical importance of environmental sounds and of the limitations in our current knowledge. While many aspects of environmental sound perception remain robust in older listeners, a number of age and hearing loss related deficits may contribute to increasing psycho-social difficulties encountered by older adults with hearing loss, with implications for individual safety and quality of life (Hamel et al. 2020; Bliss 2000; Dixon et al. 2020). Within the patchwork of subjective experiences of one's daily life, much remains unknown about contributions of environmental sounds to the person's movements and interactions across modalities including touch, taste, vision. A better understanding of the role environmental sounds play in the perception of objects and events in one's surroundings can be instrumental in the advancement of general models of meaningful sound processing. It can also contribute to the development of effective diagnostic tests and rehabilitative strategies for prevention and treatment of hearing loss and age-related cognitive changes.

Cross-References

- ▶ [Acoustic Timbre Recognition](#)
- ▶ [Auditory Memory](#)
- ▶ [Auditory Perceptual Organization](#)
- ▶ [Auditory Prosthesis](#)
- ▶ [Masking and Masking Release](#)
- ▶ [Music Processing in the Brain](#)
- ▶ [Neural Coding of Speech Sounds](#)
- ▶ [Peripheral Nerve Interface Applications, Cochlear Implants](#)

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Enzyme Kinetics, Modeling of

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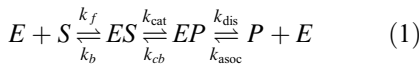
Definition

Mathematical formulation of the rates of chemical reactions that are catalyzed by enzymes, which are molecules that are regenerated as part of the chemical reaction.

Detailed Description

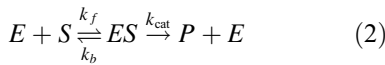
Models of reaction–diffusion systems consist of bimolecular reactions, enzyme reactions, and diffusion. An enzyme is a molecule that facilitates a reaction or transformation of a substrate molecule into a different molecule(s), known as the product. For example, ATP can be transformed into cAMP + PPi spontaneously at an extremely low rate; adenylyl cyclase is an enzyme that greatly facilitates the transformation. The theory behind enzyme reactions is that a large energy barrier prevents a reaction from occurring spontaneously, and the enzyme lowers the energy barrier.

Enzyme reactions are modeled as a series of elementary reactions. First, the enzyme (*E*) and substrate (*S*) bind to each other to form the enzyme-substrate complex (*ES*). Second, the substrate is transformed into the products. Third, the product(s) dissociates from the enzyme:



If two products are created by the enzyme, then they may or may not dissociate in a particular order. For example, during conversion of ATP into cAMP, PPI is more likely to dissociate from adenylyl cyclase after the cAMP (Dessauer and Gilman 1997). In principle enzyme reactions are reversible, though the backward rate is typically extremely low.

Because the rate of catalysis is measured by observing formation of the product, most models of enzyme activity condense the catalytic step and product dissociation into a single, nonreversible step:



In the following treatment, we assume that the mass action approximation is valid. This implies that the number of molecules is great enough to be represented as a continuous valued concentration. Deriving the mathematical equations for an enzyme reaction, or indeed for any system of equations, involves (1) writing an equation for the time-dependent concentration of each molecule in the system and (2) including terms describing rates of production (with a positive sign) and rates of consumption (with a negative sign). These rates are calculated from the concentration of the reactants multiplied by the rate constant. For reaction Scheme 1, this approach produces a system of five ordinary differential equations (ODEs). The simpler system of four ODEs for the system of two enzyme reactions (Scheme 2) is

$$\begin{aligned} \frac{d[S]}{dt} &= -k_f[E] \cdot [S] + k_b[ES] \\ \frac{d[E]}{dt} &= -k_f[E] \cdot [S] + k_b[ES] + k_{cat}[ES] \\ \frac{d[ES]}{dt} &= k_f[E] \cdot [S] - k_b[ES] - k_{cat}[ES] \\ \frac{d[P]}{dt} &= k_{cat}[ES] \end{aligned} \quad (3)$$

where the square brackets $[]$ indicate the concentration of the molecule. Note that though the

catalysis was assumed irreversible, adding in a reverse catalysis term is straightforward. Solving this system of equations requires initial conditions, i.e., the quantity of enzyme, E_0 , and substrate, S_0 . In a closed system, where conservation of mass holds, the system may be simplified using conservation equations. Namely, using $[E(t)] + [ES(t)] = [E_0]$ and $[P(t)] + [S(t)] + [ES(t)] = [S_0]$, the four ODE system can be simplified to a two-ODE system:

$$\begin{aligned} \frac{d[S]}{dt} &= -k_f(E_0 - [ES]) \cdot [S] + k_b[ES] \\ \frac{d[ES]}{dt} &= k_f(E_0 - [ES]) \cdot [S] - k_b[ES] - k_{cat}[ES] \\ [P] &= [S_0] - [ES] - [S] \end{aligned} \quad (4)$$

Under certain conditions, this set of reactions can be simplified still further. The first assumption, which has already been incorporated into the system of ODEs, is that the catalysis step is irreversible. Michaelis and Menten further made the assumption that the substrate, which concentration greatly exceeds the enzyme, is in equilibrium with the ES complex; thus there is no change in the substrate concentration ($dS/dt = 0$). This results in the following equation:

$$\frac{d[P]}{dt} = \frac{k_{cat}[E_0][S]}{[S] + K_D}, \quad \text{where } K_D = \frac{k_b}{k_f} \quad (5)$$

Briggs and Haldane made a slightly different assumption called the quasi-steady-state approximation. They assumed that after initiation of the reaction, the enzyme-substrate complex is in equilibrium: $dES/dt = 0$.

$$\begin{aligned} \frac{d[P]}{dt} &= \frac{k_{cat}[E_0][S]}{[S] + K_M}, \quad \text{where } K_M \\ &= \frac{k_b + k_{cat}}{k_f} \end{aligned} \quad (6)$$

The latter is called the Michaelis-Menten equation. This is generally valid when the initial substrate concentration is much greater than the initial enzyme concentration. Also, the enzyme concentration cannot vary rapidly; else the assumption of

$d[ES]/dt = 0$ is violated. See Chen et al. (2010) for further treatment of the conditions when this is valid.

Especially when modeling signaling pathways, i.e., cascades of bimolecular and enzyme reactions, these assumptions are often violated. Since the product of one reaction is the enzyme for the next reaction, the enzyme concentration is not constant, but varies in time. Also, in some situations substrate is quite small (Ciliberto et al. 2007) or is depleted, as occurs with phospholipase C producing inositol triphosphate from the minor membrane phospholipid phosphoinositol bisphosphate (Brown et al. 2008).

In some cases it is necessary to model the effects of enzyme inhibition. There are several types of inhibition: both reversible and irreversible and both competitive (binding to the same site as the substrate) and allosteric (binding to a different site). With competitive inhibition, the enzyme can function if the substrate concentration is sufficiently high. This can be modeled with an additional reaction, where k_{bi}/k_{fi} is the affinity of the inhibitor for the enzyme (Stenesh 1992):

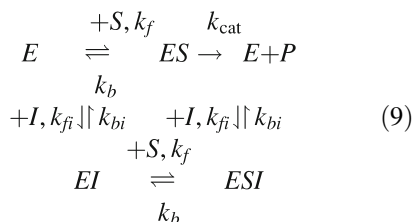


When modeling enzyme inhibition, this reaction can be included as additional two ODEs to the system of Eq. 3, or under some conditions simplified equations can be written. For example, if the enzyme cannot bind inhibitor and substrate simultaneously, the enzyme inhibitor complex undergoes no further reaction, and the inhibitor concentration is large and remains relatively constant, then an equation similar to the Michaelis-Menten equation results:

$$\begin{aligned} \frac{d[P]}{dt} &= \frac{k_{cat}[E_0][S]}{[S] + K_n \left(1 + \frac{1}{K_I}\right)}, \quad \text{where } K_M \\ &= \frac{k_b + k_{cat}}{k_f}, \quad \text{and } K_I = \frac{k_{bi}}{k_{fi}} \end{aligned} \quad (8)$$

This equation implies that a competitive inhibitor effectively increases K_M (decreases affinity of enzyme for substrate).

Allosteric inhibitors bind at a site different from the substrate-binding site, thus both the inhibitor and the substrate can bind to the enzyme simultaneously. If either S or I can bind first, the following reaction scheme occurs:



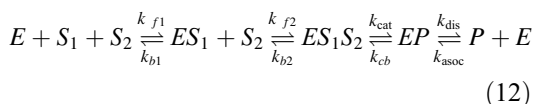
The ESI complex can have catalytic activity; however, if it does not, then again with simplifying assumptions a single equation can describe the effect of inhibition on product formation:

$$\frac{d[P]}{dt} = \frac{k_{cat}[E_0][S]}{([S] + K_n) \left(1 + \frac{I}{K_I}\right)} \quad (10)$$

where K_I and K_M are as defined in Eq. 8. This is known as noncompetitive inhibition (Stenesh 1992). If the inhibitor will bind only to the ES complex, then uncompetitive inhibition results:

$$\begin{aligned} \frac{d[P]}{dt} &= \frac{k_{cat}[E_0][S]}{K_n + [S] \left(1 + \frac{I}{K_I}\right)}, \quad \text{where } K_I \\ &= \frac{k_{bi}}{k_{fi}} \end{aligned} \quad (11)$$

All of the above assume that the enzyme requires only a single substrate. In some cases the enzyme may require two (or more) substrates or two molecules of the same species (<http://www.chem.qmul.ac.uk/iubmb/kinetics/ek1t3.html>):



In fact, all phosphorylation reactions require two substrates – the molecule to be phosphorylated and the ATP or GTP donating the phosphate

group. A system of ODEs describing this reaction can be written using the procedure described above. Alternatively, if one of the molecules is rate limiting, e.g., the reaction speed is limited by the concentration and/or binding rate of one of the substrates (known as the rate-limiting substrate), and the other substrate is in excess and/or binds rapidly, then it is often not included in the system of ODEs.

When modeling enzyme reactions involving low numbers of molecules, as occur in small structures such as dendritic spines, then a stochastic approach is often applied. Under these conditions, the assumptions used to simplify the equations often are not valid (Tzafriri and Edelman 2005; MacNamara et al. 2008). Instead of writing equations describing the change in concentration, the reaction master equation is a set of equations describing the probability of change in molecule number:

$$\frac{\partial P(x, t|x_0, t_0)}{\partial t} = \sum_{j=1}^R [a_j(x - v_j) \cdot P(x - v_j, t|x_0, t_0) - a_j(x) \cdot P(x, t|x_0, t_0)] \quad (13)$$

where $\mathbf{x}$ is a vector of molecule quantities and $a_j(\mathbf{x}) dt$ is the propensity of reaction j during the infinitesimal time interval dt (e.g., $a_j(\mathbf{x}) = k_j x_1 dt$ for a unimolecular reaction involving species S_1 and $k_j x_1 x_2 dt$ for a bimolecular reaction involving species S_1 and S_2). The stoichiometry matrix, $\mathbf{v}$, specifies the change in population i when the j th reaction occurs. This formulation includes both enzyme reactions and bimolecular reactions. This equation cannot be solved except for trivial systems, but Monte Carlo techniques are typically applied to generate trajectories (valid solutions).

Cross-References

- [Bimolecular Reactions, Modeling of](#)
- [Diffusion Equation](#)
- [Stochastic Simulators](#)

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Epidural Spinal Cord Stimulation

► [Epidural Stimulation](#)

Epidural Stimulation

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Synonyms

[Epidural spinal cord stimulation](#); [Epidural stimulation of the spinal cord](#); [Spinal electrical stimulation](#)

Definition

Epidural stimulation is the mode of electrical activation of neuronal structures by electrodes implanted in the epidural space. Theoretically, epidural electrodes can be placed anywhere overlying the dural mater of the nervous system, but they typically have been placed over the spinal cord or overlying the cortical region of the brain. Clinical application of epidural stimulation is connected with pain control, treatment of spasticity, and regulation of motor functions after neurological disorders. Another newly developed application of epidural stimulation is to facilitate improved sensory-motor function after paralysis as a result of spinal cord injury. A third application of epidural stimulation that is emerging is its use as a chronically implanted device to be used for a neurophysiological assessment of functional connectivity along specific descending and ascending sensory and motor tracts. This can be particularly useful in assessing the severity and location of neural injuries.

Detailed Description

Analgesic Effect Induced by Epidural Stimulation

Although the mechanisms of analgesic action of epidural stimulation of the spinal cord are unknown, one hypothesis is that selected frequencies and strengths of stimulation can obtain an analgesic effect by releasing neurotransmitters (GABA, glutamate, serotonin), and potentially suppressing the hyperexcitability of spinal neurons (Oakley and Prager 2002). Another hypothesis is that the chronic levels of some stimulation parameters can directly impose an analgesic effect biophysically by changing the electrical conductivity of axonal and dendritic projections of neurons (Guan et al. 2010).

Spinal Structures Activated by Epidural Stimulation

It has been known for several decades that stimulation of the spinal cord with electrodes placed

epidurally over selected spinal segments can be used to stimulate spinal networks. There has been a significant effort and some success in modeling current penetration within the spinal cord. Ideally, we need to know how a given intensity, frequency, pulse waveform of the stimulation, given the physical characteristics of the electrode and the conductivity characteristics of the multiple types of tissues (e.g., skin, subcutaneous fat, bone, the dura mater cerebrospinal fluid, vasculature), generates a given effect on specific *neural* structures. Based on computer modeling data it has been suggested that the order of excitation of spinal elements during epidural stimulation applied to posterior surface of the spinal cord is the following. First, the large myelinated fibers entering through the dorsal roots will be activated, then myelinated fibers of dorsal columns (Coburn 1985; Holsheimer 2002, Finite Element Modeling for Extracellular Stimulation elsewhere in this Encyclopedia).

Pain Control by Epidural Stimulation

The most experience with epidural stimulation of the spinal cord, by far, has been its use in efforts to suppress chronic pain (Shealy et al. 1967; Barolat 2000). The mechanism for pain suppression remains poorly understood except to say that it generates some level of anesthesia of the underlying neural structures and perhaps to areas where these neural structures may project. According to the gate theory the electrical spinal cord stimulation activating the large afferent fibers in dorsal roots close the “gate” eliminating painful inputs to the spinal cord (Melzack and Wall 1965).

Thousands of stimulators and electrode arrays are chronically implanted annually in subjects with spinal cord injury as well as for other pain disorders. As a medical intervention strategy for treating pain these implants have proven to have varying degrees of success, some being extremely successful others being ineffective. In terms of safety and durability these chronic implant procedures have been proven to be relatively routine, safe and functional for years.

Neuromodulation of Locomotor Behavior by Epidural Stimulation

Epidural electrodes placed on the spinal cord was proven to be effective in inducing locomotion in decerebrated animals more than two decades ago (Iwahara et al. 1991). In this preparation bipolar electrodes can be placed over cervical or lumbar segments to induce locomotor-like movements. More recently these epidural electrodes have also been used to neuromodulate the physiological state of different networks along the length of the spinal cord in a manner that enables rather than directly induces animals with complete paralysis to regain the ability to step in highly coordinated fashions (Gerasimenko et al. 2008). Following a complete transection of the spinal cord at the mid-thoracic level, with motor subthreshold or near threshold levels of epidural stimulation, the hind limbs of the rat can step forwards backwards or sideways and readily adjust to the speed of the treadmill belt (Courtine et al. 2009). To accomplish this, in essence, the epidural stimulation neuromodulates the properties of the spinal circuitry so that the spinal circuitry can interpret and subsequently execute the motor patterns necessary to accommodate the external mechanical conditions which is continuously monitored by a range of proprioceptors and cutaneous fibers. Again, which neural structures and how the specific structures are being neuromodulated at the cellular and network level are poorly understood. It is highly significant, however, that not only can this epidurally mediated neuromodulation facilitate standing and stepping in laboratory animals, but this same approach is proving to be highly successful in humans even with complete paralysis to regain independent standing and even some voluntary control of the lower limbs (Harkema et al. 2011).

This epidurally mediated neuromodulation is now being tested for a variety of other functions. For example, there is reason to think that neuromodulatory techniques as used to facilitate posture and locomotion could also be effective in modulation of the cervical spinal cord to improve upper limb function. Neuromodulatory interventions using epidural electrodes can be used also in conjunction with motor training to enhance rehabilitative procedures. Another valuable use of

epidurally implanted electrodes that is proving to be significant is its application as a neurophysiological tool for assessing in vivo the ability of the spinal circuitry to process the cutaneous and proprioceptive input to the spinal cord while the subject is performing a specific motor task (Shah et al. 2012).

Another application of chronically implanted epidural electrodes has been demonstrated by placing electrode arrays over the motor cortex. These type of implants can be used as an in vivo assessment tool for testing descending as well as ascending sensory-motor pathways when the subject is actually performing a motor task (Suner et al. 2005). And given the evidence that activity can be used to modulate the development of new neural supraspinal connections following a spinal or brain stem injury to the motor system, it has the potential for serving as a facilitator of enhancing supraspinal-spinal interconnections over a period of weeks.

Cross-References

► [Spinal Stimulation for Parkinson Treatment](#)

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Epidural Stimulation of the Spinal Cord

► Epidural Stimulation

Epilepsy, Neural Population Models of

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Definition

Epilepsy is a set of neurological disorders and syndromes characterized by recurrent seizures. Neural Population Models can serve as

biomathematical representation of an abnormal neuronal assembly by altering parameters to reproduce epileptiform activity. Typically, parameters related to excitatory or inhibitory synaptic transmission can be modified (with respect to physiological values) to generate events that match those actually observed in local field potentials or in the EEG during ictal (seizures) or interictal (outside seizures) periods.

Detailed Description

Epilepsy is a pathological condition in which the nature of the interactions between neurons and the properties of neurons themselves are altered. These alterations lead to the development of epileptogenic networks in the brain over which transitions from normal to epileptic activity can spontaneously occur. Epileptogenic networks consists in extended networks of neurons characterized by abnormal synchronization properties (as revealed by synchrony measures performed on intra- and/or extra-cellular signals) (Jiruska et al. 2013) and by hyperexcitability (as revealed by excessive firing) (Babb et al. 1984).

Neural population models (NPMs) have intrinsic properties that are particularly suited in the context of epilepsy. First, and conversely to detailed approaches, NPMs are not based on the explicit representation of each single neuron. They assume that neurons in a given brain area are organized as a population, itself composed of interconnected sub-populations (for instance, pyramidal cells and interneurons in the cortex). Ensemble dynamics are rising from average synaptic interactions between interconnected sub-populations. Therefore, within a sub-population high synchronization between neurons is implicitly assumed. This high synchronization, also referred to as hyper-synchronization, is often encountered during epileptic activity. Second, excitability conditions can be easily modified in NPMs (through the average amplitude of post-synaptic potentials or through the average number of synaptic contacts between sub-populations) allowing for the simulation of hyperexcitable systems. Finally, individual NPMs can be easily coupled (Wendling et al. 2000) to form for

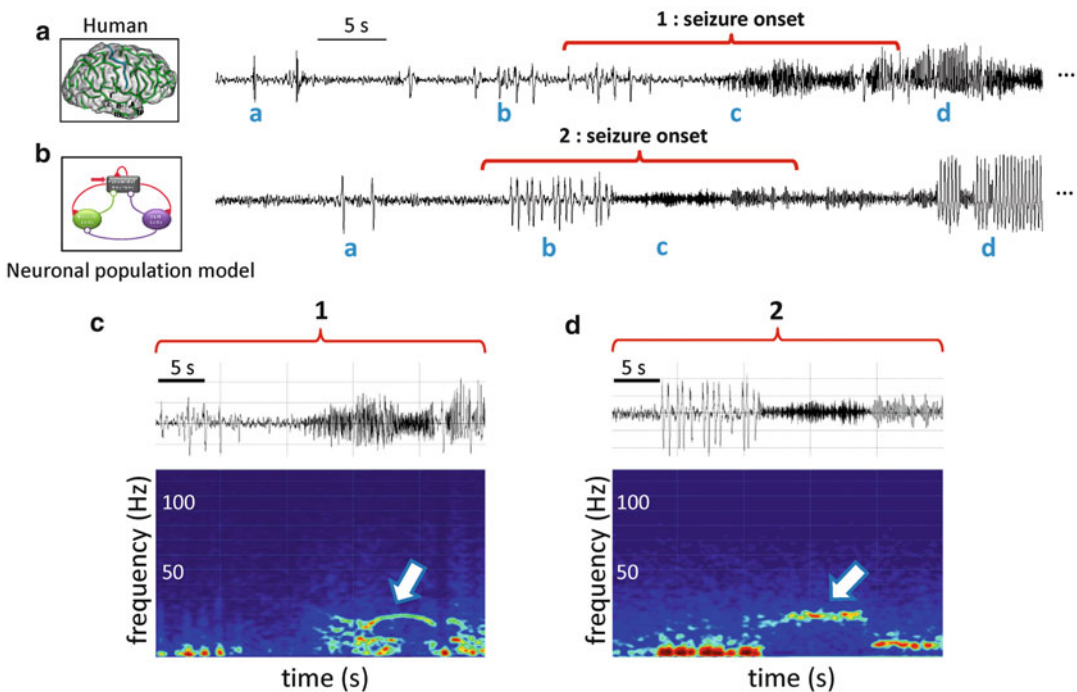
large-scale epileptic systems as those encountered in partial epilepsies (see for instance (Bartolomei et al. 2001) for temporal lobe seizures) or in generalized epilepsies (see for instance (Robinson et al. 2002) for absence seizures).

NPMs in Partial and Generalized Epilepsies

The two sections that follow are intended to provide examples of insights gained from NPMs in the context of partial and generalized epilepsies. Readers may refer to (Suffczynski et al. 2006b; Lytton 2008; Soltesz and Staley 2008) for more detailed description of neuronal population models as used in the context of epilepsy.

In partial epilepsies, these models were also used to investigate the interictal to ictal transition. Wendling and co-workers showed how a generic neuronal population model can be modified (i) to better approach the specific cytoarchitecture of brain structures like the hippocampus (Wendling et al. 2002), the enthorhinal cortex (Labyt et al. 2006) or the neocortex (Molae-Ardekani et al. 2010) and (ii) to reproduce electrophysiological patterns recorded in these structures during the transition to seizure.

An example is provided in Fig. 1 in the context of mesial temporal lobe epilepsy (MTLE). As illustrated (Fig. 1a), the transition from interictal to ictal activity is characterized by first the emergence of sporadic spikes (a), and then by a rhythmic spiking activity (b) followed by a fast activity (c) which is generally considered as the onset of



Epilepsy, Neural Population Models of, Fig. 1 Epilepsy, Neural Population Models of (a) Depth-EEG signal recorded from hippocampus in a patient with temporal lobe epilepsy (TLE) during the interictal to ictal transition. (b) LFP simulated with the neuronal population model described in (Wendling et al. 2005) when one inhibition-related parameter is gradually decreased as a function of time. Lower case letters indicate the type of

dynamics observed in LFPs: sporadic spikes (a), rhythmic spikes (b), fast activity (c), and, ictal activity (d). (c, d) Time-frequency representations (spectrograms) focusing on the typical fast activity occurring at the onset of the seizure. In both real and simulated signals, a narrow band signal (arrow) in the low gamma frequency band is generated (See text for details)

the seizure. This fast onset activity is typically in the beta or low gamma EEG frequency band (15–40 Hz) and gradually slows down in the frequency domain. It usually indicates a transition to an ictal narrowband highly-rhythmic high-amplitude activity (mostly within the EEG theta band, 5–10 Hz) (d). This typical electrophysiological pattern was investigated using NPMs (Wendling et al. 2005). As illustrated (Fig. 1b), the gradual decrease of the synaptic gain in the inhibitory loop leads the NPM to generate a typical sequence of activities reflected in real depth-EEG signal during the transition to seizure: normal background activity, sporadic spikes (a), rhythmic spikes (b), fast activity (c), ictal activity (d). The visual inspection of simulated signals shows that real waves are quite accurately reproduced by the model. Overall, insights were gained about excitability changes during transition to seizures MTL: the conjunction of increased excitation with gradual disinhibition leads to ictal activity in the proposed NPM of the hippocampal circuit. In addition, as this NPM includes two subsets of inhibitory interneurons (targeting dendritic and somatic receptors of pyramidal cells), observed dynamics and transitions could be explained. In particular, the fast seizure onset activity could be related to the fast feedback inhibitory loop present in the NPM. Experimental validation was brought afterwards (Gnatkovsky et al. 2008).

In the context of generalized epilepsies, NPM-based representations of the thalamo-cortical system were also proposed (Suffczynski et al. 2001, 2006a; Breakspear et al. 2006; Roberts and Robinson 2008). Models were designed accounting for interactions between neocortical and thalamic circuits. Mechanisms of transition between background EEG activity and rhythmic spike-wave discharges were investigated (Marten et al. 2009) and model predictions were compared with results obtained in different experimental models of absence epilepsy or in human (Crunelli et al. 2011). In particular, Lopes da Silva and co-workers obtained mechanistic insights regarding the generation of spike and wave discharges (SWs), as observed in absence seizures (Suffczynski et al. 2004). These results were

obtained through model simulations and system analysis. Authors found that SWs appear and stop spontaneously without any change of model parameters. Bifurcation analysis showed that the thalamo-cortical network exhibits bistable dynamics and attractor changes depend on the noise present in the network. As the distributions of ictal and seizure free epoch durations are exponential, authors concluded that transitions between the two stable states (background, ictal) occur randomly over time. This model prediction was validated using experimental data from animal models of absence epilepsy. Finally, as the sudden onset of large paroxysmal activity is triggered by a stochastic process, the occurrence of this type of seizures is unpredictable per definition.

Cross-References

- [Bifurcations, Neural Population Models and](#)
- [Epilepsy: Abnormal Ion Channels](#)
- [Epilepsy: Computational Models](#)
- [Phase Transitions, Neural Population Models and](#)
- [Slow Oscillations and Epilepsy: Network Models](#)
- [Transfer Function, Electrocardiac](#)

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Epilepsy: Abnormal Ion Channels

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Synonyms

[Channelopathy](#); [Excitability defect](#); [Excitability disorder](#); [Ion channel mutation](#)

Definition

A major unit in computational multi-scale modeling in epilepsy is the ion channel. Ion channels can be represented in silico by discrete mathematical formulas describing their biophysical properties while detecting and responding to a stimulus. The stimulus causes the channel protein to undergo a series of three-dimensional conformation changes which opens or closes the channel which regulates ion flow through the transmembrane pore formed by alpha-helix polypeptide subunits.

Detailed Description

Ion Channel Function

Fundamentally, an ion channel acts as an energetically favorable pathway for small charged molecules (ions) to pass through the cell membrane (Hille 1984). Ion channels are integral transmembrane proteins that exist as oligogenic macromolecular complexes including a pore-forming alpha subunit and modulatory and accessory subunits (Sharman et al. 2013; Alexander et al. 2011). Functionally, an ion channel responds to a stimulus, which may be mechanical (e.g., stretch), chemical (e.g., a neurotransmitter), or electrical (e.g., change in transmembrane voltage). This causes the channel to open a selectively permeable low-resistance path

for charged ionic species, either anionic (chloride (Cl^-)) or cationic (calcium (Ca^{2+}), potassium (K^+), sodium (Na^+)), or both (e.g., Ih). The ions pass from one side of the lipid bilayer to the other, down their electrochemical gradient (Hille 1984).

Gene mutations which encode missense amino acid substitutions, or produce premature stop codons resulting in truncated (shortened) proteins, impact static and dynamic ion channel function (Lerche et al. 2013; Lehmann-Horn and Jurkat-Rott 1999). Such changes may be associated with either inherited or sporadic epilepsy. In the latter case, although the channel variant is inherited, it is only part of a confluence of multiple factors that produce the acquired pathology. Changes in the biophysical properties of ion channel function can be used to investigate and/or define structure/function relationships in ion channel proteins using homology models and/or used to populate and assess function of computer models of neuron and network models (Capener et al. 2002; Case et al. 2012).

Epilepsy as an Excitability Disorder

Epilepsy is an excitability disorder characterized by abnormal synchronization of populations of cortical neurons. An excess of excitation and/or a change in neuronal network inhibition can lead to the electrographic hyperexcitability defect (England et al. 2012a, b). Ion channel gene mutations in both mouse and man have been shown to cause both inherited and sporadic forms of epilepsy through disrupted ion channel function (Noebels 1999; Reid et al. 2009; Mulley et al. 2003). Computational models of ion channel mutations in epilepsy have functional consequences which can be simulated by looking at homology models of three-dimensional protein structure. One can also predict aberrant cellular and/or network behavior based on the biophysical parameters of the mutant ion channel protein, and on its interactions with other ion channels.

Homology Models of Mutant Ion Channels

Homology models of ion channel proteins allow determination of the tertiary protein structure resulting from an amino acid substitution encoded by a non-synonymous genetic variant (a synonymous mutation leaves the amino acid unchanged) (Ravna and Sylte 2012). These models are particularly useful because ion channel proteins, massive macromolecular complexes that span the lipid membrane, are not amenable to standard crystallographic techniques (Capener et al. 2002). In a homology model, amino acid sequence similarity to proteins of known structure is combined with free-energy minimization calculations to optimize the energetics of polypeptide packing (Minor Jr 2007). These refined structural models offer an informed *in silico* approximation of tertiary protein-protein interactions of ion channel domains. Models of ion channels harboring missense mutations frequently focus on regions of high conservation (e.g., voltage sensor motif, ion selectivity filter) where physiochemically related protein structures can be used to predict disruption of polypeptide secondary structure (e.g., salt bridge neutralization, proline kink in transmembrane alpha-helix) as an indicator of pathogenic consequence (e.g., using PolyPhen or SIFT software, which are polymorphism phenotyping prediction tools) (Adzhubei et al. 2013; Flanagan et al. 2010).

Epilepsy Mutation Causing Dysfunction of Ion Channels in Neuronal and Network Models

Hyperexcitable epilepsy-related cell and network models have been developed which integrate genetic, biological, and pharmacological data. Ion channels are integral components of many of these models because of multiple feedback mechanisms: they both regulate and respond to the changes in transmembrane voltage. Ion channels are readily described by mathematical formulas which describe their biophysical responses (e.g., kinetics of channel opening) during dynamic

changes in membrane potential and the regulation of ion passage through the channel pore. When the biophysical parameters for epilepsy mutation containing ion channels (e.g., Nav1.1) are used to populate *in silico* models, changes in cellular signaling (e.g., action potential duration, spike frequency) can be observed. These predictions can then be tested by comparison with *in vivo* and *in vitro* data (Thomas et al. 2009; Mulley et al. 2005).

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Epilepsy: Computational Models

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Detailed Description

Epilepsy is a serious neurological disorder characterized by spontaneous recurrent seizures. In the electroencephalogram (EEG) of patients with epilepsy, one may observe seizures (ictal

events) and interictal events, e.g., epileptic spikes or spike-waves. These events are characterized by a short duration and rapid onset and offset. The real problem is that about 30% of the current population of 60 million patients with epilepsy does not respond to any treatment (Kwan and Brodie 2000). This problem is mostly due to an incomplete understanding of the mechanisms that underlie this pathology (e.g., van Drongelen 2007). As is the case for many other neurological diseases, this directly relates to a poor understanding of network function in general. Because of lack of experimental tools for studying network behavior at sufficient scale with the associated detail (e.g., van Drongelen 2010a,b), there is a significant role for modeling in this field (e.g., Blenkinsop et al. 2012; Cosandier-Rim    et al. 2010; Goodfellow et al. 2012; Lytton et al. 1997; Lytton and Sejnowski 1991; Lopes da Silva 2008; Lytton 2008; Soltesz and Staley 2008; Touboul et al. 2011; Traub and Llinas 1979; Traub et al. 1994; van Drongelen et al. 2004, 2005, 2006, 2007, 2008; Wendling and Chauvel 2008; Wendling et al. 2012).

Why Modeling in Epilepsy/Neuroscience?

Understanding the function of neuronal networks is a frontier in current neuroscience. Our lack of fundamental understanding of network function in the nervous system prevents us from linking neuronal activity to higher level physiologic and pathologic behavior. Although compound activity of huge networks can be captured by the EEG or possibly by functional magnetic resonance imaging (fMRI), current experimental techniques in neuroscience cannot record the individual activity of cells forming larger networks (>1,000 neurons) with sufficient resolution in the time domain (<1 ms). Due to the lack of such techniques, there is a real need for theoretical and computational models in neuroscience because they can provide a framework for the integration of experimental data. In addition, models provide an efficient tool for generating and testing series of hypotheses; to cite Abbott (2008), "A skillful theoretician can formulate, explore, and often

reject models at a pace that no experimental program can match."

Modeling of Neuronal Network Activity

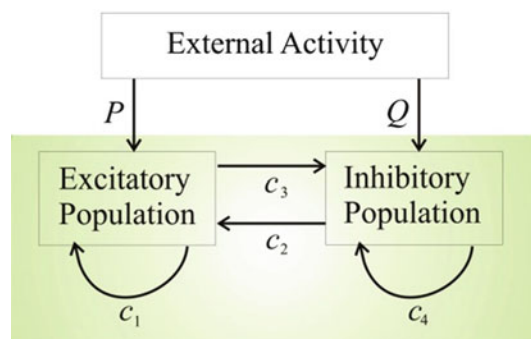
Node-Based Models When modeling neuronal networks, one can start from the network nodes, i.e., the neurons, or make direct assumptions at a higher organization level, i.e., the population activity. In the first case, the bottom-up approach, one must decide how to model the nodes. Simple on/off switches are the most abstract models of neurons in networks. The underlying hypothesis of this approach is that, for some of the aggregate behavior, the network properties themselves are of principal interest while the details of the cellular properties (beyond having active and inactive states) are irrelevant (McCulloch and Pitts 1943; Little 1974; Hopfield 1982; Benayoun et al. 2010; Wallace et al. 2011). Many network models that use the bottom-up approach include more complex representations for the nerve cells and their connections. These representations may vary from a simple IF model to compartmental models including biophysically realistic channels (e.g., van Vreeswijk et al. 1994; van Vreeswijk 1996; Olmi et al. 2010; Tattini et al. 2012; Izhikevich and Edelman 2008; Traub and Miles 1991; Traub et al. 2005; Lytton and Sejnowski 1991; De Schutter and Bower 1994; van Drongelen et al. 2005, 2006, 2007; Markram 2006).

Population-Based Models A different family of network models describes aggregate behavior of neuronal populations. Although the components of these models are derived from or inspired by the neuronal function, they do not explicitly consist of a network of individual agents. This approach was pioneered by Wilson and Cowan (1972, 1973). Their result is a nonlinear, two-dimensional model describing the dynamics of excitatory and inhibitory activity. The expressions for the population activity are based on assumptions about cellular statistics such as the distribution of neuronal excitability. The initial 1972 Wilson-Cowan model describes only the

time-dependent dynamics of the neural populations, whereas their 1973 paper includes a spatial component to this model. In the same decade, Nunez proposed models of cortical networks to explain and describe the electroencephalogram (EEG) representing compound activity of millions of nerve cells (Nunez 1974, 1995; Nunez and Srinivasan 2006a, b). This work focused on the synaptic activities in the cortical pyramidal cell population since they are considered to be the major contributors to the mammalian EEG. To describe cortical activity, Nunez included inhibitory and excitatory populations and used linearized relationships to describe their interactions. Since the early 1970s, many models have been inspired by the Wilson–Cowan approach and the models by Nunez. Examples are the models by Lopes da Silva et al. (1974) and van Rotterdam et al. (1982), the Jansen neural mass model (Jansen and Rit 1995; Grimbert and Faugeras 2006), and Freeman’s models of the olfactory system (Freeman 1987; Chang et al. 1998). More recent examples are the models by Wendling and co-workers (e.g., Wendling and Chauvel 2008), Liley and Bojak (2005), van Albada and Robinson (2009), and Hindriks and van Putten (2012). A model developed by Jirsa and Haken (1997) produces a field equation for the network activity generated by a cortical surface and can be considered a synthesis of the different population model approaches. In part due to increased access to computer technology facilitating the analysis of nonlinear dynamics, the original Wilson–Cowan approach and its derived models are being “rediscovered” (Destexhe and Sejnowski 2009).

The Wilson–Cowan Model The first model by Wilson and Cowan (1972) is exclusively temporal and describes the behavior of two neuronal populations – one excitatory and one inhibitory – embedded in neural tissue. In the Wilson–Cowan model, population properties are derived from assumed statistics of the neurons (Wilson and Cowan 1972). Each population receives input from itself, the other population, and external

sources. The input to a population affects the neurons of that population that are available (the inactive proportion of the population). The model is nonlinear as the level of excitation is related to the output activity through a sigmoidal function S . In a 2nd version of the model that will not be further discussed here, Wilson and Cowan (1973) extended their model to include the spatial component as well. Instead of formulating the model from underlying statistical properties, a coarse-grained version of the model can be directly derived from the diagram in Fig. 9. Two populations, the excitatory and inhibitory, are coupled with strengths c_1 – c_4 . The external population affects the excitatory and inhibitory networks with strengths P and Q . Denoting excitatory activity by E and inhibitory activity by I , the excitatory population in Fig. 1 receives input that can be quantified as $c_1E - c_2I + P$. This input of the population is converted to an output expression via the sigmoid function $S_e\{\dots\}$. In most followers of their approach, such a sigmoid curve is employed to represent conversion from membrane potential to spike rate and/or vice versa. In the Wilson–Cowan approach, the sigmoid curve represents the cumulative distribution



Epilepsy: Computational Models, Fig. 1 Diagram of the Wilson–Cowan model containing excitatory and inhibitory populations. The coupling strength between the populations is denoted with constants c_1 – c_4 , and external activity is symbolized by P and Q . Note that the model contains nonlinear functions to relate input and output for each population (not shown in the diagram) (From van Drongelen (2013))

of the probability that a neuron will fire at a given input, i.e., the distance between membrane potential and firing threshold. Further, assuming that the unavailable part of the population, i.e., the active + refractory portion, is proportional (by a fraction r_e) to the activity level E , then the receptive population (available portion of E) is $1 - r_e E$.

The formalism for population activity also must describe spontaneous decay proportional to E , reflecting that a non-stimulated group of neurons converge to a base level of activity (zero, reflecting a low level of spontaneous activity in this model). Finally, all changes dE/dt are weighted by the time constant of the neuronal population τ_e . Putting this all together, the expression for excitatory activity becomes

$$\underbrace{\tau_e}_{\text{Excitatory time constant}} \frac{dE}{dt} = - \underbrace{E}_{\text{Decay}} + \underbrace{(1 - r_e E)}_{\text{Available population}} \underbrace{\text{Sigmoid}}_{\text{Sigmoid}} \underbrace{\{c_1 E - c_2 I + P\}}_{\text{Input}} \quad (1)$$

A similar approach for the inhibitory population yields

$$\tau_i \frac{dI}{dt} = -I + (1 - r_i I) \text{Sigmoid}\{c_3 E - c_4 I + Q\} \quad (2)$$

Considering that this model is two dimensional and nonlinear, it is capable of exhibiting a variety of behaviors including a steady activity scenario, oscillatory activity with damping, and limit cycles.

A detailed bifurcation analysis of the Wilson–Cowan network is given in Borisjuk and Kirilov (1992). In this entry the bifurcation curves of the type Andronov–Hopf, saddle separatrix, and double limit cycle are computed in the parameter plane with P and c_3 as parameters.

Neural Mass Models Inspired by the Wilson–Cowan Approach The model described by Lopes da Silva et al. (1974) is a model of thalamus and one of the first that is inspired by the Wilson–Cowan approach. A similar treatment of the mesoscopic model, with altered synaptic function, was given by van Rotterdam et al. (1982). The base model describes a thalamic network. However, the populations are identical to the ones in the cortical Wilson–Cowan model: one excitatory and one inhibitory cell group.

The Wilson–Cowan equations (Wilson and Cowan 1972) and Lopes da Silva et al.’s approach (Lopes da Silva et al. 1974) inspired many other models. Instead of considering individual neurons, these models determine the activity of coupled populations of nerve cells, each population representing a neural mass. A very basic model, using two populations representing a coupled excitatory and inhibitory network, is described by Dayan and Abbott (2001, pp. 265–270). The rate of change for each network is negative proportional to its activity level and proportional to the input it receives from itself, the other population, and an external input. This results in a set of two coupled differential equations that describe the activities v_E and v_I of the excitatory and inhibitory populations E and I :

$$\tau_E \frac{dv_E}{dt} = -v_E + \{M_{EE}v_{EE} - M_{EI}v_I + \gamma_E\} \quad (3)$$

$$\tau_I \frac{dv_I}{dt} = -v_I + \{-M_{II}v_I - M_{IE}v_E - \gamma_I\} \quad (4)$$

M_{XX} are the coupling strengths between the populations, τ_X denote the time constants, and γ_X represent external inputs (X denotes the E or I population). Although the model seems to be linear, their model is actually nonlinear because $v_E \geq 0$ and $v_I \geq 0$. Therefore, their model is capable of generating limit cycles.

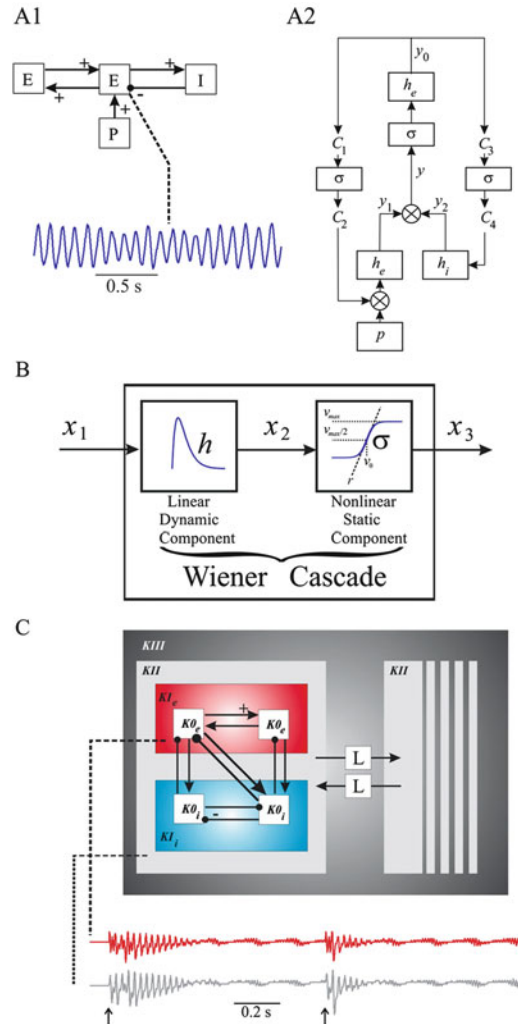
Jansen’s neural mass model (Jansen and Rit 1995) is applied by Grimbert and Faugeras (2006) to create a cortical network unit (Fig. 2a).

It is a temporal model of neuronal populations inspired by the Lopes da Silva et al. (1974) approach where each population is represented by a Wiener cascade (van Drongelen 2010a,b, Chaps. 2–5): a dynamic linear component, modeling the synaptic conversion process, and a non-linear static component that represents the conversion of membrane potential to spike rate (Fig. 2b). As it can be seen in Fig. 2b, input x_1 (input spike rate) is first convolved with the unit impulse response (UIR) h of the linear dynamic component, the result $x_2 = x_1 \otimes h$ (population membrane potential; $\otimes$ -convolution) is subsequently converted with a static sigmoid to produce output $x_3 = \sigma(x_2)$ (output spike rate). The structure of the model by Grimbert and Faugeras (2006) is similar to the canonical cortical model of Douglas and Martin (1991) in the sense that it also includes two excitatory populations E , one inhibitory population I , and an external input P . The development of the equations that govern the activities is straightforward. First, we use the UIR to write a convolution expression. Again, the synapse is considered a linear system, and in this model, the synaptic impulse response function is defined as an alpha function (as in van Rotterdam et al. 1982):

$$h(t) = \begin{cases} \alpha \beta t e^{-\beta t} & t \geq 0 \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

in which α and β are population-specific constants.

The authors employ a static nonlinearity for the membrane potential to pulse rate conversion, a sigmoid curve $\sigma(v)$ (Fig. 2b). In this study it is defined as a Boltzmann function with maximum rate $v_{\max}$, slope r , and a 50% level threshold v_0 : $\sigma(v) = \frac{v_{\max}}{1 + e^{-(v-v_0)}}$. This completes the formalism for one population, i.e., a single Wiener cascade in Fig. 2b. The pair of ODEs plus the static nonlinearity can be defined for each of the three populations in the neural mass model (two excitatory and one inhibitory, Fig. 2a). This means we will have a pair of 1st-order differential



Epilepsy: Computational Models, Fig. 2 Neural mass models. (a) A diagram of the model of a cortical unit employed by Grimbert and Faugeras (2006) and a sample trace showing an oscillation similar to an EEG alpha rhythm. Panel (A1) shows and inhibitory how excitatory networks are connected. Details of the model are shown in (A2); h_e and h_i are the synaptic unit impulse responses; the σ modules are the sigmoid functions translating membrane potential into firing rate; C 's are coupling constants; y 's are defined in Eq. 6. (b) Representation of a Wiener cascade used to model a population of nerve cells. The Wiener cascade consists of a linear dynamical module and a static nonlinear one. (c) Schematic representation of the model described by Freeman (1987) and sample traces showing chaotic behavior of the impulse responses (impulse input – arrows) (Modified from van Drongelen (2013))

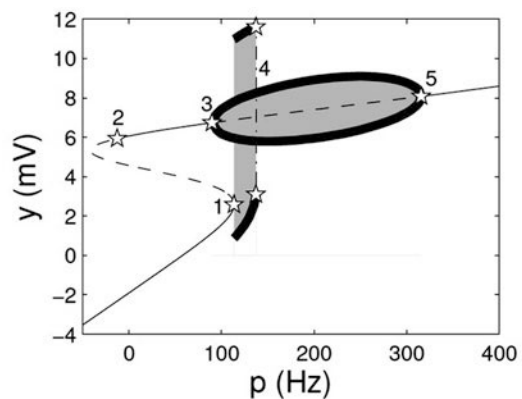
equations per population, generating a total of six equations (Eq. 3 in Grimbert and Faugeras 2006):

$$\begin{aligned} \dot{y}_0(t) &= y_3(t) & \dot{y}_3(t) &= Aa & \sigma(y_1(t) - y_2(t)) - 2a & y_3(t) - a^2 y_0(t) \\ \dot{y}_1(t) &= y_4(t) & \dot{y}_4(t) &= Aa & \{p(t) + C_2 \sigma(C_1 y_0)\} - 2a & y_4(t) - a^2 y_1(t) \\ \dot{y}_2(t) &= y_5(t) & \dot{y}_5(t) &= BbC_4 & \sigma(C_3 y_0) - 2b & y_5(t) - b^2 y_2(t) \end{aligned} \quad (6)$$

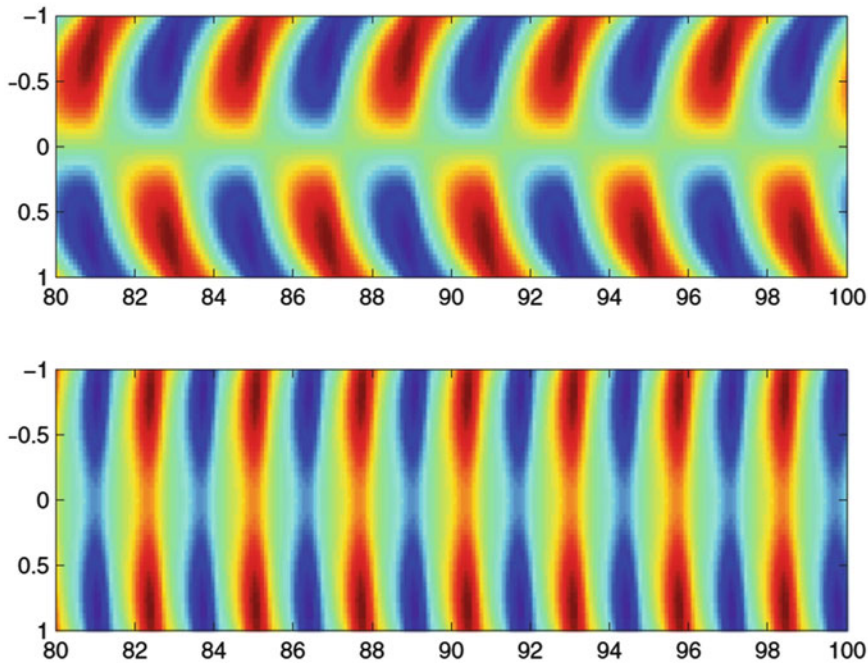
In Eq. 6, the function $p(t)$ can be taken constant, i.e., $p(t) = p$, whereupon bifurcation analysis can be performed. This is done in [37]. It turns out that a low and a high steady state can stably coexist. On the upper branch there are two values at which a Hopf bifurcation occurs. The first one produces through a subcritical Hopf bifurcation for increasing values of p an unstable branch of periodic orbits that regains stability through a saddle node of cycles and disappears in a homoclinic orbit. This yields a narrow band of p -values for which stable, large amplitude, low-frequency (1–5 Hz) periodic orbits exist. The second Hopf bifurcation point is supercritical, yielding a stable small amplitude periodic orbit with frequency in the alpha range. This orbit disappears again in a supercritical Hopf bifurcation at a higher value of p (see Figs. 4 and 5 in Grimbert and Faugeras (2006)); for convenience, the latter is replicated here (Fig. 3).

The parameters $y_0 - y_2$ denote the membrane potentials, and A, a, B, b are the constants in the population-specific alpha functions. Note that in these equations, some outputs y and sigmoid functions are weighted by connectivity strengths $C_1 - C_4$. The focus of this entry is on the variable y , the aggregate membrane potential of the main population, which is thought to be proportional with the local field potential. A simulation using the following parameters $A = 3.25$, $a = 100$, $B = 22$, $b = 50$, $C_1 = 135$, $C_2 = 0.8 * C_1$, $C_3 = 0.25 * C_1$, $C_4 = 0.25 * C_1$, $v_{\max} = 5$, $r = 0.56$, and $v_0 = 6$ shows a signal that is similar to the EEG alpha rhythm (Fig. 2a).

Network Models with Conduction Delays The models created by Freeman in the 1980s used a combined network modeling and experimental approach to study the electrical activity in rabbit olfactory system. Although Freeman's approach may not have been directly inspired by the Wilson–Cowan equations and/or the models by Lopes da Silva and co-workers, the fundamental building blocks of his model are neural masses. The appeal of Freeman's approach is that it is strongly based on the anatomy of the olfactory system and that he relates modeling results to electrophysiological experiments. As compared to the previous models, a unique addition is that it contains latencies L1–L4, modeling the conduction delays occurring in-between populations (Freeman 1987). Ordinary differential equations



Epilepsy: Computational Models, Fig. 3 Diagram of the stable fixed points and limit cycles in the model by Grimbert and Faugeras (2006). Copy of Fig. 5 in the original paper. Stars indicate the start of two simulated trajectories



Epilepsy: Computational Models, Fig. 4 Bistability near a double Hopf bifurcation in a scalar neural field equation. The patterns show the asymptotic behavior for

different initial conditions. For the parameter settings, see van Gils et al. (2013)

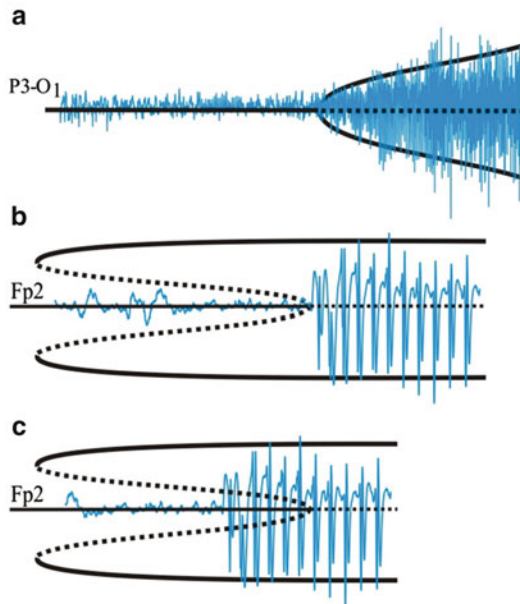
need initial values, whereas delay differential equations require initial functions to determine the solution in future time. This makes it to an infinite dimensional system, even if it is a scalar equation. There is a well-developed theory for delay equations. Local bifurcation theory, for instance, is available after a center manifold reduction. It is a given that delays in the nervous system occur because of the finite conduction velocity of nerve fiber activity. In addition to Freeman's model, several others have explored the role of these delays or included the delays in the formalism (e.g., Foss et al. 1996; Milton 2000, 2012; Visser et al. 2010, 2012).

In his models, Freeman describes different population levels. The most basic population type is defined as $K0$: a subset of noninteracting neurons, either all excitatory ($K0_e$) or inhibitory ($K0_i$). Coupled $K0$ networks create the KI level. In Freeman's terminology, two $K0_e$ modules give a KI_e module, and a pair of $K0_i$ gives one KI_i (Fig. 2c). The next level is the KII

population, i.e., coupled KI_e and KI_i units. The distance between KII populations can be large enough that conduction delays cannot be neglected. These delays are indicated by L in Fig. 2c. Finally, when KII sets are interconnected, a $KIII$ set is created. In Freeman (1987), there are three coupled KII sets: the olfactory bulb, the anterior olfactory nucleus, and the prepyriform cortex. The connections in this set are longer in range so that lags (latencies) were incorporated.

Neural Fields and Effects of Delays

Due to intrinsic delays of axons, synapses, and dendrites in the natural system, the role of delays in spatiotemporal dynamics of neural activity has received considerable attention (Liley et al. 2002; Hutt et al. 2003; Hutt and Atay 2005; Roxin et al. 2005; Venkov et al. 2007; Hutt and Atay 2007; Hutt 2008; Coombes et al. 2007; Coombes and Laing 2009; Coombes 2010).



Epilepsy: Computational Models, Fig. 5 Can seizure onset be modeled with a Hopf bifurcation? (a) A partial complex seizure spreads and grows in amplitude, suggesting one might model it with a supercritical Hopf bifurcation. (b) A generalized seizure occurs suddenly and at full amplitude, similar to a supercritical Hopf bifurcation. (c) Note that the same seizure as in panel (b) can also be explained by a perturbation in a bistable regime associated with the subcritical Hopf bifurcation. In this case the transition into the seizure state is not a bifurcation but due to a change of basin of attraction (e.g., Milton and Jung 2003) (From van Drongelen (2013))

With $p \geq 1$ populations consisting of neurons that occupy fixed positions in a nonempty, bounded, connected, open region $D \subset \mathbb{R}^n$. For each $i = 1 \dots p$ let $V_i(t, r)$ be the membrane potential at time t , averaged over those neurons in the i th population positioned at $r \in D$. These potentials are assumed to evolve in the absence of time-dependent external stimuli according to the system of integrodifferential equations.

$$\frac{\partial V_i}{\partial t}(t, r) = -\alpha_i V_i(t, r) + \sum_{j=1}^p \int_D J_{ij}(r, r') S_j(V_j(t - \tau_{ij}(r, r'), r')) dr' \quad (7)$$

for $i = 1, \dots, p$. The intrinsic dynamics exhibit exponential decay with $\alpha_i > 0$ for $i = 1, \dots, p$.

The propagation delays $\tau_{ij}(r, r')$ measure the time it takes for a signal sent by a type- j neuron located at position r' to reach a type- i neuron located at position r . The functions S_j translate the mean membrane voltage of the j th population into a firing rate. The connectivity functions $J_{ij}(r, r')$ describe how type- j neurons at position r' are connected to type- i neurons at position r . Spectral and stability properties of stationary solutions using methods from functional analysis were obtained in (Veltz and Faugeras 2010; Faye and Faugeras 2010; Veltz and Faugeras 2011). In van Gils et al. (2013), equations of this type are described as abstract delay differential equations. The theory for dual semigroups makes it possible to apply the center manifold reduction and to compute local bifurcations (e.g., Fig. 4).

Application to Epilepsy

Although there are many clinical types of seizure (Berg et al. 2010), the seizure activity in the EEG is often characterized by rhythmic activity usually lasting for minutes. Examples of typical seizure onset activity are depicted in Fig. 5. In contrast, interictal spikes and waves are sudden, short bursts of electrical activity. Although there are exceptions, in between the epileptiform events (i.e., seizures, spikes, waves), the EEG of patients with epilepsy cannot be distinguished from normal EEG patterns. Because epilepsy is characterized by its EEG patterns representing large networks, it is impossible to define epileptiform activity at the level of single neurons or even small networks. Although there seem to be cellular activity patterns frequently found in epileptic brain tissue, such as the paroxysmal depolarization shift (PDS), it is by no means clear how these PDSs relate to the typical network phenomena in epilepsy. The oscillatory activity of cells and small networks is of general interest to the neuroscientist but equally of interest in epilepsy research. However, at this level the distinction between normal and pathologic oscillatory activity is unclear. At the scale of large networks, as reflected in the EEG signal, the distinction between normal and abnormal is not without

problems but definitely easier to make. This makes the study of networks at mesoscopic and macroscopic scales of particular interest in epilepsy research. Based on the activity patterns observed in patients with epilepsy, an effective network model should be able to explain:

1. Normal and epileptiform states
2. Prototypical oscillations and bursts
3. Transitions between the states

From these properties a few general conclusions about the nature of the model can be determined. First, a model of neuronal population activity must be at least two dimensional to explain oscillations. Second, transitions between normal and epileptiform activity can be modeled by a bifurcation in a nonlinear dynamical system. Of course there are many bifurcations that could explain sudden onset and offset of seizure-like oscillations. Examples using the simplest candidate, co-dimension-1 bifurcations transitioning a system between steady state and oscillatory behavior and the sub- and supercritical Hopf bifurcations (Strogatz 1994), are shown in Fig. 5. In this figure, the two top panels show the bifurcation superimposed on seizure activity; the bottom panel indicates that in case of the subcritical scenario, the transition can also occur if the system exceeds the boundary between the basins of attractors (one attractor being the stable node and the other the stable limit cycle) (Milton and Jung 2003).

Some of the models employed in epilepsy research go beyond the minimalistic approach of two dimensions. The detailed simulation models with compartmental neuron models with realistic ion channels may have hundreds of parameters. Independent of the level of complexity of the network models, it is important to know if the neuron model itself is capable of oscillatory activity so that the individual network node can be a pacemaker for oscillation.

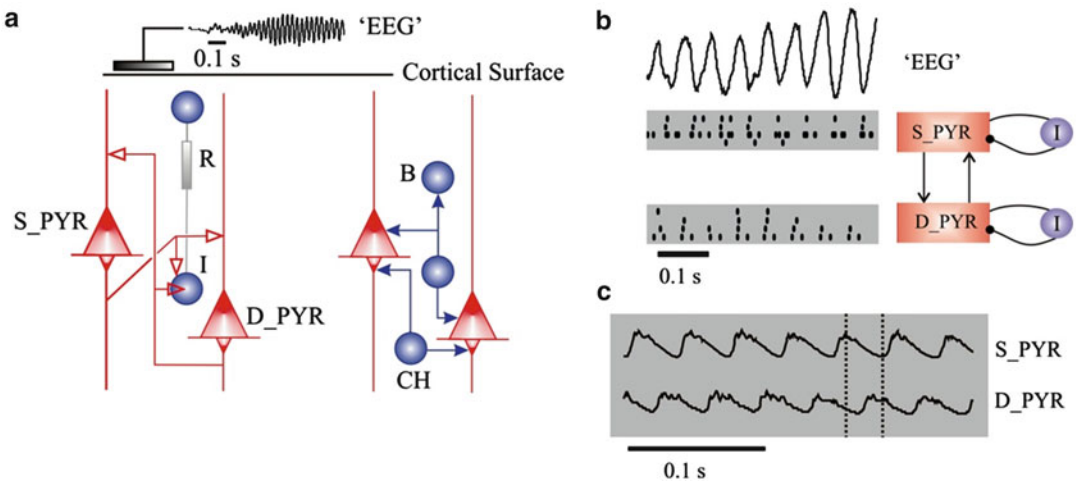
Node-Based Models Models built from cellular models have frequently been employed to study epileptiform behaviors in hippocampus and

neocortex (Lytton et al. 1997; Lytton and Sejnowski 1991; Lytton 2008; Traub and Llinas 1979; Traub et al. 1994; van Drongelen et al. 2004, 2005, 2006, 2007, 2008). In these models, excitatory and inhibitory parameters can be varied at individual or global levels while effects on neural synchrony and overall network activity can be determined. The advantage of this approach is that activity patterns can be directly linked to intrinsic membrane function and synaptic properties that can be modulated experimentally (van Drongelen et al. 2005) or used to evaluate anticonvulsant treatment. An example of the latter application of modeling for antipsychotic treatment was described by Siekmeier and van Maanen (2013). Ultimately, this type of result might help to establish a rational approach to anticonvulsant treatment.

An example of a node-based model is shown in Fig. 6a. This network model includes two different types of pyramidal neurons and four types of inhibitory cells. The currents generated by the individual nodes are used to simulate an EEG signal. Although the model creates a detailed overview of activity at both cellular and network levels, this detail also creates complexity that makes it difficult to interpret the findings. To gain a fundamental insight in the neuronal network processes in detailed simulations, one can average activities originating in different populations (Fig. 6c) (van Drongelen et al. 2006) or construct mathematical equivalents of such averaged activities (Fig. 6b) (Visser et al. 2010).

Population Models and Epileptiform

Activity Here, we examine the population models we described in Section 4 for their capability of generating seizure-like behavior. The Wilson–Cowan (1972) model is both nonlinear and two dimensional and is therefore capable of showing a range of behaviors that include limit cycles (Fig. 10) and transitions from stable behavior to an oscillatory one. The Wilson–Cowan model satisfies the three criteria of an effective network model for studying epilepsy described in the previous section. In addition, it is also a minimal model because the two dimensions (E and I ,

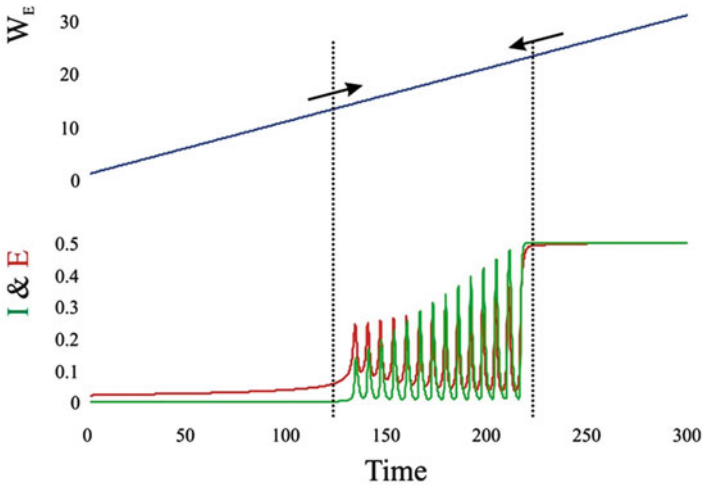


Epilepsy: Computational Models, Fig. 6 Model of neocortex. The detailed model (after van Drongelen et al. 2006) is outlined in diagram (a). The excitatory populations consist of superficial (*S_PYR*) and deep (*D_PYR*) pyramidal cells, and the inhibitory neuron type (*I*) consists of populations of basket cells (*B*) and chandelier cells (*CH*). The weighted sum of all soma currents is used as the “EEG” signal (top, panel a). The excitatory connections of the microcircuitry are shown in the left part and the inhibitory synapses in the right part of panel (a).

Panel (b) depicts a detail of the EEG during seizure-like oscillation in the “EEG” and the associated raster plots of the *S_PYR* and *D_PYR* populations. The simplified network version, after Visser et al. (2010), where only excitatory pyramidal cells and inhibitory neuronal populations are considered, is shown in the right part of panel (b). (c) The average membrane potentials of both pyramidal cell populations show that the activities of the deep *S_PYR* and *D_PYR* populations alternate during seizure-like oscillation (From van Drongelen (2013))

Epilepsy: Computational Models, Fig. 7

Bifurcations, caused by a gradually varying excitatory coupling (blue, top trace), creating a seizure-like epoch in population activity governed by the Wilson–Cowan equations (excitatory population – red and inhibitory population – green) (From van Drongelen (2013))



Eqs. 1, 2) are minimally required to include oscillation and the nonlinearity (sigmoids S_e and S_i) is essential for the existence of sudden transitions (bifurcations) between non-oscillatory and oscillatory states. An example of how a gradually changing excitatory coupling (represented by

constants c_1 and c_3 in Fig. 9) can cause sudden transitions of the population activity is depicted in Fig. 7. Interestingly, it can be seen that, depending on the initial state, oscillations may occur with both increasing and decreasing strength of the coupling (arrows, Fig. 7).

The modeling approach by Lopes da Silva et al. (1974) was used to formulate the Jansen neural mass model, which was later examined for epileptic behavior by Grimbert and Faugeras (2006). Several versions of neural mass models were recently investigated (Blenkinsop et al. 2012; Goodfellow et al. 2012; Touboul et al. 2011; Wendling and Chauvel 2008; Wendling et al. 2012). Because these neural mass models are at least two dimensional and nonlinear (e.g., see Eq. 6), they are capable of displaying transitions between activities associated with a stable node and oscillations or even chaotic behavior if they have three or more dimensions. The neural mass models by Freeman (1987) are capable of displaying these behaviors as well since they are both relatively high dimensional and nonlinear. However, due to Freeman's parameter choices, the isolated *K0* populations (Section 4.3.2) show stable behavior only. Using Freeman's choice of parameters, the model displays chaotic behavior similar to ongoing discharges during a seizure (Fig. 2c).

Linearized models do not support bifurcations and therefore fall short in explaining a critical aspect of epilepsy (seizure onset and offset). The linearized model of Nunez (1974, 1995) has this shortcoming. Nonetheless, it is useful to check if it supports oscillatory activity. First, the oscillatory activity can model ongoing seizure activity. Second, the point where an unstable oscillation arises in a linearized system is an indicator for a Hopf bifurcation in the full nonlinear model.

Conclusion

In the previous sections, a variety of modeling approaches used in neuroscience has been presented. As shown in Section 5, most models are capable of explaining aspects of epileptiform behavior. Interestingly, some of these explanations are counterintuitive (e.g., Lytton 2008; Ullah and Schiff 2009). Considering the rich repertoire of model behaviors, it is not surprising that a single approach to treatment, such as adjusting the excitation–inhibition balance, is likely to fail.

A common theme in the different models is that oscillatory behavior arises from the force term in the differential equations; in the neuronal networks, these force terms may represent membrane currents of the cells that create an oscillatory input and/or the properties of the network that embeds them. A logical next step would be to create a systematic summary of hypothetical mechanisms leading to epileptiform activity and to examine them in experimental models and clinical cases.

In general, the interest in and acceptance of modeling in neuroscience is growing (e.g., Abbott 2008; Destexhe and Sejnowski 2009). However, an important roadblock for the application of modeling is that, in part due to the complexity of the nervous system, there is little consensus amongst neuroscientists on what properties are to be considered critical in a theoretical approach. For this reason, traditionally, the neuroscientist prefers “realistic models” in which many experimental details are represented. Of course, in this sense, the skeptical neuroscientist is right that all models are wrong, i.e., no model fully captures reality, both by design and because some details are simply not known. To cite Rosenblueth and Wiener (1945), “the best material model for a cat is another, or preferably the same cat.” It is obvious that such a “best material model” is not the most helpful tool for a theoretical study of specific aspects of cat behavior because it clearly contains too much detail. Similarly, if one models traffic flow, one probably wouldn't include some details (e.g., color of the cars) while including others (e.g., number of traffic lanes between suburbs and industrial zones). Just like in physics, when modeling in biology, it is good to recall Einstein's dictum: “models should be as simple as possible, but not more so” (e.g., May 2004). Due to simplifications, models do not include all possible parameters, but they can nonetheless be very useful because they allow us to make predictions and they may generate uncluttered insight into the critical components of the underlying mechanisms of the modeled process. Of course, the above general statements are valid for modeling in neuroscience, whether we deal with models that describe the microscopic details of cellular function or ones that deal with the macroscopic

networks of billions of nerve cells in the human brain.

In spite of the necessary simplifications required in modeling, there are limitations in the models reviewed here; they neglect many aspects that play important roles. A critical part of the dynamics of neuronal networks is determined by synaptic plasticity, i.e., the change in network connection strength. These changes play a crucial role in the process of learning but, when pathologic, may also contribute to diseases such as epilepsy. It was more than a half century ago that Hebb (1949) recognized this and postulated his law. Hebb's law describes how synaptic coupling strength depends on local activity. It is often presented in a simplified form as: "neurons that fire together wire together." Much later, an experimental approach has confirmed the existence of activity-dependent plasticity at the level of the coupling between nerve cells, i.e., the synapse (e.g., Bi and Poo 2001; Woodin et al. 2003). Here, the plastic changes appeared to depend on the timing of the action potential (spike) activity of the pre- and postsynaptic neurons and are therefore also called spike-timing-dependent plasticity (STDP). STDP has been used in simulations to find appropriate synaptic strength (e.g., Izhikevich and Edelman 2008) effectively as a parameter estimation technique. It is fairly obvious that if connections between excitatory neurons that fire together also wire together (i.e., get strengthened), it represents a positive feedback mechanism, which may lead to instability and possibly seizure-like hyperactivity (Beenhakker and Huguenard 2009). Therefore, under normal physiological conditions, there must be additional mechanisms counteracting this positive feedback. Recently, an interesting attempt was made to analyze effects of plasticity of inhibitory synapses at the population level and successfully relate it to the network's balance between excitation and inhibition (Vogels et al. 2011). Since this model describes strengthening of the inhibitory connection, the instability issue does not arise here. Although plasticity is an important aspect of network behavior, the models reviewed here did not include it as one of the properties. Plasticity and many other aspects involved in nervous system

function, such as the role of glia (e.g., Volman et al. 2012), remain to be investigated.

Finally, one important conclusion is that there is not "a best approach" when modeling neural function. For example, nonlinear models can help us to understand specifics such as sudden transitions, but linear ones are more suitable to analyze subthreshold properties such as oscillation. The linearized versions of the models also make it easier to see similarities between the models across different levels of organization. Another example, complex models can be studied with simulations; they are more complete since they can deal with more parameters than the more abstract models used for mathematical analysis. However, both have a place and they can be complementary. Analysis of simplified mathematical models can generate fundamental insight in spite of the fact that they lack detail. Simulation can be too complex to directly generate such fundamental insight into the interaction of the ongoing processes, but they have the advantage to be closer to reality. This property appeals to the experimenter since it may produce data with a temporal-spatial resolution that isn't (yet) feasible experimentally. In this context, the ultimate goal in understanding neural networks in physiological and pathological states is to create a framework of experimental models, detailed simulations, and mathematical formalisms that allow us to understand and to predict dynamics of network activities including state transitions, i.e., results in one model can be used to inspire work in another type of model. In the case of analyzing a heterogeneous network disease such as epilepsy, modeling can provide an overview of hypothetical network mechanisms involved in ictal activity that can be employed as a guide for experimental and clinical investigation.

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Further Reading

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Equilibrium Following Cochlear Implantation

► [Vestibular Function After Cochlear Implantation](#)

Equilibrium Neural Network

► [Hopfield Network](#)

Equilibrium Potential

► [Nernst Equation](#)

Equivalent Cylinder Model (Rall)

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Definition

The equivalent cylinder model is a means to reduce the complex branching structure of a dendritic tree to a simple cylinder by making a set of assumptions about the morphological and electrotonic properties of the dendrites, allowing tractable mathematical analyses that can provide useful insights into dendritic function.

Detailed Description

It is difficult to gain mathematical insight into the function of complex branched dendritic trees. Analysis requires that the cable equation be solved for each dendritic segment, given boundary conditions at the ends of the segments, plus an initial condition. Mathematical solutions become unwieldy, even with small numbers of dendritic segments (see ► [“Cable Equation”](#) entry). In 1962, Rall showed that with a few assumptions complex dendritic morphology could be reduced to a simple cylinder. This simplification is known as Rall’s equivalent cylinder model, and its application has provided much insight into neuron function.

Motivation

The mathematical arguments for reduction of a complex tree to a cylinder are given in Rall (1962a, b, 1964). Here, we will motivate this reduction by considering the simple case of a cable that branches into two daughter segments and showing how this can be reduced to a single cable (Fig. 1). The boundary condition at the end of the parent cable is a leaky end with a leak conductance G_L equal to the sum of the input conductances of the two daughter cables $G_1 + G_2$. Can we construct a single cable having input conductance $G_1 + G_2$ but also having the same diameter as the parent cable?

Recall that the input conductance, G_N , for a finite cylinder is (see entry ► “Cable Equation”)

$$G_N = G_\infty \tanh(l/\lambda) = \frac{\tanh(l/\lambda) d^{3/2}}{(2/\pi)\sqrt{R_{in}R_a}}.$$

Then, the sum of the input conductances of the two daughter cables (1 and 2 in Fig. 1) is

$$G_{N1} + G_{N2} = \frac{\pi}{2\sqrt{R_{in}R_a}} \left\{ \tanh\left(\frac{l_1}{\lambda_1}\right) d_1^{3/2} + \tanh\left(\frac{l_2}{\lambda_2}\right) d_2^{3/2} \right\}.$$

The input conductance of a single cable (3 in Fig. 1) is

$$G_{N3} = \frac{\pi}{2\sqrt{R_{in}R_a}} \left\{ \tanh\left(\frac{l_3}{\lambda_3}\right) d_3^{3/2} \right\}$$

Now suppose that R_m and R_a are the same in all cylinders and suppose that the electrotonic lengths of the cylinders are also the same, that is, $l_1/\lambda_1 = l_2/\lambda_2 = l_3/\lambda_3$. Then, $G_{N3} = G_{N1} + G_{N2}$

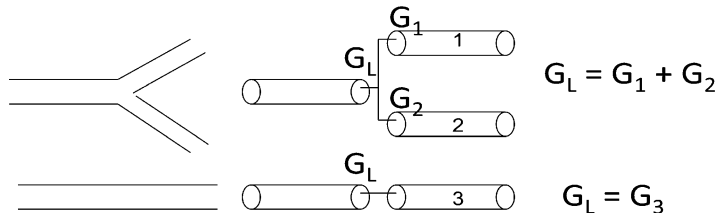
when $d_3^{3/2} = d_1^{3/2} + d_2^{3/2}$. This is called the “3/2 rule.” Thus, we can construct a single cable equivalent to two cables that also has the same diameter as the parent cable if the above assumptions are satisfied, the “3/2 rule” is satisfied, and d_3 equals the parent cable diameter.

Rall’s model

Rall (1962a, b, 1964) formally stated the conditions for the reduction of a branched dendritic tree to an equivalent cylinder as follows:

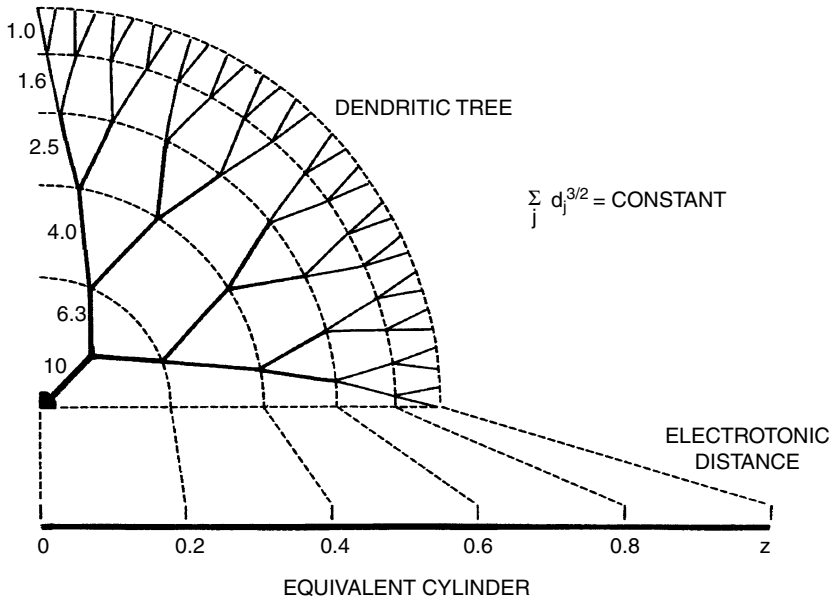
1. R_m and R_a are the same in all branches.
2. All terminal branches end with the same boundary condition (typically sealed end).
3. All terminal branches end at the same electrotonic distance, L , from $x = 0$ ($L = \sum \ell_i/\lambda_i$ is the same for all paths from $x = 0$ to all tips).
4. At every branch point, the diameter of the parent branch and its daughter branches must satisfy the relationship $d_{\text{parent}}^{3/2} = \sum d_{\text{daughters}}^{3/2}$.
5. Any dendritic input at a particular location must be delivered proportionally to all branches at the same electrotonic distance.

It should be noted that the daughter branches do not have to have the same diameters and that branches do not have to occur at the same electrotonic distances as shown, for convenience, by the symmetrical branching pattern in Fig. 2. Furthermore, the conditions above do not require branches to have the same physical length. Importantly, as can be seen from the equations following Fig. 1, the conditions above preserve



Equivalent Cylinder Model (Rall), Fig. 1 Can we replace segments 1 and 2 with an equivalent segment 3? G_L is the leak conductance at the end of the parent segment,

which must equal the sum of the input conductances of the daughter segments



Equivalent Cylinder Model (Rall), Fig. 2 Collapsing a dendritic tree to an equivalent cylinder. (Reproduced from Rall (1964))

both membrane area and input conductance of the original dendritic tree in the equivalent cylinder.

Do dendritic trees satisfy these constraints? The first condition that R_m and R_a are the same in all branches is reasonable as a first approximation although R_m and to a lesser extent R_a may be nonuniform. The second condition that all terminals end with the same boundary condition is reasonable. The third condition that all terminal branches end at the same electrotonic distance is likely to be violated. For example, the short basilar and long apical dendrites of pyramidal cells do not end at the same electrotonic distance. Motoneurons, which might appear at first glance to be good candidates for reduction to equivalent cylinders, have some branches terminating sooner than others, making a cylinder followed by a tapering cable a more appropriate representation. The fourth condition, the “3/2 rule”, was never claimed by Rall to be a rule of nature, but it happens to be satisfied in many dendritic trees, but also not in others. If the

“3/2 rule” is satisfied, there is impedance matching at branch points and no possible “reflections.” Voltage attenuation in the soma-to-distal direction proceeds smoothly. If the “3/2 rule” is not satisfied, then there are abrupt changes in attenuation at the branch point in the soma-to-distal direction. If daughter diameters are thinner than the “3/2 rule,” then voltage attenuation will be less steep before the branch point and more steep after the branch point than would be the case if the rule were satisfied. If daughter diameters are thicker than the “3/2 rule,” the opposite occurs; voltage attenuation will be steeper before the branch point and less steep after the branch point than when the “3/2 rule” is satisfied. This might have important implications for the relative effectiveness of inhibition delivered at the soma for changing the voltage at distances away from the soma. The fifth condition is required only when we consider inputs not at the soma. It is clearly not going to be satisfied generally. Nevertheless, superposition methods have been used in

conjunction with the equivalent cylinder model to deal appropriately with inputs on a single branch (Rall and Rinzel 1973; Rinzel and Rall 1974). Despite potential violations of the underlying assumptions, the equivalent cylinder model provides an excellent first approximation of the structure of dendritic trees and has proved to be an exceptional model for providing insights into neuronal function.

Cross-References

► [Cable Equation](#)

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Equivalent Partial Differential Equations (PDEs)

► [Propagator, Axonal](#)

ERK1, 2

► [Extracellular Signal-Regulated Kinases, Models of](#)

Estimating Information-Theoretic Quantities

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Definition

Information theory is a practical and theoretic framework developed for the study of communication over noisy channels. Its probabilistic basis and capacity to relate statistical structure to function make it ideally suited for studying information flow in the nervous system. It has a number of useful properties: it is a general measure sensitive to any relationship, not only linear effects; it has meaningful units which in many cases allow direct comparison between different experiments; and it can be used to study how much information can be gained by observing neural responses in single trials, rather than in averages over multiple trials. A variety of information-theoretic quantities are in common use in neuroscience (see entry ► [“Summary of Information-Theoretic Quantities”](#)). *Estimating* these quantities in an accurate and unbiased way from real neurophysiological data frequently presents challenges, which are explained in this entry.

Detailed Description

Information-Theoretic Quantities

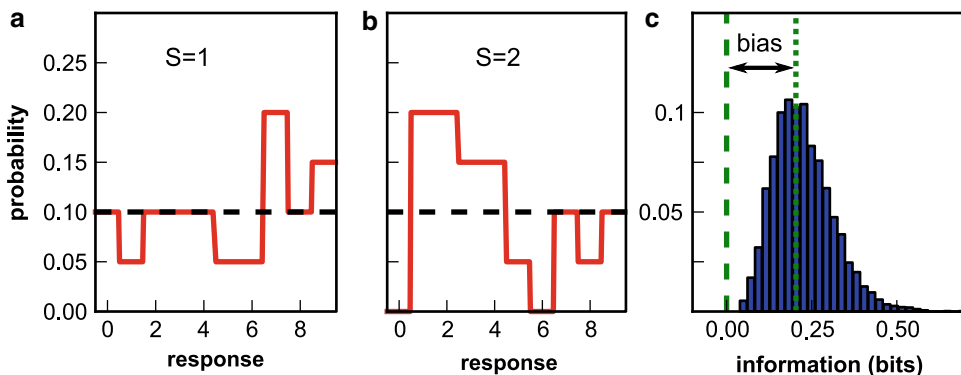
Information theory provides a powerful theoretic framework for studying communication in a

quantitative way. Within the framework, there are many different quantities to assess different properties of systems, many of which have been applied fruitfully to analysis of the nervous system and neural communication. These include the entropy (H , which measures the uncertainty associated with a stochastic variable), mutual information (I , which measures the dependence relationship between two stochastic variables), and several more general divergence measures for probability distributions (Kullback–Leibler, Jensen–Shannon). For full definitions and details of these quantities, see the ► [“Summary of Information-Theoretic Quantities”](#) entry.

The Finite Sampling Problem

A major difficulty when applying techniques involving information-theoretic quantities to experimental systems is that they require measurement of the full probability distributions of the variables involved. If we had an infinite amount of data, we could measure the true stimulus–response probabilities precisely. However, any real experiment only yields a finite number

of trials from which these probabilities must be estimated. The estimated probabilities are subject to statistical error and necessarily fluctuate around their true values. The significance of these finite sampling fluctuations is that they lead to both statistical error (variance) and systematic error (called limited sampling bias) in estimates of entropies and information. This bias is the difference between the expected value of the quantity considered, computed from probability distributions estimated with N trials or samples, and its value computed from the true probability distribution. This is illustrated in Fig. 1, which shows histogram estimates of the response distribution for two different stimuli calculated from 40 trials per stimulus. While the true probabilities are uniform (dotted black lines), the calculated maximum likelihood estimates show some variation around the true values. This causes spurious differences – in this example, the sampled probabilities indicate that obtaining a large response suggests stimulus 1 is presented – which result in a positive value of the information. Figure 1c shows a histogram of information values obtained from many simulations of this system. The bias constitutes a significant practical problem because



Estimating Information-Theoretic Quantities, Fig. 1 The origin of the limited sampling bias in information measures. (a, b) Simulation of a toy uninformative neuron, responding on each trial with a uniform distribution of spike counts ranging from 0 to 9, regardless of which of the two stimuli ($S = 1$ in (a) and $S = 2$ in (b)) is presented. The black dotted horizontal line is the true response distribution; solid red lines are estimates sampled from 40 trials. The limited sampling causes the appearance of spurious differences in the two estimated conditional

response distributions, leading to an artificial positive value of mutual information. (c) The distribution (over 5,000 simulations) of the mutual information values obtained (without using any bias correction) estimating Eq. 1 from the stimulus–response probabilities computed with 40 trials. The dashed green vertical line indicates the true value of the mutual information carried by the simulated system (which equals 0 bits); the difference between this and the mean observed value (dotted green line) is the bias (Redrawn with permission from Ince et al. (2010))

its magnitude is often of the order of the information values to be evaluated and because it cannot be alleviated simply by averaging over many neurons with similar characteristics.

Direct Estimation of Information-Theoretic Quantities

The most direct way to compute information and entropies is to estimate the response probabilities as the experimental histogram of the frequency of each response across the available trials and then plug these empirical probability estimates into Eqs. 1, 2, and 3. We refer to this as the “plug-in” method.

The plug-in estimate of entropy is biased downward (estimated values are lower than the true value), while the plug-in estimate of information shows an upward bias. An intuitive explanation for why entropy is biased downward comes from the fact that entropy is a measure of variability. As we saw in Fig. 1, variance in the maximum likelihood probability estimates introduces extra structure in the probability distributions; this additional variation (which is dependent on the number of trials from the asymptotic normality of the ML estimate) always serves to make the estimated distribution less uniform or structured than the true distribution. Consequently, entropy estimates are lower than their true values, and the effect of finite sampling on entropies is a downward bias. For information, an explanation for why bias is typically positive is that finite sampling can introduce spurious stimulus-dependent differences in the response probabilities, which make the stimuli seem more discernible and hence the neuron more informative than it really is. Alternatively, viewing the information as a difference of unconditional and conditional entropies (first two expressions of Eq. (2) in ► “Summary of Information-Theoretic Quantities”), the conditional entropy for each stimulus value is estimated from a reduced number of trials compared to the noise entropy (only the trials corresponding to that stimulus), and so its bias is considerably larger. Since entropy is biased down and the conditional entropy term appears with a negative sign, this causes the upward bias in information.

In the above explanations for the source of the bias, the source is the variability in estimates of

the probability distributions considered. Variance in the maximum likelihood histogram estimators of the probabilities induces additional “noise” structure affecting the entropy and information values.

Asymptotic Estimates of the Limited Sampling Bias

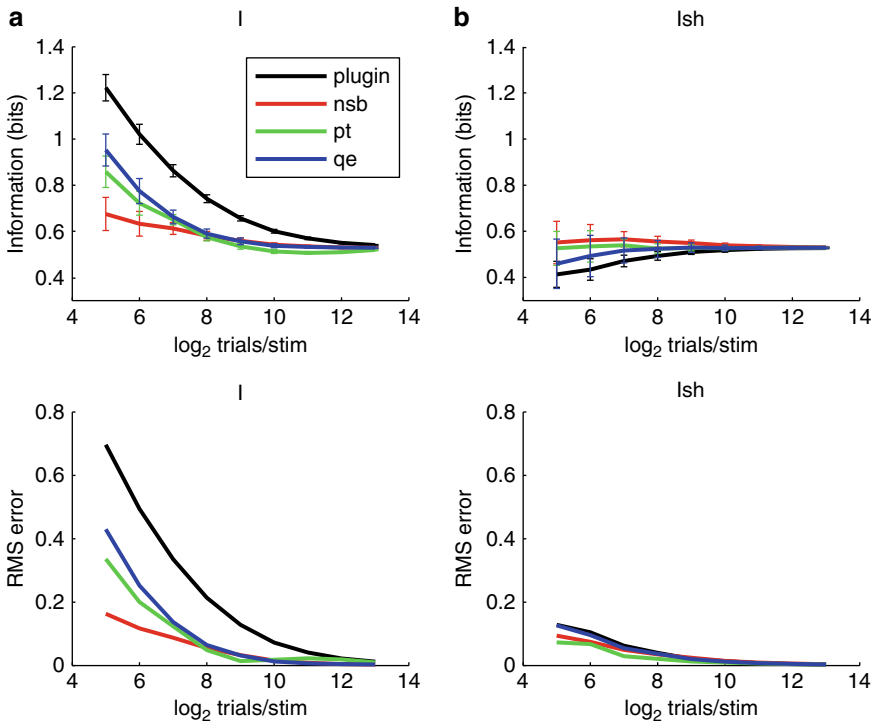
To understand the sampling behavior of information and entropy better, it is useful to find analytical approximations to the bias. This can be done in the so-called asymptotic sampling regime. Roughly speaking, this is when the number of trials is “large.” More rigorously, the asymptotic sampling regime is defined as N being large enough that every possible response occurs many times: that is, $N_s P(r|s) \gg 1$ for each stimulus–response pair s, r such that $P(r|s) > 0$. In this regime, the bias of the entropies and information can be expanded in inverse powers of $1/N$ and analytical approximations obtained (Miller 1955; Panzeri and Treves 1996). The leading terms in the biases are, respectively,

$$\begin{aligned} \text{BIAS}[H(R)] &= \frac{-1}{2N \ln(2)} [\bar{R} - 1] \\ \text{BIAS}[H(R|S)] &= \frac{-1}{2N \ln(2)} \sum_s [\bar{R}_s - 1] \\ \text{BIAS}[I(S; R)] &= \frac{1}{2N \ln(2)} \left\{ \sum_s [\bar{R}_s - 1] - [\bar{R} - 1] \right\} \end{aligned} \quad (1)$$

Here, $\bar{R}_s$ denotes the number of relevant responses for the stimulus conditional response probability distribution $P(r|s)$ – i.e., the number of different responses r with nonzero probability of being observed when stimulus s is presented. $\bar{R}$ denotes the number of relevant responses for $P(r)$ – i.e., the number of different responses r with nonzero probability of being observed across all stimuli. In practice, $\bar{R}$ is usually going to be equal to the number of elements constituting the response space R . If a response never happens across all stimuli, it can be removed from the sum over r in the calculation of each entropy term and thus removed from the response set R . However, $\bar{R}_s$ may be different from $\bar{R}$ if some responses occur only with particular stimuli.

Although valid only in the asymptotic regime, Eq. 1 sheds valuable light on the key factors that control the bias. First, Eq. 1 shows that the bias of $H(R|S)$ is approximately S times bigger than that of $H(R)$. This means that in the presence of many stimuli, the bias of $I(S;R)$ is similar to that of $H(R|S)$. However, $I(S;R)$ is a difference of entropies, and its typical values are much smaller than those of $H(R|S)$. This implies that bias correction methods must be validated on the performance of information and not only on entropies because in many cases, the bias may be proportionally negligible for entropies but not the information. Second, Eq. 1 shows that the bias is small when the ratio $N_s/\bar{R}$ is big, i.e., more trials per stimulus than possible responses. This is because assuming that the number of trials per stimulus is approximately constant and $\bar{R}_s$ is approximately equal to $\bar{R}$, the bias of $H(R|S)$ is approximately

$\bar{R}/[2N_s \ln(2)]$. Thus, $N_s/\bar{R}$ is the crucial parameter for the sampling problem. For example, in the simulations of Fig. 2, with $\bar{R} = 2^8$, the bias of $I(S;R)$ became negligible for $N_s \geq 2^{13}$ (i.e., $N_s/\bar{R} \geq 32$). Second, Eq. 1 shows that even if N_s is constant, the bias increases with the number of responses $\bar{R}$. This has important implications for comparing neural codes. For example, a response consisting of a given number of spikes can arise from many different possible temporal patterns of spikes. Thus, $\bar{R}$ is typically much greater for a spike-timing code than for a spike count code, and it follows from Eq. 1 that the estimate of information conveyed by a spike-timing code is more biased than that measured for the same neurons through a spike count code. If bias is not eliminated, there is therefore a danger of concluding that spike timing is important even when it is not.



Estimating Information-Theoretic Quantities, Fig. 2 Performance of various bias correction methods. Several bias correction methods were applied to spike trains from eight simulated somatosensory cortical neurons. The information estimates (upper panels) and root mean square (RMS) error (lower panels) are plotted as a

function of the simulated number of trials per stimulus. (a) Mean $\pm$ SD (upper panel; over 50 simulations) and RMS error (lower panel) of $I(S;R)$. (b) Mean $\pm$ SD (upper panel; over 50 simulations) and RMS error (lower panel) of $I_{sh}(S;R)$

A further important feature of Eq. 1 is that although the bias is not the same for all probability distributions, in the asymptotic sampling regime, it depends on some remarkably simple details of the response distribution (the number of trials and the number of relevant responses). Thus, Eq. 1 makes it possible to derive simple rules of thumb for estimating the bias magnitude and compare the relative bias in different situations. As detailed in the next section, the simplicity of Eq. 1 can also be exploited in order to correct effectively for the bias (Panzeri and Treves 1996).

Bias Correction Methods

A number of techniques have been developed to address the issue of bias and allow much more accurate estimates of information-theoretic quantities than the “plug-in” method described above. Panzeri et al. (2007) and Victor (2006) provide a review of such methods, a selection of which is briefly outlined here.

Panzeri–Treves (PT)

In the so-called asymptotic sampling regime, when the number of trials is large enough that every possible response occurs many times, an analytical approximation for the bias (i.e., the difference between the true value and the plug-in estimate) of entropies and information can be obtained (Miller 1955; Panzeri and Treves 1996; Eq. 1). The value of the bias computed from the above expressions is then subtracted from the plug-in estimate to obtain the corrected value. This requires an estimate of the number of relevant responses for each stimulus, $\bar{R}_s$. The simplest approach is to approximate $\bar{R}_s$ by the count of responses that are observed at least once – this is the “naïve” count. However, due to finite sampling, this will be an underestimate of the true value. A Bayesian procedure (Panzeri and Treves 1996) can be used to obtain a more accurate value.

Quadratic Extrapolation (QE)

In the asymptotic sampling regime, the bias of entropies and information can be approximated as second-order expansions in $1/N$, where N is

the number of trials (Treves and Panzeri 1995; Strong et al. 1998). For example, for information

$$I_{\text{plugin}}(R; S) = I_{\text{true}}(R; S) + \frac{a}{N} + \frac{b}{N^2} \quad (2)$$

This property can be exploited by calculating the estimates with subsets of the original data, with $N/2$ and $N/4$ trials, and fitting the resulting values to the polynomial expression above. This allows an estimate of the parameters a and b and hence $I_{\text{true}}(S; R)$. To use all available data, estimates of two subsets of size $N/2$ and four subsets of size $N/4$ are averaged to obtain the values for the extrapolation. Together with the full length data calculation, this requires seven different evaluations of the quantity being estimated.

Nemenman–Shafee–Bialek (NSB)

The NSB method (Nemenman et al. 2002, 2004) utilizes a Bayesian inference approach and does not rely on the assumption of the asymptotic sampling regime. It is based on the principle that when estimating a quantity, the least bias will be achieved when assuming an a priori uniform distribution over the quantity. This method is more challenging to implement than the other methods, involving a large amount of function inversion and numerical integration. However, it often gives a significant improvement in the accuracy of the bias correction (Montani et al. 2007; Montemurro et al. 2007; Nemenman et al. 2008).

Shuffled Information Estimator (I_{sh})

Recently, an alternative method of estimating the mutual information has been proposed (Montemurro et al. 2007; Panzeri et al. 2007). Unlike the methods above, this is a method for calculating the information only and is not a general entropy bias correction. However, it can be used with the entropy corrections described above to obtain more accurate results. In brief, the method uses the addition and subtraction of different terms (in which correlations given a fixed stimulus are removed either by empirical shuffling or by marginalizing and then multiplying response probabilities) that do not change the information value in the limit of an infinite

number of trials, but do remove a large part of the bias for finite number of trials. This greatly reduces the bias of the information estimate, at the price of only a marginal increase of variance. Note that this procedure works well for weakly correlated data, which is frequently the case for simultaneously recorded neurons.

Examples of Bias Correction Performance

Figure 2a reports the results of the performance of bias correction procedures, both in terms of bias and root mean square (RMS) error, on a set of simulated spike trains from eight simulated neurons. Each of these neurons emitted spikes with a probability obtained from a Bernoulli process. The spiking probabilities were set equal to those measured, in the 10–15 ms poststimulus interval, from eight neurons in rat somatosensory cortex responding to 13 stimuli consisting of whisker vibrations of different amplitude and frequency (Arabzadeh et al. 2004). The 10–15 ms interval was chosen since it was found to be the interval containing highest information values. Figure 2a shows that all bias correction procedures generally improve the estimate of $I(S;R)$ with respect to the plug-in estimator, and the NSB correction is especially effective.

Figure 2b shows that the bias-corrected estimation of information (and RMS error; lower panel) is much improved by using $I_{sh}(R;S)$ rather than $I(R;S)$. The use of $I_{sh}(R;S)$ makes the residual errors in the estimation of information much smaller and almost independent from the bias correction method used. Taking into account both bias correction performance and computation time, for this simulated system, the best method to use is the shuffled information estimator combined with the Panzeri–Treves analytical correction. Using this, an accurate estimate of the information is possible even when the number of samples per stimulus is R , where R is the dimension of the response space.

It should be noted that while bias correction techniques such as those discussed above are essential if accurate estimation of the information is required, whether to employ them depends upon the question being addressed. If the aim is quantitative comparison of information values

between different experiments, stimuli, or behaviors, they are essential. If instead the goal is simply to detect the presence of a significant interaction, the statistical power of information as a test of independence is greater if the uncorrected plug-in estimate is used (Ince et al. 2012). This is because all the bias correction techniques introduce additional variance; for a hypothesis test which is unaffected by underlying bias, this variance reduces the statistical power.

Information Component Analysis Techniques

The principal use of information theory in neuroscience is to study the neural code – and one of the commonly studied problems in neural coding is to take a given neurophysiological dataset and to determine how the information about some external correlate is represented. One way to do this is to compute the mutual information that the neural responses convey on average about the stimuli (or other external correlate), under several different assumptions about the nature of the underlying code (e.g., firing rate, spike latency). The assumption is that if one code yields substantially greater mutual information, then downstream detectors are more likely to be using that code (the *efficient coding hypothesis*).

A conceptual improvement on this procedure, where it can be done, is to take the total information available from all patterns of spikes (and silences) and to break it down (mathematically) into components reflecting different encoding mechanisms, such as firing rates and pairwise correlations (Panzeri et al. 1999; Panzeri and Schultz 2001). One way to do this is to perform an asymptotic expansion of the mutual information, grouping terms in such a way that they reflect meaningful coding mechanisms.

Taylor Series Expansion of the Mutual Information

A Taylor series expansion of the mutual information is one such approach. For short time windows (and we will discuss presently what “short”

means), the mutual information can be approximated as

$$I(R;S) = TI_t + \frac{T^2}{2}I_{tt} + \dots \quad (3)$$

where the subscript t indicates the derivative with respect to the time window length T . For time windows sufficiently short that only a pair of spikes is contained within the time window (either from a population of cells or from a single spike train), the first two terms are all that is needed. If the number of spikes exceeds two, it may still be a good approximation, but higher-order terms would be needed to capture all of the information. One possibility is that Eq. 3 could be extended to incorporate higher-order terms; however, we have instead found it better in practice to take an alternative approach (see next section).

With only a few spikes to deal with, it is possible to use combinatorics to write out the expressions for the probabilities of observing different spike patterns. This was initially done for the information contained in the spikes fired by a small population of cells (Panzeri et al. 1999) and then later extended to the information carried by the spatiotemporal dynamics of a small population of neurons over a finite temporal word length (Panzeri and Schultz 2001). In the former formulation, we define $\bar{r}_i(s)$ to be the mean response rate (number of spikes in T divided by T) of cell i (of C cells) to stimulus s over all trials where s was presented. We then define the signal cross-correlation density to be

$$v_{ij} = \frac{\langle \bar{r}_i(s) \bar{r}_j(s) \rangle_s}{\langle \bar{r}_i(s) \rangle_s \langle \bar{r}_j(s) \rangle_s} - 1 \quad (4)$$

This quantity captures the correlation in the mean response profiles of each cell to different stimuli (e.g., correlated tuning curves). Analogously, we define the noise cross-correlation density to be

$$\gamma_{ij}(s) = \frac{r_i(s)r_j(s)}{\bar{r}_i(s)\bar{r}_j(s)} - 1 \quad (5)$$

The mutual information $I(R;S)$ can then be written as the sum of four components,

$$I = I_{\text{lin}} + I_{\text{sig-sim}} + I_{\text{cor-ind}} + I_{\text{cor-dep}}. \quad (6)$$

with the first component

$$I_{\text{lin}} = T \sum_{i=1}^C \left\langle \bar{r}_i(s) \log_2 \frac{\bar{r}_i(s)}{\langle \bar{r}_i(s') \rangle_{s'}} \right\rangle_s \quad (7)$$

capturing the rate component of the information, i.e., that which survives when there is no correlation between cells (even of their tuning curves) present at all. This quantity is positive semi-definite and adds linearly across neurons. It is identical to the “information per spike” approximation calculated by a number of authors (Skaggs et al. 1993; Brenner et al. 2000; Sharpee et al. 2004). $I_{\text{sig-sim}}$ is the correction to the information required to take account of correlation in the tuning of individual neurons or *signal similarity*:

$$I_{\text{sig-sim}} = \frac{T^2}{2 \ln 2} \sum_{i=1}^C \sum_{j=1}^C \langle \bar{r}_i(s) \rangle_s \langle \bar{r}_j(s) \rangle_s \left[v_{ij} + (1 + v_{ij}) \ln \left(\frac{1}{1 + v_{ij}} \right) \right] \quad (8)$$

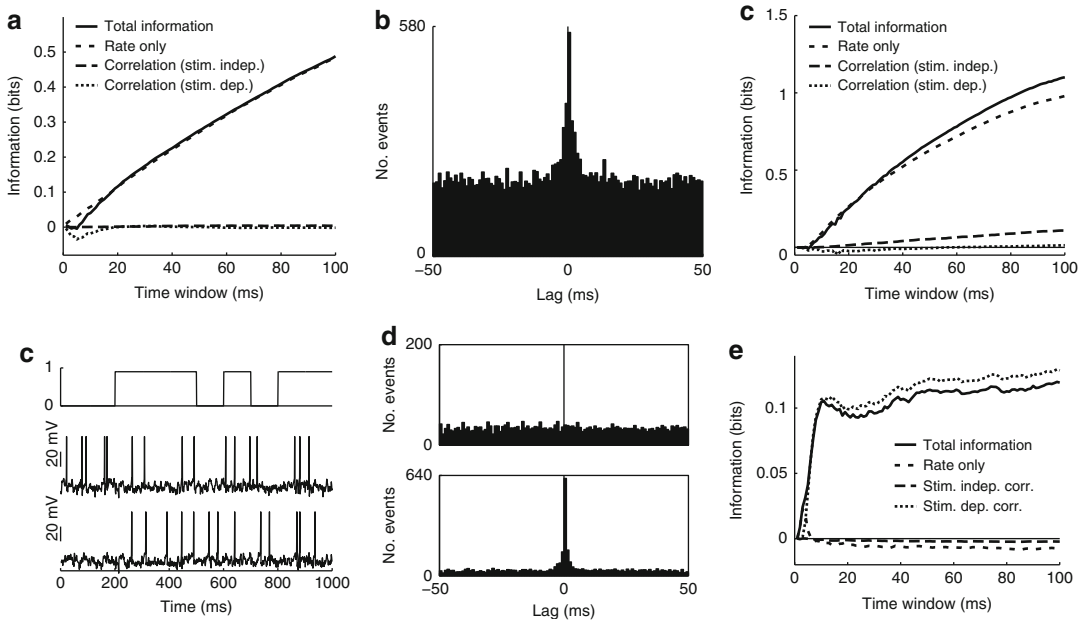
This is negative semi-definite. $I_{\text{cor-ind}}$ is the effect on the transmitted information of the average level of noise correlation (correlation at fixed stimulus) between neurons:

$$I_{\text{cor-ind}} = \frac{T^2}{2} \sum_{i=1}^C \sum_{j=1}^C \langle \bar{r}_i(s) \bar{r}_j(s) \gamma_{ij}(s) \rangle_s \log_2 \left(\frac{1}{1 + v_{ij}} \right) \quad (9)$$

$I_{\text{cor-ind}}$ can take either positive or negative values. $I_{\text{cor-dep}}$ is the contribution of stimulus dependence in the correlation to the information – as would be present, for instance, if synchrony was modulated by a stimulus parameter:

$$I_{\text{cor-dep}} = \frac{T^2}{2} \sum_{i=1}^C \sum_{j=1}^C \left\langle \bar{r}_i(s) \bar{r}_j(s) (1 + \gamma_{ij}(s)) \log_2 \left[\frac{\langle \bar{r}_i(s') \bar{r}_j(s') \rangle_s (1 + \gamma_{ij}(s))}{\langle \bar{r}_i(s') \bar{r}_j(s') \rangle_{s'} (1 + \gamma_{ij}(s'))} \right] \right\rangle_s \quad (10)$$

An application of this approach to break out components reflecting rate and correlational



Estimating Information-Theoretic Quantities, Fig. 3 Information component analysis of simulated data (for a five-cell ensemble). (a) Poisson cells, with the only difference between the stimuli being firing rate. (b) Integrate-and-fire cells, with common input due to sharing of one third of connections, resulting in a cross-correlogram as depicted in (c) contribution to the information from $I_{\text{cor}} - \text{ind.}$ (d) Integrate-and-fire cells with

two of the five cells increasing their correlation due to increased shared input, for one of the stimuli, where the others remain randomly correlated, leading to cross-correlograms shown in panel (e). Firing rates are approximately balanced between the two stimuli. This results in a substantial contribution to the information from the stimulus-dependent correlation component, $I_{\text{cor}} - \text{dep.}$ (From Panzeri et al. 1999 with permission)

coding is illustrated in Fig. 3 by application to simulated spike trains with controlled correlation. This approach has been used by a number of authors to dissect out contributions to neural coding (e.g., Scaglione et al. 2008).

This approach extends naturally to the consideration of temporal correlations between spike times within a spike train (Panzeri and Schultz 2001). Note that the Taylor series approach can be applied to the entropy as well as the mutual information – this was used to break out the effect of spatiotemporal correlations on the entropy of a small population of neural spike trains (Schultz and Panzeri 2001). While the Taylor series approach can be extremely useful in teasing out contributions of different mechanisms to the transmission of information, it is not recommended as a method for estimation of the total information, as the validity of the approximation can break down quickly as the time

window grows beyond that sufficient to contain more than a few spikes from the population. It is however useful as an additional inspection tool after the total information has been computed, which allows the information to be broken down into not only mechanistic components but also their contributions from individual cells and time bins (for instance, by visualizing the quantity after the summations in Eq. 10 as a matrix).

A More General Information Component Analysis Approach

A limitation of the Taylor series approach is that it is restricted to the analysis of quite short time windows of neural responses. However, an exact breakdown approach allowed a very similar information component approach to be used (Pola et al. 2003). In this approach, we consider a population response (spike pattern) $\mathbf{r}$ and define the normalized noise cross-correlation to be

$$\gamma(\mathbf{r}|s) = \begin{cases} \frac{P(\mathbf{r}|s)}{P_{\text{ind}}(\mathbf{r}|s)} - 1 & \text{if } P_{\text{ind}}(\mathbf{r}|s) \neq 0 \\ 0 & \text{if } P_{\text{ind}}(\mathbf{r}|s) = 0 \end{cases} \quad (11)$$

where the marginal distribution

$$P_{\text{ind}}(\mathbf{r}|s) = \prod_{c=1}^C P(r_c|s). \quad (12)$$

Compare the expressions in Eqs. 5 and 12. Similarly, the signal correlation becomes

$$v(\mathbf{r}) = \begin{cases} \frac{P_{\text{ind}}(\mathbf{r})}{\prod_c P(r_c)} - 1 & \text{if } \prod_c P(r_c) \neq 0 \\ 0 & \text{if } \prod_c P(r_c) = 0 \end{cases} \quad (13)$$

Using these definitions, the information components can now be written exactly (without the approximation of short time windows) as

$$I_{\text{lin}} = \sum_c \sum_{r_c} \left\langle P(r_o|s) \log_2 \frac{P(r_c|s)}{P(r_c)} \right\rangle_s \quad (14)$$

$$I_{\text{sig-sim}} = \frac{1}{\ln 2} \sum_r \left(\prod_c P(r_c) \right) \quad (15)$$

$$\left[v(\mathbf{r}) + (1 + v(\mathbf{r})) \ln \left(\frac{1}{1 + v(\mathbf{r})} \right) \right]$$

$$I_{\text{cor-ind}} = \sum_r \langle P_{\text{ind}}(\mathbf{r}|s) \gamma(\mathbf{r}|s) \rangle_s \log_2 \left(\frac{1}{1 + v(\mathbf{r})} \right) \quad (16)$$

$$I_{\text{cor-dep}} = \sum_r \left\langle P_{\text{ind}}(\mathbf{r}|s) (1 + \gamma(\mathbf{r}|s)) \log_2 \frac{\langle P_{\text{ind}}(\mathbf{r}|s') \rangle_s (1 + \gamma(\mathbf{r}|s))}{\langle P_{\text{ind}}(\mathbf{r}|s') (1 + \gamma(\mathbf{r}|s)) \rangle_s} \right\rangle_s \quad (17)$$

This latter component is identical to the quantity “ ΔI ” introduced by Latham and colleagues (Nirenberg et al. 2001) to describe the information lost due to a decoder ignoring correlations. It is zero if and only if $P(s|\mathbf{r}) = P_{\text{ind}}(s|\mathbf{r})$ for every s and $\mathbf{r}$.

The expressions shown above are perhaps the most useful description for obtaining insight into the behavior of the information components under different statistical assumptions relating to the neural code; however, they are not necessarily the best way to *estimate* the individual components. However, the components can also be written as a sum of entropies and entropy-like quantities, which can then be computed using the entropy estimation algorithms described earlier in this entry (Pola et al. 2003; Montani et al. 2007; Schultz et al. 2009). Note that as shown by Scaglione and colleagues (Scaglione et al. 2008, 2010), the components in Eqs. 14, 15, 16, and 17 can, under appropriate conditions, be further decomposed to tease apart the relative role of

autocorrelations (spikes from the same cells) and cross-correlations (spikes from different cells).

Maximum Entropy Approach to Information Component Analysis

The conceptual basis of the information component approach is to make an assumption that constrains the statistics of the response distribution $P(\mathbf{r}|s)$, compute the mutual information subject to this assumption, and, by evaluating the difference between this and the “full” information, calculate the contribution to the information of relaxing this constraint. By making further assumptions, the contributions of additional mechanisms can in many cases be dissected out hierarchically. As an example, by assuming that the conditional distribution of responses given stimuli is equal to the marginal distribution $P(\mathbf{r}|s) = P_{\text{ind}}(\mathbf{r}|s)$ and substituting in to the mutual information equation, one can define an information component I_{ind} . This component can then be further broken up

$$I_{\text{ind}} = I_{\text{lin}} + I_{\text{sig-sim}}. \quad (18)$$

with I_{lin} and $I_{\text{sig-sim}}$ as defined in the previous section. The correlational component, I_{cor} , is then just the difference between I_{ind} and the total mutual information. This can also be further broken up as

$$I_{\text{cor}} = I_{\text{cor-ind}} + I_{\text{cor-dep}}. \quad (19)$$

This approach can be extended further. For instance, the assumption of a Markov approximation can be made, with a memory extending back q timesteps, and the information computed under this assumption (Pola et al. 2005). More generally, any simplified model can be used, although the maximum entropy models are of special interest (Montemurro et al. 2007; Schaub and Schultz 2012)

$$P_{\text{simp}}(\mathbf{r}|\mathbf{s}) = \frac{1}{Z} \exp \left\{ \lambda_0 - 1 + \sum_{i=1}^m \lambda_i g_i(\mathbf{r}) \right\} \quad (20)$$

with parameters λ_i implementing a set of constraints reflecting assumptions made about what are the important (non-noise) properties of the empirical distribution and the partition function Z ensuring normalization. An example of this is the Ising model, which has been used with some success to model neural population response distributions (Schneidman et al. 2006; Shlens et al. 2006; Schaub and Schultz 2012). Estimation of the Ising model for large neural populations can be extremely computationally intensive if brute force methods for computing the partition function are employed; however, mean field approximations can be employed in practice with good results (Roudi et al. 2009; Schaub and Schultz 2012).

Binless Methods for Estimating Information

In applications in neuroscience, typically at least one of the random variables (stimuli or responses) is discrete, and thus the approach of discretizing

one or more of the variables is often taken. However, where stimuli and responses are both continuous (an example might be local field potential responses to a white noise sensory stimulus), it may be advantageous to take advantages of techniques better suited to continuous signals, such as kernel density estimators (Moon et al. 1995), nearest neighbor estimators (Kraskov et al. 2004), or *binless* metric space methods (Victor 2002).

Calculation of Information-Theoretic Quantities from Parametric Models

An alternative to measuring information-theoretic quantities directly from observed data is to fit the data to a model and then to either analytically or numerically (depending upon the complexity of the model) compute the information quantity from the model. Examples include analytical calculations of the information flow through models of neural circuits with parameters fit to anatomical and physiological data (Treves and Panzeri 1995; Schultz and Treves 1998; Schultz and Rolls 1999) and parametric fitting of probabilistic models of neural spike firing (Paninski 2004; Pillow et al. 2005, 2008), of spike count distributions (Gershon et al. 1998; Clifford and Ibbotson 2000), or of neural mass signals (Magri et al. 2009). It should come as no surprise that “there is no free lunch,” and although in principle information quantities can be computed exactly under such circumstances, the problem is moved to one of assessing model validity – an incorrect model can lead to a bias in either direction in the information computed.

Cross-References

► [Summary of Information-Theoretic Quantities](#)

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Estimation of Neuronal Firing Rate

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Synonyms

Bayesian estimation; Firing frequency; Kernel smoother; PSTH; Spike rate; Time histogram

Definition

Neuronal firing rate is defined as the frequency at which a neuron discharges short-duration

electrical pulses called firings or spikes, measured as number of spikes per second [sp/s] or hertz [Hz]. Because the duration of each electrical discharge is typically much shorter than interspike intervals, a spike is often idealized as a point event on the time axis. The temporal occurrence of neuronal spikes is irregular and nonreproducible even under identical stimuli. In principle, such randomness can be removed by collecting a huge number of spike trains from repeated trials and constructing a histogram of arbitrarily fine resolution for the superimposed data. However, in practice, experiments are conducted with a small number of trials over short periods during which neuronal conditions may not alter significantly. To obtain reasonable estimates from limited number of data, inferential statistics is required.

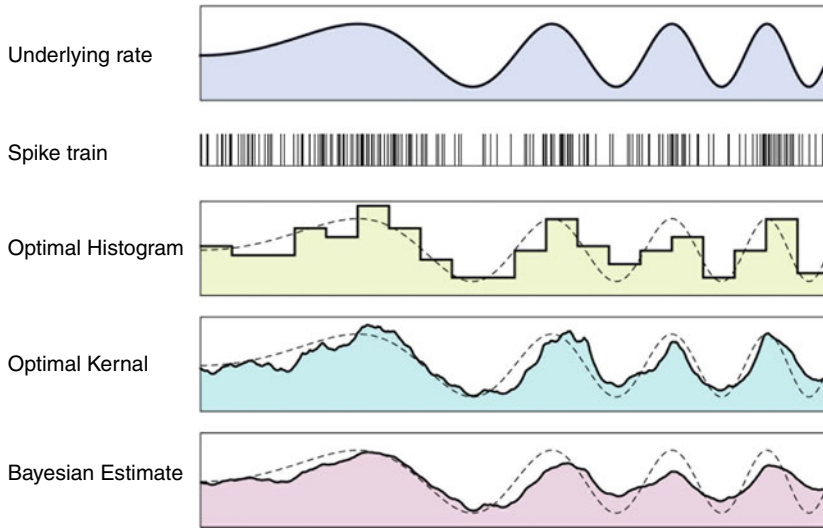
Detailed Description

Here we introduce standard rate estimators such as the histogram, kernel smoother, and Bayesian method, with instructions for selecting their binsize, bandwidth, and hyperparameters (Fig. 1).

These optimization methods assume an inhomogeneous Poisson process whereby spikes are drawn independently from some underlying rate. This assumption holds if numerous independent spike trains are superimposed (Snyder 1975; Daley and Vere-Jones 2003), but is not necessarily appropriate for analyzing one or a few spike trains. We also introduce newer methods applicable to such non-Poisson firings.

Histogram Method

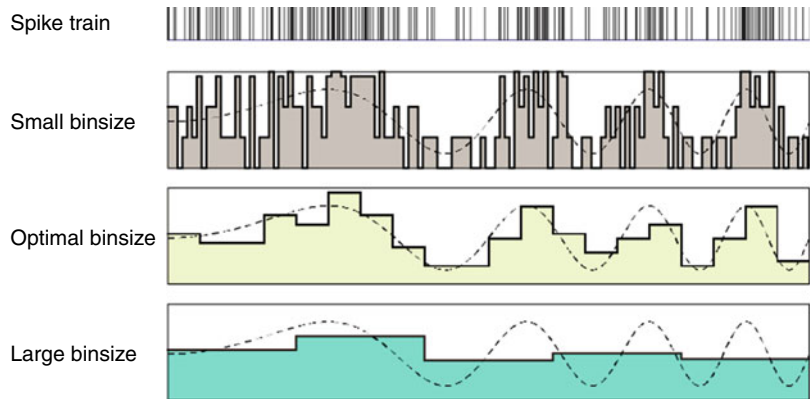
A peristimulus time histogram (PSTH) is constructed by aligning spike trains at the onset of a stimulus or certain behavioral condition and drawing tabular rectangles whose height equals the number of spikes counted in each bin (Gerstein and Kiang 1960; Abeles 1982). Each ordinate should be rescaled by dividing the spike count by the binsize and number of trials, so that its average height represents the firing rate per trial. For a



Estimation of Neuronal Firing Rate, Fig. 1 A spike train derived from the underlying rate and optimal histogram, kernel density estimate, and Bayesian estimate

obtained using web-applications provided in <http://www.ton.scphys.kyoto-u.ac.jp/~shino/toolbox/english.htm>

Estimation of Neuronal Firing Rate, Fig. 2 Time histograms constructed with small, optimal, and large bin sizes



given set of spike trains, different binsizes lead to different PSTH shapes. If the binsize is very large/small, the histogram may become too flat/spiky to represent the temporal modulation (Fig. 2). There should be an appropriate binsize for a given set of spike times, based on the goodness of fit of a PSTH to the (unknown) underlying rate.

Here we consider selecting the binsize by minimizing the mean integrated squared error (MISE) (Rudemo 1982; Shimazaki and Shinomoto 2007; Shinomoto 2010) between the histogram $\hat{\lambda}(t)$ and unknown underlying rate $\lambda(t)$, defined by $MISE \equiv \frac{1}{T} \int_0^T E(\hat{\lambda}(t) - \lambda(t))^2 dt$, where T is the entire observation interval and E refers to taking

expectation over all possible spike trains that can be realized under given rate. The height of the histogram $\hat{\lambda}(t)$ is given by the number of spikes k counted in each bin divided by the binsize Δ and number of trials n . Using the bias-variance decomposition, it was proven that the MISE can be expressed in terms of the spike count k as

$$MISE = \frac{2\langle V(k) \rangle - \langle E(k - E(k))^2 \rangle}{(n\Delta)^2} + \text{constant},$$

where V and $\langle \cdot \rangle$ refer to taking variance over all possible spike trains and averaging across all bins, respectively. Though the variance cannot be

estimated from a single spike train, if spikes are derived independently, the spike count in each bin follows the Poisson relationship $V(k) = E(k)$; as a result, this part becomes an observable quantity. The second term on the right-hand side is rewritten as $\langle E(k - E\langle k \rangle)^2 \rangle = \langle E(k - \langle k \rangle)^2 \rangle + \langle V(k) \rangle / M$, where M represents the total number of bins. Thus, the MISE can be expressed solely in terms of the expectation of spike counts,

$$\text{MISE} = \frac{E\left(2\langle k \rangle(1 - 1/2M) - \langle (k - \langle k \rangle)^2 \rangle\right)}{(n\Delta)^2} + \text{constant}.$$

Representing the expectation E as a single spike train and ignoring the correction of $1/2M$, we obtain $\text{MISE} = \frac{2\bar{k} - v}{(n\Delta)^2} + \text{constant}$ where $\bar{k} \equiv \sum k_i / M$ is the mean spike count and $v \equiv \sum (k_i - \bar{k})^2 / M$ is the spike count variance across all M bins, both of which depend on the bin size Δ . Thus, a histogram can be optimized for any given spike data, simply by minimizing this MISE.

Kernel Smoothing Method

The rate profile can also be obtained by convoluting the density kernel. $d_\Delta(t)$ with spike times

$$\{t_j\} \equiv \{t_1, t_2, \dots, t_K\}: \hat{\lambda}(t) = \frac{1}{n} \sum_{j=1}^K d_\Delta(t - t_j)$$

where n is the number of trials and K is the total number of spikes contained in all trials. The density kernel can be a rectangular boxcar function, two-sided exponential function, or Gaussian function, satisfying the normalization, $\int d_\Delta(t) dt = 1$, and possessing a finite bandwidth, $\int t^2 d_\Delta(t) dt = \Delta^2$. Generally the kernel method yields a smoother estimation than the histogram, but the goodness of fit still depends on the bandwidth Δ . The bandwidth may also be selected under the MISE minimization principle. Under the Poisson assumption, the MISE is obtained (Shimazaki and Shinomoto 2010) as follows

$$\begin{aligned} \text{MISE} &= \frac{1}{n^2} \\ &\times \left(\sum_{i,j} \phi_\Delta(t_i - t_j) - 2 \sum_{i \neq j} d_\Delta(t_i - t_j) \right) \\ &+ \text{constant}, \end{aligned}$$

where

$$\phi_\Delta(t_i - t_j) \equiv \int d_\Delta(t - t_i) d_\Delta(t - t_j) dt.$$

For a Gaussian kernel, $d_\Delta(t) \equiv (1/\sqrt{2\pi}\Delta) \exp(-t^2/(2\Delta^2))$, the convoluted function is given as $\phi_\Delta(t) \equiv (1/\sqrt{2\pi}\Delta) \exp(-t^2/(4\Delta^2))$.

The abovementioned optimization method determines a single fixed bandwidth by assuming stationary rate fluctuation. However, neurons often exhibit abrupt increase of spikes followed by gradual decrease. In such a case, a small bandwidth may detect the sharp rise, but it may add unnecessary fluctuation in the relaxation stage, whereas a large bandwidth is suitable for expressing the smooth relaxation, but it may blur the rise in firing rate. There are several methods that consider such non-stationary data with adaptive time-modulated hyperparameters; Abramson's adaptive kernel method modulates the bandwidths adaptively at the sample point (Abramson 1982); the locfit algorithm fits a polynomial to a log-density function under the principle of maximizing a locally defined likelihood (Loader 1999); BARS is a spline-based adaptive regression method on exponential family response model, expected to smooth data without missing its abrupt change (DiMatteo et al. 2001; Kass et al. 2003). Comparison of the model performances is given in Shimazaki and Shinomoto (2010).

Bayesian Methods

In the inhomogeneous Poisson process, spikes are drawn independently from the underlying spiking rate $\lambda(t)$. The probability of spiking at $\{t_j\}$ is given by Cox and Lewis (1966) and Daley and Vere-Jones (2003)

$$p(\{t_j\}|\lambda(t)) = \left(\prod_{j=1}^K \lambda(t_j) \right) \exp \left(- \int_0^T \lambda(t) dt \right).$$

The underlying rate is inferred from the given data using Bayes' formula:

$$p(\lambda(t)|\{t_j\}) = \frac{p(\{t_j\}|\lambda(t))p(\lambda(t))}{p(\{t_j\})}.$$

Here we give the prior distribution functional that penalizes the large gradient in the rate, i.e.,

$$p(\lambda(t)) \propto \exp \left(-\beta \int_0^T \left(\frac{d\lambda}{dt} \right)^2 dt \right),$$

where the hyperparameter β represents the degree of flatness of the rate, which determines the jaggedness of the estimated rate. The hyperparameter may be selected by maximizing the marginal likelihood, given by the functional integration over all possible rate processes

$$p_\beta(\{t_j\}) = \int D\{\lambda(t)\} p(\{t_j\}|\lambda(t)) p(\beta)(\lambda(t)),$$

using the expectation and maximization (EM) method (Smith and Brown 2003; Shimokawa and Shinomoto 2009). With the determined hyperparameter, we obtain the maximum *a posteriori* (MAP) estimate of the rate $\hat{\lambda}(t)$, which maximizes the posterior distribution functional.

Extension of the Method Toward Non-Poisson Data

All abovementioned optimization methods are derived under the Poisson assumption. However, neurons express non-Poissonian features in their firing patterns; in particular, spike occurrence is influenced by preceding spiking events (Shinomoto et al. 2009). Thus, the optimization methods should be revised if one requires to estimate the rate of one or a few spike trains.

The histogram optimization method was extended to accommodate non-Poisson data, by replacing the equality between the spike count variance and mean by the Fano factor (Omi and Shinomoto 2011). The Fano factor approximately equals the square of the coefficient of variation of interspike intervals obtained from a single spike train (Cox 1962). A similar idea is applicable to the Bayesian rate estimation method. It was found that the rate estimation is significantly improved or the temporal resolution of the rate profile becomes finer, if the spike train is more regular than Poisson randomness (Cunningham et al. 2008; Koyama et al. 2013).

Application Programs

The following website is dedicated to all optimizing principles introduced in this article: <http://www.ton.scphys.kyoto-u.ac.jp/~shino/toolbox/english.htm>

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Event-Driven Artificial Cochleas

► Neuromorphic Sensors, Cochlea

Evolutionary Algorithms

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Synonyms

[Evolutionary strategies/genetic algorithms](#)

Definition

Evolutionary algorithms are a family of computational approaches inspired by natural selection

that address two main topics: developing algorithms for optimization and understanding biological evolution. The former use is the more common, evolutionary algorithms being one of the main tools for parallel optimization. Indeed, they have been applied successfully to diverse optimization problems such as modeling the electrical properties of neurons (Achard and De Schutter 2006; Druckmann et al. 2007; Keren et al. 2009; Smolinski and Prinz 2009), automated writing of programs for specific tasks, and financial market modeling.

Detailed Description

The idea that natural evolution could be used as an inspiration for optimization algorithms rose in the 1950s and 1960s (Rechenberg 1965; Fogel et al. 1966; Schwefel 1977). One of the most widespread forms, genetic algorithms (GAs), was invented by J. Holland in the 1960s. At their core these algorithms are computational simulations of a simplified version of evolution: a set of individuals (a population) evolves over numerous iterations (generations) whereby the next population is determined by replicating successful solutions (individuals with high fitness) and adjusting them stochastically (mutation, crossover). There are many forms of evolutionary algorithms and their taxonomy goes well beyond the scope of this brief article. Here, we will focus mainly on genetic algorithms.

Genetic algorithms have a number of properties that make them useful optimization tools. First, they simultaneously consider a large set of solutions, thereby alleviating to some extent the problem of optimization converging on only locally optimal solutions. Since most real-world problems involve nonlinearity and complex variable interactions, there are often multiple solutions that are only local maxima, i.e., locally optimal but are not the true global optimum. Being able to simultaneously consider a large number of solutions helps to mitigate this problem since the multiple parallel solutions considered typically span a wide range of parameters, affording a more global view of the problem and

revealing the nature of local minima. Second, the formulation of genetic algorithms makes them easily parallelizable. Accordingly, they can take advantage of the increasingly common high-performance computing clusters that have dozens or even hundreds of parallel processors.

The basic operation of genetic algorithm optimization is straightforward consisting of several simple steps. Starting with an initial set of solutions, one performs multiple iterations of evaluating the current set of solutions. Then the best solutions are chosen to form the basis of the next set of solutions, in an iterative attempt to find ever better solutions (see pseudo code in Table 1). Below we briefly describe each step:

- *Evaluation (fitness selection)* – in the case of optimization, this step is typically comprised of evaluating the function to be optimized for every solution in the population. This step can be performed very effectively using parallel computing clusters since the evaluation of each solution is completely independent of the others.
- *Propagation (reproduction)* – the goal of this operation is to make multiple duplicates of successful solutions (which will later be perturbed) and eliminate poorer solutions in an effort to move towards more valuable solutions in the next generation. In the case of optimization, more successful solutions are

simply solutions with a higher fitness (or lower error value). One straightforward approach for propagating successful solution is to stochastically select which solutions will propagate according to a probability proportional to the solution’s success.

- *Evolution (mutation, crossover)* – the goal is to semi-randomly change parameter values in an effort to stochastically strike upon a more successful solution. This operation represents the main search aspect of the algorithm. Often the evolution is performed through one or both of the following operators: mutation and crossover. Mutation in principle consists simply of jittering the parameter values. Crossover operators are analogous to genetic crossover in that two “parent” solutions are combined to create a new solution that is different from either parent.

Genetic Algorithms in Practice: A Simple Binary Value Genetic Algorithm

To better understand the nature of genetic algorithms, we describe in more detail a specific implementation of a genetic algorithm, a simple binary value genetic algorithm (Holland 1992).

Consider the very simple problem of optimizing the function:

F = sin (X + Y/2) + Y - 0.5

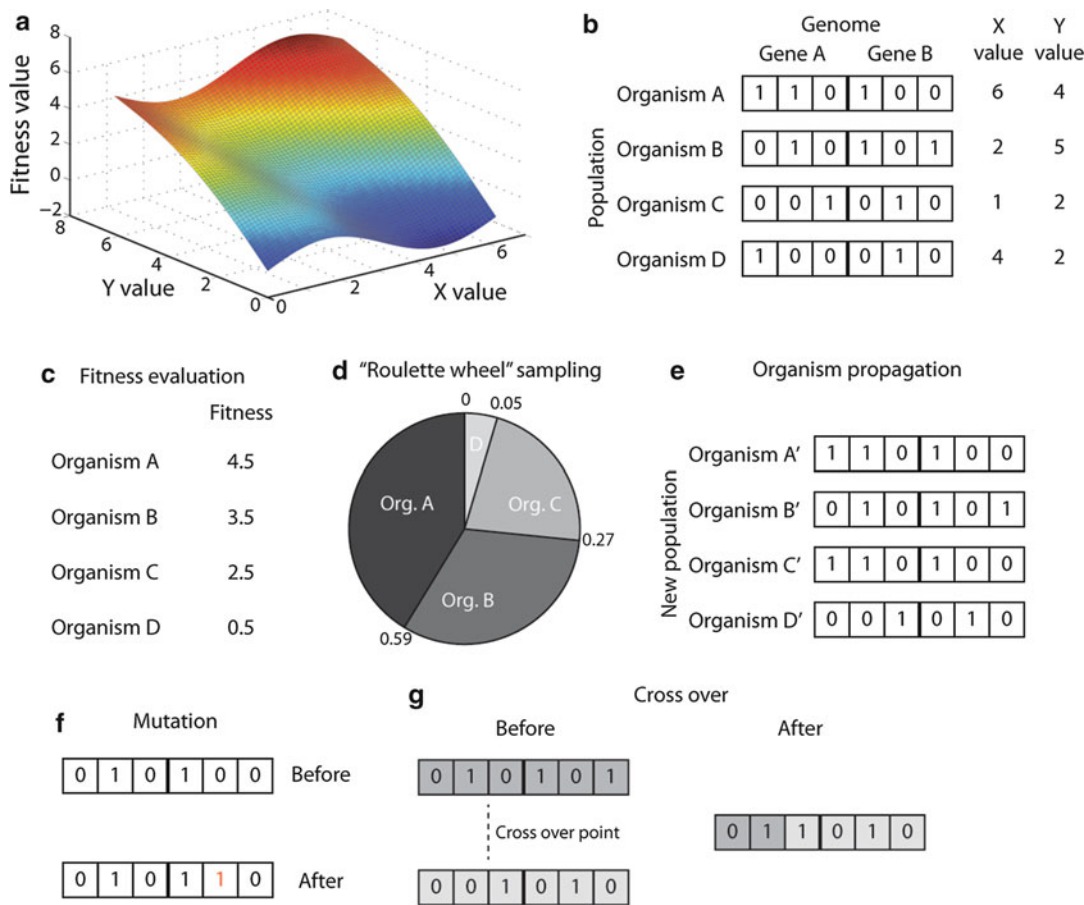
The problem has two parameters: *X* and *Y*, and we seek the values of these parameters that maximize the function *F* (Fig. 1a). Note that this function is trivial to optimize without genetic algorithms and is merely used as a simple example. Below, we describe the steps involved in running the genetic algorithm on this simple problem.

Representing a Solution

In the original genetic algorithm formulation a binary string represents each parameter value, and an ordered collection of these binary strings represents the full information that defines a

Evolutionary Algorithms, Table 1 Genetic algorithms repeatedly test a set of solutions (a population) through multiple iterations (generations). In each iteration all solutions are evaluated. Then the successful solutions are used to generate the basis for the next iteration of solutions. These tentative solutions are then perturbed stochastically to yield the next iteration of solutions and the cycle continues until it reaches a predetermined number of generations

Pseudocode for basic genetic algorithm
Initialize population
For generation in generations
For solution in solutions
Evaluate solution
Propagate successful solutions
Evolve propagated solutions



Evolutionary Algorithms, Fig. 1 Schematic representation of binary valued genetic algorithm steps. (a) Fitness function. In this example, a simple function of two parameters (X , Y) is optimized. (b) Genomes and populations. A genetic algorithm evaluates in parallel a number of tentative solutions. Solutions are referred to as organisms and the set of solutions as a population. In a binary genetic algorithm the parameter values of each solution are expressed as a string of binary numbers (depicted in squares) and referred to as an organism's genome. (c) Organism fitness. Each organism in the population is assigned a fitness value by the optimization objective. (d) Population propagation. In order to select which of the organisms will form the basis of the population in the next generation (i.e., evaluation iteration), a propagation

procedure is defined. In this case *roulette-wheel* sampling assigns a part of the range of a random variable to each solution in a manner proportional to the relative fitness of that solution. Letters denote which part of the 0–1 range is associated with each solution. Numbers correspond to the range limits for each solution. (e) New generation basis. After the propagation procedure a basis for the next generation's population is defined which will then be transformed by the genetic operators: mutation and crossover. (f) Mutation. Solutions are stochastically perturbed, in this case by a probability of flipping each bit of the genome. (g) Crossover. This genetic operator combines two solutions by joining a portion of each genome, defined by the cross-over point, from each of the two

particular solution (Fig. 1b). The analogy to biology is that each parameter corresponds to a gene, with the different values being different alleles; the entire collection of parameter values is an organism's genome.

For instance, the binary string 110 represents the value 6. Therefore, the parameter values of organism A in our example are $X = 6$, $Y = 4$ (Fig. 1b). More generally, instead of having a direct binary encoding as we have here, the binary values can be

used to represent values within a given range. A common approach is to divide the parameter range by the maximum value afforded by the binary string and have the binary number represent the fraction times the binary number value. For instance, a 3-long binary string encodes one of eight values: (0, 1, 2, 3, 4, 5, 6, 7). Therefore, if the parameter range for a particular parameter was a minimum of 1 and a maximum of 2, the value 000 would represent $1 + 0/7$, i.e., 1; the string 111 would represent $1 + 7/7$, i.e., 2; and the value 110 would represent $1 + 6/7$. Defining r as the range of the parameter value (e.g., 1–2), this can be written as:

$$X = \min(r) + (\text{binary value}) * (\max(r) - \min(r)) / (\text{number of possible binary values} - 1)$$

Initializing the Population

In order to begin running the algorithm, an initial population, i.e., an initial set of tentative solutions, needs to be generated. Typically, this is performed by setting random values to the initial parameter values. In our example one can accomplish this by flipping a coin for each binary value in the genome of each solution.

Evaluating a Solution

In this step we evaluate the fitness of all the organisms in the current population. In the case of the problem we chose, the fitness of an organism can be computed directly from its definition simply by evaluating the function F for the X and Y values defined by each solution (Fig. 1a, b) with little difficulty or computational cost (Fig. 1c). However, in more complex, real-world problems, the parameter values typically correspond to properties of some model that will then be simulated and the results of the simulation evaluated. Accordingly, solution evaluation in the more generic case is the computationally expensive part of the algorithm. Fortunately, as mentioned above it can be performed independently in parallel for each organism.

Propagating Solutions

In this step the old population (Fig. 1b, c) is transformed into a basis for the new population

(Fig. 1e). The general goal of this step is to have solutions that were found to be more successful take up a larger fraction of the new population. A simple form of propagation capturing this notion is “roulette-wheel sampling” in which each solution is assigned a fraction of a random variable’s range according to its fitness. For simplicity the random variable is typically chosen from the uniform distribution between 0 and 1.

A “roulette wheel” (Fig. 1d) is constructed by dividing each solution’s fitness by the sum of the fitness of all individuals. Specifically, the cumulative sum of the organisms’ fitness divided by the total fitness defines an allocation of the random variable range 0–1 to particular solutions (Fig. 1d). In this example, the sum of population fitness is 11 (Fig. 1c), and thus, organism A has a relative fitness of $4.5/11 = 0.41$, B a relative fitness of $3.5/11 = 0.32$, etc. In the roulette wheel organism D is thus assigned the sector from 0 to 0.045, organism C the sector from 0.045 to 0.27, organism B the sector from 0.27 to 0.59, and organism A the sector from 0.59 to 1. A solution (an organism) is selected for propagation if the random number instantiation generated is included in the organism’s sector (e.g., for organism A, if the random number generator produced a number between 0.59 and 1). The process is repeated for each organism in the new population.

Evolving Solutions

The basis for the new population generated by solution propagation is then subject to evolution before becoming the actual new population. Evolution in our example is represented by two operations – mutation and crossover. Mutation is simple – for each binary number in the genome, a probability is assigned to randomly flip the binary value at a particular location. Instantiations of the random numbers are then generated and the binary values changed accordingly (Fig. 1f). The crossover operation involves a few more steps. First, a random variable is used to pick whether crossover occurs for each solution. For a solution in which crossover is to occur, two parents need to be chosen. One parent is the one from which the solution was propagated, and the other can be

chosen randomly, for instance, by applying the roulette wheel again. Given the two parents, a random location on the genome is chosen to be the “crossover point” (Fig. 1g). Then a new organism is created by taking the genome from the first parent up until the crossover point, and the genome from the second parent from the crossover point to the end of the genome (Fig. 1g). Crossover will both trade multiple parameter values between solutions and also change the parameter value if the crossover point falls in the middle of a binary string encoding a particular parameter.

Evaluating Further Generations

At this point we have a new population with unknown fitness values, a state similar to the one just after initializing the population. In other words, we have completed the analysis of one generation. Accordingly, the genetic algorithm proceeds by iterating upon the above steps (fitness evaluation, propagation, etc.) for multiple generations. The number of generations to be evaluated can either be determined beforehand according to computational costs or generations can be iterated until a predefined success condition is achieved.

The genetic algorithm described above is just one possible implementation of the general concept (see, for instance, the journal *Evolutionary Computation* or the reference books (Goldberg 1989; Holland 1992; Mitchell 1996)). One important variant worth mentioning is the class of multi-objective optimization genetic algorithms in which the goal, like in many real-life problems, is to simultaneously optimize multiple, possibly conflicting measures of fitness (Deb 2001; see entry on ► “Multi-objective Evolutionary Algorithms”).

Theoretical Analysis of Genetic Algorithms

Beyond the empirical success of genetic algorithms as stochastic optimization approaches,

some theoretical results regarding their success can be derived. At a general level, the initial theory of genetic algorithm function, first formulated by J. Holland (1992), attributes the success of genetic algorithms to the ability to evaluate, discover, and improve building blocks of good solutions in an efficient, parallel fashion. To formalize the notion of building blocks, Holland introduced the concept of a schema. A schema is defined as a series of bits composed of three characters: 1, 0, or an *, where 0 and 1 correspond to their binary values and the asterisk corresponds to “either-1-or-0.” For instance, the schema 0**1 corresponds to all 4-bit strings that begin with a 0 and end with a 1 (e.g., 0111 or 0101).

The theoretical results concern the dynamics of the fraction of the population containing a particular schema. Specifically, whether schema associated with higher fitness values takes up larger parts of the population as the algorithm evolves through its iterations. Intuitively, this is a useful way to define whether the complex, stochastic dynamics of a genetic algorithm are indeed productive, since a good algorithm should promote good solutions. The mathematical results showing that schema tied to higher fitness indeed become more common in the population go beyond the scope of this entry but can be found in Holland’s textbook (Holland 1992).

Evolutionary Algorithms as a Tool for Understanding Natural Evolution

A less widely known application of evolutionary algorithms is theoretical analysis of simplified scenarios of natural evolution. Unlike the more generic nature of their use for optimization, genetic algorithms for analysis of evolution are quite study dependent. Therefore, we will only briefly introduce one such example (additional ones can be found in Holland 1992, Mitchell 1996).

Consider the puzzling phenomenon of the outlandish feathers of a peacock. Clearly, the feathers in and off themselves do not improve the animal's ability to survive and if anything actually impede it by higher expenditure of energy for their generation/maintenance and added difficulty in locomotion. Therefore, they may actually be detrimental to their survival, raising the question of how did such properties come about? Fisher (1958) originally suggested a qualitative solution – a “runaway process” by which a trait which initially improves survivability becomes exaggerated. The runaway nature of the process has to do with the fact that if members of a species preferentially choose partners according to some property (e.g., the elaborateness of plumage), not only will the animals with that property mate more, but their offspring are more likely to inherit the property itself (if of the sex that displays the property) or the preference for the property (if of the other sex). However, the question remains whether such a process would be stable, yielding long lasting populations that actually have such secondary traits.

This process was studied analytically by Kirkpatrick (1982) who was able to show that a whole range of steady-state equilibrium solutions exist whereby the frequency of organisms with secondary characteristics can range from either the entire population to no organisms at all (Kirkpatrick 1982). The intuition behind these solutions is that the dynamics become stable if the deficit that males suffer by having the secondary trait is offset by their mating advantage. Though it is satisfying to know that steady-state solutions with many organisms having secondary traits exist, one would like to know under which conditions the dynamics of the population develop to a state whereby secondary traits are a substantial part of the population, as we see in some species in nature. Moreover, one might be interested in examining the problem under more general assumptions than those required for the analytical solutions. Specifically, the analytical solution implicitly

assumes that each animal could mate with each other animal, an assumption that is clearly violated by the physical segregation of different animals.

To address these open questions, the study of this problem was extended by Collins and Jefferson (1992) who used genetic algorithms to simulate the evolution of individual organisms in a population of organisms. Simulating the dynamics has a number of favorable properties. First, in the simulation one can easily follow the detailed evolution of properties over time, allowing the full trajectory of the evolution of a trait in a population to be studied. In addition, more complicated assumptions, such as spatial segregation of populations, can be easily applied directly by adjusting the rules of the genetic algorithm. The simulations first confirmed that the steady-state solutions described by the analytical calculations can indeed be found when the original assumptions are used. Beyond that, the simulations showed that once the assumption regarding the ability of all animals to mate with all animals is lifted, the region of stability is found to be broader than that predicted by the analytical work. In addition, the validity of other assumptions (e.g., haploid instead of diploid organisms) was also explored, thereby advancing the understanding of sexual selection.

Summary

In summary, evolutionary algorithms, simulations of simplified models of natural evolution, are both scientific tools in their own right and general-purpose optimization approaches. Their study is an active, rich scientific field and the reader is encouraged to explore the relevant textbooks and reviews.

Cross-References

► [Multi-objective Evolutionary Algorithms](#)

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Evolutionary Strategies/ Genetic Algorithms

► [Evolutionary Algorithms](#)

Excitability Defect

► [Epilepsy: Abnormal Ion Channels](#)

Excitability Disorder

► [Epilepsy: Abnormal Ion Channels](#)

Excitability: Types I, II, and III

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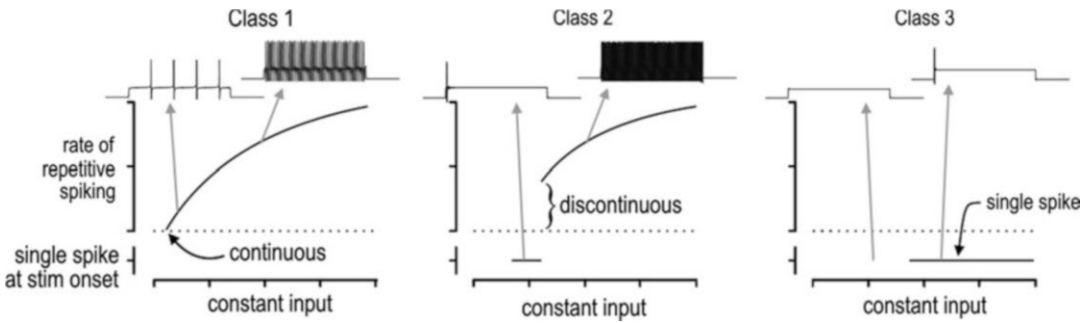
Definition

In 1948, Hodgkin distinguished between three classes of excitability on the basis of spiking patterns observed in crustacean axons. This classification scheme is still applied today because it captures fundamental differences in excitability that stem from how action potentials, or spikes, are generated. The nonlinear dynamical mechanism responsible for spike initiation in each cell class has been worked out, and the biophysical implementation of those dynamical mechanisms is reasonably well understood. Moreover, the differences in spike initiation that define each class confer differences in metrics like the phase-response curve (PRC) and spike-triggered average (STA), meaning that this simple classification scheme is predictive of important differences in neural coding.

Detailed Description

Historical Background

Based on single fiber recordings from the crab *Carcinus maenas*, Hodgkin (1948) identified three different classes of excitability. Class 1 axons were capable of spiking repetitively across a broad range of rates (5–150 spikes/s) in proportion to the stimulus intensity. Class 2 axons were also capable of spiking repetitively but across a narrower range (75–150 spikes/s),



Excitability: Types I, II, and III, Fig. 1 Defining differences in frequency-current (f - I) curves. Class 1 neurons can fire repetitively at arbitrarily slow rates, whereas class

2 neurons cannot, and class 3 neurons typically fire only a single spike even at high stimulus intensities

implying that they could not maintain slow repetitive spiking. Class 3 axons were by in large incapable of repetitive spiking and were also noted to spike at a shorter latency after stimulation than the other two classes. The differences that Hodgkin described can be readily distinguished from frequency-current (f - I) curves, as illustrated in Fig. 1: the f - I curve is continuous for class 1 neurons, discontinuous for class 2 neurons, and undefined for class 3 neurons.

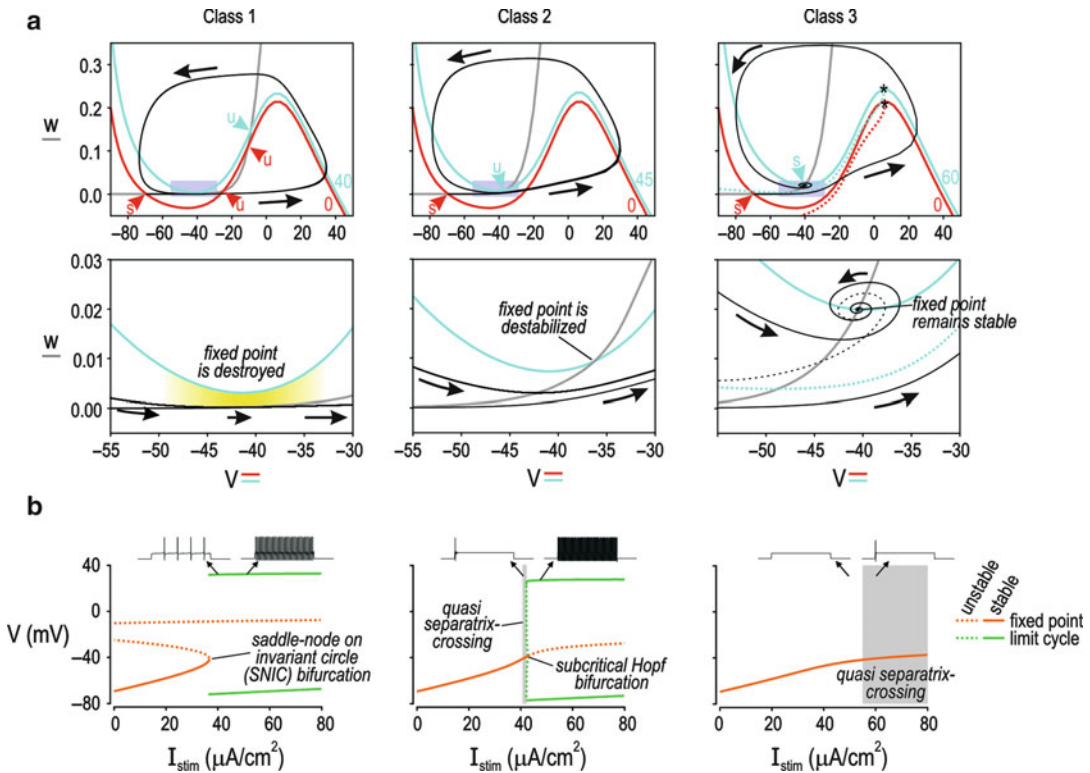
Differences in Nonlinear Dynamics

Hodgkin's classification scheme has stood the test of time because it captures fundamental differences in neuronal excitability. The distinction between continuous and discontinuous f - I curves resurfaced most notably when, in 1989, Rinzel and Ermentrout provided dynamical explanations for the emergence of zero and nonzero frequency oscillations. Using a Morris-Lecar model, they showed that repetitive spiking in a class 1 neuron arises through a saddle node on invariant circle (SNIC) bifurcation, whereas repetitive spiking in a class 2 neuron arises through a subcritical Hopf bifurcation (Rinzel and Ermentrout 1989). These nonlinear dynamical mechanisms are illustrated in Fig. 2 and are summarized below. See also Izhikevich (2007) for an in-depth discussion.

The Morris-Lecar model they used comprises only two variables, a fast activation variable V and a slower recovery variable w . Behavior of the

model can thus be explained entirely on the basis of how those two variables interact. That interaction can be visualized by plotting V against w , as shown in Fig. 2a. How the variables evolve relative to one another is explained by how the V - and w -nullclines intersect, where nullclines represent everywhere in phase space where V or w remain constant. Importantly, depolarizing stimulation shifts the V -nullcline upward and can therefore change if and how that nullcline intersects the w -nullcline.

In class 1 excitability, the V - and w -nullclines intersect at three points prior to stimulation. The left intersection constitutes a stable fixed point that controls membrane potential. Stimulation shifts the V -nullcline upward. If it is shifted far enough (i.e., if stimulation exceeds current threshold or rheobase), two of the intersection points will be destroyed and repetitive spiking ensues – this constitutes an SNIC bifurcation. In effect, so long as the stable fixed point exists, membrane potential will stay at that point; but when that point is absent (which occurs during supra-threshold stimulation), the membrane potential enters a stable limit cycle that corresponds to repetitive spiking. Importantly, the trajectory around the limit cycle slows down each time it passes close to where the stable fixed point used to exist, which translates into a reduced rate of repetitive spiking. Indeed, at the precise stimulus intensity that causes the V -nullcline to shift just far enough that the left and center fixed points fuse, a homoclinic orbit is formed and firing rate is infinitesimally small.



Excitability: Types I, II, and III, Fig. 2 Differences in the nonlinear dynamical mechanisms responsible for spike initiation. (a) Phase planes show the fast activation variable V plotted against the slower recovery variable w . Bottom panels show enlarged views of mauve-shaded regions in top panels. Colored lines show V -nullclines (i.e., conditions for which $dV/dt = 0$) and gray lines show w -nullclines (i.e., conditions for which $dw/dt = 0$). Positions at which the V - and w -nullclines intersect represent fixed points and can be stable (s) or unstable (u) based on whether trajectories move toward or away from that point. On each phase plane, the V -nullcline is represented twice: once without stimulation (red) and once during excitatory stimulation (blue). Excitatory stimulation shifts the V -nullcline upward and can qualitatively change how it intersects the w -nullcline, as summarized in bifurcation diagrams in B. (b) Bifurcation diagrams show the fixed

points and limit cycles (represented by their maximum and minimum V) as stimulus intensity I_{stim} is systematically increased. In class 1 excitability, repetitive spiking begins when the stable fixed point and its neighboring unstable fixed point are destroyed through a saddle node on invariant circle (SNIC) bifurcation. In class 2 excitability, repetitive spiking begins when the stable fixed point is destabilized through a subcritical Hopf bifurcation. In class 3 excitability, a single spike is generated when abrupt stimulation shifts the V -nullcline enough that the start of the trajectory (which corresponds to the initial stable fixed point labeled with a red s) ends up below the shifted quasi-separatrix (shown as a dotted blue curve). A quasi-separatrix crossing can also generate single spikes in class 2 neurons for intermediate stimulus intensities. See text for details (Modified from Prescott et al. (2008))

In class 2 excitability, the V - and w -nullclines intersect at a single, stable point prior to stimulation. Spiking starts when the vertical shift in the V -nullcline caused by stimulation destabilizes that point – this constitutes a Hopf bifurcation. To a rough approximation, destabilization occurs when the V - and w -nullclines intersect to the right of the local minimum in the V -nullcline, whereas the fixed point is stable when the nullclines intersect

to the left of the minimum. Local stability analysis near the fixed point should be applied to determine stability more accurately.

These changes in nullcline geometry are directly reflected in the bifurcation diagrams shown in Fig. 2b. In bifurcation analysis, a parameter of interest (such as stimulus intensity) is systematically varied to determine at what values the system qualitatively changes behavior, e.g.,

switches from quiescence to repetitive spiking. The SNIC and Hopf bifurcations described above are labeled on those diagrams. Note that class 3 excitability is not associated with a bifurcation; the single fixed point remains stable throughout the entire range of tested stimulus intensities. However, upon an abrupt increase in stimulus intensity, a single spike can be produced, as shown by gray shading. The dynamical explanation for this spike initiation mechanism was worked out (Prescott et al. 2008) and is described below.

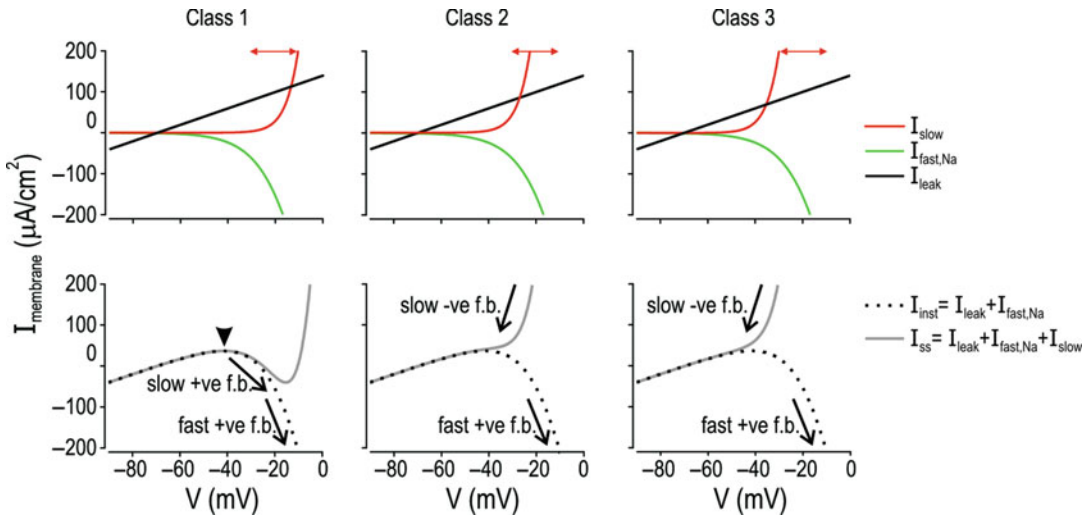
In class 3 excitability, the V - and w -nullclines intersect at a single stable point which, as already mentioned, remains stable even when stimulus intensity is very high. However, upon an abrupt increase in stimulus intensity, the V -nullcline moves instantaneously, whereas the system variables V and w lag behind. The system will move to the newly positioned stable fixed point, but can do so via different paths depending on where the trajectory starts relative to the quasi-separatrix – a boundary in phase space from which trajectories diverge. Trajectories starting below the quasi-separatrix make a long excursion around the elbow of the V -nullcline, resulting in a single spike, whereas those starting above the quasi-separatrix followed a direct, subthreshold route. Importantly, this mechanism requires that the stimulus intensity changes faster than the system variables V and w ; in geometrical terms, this means that stimulation can move the quasi-separatrix so that a point (V, w) that is above the quasi-separatrix before stimulus onset ends up below the quasi-separatrix after stimulus onset. Accordingly, this mechanism of spike initiation is referred to as a quasi-separatrix crossing because spike initiation requires that system variables cross from one side of the quasi-separatrix to the other.

Differences in Threshold Mechanism

Spike generation is essentially a two-dimensional phenomenon involving fast activation (positive feedback) to produce the rapid upstroke and slower recovery (negative feedback) to produce

the subsequent downstroke. The more important issue is to understand what happens at spike threshold. The three nonlinear dynamical mechanisms described above – the SNIC bifurcation, subcritical Hopf bifurcation, and quasi-separatrix crossing – provide that explanation, the implication being that Hodgkin's three classes of excitability reflect differences in threshold mechanism. The differences are most clearly revealed by considering local stability analysis near the fixed point in conjunction with the steady-state and instantaneous I - V curves, as illustrated in Fig. 3 and explained below.

- In class 1 excitability, $\partial I_{ss}/\partial V = 0$ at the saddle node (i.e., for just-threshold stimulation). This means that the steady-state I - V curve is non-monotonic with a local maximum above which depolarization activates net *inward* current at steady state; the negative feedback responsible for spike repolarization only begins to activate at suprathreshold potentials. Under these conditions, fast positive feedback has no slow negative feedback with which to compete at perithreshold potentials, and the voltage trajectory can, therefore, pass slowly through threshold. In fact, the net slow-activating current is inward at threshold, meaning that it cooperates (rather than competes) with fast-activating current to encourage spike initiation.
- In class 2 excitability, $-\frac{1}{C} \frac{\partial I_{inst}}{\partial V} > \frac{\phi_w}{\tau_w}$ at the unstable fixed point, meaning positive feedback (whose rate of activation is described by the left side of the inequality) outpaces negative feedback (whose rate of activation is described by the right side of the inequality) and repetitive spiking ensues. Unlike in class 1 excitability, the steady-state I - V curve is monotonic. This means that net slow-activating current is outward at threshold and competes (rather than cooperates) with fast-activating current to discourage spike initiation. Under these conditions, stimulation must not only force V high enough to activate fast-activating inward current, it must also do so fast enough that slower-activating outward current cannot catch up. It stands to reason that



Excitability: Types I, II, and III, Fig. 3 Biophysical basis for differences in spike initiation mechanism. *Top panels* show I - V curves for individual conductances comprising a modified Morris-Lecar model. *Bottom panels* show curves from *top panels* combined to give instantaneous and steady-state I - V curves. In class 1 excitability, the steady-state I - V curve has a local maximum (*arrowhead*), depolarization above which activates slow inward current. This slow positive feedback process acts cooperatively with activation of the fast sodium current, a fast positive feedback process. Under these conditions, spike initiation can occur arbitrarily slowly. In class 2 excitability, the steady-state I - V curve has no local maximum; instead,

depolarization above the local maximum of the instantaneous I - V curve causes increasing outward current. Under these conditions, slow negative feedback competes with fast positive feedback, meaning spike initiation must occur before slow negative feedback “catches up.” Class 3 excitability resembles class 2 excitability except that the outward current at perithreshold potentials is even stronger. In this example, voltage dependency of the slow conductance was varied (indicated by *red arrow* in *top panels*) to shift the model between different classes of excitability, but a multitude of other parameter changes can have equivalent effects that can be understood by the logic described above

spiking below a certain rate is disallowed since the voltage trajectory between spikes would be too slow to avoid strongly activating the slow outward current.

- In class 3 excitability, $-\frac{1}{C} \frac{\partial I_{\text{inst}}}{\partial V} < \frac{\phi_w}{\tau_w}$ at the stable fixed point. This means that at steady state, positive feedback activates too slowly to overcome negative feedback. Subthreshold activation of I_{slow} produces a steady-state I - V curve that is monotonic and sufficiently steep near the apex of the instantaneous I - V curve that V is prohibited from rising high enough to strongly activate fast inward current (I_{fast}). However, because the two feedback processes have different kinetics, a spike can be initiated if the system is perturbed from steady state: If V escapes high enough to activate I_{fast} (e.g., at the abrupt onset of stimulation), fast-activating inward current can overpower slow-activating

outward current – the latter is stronger when fully activated, but can only partially activate (because of its slow kinetics) before a spike is inevitable. In this way, a single spike is initiated before negative feedback forces the system back to its stable fixed point. Thus, like in class 2 excitability, slow-activating outward current competes with fast-activating inward current, but in class 3 excitability, the fast-activating current will only win that competition during stimulus transients. In other words, constant stimulation is never strong enough to sufficiently bias the competition in favor of fast-activating current, and constant stimulation thus never succeeds in driving repetitive spiking in class 3 neurons.

Interestingly, class 2 neurons exhibit a narrow stimulus range in which an abrupt increase in

stimulus intensity to a level that is insufficient to produce a Hopf bifurcation can nonetheless drive a single spike generated through a quasi-separatrix crossing (See Fig. 1). This has been demonstrated experimentally and implies that spike generation through two distinct mechanisms – a subcritical Hopf bifurcation and quasi-separatrix crossing – can occur in the same neuron based on different stimulus conditions. By comparison, the SNIC bifurcation cannot coexist with the other two spike initiation mechanisms. Nonetheless, a given neuron can shift between different classes of excitability (i.e., initiate spikes through different mechanisms) based on changes in its intrinsic membrane properties. In fact, different regions of the same neuron may generate spikes through different mechanisms based on subcellular variations in the densities of various ion channels.

To summarize, Hodgkin's three classes of excitability reflect differences in spike initiation dynamics. Fast-activating current is necessarily inward (depolarizing) at spike threshold. In class 1 excitability, net slow-activating current is also inward at perithreshold voltages and thus *cooperates* with fast-activating current during spike initiation. In class 2 and 3 excitabilities, net slow-activating current is outward (hyperpolarizing) at perithreshold voltages and thus *competes* with fast-activating current during spike initiation. Class 2 excitability exists if fast-activating inward current overpowers slow-activating outward current when constant stimulation exceeds threshold. Class 3 excitability exists if fast-activating inward current overpowers slow-activating outward current only during a stimulus transient, which precludes repetitive spiking during sustained stimulation.

Biophysical Basis

The fact that Hodgkin's three classes of excitability can be reproduced in a two-dimensional model demonstrates that nonlinear interaction between as few as two variables can account for the different threshold mechanisms that are the basis for each class. In other words, explaining the differences that Hodgkin described does not require complicated

models with dozens of different ion channels. That said, this does not mean that dozens of different ion channels are not contributing in one way or another to differences in excitability. Whereas currents with dissimilar kinetics interact nonlinearly, currents with similar kinetics sum linearly. Thus, net slow-activating current may, in a real neuron, comprise many different ion channels with similarly slow activation kinetics, and, likewise, net fast-activating current may comprise many different ion channels with similarly fast activation kinetics. The nonlinear interaction between the net-fast current and net-slow current could be qualitatively altered by alteration of any one of the contributing currents, meaning the class of excitability could be switched by any one of those changes. And of course ion channel inactivation is just as important as activation in determining the contribution of a given ion channel to net current. Furthermore, ultraslow processes like adaptation through slow activation of potassium currents or slow inactivation of sodium currents will modulate the fast-slow interaction; in other words, the ultraslow process can be approximated as a constant bias current over the time scale of a single fast-slow interaction (i.e., an individual spike), but that bias current will differ from one spike to the next. It stands to reason that spike initiation dynamics (ascertained in the two-dimensional subsystem) and the class of excitability that they convey will be dynamically modulated.

One point that should be stressed is that there is no unique ion channel or set of ion channels that is responsible for a given class of excitability. On the contrary, there are countless different ion channel combinations that can implement equivalent spike initiation mechanisms. In that respect, the biophysical basis for the spike initiation mechanism (and equivalently for Hodgkin's three classes of excitability) is highly degenerate. What is important is whether the fast and slow ion channels compete or cooperate during the spike initiation process.

Computational Consequences

The distinct dynamics associated with spike initiation in each of Hodgkin's three classes endows neurons with tuning to different stimulus features.

The cooperative spike initiation dynamics associated with class 1 excitability implements a low-pass filter. Spikes in class 1 neurons are thus preferentially elicited by constant or slowly fluctuating stimuli, and, as a result, those neurons tend to behave as good integrators. By comparison, the competitive spiking initiation dynamics associated with class 2 and 3 excitabilities implements a high-pass filter, although once combined with the low-pass filter implemented by membrane capacitance, the end result is band-pass filtering. Spikes in class 2 and 3 neurons are thus preferentially elicited by more rapidly fluctuating stimuli, and, as a result, those neurons tend to act as good coincidence detectors. Consistent with that description, class 1 neurons are primarily sensitive to stimulus intensity, whereas class 2 and 3 neurons are relatively more sensitive to the rate of change of stimulus intensity (Ratté et al. 2013).

Differences in tuning are directly reflected in measures such as the spike-triggered average stimulus (STA): class 1 neurons have broad, monophasic STAs, whereas class 2 and 3 neurons have biphasic STAs whose positive phase tends to be quite narrow. This is directly related to the shape of the phase-response curve (PRC), which is monophasic for class 1 neurons and biphasic for class 2 neurons (Ermentrout et al. 2007). Differences in the shape of the STA and PRC have a variety of interesting consequences (e.g., on synchronization), but that discussion exceeds the scope of the current chapter.

Summary

Hodgkin's classification of excitability is based on spiking patterns discerned over a range of stimulus intensities. This classification scheme is still widely used today, 65 years after it was initially proposed, because it captures fundamental differences in how neurons generate spikes. Spikes can arise through cooperation or competition between fast- and slow-activating currents. The biophysical basis for each spike initiation mechanism is degenerate insofar as many different ion channels contribute to the process and several different ion

channel combinations can produce equivalent excitability. What is most important is how those various ion channels interact during spike initiation. Different spike initiation mechanisms confer differences in tuning that are computationally important, thus further enhancing the utility of Hodgkin's classification scheme.

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Excitatory and Inhibitory Networks

- [Large-Scale Neural Networks: Vision](#)

Exponential Integrate and Fire Model

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Extracellular Potentials, Forward Modeling of

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Definition

Forward modeling of extracellular potentials refers to the calculation of electrical potentials recorded inside or outside the brain due to activity in neuronal (and, if relevant, glial) sources. This contrasts the “inverse” problem which amounts to estimating the underlying neural sources from recorded potentials.

Detailed Description

Extracellular potentials recorded inside or outside the brain are generated by transmembrane currents from cells in the vicinity of the recording electrode. To propagate from the membrane to a recording electrode inside the brain, the signal has to pass through brain tissue consisting of a tightly packed matrix of neurons and glial cells embedded in the extracellular medium (Nunez and Srinivasan 2006). A well-founded biophysical forward-modeling scheme based on volume-conductor theory (Rall and Shepherd 1968; Holt and Koch 1999), incorporating detailed reconstructed neuronal morphologies, allows for precise calculations of extracellular potentials – both *spikes* (the extracellular signatures of action potentials) and so-called *local field potentials* (LFPs). In *electroencephalographic* (EEG) recordings, the signal has to pass through neural tissue, dura matter, skull, and skin to reach the recording electrodes on the scalp, but the forward-modeling scheme has also been generalized to this situation.

Two-Step Forward Modeling Scheme

The modeling scheme naturally divides into two consecutive steps (Holt and Koch 1999):

1. First transmembrane currents from each neuron (and glial cells, if relevant) are calculated using multicompartmental modeling of simplified or biophysically detailed, morphological reconstructed neuron models (De Schutter 2009).
2. Next these transmembrane currents are used to calculate contributions to the extracellular potentials using a biophysical forward-modeling formula derived within so-called *volume-conductor theory* (Hämäläinen et al. 1993; Nunez and Srinivasan 2006).

Biophysical Forward-Modeling Formula

In volume-conductor theory the fundamental formula relating the contribution to an extracellular potential $\phi(t)$ recorded at position $\mathbf{r}$ from a transmembrane current $I_0(t)$ at position $\mathbf{r}_0$ is given by (Hämäläinen et al. 1993; Gratiy et al. 2017):

$$\phi(\mathbf{r}, t) = \frac{1}{4\pi\sigma} \frac{I_0(t)}{|\mathbf{r} - \mathbf{r}_0|}. \quad (1)$$

Here the brain tissue is assumed to be an infinite volume conductor, ϕ is set to be zero at a reference point infinitely far away, and σ is the *extracellular conductivity*.

This fundamental formula is derived assuming (Pettersen et al. 2012):

1. The *quasistatic approximation* of Maxwell's equations, i.e., omitting the terms with time derivatives of the electric ($\mathbf{E}$) or magnetic fields ($\mathbf{B}$).
2. A *linear* extracellular medium, i.e., $\mathbf{j} = \sigma\mathbf{E}$, where $\mathbf{j}$ is the current density, $\mathbf{E}$ the electrical field, and σ a (scalar) proportionality constant. It is further assumed that the electrical medium is
 - (a) Ohmic, i.e., no capacitive effects so that σ is independent of frequency (corresponding to a real-valued σ , that is, no imaginary component (Grimnes and Martinsen 2015),
 - (b) *Isotropic* (same in all directions), and

- (c) *Homogeneous* (same everywhere).
3. No contribution to the extracellular potential from ion *diffusion*.
 4. No contribution to the extracellular potential from *advection*, that is, ions moving by flow of the liquid in which they are suspended.

Assumption 1 seems well fulfilled for the frequencies inherent in neural activity, i.e., less than a few 1000 Hz (Hümäläinen et al. 1993; Nunez and Srinivasan 2006).

Assumption 2a has been questioned (Bédard et al. 2004), but on balance recent experiments point to a largely frequency-independent medium (Logothetis et al. 2007; Wagner et al. 2014; Miceli et al. 2017). Also, a frequency-dependent conductivity can be incorporated in the forward-modeling scheme by considering each frequency (Fourier) component separately, see Miceli et al. (2017) for an example. Assumption 2b is not always fulfilled, but the forward-model formula in Eq. (2) can be generalized to account for, for example, different conductivities in different directions (Nicholson and Freeman 1975; Logothetis et al. 2007; Ness et al. 2015). Likewise, assumption 2c is not always fulfilled, for example at interfaces between gray matter and the cortical surface where there is a discontinuity in electrical conductivity. However, the forward-model formula can be generalized to account for such discontinuities by means of the *Method of Images (MoI)* from electrostatics (Nicholson and Llinas 1971; Pettersen et al. 2006). MoI has also been used to model electrical potentials in multi-electrode arrays (MEAs) where cortical slices covered by highly conducting saline are placed on insulating chip surfaces (Ness et al. 2015; Miceli et al. 2017). Further, when the extracellular conductivities around the recording electrodes have such a complicated spatial structure that analytical forward-model formulas either do not exist or are unpractical, one can always solve the forward problem by means of *finite element modeling* (FEM) (McIntyre and Grill 2001; Mechler and Victor 2012; Lempka and McIntyre 2013; Ness et al. 2015; Miceli et al. 2017).

Assumption 3 is not always fulfilled, and if so other computational schemes must be considered (Haldnes et al. 2016), see section “[Limitations and](#)

[Generalizations](#)” below. Assumption 4 is generally expected to be fulfilled, however, as liquid flow in extracellular brain tissue is slow (Gratny et al. 2017) and the extracellular solutions essentially electroneutral.

The above forward-model formula applies to the situation with a single transmembrane current I_0 , but since electromagnetic theory is linear, contributions from several transmembrane current sources simply add up. In multicompartmental modeling where the neuron is divided into N compartments, the formula straightforwardly generalizes to

$$\phi(\mathbf{r}, t) = \frac{1}{4\pi\sigma} \sum_{n=1}^N \frac{I_n(t)}{|\mathbf{r} - \mathbf{r}_n|}, \quad (2)$$

where $I_n(t)$ is the transmembrane current (including the capacitive membrane current) in compartment n , and $\mathbf{r}_n$ is the “mean” position of the compartment, e.g., at the center of a spherical soma compartment or the mid-point of a cylindrical dendritic compartment. This scheme corresponds to the so-called *point-source* approximation (Holt and Koch 1999; Pettersen et al. 2008) since all transmembrane currents into the extracellular medium from each compartment n go through a single point. Another scheme, the more commonly used *line-source* approximation, assumes the transmembrane currents from each cylindrical compartment to be evenly distributed along a line corresponding to the cylinder axis (Holt and Koch 1999).

The above forward-modeling formulas predict potentials at point electrodes’, while real recording electrodes of course have finite physical extensions. Finite-sized electrodes appear to measure the average potential across the uninsulated electrode surface (Nelson and Pouget 2010), and a natural approximation is thus to approximate the measured potentials by the average of the computed potentials across the electrode’s surface (Lindén et al. 2014; Ness et al. 2015).

Applications

Different frequency bands of the recorded extracellular potentials contain different types of information about the underlying neural activity. The

high-frequency part of the signal ($> \sim 500$ Hz), the *multi-unit activity* (MUA), contains information about the firing of action potentials (Buzsáki 2004; Gold et al. 2006; Pettersen and Einevoll 2008), while information about how the neuron integrates synaptic inputs appears primarily contained in the low-frequency part ($< \sim 500$ Hz), i.e., the *local field potential* (LFP). The forward-modeling scheme has been used, with detailed reconstructed neuronal morphologies, to calculate both somatic spikes (i.e., extracellular signatures of action potentials) (Holt and Koch 1999; Gold et al. 2006, 2007; Pettersen et al. 2008; Pettersen and Einevoll 2008; Thorbergsson et al. 2012; Schomburg et al. 2012; Camuñas-Mesa and Quiñero 2013; Hagen et al. 2015), spikes in axonal projections (McColgan et al. 2017; Kuokkanen et al. 2018), and LFPs (Pettersen et al. 2008; Lindén et al. 2010, 2011; Schomburg et al. 2012; Leski et al. 2013; Reimann et al. 2013; Mazzoni et al. 2015; Tomsett et al. 2015; Ness et al. 2016, 2018; Hagen et al. 2016, 2017; Parasuram et al. 2016) generated by individual or populations of neurons.

Local field potentials recorded in cortex stem from populations of neurons, and detailed theoretical analysis based on the forward-modeling scheme has revealed that the level of *correlations* in synaptic inputs to the neurons surrounding the recording electrode is critical for determining the amplitudes of the recorded potentials (Lindén et al. 2011; Leski et al. 2013; Ness et al. 2018). Correlated synaptic inputs may, depending on the spatial distribution of synapses onto the neurons, substantially boost the amplitude compared to the same situation with uncorrelated inputs (Lindén et al. 2011). Further, the boosting effect is particularly prominent for low frequencies (Leski et al. 2013; Ness et al. 2018).

Charge conservation implies that $\sum_{n=1}^N I_n(t)$ in Eq. (2) is zero at all times, so that a point-neuron model (where $N = 1$) does not generate an extracellular potential (Pettersen et al. 2012). A hybrid scheme for computing LFPs from point-neuron models has thus been developed. Here the spiking dynamics is computed in point-neuron networks, while the LFP is computed in a second step using multicompartmental neuron models (Hagen et al. 2016). Further, a simplified formula for

computing LFPs generated by two-population networks of integrate-and-fire neurons has been derived (Mazzoni et al. 2015).

For the electrical potential recorded by an EEG electrode at the scalp, the forward model in Eq. (2) assuming a homogeneous electrical medium is no longer applicable due to different electrical conductivities of neural tissue, cerebrospinal fluid (CSF), skull, and scalp. However, a forward-modeling scheme can still be constructed, either by means of analytical expressions from assuming, for example, a four-sphere head model (Nunez and Srinivasan 2006; Næss et al. 2017; Hagen et al. 2018) or by numerical solutions using realistic volume conductor models (Bangera et al. 2010; Vorwerk et al. 2014). Likewise, *electrocorticographical* (ECoG) signals, that is, signals recorded with electrodes placed at the cortical surface, can be modelled either by use of MoI or by spherically symmetric head models (Hagen et al. 2018).

For further reading, see reviews in Pettersen et al. (2012) and Einevoll et al. (2013a, b).

Limitations and Generalizations

Even if spatially varying, anisotropic, and frequency-dependent electrical conductivities can be incorporated, the forward-model scheme within volume-conductor theory has several inherent limitations. For one, the scheme is not self-consistent as the extracellular potential generated by transmembrane currents change the membrane potential and thus feeds back on the neural dynamics. This feedback effect is known as *ephaptic coupling* (Holt and Koch 1999), and proper inclusion of it requires computational extensive schemes (Agudelo-Toro and Neef 2013; Tveito et al. 2017) (but see Goldwyn and Rinzel 2016). However, since the extracellular potentials typically are much smaller than a millivolt, while the membrane potentials are many tens of millivolts, this effect can in many cases be expected to be small.

Another limitation is the absence of diffusion effects: Even in the absence of transmembrane currents, spatial gradients of ion concentrations may by itself set up extracellular potentials. These can be modelled by the Kirchhoff-Nernst-Planck (KNP) scheme (Halnes et al. 2016;

Solbrå et al. 2018), or the Poisson-Nernst-Planck (PNP) scheme (Lopreore et al. 2008; Pods et al. 2013), where both extracellular potentials and ion concentrations are explicitly modeled.

Tools/Resources

- Open source Python package **LFPy** for computation of spikes, LFP, ECoG, EEG and MEG signals (Lindén et al. 2014; Hagen et al. 2018): <https://lfp.readthedocs.io/>
- Open source Python package **ViSApy** for computation of benchmarking data for spikesorting algorithms (Hagen et al. 2015): <https://github.com/espenhgn/ViSApy>
- Open source Python package **ViMEAPy** for computation of potentials recorded by micro-electrode arrays (MEAs) (Ness et al. 2015): <https://bitbucket.org/torbness/vimeapy>
- Open source Python package **HybridLFPy** for computation of LFPs generated by pointneuron networks (Hagen et al. 2016): <https://github.com/INM-6/hybridLFPy>
- Publicly available MATLAB scripts to execute the extracellular spike computations in Gold et al. (2007): <https://senselab.med.yale.edu/>
- Publicly available MATLAB tool **Vertex** for computing LFPs generated by spiking networks (Tomsett et al. 2015): <https://vertexsimulator.org/>
- Publicly available MATLAB model for studying effects of ion diffusion on LFPs (Haldnes et al. 2016): <https://senselab.med.yale.edu/modeldb/showModel.cshtml?model=190140>
- Publicly available NEURON program **LFPsim** for computing LFPs (Parasuram et al. 2016): <https://senselab.med.yale.edu/modeldb/showModel.cshtml?model=190140>
- Open source Python code to compute EEG potentials from current dipole in four-sphere head model, both with analytical formulas and FEM (Næss et al. 2017): <https://github.com/Neuroinflat/fourspheremodel>

Cross-References

- [Current Source Density \(CSD\) Analysis](#)
- [Electrocorticogram \(ECoG\)](#)

- [Local Field Potential, Relationship to Electroencephalogram \(EEG\) and Magnetoencephalogram \(MEG\)](#)
- [Local Field Potential: Relationship to Membrane Synaptic Potentials](#)
- [Local Field Potentials: Interaction with the Extracellular Medium](#)
- [Local Field Potentials: LFP](#)
- [Mesoscopic Anatomy and Neural Population Models](#)
- [Neural Population Model](#)
- [Resistivity/Conductivity of Extracellular Medium](#)
- [Transfer Function, Electrocortical](#)

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Extracellular Signal-Regulated Kinases, Models of

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Synonyms

ERK1, 2; MAPK1, 2; p42/p44 MAPK

Definition

Mitogen-activated protein (MAP) kinases consist of a family of protein kinases activated by a variety of cellular stimuli (Pearson et al. 2001). Four subfamilies of mammalian MAPK have been identified: ERK1 and ERK2: JNK; p38; and ERK5. Extracellular regulated kinase 1 and 2 (ERK1, ERK2), the original MAPK, was discovered as a kinase activity regulated by insulin. For a historical perspective on the discovery of the ERK cascade, see Blenis (1993). ERK1 and ERK2 (also known as p44 and p42 MAPK) signaling is key for the induction of synaptic plasticity and is essential for learning and memory (Thomas and Huganir 2004).

Detailed Description

The core ERK signaling module consists of a three-tiered kinase cascade: the MAPKKK Raf1 or B-Raf that phosphorylates and activates the MAPKK MEK1/2 that in turn phosphorylates and activates the MAPK ERK1/2. The small G protein Ras activates Raf, the first kinase in the cascade. Activation of guanyl-nucleotide exchange factors (GEFs) facilitates the exchange of GDP for GTP in Ras, leading to its activation. GTPase-activating proteins (GAPs) counteract this activation by enhancing the hydrolysis of GTP to GDP catalyzed by Ras itself. Ras–GTP binds to Raf, promoting its membrane association and inducing a conformational change that results in the activation of Raf. Active Raf in turn phosphorylates and activates the second kinase in the cascade MAPK/ERK kinase (MEK). MEK's only known substrate is ERK, the third kinase in the cascade. ERK is a serine/threonine kinase with a number of cytoplasmic and nuclear substrates. In the cytoplasm, active ERK phosphorylates ionic channels such as Kv4.2, other kinases such as ribosomal protein S6 kinases (RSKs), and enzymes such as phospholipase A2 (PLA2), involved in the synthesis of arachidonic acid (AA) and the phosphodiesterase PDE4, an enzyme that degrades cAMP. Nuclear targets include transcription factors such as CREB, and other kinases such as RSK-related mitogen- and stress-activated kinases (MSKs) (Reviewed by Yoon and Seger 2006).

ERK Activation in Neurons

Many of the extracellular ligands that play crucial roles in synaptic plasticity, such as growth factors, hormones, and modulatory neurotransmitters, also activate ERK. These ERK-activating ligands act through several distinct classes of cell surface receptors, such as receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), or ligand-gated ion channels. Growth factor

activation of ERK starts with the ligand-mediated tyrosine autophosphorylation of the RTK (e.g., brain-derived neurotrophic factor (BDNF) receptor TrkB) and results in the formation of a membrane-associated complex of adapter proteins that promote Ras activation via the Ras–GEF SOS.

ERK is also activated by a number of neurotransmitter receptors such as the G_q -coupled muscarinic acetylcholine receptors (mAChRs) and metabotropic glutamate receptors (mGluRs), or the G_s -coupled β -adrenergic receptor (β -AR). Activation of ERK by GPCRs coupling to heterotrimeric G proteins, G_q , G_i , and G_s , occurs by distinct mechanisms (Hawes et al. 1995; Williams et al. 1998). G_i and G_q can activate ERK via their $\beta\gamma$ subunits, while G_s activates ERK by a cAMP-dependent mechanism. For example, B-Raf can be activated by the small G protein Rap1 in response to increases in cAMP, resulting in ERK activation (Emery et al. 2013). In neurons, ERK activation also occurs through elevation of intracellular calcium, due to membrane depolarization or release from intracellular stores. For instance, glutamate opening of *N*-methyl-d-aspartate (NMDA)-type channels lead to an influx of calcium into the neuron resulting in ERK activation. Several mechanisms for calcium activation of ERK exist, including activation of calcium-sensitive Ras–GEFs, transactivation of RTKs, and activation of kinases such as PYK or PKC (Cullen and Lockyer 2002).

Computational Models of ERK Signaling in Neurons

Numerous computational models of ERK signaling have been published, exploring the different facets of this versatile signaling cascade. The ERK signaling cascade three-tiered topology and feedback regulation impart it with context-specific properties, such as ultrasensitivity, bistability, and oscillations (Ferrell Jr and Machleder 1998; Kholodenko 2000). Spatial

models of ERK have predicted an enhancement of dendritic ERK activation in response to β AR stimulation (Neves et al. 2008).

In neurons, particular attention has been given to the role of ERK interfacing with calcium signaling during synaptic plasticity. Bhalla and Iyengar (1999) developed one of the initial models of ERK in neurons, examining the possible storage of information within signaling networks underlying long-term potentiation. In this compartmental model of a CA1 hippocampal neuron, the authors explored the contribution of ERK to the maintenance of CaMKII activation after a glutamate stimulus was terminated. The model proposed the feedback loop consisting of ERK-activating PLA2, leading to increase in arachidonic acid (AA) and PKC activation. PKC can then sustain ERK active through regulation of Ras and MEK1 and MEK2. This feedback loop can give rise to bistability, as it amplifies the initial ERK activation into a sustained signal. The feedback loop involving ERK–PLA2–AA–PKC can also enhance PKA activation (as explained in the next paragraph) and thus decrease the activity of PP1, the phosphatase acting on CaMKII, promoting the phosphorylation of AMPAR. A follow-up study by Kuroda et al. (2001) developed a model of cerebellar long-term depression and included the same feedback loop involving ERK–PLA2–AA–PKC, and in this context, sustained PKC activation led to the phosphorylation and internalization of AMPAR. Other studies with similar feedback mechanisms have been further developed to include additional molecules, such as PKMzeta (Ajay and Bhalla 2004, 2007). Recently, a model of ERK regulation of PDE4 has highlighted one of the mechanism by which ERK controls AMPAR trafficking (Song et al. 2013).

ERK can also regulate synaptic plasticity by enhancing the actions of PKA. In *Aplysia*, the molecular process that enables the association of a sensory cue with a withdrawal reflex is called long-term facilitation (LTF) and is dependent on the neurotransmitter serotonin (5-HT).

5-HT activates PKA and ERK, and these two kinases regulate transcription essential for LTF by phosphorylating and activating CREB. An ERK model was developed that explored the signaling mechanism underlying LTF (Pettigrew et al. 2005). In this model, ERK modulation of PKA activity led to the coincident activation of CREB within a restricted time window. ERK was proposed to prolong PKA activation by increasing the translation of the regulatory subunit of PKA. ERK could also enhance PKA activation of CREB1 by phosphorylating CREB2, reducing its repressor activity on CREB1.

Byrne and colleagues further modified their original ERK model by abstracting the combined output of PKA and ERK pathways into a species called “inducer” (Zhang et al. 2012). The goal of this study was to use the computational model of ERK and PKA signaling to find training protocols to improve learning in *Aplysia*. They searched for 5-HT patterns of stimulation that would give rise to the most effective synergy of ERK and PKA activation and thus the highest accumulation of “inducer” and CREB activation. The identified protocol was then tested in experimental behavioral assays and shown to be significantly superior to standard protocols of learning in *Aplysia*.

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Extracellular Stimulation

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)
- [Intraspinal Stimulation](#)

Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of

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Synonyms

[Field potential](#); [Neurophonic](#)

Definition

In response to acoustic inputs (sounds), neural activity generates extracellular voltages throughout the auditory pathway. Sound-evoked extracellular voltages in the auditory brainstem – termed the *neurophonic* – exhibit distinctive temporal and spatial patterns. Computational modeling demonstrates how neural activity in an auditory brainstem region known as the medial superior olive (MSO) can produce these extracellular voltages.

Detailed Description

Extracellular Voltage Recordings in the Auditory Brainstem

An important center of auditory processing in the auditory pathway is the medial superior olive (MSO). In this nucleus, neurons receive inputs that originate from both ears. Spiking activity of MSO neurons is sensitive to the relative timing of synaptic inputs, which allows these neurons to convey information about interaural time differences, an important cue for sound source location (Grothe et al. 2010).

In addition to evoking spiking activity in MSO neurons, sounds also cause extracellular voltages (V_e) in the brainstem. Since extracellular voltages in the brain are generated by electric currents that flow through neurons and their synapses (Einevoll et al. 2013) and since sound-evoked extracellular voltages are observed in and around the MSO, it has long been hypothesized that MSO neurons are a dominant generator of these extracellular voltages. These signals – known as the *neurophonic* – can have distinctive temporal and spatial features. In response to sinusoidal acoustic input stimuli (pure tones), the neurophonic is periodic with fundamental frequency that matches the input tone. The spatial pattern of these responses resembles voltages generated by a dipole distribution of current (Galambos et al. 1959; Biedenbach and Freeman 1964; Tsuchitani and Boudreau 1964; Mc Laughlin et al. 2010). In the auditory brainstem of cats, tone-evoked V_e signals are largest for frequencies between 500 and 2000 Hz (Mc Laughlin et al. 2010) and can be observed in response to frequencies as high as 4000 Hz (Boudreau 1965).

Computational Models of Extracellular Voltages in the MSO

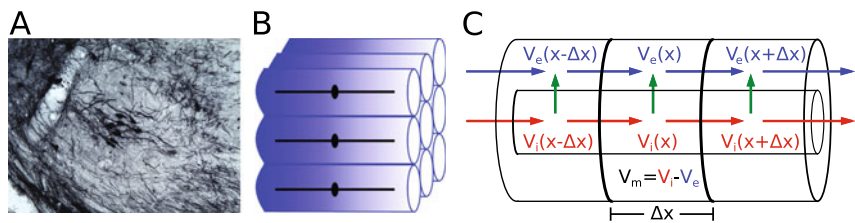
Standard models of neural activity describe the dynamics of membrane potential – the voltage difference across the cell membrane – but do not explicitly calculate the voltage outside the cell. Since extracellular voltage is the result of current flow outside of the cell, computational models of neurally generated V_e must track currents and voltages both inside and outside the cell. In principle, then, models of extracellular voltages must describe current flow throughout the brain which acts as a three-dimensional volume conductor. Models of the neurophonic have successfully simplified this problem by noting spatial symmetry in the arrangement of MSO neurons and temporal structure of inputs to MSO neurons. MSO neurons are relatively well-aligned in space with dendrites that extend, roughly, parallel to one another (Rautenberg et al. 2009). In addition, like most regions of the auditory pathway, there is a tonotopic organization in the MSO with nearby neurons tuned to similar frequencies. As a result of this orderly arrangement of MSO neurons and their synaptic inputs, it is convenient and

plausible to assume that local subpopulations of MSO neurons are nearly identical and arranged symmetrically and that nearby neurons in local subpopulation receive synaptic inputs that arrive in synchrony. In this idealized scenario, voltage inside an MSO neuron (V_i) and voltage outside (V_e) can be calculated simultaneously in coupled, one-dimensional spatial domains. The region surrounding a neuron has been termed the *virtual cylinder* of extracellular space in Goldwyn et al. (2014). These intracellular and extracellular spaces are coupled by transmembrane currents; see the schematic in Fig. 1. The use of symmetry and synchrony arguments was pioneered by Rall and Shepherd (1968) for modeling V_e in the olfactory bulb.

The anatomy and biophysics of neurons shape extracellular voltage responses. Models of MSO-generated V_e have included important biophysical details such as voltage-gated ion currents and bipolar morphology (dendrites extending away from a central soma region) (Goldwyn et al. 2014). Since spikes are small and difficult to detect in extracellular recordings in the region of the MSO, spike-generating sodium current is not thought to contribute appreciably to V_e .

The Dipole Model of MSO-Generated Extracellular Voltages

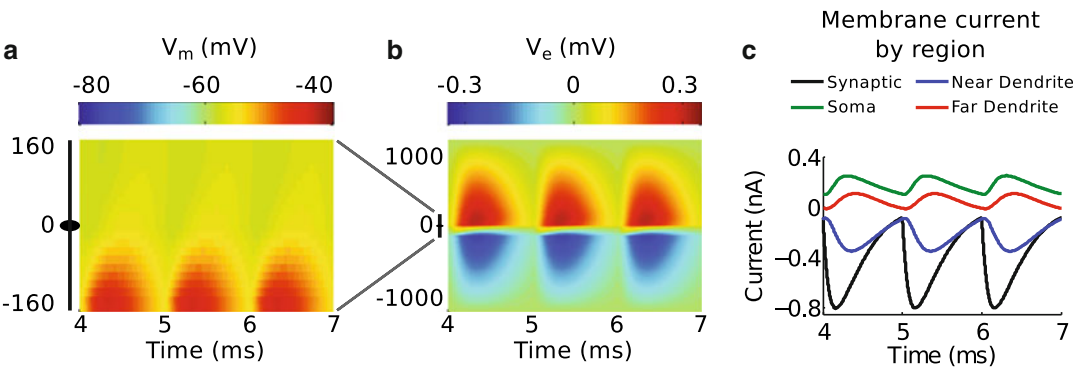
The elongated shape of MSO neurons – two dendrites, extending away from a central soma – causes MSO neurons to generate V_e in a manner similar, qualitatively, to a current dipole. A sound played to one ear evokes neural activity in the auditory nerve that is transmitted along the auditory pathway. These responses cause excitatory synaptic currents to enter as inward flows of positive ions into the dendrites on one side of a local subpopulation of MSO cells. This creates a current *sink* and a negative deflection of V_e near the sites of synapses. The principle of conservation of current requires that this inward flow be balanced, in each cell, by an outward flow of current. Consequently, the soma and dendrites on the opposite side of the MSO act as current *sources* and create positive deflection of V_e . In short, in response to sounds played to one ear, MSO neurons act similar to current dipoles. Indeed, dipole-like V_e patterns are observed in vivo (Biedenbach and



Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of, Fig. 1 Computational modeling of extracellular V_e in MSO. (a) MSO neurons are aligned in space with dendrites that extend away from cell bodies and are parallel, roughly. (b) An idealized local subpopulation of MSO neurons represented as identical cells with bipolar dendrites and spatially symmetric arrangement. Blue regions represent extracellular regions surrounding each cell. (c) Schematic of a portion of an MSO neuron, represented in a computational model as a

collection of compartments. Current inside the cell (red) determines the intracellular voltage (V_i). Current outside the cell (blue) creates extracellular voltage V_e . Assumptions of spatial symmetry of MSO neurons and temporal synchrony of neural activity in a local subpopulation allow intracellular and extracellular regions to be idealized as one-dimensional domains coupled by the flow of transmembrane current (green). (Figure reproduced from Goldwyn et al. (2014) with permission of the Society for Neuroscience)

E



Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of, Fig. 2 Simulations of MSO neuron model produce dipole-like V_e in response to 1000 Hz excitatory synaptic inputs on one dendrite. (a) Simulated membrane potential V_m . (b) Simulated extracellular voltage V_e . Note the change in spatial dimension (vertical axis) compared to (a), with the black bar indicating the location of the modeled MSO neuron. (c) Comparison of synaptic current flow (black) and net

transmembrane current flows on portions of the cell. The soma and distal dendrite are current sources (net current is positive, outward). The dendrite proximal to the synaptic input is a current sink (net current is negative, inward). Thus the MSO neuron model acts, roughly, as a current dipole in response to dendrite-targeting excitation. (Figure adapted from Goldwyn et al. (2014) with permission of the Society for Neuroscience)

Freeman 1964; Mc Laughlin et al. 2010). These spatial patterns can be reproduced in models that treat MSO neurons as current dipoles (Mc Laughlin et al. 2010) and in biophysically based models of MSO neurons (Goldwyn et al. 2014, 2017); see Fig. 2.

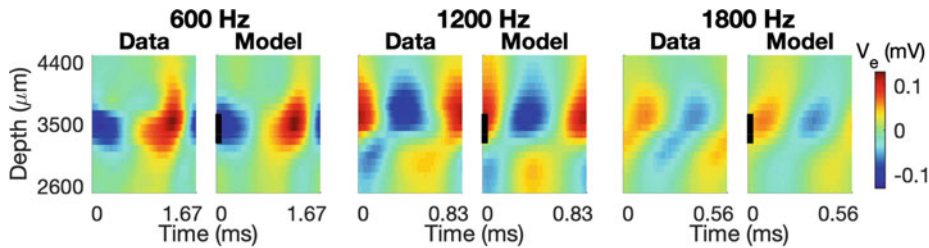
Signatures of Synaptic Inhibition in Non-dipole-Like Extracellular Voltages

Not all V_e responses are well-described by a dipole model. MSO neurons also receive soma-targeting inhibition, and computational modeling that

includes this additional current source can account for non-dipole features in V_e responses (Goldwyn et al. 2017). Combinations of soma-targeting inhibition and dendrite-targeting excitation reproduce, quantitatively, diverse and frequency-dependent neurophonic responses to pure tone stimuli, as shown in Fig. 3.

Significance of Extracellular Voltage in the MSO

The MSO is one of the first stages in the auditory pathway that combines inputs from both ears.



Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of, Fig. 3 Non-dipole features of the neurophonic accounted for in a MSO model with excitation and inhibition. Recorded and simulated V_e patterns are presented in pairs. Responses are to pure tones at three frequencies. From left to right, 600, 1200, and 1800 Hz pure tones. In experiments, tones are played to one ear (monaural); see Mc Laughlin et al. (2010) for details. In simulations synaptic inputs target two sites on the neuron: off-center (representing dendrite-targeting

excitation) and the center of the neuron (representing soma-targeting inhibition). Each panel displays cycle-averaged spatial-temporal patterns of V_e , with the period of averaging defined by the input tone. Black vertical bars in the *model* panels represent the location of the model neuron. Responses to the 1200 Hz tone are mostly “dipole-like.” Responses to 600 and 1800 Hz tones have non-dipole features. (Figure adapted from Goldwyn et al. (2017) with permission of the Society for Neuroscience)

MSO neurons play an important role, therefore, in sound localization and other aspects of binaural (“two-eared”) hearing. There are technical challenges in intracellular recording individual MSO neurons *in vivo*, although there have been recent successes (Franken et al. 2015). Recording extracellular voltages in the auditory brainstem is, therefore, a useful alternative approach to study the function of MSO neurons. Computational modeling and model-based analysis of these V_e signals provide insights into MSO activity based on this accessible source of *in vivo* data.

Computational modeling of V_e can also reveal new principles of neural activity. Extracellular voltages in the MSO can be several millivolts in amplitude. This raises a question: do MSO neurons interact via this large-amplitude, endogenously generated extracellular voltage? This type of non-synaptic neural interaction has been termed *ephaptic coupling*. Simulations of MSO neurons coupled via their endogenously generated V_e demonstrate that the neurophonic could, in principle, alter spiking activity of MSO neurons (Goldwyn and Rinzel 2016).

Cross-References

- ▶ [Auditory Evoked Brainstem Responses](#)
- ▶ [Cable Equation](#)
- ▶ [Cable Theory: Overview](#)

- ▶ [LFP Analysis: Overview](#)
- ▶ [Local Field Potential, Ephaptic Interactions](#)
- ▶ [Local Field Potential, Methods of Recording](#)
- ▶ [Local Field Potential, Relationship to Unit Activity](#)
- ▶ [Local Field Potential: Relationship to Membrane Synaptic Potentials](#)
- ▶ [Local Field Potentials: LFP](#)
- ▶ [Sound Localization in Mammals and Models](#)

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Eye-Blink Conditioning

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Synonyms

[Associative learning](#); [Eyelid conditioning](#); [Motor learning](#)

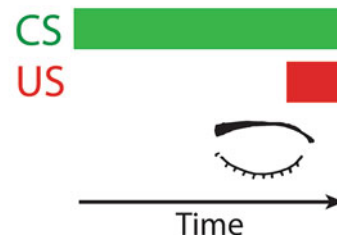
Definition

Eye-blink conditioning is both a procedure and a type of learning. The delay procedure includes the repeated presentation of a conditioned stimulus (CS) that does not elicit eyelid closure before training followed shortly (150–2000 ms) by an unconditioned stimulus (US) that elicits an eyelid closure unconditioned response (UR) before training. After repeated paired presentations of the CS and US, the organism will develop an eyelid closure conditioned response

Unconditioned Response



Conditioned Response



Eye-Blink Conditioning, Fig. 1 Diagram of eye-blink conditioning procedure and timing of the conditioned response. At the start of training, an unconditioned response (eyelid closure) occurs after the onset of the unconditioned stimulus (US). With repeated presentations of the conditioned stimulus (CS) and the US, a conditioned eyelid closure starts before the onset of the US

(CR) which precedes the onset of the US (Fig. 1). Unpaired presentations of the CS and US do not result in the development of a CR. Eye-blink conditioning therefore establishes associative learning based upon the predictive relationship between the CS and US – the CS predicts that the US is coming. It also establishes learned timing such that maximum eyelid closure for the CR is timed to the onset of the US in well-trained subjects. Eye-blink conditioning has been studied in humans, cats, dogs, ferrets, frogs, mice, monkeys, rabbits, rats, sheep, and turtles.

Detailed Description

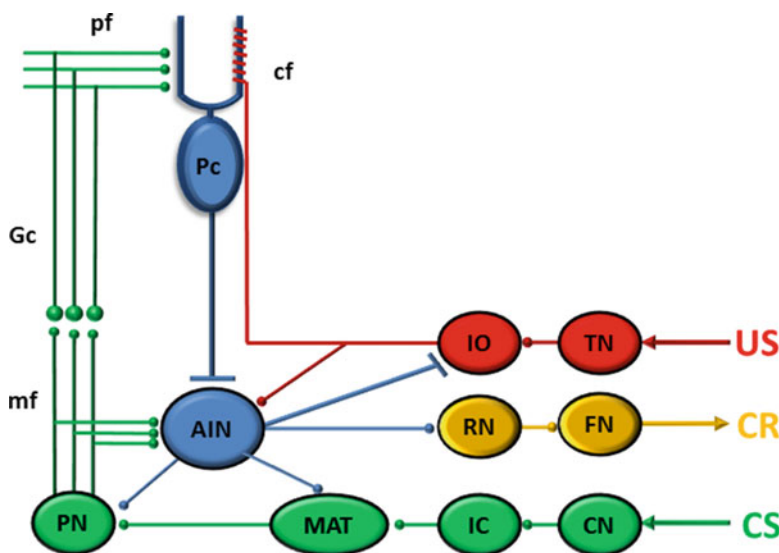
Essential Role of the Cerebellum in Eye-Blink Conditioning

Eye-blink conditioning depends on the intermediate cerebellum ipsilateral to the trained eye (McCormick and Thompson 1984). Lesions of the ipsilateral anterior interpositus nucleus block acquisition of eye-blink conditioning, even after

thousands of training trials, and completely abolish CRs acquired before the lesion. Reversible inactivation of the anterior interpositus nucleus and overlying cortex also blocks acquisition of the CR. When the reversible inactivation is ended, the rate of acquisition is the same as in animals that were not previously trained, indicating that there was no memory trace established during training (i.e., no savings) with cerebellar inactivation (Krupa et al. 1993). Cerebellar inactivation administered after the training sessions impairs eye-blink conditioning, indicating that memory consolidation is disrupted by post-training inactivation (Attwell et al. 2002). The findings of the lesion and reversible inactivation studies suggest that the memory underlying eye-blink conditioning is stored within the cerebellum (Freeman and Steinmetz 2011).

Convergence of CS and US Sensory Pathways in the Cerebellum

The neural pathways that convey CS sensory input to the cerebellum have been determined for auditory and visual stimuli (Freeman and Steinmetz 2011). The auditory CS pathway includes the lower brainstem auditory nuclei and the medial auditory thalamus (Fig. 2). The medial auditory thalamus then projects to the lateral pontine nucleus which sends its mossy fiber projection to the cerebellar cortex and nuclei. Mossy fibers synapse with granule cells in the cerebellar cortex which then send their parallel fiber projection to Purkinje cells and inhibitory interneurons. The visual CS pathway includes retina projections to the nucleus of the optic tract and the ventral lateral geniculate and projections of these nuclei to the medial pontine nuclei. The US pathway includes projections from the trigeminal nucleus



Eye-Blink Conditioning, Fig. 2 A simplified schematic diagram of the neural circuitry underlying delay eye-blink conditioning. The cerebellar anterior interpositus nucleus (AIN) and Purkinje cells (Pc) in the cerebellar cortex receive convergent input from the conditioned stimulus (CS, green) and unconditioned stimulus (US, red) neural pathways. The CS pathway for an auditory CS includes the cochlear nuclei (CN), superior olive (not shown), lateral lemniscus (not shown), inferior colliculus (IC), medial auditory thalamus (MAT), basilar pontine nuclei (PN), mossy fiber (mf) projection to the AIN and cortical granule cells (Gc), and the parallel fiber (pf) projections to Purkinje

cells. The US pathway includes the trigeminal nucleus (TN), dorsal accessory division of the inferior olive (IO), and the climbing fiber (cf) projection to the AIN and Pc. The output pathway for performance of the conditioned blink response (orange) includes the AIN projection to the red nucleus (RN) and its projection to facial motor nucleus (FN) which causes the eyelid closure conditioned response (CR). Feedback projections from the AIN to the PN, MAT, and IO regulate CS and US input to facilitate acquisition and maintain plasticity within the cerebellum. Inhibitory synapses are depicted by a flat ending. All other synapses are excitatory

to the inferior olive; the inferior olive sends its climbing fiber projection to the cerebellar cortex and nuclei (Fig. 2). The CS pathway receives positive feedback from the cerebellum to the pontine nuclei and thalamus, whereas the US pathway receives an inhibitory feedback projection from the cerebellum to the inferior olive (Fig. 2).

Cerebellar Mechanisms of Associative Learning

Computational models of cerebellar learning posit that the concurrent activation of the mossy fiber pathway and climbing fiber pathway during CS-US training trials induces synaptic plasticity. Some of the original and most influential models posited synaptic plasticity at parallel fiber-to-Purkinje cell synapses (Albus 1971; Marr 1969). More recent models posit synaptic plasticity in mossy fiber-to-interpositus nucleus synapses as well as parallel fiber-to-Purkinje cell plasticity (Li et al. 2013). Purkinje cell projections to the cerebellar nuclei are inhibitory which have led models to include synaptic depression at parallel fiber synapses with Purkinje cells. The synaptic depression produces pauses in Purkinje cell activity during the CS, which then reduces tonic inhibition of the interpositus nucleus. This release from inhibition combined with synaptic enhancement at mossy fiber-to-interpositus nucleus synapses drives an increase in interpositus nucleus activity that in turn drives premotor neurons in the red nucleus to activate the facial motor nucleus to produce the CR.

Empirical evidence supporting the models of cerebellar learning comes from neurophysiological studies. Purkinje cells show pauses in simple spike activity in vivo that develop during eye-blink conditioning (Jirenhed et al. 2007). These pauses in Purkinje cell activity are thought to be the result of synaptic depression. Neurons in the anterior interpositus nucleus show increases in activity that develop during training (McCormick and Thompson 1984), which are thought to be the result of release from Purkinje cell inhibition and synaptic enhancement. These increases in activity parallel the amplitude and time course of the CR both across training trials and within training trials (Halverson et al. 2010).

Summary

Eye-blink conditioning is a type of associative motor learning that depends on the cerebellum. Sensory inputs from the CS and US converge on neurons within the cerebellar cortex and nuclei. Paired presentations of the CS and US during eye-blink conditioning cause induction of synaptic depression between parallel fibers and Purkinje cells and synaptic enhancement between mossy fibers and anterior interpositus nucleus neurons. The synaptic plasticity within the cerebellar cortex and nuclei is the mechanisms underlying memory storage within the cerebellum.

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Eyelid Conditioning

► Eye-Blink Conditioning

F

F Current

► [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)

F1/F2 Components of Short-Term Synaptic Enhancement

► [Facilitation, Biophysical Models](#)

Facilitation

► [Short-Term Synaptic Plasticity in Central Pattern Generators](#)

Facilitation, Biophysical Models

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Synonyms

[F1/F2 components of short-term synaptic enhancement](#); [Frequency facilitation](#); [Paired-pulse facilitation](#); [Short-term synaptic facilitation](#)

Definition

Facilitation is a temporary increase in postsynaptic response to a presynaptic action potential or depolarization induced by a preceding presynaptic depolarization. It is distinguished from longer-term components of activity-dependent synaptic enhancement by its low activation threshold (a pair of action potentials is often sufficient, hence the term *paired-pulse* facilitation) and short persistence time: in most cases, facilitated response decays back to initial amplitude within less than a second after the stimulus train. Facilitation is very common in central and peripheral synapses of both vertebrate and invertebrate nervous systems; it is readily observed under conditions of low initial vesicle release probability, but is often occluded by synaptic depression when the initial vesicle release probability is sufficiently high. Biophysical models of facilitation go beyond a simple phenomenological description and often combine a model for presynaptic Ca^{2+} dynamics with a model of Ca^{2+} binding to exocytosis sites that trigger vesicle fusion.

Detailed Description

While postsynaptic effects can contribute to short-term enhancement of synaptic response, in most synapses facilitation is caused by some action of presynaptic Ca^{2+} ions entering during stimulation, which is intuitive in view of the steep nonlinear

dependence of baseline exocytosis rate on Ca^{2+} concentration ($[\text{Ca}^{2+}]$). However, simple whole-terminal accumulation of free Ca^{2+} at best provides a partial contribution to facilitation, since such residual Ca^{2+} elevation is expected to be small compared to the high concentration of Ca^{2+} near an open Ca^{2+} channel, believed to be essential for triggering exocytosis (so-called Ca^{2+} nano- or microdomain); considerable global Ca^{2+} accumulation is also inconsistent with the brief (“phasic”) nature of synaptic response. Several alternative models for facilitation have been proposed and are categorized below in terms of the respective physiological mechanism (see also reviews by Zucker and Regehr 2002; Fioravante and Regehr 2011; Hennig 2013). Notably, mechanisms 1 and 2 listed below do not require a specialized facilitation site or process, while mechanisms 3–5 rely on an extra Ca^{2+} -sensitive site which is either more remote from the Ca^{2+} channel, has a higher affinity for Ca^{2+} , or is slower than the fast low-affinity site responsible for baseline (initial) exocytosis rate and situated in close proximity to a Ca^{2+} channel. Detailed implementations of biophysical models 2–5 must include two ingredients: (1) model of Ca^{2+} dynamics (either a partial differential equation for Ca^{2+} concentration, a stochastic Monte Carlo simulation of Ca^{2+} ion movement, or a simplified ordinary differential equation description) and (2) a model of Ca^{2+} binding to Ca^{2+} sensors controlling exocytosis and its facilitation (usually described by mass-action Ca^{2+} -binding reactions).

Activity-Dependent Increase in Presynaptic Ca^{2+} Influx

The most direct facilitation mechanism is provided by the activity-dependent increase in the Ca^{2+} current through presynaptic voltage-dependent Ca^{2+} channels during the stimulus train, observed in some synapses. Such increase can be either caused by depolarization directly (Bertram et al. 2003; Brody and Yue 2000) or by

Ca^{2+} entering as a result of such depolarization and activating second messengers such as calmodulin or neuronal calcium sensor proteins, which interact with the channels and increasing their conductance (Mochida 2011). It is believed that this mechanism contributes to facilitation observed in certain conditions at the calyx of Held synaptic terminals (Catterall et al. 2013; Xu et al. 2007). However, in many synapses facilitation can be elicited without an increase in presynaptic Ca^{2+} current (Neher and Sakaba 2008).

Facilitation of Ca^{2+} Transients Through Buffer Saturation

The appealing property of the so-called buffer saturation mechanism is that it does not require any specialized facilitatory Ca^{2+} -binding site or process. Instead, facilitation in this case is explained by direct increase in local microdomain free Ca^{2+} achieved in the vicinity of a Ca^{2+} channel during each successive action potential, caused by the progressive reduction of free buffer capacity as it is gradually depleted by Ca^{2+} entering during the conditioning pulses. First proposed on the basis of computational modeling (Klingauf and Neher 1997), buffer saturation was later shown to contribute to facilitation at calbindin-positive neocortical and hippocampal synapses (Blatow et al. 2003; Burnashev and Rozov 2005) and other central synapses (Maeda et al. 1999; Felmy et al. 2003; Jackson and Redman 2003; Orduz and Llano 2007). This mechanism can also be described as a consequence of superlinear summation of small residual free Ca^{2+} accumulation, by itself too small to elicit facilitation, with the Ca^{2+} entering during an action potential; the nonlinearity of this summation is explained by the nonlinearity of the Ca^{2+} -buffer concentration relationship (Neher 1998a). Although the simplicity of this model is very appealing, its role is still under debate (Bornschein et al. 2013), and it imposes strict requirements on the properties of the Ca^{2+} buffer; in particular, simulations show that buffer saturation should be achieved in a large

portion of presynaptic terminal, which requires optimal concentrations of very fast and diffusible buffers (Matveev et al. 2004; Muller et al. 2005). Saturation of large concentration of immobile buffers would also lead to increase in Ca^{2+} transients but would produce much more pronounced elevation of free residual Ca^{2+} ; therefore immobile buffers are more likely to contribute to mechanism 4 below.

Bound Residual Ca^{2+} Accumulation

According to the bound residual Ca^{2+} model, facilitation results from the gradual increase in the Ca^{2+} -bound state of one or more Ca^{2+} sensors regulating exocytosis, rather than from an increase in free Ca^{2+} concentration, and therefore facilitation time course is entirely determined by the slow time scale of Ca^{2+} unbinding from these slow Ca^{2+} sensors that modulate exocytosis together with the fast Ca^{2+} -sensitive exocytosis trigger. This was historically the first conceptual model of facilitation first formulated by Katz and Miledi (1965) and Rahamimoff (1968), and realizations of this mechanism provided some of the first detailed models of facilitation (Yamada and Zucker 1992; Bertram et al. 1996; Delaney and Tank 1994; Dittman et al. 2000). To reconcile this mechanism with the observed sensitivity of facilitation to application of exogenous Ca^{2+} buffers, more up-to-date realistic implementation of this model involves simulations of free Ca^{2+} diffusion from the channel to the binding site, which confers to this model the required partial sensitivity to free Ca^{2+} (Yamada and Zucker 1992; Bennett et al. 2004; Matveev et al. 2006; Nadkarni et al. 2010).

Free Residual Ca^{2+} Accumulation at a Remote Site (Two-Site Model)

Although the growth of free residual Ca^{2+} is small compared to the high Ca^{2+} concentration achieved in the vicinity of a Ca^{2+} channel-vesicle complex,

it can still account for facilitation if exocytosis is assumed to be controlled by two independent Ca^{2+} -sensitive sites, one of which is located close to the channel and therefore controlled by fast microdomain Ca^{2+} transients coinciding with each action potential, and another lower-affinity Ca^{2+} -sensitive site located further away from the channel (perhaps shielded by the vesicle itself or other diffusion barrier), where the small accumulation of residual Ca^{2+} is comparable to the smaller peak Ca^{2+} reaching this more remote location. Thus, this model can be referred to as a *two-site model*. It should be noted that the presence of fixed buffers can aid in residual Ca^{2+} accumulation, since immobile Ca^{2+} buffers act as a Ca^{2+} trap, binding Ca^{2+} close to the vesicle-channel complex and slowly releasing it between action potentials (Neher 1998b). Biophysical implementations of the two-site model require simulations of Ca^{2+} diffusion and buffering (Matveev et al. 2002; Tang et al. 2000).

Calcium-Dependent Acceleration of Vesicle Mobilization

Vesicles undergo several biochemical steps such as docking and priming before becoming competent for exocytosis, and like exocytosis itself, these steps are Ca^{2+} dependent. Therefore, facilitation may arise from acceleration of such “vesicle pool mobilization” in response to Ca^{2+} elevation, increasing the number of vesicles available for release rather than increasing the probability of release of any individual vesicle (Sorensen 2004; Neher and Sakaba 2008). This mechanism would also explain acceleration of recovery from short-term synaptic depression observed in many synapses (Dittman and Regehr 1998; Stevens and Wesseling 1998; Wang and Kaczmarek 1998; Fuhrmann et al. 2004; Hosoi et al. 2007). It is possible that the last priming steps involve a geometric change in the active zone morphology, reducing the channel-vesicle distance (Gentile and Stanley 2005; Wadel et al. 2007), an effect termed “positional priming” (Neher and Sakaba 2008).

Although these effects are biologically very different from the mechanisms discussed earlier, corresponding facilitation models share formal similarities with both the two-site model and the bound- Ca^{2+} model discussed above. Namely, like in the two-site model, exocytosis is dependent on the combined action of two separate Ca^{2+} -sensitive processes, with the fast low-affinity exocytosis process sensing microdomain Ca^{2+} and ensuring phasic synaptic response, and the second high-affinity “priming” process responsible for facilitation controlled by smaller elevations of global Ca^{2+} outside of the microdomain. This mechanism also shares the characteristic property of the bound- Ca^{2+} model in that exocytosis is not in instantaneous equilibrium with local Ca^{2+} concentration, since the priming reactions are at best only slowly reversible. Earlier models of Ca^{2+} -dependent mobilization are based on ordinary differential equations (Dittman et al. 2000; Worden et al. 1997), with more recent models incorporating Ca^{2+} diffusion and buffering to account for the pronounced effects of Ca^{2+} buffering on synaptic facilitation (Millar et al. 2005; Pan and Zucker 2009).

Hybrid Mechanisms

We note that the above mechanisms are not mutually exclusive, and several of them may contribute to facilitation at a particular synaptic terminal. For example, in one of the most detailed recent studies of exocytosis and its short-term plasticity involving stochastic Monte Carlo simulations of Ca^{2+} ion dynamics, both free and bound residual Ca^{2+} accumulation contributes to facilitation (Nadkarni et al. 2010, 2012).

Other Models

A more controversial possibility is that exocytosis depends on voltage explicitly, apart from its Ca^{2+} dependence (see review by Debanne et al. 2013). In this case the fast and brief time course of exocytosis is primarily determined by the fast dynamics of membrane potential and can be achieved even if

the primary exocytosis sensor is shielded from the high Ca^{2+} microdomain or located further from the Ca^{2+} channel. In this case the exocytosis sensor’s affinity for Ca^{2+} would be sufficiently high to be sensitive to even small accumulations of residual global free Ca^{2+} , which would be comparable to peak Ca^{2+} achieved during the action potential at this remote or shielded location (Parnas et al. 1986). It is clear that this mechanism can be viewed as a modification of the free residual Ca^{2+} accumulation model (mechanism 4).

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Failure of Averaging

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Definition

Failure of averaging refers to the situation in which the behavior generated using the average of a set of measurements is not representative of the behavior of the measured population. Averaging fails when the set of parameters describing a system occupies a strongly concave-shaped region in the parameter space, so that the centroid of the distribution of measured parameters does not lie within the distribution itself. Failures of averaging may result either when individual parameters have multimodal distributions or when multiple parameters are correlated in such a manner that their joint distribution is concave. In the latter case, failure of averaging may be difficult to detect experimentally if the set of parameters whose correlations lead to failure of averaging cannot be measured simultaneously.

Detailed Description

Background and Overview

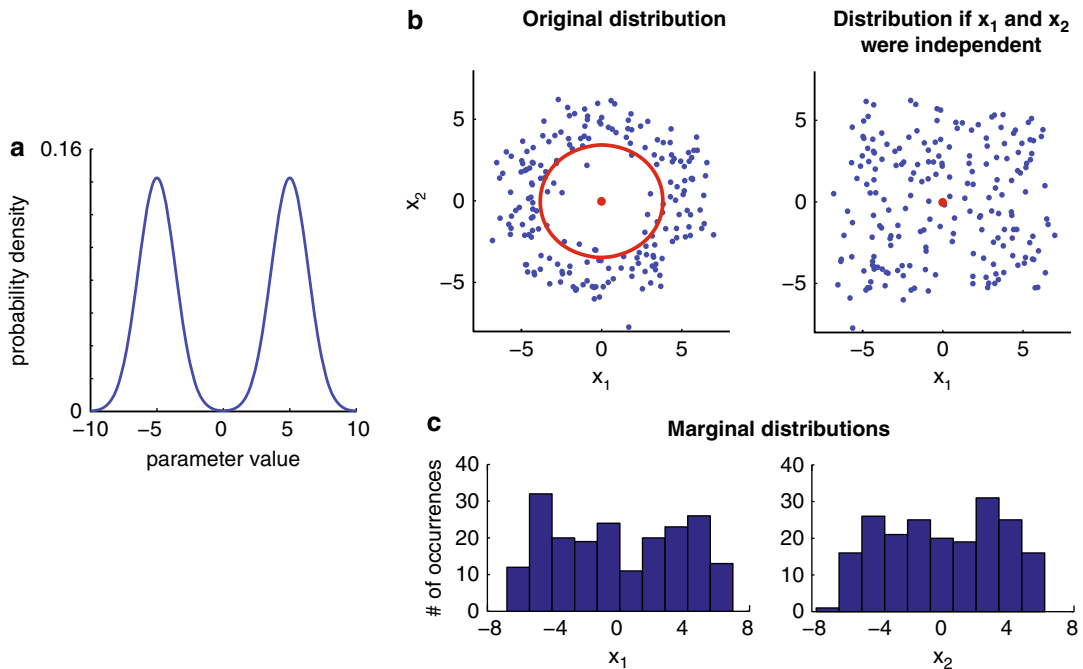
A common technique throughout the sciences is to pool data over many trials or samples and compute the average. This is commonly done to reduce variability due to measurement noise or intrinsic variability irrelevant to the signal of interest. However, this procedure can fail when the response of a system can be produced through multiple different sets of underlying parameters whose average is not typical of any individual measurement.

In the case of a system parameterized by a single variable, failure of averaging can occur if the set of stimuli that trigger a particular response

occupies a bimodal distribution. For example, if a hypothetical motion-sensitive neuron is responsive to horizontal motion with speeds around 5 m/s but is insensitive to the direction of movement, then the set of stimuli leading to an action potential may be described by a bimodal distribution similar to that shown in Fig. 1a. In this case, the strongly concave distribution is such that the mean stimulus leading to an action potential, corresponding to a stationary stimulus, never itself causes neuronal firing.

In higher dimensions, failure of averaging correspondingly can occur if the set of stimuli leading to a given response forms a concave region of parameter space so that the mean is not representative of the distribution from which it was generated (Fig. 1b, left). Furthermore, when the parameter space has a concave shape, the covariance ellipse representing one standard deviation about the mean may only minimally overlap the data from which it was constructed (red ellipse). In this case, not only does averaging together the data fail but even the second-order statistics (means and covariances) fail to characterize the data well.

More generally, the examples above show that failure of averaging occurs in situations where higher-order correlations are critical to describing the structure of a data set. In many settings, such parameter covariations may not be directly measurable, either because the measurement technique requires averaging of many samples to obtain sufficiently high signal to noise or because only a small number of system parameters can be measured at any one time. An illustration of this is provided in Fig. 1c, which shows the marginal distributions (distributions over one parameter, after summing over all samples of the other parameter) for the two-dimensional data set of Fig. 1b. Each of the parameters x_1 and x_2 individually has relatively unstructured distributions (Fig. 1c), so that it is not evident from these marginal distributions that averaging would fail so catastrophically. Indeed, taking random combinations of x_1 and x_2 leads to a relatively unstructured distribution (Fig. 1b, right), illustrating that it is the structure of the correlations in the data set that leads to a failure of averaging.



F

Failure of Averaging, Fig. 1 Geometry of failure of averaging. (a), Failure of averaging when the observed response is controlled by a single parameter, such as for the hypothetical horizontal-motion-tuned neuron discussed in the text. The parameter values leading to the response occupy a strongly bimodal distribution, so that the average is not a member of the parameter set itself. (b, c), Failure of averaging in higher dimensions. (right) The data points

(blue) occupy a concave region of parameter space that does not contain its mean (red point) or most of the region enclosed by the covariance ellipse (red ellipse). This failure of averaging is caused largely by the correlations between x_1 and x_2 because the marginal distributions of these parameters (c) and the distribution generated by randomly pairing x_1 and x_2 values (b, right) are relatively uniform

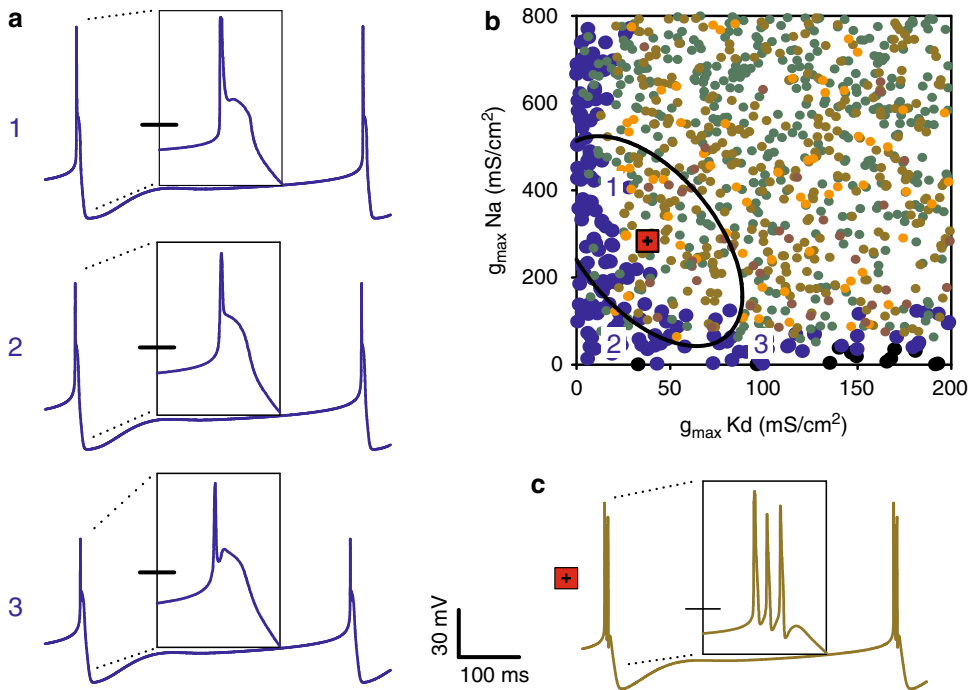
Examples of Failures of Averaging

Conductance-Based Modeling of Neurons

The electrical properties of single neurons arise from the coordinated interplay of many different types of ion channels. The maximal conductances of each of these ion channels can vary widely from cell to cell, even in identified neurons of the same cell class that exhibit similar firing properties. Traditionally, cell-to-cell variability in ionic conductance measurements was attributed to noise or independent parameter variations and was averaged away to give a single, canonical value of the maximal conductance of a given channel in a particular neuronal subtype. These canonical values were then used as the starting point for constructing conductance-based neuron models. However, a series of studies (reviewed by Marder 2011) has shown how nearly identical

behavior of single neurons or small networks can emerge from widely varying sets of underlying conductance parameters. If these conductance parameters sit in a concave region of parameter space, then a model constructed from the average of the measured conductances will not be representative of the cell's experimentally measured response.

An example of such failure of averaging, taken from a computational model of an identified neuron in the crustacean stomatogastric system (Goldman et al. 2001; Golowasch et al. 2002), is shown in Fig. 2. A brute-force search over thousands of models generated by random combinations of five different maximal conductance parameters was used to identify combinations of conductances that lead to "single-spike burster" firing patterns with a single fast Na^+ action potential riding on top of a slower Ca^{++} action potential



Failure of Averaging, Fig. 2 Failure of averaging in a conductance-based neuron model. (a, b), Voltage waveforms (a) of three examples from the L-shaped distribution of models producing one-spike bursting behavior (b). Each example has a highly similar voltage waveform even though the different examples have maximal conductance values $g_{\max} \text{Na}$ and $g_{\max} \text{Kd}$ that are high for Na and low for

Kd (point 1), low for both channels (point 2), or high for Kd and low for Na (point 3). Other data points in b correspond to non-bursting models or models with different numbers of spikes per burst. (c), A model constructed from the mean of all one-spike bursters is not itself a one-spike burster (Adapted with permission from Golowasch et al. (2002))

(Fig. 2a, three examples). When the maximal conductance values of the sodium (Na) and delayed rectifier potassium (Kd) conductances of all single-spike bursters were analyzed, they were found to individually vary over orders of magnitude and to covary such that they formed an L-shaped region in parameter space (Fig. 2b, blue points). As a result, a model constructed from the average of these single-spike bursters did not correspond to a single-spike burster but instead gave rise to a far different pattern of firing, with three spikes per burst. Mechanistically, the L-shaped region reflected that single-spike bursting activity could occur when there was insufficient Na^+ conductance to produce a second spike during the burst (Fig. 2b, low $g_{\max} \text{Na}$ values) or insufficient K^+ conductance to repolarize the action potential sufficiently to enable a second

spike during the burst (Fig. 2b, low $g_{\max} \text{Kd}$ values). More generally, this example reflects how a relatively precise behavioral output (single-spike bursting) can be produced from a broad range of underlying parameters whose strongly nonlinear correlations confound attempts to associate the behavior with a single “canonical” set of parameters such as the means of the measured population.

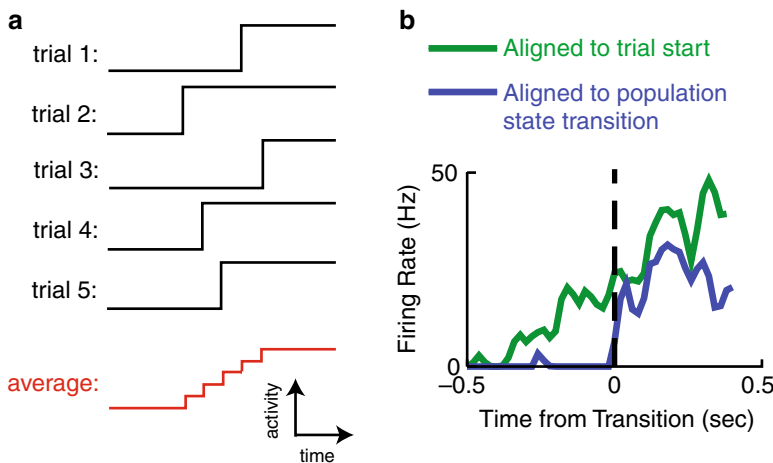
Failure of Averaging in Neural Coding

Another common setting in which failures of averaging are common is in neural coding studies. A hallmark of neurons in later stages of sensory processing is the simultaneous invariance of their responses to certain features of sensory stimuli and strong selectivity to other features. This creates problems for classic correlation-based

methods for characterizing sensory neuron responses, such as the spike-triggered average, that attempt to determine a neuron's selectivity by calculating the average stimulus that precedes a set of neuronal spikes. For example, in the case of the hypothetical speed-tuned neuron of Fig. 1a, the average stimulus preceding a spike has zero velocity and does not itself trigger spiking in this neuron. A similar failure of spike-triggered averaging occurs in the characterization of complex cells of the primary visual cortex that respond to oriented gratings of light and dark bars in a manner that is largely invariant to the phase of the alternating light and dark stripes (Touryan et al. 2002; Schwartz et al. 2006). In the case of complex cells, the use of higher-order statistics such as the spike-triggered covariance of the stimulus set can reveal the underlying selectivity. However, in higher areas of the visual system, even spike-triggered covariance analysis may fail, because cells exhibit more strongly nonlinear feature selectivity while remaining highly invariant to the pairwise correlations among stimulus elements probed by spike-triggered covariances (DiCarlo et al. 2012).

Failure of Averaging in Detecting Discrete State Transitions

A common feature in many biological systems is the presence of discrete states of activity between which a system may stochastically switch. However, differentiating between systems that encode information through continuous variations in activity versus those that utilize discrete activity states can be challenging. The problem in distinguishing such transitions is that neural spike trains are noisy, so that detecting jumps in activity typically requires averaging across many trials. This presents a problem when the time of the jump in activity varies from trial to trial, because the average of many trials can lead to the impression of a graded change in firing rate (Fig. 3a, red) even if each individual trial contains a discrete jump (Fig. 3a, black). An example of such a failure of averaging was suggested by a study of neurons in the gustatory cortex during taste processing. Recording the activity of a large ensemble of neurons revealed, on each trial, discrete transitions between a finite set of stereotyped states defined by the relative firing patterns of neurons across the electrode array (Jones et al.



Failure of Averaging, Fig. 3 Failure of trial-averaging in detecting discrete jumps in activity. (a), Cartoon example illustrating failure of trial-averaging. On each individual trial (black), activity discretely jumps to a non-zero level, but the jumps occur at different times on each trial. Averaging across trials leads to the appearance of a smooth increase in activity (red). (b), Example of failure of trial-averaging in taste processing. Averaging a single

recorded neuron's action potential discharge across trials led to an apparently graded increase in firing rate (green). Aligning instead on the multi-neuron population transition revealed a consistent, discrete jump in firing rate of this neuron at the population transition (blue). The presence and timing of the multi-neuron state transition was determined with a hidden Markov model (Adapted with permission from Miller and Katz (2010))

2007; Miller and Katz 2010). However, the times of these transitions differed markedly from trial to trial so that averaging across trials, with time aligned on the trial start, led to the appearance of graded changes in firing rate (Fig. 3b, green). Aligning instead on the state transitions identified by a multi-neuron pattern analysis revealed sharp transitions between states on a much faster time scale (Fig. 3b, blue).

Implications for Experiments

The failure of averaging demonstrated in the above examples is inconvenient for simple characterizations of data by means and variances but may not be problematic if all of the parameters of a system can be measured simultaneously and fit by a model that includes nonlinearities or higher-order statistics. However, in many biological situations, population data are either implicitly averaged by the measurement technique, such as when large numbers of cells are homogenized together to increase the signal-to-noise ratio in gene expression studies, or only a small number of system parameters can be measured simultaneously.

In the absence of simultaneous measurements of all relevant system parameters, it is important to ask whether the population means of the measured samples are likely to be representative. In the cases illustrated above, the unmeasured correlations between the parameters were highly nonlinear and caused the population mean to differ entirely from the individual samples from which it was generated. In the less extreme case, the mean parameter set might lead to an output consistent with the data from which it was determined. However, the variability around this mean would not necessarily represent noise but instead could represent the multiplicity of ways in which biological systems can produce a given output (Foster et al. 1993; Bhalla and Bower 1993; Goldman et al. 2001; Prinz et al. 2004). Given the ability of biological systems to produce desired outputs through multiple underlying mechanisms, “failure of averaging” in this broader sense may be a common occurrence.

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Faulty Integration

- [Peripheral Vision, Models of](#)

FeatureMapper

- [Topographica](#)

Feedforward Inhibition

- [Large-Scale Models of the Olfactory Bulb](#)

Fick's Second Law

► Diffusion Equation

Field Potential

► Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of

FieldML

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Definition

FieldML (Christie et al. 2009; Britten et al. 2013) is a proposed open standard data format for representing mathematical models, developed at the Auckland Bioengineering Institute (ABI) at the University of Auckland, New Zealand. It is specifically focused on multivariate spatiotemporal models and finite element method (FEM) models for biological modeling, but can be used more generally. FieldML version 0.5 is the most recent release (2012) at the time of writing, and although it already comprehensively supports the representation of a wide range of relevant models, the format is still considered under development.

Detailed Description

Introduction

Mathematical models form a core part of computational bioscience. Often these models are either represented using mathematical symbols intended to be read by humans (such as in books or research papers) or in computer programs using the

mathematical operators and syntax of a particular programming language. These approaches limit the usefulness of the model, requiring manual coding to reimplement the models in new modeling contexts and often not cleanly separating the mathematical model from the numerical methods used to compute the model.

A number of modeling formats have been created to address this problem, for example, NeuroML, CellML, and SBML. FieldML (www.fieldml.org) follows a similar approach, but with a focus on the representation of the following:

- Anatomical shape (or geometry)
- Spatially varying quantities
- Time-varying quantities
- Generalized multivariate mathematical fields

Although these biomedical focus areas have played a key role in guiding the design, FieldML is not restricted to biomedical modeling and is potentially useful in more general mathematical modeling contexts.

Overview of Data Model

FieldML top-level models are serialized to the FieldML XML format, and other data formats can be referred to from the XML for the purpose of separating bulk data from the higher-level model description. Bulk data usually consists of large numerical arrays. Underlying the XML format is the abstract FieldML data model that is independent of XML and indeed could be serialized using a different technology. The FieldML data model can also be used directly as the in-memory representation by software that processes mathematical models. This subsection gives an overview of the FieldML data model. A more detailed description of both the FieldML version 0.5 data model and the corresponding XML format is available in Britten et al. (2013).

The two main objects of interest in the FieldML data model are fields and domains. Domains are mathematical sets, possibly with additional information about their topology. An example of a domain is the set of real numbers.

Fields are mathematical functions that map values from one FieldML domain to another FieldML domain. An example of a mathematical function that could be modeled as a field would be the cosine function. Note that the term “domain of a function” is used in mathematical terminology to mean the set from which a function maps values, and similarly, the “codomain of a function” is the set into which a function maps values. The domain of the cosine function is the set of real numbers. The codomain is also the set of real numbers. Since the term domain is used for two different meanings, clarification is achieved by using the terms “FieldML domain” and “function domain” whenever confusion is possible.

The standard mathematical notation for stating that a function f has the set A as its domain and the set B as its codomain is as follows:

$$f : A \rightarrow B$$

In FieldML, fields are constructed by chaining together *evaluators*. A FieldML evaluator represents a function, and the “chaining” is essentially function composition. This will be elaborated upon later on in this section.

Evaluators

In FieldML 0.5, there are seven kinds of evaluators: argument, parameter, piecewise, aggregate, reference, external, and constant.

An *argument evaluator* essentially performs the role that a variable performs in algebraic mathematical expressions.

A *parameter evaluator* defines a function that essentially represents a numerical array by means of the array indexes being treated as the function’s parameters. The actual values of the array elements are retrieved from data sources, which are described later in detail, but essentially are bulk data, usually for numerical arrays.

A *piecewise evaluator* defines a piecewise function, where the function domain is a discrete set.

An *aggregate evaluator* defines a vector-valued function, for example, a function that takes values in three-dimensional Cartesian space.

A *reference evaluator* can be either just an alias for another evaluator or, if used in conjunction with binding (described below), represent the substitution of values into the expressions represented by a pipeline of evaluators.

An *external evaluator* declares the existence of an evaluator whose behavior is defined outside of any FieldML file. This is essentially a work-around for a current limitation of FieldML version 0.5 where common algebraic operators such as addition and multiplication are not yet supported. The work-around allows FieldML models to refer to functions that are required for the target usage, and relies on external documentation of the intended behavior and consistent implementation in all software that processes FieldML version 0.5. Although this also allows arbitrary nonstandard extension, it is discouraged. This is seen as an interim measure until the next version of FieldML is released with features that allow these functions to be defined directly in FieldML itself. The intention is that the use of external evaluators should be limited to using only those already provided in the standard library (described below) that is included as part of FieldML version 0.5.

A *constant evaluator* represents a constant value, with the restriction that it must be possible to represent the value type using standard XML string representations, which means that only text, integer, and floating point values can be represented. In combination with other evaluators, more complex constants, such as a constant vector value, can be represented.

As mentioned earlier, *binding* essentially represents the process of variable substitution in mathematical expressions. Binding can be specified as part of the specification information for reference, piecewise, and aggregate evaluators. The information provided as part of the binding syntax specifies the name of an argument evaluator and the name of any other evaluator type which will be the substitute evaluator. It represents the action of substituting every occurrence of the specified argument evaluator in the pipeline “upstream” of the host evaluator.

Domains

In FieldML version 0.5, the following constructions can be used to define domains: ensemble, Boolean, continuous, or mesh.

Note that two different domains are treated as distinct sets, even if their definitions are identical.

Ensemble is used to define finite discrete sets where the labels used for a given ensemble are either all integer labels or all string labels.

Boolean declares that a given set has exactly two members, labeled *true* and *false*. Predicate functions are used as part of the definition syntax for mesh domains (described below), and their codomain must be any domain that has been declared to be Boolean. A Boolean domain is defined in the FieldML version 0.5 standard library, and it is recommended that this be used whenever a Boolean domain is required, rather than defining additional Boolean domains.

Continuous is used to declare n -dimensional Cartesian space (however, this excludes any additional algebraic structure, such as vector addition, a distance metric, or a Riemannian metric). For dimensions higher than 1, the definition allows for an ensemble to be designated as the labels for each dimension, for example, “u, v” or “x, y, z.”

Mesh is used essentially to define a FEM mesh where all elements are the same dimension; however, the element shape may vary. Element shape is defined by reference to a predicate, which is any evaluator with a Boolean codomain. A collection of such predicates are provided in the FieldML version 0.5 standard library, and all of these are defined as external evaluators. The mesh declaration includes the definition of an ensemble that indexes the elements of the mesh and a continuous type that is used for the coordinates within each element. FieldML version 0.5 does not have a way of specifying the connectivity of the mesh. The fields over the mesh, such as the geometry field or any other fields, are defined by means of creating an evaluator pipeline. This will usually require a piecewise evaluator which depends on parameter evaluators for the degrees of freedom (DOFs) and the local to global node mapping. Hence, the connectivity information is usually present in an indirect manner.

Data Sources

Data sources allow the FieldML file to refer to bulk numerical data that is either stored in the same FieldML XML file, an imported FieldML XML file, or an external file. Data stored in external files can be stored as decimal strings in text files, or using HDF5. Parameter evaluators make reference to data sources for their data. The location of external data files is specified by URL.

Imports

Imports allow a FieldML XML file to make reference to evaluator declarations or domain declarations from external FieldML XML files. Imports require that an alias be assigned by which the imported entities are referenced. These are then treated as if they had been defined locally. Entities on which they depend are not available locally, but are nevertheless still part of the definition of the imported entities. The location of the imported XML files is specified by URL.

Imports allow FieldML models to be composed in a modular fashion, which encourages reuse and allows for duplication to be kept to a minimum.

FieldML Standard Library

The FieldML standard library serves two main purposes for version 0.5. Firstly, it provides reusable centralized definitions of evaluators and domains that are commonly required in the target application areas of computational physiology and bioengineering modeling. Secondly, in conjunction with the FieldML specification, it documents the external evaluators so that the required convention is established.

The FieldML standard library is available from http://www.fieldml.org/resources/xml/0.5/FieldML_Library_0.5.xml.

The FieldML Version 0.5 API

The FieldML version 0.5 application programming interface (API) and API implementation

were released in conjunction with the FieldML version 0.5 format. The API consists of functions for both serialization to XML and deserialization from XML. The implementation is written in C++, and bindings are provided for C++, C, Java, and Fortran 90.

Adoption

At the time of writing, known adoption of FieldML is still relatively low. The ABI hosts three software projects which have limited FieldML support. Firstly, the OpenCMISS-Zinc software library uses the FieldML API to allow for 3D interactive model visualization for a limited range of models. Secondly, the Physiome Model Repository (PMR) software allows for FieldML models stored in the model repository to be visualized using the Zinc plug-in, which is a browser plug-in based on the OpenCMISS-Zinc library. Thirdly, the OpenCMISS-Iron computational system can use the FieldML API to read in a limited range of mesh and field definitions from FieldML and can output some types of simulation results in the FieldML format also by using the FieldML API.

Cross-References

- [CellML](#)
- [NeuroML](#)
- [Physiome Repository](#)
- [Systems Biology Markup Language \(SBML\)](#)

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Figure-Ground Segregation, Computational Neural Models of

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Definition

Figure-ground segregation refers to the capacity of a visual system to rapidly and reliably pick out for greater visual analysis, attention, or awareness, or preparation for motor action, a region of the visual field (figure) that is distinct from the combined areas of all the rest of the visual field (ground). The “figure” region is often, but not necessarily, bounded by a single closed visual contour, and the figure region is often said to “own” the boundary between it and any adjacent regions. The figure region is generally experienced as “in front of” (along lines of sight) surfaces of objects that are in the ground region. Once figure-ground segmentation is achieved, the figure region often delineates a zone of additional attentive visual processing.

Detailed Description

The Importance of Figure-Ground Segregation

Visual function in animals has broadly increased in complexity and competence across eons of evolution, with figure-ground perception being among the later and more intriguing achievements of relatively sophisticated visual species.

The importance of figure-ground perception can be seen by considering its advantages to animals that have the capability, as compared to the visual limitations of animals whose visual systems do not support figure-ground perception (Land and Nilsson 2002). For example, the single-celled euglena can use its eyespot and flagellum to orient its locomotion in a light field, but it cannot take account of the edges of individual objects in the sense of figure-ground for purposes of steering. Arrays of visual receptors that sample different directions of the visual field, such as the compound eyes of insects or mammalian retinas, are needed for computing figure-ground relations. Successful figure-ground segregation can facilitate several subsequent visual tasks, such as object recognition or guidance of locomotion toward a goal or around an obstacle.

Some species of animals can perform figure-ground perception only in the presence of visual motion, while others can also do so in static environments. It must be noted that even when the environment outside an animal is perfectly still, the animal itself may be making voluntary movements at a macroscale or involuntary movements (eye tremor or microsaccades) that can help to support figure-ground segregation.

Finally, as we will see in the case of human (or, more generally, primate) figure-ground perception, the space-variant arrangement of receptors on the retina and the associated “cortical magnification” that concentrates the brain’s processing resource to the central region of the visual field are major factors both in achieving and in exploiting figure-ground perception. Voluntary eye movements to an approximate centroid of a relatively homogenous visual region can enhance the visual system’s capacity to delineate an associated figure-ground boundary and thus to perform figure-ground segregation at all. Conversely, as long as the eyes are foveating a “figure” region, a high proportion of cortical tissues is devoted to analysis of that region, courtesy of cortical magnification, thus facilitating object recognition or discrimination between two similar object categories. The ability to deploy foveal vision while performing figure-ground segregation can thus be viewed as

a “force multiplier” that enables detailed scrutiny at relatively low metabolic cost (eye movements), rather than requiring a reorientation of an entire head or actual approach of the entire body toward an environmental region.

Elementary Cues for Figure-Ground Segregation

In visual scenes with little structure, separation of figure from ground may appear as an easy or even trivial task. For example, a small dark spot on an otherwise homogenous light background is often said to “pop out” from its background in the context of a visual search task (e.g., “Find the dark spot,” Treisman and Gelade 1980). Such isolated, salient figural properties “call attention to themselves” and are effective as lures that attract saccades. A consensus of recent decades holds that regions of higher-than-average (relative to the rest of the scene) activation of certain featural qualities (e.g., of color, contrast, motion, or orientation) in visually topographic “feature maps” make such regions likely targets for attention or of overt eye movements (Wolfe and Horowitz 2017).

An important class of figure-ground phenomena occurs in cluttered visual scenes, where the achievement of figure-ground segregation can amount to the breaking of camouflage. Gibson et al. (1969) demonstrated vivid figure-ground segregation in random dot kinematograms – displays involving some combination of static and moving randomly distributed dots that are analogous in the time/motion domain to random dot stereograms. In random dot stereograms, two eyes receive related, but different, images, typically where a region of dots (the figure) is displaced in one eye’s view relative to the other eye’s view, causing a relative disparity of stimulated retinal locations that is different from the disparities of other corresponding dots in the two eyes (which form the ground).

The importance of motion to figure-ground perception of ecological scenes has been evident since, at least, the seminal paper by Lettvin et al. (1959) “What the frog’s eye tells the frog’s brain,” whose authors noted that frogs of the studied species would starve in the presence of freshly

killed flies spread on the ground before them. Nonetheless, humans and certain other species have the capacity to perform figure-ground segregation for many complex static scenes, including pictures – for which endogenous eye movements convey no additional information, as would be the case for views of actual three-dimensional environments.

The Scope of the Present Article

This article focuses on computational models of human or primate figure-ground segregation. We indicate whether models are intended to address moving or static scenes, or both, and whether they rely on binocular vision. Reasons for this focus include (1) that primate visual systems have the greatest complexity and competency among known biological systems and (2) that many machine vision systems are designed with the intent of matching if not exceeding human performance in important visual tasks. While many computer vision algorithms are designed without reference to animal examples, it makes sense to study natural visual systems for inspiration in those domains for which machine performance continues to lag, as is the case with figure-ground segregation in cluttered scenes.

What Is Border-Ownership and How Is It Related to Figure-Ground Perception?

A “figure” object and its borders occlude the objects and their borders of the background. Figure 1a shows the famous painting by Leonardo da Vinci: Mona Lisa occludes the trees, river, bushes, and other objects in the background.

The foreground borders in (Fig. 1a) obviously “belong” to the object (i.e., Mona Lisa) in front, which is the figure. The shape of the borders is often informative about the identity of the object (a human) that is depicted, which is said to “own” the border – thus figure-ground perception can be an important step on the way to object recognition. Note however that Evans and Treisman (2005) have shown that people can perform animal detection in natural scenes with great success even though they are unable to localize the animal, so figure-ground perception cannot be said to be a required step in object recognition. Rather, the *localization* of a figure’s borders and proper assignment of the ownership of associated borders are logical requirements of figure-ground segregation.

Border-Ownership Is Independent from the Polarity of Contrast Across Borders

A clever artist can devise displays in which the ownership of a border is ambiguous, leading to

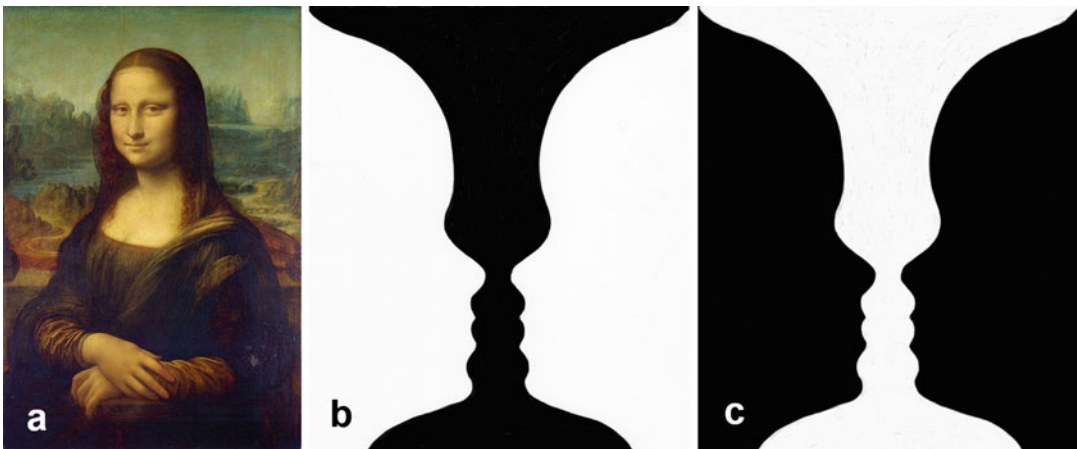


Figure-Ground Segregation, Computational Neural Models of, Fig. 1 Examples of 2D images helping formulate the concept of figure-ground segregation and border ownership, irrespective of some visual attributes such as edge contrast. (a) Mona Lisa by Leonardo da Vinci.

(Adapted from https://en.wikipedia.org/wiki/Mona_Lisa under the public domain), (b) Rubin faces/vase. (Taken from https://commons.wikimedia.org/wiki/File:Multi_stability.svg and is released under the public domain by Alan De Smet), and (c) its contrast inverted version



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Figure-Ground Segregation, Computational Neural Models of, Fig. 2 Figure-ground segregation during camouflage, when the figure and background have similar textures and their average luminance are close to each other. Such scenes can pose another level of challenge to computational models of figure-ground segregation, as the

figure borders cannot be readily detected by the lining up of the units detecting edge contrast, as tiny edge contrasts with different orientations are almost uniformly distributed. (Adapted from pixabay.com; photo is released under CC0 Creative Commons)

bistable percepts. See Fig. 1b, the Rubin (doctoral dissertation 1915) faces/vase. While consciously experiencing the faces against a black background, the borders separating the white and black areas are the face borders. Note that flipping the contrast of Fig. 1b and making the faces black and the vase white (Fig. 1c) do not change the relationship between the figure-ground separation and border-ownership, i.e., when the faces are seen against the uniform background, the borders between the black and white areas belong to the faces and the same for the vase.

A good deal of attention in introductory textbooks is devoted to bistable displays (Fig. 1b–c) when discussing figure-ground perception. Although such displays help to make an important point about the relationship between figure-ground relations and border-ownership, they are a potentially misleading starting point relative to figure-ground perception in natural scenes. In bistable displays, volitional manipulation by the viewer of semantic categories such as face or vase can “drive” a resulting percept. The bistability of labeling border-ownership is not typical of most normal perceptual settings, which are closer to the depiction of Fig. 1a. Note

also that finding boundaries is trivial in binary-valued displays with solid, connected regions, such as Fig. 1b and c, as opposed to conditions of, for example, animal camouflage (Fig. 2).

Psychophysical Antecedents of Recent Computational Neuroscience of Figure-Ground Perception

The second half of the twentieth century saw a great deal of human psychophysics devoted to the study of texture segregation, visual segmentation and grouping, and visual search.

Linking these studies – many of which sought to find fundamental visual “elements” of perception – was the goal of characterizing how, out of the “blooming, buzzing, confusion” of time-varying visual scenes, our visual systems are able to focus on relatively coherent objects of interest (figures). The texture segmentation and grouping studies characterized conditions under which perceptually continuously connected boundaries between regions could form, even in the absence of continuous differences in luminance or contrast along those boundaries (such as is evident in Fig. 2). Thus, the question of “ownership” of boundaries was often not raised.

Visual search studies, pioneered by Anne Treisman in the 1980s (Treisman and Gelade 1980) and developed since by many, most notably Jeremy Wolfe (Wolfe and Horowitz 2017), focused on describing conditions under which a region of a scene would “pop out” and thus be treated as a “figure” for subsequent processing, with the rest of the display acting as “ground.” When conditions for pop-out were not in play in a given display, search could be “guided” by top-down expectations (Wolfe and Horowitz 2017), or a number of candidate regions (Grossberg et al. 1994) might be evaluated in order of likelihood of containing the object being searched for. In scenes containing an object of search, the finding of that object, whether quickly or slowly, inevitably is accompanied by the phenomenal experience of the visible regions of that object as “figure.” A series of psychophysical studies led in turn to related paradigms involving brain imaging or electrophysiological recordings in primates, which have advanced our understanding of figure-ground perception tremendously.

Finally, an important thing to note about figure-ground perception is that, unlike the examples discussed to this point, in daily life it does not generally occur in a flat plane, such as in a picture. When we look at a spoon or cup that we are about to reach for, the surface of the object is extended and often curved in three dimensions. Tyler and Kontsevich (1995) introduced the important concept of an “attentional shroud” – a fuzzy manifold in perceptual space that envelopes the surfaces of attended objects. The shroud delineates both the limits of focal attention and also the tendency of attention to involuntarily “spread” along the visible surfaces of an attended figure, rather than into the rest of the scene (the ground). Indeed, the delineation of attentional resources for visual processing after the determination of figure-ground segregation can be viewed as an important functional reason for engaging in figure-ground segregation in the first place.

Brain Areas Involved in Figure-Ground Perception

Although figure-ground segregation is fundamental to visual perception, how the visual system

performs it is not well understood. Coding of border-ownership starts early in primate brain visual stream. A direct link between visual figure-ground perception and the responses of certain single neurons has, however, been established in the early visual system.

These cell responses may require the simultaneous activation of parts of visual areas V1, V2, and V4 (Fig. 3) acting as a functional network (Layton et al. 2012), whose neurons are monosynaptically connected to each other across visual areas (Fig. 3b). Such connections are termed *inter-areal*. On the other hand, neural connections within each area (i.e., V1, V2, etc.) are called *intra-areal*. Zhou et al. (2000) and Ko and von der Heydt (2018) have found that about half of sampled cells from primate visual areas V2 and V4 preferentially respond to borders whose ownership is related to figure-ground relations (Fig. 4). These cells are referred to as border or B-cells and have “side-of-figure” selectivity that indicates a neurophysiological correlate of percepts observed in Fig. 1b–c, namely, that a border is owned by either the region to one side (for example vase) or another of that border (face), but not both.

Temporal Dynamics of Border-Ownership Neural Response

The border-ownership-related neural response can emerge within 25 msec after the B-neuron’s response onset. In V2 and V4, the differences were found to be nearly independent of figure size up to the limit set by the size of the display (21°) that Zhou et al. (2000) used (Fig. 4). Because such a response depends on the processing of an image region that is at least as large as the figure and thus requires the transmission of information over some distance in the cortex, *these short delays constrain the functional network underlying the B-cell response and the biological plausibility of neural models.*

The short delay of the emergence of border-ownership signals constrains the contribution of inter-areal and intra-areal connections in a biologically plausible neural model that can perform figure-ground segregation (Layton et al. 2012). This is because inter-areal connections are

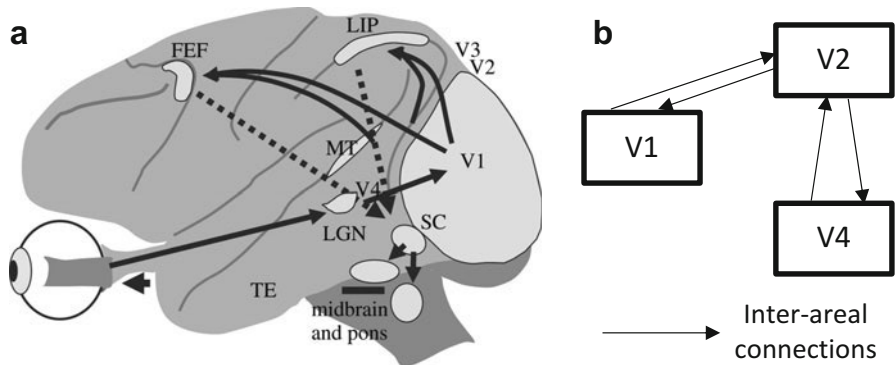


Figure-Ground Segregation, Computational Neural Models of, Fig. 3 Brain areas at some distance can be axonally connected, such as inter-areal connections between visual areas V1, V2, and V4. Inter-areal connections via myelinated axons are much faster than within area (intra-areal, unmyelinated) connections. As a result, during a stream of visual inputs, multiple brain areas can be activated within a short period of time, forming

a multiple-area network for processing the input. (a) Lateral view of the left hemisphere of a monkey brain, roughly showing the locations of V1, V2, and V4. (Adapted from Wurtz (2015) under the Creative Commons Attribution 4.0 International license). (b) A simple schema showing inter-areal and mutual connections between areas V1, V2, and V4, highlighting the fast inter-areal connections that can generate a functional multiple-area visual network

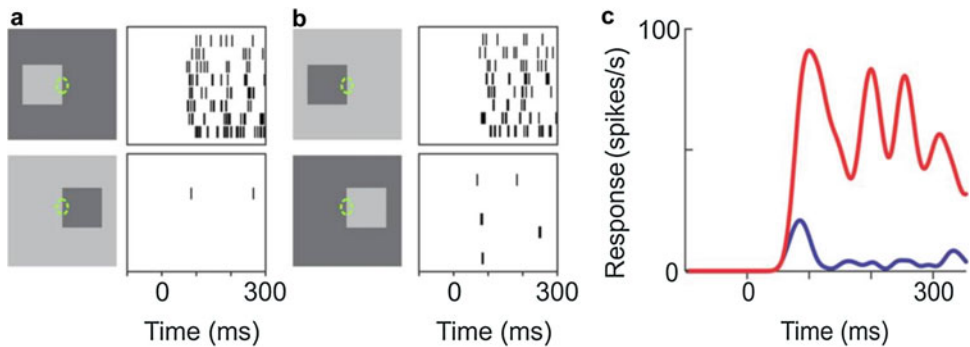


Figure-Ground Segregation, Computational Neural Models of, Fig. 4 The von der Heydt group discovered the presence of border-ownership neurons. The neuron receptive field is shown by small circle/ellipse which is over the figure edge. Local contrast (light/dark) is the same across each column and over the classic receptive field of

the neuron, yet, the neuron shows preference for figure to the left (1st row in a and b) than to the right (2nd row in a and b). Such cells, therefore, encode border-ownership, and in this particular case, left-side ownership. (Adapted from von der Heydt (2015) under CC BY License)

myelinated and transfer neural signals much faster than the intra-areal ones, and therefore, the small delays observed in border-ownership signals demand fast inter-areal connections. Researchers have proposed that B cells access global information either intra-areally, i.e., by lateral connections within a single visual cortical area, such as V2 (Zhaoping 2005), or inter-areally, i.e., where cells with larger receptive fields (e.g., V2) communicate contextual information about the scene via feedback projections to visual areas whose cells

have smaller receptive fields (e.g., V1; see the diagram in Fig. 3b). Intra-areal and inter-areal axonal conduction velocities have been estimated to be 0.3 and 3.5 m/s in early visual areas, respectively (Bullier 2001). Hence, inter-areal connections can be an order of magnitude faster than intra-areal connections for propagating information across the visual field. B-cell responses to 3° squares did not differ in latency compared to those to an 8° square, which is consistent with the use of inter-areal connections, but not intra-areal

connections, to propagate contextual figure-ground information. Although a variable amount of time is required to propagate information about a figure within a single cortical area, transmitting the information to another area with large receptive field cells could afford a roughly fixed delay irrespective of the figure size in the visual field (Layton et al. 2012). Hence, *it appears that connections within a single cortical area alone could not plausibly account for the fast global scene integration that is observed in B-cell border-ownership responses* (Layton et al. 2012), but see Zhaoping (2005), who argues otherwise.

The immediately preceding discussion is an example of an emerging paradigm shift in understanding of cortical visual processes. Most physiological studies related to cell response to luminance-based and hue-based edges of the primate visual system in the past half-century have followed the path established by Hubel and Wiesel (1962) and largely focused on the function of individual areas or subpopulations of cells *within a visual area*. Topics of such studies include how different cells in the primary visual cortex respond to luminance base edges, to the light-dark polarity of contrast, and to variations of edge orientation. It instead appears that the cortex can solve complex problems *with networks that span multiple areas*. The visual system may thus rapidly recruit an assembly of cortical areas to determine border-ownership in figure-ground segregation, a single emergent function. Neuroanatomical evidence indicates that early visual areas such as LGN, V1, V2, and V4 are massively interconnected with numerous feedforward and feedback connections (Sincich and Horton 2005, see Fig. 3b). Feedforward connections are believed to quickly propagate sensory visual information to cortical areas further up the visual hierarchy to serve a rich perception of the visual scene. Feedback projections are often said to play a modulatory role with respect to bottom-up sensory visual signals by increasing the gain of neuronal responses in attended regions and performing contextual integration. To date, few studies have hypothesized that feedback projections play a crucial as opposed to supplementary roles for the functions of early visual

cortices. It appears that the simultaneous activation of multiple areas early in the visual system not only performs modular functions that are later combined but also that such activation can collectively solve problems that individual cortical areas cannot solve alone (Layton et al. 2012).

A Teardrop Model of Figure-Ground Segregation and an Edge-Integration Model

Layton et al. (2014) presented a model of figure-ground segregation in which inter-areal feedback plays a crucial role in disambiguating a figure's interior and exterior. The model processes are based on primate receptive field scatter (jitter in receptive field center locations) and variation in receptive field sizes to generate a code for inside versus outside of a visible figure. Feedforward projections from V4 signal the curvature of object boundaries (curved contour cells), and feedback projections from visual temporal areas group neurons with different receptive field sizes and receptive field center locations in a teardrop geometry. Neurons sensitive to convex contours, which respond more when centered on a figure, balance feedforward information and feedback from higher visual areas. The model produces maximum activity along the medial axis of figures irrespective of the concavities and convexities of figure contour. The model feedback mechanism balanced with feedforward signals is crucial for figure-ground segregation and localization (Fig. 5).

Another computational approach in solving the figure-ground problem for static scenes is given by Grossberg (1993, 1994). This neural model involves feedforward and feedback interactions between cortical units that represent boundaries and surfaces at multiple spatial scales. The assignment of border-ownership drives interactions where signals for boundaries that are nearer to the viewer suppress signals for further-away boundaries in a way that supports featural visibility (lightness) of the figure region while allowing aligned segments of far boundaries to complete and support amodal completion of partially occluded surfaces. Note that, while differing in important ways from the Layton et al. (2012, 2014) models, the Grossberg (1993, 1994)

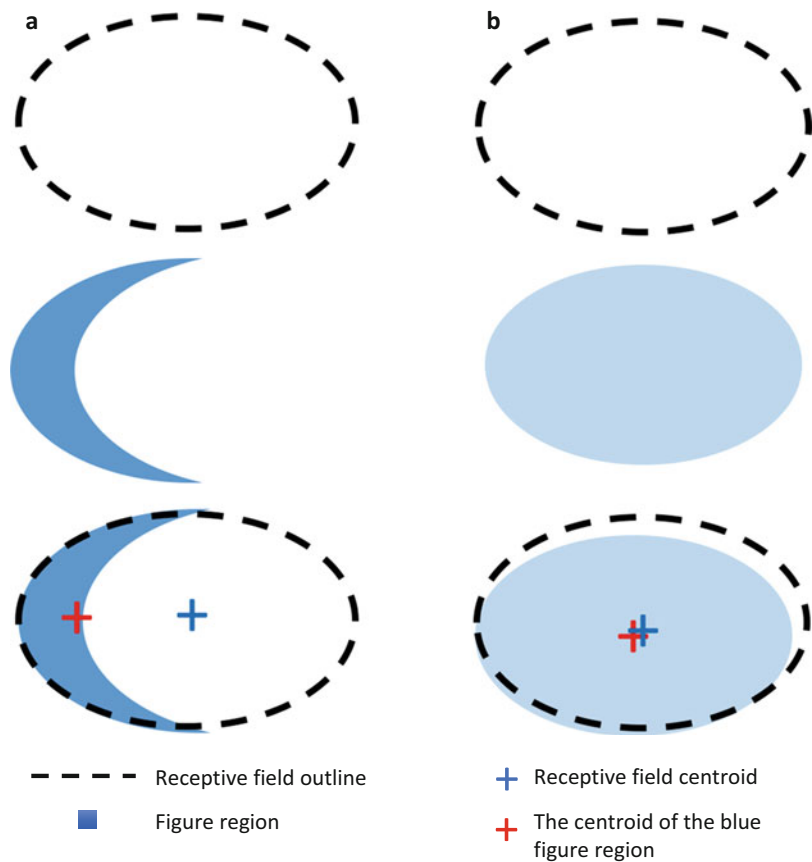


Figure-Ground Segregation, Computational Neural Models of, Fig. 5 Localizing a C-shaped (crescent moon shaped) figure is difficult from the perspective of a single neuron’s convex receptive field (shown as dotted black outlines in the top and bottom rows of the figure). The middle row shows two stimulus shapes – a concave C shape in column (a) and an ellipse in column (b). Note that the shape in (a) is darker and has a greater contrast with the white background, leading to higher activation per unit area of a neuron’s receptive field. Thus the degree of

activation of the two neurons in the third row can be approximately the same. Localization is a different matter, however. The figure centroid is shown by two red cross symbols, +, whereas the centers of the two neurons’ receptive fields are indicated by blue crosses. Localization is poor in case (a). The teardrop model of Layton et al. (2014) offers an inter-areal network to resolve figure localization in cases like in (a). Note that the areas chosen for investigation in the study described in Fig. 4 are also “C-shaped,” where the C is a block shape with right-angle corners

approach introduced the idea of cooperation and competition among representations in multiple cortical areas as a key requirement of figure-ground segregation.

A contrasting approach to modeling figure-ground segregation is taken by Kogo et al. (2010), who view figure-ground perception as a nonlinear differentiation/integration process that simultaneously accounts for border-ownership, lightness, and depth perception. A crucial step in this model is called “Integration for Surface Completion,” where estimates of depth

in a featurally homogeneous region’s interior are “filled-in” through values that are computationally propagated from signals from the region’s edges. This integration step differs with the Layton et al. 2014 approach, which depends on estimates of depth from multiple receptive fields in a higher visual area whose centroids are distributed (“jittered”) across the region’s area. Integration is a computation that would seem to “naturally” occur within a visual area, and further investigation of comparisons between classes of models employing integration versus inter-areal

feedback is needed to better understand figure-ground segregation.

Neural Responses to Texture-Defined Static Figures

Lamme (1995) is an important monkey single-unit recording study involving displays in which a figure-ground segregation is easily perceived (by humans) through differences in the orientation of texture elements. Although the receptive field of certain neurons in early visual areas of monkey lies entirely within the “figure” texture region, the neurons exhibit an enhanced firing rate compared to when the monkeys were presented a display containing a uniform texture of the neuron’s preferred orientation throughout the display.

The interior enhancement effect persists when the edges of the square are 8–10° and the modulation occurs after an 80–100 ms latency from the onset of the stimulus, which suggests *feedback from neurons with larger RFs* may be involved. A temporal analysis indicates that neural activity related to the edges of the figure emerges first, following a short latency, then interior enhancement occurs in the “late component” of the response (Roelfsema et al. 2002). A neuron that shows interior enhancement continues to fire at an elevated rate when the RF is centered at different positions within the texture-defined figure, and the firing rate drops when the RF is centered on the background. Neurons in V2 demonstrate a greater degree of interior enhancement compared to those in V1, and the magnitude of interior enhancement response is greatest in V4.

Motion-Based Figure-Ground Segregation

Fishes, frogs, moths, and snakes demonstrate adaptations in the appearance of their body to hide from predators. Through camouflage, the markings on the prey’s body cause the animal to be grouped with, rather than stand out from the surrounding. This strategy is effective as long as the animal *does not move*, because many predators and humans cannot easily detect stationary objects that resemble their surroundings in texture, color, and luminance. However, when a previously invisible animal breaks camouflage by sudden motion, humans rapidly perceive a figure

at a different depth from the surroundings, even if the texture is statistically identical. When a figure moves in front of a similarly textured background, it is said to produce kinetic occlusion (Gibson et al. 1969; Kaplan 1969). No reliable luminance contrast exists between the figure and background; there is only the relative motion between the texture patterns separated by a kinetically defined edge (kinetic edge). How do humans perceive the figure at a different depth than the background (figure-ground segregation), despite the figure and background possessing patterns with statistically identical luminance? Obviously, this is a demanding scene processing task for the primate visual system, which goes beyond simple contrast processing and is likely to involve brain areas involved in motion processing (the middle temporal area, MT, among others) as well as form processing (including V4 and probably other visual areas) to extract the moving form from visual motion cues scattered within the camouflaged scene. In this regard Layton and Yazdanbakhsh (2015) have suggested an interconnected network model of areas V1-V2-V4-MT, in which MT and V4, both monosynaptically connected to V2, process the motion and form signals, respectively. Another possible approach to motion-based figure-ground segregation is described by Barnes and Mingolla (2013), whereby motion onset and offset signals generated by accretion or deletion of texture elements via occlusion act as key gating signals for figure-ground segregation. Note that it is quite possible that the primate visual system has evolved multiple mechanisms, with partially overlapping competencies, to address the important needs of figure-ground segregation.

Need for Feedback Among Brain Areas

As noted in “the section [Temporal Dynamics of Border Ownership Neural Response](#)”, the primate visual system can rapidly recruit several cortical areas in the service of determining figure-ground relations. One way to investigate the mechanisms underlying the context-sensitive aspects of perceptual organization is the use of images that create bistable perception in which the perceptual interpretations of the image keep alternating over

time, while the physical input image is kept constant. One of the most famous images to induce perceptual bistability involving figure-ground organization is Rubin's "face-or-vase" image (Fig. 1b–c): The perceptual interpretation keeps alternating between "two faces" on the sides and a "vase" in the center, while the competing area is perceived as a part of the background. Because the perceptual switch in this case is specifically linked to the reversal of the figure-ground organization, we can call this phenomenon bistable figure-ground organization. Rubin presented his dissertation in 1915, with one of the key points that when two neighboring fields share a border, one will be seen as figure against the other as the background and that the percept of a figure is dominated by one of the fields against the other sharing that border. Pitts et al. (2011) used a Rubin faces/vase display to investigate the dynamics of figure-ground processing via EEG with humans and found that reorganization (faces to vase or back) could occur on a timescale of 200 msec or less, which allows for signals to propagate both in feedforward and feedback directions across visual areas.

Another example of bistable images is the Necker cube (Fig. 6), in which the front side of the cube swings between the top and bottom squares. Similar to Rubin vase, such a perceptual bistability can well be temporally modulated by attention, i.e., with a bit of practice, one can "will"

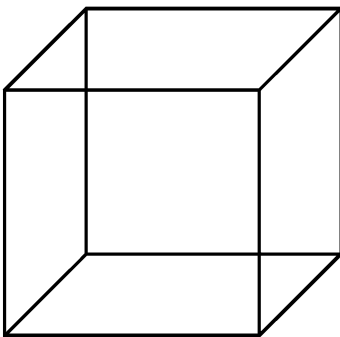


Figure-Ground Segregation, Computational Neural Models of, Fig. 6 The Necker cube is a classic example of bistable figures. Sometimes the lower square appears in front and sometimes in the back. The switch is instantaneous, showing our visual brain exhausts possible 3D alternatives which result in the same 2D projection

the top or bottom square closer and vice versa at a given time. Similarly, in Rubin faces/vase case, one can make the face or vase the figure by attention at a time. Such demonstrations further support the claim that figure-ground perception is a complex process that involves both top-down and bottom-up interactions in the primate brain. The degree of facility of such voluntary attentional switches has been exploited as potential markers for progression of Parkinson's disease (Diaz et al. 2015a, b).

"2D" Versus "3D" Displays: Figure-Ground Segregation and Stereopsis

Depth and separating a figure from background are tightly linked. A figure is generally closer in depth than the background. This brings up the question whether a figure can be purely defined and segregated from a ground area by binocular depth, with no reliance on contrast differences along an edge. Béla Julesz in 1959 generated pairs of images with random dots for which, if were shown to each eye separately, a portion of dots (e.g., forming a square) was seen at a different depth from the rest (Julesz 1971). Note that figure-ground segregation is thereby achieved, with the resulting stereoscopic border being owned by the nearer figure region. Closing each of the eyes (or just looking at each half pair instead) vanishes the percept of the circle as a figure against its background (Fig. 7). This is an example of pure stereopsis involvement (and nothing more) in forming a figure against its background. Here again, similar to the animal in camouflage case, there is no simple contrast between the figure and its background, and the figure and its borders are depth based. Are there single-cell data available for such figure-ground segregation to be used for a neural modeling approach?

Von der Heydt et al. (2000) investigated the representation of stereoscopic surfaces and edges in monkey visual cortex and whether such neural responses carry information of the figure borders and surfaces. Two key points are discovered in their work: first, if a figure like a square is generated by random dot stereogram in which there is no first-order (contrast-based) edge, the V1 cells respond to the stereoscopically defined figure

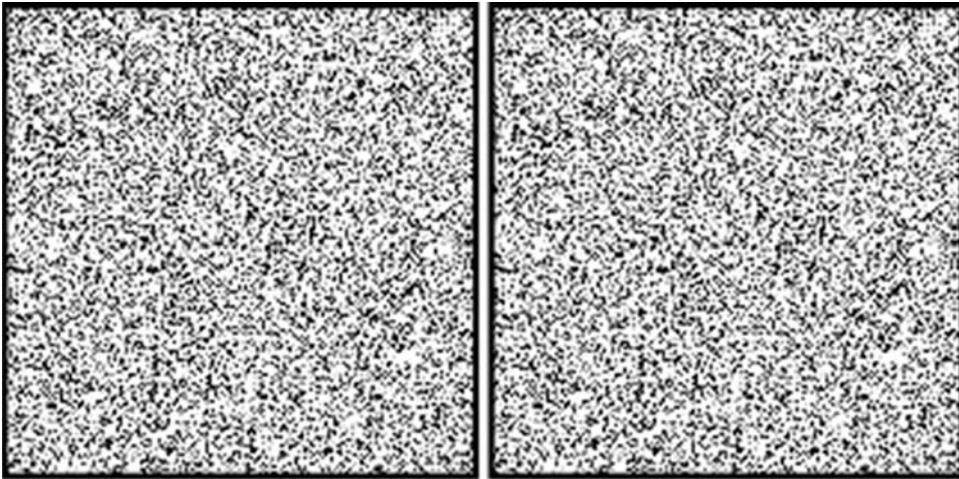


Figure-Ground Segregation, Computational Neural Models of, Fig. 7 Random Dot Stereogram. Looking at each half-pair doesn't result in seeing a particular pattern, yet, if the left and right eyes see only the left and right half-pairs, respectively, a circle in the middle appears farther. This example shows that while there is no visual border in

each half-pair, additional cues can create a pattern with clear borders. Additional cues can be stereopsis (here), motion, or large scale grouping of figure elements. (Figure is adapted from https://commons.wikimedia.org/wiki/File:Mh_stereogramm_randomdot.png under Creative Commons Attribution-Share Alike 3.0 Unported)

surface rather than to its edges; second, V2 cells respond to the stereoscopically defined edges of the figure rather than to its surface.

Conclusion

For most naturally occurring scenes, figure-ground perception is a quick, automatic, seemingly effortless, and successful process, with certain naturally occurring static images or humanly engineered camouflage being notable exceptions. Even in cases of successful camouflage, however, our visual experience is often one of a figure-ground segregation – just not the segregation that camouflage is designed to hide. Indeed, it is difficult to engineer a visual display that does not support figure-ground organization, i.e., a *ganzfeld* – a completely homogeneous light field – or very shallow gradients of luminance throughout the visual field. In contrast, if existing neural models capable of figure-ground segregation were to be challenged with a wide gamut of natural scenes, all of today's models would suffer

multiple and systematic failures, because existing neural models have been designed for a very small subset of such scenes. The diversity of the cortical networks and associated computational strategies that of our visual system uses to perform figure-ground segregation is partially revealed by variety of visual illusions, but the known class of figure/ground illusions is a particularly small and non-representative subset of natural scenes. Given that our visual system performs figure-ground segregation with its all-neural machinery capable of doing many other visual processes, understanding the underlying neural processing underlying figure-ground segregation can be indeed a difficult undertaking. It is only in recent years that “border-ownership” has been considered a “feature” to the human visual system and hence worth of study through single-unit neural recording or brain imaging. Much remains to be done.

One of the characteristics of visual neurons is their receptive fields, which are derived from the rich connectivity between neurons in different visual areas. We have not reached a sufficiently detailed understanding of the spatial and temporal

characterization of neuronal networks that perform the sophisticated task of figure-ground segregation on the order of a few tens of milliseconds. Progress in neuroanatomy and connectomics increasingly is revealing the geometry of available connections in brain networks, but a functional understanding of physiology remains constrained by several factors. One is the inherent spatial and temporal limits of each recording modality, be it single or multiunit recording, EEG, MEG, fMRI, or other modality. Another factor is that the structures of current computational neural models are far simpler than their biological counterparts, as is a virtual requirement of any progressive attempts at model-building. A satisfactory level of understanding of figure-ground segregation awaits further integrated cycles of experimentation and model development.

Before closing, we note that this article has not touched on two topics that a reader might wonder about. The first is deep learning or deep convolutional networks. Recent successes of this class of modeling architectures in object recognition are impressive in their accuracy, outperforming humans in many tasks for which a sufficient database of accurately labeled exemplars has been compiled to train the artificial neural network. Such networks have also enjoyed increasing successes in boundary segmentation and semantic segmentation, in the latter case assigning each pixel in an image the name of a category (e.g., “grass,” “road,” “sky,” etc.) that most likely is its source in an imaged scene.

Accurately finding all boundaries in a scene or semantically labeling all pixels in an image is, however, almost the exact opposite of figure-ground segregation. Animals have not evolved with the luxury of virtually limitless computational power or billions of computing cycles to before interacting with objects in their world. As noted at the start of this article, the significance of human figure-ground segregation is intimately tied to the machinery of primate vision – trying to balance the fine resolution of the fovea with a wide field of view, creating the tradeoffs of eye movements and cortical magnification.

Our default mode of visual scanning is to focus on one object at a time for a few hundred milliseconds, taking in “at a glance,” or perhaps with a handful of saccades, the important characteristics of each “figure” that we scrutinize in turn. It is thus not reasonable to expect computational approaches that treat large images as translationally uniform arrays of pixels to be informative about human figure-ground segregation. With this said, any machine vision algorithm that is designed to specifically segment an image into two regions, with one completely surrounded by another, can be said to be addressing the figure-ground problem in some way. A particular relevant example is that of Sarti et al. (2000) which uses a “seed” location (analogous to a point of foveation) to drive completion of illusory boundaries through an algorithm that uses partial differential equations and level-set methods. Such approaches, however, can be better characterized as machine algorithms “inspired by” primate neuroscience than as computational models “of” primate visual function, which is the focus of the present article.

The other topic is neural synchrony, which has been proposed as a coding strategy underlying perceptual binding between disparate regions of the visual field (Wolf Singer 1999). Dong et al. 2008 have reported that synchrony depends on the border-ownership selectivity of the neuron pairs being recorded. Neural synchrony has become a bit of a “field unto itself,” with controversies about methods and meaning of results that are not at all related to figure-ground perception. Moreover, even if it were conclusively shown that, during figure-ground perception, neurons coding a figure fire synchronously while those coding the ground fire in anti-phase with the neurons coding the figure but in synchrony with each other, a key question would remain: How did each member of each population get recruited to fire when it did, as opposed to some other time? In other words, what functional receptive field properties underlie the “sorting” of parts of the visual field into figure and ground? This article has focused on the latter questions.

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Filtering

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Final Neurons of the Descending Auditory System

- [Physiology and Function of Cochlear Efferents](#)

Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease

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Definition

Hypokinetic motor symptoms of Parkinson's disease are associated with elevated synchronization of neural oscillations in the beta frequency band. This synchronization is intermittent and exhibits specific temporal patterning. The properties of the

fine temporal structure of this synchrony may help to understand the mechanisms behind pathological neurophysiology of Parkinson's disease and assist in the development of adaptive brain stimulation techniques to suppress pathological neural activity.

Detailed Description

Neural oscillations and synchrony are believed to be important for various physiological and pathological phenomena in the brain (Buzsáki and Draguhn 2004; Colgin 2011; Fell and Axmacher 2011; Buzsáki and Schomburg 2015; Fries 2015; Harris and Gordon 2015) and have been extensively studied by using approaches and methods of computational neuroscience. Excessively strong or weak synchrony and oscillations of neuronal activities are presumably related to several motor and cognitive disorders (e.g., Schnitzler and Gross 2005; Uhlhaas and Singer 2006; Hammond et al. 2007; Oswal et al. 2013; Pittman-Polletta et al. 2015; Spellman and Gordon 2015), one of the prominent examples being Parkinson's disease.

Synchrony of Neural Oscillations in Parkinson's Disease

Parkinson's disease is a major neurological disorder characterized by degeneration of midbrain dopaminergic neurons resulting in a set of movement-related symptoms as well as other symptoms. The hallmark of Parkinson's disease is overall slowness of movement. This slow, hypokinetic behavior involves bradykinesia, akinesia, and rigidity (slowness of ongoing movement, slowness of movement initiation, and stiffness of joints). The etiology of Parkinson's disease is still a challenging question and perhaps involves different mechanisms outside of the basal ganglia. Nevertheless, the midbrain dopamine deficiency and accompanying slowness of movement are associated with excessive synchrony of neural oscillations in the basal ganglia (as well as the cortex, a major input to the basal ganglia) in the beta frequency band, usually

defined as 13–30 Hz (Brown 2003; Hammond et al. 2007; Bogacz 2014).

There are different views regarding the origin of the basal ganglia beta oscillations (local, cortical, striatal, or a mixture of all of them), the way how they mediate the movement, and whether they are in a direct causal connection with motor symptoms of Parkinson's disease. However, excessive beta oscillations and synchrony within the basal ganglia and between the basal ganglia and the cortex are observed in Parkinson's disease patients (Marsden et al. 2001; Cassidy et al. 2002; Fogelson et al. 2005; Hirschmann et al. 2011; Litvak et al. 2011; Ahn et al. 2015) and animal models of Parkinson's disease (Sharott et al. 2005; Mallet et al. 2008; Stein and Bar-Gad 2013). The level of synchrony and the power of beta oscillations are changed during movement and movement-related tasks (Cassidy et al. 2002; Levy et al. 2002; Brown 2003; Amirnovin et al. 2004; Kühn et al. 2004; Williams et al. 2005) and are reduced by treatments such as levodopa or deep brain stimulation in subthalamic nucleus (STN) (Silberstein et al. 2005; Stoffers et al. 2008).

Temporal Patterning of Synchronized Activity

The studies (such as discussed above) report elevated yet still moderate synchrony strength at rest. Thus, elevated synchrony in Parkinson's disease is not perfect (at least it does not stay perfect for prolonged intervals of time). This means the synchrony is stronger for some intervals of time and weaker (or nonexistent) for other intervals of time. It exhibits temporal variations changing from potentially very high to very low levels or from synchronized to desynchronized states. Even though it may average into some moderate synchrony strength overall, few long intervals of synchronized activity may be functionally different from many short synchronized episodes. In other words, different temporal patterns of neural synchrony may be related to different symptoms or conditions of the brain.

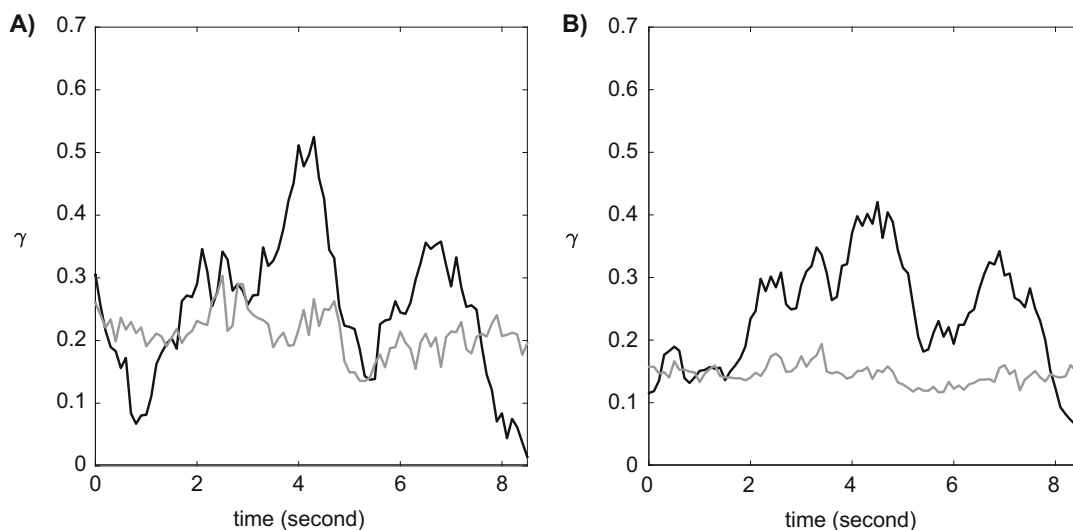
Synchronization of oscillations is a phenomenon which is not local in time and implies repetitive coordination of dynamics of coupled oscillators. There are multiple ways to define it

in mathematical terms (e.g., Pikovsky et al. 2001). It may be impossible to claim that signals or oscillators are synchronized at a particular time instant. However, it is possible to consider the synchronization, for example, measured as a phase-locking strength, over relatively short sliding time windows (especially if one can estimate the statistical significance of the phase-locking measured in this way). Moreover, recent time series analysis developments lead to a way of detecting whether the signals are in synch at each cycle of oscillations, provided there is overall statistically significant level of synchrony (Ahn et al. 2011; Rubchinsky et al. 2014). This approach considers time windows of intermittently synchronized activity to reconstruct the synchronized state from the data. Then, it is possible to check if the oscillations are close to this synchronized state or not at each cycle of oscillations. Statistic of distributions of durations of synchronized and desynchronized episodes reconstructed in this way provides a quantitative description of how synchronous dynamics is patterned in time (Ahn et al. 2011; Rubchinsky et al. 2014).

Temporal Patterns of Neural Synchrony Observed in Parkinsonian Patients

Application of this time series analysis approach to the recordings from the basal ganglia of patients with Parkinson's disease revealed high degree of temporal variability of neural synchrony in the beta frequency band (the references above regarding synchronization and oscillations in Parkinson's disease point to the association of beta-band activity, low dopamine status, and hypokinetic motor symptoms). The analysis of the phase-locking strength over a sliding time window of short length (about 1 s long, that is, about 20 cycles of oscillations) shows substantial variability of synchronization strength, which is going above and below significance level (Rubchinsky et al. 2012), where the latter was computed via phase-randomized surrogates (Hurtado et al. 2004), Fig. 1.

Each point at the graphs in Fig. 1 is not an "instantaneous" phase-locking strength; rather it represents phase-locking strength over a



Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease, Fig. 1 Dynamics of synchronous activity in the basal ganglia in a parkinsonian patient. Black line is the

phase-locking strength computed over a time window of 1 s (a) and 1.5 s (b). The gray line is the 95% significance level computed with phase-randomized surrogate data. (See the details of the analysis in Rubchinsky et al. 2012)

preceding time window involving tens of oscillatory cycles. It is possible to further improve the temporal resolution (although with some limitations) by adopting a different approach to analysis of the time series. Taking a very long time window, one can find out if there is some (statistically significant) strength of the phase-locking. This essentially provides a description of the synchronized state (the existence of certain preferred phase lag between the signals). Then, at each cycle of oscillations, one can detect if the oscillations are close to this synchronized state (then the signals are synchronized) or not close (then the signals are desynchronized). A way to formalize this approach is described in Ahn et al. (2011) and Rubchinsky et al. (2014). Going from observables to the phase space, this approach looks at whether the system of coupled oscillators is close to a synchronization manifold or not. Then one can measure the statistics of synchronized and desynchronized intervals leading to a description of variation of synchrony on very short time scales.

Analysis of microelectrode recordings from STN and internal globus pallidus (GPi) in parkinsonian patients provided a quantification of this

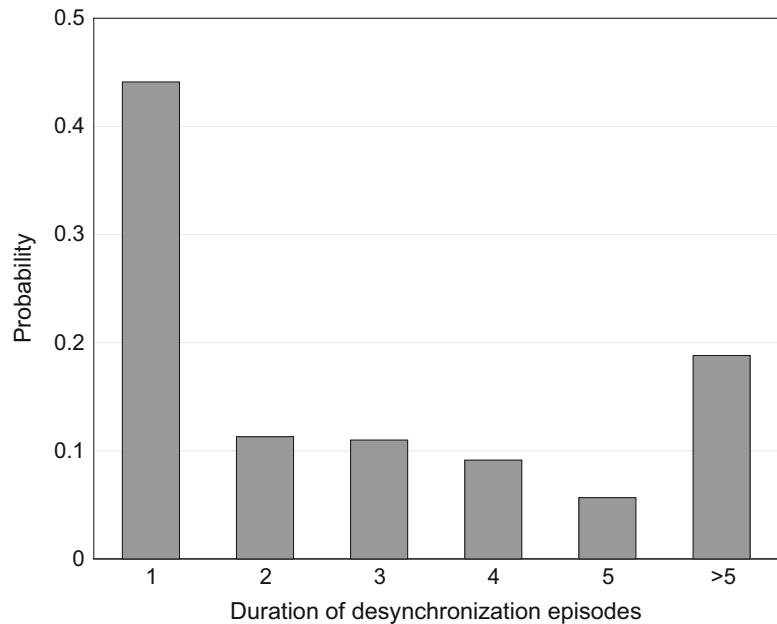
variability (Park et al. 2010; Ratnadurai-Giridharan et al. 2016). The distribution of durations of desynchronized events has a characteristic decaying form and is statistically similar for different locations in the parkinsonian basal ganglia (Fig. 2).

Furthermore, properties of the distributions of the desynchronization durations are correlated with the dopaminergic medication-induced improvements in the motor activity in parkinsonian patients (Ahn et al. 2018), pointing to its potential relevance to parkinsonian motor symptoms. Other studies indicate that transient synchrony states affect the motor performance in parkinsonian patients (Tinkhauser et al. 2020). Thus, the temporal evolution of cortical and basal ganglia synchronization rather than its time-average values may be critical for the parkinsonian neurophysiology (Cagnan et al. 2019).

Also, it is worth noting that parkinsonian tremor, while being distinct from hypokinetic symptoms in presentation and in mechanisms, also exhibits specific temporal patterning of synchronization with tremor-related neural activity in the basal ganglia (Hurtado et al. 2005).

Fine Temporal Structure of Synchronization of Neural Oscillations in the Basal Ganglia in Parkinson's Disease,

Fig. 2 Distribution of the durations of desynchronizations between spiking units and LFPs from the subthalamic nucleus of PD patients at the beta frequency band. Duration is measured in the number of cycles of oscillations. (See the details of the analysis in Rubchinsky et al. 2012)



Computational Modeling of the Mechanisms of the Intermittent Synchrony in Parkinsonian Basal Ganglia

There may be several potential factors behind the intermittent synchrony of neural oscillations. For example, the oscillations may go in and out of synchronized state because of noise (synaptic noise, channel noise, noisy inputs, etc.), fluctuations of coupling strength (synaptic plasticity), or insufficient synaptic coupling strength (strong enough to promote some degree of synchrony, but not strong enough to completely stabilize synchronized state). The episodic nature of the oscillations (which may be a generic phenomenon, Jones 2016) may, of course, be a factor too.

Simulations of conductance-based models of subthalamo-pallidal network of the basal ganglia suggested that the moderately elevated (due to the lack of the dopamine) synaptic strength of some dopamine-modulated synapses may lead to the synchronized dynamics with temporal patterns similar to those in the experiments (Park et al. 2011). Computational modeling of the parkinsonian basal ganglia is a complex field of research with multiple and sometimes contradictory models (Rubin 2017), of which these numerical studies are not an exception. However, they

compared not only the average synchrony strength but also the rates of transitions between synchronized and desynchronized states, thus comparing the structure of the phase space of the experimental system and that of the model. Further modeling indicates that dopaminergic degeneration-induced changes in the cellular properties of the basal ganglia cells may work cooperatively with this phenomenon (Park and Rubchinsky 2012) and the beta-band activity coming from the cortex may further facilitate synchronized beta oscillations locally generated in the subthalamo-pallidal circuits (Ahn et al. 2016).

An interesting observation of these modeling studies (Park et al. 2011) was that the dynamics with the realistically patterned synchronized oscillations is located (in the space of parameters) on the border of the synchronized and desynchronized dynamics. Therefore, the highly variable evolution of neural synchrony in the basal ganglia in Parkinson's disease may be indicative of the propensity of these brain circuits to express the transient episodes of synchronized beta-band activity, which is a physiological phenomenon in the healthy state (Engel and Fries 2010). The pathological low-dopamine state

would present itself in the network, which is more strongly connected than the healthy one and exhibits ongoing intermittent synchrony instead of the functional ability to generate brief episodic synchronous dynamics only when needed (Park et al. 2011; Rubchinsky et al. 2012).

Intermittent Oscillations and Synchrony in Parkinson's Disease and Adaptive Deep Brain Stimulation

One of the techniques to treat the symptoms of Parkinson's disease is deep brain stimulation (DBS). DBS delivers electrical stimulation to subcortical brain areas via implanted electrodes. In the case of Parkinson's disease, the targets include STN and GPi (Wichmann and DeLong 2006; Kringsbach et al. 2007). The conventional DBS delivers relatively high-intensity current, and experimental evidence suggests that it may work by suppressing oscillations and/or synchronization of neural activity in the beta band (e.g., Wingeier et al. 2006; Kühn et al. 2008). This naturally brings the issue of using stimulation only when oscillations or synchrony is relatively strong, that is, using stimulation adaptively as a control tool (see, for example, Schiff 2012). Some approaches of adaptive DBS have been tested clinically, yielding promising results (e.g., Little et al. 2016). Understanding the nature of the intermittently synchronized oscillatory neural activity in the parkinsonian basal ganglia and its relation to parkinsonian motor symptoms may facilitate the model-based development of more efficient adaptive DBS strategies.

Cross-References

- [Basal Ganglia: Beta Oscillations](#)
- [Basal Ganglia: Globus Pallidus Cellular Models](#)
- [Basal Ganglia: Overview](#)
- [Basal Ganglia: Subthalamic Nucleus Cellular Models](#)
- [Computational Model-Based Development of Novel Stimulation Algorithms](#)
- [Computational Models of Deep Brain Stimulation \(DBS\)](#)

- [Deep Brain Stimulation \(Models, Theory, Techniques\): Overview](#)
- [Local Field Potential and Deep Brain Stimulation \(DBS\)](#)
- [Local Field Potential and Movement Disorders](#)
- [Parkinson's Disease: Deep Brain Stimulation](#)
- [Phase-Locking Methods](#)
- [Subthalamopallidal Loop and Oscillations](#)

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Finite Element Modeling for Extracellular Stimulation

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Definition

Finite element modeling is an important computational tool in neural engineering to simulate neural excitation with implanted electrodes or with surface electrodes. Besides its importance for analyzing artificially generated neural activities, e.g., in the spinal cord (reference to entries

► “Finite Element Models of Transcutaneous Spinal Cord Stimulation” and ► “Paraspinal Magnetic and Transcutaneous Electrical Stimulation”), this technique is useful to interpret recorded electrical biosignals generated by neural or muscle tissue activities.

Detailed Description

Neural signals propagate as transmembrane voltage along neural structures, and thereby they cause plenty of tiny currents in any active region of the nervous system. Our understanding of neural activity by means of electrode recordings, e.g., at the surfaces of the skull (EEG), the cortex (ECoG), or intracortically with microelectrodes, is supported by modeling studies that take care of the electrical properties of the biological tissue. Important elements for such studies are the transmembrane currents which act as spatially distributed current sources, the conducting volume, and its electrical properties (Wolters et al. 2006; Zhang et al. 2006).

Extracellular electrical stimulation of the neural tissue is another important field of computational neurosciences with increasing impact in neurophysiology, neural engineering, and clinical applications (Rattay 1999; Rattay et al. 2000, 2001; Kunzel and Grill 2004; Oozeer et al. 2005; Butson et al. 2007; Ahuja et al. 2008; Stickler et al. 2009; Ladenbauer et al. 2010; Mou et al. 2012; Lai et al. 2012). A third field of interest in finite element modeling (FEM) of volume conductors is the ephaptic coupling of neural structures, that is, the influence of active membranes on the excitability of neighbored cells (Jönsson et al. 2008; Anastassiou et al. 2010).

The calculation of the electrical potential Φ in the volume conductor is based on a reduced form of Maxwell's equation which reads as

$$\nabla \cdot \left(\sigma \nabla \Phi + \epsilon \nabla \frac{\partial \Phi}{\partial t} \right) = 0 \quad (1)$$

where σ is the conductivity and ϵ is the permittivity of the medium. In many applications, neural

activities are simulated with compartment models where the transmembrane voltage V is the difference between intra- and extracellular potential, that is, $V = V_i - V_e$. Usually V is calculated with a set of differential equations of Hodgkin-Huxley type (McNeal 1976; Rattay 1990; Mainen et al. 1995; Rattay et al. 2002; Kuhn et al. 2009; Hu et al. 2009).

External Neuronal Stimulation

Most stimulation modeling studies neglect the secondary influence of the transmembrane currents of excited structures on the electrical field generated by the stimulating electrodes. For more accurate modeling see, e.g., Altman and Plonsey (1990) or Martinek et al. (2008). In the first modeling step, the excitable structures are not involved, and the electrical field is calculated with FEM or, for simple geometries, with analytical methods. During stimulation, e.g., the application of square pulses, electrode potentials are the driving elements. As intracellular current flow is not included in this first step, Φ is replaced by the extracellular potential V_e in Eq. 1:

$$\nabla \cdot \left(\sigma \nabla V_e + \epsilon \nabla \frac{\partial V_e}{\partial t} \right) = 0 \quad (2)$$

In order to reduce the computational effort, the minor contribution of the second term in Eq. 2 is often ignored resulting in the quasistatic approach with $\epsilon = 0$. However, investigations of forearm stimulation demonstrated the importance to incorporate tissue capacitance for voltage-regulated transcutaneous stimulation. As consequence of the high skin capacitance, the extracellular potential at the nerve significantly dropped during the applied course of the pulse (Kuhn et al. 2009). In cases of implanted electrodes, the quasistatic approach deviated less than 6% in comparison with the full solution of Eq. 2. Nevertheless, the electrode tissue interface may cause quite different voltage profiles for current- or voltage-controlled stimulation (Miocinovic et al. 2009; Goo et al. 2011).

Second Spatial Derivative of V_e and Current Density Are Used to Predict Regions of Spike Initiation

The goal of many volume conductor studies is the analysis of stimulus-recruitment relations. A common question, e.g., in deep brain stimulation, is as follows: What is the volume of neural tissue activated? The key point of this section is how the FEM output in the region of interest can be used in the second evaluation step for a recruitment analysis of the stimulated tissue. Several criteria are discussed in the following.

Current density criterion. A simple answer for step two comes from the Hodgkin-Huxley formulation where transmembrane currents are computed for 1 cm² of the axon membrane, and, consequently, the physical unit of the stimulus is also current density. With this fact in mind, one can assume that spike initiation occurs within a volume around the electrode where current density exceeds a threshold value. In an infinite homogeneous medium, a monopolar spherical electrode causes current densities proportional to $1/r^2$, where r is the distance from the center of the electrode to the point of interest. In other words, in this simplest approach, spike initiation at distance r demands for electrode currents proportional to r^2 . Interestingly, a quite linear relationship between electrical conductivity data and data from diffusion tensor MRI (DTI) of human brain regions (Tuch et al. 2001) demonstrated essential variations in the direction-dependent conductivity. This relationship allows an improvement in simulating the activated volumes in comparison with the spherical borders of the simplest approach. Thus, the borders of activation can be replaced by patient-specific surfaces based on FEM that combine the body and electrode geometry data with DTI (Butson et al. 2007).

The morphometric and electrical cell data is often disregarded in FEM analysis due to the variety in tissue shapes and other details not available in the living human brain, and this is a great

limitation. From extraneural peripheral nerve stimulation, it is known that thick fibers are recruited easier than thinner ones. This phenomenon is called reverse recruitment order as it reverses the natural recruitment sequence (Blair and Erlanger 1933). This phenomenon is an example that demonstrates the weakness of simple approaches which ignores all the electrical properties of nerve cells but uses current density or any other parameter of the volume conductor as recruitment criterion.

Threshold voltage criteria. Several of the early FEM studies published the potential distribution in the body part of interest when stimulated with surface or implanted electrodes. Guided by the threshold voltage hypothesis – an action potential is initiated as soon as the membrane voltage exceeds a value of about 20 mV above the resting state – they had no simple method to define a threshold value for the external potential. Another approach is based on a threshold value for the electrical

field (Kasi et al. 2011). Quite different electrode currents are obviously calculated for the same neural stimulation task depending on the evaluation criteria as the iso-contours of current density, electrical potential, and electrical field are not the same.

Activating Function Criterion

Many modelers prefer a two-step method in order to compute responses of excitable cells to electrical stimulation. In the first step, the electrical field in the volume conductor is calculated. In the second step, a compartment model of a target cell is evaluated. This method is computationally extensive, but it shows the complete spatial and temporal excitation and conduction process of a cell for a given electrode situation. A compartment model is a network of resistances and capacitances, where the current to the center of compartment n consists of the following components: a capacitive current, ion currents across the membrane, and intracellular currents to neighbored compartments. Current flow in compartment n results in

$$\frac{dV}{dt} = \left[-I_{ion,n} + \frac{V_{n-1} - V_n}{R_{n-1}/2 + R_n/2} + \frac{V_{n+1} - V_n}{R_{n+1}/2 + R_n/2} + \frac{V_{en-1} - V_{en}}{R_{n-1}/2 + R_n/2} + \frac{V_{en+1} - V_{en}}{R_{n+1}/2 + R_n/2} / C_n \right] \quad (3)$$

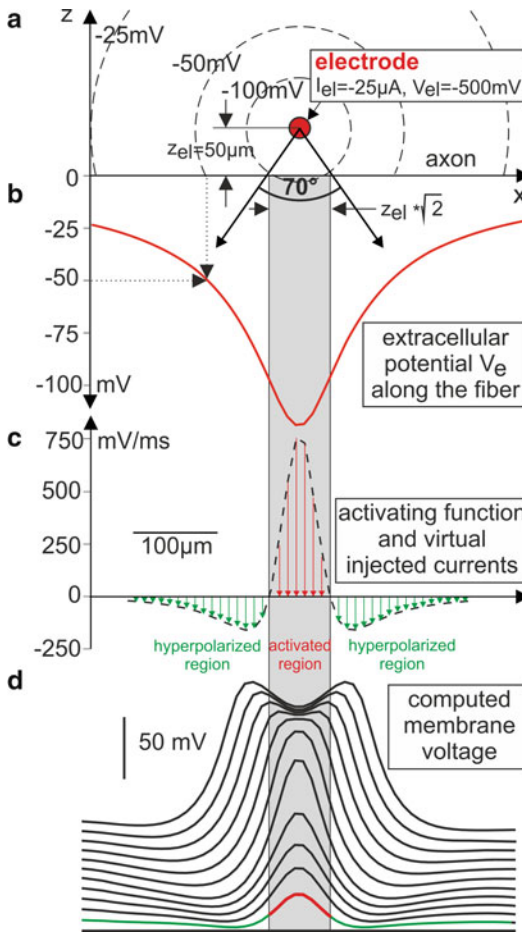
with transmembrane potential V , ion current I_{ion} , axial resistance R , and membrane capacity C . The direct stimulating influence of the extracellular potential on compartment n is defined by the activating function f (Rattay 1999) which is the driving term of the differential Eq. 3:

$$f_n = \left[\frac{V_{e,n-1} - V_{e,n}}{R_{n-1}/2 + R_n/2} + \frac{V_{e,n+1} - V_{e,n}}{R_{n+1}/2 + R_n/2} / C_n \right] \quad (4)$$

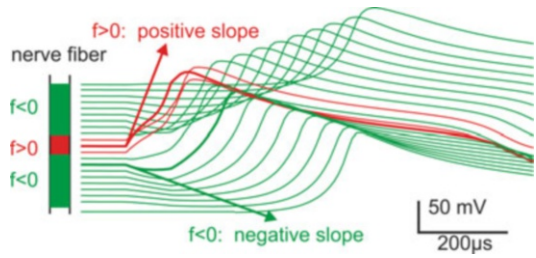
For a fiber with constant diameter d , constant compartment length Δx , intracellular resistivity r_i , and specific capacity c , Eq. 4 is reduced to

$$f_n = \frac{d}{4c\rho_i} \cdot p \frac{V_{en-1} - 2V_{en} + V_{en+1}}{\Delta x^2}. \quad (5)$$

All terms within the brackets of Eqs. 3 and 4 are currents. Therefore, neglecting the weighting factor $1/C$, the stimulating influence of the activating function f can be interpreted as an injected virtual current in every compartment. In regions where this current is positive, the membrane depolarizes, and where it is negative, it tends to hyperpolarize. For the case of a long straight excitable fiber (axon, dendrite, or muscle fiber) with constant diameter, Fig. 1 explains the activating function concept for cathodic stimulation on the basis of virtual current injection. Note that the second term on the right side of Eq. 5 is the second difference quotient of the extracellular potential along the fiber. With $\Delta x \rightarrow 0$, f becomes proportional to the second derivative of V_e , and therefore $d^2 V_e / dx^2 > 0$ indicates the regions for spike initiation.



Finite Element Modeling for Extracellular Stimulation, Fig. 1 Extracellular stimulation of a straight unmyelinated axon with a small spherical electrode. (a) Geometry and isopotentials, simulated for an equivalent point source $50 \mu\text{m}$ above a fiber positioned at the x-axis. (b) Extracellular potential $V_e = \rho_e I_{el} / 4\pi r$ with $r = \sqrt{(x - x_{el})^2 + z_{el}^2}$ is used to calculate the activating function. (c) A fiber with $d = 1 \mu\text{m}$ and compartment length $\Delta x = 10 \mu\text{m}$ results in a peak activating function value of 740 mV/ms . According to Eq. 5, this is the slope of the membrane voltage in the compartment below the electrode at the beginning of the $-25 \mu\text{A}$ pulse. According to Eq. 4, the virtual currents are $f_n C_n$. With $C_n = d\pi\Delta x c = 3.14159 \times 10^{-7} \mu\text{F/cm}^2$ and specific membrane capacity $c = 1 \mu\text{F/cm}^2$, the maximum injected current is 232 pA at the center of the activated region. As the length of the activated region ($1.414 \cdot z_{el}$) is defined by an angle of 70° (Rattay 1986), this region increases in a linear way with the electrode distance. (d) Vertically shifted transmembrane voltage profiles in time steps of $200 \mu\text{s}$. The first response of the neuron at the beginning of the stimulus pulse is proportional to the activating function shown in C: hyperpolarized and depolarized regions in green and red, respectively

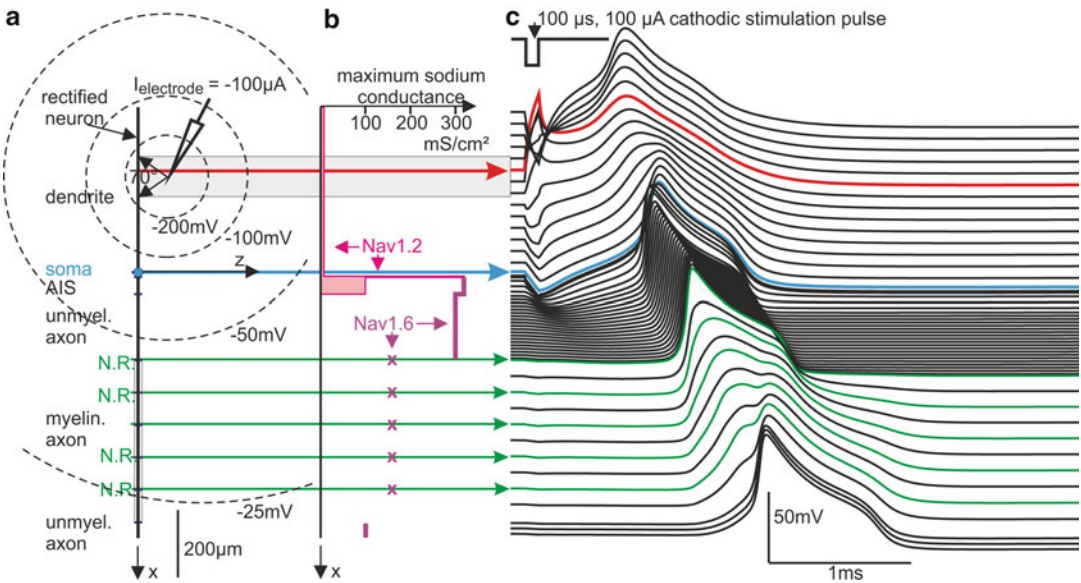


Finite Element Modeling for Extracellular Stimulation, Fig. 2 Hyperpolarized (green) and depolarized (red) regions of a stimulated axon (left) and voltage profiles as functions of time for the compartment model shown in Fig. 1 (right). Every line shows the transmembrane voltage of a compartment as function of time with a vertical shift according to the position of the compartment. The axon is for $100 \mu\text{s}$ in the resting state before it is stimulated with a cathodic $100 \mu\text{s}$ pulse as in Fig. 1d. The compartment closest to the cathodic electrode has the largest activating function value, and it is the spike initiation site (thick red line). As predicted by Fig. 1c, the largest slope in the red region ($f > 0$) is about four times the value of the largest green slope indicated by the green arrow. Therefore, a change of stimulus polarity needs about four times larger electrode threshold currents. This theoretical result for extracellular axon stimulation (Rattay 1986) is in accordance with experimental observations (Ranck 1975)

We assume that the axon is at rest before a stimulus is applied (Fig. 2). During this resting phase, the sum of the first three terms at the right side of Eq. 3 is zero, and consequently the activating function quantifies the slope of membrane voltage at stimulus onset in every compartment. The activating function is the rate of transmembrane voltage change and it has the unit mV/ms . Note that the activating function predicts the reverse recruitment order phenomenon as the scaling factor of f is proportional to fiber diameter d (Eq. 5).

Stimulus Threshold Current Depends Also on Type and Densities of Ion Channels

The activating function concept is an essentially better predictor for spike initiation than all the other methods presented at the beginning of the last section. The activating function is a fascinating concept because of its simplicity to predict regions of excitation in a target neuron without



Finite Element Modeling for Extracellular Stimulation, Fig. 3 Cathodic microelectrode stimulation at the dendrite of a rectified pyramidal cell. **(a)** The non-branching model cell consists of the following functionally different segments: dendrite, soma, axon initial segment (AIS), unmyelinated axon, myelinated axon with active membranes in the nodes of Ranvier (NR), and an unmyelinated terminal. **(b)** Two types of sodium channels enable initiation and conduction of spikes. High-threshold Nav1.2 channel densities represented by the maximum conductance (*magenta*) exist in the upper part of the neuron until AIS and low-threshold Nav1.6 channels (*purple*) from AIS until the axon terminal. Note that high concentrations from axon hillock until myelination exceed even that of nodes of Ranvier by a factor 2, whereas in soma and dendrite, a

uniform maximum sodium conductance of 8 mS/cm² is assumed (Hu et al. 2009). **(c)** Transmembrane voltages as functions of time. Electrode tip is assumed 300 μm from the soma and 80 μm from the axis ($x_{el} = 300 \mu\text{m}$, $z_{el} = 80 \mu\text{m}$) in a homogeneous medium with resistivity $\rho_e = 300 \Omega \cdot \text{cm}$. At this distance the electrical field has a direct depolarizing effect only within the gray-shaded region where the slopes at stimulus onset in **(c)** are positive. Spike is initiated in the compartment closest to the electrode (*red*) and propagates in both directions. When intracellular currents cross the soma (*cyan*), they activate the low-threshold regions in the axon, and therefore action potential peaks appear earlier in these axon compartments than in the soma and the last presomatic dendritic compartments

using knowledge about the ion channel compositions of the excitable membranes. However, simulating the gating processes of the cell membrane is needed for further improvements of cell response prediction.

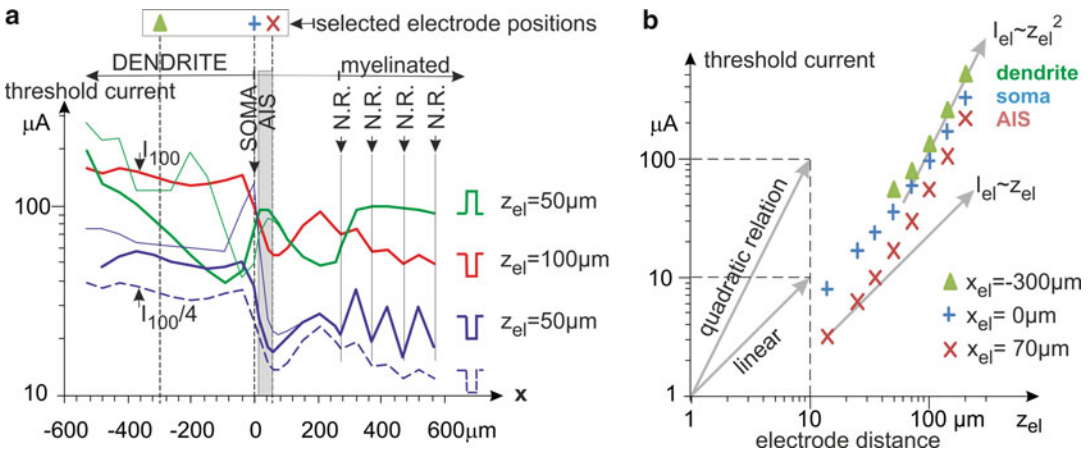
The important impact of ion channel compositions in the functionally different segments of a stimulated neuron is demonstrated with the following examples. In order to reduce geometric influences, microelectrode stimulation of a cortical pyramidal cell is simulated by a non-branching rectified model cell. Ion channel gating dynamics and more details about electrical and geometrical data are given in Rattay and Wenger (2010). Even the low density of high-threshold sodium channels (Nav1.2) enables a conducted spike to be

initiated within the dendrite (Fig. 3). For this electrode position close to the dendrite, the positive values of the activating function are found within a small region in the dendrite as predicted by the 70° limit shown in Fig. 1. An interesting phenomenon appears when the dendrite is passive or also when the sodium channel density is reduced in the modeled neuron below a critical value needed for action potential conductance. In such cases where the stimulating microelectrode is in front of the soma, the neuron is not excitable with negative pulses. This phenomenon becomes effective for the model assumptions when the electrode-dendrite distance is reduced because current influx within a shortened active zone (defined by the 70° borders, Fig. 1) cannot excite

the neighboring hyperpolarized regions. Surprisingly, this failure effect is more pronounced for thicker fibers. This is in contrast to the reverse recruitment order for excitable fibers. For details see Rattay and Wenger (2010).

In the next example, the electrode is moved in constant distance along the axis of the neuron. Several phenomena can be observed (Fig. 4a). (i) The distal end of the axonal initial segment with high Nav1.6 channel density is very sensitive to cathodic stimulation, and this is a preferred site of spike initiation. (ii) The neuron is even more excitable at the third and fourth nodes of Ranvier despite the essentially lower ion channel densities. It is a general property that myelinated axons are easier to excite than unmyelinated ones which is a consequence of higher activating function values in nodes of Ranvier that are favored by the properties of the internodes (Rattay 1986, 1990, 1999). (iii) Moving the electrode along the thick dendrite in a distance of 100 μm from the neuron axis

needs about twice the threshold current in comparison to the positions along the axon. (iv) The thresholds in 50 μm distance are higher as expected according to the prediction of the quadratic rule proposed in the literature (Stoney et al. 1968; Tehovnik et al. 2006; Butson et al. 2007), shown by dashed blue line in Fig. 4a and by Fig. 4b. (v) Electrodes above the center of an internode need doubled threshold currents compared to positions above a node of Ranvier. This node-internode threshold relation known from peripheral nerve stimulation becomes more and more pronounced when electrode-fiber distance is reduced (Rattay 1987). (vi) Within a dendritic region ($-149 \mu\text{m} < x_{el} < -37 \mu\text{m}$), anodic threshold is lower than cathodic which is in agreement with experiments (Ranck 1975) and theory (Rattay 1999). (vii) Anodic threshold current of the 5 μm diameter dendrite example increases in an exponential way with distance from the soma (comp. the rather linear relation of the left part of



Finite Element Modeling for Extracellular Stimulation, Fig. 4 Threshold current as a function of electrode position for monophasic 100 μs pulses for the model neuron of Fig. 3. (a) When the microelectrode tip is moved from left to right in constant 100 μm distance to the neuron axis, cathodic threshold current (red line, marked as I_{100}) is rather constant along the dendrite, but threshold decreases quickly before arriving at the soma ($x_{el} = 0$) with a local minimum at the distal end of the AIS (AIS is marked as gray region). The zigzag line demonstrates low thresholds when the electrode is just above a node of Ranvier. For half the axial distance ($z_{el} = 50 \mu\text{m}$), cathodic threshold (blue line) is similar in shape with the broken blue line which is the prediction for a quadratic current distance rule ($I_{100}/4$ is

a vertical shift of the red I_{100} line, corresponding to the factor 1/4 of the logarithmic scale). However, two discrepancies are characteristic: full blue line values are always higher and, second, the threshold ratio for nodal and internodal positions is increased. Anodic stimulation (green line) does neither favor positions above nodes nor the vicinity of the AIS. Thin green and blue lines show threshold predictions when the dendritic diameter is reduced from 5 to 1.25 μm . (b) Radial current distance relations for three selected positions as marked in (a): middendritic, soma, and distal end of AIS. Indicated by the slopes of the gray arrows, in all three cases, there is a clear trend from a linear to a quadratic relation when electrode distance is increased in radial direction

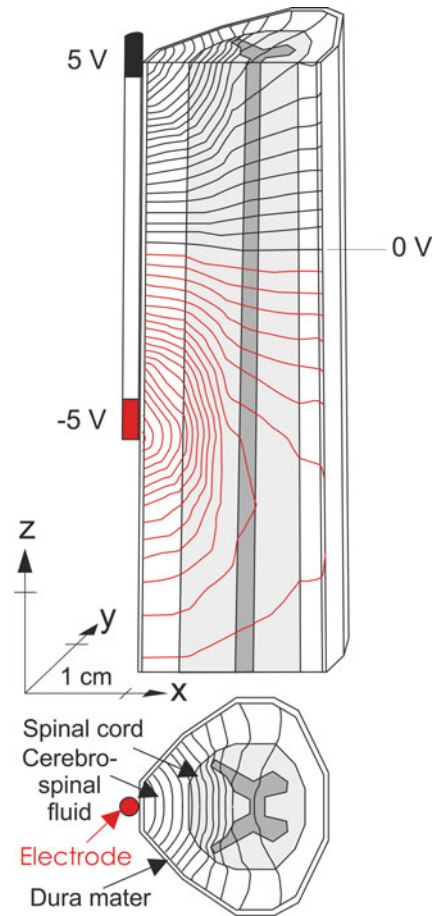
the green line in the logarithmic current scaling of Fig. 4a). The thin dendrite has another threshold characteristic as explained below. (viii) The extreme node-internode threshold fluctuations seen for cathodic pulses are lost when pulse polarity is reversed. (ix) In general thin dendrites have higher thresholds (comp. thin and thick green and blue lines in Fig. 4a).

Stimulation of the Lumbar Spinal Cord with Epidural Electrodes

In the following modeling example, we analyzed which neural elements are primarily excited in order to explain observations during human lumbar cord stimulation (Dimitrijevic et al. 1998; Minassian et al. 2007, ▶ “Paraspinal Magnetic and Transcutaneous Electrical Stimulation” in this encyclopedia). As described above, we used a two-step procedure for this task. In the first step, isopotentials are computed with finite element software ANSYS for a typical position of a bipolar electrode as implanted in paralyzed patients (Fig. 5). The stimulator (Itrel 3, model 7425, Medtronic) delivered continuous, non-patterned stimulation with 1–10 V at 2.2–130 Hz and asymmetric biphasic pulses with a 210 μ s main pulse and a long second pulse for avoiding charge accumulation. Because of its overlength, the influence of the second pulse can be neglected in this quasi-static approach, and all presented conclusions could be done with a single finite element evaluation.

The compartment models of the target neurons are based on the CRRSS (Chiu-Ritchie-Rogart-Stagg-Sweeney) model in the form described in Rattay (1990) and Rattay et al. (2002). The resulting differential equations were evaluated with software ACSL. Spike initiation points were also analyzed with the activating function concept.

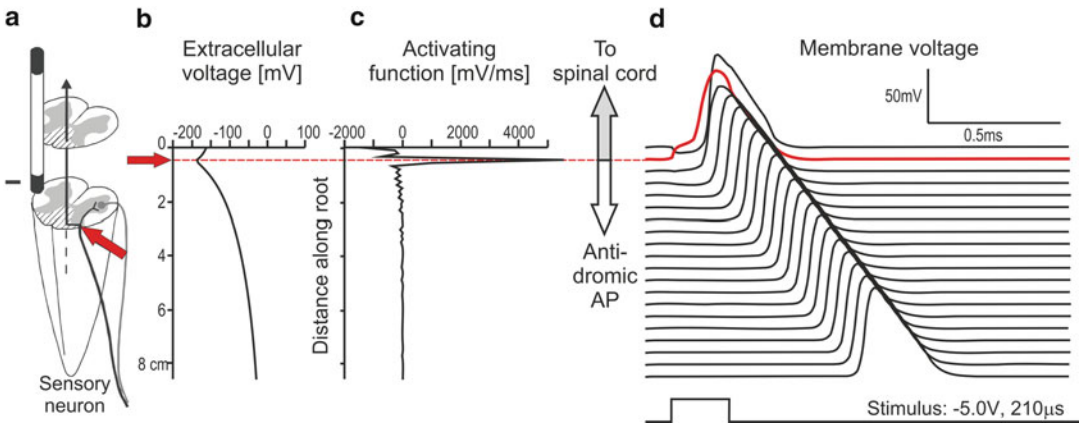
The purpose of our investigations was to find which neural elements are the primarily excited ones. First ideas are guided by the general knowledge that myelinated fibers are easier to excite than the unmyelinated. Moreover, thick axons have lower thresholds than thin axons, a fact that



Finite Element Modeling for Extracellular Stimulation, Fig. 5 Potential distribution within the dural sac is computed with the finite element method for bipolar stimulation with an implanted electrode. The volume of interest has to be embedded into a larger volume in order to use appropriate boundary conditions, e.g., a cylindrical body segment (not shown, with no current flow components across the surface). Axons close to the cathode (*red potential lines*) are preferred targets for stimulation

is deduced from the weighting factor $d/4r_i c$ in Eq. 5. Therefore, the thick sensory afferents may be most sensitive to low stimuli. However, it could be that the thinner dorsal column fibers are even more sensitive as they may be closer to the electrode at the thoracic level. Such fibers are comparable in diameter and position with the vertical branches of our target neuron marked by red arrow in Fig. 6a.

The activating function concept shows two closely neighbored hot spots in the afferent



Finite Element Modeling for Extracellular Stimulation, Fig. 6 (a) Three-dimensional view of the lower spinal cord with a sensory fiber (within the posterior root, curved trajectory) and its axonal branches in the back side of the spinal cord (hatched area, vertical arrow) with a single synaptic connection to a motoneuron. Red arrows and red line indicate the hot spot for the spike initiation at the site where the posterior root fiber enters the spinal cord.

(b) Extracellular voltage generated by epidural stimulation, (c) activating function, and (d) membrane voltage for an S1 posterior root fiber stimulated 4% above the characteristic fiber threshold with a midsagittal electrode at L4 spinal cord level. Note that the positive part of the activating function is restricted to a single node of Ranvier (peak). In this hot spot an action potential is generated that propagates into the spinal cord and in antidromic direction

rootlet fibers: the regions with sharp curvature before the entry point in the spinal cord and the entry point itself where a sudden change of the electrical conductivity at the interface between two media supports the initiation of action potentials. Both cases result in large values of the second spatial derivative of V_e and thus of the activating function. Computer evaluations with the full system of differential equations demonstrated that with the applied stimulus intensities, spikes can typically be generated in rootlets which enter the spinal cord up to 2 cm below the level of the cathode, but there is no spike initiation in the dorsal columns in the case of lumbar stimulation.

Other candidates for spike initiation for epidurally placed lumbar spinal cord electrodes are the AIS of spinal interneurons and their myelinated axonal segments. A comparison with Fig. 4a shows that AIS excitation has about the same threshold as the nodes of Ranvier. As the axons of the interneurons are essentially thinner than that of the Ia afferents and even thinner than the dorsal column fibers, model interpretation

predicts significantly larger thresholds for interneurons than for thick axons in sensory rootlets.

Further details and related explanations are found in entries ► [“Paraspinal Magnetic and Transcutaneous Electrical Stimulation”](#) and ► [“Finite Element Models of Transcutaneous Spinal Cord Stimulation”](#)

Conclusions

Finite element evaluation of the electrical field is an important tool for modeling nerve stimulation. The most important question in this context is which of the FE output data should be used to quantify the recruitment order of the excitable tissue. In this entry, it was shown that current density is not a good indicator, but it is of value for a rough approach if no information is available about geometrical and electrical details of the involved neural structures. Better insights can be found from the activating function concept and from the compartment.

Spatial differences in ion channel compositions within a single neuron can cause surprising phenomena. Such phenomena can be detected when all differential equations of the compartment model of a target neuron are evaluated. On the other hand, some remarkable observations about spike initiation sites are based on geometric configurations that can be explained with FEM. An example is that hot spots in sensory afferents stimulated with implanted epidural lumbar cord electrodes can be the same when transcutaneous stimulation is applied (Ladenbauer et al. 2010; Danner et al. 2011; ► “Finite Element Models of Transcutaneous Spinal Cord Stimulation” in this encyclopedia). The effect is surprising as both the larger distance to the axon and the larger electrode size of the surface electrode suggest a poor focusing effect in comparison with the implanted electrodes.

Another surprising phenomenon which was recently discovered is the rather poor focal stimulation success with microelectrodes. Low-current stimulation produces a sparse and distributed set of activated cells often with distances of several hundred micrometers between the cell bodies and the microelectrode (Histed et al. 2009). A reasonable hypothesis to explain the sparsely distributed population of somas results from a computer simulation analysis based on a rather dense concentration of collaterals of many neurons in the close surrounding of the electrode tip. These thin axons and dendrites are capable of generating an ongoing nerve impulse or activating the distant AIS via intracellular current flow. Therefore, the cell bodies of stimulated cells can be situated within a distance of several hundred micrometers or more relative to the electrode tip, whereas most of the cell bodies closer to the electrode have a small probability to be activated (Rattay and Wenger 2010). A similar conclusion is reported concerning the spinal cord. Previous studies demonstrated that extracellular stimulation within the spinal cord activates fibers in passage at lower stimulus intensities than neuronal cell bodies (Renshaw 1940). Action potentials elicited in localized terminal branches of afferents

are assumed to spread antidromically to all terminal branches of the afferents and transsynaptically excite motoneurons and interneurons far away from the stimulation site (Gaunt et al. 2006).

Cross-References

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)
- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

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Finite Element Modeling of Electrical Stimulation Using Microelectrodes

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Definition

Extracellular electrical neural stimulation consists in injecting a current through an electrode located in a neural tissue. A potential field is created in the tissue, which influences the membrane potential of neural elements. The membrane response depends on the shape of the potential field around the neuron, which depends itself on the electrode configuration. Finite element models (FEM) are numerical models that can be used to compute the potential field and predict the effect of a given electrode configuration. These models are based on a description of the geometry and the electrical properties of the conductive media and specific constraints on their boundaries.

Detailed Description

Electrical stimulation of neural tissues has been extensively used for decades. More recently, an increasing interest has grown to build neural prosthesis based on arrays of microelectrodes to restore functional activity in the damaged central nervous system. The fine use of electrical microstimulation requires prior analysis of how the potential field is generated in a tissue. The stimulating field generated by a given electrode configuration can be

calculated using FEM approaches (McIntyre and Grill 2001). For this purpose, different commercial software are available.

Building a FEM model requires the following steps:

1. Creating the geometry of the model comprising all the conductive volumes constituting the neural tissue and surroundings. The geometry of these volumes is meshed in 3D into elementary elements (e.g., tetrahedrons) on the vertices and edges of which the electrical potential is calculated.
2. Setting volume equations. Classically, each volume is considered homogenous with a conductivity value σ (e.g., $\sigma = 0.1 - 0.4$ S/m for the neural tissue – see (Ranck 1963; Ranck and Bement 1965)). Under the quasi-static approximation (Hamalainen et al. 1993), the equation governing the computation of the electrical potential V in this volume is the Laplace equation:

$$\nabla \cdot \sigma \nabla V = 0 \quad (1)$$

3. Setting boundary conditions between conductive volumes. At the boundary between two conductive volumes having different conductivities σ_1 and σ_2 , the normal component of the current density is conserved (Plonsey 1969), which can be represented by the following boundary equation:

$$\sigma_1 (\nabla V \cdot \mathbf{n})_1 = \sigma_2 (\nabla V \cdot \mathbf{n})_2. \quad (2)$$

4. Setting boundary conditions to insulating boundaries. Boundaries through which no current flows are represented by the homogenous Neumann boundary equation:

$$\sigma \nabla V \cdot \mathbf{n} = 0 \quad (3)$$

5. Setting boundary conditions on the surfaces of active electrodes. In order to correctly calculate the potential field V in the tissue, the electrode-tissue impedance can be explicitly incorporated into the boundary condition at the interface (Heuschkel et al. 2002). This

requires the use of the following Robin boundary condition (Joucla and Yvert 2009, 2012):

$$\sigma \nabla V \cdot \mathbf{n} = g \cdot (V_{\text{metal}} - V), \quad (4)$$

where g is the surface conductance of the electrode and V_{metal} is the voltage applied to the electrode. This equation, which takes into account the potential drop at the electrode-tissue interface, states that, at a given location on the electrode, the current flowing through the interface (left-hand side) is the product of the potential drop by the surface conductance of the interface (Ohm's law, right-hand side).

Once the model is built, the electrical potential V is calculated by solving Eq. 1 under the specified boundary conditions. It should be noted that the potential field only provides a first description of the effect of a stimulation. In particular, the neural response could further be calculated. This can be done by embedding a compartment neuron model into the stimulating field and computing the response of the membrane to the field (McIntyre and Grill 2002; Joucla and Yvert 2009). For such approach, the NEURON software environment can be used (Hines and Carnevale 1997). Alternatively, a whole finite element model can be built, in which the neuron is introduced in the model as a subsequent conductive volume on the surface of which the dynamical equations governing the membrane response are incorporated through dedicated boundary conditions under a thin film approximation (Joucla et al. 2014).

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Finite Element Models of the Spine

► Biomechanical Model of Low Back Pain

Finite Element Models of Transcutaneous Spinal Cord Stimulation

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Synonyms

Dorsal root stimulation; Extracellular stimulation; Paraspinal electrical stimulation; Paravertebral electrical stimulation; Percutaneous spinal cord

[stimulation](#); [Posterior root stimulation](#); [Transcutaneous spinal cord stimulation](#); [Transspinal electrical stimulation](#); [Volume conductor model](#)

Definition

Transcutaneous spinal cord stimulation (SCS) is a noninvasive method to electrically stimulate afferent structures of the human lumbar spinal cord. These are the same neural targets as predominantly activated by epidural implants. Biophysical principles derived from computer simulations contributed to the identification of the directly activated neural structures. These simulations combine finite element (FE) models with nerve fiber models and the activating function concept. The transcutaneously generated electric field is inherently non-focal, and thus, nerve fiber activation relies on inhomogeneities of the volume conductor and the anatomical paths of the target fibers relative to the electric field. The anatomy, its electrical properties, and the neurogeometry cause localized low-threshold sites within the widespread field and allow for the observed selective stimulation. Computer simulations are crucial for understanding the neuromodulative effects of transcutaneous SCS resulting from the trans-synaptic activation of the spinal cord neural circuits and for further improving the stimulation technique.

Detailed Description

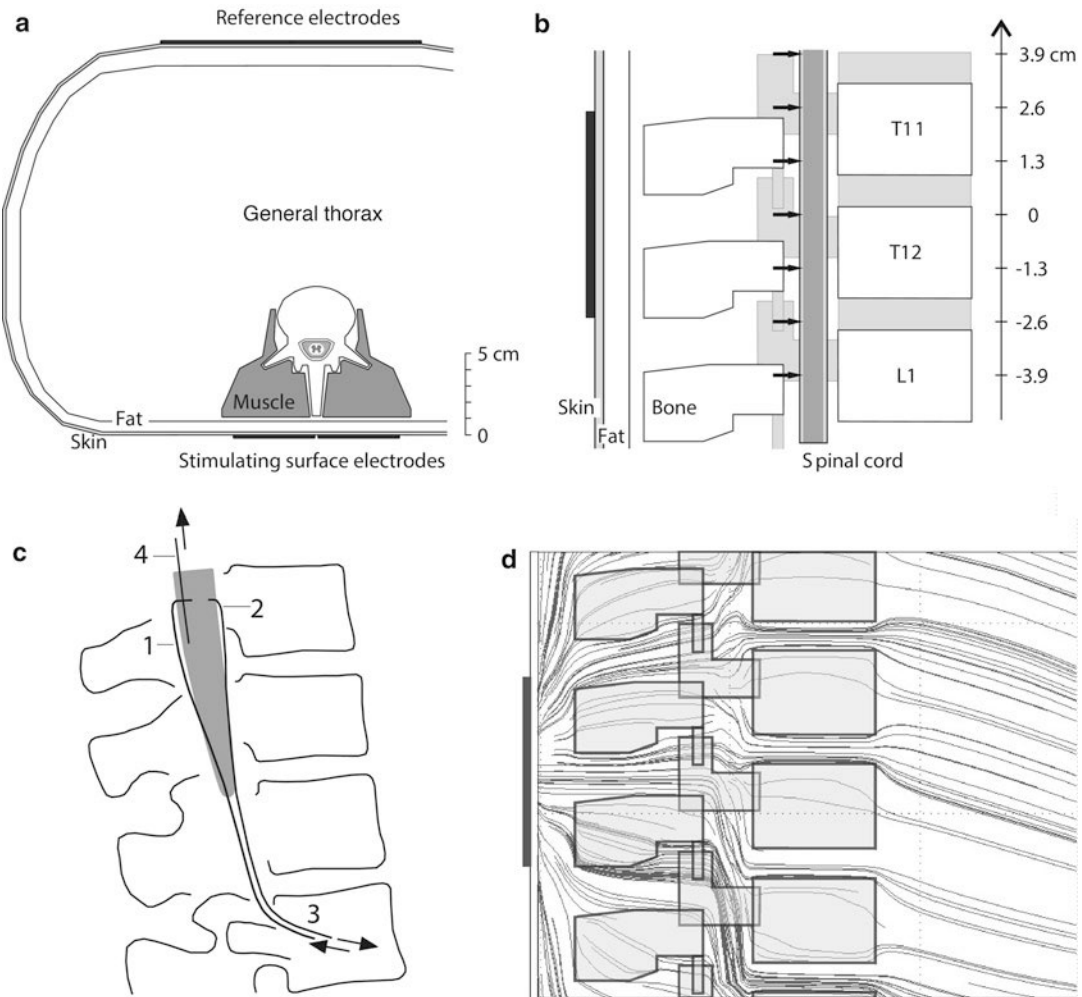
Epidural SCS involves the activation of neural target structures by leads placed in close distance of a few millimeters to the posterior aspect of the spinal cord. In transcutaneous SCS, the same deeply located neural structures are targeted from a distance of several centimeters from the body surface. Compared to the neural structures, the stimulating skin electrodes are large. Several anatomical structures between the electrodes and the spinal cord introduce electrical inhomogeneities and anisotropies, which in turn influence the generated electric potential. Yet, electrophysiological studies showed that transcutaneous SCS

reliably and selectively stimulates similar neural structures as with epidural electrodes, i.e., sensory fibers within the posterior roots and rootlets (Minassian et al. 2011).

Computer simulations that calculate the generated electric potential and its effect on neural structures are essential in understanding the immediate effects of SCS (Holsheimer 1998). The problem of calculating the electric potential distribution in a complex volume conductor can be mathematically formulated by partial differential equations. Due to the geometrical complexity and inhomogeneities of the anatomical structures, these equations are usually only tractable by applying numerical approximation methods such as the finite difference, FE, boundary element, or multigrid method (Johnson 1997).

Here, the application of the FE method is elaborated for the approximation of the produced electric potential while assuming quasi-stationary conditions (for details on the FE method, see elsewhere in this book, Rattay: Finite Element Model of Volume Conductor). A model is always an abstraction of the reality and can represent only rather simple anatomical properties, can model average dimensions, or can be tailored to an individual subject. Current models of transcutaneous SCS (Ladenbauer et al. 2010; Danner et al. 2011) cover a general case with a rather simple geometry.

As opposed to models of epidural SCS where most of the generated currents flow inside the spinal canal, the spine and its geometry are paramount for calculating the electric potential across the neural target structures produced by the skin electrodes. The simplified model must include anatomically realistic regions of the soft tissues in-between the bony structures with comparably high conductivities, thus allowing for current penetration of the canal. Structures below the electrode (i.e., the skin, subcutaneous fat, paraspinal muscles) and the spine, including the ligaments and intervertebral disks, are influencing the produced field near the target structures and thus need to be included in the model of transcutaneous SCS. Furthermore, the detailed anatomical properties of structures inside the spinal canal (e.g., the spinal cord gray and white matter, spinal nerves,



Finite Element Models of Transcutaneous Spinal Cord Stimulation, Fig. 1 Volume conductor (VC) model geometry and the paths of the simulated axons. (a) Cross section of the VC model. (b) Midsagittal section showing the relation between the spine, spinal cord, and intervertebral disks and the transcutaneous paraspinal electrode (black). Model fiber entry and exit levels

into the spinal cord are marked with *arrows*. (c) Sketch of the posterior (1) and anterior root fibers (2), joining together at the intervertebral foramina (3), and of the posterior columns (4) in relation to the spinal geometry. (d) Computer-simulated current flow within a 2 mm layer at the midsagittal plane (Reproduced from Danner et al. (2011) with permission from Wiley Periodicals, Inc.)

cerebrospinal fluid, epidural space) need to be modeled. Figure 1a, b illustrates the model geometry, Fig. 1c is a sketch of potential target fibers, and Fig. 1d shows computed current flow lines.

In a further step, the electric potential computed by the FE models is evaluated along determined paths, representing the geometry of potentially excitable neural structures. The excitability of nerve structures depends on several factors. The soma is hard to excite due to its relatively

high membrane capacitance (Rattay 1999). The activation thresholds of myelinated nerve fibers are lower than that of unmyelinated ones and are lower for nerve fibers of larger diameters (Ranck 1975). Thus, large-diameter myelinated axons can be preferentially selected for the simulation as target structures.

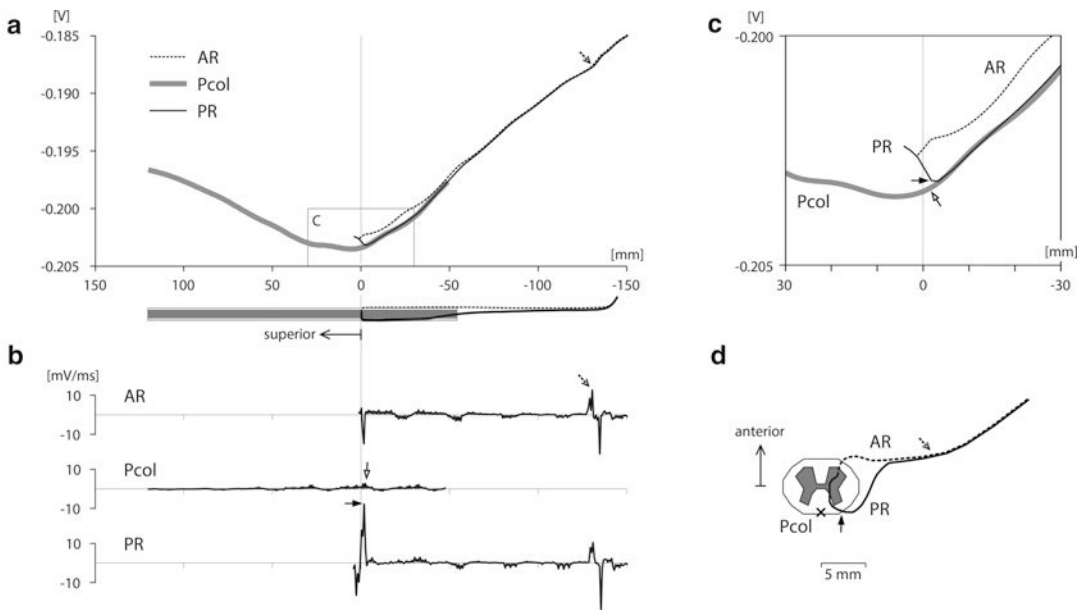
The stimulation effects on the target neural structures can be estimated from the activating function concept (Rattay 1999), which states that

the de- and hyperpolarization induced by an externally applied electric field is proportional to the second-order spatial differential of the electric potential (or the negative going, first-order differential of the electric field) along the nerve fiber. Thus, the spatial trajectory of the fibers relative to the field and the traversal of media of different conductivities greatly influence the excitability. Nerve fiber models can be used to identify the activation thresholds and simulate the influence of the fine structure of the neurons (esp. branchings and collaterals; Struijk et al. 1992). Note that all aforementioned factors can predominantly introduce de- as well as hyperpolarizations along the axons; the direction of the effect on the activation thresholds depends on the fiber's path relative to the electric field. More precisely,

convex fiber bends relative to the cathode, traversals of a fiber from a medium with high to one with low conductivity (as seen from the cathode), and fiber collaterals away from the cathode increase the excitability, whereas the respective opposite direction would decrease the excitability.

Computer simulations of transcutaneous SCS showed that the abovementioned factors are paramount for the activation of spinal neural structures through surface electrodes (Ladenbauer et al. 2010; Danner et al. 2011). Hot spots of maximal depolarization were identified at the entry point of the posterior rootlets into the spinal cord, at the entry/exit point of the posterior and anterior roots into/from the spinal canal (Fig. 2), and at the branching points of the collaterals from the posterior column fibers. This is somewhat

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Finite Element Models of Transcutaneous Spinal Cord Stimulation, Fig. 2

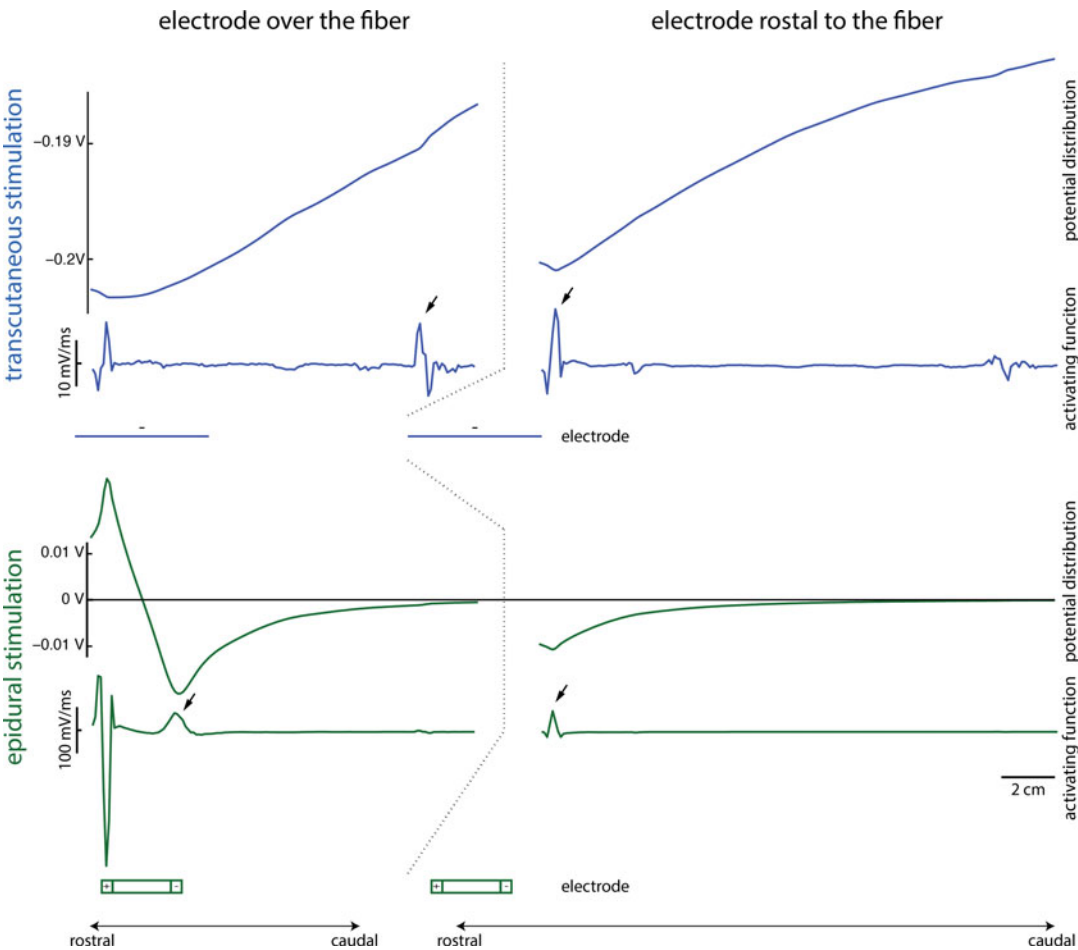
Stimulation effect evaluated along sensory structures and motor fibers of the spinal cord and roots. Low-threshold sites are caused by anatomical influences. The straight posterior column (Pcol) fiber shows only slight deviations from zero in its activating function, whereas the fibers in the posterior (PR) and anterior root (AR) are subject to strong de- and hyperpolarization at their entry/exit into/from the spinal cord and canal, respectively. (a) Extracellular potential along selected target fibers generated by transcutaneous stimulation at -1 V. The Pcol fiber is located medially and superficially in the white matter. The abscissa is the distance along the fiber

trajectories from the level of the center of the stimulation electrode. Anatomical relations of the PR and AR fiber are illustrated below the abscissa. (b) Activating functions corresponding to cases in (a). (c) Enlarged view of the box in (a). (d) Top view of the trajectories of the AR and PR fibers and of the simulated Pcol fiber location (x). Arrows indicate the lowest threshold sites. Threshold of the fibers with the paraspinal electrode acting as the cathode, calculated using the model of McIntyre et al. (2002): PR, 16.7 V; AR, 51.7 V; Pcol, 67.4 V (Reproduced from Danner et al. (2011) with permission from Wiley Periodicals, Inc.)

different to epidural SCS, where the points of strongest depolarization are close to the cathode and depend only on anatomically induced hot spots if the leads are located rostral to the fiber's entry point into the spinal cord (Fig. 3). Furthermore, epidural SCS was shown to be more selective (Ladenbauer et al. 2010). For transcutaneous SCS, the computer simulations suggest that with increasing intensity, first fibers in the posterior roots, followed by fibers in the anterior

roots, and eventually fibers in the posterior columns are stimulated.

To summarize, modeling transcutaneous stimulation of the lumbar spinal cord helps to identify the directly activated structures, provides explanations for their selective activation by the distant stimulation, and predicts their recruitment order and points of spike initiation. A more general principle was highlighted. The field produced by a distant electrode in a homogeneous medium would be too non-focal to effectively



Finite Element Models of Transcutaneous Spinal Cord Stimulation, Fig. 3 Stimulation effect (1 V) of transcutaneous and epidural electrodes located over and rostral to the posterior root fibers. The two low-threshold sites (entry into the spinal cord and the canal, respectively) can be seen in case of transcutaneous stimulation. Proximity of the electrode to these hot spots increases the amplitude of the corresponding parts of the activating function.

In case of epidural stimulation, the electrode placed over the fiber introduces strong, local deflections of the potential distribution and the activating function at the level of the contacts of the electrode, whereas the electrode located rostral to the fiber introduces an electric potential and activating function along the fiber similar to those in case of transcutaneous stimulation. Arrows indicate the spike initiation sites

activate neural structures. Rather, the anatomical properties of neurons and their surrounding tissue allow for strong and localized depolarization. Modeling will further contribute to the development of new, improved, and/or tailored stimulation techniques.

Cross-References

- [Finite Element Modeling for Extracellular Stimulation](#)
- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

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Firing Frequency

- [Estimation of Neuronal Firing Rate](#)

First-Spike Latency

- [Somatosensory Neurons: Spike-Timing](#)

Fitzhugh–Nagumo Model

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Definition

The FitzHugh–Nagumo (FHN) model is a mathematical model of neuronal excitability developed by Richard FitzHugh as a reduction of the Hodgkin and Huxley’s model of action potential generation in the squid giant axon (FitzHugh 1955). Nagumo et al. subsequently designed, implemented, and analyzed an equivalent electric circuit (Nagumo et al. 1962).

In its basic form, the model consists of two coupled, nonlinear ordinary differential equations, one of which describes the fast evolution of the neuronal membrane voltage, the other representing the slower “recovery” action of sodium channel deinactivation and potassium channel deactivation. Phase plane analysis of the FHN model provides qualitative explanations of several aspects of the excitability exhibited by the Hodgkin–Huxley (HH) model, including all-or-none spiking, excitation block, and the apparent

absence of a firing threshold. A version of the FHN equations which adds a spatial diffusion term models the propagation of an action potential along an axon as a traveling wave. Due to their relative simplicity and ease of geometric analysis, the FHN model and its variants are commonly used in neuroscience, chemistry, physics, and other disciplines as simple models of excitable dynamics, relaxation oscillations, and reaction–diffusion wave propagation.

Detailed Description

Mathematical Model

FitzHugh constructed the FHN equations by slightly modifying the cubic Bonhoeffer–van der Pol model of relaxation oscillations. The original van der Pol equation is a second-order linear differential equation:

$$\ddot{V} + (V^2 - 1)\dot{V} + \phi V = 0, \quad (1)$$

which may be written as two first-order equations by applying the Lienard transformation: $W = -\dot{V} + V - V^3/3$:

$$\dot{V} = V - V^3/3 - W \quad (2a)$$

$$\dot{W} = \phi V. \quad (2b)$$

For all $\phi > 0$, the origin in system Eq. 2 is an unstable fixed point surrounded by a globally stable limit cycle. FitzHugh’s modification to Eq. 2 added linear terms which shifted the fixed point and made it stable (FitzHugh 1955):

$$\dot{V} = V - V^3/3 - W + 1 \quad (3a)$$

$$\dot{W} = \phi(V + a - bW). \quad (3b)$$

Here a , b , and ϕ are positive constants; FitzHugh’s original values were $a = 0.7$, $b = 0.8$, and $\phi = 0.08$.

The variable V is taken to represent the membrane potential of the neuron, the parameter I is the applied current, and W is a “recovery” variable

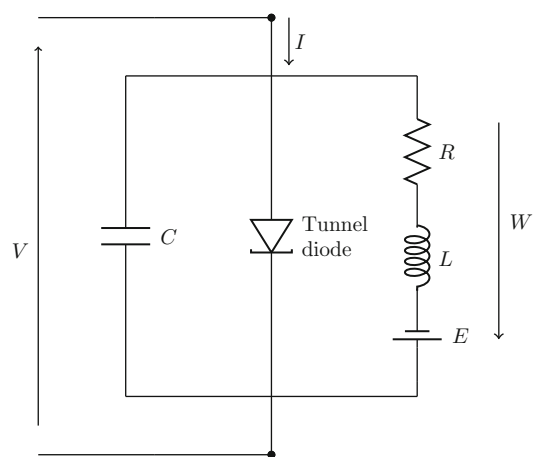
which represents the combined effects of sodium channel deinactivation and potassium channel deactivation.

There is a separation of timescales between the two variables that is set by the parameter ϕ , normally taken to be much smaller than unity in order to produce relaxation oscillations. That is, the evolution of V , as determined by Eq. 3a, occurs on a timescale of order $O(1)$, and, following Eq. 3b, W evolves on a timescale of order $\phi \ll 1$ (except at transitions; see below). Hence, V and W are referred to as the *fast* and *slow* variables, respectively.

Nagumo’s Circuit Model

Using an electric circuit that included a tunnel diode, Nagumo, Arimoto, and Yoshizawa qualitatively modeled a number of axonal behaviors (Nagumo et al. 1962). The circuit consists of a capacitor (representing membrane capacitance) and a tunnel diode (representing the nonlinear dynamics of the fast membrane current) in parallel with a resistor (representing channel resistance), an inductor, and a battery (these last three components being in series). The dynamics of the tunnel-diode circuit shown in Fig. 1 are described by the equations:

$$CV\dot{V} = I - F(V) - W \quad (4a)$$



Fitzhugh–Nagumo Model, Fig. 1 Nagumo et al.’s electric circuit. (Adapted from Nagumo et al. (1962))

$$L\dot{W} = E - RW + V, \quad (4b)$$

where C is the circuit's capacitance, R is the circuit's resistance, E is the battery's potential, L is the circuit's inductance, and I is an applied current. The variable V represents the voltage drop across the entire circuit, and the variable W represents the current through the resistor–inductor–battery circuit branch.

The $F(V)$ term expresses the current flowing through the tunnel diode as a function of voltage across it. When $F(V)$ is cubic, Eq. 4 may be easily transformed into Eq. 3; if R is eliminated from the circuit, one obtains the van der Pol Eq. 1. Thus FitzHugh's equations and Nagumo's circuit model are equivalent.

Phase Plane Analysis

The (fast) V -nullcline, given by

$$W = V - V^3/3 + I, \quad (5)$$

and the (slow) W -nullcline, given by

$$W = (V + a)/b, \quad (6)$$

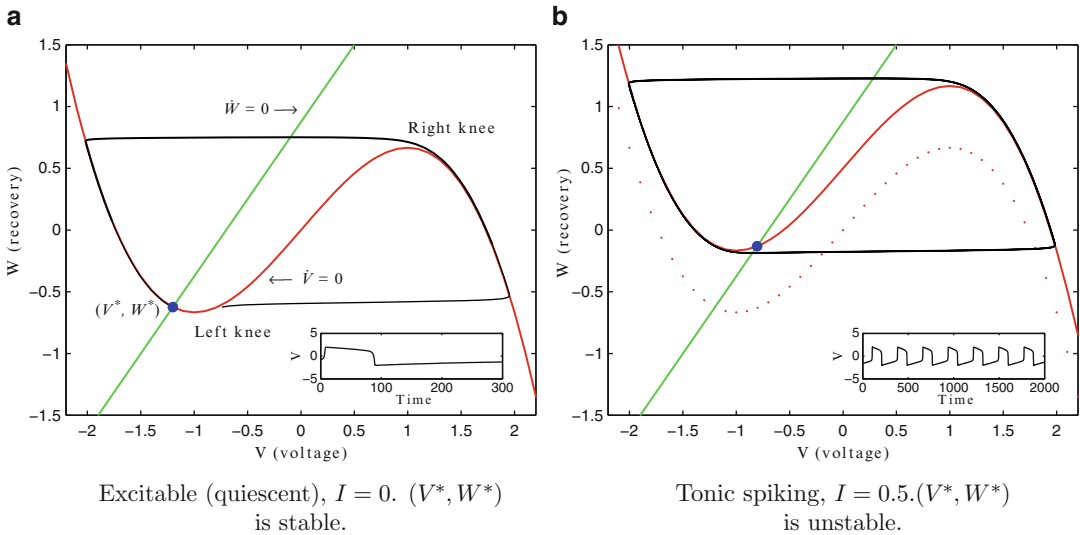
are the phase plane structures which organize the FHN system's dynamics. The (left) local minimum and (right) local maximum of the cubic V -nullcline are typically referred to as its “knees.” The knees divide the V -nullcline into three “branches,” left, middle, and right.

The fixed point of the FHN system is located at the intersection of the nullclines. (Under conditions $1 - 2b/3 < a < 1$, $0 < b < 1$, and $b > \phi^2$, there is exactly one fixed point.) The fixed point is stable for low values of applied current I , when it lies on the left branch of the V -nullcline, so that the system remains at rest unless perturbed (quiescence), as shown in Fig. 2a. As I increases, the V -nullcline shifts upward, and the location of the equilibrium shifts toward the middle branch. As the fixed point reaches the left knee of the V -nullcline, it undergoes a Hopf bifurcation, and a limit cycle is born. Thus, for sufficiently large values of I ,

the FHN system simulates tonic spiking, as shown in Fig. 2b.

Near the V -nullcline, $\dot{V}$ is approximately zero, so that motion in the $\dot{W}$ direction predominates, though it is slow because the small parameter ϕ in the $\dot{W}$ equation keeps the magnitude of W very small. Trajectories typically crawl down the left branch and up the right branch of the V -nullcline until they arrive at one of the knees. Once past a knee, the magnitude of $\dot{V}$ rapidly increases, while the magnitude of $\dot{W}$ remains small. The trajectory quickly traverses the region between the left and right branches, so that there is a large change in V in a very short time but very little change in W . Portions of trajectories between branches appear almost horizontal, and they become more nearly horizontal as ϕ decreases. These rapid changes in V as the trajectories switch branches mimic the rapid up- and down-swings of depolarization and hyperpolarization during action potentials, as can be seen in the insets of Fig. 2a, b. The separation of timescales between the V and W variables, as set by ϕ , is necessary for this action potential-like behavior and is the essential characteristic of relaxation oscillations.

When a brief positive current stimulus is applied to the quiescent FHN system, the (unperturbed) fixed point (V^*, W^*) is no longer a fixed point of the perturbed system, and thus the system's state begins to change. (Compare the locations of the fast nullclines and equilibria in Fig. 2a, b.) If its trajectory moves sufficiently far away from the fixed point before the stimulus ends, it will continue to make a large excursion around the right branch of the V -nullcline before returning to the original fixed point, as described above. This behavior models the action potential response of real neurons to depolarizing current pulses. Shifting the initial condition from (V^*, W^*) to $(V^* + V_{stim}, W^*)$ (to the right of the threshold curve near the middle branch of the fast nullcline; see below) produces a largely identical excursive trajectory (see Fig. 2a) and is the most common way to simulate single action potential production in response to external stimulus.



Fitzhugh–Nagumo Model, Fig. 2 Phase planes and sample trajectories for the FHN model Eq. 3 showing quiescence (**a**, left) and tonic spiking (**b**, right). The cubic fast nullcline ($\dot{V} = 0$) is red, the linear slow nullcline ($\dot{W} = 0$) is green, and the equilibrium point (V^*, W^*) is

denoted by a blue dot. Insets show voltage versus time for the sample trajectories in black. The fast nullcline for $I = 0$ is shown as the dotted red cubic curve in **b** for comparison

Geometric Explanation of Spike Generation Phenomena in the Hodgkin–Huxley Model

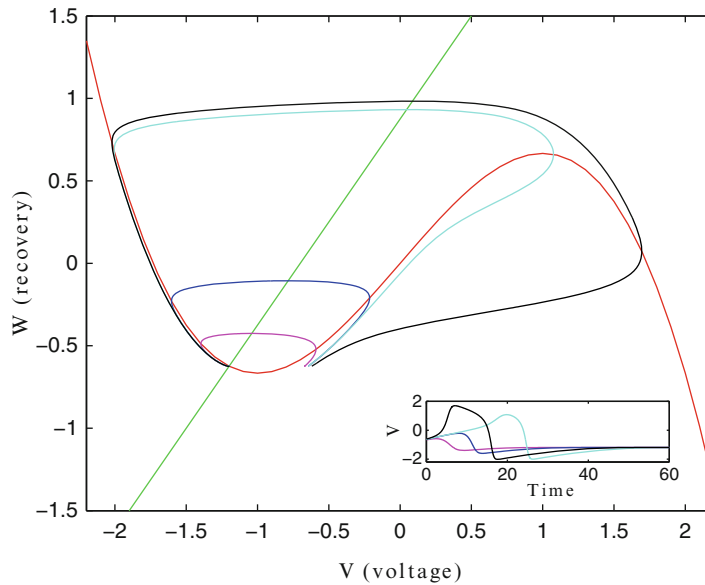
A number of phenomena which are characteristic of action potential generation in HH-style neuronal models – and, to some extent, in real neurons as well – were first explained by FitzHugh using the FHN model. FitzHugh varied I to simulate stimulation of a neuron by a constant current (setting $I = I_0$ for time $t > 0$) and by rectangular (constant step) currents of various durations (setting $I = I_0$ for time $T_{\text{on}} < t < T_{\text{off}}$) and then studied the FHN model’s response. He discovered that sufficiently large constant current produces spike trains (tonic spiking) via the mechanism described above. He modeled and analyzed other action potential response phenomena with either brief, rectangular, depolarizing (positive) stimuli or with slow current ramps (linearly varying I).

Threshold Phenomena, Small-Amplitude Spikes, and Refractoriness

FitzHugh noted that in the FHN model no single value of V acts as a threshold separating all-or-

none, action potential-like responses to stimulation from quiescent or subthreshold responses. Rather, a curve in the (V, W) plane forms a “quasi-type” threshold, such that for any given value of the recovery variable W_0 , there is a corresponding membrane voltage V_0 which the stimulus must exceed in order to evoke an action potential response (FitzHugh 1955). Trajectories starting to the right of the threshold curve simulate action potentials, while those starting to left of the threshold curve return to the left branch of the fast nullcline without producing a large action potential-like excursion (Fig. 3). Stimuli which fail to shift trajectories past the threshold curve result in small-amplitude trajectories or “bumps” in membrane potential, in both the HH and FHN models. Similar stimulation of biological neurons more typically produces either no response or a very negligible one.

The threshold curve lies near, but not on, the middle branch of the V -nullcline; it is very difficult to trace accurately using standard numerical integration techniques. (The threshold is in fact a canard trajectory which may be computed numerically using continuation methods (Desroches



Fitzhugh–Nagumo Model, Fig. 3 Weak stimuli (current or voltage perturbations) fail to move the system across the quasi-threshold for firing an action potential, resulting in small-amplitude voltage “bumps” (*magenta, blue trajectories*). Sufficiently large stimuli cross the threshold to produce full action potential responses (*black*

trajectory). For intermediate levels of stimulation which leave the system almost exactly at threshold, the system may track the quasi-threshold curve (near the middle branch of the V -nullcline) before turning *left* (no action potential) or *right* (near action potential, cyan trajectory)

et al. 2013)). Because of the difficulty determining whether trajectories would veer to the left or right near the threshold curve, FitzHugh labeled that region of the phase plane “no man’s land.” The HH model has been shown numerically to have a complicated quasi-type spike threshold as well (Guckenheimer and Oliva 2002).

Stimulation by positive current has no discernible effect during the hyperpolarizing downswing of an action potential in both real and HH model neurons. During the repolarization phase, immediately following the downswing, much larger depolarizing input is needed to produce a second action potential than that required for generating the original action potential. These phenomena are termed absolute and relative refractoriness, respectively, and are typically explained in terms of the inactivation of the sodium channels required for depolarization. Phase plane analysis of the FHN model provides a complementary geometric explanation. The FHN model exhibits absolute refractoriness during the period that a trajectory is “jumping” from the right

(depolarized) branch to the left (hyperpolarized) branch of the fast nullcline, and it exhibits relative refractoriness, while the trajectory crawls down the left branch of the fast nullcline toward the equilibrium point (repolarization).

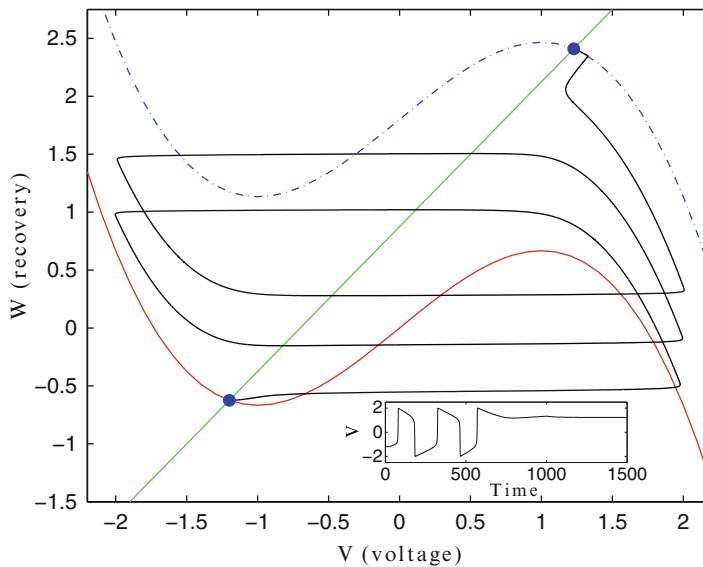
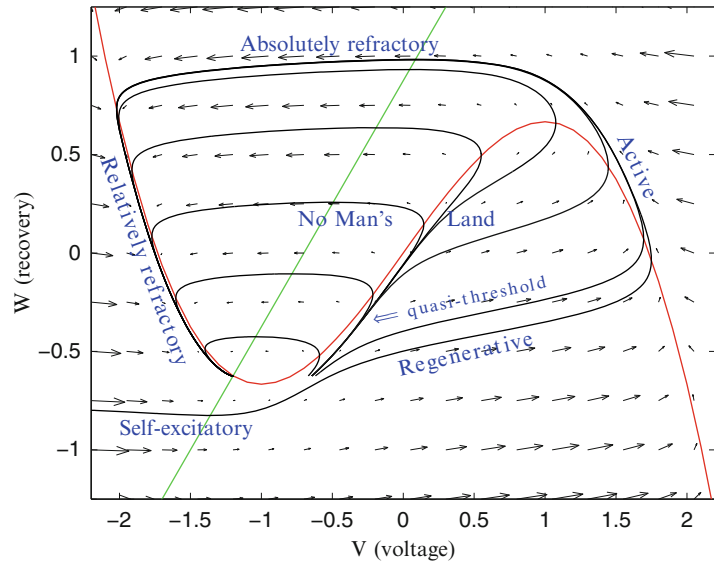
FitzHugh summarized his exploration of the FHN model’s response to brief depolarizing stimulus with a diagram similar to Fig. 4 (FitzHugh 1955, 1961).

Excitation Block

Applying positive external current shifts an HH neuron from quiescence to tonic spiking. In the FHN model, raising I moves the V -nullcline upward and induces repetitive firing as described above. If the magnitude of the stimulus is increased sufficiently, the fixed point will move to the right of the rightmost knee of the V -nullcline and become stable. The periodic orbit corresponding to repetitive spiking will be destroyed in a Hopf bifurcation, and the system will settle into a quiescent state at an elevated resting voltage. Thus, excitation of sufficient

Fitzhugh–Nagumo

Model, Fig. 4 Phase plane map associating FHN system behavior with initial conditions. (Adapted from Fitzhugh 1961)



Fitzhugh–Nagumo Model, Fig. 5 Excitation block: as the applied current I is rapidly increased, the V -nullcline rises and the system passes through a bifurcation whereby the fixed point becomes unstable and a stable periodic orbit is born. So long as the fixed point remains between the two

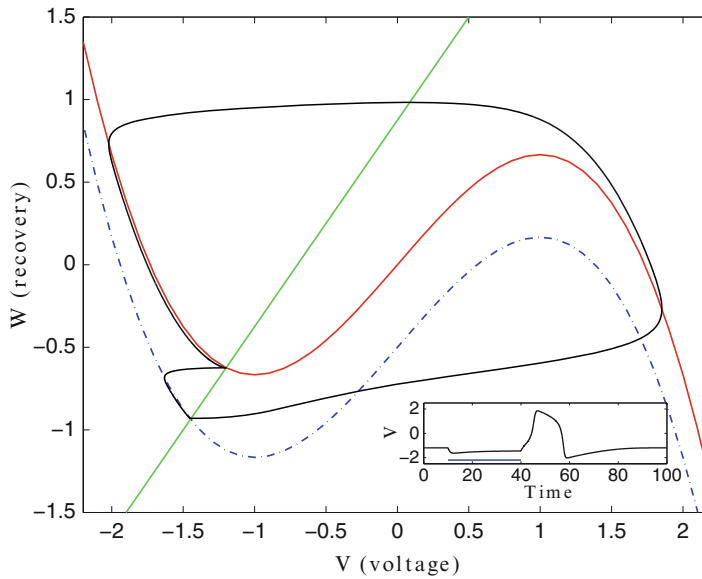
knees, the system spikes repetitively. Once I is sufficiently high for the fixed point to pass the *right knee*, the stable periodic orbit is destroyed, and the system is attracted to the new, depolarized stable equilibrium. Spiking stops and the membrane voltage remains at an elevated plateau

strength can block the production of spikes (Fig. 5).

Post-inhibitory Rebound Spiking

This phenomenon is also called “anodal break excitation” in older literature. Applying hyperpolarizing current (decreasing I) moves the

V -nullcline downward, maintaining the stability of the fixed point while shifting it down and to the left. When the hyperpolarizing current is turned off, the system is no longer at its fixed point but rather in a state where $\dot{V}$ and $\dot{W}$ are both positive (the “self-excitatory” region in Fig. 4). The system then follows a large excursive



Fitzhugh–Nagumo Model, Fig. 6 Post-inhibitory rebound spiking: injecting negative (hyperpolarizing) applied current I lowers the V -nullcline (red curve) to a new, hyperpolarized level (dotted blue curve) and moves the stable fixed point to a lower voltage level in what would

be the “self-excitatory” region of the phase plane, relative to the unperturbed system with $I = 0$. When the applied current is released, the V -nullcline and fixed point immediately return to their previous positions, and the system travels along a spike trajectory before returning to rest

trajectory around the right branch of the V -nullcline, firing off an action potential in response to the release of inhibition (Fig. 6).

Spike Accommodation

If the applied current I is raised slowly enough in the HH model, the neuron does not fire an action potential. Instead, the neuron remains quiescent, yet excitable, while the resting membrane potential rises. The same phenomenon is seen in the FHN model: as I increases, the V -nullcline shifts upward, and the equilibrium point shifts rightward, losing stability after it passes the left knee. If the shift is slow enough, the trajectory that began at the unperturbed fixed point will remain very close to the moving intersection (now unstable) of the fast and slow nullclines and will present itself as a slow rise in the resting membrane voltage over time (Fig. 7a). During this transition, very tiny perturbations may cause an action potential. Once the intersection of fast and slow nullclines passes the right knee, the fixed point will again be stable, and the system will remain at

an elevating resting membrane potential. The maximum rate of change for I which will produce spike accommodation depends in part on the separation of timescales, as set by ϕ , since it determines the separation between the spike threshold curve and the middle branch of the V -nullcline (Fig. 7b).

Other Forms of the FHN Model

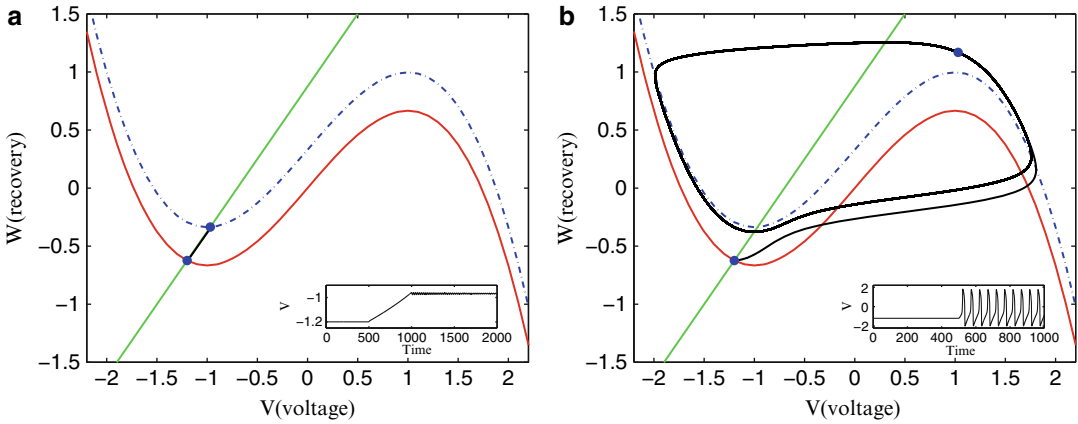
Alternative Formulations

Other formulations of the FHN equations are frequently encountered in the literature. FitzHugh also wrote his model as

$$\dot{x} = c(y + x - x^3/3 + z) \quad (7a)$$

$$\dot{y} = -(x - a + by)/c, \quad (7b)$$

with the constraints that a , b , and c were positive constants satisfying $1 - 2b/3 < a < 1$, $0 < b < 1$, and $b < c^2$ (FitzHugh 1961). This formulation



Fitzhugh–Nagumo Model, Fig. 7 Spike accommodation: increasing the applied current I raises the V -nullcline (red curve, $I = 0$) to a level where the fixed point is unstable (dotted blue curve, $I = 0.5$). When current is

increased very slowly, the membrane voltage tracks the unstable fixed point (a, left). A more rapid current ramp produces a spike as the system is unable to track the unstable fixed point (b, right)

produces a phase plane that is left–right reversed from the figures presented in this article for the FHN system Eq. 3.

Another common reformulation of Eq. 3 is

$$\dot{V} = V(1 - V)(V - \alpha) - w + I \quad (8a)$$

$$\dot{W} = \epsilon(V - \gamma W), \quad (8b)$$

with $\epsilon \ll 1$ and $0 < \alpha < 1$. In this version, the horizontal intercepts of the V -nullcline are conveniently located at 0, α , and 1.

Generalized FitzHugh–Nagumo Systems

Planar dynamical systems which have:

- I. A separation of timescales, i.e., one fast and one slow variable, say, v and w .
- II. A “cubic-like” fast variable nullcline, say, $f(v, w) = 0$.
- III. An approximately linear, monotonic slow variable nullcline, say, $g(v, w) = 0$, which intersects the fast variable nullcline exactly once, may be said to be “generalized FitzHugh–Nagumo systems.” That is, they take the form:

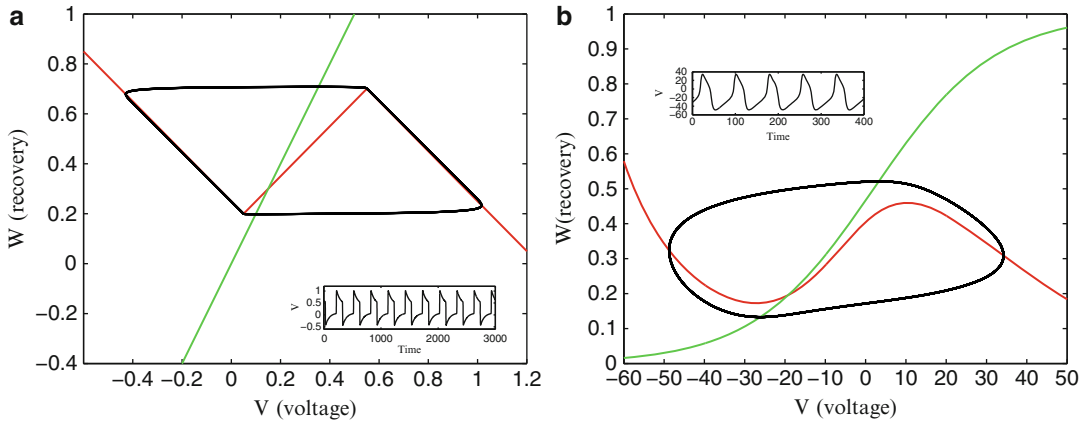
$$\dot{v} = f(v, w) \quad (9a)$$

$$\dot{w} = \epsilon g(v, w) \quad (9b)$$

with $0 < \epsilon \ll 1$. By “cubic-like,” we mean that f is continuous; that there is a single, finite interval of w values for which $f(v, w) = 0$ is satisfied by three v values; and outside that interval $f(v, w) = 0$ generically takes a single v value (Keener and Sneyd 2009) (Fig. 7). Generalized FHN models exhibit dynamics that are equivalent or similar to the canonical FHN model within some range of parameters, but they may have different bifurcation structures. Examples of generalized FHN systems include the piecewise linear models of McKean (approximations of system (Eq. 8a; see Fig. 8a) (McKean 1970; Tonnelier 2003) and Rowat and Selverston (1997) and the Morris–Lecar model (Fig. 8b) (Morris and Lecar 1981)).

Fast–Slow Approximation of Hodgkin–Huxley Dynamics

FitzHugh intended his model to capture the qualitative dynamics of the Hodgkin–Huxley equations during action potential generation. The FHN model approximates the dynamics present in the fast–slow phase plane of the HH equations.



Fitzhugh–Nagumo Model, Fig. 8 Phase planes for the piecewise linear McKendrick model (a, left) and the biophysically realistic Morris–Lecar model (b, right).

Note the cubic-like fast nullclines (red) and the (approximately) linear slow nullclines intersect exactly once; these are generalized FHN systems

The connection between the FHN and HH models can be seen in the following derivation, adapted from Keener and Sneyd (Keener and Sneyd 2009). (FitzHugh gave a similar explanation of the models' connection in FitzHugh (1961)).

The four-dimensional HH model (with variables V , m , n , h) may be reduced to a planar system with one fast variable (V , membrane voltage) and one slow variable (n , potassium activation) as follows. First, sodium activation m is

assumed to equilibrate instantaneously, so that $m = m_\infty(V)$, i.e., the sodium activation timescale is faster than the membrane voltage timescale. Second, the levels of potassium channel activation and sodium channel inactivation are assumed to change on the same timescale and to maintain an approximately constant sum over the course of an action potential, i.e., $h(t) + n(t) \approx 0.8$.

Under these two assumptions, the HH equations reduce to

$$\begin{aligned} \dot{V} &= f(V, n) \\ &= -\left(g, K^{n^4}, (V - E_K), +, gN, a^{m^3}, (V), (0.8, -, n), (V, -, E_{Na}), +, gL, (V, -, V_L)\right)/c \end{aligned} \quad (10a)$$

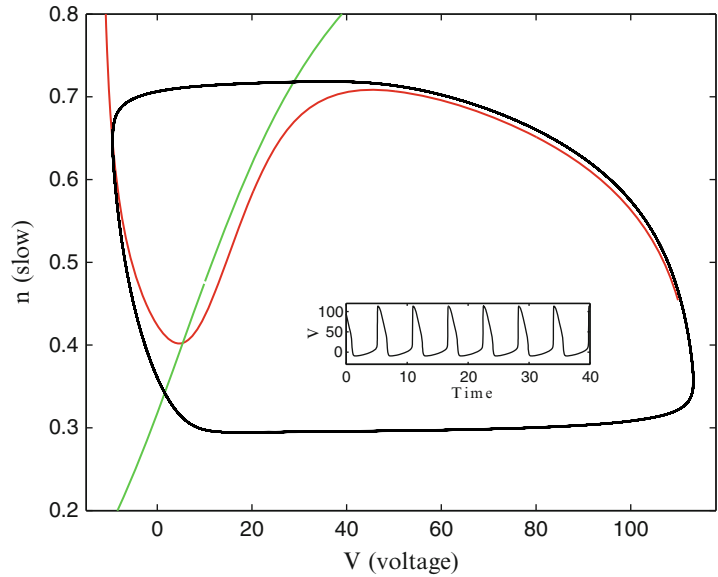
$$\begin{aligned} \dot{n} &= g(V, n) \\ &= \alpha_n(V)(1 - n) - \beta_n(V)n \end{aligned} \quad (10b)$$

Now (I), there is a wide (though implicit) separation of timescales between the fast and slow variables; (II) $f(V, n) = 0$ is “cubic-like” according to the definition above; and (III) $g(V, n)$ is monotonically increasing, is approximately linear near $f(V, n) = 0$, and intersects $f(V, n) = 0$ exactly once.

Thus, in the fast–slow phase plane, the HH model Eq. 10 is a generalized FHN system, and its behavior and analysis are essentially identical to that of the FHN model (Fig. 9). Note that the “recovery” role played by the slow variable n in the reduced HH Eq. 10 matches the physiological role played by potassium channels in helping to counteract excitation and reset the neuron's membrane potential back to the resting potential.

Fitzhugh–Nagumo

Model, Fig. 9 Phase plane for the fast–slow reduction of the Hodgkin–Huxley equations with parameters set for tonic spiking. Note the *cubic-like shape* of the fast V -nullcline and the *linear shape* of the slow n -nullcline

**FitzHugh–Nagumo Model of Spike Propagation (Traveling Waves)**

With the addition of a diffusion term, the FHN Eq. 3 may be adapted to provide a model of the spatial propagation of an action potential along an axon. Under appropriate boundary conditions to support a traveling wave solution (describing the propagation of the leading edge of the action potential), the equations become

$$V_t = V_{xx} + F(V) - W + I \quad (11a)$$

$$W_t = \phi(V + a - bW) \quad (11b)$$

where

$$F(V) = V^3/3 - V.$$

For traveling wave solutions of the form $V = V(x - ct) = V(\xi)$ and $W = W(x - ct) = W(\xi)$, V and W must satisfy

$$V_\xi = U \quad (12a)$$

$$U_\xi = W - F(V) - cU \quad (12b)$$

$$W_\xi = \frac{\phi}{c}(bW - V - a) \quad (12c)$$

Nagumo et al. first studied the system Eq. 12, taking $F(V)$ to be cubic and $b = 0$ (Nagumo et al. 1962). They found numerical evidence of two traveling wave solutions (homoclinic orbits) when ϕ was sufficiently small. Their numerical results indicated that only the higher-velocity solution was stable and that above a critical value of 0 no traveling wave solutions existed. FitzHugh's later numerical studies reached similar conclusions for $F(V) = V^3/3 - V$ and $b \neq 0$ (FitzHugh 1968). These numerical results have been confirmed analytically (see Scott (1975) for a fuller discussion).

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Flicker-Induced Phosphenes

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Definition

Flicker-induced phosphenes are visual hallucinations – often of simple geometric forms – induced by temporal modulation of spatially unstructured light. Theory suggests that they arise through a combination of resonance and lateral inhibition.

Detailed Description

Experimental Background

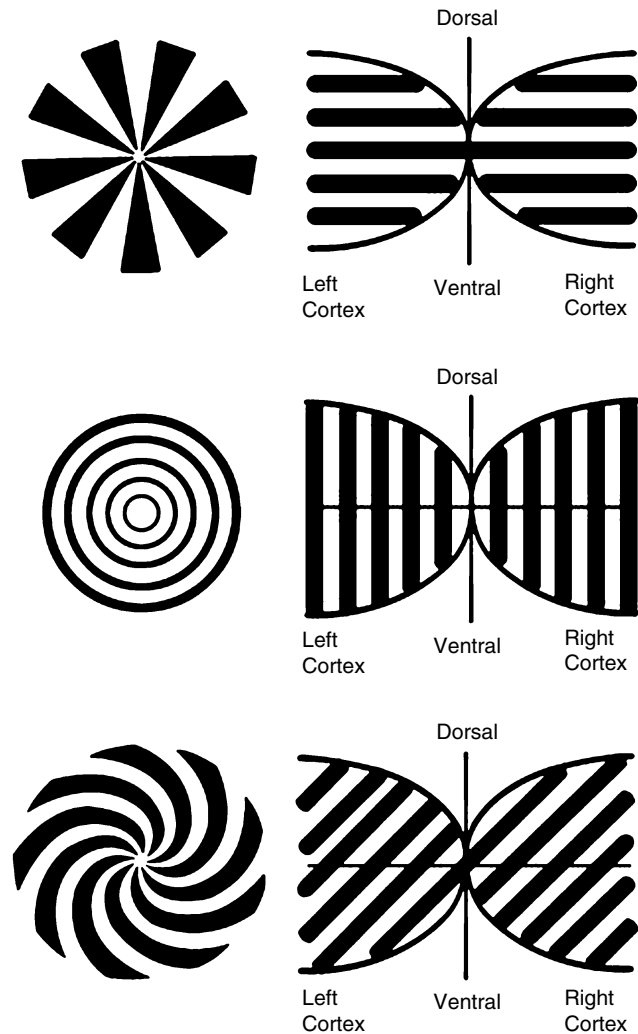
Flicker-induced hallucinations are sometimes called phosphenes to distinguish them from the over-sensationalized hallucinations linked to the five melodramatic Ds: drugs, dementia, dreams, delirium, and sensory deprivation. Flicker phosphenes were discovered by Purkinje in 1819 while fanning his fingers between his eyes and a gas

light; Brewster (the inventor of the kaleidoscope) noticed similar forms while racing past a sunlit fence with his eyes closed. Fechner and Helmholtz, who used rotating black-and-white disks as weak flicker sources, reported mainly pastel-colored hexagonal and rhomboidal lattices. In modern studies, many observers of strobe lights and flickering displays also report fan-shape, spiral, and concentric circular patterns. These shapes, together with lattices, are known as Klüver form constants and are also seen in migraine, occipital epilepsy, transcranial electric/magnetic stimulation of visual cortex, Charles Bonnet syndrome, binocular ocular pressure, and during early stages of some drug intoxications (Klüver 1966; Billock and Tsou 2012). Ermentrout and Cowan (1979) posited a revealing neural correlate to Klüver patterns: because of a nonlinear mapping between visual space and visual cortex, fan shapes, spirals, and concentric circles all map to visual cortex as gratings of parallel stripes of neural activation (Fig. 1). Scrolling cortical patterns correspond to rotating or pulsating hallucinations. Perceptual lattices can be formed by superposition of neural stripe patterns. Simpler phosphenes like “doughnuts,” wedges, “bowties,” and single arcs all map to single cortical stripes of varying orientation. Thus, if a pattern formation process on visual cortex can produce stripes of activity on visual cortex, the orientation of the induced stripe (s) predicts the nature of the observed hallucination. Ermentrout and Cowan (1979) showed that a simple excitatory-inhibitory neuronal network can produce cortical stripe patterns, and Bressloff et al. (2001) extended this model to simulate some more complicated illusory textures.

Less temporal modulation is required to induce phosphenes with two eyes than one; when one eye is flickered and the other eye is patched, the two eyes alternate in perceptual dominance. During flickered-eye dominance, geometric patterns are generally seen; during patched-eye dominance, observers report blob-like, boiling-like, and swirling amorphous forms that Smythies (1960) called “dark phase patterns.” Billock and Tsou (2007) reported similar patterns that appeared briefly before fan-shape hallucinations in an apparent motion experiment.

Flicker-Induced Phosphenes,

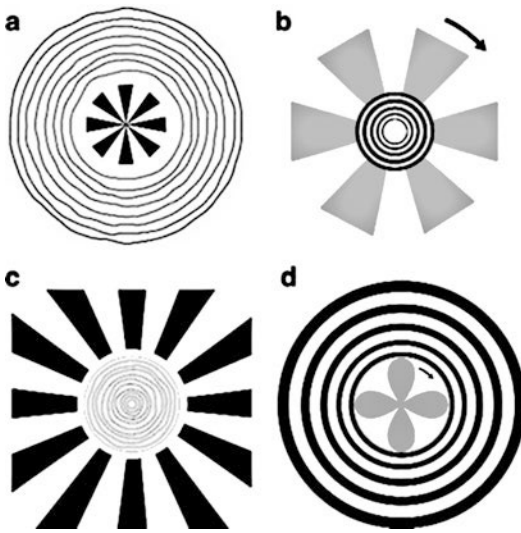
Fig. 1 Typical patterns seen during flickering light and their transformation to cortical coordinates



Precision of flicker is not critical – even random flicker has been used; however, average flicker frequency does matter: Remole (1973) measured contrast required to induce geometric patterns and found resonance-like tuning functions with maximal sensitivity at about 10–18 Hz. Studies differ on what is seen at any given flicker frequency (for a recent example, see Allefeld et al. 2010); in our experience, lattices are more common at low rates (e.g., 8–12 Hz), and geometric patterns are more common at slightly higher rates. Color is common but unpredictable. If the sluggish photoreceptors are bypassed by driving the optic nerve electrically, hallucinations (crescents, horseshoes, smoke ringlike, etc.) are produced by

rates as high as 210 Hz in light-adapted eyes (Wolff et al. 1968).

Although particular phosphenes appear unpredictably, placing a physical pattern in an adjacent field can bias flicker-induced pattern formation to an orthogonal percept, e.g., physical bull's-eyes induce illusory fan shapes (Billock and Tsou 2007, 2010; Fig. 2). Curiously, there is a visibility hierarchy, with fan shapes easiest to induce, then circles, and then spirals. Together with MacKay's (1978) afterimage experiments, this suggests a perceptual opponency between concentric circles and fan shapes and between clockwise and counterclockwise spirals – an opponency also found for perception of physical



Flicker-Induced Phosphenes, Fig. 2 Patterns inducing their complements

patterns under some conditions. Experiments and evidence adduced from other hallucinatory conditions suggest a natural spatial scale for hallucinatory features of about 1–2 mm on visual cortex (comparable to human orientation column width and hypercolumn spacing) and a natural temporal scale of 10–20 Hz (comparable to the EEG alpha and beta bands). Intriguingly, when flicker is synchronized to the subject's alpha rhythm, illusory pattern formation is significantly faster than for unsynchronized trials (Shevelev et al. 2000).

Theory

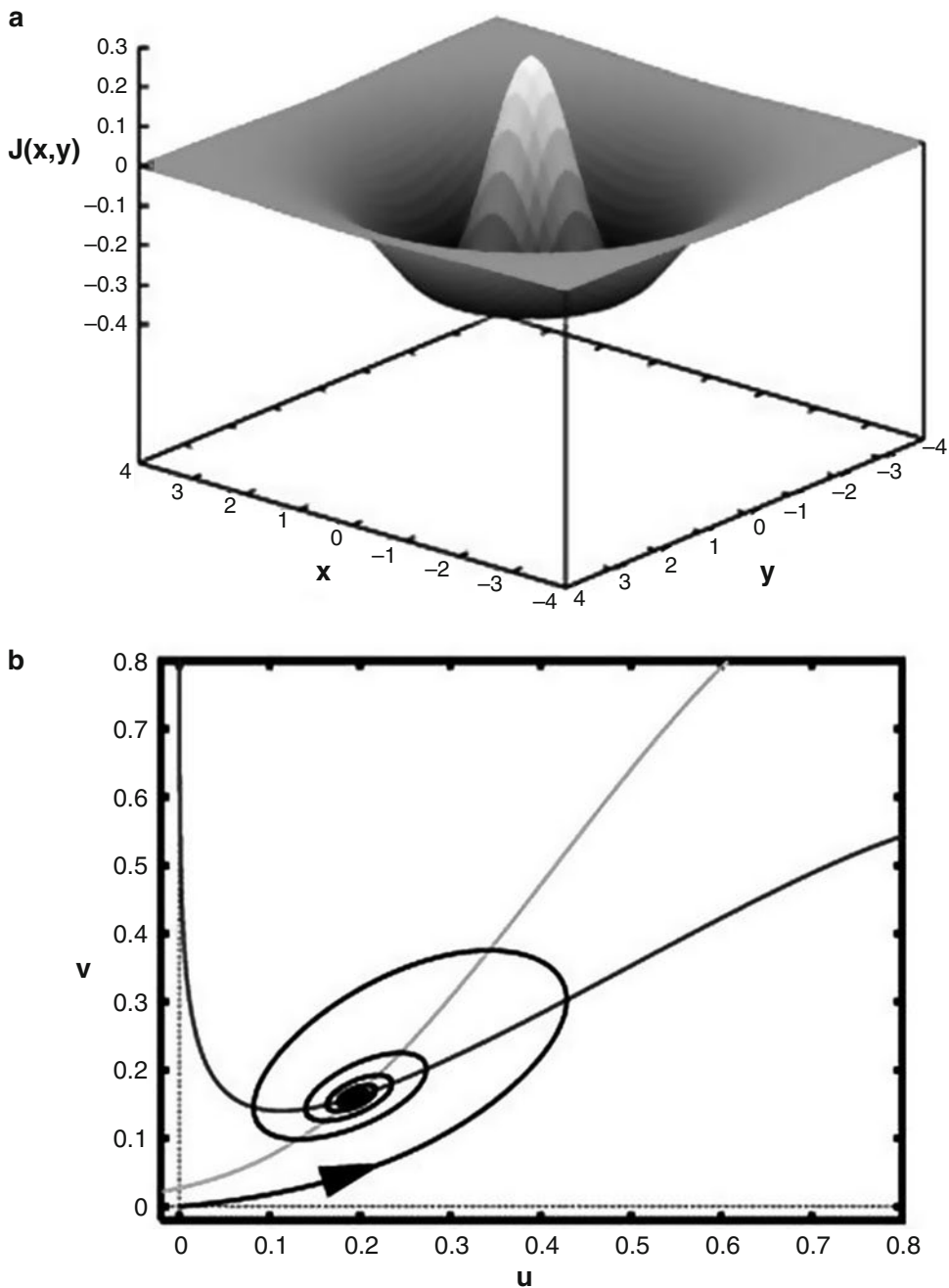
The key concept in almost every pattern forming system is *lateral inhibition* in space; that is, local activity at one point in space induces activity to nearby neurons but suppresses those more distantly. It is sometimes called a *Mexican hat* (see Fig. 3a). Flicker phosphenes are induced in a limited band of frequencies so this suggests that there is some type of resonance. Rule et al. built on the Ermentrout and Cowan work by adjusting parameters of that model to have some stronger resonance properties. They considered a population of excitatory and inhibitory neurons arranged in a two-dimensional lattice with spatially decaying connections:

$$\begin{aligned}\tau_e \frac{\partial u(x,y,t)}{\partial t} &= -u(x,y,t) + F(\alpha_{ee} J_e(x,y) * u(x,y,t) \\ &\quad - \alpha_{ei} J_i(x,y) * v(x,y,t) - \theta_e + I_e(t)) \\ \tau_i \frac{\partial v(x,y,t)}{\partial t} &= -v(x,y,t) + F(\alpha_{ie} J_e(x,y) * u(x,y,t) \\ &\quad - \alpha_{ii} J_i(x,y) * v(x,y,t) - \theta_i + I_i(t)).\end{aligned}\quad (1)$$

Here, $J_e(x,y) * u(x,y,t)$ is the two-dimensional spatial convolution of the connection strength, J_e , with the excitatory neural activity, $u(x,y,t)$. (The inhibitory activity is $v(x,y,t)$.) Both J_e and J_i are Gaussians with the spatial decay of J_e shorter than that of J_i so that the net effect is a Mexican hat. $I_e(t)$, $I_i(t)$ are spatially uniform inputs to the excitatory and inhibitory populations. In absence of stimuli, there is a stable homogeneous rest state, $u(x,y,t) = \bar{u}$, $v(x,y,t) = \bar{v}$, and perturbations of this decay to the rest state with a frequency of about 12 Hz (see Fig. 3b).

Keeping in mind Fig. 1, we see that pinwheels and bull's-eye patterns correspond to vertical and horizontal stripes in cortical coordinates. Diagonal patterns in cortical coordinates transform to spiral patterns of perception and lattice, and honeycomb cortical patterns transform to distorted lattices of similar patterns. Thus, to model flicker-induced patterns, we want our cortical network to generate simple geometric patterns like hexagons, rectangles, and stripes of various orientations.

Our network is spatially homogeneous in the sense that homogeneous inputs and initial conditions lead to homogeneous outputs. However, small amounts of noise or heterogeneity will break this symmetry. If the homogeneous system is stable, then the small effects will be dampened and ameliorated. However, if the homogeneous state is unstable, then certain spatial modes will be amplified and patterns will form. Rule et al. (2011) showed that with the parameters as in Fig. 3, patterns emerged at specific frequencies and only in a limited range. By looking at spatially periodic perturbations of the homogeneous state, they were able to compute boundaries in the period and amplitude of the stroboscopic flicker where the homogeneous pattern was



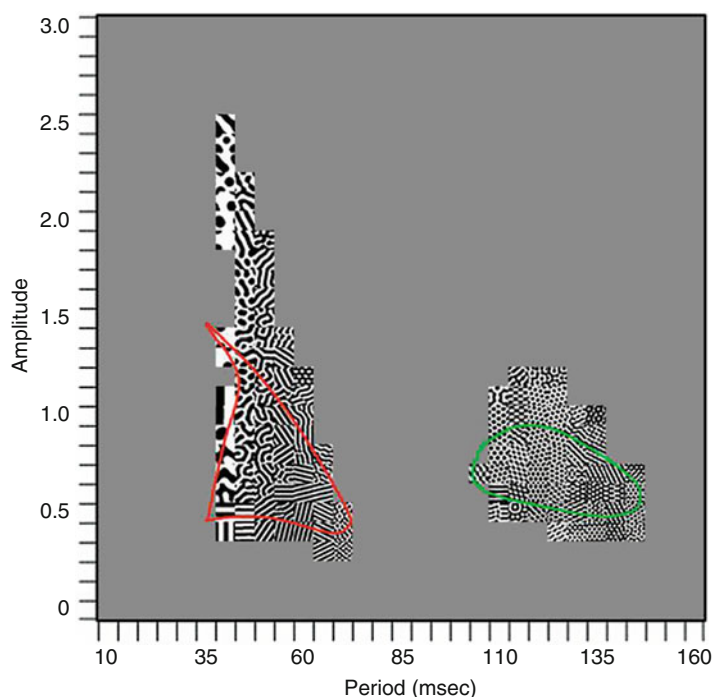
Flicker-Induced Phosphenes, Fig. 3 (a) Mexican hat connectivity pattern and (b) phase-plane showing damped oscillations

unstable. They also simulated equations (see Eq. 1) as the period and amplitude of the stimulus varied. Fig. 4 shows the results of these

simulations. At high frequencies of light (low periods), the patterns are stripes while at low frequencies (periods larger than 100 ms), they

Flicker-Induced Phosphenes,

Fig. 4 Phase diagram of spontaneous flicker-induced patterns as the amplitude and period of the stimulus vary. Contours represent the linear stability theory



are dominated by hexagonal and rectangular patterns. However, note that both classes of patterns are seen in both low and high frequency flicker. This figure also shows the boundaries computed by a stability analysis of the homogeneous state. The boundaries guarantee that within them, the homogeneous state is unstable and outside of them, it is stable. Patterns seen on the outside of the boundaries are numerical inaccuracies; more accurate simulations at the border confirm the stability of the resting state.

In Pearson et al. (2016), the authors further tested the idea that flicker phosphenes arise from a dynamic instability by reducing the stimulus space to effectively one-dimension. The authors flickered only an annulus and subject then reported that there were periodic blobs that rotated in either a clockwise or counterclockwise manner. They suggested the rotation was a consequence of the activation of motion selective neurons by the perceived spatially periodic flickering hallucination.

In sum, flicker phosphenes have been known and enjoyed for centuries. Using classic ideas of pattern formation coupled with resonance in the

temporal domain, these beautiful patterns can be explained with very few assumptions.

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Flip-Flop

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Fly Lobula Plate Tangential Cells (LPTCs), Models of

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Definition

A network of around 60 highly interconnected interneurons, the lobula plate tangential cells (LPTCs), is at the core of optic flow calculations in the fly visual system. Exquisite data is available

for these cells on their anatomy and electrophysiology *in vivo*, including the characterization of responses to visual stimulation. Consequently, it has been possible to derive models that reproduce the morphology and the detailed electrophysiology of the cells within the network and to associate the features of the network to optic flow computations that it performs. The LPTC network therefore is a prime example of a neural circuit where sophisticated computations, connectivity schemes, and anatomy are understood in a unifying manner.

Detailed Description

Circuit Overview of the Lobula Plate

The lobula plate in the fly is a neural center for course control during flight (Borst and Haag 2002). It encodes visual motion information in a retinotopic manner: Neighborhood relationships in the visual field are conserved within the lobula plate neuropil. Dendritic calcium signals in LPTCs in response to visual motion stimulation reveal this retinotopy (Borst and Egelhaaf 1992). Furthermore, the lobula plate divides into four layers that represent local motion in different directions (right, left, upward, and downward). The biophysics that lead to such an organization, i.e., the computation of local motion information, are currently being unraveled (Eichner et al. 2011; Hassenstein and Reichardt 1956; Maisak et al. 2013; Reichardt 1961; Takemura et al. 2013). The topographic two-dimensional arrangement of the lobula plate provides a structured substrate for the calculation of optic flow features. Dendrites of LPTCs cover large areas of the lobula plate to integrate local motion information. The receptive fields of LPTCs are therefore closely related to their dendritic anatomical layout. Sophisticated optic flow responses ultimately result from combining responses of individual LPTCs by means of a precise network of connections.

The network of LPTCs in the fly is accessible to detailed electrophysiological and anatomical analysis (Borst 2012; Borst et al. 2010; Borst and Haag 2002). When opening the back of the

fly's head, the lobula plate lies flat in full view. Extracellular spikes from the so-called H1 cell, one of the most prominent members of the LPTC family, can easily be isolated and recordings can be sustained over the course of many hours in the living fly (de Ruyter van Steveninck and Bialek 1988). This has led to the H1 cell being a model system for neural coding and information theory (Bialek et al. 1991; Borst and Haag 2001; Rieke et al. 1999). Other LPTCs such as the Horizontal System (HS), Vertical System (VS), and Centrifugal Horizontal (CH) cells are accessible to intracellular electrophysiology using sharp electrodes inserted in their large axons (Hausen 1982a, b). Multiple simultaneous intracellular recordings in conjunction with calcium imaging allowed for studying connections between LPTCs directly (e.g., Haag and Borst 2001, 2002, 2004).

These studies led to the description of a large number of specific connections between different LPTCs within the lobula plate (Borst et al. 2010), as well as a number of heterolateral connections linking both sides of the brain (Farrow et al. 2006; Haag and Borst 2001, 2008). Finally, the readout of optic flow information via descending neurons and the flight control circuitry have been studied in great detail (Geiger and Nüssel 1981; Haag et al. 2007, 2010; Wertz et al. 2008, 2012). A unifying network consisting of simplified LPTC model cells has recently been published (Borst and Weber 2011).

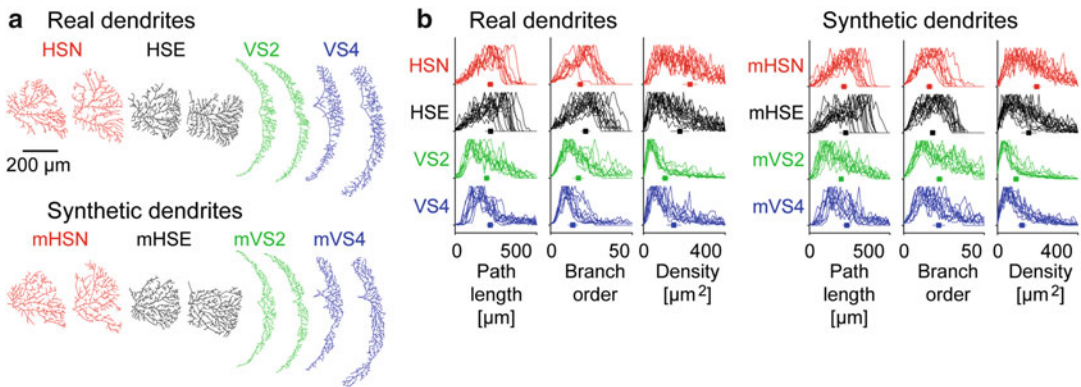
Morphological Models of LPTCs

When filled with a cellular dye, individual LPTCs are uniquely identifiable on the basis of their shape alone. They are therefore ideal candidates to study the relationship between structure and function in dendrites. On the other hand, the dendritic branching patterns of any particular identifiable LPTC do not match precisely when compared in different individuals (Hausen 1982a), indicating that any blueprint for an LPTC's dendritic structure, if it exists, is stochastic in nature. A novel kind of morphological model can reproduce LPTC dendritic structures

(Cuntz et al. 2007a, 2008). The model is based on the intuitive idea that the area covered by the dendritic tree, the so-called dendritic field (Hausen 1982a), determines the dendritic tree structure to a large extent (Cuntz 2012). Synthetic dendritic trees are grown to fill the dendritic fields while housekeeping both the total amount of wiring and the conduction times within the dendrites (Cuntz et al. 2007a). The resulting synthetic dendrites (Fig. 1a) yield quantitatively similar inner branching parameter distributions as their real counterparts (Fig. 1b). Since the same branching model is valid for all cell types, this indicates that the growth principles are similar in different LPTC types and their branching statistics are therefore determined by the dendritic field alone (Cuntz et al. 2008). This type of morphological model has since been shown to reproduce the dendritic and axonal shape of many neurons in a variety of species, cell types, or developmental stages (Budd et al. 2010; Cuntz et al. 2010, 2012).

Single-Cell LPTC Compartmental Models

Detailed compartmental models exist for the three main LPTC types: the HS, VS, and CH cells. These single-cell models include passive properties (Borst and Haag 1996), active properties (Haag et al. 1997), and the responses to large-field visual motion stimulation (Haag et al. 1999). These three LPTC types respond to visual stimulation with graded membrane potential deflections, depolarizing when a stimulus is moved in the preferred direction and hyperpolarizing when the stimulus is moved in the anti-preferred direction. The active models therefore do not produce full-blown action potentials but rather small spikelets as well as rebound spikes after strong hyperpolarization due to a specialized sodium-dependent potassium channel (Haag et al. 1997; note a typo in this paper: the sodium reversal potential should be 100 mV instead of 200 mV; see also Neuron model files at www.treestoolbox.org/hermann/). A number of computations were identified by studying HS and VS cells electrophysiologically in combination with corresponding models. First, it was shown



Fly Lobula Plate Tangential Cells (LPTCs), Models of, Fig. 1 Morphological models of HS and VS cells. (a) Example synthetic dendrites (bottom) grown within the dendritic fields of their real counterpart (top). Synthetic dendrites are marked by an “m” preceding HSE (black), HSN (red), VS2 (green), and VS4 (blue). (b) Some typical branching statistics for real dendrites (left) and synthetic dendrites (right). Each cell is represented by one distribution histogram and mean values (filled squares) with error

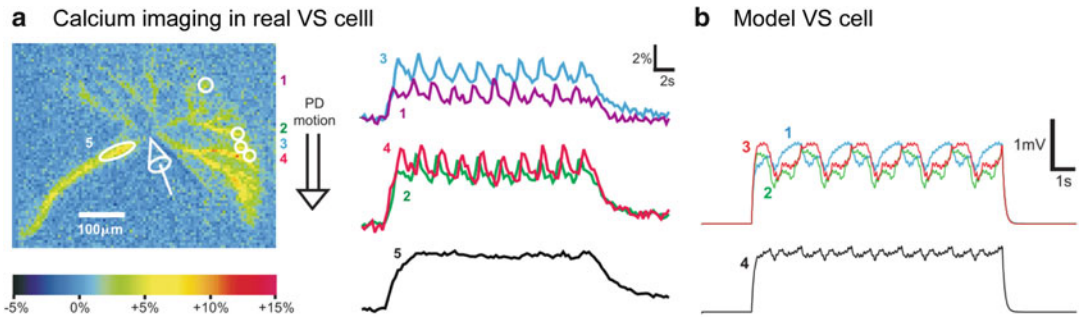
bars (standard deviation between individual dendrites) are shown. The branching statistics here are (1) path length to root values for all topological points, (2) branch order values, and (3) surface area values assigned to each topological point after Voronoi segmentation. The latter quantifies how homogeneously the topological points are distributed (Modified from Cuntz et al. (2008))

that the small spikelets in HS and VS cells enhance the transmission of high-temporal-frequency signals that would otherwise be filtered out by the time constant of the membrane (Haag and Borst 1996). Second, local irregularities in the motion signal are filtered out by spatial integration in the dendrite (Fig. 2a), a prime example for a functional interpretation of dendritic morphology (Single and Borst 1998). This feature was reproduced in the corresponding passive compartmental model (Fig. 2b), indicating that the passive membrane filtering properties in combination with the morphological structure are sufficient to explain this computationally relevant aspect of dendritic integration.

Dendritic Networks Performing Image Processing Operations

The fact that the motion image is represented in LPTC dendritic activity allows for image processing operations to be applied directly in the dendrites. The CH cell, for example, does not receive visual inputs directly from local motion elements in the lobula plate but indirectly via electrical synapses from the overlapping dendritic

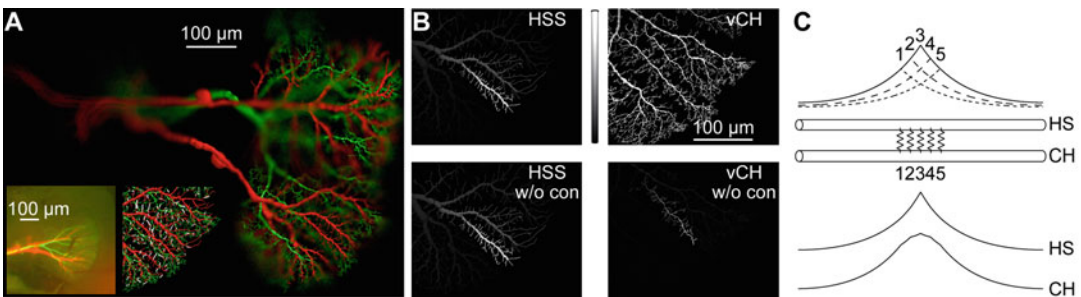
trees of HS cells (Haag and Borst 2002). A corresponding network model (Cuntz et al. 2003) was designed to accommodate active compartmental models of a ventral CH (vCH), an equatorial HS (HSE), and a southern HS (HSS) cell (Borst and Haag 1996; Haag et al. 1997) (Fig. 3a). When the dendrites are connected to each other with spatially distributed electrical synapses at the overlapping sections of their dendritic trees, the model predicts a blurring effect (Fig. 3b) that has previously been reported in experiments measuring dendritic calcium signals (Dürr and Egelhaaf 1999; Haag and Borst 2002). The model is consistent with the experimentally observed current transfer function, the temporal filtering of sharp transients such as spikelets, and the comparably small decrease in CH cell input resistance during full-field visual stimulation. CH cells also possess inhibitory (Meyer et al. 1986) dendritic output synapses (Gauck et al. 1997). The blurred motion image, as represented in the CH cell dendrites, is passed onto Figure Detection (FD) cells (Egelhaaf 1985a, b, c) via these inhibitory dendritic synapses. This puts the unique properties of the CH cell into a functional context. Subtracting the CH cell’s blurred motion image from the FD cell’s own local motion detector input



Fly Lobula Plate Tangential Cells (LPTCs), Models of, Fig. 2 Dendritic integration of visual motion. (a) Calcium responses to wide field visual stimulation using a grating. For four dendritic locations (1–4), the calcium signal exhibits local fluctuations of the brightness pattern similar to those of the drifting periodic grating. These

fluctuations are filtered out by dendritic integration in the calcium signal recorded at the level of the axon (5). (b) This scenario is reproduced in a passive model of a VS cell using simulated local motion detector inputs (1–3: dendritic locations, 4: axonal location) (Modified from Single and Borst (1998))

F



Fly Lobula Plate Tangential Cells (LPTCs), Models of, Fig. 3 Computation in a dendritic network of LPTCs. (a) Realistic compartmental models of a ventral CH (vCH) cell (green), connected to an HSS and an HSE cell (red). (Left Inset) Original fluorescent staining for comparison. (Right Inset) Location of electrical synapses (white) used for these analyses. (b) Membrane potential spread in the HSS model (top left) and vCH model (top right) after local current injection into HSS. In the bottom panels, potential spread is shown similar to top panels but with unconnected cells; current was injected in HSS (bottom left) and vCH

(bottom right). (c) Two cylinders (HS and CH) are connected by five linear conductances surrounding the location of current injection. In HS the signal spreads following an exponential decay while the CH spread is broader (bottom traces). Since the CH signal is smaller than the HS signal, both were normalized to their maximum value. The spread within the CH cell can be approximated as the sum of the currents through each individual conductance (top traces) spreading passively within the CH cell (Modified from Cuntz et al. (2003))

leads to a sharpening of the original image, equivalent to an enhanced motion contrast. This is consistent with selective laser ablation experiments of the CH cell after which the small-field selectivity of FD cells is eliminated (Warzecha et al. 1993).

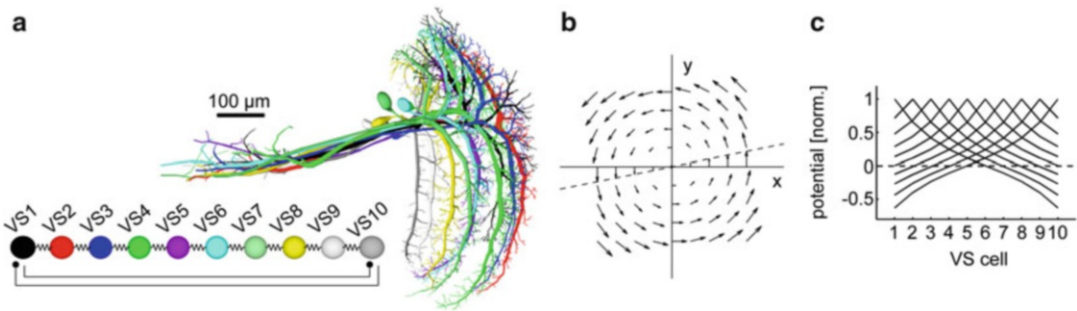
The spatial low-pass filter in this LPTC dendritic network is based on a general feature of distributed electrical or chemical synapses. The potential in the second cell is filtered by the membrane of both cells in a sequential manner corresponding to a convolution of the signal

with a kernel determined by the filtering properties of both cells (Fig. 3c). Let $f_1(x)$ and $f_2(x)$ describe the spatial impulse response in the first and in the second dendrite, respectively:

$$f_1(x) = e^{-|x|/\lambda} \quad (1)$$

$$f_2(x) = (1 + |x|/\lambda)e^{-|x|/\lambda} \quad (2)$$

where x represents the dendritic location and λ is the length constant of the dendritic cable. These



Fly Lobula Plate Tangential Cells (LPTCs), Models of, Fig. 4 Computation in axonal network between VS cells. (a) Ten VS cells as obtained from 2-photon image stacks and for which detailed compartmental models were reconstructed. Cells were placed manually according to their position in the lobula plate with neighboring dendritic arborizations slightly overlapping. Suggested connectivity scheme from Haag and Borst (2004) with adjacent cells

coupled electrically between their axons and distal cells inhibiting each other (*schematic-filled spots*). (b) Idealized optic flow field for self-rotation. The vertical components scale linearly with the x-axis (*dashed line*). (c) Voltage transfer (normalized amplitudes) from all different VS cells at the location of the synapses in the axon terminal (Modified from Cuntz et al. (2007b))

equations show that the relative spatial attenuation in the second cell is much smaller than in the first one: $f_1(x = \lambda) = 1/e$ and $f_2(x = \lambda) = 2/e$ (see Cuntz et al. 2003 for details). The filtering by the membrane corresponds to a spatial low-pass (blurring), which in the second cell filters out more high frequencies because of the larger space constant. The amount of blurring is determined by the length constant λ of both cells which in turn depends on the dendritic anatomy as well as on the axial and transmembrane resistance (Rall 1959).

Axonal Networks Extracting Optic Flow Features

As illustrated in the preceding example, the precise location of the synapses and the geometrical arrangement of dendrites and axons within the network are crucial for some of the computations that occur in the lobula plate. The network of VS cells (Fig. 4a) is another example for this type of highly selective connectivity. Their dendrites sequentially cover slightly overlapping stripes along the rostrocaudal axis of the lobula plate. However, apart from the expected sensitivity of their responses to vertical motion in large vertical stripes of the visual field, VS cells exhibit more complex receptive fields reaching beyond the

receptive field size expected from the retinotopic location of their dendrites (Krapp et al. 1998; Krapp and Hengstenberg 1996; Laughlin 1999). The complex receptive fields of VS cells roughly match the optic flow that occurs during rotational flight maneuvers of the fly around its own axis (rolling rotation, see Fig. 4b).

How do these properties arise? A number of experiments have indicated that VS cells are connected to each other via their axons in a chain-like manner (Farrow et al. 2005; Haag and Borst 2004, 2005). Moreover, distant VS cells inhibit each other reciprocally. After tuning synaptic conductances and membrane parameters in a network of anatomically realistic VS compartmental models (Fig. 4a), the observed current transfer between VS cells in the network and other experimental measures are reproduced in detail (Cuntz et al. 2007b; Elyada et al. 2009). Interestingly, the VS network thereby effectively implements a triangular filter (Fig. 4c). The linear potential decay is the result of a superposition of the potential decaying exponentially from VS1 to more distal VS cells and the same potential inverted via the inhibition decaying exponentially backward from the distal VS cell to the VS1 cell (Cuntz et al. 2007b; Weber et al. 2008). A triangular filter possesses the interesting characteristic of linearly interpolating the inputs. In this way, the VS network

incorporates prior knowledge about the linear relationship of rotational optic flow vectors with horizontal disparity: Fig. 4b clearly shows this linear relationship in the rotational optic flow field (dashed line). Descending neurons that collect the signals from VS cells have been identified and robustly read out the axis of rotation (Wertz et al. 2009).

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fMRI BOLD, Neural Population Models of

► [Neuroimaging, Neural Population Models for](#)

Fokker-Planck Equation

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Synonyms

[Convection-diffusion equation](#); [Drift-diffusion equation](#); [Forward Kolmogorov equation](#); [Smoluchowski equation](#)

Definition

The Fokker-Planck equation (FPE) is a partial differential equation that describes the temporal evolution of the probability distribution of a stochastic variable. It is useful to describe the membrane potential distribution of a neuron receiving stochastic inputs. In this context, it has been used

to determine stationary firing rates as well as neuronal responses to time-dependent stimulations. Beyond its application to single neuron dynamics, the FPE is useful to analyze in a self-consistent way the behavior of an ensemble of interacting spiking neurons and in particular the emergence of neural rhythms.

Historical Remarks

The Fokker-Planck equation is named after Adriaan Fokker and Max Planck who introduced it to describe the time evolution of the velocity probability distribution for a Brownian particle. Marian Smoluchowski used it to analyze the position distribution of Brownian particles when the particle motion is strongly damped. It was also introduced by Andrei Kolmogorov as the equation governing the evolution of the probability distribution of general memoryless stochastic process (Markov process). An important early use of the FPE was Kramers's analysis of the thermal escape rate of a particle over a potential barrier (see Chandrasekhar (1943) for an early classic review).

The stochastic character of neuronal activity has been recognized and quantified for over half a century. Stochastic models of neuronal spiking were developed from the early 1960s (see Tuckwell (1988) for a detailed exposition), but the usefulness of the FPE in this context has been recognized more recently (see Brunel and Hakim (2008) and references therein).

The Fokker-Planck Equation for a Neuron Receiving Noisy Inputs

The temporal evolution of the membrane potential of a neuron can be described with different degrees of complexity and realism. The simplest spiking neuron models use the membrane potential V as their only variable. They usually combine an evolution equation

$$C \frac{dV}{dt} = -F(V) + I(t) \quad (1)$$

where C is the membrane capacitance, $I(t)$ represent the input current, and $F(V)$ represents the intrinsic membrane dynamics, with a spike reset mechanism to account for the repolarization after action potential emission: when V reaches a threshold V_T , an action potential is deemed to be emitted, and the membrane potential is instantaneously reset at $V_R < V_T$. The classical leaky integrate-and-fire (LIF) model uses a linear F representing a passive membrane of conductance g , $F(V) = gV$ (Lapicque 1907; Knight 1972). Nonlinear F s can be used to represent the voltage-gated opening of (sodium) channels as, e.g., $F(V) = gV - g\Delta_T \exp.[(V - V_s)/\Delta_T]$, in the exponential integrate-and-fire (EIF) model where Δ_T quantifies the sharpness of action potential initiation (Fourcaud-Trocmé et al. 2003).

In many situations, $I(t)$ can be split into an average $\mu(t)$ and a fluctuating noise term $\eta(t)$. When the fluctuating term $\eta(t)$ is well approximated by a white noise, Eq. 1 becomes a particular type of stochastic differential equation, called a Langevin equation. The evolution of the probability distribution $P(V, t)$ of V is then described by the Fokker-Planck equation associated to Eq. 1:

$$C \frac{\partial P}{\partial V} = \frac{\partial}{\partial V} [(F(V) - \mu(t))P(V)] + \frac{\Delta(t)}{2} \frac{\partial^2 P}{\partial V^2} \quad (2)$$

where $\Delta(t) > 0$ measures the amplitude of noise fluctuations, $\langle \eta(t)\eta(t') \rangle = \Delta(t)C\delta(t - t')$. The two terms on the right-hand side of Eq. 2 correspond, respectively, to a deterministic drift term induced by the membrane dynamics and the mean input and a diffusion term coming from the fluctuating part of the input. We have supposed that the mean and variance of the noisy inputs are time dependent since that is useful for some applications, as explained below.

Probability is conserved by the FPE, and a probability current $j_P(V, t)$ is associated to Eq. 2:

$$j_P(V, t) = \frac{-F(V) + \mu(t)}{C} P(V) - \frac{\Delta(t)}{2C} \frac{\partial P}{\partial V} \quad (3)$$

The resetting of the action potential imposes boundary conditions at the action potential

threshold V_T and reset V_R . First, it gives an absorbing boundary condition at V_T , $P(V_T) = 0$. Second, the probability is continuous at the reset potential, but its derivative is discontinuous: there is an entering current at reset potential equal to the exiting probability current through the threshold potential. That is,

$$\frac{\partial P}{\partial V}(V_T, t) = \frac{\partial P}{\partial V}(V_R^+, t) - \frac{\partial P}{\partial V}(V_R^-, t) \quad (4)$$

where the subscript $\pm$ denote the limiting values of the function from upper/lower values of its argument.

Finally, the neuron instantaneous firing rate $r(t)$ is given by the instantaneous probability current through threshold potential:

$$r(t) = -\frac{\Lambda(t)}{2C} \frac{\partial P}{\partial V}(V_T, t) \quad (5)$$

Some Applications

The Fokker-Planck formalism has proven useful for the analysis of single neuron and network dynamics in the presence of noise. We mention a few applications of the formalism in the following.

Stationary Firing Rates and F-I Curves

The simplest application of the FPE is the determination of the steady discharge rate of a neuron submitted to stochastic inputs. In a steady situation, the time derivative in Eq. 2 vanishes. A first integration simply gives that the probability current is constant in the two membrane potential intervals, between threshold and reset, $V_R < V < V_T$, and below threshold, $V < V_R$. The current actually vanishes in this second interval (as the probability of finding a very negative membrane potential does). A second integration then allows the determination of the membrane potential probability distribution. Normalization of the total probability fixes the constant probability current between reset and threshold and determines the steady discharge rate r_s :

$$\frac{1}{r_s} = \frac{2C}{\Delta} \int_{V_R}^{V_T} dU \int_{-\infty}^{V_T} dV \exp \left\{ \frac{2}{\Delta} \int_V^U dW [F(W) - \mu] \right\} \quad (6)$$

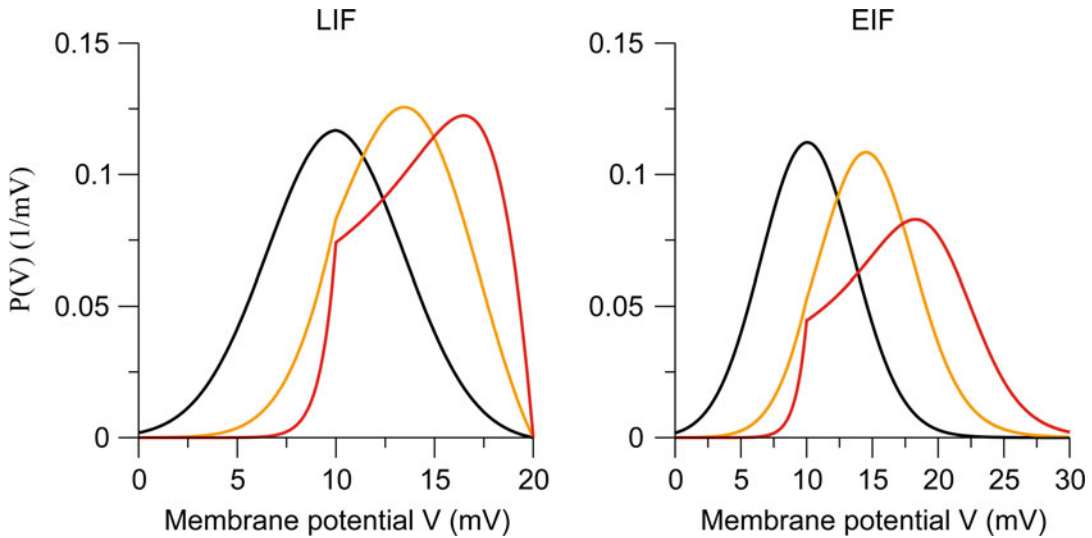
This calculation in essence dates back to Kramers's computation of the thermal mean escape time of a particle over a potential barrier (Kramers 1940) and is classic in the present context (see Tuckwell (1988) for early references and Burkitt (2006) for a recent survey). The obtained membrane potential distributions for the LIF and EIF neuron models are shown for illustration in Fig. 1.

Responses to Stimulation in the Presence of Noisy Inputs

A major question in neuroscience is how neurons respond to time-dependent inputs. This question is in particular relevant to the understanding of the speed of information processing in sensory systems. It is therefore useful to determine how a neuron responds to a particular input, the signal $s(t)$, in the presence of other “distracting” inputs. Since the neuron response is provided by its output spikes, this leads to analyze how the neuron spike rate is modified by the signal $s(t)$. This can be performed using Eq. 2 when the distracting inputs can be modeled as white noise. For weak signals, the ensuing spike rate modulation $r_1(t)$ is small, and it is linearly related to the signal through a “spike rate response” function R :

$$r_1(t) = \int_{-\infty}^t dt' R(t-t') s(t') \quad (7)$$

The function R can be determined by linearizing the FPE Eq. 2 and solving the resulting linear equation. This is conveniently performed in Fourier space, i.e., by considering periodic signals of different frequencies ω . Responses to both a varying mean $\mu(t)$ and a varying fluctuation amplitude $\sigma(t) \Delta(t)$ have been computed. For instance, for the simplest LIF model subjected to current inputs, one obtains



Fokker-Planck Equation, Fig. 1 Probability distribution of the membrane potential for the LIF model (*left panel*) and the EIF model (*right panel*) and for stationary input mean $\mu(t) = \mu_0$ and variance $\Delta(t) = \Delta_0$. Parameters: $C/g = 20$ ms, $V_T = 20$ mV, $V_R = 10$ mV, $\Delta_T = 2$ mV, $\mu_0/g = 10$ mV (black curves), 15 mV (orange curves), 25 mV (red curves), and $\sqrt{\Delta_0/g} = 5$ mV. Note that in the LIF model, the distribution is confined to $V < V_T$. It reaches zero at

threshold, and the firing rate is proportional to the slope of the distribution at threshold. On the opposite, for the EIF model, the distribution is nonzero for any V and has an exponential tail at large Vs. For inputs that are in the subthreshold range $\mu_0/g < V_T$, the distributions are close to a Gaussian. For larger inputs, the distribution is strongly affected by spiking (see the cusp at $V = V_R$ due to the probability flux proportional to the firing rate)

$$R_1^{(LIF)}(t) = \int \frac{d\omega}{2\pi} \exp(i\omega t) \tilde{R}_1^{LIF}(\omega), \quad (8)$$

where $R_1^{(LIF)}(\omega)$ can be expressed in terms of a combination of hypergeometric functions (see Brunel and Hakim (2008) for a review). A compendium of different response functions for the LIF and EIF models can be found in Richardson (2007), as well as an efficient numerical method to compute such functions.

Self-consistent Analysis of a Network of Neurons

The FPE gives the probability density of neurons submitted to stimuli that are independent representatives of the same stochastic process. However, it can also be used to analyze in an approximate way the dynamics of a set of interacting neurons by neglecting correlations between neurons, the so-called mean field

approximation. This has served for instance to characterize the spontaneous activity of neurons in a network. It has also been used to determine the parameters region where the neural activity of an ensemble of neurons is spontaneously oscillatory and gives rise to neural rhythms (for more details, see the ► “Population Density Model” long entry).

Some Generalizations

Equation 2 is the simplest form of the FPE for one scalar stochastic variable. More general FPEs can be easily written for multidimensional stochastic evolution. In the context of neuronal evolution, these descriptions arise naturally as soon as several variables are used to describe the neuron dynamics, as in the basic Hodgkin-Huxley model. However, multidimensional FPEs are notoriously more difficult to mathematically analyze than the single variable FPE and their use has been much more limited.

One such case is the use of the Fokker-Planck formalism to study the consequence of membrane resonance at a particular frequency. Resonance can arise for instance when a slow conductance opposes membrane potential changes. In this case, the slowness of the second variable allows for a simple analysis by a reduction of the two-variable model to an effective one-variable model (Richardson et al. 2003).

Colored noise provides another case of interest. The filtering effect of synaptic dynamics replaces, for instance, the white noise η in Eq. 1 by a colored noise. In a minimal description, this can be taken to be an Ornstein-Uhlenbeck process with correlation time τ , and it naturally leads to a two-variable Fokker-Planck description. The analysis performed in the small τ limit shows that noise correlation has important consequences on the high-frequency behaviors of spike rate responses (Brunel et al. 2001).

Finally, the neuronal dynamics can be approximated by a diffusion process only under the approximation that the neuron is submitted to small and numerous independent synaptic inputs. While this appears justified in several in vivo situations, it remains to be assessed whether the “shot noise” case of a few sizable inputs proves more appropriate in other cases (Richardson and Swarbrick 2010).

Cross-References

► [Population Density Model](#)

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Forced Texture Processing

► [Peripheral Vision, Models of](#)

Forward and Inverse Problems of MEG/EEG

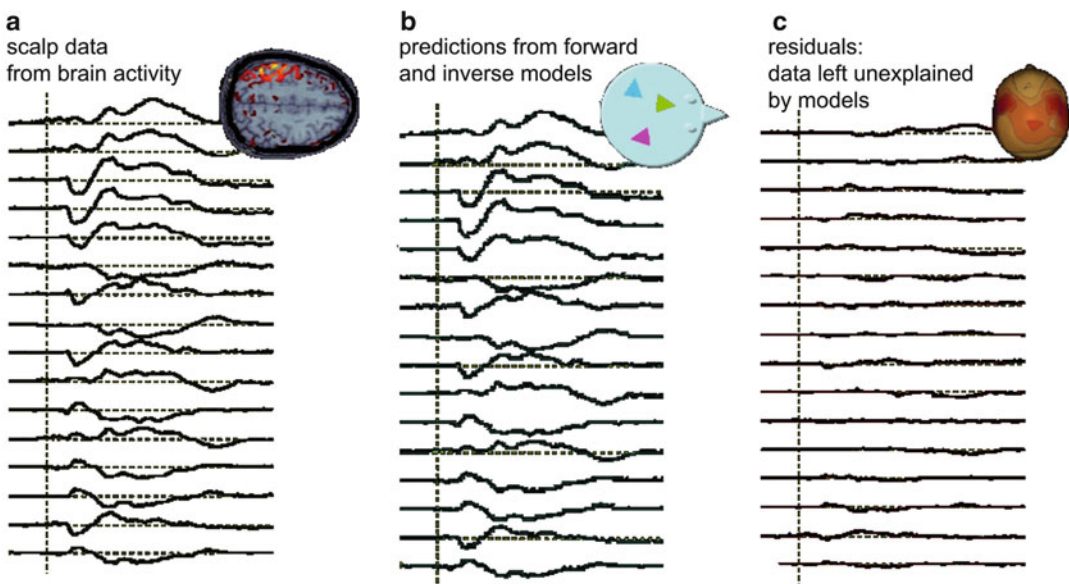
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Definition

The quantitative analysis of scalp MEG and EEG data continues to generate a very diverse body of research based on the characterization of time-resolved brain activity. Some questions however require a more direct assessment of the anatomical substrate of cerebral dynamics. In many cases, modeling the neural generators of scalp MEG/EEG data is the method of choice. From a

methodological standpoint, MEG/EEG source modeling is an “inverse problem”: a ubiquitous concept in many fields, from medical imaging to geophysics (Tarantola 2004). It builds a framework that helps conceptualize and formalize the fact that, in experimental sciences, models are confronted with observations to test a set of hypotheses and/or to estimate some parameters that were originally unknown. Parameters are quantities that can be changed without fundamentally invalidating the theoretical model. Predicting observations from a model with a given set of parameters is called *forward* modeling. The reciprocal situation where observations are used to estimate some unknown model parameters is an *inverse* modeling problem. The neural sources of scalp signals can be defined in terms of their anatomical location and current-flow orientation in space and amplitude variations in time, which represent the primary unknown parameters of MEG/EEG inverse modeling. To enable the latter, it is crucial to capture how these parameters

contribute to scalp data. Hence, MEG/EEG forward modeling consists in predicting the electromagnetic fields and potentials generated by any arbitrary source model, for any possible location, orientation, and amplitude parameter values. In practice, MEG/EEG forward modeling assumes that some additional key parameters are known, hence are not estimated from the data: the geometry of the head, conductivity of the tissues, sensor locations, etc. (Fig. 1). Importantly, it is established that the general inverse problem consisting in characterizing the sources that generate electromagnetic fields outside a volume conductor has an infinite number of solutions. This issue of nonuniqueness is not specific to MEG/EEG: astrophysicists, for instance, face the same issue to determine the distribution of mass inside a planet by measuring its external gravity field. Hence in principle, an infinite number of source models can fit equivalently any set of MEG and EEG observations. Fortunately, this conundrum is addressed with the powerful



Forward and Inverse Problems of MEG/EEG, Fig. 1 Principles of MEG/EEG forward and inverse modeling: (a) some unknown brain activity generates magnetic fields and electrical potentials at the surface of the scalp. This is illustrated by *black* traces of time series representing measurements on a subset of sensors. (b) A naive illustration of forward and inverse models is

shown, with colored arrowheads as ECDs inside a spherical head geometry. The free parameters of each ECD, e.g., location, orientation, and amplitude, are adjusted by inverse modeling. (c) Residuals, i.e., the difference between the original data and the measures predicted by a source model, are minimized by the inverse modeling procedure

mathematics of regularization, which formalizes how additional contextual information can complement a basic theoretical model and guarantee uniqueness and robustness in the determination of its unknown parameters. A considerable amount of research has been produced on practical methods for MEG/EEG forward and inverse modeling. They actually reduce to a handful of classes of approaches, which are now well identified and contribute to making MEG and EEG source imaging a major neuroimaging technique (Salmelin and Baillet 2009).

Detailed Description

MEG and EEG Forward Modeling

Model of Neural Sources

MEG and EEG forward modeling requires two basic models that are bound to work together in a complementary manner: a physical model of neural sources and a model that predicts how these sources generate electromagnetic fields outside the head. The canonical source model of the net primary intracellular currents within a neural assembly is the electrical current dipole. The adequacy of a simple equivalent current dipole (ECD) model as a building block of cortical current distributions was originally motivated by the topography of scalp MEG/EEG data, which typically consists of dipolar patterns of inward/outward magnetic fields and positive/negative electrical potentials. From a historical standpoint, the ECD model derived from extensive previous work in electrocardiography, where dipolar field patterns are also omnipresent (Geselowitz 1964). However, the complexity of the spatio-temporal dynamics of brain activity is more challenging than that of “cardiac traces.” Therefore, more generic alternatives to the ECD model have been proposed either as higher-order multipoles (Jerbi et al. 2004) also derived from cardiographic research or densely distributed source models (Wang et al. 1992). In the latter case, a large number of ECDs are distributed in the entire brain volume or spatially constrained to the cortical surface, thereby forming a dense grid of

elementary sites of activity, the amplitudes/intensities of which are determined from the data. This latter approach is now the prominent technique of choice for MEG and EEG source imaging (Salmelin and Baillet 2009). To understand how these elementary source models generate signals that are measurable using external sensors, further forward modeling of the sensor array and of the electromagnetic properties of head tissues is required.

MEG/EEG Sensor Arrays

Sensor locations can be readily measured with state-of-the-art MEG devices and ancillary EEG equipment. Sensor locations may also be approximated from montage templates; however, this is suboptimal with respect to the accuracy of subsequent source estimation (Schwartz et al. 1996). This is critical with MEG, as the subject is relatively free to position his/her head within a sensor array of fixed size and shape, although movement compensation techniques have been proposed. Further detailed modeling of the sensor geometry, pickup technology, and online noise-attenuation processes is state-of-the-art in the field.

Head Modeling

Quasistatic Assumptions MEG and EEG forward modeling also consists in identifying the influence of the head geometry and of the electromagnetic properties of its tissues on data formation. This last step is popularly coined “head modeling.” For a given model of elementary neural currents and sensor array, the physics of MEG and EEG are ruled by the theory of electrodynamics (Feynman 1964), which reduces in MEG to Maxwell’s equations and to Ohm’s law in EEG, under quasistatic assumptions. These latter consider that the propagation delay of the electromagnetic waves from brain sources to the MEG/EEG sensors is negligible. The reason is the relative proximity of MEG/EEG sensors to the brain with respect to the expected frequency range of neural sources (up to 1 kHz) (Hämäläinen et al. 1993). This is a very important, simplifying assumption, which has immediate consequences on the computational aspects of MEG/EEG head

modeling. Indeed, the equations of electro- and magnetostatics determine that there exist analytical, closed-form solutions to MEG/EEG head modeling when the head geometry is considered spherical. Hence, the simplest and consequently by far most popular model of head geometry in MEG/EEG consists of concentric spherical layers: with one sphere per major category of head tissue (scalp, skull, cerebrospinal fluid, and brain).

Simplified, Spherical Head Geometry The spherical head geometry has further attractive properties for MEG in particular. Quite remarkably indeed, spherical MEG head models are insensitive to the number of shells and their respective conductivity: a current source within a single homogeneous sphere generates the same MEG fields as when located inside a multilayered set of concentric spheres with different conductivities. The reason for this is that conductivity only influences the distribution of secondary volume currents that circulate within the head volume and which are impressed by the original primary neural currents. The analytic formulation of Maxwell's equations in the spherical geometry demonstrates that these secondary currents do not generate any magnetic field outside the volume conductor (Sarvas 1987). Consequently, the conductivity and radius of each spherical layer have no influence on the measured MEG fields, which is not the case in EEG. This is considered a major advantage for MEG.

Geometrical registration to individual MRI anatomical data improves the adjustment of the best-fitting sphere geometry to the participant's head. A spherical head model can be optimally adjusted to the head geometry or restricted to regions of interest, e.g., posterior regions for visual studies. Another remarkable consequence of the spherical symmetry is that radially oriented brain currents produce no magnetic field outside a spherically symmetric volume conductor. For this reason, MEG signals from currents generated at the gyral crests or sulcal depths are attenuated, with respect to those generated by currents flowing perpendicularly to the sulcal walls. The difference in sensitivity to source orientation is another important contrast between MEG and

EEG (Hillebrand and Barnes 2002). Finally, the amplitude of magnetic fields decreases faster than electrical potentials' with the distance from the generators to the sensors. Hence, it has been argued that MEG is less sensitive to mesial and subcortical brain structures than EEG. An increasing body of experimental evidence and modeling efforts has shown however that MEG can detect neural activity from deeper brain regions (Attal and Schwartz 2013).

Realistic Head Geometry Although spherical head models are convenient, they are poor approximations of the human head shape, which impacts the accuracy of MEG/EEG source estimation (Stenroos et al. 2014). The use of more realistic head geometries, which requires solving Maxwell's equations with numerical methods, has also been proposed. Boundary element method (BEM) and finite element method (FEM) are generic numerical approaches to the resolution of continuous equations over discrete space. In MEG/EEG, geometric tessellations of the different envelopes forming the head tissues need to be extracted from the individual MRI volume data to yield a realistic approximation of their geometry. In BEM, the conductivity of tissues is supposed to be homogeneous and isotropic within each envelope. Therefore, each tissue envelope is delimited using surface boundaries defined over a triangulation of each of the segmented envelopes obtained from MRI. FEM assumes that tissue conductivity may be anisotropic (such as the skull bone and the white matter); therefore, the primary geometric building block needs to be an elementary volume, such as a tetrahedron (Marin et al. 1998).

In practice, the FEM's tessellation step remains tedious and complicated. However, efficient implementations of BEM have been derived recently (e.g., Kybic et al. 2005) and are now readily available in several commercial and academic software applications (Baillet et al. 2011).

An important caveat, especially for EEG, is realistic head modeling also depends on the correct estimation of tissue conductivity values, which are difficult to access *in vivo*. Methods of impedance tomography have been proposed with MRI (Tuch et al. 2001) and EEG (Goncalves et al.

2003) but have had limited practical impact so far. Hence, conductivity values from *ex vivo* models are conventionally considered in MEG and EEG head models (Geddes and Baker 1967).

MEG/EEG Source Modeling

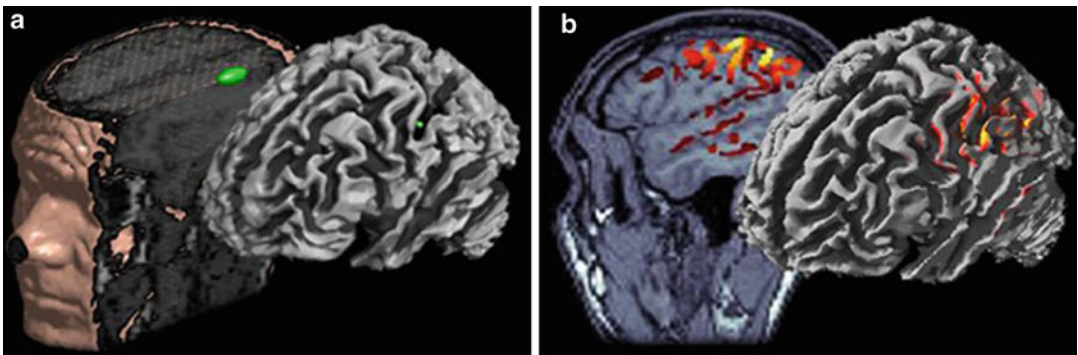
Source Localization Versus Source Imaging

The localization approach to MEG/EEG source estimation assumes that brain activity at any time instant is generated by a relatively small number (a handful, at most) of brain regions. An elementary model, such as an ECD accounting for the local distribution of neural currents, is typically used for each source. The resulting elementary sources can then be overlaid to the subject's MRI volume, for visualization and interpretation. Source localization models are therefore compact representation of distributed physiological currents. Although extremely popular in the 1980s and 1990s, this type of approach is now being gradually abandoned in favor of image-based, distributed inverse models, which are better adapted to streamlined analyses of cohorts of subjects.

MEG/EEG source imaging techniques were inspired from the methods and algorithms contributed by research in image restoration and reconstruction in other fields (early digital imaging, geophysics, and other biomedical imaging techniques). Synoptic images of neural current density are obtained using a dense grid of current dipoles distributed as voxel-like current intensity elements over the entire brain volume or limited to the cortical gray matter surface. The imaging procedure is an estimation of the time-resolved amplitude changes of all elementary currents. Hence, in contrast to the localization model, there is no intrinsic sense of distinct, active source regions *per se*. Explicit identification of activity issued from discrete brain regions usually necessitates subsequent analysis, such as empirical or inference-driven amplitude thresholding. In that respect, MEG/EEG source images are essentially similar to the maps obtained in fMRI, with the benefit of time resolution however (Fig. 2).

Beamforming

The first alternatives to source localization were inspired by radar and sonar data analysis, which also concerns array signal processing. MEG and



Forward and Inverse Problems of MEG/EEG, Fig. 2 Inverse modeling: source localization (a) versus imaging (b) approaches. Source localization consists in decomposing the MEG/EEG generators using a handful of equivalent current dipoles (*ECD*). This is illustrated here from experimental data testing the somatotopic organization of primary cortical representations of hand fingers. The parameters of the single *ECD* have been adjusted on the [20, 40] ms time window following electrical stimulus onset at a given hand finger. The *ECD* was found to

localize along the contralateral central sulcus as revealed from the 3D rendering, after registration to the individual anatomy obtained with MRI. In the imaging approach, the source model is spatially distributed using a large number of *ECD*s. Here, a surface model of MEG generators was constrained to the individual brain surface extracted from T1-weighted MR images. Elementary source amplitudes are interpolated onto the cortex, which yields an image-like distribution of the amplitudes of cortical currents

EEG source scanning techniques have therefore emerged: they proceed by systematically sifting through the brain volume to evaluate how a pre-determined elementary source model would fit the data at every voxel while “blocking” contributions from other sources elsewhere in the brain. Hence, these techniques are also known as spatial filters and beamformers (the simile is a virtual beam directed toward a specific brain region) (Spencer et al. 1992; Hillebrand et al. 2005). In theory, beamformers cannot properly detect signal sources that are strictly synchronized; they are also dependent on the prior characterization of second-order noise vs. signal statistics, which may be challenging in practice (Wax and Anu 1996). Nevertheless, beamforming has now become a popular technique for MEG and EEG source imaging.

Distributed Source Imaging

Imaging source models consist of distributions of elementary dipole sources in the brain volume or on the cortex, generally with fixed locations and orientations (Dale and Sereno 1993; Lin et al. 2006). The parameters to estimate through inverse modeling at each time point are therefore the amplitudes of thousands of elementary dipoles given only tens or a few hundreds of data points. Consequently, this image reconstruction inverse problem is dramatically underdetermined and needs to be supplemented by a priori information. The addition of relevant priors can be properly formulated with the mathematics of regularization, reviewed in the context of MEG and EEG (Baillet et al. 2001). The priors on the source image models may take multiple faces, e.g., in order to promote current distributions with spatial and temporal smoothness, or to penalize solutions with current amplitudes that are not physiologically plausible, or to fit with fMRI activation maps, or to prefer source image models made of piecewise homogeneous active regions, etc. Well-chosen priors may also guarantee the uniqueness of the optimal solution to the imaging inverse problem. Overall, weighted minimum-norm image models are the most popular in the field: they are relatively robust to noise and head model approximations, generate centimeter resolution

images, and are fast to compute. Note that the selection of a particular set of image priors is quite subjective. However, methods have emerged to approach model selection in an in-principle manner (Daunizeau et al. 2006).

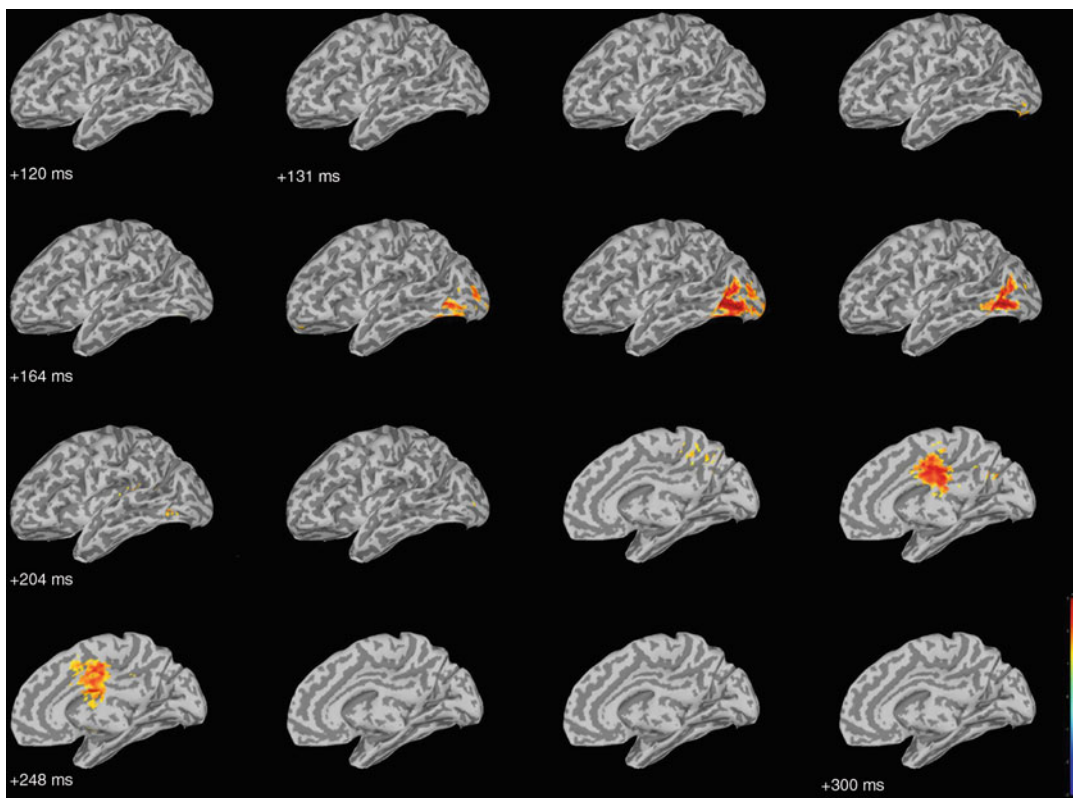
Appraisal of MEG/EEG Source Models

Modeling implies dealing with uncertainty, and MEG/EEG forward and inverse modeling has uncertainty everywhere: data are complex and contaminated with various nuisances, source models are simplistic, and head models are obtained from approximated geometries and conductivity properties. The determination of error bounds and confidence intervals on the estimated parameter values is an important issue, which has been researched with either parametric methods (Mosher et al. 1993) or nonparametric resampling techniques (Baryshnikov et al. 2004; Darvas et al. 2005).

Statistical inference and hypothesis testing are other important aspects of the appraisal of MEG and EEG source models; they directly address the neuroscience question that has motivated data acquisition and the experimental design (Guilford and Fruchter 1978). In the context of MEG/EEG, the population samples supporting inference are either trials or subjects, for hypothesis testing at the individual and group levels, respectively. Here too, parametric (Kiebel et al. 2005) and nonparametric (Nichols and Holmes 2002; Pantazis et al. 2005) approaches to statistical inference have been proposed, with the important concern of multiple-hypothesis testing (e.g., at thousands of source locations) kept under control (Fig. 3).

Conclusion

The convergence of forward and inverse modeling techniques with statistical inference solutions has brought electromagnetic source imaging to a considerable degree of maturity that is comparable to other neuroimaging techniques (Lopes da Silva 2013). The practical impact of methods for MEG/EEG data analysis has been considerably multiplied by the emergence of major commercial



Forward and Inverse Problems of MEG/EEG, Fig. 3 MEG source imaging of the response to the presentation of a visual target in a rapid serial visual presentation paradigm. The images show a slightly smoothed version of one participant's cortical surface. Colors encode the contrast of MEG source amplitudes between responses

to target versus control faces. Salient visual responses are detected in the target condition by 120 ms and rapidly propagate anteriorly. By 250 ms and thereafter, strong posterior cingulate responses are detected. The latter are the main contributors of the brain response to target presentation

and academic software applications (Baillet et al. 2011).

The complexity in the data obtained with MEG/EEG source analysis is a direct reflection of the intricate brain dynamics that unfold over multiple spatial and temporal scales. For this reason, MEG and EEG imaging has become a truly unique neuroimaging technique for revealing the fundamental large-scale mechanisms that underlie brain functions and dysfunctions.

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Forward Kolmogorov Equation

- [Fokker-Planck Equation](#)

Forward-Generative Models of Functional Neuroimaging Data

- [Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism](#)

Frequency Facilitation

- [Facilitation, Biophysical Models](#)

Frequency Tuning Curves

- [Spectrotemporal Receptive Fields](#)

Functional Magnetic Resonance Imaging (fMRI), Neural Population Models of

- [Neuroimaging, Neural Population Models for](#)

Functional Network Observations of Diseased Brain States

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Definition

A functional network represents the measured associations between activities recorded from separate brain regions. Many diseases may alter, or be caused by, changes in brain functional connectivity.

Detailed Description

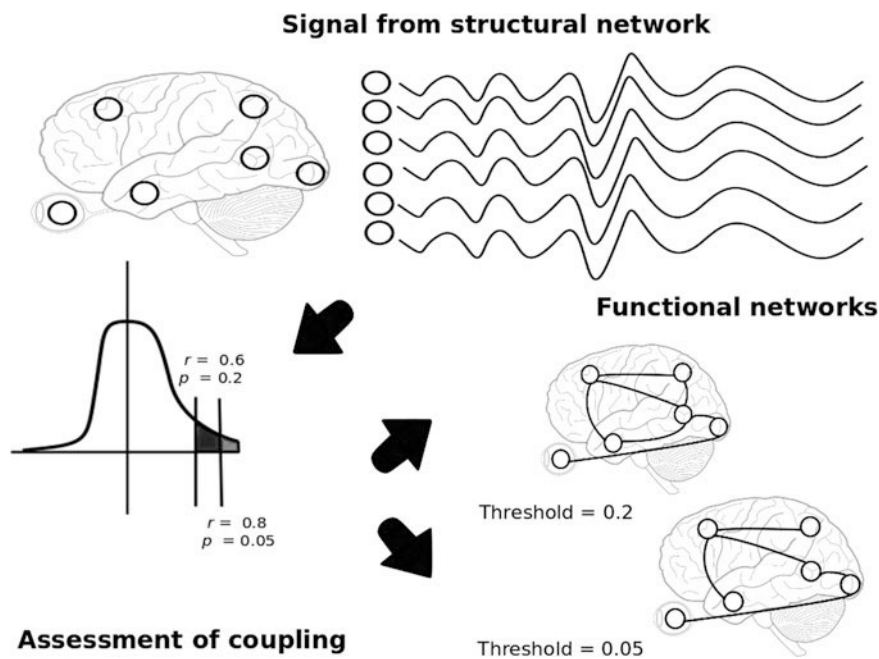
An increasingly popular approach in computational neuroscience has been to conceptualize neural networks as mathematical graphs (i.e., collections of nodes and edges) with nodes representing spatially localized brain regions. Such networks typically fall into two categories: structural networks, in which an edge corresponds to a well-defined anatomical feature, such as a synapse or axon bundle, and functional networks, in which an edge corresponds to a statistical association between measured signals recorded at each node. Functional and structural networks are interdependent – functional networks represent dynamically active subsets evolving on an underlying structural network. Experimental and simulated lesions (i.e., node removals) demonstrate that structural connectivity at a removed site is highly predictive of the extent of functional disruption (Sporns 2010).

The inference of a functional network from time-series data requires a number of choices

(see Fig. 1). These include the following: (1) **Choice of a signal that reflects meaningful neural activity at each node.** Many imaging modalities in neuroscience exist, such as the electroencephalogram (EEG), magnetoencephalogram, functional magnetic resonance imaging (fMRI), and positron emission tomography. (2) **Choice of a coupling statistic to assess associations between the collected activities.** These statistics include linear measures of association (such as the cross-correlation or coherence), generalized linear models, and nonlinear measures. (3) **Choice of a threshold in the coupling statistic.** A high threshold leads to fewer connections as well as fewer false detections.

Functional networks are typically understood in terms of their connectivity, which is quantified by graph measures (see Table 1). For instance, a small-world network is defined by the presence of local interconnectivity between nodes together with a few long-distance connections or “shortcuts” through the network (Watts 2004). These properties are captured by (1) a high degree of clustering (i.e., an abundance of local connections) and (2) a small average path length due to the existence of shortcuts. Such a network is of particular interest in neuroscience, where it has been suggested that the mammalian brain – a hierarchy of parallel local circuits – adheres to a small-world architecture (Sporns 2010). Nested within these choices are other subtle issues such as experimental design, signal processing (e.g., smoothing, artifact removal), and identification of epochs of interest.

A recent development is the use of network-theoretic approaches to study complex neuropathologies such as epilepsy, Alzheimer’s disease (AD), schizophrenia, and autism (Sporns 2010). In each case, neurobiological substrates have been hypothesized, but the bridge between microscopic mechanisms and macroscopic dysfunction manifest in brain signals remains unclear. The goal is to illuminate the issue by relating structural and functional networks. These efforts are only just beginning, but network measures appear to be reliable indicators of disease in a handful of cases. For example, it has been shown that small-world network metrics are significantly



Functional Network Observations of Diseased Brain States, Fig. 1 Illustration of the progression from structural network to functional network. This procedure relies on collecting representative signal from each region of interest (*top*) and identifying significant coupling through

a statistical hypothesis test (*bottom left*). The result is a functional network (*bottom right*). Note that different hypothesis tests (due, e.g., to different choices of threshold) lead to different networks

Functional Network Observations of Diseased Brain States, Table 1 A summary of five connectivity measures commonly associated with graph elements. By taking

averages, one can also compute characteristic measures for an entire graph

Measure	Defined on	Definition	Comments
Degree	Nodes	Number of incident edges	Highly predictive of several other measures.
Clustering coefficient	Nodes	Actual connections among directly adjacent nodes / Potential connections	Relatively large in ‘small-world’ network
Path length	Node pairs	Length of shortest path between two nodes; undefined if nodes are not connected	Relatively short in ‘small-world’ network
Betweenness centrality	Nodes	Fraction of times a node appears in the set of shortest paths	Can be defined similarly on edges
Motif frequency	Sup-graphs	Number of times a particular subgraph (motif) appears	Allows the analyst to identify and focus upon specific patterns of interest

different when generated from fMRI and MEG data recorded from patients with AD and that these features correlate with mini-mental status test scores. The AD network has a larger clustering coefficient (implying abnormally high local efficiency) and longer path length (implying

decreased global efficiency) compared to the healthy network (Bianchi et al. 2010). Another potential use of network analysis is to identify the seizure onset zone (SOZ) in patients with partial epilepsy. It has been suggested that during seizure, patterns of functional coupling change

more drastically within the SOZ than outside it (Kolaczyk 2009). Furthermore, a consistent observation across AD, schizophrenia, and autism is functional network differences in frontotemporal areas – especially the posterior cingulate cortex and frontal midline. In most cases, coupling is reduced, consistent with the deficits in working memory, attention, and executive function observed in each disease. The same diminished functional coupling may also be a feature of attention deficit and hyperactivity disorder (ADHD). Additionally, a significant increase in functional coupling in frontotemporal areas has been reported in schizophrenia patients as well as their relatives, suggesting a possible genetic basis. This increase has been interpreted as a deactivation failure of the task-negative (i.e., “daydreaming”) network, perhaps offering a broad link between biology and behavior. Nevertheless, significant work remains to be done.

Conclusions

Brain imaging studies generate increasingly large data sets. Indeed, simultaneous recording paradigms now incorporate multiple spatial scales (e.g., single-cell/LFP/ECOG) and multiple modalities (e.g., EEG/fMRI). Network theory – a rich, graph-based language for describing complex systems – offers a promising avenue for analyzing complicated statistical relationships in these data sets.

Cross-References

- [Determining Network Structure from Data: Nonlinear Modeling Methods](#)
- [Network Theory in Neuroscience](#)

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Functional Neuroscience: Cortical Control of Limb Prostheses

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Synonyms

[Brain-computer interfaces](#); [Brain-machine interfaces](#); [Neuroprostheses](#)

Definition

Cortical control of limb prostheses is a specific type of brain-machine interface (BMI) used to provide motor functions similar to those performed by the upper limbs, such as reaching and grasping. BMIs (also called brain-computer interfaces or BCIs) use neural activity to control external devices. Cortical control of limb prostheses is intended to restore motor function to patients with motor disabilities by allowing the activity of intact brain areas to control the movements of a new actuator.

Detailed Description

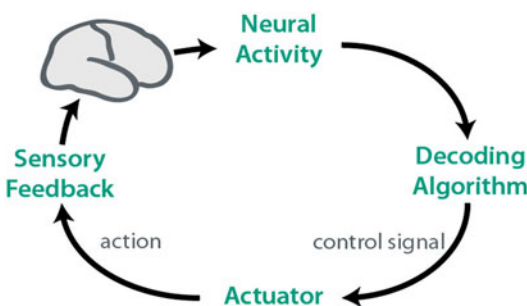
BMIs use neural activity from the brain to control external devices (see Fig. 1). This diverse tool has many potential applications. One of the most promising is for the recovery of motor function, where neural activity recorded from intact areas of the central nervous system could be used to restore function to patients with motor disabilities. BMIs could be used to restore motor function for patients with complete paralysis (e.g., due to spinal cord injury or amyotrophic lateral sclerosis), provide control for new end-effectors (e.g., for amputees), or facilitate motor rehabilitation for patients with severe damage to the motor system (e.g., due to stroke). Here, we focus on BMI applications for controlling limb prostheses, where the goal is to restore reaching and/or grasping functions naturally performed by the upper limb.

Cortical neuroprostheses show great potential for motor restoration, with many successful demonstrations of animals and human subjects controlling devices ranging from computer cursors to robotic arms with neural activity (Lebedev and Nicolelis 2006; Schwartz et al. 2006; Schalk and Leuthardt 2011; Wolpaw and Wolpaw 2012; Bensmaia and Miller 2014). Each successive demonstration has improved significantly, both in the provided control accuracy and complexity (e.g., number of degrees of freedom (DOFs) controlled). However, many challenges remain before such devices will be clinically viable solutions for

patients (del R Milan and Carmena 2010; Gilja et al. 2011; Lu et al. 2012). These include improving the movement control provided by BMIs, developing ways to include sensory feedback of movement (i.e., tactile and proprioceptive sensation), and improving neural recording technologies to be practical and safe for real-world settings. Research in each of these interrelated areas is ongoing.

There are many potential implementations of limb cortical prostheses. The key system components are: (1) a method to acquire neural signals, (2) an algorithm to translate neural activity into a control signal (often called a “decoder”), (3) a controlled actuator, and (4) mechanisms to provide feedback to the user. These components, together, create a full BMI system, as illustrated in Fig. 1.

By providing the user with feedback, BMIs create a “closed-loop” control system. This allows the user to move the actuator as desired to accomplish movement goals, much as we naturally move our limbs. Early approaches to BMIs aimed to develop BMI systems that could mimic the natural motor system. For instance, much attention has been directed toward creating decoding algorithms capable of predicting limb movements from neural activity for BMI applications (Jackson and Fetz 2011). However, the presence of feedback in closed-loop contributes significantly to BMI performance via biofeedback mechanisms (Wolpaw et al. 2002; Wolpaw 2007; Fetz 2007; Jackson and Fetz 2011; Green and Kalaska 2011). That is, subjects can volitionally control neural activity to achieve desired actuator movements. Similarly, there are many differences between current BMIs and the natural motor system, which may cause differences in evoked neural activity during natural limb motion and BMI control (Orsborn and Carmena 2013; Golub et al. 2016; Orsborn and Pesaran 2017). Thus, more recent approaches to BMI development focus on designing BMI systems that can be readily controlled in closed-loop, rather than explicitly mimicking the natural neural control of limb movements. For instance, mechanisms such as neural plasticity and/or adaptive algorithms that learn user strategies are being heavily explored



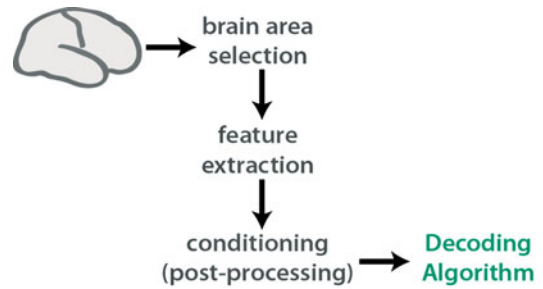
Functional Neuroscience: Cortical Control of Limb Prostheses, Fig. 1 Closed-loop BMIs use neural activity to control movement actuators. The presence of sensory feedback to the user creates a closed-loop control system

(Green and Kalaska 2011; Jackson and Fetz 2011; Wolpaw and Wolpaw 2012).

There are a variety of ways to construct a BMI, with variations on the four primary components and the system architecture. Systems have been developed with a wide range of neural signals, decoding algorithms, controlled devices, and forms of user feedback. What's more, there are many different ways to facilitate the control. For instance, neural activity can control movement kinematics directly (e.g., predicting the actuator's position or velocity), or be used to specify a general class of movement (e.g., moving right versus left). The design choices of a BMI system will ultimately influence its performance and path toward clinical translation. Below, we survey the different methodologies used for upper-limb BMIs, discussing key aspects of each BMI system component. Due to the vast variety of approaches in the field, we particularly emphasize methods based on intracortically-recorded neural activity. Methods primarily used in noninvasive BMI systems are discussed briefly with references to additional information.

Recorded Neural Activity

BMIs require a signal from the brain to facilitate actuator control. Obtaining these signals requires several design choices, including: (1) the method used to obtain the signals, (2) the brain regions selected for control, and (3) determining how to analyze the recorded signals. There are a variety of different methods to obtain neural signals, which capture different aspects of neural activity at different spatial and temporal scales. There are also a variety of brain regions that might be useful for BMI applications. Once the type and source of neural signals are chosen, these signals must be interpreted. That is, features thought to be informative about neural states must be extracted from the raw recorded signal. Note that this processing is separate from "decoding" control signals. The steps inherent in obtaining a neural signal from the brain are illustrated in Fig. 2. Below, we briefly survey commonly used recording methods, the features most commonly analyzed from these



Functional Neuroscience: Cortical Control of Limb Prostheses, Fig. 2 The processing required for obtaining neural signals from the brain. For a given recording method, neural signals require (1) selecting brain regions to record from, (2) extracting meaningful features from the signals, and (3) any additional necessary processing on the signals. These signals are then input into the BMI decoder for translation to a control signal

recording methods, and brain regions frequently used for BMI control.

Recording Methods

There are a variety of neural recording methods, each with advantages and disadvantages. Important considerations for BMI applications include: (1) the ability to reliably extract a control signal for movement, (2) spatial resolution, (3) temporal resolution, (4) the invasiveness, and (5) longevity of the signal for long-term prosthesis use.

Obtaining a signal with sufficient information to provide reliable control signals for the actuator is essential for BMI applications. Neural activity from motor-related brain areas, which modulate activity during executed or imagined movements, are commonly used. However, the signals do not explicitly have to be related to natural movement as long as the user can reliably modulate them to control the actuator (see below for discussion of signal source selection). The signals' spatial and temporal resolution are related to their information-content. Recording methods with low spatial resolution limit the number of independent signals that can be recorded from the brain, which in turn shapes the number of control signals that can be obtained to move the actuator. For example, a recording method that yields a single neural feature can only be used to control a prosthesis with one DOF. Similarly, the temporal resolution of a signal limits how frequently

control signals are obtained, shaping the time-scale of the BMI system. The spatial and temporal resolution of the neural recording method may also be related to a subject’s ability to directly control the neural signal. For instance, subjects controlling BMIs operated with low-spatial resolution neural signals like electroencephalography (EEG) often report mental fatigue. There is also a wide range of subject ability in reliably modulating EEG signals (Allison and Neuper 2010). However, the relationship between neural signal properties and user control is still an open question under significant investigation.

The other key considerations for neural signal selection relate to the translating cortical prostheses to clinical applications in humans. The degree of invasiveness – whether surgery is required, and the degree of medical risk associated with the procedures – is a key concern. Moreover, human patients will require neuroprostheses that function throughout their lifetime, making it essential to be able to record viable signals long term (years to decades). Existing invasive methods, such as intracortical implanted electrode arrays, often show signal decay over time in part due to physiological reactions to the implant (Schwartz et al. 2006; Otto et al. 2012).

Table 1 surveys electrical recording methods commonly used for BMI and their invasiveness, longevity, and spatial resolution. Extensive discussion of signal selection for cortical prostheses applications can be found in Andersen et al. (2004), Schwartz et al. (2006), Otto et al. (2012), and Wolpaw and Wolpaw (2012). Discussion of nonelectrophysiological methods and their properties can also be found in Ramsey (2012) and Srinivasan (2012).

Common Signal Types and Feature Extraction

Each recording method produces varied types of neural signals. How these signals are treated and analyzed varies significantly across methods. Here, we briefly discuss the types of signals commonly used for BMI applications. We focus on electrophysiological recording methods, as these are the most commonly used approaches in BMI. However, magnetic signals like magnetoencephalography (MEG) or metabolic neural signals such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) may also be useful for BMI applications. These methods and their applications in BMI have been reviewed in Ramsey (2012), Srinivasan (2012), and Sitaram et al. (2012).

Similarly, many BMIs use signal conditioning or “preprocessing” methods to transform neural features into more advantageous signals for decoding. For instance, dimensionality-reduction techniques can be used on neural ensemble data prior to decoding (Krusienski et al. 2012). We focus primarily on feature extraction itself, and refer the reader to Bashashati et al. (2007), and Krusienski et al. (2011, 2012) for thorough discussion and review of preprocessing methods and issues.

Action-Potentials

Action-potentials of neurons are one type of signal recorded from intracortical electrodes. Because action potentials (or spikes) are “all or nothing” events, these signals are binary. Information is conveyed by the times of action potentials, commonly called a spike-train. The most commonly used feature of spike trains is the firing rate. This captures the frequency of spikes. The firing rate of a neuron at a given time can be

Functional Neuroscience: Cortical Control of Limb Prostheses, Table 1 Electrical recording methods and signals, their spatial scale, and invasiveness. Data is summarized from Schwartz et al. (2006) and Nunez (2012). Abbreviations: EEG electroencephalography, ECoG electrocorticography

Method	Signal type	Scale (mm)	Invasiveness
EEG	Scalp potential	>10	Noninvasive
ECoG	Cortical potential	0.1–10	
Intracortical electrode	Local field potential	0.1–1	Invasive
	Action potentials	0.1	

estimated by counting the number of spikes occurring in a small window ΔT . This is commonly referred to as “binning,” and ΔT represents the bin width (Dayan and Abbott 2001; Krusienski et al. 2012). Firing rate, however, ignores additional information that may be contained in the precise timing of a neuron’s action potentials. Methods to extract information about spike timing have also been employed in BMI applications. For example, point-process models attempt to model a neuron’s temporal firing properties (Dayan and Abbott 2001; Brown et al. 2004; Krusienski et al. 2012).

Action potential signals can be recorded from several different sources. An individual intracortical electrode typically records the activity of a small population of nearby neurons. Electrophysiology techniques and spike-sorting algorithms can be used to isolate the spiking of individual neurons from these signals (Miller and Hatsopoulos 2012). Alternately, the activity of several neurons might be combined together into so-called “multi-unit” activity. Both single- and multiunit neural activity has been used in BMI applications.

Field Potentials

Field potential signals represent the electric fields produced by brain activity. They can be measured at several different scales with various recording methods (Nunez 2012). Intracortical electrodes record microscale potentials called local field potentials (LFP). Electrocorticography (ECoG) methods record mesoscale potentials. And EEG can be used to record macroscale fields. One key difference between each of these methods (and scales of field potentials) is the volume of neural activity contributing to the recorded field potential. LFP signals are thought to reflect local synaptic activity near the recording electrode, while EEG signals reflect aggregate activity of large areas of cortex (on the order of 10 mm) (Schwartz et al. 2006; Nunez 2012).

While the underlying source of these signals varies across recording methods, the signal itself is fundamentally the same. It is a continuous-valued, time-varying voltage signal. There are several different types of features commonly

analyzed in field potential signals. Typically, the signals are analyzed in the time or frequency domain (Krusiensi et al. 2012). Temporal features refer to the voltage amplitude over time. Frequency-based features, instead, analyze the spectral information contained within the field potential. Field potential signals commonly show amplitude- and frequency-modulated oscillations that are thought to be informative of neural processes. Thus, the amplitude and/or phase of field potential signals in different frequency ranges can provide useful features for BMI. There are many different methods for estimating spectral components, which are reviewed in Krusienski et al. (2011, 2012). Both temporal and spectral field-potential features must be estimated over time. As with action potential signals, this is typically accomplished by “binning” the signal into small intervals of time. For spectral features, however, this is particularly challenging since the ability to estimate a signal’s spectral components is heavily dependent on the bin sized used (Hayes 1996).

Brain Regions

Another important consideration in BMI applications is what brain region(s) are used for control. Cortical neuroprostheses for reaching and grasping have primarily targeted motor cortical areas. Lower spatial-resolution methods like EEG typically use electrodes centered over motor and sensory areas. Intracortical prostheses commonly implant electrodes in the primary and premotor cortices in areas related to hand and/or arm movement. Many cortical areas are involved with movement, and show a variety of different relationships to movement, which are still under investigation (Riehle and Vaadia 2005; Miller and Hatsopoulos 2012). Pre-motor, supplementary motor, and parietal areas generally show stronger relationships to planned movement goals, rather than executed movements that are represented strongly in primary motor cortices. The types of motor representations and reference frames of movement planning (e.g., planning in visual versus body-centric coordinates) are also thought to differ across areas (Andersen et al. 2010). As such, the neural areas implanted will

influence control. Brain regions may be better suited to different types of BMI architectures or decoders. For example, goal-based signals might be most useful for discrete-movement decoding (Andersen et al. 2010). Intracortical activity from many different motor areas has been used for BMI applications. Additional research is needed to understand if and how BMI control is influenced by brain region. It may also be possible to combine neural activity from multiple brain areas and of different types, though this remains to be carefully investigated.

While the majority of research targets motor areas, BMIs can be controlled with any neural signal. Nonmotor-related BMI systems have been implemented using a variety of brain areas, based on the principles of biofeedback (Fetz 2007).

Controlled Devices (Actuators) and Forms of Control

Neural signals can be used to control a variety of different actuators and with a range of different control schemes. To-date, BMIs have been implemented to control virtual objects like computer cursors, anthropomorphic robots, mobility-based robots, and the user's native limbs via muscle stimulation. Each of these actuators has different potential utility. The properties of the actuator will also influence the complexity of control and the most suitable control algorithms. Movements are described by both kinematic and dynamic properties of the actuator. The movement variables directly controlled by cortical input can be varied. For instance, the neural signal can be used to specify the actuator's position or velocity, or both. Moreover, the coordinate system of control must be considered. Actuators with multiple DOFs, like an anthropomorphic limb-like robot, can be controlled by the end-point or via individual joints (Schwartz et al. 2006). Below, we survey actuators and types of control that have been used in BMI.

Control of virtual objects may be useful for allowing paralyzed individuals to interact with computers. This is of particular interest for

patients with severe paralysis such as tetraplegia (paralysis of all limbs and torso). Virtual cursors also have simplified dynamics compared to real-world actuators that interact with objects within the environment. As such, many preliminary demonstrations of BMI have focused on cursor control. These systems typically use kinematic control implemented in Cartesian space. For example, neural activity is commonly used to control the velocity or position of a cursor moving in two dimensions on a computer screen.

More recent research has focused on cortical control of real-world devices. These systems may have more wide-ranging uses for paralyzed individuals, as they would allow them to interact with the real-world to perform tasks of daily living. Neural activity has been used to control mobility-based robots, like wheelchairs (del R Milan and Carmena 2010). Anthropomorphic robots – robotics with similar appearance and function to human arms – have also been used for BMI (Hochberg et al. 2012; Collinger et al. 2012; Wodlinger et al. 2015). Cortical activity can alternatively be used to drive movements of the user's own body. Functional electrical stimulation (FES) uses electrical stimulation of motor nerves to elicit contractions of muscles, and can be used to evoke movements in paralyzed individuals (Peckham and Knutson 2005). Recent work has investigated using cortical activity to control FES stimulation (Moritz et al. 2008; Ethier et al. 2012). The goal of this approach is to restore natural motor function to paralyzed individuals. This method has been successfully demonstrated in paralyzed animal models.

Robotic and FES-based systems can significantly increase the control complexity of the BMI. First, they typically include many more DOFs than virtual systems. For instance, robots incorporating a shoulder, elbow, wrist, and basic hand grasping include seven DOFs. Incorporating more complex hand movements further expands the number of DOFs. FES systems for upper-limb movement restoration commonly target a minimum of eight muscles (Peckham and Knutson 2005), and more may be necessary for more refined motor control. It is currently unclear if existing BMI approaches will scale as the number

of controlled variables increases. Furthermore, these real-world systems have more complex dynamic properties than cursors which may influence control. For example, biological factors such as muscle fatigue change the relationship between muscle stimulation and evoked movement over time (Peckham and Knutson 2005; Peckham and Kilgore 2013).

There are also many potential control variables in more complex systems. Neural activity can be used to directly set the muscle activations or robot joint movements. Such a scheme allows for the most flexible control, as the user can directly influence all aspects of movement, at the cost of system complexity. Alternative control schemes can be developed to reduce the system complexity. Neural activity could specify kinematic or dynamic parameters of movement in a simplified coordinate system, and algorithms translate these commands into actuations of muscles/joints. For instance, a user could control the end-point position of a robotic limb, and each individual joint position is determined algorithmically. Such methods require assumptions about basic movement properties due to the redundancy in the system (Schwartz et al. 2006; Ting et al. 2012). That is, there are several possible joint configurations that lead to the same end-point position. Hence, these methods constrain the BMI's movement repertoire. Similarly, it may be possible to use "shared-control" where neural activity and automated controls are combined (del R Milan and Carmena 2010). These methods may simplify control of more complex systems, though little work has been done to understand if and how the actuator's properties and control schemes influence closed-loop control.

Decoding Algorithms

Many different decoding algorithms have been used for BMI. The decoding algorithm maps recorded neural activity into a control signal for the actuator. As discussed above, the types of neural and control signals used can be varied. Similarly, the structure of the decoding algorithm is an important design consideration for

developing cortical prostheses. The BMI system architecture – particularly the controlled actuator and neural signal properties – will shape the type of algorithms used.

BMI algorithms can be grouped into several different classes: continuous variable versus discrete movement prediction, generative versus discriminative approaches, and linear versus nonlinear methods. Continuous variable prediction uses neural activity to estimate a continuous-valued movement variable (e.g., end-point velocity), while discrete movement prediction maps neural activity to one of a limited set of movement options (e.g., one of eight target positions). Generative (or inference-based) methods aim to model the relationship between neural activity and movement parameters, which then allows for prediction. Discriminative methods, instead, establish relationships between observed neural activity and movement parameters without learning an underlying model. That is, they perform pattern recognition. Discriminative algorithms, then, are most commonly used for discrete predictions where a limited number of patterns must be learned. Finally, linear decoders use a mapping between neural activity and movement parameters that is linear, while nonlinear decoders use nonlinear mappings.

Below, we overview commonly used classes of algorithms, focusing primarily on continuous-valued prediction methods that are most commonly used in intracortical-BMI applications. The space of algorithms used to predict movement from neural activity is large, and thus we focus primarily on algorithms that have been successfully used in closed-loop BMI applications. Many more algorithms have been explored for open-loop predictions of movement. We also focus on methods for decoding neural signals, independent of their form. Types of signals, features extracted from them, and preprocessing are discussed briefly in section "Recorded Neural Activity." This should not be considered an exhaustive list. Reviews surveying BMI decoding and preprocessing approaches can be found in Schwartz et al. (2001, 2006), Schwartz (2004), Bashashati et al. (2007), Lotte et al. (2007), and McFarland and Krusienski (2012).

Commonly Used Continuous Algorithms

Continuous BMI decoding algorithms translate neural activity into a continuous movement control variable, such as position or velocity.

Direct Mapping

One simple decoding algorithm is to directly use the neural signal, or a linear scaling thereof, for the control signal (see, for instance, Fetz 2007). An example is using the EEG power in two different frequency bands to control the horizontal and vertical velocities of a cursor moving on a screen. Mathematically, these transforms can be described as

$$Y = aX + b$$

where Y and X are the control and neural signals, respectively, and a and b are scaling factors. This basic approach can also use a scaled version of summed neural signals. For instance, the mean firing rate of a small population of neurons can be used as a control signal. While this class of decoders is generative (because it assumes a model for neural activity's relationship to movement), these decoders often do not directly attempt to mimic how neural activity relates to movement in the natural motor system. That is, they are typically not trained using neural and movement data. Instead, parameters are most often specified by the experimenter, imposing a potentially artificial relationship between neural activity and movement.

Population-Vector and Optimal-Linear Estimators

Neurophysiology research in motor cortex revealed that neural activity (particularly single- and multiunit activity in the motor cortices) exhibits cosine tuning to movement parameters such as end-point position and velocity (Miller and Hatsopoulos 2012). That is, a given unit's activity f can be modeled as:

$$f = b_0 + m(\vec{p} \cdot \vec{d})$$

where $\vec{d}$ is movement direction vector, $\vec{p}$ is a cell's preferred direction, b_0 is the baseline

activity, m is the unit's modulation depth. Different neural signals can have different modulation depth, preferred direction, and baseline parameters.

The population-vector algorithm (PVA) and related variants fit cosine tuning models to units, and sum the units' activity weighted by their respective preferred directions to decode movement. Mathematically, the population vector algorithm can be described as:

$$\vec{D} = \sum_{i=1}^N r_i \vec{p}_i = \sum_{i=1}^N \left(\frac{f_i - b_{o,i}}{m_i} \right) \vec{p}_i$$

where $\vec{D}$ is the decoded movement vector, r_i and $\vec{p}_i$ are the normalized-activity and preferred direction of unit i (respectively), and N is the total number of units used for decoding. Normalized activity r_i represents the unit's modulation relative to its baseline activity, scaled by its modulation. The PVA can thus be viewed as giving each unit a "vote" in the resulting movement direction, which is scaled by its modulation. This algorithm has been used to decode a variety of different movement signals, including position, or velocity, and in joint or Cartesian coordinate frames (Dayan and Abbott 2001; Schwartz et al. 2001; Miller and Hatsopoulos 2012; Krusienski et al. 2012).

Training a PVA requires estimating the tuning parameters (b_0 , m , and $\vec{p}$) of each unit. Linear regression techniques can be used to estimate these parameters.

The PVA assumes a uniform distribution of preferred directions, which may not be true for small numbers of units. The optimal linear estimator (OLE) is a variant of the PVA that corrects for nonuniformities in the preferred direction. The OLE decoder has the same form as the PVA, but differs in how the preferred directions are estimated to correct for bias due to nonuniformity. Details can be found in Dayan and Abbott (2001), and Schwartz et al. (2001).

The PVA and OLE are generative decoders. Also note that these algorithms could be used to predict discrete movements (i.e., to one of a set number of targets), rather than continuous movement parameters.

Wiener Filter

The Wiener filter is a linear time-invariant filter (Hayes 1996). BMI applications typically use the discrete filter implementation. The discrete Wiener filter models movement properties $\mathbf{Y}(t)$ as a linear function of past neural activity $\mathbf{X}(t)$:

$$\mathbf{Y}(t) = \mathbf{b} + \sum_{i=-m}^n \mathbf{a}(i)\mathbf{X}(t-i) + \boldsymbol{\epsilon}(t)$$

$$\mathbf{Y} = \mathbf{X}\mathbf{A}$$

where $\mathbf{a}(i)$ are filtering constants at time-lag i , $\mathbf{b}$ is a vector of offsets, and $\boldsymbol{\epsilon}(t)$ is a noise term. The filter uses neural activity across time-lags $[-m, n]$. This can alternately be expressed in matrix form, where $\mathbf{X}$ is a matrix of neural activity where each column is a different unit and rows are time-lagged data and $\mathbf{A}$ is a matrix of the corresponding filter coefficients. Online BMI applications must be causal filters, using only data from the past to predict current/future events. However, open-loop off-line predictions can use noncausal filtering. Wiener filters use the temporal dynamics of neural activity in their predictions, which can be beneficial for increasing decoding power. It also makes these filtering approaches best suited to continuous variable prediction in real-time BMI applications. Wiener filters can be used to predict a variety of different movement variables, including kinematics or dynamics in joint or Cartesian space.

Training a Wiener filter requires setting the filtering constants (matrix $\mathbf{A}$). The coefficients that minimize least-squared error are given by

$$\mathbf{A} = \text{inv}(\mathbf{X}_{\text{train}}^T \mathbf{X}_{\text{train}}) \mathbf{X}_{\text{train}}^T \mathbf{Y}_{\text{train}}$$

where $\mathbf{X}_{\text{train}}$ and $\mathbf{Y}_{\text{train}}$ are vectors of neural and kinematic training data, respectively.

Kalman Filter

The Kalman filter is a linear filter that predicts the state of a system by modeling the state dynamics and their relationship to observed variables (Hayes 1996). In BMI applications, the Kalman filter is used to predict movement variables based on observed neural activity (Schwartz 2004). The

filter models the underlying dynamics of movement (i.e., given a particular end-point position at time t , what is the most likely end-point position at $t + 1$). It also models the relationship between measured neural activity and movement. The final filter estimate is a combination of estimates based on the dynamics model and neural activity measurements.

The KF assumes linear state evolution (1) and state observation models (2):

$$x_t = \mathbf{A}x_{t-1} + w_t$$

$$y_t = \mathbf{C}x_t + q_t$$

where x_t and y_t represent the movement variables and recorded neural activity at time t , respectively. $w_t \sim N(0, \mathbf{W})$ and $q_t \sim N(0, \mathbf{Q})$ are noise terms. The filter is thus specified by the matrices $\mathbf{A}$, $\mathbf{W}$, $\mathbf{C}$, and $\mathbf{Q}$, which are estimated using training data. Based on these models, the Kalman filter recursively estimates the current movement variables x_t based on both the past observed movements ($x_{t-1}, \dots, x_0$) and currently observed neural activity y_t . The recursive estimation scheme is as follows:

1. Estimate of movement variables based solely on state-evolution model (a priori estimate):

$$\hat{x}_{t|t-1} = \mathbf{A}x_{t-1}$$

2. Estimate the covariance (uncertainty) of the a priori estimate:

$$\mathbf{P}_{t|t-1} = \mathbf{A}\mathbf{P}_{t-1}\mathbf{A}^T + \mathbf{W}$$

3. Compute the expected neural activity corresponding to the a priori estimated movement, and the difference between the expected and observed neural activity (measurement residual):

$$\tilde{y}_t = y_t - \mathbf{C}\hat{x}_{t|t-1}$$

4. Compute the covariance (uncertainty) of this measurement residual:

$$\mathbf{S}_t = \mathbf{C}\mathbf{P}_{t|t-1}\mathbf{C}^T + \mathbf{Q}$$

5. Compute an estimate of kinematics incorporating the recorded neural activity (a posteriori estimate):

$$\begin{aligned}\hat{x}_t &= \hat{x}_{t|t-1} + \mathbf{K}\tilde{\mathbf{y}}_t \\ \mathbf{K} &= \mathbf{P}_{t|t-1}\mathbf{C}^T\mathbf{S}_t^{-1}\end{aligned}$$

6. Compute the covariance (uncertainty) of the a posteriori estimate:

$$\mathbf{P}_t = (\mathbf{I} - \mathbf{K}_t\mathbf{C})\mathbf{P}_{t|t-1}$$

Because the Kalman Filter is recursive, it is an infinite-length filter – that is, neural activity at a given time can influence all future predicted movements. By comparison, the length of the Wiener filter (i.e., the number of lags) is a design parameter and is typically set to be finite. The standard Kalman filter only analyzes the neural activity at the current time for prediction. However, n th order extensions to the KF can be used to incorporate time-lagged data as well (Haykin 2002). Because the Kalman filter is designed to incorporate temporal dynamics, it is best suited to continuous decoding.

Training a Kalman filter requires specifying the matrices $\mathbf{A}$, $\mathbf{W}$, $\mathbf{C}$, and $\mathbf{Q}$. These can be estimated using maximum-likelihood estimation methods, which create optimal filters in the least-squares sense. There are also alternative methods to fit filter matrices while constraining the temporal dynamics of the system. For instance, if predicting position and velocity movement variables, it may be desirable to design a Kalman filter that incorporates causal physics (i.e., position is the integral of velocity).

Other Nonlinear Algorithms

Linear algorithms, such as those presented above, are the most prevalent in real-time BMI applications, in part due to their computational simplicity. However, several different nonlinear algorithms have been applied to the problem of predicting movements from neural data. They are briefly summarized here. There are several possible ways to extend the above-described filters to

incorporate data nonlinearity. Nonlinear Kalman filters are a particular example (Haykin 2002). Direct mapping techniques can also use nonlinear functions to map a neural signal into the control signal. There have also been nonlinear Bayesian extensions of the Population Vector Algorithm proposed (Dayan and Abbott 2001; Schwartz 2004).

Similarly, there are many new statistical methods being developed to incorporate Bayesian and maximum likelihood estimation methods to BMI decoding (Dayan and Abbott 2001; Brown et al. 2004; Krusienski et al. 2012). Such models may benefit from incorporating, for instance, models of temporal firing of individual neurons (commonly called point-process models) and/or correlation structures across different neural signals.

Another interesting class of decoding algorithms is artificial neural networks (ANNs). ANNs are interconnected networks of artificial neurons, which can perform linear or nonlinear computations based on their inputs, and with varying connection architectures (Haykin 2009). These networks, thus, can be used to model a variety of data, including highly nonlinear and complex relationships. Feed-forward NNs have directed connections between units such that there are no “cycles” (i.e., starting at a given neuron and moving along its connections, there is no way to return to that neuron). These networks are most common, as they are typically the easiest to train. Recurrent NNs (which include cycles) can demonstrate much more complex and dynamic behaviors, and thus may also be particularly interesting for BMI applications. However, due to their computational complexity, they have only recently been used for closed-loop studies (Sussillo et al. 2012).

Finally, musculoskeletal and neuromechanical models have also been explored for BMI decoding (Kim et al. 2007; Heliot et al. 2010). Musculoskeletal model-based decoders create a biomechanical model of the limb, and use neural activity to drive movements of the model. For instance, neural activity could be used to control the virtual muscles. Neuromechanical models that model properties of the spinal cord (e.g.,

incorporating short-loop reflexes) may also be useful for BMI applications. Incorporating the biomechanical properties of the natural motor system into the decoder may provide beneficial control properties, though closed-loop studies fully exploring these algorithms remain to be done.

Commonly Used Discrete Algorithms

Discrete BMI decoding algorithms translate neural activity into a discrete movement control variable; for instance, decoding a leftward versus rightward movement or a movement to one of a list of candidate locations. Discrete approaches use classification algorithms, which define candidate movement classes (e.g., a list of possible reaching targets) and the neural activity associated with each class. The algorithm then determines the most suitable class based for newly observed neural activity.

There are a wide variety of classification schemes, many of which have been explored in BMI applications. Below, we briefly summarize classification methods in BMI. A thorough algorithm survey and discussion of their strengths and limitations can be found in Lotte et al. (2007), and McFarland and Krusienski (2012).

Linear, discriminative approaches like linear discriminant analysis (LDA) and support vector machines (SVM) are very popular. These methods define hyperplanes that divide data into classes, though they differ in how the hyperplanes are defined. Artificial Neural Networks (ANNs; see section “[Other Nonlinear Algorithms](#)”) can also be used for classification, and many different architectures have been explored in BMI. LDA, SVM, and ANNs are static classification methods, using the neural data from a single time-point for prediction. Dynamic classifiers, instead, use temporal dynamics of neural activity in classification. Hidden Markov models (HMMs) are one class of dynamic classifiers, which determine the likelihood of particular classes based on observed sequences of neural activity.

Each classification method has advantages and disadvantages. One key concern in classification is issues of dimensionality, because the amount of data needed to reliably train a decoder depends strongly on the number of classes being decoded.

Similarly, a decoder varies significantly in their sensitivity to data noise and variance. Recent efforts suggest that combining multiple classification schemes, each with different strengths and weaknesses, may be a particularly beneficial approach in BMI (Lotte et al. 2007).

Decoder Training

There are several possible ways to determine decoder parameters. Decoders are typically trained using supervised methods, where a set of recorded neural data and the corresponding movement variables are known. This training data can be collected as subjects make, observe, or imagine making movements. In clinical applications for individuals with motor disabilities, motor observation or imagery are the only options for collecting training data sets. Natural arm movements, however, may be used in BMI research with able-bodied animal or human subjects.

It is also possible to train many decoders in closed-loop settings. Many groups have developed methods to modify a decoder's parameters as a subject operates a BMI in closed-loop (reviewed in McFarland et al. (2011) and Dangi et al. (2013)). This approach typically uses methods from adaptive filtering. The goal is to dynamically modify the decoder parameters to increase performance over time. This can be achieved by examining a user's neural activity and the movements of the BMI during closed-loop control, and modifying the decoder based on this performance. Supervised approaches use knowledge of what the subject's intentions to correct decoding errors. Unsupervised methods, based on adaptive filtering methods to correct decoding biases, can also be used. Decoder adaptation has several possible uses, including training new decoding algorithms, increasing performance in closed loop, and combating nonstationarity of neural signals over time (Orsborn et al. 2014).

Methods for Providing User Feedback

Closed-loop BMI operation requires that the user have feedback about the actuator movement. This allows the user to perform goal-directed actions with the neuroprostheses. There are several

possible ways to provide this feedback. To date, the majority of BMIs have provided feedback using sensory pathways that are intact even in patients with motor disabilities. For instance, visual feedback of actuator movement can be used to guide movements. Intact pathways can also be used for sensory substitution, where a sensory pathway is used to “display” information different from the usual modality. For example, auditory feedback could be used to convey how much force an actuator is applying, substituting tactile feedback with audition (Schwartz et al. 2006).

Natural and substitutive sensory feedback, however, may have limitations as the complexity of the controlled actuator increases and the amount of feedback required for robust control expands. In natural reach and grasp, proprioceptive and tactile feedback is critical for dexterous movements (Sabes 2011). Incorporating rich somatosensory feedback, then, may be critical for creating viable clinical limb neuroprostheses (Lebedev and Nicolelis 2006; Schwartz et al. 2006; del R Milan and Carmena 2010).

An alternative or additional approach is sensory restoration, aiming to provide sensory information into the central nervous system directly. One promising method for sensory restoration is neural stimulation (Lebedev and Nicolelis 2006; Schwartz et al. 2006; Bensmaia and Miller 2014). Stimulation can be accomplished in a variety of ways. The most popular method for BMI sensory stimulation is intracortical microstimulation (ICMS), where action potentials are evoked from small populations of neurons by injecting small currents into neural tissue using intracortical electrodes. Stimulation of neural tissue has been shown to evoke sensory percepts in animals and humans. Moreover, recent work shows that these artificially-evoked sensory percepts can be combined with other natural sensory stimuli to perform motor- and BMI-control tasks (Venkatraman and Carmena 2011; O’Doherty et al. 2011; Dadarlat et al. 2015). However, these demonstrations are limited to relatively simple forms of feedback. How to convey the rich sensory feedback necessary to represent complex effectors is still unclear. Research into

sensory restoration is ongoing (Bensmaia and Miller 2014).

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Functional Vision

► [Prosthetic Vision, Assessment](#)

G

G Protein Linked Receptors

► [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

GABA-A Receptor Conductance Models

► [Gamma-Aminobutyric Acid Type-A \(GABA-A\) Receptors, Kinetic Models](#)

Gamma Rhythm, Neural Population Models of the

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Definition

The classical definition of gamma activity in the electro- and magnetoencephalogram (EEG/MEG) includes all high frequency (>30 Hz) oscillations of brain activity. One can further distinguish the “gamma rhythm” proper, meaning band-limited oscillations of 30–80 Hz with a typical frequency of about 40 Hz, from so-called high gamma

(80–200 Hz) broadband and other, even faster, activity. These high frequency rhythms have been scrutinized extensively, since they become prominent during cognitive tasks. In particular, they often appear to phase lock across distant brain sites, which has led to speculations about their role in integrating distributed neural activity. Neural population models (NPMs) have been used to address the genesis and function of gamma rhythmicity: On one hand, the underlying physiology and the dynamic mechanisms by which gamma activity emerges have been studied in detail. On the other hand, the cognitive aspect has been investigated with functional processing models, mostly for visual feature representation and pattern recognition. As the experimental focus is currently shifting towards high gamma, we can expect that future modeling with NPMs will follow suit.

Detailed Description

Among the classical frequency bands of the EEG/MEG, which also include delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz), “gamma” has been the label assigned to all rapid (>30 Hz) oscillations of electrocortical brain activity (Jasper and Andrews 1938). The amplitude of these oscillations in the EEG/MEG is typically small compared to the lower frequency rhythms. For the sake of

definiteness, often a gamma frequency of around 40 Hz has been discussed in the literature. However, the central frequency of this band-limited brain activity is quite variable in the range of 30–80 Hz, with a bandwidth of about 20 Hz (Muthukumaraswamy et al. 2010; Ray and Maunsell 2011; van Pelt et al. 2012).

A classification of related high frequency phenomena is currently emerging: Firstly, above 600 Hz the dominance of synaptic processes in the electrophysiological signal comes to an end. This “ultrafast activity” (>600 Hz) is related to synchronized bursts (Curio 2005; Hughes 2008) and indexes action potentials (Schroeder et al. 1998, 2001). “Fast activity” (200–600 Hz), like the fast ripples in hippocampus associated with epilepsy (Dzhala and Staley 2004), is likely of similar kind and could be created by multiplexing of synchronous neural firing at lower frequencies (Kohling and Staley 2011). Finally, a so-called “high gamma” band (80–200 Hz) has been identified, which shows very clear power augmentation in task-related brain regions (Brindley and Craggs 1972; Crone et al. 2011), as well as power suppression in the default mode network (Ossandon et al. 2011). It may be an even cleaner signal of cognitive activity than the classical gamma rhythm (Foster et al. 2012). There is, however, currently no agreement in the literature about real or convenient frequency limits between these classes of activities. Furthermore, muscle artifacts with their spectral bandwidth of about 20–300 Hz may compromise noninvasive studies of high frequency neural activity (Muthukumaraswamy 2013). EEG/MEG data hence need to be controlled carefully against potential electromyographic contamination.

A qualitative distinction between the conventional gamma rhythm and the high gamma activity can be made: The latter is not band limited but truly broadband, basically appearing across the entire frequency range without a clear center frequency. We have used 80 Hz above to separate the gamma rhythm from high gamma. However, one might record gamma rhythms with center frequencies of up to 100 Hz and conversely find high gamma broadband changes down to 50 Hz. Furthermore, these brain activities are not mutually

exclusive but can occur simultaneously. It has been suggested that broadband power augmentation actually extends all the way down into the low frequency bands but is in practice masked there by simultaneous narrowband power decreases induced by subcortical regions (Manning et al. 2009; Miller et al. 2007). A different possibility is that the broadband high gamma signal is really just the gamma rhythm observed at higher frequencies. According to this hypothesis spatially more compact neural groups generate higher frequencies (cf. Pfurtscheller and Cooper (1975)), and different such groups would operate at different central frequencies. The recorded signal would sample many such groups as a consequence of volume conduction through tissue, effectively integrating these band-limited processes into one broadband response (Crone and Hao 2002; Crone et al. 2011).

Gamma rhythms became a popular research topic through their apparent association with cognitive function in the cortex (Bressler and Freeman 1980; Galambos et al. 1981; Gray and Singer 1989; Spydell et al. 1979). The appearance of *synchrony* between gamma rhythms in separate parts of the brain has been a particular research focus both for experimental studies (Bressler et al. 1993; Fries et al. 2001, 2008; Gray et al. 1989; Pesaran et al. 2002; Rodriguez et al. 1999; Schoffelen et al. 2005; Tallon-Baudry et al. 1997; Varela et al. 2001) and for theoretical speculations (Engel et al. 1992, 2001; Fries 2005; Singer and Gray 1995; von der Malsburg and Schneider 1986). Additional experimental and theoretical contributions of Freeman and collaborators have been conveniently summarized in a series of papers (Freeman 2003a, b; Freeman et al. 2003; Freeman and Burke 2003; Freeman and Rogers 2003). Furthermore, several comprehensive reviews can be consulted for an overview (Başar 2013; Bastiaansen and Hagoort 2006; Fell and Axmacher 2011; Lee et al. 2003; Tallon-Baudry and Bertrand 1999; Whittington et al. 2000).

Gamma synchrony means that the activity at two different locations in the brain is *phase locked*, with the relative phase between the local gamma waves remaining constant. Initial reports even suggested *zero-lag synchrony*, i.e., in spite of

a physical separation, the relative phase appeared to be zero (Castelo-Branco et al. 1998; Frien et al. 1994; Gross et al. 2004; Rodriguez et al. 1999; Roelfsema et al. 1997). This has led to speculations about the presence of a neural “relay,” for example, thalamus, which could create the appearance of zero lag between two cortical sites (Gollo et al. 2010; Theyel et al. 2010; Vicente et al. 2008; Viriyopase et al. 2012). However, more recent experimental evidence shows non-zero lags (Gregoriou et al. 2009), and a recent review (Uhlhaas et al. 2009) suggests that previous zero-lag results were mostly due to measurements at short distances and experimental difficulties in detecting short lags (Havenith et al. 2009; König et al. 1995; Nikolic 2007; Schneider and Nikolic 2006).

The unique functions speculatively attributed to gamma activity – like binding distributed neural groups into a single task, coding information by using the phase as clock, or gating the communication between distinct neural groups through coherence (Engel et al. 2001; Fries 2005, 2009; Fries et al. 2007; Singer 1999; Uhlhaas et al. 2009; Womelsdorf et al. 2007) – may be an over-interpretation of available data. The variability of the gamma rhythm (Ray and Maunsell 2010), its apparent randomness (Xing et al. 2012), and its disruption through combining stimuli (Lima et al. 2010) could suggest that the gamma rhythm is a reflection of, rather than a means for, cognition. For example, it could reflect the balance of excitation and inhibition at a basic level of processing driven by attention (Brunel and Wang 2003; Niebur et al. 2002; Ray et al. 2013).

While functional interpretations remain rather speculative, the gamma rhythm certainly provides a unique window on brain physiology. Gamma activity is likely driven by, and hence provides experimental access to, networks of inhibitory interneurons (Bartos et al. 2007; Buzsáki and Chrobak 1995; Hasenstaub et al. 2005). There is also a clear correlation between task-related increases in gamma activity and augmentations of the functional magnetic resonance imaging signal (Lachaux et al. 2007; Logothetis et al. 2001; Mukamel et al. 2005; Niessing et al. 2005; Nir et al. 2007), unlike for lower frequency rhythms.

Finally, local field potentials (LFPs), which are the underlying source for the EEG signal, appear to be generated by neural populations at typical scales of around 0.3–0.5 mm when oscillating at gamma frequencies (Berens et al. 2008; Ray and Maunsell 2010). Thus, one can expect gamma activity to be a phenomenon that can be well described with NPMs.

A number of works have addressed gamma activity within the NPM framework. Early results by Zhadin (1984, 1994, 1996) identified a strengthening of gamma activity with cortical excitation and suggested a scaling of frequencies between species with the number of involved cortical cells. König and Schillen provided a comprehensive analysis how visual features can be represented by neural assemblies synchronizing and desynchronizing with gamma oscillations (König and Schillen 1991; König et al. 1992; Schillen and König 1991, 1994). Several other groups also achieved visual processing and pattern recognition using NPM activity compatible with gamma rhythmicity (Campbell and Wang 1996; Grannan et al. 1993; Grossberg and Somers 1991; Hirakura et al. 1996; Horn et al. 1991; Malsburg and Buhmann 1992; Schuster and Wagner 1990; Wang 1995; Yamaguchi and Shimizu 1994). While applications to the visual system are by far the most popular, Baird (1986) has modeled pattern recognition in the olfactory bulb similarly. Finally, Sabatini et al. (2004, 2005) used a continuum approach with an excitatory diffusive term to model visual association fields.

Based on an earlier cortical model (Wright and Liley 1995), Wright and colleagues modeled gamma activity arising from an increase in cortical activation in the presence of inhibitory feedback, as well as zero-lag synchrony supported by long-range excitatory couplings (Chapman et al. 2002; Wright 1997, 1999; Wright et al. 2000). These simulations reproduced qualitatively the results of visual experiments made with moving bars. Cortical synchrony did not require nonlinear gamma activity, but spatially segregated phase patterns could be locked together by triggering it through increasing excitation. Wright (2009, 2011) has consolidated this approach with further parametric studies. In partly overlapping work,

Robinson and collaborators (Robinson et al. 1998, 2001; Wright et al. 2001, 2003) on one hand found that the introduction of reversal potentials led to the appearance of robust gamma resonances (Rennie et al. 2000). On the other hand also improved cortico-cortical activity propagation could lead to spectral enhancements in the gamma range in their model, if the system was marginally stable (Robinson 2005, 2006).

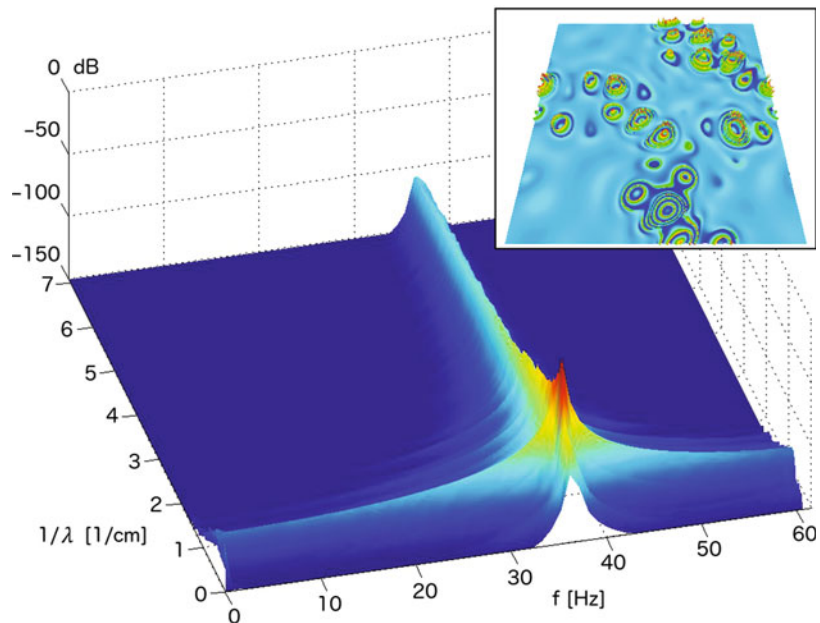
The emergence of spatiotemporal patterns in gamma frequencies, including rotating spiral waves and chaos, was studied by Destexhe (1994). Complex activity arose in spite of an isotropic and homogeneous model structure. Large network size, as well as nonzero conduction delays and sufficiently strong connectivity, was crucial for obtaining these responses. Bojak and Liley (2007) showed that bifurcations from regular alpha oscillations could create localized gamma “hot spots” within about 150 ms, which were furthermore phase-locked with each other; see Fig. 1. It should be noted that their model included reversal potentials (Liley et al. 2002) and that eliciting gamma responses required only relatively minor increases to excitatory thalamic input, compatible with the fact that only 5–10% of all axon terminals in the cortex are thalamic

(Peters 2002). Finally, the model of Steyn-Ross et al. (2009) also needed rapid feedback through reversal potentials to create phase-locking gamma instabilities. They showed that diffusive dynamics due to inhibitory gap junctions increases the spatial extent of such gamma “hot spots.”

It is generally believed that any physiologically accurate model of cognition will have to explain the concurrent appearance of gamma rhythms and related high frequency phenomena in the brain. However, there is a danger in overcommitting to the current state of experimental investigations. Zero-lag synchrony at a distance, once considered to be a crucial feature of gamma rhythmicity, now appears to be mostly an artifact of special circumstances and measurement limitations. Current experimental studies also favor the role of broadband high gamma over the band-limited gamma rhythm for tracking cognitive states. In the face of such changes, it seems prudent for modelers to clarify the physiological mechanisms and relationships of these various high frequency phenomena in the brain first. Nevertheless, the association with cognition makes gamma activity a particularly attractive research field and a testing ground for novel, and potentially far reaching, speculations about the human mind.

Gamma Rhythm, Neural Population Models of the, Fig. 1

Phase-locked “hot spots” emerging on a $(51.2 \text{ cm})^2$ cortical grid (*inset*) after a bifurcation from regular alpha rhythms oscillate with a gamma frequency of approximately 40 Hz (Bojak and Liley 2007). The radial power spectrum (Bojak and Liley 2005) is shown in decibel



Cross-References

- [Bifurcations, Neural Population Models and](#)
- [Coordination Dynamics](#)
- [Electrocorticogram \(ECOG\)](#)
- [Embodied Cognition, Dynamic Field Theory of](#)
- [Gamma and Theta Oscillations, Hippocampus: Overview](#)
- [Gap Junctions, Neural Population Models and](#)
- [Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)
- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Hippocampus, Theta, Gamma, and Cross-Frequency Coupling](#)
- [Local Field Potential, Relationship to Unit Activity](#)
- [Local Field Potential, Synchrony of](#)
- [Local Field Potentials: LFP](#)
- [Neural Population Model](#)
- [Neuroimaging, Neural Population Models for](#)
- [Pattern Formation in Neural Population Models](#)
- [Phase Transitions, Neural Population Models and](#)

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Gamma-Aminobutyric Acid Type-A (GABA-A) Receptors, Kinetic Models

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Synonyms

[GABA-A receptor conductance models](#)

Definition

GABA-A receptors are the predominant inhibitory neurotransmitter receptors in the CNS and are protein complexes consisting of an extracellular domain where the neurotransmitter GABA binds to activate a membrane-spanning chloride-selective ion channel. They are often localized in postsynaptic clusters and, upon activation, produce an inhibitory postsynaptic current or potential (IPSC/P). They are the main target for benzodiazepines and general anesthetics, as well as the locus of harmful mutations often associated with epilepsy (Macdonald and Olsen 1994; Cromer et al. 2002). The timecourse of the IPSC is critical in shaping the temporal dynamics of circuit function, including the frequencies of

population rhythms (Whittington et al. 2000). The timecourse of the IPSC, in turn, is shaped by the kinetic properties of the GABA-A receptor complex (Jones and Westbrook 1995).

Most GABA-A receptor conductance models, or kinetic models, are systems of coupled ordinary differential equations that predict the probability of channel state occupancies as a function of time in response to GABA binding and their modulation by drugs or mutations. Such models are important for (a) understanding the regulation of neural function by inhibitory signaling, (b) for understanding the biophysics and pharmacology of GABA-A receptors and related receptors (e.g., nAChRs, GlyRs, 5HT3Rs), and (c) for theoretical advances including accurate computational modeling of neural circuit function and rational drug design.

Detailed Description

Like other kinetic modeling approaches, modeling of GABA-A receptors typically involves enumerating the conformational states available to the protein (e.g., unbound, bound with GABA, open, desensitized, etc.) and assigning transition rate constants between states based on experimental evidence, mostly derived from voltage-clamp measurements of currents in response to application of GABA under varied experimental conditions. The specific conditions that produce the data constrain the type of model that can be developed, each with its own advantages and limitations.

Macroscopic Versus Microscopic Evidence

The most common data available consist of “macroscopic” responses to GABA application (i.e., the ensemble summed current through a large number of receptors), as are produced in two-electrode voltage-clamp experiments in oocytes, or whole-cell recording from HEK293 cells or neurons, or outside-out patch recordings in response to rapid solution exchanges. Such experiments can yield dose–response relations or

reveal the average timecourse of the receptor response, but in general do not directly reveal what states are available or the transition rate constants between states, because the shapes of these responses are determined by the entire combination of states and transitions rather than any single one.

In contrast, one can obtain some “microscopic” information (i.e., direct measurement of state transitions) by observing the statistics of opening and closing of a single ion channel in response to GABA application, for example, in outside-out patch recordings under either steady-state conditions or in response to rapid solution exchange. However, this information is also limited because it is restricted to analysis of transitions between open and closed states. Transitions between two closed states (e.g., unbound to bound or bound to desensitized) are not directly observable in single channel records.

Therefore, neither ensemble measurements nor single channel measurements are sufficient to reveal directly the full underlying microscopic structure of receptor kinetics. The states and transition rates must be inferred by fitting candidate models to the data.

What Does a GABA-A Receptor Kinetic Model Need to Explain?

The most common data available consist of dose–response curves of peak macroscopic current versus GABA concentration that can be fit with a simple two-state model (unbound $\leftrightarrow$ bound) such as that embodied by the Hill equation, where the main free parameters are the affinity constant ($K_d = k_{\text{off}}/k_{\text{on}}$) and a slope factor (n), such that the individual rate constants cannot be uniquely specified. However, lacking rate constants, the resulting model does not allow prediction of the timecourse of current, for example, the shape of the IPSC. The timecourse of macroscopic currents reveals that desensitization occurs, and single channel experiments reveal directly that there are many closed and open states; thus a two-state model is inherently inaccurate. A comprehensive model should be able to account

not only for the macroscopic dose–response curve but also for the number and dwell times of open and closed states observed in single channel recordings, as well as states that cannot be unambiguously quantified in most single channel recordings such as long desensitized states. An accurate model should also provide the forward and backward rate constants for transitions between any pair of states.

These issues are relevant because each state in a model is meant to represent a distinguishable physical conformation of the protein, and the rate constants are logarithmically proportional to the energy barriers between conformations. Furthermore, an accurate model should be able to predict synaptic responses and their alteration by drugs or mutations that alter neuronal computations and behavioral states.

No current model accounts for all of the available data. Existing models tend to be biased toward explaining the specific experiments that produced them. Many features of these models are compatible with each other, but in some cases they produce conceptually different interpretations that either cannot be distinguished from each other based on available evidence or directly conflict with each other.

Cooperativity Models

One class of models is similar to the classical Monod-Wyman-Changeux (MWC) model of cooperative binding, in which the receptor can transition between open, closed, and desensitized states in the absence of modulators such as GABA, benzodiazepines, or anesthetic drugs, but the equilibrium between the different states is altered by the binding of each modulator (Forman 2012). These models are based largely on data from peak dose–response curves (i.e., the maximum current response produced by different GABA concentrations), in the presence and absence of drugs or mutations that modulate receptor function, although in some cases the timecourse of the response is also taken into account (Scheller and Forman 2002). A major advantage of these models is that they naturally lend themselves to treating interactions between the numerous modulatory

sites on GABA-A receptors, via the central underlying concept that all binding sites and gates are energetically coupled to each other such that a transition at any site affects the probability that all other sites will undergo a transition, according to some set of coupling constants. However, a limitation of these models is that transitions are often expressed as equilibrium constants rather than rate constants (but see Scheller and Forman 2002) or that they consider only a small subset of the states that are known to exist.

Stationary Microscopic Kinetic Models

Another class of models focuses on explaining the dwell times and connectivity among states based on the statistics of channel opening and closing observed in single channel records from excised patches collected under true steady-state conditions (Macdonald and Twyman 1992). One advantage of these models is that they make few a priori assumptions about connectivity; for example, they do not insist that all transitions are possible but rather infer connectivity from correlations between observed events. Another advantage is that they account quantitatively for the highly detailed single channel data and can predict certain aspects of macroscopic responses such as dominant features of the IPSC timecourse. A disadvantage is that transitions between closed states, for example, the initial GABA binding step or entry/exit from long desensitized states, are not directly observable in single channel records, and estimation of long closed dwell times in general may be confounded by uncertainty about the number of receptors present in the patch. Thus, the binding rates may depend on the specific model used, and long desensitized states are often omitted for simplicity. Another disadvantage is that extension of such models to account for multiple modulatory interactions becomes unwieldy.

Nonstationary Macroscopic/Microscopic Kinetic Models

A third class of models focuses primarily on explaining the timecourse of the IPSC and other

nonstationary macroscopic phenomena, based on model fitting to the kinetics of responses to transient GABA applications (Jones and Westbrook 1995; Haas and Macdonald 1999; Burkat et al. 2001), often using single channel data as well to directly constrain certain rate constants. In addition to providing predictions of IPSC details, these models also have the advantage of explicitly including desensitized states. In certain circumstances, estimates of binding rates can also be obtained (Jones et al. 1998). Disadvantages are that they are often not sufficiently detailed to account for all of the single channel observations and that their extension to multiple modulatory interactions are also unwieldy.

Pre-activation Step Models

A relatively recent concept in interpreting kinetic data on GABA-A receptors is the idea, first introduced for glycine receptors (Burzomato et al. 2004), that one or more so-called “flip” or pre-activation steps follow GABA binding but precede gating. These models are in some ways a hybrid of previous approaches, in that they incorporate elements of the MWC cooperativity mechanism, but the original versions were derived from stationary microscopic single channel kinetics and later adapted to GABA-A receptors based on peak dose–response curve data (Gielen et al. 2012). A major advantage is that, with minor modifications of coupling constants, they can account for differences in efficacy between full and partial agonists and the effects of certain allosteric modulators. A disadvantage that they share with the first two classes is that long desensitized states are often not included. Also, the estimated dwell times of the “flip” states tend to be too brief to resolve directly.

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Gap Junctions in Small Networks

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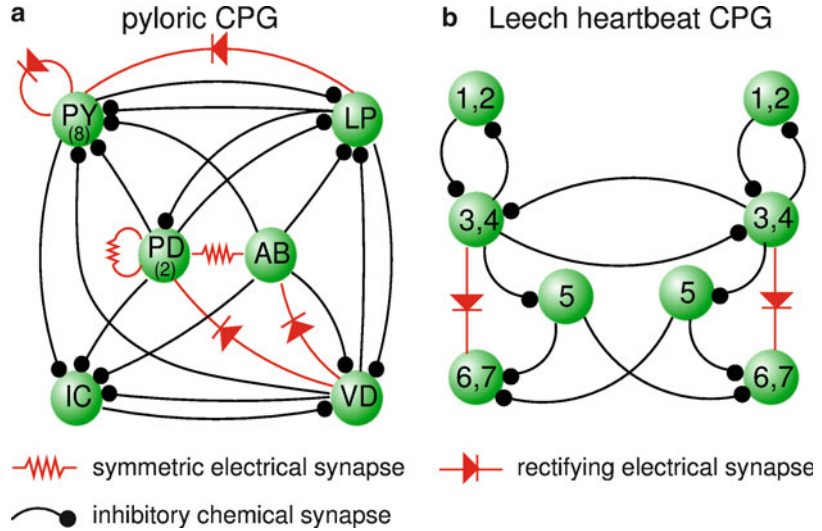
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Background/History

Gap junctions are electrical connections between cells that are not primarily gated by chemicals. One of the first accounts of gap junctions was in the crayfish escape system (Furshpan and Potter 1959). Even though the existence of gap junctions

Gap Junctions in Small Networks,

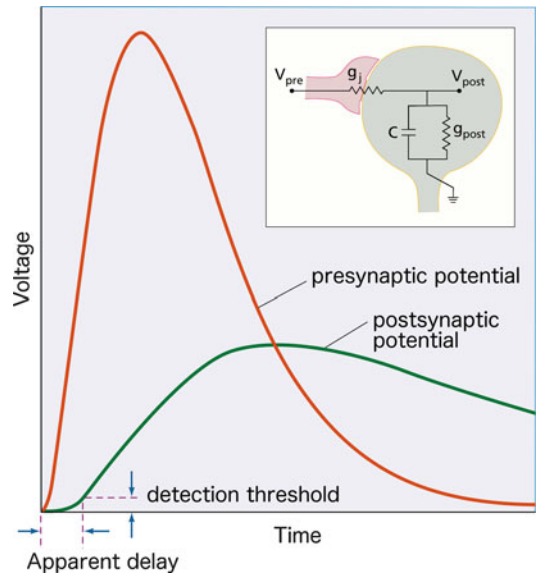
Fig. 1 Examples of small networks where gap junctions play important roles, the crustacean pyloric CPG (a) and the leech heartbeat CPG (b). (a) was created based on Mulloney (1987) and Johnson et al. (2005); (b) was created based on Weaver et al. (2010)



in vertebrates was established in the same year (Bennett et al. 1959), much of the early work on electrotonic coupling has been carried out in small invertebrate circuits. Gap junctions in the mammalian brain were discovered only in the 1970s (see Llinas 1985) and their relevance was appreciated even later.

Typical model systems for the study of gap junctions in small circuits are the crustacean pyloric CPG (Fig. 1a), the *Tritonia* swimming CPG, and the leech heartbeat CPG (Fig. 1b), among others (see Bennett (1977) for review).

Gap junctions are composed of a number of individual electrical channels consisting of two half channels formed of six subunits, provided by each of the connected cells. There are two separate families of proteins that can act as subunits of a gap junction channel: pannexins (originally named innexins when first discovered in insects but later renamed when also discovered in chordates) and connexins, which have thus far only been found in vertebrates. Though having unrelated sequences, proteins of both families have similar 4-trans-membrane domain structure (Panchin 2005; Sáez and Nicholson 2009) for more details. Current flows in the form of ions through the pores of the channels, determined to a first approximation by Ohm's law. Figure 2 illustrates the basic electrical properties of a gap junction.



Gap Junctions in Small Networks, Fig. 2 Typical transmission of membrane potential deflections through a gap junction. The attenuation of the signal and the apparent delay can be understood from the finite input resistance and capacitance of the postsynaptic cell (see inset). The result is an effective low-pass filter (Reprinted (with modifications) by permission from Macmillan Publishers Ltd.: Nat. Neurosci. 3: 7–9, copyright 2000)

The overall conductance of the gap junction is determined by the number of channels in it and the single-channel conductance. The latter has been found to be on the order of 50 pS in neonatal rat heart cells (Burt and Spray 1988), and,

interestingly, individual single channels appear to open and close randomly (Burt and Spray 1988) like other ligand- or voltage-gated channels, i.e., the single channels in a gap junction are not just passive pores in the membrane.

In computational neuroscience, gap junctions are often modeled as simple ohmic conductances between cells. As such they are both inhibitory and excitatory and bidirectional. However, from their first discovery, it has been clear that they are much more complex in reality:

1. Furshpan and Potter's experiments (1959) showed that the gap junctions between the giant axon and giant motor fibers in the crayfish are rectifying, only transmitting currents when the giant axon was depolarized. It is worth keeping in mind that a majority of gap junctions are, however, non-rectifying.
2. Gap junctions are typically low-pass filters, which leads to an appreciable attenuation of the postsynaptic potential elicited by presynaptic spikes (Fig. 2). Interestingly, this phenomenon can render them inhibitory if the effect of the fast, depolarizing part of the presynaptic potential is reduced and a longer and slower after-hyperpolarization is transmitted much more efficiently (see Bennett and Zukin 2004).
3. Gap junctions can be voltage-gated beyond the linear voltage dependence of Ohm's law. Spray et al. (1981) showed that gap junctions between amphibian blastomeres have strong voltage dependence, likely due to the movement of charge within the channel molecules. In contrast to other types of voltage-gated channels, this voltage dependence is mainly determined by the voltage difference between the connected cells rather than the absolute membrane potentials.
4. Gap junctions can be modulated by chemical synapses, for example, in the feeding system of the mollusc *Navanax* (Spira et al. 1980) and the escape motor circuit of teleost fish (Yang et al. 1990). In *Navanax*, for example, gap junction-coupled neurons can essentially be functionally decoupled if separate depolarizing input transiently lowers the input resistance of one of the coupled cells and so largely suppresses any effects of trans-junctional currents.
5. The conductance of gap junctions can depend on extracellular acidity and intracellular Ca^{2+} concentration (Spray and Scemes 1998).
6. It has been shown in vertebrates that the behavior of gap junctions can be altered by phosphorylation of connexins (Musil et al. 1990; Lampe and Lau 2004).

Hypothesized Functions in Small Networks

The most obvious and first to be described function of gap junctions is fast synaptic transmission, for example, in time-critical escape or startle responses (Furshpan and Potter 1959). Another very prominent suggested function is synchronization or coordination of neuronal activity. Egelhaaf and Benjamin (1983) investigated the role of electrotonic coupling between so-called peripheral bursters, intrinsically bursting cells in the nervous system of the snail *Lymnaea stagnalis*. They found that strong coupling between ipsilateral cells led to 1:1 entrainment, such that cells functioned as a single unit. Weaker, contralateral electrotonic connections in contrast led to more rich coordinated activity with changing regimes of 1:1 and 1:2 synchronization.

The formation of single functional unit through strong electrical coupling has been established in the crustacean pyloric CPG, where a pair of pyloric dilator (PD) motoneurons and the anterior burster (AB) neuron form a tightly coupled functional unit (Fig. 1).

A less intuitive function of gap junctions was suggested by Gettings and Willows (1973) in the *Tritonia* pleural ganglia. In this system a group of about 30 trigger group neurons (TGN) are electrically coupled and exhibit accelerating bursting activity. The bursting ends in a synchronous spike in many of the neurons, mediated by the electrical coupling. Burst termination was related to a prolonged after-hyperpolarization of all neurons due to the simultaneous hyperpolarization in many neurons and the ensuing absence of repolarizing currents through the electrical coupling. This is a nice example where the interaction of cellular properties (after spike hyperpolarization) in conjunction with the electrical coupling

generates important and unexpected effects (burst termination in the population of TGN).

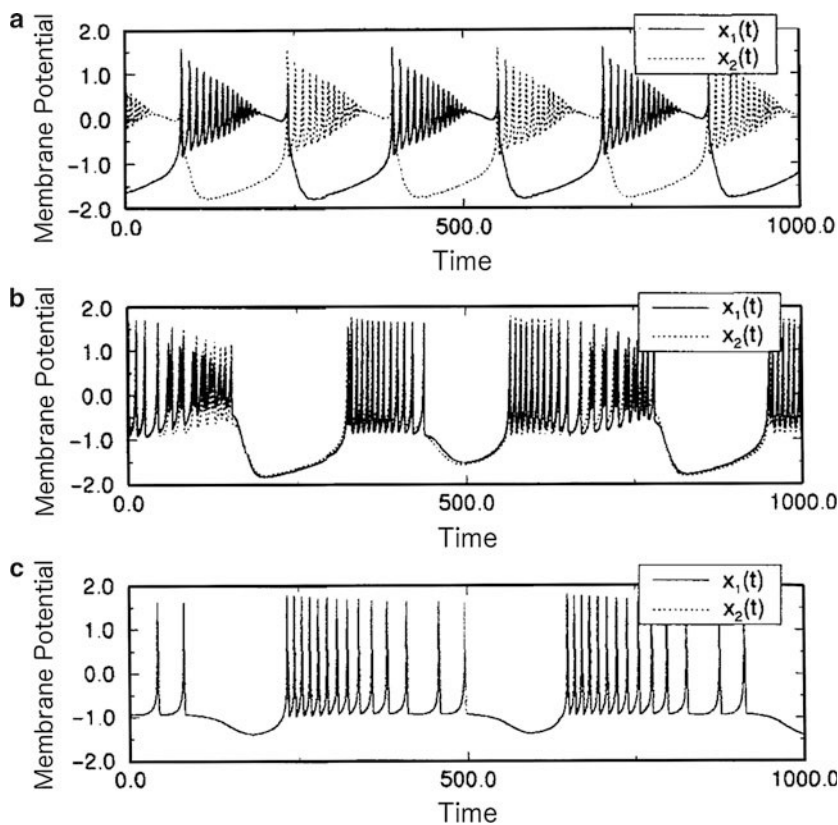
Another example of such nontrivial interactions is the combination with chemical synaptic transmission that has been posited to underlie the precise phase relationships in the leech heartbeat CPG (Weaver et al. 2010); see Fig. 1 and the discussion of this work in the next section.

Theoretical Work

A major theme in theoretical and computational work on the role of gap junctions has been synchronization.

Abarbanel et al. (1996) investigated the dynamics of electrically coupled chaotic bursting

neuron models, inspired by the PD neurons in the lobster pyloric CPG (Fig. 1a). They were able to show analytically that the neurons will synchronize perfectly for strong enough coupling while the joint dynamics remained chaotic. For less strong coupling, they identified several distinct regimes of synchronization, including in-phase burst synchronization (but no synchronization of spikes) and, surprisingly, out-of-phase burst synchronization (Fig. 3). Similar effects were also seen in neurons with regular activity (Sherman and Rinzel 1992). Subsequently, Elson et al. (1998) showed that these synchronization regimes can be observed in the lobster pyloric CPG when the electronic coupling between PD neurons is manipulated by the introduction of a simulated additional (or compensatory) electrical coupling



Gap Junctions in Small Networks, Fig. 3 Synchronization phenomena in two electrically coupled chaotic bursting model neurons. Depending on the coupling strength and the properties of the bursting cells, symmetric electrical coupling leads to out-of-phase

synchronization (a), burst synchronization (b), or complete, spike-by-spike synchronization (c) (Reprinted by permission of MIT Press Journals from Abarbanel et al. (1996), © 1996 Massachusetts Institute of Technology)

with dynamic clamp. Similarly, electrically coupled electronic neurons exhibit the same synchronization regimes (Pinto et al. 2000).

Other computational work addressed the role of rectifying gap junctions in regulating the phase relationships of phasic bursting in a model of the leech heartbeat CPG (Fig. 1b). In the medicinal leech, the two tubular hearts operate in two different modes – synchronous contractions in one and a peristaltic rear to front contraction in the other – and the mode of operation swaps between the two hearts regularly. Weaver et al. (2010) showed in a model that only the interaction of inhibitory chemical and electrical connections could reproduce this complex phasing between motoneuron activities on the two sides. Neither inhibitory synapses nor electrical synapses were sufficient on their own. This gives us a glimpse on the potential additional complexity of gap junction function if they interact with other synaptic connections and/or intrinsic cell properties.

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Gap Junctions, Neural Population Models and

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Definition

Gap junctions, also known as electrical synapses, provide a means of direct, diffusive neuron-to-neuron communication; this information flow is completely separate from action potential-mediated signaling via chemical synapses. Gap junctions are connexin protein structures that connect the interiors of adjoining cells allowing free flow of transmembrane current. Gap junctions are found in most animal tissues and are widely expressed throughout the mammalian brain, most commonly at the points of contact between dendrites of inhibitory interneurons and between glial astrocytes (Bennett and Zukin 2004). Gap junctions between pairs of excitatory pyramidal cells are rare.

Gap junctions can be modeled as simple Ohmic-resistive connections between neighboring neurons. To date, almost all modeling studies have investigated the bulk effects of resistive coupling among cortical neurons by assembling large networks of discrete spiking neurons, and none of these have considered how resistive coupling might be incorporated into a neural-mass (mean-field) continuum of excitable tissue. The single exception is the mean-field gap-junction model of Steyn-Ross et al. (2007, 2008, 2009, 2010, 2011, 2012, 2013). The continuum population approach allows predictions regarding neural activity and state changes that should be discernible at the scale of EEG electrodes.

Detailed Description

Network Effects of Neuron-to-Neuron Diffusion

Most modeling studies have incorporated gap junctions as resistive connections between pairs of neurons that have been assembled into a neural network of several hundreds or perhaps thousands of individual Hodgkin-Huxley (or similar) spiking neurons. We refer to such networks as “neuron-by-neuron” models to distinguish them from the “mean-field” or population-based approach that describes a spatially averaged continuum of excitable tissue (see next section).

If two adjoining neurons, labeled j and k , are coupled by a resistive gap-junction channel, a current proportional to the voltage difference between those neurons will flow through the gap junction, $I_{\text{gap}} \propto (V_k - V_j)$. This gap current will sum with any ionic flows resulting from action potentials arriving at chemical synapses, I_{syn} , giving a total current entering the capacitive membrane of neuron i as

$$C \frac{dV_j}{dt} = I_{\text{syn}} + I_{\text{gap}} \quad \text{with} \quad I_{\text{gap}} = g \cdot (V_k - V_j) \quad (1)$$

where C is the membrane capacitance and g is the conductance of the gap-junction channel.

It is clear from Eq. 1 that the gap current between coupled neurons can only disappear if the gap-channel conductance g is zero (i.e., the channels are completely blocked) or when the voltage difference $(V_k - V_j)$ between cells is zero, implying that the neuron pair is completely synchronized with identical membrane voltages. Thus, the presence of gap currents will tend to align neuron behaviors, not only during sub-threshold fluctuations but also during periods of active firing. Synchronized behavior has been observed in whole-cell recordings of gap-junction-connected GABAergic (inhibitory) neurons in the cortex (Galarreta and Hestrin 1999; Tamás et al. 2000; Beierlein et al. 2000) and confirmed theoretically in many numerical simulations of conductance-based neuron-by-neuron

networks of interneurons (Traub 1995; Traub et al. 2000; Skinner et al. 1999; Kopell and Ermentrout 2004).

In summary, these modeling works indicate that – although interneuronal gap junctions tend to synchronize neuronal oscillations – they do not instigate global oscillations. This is consistent with mean-field investigations showing that interneuronal gap junctions can modulate GABAergic-generated rhythms to produce phase-coherent activity across the cortical field (Steyn-Ross et al. 2010, 2012).

Although most neural gap junctions form between the dendrites of interneurons, there have been reports of axo-axonal junctions between principal neurons in the hippocampus (Schmitz et al. 2001; Nagy 2012). Network modeling by Traub et al. (2001, 2002) suggests that such connections can generate the fast ripple oscillations seen prior to and during epileptic seizure events and may have a role in epileptogenesis.

Modeling Gap-Junction Diffusion in a Neural Population

Rather than tracking the detailed behavior of individual neurons within a network, continuum models of the cortex describe the spatially averaged activity of large populations of neurons. The neural equations are then expressed in terms of a notional population-averaged neuron represented as an RC integrator of membrane resistance R_m and capacitance C_m , charged by a battery of voltage V^{rest} , the cell's resting potential (see Fig. 1). The neuron's membrane voltage V_m is perturbed by input currents entering from chemical synaptic sources (arising from action potential events) and from gap-junction channels.

From Kirchhoff's law, the total input current I_{in} from chemical and diffusive sources equals the sum of the resistive and displacement currents owing to “ground” (i.e., the extracellular space):

$$\begin{aligned} I_{\text{syn}} + I_{\text{gap}} &= I_{\text{in}} \\ &= (V_m - V^{\text{rest}})/R_m + C_m \frac{dV_m}{dt} \quad (2) \end{aligned}$$

Each neuron receives diffusive inputs from its gap-junction-coupled neighbors. If this per-neuron region of diffusive sensitivity has area a , then using simple Ohm's law arguments, Steyn-Ross et al. (2007) showed that the gap current is given by

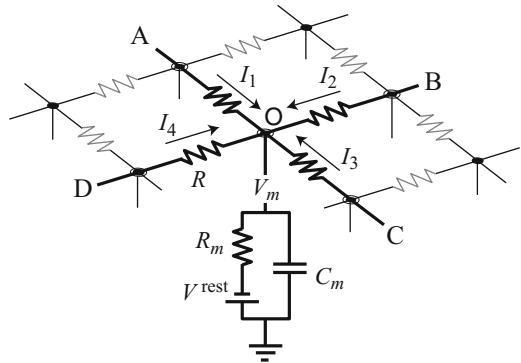
$$I_{\text{gap}} = \frac{a}{R} \left[\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right] V_m \equiv \frac{a}{R} \nabla^2 V_m \quad (3)$$

where effective coupling resistance R (shown in Fig. 1) is a fraction of the single-channel gap-junction resistance R_{gap} :

$$R = \frac{R_{\text{gap}}}{N/4}$$

Here, N is the average number of gap junctions per neuron; this is reduced by a factor of 4 on the assumption that these gap junctions are uniformly distributed across each of the four rectangular-grid directions. After substituting Eq. 3, and defining membrane time constant $\tau = R_m C_m$, Eq. 2 can be rearranged to read as

$$\tau \frac{\partial V_m}{\partial t} = (V^{\text{rest}} - V_m) + I_{\text{syn}} R_m + D \nabla^2 V_m \quad (4)$$



Gap Junctions, Neural Population Models and, Fig. 1 Cortical sheet modeled as a 2-D rectangular network of diffusively coupled neurons. The neuron at origin O receives diffusive currents $I_{\text{gap}} = (I_1 + I_2 + I_3 + I_4)$ from four neighboring diffusion cells via coupling resistances R determined by the density and spatial distribution of gap-junction channels (chemical synaptic currents not shown). (Figure modified from Steyn-Ross et al. 2007)

where $D = \frac{aN}{4} (R_m/R_{\text{gap}})$ is the diffusive coupling strength, carrying dimensions of area, so that the ratio D/τ is a diffusion coefficient for voltage change: in time t , a voltage perturbation will diffuse through rms distance $\sqrt{4Dt/\tau}$ on a two-dimensional cortical sheet.

In application, Eq. 4 would be written as a pair of partial differential equations representing the neuron-average soma voltages [i.e., $V_m \rightarrow (V_e, V_i)$] for the excitatory and inhibitory populations, respectively, with distinct diffusion strengths [$D \rightarrow (D_{ee}, D_{ii})$]. In addition, each population receives chemical synaptic current I_{syn} via an incoming flux of both excitatory and inhibitory spike events: $I_{\text{syn}} \rightarrow (I_{ee} + I_{ie} + I_{ei} + I_{ii})$, where, e.g., I_{ie} signifies inhibitory synaptic current entering the excitatory population. Each of these currents is computed as a convolution of the spike rate with a response function (usually biexponential) representing postsynaptic ion-channel kinetics (Destexhe et al. 1989; Steyn-Ross et al. 2009), modulated by the relevant ionic reversal potential (Liley et al. 1999; Rennie et al. 2000).

Estimation of Gap-Junction Coupling Strength

For layers 2 and 3 of cat visual cortex, Fukuda et al. (2006) counted ~ 400 large (L-type) inhibitory interneurons per mm^2 with each neuron making 60 ± 12 (mean $\pm$ SD) gap junctions with neurons of the same type. They reported that serially interconnected neurons could be traced through multiple gap junctions to form a dense, homogeneous syncytium that extended over many columns of the visual cortex. Using the Fukuda data, Steyn-Ross et al. (2007) estimated an upper bound for inhibitory-to-inhibitory ($i-i$) diffusion coupling strength of $D_{ii} \lesssim 0.6 \text{ cm}^2$, but acknowledge considerable uncertainty in this value given that:

- Detection of gap junctions is technically challenging; estimates for gap-junction abundance in cerebral cortex have been increasing over time as laboratory techniques become more sensitive and discriminating.

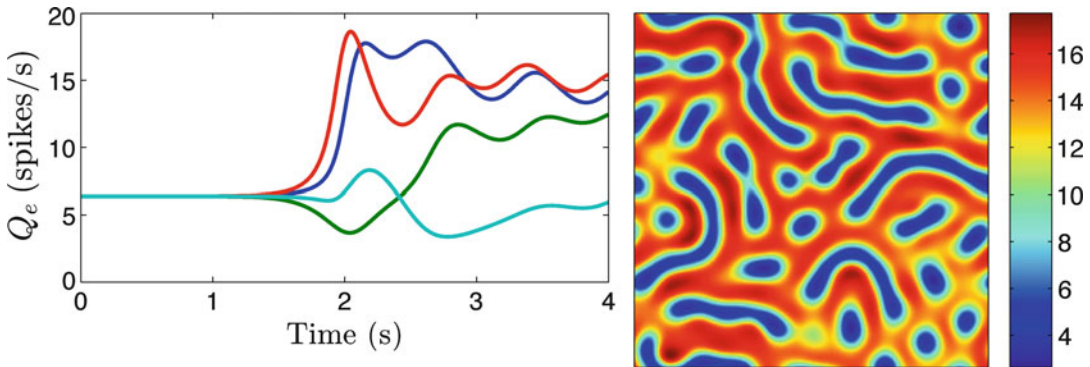
- Fukuda et al. (2006) only counted connexin-36 (Cx36) junctions; however, there are many other connexin and pannexin types (e.g., Cx32, Cx43) connecting pairs of neurons, pairs of glial cells, and neuron-glial pairs (Nadarajah et al. 1996).
- The value for a , the lattice area of diffusive reception, is sensitive to the shape of the assumed connectivity kernel (e.g., Gaussian vs. top hat).
- The assumed values for membrane resistance $R_m \approx 7.1 \text{ G}\Omega$ and channel resistance $R_{\text{gap}} \approx 290 \text{ M}\Omega$ are average values; these are likely to change dynamically with neuronal activity (Koch 1999; Palacios-Prado et al. 2013).

Unlike the case for inhibitory neurons, there are very few reports for gap-junction connectivity between *excitatory* neurons (Schmitz et al. 2001) and none suggesting the existence of a dense network of e-to-e resistive connections. This implies that, relative to $i-i$ coupling, $e-e$ diffusive coupling strength is very weak: $D_{ee} \ll D_{ii}$.

Implications of a Gap-Junction Syncytium

The inclusion of nearest-neighbor diffusion terms transforms the mean-field cortical model into a set of reaction-diffusion equations similar to those seen in nonlinear chemical dynamic systems (e.g., Brusselator). Since inhibitory diffusion strongly dominates excitatory diffusion, conditions are favorable for the emergence of a Turing instability (Turing 1952) leading to the spontaneous formation of spatially organized patterns of neural activity (see Fig. 2).

This Turing spatial instability can interact with a Hopf temporal instability arising from a slowing of the inhibitory responsiveness at GABA chemical synapses, producing spatiotemporal patterns that may underlay the slow activity modulations seen in functional MRI recordings of the default background state of the resting cortex (Steyn-Ross et al. 2009). Reduction of $i-i$ gap-junction diffusivity weakens the Turing instability, thus allowing GABA-mediated Hopf oscillations to



Gap Junctions, Neural Population Models and, Fig. 2 Numerical simulation of mean-field cortical equations that include both chemical and electrical (gap-junction) synapses on a 2-D grid with periodic boundaries. Diffusion strengths are $[D_{ee}; D_{ii}] = [0.01; 1.0]$ cm^2 . *Left*: time series showing excitatory firing rate Q_e at four

equally spaced points down the midline of the grid. *Right*: bird's-eye view of Q_e activity after 4 s. Grid resolution is 240×240 , representing a 25×25 -cm cortical sheet. *Color bar* shows firing rate in spikes/s (see Steyn-Ross et al. (2013) for model details and computer codes)

dominate, predicting global seizure in the limit of strongly suppressed inhibitory diffusion (Steyn-Ross et al. 2012). However, the role of gap junctions in seizure initiation and spread is controversial (Voss et al. 2011), with some researchers reporting seizure suppression with blockage of gap junctions (e.g., Carlen et al. 2000; Jin and Chen 2011), while others find that blockers increase seizure propensity (Yang and Ling 2007; Jacobson et al. 2010).

Nonlinear Turing–Hopf interactions may also be important for the genesis of the large, irregular ~1-Hz slow oscillations that characterize the unconsciousness of deepest slow-wave sleep and of drug-induced general anesthesia (Steyn-Ross et al. 2013).

Cross-References

- Anesthesia, Neural Population Models of
- Bifurcation Analysis
- Bifurcations, Neural Population Models and
- Chaos, Neural Population Models and
- Epilepsy, Neural Population Models of
- Neural Population Model
- Pattern Formation in Neural Population Models
- Phase Transitions, Neural Population Models and
- Sleep, Neural Population Models of

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Gating Current

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Definition

Gating current is the component of the neuronal transmembrane current due to the movement of charges attached to voltage-gated ion channels.

Detailed Description

Physical Basis

The proteins making up ion channels are arranged into subunits, which are further organized into segments. About a third of the amino acid residues in the S4 segments of voltage-gated ion channels are positively charged arginine and lysine. These gating charges are acted on by the electric field across the membrane, with the force changing the stability of ion channel conformations. The movement of the gating charges perpendicular to the membrane during conformation changes is the gating current. This is distinct from the ionic current, the current due to ions flowing through the channel pore.

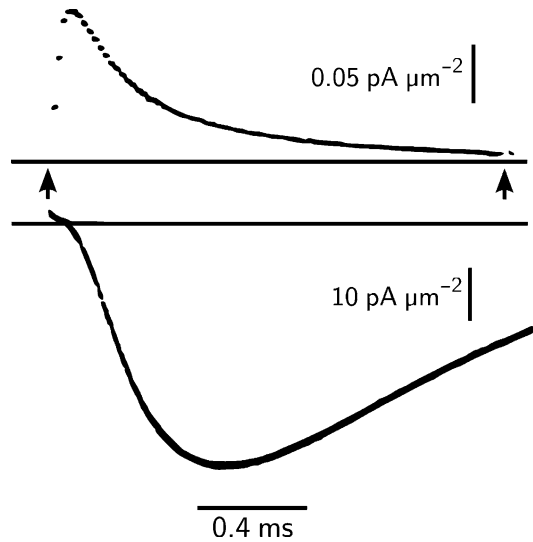
The theory of ion channels opened and closed via gating charges was postulated by Hodgkin and Huxley (1952), although they used the term “gates” rather than “ion channels.” They predicted that gating current associated with a channel opening will flow just before the ionic current starts to flow through the newly opened channel.

Measurement

Gating current was first measured in the 1970s (Armstrong and Bezanilla 1973). To measure the relatively small gating current, the ionic current has to be reduced, either by using channel blockers or reducing the concentration of permeant ions, and multiple recordings had to be averaged. During a depolarizing voltage step (Fig. 1), the gating current is outward since the positively charged residues are moving outward. As predicted by Hodgkin and Huxley, the gating current leads the ionic current.

Equivalent Gating Charge

The equivalent gating charge is the integral of the gating current that flows when the ion channel moves from the closed to open state. The equivalent gating charge gives the number of charges that would have to move all the way across the membrane when an ion channel opens or closes.



Gating Current, Fig. 1 Measurement of sodium gating current in squid axon by Armstrong and Bezanilla (1973). The *upper trace* is the gating current averaged over 2000 presentations of a voltage step from -70 to 0 mV. This is measured in artificial seawater in which sodium has been replaced by the impermeant ion Tris and potassium by cesium ions, which are impermeant. The *lower trace* is the ionic current seen in artificial seawater containing sodium. The gating current is seen to lead the sodium current. (Reproduced by permission from Macmillan Publishers Ltd: Nature 242, 459–461 ©1973. Note: permission is needed from Macmillan, publishers of Nature)

In principle, the equivalent gating charge could be made up of many charges moving a fraction of the transmembrane distance, but in fact a number of charged residues on the S4 segment of voltage-gated channels do move across the whole membrane (Hille 2001).

On the basis of the steepness of the activation curve of squid sodium channels, Hodgkin and Huxley (1952) predicted that the equivalent gating charge was around six elementary charges. This prediction is derived by considering the two components of the work required to move a gate (see ► “Hodgkin-Huxley Model”) from its closed position to its open position for a given membrane potential V :

- w , the work required were there no electric field (i.e., if $V = 0$)
- $-z_g e V$, the work required to move z_g equivalent gating charges, each with elementary charge e , across the membrane

From Boltzmann's principle, at equilibrium the ratio of the probability O of a gate being the open position to the probability C of it being in the closed position is

$$\frac{O}{C} = \exp(-(w - z_g eV)/k_B T) \quad (1)$$

where T is the temperature in kelvin and k_B is Boltzmann's constant. Given that $O + C = 1$, the fraction of gates in the open position is

$$O = \frac{1}{1 + \exp((w - z_g eV)/k_B T)} \quad (2)$$

This is a sigmoid curve, and by fitting it to the data for the open probability for the sodium m gate, Hodgkin and Huxley determined that $z_g \approx 6$.

Modern estimates of the equivalent gating charge are in the range of 12–16 elementary charges per potassium channel, 8–15 charges per calcium channel, and around 12 charges per sodium channel (Hille 2001). The equivalent gating charge is thus much smaller in magnitude than the typical number of ions that flow through a channel pore during an action potential or post-synaptic current.

Applications for Computational Neuroscience

The gating current is usually negligible compared to ionic currents and therefore tends not to be modelled explicitly. However, gating current recordings can be used to make inferences about the structure of ion channels. For example, recordings of gating currents from squid giant axon sodium channels do not follow the form predicted by Hodgkin and Huxley (1952) and therefore lead to a more complex model of the channel, in which activation occurs in several steps (Patlak 1991; Hille 2001).

Cross-References

► [Hodgkin-Huxley Model](#)

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GEneral NEural Simulation System

► [GENESIS, the GEneral NEural Simulation System](#)

Generalized Linear Models for Point Process Analyses of Neural Spiking Activity

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Definition

Point process-generalized linear model. An adaptation of the generalized linear model framework to point processes using local Bernoulli or local Poisson models to analyze the relationship between neural spiking activity and relevant covariates such as putative stimuli and spike history.

Detailed Description

Most systems neuroscience experiments entail applying a stimulus and measuring the response which is commonly the spiking activity of one or more neurons (Brown et al. 2004; Paninski 2004; Truccolo et al. 2005; see entries ► “Spike Train,” ► “Spike Train Analysis: Overview”). The typical objective of the experiment is to define how spiking activity in a given brain area changes in response to the stimulus under a range of different conditions. From a statistical standpoint, this type of experimental design requires a regression model in which the observations can be spiking activity and the regressors can be the stimulus and any other relevant covariates. The generalized linear model (GLM) provides such a framework.

The standard linear regression model assumes observations with Gaussian errors. The GLM is an extension of the regression model to observations from any probability model in the exponential family (McCullagh and Nelder 1989). The exponential family includes many of the probability models commonly used in statistical analyses such as the Gaussian, Bernoulli, binomial, Poisson, gamma, and inverse Gaussian (DeGroot and Schervish 2012). The GLM is constructed by writing the exponential family model in canonical form and expressing the natural parameter as a linear function of the covariates. For example, the natural parameters are μ for the Gaussian, $\log \lambda$ for the Poisson, and $\log[p/(1 - p)]$ for the Bernoulli and the binomial. Relating the natural parameter to the regressors as a linear function defines the natural link for the GLM. The GLM offers several appealing features. Computation of the maximum likelihood estimate of the parameters can be carried out efficiently using iteratively reweighted least squares. For the Gaussian linear model, the iteration converges in one step to the exact least squares solution. The sum of squares in the standard analysis of variance generalizes in the GLM framework to the deviance which equals $-2 \times \log$ of the maximized likelihood function.

Brillinger showed that by modeling a neural spike train recorded a stimulus response experiment as a point process defined in terms of its conditional intensity function then GLM framework could be adapted to analyze this class of data

(Brillinger 1988). A point process is a binary (0–1) process observed in continuous time. In a small time interval, the product of the conditional intensity function times the time interval defines the probability of an event, or a 1, in the small time interval conditional on the history of the point process up to that time (Brown et al. 2003; Daley and Vere-Jones 2003). The conditional intensity function is therefore a history-dependent generalization of the rate function of Poisson process. In this way, a point process is a generalization of a Poisson process that allows history dependence, and like an inhomogeneous Poisson process, dependence on other covariates as well. The conditional intensity function is chosen as the quantity to model because it completely characterizes the point process. An alternative would be to model the interspike interval distribution. Use of the conditional intensity function is more flexible. Moreover, it is easy to show that the conditional intensity function specifies the interspike interval distribution and vice versa (Truccolo et al. 2005; Brown et al. 2003).

To apply the GLM framework to a neural spike train analysis, the spike train is modeled as a point process in which either the log of the conditional intensity function or the logit of the conditional intensity function times a small time interval is expressed as a linear function of the covariates of interest (Truccolo et al. 2005; Brillinger 1988). Time is discretized into non-overlapping mutually exclusive subintervals so that any subinterval contains at most one observation which is a 1 if there is a spike or a 0 if there is no spike. Each subinterval then defines a local Bernoulli model or a local Poisson model with only a 0 or 1. A Taylor series analysis of the local Bernoulli model for sufficiently small subintervals shows that it is equivalent to the local Poisson model. The joint distribution of the neural spike train data or, equivalently, the likelihood function of the model parameters is given by the product of the conditional probabilities of a spike or no spike defined by the local Bernoulli or the local Poisson model. For this reason, the data may be highly dependent, yet the likelihood function resembles the likelihood function of a product of Bernoulli or a product of Poisson random variables. Hence, by formulating a point process model in terms of a

conditional intensity function in discrete time, the Bernoulli or Poisson GLM can be used to fit a regression model relating the neural spiking activity to any covariates of interest, such as a putative stimulus or spiking history. This approach to neural spike train data analysis is termed point process GLM framework.

Berman, who also proposed the point process GLM framework (Berman and Turner 1992), suggested that goodness of fit for these models could be assessed using the time-rescaling theorem, which states that integrating the conditional intensity function between spike times transforms the interspike intervals into independent exponential random variables with rate 1 (Berman and Turner 1992; Berman 1983; Brown et al. 2002). To evaluate goodness of fit, the exponential structure in the transformed interspike intervals can be assessed using Kolmogorov-Smirnov plots (Berman and Turner 1992; Berman 1983; Brown et al. 2002; Ogata 1988). Independence can be assessed approximately by transforming the putative exponential or uniform random variables to Gaussian random variables and analyzing the autocorrelation function (ACF) (Czanner et al. 2008). If the autocorrelation function is not appreciably different from zero, as assessed by common ACF confidence interval formula, then we can infer that the original transformed interspike (putative exponential) intervals are approximately independent up to the order of the ACF that was analyzed.

The GLM can be used to analyze ensemble neural spiking activity to account of interactions among neurons in the ensemble and addition to any relevant covariates (Chornoboy et al. 1988; Okatan et al. 2005; see entry ► [“State-Space Models for the Analysis of Neural Spike Train and Behavioral Data”](#)). The GLM framework can be used to conduct Granger causality analyses for neural spike trains (Kim et al. 2011; see entries ► [“Correlation Analysis of Parallel Spike Trains,”](#) ► [“Dynamic Causal Modelling with Neural Population Models,”](#) ► [“Information Geometry as Applied to Neural Spike Data”](#)). Multivariate model extensions of the GLM using log linear models (Kass et al. 2011; Shimazaki et al. 2012) or simultaneous event multivariate point process (SEMPP) (Ba et al. 2014) models to analyze

synchrony in ensembles of neural spike trains at an arbitrary time resolution are now being developed (see entries ► [“Applications of Information Theory to Analysis of Neural Data,”](#) ► [“Information Measures of Redundancy and Synergy in Neural Activity”](#)). The SEMPP models use a marked point process representation to simulate ensemble neural spiking activity and can be fit using the multinomial extension of the iteratively reweighted least squares algorithm (Ba et al. 2014).

Cross-References

- [Applications of Information Theory to Analysis of Neural Data](#)
- [Correlation Analysis of Parallel Spike Trains](#)
- [Dynamic Causal Modelling with Neural Population Models](#)
- [Information Geometry as Applied to Neural Spike Data](#)
- [Information Measures of Redundancy and Synergy in Neural Activity](#)
- [Spike Train](#)
- [Spike Train Analysis: Overview](#)
- [State-Space Models for the Analysis of Neural Spike Train and Behavioral Data](#)

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GENESIS, the General NEural Simulation System

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Synonyms

GEneral NEural Simulation System

Definition

GENESIS (The *GEneral NEural Simulation System*) is a simulation environment for constructing realistic models of neurobiological systems at many levels of scale including subcellular processes, individual neurons, networks of neurons, and neuronal systems (Wilson et al. 1989; Bower 1992; Bower and Beeman 2006; Beeman 2013). First released to the public in July 1990, it was one of the first simulation systems specifically designed for modeling nervous systems and also one of the first open-source software projects in computational biology. As a consequence, the GENESIS software system has benefited from many different contributors and has been responsible for many technical innovations and advancements.

Detailed Description

GENESIS is written in C and was originally developed for UNIX platforms (Wilson et al. 1989), although it now also runs under Mac OS and with Windows under the Cygwin environment. Originally developed in the author's laboratory at Caltech, the system was first released in June of 1988 in association with the first annual Methods in Computational Neuroscience Course at the Marine Biological Laboratory in Woods Hole, MA and then released as full source code to the public via anonymous FTP in July 1990. GENESIS version 2.0 was released in August 1995, with the latest update (version 2.3) released in May 2006 (available through the web site <http://sourceforge.net/projects/genesis-sim>). GENESIS Version 3.0 (G-3) is currently in beta release (<http://genesis-sim.org>) and represents a backwards compatible but complete restructuring of the software system.

From the outset, GENESIS design has predicated on several assumptions regarding computational neuroscience. These include: (1) the construction of computer models based on actual anatomy and physiology would be essential to understanding the computational organization of the nervous system (Bower 1991b, 1992, 2005, 2013; Bower and Beeman 2007);

(2) understanding nervous system function would depend on being able to construct and link models at many different levels of biological scale (Bower 1991a). (3) growth of the modeling system would depend on the ability of individual modelers to develop and share model features and components; (4) the system should be as machine independent as possible; (5) successful use would depend on a graphical interface supporting users with a range of computer expertise (Uhley et al. 1989; Bhalla 1998); (6) considerable time, effort, and resources would need to be committed to user support; and (7) in order to build modeling expertise within the neuroscience community GENESIS should support use in education as well as research (Fig. 1 from Bower and Beeman 1994).

The commitment of the GENESIS project to educational use is reflected in its first release in the inaugural year of the Methods in Computational Neuroscience course at the Marine Biological Laboratory in Woods Hole, MA, as well as in

subsequent courses offered in Europe, Asia, and Latin America. The tutorials developed for those courses provided the basis for “The Book of GENESIS” published in two editions (Bower and Beeman 1994, 1998). That book (now available as a free download: <http://www.genesis-sim.org/GENESIS/bog/bog.html>), was written both to support undergraduate and graduate education in computational neuroscience as well as an introduction to modelers interested in using GENESIS for research.

The development of educational tutorials has continued, with web-based tutorials for both GENESIS 2.3 and G-3. The GENESIS Documentation Home Page (<http://genesis-sim.org/userdocs/documentation-homepage/documentation-homepage.html>) contains links for documentation and tutorials for both versions. The “Ultimate GENESIS Tutorial Distribution” (<http://genesis-sim.org/GENESIS/UGTD.html>) is a complete self-paced GENESIS modeling course, combined with GENESIS 2.3 distributions and installation instructions.

GENESIS, the GEneral NEural Simulation System, Fig. 1 Original cover for the Book of GENESIS (first edition) (used with permission Bower and Beeman 1994)



It provides an easy way to get everything for GENESIS 2.3 by downloading a single package.

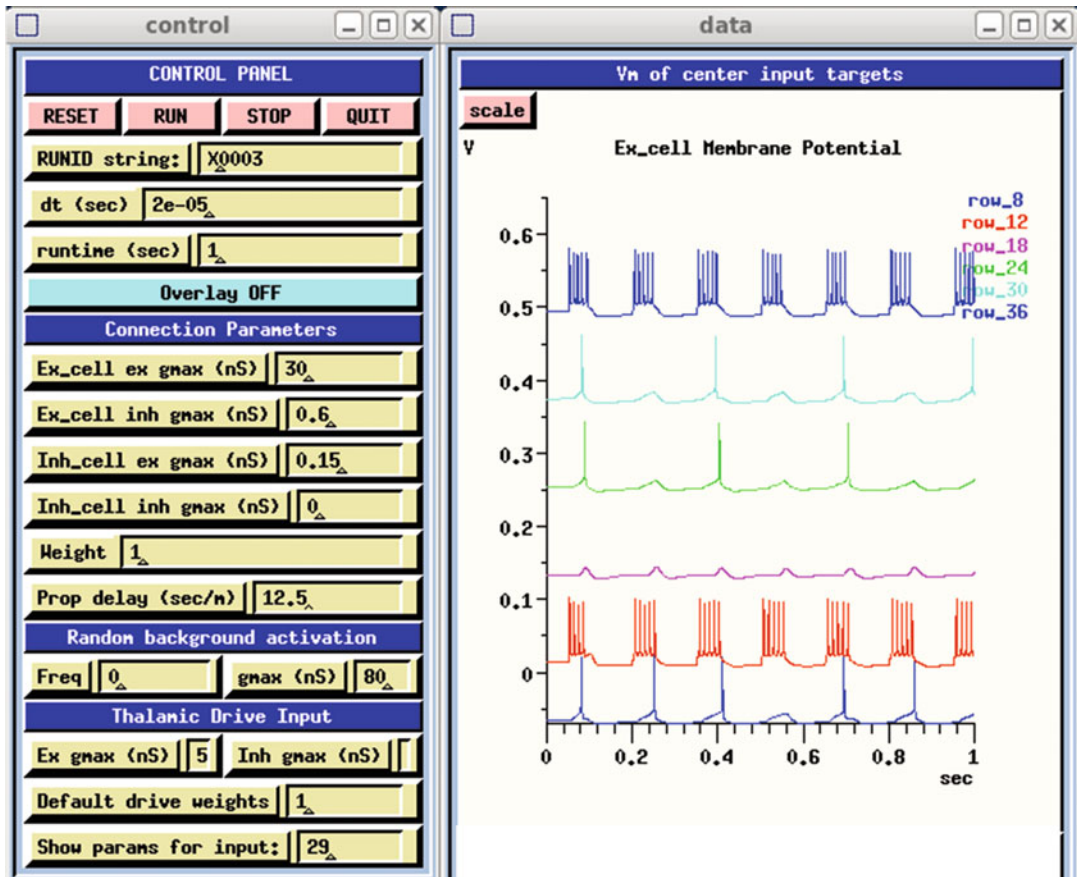
As one of the first neural simulations systems, the GENESIS project has also had a long history of innovation in the application of numerical simulation techniques to computational neuroscience. For example, GENESIS was one of the first open software systems in computational biology (Wilson et al. 1989); was the first simulation system supporting realistic modeling across a wide range of scales from large scale networks (Wilson and Bower 1989, 1991, 1992) to single neurons (De Schutter and Bower 1992) to subcellular (Blackwell et al. 2013); has fostered the application of new numerical simulation techniques for neurobiological modeling (Vanier and Bower 1999; Eichler West et al. 1997), was the first simulation system to promote quantifying parameter searches and modeling results (Bhalla and Bower 1993; Eichler West et al. 1997; Vanier and Bower 1996, 1999; Baldi et al. 1998); was one of the first computational modeling systems to be adapted for use on parallel computers (Bower et al. 1988; Nelson et al. 1989; De Schutter and Bower 1992), and was the first system to link geographically remote computers together in a single neuronal simulation (Leigh et al. 1993). The GENESIS project was also the first to propose standards against which to judge the speed and reliability of neural simulators (Bhalla et al. 1992, 1993), and was one of the first simulation systems to adopt the Python object-oriented declarative scripting language (Vanier 2001 thesis). From a user perspective, the GENESIS group was the first to develop a graphical interface specifically for use by neurobiologists for modeling (Uhley et al. 1990; Bower and Hale 1991; Forss et al. 1999), was the first to use virtual reality visualization techniques (Leigh et al. 1995), and was the first to use the Internet in support of intercommunication between neurobiologists and their modeling efforts (Leigh et al. 1995). The GENESIS project has pioneered the development of tools to convert neurobiological data into usable forms for models (West et al. 1997) and also pioneered the use of modeling databases as sources of biological data (Hucka et al. 2002). From the outset, the

GENESIS development group has also promoted and supported efforts to provide interoperability between neural simulators (Beeman and Bower 2004; Cannon et al. 2007; Crook et al. 2013), beginning with the Modelers Workspace project (www.modelersworkspace.org), which drafted and promoted the first markup language for realistic neural modeling (Goddard et al. 2001). That initial effort subsequently provided the foundation for the development of NeuroML (Crook et al. 2007; Gleeson et al. 2010) (<http://neuroml.org>), which, in turn, has fostered the development of simulator interoperability tools including neuroConstruct (Gleeson et al. 2007).

A Modeler's View of GENESIS

From the standpoint of a modeler who is implementing a neural model with GENESIS version 2.3 or 3.0, the object oriented interface presented to the user is one of its most useful features. The design of GENESIS simulations and their Graphical User Interfaces are based on a “building block” approach. Simulations are constructed from modules that receive inputs, perform calculations on them, and then generate outputs. Model neurons are constructed from compartments to which are added variable conductance ion channels forming multi-compartmental neurons of any desired level of complexity. Neurons can then be linked together to form neural circuits of any size. A high level scripting language is used to recognize commands for combining these objects into neuron, network or system level models, and to optionally create a custom GUI for the simulation, as shown in Figs. 2 and 3. GENESIS has also been adapted to modeling subcellular structures as well (Blackwell et al. 2013).

This object-oriented approach is central to the generality and flexibility of the system, as it allows modelers to easily exchange and reuse models or model components. In addition, it makes it possible to extend the functionality of GENESIS by adding new commands or simulation components to the simulator, without having to modify the GENESIS base code itself.



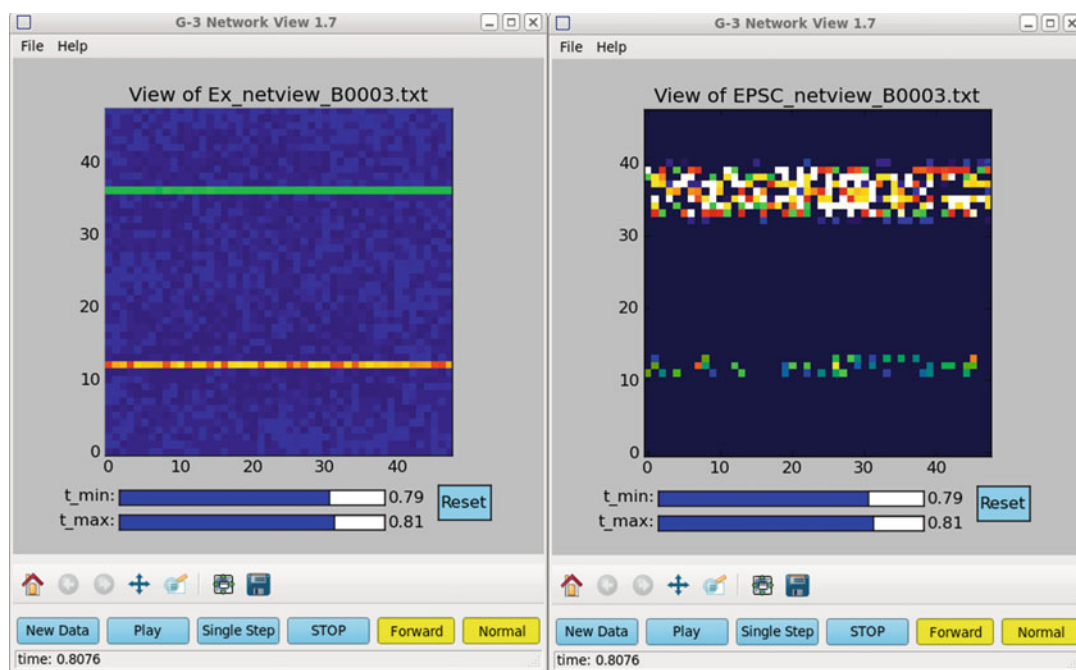
GENESIS, the GEneral NEural Simulation System, Fig. 2 A GUI for running a network simulation scripted with GENESIS 2.3

GENESIS 3 (G-3)

After the release of GENESIS 2.3, development efforts shifted to re-implementing GENESIS as a true twenty-first century simulation system (Beeman 2013), while preserving the most desirable features of the present version. This effort, known as GENESIS 3.0, or G-3, is intended to take simulator interoperability as well as flexibility in simulator design, development and use to a new level. With G-3 the GENESIS development group has completely restructured the historical monolithic core of GENESIS and reimplemented the system as a collection of independent software components. Based on the modular CBI architecture (Cornelis et al. 2012a), G-3 consists of a set of largely independent components which can be

used either individually or in combination to perform the functions desired in running a particular simulation. Keeping with the original design objectives for the GENESIS project, this modularization considerably enhances the ability to run models across different levels of biological scale, and greatly facilitates interactions between those levels.

By separating user-specified model description from their machine level implementation, G-3 simplifies the development of new mathematical solvers and other run-time software components. This separation also allows for an assessment of model structure independent of its algorithmic implementation, providing among other advantages, the opportunity to build a new form of model-based publication system (Cornelis et al.



GENESIS, the General NEural Simulation System, Fig. 3 View of the network membrane potential and summed excitatory post-synaptic currents produced by

the simulation in Fig. 1. This was produced by the G-3 Python 'netview' tool

2010). Through its modularization G-3 allows simulations to be run locally and/or distributed over networks (Coop et al. 2010). The use of multiple parsers for scripting simulations allows G-3 to maintain backwards compatibility with GENESIS 2.3, and to support the use of scripts written in modern scripting languages such as Python. The modular CBI architecture also provides a template for interacting with and even incorporating other software systems (Cornelis et al. 2012b). As the first truly modular neural simulation system, G-3 provides a plastic and extensible framework that is designed to represent the next step in evolution of simulation systems for computational neuroscience (Brette et al. 2007; Beeman 2013).

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GHK Current Equation

- [Goldman-Hodgkin-Katz Equations](#)

GHK Voltage Equation

- [Goldman-Hodgkin-Katz Equations](#)

Gillespie Algorithm for Biochemical Reaction Simulation

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Synonyms

[Stochastic Simulation Algorithm \(SSA\)](#)

Definition

The Gillespie Algorithm, also known as the Stochastic Simulation Algorithm (SSA), is a computer-oriented procedure for simulating the changes in the molecular populations of chemical species in a chemically reacting system. The algorithm requires the reactant molecules, typically solute molecules in a sea of many much smaller solvent molecules, to be dilute and well-mixed throughout the containing volume. In contrast to the traditional differential equations of chemical kinetics, which imposes not only those requirements but also the requirement that the molecular populations be very large, the SSA simulates the occurrence of individual reaction events in a way that properly reflects their inherent randomness. That randomness is often important for the relatively low molecular populations that commonly occur in cellular systems.

Since the middle of the nineteenth century, ordinary differential equations (ODEs) have been the standard mathematical tool for modeling the way in which molecular populations in chemically reacting systems evolve in time. The broad success of that modeling strategy is, however, a little surprising: ODEs prescribe a behavior that is

continuous and deterministic, yet molecules come in whole numbers, and they react chemically in ways that are largely random. Those features can be important when the molecular populations of some key reactants are relatively small, as in a biological cell.

The stochastic simulation algorithm (SSA), also known as the Gillespie algorithm (Gillespie 1976, 1977), is a procedure for numerically modeling the evolution of certain chemically reacting systems that takes proper account of the system's inherent discreteness and randomness. In the limit of infinitely large molecular populations that discreteness and randomness become imperceptible, and the SSA reduces to the ODEs of conventional deterministic chemical kinetics (Gillespie 2009a; Gillespie et al. 2013). Since those ODEs are thus a limiting approximation of the SSA, we cannot use them to derive the SSA. An honest derivation of the SSA must look to molecular physics to see how chemical reactions actually occur, and then adopt a mathematical formalism that accurately describes that physics.

The system of concern here is a collection of molecules of N chemical species $S_1, \dots, S_N$ which are confined to some volume Ω at some temperature T and which are undergoing M chemical reactions $R_1, \dots, R_M$. The goal is to numerically simulate the time evolution of $\mathbf{X}(t) \equiv (X_1(t), \dots, X_N(t))$, where $X_i(t)$ is the (integer) number of S_i molecules in Ω at time t . Importantly, each reaction R_j is assumed to be “elemental,” in that its occurrence as a physical event is effectively instantaneous on the time scale of interest. In cellular chemistry such reactions will practically always be one of two types: either unimolecular, in which a molecule suddenly experiences internal changes that alter its chemical character; or bimolecular, in which a chemical change is immediately triggered by the collision of two molecules. Trimolecular and reversible reactions in cells practically always occur as a series of two or more elemental reactions.

The unimolecular reaction $R_j : S_i \rightarrow \dots$ is inherently nondeterministic, usually for quantum mechanical reasons; there is no deterministic rule that predicts when a given S_i molecule will so react. But molecular physics implies that

the probability that a given S_i molecule will undergo this reaction in the next infinitesimally small time dt can usually be written $c_j \cdot dt$, where c_j is some constant (independent of both t and dt) that depends on the microphysical properties of an S_i molecule. Summing the probability over all $X_i(t)$ S_i molecules in Ω at the current time t then allows us to conclude, by the adding law of probability, that $X_i(t) \cdot c_j dt$ is the probability that an R_j event will occur somewhere inside Ω in the next dt .

The bimolecular reaction $R_j : S_i + S_k \rightarrow \dots$ is more problematic. A relatively simple physics argument (Gillespie 1976) shows that if the reactant molecules comprise a well-mixed dilute gas, then the probability that a randomly chosen $S_i - S_k$ molecular pair will undergo this reaction in the next dt can be written $c_j \cdot dt$, where the constant c_j is an explicit function of the physical properties of the two molecules, the system temperature T , and the system volume Ω . This dilute gas result was later extended (Gillespie 2009b; Gillespie and Seitaridou 2012) to the more biologically relevant case in which the S_i and S_k molecules are solute molecules in a well-mixed dilute solution with many smaller chemically inert solvent molecules. The c_j for the solution case is given by a more complicated formula than the c_j for the gas case; however, both are inversely proportional to Ω (whereas the c_j for a unimolecular reaction is independent of Ω). Moreover, the solution phase c_j limits to the gas phase c_j when the sum of the diffusion coefficients of the S_i and S_k molecules is sufficiently large. Summing the single-pair bimolecular reaction probability $c_j dt$ over all distinct pairs of S_i and S_k molecules in Ω at the current time t gives $X_i(t)X_k(t) \cdot c_j dt$ for the probability that an R_j event will occur in the next dt when $k \neq i$, or $\frac{1}{2}X_i(t)(X_i(t) - 1) \cdot c_j dt$ if $k = i$.

Thus, at least for chemical systems in which the reactant molecules are dilute and well-mixed in a bath of many much smaller chemically inert molecules, there will exist for each elemental reaction R_j a function a_j of the current species populations $\mathbf{x} = (x_1, \dots, x_N)$ which is such that $a_j(\mathbf{x}) \cdot dt$ gives the probability that an R_j event will occur somewhere inside Ω in the next infinitesimal time interval $[t, t + dt)$. This function a_j is

called the propensity function for reaction R_j because it quantifies the propensity for R_j to fire. It has the form $a_j(\mathbf{x}) = c_j x_i$ for a unimolecular reaction, and the forms of either $a_j(\mathbf{x}) = c_j x_i x_k$ or $a_j(\mathbf{x}) = c_j x_i (x_i - 1)$ for a bimolecular reaction.

Propensity functions are closely related to the “reaction rates” of deterministic chemical kinetics; however, the latter are derived from the former, not vice versa. Whether propensity functions exist for other kinds of cellular environments, such as where the reactant molecules are not dilute or where they move by active mechanisms along actinic pathways, and if so what forms such propensity functions take, are questions that can be answered only by a careful analysis of the underlying molecular physics of the specific situation.

Each reaction channel R_j is mathematically defined not only by its propensity function $a_j(\mathbf{x})$ but also by its state-change vector $\mathbf{v}_j \equiv (v_{1j}, \dots, v_{Nj})$. Here, v_{ij} is the (signed integer) change in the molecular population of species S_i caused by one R_j event, i.e., an R_j reaction induces the state change $\mathbf{x} \rightarrow \mathbf{x} + \mathbf{v}_j$. The SSA asks, and then answers, the following question: Assuming propensity functions exist, then given the system is in state $\mathbf{x}$ at the current time t , at what time $t + \tau$ will the next reaction in the system occur, and which R_j will that next reaction be? Since the probabilistic character of the propensity functions implies that τ and j must be random variables, the answer to this question can be supplied only by the joint probability density function (PDF) of τ and j . That function is denoted by $p(\tau, j | \mathbf{x}, t)$, and it is defined so that $p(\tau, j | \mathbf{x}, t) \cdot d\tau$ gives the probability that the next reaction event in the system will occur in the infinitesimal time interval $[t + \tau, t + \tau + d\tau)$ and will be a reaction R_j . From the definition of the propensity function, it can be proved using only the laws of probability that (Gillespie 1976)

$$p(\tau, j | \mathbf{x}, t) = e^{-a_0(\mathbf{x})\tau} a_j(\mathbf{x}),$$

where $a_0(\mathbf{x}) \equiv \sum_{k=1}^M a_k(\mathbf{x})$. The SSA is thus the following computational procedure:

1. In state $\mathbf{x}$ at time t , evaluate (as necessary) $a_1(\mathbf{x}), \dots, a_M(\mathbf{x})$ and their sum $a_0(\mathbf{x})$.

2. Generate two random numbers τ and j according to the above joint PDF.
3. Actualize the next reaction by replacing $t \leftarrow t + \tau$ and $\mathbf{x} \leftarrow \mathbf{x} + \mathbf{v}_j$.
4. Record $(\mathbf{x}, t)$. Return to step 1, or else end the simulation.

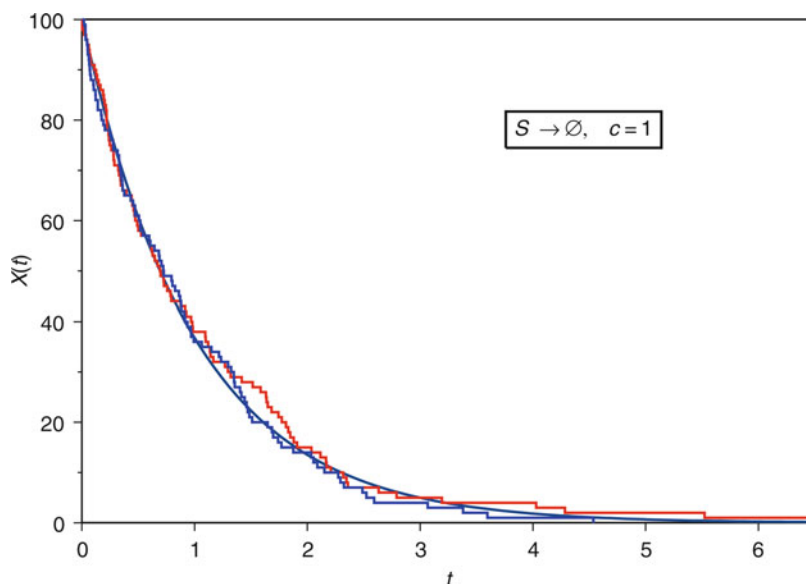
Step 2 of the SSA can be implemented using any of several different exact “methods.” Two such methods were presented in Gillespie (1976): the direct method, which follows from a straightforward application of the well-known inversion Monte Carlo generating technique to the above joint PDF, and the first reaction method, which is less straightforward but nonetheless exact. The direct method is usually more efficient, and it goes as follows: Draw two unit-interval uniform random numbers u_1 and u_2 and take

$$\tau = \frac{1}{a_0(\mathbf{x})} \ln \left(\frac{1}{1 - u_1} \right),$$

$j =$ the smallest integer satisfying $\sum_{k=1}^j a_k(\mathbf{x}) > u_2 a_0(\mathbf{x})$.

Figure 1 shows the results of two SSA runs for the simple reaction $S \rightarrow \emptyset$ obtained using this method. Other exact methods of implementing step 2 have been developed that offer certain computational advantages in special situations. Notable among these are the next reaction method (Gibson and Bruck 2000), the optimized direct method (Cao et al. 2004), the sorting direct method (McCollum et al. 2006), the modified next reaction method (Anderson 2007), and the composition-rejection method (Slepoy et al. 2008). A critique of the efficiencies of these and several other methods is given in (Mauch and Stalzer 2011).

The strength of the SSA is also its weakness: simulating the occurrence of every reaction event one at a time, no matter what method is used to implement step 2, often requires too much computer time. One approximate strategy for getting around that problem is a procedure called tau-leaping (Gillespie 2001), a much improved version of which is described in (Cao et al. 2006) and (Gillespie 2008). Tau-leaping solves some, but



Gillespie Algorithm for Biochemical Reaction Simulation, Fig. 1 The red and blue stair-step curves show the results of two independent runs of the SSA for the chemical reaction $S \xrightarrow{c} \emptyset$ with $c = 1$ and $x_0 = 100$. In this simple one species/one reaction example, $a(x) = x$ and $\nu = -1$. After each generation of a value for τ using the direct method formula, t was increased by τ and the population was decremented by 1. Note that the trajectory thus produced

is complete, since the population stays constant between successive reactions. The smooth black curve is the solution $x_0 \exp(-ct)$ of the traditional ODE for this reaction, $dX(t)/dt = -cX(t)$. It shows the average of infinitely many trajectories; however, any single trajectory will always have the discrete-stochastic character of the two colored curves

not all, of the slowness problems of the SSA. It is also important because it provides a logical bridge between the SSA and the ODEs of traditional chemical kinetics, since it reduces to those ODEs in the limit of an infinitely large system (Gillespie 2009a; Gillespie et al. 2013).

Relaxing the “well-mixed” requirement of the SSA requires expanding the definition of the system’s state to include information on where the reactant molecules are inside Ω . One way of doing that is to imagine Ω to be subdivided into K identical subvolumes or voxels $\Omega_1, \dots, \Omega_K$, which are small enough that the well-stirred condition holds inside each Ω_k . The M nominal reactions $\{R_j\}$ are then replaced by the MK reactions $\{R_{jk}\}$, where R_{jk} is reaction R_j inside voxel Ω_k . The propensity function for R_{jk} is a_j , but now referred to as Ω_k and regarded as a function of $\mathbf{x}_k = (x_{1k}, \dots, x_{Nk})$, where x_{ik} is the current number of S_i molecules inside Ω_k . And the state-change vector

for R_{jk} is $\boldsymbol{\nu}_j$, but now confined to the space of $\mathbf{x}_k$. Diffusion of a single S_i molecule from voxel Ω_k to an adjacent voxel Ω_l is modeled as a “diffusive transfer reaction” R_{ikl}^d whose propensity function is $\kappa_i x_{ik}$, where κ_i is a constant chosen to agree with the diffusion equation (Gillespie and Seitaridou 2012), and whose state-change vector decreases x_{ik} by 1 and increases x_{il} by 1. Since diffusion between voxels is mathematically modeled in the same way (using propensity functions) as the chemical reactions inside voxels, the system can be simulated using the SSA with the following straightforward replacements: the N -dimensional state vector $\mathbf{x} = \{x_i\}$ is replaced by the NK -dimensional state vector $\{x_{ik}\}$, and the M reactions $\{R_j\}$ are replaced by the MK chemical reactions $\{R_{jk}\}$ plus the $2NB$ diffusive transfer reactions $\{R_{ikl}^d\}$, where B is the total number of boundary surfaces between adjacent subvolumes.

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GIRK Channels

- [Inward Rectifier Potassium Channels](#)

Glomerular Layer

- [Large-Scale Models of the Olfactory Bulb](#)

Goldman-Hodgkin-Katz Equations

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Synonyms

[GHK current equation](#); [GHK voltage equation](#)

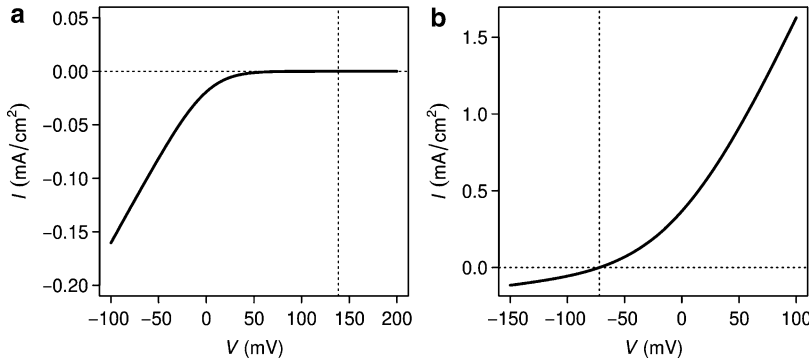
Definition

There are two Goldman-Hodgkin-Katz (GHK) equations: the GHK voltage equation and the GHK current equation. The GHK voltage equation gives the membrane potential expected to result from multiple ion species at differing concentrations on either side of the membrane. The GHK current equation gives the transmembrane current of an ion species expected at a given membrane potential for a given concentration of the ion on either side of the membrane. Both equations are derived from the Nernst-Planck equation with a constant field assumption in the membrane. This assumption is not generally true in ion channels, but the equations are a useful approximation for neuronal modelling.

Detailed Description

Physical Basis

The GHK equations apply when one or more ion species exist on both sides of a membrane permeable to them. The electrical and diffusive influences on each ion are not necessarily at equilibrium, and thus there can be a net flow of



Goldman-Hodgkin-Katz Equations, Fig. 1 I - V characteristics computed from the GHK current equation. (a) Calcium at an intracellular concentration of 10^{-4} mM and extracellular concentration of 10 mM. The dotted vertical

line indicates the equilibrium potential calculated from the Nernst equation. (b) Potassium at an intracellular concentration of 400 mM and an extracellular concentration of 20 mM.

each ion species through the membrane. This is in contrast to the situation in which there is an equilibrium between electrical and diffusive influences on an ion species, in which case the Nernst equation applies. The GHK equations are derived from a theory in which it is assumed that the electric field in a membrane is constant. This is not generally true (Hille 2001), but the GHK equations are nevertheless a good approximation for describing current flow through ion channels.

The GHK Current Equation

The GHK current equation (Goldman 1943; Hodgkin and Katz 1949) for an ion species X gives the per-unit area current I_X carried by that ion as a function of the permeability P_X of the membrane to the ion, the membrane potential V , the intracellular and extracellular concentrations of the ion $[X]_{\text{in}}$ and $[X]_{\text{out}}$, and the valency z_X of the ion:

$$I_X = P_X z_X F \frac{z_X F V}{RT} \left(\frac{[X]_{\text{in}} - [X]_{\text{out}} e^{-z_X F V / RT}}{1 - e^{-z_X F V / RT}} \right)$$

where F is Faraday's constant, R is the molar gas constant, and T is the temperature in kelvins. By convention, a positive current is defined as an outward flow of positive charge and a negative current as an inward flow of positive charge.

A plot of the GHK calcium current versus the membrane potential (an I - V characteristic) is

shown in Fig. 1a. When the membrane potential is equal to the equilibrium potential for calcium, as given by the Nernst equation, the current is equal to zero. When the membrane potential is less than the equilibrium potential, the current is inward (negative), and when the membrane potential exceeds the equilibrium potential, it is outward (positive). The inward currents are much greater than the outward currents, demonstrating inward rectification. The greater the difference between the intracellular and extracellular concentrations, the greater the degree of rectification. An I - V characteristic for potassium (Fig. 1b) shows a much weaker degree of outward rectification. Inward rectification occurs when the extracellular concentration of the ion exceeds the intracellular concentration.

The GHK Voltage Equation

The GHK voltage equation describes the equilibrium potential reached when multiple ion species exist in solution around a membrane that is permeable to each species. It is derived from the GHK current equations by computing the value of the membrane potential at which the sum of all ionic currents across the membrane is zero. Note that this does not mean that each ion species is in equilibrium, since the membrane potential is likely not to correspond to the equilibrium potential of any one species.

For a membrane permeable to sodium, potassium, and chloride ions, the GHK voltage equation derived from the GHK current equations is

$$V = V_{\text{in}} - V_{\text{out}} \\ = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{\text{Na}}[\text{Na}^+]_{\text{out}} + P_{\text{Cl}}[\text{CT}]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{\text{Na}}[\text{Na}^+]_{\text{in}} + P_{\text{Cl}}[\text{CT}]_{\text{out}}}$$

where P_K , P_{Na} , and P_{Cl} are the membrane permeabilities to K^+ , Na^+ , and Cl^- , respectively. Note that within the logarithmic term the outside and inside concentrations of cations (K^+ and Na^+ in this case) are on the numerator and denominator, respectively, whereas it is the other way round for the anions (Cl^- this case). The form of this equation is possible because all the ions are monovalent. It is also possible to derive a GHK voltage equation that includes monovalent and divalent ions, but its form is more complex, as it involves the solution of a quadratic equation.

Derivation

Hille (2001) and Johnston and Wu (1995) present accessible derivations of the GHK current equation.

Cross-References

► [Nernst Equation](#)

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Granule Cells

► [Large-Scale Models of the Olfactory Bulb](#)

Graph Analysis

► [Connectivity Analysis in Normal and Pathological Brains](#)

Graph Theory in Neuroscience

► [Network Theory in Neuroscience](#)

Gravity Analysis of Parallel Spike Trains

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Definition

The gravity representation is a mapping of the spiking activity of N neurons into a mechanical model. The method originated with an effort to measure plant similarity (Wright 1977). In the present context, each neuron is represented by a particle moving in an N -dimensional space. Action potentials produce transient “charges” on the particle which corresponds to the neuron which fired. The particles move according to forces caused by attraction or repulsion of the charges; any near-coincidence structure in the neuronal firing is transformed into aggregation of the model particles. The speed and dynamics of the clustering process can be interpreted in terms of the dynamics of the underlying neuronal interactions. The gravity representation is mostly useful as a screening stool to identify interacting neurons that should be further studied.

Detailed Description

In the N -dimensional space, the initial position of the i -th particle along the j -th axis is given by

$$\mathbf{x}_i^j = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases} \quad (1)$$

The charge on particle i at time t is given by

$$q_i(t) = \sum_k K(t - T_k) - \lambda_i \quad (2)$$

Here T_k are the times of the spikes fired by this cell, and $K(t)$ is a kernel function which is convolved with the spike train. The kernel function is assumed to have unit area and is frequently taken as a simple decreasing exponential with a time constant τ .

Particle positions are adjusted according to the pairwise attractions between particles. Thus, using a discrete time step of δt , the position update rule is

$$\mathbf{x}_i(t + \delta t) = \mathbf{x}_i(t) + \kappa \delta t \sum_{j \neq i} Q_{i,j} \frac{\mathbf{x}_j - \mathbf{x}_i}{|\mathbf{x}_j - \mathbf{x}_i|} \quad (3)$$

where

$$Q_{i,j} = q_i q_j \quad (4)$$

Note that this is an update rule that has velocity rather than acceleration proportional to attractive force. In real physical systems, this would only occur over a narrow range of conditions for particles moving in a viscous medium.

With the above equations, there will be aggregation of the particles representing approximately synchronously firing neurons, while particles representing independent neurons will remain roughly near their starting points in the N -dimensional space. Such aggregations cannot be directly visualized because they are N -dimensional and their detection is generally a problem in cluster analysis. However, we have found several simple and useful graphical methods that reduce the dimensionality for visualization (Gerstein et al. 1985; Dayhoff 1994; Gerstein 2010).

A useful visualization method graphs the time course of the distance between particles for each pair of particles. The distance between any two particles in the N space is a vector quantity, but here we will consider only its magnitude. For N neurons there will be $N(N-1)/2$ intra-pair distance trajectories. The trajectories for pairs involving independent neurons will remain (noisily) at the initial distance value; trajectories for pairs involving synchronous neurons will slope downwards at rates related to the strength of the synchrony.

Projection of the N -dimensional system to a two-dimensional plane loses information, can produce spurious particle aggregation, and must be carefully checked against the pair distance data. However, such projection allows direct visualization of the development of the particle movements and their interpretation in terms of neuronal interactions. We have found a simple geometric projection convenient for small numbers of neurons (e.g., $N < 20$). Here the projection plane is determined by the centers of gravity of various particle combinations and hence is a dynamic rather than a fixed plane (Gerstein and Aertsen 1985).

Many variations of the basic gravity rules serve particular analysis purposes and can be found in the original literature (e.g., Baker and Gerstein 2000). One example is to use two different kernels for the “charge” on each particle, one for when the particle is being moved (i in Eq. 3) and the other for when the particle is one of the movers (j in Eq. 3). If these two kernels are, respectively, a falling exponential and a rising exponential, the i particle will move only when it represents a pre-synaptic neuron.

The greatest utility of the gravity representation is the identification of those neurons in an ensemble recording that are interacting (as evidenced by their timing relations) as illustrated, e.g., in Maldonado and Gerstein (1996), Lindsey et al. (1992, 1997), and Arata et al. (2000) and hence worthy of more detailed study. However, the basic method is limited in its ability to define the nature of the neuronal

interactions and the detailed diagram of the effective connectivities.

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Spatial Temporal Spike Pattern Analysis](#)
- [Unitary Event Analysis](#)

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Green's Function, Axonal

- [Propagator, Axonal](#)

H

H - Current

- [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)

Haken-Kelso-Bunz Model

- [Coordination Dynamics](#)

HCN Channels Hyperpolarization-Activated Current

- [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)

Hearing

- [Auditory Processing in Insects](#)

Heat Equation

- [Diffusion Equation](#)

Hebb's Postulate of Learning

- [Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits](#)

Hebbian Conditioning Paradigms

- [Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits](#)

Hebbian Learning

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Definition

Hebbian learning is a form of activity-dependent synaptic plasticity where correlated activation of pre- and postsynaptic neurons leads to the strengthening of the connection between the two neurons. The learning principle was first proposed by Hebb (1949), who postulated that a presynaptic neuron A, if successful in repeatedly activating a postsynaptic neuron B when itself (neuron A) is

active, will gradually become more effective in activating neuron B. The concept is widely employed and investigated in both experimental and computational neuroscience.

Detailed Description

In this article, we will review computational formulations and theoretical bases of Hebbian learning and its variants. We will also briefly review neurobiological underpinnings of Hebbian learning. See Frégnac (2003), Gerstner and Kistler (2002), Shouval (2007), and Dayan and Abbott (2001) for a more in-depth review of this topic.

Basic Formulations

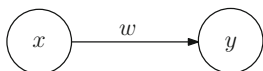
The formulation in this subsection closely follows that of Dayan and Abbott (2001). Consider a presynaptic neuron with activity x and a postsynaptic neuron with activity y connected by a synapse with weight (strength, efficacy) w , as shown in the figure below (Fig. 1). The activities and weights are commonly represented with positive real numbers.

The simplest formulation of Hebbian learning based on the above configuration results in the following weight update rule

$$\frac{dw}{dt} = \eta xy, \quad (1)$$

where the learning rate η is a small fixed positive value. This rule requires that both presynaptic and postsynaptic neurons are active in order to adjust the connection weight, thus faithfully implementing Hebbian learning.

When there are multiple input neurons feeding into a single output neuron (Fig. 2), all the incoming weights can be represented as a column vector $\vec{w}$, and averaging ($\langle \cdot \rangle$) over multiple input vectors,



Hebbian Learning, Fig. 1 A single presynaptic neuron connected to a single postsynaptic neuron

Eq. 1 can be written as the input correlation matrix (Q) times the weight vector.

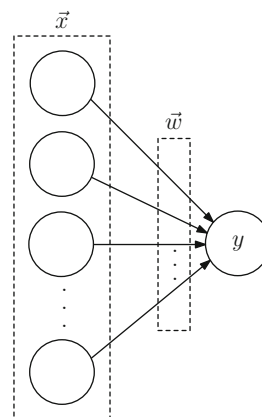
$$\frac{d\vec{w}}{dt} = \langle \vec{x} \vec{x}^T \rangle \vec{w} = Q \vec{w}, \quad (2)$$

since $y = \vec{w}^T \vec{x}$. Thus, this learning rule is often called the “correlation-based rule.”

An obvious shortcoming of this approach is that the weight will increase (synaptic potentiation) without bound, since every time weight is updated, the value is incremented by a positive quantity. One quick way to overcome this problem is to impose thresholds θ_x and/or θ_y (see, e.g., Linsker 1988; for a review, see Frégnac 2003; Shouval 2007)

$$\frac{d\vec{w}}{dt} = \eta (\vec{x} - \vec{\theta}_x) (y - \theta_y), \quad (3)$$

so that neuronal activity falling below the threshold would result in a decrease in the synaptic weight (synaptic depression; see Stent 1973 for a discussion on such thresholding mechanisms). Note that when Eq. 3 is generalized to multiple inputs as in Eq. 2 and the thresholds are set to the mean input vector or the mean output value, the input correlation matrix Q is replaced by the input covariance matrix C (the “covariance rule”; see Sejnowski 1977). However, this kind of threshold mechanism alone (when the threshold is fixed) is not enough to prevent unchecked growth of the synaptic weight (Dayan and Abbott 2001).



Hebbian Learning, Fig. 2 Multiple presynaptic neurons connected to a single postsynaptic neuron

Preventing Unbounded Growth of the Synaptic Weight

There are two types of mechanisms to limit unbounded growth in synaptic weight: (1) adaptive threshold and (2) weight normalization.

A representative example of the adaptive threshold-based approach is the BCM (Bienenstock, Cooper, and Munro) rule (Bienenstock et al. 1982), where a variant of Eq. 3 is used ($\vec{\theta}_x = \vec{0}$), along with a threshold adaptation rule (on the postsynaptic threshold θ_y) that depends on the output activity y . Following the formulation in Dayan and Abbott (2001), we get

$$\frac{d\theta}{dt} = \eta_\theta (y^2 - \theta_y), \quad (4)$$

where η_θ is a fixed adaptation rate for the threshold update rule.

Weight normalization-based approaches basically impose constraints on synaptic plasticity (Miller and MacKay 1994; von der Malsburg 1973) and can be classified further into two types where (1) the sum of weights is kept constant or (2) the sum of squares of the weights (or the square root of it, i.e., the length of the weight vector) is kept constant. Such normalization can be done by simply updating all the weights based on the basic learning equation (Eq. 1) and then dividing all weights with the sum of weights or the sum of squared weights. Alternative implementations of these two types take a dynamic form, where the terms that are involved in weight normalization are directly built into the dynamic learning equation. In this context, the sum of weight-based normalization is also called subtractive normalization, and the sum of squared weight-based one called multiplicative normalization (Miller and MacKay 1994). The latter, which is based on a power series expansion of the division by sum of squared weights (length of weight vector, to be more precise) approach, leads to Oja's rule (once the higher order terms are dropped)

$$\frac{d\vec{w}}{dt} = \eta (y\vec{x} - y^2\vec{w}), \quad (5)$$

where the first term on the right-hand side ($y\vec{x}$) implements basic Hebbian learning, while the second term ($-y^2\vec{w}$) serves the normalization function (Oja 1982).

Theoretical Perspectives

Hebbian learning has been intensively analyzed for its theoretical, computational properties. The key question in this case is what kinds of optimization principles are implemented by the Hebb rule.

One of the earliest discoveries in this respect was made by Oja (1982), where the formulation in Eq. 5 was shown to converge to the first principal component of the inputs (the eigenvector of the input correlation matrix with the largest eigenvalue; also see Amari 1977). Subsequent analysis by Linsker (1988) showed that Hebbian learning can serve various optimization functions: (1) maximize the postsynaptic neuron's activity variance (cf. Oja 1982), (2) maximize variance in the postsynaptic neuron's activity while minimizing the variance due to processing noise, and (3) maximize information preservation between the presynaptic and postsynaptic neurons' activity (i.e., maximize the mutual information between the input and the output).

General learning algorithms such as self-organizing maps (SOM), Hopfield network, error backpropagation learning, temporal difference learning, and independent component analysis can also be interpreted under a Hebbian learning framework (see Kohonen 1993; Hopfield 1982; Xie and Seung 2003; Rao and Sejnowski 2001; Hyvärinen and Oja 1998, respectively).

Neurobiological Underpinnings

Hebbian learning has served as an important theoretical construct to guide experimental research. Efforts in this direction led to the discovery of long- and short-term synaptic plasticity that appears to embody a Hebbian principle, most notably in the hippocampus. A comprehensive

review of long-term synaptic plasticity (long-term potentiation, long-term depression) can be found in Bliss and Collingridge (1993), Dudek and Bear (1992), and a similar treatment of short-term plasticity (spike timing-dependent plasticity) in Caporale and Dan (2008). Here, we will briefly go over some of the main findings reviewed in these articles.

Long-term potentiation (LTP) refers to a prolonged increase in synaptic efficacy (weight) following high-frequency stimulation (Bliss and Collingridge 1993). The phenomenon was first discovered in the hippocampus, and the *N*-methyl-d-aspartate (NMDA) receptor, a subtype of glutamate receptor, is known to play a key role, as well as the intracellular Ca^{2+} concentration. Long-term depression (LTD), on the other hand, is a phenomenon where low-frequency stimulation leads to a prolonged decrease in synaptic efficacy (Dudek and Bear 1992). An interesting fact is that these phenomena seem to be governed by some type of activity threshold. These mechanisms, together, are believed to form the cellular basis of Hebbian learning (see Beggs 2000 for a statistical analysis of LTP and LTD and their relation to the BCM rule). Experimental findings also suggest how weight normalization could be done at these synapses: it has been shown that changes in the efficacy of a single synapse can have a scaling effect on other synapses in the same neuron. This mechanism is called homeostatic plasticity (see Turrigiano 1999 for a review). Finally, a spike timing-dependent mechanism that seems to embody Hebbian principles has been found, where the relative ordering of pre- and postsynaptic events leads to an asymmetric behavior – potentiation or depression – depending on the causal order of events. This is known as spike timing-dependent plasticity, and it is being actively investigated in relation to Hebbian learning (see Caporale and Dan 2008 for a review).

Applications of Hebbian Learning

Hebbian learning and similar mechanisms have found wide usage, including unsupervised learning tasks and modeling cortical development (see,

e.g., Miikkulainen et al. 2005). See McClelland (2006) for a discussion of applications of Hebbian learning in biological and psychological development.

Cross-References

- ▶ [Anti-Hebbian Learning](#)
- ▶ [Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits](#)
- ▶ [Spike-Timing Dependent Plasticity, Learning Rules](#)

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Hebbian Plasticity

- [Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits](#)

Heptahelical Receptors

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Heteroassociative Networks

- [Olfactory Cortical Associative Memory Models](#)

Hierarchical Models of the Visual System

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Synonyms

[Deep learning architectures](#); [Hubel and Wiesel model](#); [Large-scale models of the visual system](#); [Simple-to-complex hierarchies](#); [Ventral stream](#)

Definition

Hierarchical models of the visual system are neural networks with a layered topology. The receptive fields of units (i.e., the region of visual space to which units respond) at one level of the hierarchy are constructed by combining inputs from units at a lower level. After a few processing stages, small receptive fields tuned to simple stimuli get combined to form larger receptive fields tuned to more complex stimuli. Such an anatomical and functional hierarchical architecture is a hallmark of the organization of the visual system. In feedforward networks, information flows in a bottom-up fashion – from lower to higher processing stages. In feedback networks, information is able to dynamically reenter processing stages via recurrent connections. Feedback connections can be broadly divided between horizontal or lateral connections within processing stages and top-down connections from higher onto lower processing stages.

Since the pioneering work of Hubel and Wiesel (1962), a variety of hierarchical models have been proposed, from relatively small-scale models of the primary visual cortex to very large-scale (system-level) models of object and action recognition, which account for visual processing in entire visual streams. The term “model of the visual system” is generally reserved for

architectures that are constrained in some way by the anatomy and the physiology of the visual system (with various degrees of realism). Deep convolutional networks are architecturally similar neural networks that have led to impressive results in a wide range of engineering disciplines, from computer vision to natural language processing, and artificial intelligence more broadly.

Detailed Description

The feedforward flow of visual information in the ventral stream of the visual cortex is carried by ascending projections from the retina, through the lateral geniculate nucleus (LGN) of the thalamus to the primary visual cortex (V1) and extrastriate visual areas, V2 and V4, and culminating in the inferotemporal (IT) cortex. In turn, IT provides a major source of input to the prefrontal cortex (PFC), which is involved in linking perception to memory and action (see DiCarlo et al. 2012, for review). A single feedforward pass through the visual cortex rapidly produces a coarse image representation sufficient for rapid object classification. Evolutionarily, such rapid feedforward processing might have been enabled the split-second detection of predators necessary for survival (Thorpe et al. 2001).

The function of feedback/recurrent connections are less well understood. By “feedback,” we mean those connections which carry information either from a higher to a lower cortical area (top-down feedback) or within a cortical area (lateral or horizontal feedback). Top-down feedback is mediated by descending projections connecting, for example, V2, V4, and IT to V1 or V1 to LGN (see Pennartz et al. 2019, for a review). These descending projections generally outnumber ascending ones. It is speculated that feedback serves primarily to modulate rather than drive activity in lower areas (Gilbert and Li 2013). Accordingly, circuits with recurrent connections have been implicated in the dynamic maintenance of image representations via attention and working memory (Gazzaley and Nobre 2012) and other modulatory processes (Lamme et al. 1998;

Angelucci and Shushruth 2013; Gilbert and Sigman 2007).

The goal of hierarchical models of the visual cortex is to explain how cortical anatomy and physiology, particularly the hierarchical arrangement of visual areas, give rise to complex visual behaviors including object recognition. Such models can be broadly classified into feedforward and feedback varieties and have their origin in computational neuroscience, where biological realism is the primary concern. Recently, however, computer vision models, notably deep convolutional neural networks (CNNs), have emerged as the best predictors of neural activity (see Serre (2019) for a review), despite their being largely unconstrained by biology.

First, we will provide an overview of feedforward hierarchical models of the visual cortex. One of the primary objectives of these models is to explain rapid visual categorization (see Serre (2016) for a review). Consequently, feedforward hierarchical models must address the ability of feedforward cortical pathways to extract features which are both selective for natural object recognition and invariant to irrelevant image transformations, including pose and illumination. The balancing of these two factors is sometimes called the “invariance-selectivity” trade-off (Geman 2006). Second, we will turn to feedback models of visual processing. These network models seek to explain how an initial, coarse feedforward representation can be dynamically manipulated with executive, mnemonic, and other processes. Finally, we will briefly discuss the problem of learning in hierarchical models.

Feedforward Hierarchical Models

Feedforward hierarchical models of the visual system have a long history starting with Marko and Giebel (1970)’s homogeneous multilayered architecture and later Fukushima (1980)’s neocognitron. One of the key principles in the neocognitron and other modern hierarchical models originates from the pioneering physiological studies and models of Hubel and Wiesel (1962). In these networks, the receptive fields of units at one

level of the hierarchy are constructed by combining inputs from units at a lower level. Numerous feedforward models of the ventral stream of the visual system have been described since the neocognitron to account for the organization and the neurophysiology of the ventral stream of the visual cortex. These models can be coarsely divided into conceptual proposals (Biederman 1987; Perrett and Oram 1993; Hochstein and Ahissar 2002) and neurobiological models (e.g., Wallis 1997; Mel 1997; Riesenhuber and Poggio 1999; Ullman et al. 2002; Thorpe 2002; Amit and Mascaro 2003; Wersing and Koerner 2003; Serre et al. 2007; Masquelier and Thorpe 2007). Similar hierarchical models have also been proposed to explain motion processing in the dorsal stream of the visual cortex (e.g., Simoncelli and Heeger 1998; Grossberg et al. 1999; Perrone and Thiele 2002; Giese and Poggio 2003; Rust et al. 2006; Jhuang et al. 2007; Pack and Born 2008; Mineault et al. 2012).

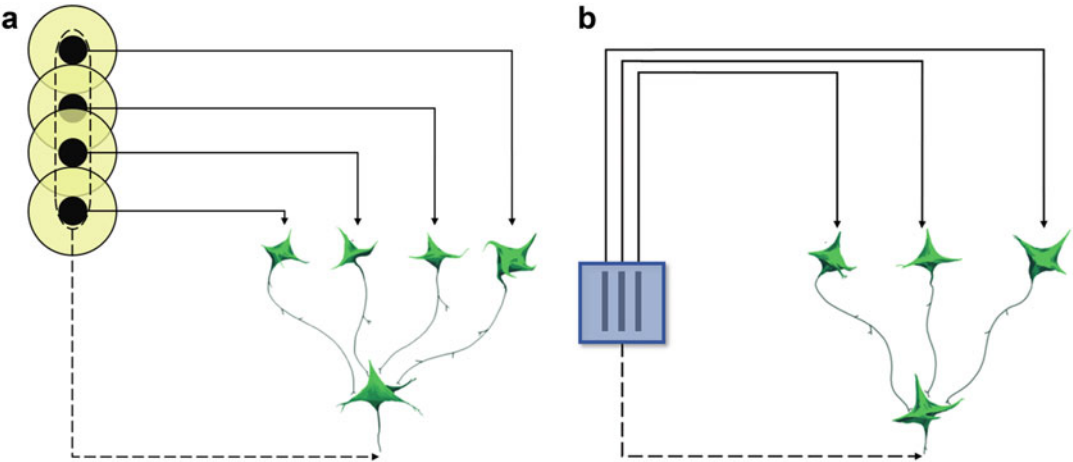
Somewhat independently, convolutional neural networks (CNNs) and other deep learning architectures have been developed in computer vision (see LeCun et al. 2015, for review). CNNs typically involve two processing stages: a feature extraction stage, in which visual information is passed through layers of computing units having small receptive fields, and a classification stage, in which the resultant features are combined by “fully connected” units having global receptive fields. In the most common computer vision setting, the parameters of these models are gradually adjusted by the backpropagation algorithm to minimize classification error on a large data set of labeled images. After supervised training, the network approximates a function from the space of natural images to a set of discrete object labels. These neural networks do not mimic the organization of the visual system in detail, but biology is often cited as a source of inspiration, and they nevertheless provide a better fit to experimental data than earlier biological models (Yamins et al. 2014).

Modeling of feedforward pathways in the visual cortex begins with the description of primary visual cortex by Hubel and Wiesel (1962). Hubel and Wiesel famously described two

functional classes of cortical cells: simple cells, which respond to oriented stimuli (e.g., bars, edges, gratings) at particular orientations, and complex cells, which, while also tuned to oriented stimuli, tend to have larger receptive fields and exhibit some tolerance to the exact position of the stimulus within their receptive fields. A V1-like circuit is shown in Fig. 1, which connects a complex cell to an array of simple cells tuned to the same feature at neighboring locations.

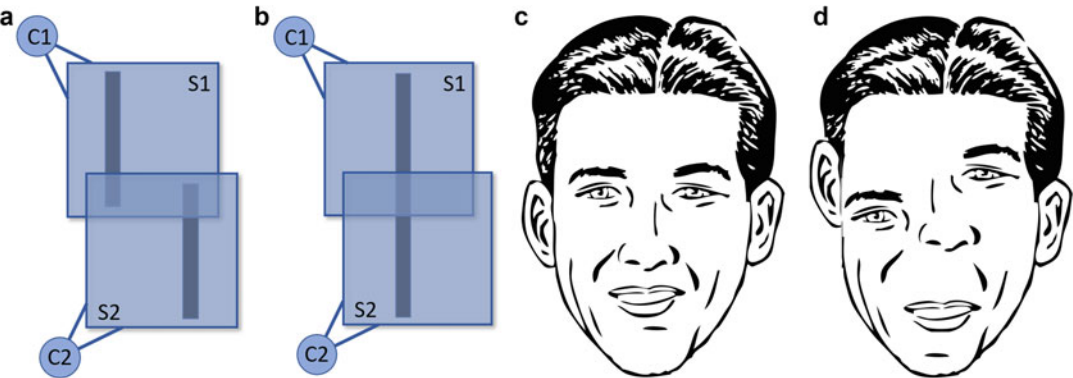
Though such models help to explain the basic invariance properties of key neural circuits, they do not explain the careful balance of invariance and selectivity needed to solve the problem of natural object recognition. To understand the limitation of these circuits more clearly, consider the following classic example of Geman (2006) (Fig. 2). A collection of simple cells are tuned to vertical bars. One subset, S1, of these cells feeds into complex cell, C1, and an overlapping subset, S2, feeds into complex cell C2. One of the proposed functions of complex cells in the visual system is the gradual introduction of invariance, since, for example, C1 and C2 will be as active when presented with two bars in the configuration of Fig. 2a as they will when presented with the configuration of Fig. 2b. In other words, the activation patterns of C1 and C2 cannot distinguish between a broken and a continuous line. This problem generalizes: a V1-like circuit consisting of a few face features with tolerance to small translations will tend to detect faces (Geman 2006) even when it should not (Fig. 2c vs. 2d). Such a circuit appears to be insufficient to fully achieve selective and invariant object recognition.

Contemporary feedforward models of the visual cortex partially resolve this “invariance-selectivity” dilemma by introducing further, “deeper,” processing stages, each with numerous learned filters. These models are an extension of the Hubel and Wiesel’s circuit from V1 to higher areas of the ventral stream. They come in numerous forms, differing in their specific wiring and neuronal operations. However, common to most of these network models are three key ingredients: (1) a cascade of linear filters each followed by (2) a pointwise nonlinearity which introduces



Hierarchical Models of the Visual System, Fig. 1 Hubel and Wiesel model. (a) Receptive field (RF) of a simple cell (lower green cell) obtained by selectively pooling over afferent center-surround cells (upper green cells) aligned along a preferred axis of orientation (vertical shown here). (b) At the next stage, a complex cell (lower green cell) RF can be obtained by selectively pooling over afferent simple cells (upper green cells) with

the same preferred orientation (vertical). Shown here is a complex cell RF obtained by pooling over position to build tolerance to translation of the preferred stimulus, but a more complete model of a complex cell would also include pooling over simple cells tuned to slightly different spatial frequency and phases (Rust et al. 2005; Chen et al. 2007). (Modified from Hubel and Wiesel (1962))



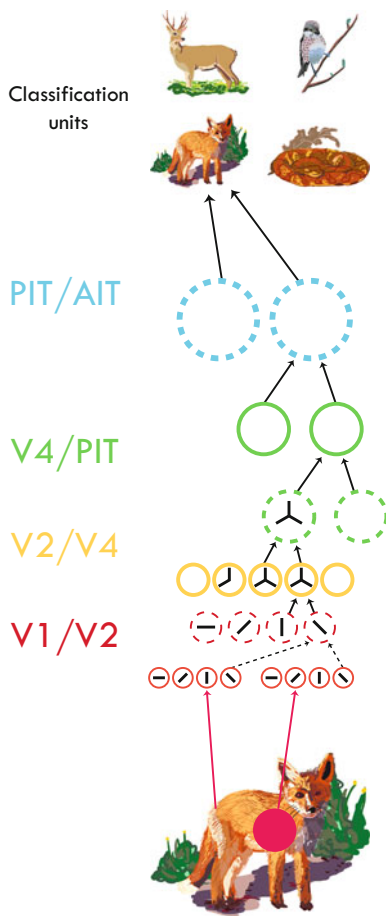
Hierarchical Models of the Visual System, Fig. 2 The invariance-selectivity trade-off. Two complex cells C1 and C2 pool over overlapping sets of simple cells tuned to vertical bars. Being translation invariant, the cells respond identically to the broken bars in (a) as they to the continuous bar in (b). Similarly, a collection of complex cells

tuned to face parts may erroneously detect a full face (c) if facial components are subject to small translations (d). See Geman (2006) for details. Arguably, the visual system avoids these false alarms for thousands of fine-grained object categories while remaining invariant to irrelevant image nuisances, like illumination, contrast, and pose.

tolerance to noise and (3) gradual, intermittent max/average pooling for translation invariance (see Mallat 2016, for a theoretical justification of these three parts). The result is an architecture which gradually builds hierarchical compositions of visual features up to and including natural

objects. Such a feature hierarchy is depicted for the case of Hmax, a classical hierarchical model of visual processing (Riesenhuber and Poggio 1999; Serre et al. 2007), in Fig. 3.

A general wiring diagram of a feedforward model of the visual system is shown in Fig. 4.



Hierarchical Models of the Visual System, Fig. 3 Sketch of the Hmax hierarchical model of visual processing. Acronyms: V1, V2, and V4 correspond to primary, second, and fourth visual areas and PIT and AIT to posterior and anterior inferotemporal (IT) areas, respectively (tentative mapping with areas of the visual cortex shown in color, parietal cortex and dorsal stream not shown). The model relies on two types of neural operations: a max-like pooling operation (shown in dash circles) over similar features at different positions and scales to gradually build tolerance to affine transformations and a convolution (also called tuning) operation (shown in plain circle) over multiple features to increase the complexity of the underlying representation. Since it was originally developed Riesenhuber and Poggio (1999), the model was shown to explain a number of new experimental data (see Serre and Poggio 2010, for a review). However, today this model and similar architectures have been superseded by deep convolutional networks that have been shown to provide a better fit to neural data along the ventral stream of the visual cortex (Serre 2019)

A layer of simple cells is conceived as a bank of feature detectors, each selecting for one of K different features within a local neighborhood centered at spatial location, u , in the layer's input (see Ullman and Soloviev 1999, for a discussion of the biological realism of this architecture). Each simple cell computes a weighted sum of afferent unit activities,

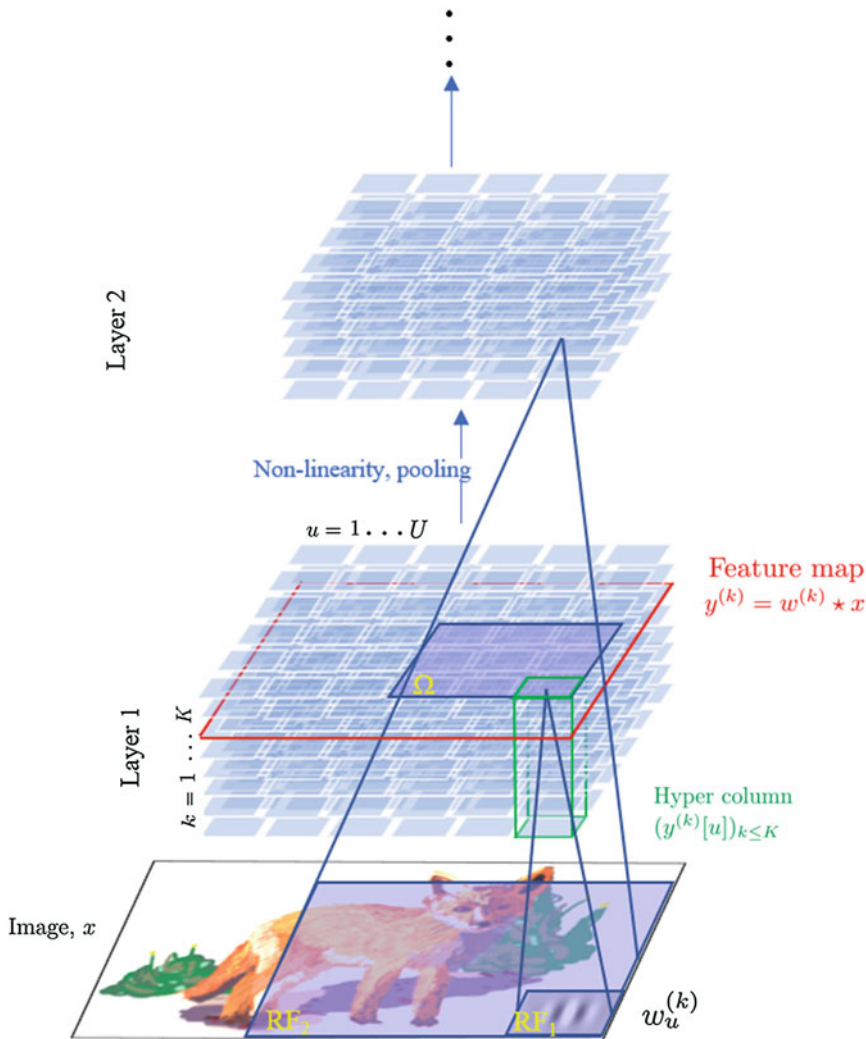
$$y_u^{(k)} = \sum_{v \in \Omega_u} w_v^{(k)} x_v, \quad (1)$$

where k indexes the particular feature to which the simple cell is tuned, Ω_u are the locations of afferent units in the input pool, x_v are those units' activities, and w_v are the synaptic weights connecting each afferent to the simple cell target. The scalar $y_u^{(k)}$ is analogous to an average firing rate of the simple cell. Since feature detectors are replicated at each spatial location, the output of a simple cell layer can be modeled as a convolution of the afferent signal, x , with a bank of features $\{w^{(k)}\}_{k=1}^K$ of small support:

$$y^{(k)} = w^{(k)} \star x.$$

The pattern of activations $y^{(k)}$ for a given k is called a feature map (Fig. 4, red rectangle). Note that we have written the output of a layer of simple cells as a 2D convolution, though, in general, the summation can be taken across many dimensions, including time, input channels, eye dominance, etc.

The vector $(y_u^{(k)})_{k=1}^K$ for a fixed location, u , is called a hypercolumn (Fig. 4, green prism) and represents an encoding of the afferent activity with respect to the features $\{w^{(k)}\}$. In the primary visual cortex, these local descriptors are well modeled by Gabor wavelets (as shown in RF₁ in Fig. 4), tuned to different orientations and scales, and these filters often emerge in models trained on natural images, especially when activity in the network is encouraged to be sparse (Olshausen and Field 1996; Lee et al. 2008). Iteratively combining the supports of filters throughout the hierarchy which feed into a given unit yields its receptive field; e.g., in Fig. 4, the shaded region RF2 is the union of receptive fields of its afferent



Hierarchical Models of the Visual System, Fig. 4 Feedforward wiring diagram. Hierarchical

models of the visual system are characterized by multiple stages of processing whereby units in one stage (shown as squares) pool over the response of units from the previous stage. Each stage computes a convolution of the previous stage with a bank of K filters, and a unit's activity is the

output of this convolution at a given location. The convolution with a given filter is called a *feature map* (e.g., the outputs of cells in the red square). The set of feature activations at a given location is called a *hypercolumn*. The output of a layer is passed through a pointwise non-linearity and max or average pooling, after which it forms the input for another bank of filters. See text for details

units in Ω . Comparing the size of RF_1 and RF_2 , we see that iterative pooling in this manner gradually increases the size of receptive fields as one proceeds up the feature hierarchy.

The output of a simple cell layer is typically passed through a pointwise nonlinearity, ρ , called an activation function in order to provide some robustness to noise and increase the expressiveness of the visual representation:

$$\begin{aligned} \hat{y}^{(k)} &= \rho(y^{(k)}) \\ &= \rho(w^{(k)} \star x). \end{aligned} \quad (2)$$

Typical choices for ρ include rectification, logistic, or hyperbolic functions. The standard choice in computer vision for ρ is zero rectification. In this context, a scalar bias, b , on the output of a simple cell layer functions as a spiking

threshold, since $y_u = \max(0, (w * x)_u - b) > 0$ only when $(w * x)_u > b$. A model neuron which passes a linear combination of its afferents through a pointwise nonlinearity is called a linear-nonlinear (LN) neuron (Simoncelli et al. 2004). The LN model has been shown to account for a host of experimental data (Rieke et al. 1997), and it has been shown that in many cases, biophysically more realistic, spiking neuron models can be reduced to a simple LN cascade (Ostojic and Brunel 2011).

Extensions of the LN cascade include the addition of a normalization stage (Heeger 1993; Carandini and Heeger 1994), in which the response y_u of the neuron is divided by a factor that typically includes the summed activity of a pool of neurons:

$$y_u = \frac{\sum_{v \in \Omega_u} (w_v x_v)^p}{\epsilon + \left(\sum_{v' \in \Omega'_u} x_{v'}^q \right)^r}, \quad (3)$$

where $\epsilon \ll 1$ is a constant to avoid zero-division. The pool of neurons Ω'_u used for normalization may correspond to the same pool of neurons Ω_u which shape the classical receptive field or may extend beyond to account for extra-classical receptive field effects (Series et al. 2003). Normalization circuits were originally proposed to explain the contrast response of cells in the primary visual cortex and are now thought to operate throughout the visual system and in many other sensory modalities and brain regions (see Carandini and Heeger 2012, for a review).

Complex cell layers filter their input with a fixed low-pass or max filter, the latter of which is the standard in computer vision. If a max-pooling unit at location u receives input from a pool of afferent units Ω_u , then the unit outputs

$$y_u = \max_{v \in \Omega_u} \{x_v\}, \quad (4)$$

where x is itself usually the activity of a simple cell layer. Interestingly, maximum, Gaussian, sigmoid, and other types of cell tuning can all be

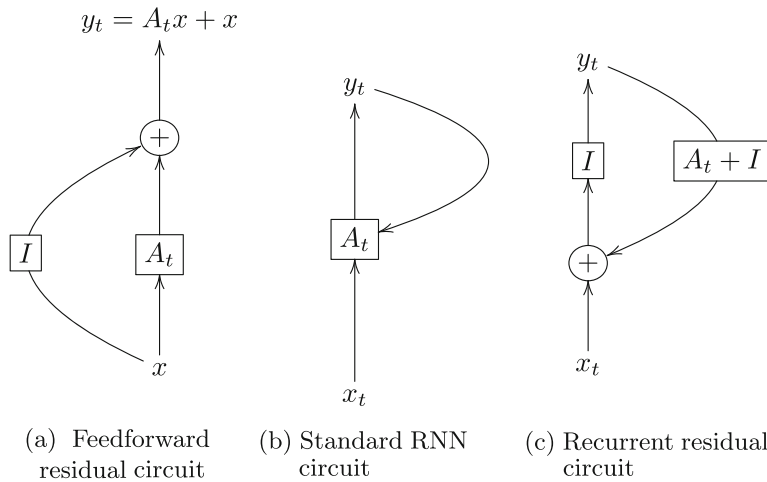
approximated by various forms of Eq. 3 depending on the values of the static nonlinearities p , q , and r in the underlying neural circuit. By adjusting these nonlinearities, Eq. 3 can approximate better a maximum or other tuning functions (see Kouh and Poggio 2008, for details).

While recent work has suggested that simple and complex cells may represent the two ends of a continuum instead of two discrete classes of neurons (see Ringach (2004) for a discussion), this dichotomy is probably not critical for hierarchical models of the visual system. Indeed, some computational models do not distinguish between simple and complex cell pooling (O'Reilly et al. 2013).

Deep convolutional neural networks with an architecture similar to that of Fig. 4 have achieved impressive results in image classification, by some measures surpassing human performance (He et al. 2015). Many of the most powerful contemporary networks are “ultra-deep,” extending the linear-nonlinear cascade to hundreds or even thousands of layers (He et al. 2016). Often, these models are only superficially deep, as they employ “skip” connections to bypass several layers, similar to the ascending projections from V2 to IT or V1 to V4 (Nakamura et al. 1993). During training, these “residual networks” (He et al. 2015) essentially learn to adjust their processing depth to best suit a given task. For example, imagine that pairs of linear-nonlinear stages are grouped into blocks indexed by t , so that the output of the t th block is given by the nonlinear operator A_t :

$$A_t x = \rho(w_{t,2} \star \rho(w_{t,1} \star x)), \quad (5)$$

where $w_{t,1}$ and $w_{t,2}$ are two kernels of synaptic weights interleaved by pointwise nonlinearities. Skip connections add the input to this operator to the output: $A_t x + x$. Suppose that the true function to be learned by this block is $F(x)$. In an ultra-deep system, the optimal function for this block may very well be the identity map, $F(x) = x$. Bypass connections in residual nets (Fig. 5a) accelerate the learning of these identity maps since they allow the training algorithm to alternatively learn zero “residual” functions



Hierarchical Models of the Visual System, Fig. 5 Residual and recurrent circuits. (a) A residual net contains skip connections that allow a copy of activity x to bypass the t th block of layers, here encoded in the operator A_t . The copied activity, x , is then added to the output of the bypassed layers, $A_t x$, in the hopes that the model will more easily learn that the A_t operator is often the

zero operator. (b) A recurrent circuit runs in time and updates its persistent state by integrating incoming information: $y_t = A_t y_{t-1} + x_t$. (c) A residual net can be reformulated as a particular recurrent network (Liao and Poggio 2016), where the t th residual block is the state of the recurrent circuit at time t .

$$F(x) - x = A_t x. \quad (6)$$

After training, many of the A_t will have converged to the zero operator, allowing data to essentially skip a layer as the network performs a feedforward pass.

Despite being unconstrained by neurophysiology, currently the best feedforward models of visual cortical activity are deep convolutional networks developed by the computer vision community. Early computational neuroscience work started with AlexNet (Krizhevsky et al. 2012) and ZFNet (Zeiler and Fergus 2014), which were shown to improve the fit to neural data in intermediate and higher areas of the ventral stream of the visual cortex even if they were optimized for task performance (e.g., image classification accuracy) instead of neural prediction directly (Cadieu et al. 2014; Khaligh-Razavi and Kriegeskorte 2014). A recent study (Cadena et al. 2019) has shown that intermediate layers from the VGG network of Simonyan and Zisserman (2014) provide a better fit to V1 monkey electrophysiology data compared to simpler linear-nonlinear models. Work by Hong et al. (2016) has also shown that

multiple image properties beyond object categories (e.g., object position, 3D size, and pose) remain relatively well encoded in higher processing stages in both neural and CNN representations. This provides further evidence that visual hierarchies are able to learn visual representations that are invariant to task-irrelevant transformations while maintaining information for task-relevant ones.

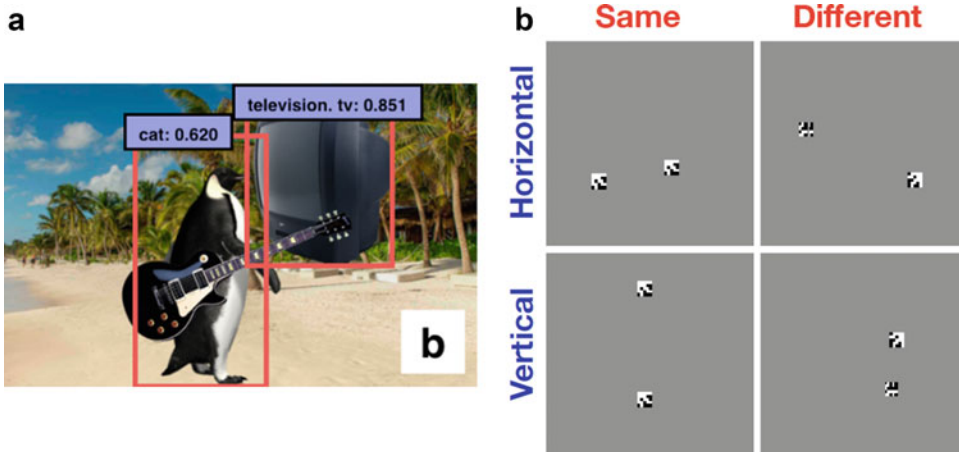
Further evidence for hierarchical processing in object recognition comes from studies that have shown that the depth of convolutional layers that provides the best goodness of fit with brain data increases along the ventral visual stream (Cichy et al. 2016; Devereux et al. 2018; Guclu and van Gerven 2015; Kalfas et al. 2017; Khaligh-Razavi and Kriegeskorte 2014; Yamins et al. 2014). Similar results were also reported for scene recognition (Cichy et al. 2017; Greene and Hansen 2018) and action recognition (Güçlü and Gerven 2017) with spatiotemporal CNNs trained for action recognition (Tran et al. 2015). Interestingly, the goodness of fit between brain data and fully connected layers tends to be lower than with convolutional layers (Kalfas et al. 2017), a result consistent with a behavioral study that has

compared CNNs with human behavioral decisions during a rapid categorization task (Eberhardt et al. 2016). This result also seems consistent with a recent object naming study (Devereux et al. 2018) that has shown that a network model of semantics, explicitly trained to learn a mapping from the convolutional layers of a CNN onto object semantic attributes, was better able to explain functional magnetic resonance imaging (fMRI) activation patterns in higher visual areas compared to either convolutional or fully connected layers. CNNs have also been used to synthesize patterns of fMRI activations, which were then used to reproduce classic functional brain-mapping experiments, from recovering retinotopic maps in early visual areas to replicating the known faces-versus-places BOLD contrast in higher areas (Eickenberg et al. 2017).

Recurrent Models

To date, most existing hierarchical models of visual processing – from the perspectives of both biological and machine vision – are instances of

feedforward models (Serre 2019). These models have been useful in exploring the power of fixed hierarchical organization as originally suggested by Hubel and Wiesel (1962). However, the limitations of feedforward networks, in terms of their correspondence to both cortical function and anatomy, are becoming increasingly obvious. For example, convolutional networks can be easily tricked into incorrectly detecting objects in ways that biological vision cannot, either by placing familiar objects in unfamiliar arrangements (Fig. 6a; see Rosenfeld et al. (2018)) or even by adding minute perturbations to images (Szegedy et al. 2013; Geirhos et al. 2018). Evidently, deep feedforward nets have not fully resolved the invariance-selectivity dilemma and its attendant high false alarm rate. These networks also struggle to learn simple visual reasoning tasks which are trivial for humans, notably those in which arbitrary objects must be compared (Fig. 6b; see Kim et al. 2018). This limitation suggests feedforward models of the visual system cannot easily emulate humans' ability to flexibly construct innumerable structured descriptions of the visual world (Fodor and Pylyshyn 1988; Geman



Hierarchical Models of the Visual System, Fig. 6 Limitations of feedforward models. (a) A feedforward model can be trained to high accuracy on hundreds of object classes, and yet the resulting network still misclassifies objects when placed in unfamiliar arrangements. Here, the YOLO object recognition and localization deep network (Redmon et al. 2016) mistakes a penguin for a cat because of a partially occluding guitar. (See Rosenfeld et al. (2018) for a systematic analysis of

this effect; image credit: Junkyung Kim.) (b) Kim et al. (2018) found that feedforward models could easily solve spatial reasoning problems, like determining whether two random patterns are arranged vertically or horizontally (vertical axis), but had a comparatively more difficult time solving same-different tasks such as determining whether an image contains two identical, but arbitrary, patterns (horizontal axis)

et al. 2015). Naturally, feedforward models do not help explain the copious feedback and lateral connections in the visual cortex or the executive and mnemonic processes they support. Contemporary CNNs can also have hundreds of processing stages, counting skip connections, whereas the ventral stream contains a dozen or fewer. In fact, the classification accuracy of feedforward networks begins to decorrelate with human behavior after a few layers (Eberhardt et al. 2016).

Could the functional and anatomical limitations of feedforward models of the visual system be connected? Geman (2006), for instance, claims that selectivity in natural vision arises not from the learning of a large dictionary of complex visual features but rather from the dynamical construction of representations out of simple parts using recurrent connections. Recent work in recurrent neural networks (RNNs) has partially corroborated this intuition and shown that models with feedback connections are both functionally superior to feedforward networks on some tasks (Linsley et al. 2018) and better predictors of cortical activity (Nayebi et al. 2018; Kar et al. 2019).

An RNN is built from circuits with cyclical connections. For example, if x_t is a signal at time t , then such a circuit could compute

$$y_t = A_t y_{t-1} + x_t, \quad (7)$$

where A_t is a potentially nonlinear, time-dependent operator (Fig. 5b). y_t is a persistent or hidden state of the circuit which accumulates information from x_t over time. An additional operator can provide a readout or classification layer: $o_t = B_t y_t$. The principal advantage of networks built from these circuits is that the system can perform stateful computations based on the information stored in the persistent activity y_t . For example, given a memory-data combination, (y_t, x_t) , a network could learn to sequentially suppress or enhance different regions of the visual field, giving rise to exactly the kind of attentional mechanisms capable of disambiguating a cluttered scene (Treisman and Gelade 1980; Evans and Treisman 2005), as in Fig. 6a, or detecting the relations in Fig. 6b

(Donderi and Zelnick 1969; Clevenger and Hummel 2014).

Importantly, a version of the dynamical system in Eq. 7 is equivalent to the ultra-deep residual networks discussed above. If $x = x_0$, $x_t = 0$ when $t > 0$, $y_0 = 0$, and we consider the circuit in Fig. 5c with operator $A_t + I$, then we find

$$\begin{aligned} y_1 &= (A_1 + I)0 + x_0 = x \\ y_2 &= (A_2 + I)y_1 + 0 = A_2 x + x \\ y_3 &= A_3 y_2 + y_2 \\ &\vdots \end{aligned}$$

We observe that the operator A_t corresponds to the function embodied by blocks in a residual network, so that the t th block in the hierarchy is also the t th sequential operation in the recurrent circuit of Fig. 5c. In other words, an ultra-deep residual network can be “folded” into a shallow recurrent circuit (see Liao and Poggio 2016, for details). This suggests that the relatively shallow visual cortex could match the performance of ultra-deep feedforward systems by using recurrent connections through time.

Contemporary recurrent models of the visual cortex elaborate on the basic RNN structure by hierarchically stacking recurrent circuits, introducing lateral connections within a layer and top-down connections between layers, and allowing the system to gate activity. This last operation, known primarily for its use in long short-term memory (LSTM) networks (Hochreiter et al. 1997) and, later, gated recurrent units (GRUs) (Cho et al. 2014) for natural language processing, enables a network to selectively delete and append information to its persistent state. Linsley et al. (2018) recently developed a recurrent network model with lateral connectivity and gating to mimic the contour integration and object segmentation capabilities of humans in cluttered scenes (Grossberg and Mingolla 1985; Field et al. 1993; Grossberg and Raizada 2000; Grossberg and Williamson 2001). Further, Nayebi et al. (2018) and Kar et al. (2019) found that convolutional networks augmented with recurrent connections had improved performance in image classification and could predict recordings of primate IT activity

better than a feedforward baseline. These attempts to model the visual system with recurrent networks are promising, though this line of research is still in its infancy compared to feedforward modeling.

Learning

Modeling the visual system with recurrent networks is a tantalizing proposition, since RNNs are Turing-equivalent and can therefore theoretically compute any function given enough time (Hyötyniemi 1996). This is to say nothing of how this function is learned, however. Learning is the domain where differences between computational and biological models are at their starkest. In particular, CNNs are typically trained by supervision with gradient descent on millions of labeled images, whereas training in the visual system likely occurs by some combination of unsupervised and reinforcement learning. Differences with biological vision seem all the greater in light of recent evidence indicating that face preference (Reid et al. 2017), category selectivity (van den Hurk et al. 2017), and basic reasoning (Martinho and Kacelnik 2016) can require little to no visual experience to function properly.

Even the basic mechanisms of error propagation seem difficult to implement in a biologically plausible manner. Backpropagation of error has traditionally been considered biologically unrealistic since it would seem to require that feedforward connections be mirrored by identical feedback connections. Any mechanism for computing error in cortex would have to know the weights of the feedforward pathway, a dilemma known as the “weight transport” or “weight symmetry” problem (Grossberg and Mingolla 1987). However, Liao et al. (2015) found that feedforward and feedback weights need not be symmetric for successful training as long as the network was trained with batch normalization (Ioffe and Szegedy 2015) and the magnitudes of gradient updates were discarded. Further, Bengio et al. (2015) argues that spike-timing-dependent plasticity (STDP; see Sjöström and Gerstner

(2010)) is equivalent to gradient descent for a particular variational algorithm.

Though these results assuage some fears about basic error propagation in the cortical setting, they do not address the implausibility of direct supervision. A complete computational model of the visual system will have to integrate the feedforward and feedback mechanisms discussed above with methods from unsupervised learning, for example, predictive coding (Rao and Ballard 1999). See Marblestone et al. (2016) for an extensive review on the neuroscientific implementation of deep learning algorithms.

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High-Conductance State

- [Balanced State](#)

Higher-Order Correlation

- [Statistical Evaluation of Spatio-temporal Spike Patterns](#)

High-Frequency Nerve Block

- [Peripheral Nerve Stimulation Technique, Nerve Block](#)

High-Frequency Stimulation

- [Parkinson's Disease: Deep Brain Stimulation](#)

High-Voltage Paraspinal Electrical Stimulation

- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

High-Voltage Percutaneous Electrical Stimulation

- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

High-Voltage-Activated Calcium Channels

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Synonyms

Cav1.1–4 “long-lasting” type (L type); Cav2.1 “Purkinje” type (P/Q type); Cav2.2 “non-L type” (N type); Cav2.3 “residual” type (R type); High-voltage-gated calcium channels

Definition

Calcium channels are one of the oldest members of the voltage-gated channel family (Anderson and Greenberg 2001) and are ubiquitous among excitable cells. Calcium channels are composed of a specialized structure, a complex protein placed to bridge the intracellular and extracellular media across the lipidic cell membrane. Under the control of the difference of potential across the cell membrane (membrane voltage or V_m) and biochemical pathways, these channels finely control the flow of calcium (Ca^{2+}) ions into excitable and non-excitable cells. The Ca^{2+} channels (Cav) are divided into different subfamilies based on their subunits types and assembly, which leads to the creation of channels with different kinetic properties and distinct function in specific sections of the cells.

Like sodium (Na^+) or potassium (K^+) channels, Ca channels show a voltage dependence of their gating variables. Their large family, 10 genetically identified types, can be roughly divided into two classes based on the range of the membrane voltage in which Ca channels open: low (LVA) and high voltage activated (HVA). HVA calcium channels contribute to neuronal excitability providing multiple functional complements to action potential generation and subthreshold integration of input. The ability of HVA calcium channels to mediate ion entry has been used by the evolution for many different purposes: from action potential generation in lower eukaryotes to fine-tuned synaptic control in higher species and from muscular contraction to hormone release and genetic expression (Anderson and Greenberg 2001).

Detailed Description

A cell is a living organism which requires an enclosed place to live, a complex system able to capture nutrients from the outer medium and to dispose of the waste produced by the cell activity. All animal cells are surrounded by a double-layered membrane able to define where, what, and when a specific substance can pass across it and in which direction. Under physiological

condition, only gases, like oxygen and CO₂, and only small uncharged polar molecules, like water or alcohol, can diffuse through the membrane. These substances are fundamental for the life of all cells and so they can diffuse freely, from the extracellular side to the cytoplasmic side and backward. In the case of ions, the lipidic membrane keeps a tight control of their flux maintaining their differential concentration across the membrane at specific levels taking advantage of complex mechanisms as internal stores, ion pumps (PMCA), or sodium-calcium exchanger (NCX). In the specific case of Ca²⁺ ions, the cellular mechanisms act to maintain a low Ca²⁺ concentration in the cellular cytoplasm and a high concentration in the extracellular matrix. The internal quantity must be kept strictly under control, as intracellular Ca²⁺ is able to activate an enormous series of local biochemical pathways, some of which are able to activate enzymes used during synaptic plasticity or to regulate other ions channels. Some others are connected with gene expression or initiate the apoptosis process leading to cell death.

Role of HVA Ca in Neuronal Dynamics

Calcium channels play a large number of key roles in neurodynamics. They can shape regenerative action potentials, provide exclusive contribution to the generation of action potentials like in cardiac pacemaker cells, and finely control the release of a single vesicle from a presynaptic terminal. In general, Ca²⁺ channels are involved in contraction, secretion, and gating. In many cell types, N/P-type HVA Ca channels contribute to the generation of after-hyperpolarization currents by increasing intracellular Ca concentration and activating K⁺ channels. In motoneurons, N/P-type Ca HVA channels contribute to the generation of after-hyperpolarization currents (Venugopal et al. 2012). In the same neurons, L- and N-channel types also couple with Ca-dependent potassium currents to increase the gain and the rate of spike frequency (Umemiya and Berger 1994). L-type calcium channels control the spontaneous activity in neurons as P/Q-type channels do in Purkinje

cells (Womack et al. 2004). In unipolar brush cells, the L-type channels help in intensifying the response induced by synaptic activity (Diana et al. 2007).

History of Names

The subfamily of HVA Cav is composed of four types: L type, P/Q type, N type, and R type. These names were given to define one specific characteristic of each channel. The L type (Cav1.1-4) is called “long lasting” because the channel remains open for a long time. This channel can be found in neurons, muscles and, above all, in the cardiac action potential generation where they play the important role of sustaining it. The P type (Cav2.1) has been called in this way by the researcher who finds it, for the first time, in cerebellar Purkinje cell (Llinas et al. 1989). This channel takes over 2 s to enter the inactivated state and this can be seen as a way, for PC, to integrate the synaptic activity over a very long timeframe. The original definition for the N type (Cav2.2) was “non-L-type” calcium channel, but now it is defined as “neuronal type” and is localized primarily in the presynaptic side of CNS synapses. The R type (Cav2.3) is called “residual” because, after blocking any other type of calcium channel with any possible toxin/drug, this channel type is still able to allow a residual calcium current (Wilson et al. 2000). For a full summary of exact names of the channel family and subunits consult the database published by Sharman et al. 2013.

Channel Subunits

A voltage-gated ion channel is composed of four proteins (called subunits) which, together, form a specific quaternary structure: a tetramer. The tetramers can be defined as homotetramers, if the subunits are all of the same type, or heterotetramers, if two or more are different. The HVA subfamily is composed only of heterotetramers. The most important subunit is $\alpha 1A$ ($\alpha 1A$) which is responsible for the selectivity of the ion

pore; it is able to sense membrane voltage changes and it provides a binding site for drugs and toxins. The auxiliary $\alpha 2$ ($\alpha 2$) and the delta (δ) subunits are very important, in the channel setup. $\alpha 2$ is able to cluster with $\alpha 1$, enhancing the channel conductance, the balance between activation and inactivation time constants, and the shift of the inactivation curve toward hyperpolarized voltages. $\alpha 2$ is coexpressed with a delta subunit (δ) that anchors the channel to the cell membrane. To give specific kinetic characteristic and to complete the tetramer, the channel incorporates one out of two types of modulatory auxiliary subunits called beta (β) and gamma (γ). There are four known isoforms of β subunit which are able to modify, even more, the activation and inactivation kinetics of any HVA channel. In Purkinje cell, the presence of β subunits can change, in a very specific way, the inactivation timing (Richards et al. 2007). Instead, the presence of γ , instead of β , subunits is responsible for the reduction of activation/inactivation kinetics and enhancement of inhibitory kinetics (Arikkath and Campbell 2003). The subunits' composition can be different for each member of the Ca^{2+} subfamily. For example, L-type channels can be composed of the combination of four out of all the available subunit types ($\alpha 1A$, $\alpha 2$, δ , β , γ), forming distinct tetramers. Conversely, P-type channels are usually composed only of $\alpha 1A$, $\alpha 2$, δ , and β subunits. Only in a few cases, the γ subunit is included in the P-type tetramer. Pushing to a higher level of complexity the range of possible properties of each channel, each subunit has different splicing alternatives giving rise to a series of subunits with slightly different biophysical properties. The existence of 10 variations of $\alpha 1A$, four $\alpha 2\delta$ complexes, four auxiliary β , and eight γ subunits is known (Catterall 2000; Tedford and Zamponi 2006).

Biophysics of HVA Calcium Channels

HVA Ca channels are sensitive to membrane voltage and to the intracellular Ca^{2+} concentration. Voltage gating is responsible of conformational changes leading to channel transitions into

or from the open, closed, or inactivated state. The intracellular Ca^{2+} concentration controls transitions from closed or open states to the inactivated state (for an example, see L-type Markov model: Mahajan et al. 2008). In spite of the large dataset available on Ca^{2+} channels conformational changes, the state of the art on their computational modeling is mainly focused on using the Hodgkin and Huxley formulation. In these computational models, Ca^{2+} channels show activation and inactivation dynamics dependent on voltage changes only, discarding the dependence of inactivation on the intracellular Ca^{2+} concentration.

An example for HVA calcium currents is L-type (slow inactivating calcium currents) high-voltage-activated calcium currents of unipolar brush cells. The channel is a Hodgkin-Huxley-based model; the source of the model is from granule cell model (D'Angelo et al. 2001) where the channel kinetics was modified for UBC-specific properties (as published in Diana et al. 2007). The alpha and beta rate function equations are listed in Table 1:

$$I_{Ca} = \bar{g} \cdot s^2 \cdot u \cdot (V - E_{Ca})$$
$$\frac{ds}{dt} = \alpha_s \cdot (1 - s) - \beta_s \cdot s$$
$$\frac{du}{dt} = \alpha_u \cdot (1 - u) - \beta_u \cdot u$$

The models currently available for HVA calcium channels are listed in Table 2. Collecting sound experimental data and modelling these kind of ion channels is a difficult task due to their complexity, modulatory mechanisms, and permeability properties.

High-Voltage-Activated Calcium Channels, Table 1 HH-based model of HVA Ca (L-type) ion channels

Transition rates	$\alpha(S^{-1})$	$\beta(S^{-1})$
Activation (s)	$0.05 \cdot e^{(v+29.1)/15.9}$	$0.08 \cdot e^{-(v+18.7)/25.6}$
Inactivation (u)	$0.001 \cdot e^{-(v+48)/18.2}$	$0.001 \cdot e^{(v+48)/83}$

High-Voltage-Activated Calcium Channels, Table 2 Available computational models of HVA Ca ion channels

HVA Ca channel type	HH model	Markov chain model
Cav1.1–4 (L type)	D’Angelo et al. (2001)	Mahajan et al. (2008)
Cav2.1 (P type)	Anwar et al. (2010)	–
Cav2.2 (N type)	–	Buraei et al. (2005)
Cav2.3 (R type)	Wolf et al. (2005)	–

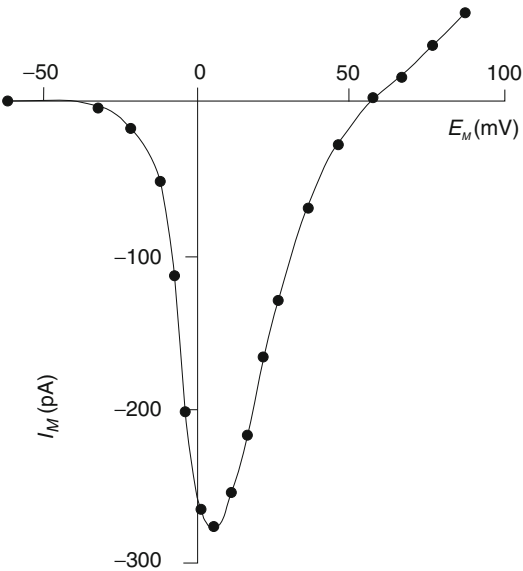
Modulation of Biophysical Properties

The biophysical properties of the calcium channels are subject to modulation by many intracellular pathways. Among those the calmodulin (CaM) plays a relevant role as it binds to L-, N-, P/Q-, and R-type Ca^{2+} channels. CaM-mediated effects are widespread in the calcium channel family translating the overall neuronal activity measured by intracellular Ca^{2+} accumulation into short-term changes of gating properties leading to facilitation or inactivation. Many different computational models of CaM are currently available (Pepke et al. 2010), but they are not ready for use in the main neuronal simulators (neuron, genesis, etc.). Unfortunately, a computational model of the interaction of CaM with one of the HVA Ca^{2+} channels is not currently available.

Calcium Channel Permeability

Current-voltage relationship for voltage-gated ions is always nonlinear. The voltage dependence of ionic channels emerges from three components: the driving force acting on each ion, the ionic channel permeability, and the probability that a channel is in its open state. The Ca^{2+} current follows the concentration gradient of $[\text{Ca}^{2+}]$, in physiological conditions 10^4 – 10^5 times lower inside the cell than outside, resulting in an inward current (Tsien et al. 1988).

The thermodynamic reversal potential of Ca^{2+} is +128 mV (according to Nernst equation; Hille



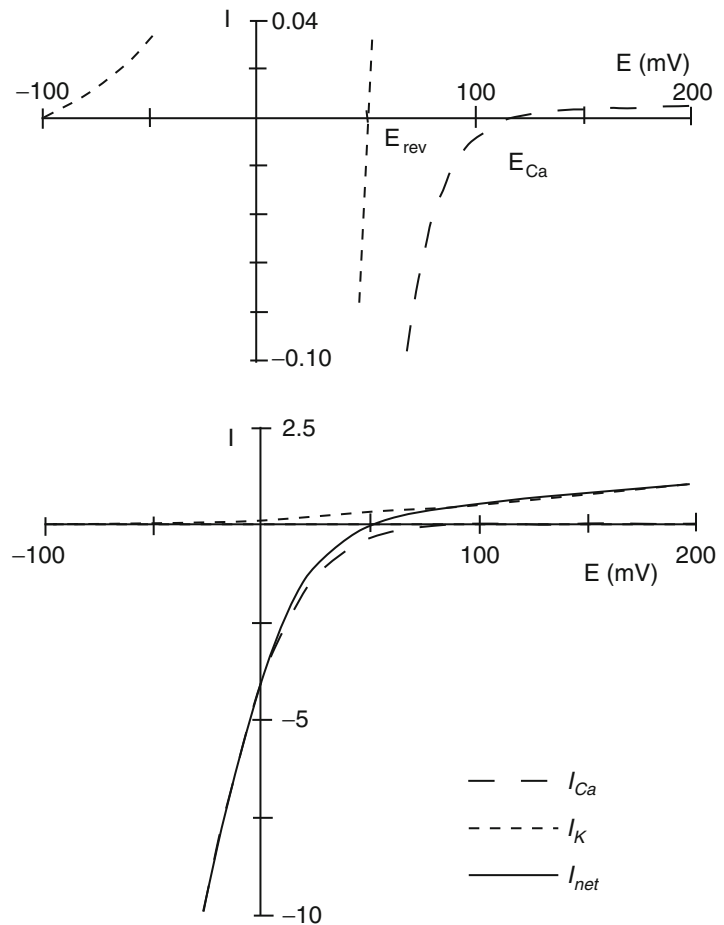
High-Voltage-Activated Calcium Channels, Fig. 1 IV curve of Ca under experimental observation of chromaffin cell. (Adapted from Hille 2001)

2001), but the observed experimental value is around +54 mV (Fig. 1) (according to Goldman-Hodgkin-Katz (GHK) equation; Hille 2001). This discrepancy is explained by considering that this channels are permeable to Ca^{2+} ions and slightly permeable to K^{+} ions ($\text{P}_{\text{K}}/\text{P}_{\text{Ca}} = 1/1,000$). Although K^{+} ions permeability is low, the high concentration of K^{+} ions yields a significant contribution to the reversal potential of the HVA Ca currents. When the membrane potential goes more in positive than 0 mV, the resulting reversal potential of the HVA Ca current is dominated by K^{+} rather than by Ca^{2+} ions (Hille 2001; Tsien et al. 1987).

This counterintuitive behavior emerges from the fact that in the cytoplasm, K^{+} ions are 10^6 times more concentrated than Ca^{2+} ions. Therefore, the far lower permeability Ca^{2+} channels to K^{+} than Ca^{2+} ions must counteract an extremely large number of K^{+} ions trying to access the channel. The dotted line in Fig. 2 shows the predicted K^{+} current in flowing through Ca^{2+} channels in the case of a low K^{+} permeability, i.e., 1/1000 of the Ca permeability (assuming that the GHK equation applies). The total current carried by K^{+} and Ca^{2+} ions in this hypothetical example

High-Voltage-Activated Calcium Channels,

Fig. 2 Example: individual K^+ ions (*dotted line*) and Ca^{2+} ions (*dash line*) permeable through calcium channel. Net current passes through Ca channel (*solid line*). (Adapted from Hille 2001)



H

is drawn as a solid line. This would be the experimentally observable net current. The IV curve is less curved than for Ca^{2+} current alone and the reversal potential (+52 mV) is no longer equal to its thermodynamic value. As is probably the case for all real channels, the reversal potential here includes a weighted contribution from several ions (Hille 2001; Tsien et al. 1987).

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High-Voltage-Gated Calcium Channels

► High-Voltage-Activated Calcium Channels

Hill's Model

► Hill's Model for Muscle Physiology and Biomechanics

Hill's Model for Muscle Physiology and Biomechanics

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Synonyms

Hill's model; MATLAB; Muscle

Definition

Computational models of muscles serve as important tools to understand the musculoskeletal physiology and biomechanics. Such models have been widely implemented in a variety of simulation platforms and incorporate varying degrees of physiological details. This entry summarizes a simplified two-component biomechanical muscle model, first described by A. V. Hill in 1938, popularly known as the *Hill's muscle model*. The Hill's model provides thermodynamically constrained quantitative relationships between

muscle length, shortening velocity, force, and heat released during a muscle contraction. The model description, simulations, and MATLAB script provided here highlight the computational features of the Hill's muscle model.

Detailed Description

Biomechanical Components of Muscle Force Generation

Muscle cells contract to produce movement. During a contraction, the shortening of a muscle cell results in tension or force production. The basic structural components involved in force production consist of a *series elastic element* and a *contractile element*. The series elastic element is composed of tendons and aponeurosis. Tendons are tough extensions of the muscles, and aponeurosis is thin sheets of tissue that attach the muscle to the bone. The contractile element is composed of sarcomeres which consist of thin actin filaments and thick myosin filaments. The sarcomeres form subunits called myofibrils which are long filaments bundled into muscle fibers (see Fig. 1). The myosin heads of the thick filament form crossbridges with the adenosine triphosphate (ATP) binding sites on the thin actin filaments. To produce force in the muscle cell, the filaments slide past each other when bound to ATP. More details on muscle biology, molecular mechanisms, and dynamics of force generation can be found in (Enoka and Pearson 2013).

In his seminal paper (1938), A.V. Hill details his extensive experiments measuring the length,

velocity, force, and the energy released during muscle contractions (Hill 1938). Based on such physiological measures, Hill proposed a mathematical relationship between energy, force, and velocity of muscle shortening/lengthening (also see (Holmes 2006)). It is noted that the details of muscle biology were unknown at that time.

Model Description

A Two-Component Biomechanical Model for Force Production

A highly simplified biomechanical muscle model conceived by A.V. Hill consists of series elastic and contractile elements as shown in Fig. 2.

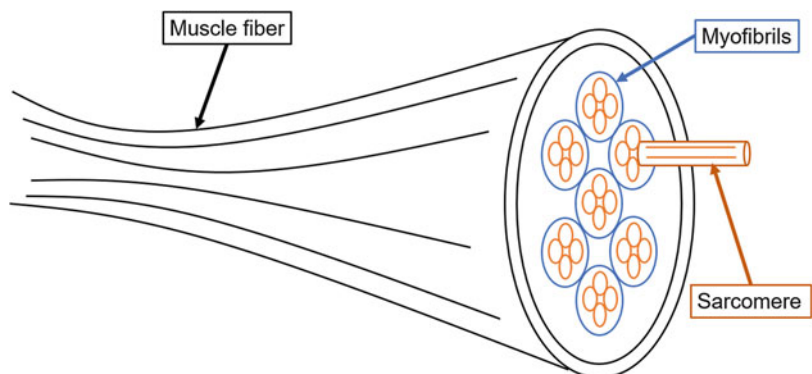
The series elastic element is assumed to be a spring-like structure with length, L_{se} , and the length of the contractile element is given by L_{ce} such that, the total muscle length, L , is:

$$L = L_{ce} + L_{se}$$

During an isometric contraction, the L_{ce} gradually reduces to mimic shortening of the contractile element. In parallel, the L_{se} gradually increases (muscle stretch), to account for the constant muscle length. The contraction force of L_{ce} is exactly the same as the stretching force of L_{se} . Such a force, P is assumed to be proportional to the stretch in L_{se} (Hooke's Law) as given below (also see Loiselle et al. 2008).

$$P = \alpha(L_{se} - L_{se}(0))$$

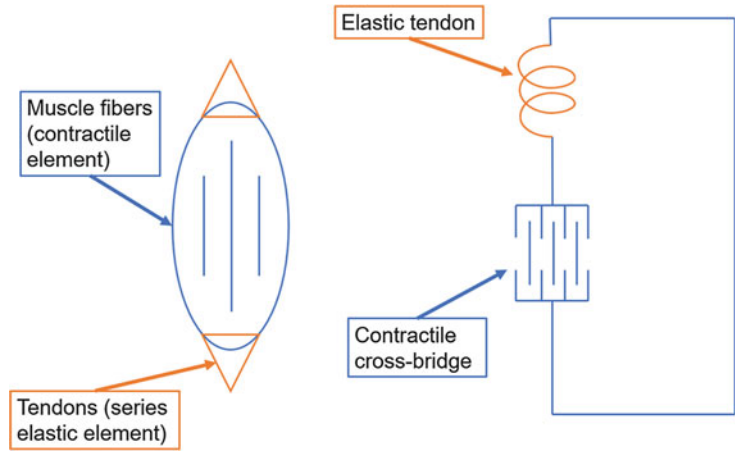
Hill's Model for Muscle Physiology and Biomechanics, Fig. 1 Structural components of a muscle. Schematic illustrating the main structural components of a muscle



Hill's Model for Muscle Physiology and Biomechanics,

Fig. 2 Biomechanical components of a muscle.

A schematic showing the biomechanical equivalence of the structural components of a muscle



where α is the spring constant and $L_{se}(0)$ is the length of the series elastic element before the contraction. The rate of change in L is therefore:

$$\frac{dL}{dt} = \frac{dL_{ce}}{dt} + \frac{dL_{se}}{dt} = v_{ce} + \frac{dL_{se}}{dt}$$

where v_{ce} is the shortening velocity of the contractile element. Similarly, the rate of change of P is given by:

$$\frac{dP}{dt} = \alpha \frac{dL_{se}}{dt}$$

From the above, it is noted that during length changes, the force P responds to length change primarily in L_{se} . For isometric contractions, in which the total muscle length is held constant, the contractile element subsequently readjusts to restore the L_{se} and therefore the force, P .

Heat Released and Force-Velocity Relationship

The original formulation for the force-velocity relationship given by A.V. Hill was based on the measurements of heat released during muscle shortening. The heat released depends on the distance (x) and velocity (v) of shortening. To measure these relationships, Hill's experiments consisted of testing the effect of different shortening velocities on the heat released during shortening. To achieve a consistent initial condition, he

began at the tetanic force, P_0 , during an isometric contraction and subsequently measured the heat released during muscle shortening for varying loads (P) (also see Figs. 4, 5, and 6). The heat released during muscle shortening is given as ax , $g.cm$, where a was experimentally determined to be a constant and has the unit of force. Next, if P of load is lifted by the muscle, the work done is given as Px , $g.cm$.

The total energy in excess of the isometric contraction is given as:

$$h = (P + a)x, \text{ in } g.cm$$

The rate of change in energy is therefore written as:

$$\frac{dh}{dt} = (P + a) \frac{dx}{dt} = (P + a)v$$

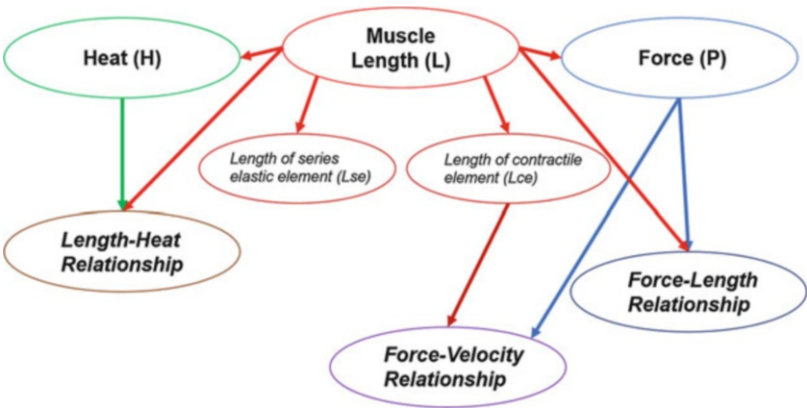
Experimentally, Hill found that this rate of change of energy release increased linearly as the load, P , diminished such that it was zero when $P = P_0$. This relationship is known as the famous Hill equation and relates the rate of heat released during muscle shortening to the corresponding load/force, as given below:

$$(P + a)v = b(P - P_0)$$

where b is the slope of the above linear relationship. The constant b is defined as the absolute rate of energy liberation.

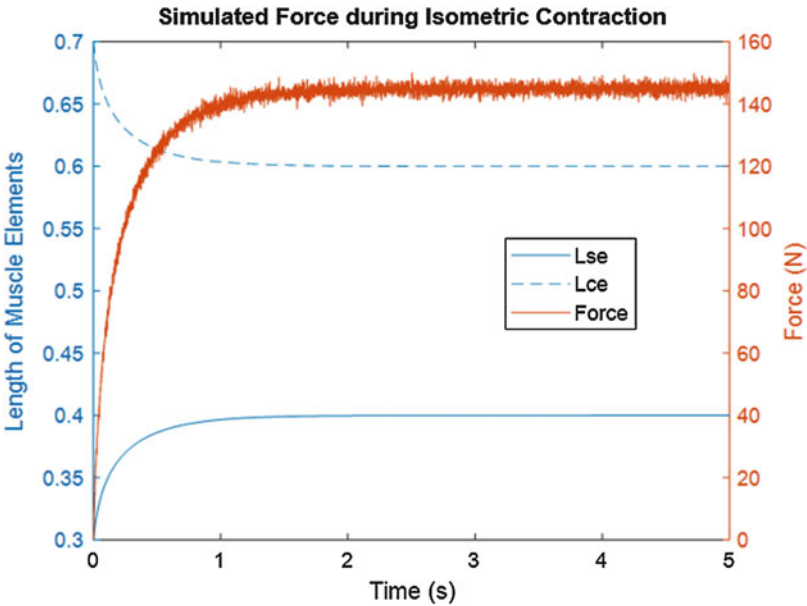
Hill's Model for Muscle Physiology and Biomechanics, Fig. 3

A flow chart of the computational steps of Hill model. The model input is the assumed muscle length (L), and outputs include lengths of the series elastic and contractile elements, velocity, force, and heat released. The ovals indicate computational steps



Hill's Model for Muscle Physiology and Biomechanics, Fig. 4

Force-Length Relationship. In the above simulation, L_{se} was set to 30 % of the total muscle length, L . The simulation included motor noise in order to more realistically model physiological force production



Model Simulations

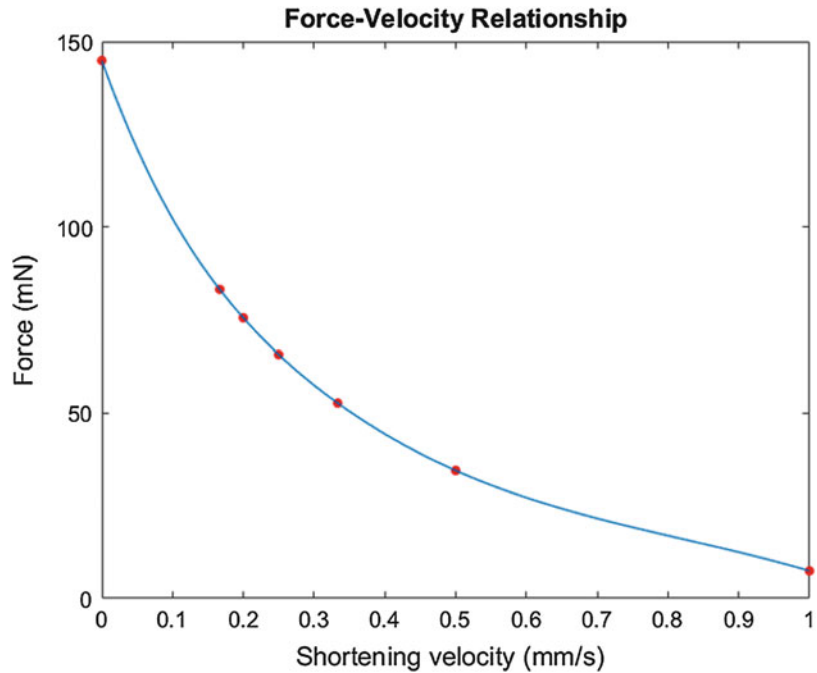
Figure 3 illustrates a flow diagram of the computational steps of the two-component biomechanical muscle model. The changes in muscle length (L) are translated into force (P) and heat production (H). The model reproduces known physiological relationships between these quantities. The description here is restricted to isometric conditions where the muscle length is

held constant to generate a corresponding steady-state force.

Force-Length Relationship

Figure 4 illustrates the force generation during an isometric contraction. In this simulation experiment, the initial length L_{se} is set 30% of the total length L at rest, such that the L_{ce} is at 70% of L ; note that the force is zero. To mimic

Hill's Model for Muscle Physiology and Biomechanics,
Fig. 5 Relationship between force and shortening velocity. Red circles show the steady-state force for different values for shortening velocity in individual simulations. The blue line shows a regression fit highlighting an inverse force-velocity relationship



muscle shortening during an isometric contraction, the value of L_{ce} is reduced to 60% of L . Note that this change in length is not instantaneous but has an initial transitory phase as L_{ce} shortens and L_{se} increases to ensure L is constant. Correspondingly, the force, P , increases. After stabilization of L_{ce} and L_{se} , the force P saturates at the steady-state value of the isometric contraction. A white noise was added to the force function in these simulations to match realistic conditions.

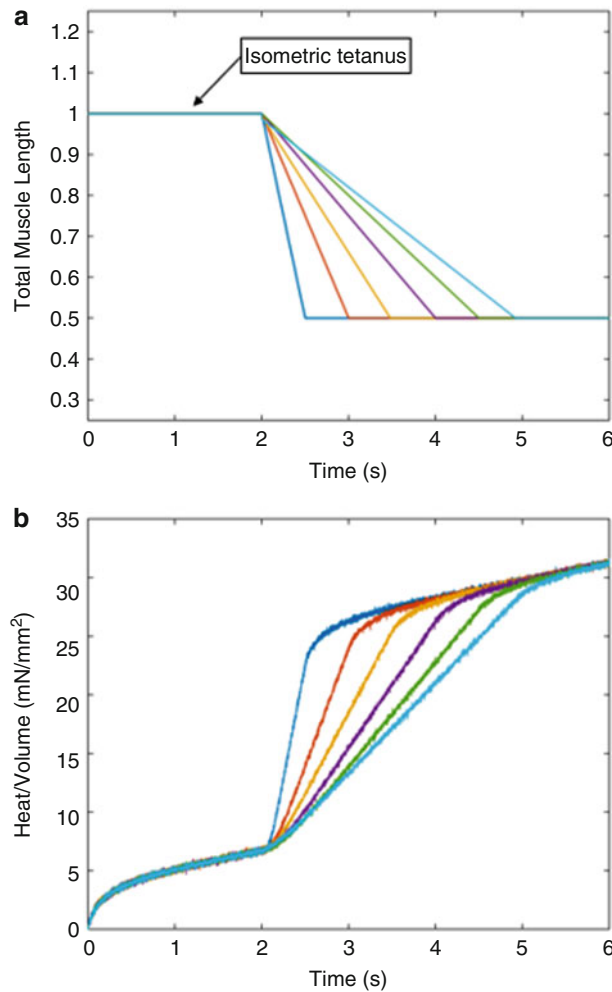
Force-Velocity Relationship

Hill empirically demonstrated that when held at the tetanic condition during an isometric contraction, subsequent increases in muscle load, P , decreased the shortening velocity, v , of the muscle over a distance, x , cm. Such experiments can be simulated in the model to reproduce this force-velocity relationship. As shown in Fig. 5, beginning at an isometric force of 150 mN, the shortening velocity, v mm/s, was changed from a value 0 to 1 in repeated simulations to compute the resulting steady-state

force. This inverse force-velocity relationship is summarized by an exponential regression fit as shown in the figure.

Length-Heat Relationship

Hill demonstrated that the heat released during muscle shortening is independent of the shortening velocity. This critical aspect on the thermodynamics of isometric contraction is illustrated by the simulations in Fig. 6. The muscle model was released from an isometric tetanus at 2 s and was subject to different shortening velocities as shown in Fig. 6a. The corresponding heat liberated as shown in Fig. 6b depends only on the shortening distance x (here, $x = 0.5$ mm) and not on the shortening velocity. Specifically the total amount of heat released due to muscle shortening was the same across all of the simulations, despite varying shortening velocities. These results demonstrate that the shortening distance x is a crucial determinant of the energy released by the muscle. When held in completely isometric conditions, the energy released is zero because there is no change in distance.



H

Hill's Model for Muscle Physiology and Biomechanics, Fig. 6 Force-Velocity and Length-Heat Relationships. (a). The muscle was held in isometric tetanus for 2 s, after which it was subject to different shortening velocities. From right to left, the shortening velocities shown are 1 mm/s, 0.50 mm/s, 0.33 mm/s, 0.25 mm/s, 0.20 mm/s, and 0.17 mm/s. After undergoing a period of shortening, all of the simulations ended at the same final length, which

was $\frac{1}{2}$ of the original length of the muscle at isometric tetanus. (b) The heat released by the muscle for the different shortening velocities in (a) is plotted (heat responses are color matched with traces in a). Over shorter periods of shortening, the rate of energy released is higher or reaches the maximal level more quickly; for this simulation, the end length was the same and notes that the energy released at the end of shortening is the same across all trials

Conclusion

Computational models of muscles help explain the principles of muscle physiology and force generation. The Hill model described here offers insights into the

relationships between muscle length, force, velocity, and heat released based on the classic experiments by A. V. Hill (1938). The model is useful to begin understanding the quantitative aspects of muscle physiology and biomechanics.

Appendix

Model Implementation Using MATLAB

```

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%% Hill Muscle Model %%%%%
%%%%% Jakob von Morgenland %%%%%
%%%%% The Hill Muscle Model and its
Implementation (JVM and SV) %%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

```

```

        i=length(t);
    end
end
[P2,H2,Lse2,Lce2] = hill(L2,t);
Pss(j)=P2(length(t)-1);
end

```

Hill Function

```
function [P,H,Lse,Lce] = hill(L,t)
```

Preparing Inputs for the Hill Function

```

t=0:0.001:5;
% time from 0 to 5 seconds with 0.001
time step
L=ones(length(t),1);
% initializing length of muscle to 1
L2=ones(length(t),1);
m=[-1,-0.5,-1/3,-0.25,-0.2,-1/6]
% theoretical slopes for linear
velocity equations
yint=[3,2,1.66,1.5,1.4,1.32]
% calculated y-intercepts for linear
velocity equations
vel=[1,0.5,1/3,0.25,0.2,1/6,0]
% theoretical velocity values derived
from slope calculations
%not used in rest of simulation, included for
reference for force-velocity graph
force=[7.437,34.51,52.68,65.71,
75.52,83.16,144.9]
% calculated force values derived from
simulations using theoretical velocity
values

```

Input-Output Relationship for Hill Model

```

[P,H,Lse,Lce] = hill(L,t);
% Inputs = muscle length (L) and time (t)
% Outputs = force (P), heat (H), and the
individual element lengths (Lce and Lse)

```

For Loop to Determine Force-Velocity

Relationship

```

for j = 1:length(m)
    for i = 1:length(t)-1
        if t(i)<2
            L2(i)=1;
        else
            if t(i)>= 2
                L2(i)=yint(j)+m(j)*t(i);
            end
        end
        if L2(i) < 0.5
            L2(i)=0.5;
        end
    end
end

```

Model Parameters

```

a = (380*.098); % shortening and heat
excess proportionality constant
b = 0.325; % excess energy and steady-
state force proportionality constant
P0 = a/0.257; % initial force in
isometric contraction
alpha = P0/0.1; % spring constant for
series elastic element
Lse0 = 0.3; % initial length of the
series elastic element
k = a/25; % heat production constant

```

Initialize Arrays for Outputs

```

Lse = zeros(length(t),1);
Lce = zeros(length(t),1);
Lse(1,:) = Lse0;
Lce(1,:) = 1-Lse0;
H = zeros(length(t),1);
P = zeros(length(t),1);

```

Solver for Length Input into Hill Model

```

for j = 2:(length(t))
    dt = (t(j)-t(j-1));
    dL = (L(j)-L(j-1));
    dP = alpha*((dL/dt)+b*((P0-P(j-1))/(
(a+P(j-1))))*dt;
    P(j) = P(j-1)+dP;
    H(j) = H(j-1)+(k+a*b*((P0-P(j-1))/(
(a+P(j-1))))*dt;
    Lse(j) = Lse0+P(j-1)/alpha;
    Lce(j) = L(j)-Lse(j);
end

```

Creates Noise for More Realistic Output

```

for i = 1: length(H)
    H(i) = H(i)+(k/10)*randn(1);
    P(i) = P(i)+(P0/100)*randn(1);
end
end

```

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Further Reading

Nature-Springer Encyclopedia of Neuroscience

Hippocampal Cognitive Prosthesis

► [Hippocampal Memory Prosthesis](#)

Hippocampal Memory Decoding Model

► [Memory Decoding Model](#)

Hippocampal Memory Prosthesis

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Synonyms

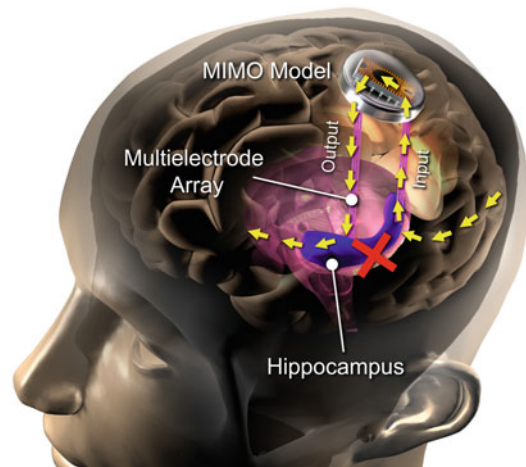
[Hippocampal cognitive prosthesis](#); [Hippocampal prosthesis](#)

Definition

Hippocampal memory prosthesis is a brain-machine interface device developed for restoring or enhancing memory functions (Berger et al. 2010, 2011, 2012; Hampson et al. 2012, 2013; Song et al. 2006). It is designed to circumvent damaged hippocampal regions by re-establishing the transformation of spike trains performed by a normal population of hippocampal neurons. The objective is to restore long-term memory function in a stimulus-specific manner using a multi-input, multi-output (MIMO) nonlinear dynamical model (Fig. 1).

Detailed Description

The hippocampus is responsible for the formation of new long-term episodic memories (Milner 1970; Squire and Zola-Morgan 1991; Eichenbaum 1999). It receives signals carrying short-term memories from neocortices and transforms them with its feedforward pathways into signals that can be stored as long-term memories back in neocortices. Degeneration and malformation of hippocampal neurons are the underlying



Hippocampal Memory Prosthesis, Fig. 1 A conceptual illustration of the hippocampal memory prosthesis for restoring memory functions. The hippocampal memory prosthesis bypasses a damaged region by reinstating output spike trains from input spike trains using a biomimetic multi-input, multi-output (MIMO) model

cause of the memory disorders associated with stroke, epilepsy, dementia, and Alzheimer's disease.

The hippocampal memory prosthesis is a biomimetic system that consists of three components: (1) a multielectrode array for recording the ensemble spike trains from an upstream hippocampal region, e.g., CA3, (2) a computational unit with a MIMO nonlinear dynamical model for predicting the output (e.g., CA1) ensemble spike trains based on the ongoing input (e.g., CA3) ensemble spike trains, and (3) an electrical stimulator for stimulating the downstream hippocampal region, e.g., CA1, with the predicted output spatiotemporal patterns of spikes.

The MIMO nonlinear dynamical model of input-output spike train transformation takes the form of the sparse generalized Laguerre-Volterra model (Song and Berger 2010; Song et al. 2009a, b, 2013, 2018; Fig. 2). A MIMO model is a concatenation of a series of multi-input, single-output (MISO) models that each can be considered a physiologically plausible spiking neuron model (Song et al. 2006, 2009a). Each MISO model consists of (a) a MISO Volterra kernel model transforming the input spike trains (x) to the synaptic potential u , (b) a Gaussian noise term capturing the stochastic properties of spike generation, (c) a threshold for generating output spikes, (e) an adder generating the pre-threshold membrane potential w , and (d) a single-input, single-output Volterra kernel model describing the output spike-triggered feedback nonlinear dynamics. The second-order self-kernel model can be mathematically expressed as:

$$w = u(k, x) + a(h, y) + \varepsilon(\sigma)$$

$$y = \begin{cases} 0 & \text{when } w < \theta \\ 1 & \text{when } w \geq \theta \end{cases}$$

$$u(t) = k_0 + \sum_{n=1}^N \sum_{\tau=0}^{M_k} k_1^{(n)}(\tau) x_n(t - \tau) + \sum_{n=1}^N \sum_{\tau_1=0}^{M_k} \sum_{\tau_2=0}^{M_k} k_{2s}^{(n)}(\tau_1, \tau_2) x_n(t - \tau_1) x_n(t - \tau_2)$$

$$a(t) = \sum_{\tau=1}^{M_h} h(\tau) y(t - \tau)$$

The zero-order kernel, k_0 , is the value of u when the input is absent. First-order kernels $k_1^{(n)}$ describe the linear relation between the n th input x_n and u , as functions of the time intervals (τ) between the present time and the past time. Second-order self-kernels $k_{2s}^{(n)}$ describe the second-order nonlinear relation between pairs of spikes in the n th input x_n as they affect u . N is the number of inputs. h is the linear feedback kernel. M_k and M_h denote the memory lengths of the feedforward process and feedback process, respectively. Additional model terms such as the second-order cross-kernels and third-order kernels can also be included.

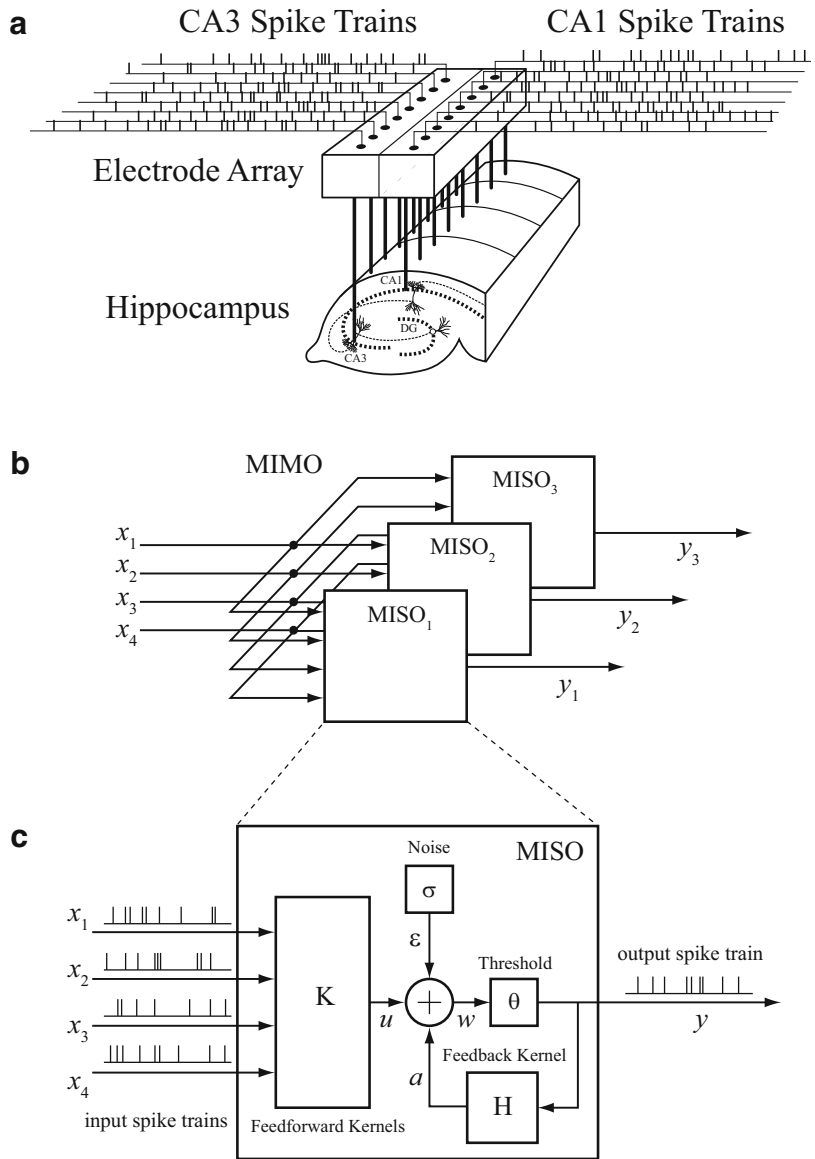
To facilitate model estimation and avoid overfitting, the Volterra kernels are expanded with basis functions b such as Laguerre basis or B-spline basis (Song et al. 2006, 2009a, b):

$$u(t) = c_0 + \sum_{n=1}^N \sum_{j=1}^J c_1^{(n)}(j) v_j^{(n)}(t) + \sum_{n=1}^N \sum_{j_1=1}^J \sum_{j_2=1}^J c_{2s}^{(n)}(j_1, j_2) v_{j_1}^{(n)}(t) v_{j_2}^{(n)}(t) \\ a(t) = \sum_{j=1}^L c_h(j) v_j^{(h)}(t)$$

where $v_j^{(n)}(t) = \sum_{\tau=0}^{M_k} b_j(\tau) x_n(t - \tau)$, $v_j^{(h)}(t) = \sum_{\tau=1}^{M_h} b_j(\tau) y(t - \tau)$, $c_1^{(n)}$, $c_{2s}^{(n)}$, and c_h are the sought expansion coefficients of $k_1^{(n)}$, $k_{2s}^{(n)}$, and h , respectively (c_0 is equal to k_0). J is the number of basis functions.

To achieve model sparsity, the coefficients are estimated with a composite likelihood estimation method, e.g., group LASSO (Song et al. 2013, 2018). In maximum likelihood estimation (MLE), model coefficients are estimated by minimizing the negative log likelihood function

Hippocampal Memory Prosthesis, Fig. 2 Multi-input, multi-output (MIMO) model for hippocampal CA3-CA1 population dynamics. **(a)** schematic diagram of spike train propagation from hippocampal CA3 region to hippocampal CA1 region. **(b)** MIMO model as a series of multi-input, single-output (MISO) models. **(c)** structure of a MISO model



H

$-l(c)$. In group LASSO, the composite penalized criterion is written as

$$\begin{aligned}
 S(c) &= -l(c) + \lambda \left(\sum_{n=1}^N \|c_1^{(n)}(j)\|_2^1 + \sum_{n=1}^N \|c_{2s}^{(n)}(j_1, j_2)\|_2^1 \right) \\
 &= -l(c) + \lambda \left(\sum_{n=1}^N \left(\sum_{j=1}^J c_1^{(n)}(j)^2 \right)^{\frac{1}{2}} \right. \\
 &\quad \left. + \sum_{n=1}^N \left(\sum_{j_1=1}^J \sum_{j_2=1}^{j_1} c^{(n)}(j_1, j_2)^2 \right)^{\frac{1}{2}} \right)
 \end{aligned}$$

where $\lambda \geq 0$ is a tuning parameter that controls the relative importance of the likelihood and the penalty term. When λ takes on a larger value, the estimation yields sparser coefficients. λ can be optimized with a multifold cross-validation method. The MIMO model is validated with the Kolmogorov-Smirnov test based on the time-rescaling theorem.

The hippocampal memory prosthesis has been tested in rodents and nonhuman primates performing memory-dependent behavioral tasks

such as the delayed nonmatch-to-sample (DNMS) task and the delayed match-to-sample (DMS) task (Berger et al. 2011, 2012; Hampson et al. 2012, 2013). Recently, its application was successfully demonstrated in human epilepsy patients (Song et al. 2018; Hampson et al. 2018). Results showed that MIMO model-derived electrical stimulation delivered to the hippocampal CA1 region during the sample phase of DMS trials facilitated short-term memory by 37% during the task. Longer term memory retention was also tested with a delayed recognition (DR) task. Across multiple subjects, the stimulated trials exhibited significant improvement (35%) in both short-term and long-term retention of visual information.

Applications

Damage to the hippocampus and surrounding regions of the medial temporal lobe can result in a permanent loss of the ability to form new long-term memories. Because the hippocampus is involved in the creation but not the storage of new memories (Milner 1970), long-term memories formed before the damage often remain intact, as does short-term memory. The anterograde amnesia so characteristic of hippocampal system damage can result from stroke or epilepsy and is one of the defining features of dementia and Alzheimer's disease. There is no known treatment for these debilitating cognitive deficits. Damage-induced impairments in temporal lobe function can result from both primary or invasive wounds to the brain, and from secondary or indirect damage, such as in traumatic brain injury. Temporal-lobe damage-related memory loss is particularly acute for military personnel in war zones, where over 50% of injuries sustained in combat are the result of explosive munitions, and 50–60% of those surviving blasts sustain significant brain injury, most often to the temporal and prefrontal lobes. Rehabilitation can rescue some of these lost faculties, but for moderate to severe damage, there are often substantial long-lasting cognitive disorders. Damage-induced loss of fundamental memory and organizational thought processes severely

limit patients' overall functional capacity and degree of independence, and impose a low ceiling on the quality of life. Given the severity of the consequences of hippocampus and/or temporal lobe damage-induced cognitive impairments, and the relative intransigence of these deficits to current treatments, the hippocampal memory prosthesis provides a solution to the problem of severe memory deficits with its MIMO model-driven, bi-directionally communicates with the functioning brain.

Cross-References

- [Cortical Motor Prosthesis](#)
- [Memory Decoding Model](#)
- [Somatosensory Prosthesis](#)

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Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)

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Definition

Oscillations result from synchronization of the underlying neural network. When a neuron fires action potentials at regular intervals, this leads to a periodic change in the membrane potential of its target cells. This periodic change only

shows up in the local field potential (LFP) or electroencephalographic (EEG) signal on the scalp if a sufficient number of neurons fire at roughly the same time, i.e., when they are synchronized.

What causes neurons to synchronize their spiking activity? This question has been extensively studied for gamma oscillations (30–90 Hz) in the hippocampus, mostly *in vitro* (i.e., in slices containing the hippocampus). Gamma oscillations were found to be induced in hippocampal slices under three different sets of conditions, leading to the identification of three gamma-generating mechanisms. Two mechanisms were named after the cell types involved in generating the oscillations: Interneuron Network Gamma, or ING, and Pyramidal Interneuron Network Gamma, or PING. The third mechanism, referred to as sparse and persistent gamma (PG), was named after its key characteristics, which distinguish it from both ING and PING.

Interneuron Network Gamma arises due to recurrent inhibitory coupling and is independent of principal cell firing. Synchrony can be achieved when the interneurons are driven to spike, inhibiting the group of neurons they project to. The targeted neurons recover from this inhibition at roughly the same time scale, delaying their spikes and hence increasing the likelihood of synchronized spiking after inhibition has decayed sufficiently.

Interneuron firing is also required in the PING mechanism, but there the interneurons are recruited by synchronized pyramidal cell spiking. Hence, the interneuron volley is always preceded by a pyramidal cell volley. PING is associated with high pyramidal cell firing rates.

While ING and PING are thought to be transient phenomena, induced by strong depolarizing inputs, sparse gamma is a long-lasting rhythm. Like ING, it does not require a high pyramidal cell firing rate; however, it is affected by modulation of excitatory synapses. Sparse gamma is therefore thought to depend on both pyramidal cell and interneuron activity, but is mediated by different connections than the PING and ING mechanisms.

Detailed Description

Hippocampal Oscillations: An Introduction

When an electrode is placed in between or close to a group of neurons, a time-varying local field potential signal (LFP) is recorded (Buzsáki et al. 2012). The LFP recorded *in vivo* typically shows periods of high and low amplitude following each other in a regular pattern. This pattern is known as an oscillation. Oscillations can be measured throughout the brain. When the power spectral density of the signal is computed and plotted, it becomes apparent that oscillations can have diverse characteristics. First, the brain's activity spans a range of frequencies, from a fraction of a Hertz up to 200 Hz (Buzsáki and Draguhn 2004). Second, power can differ between frequency bands and change over time. Oscillations have been linked to numerous brain functions, sparking great interest in the neurosciences in the past decades (Buzsáki and Draguhn 2004). Hippocampal oscillations have received a lion's share of the attention. Two frequency bands are particularly prominent and easy to distinguish in hippocampal activity: the theta band (4–10 Hz) and the gamma band (30–80 Hz, Buzsáki and Draguhn 2004). A link was discovered early on between these frequency bands and spatial navigation memory, making the study of these rhythms highly relevant (Buzsáki and Moser 2013).

Oscillations have been studied extensively in hippocampal slices of rodent brains (*in vitro*), mostly in rat. Several stimulation protocols were found to produce gamma oscillations in these slices (Whittington et al. 2011), which will be described in the next section. It allowed for the identification and description of three gamma-generating mechanisms. These mechanisms have since been studied using computer models (*in silico*) and in awake, behaving animals (*in vivo*). The mechanism behind the generation of theta oscillations is still debated, despite its putative role in spatial navigation and extensive studies into phase coding. Several models have been identified that can produce theta rhythms, but their relevance to hippocampal oscillations is unclear (see Kopell et al. 2010 and elsewhere in this encyclopedia). Here, we focus on generation of gamma oscillations, as the underlying

mechanisms are more delineated. We review the results from *in vitro*, *in vivo*, and *in silico* experiments and give a state-of-the-art description of the three gamma-generating mechanisms as well as their differences and similarities. We will also touch on the functional relevance of these mechanisms.

Three Types of Gamma Oscillations in *In Vitro* Measurements

In hippocampal slices, generation and modulation of gamma rhythms has been systematically studied by applying electrical stimulation and pharmacological manipulations. Tetanic electrical stimulation, in which a series of short pulses is applied via an electrode in the slice, induces short-lived gamma rhythms (Gloveli et al. 2010). Pharmacological manipulation is achieved by applying agonists or antagonist of membrane receptors in the bath solution in which the slice is kept. Activation of several membrane receptors, such as metabotropic glutamate receptors (mGluR), muscarinic acetylcholine receptors (mAChR), and kainate receptors (KAR, an ionotropic glutamate receptor), was shown to lead to gamma oscillations in hippocampal slices, as can an increase in bath concentration of potassium, which depolarizes the cells. Oscillations could be evoked in both the first and third cornu ammonis region (CA1 and CA3) in hippocampus, as well as in other parts of the hippocampal formation, such as dentate gyrus and entorhinal cortex (Gloveli et al. 2010).

To shed light on the mechanism behind the evoked oscillations, the role of inhibitory interneurons and principal cells was studied by selective blocking of synaptic transmission. To block excitatory synaptic transmission, the AMPA receptor antagonist NBQX was applied, while inhibitory synapses were blocked with the GABA_A receptor antagonist bicuculline. Gamma oscillations were absent when GABA transmission was blocked, independent of the area or stimulation protocol that was used (Whittington et al. 1995; Fisahn et al. 1998; Bartos et al. 2007). This finding indicates a critical role for inhibitory interneurons in the generation of gamma oscillations in

hippocampus. The oscillation frequency and power was affected when the strength and duration of GABA signalling was increased by adding benzodiazepines or barbiturates, which allosterically activate the GABA_A receptor (Bartos et al. 2007).

Surprisingly, when blocking AMPA transmission, mGluR-induced gamma oscillations in CA1 and CA3 remained (Whittington et al. 1995), but under these conditions mAChR-induced oscillations in CA3 and tetanically induced oscillations were abolished (Fisahn et al. 1998). Potassium-induced oscillations in both CA1 and CA3 were reduced, but not completely blocked.

By adding AMPA antagonists (Bartos et al. 2007). The results indicate that there are different types of dependence of the evoked gamma oscillations on principal cell (PC) activity. Hence, there are multiple gamma-generating mechanisms in these slices.

As the described data were all collected in the CA3 region of hippocampus, the results cannot be explained by differences in the anatomy of the underlying network. Instead, the stimulus protocols are expected to differ in the type of sub-network or the cell types they recruit and/or in the extent to which those are recruited during stimulation. For instance, while mGluRs and KARs are mostly found on interneurons, activation of AChRs by application of carbachol is known to activate pyramidal cells. In the mAChR activation protocol, interneurons are therefore entirely dependent on AMPA-mediated transmission for their activation, explaining the lack of oscillatory activity in the presence of AMPA receptor antagonists as a lack of interneuron recruitment.

Apart from their dependence on AMPA synaptic transmission, the rhythms obtained with different stimulation protocols differed in other characteristics as well, for instance:

- PC firing rate: pyramidal cells were found to fire either at gamma frequency or at only a few Hertz.
- Duration: electrical stimulation and potassium application produce gamma oscillations which last for seconds or minutes, while, for instance, mAChR-induced gamma can last for hours.

- Dependence on gap junctions: mAChR-induced oscillations in CA3 and potassium-induced oscillations in CA1, among others, have been shown to be dependent, to some extent, on the presence of gap junctions (pores that electrically couple adjacent neurons).
- Frequency range: different frequency bands have been found to coexist in CA1 recordings (Buzsáki and Wang 2012). Furthermore, the frequency versus stimulation amplitude curve of differently induced rhythms has different shapes, peaking at different frequencies within the gamma band (Whittington et al. 2011).

Based on these characteristics and subsequent modelling studies, the rhythms found *in vitro* have been collapsed into three groups (Whittington et al. 2011):

- Interneuron Network Gamma (ING): transient rhythms that are produced by direct stimulation of interneurons.
- Pyramidal Interneuron Network Gamma (PING): transient rhythms that are produced by stimulation of the pyramidal cells. PING is associated with high PC firing.
- Sparse or persistent gamma (PG): it requires PC firing, but at low firing rates. As the name suggests, persistent gamma is long lasting.

In the next three sections, the characteristics of each of the gamma-generating mechanisms are discussed in detail. Computer models of the three mechanisms are used to study what underlies their differences and similarities. It is important to keep in mind that these rhythms are not mutually exclusive. Instead, *in vivo* activity is likely to be composed of a mixture of the three, with the current state depending on what input was received and perhaps the computations that need to be performed.

Cell Types Involved in the Gamma Rhythm

As was shown in the preceding section, generation of gamma oscillations was disrupted when

GABA-mediated synaptic transmission was blocked, as well as, for some rhythms, when AMPA transmission was blocked. These findings indicate a crucial role for GABAergic interneurons in gamma generation. Though interneurons only make up a small portion of the total number of neurons in hippocampus, their diversity is much larger than that of pyramidal cells. Interneuron cell types are distinguished based on their electrophysiological, molecular, and morphological characteristics (see Klausberger and Somogyi (2008) for a review).

To identify the interneuron cell types involved in hippocampal gamma, two approaches can be considered. First, one can take a bottom-up approach and study the behavior of different interneuron types in a slice that is showing gamma oscillations by recording from individual neurons.

Several cell types were found to be active in accordance with the gamma cycle. Basket cells that express the calcium-binding protein parvalbumin (PV+ basket cells) were found to spike in synchrony with the gamma rhythm (quantified using the spike-field coherence, Gloveli et al. 2010; Buzsáki and Wang 2012). These cells were found to evoke gamma phase-locked IPSPs in the soma of connected pyramidal cells (Buzsáki and Wang 2012). The involvement of basket cells in gamma generation is supported by the properties of this cell type: basket cells are abundant (approx. 20% of the interneurons, Bartos et al. 2007), are densely connected to both each other and pyramidal cells (Bartos et al. 2007; Mann and Paulsen 2007), have been found to resonate at gamma frequency and spike at these high frequencies without adaptation (Bartos et al. 2007; Buzsáki and Wang 2012), and innervate the soma of pyramidal cells, making them perfectly suited for controlling spike timing, but not integration (which occurs in the dendrites), of the pyramidal cells (Mann and Paulsen 2007).

Other interneuron types that were found to co-activate with the gamma rhythm are, among others, bistratified and trilaminar interneurons. Bistratified cells showed a very high spike-field coherence and target the proximal dendrites of pyramidal cells (Klausberger and Somogyi

2008). The proximal dendrites have been found to resonate at gamma frequency (Whittington et al. 2011). Bistratified cells might therefore produce a very effective synchronizing signal, despite a low abundance. Trilaminar cells innervate neighboring areas in hippocampus and are therefore thought to play a role in the spatial spread of gamma oscillations (Whittington et al. 2011).

A second approach to identifying cell types involved in gamma generation is a top-down approach, which works by identifying which cell characteristics form the minimal requirements for gamma generation. This was studied using models of the different gamma-generating mechanisms. From these models it became clear that interneurons require fast kinetics to have an effective synchronizing effect and preferably innervate the soma or the dendritic elements close to the soma (Whittington et al. 2011). These requirements match the characteristics of basket cells, marking them as the key element to synchronization in the gamma frequency range.

Interneuron Network Gamma (ING)

The Interneuron Network Gamma (ING) mechanism is the simplest form of gamma generation. ING can be found in a model network comprised only of interneurons, as the rhythm's generation is independent of principal cells. When a drive is applied – that is, a current is injected at the soma – to the interneurons, the cells depolarize, causing them to spike at high rates. Subsequently, downstream neurons are inhibited and their firing is delayed. The projections from a neuron are divergent, meaning each neuron projects to a number of downstream neurons, causing the inhibitory effect of a spike to spread to a (small) part of the population (Bartos et al. 2007). When spikes of several neurons coincide, forming a volley, target neurons of all the neurons in the volley will be inhibited and recover from this inhibition at roughly the same point in time. Subsequent spiking of this group of target neurons is more likely to be synchronized than

before the volley, due to the synchronized inhibition. Synchrony will therefore spread through the population and oscillations can emerge (Tiesinga and Sejnowski 2009).

The ING mechanism has been extensively studied using computer models. An influential model, named after its developers, is the Wang-Buzsáki model (W-B model). It incorporates a network of conductance-based point model neurons that resemble PV+ basket cells (Wang and Buzsáki 1996). The model neurons are connected by model GABAergic synapses, with every neuron projecting to all other neurons in the network (all-to-all connections). When the interneurons are depolarized, the model shows robust oscillations in the lower gamma range within five or six cycles after stimulus onset (Fig. 1a). Replacing the all-to-all connectivity by a sparser, random connection matrix, also leads to synchrony, provided that there is enough convergence of inhibition to inhibit spiking in the downstream neurons (Fig. 1b).

The Wang-Buzsáki model demonstrates the ING mechanism in its purest form. From the model we can conclude that generation of gamma oscillations via the ING mechanism has only three requirements (Buzsáki and Wang 2012):

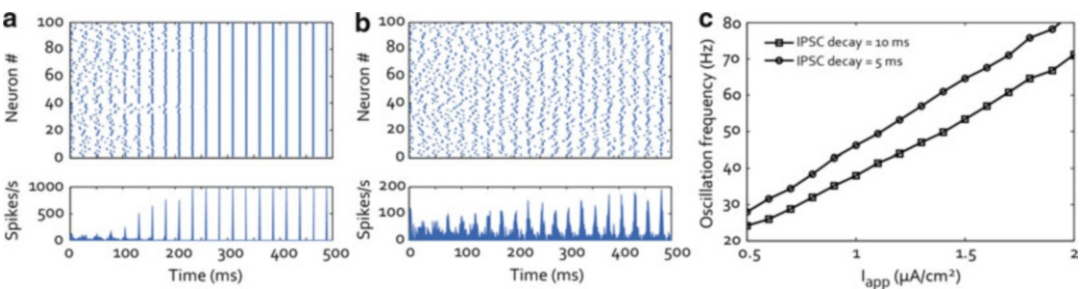
- Recurrent connections between inhibitory interneurons

- A time constant, due to transmission via GABA_A receptors, spreading the inhibition out in time
- Sufficient depolarization of the interneurons

The frequency of the emerging gamma oscillations in an ING network is determined by the time scale of inhibition and the level of depolarization of the interneurons. Neurons are ready to start a new volley when the drive to the neurons can overcome the remaining inhibition from the previous volley. Long decay time constants for the inhibitory postsynaptic currents (IPSCs) therefore lead to slower oscillations, or lower frequencies. A high drive, on the other hand, is able to balance out a much higher level of remaining inhibition and therefore shifts the next volley forward in time, increasing the oscillation frequency (Fig. 1c).

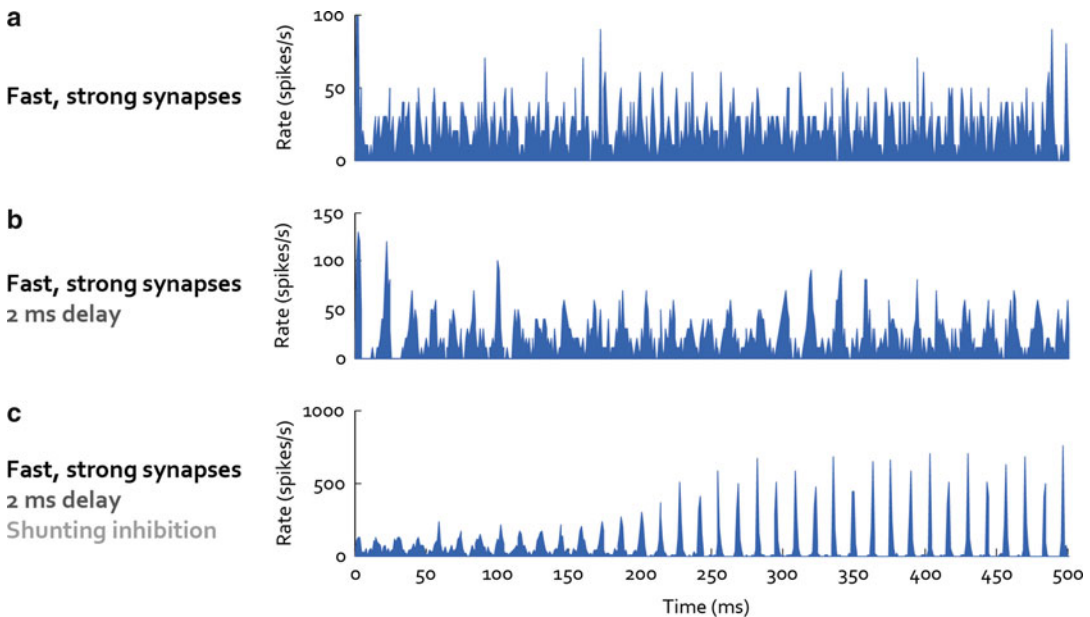
The Wang-Buzsáki model can provide great insight and is easy to study. When comparing it to the biological system, however, some discrepancies between model and experimental data need to be acknowledged. First, the time constant of the GABA_A receptors in the model was chosen to be 10 ms. Experimental data suggest that IPSCs due to basket cell – basket cell connectivity.

Have much shorter time constants, in the order of 1–2 ms (Bartos et al. 2007; Whittington et al. 2011), which is compensated by a high IPSC amplitude (Bartos et al. 2007). Decreasing the



Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Fig. 1 The Wang-Buzsáki model. (a) The W-B model with synapses with a 10 ms IPSC decay time constant and all-to-all connectivity shows rapid synchronization. Within five to six cycles, the population reaches full synchrony, in which all neurons spike within a close proximity. (b) With heterogeneity in the drive to the neurons and a connection probability of 60%, the network still

shows synchrony, but spike times are more variable. (c) The oscillation frequency (vertical axis) of the population in the W-B model depends on two factors: the frequency increases with the (average) drive to the neurons (horizontal axis) and increases with a shorter IPSC decay time (compare 10 ms decay time constant (squares) to 5 ms decay time constant (circles)). (Circuit model as described in Wang and Buzsáki (1996))



Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Fig. 2 The behavior of the Wang-Buzsáki model network is highly sensitive to the synapse parameters. (a) Fast, strong synapses, as suggested by experimental data, disrupt the oscillations in the Wang-Buzsáki model (compare Fig. 1b). (b) Oscillatory activity can be restored

by introducing a 2 ms synaptic delay in the model. (c) Changing the reversal potential of the GABA_A-mediated transmission from hyperpolarizing to shunting leads to increased levels of synchronization for strong synaptic connections and high oscillation frequencies. (Circuit model as described in Wang and Buzsáki (1996))

IPSC time constant and increasing the amplitude in the W-B model disrupts the oscillations (Fig. 2a). However, when synaptic delays between the synapses are introduced in the model, stable oscillations do occur, despite the fast IPSCs (Fig. 2b).

A second discrepancy between the W-B model and the hippocampal network is the resilience of the oscillatory activity to noise and heterogeneity in the network. Noise and heterogeneity in the tonic drive leads to variation in spike rate between neurons and makes periodic activity of individual neurons less reliable. In the W-B model, oscillations break down when the variance in drive to the neurons is larger than 5% of the mean drive (Bartos et al. 2007). Such small variability is not likely to be achieved *in vivo*, and from recordings during *in vitro* mGluR-induced oscillations, the variability in the drive across neurons is estimated to be 35% (Bartos et al. 2007). Two adjustments to the model have been found to make it less sensitive to variability in the drive: the addition of gap

junctions (Whittington et al. 2011) and changing the synapses from hyperpolarizing to shunting (Bartos et al. 2007). Gap junctions electrically couple neighboring neurons and allow activation to spread to adjacent cells almost instantaneously. Gap junctions therefore have a homogenizing effect: neighboring cells are more likely to spike simultaneously when they are electrically coupled, even if they receive different tonic drives. Gap junctions have been found to occur between basket cells, both with electron microscope imaging and with paired electrical recordings. Transgenic mice missing the gene for the most common gap junction pore protein, Connexin-36, still have mGluR-induced oscillations in CA3, but with a reduced power (Bartos et al. 2007).

Shunting inhibition has also been found to have a homogenizing effect, but through a slightly more complex mechanism than gap junctions. For shunting synapses, the reversal potential of the synaptic current is between the resting membrane

potential and the spike threshold, which has been indicated to be the case for GABA_A receptors (Mann and Paulsen 2007). In comparison, for hyperpolarizing synapses, the synaptic reversal potential is below the resting membrane potential, causing a cell at rest to hyperpolarize when the GABA_A receptor-mediated channels open. For shunting synapses, a cell at rest will not hyperpolarize, but depolarize, though not enough to reach spike threshold. Despite its depolarizing effect, shunting synaptic events prevent the postsynaptic cell from spiking, due to the increased conductance of the cell membrane, and hence, the term “inhibition” is appropriate. At low levels of excitation, the effect of increased conductance is small and the net effect of shunting is excitatory (Bartos et al. 2007). Therefore, the effect of shunting is drive dependent, with high drive leading to inhibition and low drive leading to excitation, hence homogenizing the activity of the neurons in the network if the synaptic connections are strong enough (Fig. 2c). The result is a highly synchronized population activity, but the resulting oscillations have a high frequency. The relevance of gap junctions and shunting in the generation of oscillations *in vivo* still remains to be determined. Furthermore, the potential involvement of other interneuron cell types as a stabilizing agent has so far not been considered in models (Mann and Paulsen 2007).

In the brain, interneurons do not form an isolated network. Instead, they are densely connected to (local) pyramidal cells. How do projections to and from pyramidal cells affect the ING mechanism? To test this, the W-B model has been extended with 400 pyramidal cells. In this model, when the interneurons are depolarized, while the pyramidal cells only receive a small drive, oscillations will occur via the ING mechanism (Fig. 3a). In agreement with experimental results, pyramidal cells have a low firing rate, while the interneurons spike at frequencies of a few tens of Hertz. When the connections from the pyramidal cells to the interneurons are broken, the oscillatory activity is not affected (Fig. 3b), but with broken interneuron-interneuron connections, the oscillation disappears (Fig. 3c). This indicates that the oscillation is only dependent on the

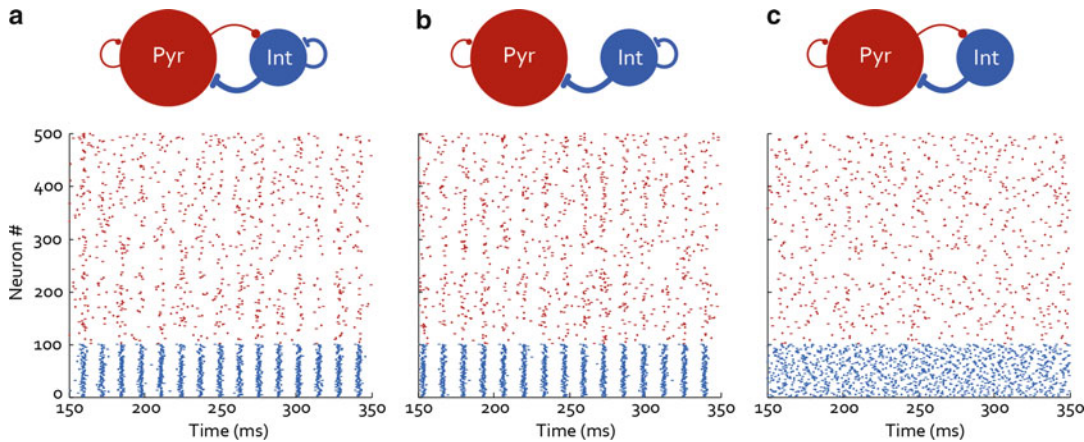
depolarization of the interneurons and not the input from the pyramidal cells, setting it apart from the PING and sparse mechanisms. We will now study those mechanisms in detail, before returning to the ING model and comparing the features of the three mechanisms.

Pyramidal Interneuron Network Gamma (PING)

The PING mechanism is thought to be recruited during sensory stimulation and could potentially play an important role in computation and communication in sensory processing areas (Whittington et al. 2011). A PING cycle starts when the pyramidal cells receive a strong input that drives them to spike. Some neurons will spike at roughly the same time. Pyramidal cell projections are highly convergent onto interneurons, with each interneuron receiving projections from approximately 1500 pyramidal cells (Whittington et al. 2011). The pyramidal cell activity triggers the interneurons to spike and thereby inhibits further activity in the pyramidal cells and interneurons they project to. The depolarization of the pyramidal cells can only trigger subsequent spikes when the inhibition has sufficiently decayed, delaying the spikes of the pyramidal cells and synchronizing them near the onset of the next cycle.

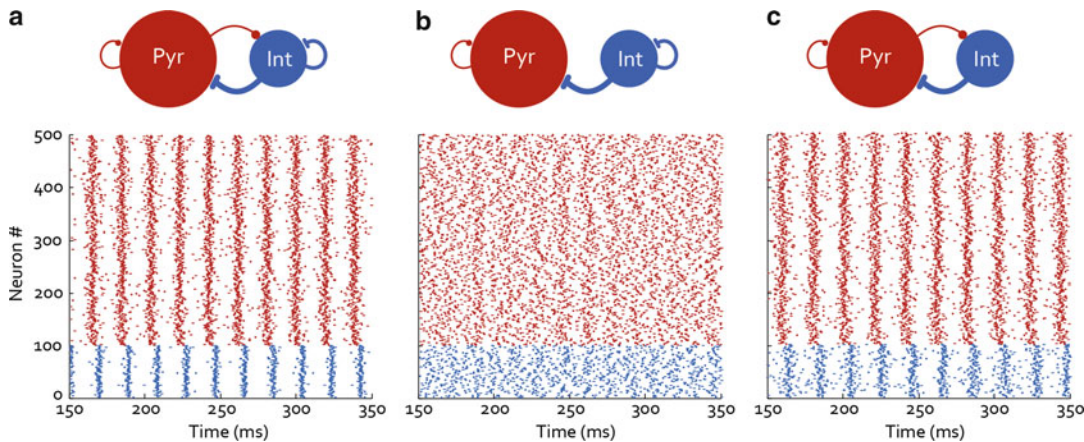
PING can be induced *in vitro* by applying a short period of pulsed electrical stimulation (tetanic stimulation) via an electrode in the slice (Whittington et al. 2011). This oscillation is short lived (Kopell et al. 2010) and is associated with high spike rate of both interneurons and pyramidal cells (Whittington et al. 2011). Both cell types spike approximately once per cycle, with the pyramidal cells always spiking before the interneurons, a pattern that has also been observed in *in vivo* recordings (Tiesinga and Sejnowski 2009; Buzsáki and Wang 2012).

The characteristics of the PING mechanism have been studied with a model that is similar to the two-population model described for the ING model. PING oscillations occur when the cell populations spike at a specific firing rate ratio



Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Fig. 3 (a) ING mechanism in a two-population model, including pyramidal cells. (b) Breaking the connections between the pyramidal cells and the interneurons does not affect the oscillations. (c) Breaking the connections between the interneurons disrupt the oscillations, even if the interneuron drive is compensated for the

reduced inhibition, as shown here. Circuit model as described in Roberts et al. (2013), with a connection probability between interneurons of 40% and $I_e = 1.5 \mu\text{A}/\text{cm}^2$ and $I_i = 3 \mu\text{A}/\text{cm}^2$ for A and B, $I_i = 1 \mu\text{A}/\text{cm}^2$ for C. I_e and I_i correspond to the average depolarizing currents injected into the excitatory and inhibitory cells, respectively



Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Fig. 4 (a) PING mechanism shown in a two-population model. As expected, the pyramidal cells produce a synchronized volley, followed by a volley of the interneurons at a short delay. (b) Breaking the connections between the pyramidal cells and the interneurons abolishes the oscillation, even if the interneurons are compensated for the reduced excitation through an additional

depolarizing current, as shown here. (c) Breaking the connections between the interneurons does not disrupt the oscillations, though spiking becomes somewhat more variable. The level of interneuron depolarization is increased to compensate for the reduced inhibition. Circuit model as described in Roberts et al. (2013), with $I_e = 2 \mu\text{A}/\text{cm}^2$ and $I_i = 1 \mu\text{A}/\text{cm}^2$ for A, $I_i = 2 \mu\text{A}/\text{cm}^2$ for B, and $I_i = 0.5 \mu\text{A}/\text{cm}^2$ for C

(Tiesinga and Sejnowski 2009), with isolated pyramidal cells spiking at or above gamma frequency (Fig. 4a). In the model, the origin of the oscillations can easily be checked by breaking the projections from the pyramidal cells to the

interneurons. Breaking the connections disrupts the oscillatory activity, indicating that the pyramidal cells are essential for its generation (Fig. 4b). Furthermore, oscillations can be found when there is no drive to the interneurons or when the

connections between the interneurons are broken (Fig. 4c), provided that the interneurons receive enough synaptic input from the pyramidal cells.

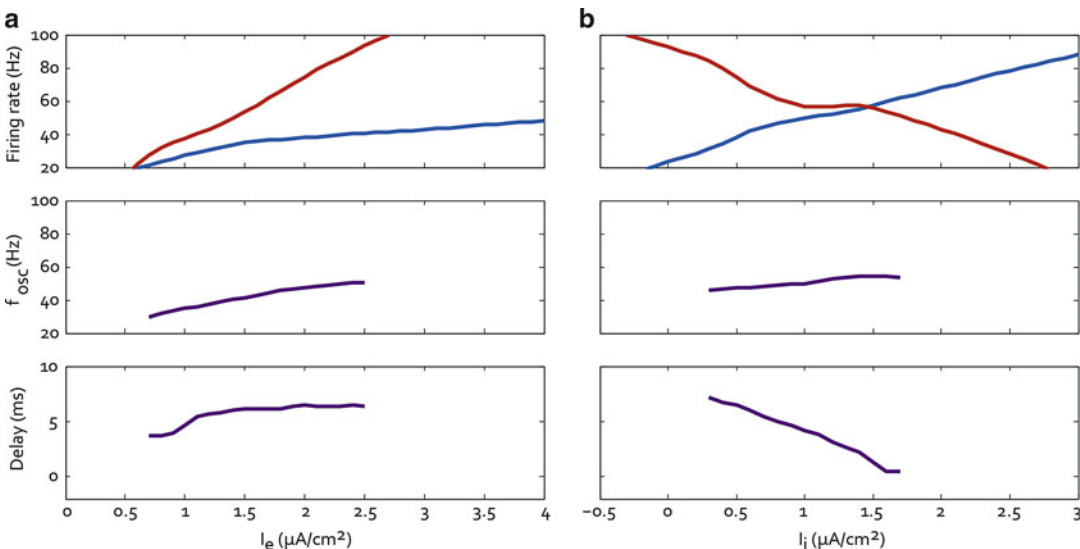
As in the *in vitro* and *in vivo* recordings, in the PING model pyramidal cells spike first, while the interneurons follow at a delay of a few milliseconds (Fig. 4a). The oscillation frequency in the population is the result of both the interneuron delay and the latency between the interneuron volley and the next pyramidal cell volley. The latency between the interneuron volley and the next pyramidal cell volley is determined by the time it takes the pyramidal cells to overcome the inhibition. It can be decreased by increasing the drive to the pyramidal cells, as shown by an increase in oscillation frequency (Fig. 5a, middle). Also, to some extent, the strength of the GABAergic synapses onto the pyramidal cells plays a role (Kopell et al. 2010), respectively slowing down and speeding up the oscillation. An increase in depolarization will cause the pyramidal cells to spike at a higher rate (Fig. 5a, top) and, in turn, drive the interneurons to increase

their spiking (Fig. 5a, top). As long as the ratio between pyramidal cell firing and interneuron firing is maintained, the populations will show synchrony and the oscillation frequency increases. For *in vitro* recordings, it was established that increasing the drive to the pyramidal cells leads to an increase in the oscillation frequency from 15 to about 60 Hz (Whittington et al. 2011).

The model also makes predictions for the effect of changing the drive to the interneurons. When the drive to the interneurons is increased, interneuron firing is increased, while pyramidal cells show less firing due to the increased inhibition. The model predicts three possible outcomes of changing the interneuron drive (Fig. 5b):

- When the ratio between pyramidal cell firing and interneuron firing becomes too low (i.e., high interneuron firing rates), synchrony is lost.
- When the ratio of pyramidal cell to interneuron firing enters the right range, synchronized oscillations emerge and the populations are

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Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Fig. 5 The effect of an increase in the tonic drive depends on the cell type to which it is applied. (a) Increasing the drive to the pyramidal cells increases the firing rate (top) of both the pyramidal cells (red) and the interneurons (blue) and increases the oscillation frequency (middle), while the delay between pyramidal cell volley and

interneuron volley is largely unaffected (bottom). (b) Increasing the drive to the interneurons increases their firing rate, while the pyramidal cell firing is reduced (top). The oscillation frequency is only slightly affected (middle), but the delay between the pyramidal cell and interneuron volleys is markedly reduced (bottom). (Circuit model as described in Roberts et al. (2013))

locked to the oscillations. On this “step,” the oscillation frequency does not change, but the delay between pyramidal cell volley and interneuron volley decreases (Tiesinga and Sejnowski 2010).

- For low interneuron firing, the inhibition cannot keep the pyramidal cells in check and synchrony is lost.

To conclude, the model predicts a change in the overall synchronization in the network with the interneuron drive. In experiments, under certain conditions, depolarizing the interneurons was found to enhance synchronization (Whittington et al. 2011).

Sparse or Persistent Gamma (PG)

The third mechanism for gamma generation has been named after two important characteristics of its activity pattern. PG is associated with low (sparse) pyramidal cell spiking, and it can last for hours. Its duration sets it apart from the ING and PING mechanisms, which are thought to be transient phenomena. Apart from this, the activity pattern of PG initially seems similar to that of ING: the interneurons spike at high firing rates (5–20 Hz, Traub et al. 2000), whereas pyramidal cells have low firing rates, between 0 and 4 Hz, and spike stochastically (Kopell et al. 2010; Whittington et al. 2011).

A more detailed study of PG brings to light important discrepancies between ING and PG. Surprisingly, genetically modified mice with ablated inhibitory synapses between PV+ basket cells still show strong persistent gamma rhythms. So, unlike ING, interneuron-interneuron interactions via chemical synapses are not essential for rhythmogenesis in PG (Whittington et al. 2011). Furthermore, when the membrane potential of individual interneurons is recorded during PG, large excitatory postsynaptic potentials (EPSPs) are found. This finding makes the PG mechanism inherently complex: how can rare and stochastic pyramidal cell spikes lead to strong excitatory inputs that drive the network to oscillate?

A possible origin of large EPSPs in interneurons during PG can be found in the presence of gap junctions. Gamma oscillations were found to be abolished when transmission via gap junctions was reduced through application of a general gap junction blocker (Whittington et al. 2011). Again, specifically blocking the connections between interneurons did not affect the oscillations, indicating that the gap junctions involve pyramidal cells. In agreement with this finding, recordings from pyramidal cells during PG reveal a high number of spikelets (Whittington et al. 2011): short transient depolarizations of the soma that resemble action potentials, but have a smaller amplitude. Spikelets are thought to result from action potentials in cell compartments that are electrotonically far from the soma. Therefore, it was hypothesized that there are axo-axonal gap junctions between pyramidal cells. These gap junctions could explain the strong EPSPs recorded in interneurons, while they could also give rise, via antidromic spikes, to the spikelets measured in the pyramidal cell soma.

Models with axo-axonal gap junctions between the pyramidal cells generated persistent gamma oscillations. However, nested within the gamma cycles, a very fast oscillation (VFO) is found. These VFOs have been observed under some experimental conditions (Whittington et al. 2011), but their significance is unclear. Another modelling study showed that oscillations with the characteristics of PG can also be obtained in a model without axo-axonal gap junctions. Here, a strong convergence from pyramidal cells to interneurons and a noisy external drive were sufficient to explain the strong EPSPs found in interneurons during PG (Kopell et al. 2010). A high noise level is thought to facilitate oscillatory behavior, as it can push the neurons to a subthreshold resonance regime: the noisy drive allows for spiking while keeping the average membrane potential at a relatively low level. Subthreshold resonance is found to be more pronounced at these lower membrane potentials, pushing the network toward an oscillatory state (Wang 2010). The mechanism underlying PG remains a topic of further discussion.

Comparing ING, PING, and Sparse Gamma

In the previous sections, a wide range of characteristics of ING, PING, and PG were discussed. In Table 1, the characteristics are summarized. Apart from these differences, a characteristic frequency response curve was identified *in vitro* for each of the mechanisms (Whittington et al. 2011). When the stimulation intensity increased, the three mechanisms showed distinct frequency changes. For low drive, the ING mechanism produced low oscillation frequencies, which increased to around 50 Hz and then decreased again for high stimulus powers. Unlike ING, induced PING showed a steady increase of gamma frequency with stimulus power, while PG showed no changes at all.

Given the characteristics in Table 1, it is possible, in principle, to distinguish between the three mechanisms in modelling studies: breaking the connections from pyramidal cells to interneurons should disrupt the PING and PG models, but not ING. PG and PING should be separable on the basis of the pyramidal cell firing pattern: while in PING pyramidal cells fire at high rates and are synchronized into a volley before interneuron firing, for PG the pyramidal cells spike sparsely and irregularly.

For experimental studies, the distinction between the three mechanisms is not trivial.

While the difference in pyramidal cell spike pattern between PING and PG is still a valid criterion, the distinction between ING and PG is not possible based on a spiking signature alone. Furthermore, how do we distinguish between a PING mechanism and an ING mechanism with a large but irrelevant pyramidal cell drive?

To allow for *in vivo* separation of the three mechanisms, we need to identify modulations of the network and its inputs that (1) can be performed without disrupting the functional properties and qualitative behavior of the network and (2) are feasible with the current technical possibilities. A possible approach is to apply optogenetic stimulation to specific cell types. For instance, stimulation of interneurons has a differential effect on the PING and ING mechanisms, as predicted from the models. For the ING mechanism, increasing the drive is predicted to increase the oscillation frequency, while for PING, it is expected to alter either the level of synchrony or the delay between pyramidal cells and interneurons. Selectively driving the pyramidal cells is expected to increase the oscillation frequency in the PING, but not the ING mechanism, where it will only affect the firing of the pyramidal cells. This modulation is hard to achieve pharmacologically, as it is not possible to drive the pyramidal cells without affecting the interneurons. However, when only pyramidal cells express

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Hippocampal Oscillations, Mechanisms (PING, ING, Sparse), Table 1 Summary of ING, PING, and PG characteristics

Characteristic	ING	PING	PG
<i>Interneuron firing</i>	Near gamma freq.	Near gamma freq.	Near gamma freq.
<i>Pyramidal cell firing</i>	Low (<5 Hz)	At or above gamma freq.	Low (<5 Hz)
<i>Duration</i>	Short (seconds)	Short (seconds)	Long (hours)
<i>Blocked by GABA_A antagonist</i>	Yes	Yes	Yes
<i>Blocked by AMPA antagonist</i>	No	Yes	Yes
<i>Modulated by gap junction blocker</i>	Yes	No	Yes
<i>Large EPSPs in interneurons</i>	No	Yes	Yes
<i>Increase of stimulus power in vitro</i>	Peak around 50 Hz for intermediate stimulus amplitudes	Oscillation frequency increased with power	No noticeable changes

channelrhodopsin, it is possible to apply cell type-specific optogenetic stimulation. A similar approach would allow one to distinguish ING from PG *in vivo*, but more insight into the PG mechanism is required before solid predictions can be made. With those approaches, it would be possible to identify the input conditions that lead to the recruitment of the different mechanisms. Also, the possibility of coexistence of and interactions and transitions between the mechanisms and their activity signatures should be studied further, as these questions are relevant in understanding the function of the different mechanisms.

Gamma Rhythms and Cell Assemblies

The abundance of oscillations in the brain suggests a strong link, either causal or coincidental, to function. Several possible functional relations have been suggested for gamma oscillations. The possibility of a temporal code, in which the timing of a spike relative to the oscillatory background encodes information, was recognized early on (Buzsáki and Draguhn 2004). A more compelling possibility is the dynamic formation of neurons or local networks into functionally distinct assemblies. An assembly marks a temporary partnership between groups of neurons that extends across multiple gamma cycles and does not require direct synaptic connections. The formation of assemblies potentially improves computation and facilitates synaptic plasticity and communication (Buzsáki and Draguhn 2004).

The mechanisms underlying transient assembly formation have recently been explored in modelling studies. In both the ING (Buzsáki and Wang 2012) and the PING (Kopell et al. 2010) mechanisms of gamma generation, cell assembly formation can result from heterogeneity in the input to the cells. Heterogeneity causes the pyramidal cells in a population to spike at different phases of the gamma cycle: pyramidal cells receiving a strong input will spike early, while more weakly driven cells fire late in the gamma cycle. If the strongly driven pyramidal cells are numerous and/or synchronized enough,

they will recruit inhibition and spiking of weakly driven neurons is suppressed. This way, two or more cell assemblies are formed. As long as the activity of the neurons is able to “reset” completely within a gamma cycle or, in other words, if inhibition is the longest timescale in the system, the temporal ordering of spikes is maintained as long as the input pattern is maintained (Kopell et al. 2010).

Interactions between the gamma rhythm and oscillation with other frequencies are also considered important for assembly formation. At larger spatial scales, the interaction between the theta and gamma rhythms is thought to lead to synchronization between distant areas, for instance, across hippocampal hemispheres or between cortex and hippocampus (Buzsáki and Wang 2012). The local gamma rhythm can lock to the cycles of the more spatially extended theta rhythm, leading to a spatial spread of gamma synchronization, at least in models (Kopell et al. 2010).

Cross-References

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- ▶ [Local Field Potential, Synchrony of](#)
- ▶ [Local Field Potentials: LFP](#)

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Hippocampal Prosthesis

► Hippocampal Memory Prosthesis

Hippocampal Theta, Gamma, and Theta/Gamma Network Models

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Definition

Hippocampal theta, gamma, and theta/gamma network models refer to mathematical models of networks that are able to generate oscillations within the theta (4–12 Hz), gamma (25–140 Hz), and nested theta/gamma frequency ranges in the hippocampus.

The focus is on network models consisting of biophysically motivated cell models in the hippocampus that are concerned with network rhythm generation.

This entry discusses some common motives involved as well as questions that arise in constructing these network models, provides a tabular summary of existing theta/gamma network models, and gives further details of some of the network models.

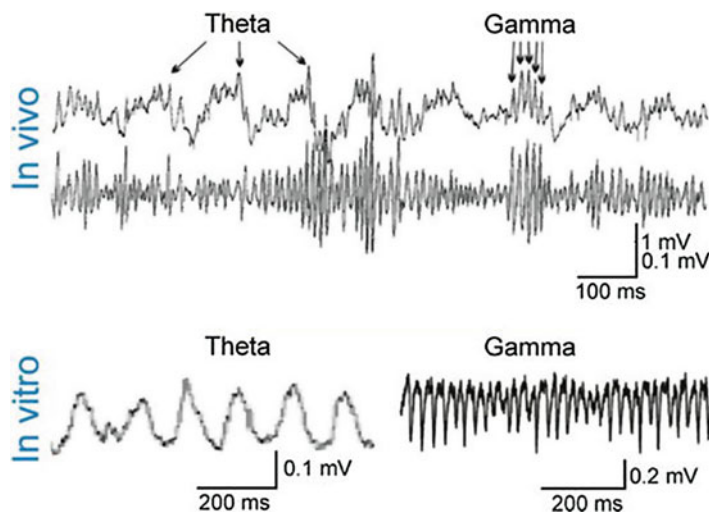
Detailed Description

Coordinated neural activity may provide a temporal structure with which information can be processed and transmitted and can be reflected in

recordings of population activity, such as those of the local field potential (LFP). Indeed, links between network oscillations and behavior have been shown, particularly with respect to network rhythms of the hippocampus. Most notably, hippocampal theta (4–12 Hz) and gamma (25–140 Hz) rhythms are recorded during exploratory behavior and REM sleep and are thought to be critically involved in certain forms of cognition, such as feature binding, temporal encoding, decision making, spatial navigation, and episodic memory (Singer 1999; Traub et al. 1999; Salinas and Sejnowski 2001; Buzsáki 2002; Womelsdorf et al. 2007; Tort et al. 2008; Colgin and Moser 2010). In vivo, gamma rhythms are generally temporally nested within the slower theta rhythm and are termed theta/gamma rhythms (Fig. 1) (Bragin et al. 1995; Montgomery et al. 2008). Although experiments have provided much insight into how these oscillations may come about (Buzsáki 2002; Colgin and Moser 2010; Wang 2010; Colgin 2013) (see ► “Hippocampus, Theta, Gamma, and Cross-Frequency Coupling” for more details), a precise understanding of their

generation, in particular theta and theta/gamma, remains unclear.

Theta and theta/gamma network rhythms are generated intrinsically and endogenously in a complete rat hippocampal preparation in vitro (Goutagny et al. 2009; Jackson et al. 2011) and can be induced in in vitro hippocampal slice preparations through pharmacological manipulation (Fisahn et al. 1998; Gillies et al. 2002), thereby facilitating recordings of network rhythms. The hippocampus has a structured architecture, where cell bodies are often constrained to lie in a single layer, and dendritic trees and axonal projections compose well-defined laminae. This provides a setting in which one can target and identify particular cell types and permits simultaneous recordings of network and cellular levels to be done with relative ease. Thus, a plethora of experimental work focuses on cellular functioning in hippocampal network oscillations, providing a platform with which one can construct experimentally based models to gain insight into hippocampal rhythmogenesis. Modeling a theta, gamma, or theta/gamma network simplifies the complicated biological system due to a



Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 1 Hippocampal theta and gamma oscillations in vivo (*top*) and in vitro (*bottom*). In vivo, gamma oscillations can be seen nested inside the slower theta oscillations (theta/gamma) in field recordings of the dentate gyrus during exploratory waking. In vitro, the theta and gamma oscillations shown were recorded

under pharmacological manipulation in the CA1 and CA3 areas (With kind permission from Springer Science+Business Media: *Hippocampal Microcircuits* (Cutsuridis, V., Graham, B., Cobb, S. & Vida, I., eds.), Part I, Chapter 8, 2010, pp. 247–276, T. Gloveli, N. Kopell, and T. Dugladze, “Neuronal activity patterns during hippocampal network oscillations *in vitro*,” Fig. 1a, c, d)

focus on particular rhythms, permitting theoretical and/or computational analyses to parse out fundamental mechanisms of the network. With such mechanistic insight, models help understand not only hippocampal rhythm generation but also pathological states that are associated with hippocampal rhythm changes. Further, model mechanisms could yield insights into rhythm generation in other brain regions.

Building Network Models and Complications Involved

Which Cell Types to Include?

The goal of many hippocampal network models is to gain a mechanistic understanding of the cellular contributions to intrinsically generated hippocampal network rhythms (e.g., Gloveli et al. 2005; Wulff et al. 2009). Thus, a first step in building a network model is to decide which cell types should be included. This is not a straightforward task: although excitatory cells far outnumber inhibitory (releasing γ -aminobutyric acid or GABAergic) interneurons, inhibitory cell networks with tonic depolarization have been shown to generate gamma oscillations (Whittington et al. 1995; Buzsáki and Wang 2012). Thus, explicitly including excitatory cells in network models may not always be critical to rhythm generation. In addition, a number of different inhibitory (GABAergic) interneuron types may be involved in local hippocampal oscillations (Klausberger and Somogyi 2008), and how critical each cell type is to rhythm generation is yet to be determined. These interneuron types exhibit a wide diversity of morphologies, synaptic targets, and firing properties (Freund and Buzsáki 1996; McBain and Fisahn 2001).

Fast-firing interneurons in particular have been suggested to play an essential role in hippocampal theta, gamma, and theta/gamma rhythms (Ylinen et al. 1995; Penttonen et al. 1998; Bartos et al. 2001; Freund 2003; Wulff et al. 2009; Colgin and Moser 2010; Gulyás et al. 2010; Jackson et al. 2011; Belluscio et al. 2012). These fast-firing cells are most often regarded as parvalbumin-positive (PV+) basket cells, although other fast-firing interneurons may also contribute to these rhythms

(e.g., PV+ axo-axonic and bistratified cells). Oriens-lacunosum-moleculare (O-LM) interneurons have their cell bodies constrained to the stratum oriens, but their axonal projections target the distal dendrites of pyramidal cells in the stratum lacunosum-moleculare. Maccaferri and McBain (1996) showed that they tend to fire spontaneously at theta frequencies (but see Kispersky et al. 2012) and are therefore thought to play an important role in theta oscillations. Furthermore, more models exist of O-LM and PV+ interneurons than of other interneuron types (see ► “Hippocampus, Model Inhibitory Cells”). This is true for a number of reasons, including ease of recordings and prevalence of interneurons. For example, O-LM and PV+ cells are more numerous in the CA1 region than some other interneuron types, such as cholecystikinin (CCK) and vasoactive intestinal protein (VIP) interneurons (Jinno and Kosaka 2006). Consequently, fast-firing and O-LM interneurons are the most common interneuron types to be included in theta, gamma, and theta/gamma hippocampal network models. However, it remains to be seen whether other interneuron types are critically involved in the generation of these local rhythms.

How to Model Individual Cells?

Neurons are often represented either by simple spiking models (e.g., the leaky integrate-and-fire model. See ► “Integrate and Fire Models, Deterministic” in this Encyclopedia) or by conductance-based models (Skinner 2006). The computational efficiency of simple spiking models, such as the leaky integrate-and-fire model and the Izhikevich model (Izhikevich 2003), makes them good candidates for examining network dynamics (e.g., Ferguson et al. 2013). However, to address more biophysically detailed questions, conductance-based neuron models are used (e.g., Orbán et al. 2006).

The level of detail incorporated in conductance-based neuron models varies greatly depending on the question at hand and on the availability of experimental data. Firing properties, ion channel densities and kinetics, and synaptic transmission have been studied extensively in hippocampal excitatory cells, and therefore many detailed

multi-compartment models of these cells exist (see ► [“Hippocampus, Model Excitatory Cells”](#)). Depending on the question being addressed, some network models will incorporate these highly detailed excitatory cell models (e.g., Orbán et al. 2006), while others will prioritize computational efficiency and use simpler models (e.g., Wulff et al. 2009). However, much less is known about the various interneuron types involved. This, in combination with the need for computational efficiency in large networks, commonly leads to the use of simple single-compartment conductance-based models to represent hippocampal interneurons in these network models (see ► [“Hippocampus, Model Inhibitory Cells”](#) for some examples).

How Is the Network Connected?

Additional considerations arise for modeling the connectivity of the network. For example, synaptic connections from fast-firing basket cells to O-LM interneurons have yet to be shown experimentally. Some network models assume that this connection exists (e.g., Gloveli et al. 2005; Tort et al. 2007; Wulff et al. 2009), while others assume it does not (or is not a critical connection) (e.g., Orbán et al. 2006; Neymotin et al. 2011). O-LM interneurons have been shown to synapse onto PV+ interneurons (Katona et al. 1999), but the strength of this connection, and whether this synapse plays a critical role in local rhythms, remains unclear. Therefore, some models include this connection (e.g., Gloveli et al. 2005; Orbán et al. 2006; Tort et al. 2007; Wulff et al. 2009), while others do not (e.g., Neymotin et al. 2011). Synaptic strengths and kinetics of the connections need to be considered as well. For example, Bartos et al. (2002) used a much smaller time constant for recurrent fast-spiking interneuron inhibitory postsynaptic current (IPSC) dynamics than Wang and Buzsáki (1996), which influences both coherence and frequency of the oscillations.

Further, topology or architecture aspects need to be taken into consideration (Feldt et al. 2011). This is challenging as it is not simply the issue of whether there are full (all-to-all) or partial connections between different cell types that can strongly influence the network dynamics. Multiple afferents generally target individual cells (a cell's

convergence), and that cell in turn targets multiple postsynaptic cells (its divergence). This, as well as particular structural motifs (► [“Hippocampus, Model Network Architecture”](#)), can also strongly influence network rhythms.

How Many Cells Are Needed to Represent a Population?

Due to computational constraints, hippocampal network models often incorporate a minimal number of cells for each cell type. However, the “minimal” number of cells needed to represent a population is not clear and will depend on the question being addressed. Thus, many different choices have been made. For example, Gloveli et al. (2005) represent a population of pyramidal cells with a single pyramidal cell model, while Neymotin et al. (2011) represent the pyramidal cell population with 800 cell models. Furthermore, the proportion of the various cell types in the network model could be considered. One may choose the number of each cell population to be proportional to that which is observed experimentally or may make assumptions about the role or influence of a particular cell population during the network rhythm. Regardless, such decisions need to be made.

Overall, important choices must be made about which cell types to include in one's network model, the type of model used to represent them, the connectivity and architecture of the network, and the network size. These choices will ultimately affect the network output and the mechanisms involved in the network model rhythm generation.

Gamma Models

Many models of population gamma have been developed and used (see Buzsáki and Wang 2012 review). Based on both experimental and modeling work, there is a well-developed conceptual understanding of how gamma rhythms are generated in neuronal networks. These mechanisms are described in detail in ► [“Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)”](#). Briefly, two distinct gamma-generating mechanisms have been discussed extensively:

interneuron network gamma (ING) and pyramidal-interneuron network gamma (PING). In the ING mechanism, gamma is generated by a network of recurrently connected inhibitory interneurons. This gamma is independent of phasic pyramidal cell firings, although the interneurons do require a depolarizing drive. The frequency and coherence of the gamma generated are dependent on the amount of recurrent connectivity in the network, the excitatory drive to the interneurons, and the decay time constant of the inhibitory postsynaptic potentials (IPSPs). Conversely, the PING mechanism requires the interaction between principal cells and inhibitory interneurons but does not require recurrent connections among the interneurons. PING networks require specific firing ratios between the pyramidal and the interneuron populations, and oscillations only occur when principal cells have high firing rates (i.e., they must fire at or above gamma frequencies). The majority of theta/gamma models created thus far have utilized this PING mechanism. Physiologically, gamma may be generated by a combination of mechanisms, including ING and PING. See the “Further Reading” section for PING/ING model references.

Theta Models

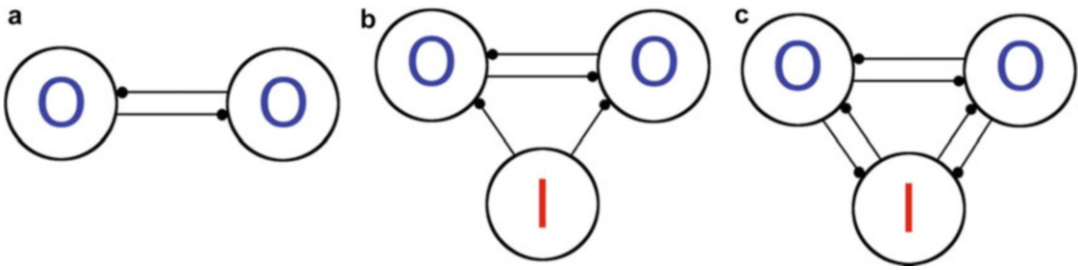
Maccaferri and McBain (1996) showed that a hyperpolarization-activated (h) current in oriens-alveus interneurons is involved in the generation of spontaneous spiking activity at theta frequencies. Since then, these cells have been seen as a potential pacemaker for intrinsic hippocampal theta rhythms. In 2002, Gillies and colleagues produced atropine-resistant theta oscillations in the CA1 region of *in vitro* hippocampal slice preparations by applying a metabotropic glutamate agonist and an α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blocker. During this pharmacologically induced CA1 theta oscillation, Gillies et al. (2002) implicated oriens-lacunosum-moleculare (O-LM) interneurons, and specifically h-currents in these cells, as a critical component of this theta generation.

Rotstein et al. (2005) constructed an inhibitory interneuron-based hippocampal network model to determine whether h-currents in O-LM interneurons could be responsible for the theta generation described by Gillies et al. (2002). Using single-compartment O-LM cell models (O) with h-channel dynamics, they tested whether a network of two cell models (Fig. 2a) could produce network theta oscillations. They found that although their models individually fired intrinsically at 12 Hz, the two cells could not produce a robust coherent rhythm. When a fast-spiking cell model (I) provided common inhibition to the O cell network (Fig. 2b), it robustly entrained and synchronized the O cells only when I cells were firing at theta frequencies. Furthermore, if feedback was provided from O to I cells (Fig. 2c), the network produced robust and coherent theta oscillations. Their findings did not depend critically on network size, but did on the presence of h-currents in their O cell model and the absence of this current in their I cell model.

It is important to note that in 2012, Kispersky and colleagues demonstrated in hippocampal slice preparations that O-LM cells do not fire preferentially at theta frequencies when injected with broadband artificial synaptic inputs but do phase-lock well to theta-modulated inputs. They also showed that O-LM phase-locking to theta frequencies was not due to h-currents (Kispersky et al. 2012). Therefore, the importance of O-LM cells for theta rhythm generation may not be as great as early models predicted. However, O-LM cells with their biophysical characteristics that include h-currents may predispose the system to phase-lock to high or low theta frequency inputs (Sekulić and Skinner 2017).

Theta/Gamma Models

A number of models that aim to gain insight into theta rhythm generation have also investigated the mechanisms involved in local hippocampal nested theta/gamma oscillations. These models have, in general, focused on three cell types: pyramidal cells, fast-spiking basket cells, and O-LM interneurons. They have investigated various



Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 2 Schematics depicting the various network models used in Rotstein et al. (2005). Here, “O” represents their single-compartment oriens-lacunosum-moleculare (O-LM) cell model, which fires intrinsically at theta frequencies (12 Hz), and “I” represents their fast-spiking interneuron model. *Black filled circles*

represent inhibitory connections. (a) Two O cell models do not produce coherent theta oscillations. (b) A single I cell provides common inhibition to two connected O cells. Here, theta oscillations were coherent when I cell firings were at theta frequencies. (c) Robust and coherent theta oscillations were produced in a network of two O cells and an I cell with all-to-all connections

questions concerning the mechanisms underlying theta/gamma rhythm generation, and thus, due to the consideration of different issues, as well as the consideration of various underlying assumptions, the network models used differ.

We summarize these theta/gamma network models in Table 1. For simplicity, and as done by some authors, we use E, I, and O for models of pyramidal cells, fast-spiking interneurons, and O-LM cells, respectively. Unless otherwise noted, the I cell models used are from Wang and Buzsáki (1996). The O cell models used are comparatively presented elsewhere (► “[Hippocampus, Model Inhibitory Cells](#)”). The basis of the E cell models is given in footnotes. Connections included between different cell types are shown, but further specifics of their architecture are not described in the table. Here, we describe a few of these theta/gamma network models, and their experimental motivation, in more detail.

Wulff et al. (2009): Fast Inhibition onto Parvalbumin-Positive (PV+) Interneurons Is Required for Theta/Gamma Coupling

Rotstein et al. (2005) showed that their inhibitory network model required mutual connections between their O cells and their fast-spiking I cells for theta generation. To investigate this further, Wulff et al. (2009) employed both experimental techniques and computational modeling to determine the precise role of inhibition onto parvalbumin-positive (PV+) interneurons, of

which fast-spiking basket and axo-axonic interneurons make up the majority (~75% collectively; Baude et al. 2007). First, they genetically modified mice in which fast GABA_A receptor-mediated inhibition was removed from PV+ interneurons and found that theta oscillation and theta/gamma oscillation coupling in vivo were dependent on this synaptic input. Second, they created a mathematical network model to determine if these changes to theta and theta/gamma coupling were due to ablated connections within an intra-hippocampal theta-generating network.

Their network model consisted of a single E cell, I cell, and O cell (see Fig. 3a and Table 1), where the O cell was representative of a cell that preferentially spikes at theta frequency, but not necessarily an O-LM interneuron. The E cell was representative of a population of pyramidal cells and thus fired intrinsically at the population frequency (i.e., gamma). As with the model in Rotstein et al. (2005), the $O \leftrightarrow I$ network produced theta oscillations. In addition, gamma was generated through a mechanism involving the $E \leftrightarrow I$ network (pyramidal-interneuron network gamma or PING. ► “[Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)”). To mimic their experimental protocol, they removed the inhibitory synapses onto the I cell (by setting the maximal synaptic conductance strength of the $O \rightarrow I$ and the $I \rightarrow I$ connections to zero) (Fig. 3b). Consistent with their experimental results, without these fast inhibitory synapses,

Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Table 1 Theta/gamma network models

References	Cell types	Number of compartments in biophysical model	Network size	Connections included
White et al. (2000)	I, O ^a	1	50, 50	I → O, O → I
Tiesinga et al. (2001)	E, ^b I	2, 1	50–500, 100	E → I, I → E E → E, I → I
Gloveli et al. (2005)	E, ^c I, ^d O	2, 1, 1	1, 2, 2	E → I, E → O I → E, I → O, I → I O → E, O → I
Orbán et al. (2006)	E, ^e I, O	256, 1, 1	15, 100, 70	E → I, E → O I → E, I → I O → E, O → I
Tort et al. (2007)	E, ^f I, O	5, 1, 1	1–80, 5–50, 5–50	E → I, E → O I → E, I → O, I–I O → E, O → I
Wulff et al. (2009)	E, ^g I, O	1, 1, 1	1, 5, 15	E → I, E → O I → E, I → O, I → I O → E, O → I
Neymotin et al. (2011)	E, ^h I, O	5, 1, 1	800, 200, 200	E → I, E → O I → E, I → I O → E

^aA single mathematical model is used to represent I and O cells (White et al. 1998), but I and O cells are considered as two different inhibitory cell populations based on differences in their synaptic kinetics. Although I cells are considered to be basket cells, O cells are not necessarily O-LM interneurons

^bAdapted from Pinsky and Rinzel (1994)

^cAdapted from the I cell in Rotstein et al. (2005)

^dRotstein et al. (2005)

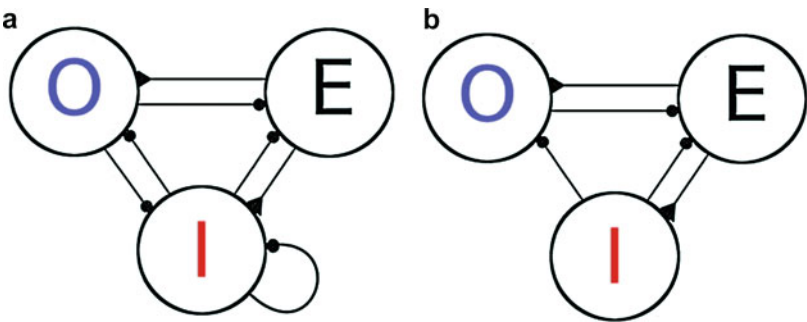
^eAdapted from Warman et al. (1994) but included h-current based on Magee (1998)

^fAdapted from Migliore et al. (2004)

^gErmentrout and Kopell (1998), which is a reduction of Traub and Miles (1991)

^h(Tort et al. 2007), which is adapted from Migliore et al. (2004)

Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 3 A schematic of the network model in Wulff et al. (2009). Their network model consisted of one excitatory cell model (*E*), five fast-firing inhibitory cell models (*I*), and 15 models of cells that spike preferentially at theta frequencies (*O*). *Black filled circles* represent inhibitory connections, and *black filled triangles* represent excitatory connections. (a) The Wulff et al. (2009) theta-gamma-generating network model had all-



to-all connections among the cell populations, as well as recurrent connections among the I cell population. (b) To mimic their experimental protocol, where GABAergic synapses onto fast-spiking interneurons were ablated, they set their O–I and I–I connection strengths to zero. Here, they observed attenuated theta oscillations and a reduction in the modulation of gamma amplitude and frequency by theta

their network model had attenuated theta oscillations and a large reduction in gamma amplitude and frequency modulation by the theta phase. Thus, their model implicates an intra-hippocampal network as responsible for the reduced theta and theta/gamma coupling seen in their genetically modified mice.

Gloveli et al. (2005) and Tort et al. (2007): O-LM Cell Morphology Affects Theta/Gamma Rhythms Across the Longitudinal Axis

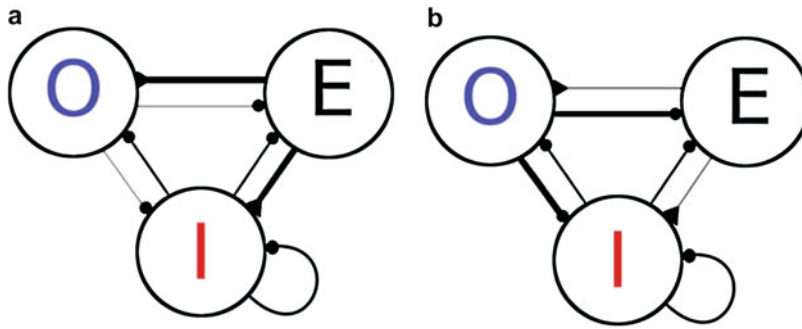
Andersen et al. (1971) showed that the hippocampus is composed of multiple laminae that are arranged in parallel across the longitudinal axis, indicating that there may be multiple functional units organized across this axis. It is possible that, due to the diversity of interneuron types, a particular class may have the appropriate axonal arbor to serve as a connection between these distinct segments. Experimental and modeling work suggests that O-LM cells may comprise a critical component of local hippocampal theta oscillations (Maccaferri and McBain 1996; Gillies et al. 2002; Rotstein et al. 2005). Gloveli et al. (2005) investigated this possibility by examining the axonal arborization of biocytin-filled O-LM cells in the CA3 region of the hippocampus and found that these cells branched most extensively in the longitudinal direction. In fact, they formed clusters across this axis, indicating that they may serve to connect distinct functional units. Gloveli et al. (2005) also determined that gamma was the dominant field network activity in the CA3 of transverse slices, theta was predominant in longitudinal slices, and theta and gamma were both clearly present in coronal slices. Thus, they created a network model to determine whether the distinct longitudinal trajectory of O-LM cell axons could explain this difference in network oscillation generation in the various slice preparations.

As Rotstein et al. (2005) proposed that both O-LM cells and fast-spiking interneurons were required for network theta oscillations, and Ermentrout and Kopell (1998) suggested that pyramidal cells may also be necessary for gamma oscillations (► “Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)”),

Gloveli et al. (2005) created a network model of two O-LM cell models (O), two fast-spiking interneuron models (I), and a single two-compartment (one somatic and one dendritic compartment) pyramidal cell model (E) (as in the network in Fig. 3a), where the O cell model was connected to the dendritic compartment of the E cell model and the I cell model was connected to the somatic compartment of the E cell model. The O-LM cell model was adapted from Saraga et al. (2003), included an h-current, and fired spontaneously at approximately 10 Hz. To model the transverse slice, synaptic connections from E cells were stronger than in the model longitudinal slice (Fig. 4a). This was done to reflect the transverse distribution of pyramidal cell axon collaterals. Conversely, in the model longitudinal slice, synaptic connections from O cells were stronger than in transverse slices to reflect the longitudinal organization of O-LM axon collaterals (Fig. 4b). In the model coronal slices, the synaptic connections had strengths in between those of the longitudinal and transverse slices.

The Gloveli et al. (2005) network model used the non-spiking dendritic compartment of their E cell model to compare with their experimental network oscillations. Similar to what they found experimentally, their model coronal slices produced theta-modulated gamma. Here, the gamma synchrony was produced by the E and I cell interactions (► “Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)”). E and I fired synchronously, but in order to do so, the E cell was required to fire at gamma frequencies. Theta modulation required O-LM cells to fire at theta frequencies and required connections between O and I cells (as in Rotstein et al. 2005). In the model longitudinal slice, all cells fired at theta frequencies due to the strong theta-modulated input from O-LM cells. In the model transverse slice, E and I were synchronized at gamma frequencies, and O remained firing at theta, due to the weak O-LM cell inputs. They noted, however, that these results may be specific for CA3, as CA1 O-LM cells have been shown to extend along both the transverse and longitudinal axes (Sik et al. 1995).

Based on the hypothesis that O-LM cells could connect distinct functional units across the



Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 4 A schematic of the (a) transverse and (b) longitudinal network models in Gloveli et al. (2005). The model networks were represented by a two-compartment excitatory cell model (E), two fast-spiking inhibitory cell models (I), and two O-LM cell models (O). Black filled circles represent inhibitory connections, and black filled triangles represent excitatory connections. Thick (thin) black lines represent connection strengths

that were increased (decreased) to mimic the different slice configurations. (a) In the network model representing the transverse hippocampal slice, E–O and E–I connections were stronger, and connections from the O cell were weaker, than in the longitudinal slice model. (b) In the network model of the longitudinal slice, synaptic connections originating from the E cells were weaker, and those from the O cells were stronger, than in the transverse slice model

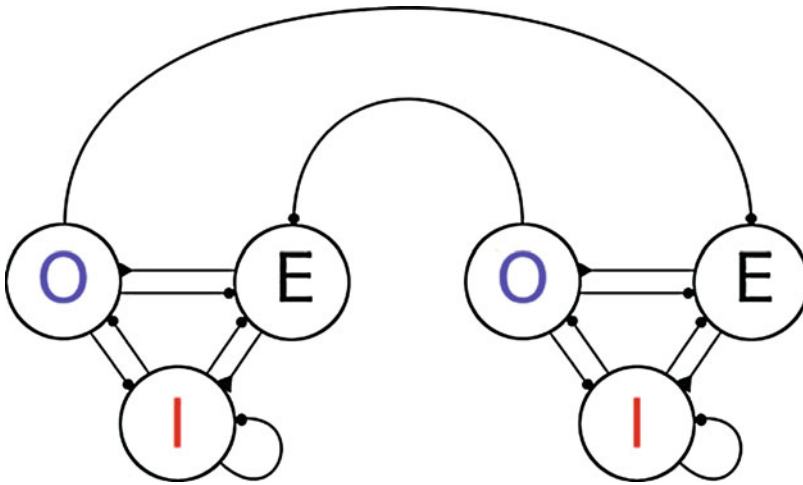
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longitudinal axis, Tort et al. (2007) created a network model to investigate whether O-LM cells could coordinate multiple cell assemblies. To do so, they created “modules” of networks similar to those of Gloveli et al. (2005) (but with some changes, such as a five-compartment E cell model and a larger network size). The model local field potential (LFP) of each module was set to be the membrane potential of a “passive” pyramidal cell model (an E cell model that did not spike due to the absence of an external drive current). Each module was then connected to a neighboring module through O cell connections to distal E cell compartments (representing the longitudinal distribution of the O-LM cell projections) (Fig. 5). Tort et al. (2007) found that each module produced theta-modulated gamma firing in a functionally similar manner to Gloveli et al.’s (2005) model: the I and E cells produced synchronized gamma firing (► “[Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)”), and the O cell models fired in clusters at theta frequencies. Through across-module O to E cell connections, multiple gamma assemblies could be formed. Modules would synchronize with each other when a subset of their cells received a similar drive, as long as each module exhibits PING (requiring E cells to receive enough drive to fire at

least as fast as I cells). Thus, Tort et al. (2007) propose that O-LM cells in the CA3 region can bring about gamma synchronization of distinct modules along the longitudinal axis.

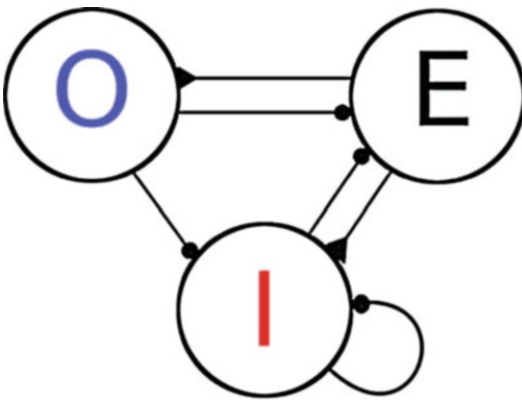
Orbán et al. (2006): The Effect of Hyperpolarization-Activated (h) Currents in Pyramidal and O-LM Interneurons on Theta/Gamma Generation

Gillies et al. (2002) implicated O-LM interneurons, and specifically their h-currents, as a critical component of a pharmacologically induced CA1 theta oscillation in slice preparations. Indeed, theta oscillations in this experimental model were sensitive to blockade of h-currents (Gillies et al. 2002). Since then, h-currents have been incorporated as an essential part of O cell models in networks of hippocampal theta and theta/gamma generation (e.g., Rotstein et al. 2005; Gloveli et al. 2005). However, h-currents also exist in pyramidal cells, where it is tonically active at resting membrane potentials (Magee 1998). In addition, for depolarized membrane potentials, pyramidal cells have intrinsic resonant properties at the theta frequency (Strata 1998). Thus, Orbán et al. (2006) created a network model to determine whether h-channel activation could pace theta oscillations in the hippocampus, and compared



Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 5 A schematic of the network model from Tort et al. (2007). Tort et al. (2007) created “modules,” where each module consisted of a network of models representing O-LM cells (*O*), excitatory cells (*E*), and fast-spiking interneurons (*I*). Two modules are shown

in the schematic. Each module was connected through O–E connections, representing the longitudinal distribution of O-LM cell projections. *Black filled circles* represent inhibitory connections, and *black filled triangles* represent excitatory connections



Hippocampal Theta, Gamma, and Theta/Gamma Network Models, Fig. 6 A schematic of the network model in Orbán et al. (2006). Their network model consisted of 15 excitatory cell models (*E*), 100 fast-spiking inhibitor cell models (*I*), and 70 O-LM cell models (*O*). *Black filled circles* represent inhibitory connections, and *black filled triangles* represent excitatory connections. Unlike previous hippocampal theta-/gamma-generating network models, they did not include an I–O connection

h-current activation in *E* and *O* cells to determine how they affected theta/gamma rhythms.

Orbán et al. (2006) created a network model consisting of *E*, *O*, and *I* cells (Fig. 6). In contrast with other theta/gamma models, they did not include a synaptic connection from *I* to *O* cells

and used a detailed 256-compartment model with h-current dynamics to represent the *E* cells. They used their model to study the components necessary for theta generation and explored the effects of interactions between individual neuron populations. They found that *I* to *O* cell connections were not necessary for theta/gamma generation, although they may have an effect on the stability of the oscillation. Constant depolarizing current injected into *E* cells increased the field frequency; however, it was only slightly affected when they did so with *O* cells. In addition, eliminating h-currents in both *E* and *O* cells caused theta frequency modulation of neuronal populations to disappear. However, reducing the maximal conductance strength of h-channels in *O* cells did not reduce theta amplitude, whereas blocking these channels in *E* cells resulted in a large decrease in theta amplitude. Thus, Orbán et al. (2006) have implicated pyramidal cell h-currents, rather than O-LM cell h-currents, as an important component to hippocampal theta oscillations and have indicated that potential connections from O-LM cells to fast-firing interneurons do not play a critical role.

There are a few hippocampal theta-/gamma-generating network models that we have not described in detail above (see Table 1) but are

briefly described here. White et al. (2000) investigated whether slow GABAergic synapses, generated by a distinct group of interneurons, could be responsible for the slow theta rhythmicity. Tiesinga et al. (2001) used E cell model networks (which occasionally included I cells) to examine the known physiological effects of carbachol on the muscarinic and calcium-dependent potassium currents of pyramidal cells and on the strengths of excitatory postsynaptic potentials. Finally, Neymotin et al. (2011) used a 1200 cell network of E, I, and O cells to investigate the effects of ketamine (an *N*-methyl-D-aspartate receptor, or NMDAR, antagonist) on CA3 theta/gamma rhythms. Although they primarily used extrinsic inputs to pace the theta oscillations, they found that their hippocampal network could produce intrinsic theta/gamma oscillations when this external drive was removed and that connections between O and I cells were not required for this internally generated rhythm. Furthermore, they found that the experimental effect of ketamine on theta/gamma rhythms could only be reproduced in the model with the reduction of NMDAR in their O cells. Thus, their network model predicted that NMDARs in O-LM interneurons play an important role in ketamine effects on theta/gamma oscillations, and the authors suggested that this effect may be reversed with a continuous inward current to these cells (Neymotin et al. 2011).

Overall, theta-/gamma-generating network models have focused on the dynamics between O-LM interneurons, fast-spiking interneurons, and pyramidal cells. However, the critical components required for these models have not been settled upon: the connectivity of these cell types and the role of particular ion channels remain unclear. Further experimental and modeling studies should be done to address these issues.

Models for an Intrinsic Theta Rhythm Experimental Context

It has been shown that theta and theta/gamma rhythms can spontaneously emerge in an intact whole hippocampus preparation *in vitro* (Goutagny et al. 2009; Jackson et al. 2011). This

implies that rhythmic drive to the hippocampus is not necessary for the hippocampus to exhibit rhythmic output. Network models based on this whole hippocampus preparation have been developed (Bezaire et al. 2016; Ferguson et al. 2017). Ferguson et al. (2017) used single-compartment Izhikevich-type cellular models with explicit links to the data for the pyramidal (E) cells and fast-firing inhibitory (I) cells (Ferguson et al. 2013, 2015b). They showed that the essence of the intrinsic theta rhythm generation in CA1 hippocampus occurred in E-I networks in which the pyramidal cells were minimally connected, and there was spike frequency adaptation and post-inhibitory rebound in the pyramidal cells. The more detailed network CA1 microcircuit model of Bezaire et al. (2016) had eight types of inhibitory cells and pyramidal cells with multi-compartment representations, and network connectivity and cellular specifics were based on an extensive knowledge base of the experimental data (Bezaire and Soltesz 2013). The full-scale CA1 microcircuit model exhibited theta and theta/gamma rhythms.

Related (Theta/Gamma) Models and Further Considerations

Experimental work has suggested that synchronization of theta oscillations in the hippocampus is brought about by a primarily extrinsic mechanism, since, for example, septal neurons fire in synchrony with hippocampal theta, and lesions to the medial septum significantly decrease the amplitude of theta oscillations (Petsche et al. 1962; Buzsáki 2002). Thus, some investigate theta modulation, and not generation, of hippocampal circuits. These models incorporate an external drive (from, e.g., the medial septum or the entorhinal cortex) to pace the hippocampal rhythm (e.g., Kunec et al. 2005; Cutsuridis et al. 2010; Cutsuridis and Hasselmo 2012; Pastoll et al. 2013). Theta inputs via non-extrinsic inputs have also been investigated, and these models showed that distally projecting inhibitory cells could control the power of theta rhythms (Chatzikalymniou and Skinner 2018; Ferguson et al. 2015a). Network models may also examine theta/gamma modulation in using non-

biophysically motivated cell models. For example, Pastoll et al. (2013) created a network of integrate-and-fire neurons, where each model received an external current source (composed of the sum of constant background activation, theta-modulated current, velocity modulation current, and hippocampal place field input) to create an attractor network model.

In conclusion, many theta and theta/gamma network models exist, and mechanisms for their generation are beginning to emerge. However, more work is needed for us to obtain a complete understanding of how theta and theta/gamma oscillations in the hippocampus are produced.

Cross-References

- [Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)
- [Hippocampus, Model Excitatory Cells](#)
- [Hippocampus, Model Inhibitory Cells](#)
- [Hippocampus, Model Network Architecture](#)
- [Hippocampus, Theta, Gamma, and Cross-Frequency Coupling](#)
- [Integrate and Fire Models, Deterministic](#)

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Hippocampome.org

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Definition

Hippocampome.org is a freely accessible, comprehensive knowledge base of neuron types in the rodent hippocampal formation (dentate gyrus (DG), CA3, CA2, CA1, subiculum (Sub), entorhinal cortex (EC)) (Wheeler et al. 2015). Built upon extensive data mining of scientific literature, neuron types are discriminated by their primary neurotransmitters, axonal and dendritic patterns, synaptic specificity, electrophysiology, and molecular markers. All annotated properties are individually supported by specific evidence in peer-reviewed publications. Hippocampome.org is the basis for a probabilistic atlas of the entire synaptic blueprint of the rodent hippocampus (Ascoli 2010).

Detailed Description

Hippocampome.org is a powerful, groundbreaking resource of knowledge, distilled from hundreds of scientific articles and integrated

into a framework of morphologically defined neuron types. Hippocampome.org distinguishes well over 100 neuron types, which are defined in part by their axonal and dendritic expanse into the 26 cytoarchitectural parcels of the hippocampal formation: DG outer stratum (s.) molecular, inner s. molecular, s. granulosum, hilus; CA3 s. lacunosum-molecular, s. radiatum, s. lucidum (SL), s. pyramidale (SP), and s. oriens; 4 each in CA2 and CA1 (same as CA3 except SL); Sub s. molecular, SP, polymorphic layer; and EC layers I–VI. For these neuron types, the annotated evidence supports well over 10,000 distinct “pieces of knowledge” regarding not only the presence or absence of their axons or dendrites within any of the 26 parcels, but also the expression or non-expression of molecular markers, including data leveraged from the Allen Brain Atlas (Hamilton et al. 2017b), individual electrophysiological properties, and known and potential connectivity (Rees et al. 2016).

All of the accumulated and collated knowledge of these neuronal properties are fully browsable and searchable. In browse mode, Hippocampome.org provides summaries of its information in the form of fully clickable matrices. Searching for neuron types is accomplished through selections from dynamically updated pull-down menus of any of the annotated properties, and compound queries can be crafted with AND & OR Boolean connectors. Searches can also be conducted using PubMed identifiers, author names, neuron names/synonyms, original firing patterns, and neuron terms (Hamilton et al. 2017a). Returned results contain full bibliographic information, a link to the article with a pointer to the specific evidence location within, and a list of neuron types with information from the article.

The human- and machine-readable knowledge contained in Hippocampome.org will be leveraged to formulate a detailed computational model of the entire rodent hippocampal formation. Computer simulations will initially involve the simplified formalism of Izhikevich models and parameters (Venkadesh et al. 2018). The simulations also will leverage information such as firing pattern

phenotypes (Komendantov et al. 2018), neurite lengths, and neuron type counts to fill in the details of the model. As technology advances and computing power continues to increase, more biophysically detailed modeling will become feasible. In conjunction with the growth in simulation complexity, Hippocampome.org will continue to expand its compendium of openly shared, annotated knowledge and help to advance the bounds of neuroinformatics as a whole.

Cross-References

- ▶ [Databases and Data Repositories in Computational Neuroscience: Overview](#)
- ▶ [NeuroElectro Project](#)
- ▶ [NeuroMorpho.Org](#)
- ▶ [Neuroscience Information Framework \(NIF\)](#)

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Hippocampus, Model Excitatory Cells

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Definition

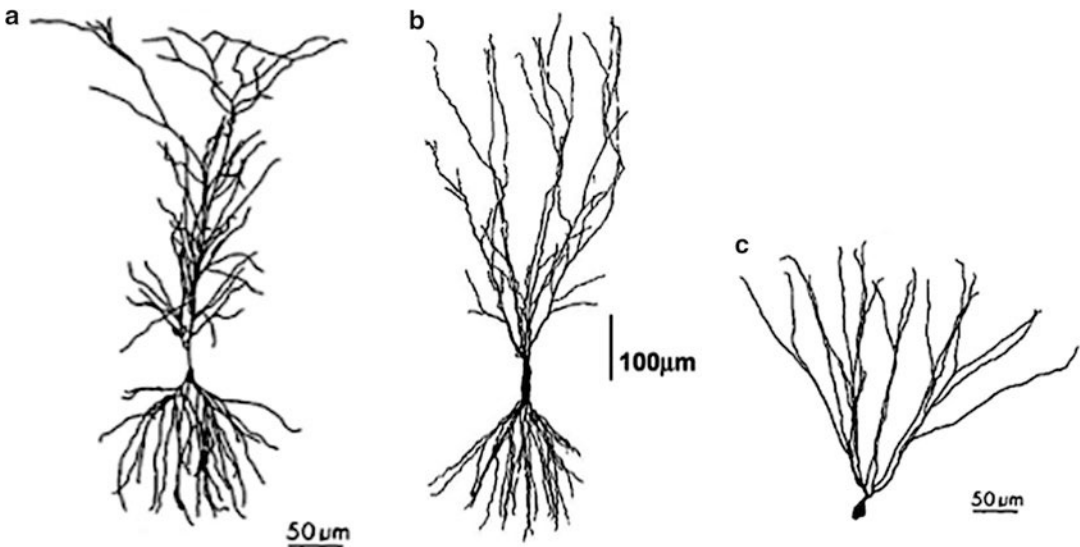
Hippocampus, model excitatory cells refer to mathematical models of neurons that are designed to represent excitatory neurons in hippocampus. Here, we focus on biophysically motivated

models of excitatory cells in the hippocampus proper (specifically the CA1 and CA3 pyramidal cells) and the granule cells of the dentate gyrus (DG). This article discusses some common motives for constructing these models and describes a few frequently used models in more detail.

Detailed Description

Introduction

Three principal hippocampal excitatory cell types are CA1 pyramidal cells, CA3 pyramidal cells, and granule cells of the DG (Fig. 1). These cells depolarize their postsynaptic targets through glutamatergic transmission of three main types of ionotropic receptors: α -amino-3-hydroxy-5-methyl-isoxazole-propionic acid (AMPA), kainate, and *N*-methyl-d-aspartate (NMDA). This is in contrast to hippocampal interneurons, which inhibit their postsynaptic targets through



Hippocampus, Model Excitatory Cells, Fig. 1 The morphology of principal cells of the CA1, CA3, and dentate gyrus. **(a)** A CA1 pyramidal cell. **(b)** A CA3 pyramidal cell. Note that the cell soma is larger than in CA1 pyramidal cells, but the cell does not have the large primary apical branch. **(c)** A dentate granule cell. The cell body is not pyramidal-like, and they have a single conical dendritic tree. **((a, c)** With kind permission from Springer Science+Business Media: *Hippocampal Microcircuits* (Cutsuridis,

V., Graham, B., Cobb, S. & Vida, I., eds.), Part I, Chapter 2, 2010, p. 27–67, I. Vida, “Morphology of Hippocampal Neurons,” Fig. 2B, D. **(b)** With kind permission from Springer Science+Business Media: *Hippocampal Microcircuits* (Cutsuridis, V., Graham, B., Cobb, S. & Vida, I., eds.), Part I, Chapter 12, 2010, p. 353–374, M. Migliore, G.A. Ascoli, and D.B. Jaffe, “CA3 Cells: Detailed and Simplified Pyramidal Cell Models,” Fig. 1e)

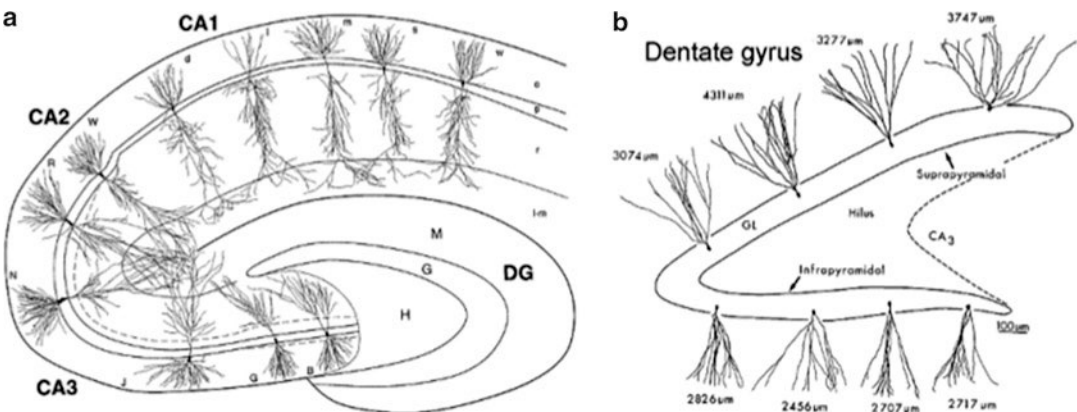
γ -aminobutyric acid (GABA) receptors (for inhibitory cell models, see ► “[Hippocampus, Model Inhibitory Cells](#)”). We note that hilar mossy cells also excite their postsynaptic targets, but due to the lack of experimental characterization of these cells relative to the other three cell types and the fact that very few models of these cells exist, we do not discuss them in this article.

Why Do We Care About Hippocampal Excitatory Cells?

Much of our general knowledge about neuron structure and function is derived from studies of excitatory cells in the hippocampus. This is most notably true because the hippocampus has a structured architecture, where principal cell bodies lie in a single layer, and dendritic trees and axonal projections compose well-defined laminae (Fig. 2). These organized layers create identifiable current sinks and sources, which facilitate extracellular recordings of local field rhythms in both *in vivo* and *in vitro* preparations. In addition, the predictable location of principal cell bodies simplifies the identification process for intracellular recordings. Excitatory axonal projections between hippocampal regions are constrained within these laminae (e.g., Schaffer collaterals from CA3 to CA1 are located in the stratum radiatum and stratum

oriens), providing a means to stimulate principal cells to study synaptic transmission, integration, and plasticity. Indeed, long-term potentiation (LTP) was discovered in the dentate gyrus (DG) of the hippocampus (Lømo 1966), and most recent LTP studies have taken place in the CA1 region. The hippocampus is known to play an important role in learning and memory, and thus understanding synaptic plasticity as a mechanism of these processes is essential. Furthermore, the hippocampus, and principal cell activity, have been implicated in playing a large role in a number of neurological diseases, such as epilepsy and Alzheimer’s (Bruton 1988; Braak and Braak 1991). Finally, experimental work in this area is also facilitated because *in vitro* hippocampal slice preparations can remain alive and healthy for extended periods, permitting lengthy recordings of this easily accessible neuronal activity.

CA1 pyramidal cells, CA3 pyramidal cells, and DG granule cells comprise the majority of the neurons in their respective regions, and thus excitatory cell activity is likely to strongly influence local network rhythms. Understanding excitatory cell activity may provide insight into the mechanisms underlying the generation of behavior-dependent local field oscillations, which are thought to play an essential role in



Hippocampus, Model Excitatory Cells, Fig. 2 A schematic showing the structured organization of the hippocampus, with principal cell bodies restricted to particular laminae. (a) Pyramidal cells of the CA1, CA2, and CA3 area. Cell bodies lie in the stratum pyramidale. (b) Cell bodies of dentate granule cells lie in the stratum

granulosum. (With kind permission from Springer Science+Business Media: *Hippocampal Microcircuits* (Cutsuridis, V., Graham, B., Cobb, S. & Vida, I., eds.), Part I, Chapter 2, 2010, p. 27–67, I. Vida, “Morphology of Hippocampal Neurons,” Fig. 2A, C)

many aspects of learning and memory, such as feature binding, temporal encoding, and spatial navigation (Buzsaki 2002; Colgin and Moser 2010).

Overall, the vast number of studies involving hippocampal excitatory cells has furthered our understanding of intrinsic cell functioning, synaptic transmission, synaptic integration, synaptic plasticity, network oscillations, and the role of neural activity in behavior and disease. This plethora of knowledge provides an excellent platform to build well-constrained models to address a variety of questions about cell functioning.

Why Build Hippocampal Excitatory Cell Models?

Hippocampal excitatory cell models allow us to systematically explore a specific question in a simplified setting. In many cases, these questions are difficult or impossible to fully explore experimentally. For example, Vetter et al. (2001) explored the effect of morphology on action potential propagation. By building multi-compartment models from three-dimensional reconstructions of rat CA1/CA3 pyramidal cells and DG granule cells (among others) and by using the same active and passive ion conductances across cell models, they were able to isolate the effects of dendritic morphology on the efficacy of signal propagation. Another feature that is more easily explored in models than in experiment is how the distribution of ion channels across the neuron affects its activity (e.g., Hoffman et al. 1997). One can explore the role of specific synaptic or intrinsic properties on spiking patterns (such as bursting, adaptation, after-depolarizing potentials, etc.) through mathematical models (e.g., Traub and Llinás 1979; Traub 1982; Warman et al. 1994; Pinsky and Rinzel 1994) or investigate how the activation of particular ion channels shapes the efficacy or weight of postsynaptic signals (e.g., Lipowsky et al. 1996). Models can also be used to study passive cable properties (e.g., Major et al. 1994; Schmidt-Hieber et al. 2007; Baker et al. 2011). In addition, excitatory cell models can be used to study the role of principal cells in network oscillations (e.g., Gloveli et al. 2005). Therefore, models can help us understand

cellular and network mechanisms and guide future experiments. Their power lies in their predictive capabilities and the generation of hypotheses.

How Do We Model These Excitatory Cells?

How one constructs a neuron model depends on the question at hand and on the availability of experimental data. For details of different approaches to constructing neuron models, see articles referenced in the “Further Reading” section. In general, neuron models can be divided into three categories based on their level of biological abstraction: rate-based models, simple spiking models, and biophysical models. Rate-based models are the simplest of the three and describe a cell by its firing rate as a function of time (e.g., Wilson and Cowan 1972). As these models are constructed based on the firing rate alone, they will not be discussed in this article.

Spiking models focus on representing the firing behavior of the neuron. Although some spiking models rely on a simple threshold method, such as the leaky integrate-and-fire model (see “Integrate and Fire Models, Deterministic”), others aim to reproduce more complex firing patterns (e.g., Izhikevich 2003). Thus, in choosing a spiking model, one must determine the amount of desired computational efficiency, as well as the key properties of the neuron that one wishes to capture (e.g., the frequency-current profile, bursting, adaptation, spike shape). The computational and mathematical simplicity of these spiking models makes them good candidates for examining network dynamics (e.g., Dur-e-Ahmad et al. 2012).

Biophysical models describe the dynamics of a cell’s membrane potential, where the cell’s ion channels are represented by conductances, and the cell’s lipid bilayer through a capacitor (see Skinner 2006 for more details). These models can vary greatly in the level of detail incorporated, and choices about the model’s complexity will depend on the question being addressed. For example, if one is investigating how ion channel properties on oblique dendrites affect cell activity (e.g., Migliore et al. 2005), one would require a multi-compartment model that represents a cell’s

detailed morphology. Of course, the dynamics and distribution of every receptor and ion channel type involved in hippocampal excitatory cell functioning are not known. Therefore, choices must be made as to which channels to include, how to constrain their kinetics, and how they are distributed. However, in other cases when computational efficiency and simple dynamics are prioritized to facilitate analyses or to construct large networks, one may prefer to use a simpler single-compartment model. Therefore, before constructing a neuron model, a number of difficult choices must be made.

Due to the abundance of experimental data that currently exists for hippocampal excitatory cells and the large number of experimental questions that remain, many different models of these cells have been created (e.g., see ModelDB: <http://senselab.med.yale.edu/modeldb/FindByRegionList.asp>). Many models are created by expanding or reducing existing models or are derived based on properties from multiple models. Therefore, instead of attempting to address every model, we will highlight a few of the commonly used ones and the various questions they have helped address.

CA1 Pyramidal Cell Models

CA1 pyramidal neurons are arguably the most studied class of neuron in the brain, both functionally and structurally. It is generally easier to keep these cells healthy in slice preparations than those in the adjacent CA3 area, which contributes to the vast number of recordings from this area (Spruston and McBain 2007). The structurally homogeneous Schaffer collateral inputs from CA3 to CA1 provide a pathway that is easily stimulated to investigate synaptic activation and plasticity in CA1 pyramidal cells. In addition, these neurons have relatively large primary apical dendrites (Fig. 2a), which permit dendritic patch-clamp recordings. Thus, studies of CA1 pyramidal cells have increased our understanding of principal cell functioning in many ways.

Due to the large amount of research focused on CA1 pyramidal cells, they provide a great starting

point at which models can be used to investigate specific questions about how certain properties affect cell functioning. Thus, many of the commonly used CA1 pyramidal cell models are detailed multi-compartment biophysical models. However, simple models have also been constructed to explore cellular and network dynamics with computational ease (e.g., Ferguson and Campbell 2009). Many different questions have been addressed with CA1 pyramidal models, such as how different active ionic conductances influence spike shape and firing properties (e.g., Traub and Llinás 1979; Warman et al. 1994), and the role of particular axonal ion channels in action potential initiation (e.g., Royeck et al. 2008).

We discuss three models here that are used to explore: (1) the effects of channel distribution on cell activity, (2) how synaptic signals are integrated, and (3) how channel dynamics and oblique dendrites interact to affect action potential propagation.

Hoffman et al. (1997): Effects of K-A Distribution on Action Potential Generation and Excitatory Post-synaptic Potential Shape

Through a series of somatic and apical dendritic patch-clamp recordings, along with the use of a variety of channel blockers, Hoffman et al. (1997) revealed that CA1 pyramidal cell dendrites contain a high density of transient A-type potassium ion channels (K-A). This increased density was shown to prevent action potential generation in the dendrites, to limit the amplitude of back-propagating action potentials, and to reduce excitatory postsynaptic potentials (EPSPs). Hoffman et al. (1997) created a CA1 pyramidal model to investigate how an increased density of K-A channels in the dendrites may interact with other ion channels to produce these features.

A reconstruction of a hippocampal pyramidal neuron was used to construct the morphology of the pyramidal cell model. They chose to include only sodium channels (Na), delayed rectifier potassium channels (K-DR), and two K-A channels: a proximal channel used within 100 μm from the soma and a distal channel for distances greater than 100 μm from the soma. While the Na and K-DR channels were distributed uniformly

throughout the soma and dendrites of the neuron model (and increased tenfold in the axon), the peak conductance strength for both K-A channels increased with distance from the soma. The Na and K-A conductances were set to reproduce their experimentally determined K-A to Na ratio of ~3:1, whereas their K-DR conductance was set to repolarize the action potential in the absence of K-A channels. Since one can easily change the distribution and strength of ion channels in a neuron model, this computational modeling approach allowed them to investigate how this experimentally determined distribution of K-A channels affects action potential amplitude and EPSP propagation toward the soma.

The authors found that by incorporating K-A channels in their model, their experimental findings were reproduced: somatic action potentials were generated, they decreased as they propagated toward the dendrites, and EPSP amplitudes were reduced. Interestingly, by pairing simulated EPSPs onto a single branch with a back-propagating action potential, they showed that action potential amplitude was significantly boosted in the branch receiving the input. This occurred because K-A channels are susceptible to rapid depolarization-induced inactivation during subthreshold input. This inactivation allowed an increase in Na activation, which boosted the amplitude of the action potential. Through this mechanism, the propagation of action potentials into specific branches of the dendritic tree may be regulated by synaptic inputs and may thereby play a role in synaptic plasticity.

Poirazi et al. (2003): Rules of Synaptic Integration

Conflicting reports of synaptic integration rules have brought into question how pyramidal cells process information (e.g., Nettleton and Spain 2000; Cash and Yuste 1999). Poirazi et al. (2003) built a computational model to assess whether arithmetic summation in CA1 pyramidal cells is best represented by linear or nonlinear integration rules. They also set out to determine whether particular aspects of experimental design may have contributed to the conflicting reports. Computational modeling provided an ideal forum

to answer these questions, as they could precisely control the number, location, and types of synapses, and record the postsynaptic responses from any location on the model neuron simultaneously.

In this highly detailed model, Poirazi et al. (2003) used a reconstructed CA1 pyramidal cell to create the morphology of the model neuron (consisting of 183 compartments) and included 17 different ion channels (leak, somatic/axonic sodium, dendritic sodium, somatic/axonic delayed rectifier potassium (K-DR), dendritic K-DR, proximal A-type potassium (K-A), distal K-A, M-type potassium, a mixed conductance hyperpolarization-activated channel, T-type calcium, somatic R-type calcium (Ca-R), dendritic Ca-R, somatic L-type calcium (Ca-L), dendritic Ca-L, slow calcium-dependent potassium (K-AHP), medium K-AHP, and persistent sodium) and four types of synapses (AMPA, NMDA, GABA_A, GABA_B). Where possible, channel kinetics were taken from studies where individual channel properties, such as activation and inactivation curves, time constants, and location-dependent densities, were investigated (e.g., K-A dynamics from Hoffman et al. 1997). In addition, they validated their model with a number of tests to ensure that it produced output similar to that observed experimentally. For example, they tested the effect of the hyperpolarization-activated mixed cation current (h current) on input resistance and steady state voltage propagation and compared with the results from Magee et al. (1998).

The authors simultaneously recorded from the soma and dendrites of the neuron model. They compared their results using two different response measures, two different stimulus protocols, and two different spatial integration conditions. They found that the neuron's response to paired inputs was well described by the sum of nonlinear subunit responses, where the subunit response represents that of the dendritic branches. They also suggested a number of ways in which experimental design choices may influence one's conclusions regarding synaptic integration rules.

Many subsequent studies have either used this model or a modified version of it (e.g., Cutsuridis et al. 2010; Dyhrfeld-Johnsen et al. 2008). Other

studies have used properties of this model to create their own models (e.g., Narayanan and Johnston 2007; Bianchi et al. 2012; Ashhad and Narayanan 2013).

Migliore et al. (2005): Action Potential Propagation Into/from Oblique Dendrites

Hoffman et al. (1997) demonstrated that A-type potassium (K-A) channel densities increased in the primary apical dendrites of CA1 pyramidal cells, and through calcium-imaging experiments. Frick et al. (2003) suggested that the density of these channels may be especially high in oblique apical dendrites. However, the precise biophysics of K-A currents in the oblique dendrites remained unclear. More specifically, the effects of the morphology of oblique dendrites (i.e., the geometry at branch point, the distance from the soma, etc.), in combination with dendritic K-A channel properties, on action potential propagation into and from oblique dendrites were not well understood. As CA1 pyramidal cell oblique dendrites comprise the majority of apical tree surface area and are the main target of CA3 Schaffer collaterals, their functional role in shaping neural activity is important to understand. However, these dendrites are very thin, and thus it is very difficult to record their electrical properties. Thus, this problem is best addressed with computational modeling, as multiple morphologies and dendritic distributions of K-A channels can be easily explored.

Migliore et al. (2005) used 27 reconstructed three-dimensional morphologies of rat CA1 pyramidal cells. The same uniform passive properties were used for all neurons. They included four channel types: sodium (Na), delayed rectifier potassium (K-DR), K-A, and hyperpolarization-activated h. Na and K-DR were distributed uniformly over the entire basal and apical dendritic tree. However, because the K-A and h distributions in oblique dendrites have not been characterized experimentally, their peak conductances were distributed in the model in three separate ways. In the first set of simulations, K-A and h peak conductances were increased linearly across the whole dendritic tree. In the second, K-A and h peak conductances increased in the main apical trunk, but were set to be constant (and were

determined by the value at the point of attachment to the main trunk) in the rest of the dendritic tree. In the final case, h peak conductance was increased linearly across the dendritic tree (as in the first case), but K-A peak conductance was increased threefold in each oblique with respect to its value at the point of attachment.

They found that individual oblique dendrites regulated local action potential forward and backward propagation. The local morphology of the obliques had the most effect on forward propagation, whereas the distribution of K-A channels influenced backward action potential propagation the most. They also found that somatically generated action potentials propagating toward the dendrites invade the oblique branches in an all-or-none fashion. This process was highly regulated by local K-A distributions. In fact, their model predicted that the distribution of h and K-A channels in the oblique dendrites can even affect the antidromic propagation of action potentials into the main apical shaft. However, an increase in h channels would facilitate action potential back propagation, whereas an increase in K-A channels would impede it. Overall, their model showed that signal propagation in CA1 pyramidal cells would be greatly affected by the morphology of their oblique dendrites, as well as their K-A and h channel distributions along them.

CA3 Pyramidal Cell Models

Although the properties and distributions of voltage-gated channels have been reasonably well characterized in CA1 pyramidal cells, less is known about those in CA3. One of the contributing factors to this is that CA3 pyramidal apical dendrites bifurcate closer to the stratum pyramidale and therefore lack the significant primary apical dendrite found in CA1 pyramidal cells (Spruston and McBain 2007) (Fig. 2b). As a result, CA3 pyramidal cell models are more theory driven than those of CA1. Due to the lack of experimental data compared with CA1 pyramidal cells, particular channel kinetics of CA3 pyramidal cell models are occasionally derived from CA1 pyramidal cells (e.g., Baker and Olds 2007;

Hemond et al. 2008), and the focus of many CA3 pyramidal models is on cell firing patterns (e.g., Traub 1982; Traub et al. 1991; Migliore et al. 1995; Hemond et al. 2008). CA3 pyramidal cell models have been adapted directly from CA1 pyramidal cell models (e.g., Tort et al. 2007 based on a reduction of Migliore et al. 2004), and general pyramidal cell models have been constructed based on properties and morphologies of both CA1 and CA3 pyramidal cells (e.g., Jaffe et al. 1994).

One of the major differences between CA1 and CA3 pyramidal cells is their network configuration. CA1 pyramidal cells form very few recurrent connections (~1%) (Knowles and Schwartzkroin 1981; Deuchars and Thomson 1996), whereas CA3 pyramidal cells are highly interconnected (Amaral and Witter 1989; Amaral et al. 1990). Thus, some network models use one type of pyramidal cell model for both CA1 and CA3 networks and alter only the number of recurrent connections among the neurons in each region (e.g., Taxis et al. 2012). However, CA1 and CA3 pyramidal cells do have some difference in their firing profiles and intrinsic properties, and these differences may be important depending on the question being investigated. For example, bursting is more prominent in CA3 pyramidal cells (Schwartzkroin 1978; Wong and Prince 1978), and their membrane time constant is considerably slower (Spruston and Johnston 1992). Here, we discuss in more detail a few models that are built to further our understanding of the mechanisms involved in CA3 pyramidal cell firing patterns.

Traub et al. (1991): Firing Patterns

Traub et al. (1991) set out to create a model that captured the electrical properties of a CA3 pyramidal cell, aiming to provide insight into the mechanisms underlying its complex firing patterns. Their group had previously constructed a CA3 pyramidal cell model that produced bursting and spiking patterns similar to those recorded experimentally (Traub 1982). However, in contrast with CA3 pyramidal cell recordings *in vitro* (Wong and Prince 1981), their 1982 model was not able to switch from repetitive bursting to repetitive single action potentials with increased

depolarization. In addition, under certain conditions, network models built with their pyramidal cell model were expected to produce synchronized multiple bursts, but did not unless some ad hoc properties of the synapses or axons were assumed (Traub et al. 1984). Traub's group hypothesized that these failures could be because the model was unable to generate dendritic calcium spikes. This, along with new data from whole-cell and calcium-imaging experiments (Kay and Wong 1986; Regehr et al. 1989), motivated the authors to construct a new CA3 pyramidal cell model. They aimed to understand the conditions under which this cell might switch between modes of firing, and to determine the essential properties for the synchronization of multiple bursts in a network of CA3 pyramidal cells.

Traub et al. (1991) therefore constructed a model where the basilar and apical dendrites are each represented by an equivalent cylinder and, together with the soma, comprise 19 compartments. They included six voltage-gated channel types (sodium, calcium, delayed rectifier potassium, A-type potassium, long-duration Ca-dependent potassium, and short-duration calcium- and voltage-dependent potassium (K-C)) and attempted to constrain model kinetics with experimental data as best as possible. Thus, for the first five channel types, model kinetics were taken from voltage-clamp data from isolated hippocampal pyramidal cells. Due to the availability of data, many of the recordings were from CA1 pyramidal cells from guinea pig (e.g., Kay and Wong 1987; Sah et al. 1988; Numann et al. 1987). Although K-C channels were known to exist in CA1 pyramidal cells (Numann et al. 1987), their kinetics were unclear, and thus model kinetics were based on recordings from bullfrog sympathetic neurons (Adams et al. 1982). For network model simulations (consisting of 100 pyramidal cell models), they included a fast excitatory synapse model in two compartments and a slow voltage-dependent synapse (representing an NMDA receptor) in one compartment. Once the kinetics of the channels were defined, they decided upon distributions of peak conductance values that reproduced a

number of current-clamp recordings. Using these fixed parameters, they analyzed how each voltage-gated channel type contributed to the cell model's firing patterns.

The model successfully reproduced a number of electrical properties that are characteristic of CA3 pyramidal cells, such as its ability to generate large dendritic calcium spikes. When somatic depolarizing currents were applied and gradually increased, the model also reproduced the transition from low frequency bursting to high-frequency repetitive firing that is seen in pyramidal cells *in vitro* (Wong and Prince 1981). The network model produced synchronized bursts, although the shape of the bursts was not completely as desired. The model also produced a number of predictions, including that NMDA blockers should suppress secondary (but not primary) bursts and that a novel firing pattern may exist during tonic depolarizing dendritic stimulation.

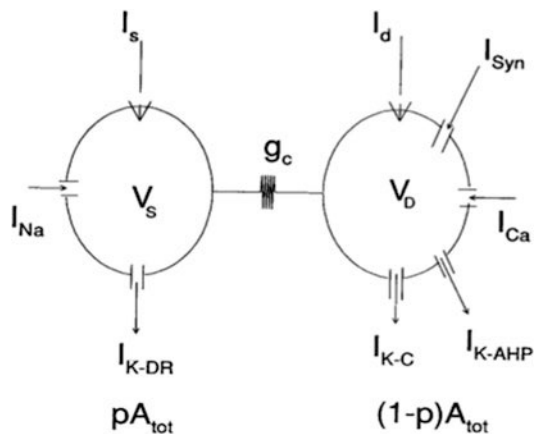
Pinsky and Rinzel (1994): Firing Patterns in a Reduced Model

Although Traub et al.'s (1991) model (referred to here as Traub's model) reproduced many complex firing patterns of a CA3 pyramidal neuron, the precise biophysical mechanisms required to produce this behavior remained unclear. One can parse out the key mechanisms of a system by creating a minimal mathematical description that accounts for its essential characteristics. With this in mind, Pinsky and Rinzel (1994) created a two-compartment model as a reduction of Traub's 19-compartment model of a CA3 pyramidal cell. Such a minimal model allowed them computational freedom to perform a thorough analysis of the effect of the electrotonic coupling parameters on spiking behavior. They used their model to create a network model and compared the key firing properties of their single-cell and network model with those of Traub et al. (1991).

To construct the two-compartment model, Pinsky and Rinzel noted that the fast-spiking currents, sodium (Na) and delayed rectifier potassium (K-DR), in Traub's model were restricted to the soma and proximal dendritic compartments, whereas the majority of the calcium currents

were in the distal dendritic compartments. Thus, Pinsky and Rinzel created a "soma-like" compartment containing the fast-spiking currents (Na and K-DR) and a "dendrite-like" compartment containing excitatory synaptic currents, the calcium (Ca) current, the calcium-activated potassium current (K-C), and the potassium afterhyperpolarization current (K-AHP). They used the same voltage-gated current kinetics as in Traub et al. (1991). Electrotonic coupling was described by two parameters: one that represented the coupling strength and one that represented the percentage of total area in the "soma-like" compartment (see Fig. 3).

Pinsky and Rinzel found that their simple two-compartment model reproduced several of the major stimulus-response features of Traub's



Hippocampus, Model Excitatory Cells, Fig. 3 A schematic of Pinsky and Rinzel's (1994) two-compartment model of a CA3 pyramidal cell. The soma-like compartment has a sodium (I_{Na}) and potassium delayed rectifier (I_{K-DR}) currents, whereas the dendrite-like compartment contains the calcium (I_{Ca}), calcium-activated potassium (I_{K-C}), potassium afterhyperpolarization (I_{K-AHP}), and synaptic (I_{Syn}) currents. Each compartment also receives an applied current (I_s and I_d for somatic and dendritic compartments, respectively). The coupling strength of the two compartments is given by g_c , where A_{tot} is the total cell membrane area, and p is the proportion of cell area taken up by the soma. The membrane potentials of the somatic and dendritic compartments are represented by V_s and V_D , respectively. (With kind permission from Springer Science+Business Media: *J Comput Neurosci*, "Intrinsic and network rhythmogenesis in a reduced Traub model for CA3 neurons," vol 1, 1994, p. 39–60, P.F. Pinsky and J. Rinzel, Fig. 1A)

model, such as the generation of bursts for weak steady depolarizing current drive to the soma and repetitive single action potentials for a larger drive. They found that steady dendritic stimulation could produce higher frequency bursting than steady somatic input and that bursting only occurred when the coupling strength was within an intermediate range. Bursting depended on having the lower threshold fast currents (Na, K-DR) in electrically separate compartments from the higher threshold slow currents (Ca, K-C, K-AHP), and thus bursting could not occur when they were too strongly or weakly coupled. Similar to Traub et al.'s (1991) network model, Pinsky and Rinzel's network simulations produced synchronized bursting through the stimulation of a single cell. Interestingly, they found that the network quickly desynchronized when the fast excitatory synapses were blocked, even when the network was homogeneous, due to intrinsically chaotic burst dynamics.

Due to the fact that this model captures many complex firing features of CA3 pyramidal cells and is computationally efficient, a number of studies have incorporated this model into their work (e.g., Huang et al. 2007; Taxidis et al. 2012).

DG Granule Cell Models

Dentate gyrus granule cells have properties that make them quite unique from CA1 and CA3 pyramidal cells. Notably, they are not pyramidal in morphology: they have a small cell body with a single conical dendritic tree (Fig. 2c). Unlike pyramidal cells, under healthy conditions, DG granule cells do not form recurrent connections (Claiborne et al. 1986). They are densely packed in the stratum granulosum and therefore outnumber CA1 or CA3 pyramidal cells (West et al. 1991). However, due to their more hyperpolarized resting membrane potential (Penttonen et al. 1997; Spruston and Johnston 1992; Staley et al. 1992), they have low spontaneous rates of firing under most conditions (Penttonen et al. 1997). Thus, recordings of DG granule cell firing patterns can be difficult to obtain *in vivo*. In addition, DG granule cell dendrites are small in diameter,

making them hard to record and therefore limiting the number of studies of dendritic action potential propagation. Thus, there are many questions left to be addressed by experiments and modeling.

Computational models have attempted to further our general understanding of DG granule cell functioning. For example, Vetter et al. (2001) used computational modeling to examine the effects of DG granule cell morphology on action potential propagation. Yuen and Durand (1991) used ion channel properties from other neuron types in their DG granule cell model and investigated what modifications in these channel properties were necessary to reproduce experimentally determined firing patterns. Also, Rusakov et al. (1996) created a DG granule cell model to investigate how spine changes would affect synaptic efficacy, and Ferrante et al. (2009) described how feed-forward inhibition may help shape the neuronal input/output relationship.

Although DG granule cells do not synapse onto each other under healthy conditions (Claiborne et al. 1986), recurrent excitatory circuits have been shown to emerge in epileptic rats (Lynch and Sutula 2000). Here, we describe in more detail a network model that attempts to understand the effect of DG granule cell axonal sprouting and network connectivity on network activity. This model contains four different cell types: DG granule cells, hilar mossy cells, inhibitory basket cell interneurons, and hilar perforant path-associated (HIPP) interneurons. Although the hilar mossy cells are excitatory hippocampal cells, much less experimental work has been done to characterize these cells than on CA1 and CA3 pyramidal and on DG granule cells. Because of this, few models of these mossy cells exist, and details with which to constrain the models are relatively minimal. Thus, we will focus our attention on the DG granule cell model of this DG network model.

Santhakumar et al. (2005): The Effects of Axonal Sprouting on Network Dynamics

The axons of DG granule cells, denoted "mossy fibers", have been shown to sprout due to persistent seizures and head trauma (Golarai et al. 2001; Santhakumar et al. 2001). This sprouting is associated with hyperexcitability of the DG, although

the precise mechanisms of this increased activity are unknown. In particular, it is unclear whether a small amount of sprouting, as is seen in experiments (Santhakumar et al. 2001), can lead to seizure activity. Therefore, Santhakumar et al. (2005) created a computational network model containing DG granule cells to investigate how mossy fiber sprouting (as well as mossy cell death) contributes to network activity (Santhakumar et al. 2005).

Santhakumar et al. (2005) created network models of the DG, based on a 2000:1 scaling down of four major cell types in the DG. The DG granule cell model was adapted from a previously constructed model by Aradi and Holmes (1999) and consisted of nine compartments and a number of voltage-gated channels (sodium; fast and slow delayed rectifier potassium; A-type potassium; L-, N-, and T-type calcium; calcium-dependent potassium; and calcium- and voltage-dependent potassium). As DG hyperexcitability is known to remain in the presence of NMDA blockers (Santhakumar et al. 2000), only AMPA and GABA_A synapses were included. The authors carefully chose their network sizes and network convergences and divergences in accordance with available experimental quantities and considered both topological (incorporating the axonal distribution of cell types) and non-topological (postsynaptic targets were selected at random) networks. Mossy fiber sprouting was modeled through the addition of connections from DG granule cells to DG granule cell proximal dendrites.

Simulations indicated that in the topological networks, even a low degree of mossy fiber sprouting was sufficient to induce seizure-like activity in the DG in response to perforant path stimulation. The spatially restricted axonal distribution of the sprouted mossy fibers played a pivotal part in determining the spread of network activity during seizures in the DG.

Concluding Statement

It is clear that many experimental details of hippocampal excitatory cells exist and that many

specific questions about these cells have been addressed with models. However, further aspects, such as cellular, biochemical mechanisms (e.g., Kim et al. 2010), can also be considered. Furthermore, mathematical models are always simplifications of the biology, and so, when constructing models, it is important to be aware of and to be clear about the constraints and assumptions made. These details and rationales become especially important when creating subsequent models by expanding or reducing previously constructed models. In this way, linkages between experiment and modeling can remain clear, and cycling between the two becomes feasible.

Cross-References

- [Hippocampus, Model Inhibitory Cells](#)
- [Integrate and Fire Models, Deterministic](#)

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Hippocampus, Model Inhibitory Cells

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Definition

Hippocampus, model inhibitory cells refer to mathematical models of neurons that are designed to represent (GABAergic) inhibitory interneurons in the hippocampus. Specifically, biophysically motivated models of interneurons located in the CA1, CA3, and dentate gyrus (DG) regions of the

hippocampus are described. These cellular models have been developed for two main purposes: (i) to examine how their biophysical characteristics affect and control electrophysiological output and (ii) to examine network output given the modeled cellular characteristics. This entry summarizes a comprehensive set of such models.

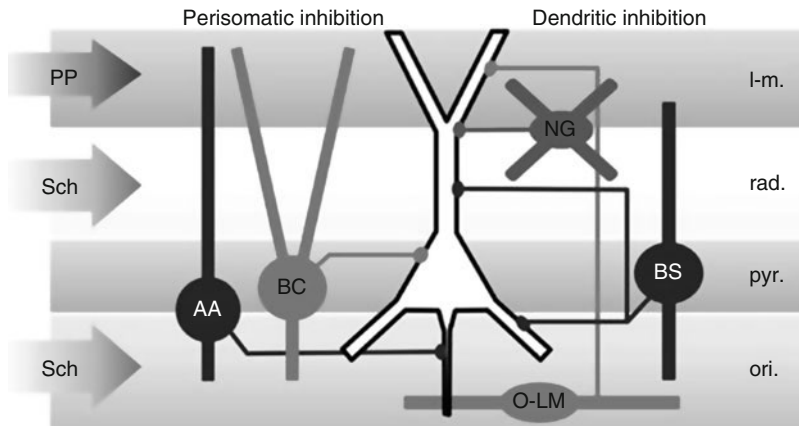
Detailed Description

Introduction and Background Context

The brain consists of two classes of neurons, excitatory and inhibitory cells. Excitatory cells were typically thought to be long ranging with their connections, whereas inhibitory cells were viewed as “local circuit neurons” or interneurons (Shepherd 2003). Today, it is clear that this is not necessarily the case, as some inhibitory cell types have long extensions (e.g., see Jinno et al. 2007). Regardless, the “interneuron” terminology is often used synonymously with “inhibitory cell.”

Inhibitory cells or interneurons in the mammalian brain are also termed GABAergic since their primary neurotransmitter is GABA, which causes an inhibitory, hyperpolarizing response in the postsynaptic cells when GABAergic receptors are activated there. It is now known that even though inhibitory cells represent a much smaller percent of neurons, they exhibit a much wider diversity in their characteristics, relative to excitatory cells (e.g., see Freund and Buzsáki 1996; McBain and Fisahn 2001). Interneurons have distinct morphologies located in various cortical layers, have different axonal targets, express different calcium-binding proteins, and exhibit different firing properties. Determining the functionality of this diversity is challenging (e.g., see Freund and Kali 2008; Kepecs and Fishell 2014). In addition, efforts to systematically classify these diverse GABAergic cells are ongoing (Ascoli et al. 2008; DeFelipe et al. 2013).

The hippocampus (Andersen et al. 2006; Ben-Ari and Represa 2009) has been a heavily studied brain structure due to its experimental accessibility with the slice preparation. Moreover, it expresses several rhythmic and population activities that are correlated with normal (e.g., learning



Hippocampus, Model Inhibitory Cells, Fig. 1 Schematic illustrating two main classes of interneuron types in hippocampus CA1, based on their post-synaptic targets. Also schematized are the layers (I-m., rad., pyr., ori.) where the cell bodies are found and where their targets go, as well as input coming from other regions (perforant path *PP*, Schaffer collaterals (*Sch*)). The first class (shown on the *left*) are interneurons that target perisomatic regions of the excitatory, pyramidal cell. They include basket cells (*BC*, targets: soma and proximal dendrites) and axo-axonic cells (*AA*, targets: axon initial

segments). The second class (shown on the *right*) are interneurons that target dendritic regions. They include bistratified cells (*BS*) that innervate the mid-distal dendrites, neurogliaform (*NG*) interneurons that target apical dendrites, and O-LM interneurons that target the distal apical dendrites (I-m. layer). (With kind permission from Springer Science+Business Media: *Hippocampal Microcircuits* (Cutsuridis, V., Graham, B., Cobb, S. & Vida, I., eds.), Part I, Chapter 2, 2010, p.27–67, I. Vida, “Morphology of Hippocampal Neurons,” Figure 4)

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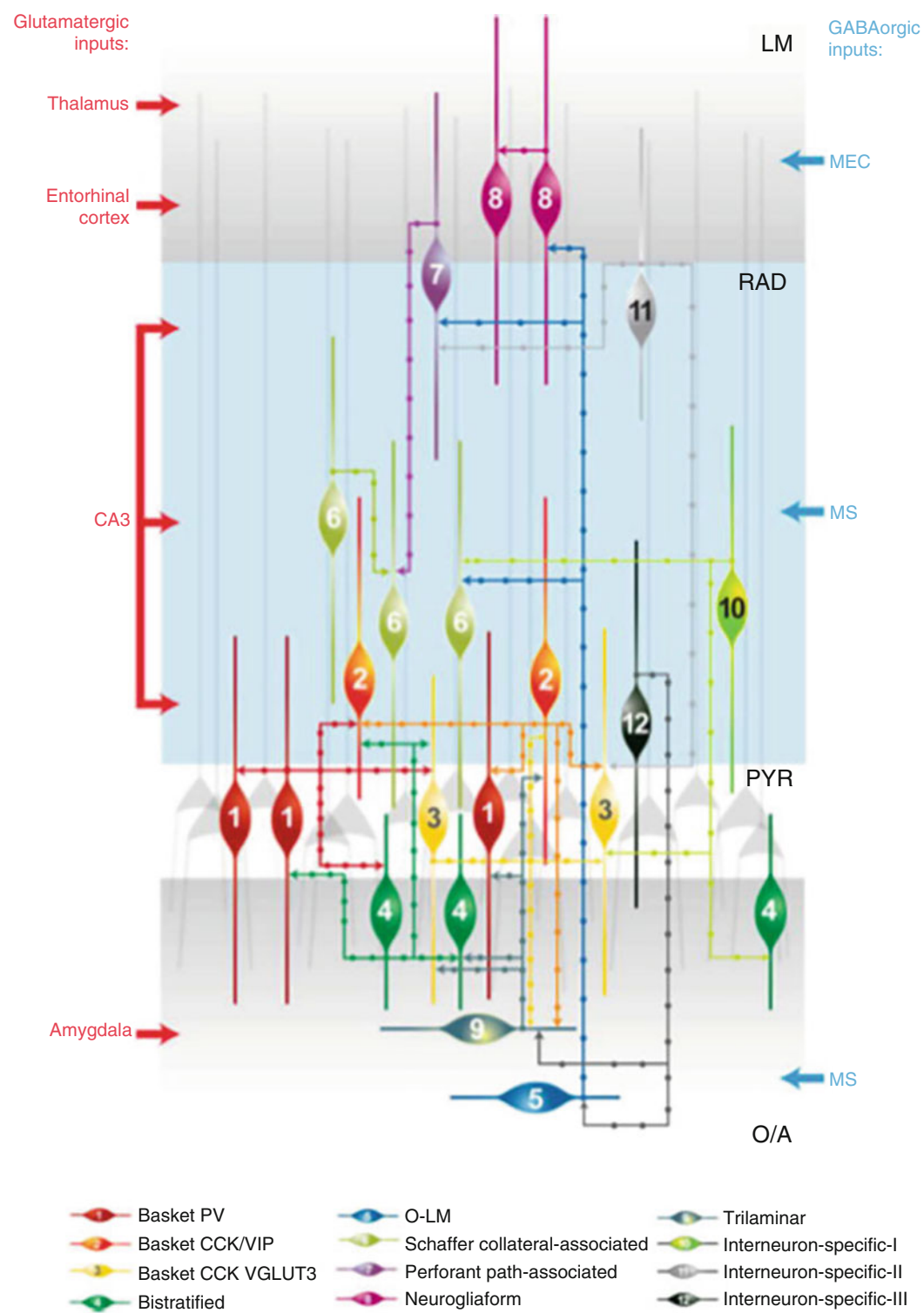
and memory) and pathological states (e.g., epilepsy, Alzheimer’s) and in which interneurons appear to have critical, controlling roles (e.g., see Krook-Magnuson et al. 2013). Figures 1 and 2 illustrate several types of interneurons in the hippocampus, either from a dendritic- versus perisomatic-targeting perspective (Fig. 1) or from an interneuron-targeting perspective (Fig. 2). Much work continues to uncover the richness of interneuron diversity (e.g., see Chamberland and Topolnik 2012), and it is clear that we still have much to learn to be able to appreciate and thus understand the functionality of this interneuron diversity.

Mathematical and computational modeling is an essential tool in neuroscience today, and there are many types of mathematical models of neurons ranging from abstract to detailed (Brunel and Hakim 2009). The rationale behind the choices one makes in using a certain type of model naturally depends on the question being addressed. Since the hippocampus expresses several different rhythmic activities, the research questions that are typically considered, in which mathematical

models of hippocampal interneurons are used, either directly or indirectly involve the generation and/or modulation of rhythmic, population activities. Furthermore, it is clear that interneurons play distinct and particular roles in rhythmic activities such as theta and gamma rhythms (► “Hippocampus, Theta, Gamma, and Cross-Frequency Coupling”; ► “Hippocampal Theta, Gamma, and Theta/Gamma Network Models”) (e.g., Klausberger and Somogyi 2008) making them an important focus in modeling studies.

Cellular Models

The amount of detail in a cellular model needs to be enough to allow speculations, hypotheses, and predictions to emerge for future experiments. Interneuron models are either primarily concerned with how inhibitory cells contribute to network rhythms/population oscillations or with characteristics of the individual cells that affect the networks in which they reside. As such, the models tend to be multi-compartment in nature and more detailed for the latter, but not exclusively. Clearly, the more detail that is included in individual cell



Hippocampus, Model Inhibitory Cells, Fig. 2 (continued)

models, the more likely one can adequately represent the characteristics of particular interneurons. However, more detail requires more equations and more parameters which require experimental constraints. In this entry, we tabulate cellular models that have been developed to represent interneurons in CA1, CA3, and DG regions of the hippocampus. Given the cellular, identifiable focus we take, the models are necessarily biophysical in nature, but not always entirely. In particular, the fast-spiking model developed by Ferguson et al. (2013) does not specifically include voltage-gated channels (VGCs), but it does capture spiking characteristics taken directly from experiment. We note that much simpler, cellular representations are used in some studies to allow large networks to be examined along with detailed mathematical analyses (e.g., see Brunel and Hansel 2006; Ledoux and Brunel 2011). The use of identifiable, inhibitory cell-type models is not a focus in such studies.

An anatomically distinct characteristic of hippocampal interneurons, which is likely to be functionally relevant, is the layer-specific targeting of its axons. Specifically, some interneurons preferentially target somatic regions of pyramidal cells, and others target dendritic regions (see Fig. 1). Given this, as well as the range of developed models that exist, we group the models into three tables. Table 1 encompasses models of fast-spiking, basket cell-type interneurons that target perisomatic regions of pyramidal cells. For example, this table includes parvalbumin-positive (PV+) basket cells. We also note that earlier models of hippocampal inhibitory cells are included in this table, as they were developed to be fast spiking (relative to pyramidal cell firing). Indeed, experimental studies often differentiate excitatory and

inhibitory cells based on whether they are fast spiking or not. However, it is now clear that several inhibitory cell types (e.g., Ivy cells – Fuentealba et al. 2008) are not fast spiking. Table 2 encompasses models of interneurons with horizontal dendrites so that their cell bodies and dendrites are in the same layer. These cells target more distal regions of the pyramidal trees. Most of the models in this table are the distal dendrite-targeting oriens–lacunosum-moleculare (O–LM) cells. Table 3 encompasses models of other interneuron types.

For each model in each of the three tables, we identify five aspects:

- (i) The biological interneuron type that the model represents. In some cases, the type is implied.
- (ii) The mathematical model type, identified in three possible ways.
Simple, such that particular biophysical details are not present.
Biophysical and whether *single-* or *multi-compartment* model. The current types (see Glossary) that are included in the model are specified.
Derivative, which could mean *subsequent* use of a given model in another study, typically a network situation, *simplification* of a given model, *adaptation* of a given model, or *expansion* of a given model. The identification of this *derivative* type is meant to be particular and not loose such as when various aspects of various models are used.
- (iii) The experimental basis, considered in three ways. We note that experimental data is obtained from rodents.

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Hippocampus, Model Inhibitory Cells, Fig. 2 Schematic representation of synaptically connected GABAergic inhibitory circuits in the CA1 hippocampal area. Schematic illustrating interneurons that connect to other interneurons in hippocampus CA1. The main excitatory (glutamatergic) inputs are shown on the left, and the main long-range inhibitory (GABAergic) that contact CA1 interneurons are shown on the right. CCK cholecystokinin, LM stratum lacunosum-moleculare, O/A

stratum oriens/alveus, O–LM oriens–lacunosum-moleculare cell, PV parvalbumin, PYR stratum pyramidale, RAD stratum radiatum, VGLUT3 vesicular glutamate transporter 3, VIP vasoactive intestinal peptide. (With kind permission of the authors: Figure 1 as originally published in Chamberland S, Topolnik L (2012) Inhibitory control of hippocampal inhibitory neurons. Front Neurosci 6:165. doi:<https://doi.org/10.3389/fnins.2012.00165>)

Hippocampus, Model Inhibitory Cells, Table 1 Fast-spiking interneurons, PV+ basket cells

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA3 interneuron	Biophysical, multi-(Na, K-D)	Passive – generic	Network (carbachol-driven population rhythms)	Traub et al. (1992)
		Active – generic		
		f-I – yes		
CA3 SP interneuron	Biophysical, multi-(Na, K-DR, K-Ca, K-AHP, K-A, Ca-L)	Passive – generic	Intrinsic (active, VGCs in dendrites, and spike transduction)	Traub and Miles (1995)
		Active – generic		
		f-I – yes		
*CA3 SP interneuron	Derivative, subsequent (Traub 1995)		Network (population bursts with dendritic GJ coupling)	Traub (1995)
CA1 ^a fast-spiking basket cell	Biophysical, single-(Na, K-DR)	Passive – generic	Network (gamma rhythms)	Wang and Buzsáki (1996)
		Active – generic		
		f-I – yes		
*CA1 fast-spiking basket cell	Derivative, subsequent (Wang and Buzsáki 1996)		Network (gamma rhythms)	Bartos et al. (2007) ^b
CA3 interneuron	Biophysical, multi-(Na, K-DR)	Passive – generic	Network (GABAergic modulation of place field development)	Wallenstein and Hasselmo (1997)
		Active – generic		
		f-I – no		
CA1 ^c fast-spiking interneuron	Biophysical, single-(Na, K-DR)	Passive – generic	Network (loss of synchrony mechanisms)	White et al. (1998)
		Active – generic		
		f-I – no		
*CA1 fast-spiking interneuron	Derivative, subsequent (White et al. 1998)		Network (theta/gamma rhythms)	White et al. (2000)
DG basket cell	Biophysical, multi-(Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific	Network (DG hyperexcitability, mossy fiber, and mossy cell changes)	Santhakumar et al. (2005)
		Active – specific		
		f-I – yes		
*DG basket cell	Derivative, subsequent (Santhakumar et al. 2005)		Network (DG hyperexcitability, topology changes)	Morgan and Soltesz (2008) ^d
CA1 basket cell	Biophysical, multi-(Na, K-DR)	Passive – generic	Network (active, VGCs in dendrites, and synchrony with dendritic GJ coupling)	Saraga et al. (2006)
		Active – generic		
		f-I – no		
*CA1 basket cell	Derivative, adaptation (Saraga et al. 2006)		Network (predicting synchrony with dendritic GJ coupling)	Zahid and Skinner (2009)
DG fast-spiking PV+ basket cell	Biophysical, multi-(Na, K-DR, h-sag)	Passive – specific	Intrinsic ^e (EPSP and spiking properties)	Hu et al. (2010)
		Active – specific		
		f-I – no		
CA1 basket cell	Biophysical, multi-(Na, K-DR, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – generic	Network (encoding and retrieval in CA1 theta rhythm microcircuit)	Cutsuridis et al. (2010)
		Active – generic		
		f-I – no		
CA1 basket cell	Biophysical, single-(Na, K-DR, K-A)	Passive – generic	Network (GABAergic contributions during theta – gating, timing, and phase precession)	Cutsuridis and Hasselmo (2012)
		Active – generic		
		f-I – no		

(continued)

Hippocampus, Model Inhibitory Cells, Table 1 (continued)

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA1 PV+ fast-spiking	Simple, single-	Passive – specific	Network (gamma rhythms)	Ferguson et al. (2013)
		Active – N/A		
		f-I – yes		
CA1 PV+ basket cell	Biophysical, multi-(Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific Active – generic f-I – yes	Network (theta, gamma rhythms)	Bezaire et al. (2016)

^aPutatively CA1 due to connectivity aspects used
^bThis is a review paper but chosen as a “representative” of the many papers that have subsequently used the Wang and Buzsáki (1996) model
^cStated to be applicable to CA1
^dOther derivative model references can be found in Morgan and Soltesz (2010)
^ePassive model characteristics from Nörenberg et al. (2010)

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Passive properties, considered to be *generic* or *specific* in terms of the particular biological cell type being represented.

Active properties or VGCs (current types), considered to be *generic* or *specific* in terms of the particular biological cell type. *Specific* is used if at least one of the current types is based on data specific to the biological cell type.

Frequency response to injected current or current clamp responses, i.e., *f-I* output curve, considered as *yes* or *no*. *Yes* is specified if the *f-I* curve is shown or if at least two examples of model firing are shown so that it can be seen how firing changes with different levels of injected current. This aspect is chosen because the steepness of *f-I* curves is an important factor to consider in the control of network dynamic output. However, note that all models show firing output that matches experiment in some way.

(iv) Functional aspect considered with the model.

Intrinsic – means that the inhibitory cell model was used to examine how its biophysical characteristics affect and control electrophysiological output (with summarizing specifics given).

Network – means that the particular inhibitory cell model was used when examining

network output (with summarizing specifics given). Also, note that the model network may include other inhibitory cell types as well as excitatory cells with the given inhibitory cell model.

(v) Reference where the given model is described.

Given that we focus this entry on models of identifiable hippocampal interneuron types (as described above), the models given in the tables are a reasonably comprehensive listing. However, we have not included models where only passive properties were considered and only a selection of *derivative* model types is given. We present the models in the tables in a chronological order (of paper publication) with the exception that *derivative* models are presented immediately following the given model and are shown as a shaded entry as well as being starred (*) to highlight that it is a derivative model and not presented in chronological order in the tables.

Considerations

As tabulated above, it is clear that many different models of hippocampal interneurons have been developed, although new “types” of interneurons are still being defined so that models would not yet exist. All biological cell types modeled, except for the non-PV+ Ivy cells, can be found in the schematics of Figs. 1 and 2. We note that although the majority of models include biophysical VGCs,

Hippocampus, Model Inhibitory Cells, Table 2 Horizontal dendrites, distal dendrite-targeting interneuron types

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA1 O–LM interneuron	Biophysical, multi- (Na, K-DR, K-A, h-sag)	Passive – specific	Intrinsic (active, VGCs in dendrites, and spike propagation)	Saraga et al. (2003)
		Active – specific		
		f-I – yes		
*CA1 O–LM interneuron	Derivative, simplification to single- (Saraga et al. 2003)		Network (theta/gamma rhythms)	Gloveli et al. (2005) ^a
DG HIPP interneuron	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, h-sag)	Passive – specific	Network (DG hyperexcitability, mossy fiber, and mossy cell changes)	Santhakumar et al. (2005) ^b
		Active – specific		
		f-I – yes		
CA3 O–LM interneuron	Biophysical, single- (Na, Na-p, K-DR, h-sag)	Passive – generic	Network (theta-phase separation, encoding, and retrieval in CA3)	Kunec et al. (2005)
		Active – generic		
		f-I – no		
CA1 O–LM interneuron	Biophysical, single- (Na, Na-p, K-DR, h-sag)	Passive – generic	Network (theta rhythm)	Rotstein et al. (2005)
		Active – generic		
		f-I – no		
CA1 O–LM interneuron	Biophysical, multi- (Na, K-DRf, K-DRs, K-A, K-Ca, K-M, Ca-T, Ca-L, h-sag)	Passive – specific	Intrinsic (K-M current control of spiking)	Lawrence et al. (2006)
		Active – specific		
		f-I – yes		
CA1 O–LM interneuron	Biophysical, multi- (Na, K-DR, K-A, h-sag)	Passive – generic	Network (encoding and retrieval in CA1 theta rhythm microcircuit)	Cutsuridis et al. (2010)
		Active – generic		
		f-I – no		
CA3 O–LM interneuron	Biophysical, single- (Na, K-DR, K-Ca, Ca-L, h-sag)	Passive – generic	Network (theta/gamma rhythms)	Neymotin et al. (2011)
		Active – generic		
		f-I – no		
CA1 O–LM interneuron	Biophysical, single- (Na, Na-p, K-DR, h-sag)	Passive – generic	Network (GABAergic contributions during theta – gating, timing, and phase precession)	Cutsuridis and Hasselmo (2012)
		Active – generic		
		f-I – no		
CA1 SOM+ interneuron	Simple, single-	Passive – specific Active – N/A f-I – yes	Network (theta rhythms)	Ferguson et al. (2015)
CA1 O–LM interneuron	Biophysical, multi- (Na, K-DRf, K-A, h-sag)	Passive – specific Active – generic f-I – yes	Network (theta, gamma rhythms)	Bezaire et al. (2016)

^aOther derivative model references include Tort et al. (2007) and Wulff et al. (2009)

^bSee Table 1 for derivative model articles

the majority of them do not have an experimental basis that is specifically tied to the biological cell type. Also, more detailed, multi-compartment, biophysical models are not necessarily more specific. While the reasons for this could be multiple, it is often the case that modelers do not have direct access to experimental data, which is probably due to insufficient interactions between modelers and experimentalists. However, a main reason is due to the active and “fluid” interneuron

field, making it challenging to be clear about experimental data and particular cell types. Coupled with the technical limitations of acquiring data from particular cell types, one cannot expect to have experimental constraints for all model aspects. This is in contrast to hippocampal, excitatory cell models where much more experimental data is available, and specific questions have been considered (in this entry ► “Hippocampus, Model Excitatory Cells”).

Hippocampus, Model Inhibitory Cells, Table 3 Other interneuron types

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA1 O/A interneuron	Biophysical, single- (Na, Na-p, K-DR, K-D)	Passive – generic	Network (synchronized bursting with GJ and inhibitory coupling)	Skinner et al. (1999)
		Active – generic		
		f-I – no		
*CA1 O/A interneuron	Derivative, expansion to multi- (Skinner et al. 1999)	f-I – yes	Intrinsic (K-D current control of bursting)	Saraga and Skinner (2002)
CA1 ^a O/A CB+ interneuron	Biophysical, single- (Na, K-DR, K-Ca, Ca-L, h-sag)	Passive – generic	Network (septo-hippocampal theta rhythms)	Wang (2002) ^b
		Active – generic		
		f-I – no		
CA1 LM/RAD interneuron ^c	Biophysical, single- (Na, Na-p, K-DRf, K-DRs, K-A, K-D)	Passive – specific	Intrinsic (subthreshold MPO generation)	Morin et al. (2010)
		Active – specific		
		f-I – no		
*CA1 LM/RAD interneuron	Derivative, subsequent (Morin et al. 2010)	f-I – yes	Network (reliable theta-frequency spiking in virtual networks)	Sritharan and Skinner (2012)
CA1 AAC	Biophysical, multi- (Na, K-DR, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – generic	Network (encoding and retrieval in CA1 theta rhythm microcircuit)	Cutsuridis et al. (2010)
CA1 BSC		Active – generic		
		f-I – no		
CA1 AAC, CA1 BSC	Biophysical, single- (Na, K-DR, K-A)	Passive – generic	Network (GABAergic contributions during theta – gating, timing, and phase precession)	Cutsuridis and Hasselmo (2012)
CA1 Ivy cell		Active – generic		
		f-I – no		
CA1 NGL cell	Biophysical, single- (Na, K-DR)	Passive – generic	Network (GABAergic contributions during theta – gating, timing, and phase precession)	Cutsuridis and Hasselmo (2012)
		Active – generic		
		f-I – no		
CA1 IS3 cell	Biophysical, multi- (Na, Na-p, K-DRf, K-A)	Passive – specific	Intrinsic (determining biophysical properties and spike generation control)	Guet-McCreight et al. (2016)
		Active – generic		
		f-I – no		
CA1 AAC	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		
CA1 BSC	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		
CA1 CCK+ basket cell	Biophysical, multi- (Na, K-DRf, K-DRs, K-A, K-Ca, K-AHP, Ca-L, Ca-N, h-sag)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		
CA1 Ivy cell	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		
CA1 NGF cell	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, Ca-N)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		
CA1 SCA interneuron	Biophysical, multi- (Na, K-DRf, K-DRs, K-A, K-Ca, K-AHP, Ca-L, Ca-N, h-sag)	Passive – specific	Network (theta, gamma rhythms)	Bezaire et al. (2016)
		Active – generic		
		f-I – yes		

^aReferred to as CA1^bThis entry also included a MS non-cholinergic model, and derivative models of it representing hippocampal interneurons are in Hajós et al. (2004) and Orbán et al. (2006)^cThe LM/RAD acronym was used by the authors for this interneuron type, but likely part of SCA interneuron types (see Vida 2010)

For inhibitory cell models in the hippocampus, it is essential that the experimental and biological basis be specified, so that future models can more fully take advantage of existing ones. While this should be the case for any model, it is even more so for these diverse, inhibitory cell populations, which are developmentally regulated (see Tricoire et al. 2011), and where diversity and function are probably linked (see Leão et al. 2012).

Cross-References

- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Hippocampus, Model Excitatory Cells](#)
- [Hippocampus, Theta, Gamma, and Cross-Frequency Coupling](#)

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Glossary

Biophysical: Types of Currents as Given in “Mathematical Model Type”

Ca-L	L-type calcium. Also referred to as high threshold type, non-inactivating
Ca-N	N-type calcium
Ca-T	T-type calcium. Also referred to as low threshold type, inactivating, and associated with post-inhibitory rebound
h-sag	Hyperpolarization-activated (sag) inward
K-A	A-type, transient potassium
K-AHP	AHP potassium. Only calcium dependent, not voltage dependent, apamin sensitive, sometimes referred to as SK, and responsible for slow AHP, but could also be part of medium AHP
K-Ca	Calcium-dependent potassium. Calcium and voltage dependent, sometimes referred to as BK and responsible for fast AHP aspects
K-D	Slowly inactivating potassium
K-DR	Delayed rectifier potassium. HH type

K-DRf	Fast delayed rectifier
K-DRs	Slow delayed rectifier
K-M	Muscarinic, potassium
Na	Sodium. Transient, HH type
Na-p	Persistent sodium

Other Acronyms Used

AAC	Axo-axonic cell
AHP	Afterhyperpolarization
BSC	Bistratified cell
CB+	Calbindin positive
CCK+	Cholecystokinin positive
DG	Dentate gyrus
EPSP	Excitatory postsynaptic potential
GABA	γ -aminobutyric acid
GJ	Gap junction
HH	Hodgkin–Huxley
HIPP	Hilar perforant path associated
IS3	Interneuron-specific-III
LM/RAD	Lacunosum-moleculare/radiatum
MPO	Membrane potential oscillation
MS	Medial septum
N/A	Not applicable
NGL	Neurogliaform
O/A	Oriens/alveus
O-LM	Oriens–lacunosum/pyramidale
PV+	Parvalbumin positive
SCA	Schaffer collateral associated
SOM+	Somatostatin positive
SP	Stratum pyramidale
VGC	Voltage-gated channel

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Hippocampus, Model Network Architecture

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Definition

Hippocampus, Model Network Architecture refers to the mathematical models used to describe cell connectivity and activity in computational models of the hippocampus. Models of the hippocampus contain two main components: (1) the structure of connections between the cells/regions and (2) the cell types used as the building blocks of the model.

Detailed Description

Basic Hippocampal Anatomy

The hippocampus proper is composed of three subregions: CA1, CA2, and CA3. However, many models actually represent the hippocampal formation, which additionally includes the dentate gyrus (DG), subiculum (SUB), presubiculum, parasubiculum, and entorhinal cortex (EC) (Amaral and Lavenex 2006). Many hippocampal models focus on the representation of a single subregion or the interactions between regions. One aspect of the hippocampus that differentiates it from other cortical regions is that connections between subregions tend to be unidirectional, creating loops of which have important implications for information processing. This is especially important given that the hippocampus is involved in functions such as memory, learning, and spatial navigation. Because much of the available experimental data regarding hippocampal structure comes from studies of mice and rats, most computational models are based on what is known about the structure of the rodent hippocampal formation.

Anatomical Structure/Connectivity

The basic connectivity of the hippocampus is generally simplified to represent the following interactions between subregions. The hippocampus receives input from the cortex to the EC. The EC projects to the DG, CA3, CA1, and the SUB through the perforant pathway. The DG sends mossy fibers to CA3, and CA3 in turn projects to CA1. CA1 then projects to the SUB as well as back to the EC, and the SUB also projects back to the EC. The exact nature of these connections can further be deconstructed, and other less prominent connections also exist. Please refer to the “Further Reading” section for references describing the connectivity in more detail.

Cell Types

The hippocampus is composed of excitatory principal cells, inhibitory interneurons, and glial cells. Many models include excitatory and inhibitory cells, but often exclude the contribution of glial cells. However, as recent experimental data

emphasizes the importance of glial-neuronal interactions (Volterra and Meldolesi 2005), more computational models are attempting to include these cells, especially in models of disease such as epilepsy (Volman et al. 2012).

The most studied principal cells of the hippocampus include the pyramidal cells of CA1 and CA3 and the granule and mossy cells of the DG, and detailed biophysical models of these cells have been developed (Vida 2010).

There is a vast diversity of interneurons in the hippocampus (Freund and Buzsaki 1996; Kullmann 2011), and new experimental techniques continue to lead to the classification of new subtypes of these GABAergic cells. Interneurons are normally classified based on their morphology, neurochemical markers, and electrophysiological properties (Ascoli et al. 2008). However, recently, a new class of “hub cells” was functionally identified and could be identified as early-born neurons suggesting that birth date/location of cells might also be important in the classification of interneurons (Bonifazi et al. 2009; Picardo et al. 2011). Biophysical models of the hippocampus often attempt to include interneurons, and detailed models of some subtypes such as basket cells and OLM neurons have been developed (Skinner and Saraga 2010a), but due to the current lack of experimental knowledge about this class of cells, it is difficult to include detailed models of all of the relevant cell types.

While some computational models are based on detailed representations of the cell types found in the hippocampus, many models choose to instead use simplified representations of cells and implement neurons as simply excitatory or inhibitory. For more information, see the “Further Reading” Section.

Types of Models

Because hippocampus is highly organized and complex structure, the first decision that must be made in defining a computational model of the hippocampus is the level of detail that one would like to include. As in all computational models, this will be dependent on the type of questions that

the model is intended to address and the computational power available. The goal of all hippocampal models is to aid in our understanding of hippocampal functioning. Because the hippocampus has been implicated in a wide variety of tasks and diseases, different models choose different levels of abstraction in order to elucidate potential mechanisms that give rise to observed behaviors. One way of classifying hippocampal models is by the level of abstraction used to model cells. In this case, models can roughly be divided into three categories: biophysical models, spiking neuron models, and firing rate models.

Biophysical Models

Biophysical models are composed of cell types whose dynamics are normally derived from Hodgkin-Huxley-type equations. These models can include multiple compartments and sometimes are based off of detailed cell morphology.

A highly detailed biophysical model of the DG was developed (Santhakumar et al. 2005; Dyhrfjeld-Johnsen et al. 2007) and expanded to include over one million cells (Schneider et al. 2012). This model can be implemented in reasonable time using parallel processing and has been used to study the effects of structural network changes associated with epilepsy. In CA1, Olypher et al. simulated a 1 mm patch to study input–output transformations (Olypher et al. 2012), and Cutsuridis et al. implemented a microcircuit model of CA1 to study memory storage and consolidation (Cutsuridis et al. 2010). Ibarz et al. looked at how populations of pyramidal cells can contribute to high-frequency oscillations (Ibarz et al. 2010), while Baker and Olds used realistic spike train stimulations of a highly detailed CA3 pyramidal cell to study phase precession of place cells (Baker and Olds 2007).

The variation in scale of each of these studies demonstrates the different approaches taken in using computational modeling to study hippocampal function. While some strive to include as much detail as possible and take advantage of parallel computing, others prefer to use smaller but still detailed models to tease out the effects of particular parameters. However, in all of these

models, it should be noted that there are still levels of detail that are left out.

Spiking Neuron Models

Instead of implementing biophysical models of neurons, some models prefer to use highly simplified neuronal representations that reflect the oscillatory nature of neurons and often rely on the concept of a threshold value at which the neuron is said to fire an action potential. Perhaps the most well-known spiking neuron model is the leaky integrate-and-fire neuron (Gerstner and Kistler 2002). Because of the simplicity of this type of neuron, models that implement integrate-and-fire neurons can focus on network interactions, heterogeneity, and specific patterns of connectivity without the additional complexity that comes from biophysical neuronal models.

Spiking neuron models have been used to study memory formation (Feldt et al. 2010a), the effects of network structure on the integration of newly generated neurons (Schneider-Mizell et al. 2010), phase precession of place cells (Tsodyks et al. 1996), temporal sequence compression (August and Levy 1999), and interactions between grid and place cells (Jay et al. 2010).

Firing Rate Models

Firing rate models represent a further abstraction of neuronal dynamics and represent cells by their firing rate as a function of time (Dayan and Abbott 2001). These models are often extensions of the Wilson and Cowen model (Destexhe and Sejnowski 2009; Wilson and Cowan 1972) and have been used to explore rephrasing of oscillations in CA3 and the DG (Akam et al. 2012). Firing rate models are often used to study hippocampal memory formation.

Models of Disease

The hippocampus has been implicated in a variety of diseases, and computational models have been employed to study the differences between healthy and pathological network functions. Multiple computational studies have therefore looked

at how changes in hippocampal architecture relate to seizure development in epilepsy (Case and Soltesz 2011; Soltesz and Staley 2008). In temporal lobe epilepsy, cell death and mossy fiber sprouting in the DG have been linked to the development of spontaneous seizures. By incorporating these changes into a previously developed biophysically motivated model of the DG, Morgan and Soltesz used the injured version of the model to predict a role of highly connected hub cells in seizure dynamics (Morgan and Soltesz 2008). Netoff et al. showed that progressively increasing the number of long-range connections in a small-world network model of epilepsy causes the network to transition from normal to seizure and bursting states (Netoff et al. 2004).

Hippocampal atrophy also plays a large role in Alzheimer's disease, and computational models have been used to explore the progression of the disease (Hasselmo 1997) and how changes in hippocampal network architecture can affect memory (Gluck et al. 2006). Additionally, models have explored how alterations in ion channels can lead to observed changes in the theta rhythm of Alzheimer's patients (Zou et al. 2011).

Functional Structure

A main difficulty encountered in developing models of the hippocampus is the lack of knowledge about the exact anatomical connectivity at the level of individual neurons. Often, model neurons are placed in one-dimensional chains or on two-dimensional grids that neglect the unique spatial properties of hippocampal structure. However, an advantage of computational models is that unlike the connectivity of the brain, the exact model connectivity is known, and in both cases, the dynamics of the neurons can be observed. It can therefore be useful to explore a new type of network structure called functional structure or functional connectivity (Feldt et al. 2011).

Functional structure is derived from statistical relationships between neurons. A connection is

said to exist between neuron A and neuron B if they meet some statistical requirement such as synchronous firing. Functional connectivity can sometimes be related to the underlying anatomical connections, although this is not necessarily the case as one can imagine a situation where common inputs to the cells might cause them to fire synchronously even though the two cells are not themselves connected.

By studying the functional connectivity of synchronous network events in the developing hippocampus, the Cossart lab identified the presence of hub (highly connected) neurons that also display a widespread axonal arborization (Bonifazi et al. 2009; Picardo et al. 2011). The Zochowski lab developed the Functional Clustering Algorithm (FCA) that detects groups of synchronously firing neurons and used this to study memory consolidation (Feldt et al. 2009) and the relationship between structure and dynamics in hippocampal cultures (Feldt et al. 2010b). The algorithm was also applied to chronically epileptic networks to show that these networks are composed of spatially clustered synchronous neuronal assemblies (Feldt Muldoon et al. 2013).

Comparison of functional structure derived from model and experimental data can be useful in model validation and help in our understanding of the relationship between neuronal structure and dynamics.

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Hippocampus, Theta, Gamma, and Cross-Frequency Coupling

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Definition

The hippocampus is a prominent brain structure in the medial temporal lobe known to be important for episodic memory function. Theta (3–12 Hz) and gamma rhythms (25–160 Hz) commonly refer to specific frequency bands of EEG or local field potential (LFP) activity that is generated by neural circuits in the hippocampus during periods of increased neural activity. These neural rhythms function to organize hippocampal spike timing using different temporal scales.

Detailed Description

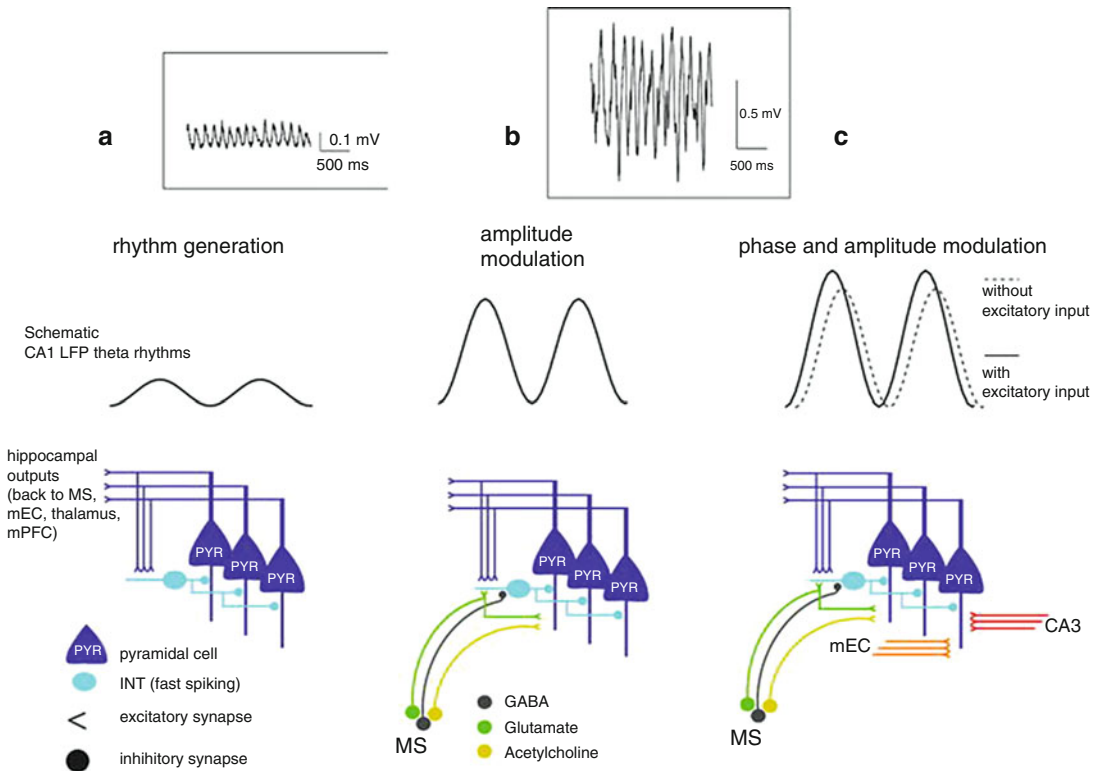
Brain rhythms play an important role in spike timing and brain communication (Buzsaki 2006; Gray et al. 1989; O'Keefe and Recce 1993). Different brain regions produce distinctly different brain rhythm frequencies that are thought to reflect unique forms of processing important for the localization, parceling, and routing of information within and between regions. Delta (~0.5–2 Hz), theta (3–12 Hz), beta (15–25 Hz), and gamma rhythms (25–160 Hz) have been investigated for decades. It is now known that theta, gamma, as well as the coupling between these rhythms are important for different brain processes such as episodic memory (Axmacher et al. 2010; Belluscio et al. 2012; Canolty et al. 2006; Fuentemilla et al. 2010; Fujisawa and Buzsaki 2011; Lakatos et al. 2005; Tort et al. 2009). Theta and gamma rhythms have been described in both rodent and primates suggesting that brain rhythms and brain rhythm coupling could serve more general brain functions conserved across species.

Theta Rhythms

Theta rhythms (3–12 Hz) arise from the temporal neocortex and hippocampus during active processing of sensory information, during movement, and during rapid eye movement (REM) sleep (Bland and Oddie 2001; Buzsaki 1996; Kramis et al. 1975; Montgomery et al. 2008; Vanderwolf 1969).

How Are They Generated?

Theta rhythms in the hippocampus are generated by a combination of glutamatergic, GABAergic, and cholinergic inputs together with local activity emerging from the spontaneous activity of interneurons and pyramidal cells (Fig. 1) (Bragin et al. 1995; Charpak et al. 1995; Gloveli et al. 2005; Goutagny et al. 2009; Kocsis et al. 1999; Konopacki et al. 1987; Lawson and Bland 1993; Winson 1978). The firing patterns of neurons throughout the brain have been shown to be correlated with hippocampal theta rhythms including those neurons near theta generators in the temporal lobe (Chrobak and Buzsaki 1998; Dickson



Hippocampus, Theta, Gamma, and Cross-Frequency Coupling, Fig. 1

An oversimplified and reductionist model of theta rhythm generation in hippocampal CA1 and subiculum. (a) The minimal circuits required for theta are pyramidal cells and interneurons (Cobb et al. 1995; Goutagny et al. 2009). Activity in CA1 networks will spontaneously give rise to self-generated theta rhythms. The waveform shown above is an example of LFP trace in CA1 without any afferent inputs from the mEC, CA3, or medial septum (MS). (b) The GABAergic inputs from the medial septum are involved in synchronizing these separate intrinsic hippocampal oscillators and therefore creating larger network rhythms. The role of neurons expressing acetylcholine is unclear, although these cells do appear to be crucial for theta generation under urethane anesthesia. The role of glutamate containing MS afferent is currently unknown. Cholinergic and glutamatergic inputs arise throughout the CA1 network, whereas the GABAergic MS inputs are highly

localized to hippocampal interneurons. (c) The afferent excitatory inputs from CA3 and the mEC increase theta power, due to increases in dendritic current influx arising from strong excitatory synapses. These inputs are more likely to have a role in phase modulating the intrinsic rhythms, by slightly advancing (as illustrated) the phase of the rhythms shaped by endogenous- and MS-mediated processes. Phase delays are of course also possible. CA3 and mEC form synapses in different parts of the apical dendrites and therefore can exert their phase and amplitude modifying influence via different mechanisms. The raw data above (b, c) is an example LFP trace taken from CA1 of a freely moving rat. This schematic does not take into account active intrinsic somatic or dendritic conductances to the generation of theta. In addition, numerous subcortical regions modify theta rhythm frequency and amplitude through actions on the MS and local hippocampal circuits. For a review, see Bland and Oddie (2001)

et al. 2000, 2003; Konopacki et al. 1987; Mizuseki et al. 2009) and in connected subcortical regions such as the hypothalamus, amygdala, and striatum (Bland and Oddie 2001; Kirk et al. 1996; Pape et al. 2005; van der Meer and Redish 2011). Therefore, theta frequency activity occurs within brain-wide networks and often the theta

synchronization between regions originates in part from the hippocampus (Battaglia et al. 2011). These data suggest that the hippocampus serves as a central brain hub governing the synchronization of large-scale brain-wide networks at theta frequencies. This is further supported by large-scale brain network topological analysis

that shows that there is a concentration of information flow to the hippocampus (Mišić et al. 2014). The main theta modulating input to the hippocampus arises from the medial septum (MS). The MS sends glutamatergic, GABAergic, and cholinergic inputs to the hippocampus. Cholinergic inputs are not required for theta generation (Lee et al. 1994; Simon et al. 2006) but may contribute to initiation and termination of the theta state (Zhang et al. 2010). GABAergic inputs however have been suggested to play a more prominent role in the fine structure of theta rhythms by making synaptic contacts onto local interneurons in the hippocampus (Freund and Antal 1988), thereby creating a brief period of synchronous disinhibition in hippocampal pyramidal cell networks (Toth et al. 1997). This circuit disinhibition is thought to be responsible for providing the window within which pyramidal cells fire, creating the depolarized phase of the theta wave. Indeed, GABAergic MS lesions do reduce the amplitude of theta; however, with complete MS lesions, small theta rhythmic activity is still found within the hippocampus, and cellular activity still shows signs of theta periodicity (Brandon et al. 2011; Leutgeb and Mizumori 1999). Glutamatergic MS cells form synaptic contacts onto pyramidal cells in the hippocampus and are also likely playing a role in the septal influence on theta rhythms (Huh et al. 2010). One major open question in theta rhythm research is which cell types in the hippocampus are important for local theta generation. Several subclasses of interneurons fire phase locked to hippocampal theta (Klausberger and Somogyi 2008), and different models have ascribed various levels of importance to each interneuron class (► “Hippocampus, Model Inhibitory Cells”). Somatostatin (SOM)-positive interneurons fire at theta bursts (Klausberger et al. 2003) and receive excitatory theta frequency input from the MEC (Witter et al. 1988) as well as cholinergic input from the medial septum. SOM cells may be crucial for amplifying theta-modulated synaptic activity arising in the hippocampus from the medial septum, from the medial entorhinal cortex (MEC), or from the Schaffer collateral circuits of CA3 (Kispersky et al. 2012; Leao et al. 2012).

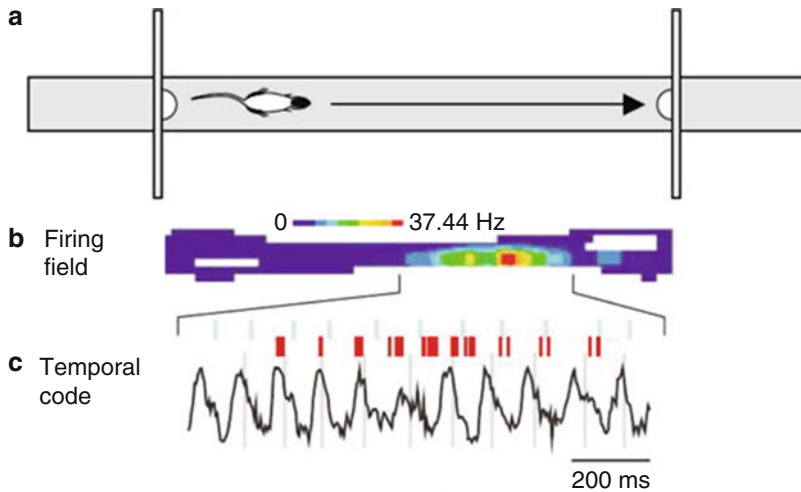
Theta Rhythms and Behavior

Theta rhythms play a key role in controlling spiking timing in the hippocampus during locomotion, during sensory processing, and during memory tasks (Kramis et al. 1975; O’Keefe and Recce 1993). Specifically, as rodents move through space, hippocampal pyramidal cells fire at an increased rate when moving through the cell’s “place field.” During the place field traversal, the firing rate increases, and cells fire at progressively earlier phases of the hippocampal theta rhythm, a phenomena termed phase precession (Huxter et al. 2003) (Fig. 2). In doing so, place cell spiking provides a phase code which can be used to indicate the animal’s position in the environment based on the theta phase of firing. The mechanism of phase precession is debated, although one theory postulates interference between an oscillatory excitation at apical dendrites and slower inhibitory oscillations acting at the soma via local interneurons (Losonczy et al. 2010; O’Keefe and Burgess 2005). However, the network mechanisms of precession are not definitively known, and there is debate regarding if precession is generated by synaptic inputs to the hippocampus or from local dynamics within hippocampal circuits (Mizuseki et al. 2009).

Grid cells in the MEC are also theta modulated and fire at theta frequencies with phase modulation to the local theta rhythm (Stensola et al. 2012). Theta rhythm communication is thought to be fundamental for communication between these different regions of the hippocampus during episodic memory processes such as spatial navigation in rodents (Buzsaki and Moser 2013).

Gamma Rhythms

Gamma frequency activity (25–160 Hz) refers to bursts of fast frequency rhythms found in spiking, LFP, EEG, and electrocorticography (ECoG) forms of time series data. The specific bandwidths change depending on the preparation, species, experimental conditions, and brain region, and likely different gamma rhythms arise from distinct circuit mechanisms. Two main frequency bands have been described and referred to as slow (~25–50 Hz) and fast (~65–140 Hz) gamma. Different brain regions often preferentially generate



reproduced from Huxter et al. 2003 with permission

Hippocampus, Theta, Gamma, and Cross-Frequency Coupling, Fig. 2 Phase precession of a hippocampal pyramidal cell on a linear track. (a) Schematic showing the path taken during the run from *left* to *right* on a representative trial. (b) The firing rate heat map showing the location versus firing rate, with the obvious location of the cell's place field. Warmer colors code for higher firing rate. (c) The relationship between the theta waves (LFP,

black) and place cell spiking (spike times indicated in *red*). Note precession of the spike relative to the theta cycle, where the spike fires at progressively earlier theta phases as the rat moves through the place field. The ticks above are the zero-crossing times of the individual theta cycles (180°). The vertical lines indicate 270° within the theta cycle (Data are reproduced from Huxter et al. (2003) with permission)

one of the two frequencies, although shifts between gamma frequencies can serve to change the communication between different regions on a rapid time scale gamma (Buzsaki and Wang 2012).

How Are They Generated?

Two main models of gamma rhythms are proposed to account for the physiological mechanisms of gamma synchrony in the brain (Buzsaki and Wang 2012) (► "Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)"). The first model, PING, requires balanced excitation and inhibition between pyramidal cells and interneurons (Csicsvari et al. 2003; Fisahn et al. 1998). In this model, excitatory pyramidal cells provide feed-forward excitation of interneurons, which then provide inhibitory feedback to the comparatively more numerous pyramidal cell population. The pyramidal cells recover from inhibition synchronously, and thus their post-inhibitory rebound spiking starts the subsequent gamma cycle by depolarizing interneurons. The second model, ING, postulates inhibitory interactions between

interneurons which can sustain gamma frequency synchronization (Buzsaki and Wang 2012; Whittington et al. 1995) via tonic depolarization of connected interneurons. No single model of gamma rhythm likely captures the heterogeneous mechanisms by which different gamma frequencies are generated. However, support for both models has been provided by different experimental data sets (Buzsaki and Wang 2012). The cell type most often associated with gamma rhythms is the parvalbumin (PV)-positive basket cell (Gulyas et al. 2010). These basket cells fire in vivo with bursts of activity at high frequencies and provide somatic inhibition to local pyramidal cells as well as other PV-positive cells. Inhibition of PV cells in the neocortex reduces local gamma rhythms (Sohal et al. 2009). However, an analysis of gamma rhythms in the hippocampus following PV cell suppression has not been reported.

Roles and Characteristics

The different frequencies (slow and fast) of gamma may arise from different network mechanisms (Bragin et al. 1995; Colgin et al. 2009) or

from different parameter regimes of the same synaptic components (Mann and Mody 2010). Different gamma frequencies can be present during different behavioral states (Ahmed and Mehta 2012; Colgin et al. 2009) and could thus serve to assist in signaling information between specific pathways. In the context of the hippocampus, gamma rhythms can be generated by intrinsic hippocampal circuits in CA3 (Bragin et al. 1995; Fisahn et al. 1998) and the subiculum (Colling et al. 1998; Jackson et al. 2011; Stanford et al. 1998) in addition to cortical regions that communicate with hippocampal circuits, including the medial entorhinal cortex (MEC) (Charpak et al. 1995; Colgin et al. 2009; Quilichini et al. 2010). Therefore, the cortex and hippocampus are wired to communicate using these gamma frequencies presumably through the phase coupling of independent gamma oscillators. Gamma frequency coherence between hippocampal regions is high during working memory tasks (Montgomery and Buzsaki 2007), suggesting gamma coherence serves to link together regions in a task-dependent manner. However, gamma rhythms *in vivo* are generally not persistent (unlike in brain slice preparations) and occur in brief bursts which are “theta modulated”; thus the amplitude of gamma follows the phase trajectory of theta rhythms (Fig. 3). This property of theta-modulated gamma is known as cross-frequency coupling or, specifically in this instance, theta–gamma coupling and provides a mechanism to simultaneously process multiple frequencies of network activity being relayed between brain areas. Further roles are described below.

Theta–Gamma Coupling

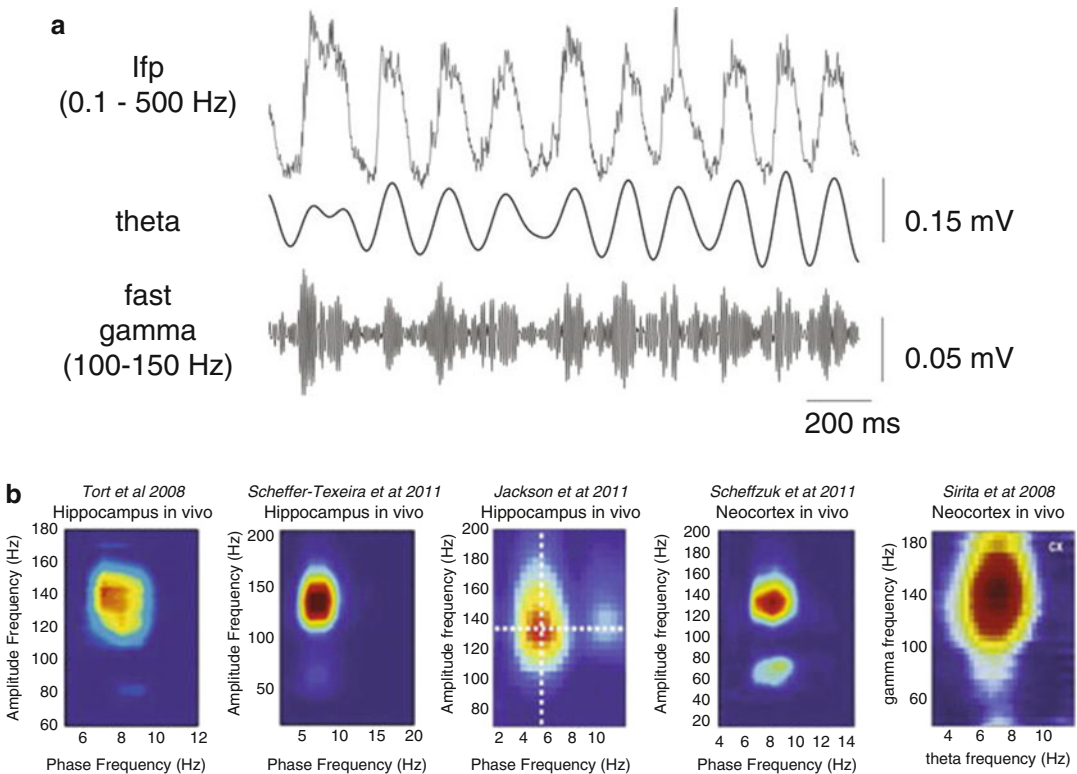
Theta–gamma coupling can be grouped into two forms: (1) phase–amplitude coupling, which refers to the phenomenon where the phase of the theta rhythm modulates the amplitude of the gamma frequency (Fig. 3), and (2) phase–phase coupling, where the phases of gamma and theta covary due to gamma waves occurring at preferred phases of theta (Belluscio et al. 2012). These forms of rhythm coordination are just two examples of cross-frequency coordination found in the brain. Theoretically, many other types of

coupling could exist (► “[Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)”).

The observation of covariation between theta phase and gamma amplitude was first quantified by Bragin and colleagues who described theta–gamma coupling in rat CA1 using LFP and single neuron recordings (Bragin et al. 1995). This original observation was not intensively followed up until Canolty and associates showed that ECoG recordings in humans demonstrated robust theta–gamma coupling and the strength of this coupling correlated with behavioral performance on memory tasks (Canolty et al. 2006). Since these reports, this interesting form of frequency multiplexing has been the subject of intense study by many experimental and theoretical neuroscientists (Axmacher et al. 2010; Belluscio et al. 2012; Canolty et al. 2006; Canolty and Knight 2010; Colgin et al. 2009; Pastoll et al. 2013; Sauseng et al. 2010; Sirota et al. 2008; Tort et al. 2009; Wulff et al. 2009). Although relatively few studies have focused on the mechanisms of theta–gamma coupling, many studies have described this phenomenon in different brain regions, in different species, and under different laboratory settings. This suggests that this cross-frequency coordination is a general property of oscillatory neural circuits and that optimal circuit function produces nonlinear coupling between different frequencies of neural activity (He et al. 2010). However, neural data analyses must be carefully done and considered in extracting cross-frequency properties (Aru et al. 2015; Hyafil 2015, 2017; Lozano-Soldevilla 2018). Bringing mechanistic and functional understanding together is clearly needed (Hyafil et al. 2015), and various modeling studies exist (► “[Hippocampus, Model Excitatory Cells](#)”; ► “[Hippocampus, Model Inhibitory Cells](#)”; ► “[Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)”).

Role in Behavior

One function of theta–gamma coupling was proposed in working memory (Lisman and Idiart 1995). During working memory tasks, individuals must maintain several items (words, digits, letters, etc.) in working memory in preparation for subsequent recall. It was proposed that the number of



Hippocampus, Theta, Gamma, and Cross-Frequency Coupling, Fig. 3 (a) Spontaneous, theta–gamma (phase–amplitude) coupling in the subiculum of the isolated hippocampus in vitro. The LFP from the deep layer of the subiculum was filtered in the theta band (3–10 Hz) and in the fast gamma band (100–150 Hz). Note that the amplitude of the gamma rhythms is modulated by a theta frequency, and increases in gamma amplitude occur near the theta peaks, demonstrating theta–gamma, phase–amplitude coupling. (b) Five examples of cross-frequency coupling analysis in different preparations (indicated above). The analysis quantifies the degree of phase–amplitude

coupling for all frequency pairs (phase x-axis vs. amplitude y-axis). The warmer colors indicate stronger coupling (modulation index) between the phase and amplitude. Note the prominent region of phase amplitude coupling near 140 Hz in all cases corresponding to the frequency band known as fast gamma, high-frequency oscillations (HFOs), or epsilon (Schomburg et al. 2012). See Tort et al. 2009 or Tort et al. 2010 (Journal of Neurophysiology) for a description of the details underlying the quantification of the phase amplitude coupling (Panel b is reproduced from Tort et al. (2013) with permission)

gamma cycles within the theta cycle set the limit on working memory capacity (roughly four to seven items). According to this theory, recently encoded items are temporarily stored in working memory by theta–gamma coupling where each item corresponds to one gamma cycle and the temporal order of item encoding is preserved by the order of each gamma cycle within the theta cycle. The encoding of more items would require the slowing of the theta cycle in order to accommodate more gamma cycles and more working memory items (Jensen and Lisman 1996). Recent data by Axmacher et al. (2010) have shown that

theta–gamma coupling is correlated with short-term memory; however, the gamma frequency also slows with increased memory load, suggesting each item to be recalled is not represented by a single gamma cycle as proposed by the original hypothesis (Jensen and Lisman 1998; Lisman and Idiart 1995). Other insights into the function of cross-frequency theta–gamma coupling have come from specifically analyzing the large-scale brain-wide dynamics of theta–gamma coupling during different memory tasks in humans (Fuentemilla et al. 2010; Jacobs and Kahana 2009; Mormann et al. 2005; Sauseng

et al. 2009). Collectively, this growing body of work has shown that when items are maintained in working memory, theta–gamma coupling is present, and the strength of theta–gamma coupling predicts the performance on the task. Additionally, the presentation of specific stimulus features during stimulus presentation is accompanied by distinct theta–gamma “signatures” where the spatiotemporal dynamics of theta–gamma is different for separate stimulus features (Jacobs and Kahana 2009).

Work in rodents has shown that in CA3 theta–gamma coupling increases as rats learn to discriminate between different spatial contexts (Tort et al. 2009). In a separate task, Tort et al. trained rats to use an auditory cue to signal the requirement of either a left or right turn on a T-maze (Tort et al. 2008). The authors found specific theta–gamma signatures at distinct spatial locations within the task maze, and that coupling reaches a maximum at the time when the cue was delivered. In addition, the cross-frequency coupling underwent a different time course in the striatum versus the hippocampus. These studies suggest that there are rapid brain-wide theta–gamma coupling changes that accompany specific parts of the task. Furthermore, this work highlights how hippocampal theta could coordinate the changes in gamma activity in other regions through inter-region theta–gamma coupling, demonstrating a more general function of theta–gamma coupling in long-range brain communication. In this regard, a landmark study has shown that hippocampal theta rhythms phase modulated gamma rhythm generators throughout the entire neocortex (Sirota et al. 2008), posing interesting and challenging new questions regarding long-range hippocampal communication through this form of cross-frequency coupling.

How Is Coupling Produced?

The coordination of both theta and gamma rhythms is most likely an emergent phenomena arising from the large-scale integrative properties of separate rhythm-generating neural networks. Gamma rhythms (Atallah and Scanziani 2009; Cunningham et al. 2003; Fisahn et al. 1998) and theta rhythms (Goutagny et al. 2009; Konopacki

et al. 1987) can be generated locally by different intrinsic hippocampal circuits. Therefore, it has been difficult to investigate the mechanisms of how these two distinct frequencies become coordinated. Mechanistically, theta–gamma coupling can be divided into the microcircuit and macrocircuit levels. Macrocircuit coupling assesses the large-scale coupling mechanisms between regions, for example, theta in one region and gamma in another (Quilichini et al. 2010; Sirota et al. 2008). Microcircuit theta–gamma coupling refers to instances where the same groups of neurons are simultaneously participating in generating both rhythms, for example, in local hippocampal or entorhinal networks where both rhythms are generated (Gloveli et al. 2005; Jackson et al. 2011; Montgomery et al. 2008; Pastoll et al. 2013). These two levels are of course not mutually exclusive, but this dichotomy provides a useful starting point for investigation and discussion of the relevant literature.

At the level of the microcircuit, hippocampal theta–gamma coupling requires pyramidal cells and interneurons, as both cell types fire and are simultaneously phase locked to theta and gamma rhythms (Bragin et al. 1995; Csicsvari et al. 1999; Senior et al. 2008). However, different subtypes of interneurons are likely differentially involved (Klausberger et al. 2003; Klausberger and Somogyi 2008; Lapray et al. 2012; Laszotzci et al. 2011). Bistratified and somatic targeting PV-positive interneurons fire phase locked to gamma rhythms (Tukker et al. 2007) while simultaneously firing phase locked to theta. Other interneuron subclasses such as the SOM interneurons phase lock to theta rhythms without phase locking to gamma (Klausberger et al. 2003; Tukker et al. 2007).

The use of optogenetics has provided the ability to causally test the role of cell types in network activity. Using these tools, it was recently shown that theta–gamma coupling in the MEC can arise through feedback inhibition between fast-spiking (FS) interneurons and layer II stellate cells (SCs) (Pastoll et al. 2013). Simultaneous theta frequency depolarization of both cell types resulted in strong excitation of interneurons, which in turn provided inhibitory feedback to produce rapid

gamma frequency IPSCs to SCs and consequently produced theta–gamma coupling both in the extracellular field potentials and in single cell membrane potential activity. Therefore, in this case the MEC theta frequency drives the occurrence and dynamics of gamma activity. In this model, theta–gamma coupling does not require synaptic connections between excitatory neurons. However, theta–gamma coupling was reduced by blockade of glutamatergic synaptic transmission because of the reduced drive onto inhibitory interneurons.

At the macrocircuit level, theta–gamma cross-regional coupling is even less well understood. Although it is well known that theta phase in the hippocampus coordinates gamma frequency activity in the striatum (Tort et al. 2008) and throughout the rostral–caudal neocortical axis (Sirota et al. 2008), very few studies have systematically tried to decipher the anatomical basis of this form of interregional brain coordination. Hippocampal outputs are mainly excitatory; however, recent data has shown long-range inhibitory–inhibitory connections from hippocampus to extra-hippocampal regions (Jinno et al. 2007) as well as GABAergic cells connecting different regions of the hippocampal formation itself (Ceranik et al. 1997; Melzer et al. 2012). It remains to be determined exactly how hippocampal theta rhythms coordinate gamma throughout numerous extra-hippocampal structures, and therefore, future experiments with cell-type-specific inactivation techniques will be required to test the mechanisms of long-range cross-frequency coupling.

Conclusions

Theta and gamma rhythms are the main oscillatory electrophysiological patterns found in the hippocampus and temporal lobe. Different forms of theta and gamma arise in different behavioral states and from different anatomical pathways and synaptic mechanisms. The coordination between frequencies can arise from coupling between theta and gamma rhythm generators, and different regions likely have

different coupling mechanisms which reflect the unique neural architecture of each region. Collectively, the simultaneous generation of these two rhythms shapes the spike timing of nearly all the pyramidal cells and interneurons in the hippocampus. Therefore, these network patterns are of utmost importance for temporal lobe functions such as episodic memory.

Cross-References

- [Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)
- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Hippocampus, Model Excitatory Cells](#)
- [Hippocampus, Model Inhibitory Cells](#)
- [Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)

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Hodgkin-Huxley Model

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Synonyms

Action potential model; Squid axon model

Definition

The Hodgkin-Huxley model is a mathematical model of current flow through ion-selective channels in neural membrane. Hodgkin and Huxley were able to describe the time behavior of the

intracellular membrane potential and the currents through potassium (K) and sodium (Na) channels with simple first-order ordinary differential equations. This was done using parameters fitted from their ► **“Voltage Clamp Technique”** measurements on the giant axon of the squid. With this model, they quantitatively described the generation of action potentials by current injection and observable behavior such as the *refractory period* and the *anode break* phenomenon. With other sets of parameters, the Hodgkin-Huxley model has been used to describe many other types of voltage-dependent ion channels and has become a standard technique in *compartmental modeling* of neurons.

Detailed Description

Background

In a series of five classic papers published in 1952, Alan Hodgkin and Andrew Huxley, along with Bernard Katz (Hodgkin et al. 1952; Hodgkin and Huxley 1952a, b, c, d), described the results of experiments on an isolated segment of the giant axon from the squid *Loligo*. For these experiments and the resulting model, Sir Alan Hodgkin and Sir Andrew Huxley were awarded the Nobel Prize in Physiology and Medicine in 1963 (shared with Sir John Eccles for his work on synaptic transmission).

Although these results, and the model that gives them a quantitative description, were concerned with the generation and propagation of action potentials in the squid axon, they form the basis of our understanding of neuronal firing in general. The story of the relationship between experiment, theory, and numerical simulation in these papers exemplifies the way that computational neuroscience combines experimental and theoretical approaches to use simulation as a tool for understanding neural systems.

The squid giant axon is specialized for the rapid conduction of action potentials that are used to trigger contractions in the squid mantle, as an escape reflex. A short piece of the axon with the ends tied off, and immersed in seawater, was the ideal preparation for these pioneering

experiments because the large diameter of 0.5 mm allowed its exploration with the tools of the time and because the variable conductance of its membrane was dominated by just two currents, sodium (Na) and potassium (K), rather than the dozens of ionic current types found in most neurons.

In this *voltage clamp* experiment, two thin silver wires were inserted along the length of the axon for 30 mm. One was used to record the internal membrane potential relative to the exterior solution. The other was connected to a feedback amplifier that measured the difference between the membrane potential and a desired “control voltage” and that injected the proper amount of current through this electrode to maintain the membrane potential at the control voltage. With this arrangement, Hodgkin and Huxley were able to measure the current needed to maintain the membrane potential at any particular level and indirectly calculate the channel conductances.

This was done with a series of voltage clamp experiments that measured both the total current and the current when the Na conductance was disabled. They eliminated the sodium current by replacing the seawater with a solution containing choline instead of sodium chloride. Modern experiments use a puffer fish neurotoxin tetrodotoxin (TTX) to block the sodium channels.

During more than 60 years since the publication of this work, many varieties of sodium-, potassium-, and calcium-selective channels, including calcium concentration-dependent potassium channels, have been discovered and studied in a wide variety of neurons. These occur in the soma and dendrites of the cells as well as the axon and are responsible for the wide variety of observed neuronal firing patterns. With appropriate parameters obtained from voltage clamp experiments, variations of the Hodgkin-Huxley model are used to simulate their behavior in detailed models of neurons.

Basis of the Model

At the time, little was known about the nature of the cell membrane or even the existence of

channels through which ions could pass. It was known that the membrane was semipermeable to ions and that it surrounded a conducting cytoplasm of comparatively low resistance. In effect, it acted like a leaky cylindrical capacitor.

Figure 1 illustrates the conceptual model behind the mathematical model.

It was also known that the concentration of sodium ions is greater outside the axon, so they have a tendency to enter. The concentration of potassium ions is greater on the inside, so they tend to leave. Metabolic processes within the cell called ionic pumps maintain this balance of concentrations.

Because of the difference in ionic concentrations, when the cell is at rest and the axon is not firing action potentials, the interior is polarized to a membrane potential E_{rest} of about 70 mV negative from that outside. This produces an attractive electrostatic force on the positively charged ions, in addition to the diffusive force produced by the concentration gradients.

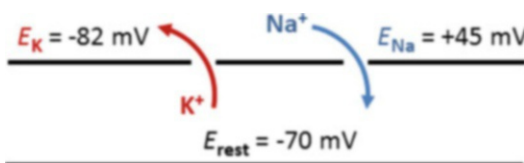
Due to its higher exterior concentration, Na has a tendency to enter the cell unless the membrane potential is raised to a high enough value so that the electrostatic repulsion of the ions cancels the osmotic force of diffusion. Hodgkin and Huxley (1952a) applied the ► “Nernst Equation” to calculate this *reversal potential* or *equilibrium potential* E_{Na} from the known interior and exterior Na concentrations and found it to be about 45 mV positive with respect to the extracellular potential. Likewise, this competition between osmotic and electrostatic forces means that potassium will tend to leave unless the membrane potential falls below the negative reversal potential E_{K} of about -82 mV relative to the exterior. Most neuroscience textbooks (e.g., Kandel et al. 2000) explain how these equilibrium potentials are calculated from the

Nernst equation and the how the rest potential can be calculated from what has become known as the Goldman-Hodgkin-Katz voltage equation.

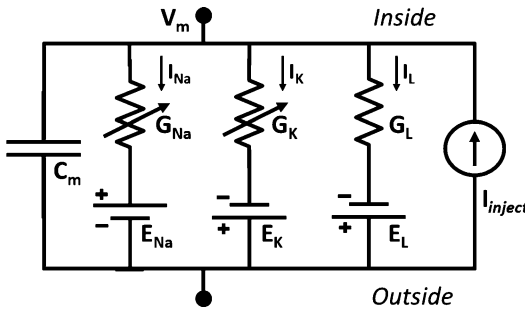
At this time, it was only their hypothesis that the interplay of the Na and K currents was responsible for the production of the action potential. From the results of the their experiments, they reasoned (and demonstrated quantitatively with their model) that depolarization of the cell (an increase in membrane potential relative to the outside) causes Na-selective channels to open, allowing Na ions to enter. This raises the potential, further increasing the conduction of the Na channels, and causes the neuron to fire an action potential. Eventually, the Na channels inactivate, and K-selective channels begin to open, causing a flow of charge out of the cell, ending the action potential. This is followed by a period of hyperpolarization to a potential below the resting potential, which is responsible for the “refractory period” during which another stimulus is unable to cause an action potential.

In Part I of the final paper of the series, Hodgkin and Huxley (1952d) reviewed the experimental results from the previous papers. They saw that the observed changes in permeability of the membrane depended on the membrane potential, and not on the current through the membrane. The channels acted in accordance with Ohm’s law, with a current proportional to the voltage drop across a channel conductance. The voltage drop for a particular ionic conductance would be the difference between the membrane potential and the equilibrium potential for that ion. That led to a model based on an electrical circuit similar to the one shown in Fig. 2.

In this figure, V_m represents the membrane potential at a point inside the axon, relative to a point outside the cell in the seawater or other extracellular fluid. The relatively nonconducting cell membrane that separates the conducting cytoplasm from the surrounding solution acts as a membrane capacitance C_m in parallel with the resistors and batteries. The membrane capacitance can be charged or discharged as current flows into or out of the compartment, changing the value of V_m . This current can come from the passage of ions through ion channels or from a current I_{inject}



Hodgkin-Huxley Model, Fig. 1 Ion flow in the Hodgkin-Huxley model



Hodgkin-Huxley Model, Fig. 2 The equivalent electrical circuit of the Hodgkin-Huxley model

through the injection electrode inserted into the axon segment.

The resistor symbols with the arrows through them represent the two variable conductances for Na and K ions. The fixed “leakage conductance” G_L represents conductance of passive channels, primarily selective for chloride ions, that have little or no voltage dependence. By convention, these are represented by a conductance, G , rather than a resistance, $R = 1/G$. Each one of these conductances has an associated equilibrium potential represented by a labeled battery.

In Part II, Hodgkin and Huxley went on to construct the mathematical model corresponding to this circuit.

The Mathematical Model

Electrical circuit theory states that the rate of change of the voltage across the capacitance is proportional to the net current that is applied to charge it, or

$$C_m \frac{dV_m}{dt} + I_{\text{ion}} = I_{\text{inject}} \quad (1)$$

where the ionic current through the three conductances is

$$I_{\text{ion}} = G_{Na}(V_m - E_{Na}) + G_K(V_m - E_K) + G_L(V_m - E_L) \quad (2)$$

These may be combined to give

$$C_m \frac{dV_m}{dt} = G_{Na}(E_{Na} - V_m) + G_K(E_K - V_m) + G_L(E_L - V_m) + I_{\text{inject}} \quad (3)$$

Readers who are familiar with electrical circuit theory may wonder why the ionic current appears on the left-hand side of Eq. 1 and why the arrows labeled with currents in Fig. 2 point from the inside to the outside. Normally, one would expect that currents that enter the cell segment, charging the capacitor to a higher potential, will be considered as positive in sign. This is the case with injection currents and with currents from neighboring segments when the circuit is extended for *compartmental modeling* of neurons. However, Hodgkin and Huxley used what has been called the “physiologists’ convention” in referring to ionic currents as positive when they are outward, not inward. Perhaps this convention arose because the currents being measured were those being provided by the clamp circuitry (I_{inject}) and are equal and opposite to the total ionic current when the voltage is held constant.

Another convention to note is that Hodgkin and Huxley gave all voltage measurements relative to the resting potential of the axon interior. Figure 1 reflects the modern convention of measuring potential differences with respect to the exterior medium. This results in the value $E_{\text{rest}} = -70$ mV and the equilibrium potentials shown in the figure. The Hodgkin-Huxley convention measures these relative to $E_{\text{rest}} = 0$.

Note that Eq. 3 will be the same, no matter which sign convention is used or which value is used as the reference for measurements of potential. Some neural simulators, such as GENESIS (Bower and Beeman 1998, 2003; Cornelis et al. 2012), consider all inward currents, including ionic currents, to be positive. The plots in the simulation examples that are shown in this entry use the Hodgkin-Huxley conventions for current sign and membrane potential.

In order to solve this equation for the time behavior of V_m , given a specified injection current, it was necessary to find equations for the time and voltage behavior of the Na and K conductances, using parameters fitted from the

voltage clamp experiments. This was the most significant aspect of the model. By performing the experiments with different values of the clamp voltage, they were able to determine the time dependence and equilibrium value of the conductances at different voltages.

Figure 3, reproduced from Hodgkin and Huxley (1952d), shows the behavior of the K conductance when the voltage is stepped to 25 mV above the rest potential and then brought back down to the rest potential. For different clamping voltages, they found different values of the maximum conductance and different time behaviors.

It would be tempting to fit the rise of the conductance to an exponential function of time, but the experimental measurements were best fitted by an exponential to the fourth power. They were able to fit the K conductance to an equation of the form

$$G_K = \bar{g}_K n^4 \quad (4)$$

where n is a dimensionless variable with values from 0 to 1, referred to here as the “activation state variable” for K. $\bar{g}_K$ is the scaling factor for K conductance, which Hodgkin and Huxley expressed in units of millimho/cm². The modern unit for conductance is Siemens (the inverse of ohm), so this would be mS/cm².

They postulated that the time behavior of n was given in terms of two voltage-dependent parameters $\alpha_n(V)$ and $\beta_n(V)$ with the differential equation

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n \quad (5)$$

Under the voltage clamp conditions shown in Fig. 3, this equation has a simple solution, governed by a single time constant τ_n for the value of n as the voltage is stepped upward:

$$n(t) = n_\infty(V) - (n_\infty(V) - n_\infty(0))e^{-t/\tau_n}. \quad (6)$$

Here, $n_\infty(V)$ represents the value of n after a long period of time after a step to voltage V , corresponding to its maximum conductance value shown in the figure. $n_\infty(0)$ corresponds to the steady conductance value at the rest potential before the voltage step. The quantities $n_\infty(V)$ and $\tau_n(V)$ are related to $\alpha_n(V)$ and $\beta_n(V)$ by

$$n_\infty(V) = \alpha_n(V)/(\alpha_n(V) + \beta_n(V)) \quad (7)$$

and

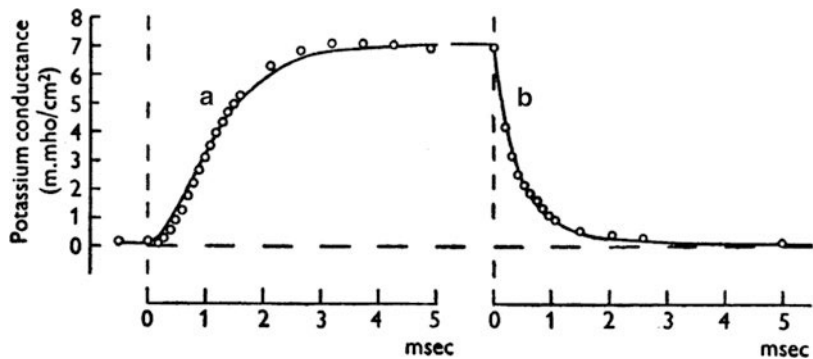
$$\tau_n(V) = 1/(\alpha_n(V) + \beta_n(V)) \quad (8)$$

The injection current is known, the leakage current depends only on the voltage and a constant value of conductance, and the Na current was eliminated. Thus, Hodgkin and Huxley could fit the values of G_L , $\bar{g}_K$, $\alpha_n(V)$ and $\beta_n(V)$ by using different values of the clamp voltage in the absence of Na ions.

Their fit for the Na conductance was a little different, because they found that at a fixed voltage, the conductance rose with time and then decreased exponentially with time, even when the clamping voltage was maintained (Hodgkin and Huxley 1952c). This required a fit to the equation

$$G_{Na} = \bar{g}_K m^3 h \quad (9)$$

Hodgkin-Huxley Model,
Fig. 3 (a) Rise of potassium conductance associated with a depolarization of 25 mV and (b) fall of potassium conductance associated with a repolarization to the resting potential. (Reproduced from Hodgkin and Huxley (1952d), Fig. 2)



Here, m is the activation variable for Na, and h is called the “inactivation state variable,” because it becomes smaller when m (and the membrane potential) becomes larger. m and h obey equations similar to the ones for n but with different voltage dependences for their steady-state values and time constants.

By conducting a similar series of voltage clamp experiments in the presence of Na, Hodgkin and Huxley were able to measure the Na current in isolation by subtracting the currents that were measured without Na. The resulting parameter fits resulted in the equations

$$\alpha_n(V) = \frac{0.01(10 - V)}{\exp\left(\frac{10 - V}{10}\right) - 1} \quad \beta_n(V) = 0.125 \exp(-V/80)$$

$$\alpha_m(V) = \frac{0.1(25 - V)}{\exp\left(\frac{25 - V}{10}\right) - 1} \quad \beta_m(V) = 4 \exp(-V/18)$$

$$\alpha_h(V) = 0.07 \exp(-V/20) \beta_h(V) = \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1}$$

The model is then fully specified with the following parameters (the reversal potentials are measured relative to the rest potential; see above):

$$C_m = 1.0 \mu\text{F}/\text{cm}^2; E_{Na} = -115 \text{mV}; E_K = +12 \text{mV}; E_L = -10.613 \text{mV}$$

$$\bar{g}_{Na} = 120 \text{ mS}/\text{cm}^2; \bar{g}_K = 36 \text{ mS}/\text{cm}^2; \bar{g}_{leak} = 0.3 \text{ mS}/\text{cm}^2$$

This detailed model of the behavior of the Na and K conductances during a voltage clamp experiment was a remarkable accomplishment. But the outstanding success of the Hodgkin-Huxley model was revealed in the third and final part of the fifth paper (Hodgkin and Huxley 1952d).

Reconstruction of Nerve Behavior

The preceding analysis and parameter fitting were applied to the solution to Eq. 3 for V_m and the coupled equations for conductances under a very unnatural stimulus, the voltage clamp. If this model correctly represents the ionic currents that are responsible for the behavior of the axon, it should be able to predict and help understand the behavior under more natural conditions of greater interest.

In Part III, Hodgkin and Huxley described their numerical solution to the coupled differential equations. The calculations were carried out on “hand-crank” mechanical calculators using a step-by-step iterative process of calculating V_m from Eq. 3 for a step forward in time, calculating new values of the state variables n , m , and h , and repeating. It took weeks to produce the results.

After verifying that their model gave an acceptable fit to the voltage clamp experiments, they went on to correctly calculate the form of the action potentials produced by a depolarizing injection pulse and quantitatively described the *refractory period* during which an axon or cell cannot be stimulated to produce an action potential and the phenomenon of *anode break*.

All of this was done with no changes to the parameters that were used to reproduce the voltage clamp results. This principle of fitting parameters to “function-neutral” experiments that are not directly related to the behavior of interest is an important one in computational neuroscience (Bower 1995). If a computational model produces behaviors that were not used to generate the model, it is possible to have some confidence that the underlying hypotheses are correct.

By the time-consuming laborious manual step-by-step numerical integration of the equations, Hodgkin and Huxley were able to plot the membrane potential during the course of an action potential and the behavior of the state variables n , m , and h . From these plots, it is possible to understand the details of action potential generation. Now, anyone with a little programming experience can reproduce and study the Hodgkin-Huxley model. The model has also

been implemented as an example or tutorial in nearly every neural simulator package.

The examples given here were generated with the GENESIS simulator (Bower and Beeman 1998, 2003) using the “Squid” Tutorial that was developed by Mark Nelson (Nelson and Rinzel 1998). The screen images are taken from a set of online lecture notes by Beeman (2008).

Reproduction of the Voltage Clamp Experiments

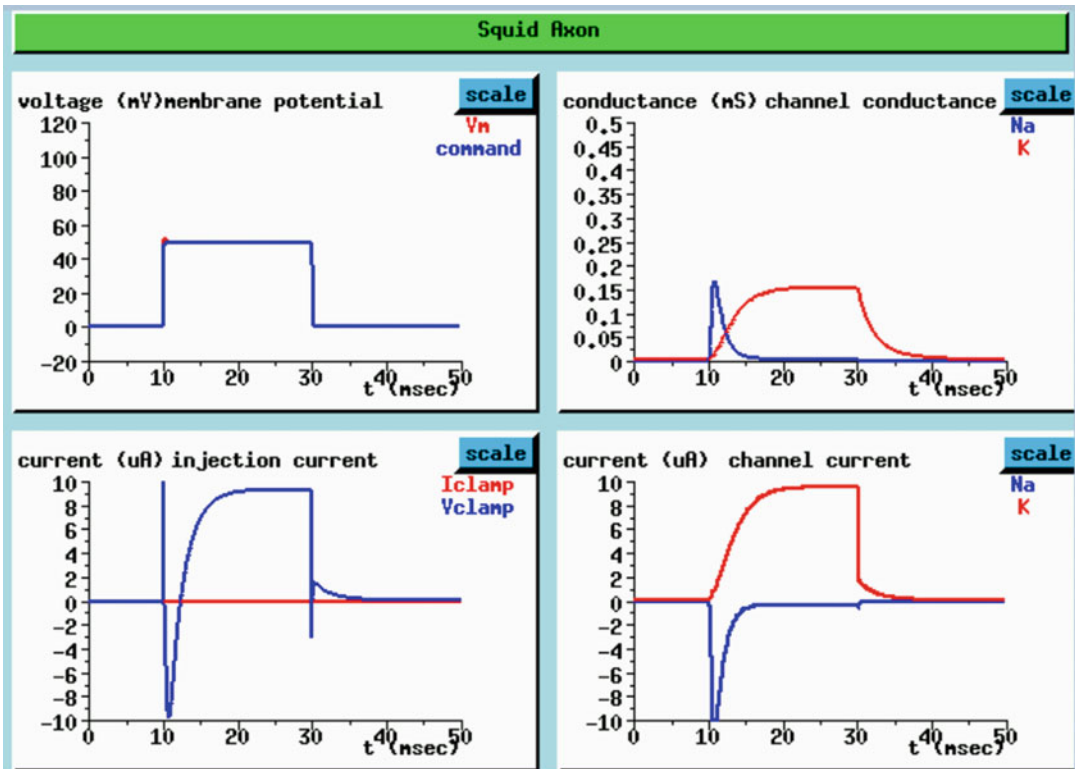
Figure 4 shows screen images from a GENESIS simulation of a voltage clamp experiment. Here, the membrane potential is held at the resting potential for 10 ms, then rapidly raised to 50 mV above the rest potential, and held for 20 ms before returning to the rest potential. In accordance with

the original Hodgkin-Huxley conventions, voltages are measured in mV with respect to the resting potential of 0, and outward ionic currents are plotted as positive.

The plots at the *UPPER LEFT* show both the “command voltage” that is applied to the voltage clamp circuitry and the resulting membrane potential. A step from the resting potential of 0–50 mV is applied after 10 ms. Note the slight difference between the two plots at the top of the step. The simulated voltage clamp circuitry follows the behavior of that used in the experiments and cannot change the membrane potential instantly.

The *LOWER LEFT* plot shows the injection current used to maintain this voltage. The very sharp initial spike is due to the large current needed to quickly charge the membrane capacitance to the clamp voltage. This can be seen from

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Hodgkin-Huxley Model, Fig. 4 Simulation of a voltage clamp experiment using the Hodgkin-Huxley model. (Reproduced from Beeman (2008) with permission from the author)

Eq. 1, where dV_m/dt is nearly infinite during the voltage step. It is followed by an inward Na current, shown as a negative current here, then an outward K current.

The channel conductance plots at the *UPPER RIGHT* reveal a rapid rise in the Na conductance, followed by a slower decay as it becomes inactivated. The K current has a much slower activation and no inactivation. There is no decay until the voltage is dropped back to zero. These conductance changes result in the channel currents shown in the *LOWER RIGHT* plots. Because the Na equilibrium potential is greater than the resting potential, the Na current flow is inward (negative). The superposition of these two currents plus the initial capacitive current gives the injection current shown at the *LOWER LEFT*.

In an actual experiment, the currents would be measured directly, separating the K current from the total current by blocking or disabling the Na current. It would then be possible to calculate the conductances, which are plotted here. In the simulation, it is done the other way around.

From the values of the conductances the channel activation and inactivation variables can be calculated and plotted. Figure 5 shows a window from the Squid Tutorial that plots these during the voltage clamp.

Notice the value of m^3 at the resting potential and the time behavior during the steps to 50 mV and back down to rest. Initially, there is a balance between the inward Na current, the outward K current, and the leakage current. At the resting potential, m (black) is small, and h (red) is fairly large. Thus, m^3h is small, but nonzero. The

K activation n (blue) is moderate in size, but is also small when raised to the fourth power.

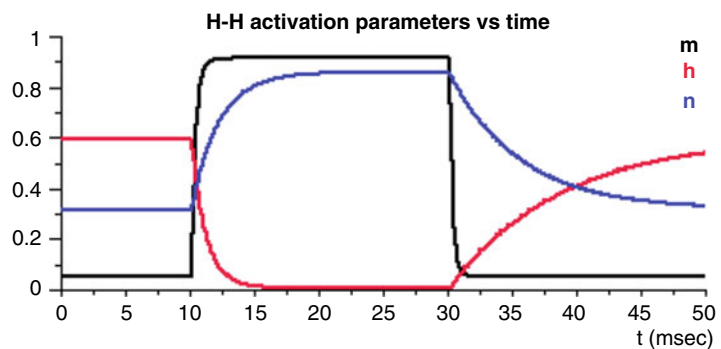
At the start of the voltage step, the depolarization causes m to increase as the Na channels open. After about 2 ms, the Na conductance inactivates and h decreases. While this is happening, the K conductance activates and n increases, leveling off to a steady value.

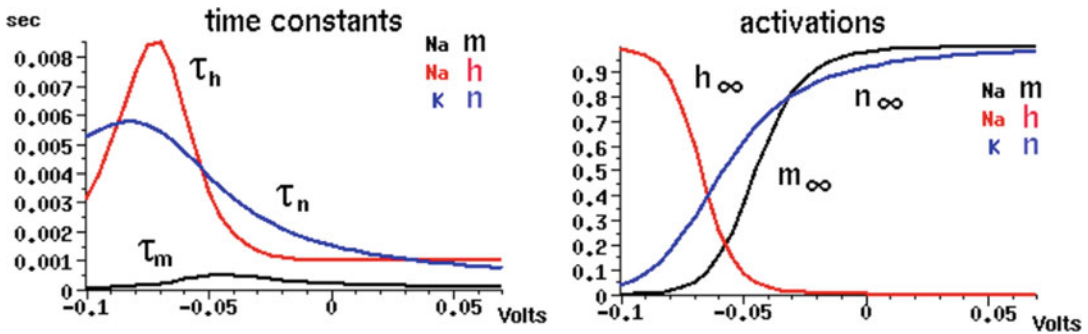
At the end of the pulse, n steadily declines toward its resting value, the Na activation rapidly drops to its original value, and the inactivation slowly returns to its original value. Note that the sodium inactivation and the potassium activation take much longer to reach their steady-state values than the sodium activation.

The key to understanding the role of these currents in the production of action potentials is to keep in mind the way that the steady-state values of the activation and inactivation variables depend on voltage and the relative magnitudes of their time constants for reaching steady state. Figure 6 shows a plot of these variables and their voltage-dependent time constants for various clamp voltages. In this plot, the resting potential is taken as -70 mV, instead of zero.

Notice that although the time constants depend strongly on voltage, the time constant for the Na activation variable m is about an order of magnitude less than that for the Na inactivation h and the K activation n throughout the entire range. This means that during an action potential, when the voltage is high and m is large, and h is supposed to be small, it will take a while for h to decrease. Also, it will take n some time to become large and contribute to the opposing K current. If it were not

Hodgkin-Huxley Model,
Fig. 5 Plots of the activation and inactivation variables during the voltage clamp: m (black), h (red), n (blue). (Reproduced from Beeman (2008) with permission from the author)





Hodgkin-Huxley Model, Fig. 6 Plots of the steady-state activation variables and time constants as a function of clamp voltage. (Reproduced from Beeman (2008) with permission from the author)

for the slower behavior of h , m^3h would be close to zero after the start of depolarization from -70 mV, and it would never be large enough to give the Na conductance needed for an action potential to form.

Post-Inhibitory Rebound

Hodgkin and Huxley's reconstruction of the action potential during a depolarizing current injection was an impressive test of the model. An even more interesting experiment is their recreation of the *anode break* or *post-inhibitory rebound* phenomenon which had been observed in squid axons after a hyperpolarizing current pulse.

Figure 7 shows plots from a simulation in which a brief current pulse of -0.1 microamperes is applied after 10 ms and held it for 20 ms. What behavior would you expect?

The plot of the membrane potential (*UPPER LEFT*) shows the typical curve for charging a capacitor with a negative current during the hyperpolarizing pulse. It starts to discharge at the end of the pulse, but instead of leveling off to the resting potential, we see a full-blown action potential, followed by hyperpolarization and then a return to the rest potential.

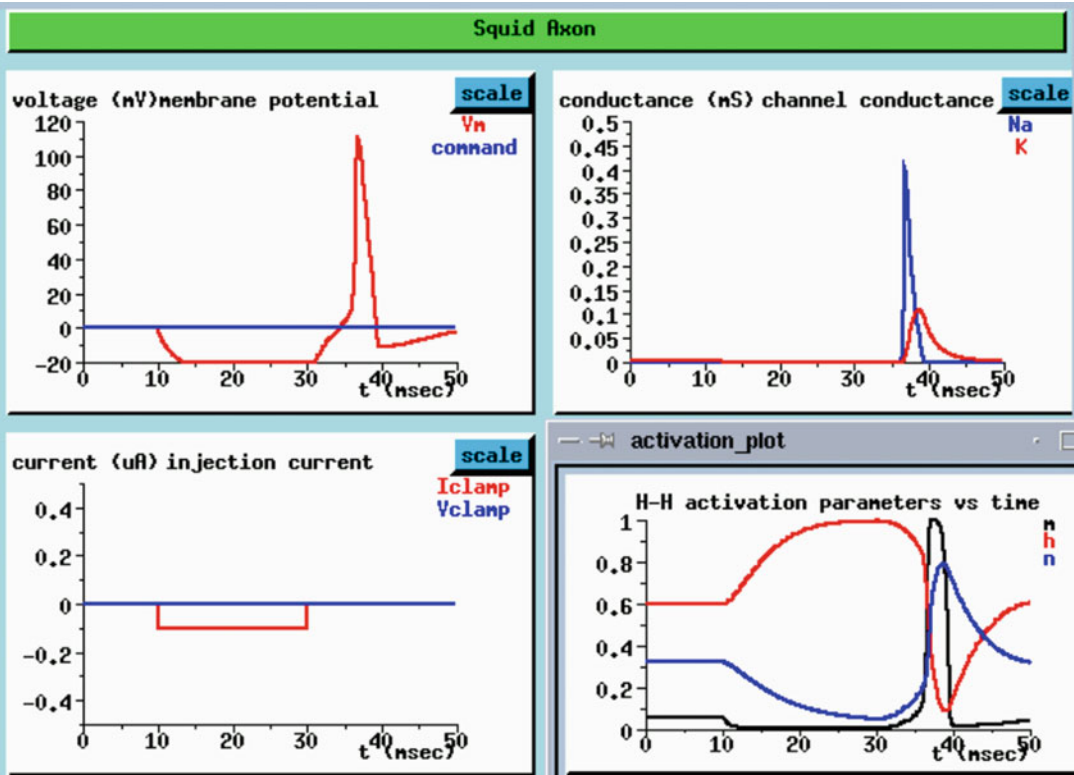
The channel conductance plots (*UPPER RIGHT*) show the conductances that one associates with an action potential – there is a sharp peak in Na conductance, followed by a broader delayed peak in the K conductance. This causes an

outward flow of current which terminates the action potential and causes the hyperpolarization. Many people find this result surprising. How can an inhibiting (hyperpolarizing) current produce an action potential if lowering the membrane potential causes the channel activations to decrease?

The plot of the activation and inactivation parameters (*LOWER RIGHT*) provides an explanation of what is happening. Before the hyperpolarizing pulse, the steady-state resting potential value of the Na activation parameter m is fairly low. The inactivation parameter h is moderately high, but the Na conductance is proportional to m^3h , so it is small and a small Na current flows into the compartment. n is small (about 0.35), so n raised to the fourth power is relatively small, and there is a slight K current in the opposite direction of the Na current.

From 10 to 30 ms, during the pulse, the cell becomes hyperpolarized, and m gets even smaller, becoming essentially zero. Although h increases, the resulting Na current is nearly zero.

At 30 ms, when the pulse has ended, the Na activation parameter m rapidly starts to increase toward its original small value. However, when it gets there, h is still very large, because of its much larger time constant for reaching its final value. This causes an increase in the Na conductance, which raises the membrane potential and allows m to increase even more. Near the peak of the action potential, h has finally decreased, and the K activation parameter n (in blue) has built up, so the action potential ends. The large value of n , and the resulting outward flow of potassium ions,



Hodgkin-Huxley Model, Fig. 7 A hyperpolarizing pulse produces anode break excitation. (Reproduced from Beeman (2008) with permission from the author)

accounts for the hyperpolarization following the action potential.

Refractory Period

Understanding this period of hyperpolarization is the key to understanding the *refractory period*, which was also analyzed by Hodgkin and Huxley. An examination of the plot of the activation state variables after the end of the action potential shows that shortly after the end of the action potential, the Na activation parameter rapidly decreases to near its resting potential value. But the inactivation parameter h is still very low, and the K activation parameter n is relatively high. It takes about another 10 ms before they get back to their original values. This interval is called the refractory period.

What would happen if we applied a depolarizing pulse during the refractory period? Imagine what would happen if the pulses were at 5 ms intervals. Not only would it be hard to get enough Na conductance to raise the membrane potential above threshold, but there would be a large K current in the opposite direction, tending to keep the cell hyperpolarized. Experiments with the simulation will confirm that at least 10 ms is required between action potentials.

Biological Basis of the Hodgkin-Huxley Model

The biological basis for the model described by Figs. 1 and 2 is now well known and understood. But is there a biological basis for the Hodgkin-Huxley form of the conductance equations? In

their model, the fourth power exponent for K activation in Eq. 4 and the third power for Na in Eq. 9 were obtained from a best-fit approximation to conductance data. They provided an explanation, but cautioned (Hodgkin and Huxley 1952d): “For the sake of illustration we shall try to provide a physical basis for the equations, but must emphasize that the interpretation given is unlikely to provide a correct picture of the membrane.”

They went on to assume that potassium ions can only cross the membrane when four similar particles occupy a certain region of the membrane. n represents the fraction of the particles in a certain position and $(1 - n)$ the fraction that are somewhere else. Then, Eq. 5 may be interpreted as a rate equation for the transition between these two states. n^4 would then be the probability that all gating particles are in the appropriate positions. They explained the Na conductance in similar terms, assuming that G_{Na} is proportional to the number of sites on the inside of the membrane which are occupied simultaneously by three activating molecules, but are not blocked by an inactivating molecule. The rates of transition between these states are given by similar rate equations for m and h .

At the time, very little was known of the nature of the cell membrane. It is notable that Hodgkin and Huxley did not use the word “channels” to describe the selective conductivity for Na and K.

During the 1960s and 1970s, Hille, Armstrong, and others introduced the idea that the two currents are carried by specific ion channels and proposed models for their ion selectivity and function. However, there was no information available at that time on the actual structure of the proteins that form the channels through the lipid membrane of the cell.

► “Patch Clamp Techniques” have provided detailed information about the response of single channels to depolarization. Measuring the current from individual channels revealed the all-or-none opening of voltage-gated channels. The continuous values of conductance predicted by the Hodgkin-Huxley model are produced by the

average behavior of very many single-channel openings and closings. More recently, Markov models (► “Markov Models of Ion Channels”) of channel dynamics have been developed that are suitable for simulations when the number of channels in a region is small enough that the fluctuations in average conductance become important.

There has been considerable progress in our understanding of the structure and function of the sodium channel, summarized in a recent review by Caterall (2012). Through the 1970s, several laboratories used neurotoxins to modify channel conductance and to identify the protein subunits of the Na channel. X-ray crystallographic and other structural analyses have now been applied to membrane proteins with a resolution down to the size of single atoms. Cloning and DNA sequencing the subunits of Na channels have provided another tool. Genes for most of the major channels have been cloned or sequenced. This information has been used to create models of the different channel proteins and to study the effects of alterations of their structure.

As a result of these studies of the Na channel protein, the voltage-dependent activation is understood in terms of the outward movement of identified gating charges, the “gating particles” of Hodgkin and Huxley. The mechanism for fast inactivation is also now understood, with functional and structural evidence for the closure of a fast inactivation gate. Although the details are much more complex than envisioned by Hodgkin and Huxley, and the “particles” are neither identical nor independent, the Hodgkin-Huxley paradigm of a small integer number of gating particles controlling the passage of ions was essentially correct.

Cross-References

- GENESIS, the GEneral NEural SIMulation System
- Markov Models of Ion Channels
- Nernst Equation

- Patch Clamp Technique
- Voltage Clamp Technique

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Hopfield Network

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Synonyms

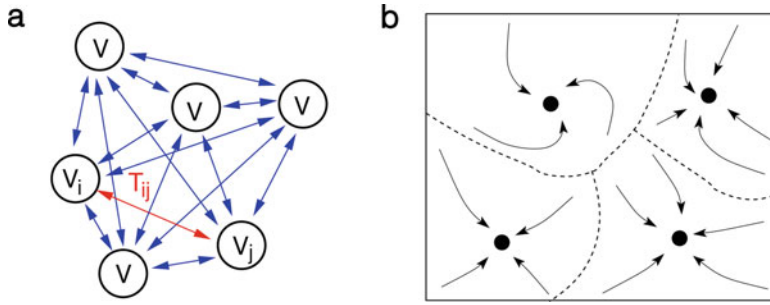
Attractor neural network; Binary neural network; Equilibrium neural network; Recurrent neural network

Definition

Hopfield model was originally introduced as the representation of a physical system, whose state in a given time is defined by a vector $\mathbf{X}(t) = \{X_1(t), \dots, X_N(t)\}$, with a large number of locally stable states in its phase space, namely, $\mathbf{X}_a$, $\mathbf{X}_b, \dots$, also called *attractors*. Starting from some initial condition within the basin of attraction of one of these minima, that is, $\mathbf{X}(0) = \mathbf{X}_a + \Delta$, the dynamics leads the system toward this minimum, that is, $\mathbf{X}(t \rightarrow \infty) \approx \mathbf{X}_a$. The model provides a rule to convert any prescribed set of system states, the so-called *memory states*, into some of these locally stable states that now carry predefined information. This procedure allows the use of the model as a general content addressable memory system. The way the system reaches one of these memories from some initial state, which falls within its basin of attraction, then determines the so-called *associative memory process* (see Fig. 1b).

Detailed Description

In the original article where the model is proposed (Hopfield 1982), the state of the physical system



Hopfield Network, Fig. 1 (a) Scheme representing a Hopfield neural network where the processing devices or neurons are represented by open circles with states defined by V_i and symmetric connections among neurons are represented by bidirectional arrows. (b) Cartoon representing a hypothetical phase space for the Hopfield

network with a set of attractors states (black circles) and their corresponding basins of attraction separated by dashed lines. The curved arrows represent possible trajectories to reach the attractors from some given initial conditions

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is defined as the state of N processing devices or *neurons*, each one having two possible states, namely, $V_i = 1$ (representing a firing neuron at maximum rate) and $V_i = 0$ (which represents a not firing neuron). The instantaneous state of the system then is defined by the vector $\mathbf{V}(t) = \{V_1(t), \dots, V_N(t)\}$ being, therefore, 2^N possible states of this type. When two neurons i and j are connected, it says there is a *synapse* among them, and the strength of such connection is defined as T_{ij} which, therefore, represents the state of such synapse. If the connection is not present then $T_{ij} = 0$. This defines the model as a neural network (see Fig. 1a). Moreover, the model assumes that the connection strengths T_{ij} include some information concerning a particular set of system states $\mathbf{V}^s$, $s = 1, \dots, n$, through the *storage prescription* (also known as learning rule)

$$T_{ij} = \sum_s (2V_i^s - 1)(2V_j^s - 1) \quad i \neq j \quad (1)$$

$$T_{ij} = 0 \quad i = j.$$

With this prescription, each neuron is connected to others neurons in the network except itself defining the so-called *fully connected network* or a *recurrent network*. The model also assumes that for each neuron there is a fixed threshold U_i for firing, so the dynamic of the physical system becomes

$$V_i = 1 \quad \text{if} \quad \sum_j T_{ij} V_j > U_i$$

$$V_i = 0 \quad \text{if} \quad \sum_j T_{ij} V_j < U_i \quad (2)$$

where the sum $\sum_j T_{ij} V_j$ is also referred as *local field*. When the model is used to study biological systems such as a neural medium, the local field is interpreted as the *synaptic current* received by a postsynaptic neuron connected with N presynaptic neurons with T_{ij} being the effectiveness of synapse (i, j) and therefore related to its synaptic conductance. The precise form of T_{ij} given in the prescription (1) can be related with modifications in time of the synaptic strength during *pairing* or training experiments which define the so-called Hebbian learning (Hebb 1949). More precisely, after the training of a particular activity state $\mathbf{V}^s$, the activities $V_i^s(t)$ and $V_j^s(t)$ of two neurons linked by a synapse induce a modification of the maximal conductance of this synapse in an amount

$$\Delta T_{ij} \propto \left[(2V_i^s(t) - 1)(2V_j^s(t) - 1) \right]_{\text{average}},$$

where the average is over the past history of both neurons. Note that the modification is positive if the training of the state s implied a positive correlation between the activities of both neurons (both

are firing) and negative on the contrary (one neuron is firing and the other is silent).

The Updating Scheme

In the original version of the model, the dynamics of each neuron is chosen to be asynchronous, random, and deterministic (i.e., in absence of noise). More precisely, each time step, a neuron is chosen at random (or using a predefined sequence) within the population and updated deterministically using rule (2). This type of neuron update is also known as *sequential updating* (Peretto 1992). There are, however, other types of updating schemes often used in the literature such as the updating of all neurons synchronously each time step, also known as *parallel updating* (Peretto 1992), or each time step choosing at random a subset of neurons within the population and updating them synchronously, also known as *hybrid updating* (see, for instance (Torres et al. 2008)). Different updating schemes determine different ways of convergence of the system toward its steady state.

Memory Capacity

In its pioneering work, Hopfield numerically computed that there is a maximum number n_c of network states V° that can be stored in network according to the prescription (1) and retrieved without severe errors. This number scaled with the size of the network as $n_c \approx 0.15 N$ for networks sizes ranging from $N = 30$ to 100 neurons. To obtain this number, Hopfield assumes that the network stored unbiased random patterns. Posterior numerical simulations of larger Hopfield networks and its extrapolation to $1/N \rightarrow 0$ resulted in a value of $n_c \approx 0.14 N$ (Volk 1998) which agrees with a theoretically value of $n_c = 0.138 N$ obtained within a statistical physics mean-field approach (Amit et al. 1987). This memory capacity can be increased assuming some conditions over the network topology and the stored patterns.

Hamiltonian Description

The Hopfield model admits a Hamiltonian description assuming that the connection strengths are symmetric $T_{ij} = T_{ji}$. In this case, one can define an energy function

$$H(\mathbf{V}) = -\frac{1}{2} \sum_{i \neq j} T_{ij} V_i V_j + \sum_i U_i V_i \quad (3)$$

describing the configurational state of the network, and which is isomorphic to the well-known long-range Ising Hamiltonian in the presence of a magnetic field when $T_{ij} = T_0 \forall ij$ and $U_i = U \forall i$. Within this framework, the term $\sum_j T_{ij} V_j - U_i$ is interpreted as the energy per neuron and it drives the dynamic of the neuron. That is, when a particular neuron i in the network changes its state according to the rule (2), there is a change in the energy of the network given by

$$\Delta H_i = -\Delta V_i \left(\sum_j T_{ij} V_j - U_i \right)$$

which implies (3) to be a monotonically decreasing function and, therefore, that the changes in the state of the network will occur until a local minimum in $H(\mathbf{V})$ is reached. This framework also allows to study the steady-state collective properties of the model using the statistical physics techniques by assuming that the network is in equilibrium with a thermal bath at temperature T that causes stochastic fluctuations of the neuron states around an equilibrium state defined by $H(\mathbf{V})$.

Cross-References

► [Boltzmann Machine](#)

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Hubel and Wiesel Model

► Hierarchical Models of the Visual System

Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights

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Synonyms

Balance control dynamics; Characterization of motor learning in continuous tracking tasks; Human stick balancing; Lévy flights to improve balance control; Skill acquisition in stick balancing; Virtual stick balancing

Definition

In human stick balance intermittency is observed (Fig. 1). Here intermittency denotes the random alternation between phases with extremely low movement amplitudes and phases with high



Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 1 A stick balanced at the fingertip

movement amplitudes. This type of intermittency is characterized by power laws in the distributions of corrective movements in real stick balancing and in virtual stick balancing (i.e., balancing an unstable target on a computer screen). These observations are commonly seen as evidence which contrasts neurological control from standard engineered controllers.

Detailed Description

Neural control mechanisms are subjected to the presence of time delays and random, uncontrolled fluctuations or noise. The interplay between noise and time-delayed control mechanisms can lead to the appearance of new phenomena which themselves are beneficial for the neural function. Here, attention is paid to the possible effects of fluctuations affecting the system parameters (Horsthemke and Lefever 1984) (parametric noise).

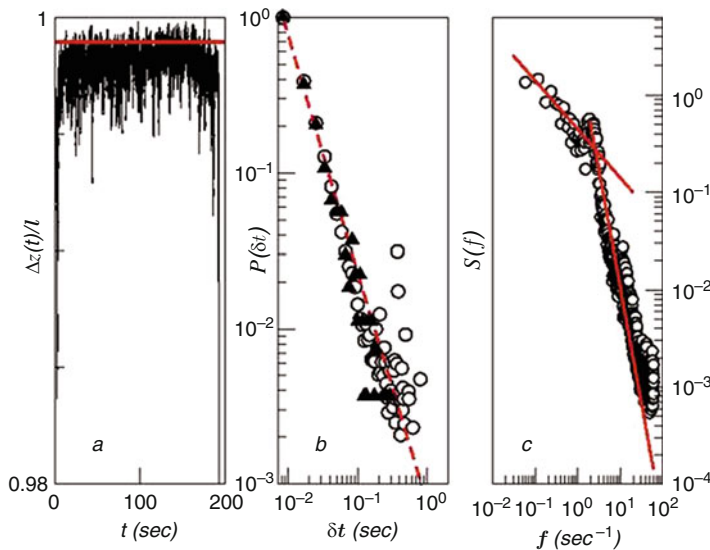
Tuning at the Edge of Stability: On-Off Intermittency in Human Stick Balancing

An important dynamical phenomenon produced by parametric noise is on-off intermittency (Platt et al. 1993) (OOI) that arises because of the fluctuating forcing of a control parameter across a stability boundary. OOI has been reported for the task of balancing a stick at the fingertip (Cabrera and Milton 2002). Stick balancing involves time-delayed control mechanisms in the presence of fluctuations. Detailed movement studies of the 3D trajectories of a balancing stick on the fingertip show that OOI allows for corrective movements on all timescales including those shorter than the physiological delay. This is interpreted as the first evidence showing how a control system can overcome the restrictions imposed by response times. From the stick trajectories, attention was paid to the quantity $\Delta z/l$, where Δz is the difference in the vertical coordinate of the upper and lower ends of the stick and l is the stick length. The dynamical behavior of a balanced stick is characterized by a highly fluctuating variable showing an intermittent temporal evolution (Fig. 2a) as evidenced by

a power-law dependence in the distribution of the times between two corrective movements (or laminar phases), δ with exponent $-3/2$ (Fig. 2b). The power spectra of the temporal series show also a power-law behavior but with exponent $-1/2$ (Fig. 2c). These exponent values are those expected for OOI (Platt et al. 1993; Venkataramani et al. 1996). The power law in δ implies that more than 98% of the times between corrective movements are shorter than the latency for the neural reflex involved in the balance control which was estimated around 100 ms (Cabrera and Milton 2002) or higher (Milton et al. 2016). Additional insights into the nature of the human neural control of stick balancing can be achieved modeling mathematically an inverted pendulum with time-delayed feedback in the presence of a parametric noise (Cabrera and Milton 2002). The model reads

$$\ddot{\theta} + \Gamma \dot{\theta} - q \sin \theta + R(t) \theta(t-1) = 0,$$

where θ is the angular deviation from the vertical, $R(t) \equiv R_0 + \xi(t)$ is a fluctuating restoring force



Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 2 (a) Temporal series for $\Delta z/l$ for a 62 cm stick balanced at the fingertip. The horizontal line is the threshold used to determine laminar phases δ . (b) Log-log plot of the power spectrum for the fluctuations in Δz characterized by a regime with power law of exponent

close to $-1/2$ (upper line). (c) Normalized laminar phase probability distribution, the triangles were obtained from a single realization, while circles describe the mean distribution from 48 realizations. The dashed line is a power law with exponent $-3/2$

with R_0 mean, and $\xi(t)$ is a zero mean Gaussian white noise, and other parameters are related to the stick physical characteristics. In this equation, $\theta(t - 1)$ accounts for the time-delayed responses where the latency time involved in the control, τ , has been normalized. A deterministic version of the model is characterized by the stability domain (with a half-moon shape) defined in the space of the variables concerning the human response (the intensity of the corrective term, R_0 , and the time delay, τ , as shown in Fig. 3a). Outside of the stability domain, the stick falls. For the values of (R_0, τ) depicted as points on the stability domain, results of integrating the model stochastic version can be seen at Fig. 3, right column. The numerical temporal series resembling the experimental one (Fig. 2a) is that obtained with (R_0, τ) tuned very close to the stability boundary (Fig. 2d). At this value, it is also possible to reproduce the power-law behavior observed in the experiment (not shown Cabrera and Milton 2002).

These findings suggest that the nervous system has an elegant solution to the stick balancing problem: (i) increasing maneuverability by tuning parameters very close to the instability (ii) where a parametric noise can give place to corrective

movements on all time scales including shorter than the time delay. These interesting results may have triggered further research and additional approaches to the problem of human stick balancing including intermittent control (Loram et al. 2011). Note that the latter denotes continuous control with discontinuous control forces, which may occur independently of intermittency, and with or without predictive control. Other recent research focused on sensory dead zones (Insperger et al. 2013) and on the related, but slightly different, problem of human upright standing control (Asai et al. 2013), among others.

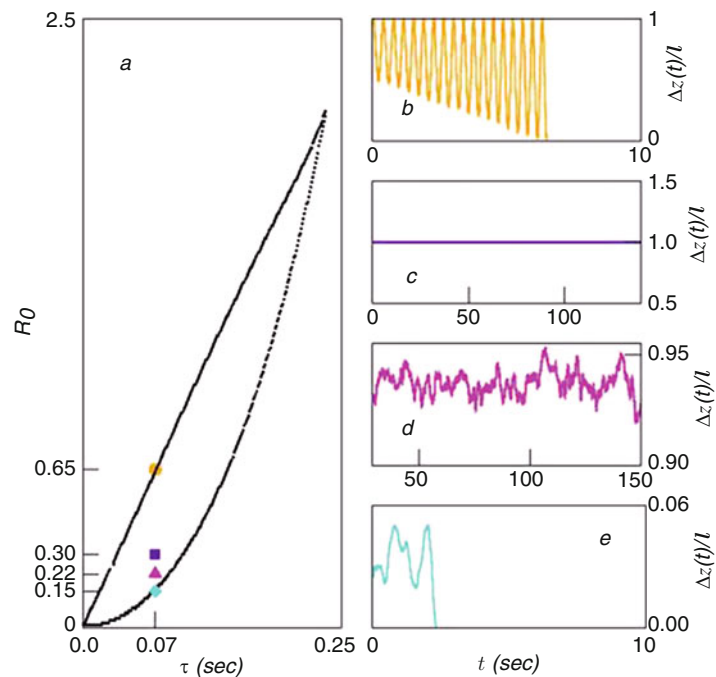
A Lévy Flight in the Fingertip

Further insights in the stick balancing task have confirmed that changes in speed made by the fingertip are described by a truncated Lévy distribution (Cabrera and Milton 2004), defining a random walk known to be optimal for performing random searches (Viswanathan et al. 2011). Furthermore, changes in the subject skill level were related to changes in the Lévy distribution (Cabrera and Milton 2004), demonstrating that motor learning in continuous tasks can be characterized by changing distributions that reflect

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Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 3 (a)

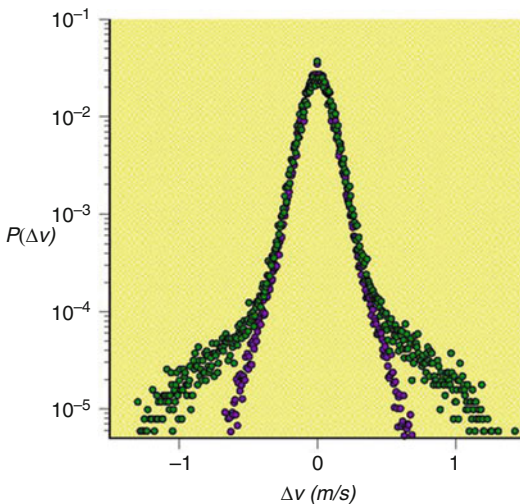
Numerically determined deterministic stability domain for the Cabrera-Milton model and example time series for the parameter choices given by the solid symbols in (a) as shown, respectively, in (b), (c), (d), and (e)



sensorimotor skill acquisition (Cabrera and Milton 2004, Cluff and Balasubramaniam 2009; Fig. 4). More recent numerical and experimental research has shown that Levy noise improves stabilization when compared with Gaussian noise in the case of a stochastic parametric system with time delay as discussed above (Gutiérrez 2015; Odonell 2015).

Virtual Stick Balancing

Virtual stick balancing (VSB) facilitates data acquisition and setup manipulations compared to real stick balancing. In a typical setup, a cursor C and a target T are displayed on a computer screen (Fig. 4). C is controlled by the subject's hand movements. T is moved by the computer according to an unstable dynamics of first or second order. Subjects are typically told to keep C and T as close together as possible. Task variations include, for example, keeping T on the screen as long as possible. Input devices include, for example, the computer mouse (Bormann et al. 2004) and the manipulandum (Mehta and Schaal 2002).

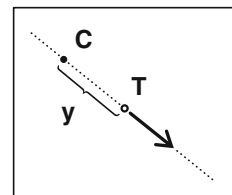


Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 4 How the probability distribution of the speed changes in the fingertip is modified by learning for a subject balancing a 62 cm stick on the fingertip. As the subject get skilled in the balancing task, the tail of the distribution gets broad (for details, see Cabrera and Milton 2004)

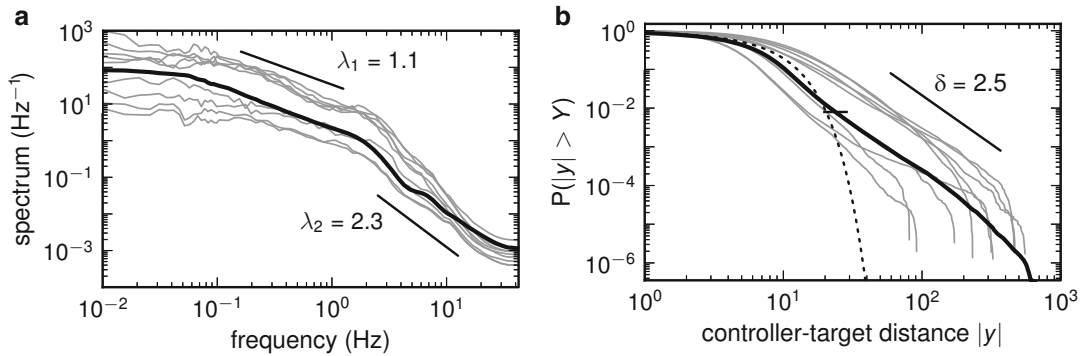
While this task is very similar to real stick balancing, there are some differences: VSB involves only visual feedback about the target, while balancing a real stick on the fingertip can involve additional haptic feedback. Furthermore, movements in real balancing are limited, for example, by the length and inertia of the subject's arm, while in VSB additional limitations include the size of the screen, the movement dimensionality, and range of the input device, or the latency of the setup.

VSB time series exhibit power laws in the spectrum (Fig. 5a) similar to those observed for real stick balancing (Bormann et al. 2004). Furthermore, VSB has been performed with different task difficulties (Milton et al. 2013). Hard tasks are comparable to balancing a stick which is shorter than 1 m. In easier tasks, subjects are able to control the target for minutes. While the variance in easier tasks is smaller than for the hard task, the shape of the distribution can be more heavily tailed (Milton et al. 2013). Here, the cumulative distributions of large distances y in between C and T (control errors) are well described by a power-law $P(y > Y) \propto |y|^{-\xi}$ with an exponent ξ in between 2 and 4 (Patzelt et al. 2007; Fig. 6). An apparent truncation for the largest events in each time series is caused by temporal correlations (see supplement to Patzelt and Pawelzik 2011): subsequent measurements are not independent.

The power-law distribution of control errors suggests that parametric noise is adjusted such that the system even in simple tasks appears to be close to a critical point: self-similar fluctuations



Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 5 A common virtual balancing setup: subjects control a mouse cursor C and have to catch a target T which is controlled by the computer. C and T can be thought of as the projections of the positions of the two ends of a stick onto the horizontal plane



Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 6 Analysis of absolute balancing errors $|y|$ in virtual balancing time series for several subjects (*thin gray lines*) and a predictive, rapidly adaptive model (*thick black lines*, Fig. 6) (Data from Patzelt and Pawelzik 2011). (a) Power spectra. The scaling exponents

$\lambda_{1,2}$ have been estimated for the model time series using linear regression. (b) Complementary cumulative distribution. *Diagonal line*: a power-law fit using the Hill estimator. *Horizontal line*: estimator cutoff. *Dotted line*: Gaussian with the same mean and variance as the model time series

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in y over up to three orders of magnitude (mm to m) are observed. This hypothesis might explain why Human VSB control parameters are often identified to be close to the edge of stability (see e.g., Matsumoto et al. 2018 for a recent example). However, it raises the question why extreme fluctuations which pose the risk of losing control are not avoided.

A suggested cause of the parametric noise is an online estimation of system parameters. The motivation for this model is evidence that certain balancing tasks are predictive (Mehta and Schaal 2002) and that humans are often capable of adapting to quickly changing environments (Patzelt et al. 2007). The model controller at each point in time makes a short-term prediction of where T is going to move. Then, it moves C in the same direction slightly faster in order to catch T (Fig. 6). The predictor compensates for reaction delays which for subjects were estimated significantly above 150 ms (Patzelt and Pawelzik 2011) and sometimes even above 300 ms (Bormann et al. 2004). The distinctive feature of this model compared to standard views on the action-perception cycle (Wolpert and Ghahramani 2000) is that the parameter of the forward model is an ad hoc estimation.

A predictive and highly adaptive controller as described above can run into an instability because successful control annihilates

observable information about the controlled system (Patzelt and Pawelzik 2011): it is only possible to predict where a stick is going to fall once it starts falling. This principle maps small control errors to large uncertainties about future dynamics and vice versa, thereby inducing self-similar fluctuations. It can be illustrated in a simple linearized example: consider a system with expected dynamics without control.

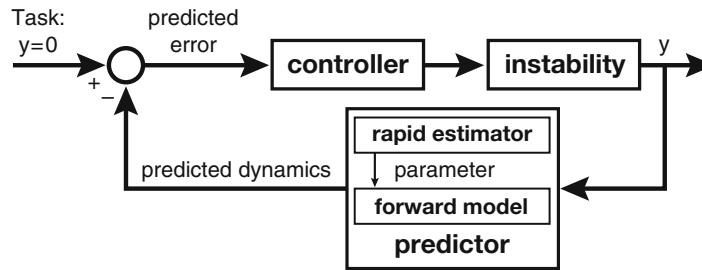
$$\dot{y}(t) = \vartheta y(t).$$

Assume that the system is observed at a given location y . Given noisy observations of y and $\dot{y}$ with respective probability distributions $p(y)$ and $p(\dot{y})$, the expected amount of information about the parameter.

$$\mathcal{I} = \frac{\langle y^2 \rangle}{\sigma_y^2}$$

vanishes if successful control moves the system towards the origin. Since $1/\mathcal{I}$ is a lower bound for the mean squared error of an unbiased estimator for ϑ , stabilization (minimizing $|y|$) evolves the system towards a critical point.

A complete balancing model involves a reaction time, an unbiased short-term parameter estimator, and an optimal forward model based on



Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights, Fig. 7 Standard models of the action-perception cycle include forward models allowing subjects to predict the future dynamics of their environment. If in addition parameters are estimated online on timescales

this prediction (Fig. 7). This model can reproduce the distribution of control errors and the power spectra of subjects in a virtual balancing task (Patzelt and Pawelzik 2011; Fig. 6). The kink in the power spectrum around 4 Hz corresponds to the reaction time of the controller. Controller memory and gain determine the scaling exponents. The model further suggests that power-law error distributions persist even after several hours of training because subjects minimize mean control errors by eliminating random local trends at the cost of rare, extreme errors. This is consistent with experimental results showing that humans can change this control strategy if incentivized (Patzelt 2014). Research involving other predictive control models also suggests that parameters at stabilities edge may reduce movement costs (Milton et al. 2016).

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Human Connectome Project

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Definition

The Human Connectome Project (HCP) is a major endeavor to map the neural pathways that underlie brain function and its variability in humans. The purpose of the HCP is to acquire and share data about the structural and functional connectivity of the human brain, the “connectome,” on the macroscopic scale ($\sim 1 \text{ mm}^3$ or greater) as analyzed using noninvasive neuroimaging in a large population of healthy adults (Van Essen and Ugurbil 2012).

Neuroimaging, behavioral, and genetic data being acquired by the HCP from 1,200 healthy adults will serve as a key resource for investigators in many fields, including neuroimaging, neuroanatomy, psychology, computational neuroscience, and network modeling. To facilitate data sharing, the HCP is developing an informatics platform comprised of the “ConnectomeDB” database for data storage, processing, and distribution and “Connectome Workbench,” a tool for data visualization and exploration.

Detailed Description

Origins of the HCP

With the goal of systematically examining human brain connectivity and its variability across the whole brain in large numbers of subjects with neuroimaging, in 2009 the NIH announced a request for applications for the Human Connectome Project. The NIH Blueprint for Neuroscience funded grants in September of 2010 to two consortia (<http://www.neuroscienceblueprint.nih.gov/connectome/>) that are taking complementary approaches. One is a 5-year grant to a consortium of ten institutions led by Washington University in St. Louis (WashU), the University of Minnesota (UMinn), and Oxford University (the “WU-Minn HCP Consortium”). This is a \$30 M effort to characterize human brain connectivity and function in 1,200 healthy subjects using four magnetic resonance imaging (MRI)-based modalities plus magnetoencephalography (MEG) along with extensive behavioral and genetic data. The second is a 3-year grant to a consortium led by Harvard/Massachusetts General Hospital and the University of California at Los Angeles focused on developing a “next-generation” 3 T MR scanner for diffusion imaging.

Overview of the HCP

The WU-Minn HCP Consortium began with extensive efforts over a 2-year period to refine and optimize acquisition and analysis methods. Data acquisition began in August 2012 on subjects drawn from a population of adult twins and their non-twin siblings, in the age range of 22–35 years. Each subject is assessed in a 2-day study visit at WashU that includes behavioral measures in a broad range of domains, blood draw for eventual genotyping, and multiple MR scanning sessions on a single, customized 3 T Connectome Scanner (Van Essen et al. 2012, 2013). A subset of 200 subjects are also being scanned at UMinn on a 7 T scanner, beginning winter 2013. For both the 3 and 7 T systems, advanced pulse sequences are used to acquire T1-weighted and T2-weighted

anatomical MRI, diffusion imaging (dMRI), resting-state fMRI (rfMRI), and task-evoked fMRI (tfMRI) scans. Seven tasks are included in the tfMRI scans aimed at identifying a maximal number of functionally distinct cortical parcels in a wide range of neural systems over the whole brain.

MEG is being acquired on a subset of 100 subjects at St. Louis University, including resting-state scans plus three task-evoked scans. MEG will provide data with higher temporal resolution

(milliseconds instead of seconds) at a coarser spatial resolution (centimeters vs. millimeters) than is available with MRI.

The HCP is advancing capabilities for analyzing brain connections capitalizing on the high-quality functional and structural image data being generated by the project. Innovative data processing and analysis pipelines are being developed and implemented as the data are collected. The data are being distributed at multiple stages of processing/analysis, giving users the ability to

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HCP Data Releases

Updated Sept 23, 2013: Q3 subjects have been added to ConnectomeDB. These datasets can be freely accessed and used by those who agree to their terms of use.

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- [Group-PCA Eigenmaps for R120+U40 Groups](#)

Dense Connectomes (33 GB each)

To avoid downloading, these files can be accessed remotely via Connectome Workbench or created locally from the Group-PCA Eigenmaps. [See Documentation](#)

- [120 Subjects \(many related\), full correlation](#)
- [120 Subjects \(many related\), mean-gray-timecourse-regressed](#)
- [40 Unrelated Subjects, full correlation](#)
- [40 Unrelated Subjects, mean-gray-timecourse-regressed](#)

[HCP Data Release Documentation: humanconnectome.org/documentation](#)

Human Connectome Project, Fig. 1 The ConnectomeDB landing page

choose the level of data on which to conduct their own analyses. HCP is also distributing the processing and analysis pipelines themselves, when fully vetted and finalized versions are available. This will enable users to run pipelines on data collected outside the HCP and directly compare it to the HCP data.

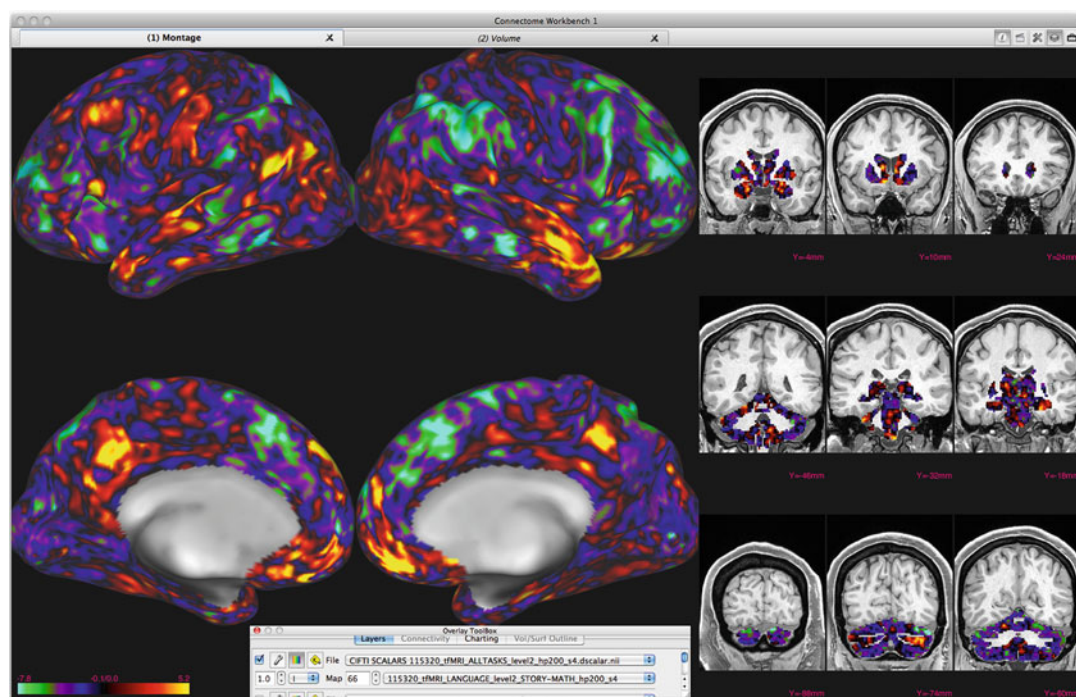
ConnectomeDB and Connectome Workbench

The HCP has built a suite of informatics tools to enable high throughput data collection, automated data processing and analysis, data sharing, and data mining and visualization (Marcus et al. 2013). A two-tiered database based on the XNAT database platform (Marcus et al. 2007) has been developed for managing and sharing large amounts of unprocessed and processed HCP data (expected to approach 1 petabyte by the end of the HCP). The HCP consortium manages data collection and quality control validation

using the private database IntraDB. Data are then moved to ConnectomeDB (<https://db.humanconnectome.org>), the HCP's externally accessible database, enabling data sharing, data mining, and discovery science by end users (Fig. 1). Customizations for the XNAT system employed by ConnectomeDB are available as pluggable modules that can be downloaded (<http://marketplace.xnat.org/>) and deployed on independent XNAT systems. In addition, the overall code for the HCP databases is open source and available on the Bitbucket version control system (<https://bitbucket.org/hcp>).

The Connectome Workbench (a.k.a. “Workbench”) brain surface and volume visualization platform has been developed to provide novel capabilities for viewing images and connectivity analysis results being produced by HCP (Fig. 2). Workbench has its origins in Caret software (Van Essen et al. 2001) but has been thoroughly redesigned with new features, many that accommodate the new CIFTI data format introduced for connectivity matrix data (<http://www.nitrc.org/>

H



Human Connectome Project, Fig. 2 Connectome Workbench GUI showing Story-Math language task activations on brain surfaces and volumes of an individual subject

projects/cifti/). The Workbench platform is comprised of an application with a graphical user interface for interactive display of data mapped to brain volumes or surfaces and “wb_command,” software run on the command line for performing various tasks related to handling and processing neuroimaging data for analysis and visualization. Workbench is open source and available for download at <http://humanconnectome.org/connectome/get-connectome-workbench.html>.

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Further Reading

More information on current developments and data releases of the WU-Minn Human Connectome Project are available at <http://www.humanconnectome.org/>

Human Stick Balancing

► [Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)

Hybrid Parameter Optimization Methods

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Definition

Hybrid parameter optimization (HPO) methods are search strategies that combine the strengths of different optimization algorithms to increase the performance of the overall parameter search process.

Detailed Description

Parameter optimization tends to be very complex, especially for the situations it is used for in computational neuroscience. Due to the many nonlinearities in neuronal systems and the large number of free parameters, the fitness landscapes tend to be highly dimensional and non-convex (Prinz et al. 2003; Achard and De Schutter 2006; Druckmann et al. 2007). Every optimization algorithm is optimal for certain shapes and sizes of the solution space (Achard et al. 2010). Unfortunately, the shape can change depending on the resolution one scans the parameters. On a macroscopic scale, the problem might look very non-convex with a lot of local minima, but close-ups around the optimal solutions could show a much more convex local environment.

The scientist who wants to use parameter optimization methods has to decide which algorithm to use. This implies having some knowledge about the shape of the parameter space. There will also be constraints on the amount of

computational resource available, so it is not only a question of finding the best values for the parameters but also a question of finding them as quickly and as efficiently as possible.

This is where hybrid optimization techniques can be beneficial. Instead of choosing one algorithm that could be suboptimal for some parts of the solution space, one combines different algorithms, sequentially or in parallel.

One example of a sequential hybrid approach would be to first apply a global search technique, like a genetic algorithm, to isolate a set of islands in the solution space that have a high fitness value, and then apply to these islands a local search algorithm, like downhill simplex (DS) method (Nelder and Mead 1965) to find the best solution for every island (Vossou et al. 2007).

When estimating neuron parameters, it can sometimes be beneficial not to give all parameters at once to a search algorithm, but rather to isolate known subproblems. The fitting process of the passive parameters (combined with typically the h-current) of a detailed neuron model does, e.g., involve much less nonlinearities. One could therefore fit these parameters first, possibly with a simpler optimization algorithm. Next these parameters can be fixed and a possibly more advanced algorithm can estimate the values for the active parameters (Roth and Bahl 2009; Keren et al. 2009).

Mitra et al. show a similar use case by combining gradient descent (GD) and DS methods (Mitra et al. 2013). In this study the GD algorithm was on its own not able to converge to the global minimum. When applying the DS method, the solution became however very dependent on the initial conditions. A hybrid algorithm that first runs the GD using just one part of the fitness function and then using that result as a starting point for the DS method overcame the disadvantages of the isolated algorithms.

Another class of hybrid optimization techniques involves the application of different algorithms in parallel. An example is an algorithm that on the fly tunes the mutation rates of a genetic algorithm based on some heuristic (Maeda and Li 2007).

Cross-References

- [Evolutionary Algorithms](#)
- [Multi-objective Evolutionary Algorithms](#)
- [Neurofitter](#)
- [Neuronal Model Output Fitness Function](#)
- [Neuronal Parameter Space Exploration](#)

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- [Computation with Serotonergic Modulation](#)

Hyperpolarization-Activated Cyclic Nucleotide Gated Channels

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Synonyms

F current; H⁻ current; HCN channels
hyperpolarization-activated current; I_h; Q current

Definition

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are membrane ion channels that are permeable to sodium and potassium ions. They open when the membrane potential hyperpolarizes and close when it depolarizes. This contrasts with the majority of voltage-gated ion channels, which open on depolarization and close on hyperpolarization. HCN channel gating can be directly modulated by cyclic nucleotides. At a molecular level, HCN channels have a structure similar to voltage-gated potassium channels. Individual subunits have six transmembrane domains and a reentrant pore loop but are distinguished by a cyclic AMP-binding domain located near to their C-terminus. Functional channels are formed by homomeric or heteromeric assembly of four subunits.

Detailed Description

HCN channels are an important and striking exception to the general rule that voltage-gated ion channels open in response to depolarization of a cell's membrane potential. Instead, HCN channels open when a cell's membrane hyperpolarizes and close when it depolarizes. Currents with these properties were first described in the heart and retina (Yanagihara and Irisawa 1980; Brown et al. 1979; Brown and DiFrancesco

1980; Attwell and Wilson 1980; Bader et al. 1979) and later found to be present in many central neurons (Halliwell and Adams 1982; Pape 1996; Robinson and Siegelbaum 2003; Biel et al. 2009). The unusual voltage dependence of these currents, which are often referred to as hyperpolarization-activated currents (I_h) (Hille 2001; Pape 1996; Robinson and Siegelbaum 2003), led to their also being called funny (I_f) (Brown et al. 1979) or queer (I_q) currents (Halliwell and Adams 1982).

Currents Through HCN Channels

HCN currents typically activate with a delay following hyperpolarization to potentials negative to approximately −50 mV. The current through HCN channels is mediated by both Na⁺ and K⁺. In physiological conditions, currents reverse polarity at potentials in the range of −20 to −50 mV (Pape 1996; Robinson and Siegelbaum 2003; Biel et al. 2009). The single channel conductance of HCN channels appears to be low, with an estimated value of approximately 1 pS (DiFrancesco 1986; Kole et al. 2006). Gating of HCN channels in response to changes in membrane potential is relatively slow. Activation time constants for HCN currents range from tens of milliseconds in some cells to greater than 1 s in others (Pape 1996; Robinson and Siegelbaum 2003; Biel et al. 2009). An instantaneous component of HCN channel activation has also been reported (Proenza et al. 2002). Elevation of intracellular cAMP shifts the voltage dependence of channel opening in a positive direction and accelerates channel opening and closing (DiFrancesco and Tromba 1988; Robinson and Siegelbaum 2003; Biel et al. 2009; Pape 1996).

The current through HCN channels (I_h) can be modeled using a Hodgkin-Huxley formalism with a single activation variable:

$$I_h = g_h m(V - E_h)$$

where g_h is the maximum conductance, V is the membrane potential, E_h is the membrane potential at which I_h reverses polarity, and m is the

activation variable, such that $\partial m / \partial t = \alpha(1-m) - \beta m$, where α and β are voltage-dependent rate constants for transitions between open and closed states of the channel. More complex gating schemes are required to account for delayed activation and cAMP modulation of I_h (Altomare et al. 2003; Wang et al. 2002).

Molecular Properties

In mammals, HCN channels are encoded by a family of four genes (Robinson and Siegelbaum 2003; Santoro et al. 1997, 1998; Ludwig et al. 1998, 1999; Vaccari et al. 1999; Seifert et al. 1999; Santoro and Tibbs 1999). Homologues of these genes have been identified in non-mammalian organisms, including sea urchin (Gauss et al. 1998), insects (Krieger et al. 1999; Marx et al. 1999), urochordates (Jackson et al. 2012), and the unicellular choanoflagellates (Cai 2012). Each gene encodes a protein with six transmembrane domains (S1–S6) and a reentrant pore loop. The membrane topology is similar to voltage-gated K^+ channels (Santoro and Tibbs 1999; Robinson and Siegelbaum 2003; Biel et al. 2009). Functional channels are formed from four subunits assembled as homomers or heteromers (Santoro et al. 2000; Chen et al. 2001; Ulens and Tytgat 2001). Just as for voltage-gated K^+ channels, the voltage sensor for HCN channels is in the S4 domain, which moves in an extracellular direction on depolarization (Vemana et al. 2004; Mannikko et al. 2002; Bell et al. 2004). Binding of cAMP relieves an inhibitory action of the cyclic nucleotide-binding domain (Wainger et al. 2001). Crystal structures of this domain identify mechanisms for the specificity of cAMP binding (Zagotta et al. 2003).

Diversity in the kinetics, voltage dependence, and sensitivity to cAMP of currents through HCN channels is achieved through several mechanisms (Santoro et al. 2000; Robinson and Siegelbaum 2003). Homomeric channels assembled from different subunits have distinct voltage dependence and sensitivity to cAMP (Ishii et al. 1999; Ludwig et al. 1999; Seifert et al. 1999; Altomare et al.

2003; Wainger et al. 2001; Santoro et al. 2000; Stieber et al. 2005; Mistrik et al. 2005). Heteromeric assembly of different subunits results in channels with properties typically intermediate between those of their constituent subunits (Altomare et al. 2003; Chen et al. 2001; Ulens and Tytgat 2001). Association with the accessory subunit protein Trip8b modifies the amplitude, kinetics, and voltage dependence of HCN currents (Santoro et al. 2004; Zolles et al. 2009). Alternative splicing of Trip8b provides further increases in the diversity of HCN current properties (Santoro et al. 2009; Lewis et al. 2009). Finally, modulation by a number of protein kinases enables further tuning of HCN currents (Pape 1996; Biel et al. 2009).

Cellular Functions

Three biophysical features of HCN currents are central to their cellular functions. First, the relatively positive reversal potential of HCN currents means that opening of HCN channels depolarizes the membrane potential. Second, as they open at relatively negative membrane potentials, HCN channels primarily influence subthreshold membrane potential activity. Third, because their kinetics are relatively slow, HCN channels oppose slow changes in membrane potential. This causes a characteristic sag-like response to current steps (Araki et al. 1961; Pape 1996). These features manifest in several distinct cellular functions. In some cells, for example, in the heart and thalamus, subthreshold activation of HCN channels contributes to pacemaking of rhythmic activity (Pape 1996). In other cells, for example, cortical pyramidal neurons, HCN channels control integration of synaptic responses (Magee 1998, 1999; Nolan et al. 2004; Robinson and Siegelbaum 2003; Biel et al. 2009). Other functions for HCN channels include promotion of membrane resonance by suppressing responses to low-frequency inputs (Nolan et al. 2007; Ulrich 2002; Hutcheon et al. 1996) and control of synaptic plasticity (Nolan et al. 2004; Tsay et al. 2007). Activity-dependent plasticity of HCN channels can modify these functions (van Welie et al. 2004; Fan et al. 2005).

Contributions to *In Vivo* Physiology, Behavior, and Disease

HCN currents contribute to pacemaking of the cardiac rhythm and acceleration of heart rate following sympathetic activation (DiFrancesco 1993; Biel et al. 2009). In the brain, direct evidence for HCN channel functions at a behavioral level comes from studies in which HCN genes are knocked out. These indicate roles for HCN1 channels in motor learning (Nolan et al. 2003), in spatial memory (Nolan et al. 2004), and in sensitivity to anesthetics (Chen et al. 2009). Pharmacological manipulations of HCN channels indicate further roles in working memory (Wang et al. 2007). There is evidence for major roles of HCN channels in several forms of epilepsy (Ludwig et al. 2003; Shah et al. 2013; Noam et al. 2011), as well as in neuropathic pain and cardiac disorders (Biel et al. 2009; Baruscotti et al. 2010), while reduction of HCN currents may promote antidepressant behavior (Lewis et al. 2011; Kim et al. 2012).

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Hypokinesia Model

► Basal Ganglia: Bradykinesia Models

Hypothesis Testing

► Significance Evaluation



Idiopathic Parkinson's Disease

► [Parkinson's Disease: Deep Brain Stimulation](#)

Imaging Analysis, Bayesian

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I_h

► [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)

Definition

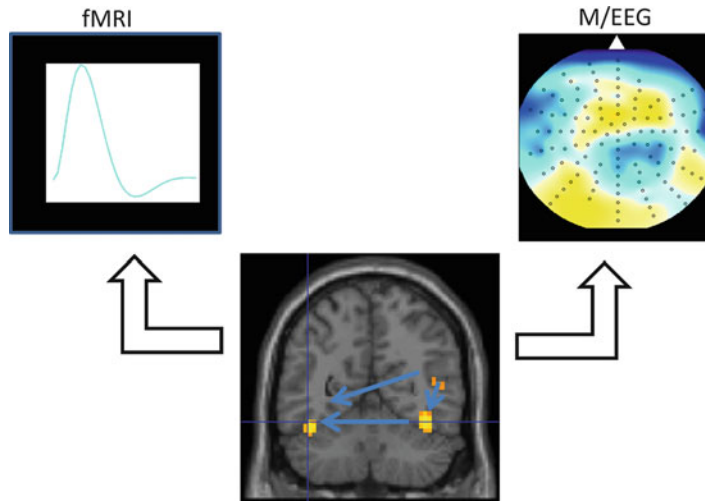
This entry refers to Bayesian methods (Gelman et al. 1995; Bishop 2006) for making inferences about neural activity from brain imaging data. This includes data from functional magnetic resonance imaging (fMRI) (Huettel et al. 2009), magnetoencephalography (MEG), and electroencephalography (EEG) (Luck 2005). These data are unique in neuroscience in that they allow, through noninvasive methods, relations to be studied between the large-scale activity of the brain and human behavior. Statistical aspects of microscopic neural activity can be estimated through Bayesian inversion of appropriate mathematical models. The methods described below have been applied to the study of a wide range of human brain functions from low-level sensory processing and sensorimotor integration to studies

Illusions

► [Visual Aftereffects, Models of](#)

ImaGen

► [Topographica](#)



Imaging Analysis, Bayesian, Fig. 1 Brain mapping identifies regions where experimental effect sizes are significantly nonzero (*orange*), as identified using the posterior distribution. Brain connectivity then explains activity in a set of regions using differential equation models with directed connections. For brain mapping, the parameters of

interest, θ , are regional activities, and for brain connectivity, they are directed pathways (*blue*). Both approaches can be applied to data, y , from *fMRI* or *MEG/EEG*. For *fMRI* this requires Bayesian inversion of a forward model describing a temporal convolution and for *MEG/EEG* a forward model describing a spatial mapping

of memory, emotion, and decision making (Friston et al. 2007b; Fig. 1).

Detailed Description

In what follows $N(x; m, V)$ denotes a multivariate Gaussian density, with mean m and covariance V , over the random variable x . Bayesian inference is used to transform prior distributions over parameters describing neuronal activity, $p(\theta)$, into posterior distributions, $p(\theta|y)$, based on neuroimaging data y .

Brain Mapping

MEG sensors, placed over the head, detect changes in magnetic fields due to changes in underlying neuronal currents. EEG electrodes, in contact with the scalp, detect voltage differences due to these same currents. For both MEG and EEG data (MEG/EEG), we can capture the relation between neuronal sources, θ , and measured signals y as a linear relation $y = L\theta$ where L is a lead field matrix derived from Maxwell's equations (Baillet et al. 2001).

These observations are assumed to be corrupted with Gaussian noise having covariance V_y . This leads to the statistical model

$$\begin{aligned} p(y|\theta) &= N(y; L\theta, V_y) \\ p(\theta) &= N(x; 0, V_\theta) \end{aligned} \quad (1)$$

Because there are many more potential brain sources (thousands) than MEG/EEG sensors (tens or hundreds), the prior $p(\theta)$ must provide sufficient constraints so that the sources can be recovered. MEG/EEG source reconstruction algorithms, such as “minimum norm,” “low-resolution tomography (LORETA),” or “multiple sparse priors (MSP),” are differentiated by their priors and estimation algorithms for approximating the posterior $p(\theta|y)$ (Wipf and Nagarajan 2009; Litvak et al. 2011).

fMRI detects changes in neuronal activity via changes in hemodynamics and the differential magnetic properties of oxygenated versus deoxygenated blood. This is known as the blood oxygen level-dependent (BOLD) effect (Huettel et al. 2009). Given the time courses of experimental conditions, we can predict the resulting fMRI

signals via temporal convolution with canonical response profiles (Friston et al. 2007b). The result of this convolution step can be captured in a design matrix X . The fMRI signal is then modeled as

$$\begin{aligned} p(Y|\theta) &= \prod_n N(y_n; X\theta_n, V_y) \\ p(\theta) &= \prod_k N(\theta_{k\cdot}; 0, V_\theta^k) \end{aligned} \quad (2)$$

where y_n is the fMRI time series at the n th spatial location, θ_{kn} is mean neuronal activity for experimental condition k at voxel n , and the prior covariance V_θ^k enforces local spatial smoothness constraints on the estimate of the k th neuronal response (Woolrich 2012). Inference about neuronal effect sizes can then be made from the posterior and displayed using posterior probability maps (PPMs) (Friston et al. 2007b). Bayesian methods also allow one to infer that a region has not activated (Woolrich 2012).

Brain Connectivity

Interactions among brain regions can be studied using a variety of statistical tools including structural equation modeling, regression methods, and principal or independent component analysis (Friston et al. 2007b). Studies of brain connectivity with fMRI that take a dynamical systems approach typically model time series, y , from a small number of regions (less than ten). These regions are selected based on previous analyses of imaging data or from knowledge of systems neuroscience (Kandel et al. 2000; Frackowiak et al. 2003).

$$\begin{aligned} p(y|\theta) &= N(y; g(x, \theta), V_y) \\ \dot{x} &= \left(A + \sum_i u_i B_i \right) x + Cu \\ p(\theta) &= N(x; m_\theta, V_\theta) \end{aligned} \quad (3)$$

where $\theta = \{A, B, C, h\}$ are model parameters. Here, x is a vector of neuronal activity in multiple brain regions, $\dot{x}$ denotes the time derivative, and

u is a vector of experimental stimuli. Connectivity is characterized by a set of “intrinsic connections,” A ; input connections, C ; and modulatory connections, B . Here B specifies which intrinsic connections can be changed by contextual variables involving, for example, changes in attentional or instructional set. The overall connectivity pattern is a scientific hypothesis about the structure of the large-scale neuronal network mediating the underlying sensorimotor or cognitive function. Such hypotheses can be compared using Bayesian model selection (Penny et al. 2004).

In the above model, neuronal activity gives rise to fMRI activity by a dynamic process described by an extended Balloon (Buxton et al. 1998) and BOLD signal model. This takes the place of the linear convolution models used in mapping studies and has the advantage of accommodating, for example, nonlinear hemodynamic saturation effects. These models are not routinely used in mapping studies due to the computational expense of fitting them at large numbers of voxels. The overall dynamic model involves a set of hemodynamic state variables, state equations, and hemodynamic parameters, h . Together these equations describe a nonlinear process, $g(x, \theta)$, that converts neuronal activity into the BOLD signal.

For MEG/EEG data, dynamical connectivity models are again usually based on activity in a small number of regions

$$\begin{aligned} p(y|\theta) &= N(y; Lx, V_y) \\ \dot{x} &= f(x, u, \theta) \\ p(\theta) &= N(x; m_\theta, V_\theta) \end{aligned} \quad (4)$$

where x is a vector of neuronal activity. This activity is driven by experimental perturbations u according to a differential equation with parameters θ . Models of event-related fields/potentials (Luck 2005) are based on variants of the Jansen-Rit model (David et al. 2006) for describing the activity of multiple cell populations within a single cortical unit. Multiple cortical units are then connected together using anatomically realistic connection rules (Felleman and Van Essen 1991) to form large-scale networks. Priors over model

parameters constrain, for example, synaptic time constants to physiological ranges. Usually, the most interesting components of the posterior distribution are those that describe changes in the long-range excitatory connections among regions (Litvak et al. 2011).

Model Inference

Bayesian inference for the above models is based on the standard corpora of approximate inference methods (Gelman et al. 1995; Bishop 2006). Due to the size of most neuroimaging data sets, with data at potentially thousands of spatial positions and hundreds of time points, deterministic methods such as variational Bayes (Bishop 2006; Friston et al. 2007a) are most often used. Methods have been developed to make inferences about families of models and effects that are consistent over a group of subjects.

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Behavioural Analysis, Bayesian](#)
- [Brain Imaging: Overview](#)
- [Cognition, Bayesian Models of](#)
- [Dynamic Causal Modelling with Neural Population Models](#)
- [Electrophysiology Analysis, Bayesian](#)
- [Multiscale Brain Connectivity](#)

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Imaging, Electron Microscopy

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Synonyms

[Electron microscopic imaging](#); [Electron microscopy](#)

Definition

Electron microscopy is the method by which electrons interact with a sample and are collected to

detect a signal or change in sample density. This density is then either transferred onto a photographic plate or digitally recorded to create an electron micrograph.

Detailed Description

Electron microscopy is an imaging technique used by those who require a higher resolution than conventional light microscopy allows. Electrons are emitted from a filament tip and are accelerated and focused into a beam that targets and interacts with a sample. Electrons are then collected, and an image is recorded based on the results of those interactions.

Applications

Electron microscopy is often applied to samples of either biological origins or inorganic materials, including metals and crystals. Biological specimens include microorganisms, fixed tissue samples, and small structures, ranging down to large molecules or proteins.

Electron microscopy plays a crucial role in neural circuit reconstruction because it is the only imaging method by which individual processes in densely stained tissue can be imaged and reconstructed at the necessary resolution of synapses. It is because of this necessity that multiple associated methods have been developed and applied to volumetric imaging through neural tissue, including focused ion beam electron microscopy (FIB-SEM), serial-section transmission electron microscopy (SS-TEM), and serial block-face scanning electron microscopy (SBEM).

Brief History

Electron microscopy is a young imaging technique, relative to light microscopy, due to the necessity of the development of high vacuums and electromagnetic lenses to focus the electron beam. The first electron microscopy lens was developed in 1926 by Hans Busch, and the first transmission electron

microscope came five years later in 1931, developed by Ernst Ruska and Max Knoll (Nobel Prize Foundation 1986). That same year, Reinhold Rudenberg patented the electron microscope. The first electron microscope, however, did not surpass the resolving power of the best light microscopes. That was developed 2 years later in 1933 for TEM by Ruska. The first SEM did not appear until 1937 when Manfred von Ardenne adapted raster scanning to the electron beam.

Types of Electron Microscopy

Transmission Electron Microscopy

Transmission electron microscopy (TEM) is a method by which thin samples, usually either positioned over a hole on a sample holder or spanning across a thin layer of Formvar film, are bombarded with an electron beam, and the resulting distribution of electrons is recorded on the opposite side of the thin section. In a transmission electron microscope (Williams and Carter 1996), the electrons are differentially transmitted through the sample based on heavy metal composition. Because heavy metals will prevent the passage of electrons, the resulting image shows an inverted image where electrons either passed through the sample or failed to do so.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) does not rely on the use of thin sections. Rather, a sample is placed under an electron beam and electrons are recorded after interacting with a limited volume below the sample surface. Based on the voltage and current of the electron beam, the interaction volume of the beam with the sample can be manipulated to achieve the desired resolution, down to 0.4 nm with the Hitachi S-5500. Most scanning electron microscopes have a resolution limit that falls between 1 and 20 nm. SEM, unlike TEM, relies on raster scanning across the sample surface.

Scanning Transmission Electron Microscopy

Scanning transmission electron microscopy (STEM) is akin to a hybrid of SEM and TEM. The STEM method relies on the transmission of

electrons through a thin sample like TEM, but uses a raster scanning process across the sample, similar to SEM. This allows for the higher resolution of TEM with serial data collection.

Sample Preparation

Inorganic, conductive samples can be viewed directly in an electron microscope without the need for further sample preparation. Even inorganic materials that lack conductivity can be coated with thin conductive films to prevent charging artifacts. Most biological samples, however, require processing before the sample is suitable for visualization with an electron microscope. Such sample preparation steps include:

- Chemical fixation
- En bloc staining
- Cryofixation (for cryo-electron microscopy)
- Dehydration
- Embedding
- Sectioning or milling
- Section staining

Advantages

The most notable advantage offered by electron microscopy is its improved resolving power over visible light microscopy because electrons have wavelengths about 100,000 times shorter than visible light photons. Electron microscopy can achieve better than 50 pm resolution, whereas visible light microscopy is generally limited by diffraction to 300 nm.

Limitations

Most forms of electron microscopy only provide grayscale images which display heavy metal contrast in the sample. In combination with X-ray microanalysis, however, samples can be assessed for elemental composition based on emitted spectra while imaging, effectively creating a “color” electron micrograph.

Because an electron beam must pass through a vacuum to prevent the electrons from being

scattered due to interactions with air, specimens must also be placed in high vacuum. For biological samples, this can pose a problem and necessitates the use of chemical fixation, staining, and resin embedding for sample stability before imaging, and each process can induce unwanted artifacts in the sample.

Scanning electron microscopy is often liable to reductions in image quality due to charging-related artifacts. Because electrons can collect on the surface of a sample, those electrons can distort the path of primary, secondary, and back-scattered electrons, creating a warped image or preventing imaging entirely. It is possible to address this limitation by imaging nonconductive samples under low-vacuum conditions with water vapor or gas to discharge the sample surface by ions formed from interaction of the vapor or gas with the electron beam. Unfortunately, the low-vacuum conditions introduce additional noise into the image due to electron skirting.

Cross-References

- [Imaging, Specimen Preparation](#)
- [Reconstruction, Electron Microscopy](#)

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Imaging, Specimen Preparation

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Definition

Before specimens can be imaged for analysis using computational neuroanatomy techniques,

they must be properly prepared. Computational neuroanatomy encompasses a wide range of analysis, and correspondingly, a wide range of specimens can be analyzed. This discussion will focus on the preparation of specimens for high-throughput 3D microscopy technologies that are being rapidly developed. Methodologies that emphasize 3D molecular and morphological imaging, including ultrahigh-resolution electron microscopy imaging, provide complementary perspectives that can be applied to computational neuroanatomy. Through such analyses, it is possible to carry out detailed descriptions of local circuits that will help further elucidate neuronal function. These microscopy technologies together with high-performance computing power that continue to be improved enable data-driven, multi-scale modeling and simulation of large-scale neuronal circuits (such as the complete connectome of the mouse (Kleinfeld et al. 2011)).

Detailed Description

Introduction

Biological specimens to be analyzed using histological methods must be stabilized or preserved so that structural relationships can be maintained throughout the data acquisition phase. Biological specimens are obtained from living organisms, and specimens can consist of the entire organism such as insects (i.e., *Drosophila* or fruit flies), nematodes (i.e., *C. elegans*), or embryos (i.e., mouse or zebra fish embryos), or specimens can be the whole central nervous system (CNS, which includes the brain and spinal cord) taken from organisms such as mouse, rat, or adult zebra fish brain. Finally, samples also can include parts of the CNS taken from larger organisms including the human brain or spinal cord. High-throughput 3D analysis for computational neuroanatomy is still practically limited to analysis of specimens that are not much larger than a cubic centimeter (1.0 cm^3), which is the approximate size of an adult mouse brain. For this description, we will focus on the preparation of tissue samples that are no larger than 1.0 cm^3 , and we will describe specimen preparation that can be used for high-throughput 3D analysis.

Fixation

Once death of an organism has occurred, cellular integrity can no longer be maintained. Enzymes located within cells are released and start to act inside as well as outside the cells leading to tissue decay or destruction. The process of fixation stops the actions of these degradative enzymes on tissue/cellular components. It is important to prevent this process of “self-digestion” or “autolysis” from occurring because it will cause tissue morphology to change or become unrecognizable and severely autolyzed tissues also do not stain properly. Most common fixatives used today function to cross-link proteins together, which inactivates enzymes and maintains structural integrity of the cells and tissues. A wide range of factors can profoundly influence fixation, and these factors can be reviewed in the histotechnology textbook by Carson and Hladik (2009).

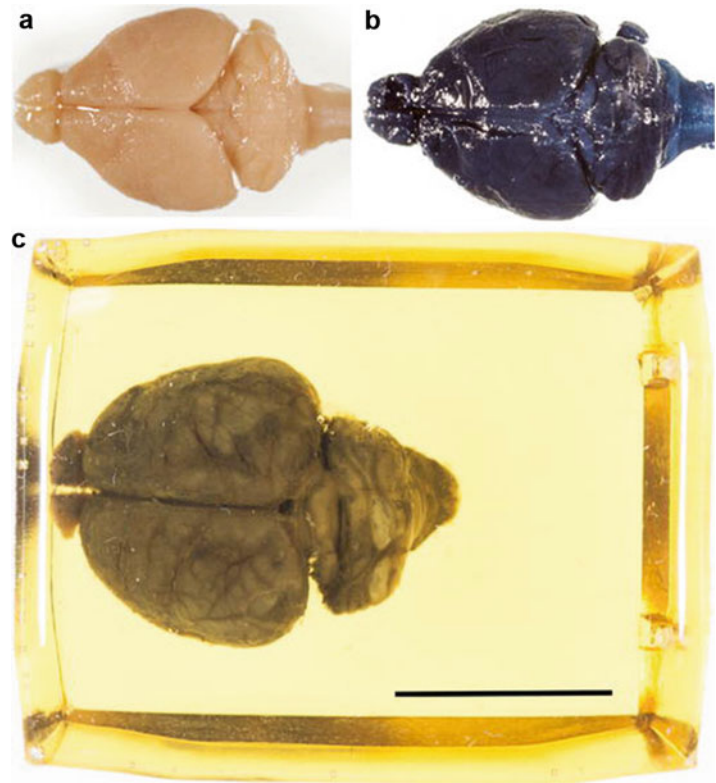
Common fixatives that are used are aldehydes such as formaldehyde (see Fig. 1a) and glutaraldehyde (Jaeger 2001). Less common fixatives that also can be used for specialized purposes are mercuric chloride (HgCl_2) and osmium tetroxide (OsO_4). All fixatives are toxic, but HgCl_2 and OsO_4 are especially so, and great care must be exercised if these fixatives are used. Formaldehyde is often used in the form of paraformaldehyde, which is a polymerized form of formaldehyde (Senda et al. 2005). Fixation should be carried out as rapidly as possible, and whole animal fixation is preferably carried out through perfusion (Mayerich et al. 2008a; Gage et al. 2012). Small pieces of tissue can effectively be fixed using immersion fixation, where the tissue, after it is excised from the body, is immersed in a fixative solution for an appropriate period of time (usually 48–96 h, depending on the volume of the tissue and the storage temperature – room temperature or refrigerated). After an appropriate time for fixation has elapsed, then the tissues can be stained.

Staining

Whole specimens can be stained either “en bloc” or using surface staining as sections of tissue are

Imaging, Specimen**Preparation, Fig. 1**

(a) Perfusion-fixed whole mouse brain, dorsal view. Brain was perfused with 10 % neutral-buffered formalin. (b) Perfusion-fixed whole mouse brain also stained en bloc with thionine. (c) Golgi-Cox-stained rat brain embedded in araldite resin. Scale bar = 1 cm and applies to all three figures



removed. Alternatively, individual neurons can be stained by injection of a dye such as biocytin (Jaeger 2001). En bloc staining refers to staining tissue components through the tissue while the tissue is still in one piece (Choe et al. 2011; Tapia et al. 2012). En bloc staining has been used to prepare electron microscopy samples for more than 30 years, but those samples have a typical volume of one cubic millimeter (1.0 mm^3), which is $1,000\times$ smaller than the volumes described in this protocol. However, en bloc staining methods have been developed using Nissl (see Fig. 1b) and Golgi-Cox staining for neurons (see Fig. 1c), using India ink to highlight blood vessels including capillaries, and heavy metal stains to produce high tissue contrast in serial sections used for field emission scanning electron microscopy (FESEM) (Jaeger 2001; Mayerich et al. 2008b; Choe et al. 2011; Tapia et al. 2012; Mikula et al. 2012). Nissl staining (typically cresyl violet or thionine dyes) stains neuronal cell bodies, while Golgi-Cox staining stains an entire neuron including the cell body as

well as its processes (dendrites and axon). India ink is used to fill the lumens of all blood vessels including the smallest blood vessels, the capillaries. Once staining is accomplished, the stained tissues can be processed for embedding in a resin that will allow the tissue to be sectioned.

Processing and Embedding

Synthetic resins such as Epon, Araldite, Spurr's resin, and LR White are commonly used to embed specimens so that thin sections ($0.5\text{--}1.0 \text{ }\mu\text{m}$) can be cut. After staining, tissues are dehydrated using graded alcohols and then immersed in an intermediate chemical (such as acetone or propylene oxide) that is miscible with alcohols and also with synthetic resins. The specimens are then infiltrated with the liquid resin before they are polymerized (see Fig. 1c). LR White is miscible with alcohol so an intermediate chemical is not needed during processing. Also, LR White does not quench fluorescence under normal processing

conditions, so it can be used for specimen prepared with fluorescence immunohistochemistry or green fluorescent protein (GFP) labeling (Luby-Phelps et al. 2003).

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Independent Component Analysis of Images

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Synonyms

Independent component analysis of natural images; Olshausen-Field model; Sparse coding of natural images

Definition

Independent component analysis (ICA) is a general machine learning method for analyzing the statistical structure of data or signals. It is based on a linear generative model with statistically independent and non-Gaussian latent variables. In computational neuroscience, it can be applied on small patches (windows) of ordinary photographic images to model their structure. The result is that the independent components are similar to the outputs of simple cells in the primary visual cortex (V1). Thus, ICA of natural images provides an interesting theory to explain why the response properties (receptive fields) of simple cells in V1 are as they are: they are adapted to the statistical structure of natural images. This supports the more general hypothesis that the visual cortex constructs an internal probabilistic model of the world and codes the incoming input efficiently.

Detailed Description

Background and Motivation

In neuroscience, some of the most interesting questions to ask are the “why” questions: Why does a system in the brain function as observed? In vision, an important instance is the question of why the receptive fields in the visual cortex are what they are. The most common target here is V1 simple cells known to have spatially localized, oriented, band-pass receptive fields.

A long-standing hypothesis is that the visual cortex is adapted to the statistical (probabilistic) properties of the typical input. Intuitively speaking, typical images that the brain receives (“natural images”) are clearly not random white noise: locations next to each other tend to have similar luminance (grayscale value), and on a more abstract level, there are many contour-like continuities in the data. The hypothesis can be formulated from the viewpoint of coding images, in which case it is called *efficient coding*, where efficiency is taken in the sense of information theory. Alternatively, a Bayesian approach assumes that the visual cortex uses an internal *prior model* of natural input to perform probabilistic inference.

The main goal in ICA of natural images is to investigate the validity of this hypothesis. We can collect a large number of natural images as digital photographs and use ICA to analyze their statistical properties, or *natural image statistics*. If the results show similarities to known V1 properties, this can be seen as evidence supporting the hypothesis of adaptation to natural image statistics, which would provide a widely applicable theory on sensory processing.

ICA Model

Independent component analysis (ICA) is a general statistical (probabilistic) model of multi-dimensional data (Hyvärinen et al. 2001), but here we explain it in terms of image modeling. Denote by $I(x, y)$ the grayscale values of a natural image with x and y indicating the horizontal and vertical pixel location. While the images analyzed

are digitized in practice, we consider the grayscale values as continuous valued here and further assume that the mean grayscale value has been subtracted.

Since we model the brain’s probabilistic prior model about the structure of natural images (and, in practice, analyze a large collection of images), I is considered a random quantity, in particular a random vector. Denote by $A_i(x, y)$ the features (also called basis vectors) which are used to model the images; learning (estimating) these features is the main goal of ICA. The number of features, denoted by k , is fixed to be equal to the number of pixels in the basic model. The starting point in ICA is to express the data as a *linear superposition* of features:

$$I(x, y) = \sum_{i=1}^k A_i(x, y) s_i$$

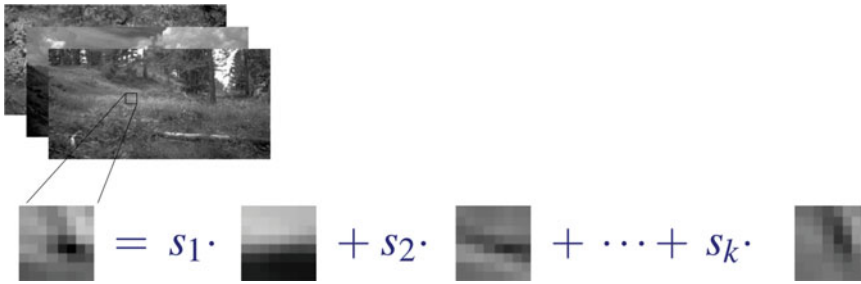
where the components s_i are the coefficients of the features in a particular image. The components s_i are random variables, since they are different from one image to another, i.e., they are random in the same sense as I , while the A_i are nonrandom quantities, constant for all images. The linear model is illustrated in Fig. 1.

Once we specify the statistical properties (i.e., probability distributions) of the random variables s_i , we obtain a model which is *statistical* (or probabilistic) in the sense that it defines a probability distribution in the space of images I . The model is also *generative* in the sense that it describes how the data can be generated by first randomly generating the s_i and then linearly transforming them into I .

What distinguishes ICA from related statistical models are the statistical assumptions that we make on the s_i . In ICA, we assume that:

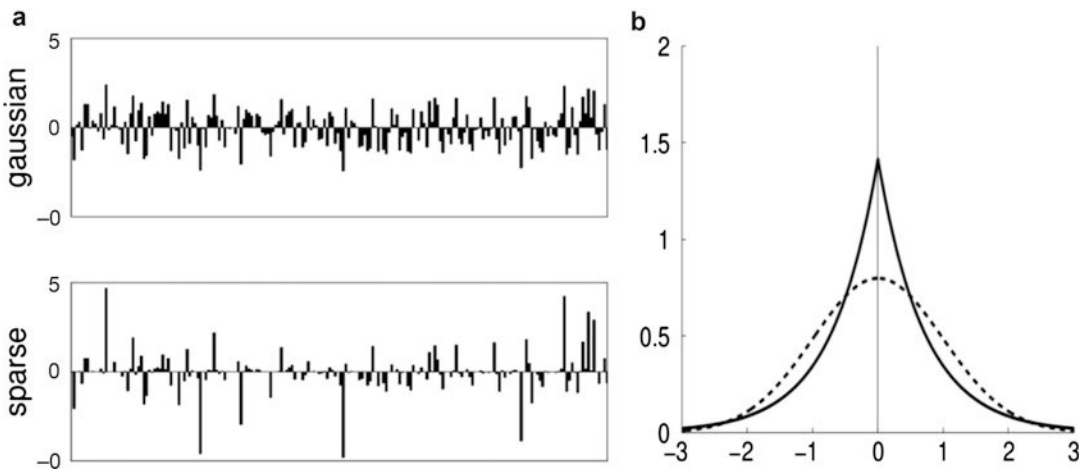
- The s_i are statistically independent from each other.
- The s_i have non-Gaussian distributions.

Especially the assumption of *non-Gaussianity* is important and sets ICA apart from classical methods such as principal component analysis (PCA) or factor analysis. Non-Gaussianity can



Independent Component Analysis of Images, Fig. 1 Illustration of linear modeling of the statistical properties of images. Given a set of large natural images, we sample small patches from them and express each as a linear superposition of the features which can be directly

plotted as image patches themselves. The goal is to learn the statistically optimal features. For illustration purposes, we have already plotted here some typical features learned by ICA



Independent Component Analysis of Images, Fig. 2 Illustration of sparsity, from Hyvärinen et al. (2009). In (a), samples are drawn from a sparse distribution and a Gaussian distribution of the same variance. The sparse variable takes more often very large values or values

very close to zero. In (b), a sparse probability density function (*solid*) is compared with the Gaussian one of equal variance (*dashed*). The sparse density has a prominent peak at zero and heavier tails (not very visible in this plot)

take many forms in general, but the fundamental form of non-Gaussianity in natural images is *sparsity*, i.e., the property that the s_i are very close to zero most of the time and only occasionally obtain very large values. Sparsity should not be confused with small variance; the difference is illustrated in Fig. 2.

Importantly, no assumptions on the A_i , other than their linear independence, are made in ICA. That is, the A_i are *not* assumed to be spatially localized or oriented or to have any specific spatial properties. Instead, the entire learning process is based on the statistical properties of the s_i . Any

specific tuning properties of the A_i are due to the statistical structure of images.

A fundamental theorem in ICA says that the model can be estimated by finding the linear features A_i which maximize the non-Gaussianity of the obtained components s_i (Hyvärinen et al. 2001). Such maximization of non-Gaussianity can be shown to be equivalent to different estimation principles such as maximum likelihood estimation, minimization of mutual information (statistical dependence) between the components, as well as maximization of information flow in a nonlinear network. (The last principle leads to an algorithm

which is often called the “infomax algorithm,” although infomax is in fact a general principle that can be used for other purposes than ICA.)

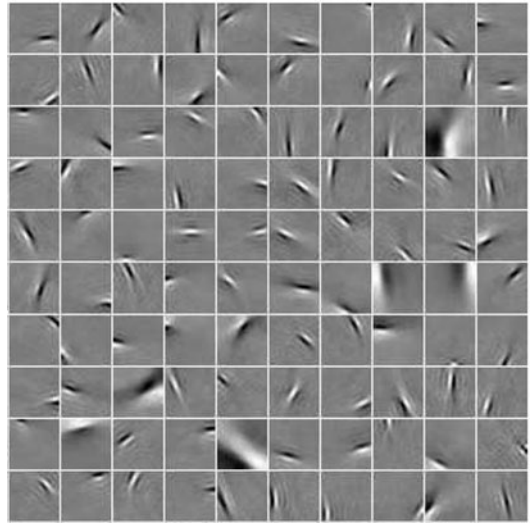
Due to the prominence of sparsity in natural images, ICA for images is essentially maximization of the sparsity of the estimated components. Thus, ICA is often called *sparse coding* in that context. The first application of ICA-like models on natural images was the Olshausen-Field sparse coding model discussed below.

Results on Natural Images

In practice, to keep the computations manageable, the natural images used in the model are very small, typically only a few hundred or thousand pixels; in other words, we model small parts of whole natural images, called patches or windows. In the simplest case we only model their grayscale values, although modeling of color and stereo images as well as video is equally possible.

Before applying the model to the data, the dimension is often reduced by principal component analysis (PCA) to reduce artifacts due to the limited pixel resolution. Such preprocessing does not change the theory in any way: The original pixels in the ICA model given above are simply replaced by the variables given by the principal components.

Results obtained by running ICA on a set of wildlife images are shown in Fig. 3. The features A_i have the characteristic properties of V1 simple cell receptive fields: they are spatially localized, oriented, and localized in spatial frequency. Alternatively, we could analyze the spatial filters which are obtained by inverting the generative model of ICA and more closely correspond to receptive fields; such spatial filters are essentially “sharper” versions of the features A_i , obtained by boosting their high-frequency content. Thus, we can consider that either the A_i or the spatial filters obtained by inversion provide a model of the linear receptive fields of simple cells, and the s_i model the actual responses. Due to the abstract nature of the ICA model, and linear models in general, the correspondence between the elements of the model and neuroscientific quantities is not quite unambiguously defined.



Independent Component Analysis of Images, Fig. 3 Some features A_i estimated by ICA from natural images, adapted from Hyvärinen et al. (2009). The size of the patches was 32×32 pixels, the number of patches was 50,000, and the PCA dimension was 256. ICA was performed by the FastICA algorithm. Each small square here corresponds to one feature A_i , which is plotted as an image patch itself; *gray* corresponds to zero, *white* to positive, and *black* to negative values. A given image patch can be constructed as a weighted sum of these A_i as in Fig. 1, where the weights s_i are different for each image patch

Extensions

The number of features can be larger than the number of pixels, which is called the case of an overcomplete basis. Furthermore, a Gaussian noise term $N(x, y)$ can be added to the generative model to model miscellaneous random effects. In both cases, the resulting features (basis vectors) are very similar to what is obtained by the basic model. Nevertheless, when the models are used for Bayesian inference, these extensions can change the results of the inference substantially. The original Olshausen-Field sparse coding model had a noise term and an overcomplete basis but is otherwise almost identical to the model described above. (The main further difference is that the Olshausen-Field model assumes the components to be sparse, while ICA allows different kinds of non-Gaussianity. However, for natural images, this hardly changes the results.)

As another extension, the components can be assumed to have limited statistical dependencies instead of being completely independent. Prominent examples of such modeling are topographic ICA (see ► [Topographic Independent Component Analysis](#)) and normalization models which explain extra-classical receptive fields including surround suppression (Simoncelli and Olshausen 2001).

Cross-References

► [Topographic Independent Component Analysis](#)

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Independent Component Analysis of Natural Images

► [Independent Component Analysis of Images](#)

Information Geometry as Applied to Neural Spike Data

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Definition

Information geometry studies invariant structures of a family of probability distributions. Such a family forms a Riemannian manifold together with a dual pair of affine connections (Amari

and Nagaoka 2000). Neural spike train data are of stochastic nature described by probability distributions. Information geometry is applied for elucidating the properties of spiking processes spread over a number of neurons as well as over time.

Detailed Description

Neuronal spike data are composed of a collection of binary variables $D = \{x_i(t)\}$, where $i = 1, \dots, n$ denote the numbers of neurons in an ensemble and t denotes the discrete time, $t = 1, 2, \dots, T$, such that $x_i(t)$ is 1 when a spike exists and 0 otherwise. The probability distribution governing $\{x_i(t)\}$ is searched for from observed data in order to elucidate temporal and spatial correlations of spikes. Since $x_i(t)$ are binary random variables, its distribution belongs to an exponential family, which is geometrically a dually flat Riemannian manifold.

Correlations and Joint Firing Rates

We first search for correlational structure in a neuronal ensemble, neglecting temporal aspects. Random variables are $\mathbf{x} = (x_1, \dots, x_n)$, where t is omitted. It is assumed that the data are generated subject to a probability distribution $p(\mathbf{x})$. Since there are 2^n firing patterns $\mathbf{x}$, the degrees of freedom of $p(\mathbf{x})$ are $N = 2^n - 1$. Hence, a probability distribution is specified by N -dimensional parameter, which forms a coordinate system in the manifold $S = \{p(\mathbf{x})\}$.

The log of probability $p(\mathbf{x})$ is expanded in a polynomial as

$$\log p(\mathbf{x}, \boldsymbol{\theta}) = \sum \theta_i x_i + \sum \theta_{ij} x_i x_j + \dots + \theta_{12\dots n} x_1 x_2 \dots x_n - \psi,$$

where ψ is the normalizing factor and the coefficients $\boldsymbol{\theta} = (\theta_1, \dots, \theta_n; \theta_{12}, \theta_{13}, \dots, \theta_{n-1n}; \dots, \theta_{12\dots n})$ are used as a coordinate system to specify probability distributions in S . Since $\log p(\mathbf{x}, \boldsymbol{\theta})$ is linear in parameter $\boldsymbol{\theta}$, such a family is called an

exponential family of probability distributions and parameter θ is called a natural or canonical parameter.

Let us use another type of parameters given by

$$\begin{aligned}\eta_i &= E[x_i], \eta_{ij} = E[x_i x_j], \dots, \eta_{12\dots n} \\ &= E[x_1 \dots x_n],\end{aligned}$$

where E denotes expectation. These parameters $\eta = (\eta_i; \eta_{ij}; \dots; \eta_{1\dots n})$ form another coordinate system of S , called the expectation parameter or joint firing rate parameters, because

$$\begin{aligned}\eta_{i_1\dots i_k} &= E[x_{i_1} \dots x_{i_k}] \\ &= \text{Prob}\{x_{i_1} = 1, \dots, x_{i_k} = 1\}\end{aligned}$$

represents the joint firing rate of neurons $i_1, \dots, i_k$.

The two coordinate systems are hierarchically organized (Amari 2001), from the first-order parameters such as

$$\theta^1 = (\theta_1, \dots, \theta_n); \eta^1 = (\eta_1, \dots, \eta_n),$$

the second-order parameters

$$\begin{aligned}\theta^2 &= (\theta_{12}, \theta_{13}, \dots, \theta_{n-1n}); \eta^2 \\ &= (\eta_{12}, \eta_{13}, \dots, \eta_{n-1n}),\end{aligned}$$

until the n th-order parameter

$$\theta^n = \theta_{12\dots n}; \eta^n = \eta_{12\dots n}$$

We use indices I, J , etc. as θ_I or η_I to denote components of θ or η , where they run over $\{1, \dots, n; 12, 13, \dots, nn-1; \dots; 1\dots n\}$. Obviously, when n neurons fire independently, all the higher-order terms $\theta^2, \dots, \theta^n$ corresponding to the expansion of log probability vanish, and parameters $\eta^2, \dots, \eta^n$ are written in the product forms of firing rates η_i of individual neurons.

Orthogonality of Parameters

The probability distribution is denoted as $p(x, \xi)$, where ξ is either θ or η in our case. The Fisher information matrix is defined by the expectation of the product of two score functions,

$$g_{IJ} = E \left[\frac{\partial}{\partial \xi_I} \log p(x, \xi) \frac{\partial}{\partial \xi_J} \log p(x, \xi) \right],$$

where I denotes components of ξ . Two parameters ξ_I and ξ_J are said to be orthogonal when their scores are not correlated,

$$E \left[\frac{\partial}{\partial \xi_I} \log p(x, \xi) \frac{\partial}{\partial \xi_J} \log p(x, \xi) \right] = 0,$$

in other words the (I, J) component G_{IJ} of Fisher information matrix vanishes. It is remarkable that parameter θ_I is orthogonal to parameter η_J for $I \neq J$. When ξ_I and ξ_J are orthogonal, changes $d\xi_I$ and $d\xi_J$ are clearly separated, because the respective changes in the score are orthogonal. The orthogonality is useful for characterizing the parameters (Nakahara et al. 2006).

Higher-Order Correlations

Let us consider the set of parameters $\eta^1, \dots, \eta^k$ consisting of the joint firing probabilities up to order k . Then, they are orthogonal to the natural parameters $\theta^{k+1}, \dots, \theta^n$ of which orders are higher than k (Amari 2001). Therefore, θ^2 is a parameter which is orthogonal to the firing rates η^1 . On the other hand, the third-order parameters θ^3 are orthogonal to the firing rates η^1 and joint firing rates η^2 of any pairs of neurons, so that they are not affected by pairwise correlations given by the joint probability of two neurons. Therefore, θ^3 represents higher-order interactions of three neurons.

This shows that θ^2 are responsible to pairwise correlations and θ^3 are responsible for triple-wise correlations which cannot be decomposed into pairwise correlations. Higher-order correlations are determined in this manner (Abeles and Gerstein 1988).

Higher-Order Interactions and Dichotomized Gaussian Distribution

The full model S includes N degrees of freedom which are too large to handle. Tractable models

are required. The Boltzmann machine, sometimes called the maximum entropy family, includes only up to the second-order interactions so that its degrees of freedom is of the order of n^2 . The dichotomized Gaussian distribution is another model, where each neuron collects information from its environment, such that its membrane potential is subject to a Gaussian distribution. Its output is 0 or 1, depending on whether it exceeds a threshold or not. So it is written as

$$x_i = \begin{cases} 1, & u_i > h, \\ 0, & u_i \leq h, \end{cases}$$

where h is the threshold and u_i are membrane potentials of neurons $i = 1, \dots, n$ which together are subject to a joint Gaussian distribution (Amari et al. 2003). The degrees of freedom of this model are order of n^2 so that the model is tractable. It is possible to fit experimental data by using the dichotomized Gaussian model (Macke et al. 2011; Yu et al. 2011). It is interesting to see dichotomization generates higher-order correlations even when there are none in a continuous random variable.

Temporal Structure of Spikes

Temporal structure of spikes is studied by using various temporal models such as the Markov model. A renewal model is often used to represent temporal structure. Let T be an interspike interval of spikes of a neuron. The renewal model assumes that a sequence $T_1, \dots, T_k$ of intervals is independently distributed. The gamma distribution is a frequently used model which has the following probability density of T :

$$p(T; \kappa, \xi) = \frac{(\xi\kappa)^\kappa}{\Gamma(\kappa)} \Gamma^{\kappa-1} \exp\{-\xi\kappa T\}.$$

It includes two parameters ξ and κ . ξ is the parameter representing the firing rate of a neuron and κ is responsible for the refractoriness after spike. It is called the shape parameter.

When both ξ and κ are constant, it is easy to estimate them from observed data. However, the

firing rate ξ usually changes over time, while the shape parameter κ is considered to be fixed. In such a case, one needs to estimate κ under the condition that ξ changes. This is a semiparametric statistical problem since the values of ξ at each interval are unknown. Information geometry is applicable in such a case too (Miura et al. 2006).

Let us assume that the values of ξ are the same at least for two consecutive intervals T_{2i} and T_{2i+1} . Then, the estimating equation of κ is given by

$$\sum_i [\log T_{2i} T_{2i+1} - 2 \log (T_{2i} + T_{2i+1}) + 2\phi(2\kappa) - 2\phi(\kappa) = 0],$$

where $\phi(\kappa)$ is the bi-gamma function. The statistics which is used for estimation is

$$S_I = \frac{1}{2} \sum_j \log \frac{4T_{2i}T_{2i+1}}{(T_{2i} + T_{2i+1})^2}.$$

This is related to Shinomoto's L_V (Shinomoto et al. 2003).

Cross-References

- Estimation of Neuronal Firing Rate
- Spike Train

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Information Measures of Redundancy and Synergy in Neural Activity

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Definition

Two descriptions of an underlying signal should be expected to be more informative than either one of the descriptions itself. However, several scenarios can be imagined. First, if the two descriptions each represent independent aspects of the underlying signal, then the two descriptions should be twice as informative as any one by itself. Second, if the two descriptions provide partially overlapping information, then the two descriptions together should be *less than* twice as informative as any one by itself. In this case, we say that the two descriptions are *redundant*. A third scenario requires a somewhat more specific setup. Namely, suppose now that each description provides a *noisy* version of the underlying signal, but with different noises. Then, it could happen that the two noises cancel each other out and, hence, that the two descriptions together are *much more* than twice as informative as any one by itself. A similar observation applies if the noises only approximately cancel each other out. In these cases, we say that the two descriptions are *synergistic*.

The next goal is to *quantify* the degree of redundancy or synergy present in a collection of signal descriptions. Many different approaches to this can be envisioned. The present note reviews the use of information measures for this purpose.

Detailed Description

Information Measures of Redundancy and Synergy

Redundancy and synergy can be quantified in many different ways. The present note concerns *information measures*, as pioneered by Shannon (1948).

Based on an intuitive understanding of Shannon's information measure, it is natural to propose the following information measure of synergy and redundancy of two neurons, neuron A and neuron B:

$$R = I_A + I_B - I_{AB} \quad (1)$$

Here, I_A is the information provided by the response of neuron A alone, I_B is the information provided by the response of neuron B alone, and I_{AB} is the information provided by both responses together. This measure appears in many sources, including Rieke et al. (1996, p. 268). We then have the following terminology:

1. If $R = 0$, the two neurons respond *independent* of each other.
2. If $R > 0$, the two neurons are said to respond in a *redundant* fashion.
3. If $R < 0$, the two neurons are said to respond in a *synergistic* fashion.

It is easy to see that R cannot be larger than $I_A + I_B$. However, a sometimes undesirable feature of this definition is that R can be arbitrarily negative irrespective of the values of I_A and I_B . To see this, it is sufficient to consider a scalar normal (Gaussian) probabilistic model. Supposing that the underlying signal has unit variance and that the responses are simply noisy versions of this signal, where the noises have unit variance and correlation coefficient ρ , we find $R = (1/2)/\log_2(4(1 + \rho)/(3 + \rho))$. As should be expected, this is maximized when $\rho = 1$, the case where the two noises are exactly equal, representing the case of maximal redundancy. However, as ρ approaches -1 , it becomes arbitrarily negative, representing the case of maximal synergy.

The literature introduces many slight variants of this quantity, particularly introducing normalization. For example, in Reich et al. (2001), Machens et al. (2001), a “redundancy index” is introduced which can be expressed as $R/\min\{I_A, I_B\}$ (where we note that Machens et al. (2001) incorporates a Gaussian probabilistic assumption into the definition). Another popular normalization is to define $r = R/I_{AB}$ as this quantity is now bounded between -1 and 1 ; see, e.g., Schneidman et al. (2003).

Finally, it should be clear that the above redundancy measure R is easily extended to many neurons: In general, it is simply the difference between the sum of the individual informations and the joint information (leveraging all neurons simultaneously for decoding).

Should We Expect Redundancy and Synergy in the Neural Code?

Let us first consider the scenario where we get to design the representation (the code) completely freely. For this scenario, Shannon has shown that when optimally representing or compressing information, the resulting descriptions will be independent of each other; hence, there will be neither redundancy nor synergy. There are two fundamental assumptions underlying his proof. First, the descriptions are deterministic functions of the underlying information. Second, the descriptions are available in full at the destination.

There appears to be a wide consensus that both of these assumptions are violated in neural systems. In particular, successive runs of the same experiment reveal variations in the descriptions, suggesting that the code is not a deterministic mapping. Moreover, there is also experimental evidence that descriptions are merged, altered, or lost in transit as they advance in the neural processing pathway. Therefore, the optimal representations need not be independent. Rather, they may be redundant or synergistic. Shannon’s information theory has not yet been fully extended to cover such scenarios, revealing only partial results to date. Therefore, contemporary information theory cannot make a clear prediction concerning the optimal degrees of redundancy or synergy in a network.

Some Experimental Studies of Redundancy and Synergy via Information Measures

Many experimental studies have identified synergy and redundancy via information measures in various parts of the neural system. We briefly discuss a few here. The beginning appears to be marked by the studies presented in Reich et al. (2001), Machens et al. (2001), Nirenberg et al. (2001), which all concern sensory modalities. To take them up in turn, in Reich et al. (2001), the authors consider the primary visual cortex in monkeys and report results on the relationship between the redundancy and the size of the considered cluster of neurons. In Machens et al. (2001), the authors consider the insect auditory pathway. They analyze the redundancy conditioned on stimulus classes and, among other findings, observe that stimuli with higher bandwidth lead to reduced redundancy. Finally, in Nirenberg et al. (2001), the authors study the importance of correlated firing in retinal ganglion cells in the mouse. They use a redundancy measure similar to R as defined above to conjecture that correlations are not important and that the cells act mostly independently.

Redundancy and synergy have also been studied in motor cortex via information measures. In Narayanan et al. (2005), the authors report widespread redundant neuron populations in the rat motor cortex. In So et al. (2012), a similar consideration is applied to the monkey motor cortex, both in natural and prosthetic motor control.

Another use of redundancy was presented in Amin et al. (2013), concerning the auditory cortex. The study compares songbirds raised in a white noise environment to controls and finds an increased redundancy in the former when natural stimuli are applied.

Computational Issues

While it is often possible to empirically assess information measures for a single neuron from usual data sets, it is much more challenging to estimate the joint information for a population of neurons. The data requirements increase

exponentially with the size of the population. To deal with this issue, a standard approach involves statistical modeling assumptions. For example, in Machens et al. (2001), the authors consider Gaussian statistical models, such that information estimates only depend on second-order statistics that can be estimated reliably from usual data sets.

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Information Processing in the Olfactory Bulb

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Definition

The information processing in the olfactory bulb refers to the ensemble of concurrent dynamics of

chemical and electrical type triggered by the interaction of odors (the information) with the olfactory mucosa and then acting to stimulate the olfactory bulb by which the encoded information arrives to the brain.

Detailed Description

The olfactory system is the pathway by which the odors (mixture of different chemical molecules, the odorants) are perceived, i.e., it performs the information processing. The key role of such a process is played by the *mitral cell*: it is the main component of the olfactory bulb. After the stimulations received from the *olfactory sensory neurons*, the mitral cell conveys the information in order to transmit it to the cerebral cortex (Linster 2014).

Referring to Kavoi and Jameela (2011), Squire et al. (2012), and Kandel et al. (2013), we describe the process from the beginning. Indeed, the information processing starts in the *olfactory epithelium* where it is possible to distinguish several types of cells among them the olfactory sensory neurons. They are small neurons provided with a long dendrite which protrudes into the mucus covering the nasal cavity. At this level, the dendrite gives rise to numerous extensions called *cilia*. These elements have receptors on their surface specialized to bind odorants by means of an hydrogen bond.

It is estimated that the human being is able to detect about 10^4 odorants, but the average number of receptors is only 350 (about). Each odorant molecule interacts with more than one type of receptor. This means that molecules of the same odorant bind a specific sequence of receptors. The surface of the olfactory neurons is provided of only one type of receptor; therefore, the coupling interaction between odorant molecules and receptors originates the activation of a set of neurons. This can be viewed as a *combinatorial code* realizing the perfect match between an odorant and a particular pattern of activated neurons. In this way, the large number of different odors can be detected by the olfactory bulb even if the number of receptors is clearly lower: indeed, each odor is encoded by means of the combinatorial code deriving from

which and how much olfactory receptors are activated during the above interaction.

The odorants' binding causes variations in the membrane potential of olfactory neurons until it attains the threshold value needed to open voltage-dependent sodium channels. This event originates the *firing* of the olfactory neuron as an action potential transmitted by means of its axon. This phenomenon is known as the *sensory response* and it is subject to the *adaptation phenomenon*; the latter can be identified as the decline of the firing rate during such response. The adaptation is essentially due to the action of calcium which activates proteins triggering a cascade of chemical reactions.

The axons of the olfactory neurons terminate on the dendrites of olfactory bulb neurons within reticular structures called *glomeruli*. Each axon terminates in only one glomerulus where it establishes a synapse with the dendrite of typical bulbar cells: the so-called *mitral cells* (Li 2013).

In each glomerulus, the axons of several thousand sensory olfactory neurons converge on the dendrites of approximately 40–50 bulbar neurons. In the glomerulus occurs the transmission of the information between the olfactory sensory neurons and the mitral cell (Migliore and McTavish 2013). This is the basis of a convergence process aimed to convey the sensory information to limited and well-defined areas of the ipsilateral cerebral hemisphere. However, the organization of sensory information is different from that of the epithelium. Although olfactory sensory neurons with the same odorant receptor are randomly scattered in one epithelial zone, their axons converge in the same glomerulus.

Each glomerulus, and each mitral neuron connected to it, receives input from just one type of sensory neuron. This organization has the advantage to maintain the arrangement of inputs in the olfactory bulb unaltered. The result is a precise arrangement of inputs from different odorant receptors. Because each odorant is recognized by a unique combination of receptors, each odorant also activates a unique combination of glomeruli in the olfactory bulb. In summary, we can say that the combinatorial scheme based on activated receptors is refined at the level of glomeruli, while retaining the information it carries.

Each glomerulus is also encircled by *periglomerular interneurons*: they receive excitatory inputs from sensory axons and make inhibitory dendro-dendritic synapses with mitral cell dendrites in that glomerulus. The periglomerular cells are considered to have a role in *signal modulation*. In the processing of stimuli, the mitral cells make an active synapse with inhibitory interneurons called *granule cells*. This connection constitutes a negative feedback in order to turn off the mitral cell itself.

Finally, the axons of the mitral cells project to the olfactory cortex. The olfactory cortex is defined as the portion of the cortex that receives the direct stimulus from the olfactory bulb and comprises five areas: the anterior olfactory nucleus, the anterior and posterior cortical nuclei of the amygdala, the olfactory tubercle, part of the entorhinal cortex, and the piriform cortex (the largest olfactory cortical area).

At the end, we can remark that the olfactory bulb plays its role as an information processor placing itself in the middle between the odor sensation and the odor perception. The sensation is the capacity to bring the information from the outside world to the nervous structures where they are analyzed, codified, and integrated with stimuli of different sensory areas (those related to the vision, the memory, the emotions) (Linster and Cleland 2014). The perception is the capacity to become aware of the information brought by the stimulus as a result of the complex elaboration made during the sensation process.

On Mathematical Modeling of Information Processing

For modeling purposes, in the previous description, we can distinguish three essential steps responsible of the information processing: (1) the impact of the odors on the olfactory mucosa, i.e., the binding of the odorant molecules in the cilia of the olfactory sensory neurons and the consequent electro-chemical reactions, (2) the interaction between the olfactory sensory neurons and the mitral cells by means of the reticular structure of glomeruli, and (3) the propagation of the stimulus from the mitral cells to the cortex. During the step (1), all concurrent dynamics produce a combinatorial code of the information

received from the outside; the code is based on the number and on the type of the activated receptors. In the step (2), taking into account the previous combinatorial code, a firing activity of specified olfactory sensory neurons occurs in the glomeruli and finally, in the step (3), the mitral cells stimulated by means of the glomeruli provide to propagate the stimulus until to the cortex.

It appears therefore evident that the incoming information is appropriately transformed, at first, into a combinatorial code which decides which and how many neurons must be involved in the information transmission, and subsequently their firing activities provide to bring the information at the level of perception. Definitively, the information processing can be viewed as a transformation in *space* (the geometry of the network and of the connections of the activated neurons) and in *time* (rate and timing of firing activities) of the input information.

Remarking that the process is still the subject of extensive studies, a very large number of papers is dedicated to mathematical models for the description, the comprehension, and the prediction of specific aspects of this complex neuronal dynamics, among them those of stochastic type (see, for instance, Burkitt (2006), Levakova et al. (2015), and reference therein). These models are characterized by the use of the *noise* to model the random fluctuations converting some additional unknown dynamics that can affect the main process. Stochastic models of networks of interacting neurons (Buonocore et al. 2014; Carfora and Pirozzi 2017) can be well adapted to represent the physical geometry of the olfactory system, its connections, and the activation scheme. Furthermore, specific models are devoted to the investigation of the neuronal code deriving from the timing and the rate of the firing activity (Buonocore et al. 2015; Shinomoto 2014; D'Onofrio and Pirozzi 2016) of all involved neurons. Moreover, the modeling of some other collateral, but not less important, phenomena also has been considered in order to improve the knowledge of this topic: the adaptation phenomenon (Buonocore et al. 2016), the feedback actions (Vidybida and Shchur 2018), multitimescale dynamics (Kobayashi et al. 2009), some other

actions that can be also represented as a sort of neuronal memory (Hodara and Löcherbach 2017; Pirozzi 2017; Abundo and Pirozzi 2018; Ascione and Pirozzi 2018), or effects of different noises in the models (D'Onofrio et al. 2018). Specific measures of information have also to be considered (see, for instance, Kostal and Shinomoto (2016), Kostal and D'Onofrio (2018), and references therein). Finally, specialized techniques of the parameters' estimation (Vich et al. 2017) reveal powerful tools to verify how well some of the above mathematical models adapt to the phenomenological evidences.

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Information Transmission by Neural Populations

- [Efficient Population Coding](#)

Inner Ear Prosthesis

- [Auditory Prosthesis](#)

Insect Olfaction: A Model System for Neural Circuit Modeling

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Definition

Insect olfactory system denotes the network of cells – including the sensory neurons located on the antennae and the interneurons located in several areas of the brain such as the antennal lobe, the mushroom body, and the lateral horn – that work together to enable the sense of smell in an insect. Here we describe this circuit and consider why it makes a good model system for computational modeling of neural circuits.

Detailed Description

Olfaction presents some difficult problems. Unlike the visual or the auditory system, whose stimuli – light or sound – can be described along the dimensions of frequency and intensity, the olfactory system works with volatile chemicals, which come in numerous shapes and sizes, defying easy description in one or a few dimensions. But, like visual and auditory stimuli, olfactory stimuli may also vary in their intensity, timing, or spatial distribution. It remains a puzzle how the brain makes sense of this multidimensional input (Laurent 2002).

Many animals, including large mammals and small insects, use odors as cues for finding food and mates or for avoiding predators. Although insects have small brains – with five orders of magnitude fewer neurons than humans – they

possess well-developed olfactory systems comparable in organization and capability to their human counterpart (Hildebrand and Shepherd 1997; Kay and Stopfer 2006). These structural and functional similarities, together with their greater amenability to experimental manipulation, make insects attractive models for studying olfaction. Ongoing experiments in several insect species including locusts, moths, flies, bees, and cockroaches are revealing not only the number, morphology, and responses of olfactory neurons but also their interactions and organization into circuits throughout the brain (Hansson 1999). For the computational neuroscientist interested in modeling neural circuits, the insect olfactory system thus provides a rare combination of simplicity of organization, richness of features, and availability of experimental data, which together allow for biologically plausible and functionally useful models. Below, we illustrate how different types of computational models have drawn upon these advantages of the insect olfactory system to further our understanding of the brain.

Insect Olfactory Anatomy and Physiology

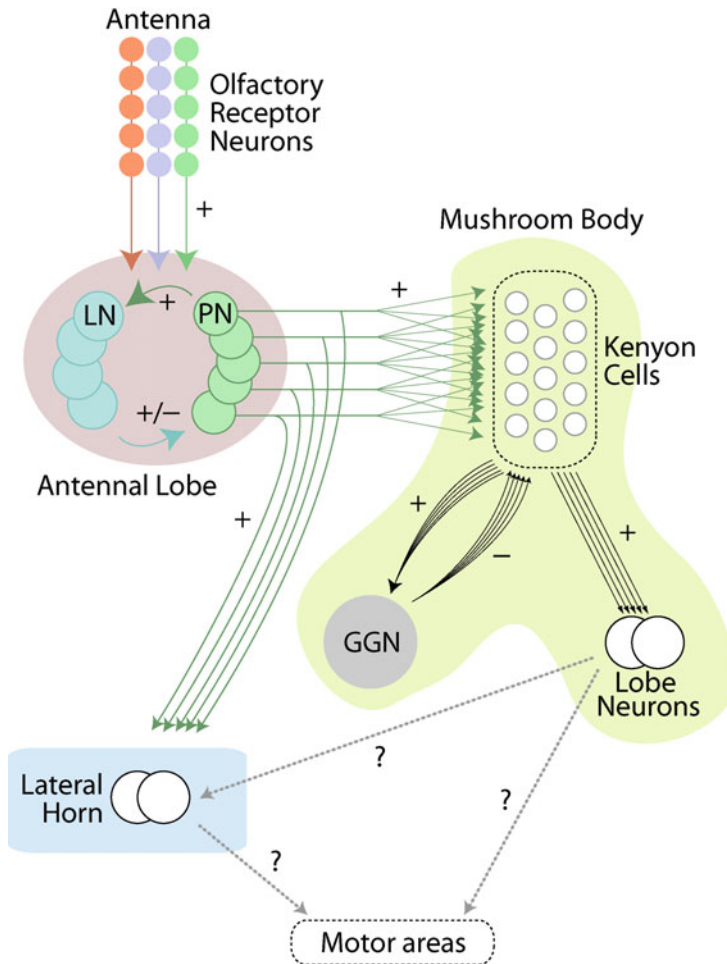
In insects, odor detection begins when odorant molecules in the environment bind to olfactory receptor neurons (ORNs) located on the antennae and other body parts. Different odorants can elicit different patterns of spiking in different but overlapping sets of ORNs. ORNs send their axons to antennal lobes in the brain (Fig. 1), where the axons synapse onto local neurons (LNs) and projection neurons (PNs) within interacting spherical neuropils called glomeruli. In locusts, tens of thousands of ORNs converge onto an estimated 300 LNs and 830 PNs. Local interactions among ORNs (excitatory), PNs (mostly excitatory), and LNs (inhibitory or excitatory) in the antennal lobe cause PN spikes to be synchronized into a fast, ~20 Hz oscillatory rhythm riding atop slower temporal patterns of spikes distributed spatially among the population of PNs. These spatiotemporal patterns encode information about odor

identity, intensity, and timing (Stopfer et al. 2003; Brown et al. 2005).

PNs convey this spatiotemporal code directly to higher olfactory centers of the brain: the mushroom body and the lateral horn (Fig. 1). In the mushroom body, PNs synapse with a large population of Kenyon cells (KCs, 50,000 in locusts). Unlike PNs, each KC responds sparsely to very few odors, with very few spikes (Perez-Orive et al. 2002). KCs send their axons to lobes of the mushroom body, converging upon a small number of neurons, some of which provide feedback to KCs, while others send their output beyond the borders of the mushroom body. In the lateral horn, PNs converge on a diverse population of neurons, all of which respond broadly to odors, and which may extract specific stimulus features such as odor intensity (Gupta and Stopfer 2012). Where information goes after the mushroom body lobe neurons and the lateral horn neurons is not completely clear. This mystery underlies an area of active research.

Computational Models in Insect Olfaction

Many types of computational models exist, and based on their primary purpose, models of the insect olfactory system may be divided into three categories: (a) feature-replication models, which try to reproduce an experimentally observed result to help understand the underlying mechanisms; (b) feature-prediction models, which extrapolate from what has been observed to predict unexplored aspects of neural circuits that can be tested later by experiments; and (c) role-detection models, which help explore the functions of experimentally observed features of neural circuits. Below we illustrate each of these categories with an example, focusing on how the model was constrained by experimental data to be biologically realistic and on what we could learn from the model about the functioning of neural circuits. We note that these three categories are not mutually exclusive; in many cases an individual model may serve multiple purposes, as we illustrate with our fourth example.



Insect Olfaction: A Model System for Neural Circuit Modeling, Fig. 1 Insect olfactory anatomy. Multiple types of olfactory receptor neurons (illustrated here with *multiple colors*) located on antennae sense odors and send their output to local neurons (LNs) and projection neurons (PNs) in the antennal lobe. Inhibitory and excitatory interactions between ORNs, LNs, and PNs help transform the sensory information into a spatiotemporal code, which is then carried by PNs to the mushroom body and the lateral

horn. In the mushroom body, the information is received by a large population of sparsely responding Kenyon cells, which then converge on the mushroom body lobe neurons. In locusts, one of the lobe neurons, the giant GABAergic neuron (GGN), helps maintain sparse responses in KCs by forming a normalizing feedback loop; other insects have similar feedback mechanisms. The targets of other lobe neurons and the lateral horns neurons are still being discovered

Models for Feature-Replication: Origin of Temporal Patterns in PNs

In PNs, the spatiotemporal codes for odors consist of elaborate cell- and odor-specific, reliable patterns of spikes, with periods of high activity interleaving periods of silence. These patterns were thought to be generated entirely by circuit interactions within the antennal lobe when provided excitation from the periphery (Wehr and Laurent 1999). However, recent experiments

showed that stimulating antennae with constant current pulses failed to generate patterns as complex as those evoked by odors (Raman et al. 2010). Further, recordings from ORNs – which provide input to PNs – revealed a diversity of temporal spiking patterns (Hallem and Carlson 2006; Raman et al. 2010). Together, these experiments suggested the patterns of spikes in ORNs may also contribute to the patterns of spikes in PNs.

To assess the relative contributions of ORNs and the antennal lobe circuit in generating the temporal patterns of PNs, Raman et al. (2010) constructed a model. The odor-elicited spiking patterns of ORNs were modeled by five parameters: amplitude, latency, rise and fall time constants, adaptation rate, and baseline firing rate; these parameters were initially set to reflect activity recorded *in vivo* and were constrained so that the combined responses of the model's ORNs matched experimentally recorded electro-antennograms, which reflect the summed activity of the antenna's receptors. The antennal lobe was represented in the model by a network of PNs and LNs, whose relative numbers, connection probabilities, and firing properties were drawn from experiments performed *in vivo*. Set in motion, the model's PNs produced realistic and complex temporal patterns when the ORNs provided realistic, temporally heterogeneous input to the antennal lobe. But, when input from the model's ORNs was reprogrammed to lack normal temporal variety, the PNs produced only simple and unrealistic responses. These results suggest that the temporal patterns of ORNs are required to drive the more elaborate temporal patterns in PNs. The model further revealed that interactions between LNs and PNs in the antennal lobe contribute to the fine-tuning of PN patterning, making the responses of different PNs to an odor more distinct over time, and synchronizing the responsive PNs into an oscillatory rhythm (Raman et al. 2010). These features may be a useful downstream for decoding the output of the PN population (Laurent 2002).

Models for Feature-Prediction

Non-synaptic Inhibition in Olfactory Sensilla

In insects and in other types of animals, ORNs reside in small, hair-like formations known as sensilla. Each sensillum encapsulates a small number of ORNs, whose dendrites bathe in a common pool of sensillar lymph and whose somata soak in a common pool of hemolymph. The potential difference between the sensillar lymph and the hemolymph drives odor-evoked

transduction in ORNs. To examine the possible consequences of housing multiple ORNs together in a sensillum, Vermeulen and Rospars (2004) created a two-part model. The first part comprised kinetic equations to analyze the binding of odor molecules and the resulting conductance changes in ORNs. The effects of these conductance changes were then analyzed in the second part of the model, represented as an electrical circuit and constrained by parameters obtained from electrophysiological recordings from sensillae (Vermeulen and Rospars 2001). This model predicted that direct electrical interactions should occur between two neighboring ORNs and that the coupling should be most effective when the ORNs maximally differ in their chemical sensitivity to an odor; such coupling would cause the presentation of the odor to produce enhanced responses in the sensitive ORN while inhibiting the insensitive ORN.

To experimentally test the possibility of non-synaptic electrical coupling between two neighboring ORNs predicted by the model, one needs to know whether a stimulating odor binds to only one ORN or to both. For technical reasons, this experiment proved difficult until recently when Su et al. (2012) used *Drosophila* genetics to do the trick. Analyzing the ab3 sensillum, which houses two neurons (A and B), Su et al. found that activating neuron A with a brief pulse of odor reduced the ongoing firing of neighboring neuron B. But when neuron A was genetically ablated, the same brief pulse of odor induced no change in neuron B, indicating that the odor affected neuron B indirectly, via neuron A. With further experiments examining synaptic connectivity and behavioral performance, the authors established that interactions between neighboring ORNs represent a form of electrical, non-synaptic lateral inhibition and that these interactions can affect behavior (Su et al. 2012).

Models for Role Detection

Maintaining Sparseness by Inhibitory Feedback

One of the neurons postsynaptic to KCs in the mushroom body lobes of locusts is the giant

GABAergic neuron (GGN). This huge cell, which is analogous to the APL neuron in *Drosophila* and to groups of recurrent neurons in other insects, receives excitatory input in the mushroom body lobe from all KCs and reflects it back as inhibitory output to KCs in the mushroom body calyx (Fig. 1), thus forming a closed negative feedback loop (Papadopoulou et al. 2011). What role does this feedback play? The odor-elicited responses of KCs are reliable and extremely sparse. Using two computational models, Papadopoulou et al. (2011) examined the role of feedback in the sparsening of KC responses. First, using a minimal, time-discrete model comprised of binary neurons, with experimentally derived population sizes and connection probabilities, Papadopoulou et al. (2011) found that high firing thresholds for KCs, in the absence of GGN feedback, could generate responses that were sparse on average, but not reliably across the entire population. Adding the GGN allowed reliably sparse responses, similar to those observed experimentally (Perez-Orive et al. 2002). Second, to take into account the fast synaptic transmission from the GGN to KCs, Papadopoulou et al. built a conductance-based model with Hodgkin-Huxley neurons, containing a tenth as many neurons as found *in vivo*, but organized with the same ratio of PNs to KCs and with the same connection probabilities as observed experimentally. This model, too, generated large fluctuations in KC responses without the GGN but reliably sparse responses with the GGN.

Until the discovery of the KC-GGN-KC feedback loop, a putative feedforward inhibitory pathway from PNs to KCs via the lateral horn was thought to underlie the sparse responses of KCs (Perez-Orive et al. 2002). A close examination of lateral horn neurons, however, found no evidence for the existence of this feedforward inhibitory pathway (Gupta and Stopfer 2012). By rigorously assembling a variety of new experimental findings, the computational models by Papadopoulou et al. explained the role of the GGN and demonstrated that a single inhibitory feedback neuron is sufficient to maintain sparseness in a large population of neurons.

Models that Serve Multiple Functions

Fast Learning in the Antennal Lobe

Sinuous odor plumes and flicking antennae conspire to provide odors to ORNs in discrete, recurring splashes rather than in smooth and constant streams. Recordings from the locust brain show that the responses of olfactory neurons change over the course of such multiple, repeated stimulus presentations: PNs come to produce fewer spikes, but these spikes tend to become more synchronized with spikes in other PNs, resulting in stronger network oscillations (Stopfer and Laurent 1999). These changes appear within a few odor presentations separated by seconds, but last for minutes, and occur independently of receptor adaptation within the antenna. They reflect a fast, short-term form of learning in the antennal lobe.

What mechanisms underlie this fast learning? Bazhenov et al. (2005) modeled the antennal lobe as a network of Hodgkin-Huxley LNs and PNs, whose relative numbers and conductances were based on available experimental data. Input from ORNs to LNs and PNs was modeled by randomly distributed spikes, constrained to generate experiment-matched membrane potential fluctuations in PNs. When activity-dependent facilitation of inhibitory synapses was added to the model's antennal lobe, it reproduced fast learning with dynamics similar to those observed in the experiments.

The success of the model was contingent upon, and thus predicted, the existence of activity-dependent plasticity at inhibitory synapses in the antennal lobe. This prediction is validated by recent results showing facilitation of specific GABAergic synapses after odor exposure in *Drosophila* (Das et al. 2011; Sudhakaran et al. 2012).

What functional role may be served by such fast learning? By manipulating the presence and extent of plasticity in the model, Bazhenov et al. (2005) identified one possible role. Noisy ORN input caused large trial-to-trial variability in the PN spike patterns in the absence of plasticity; this variability was reduced significantly when plasticity was returned to the model. These results suggest

fast learning in the antennal lobe makes olfactory responses more robust to stimulus variability, potentially enabling the animal to better recognize odors in its naturally noisy environment.

Summary

A model is a well-specified description of a complex, sometimes only partially explored system, and, as such, is expected to set aside some biological details. But should the modeler stray too far from what is known, the model may begin to lose its relevance. We assert that the utility of the computational models sampled above – in revealing the mechanisms underlying temporal patterning or fast learning, in predicting non-synaptic inhibitory coupling or activity-dependent facilitation of inhibitory synapses, and in determining the role of feedback inhibition or that of fast learning – is explained in part by a shared motif: they all were tightly constrained by available experimental data. They are just a few of the many useful models in insect olfaction, illustrating how this system, supported by a long tradition of anatomical and physiological exploration (Kenyon 1896), provides a rich platform for modeling neural circuits. These models have begun to reveal the principles of neural computation and their significance for perception, memory, and behavior (Laurent 2002; Gupta and Stopfer 2011). But there is still a long way to go before we can claim to understand olfaction, or the brain.

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Integrate and Fire Models, Deterministic

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Synonyms

Exponential integrate and fire model; Izhikevich model; Leaky integrate and fire model; Quadratic integrate and fire model

Definition

The integrate-and-fire (IF) model is a single-compartment model describing the subthreshold dynamics of the neuron membrane potential V . The spiking dynamics is marked by a spiking threshold, potential at which the neuron emits a spike. After spike emission, V is set at the neuron's reset potential. Subthreshold dynamics was initially designed to capture neuron's passive membrane properties, and its dynamics was given by a single first-order linear differential equation.

Variations around this model have been introduced to describe either spike-activated currents, more complex subthreshold dynamics, or more realistic spike initiation dynamics. These models can be two or three dimensional or include nonlinear terms. However, they are always designed to describe the relevant mechanisms with a minimal set of variables and parameters which make them suitable for large-scale simulations or detailed mathematical analysis.

Detailed Description

Leaky Integrate-and-Fire Model

The leaky integrate-and-fire (LIF) model was first introduced by Lapicque (1907) to describe mathematically neuron firing times. It is based on the idea that neuron activity can be captured by the

dynamics of its membrane potential which evolves according to neuron inputs (synaptic or current injection) and passive membrane properties (see, e.g., Eccles 1957). The main hypothesis of the LIF model is that action potential threshold and shape are invariant from spike to spike, and thus a precise description of the spike can be omitted and simply sketched by a spiking threshold. When V reaches this threshold, a spike is emitted, after which V is set at the neuron's resting membrane potential. This simple spiking dynamics captures the nonlinear input–output relationship of neurons and has been the subject of detailed mathematical analysis (Knight 1972; Tuckwell 1988).

Below spiking threshold, the membrane potential dynamics is described by the membrane passive dynamics. The equivalent electrical circuit is sketched in Fig. 1a and its main parameters are the following:

- C_m : the membrane capacitance
- g_L : the leak conductance (or equivalently its membrane resistance $R_m = 1/g_L$)
- E_L : the resting membrane potential, which is the neuron membrane potential in the absence of external stimulation

The standard equation describing the LIF model below threshold is then given by

$$C_m \frac{dV}{dt} = -g_L(V - E_L) + I(t) \quad (1)$$

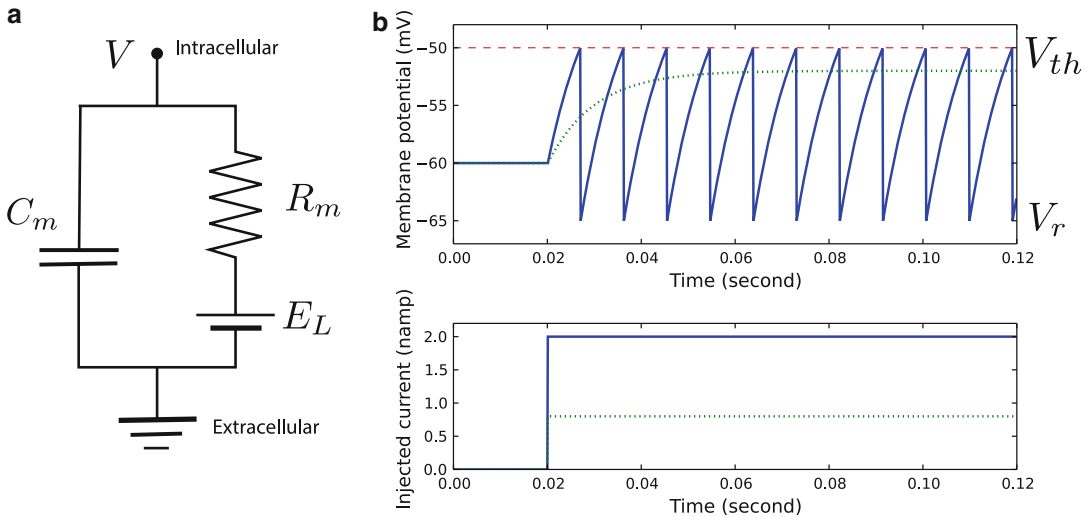
where $I(t)$ represents any external input (electrode, synaptic, etc.) to the neuron. Another common form of Eq. 1 is

$$\tau_m \frac{dV}{dt} = -(V - E_L) + R_m I(t) \quad (2)$$

where τ_m is the membrane time constant:

$$\tau_m = \frac{C_m}{g_L} = R_m C_m \quad (3)$$

The first term on the right-hand side in Eqs. 1 or 2 is called the leak current. It pulls V toward its resting membrane potential. With this term, the LIF model is the original leaky integrate-and-fire



Integrate and Fire Models, Deterministic, Fig. 1 Basis of the leaky integrate-and-fire (LIF) model. (a) Electrical RC circuit equivalent to the LIF model. (b)

Subthreshold (dashed line) and suprathreshold (full line) activation of a LIF model. LIF parameters: $E_L = -65$ mV, $\tau_m = 10$ ms, $V_r = -70$ mV, $V_{th} = -50$ mV

model (also called forgetful IF). This term is sometimes neglected in which case the model is a perfect integrator (simple integrate-and-fire model, SIF). The previous equations only describe the subthreshold membrane potential dynamics. To capture neuron spiking mechanisms, the LIF model is completed by a constant spiking threshold V_{th} , potential at which the LIF model is considered to have emitted a spike. There is no detailed description of the actual spike shape. Following a spike, the potential V is reset to a reset potential V_r . See Fig. 1b for an example of LIF membrane potential trace.

To take into account the finite width of real spikes and the neuron absolute refractory period, we can add to the LIF model a refractory period τ_{ref} . It is a period following each spike during which the model is insensitive to external inputs. At the end of this period, V is reset at V_r .

Thanks to the simple form of its equation, assuming a constant input current $I(t) = I$, the LIF model trace can be exactly computed between spikes:

$$V(t) = V_r + (R_m I + E_L - V_r) \left(1 - e^{-\frac{t}{\tau_d}}\right) \quad (4)$$

This shows that if the input current is large enough, $R_m I \geq V_{th} - E_L$, then the LIF model emits a spike after a time T such that

$$V_{th} = V_r + (R_m I + E_L - V_r) \left(1 - e^{-\frac{T}{\tau_d}}\right) \quad (5)$$

Finally we obtain the LIF f-I curve, given by

$$f(I) = \frac{1}{\tau_{ref} + \tau_{td} \ln \left(\frac{R_m I + E_L - V_r}{R_m I + E_L - V_{th}} \right)} \quad (6)$$

Note that the logarithmic shape of the f-I curve, close to rheobase (current threshold), is not typical of f-I curves found with more detailed neuron model. Besides, this simple calculation in presence of a constant external input should not mask the strong nonlinearity introduced in the model by its hard spiking threshold making analytical computations more difficult as soon as more complex dynamics are considered. However, the simplicity of the LIF model makes it useful in large-scale simulations of neuronal networks.

Extensions of the LIF Model

The LIF model captures only subthreshold dynamics governed by passive membrane dynamics and has an oversimplified spiking mechanisms which can sometimes generate rather

unphysiological behavior. Thus, many extensions of the model have been proposed to allow a description of additional features found in real neurons. We will describe here three major classes of extension:

- Currents activated during spiking, like afterhyperpolarization currents leading to spike rate adaptation
- Currents active below threshold which can generate resonant membrane properties
- More realistic spiking mechanisms allowing to better capture fast neuronal dynamics

As we will see, the common basis of all the extensions proposed for the LIF model is that they were intended to use the smallest number of parameters and the simplest equation possible to capture additional neuronal dynamics. The model proposed by Izhikevich (2003), gathering many of these extensions, can thus describe most of known neuronal spiking pattern with a very small set of parameters and first-order differential equations. It will be presented at the end of this section.

Spike-Activated Currents

In real neurons, spiking is induced by the strong activation of intrinsic sodium and potassium currents. This leads to a large fluctuation of neuron membrane potential and transient changes of ion intracellular concentration. These effects can cause other voltage-activated or ion-activated (like potassium-dependent) channels to be modulated during spiking. A common example is the activation during a spike of currents leading to spike rate adaptation. These types of currents are transiently activated during a spike but are then slowly inactivated between spikes and tend to hyperpolarize the neuron. The first version of such a current in a LIF model has been introduced by Treves (1993), and its simplest mathematical description is given by

$$\tau_m \frac{dV}{dt} = -(V - E_L) + R_m(-I_a + I(t)) \quad (7)$$

$$\tau_a \frac{dI_a}{dt} = -I_a \quad (8)$$

where the adapting current I_a is incremented by a positive constant r_a at each spike. An example of trace of an adapting LIF model is shown in Fig. 2. Note that the same formalism could be used to describe facilitating currents, leading to afterdepolarization (ADP), by changing to positive sign in front of I_a in Eq. 7. Other versions of the adapting current use a slowly decaying conductance g_a and then define $I_a = g_a(V - E_a)$ where E_a is the reversal potential of the adapting current and has to be lower than V_{th} in order to describe an hyperpolarizing current.

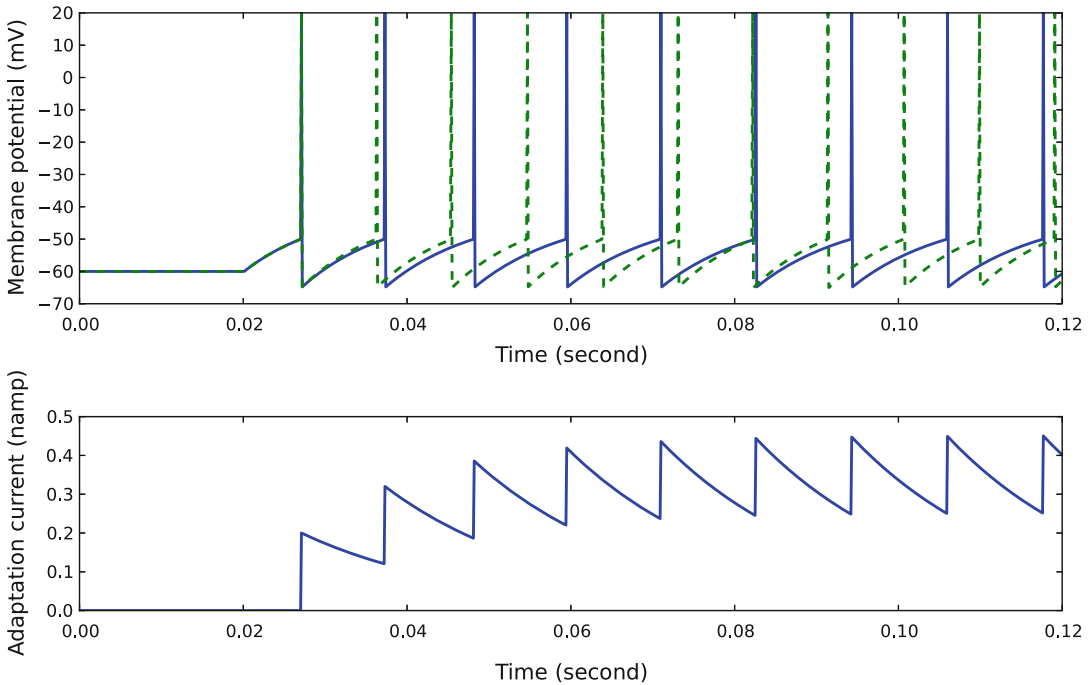
Subthreshold Voltage-Dependent Currents

In the previous section, the spike-activated current (or conductance) was not voltage-dependent between spikes. However, most of real neurons express currents which are activated in a voltage-dependent manner below the spike threshold and affect the neuron dynamics. An accurate description of this type of voltage-dependent currents generally requires to use the Hodgkin-Huxley formalism. However, it is still possible to capture the most salient effects of such currents on the neuron dynamics by restraining their analysis in a narrow voltage band (Izhikevich 2001; Richardson et al. 2003). For example, Richardson et al. (2003) showed that it is possible to linearize the full conductance equation of voltage-dependent conductances around the neuron equilibrium potential to obtain a linear system able to capture membrane potential subthreshold resonance. Adding a standard LIF spiking threshold to the linearized model gives the generalized integrate-and-fire (GIF) model. The standard equation of a GIF model is given by

$$\tau_m \frac{dV}{dt} = -(V - E_L) + R_m(-g_x W_x + I(t)) \quad (9)$$

$$\tau_x \frac{dW_x}{dt} = -W_x + (V - E_x) \quad (10)$$

We emphasize that contrary to the current used to describe spike rate adaptation, here W_x depends on V . Depending on the parameters g_x and τ_x , this allows the system to have fixed points with complex basis solutions like for the simple or damped



Integrate and Fire Models, Deterministic, Fig. 2 Adaptation in a LIF model. *Top*: potential traces of a LIF model with (*full line*) and without (*dashed line*) adaptation current. *Bottom*: buildup of the adaptation

current during spiking. Note that after a transient increase at the beginning of neuron firing, adaptation stabilizes. Adaptation parameters: $\tau_a = 20$ ms, $r_a = 0.2$ nA

harmonic oscillator. Such solutions can capture resonant properties found in real neurons (Hutcheon and Yarom 2000). In Eq. 9 we had only one additional conductance to the original LIF model, but some neuron with low and high resonant frequencies may require two or more currents in order to capture their dynamics. Details on the derivation of additional current parameters from the standard Hodgkin-Huxley equations can be found in Richardson et al. (2003).

Spike Initiation Dynamics

In the standard LIF model, the spiking mechanism is sketched by a constant spiking threshold. However, in real neurons, the action potential is initiated by a strong sodium current with a fast, but not instantaneous, activation. Both mechanisms are similar when we are only interested in slow neuron dynamics, but discrepancies can appear when looking at the response to fast-fluctuating input, for example. Thus, extensions of the LIF model

including a nonlinear term to model the non-instantaneous activation of sodium current have been proposed. The general form of these nonlinear integrate-and-fire (NLIF) models is given by

$$C_m \frac{dV}{dt} = g_L \psi(V) + I(t) \quad (11)$$

where $\psi(V)$ is a function which increases fast enough such that when V grows, it can diverge to infinity in a finite time. In this case, the spike time is given by the time of divergence of V , and it is then reset at potential V_r . It is no longer necessary to choose an arbitrary spike threshold, but for numerical simulation, a spike cutoff has to be defined assuming infinity has been reached.

Using this equation, we can define two important quantities:

- The voltage threshold V_T which is the highest steady-state voltage the neuron can sustain without emitting a spike. If ψ is convex, it is defined by $\psi'(V_T) = 0$.

- The spike shape factor Δ_T which is proportional to the curvature radius of the neuron current–voltage curve at its voltage threshold V_T . It is defined by $\Delta_T = 1/\psi''(V_T)$.

Two major classes of NLIF neurons have been used in the literature. The first one historically is the quadratic integrate-and-fire (QIF) (Ermentrout and Kopell 1986; Ermentrout 1996), also known as the theta model:

$$C_m \frac{dV}{dt} = \frac{g_L}{2\Delta_T} (V - V_T)^2 - I_0 + I(t) \quad (12)$$

For an input current below I_0 , the model exhibits two fixed points: one stable and one unstable. When the input current increases and reaches I_0 , the two fixed points merge and the neuron membrane potential is destabilized through a Hopf bifurcation which is the classical type I dynamics observed in many neuron models.

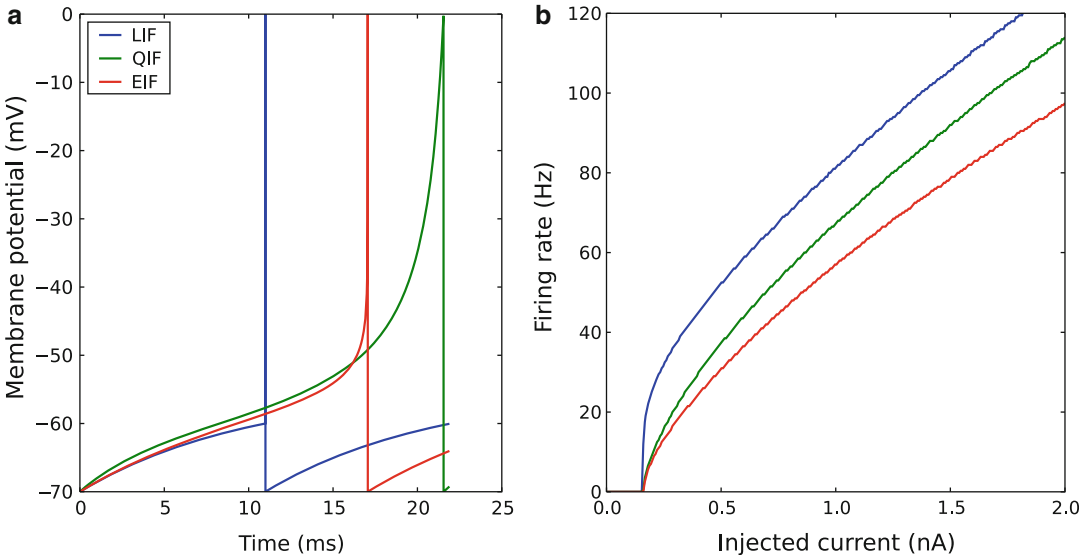
The second type of well-known NLIF neuron is the exponential integrate-and-fire model (EIF):

$$C_m \frac{dV}{dt} = -g_L(V - V_T) + g_L \Delta_T e^{\frac{V - V_T}{\Delta_T}} + I(t) \quad (13)$$

Here the divergence function is exponential which leads to a spike initiation speed intermediate between the instantaneous LIF spike and the rather slow QIF spike (see Fig. 3a). Fourcaud-Trocmé et al. (2003) have shown that this model captures best the fast dynamics of standard Hodgkin-Huxley-type models for cortical neurons, like the Wang-Buzsáki model (Wang and Buzsáki 1996).

Comprehensive IF Models

The three types of extensions presented previously describe distinct aspects of neuron



Integrate and Fire Models, Deterministic, Fig. 3 Comparison of nonlinear IF models. *Left*: comparison of LIF, QIF, and EIF spiking initiation in response to the same constant current input. We observe that the LIF neuron is very reactive and spikes as soon as it reaches the spiking threshold V_{th} . The EIF model has a smooth but sharp spike, while the QIF model has the slowest spike. *Right*: comparison of LIF, QIF, and EIF f-I curves. We observe that LIF f-I curve has a logarithmic initial portion which is a consequence of its instantaneous spiking

mechanism. QIF and EIF f-I curve initial portion have a square root shape, which depends only on V_T and Δ_T . This shape is classically observed in type I neurons. Parameters: for all models, $C_m = 1$ nF, $g_L = 0.1 \mu S$, $E_L = -65$ mV; **LIF**, *left*, $V_{th} = -60$ mV, $V_r = -70$ mV; **LIF**, *right*, $V_{th} = -63.4$ mV, $V_r = -80$ mV, $\tau_{ref} = 1.35$ ms; **QIF**, $V_T = -59.9$ mV, $\Delta_T = 3.48$ mV, $V_{th} = -30$ mV, $V_r = -62.235$ mV, $I_0 = -0.16$ nA, $\tau_{ref} = 0$ ms; **EIF**, $V_T = -59.9$ mV, $\Delta_T = 3.48$ mV, $V_{th} = -30$ mV, $V_r = -68$ mV, $\tau_{ref} = 1.7$ ms

dynamics but are not exclusive. Some studies proposed to combine them in order to produce simple but realistic neuron models. One of the simplest has been proposed by Izhikevich (2003). It is defined by

$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 - U + I(t) \quad (14)$$

$$\frac{dU}{dt} = a(bV - U) \quad (15)$$

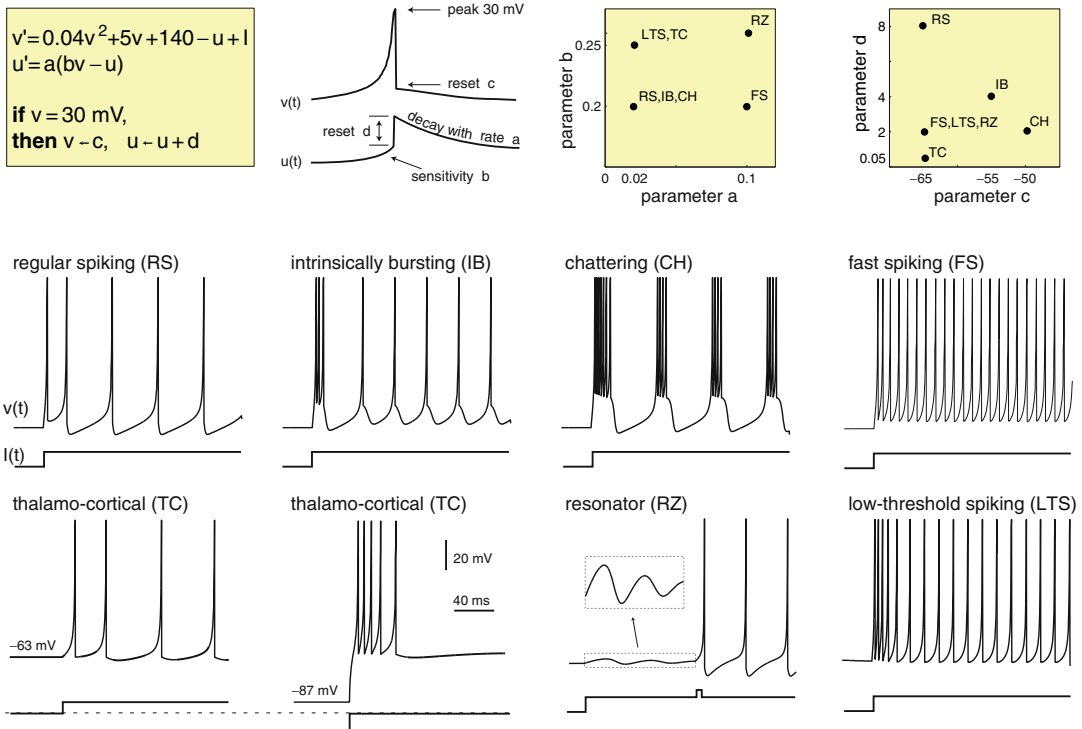
Two additional parameters are the reset $V_r = c$ and the increase d of variable U after each spike. Note that depending on the set of parameters a , b , c , d , it can include all LIF extensions previously described. Using this model, Izhikevich has shown that most of the common recorded discharge patterns could be reproduced (see Fig. 4).

A second comprehensive model is the adaptive integrate-and-fire model (Brette and Gerstner 2005). It is described by

$$C_m \frac{dV}{dt} = -g_L(V - V_T) + g_L \Delta_T e^{\frac{V - V_T}{\Delta_T}} - w + I(t) \quad (16)$$

$$\tau_w \frac{dw}{dt} = a(V - E_L) - w$$

Again, the model must be completed by a reset V_r and the increment b of the adaptive current w at each spike. This model is very similar to the model proposed by Izhikevich (2003) but its subthreshold dynamics and spike initiation dynamics are closer to standard Hodgkin-Huxley models. This facilitates the choice of the model parameters



Integrate and Fire Models, Deterministic, Fig. 4 Example of a comprehensive IF model. The model depicted in the upper equations includes subthreshold dynamics, a spiking mechanisms inspired by the QIF model, and spike-dependent adaptation. All these dynamical aspects depend only on two variables and four

parameters. Careful choices of the parameters can lead to a great variety of neuronal dynamics reminiscent of actual neuronal recordings (Electronic version of the figure and reproduction permissions are freely available at www.izhikevich.com)

based on simple experimental measurements (injection of current pulses, steps, and ramps; see Brette and Gerstner 2005 for details).

Cross-References

- [Capacitance, Membrane](#)
- [Excitability: Types I, II, and III](#)
- [Hodgkin-Huxley Model](#)
- [Theta Neuron Model](#)
- [Time Constant, Tau, in Neuronal Signaling](#)

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External Links

- http://www.scholarpedia.org/article/Adaptive_exponential_integrate-and-fire_model
- <http://www.izhikevich.org/publications/spikes.htm>

Intermittent Control

- [Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the](#)

Intermittent Control of Movement and Balance

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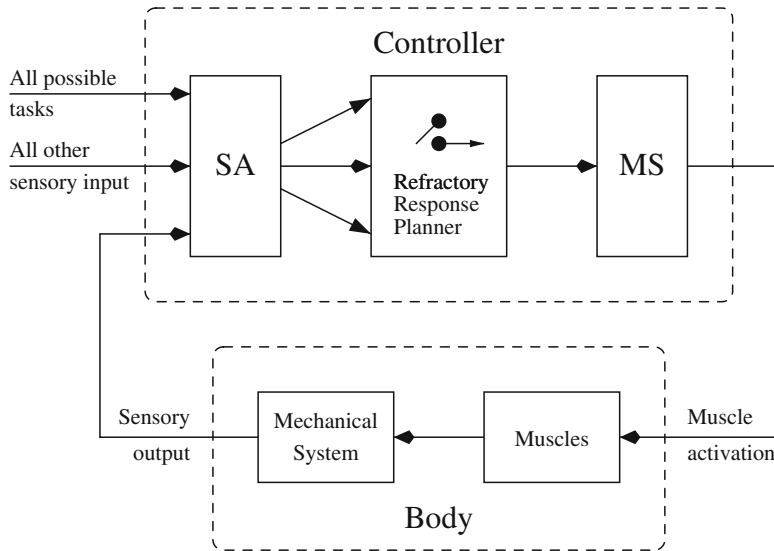
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Definition

The intermittent control hypothesis proposes that centrally integrated sensorimotor control systems cannot be described by continuous feedback but rather by a sequence of open loop trajectories determined by intermittent feedback (Fig. 1). The times at which feedback occurs, and at which the trajectories are adjusted, can in principle be at regular intervals or determined by events. The latter is termed event-driven control, and events can occur when measured states or predicted state errors exceed a threshold. The purpose



Intermittent Control of Movement and Balance, Fig. 1 Intermittent control. Sensorimotor control of sustained tasks is a process of closed loop feedback in which a controller uses sensory output to control muscle activations which determine movement of the mechanical body. The controller uses sensory analysis (SA) to estimate states and uses a motor system (MS) to generate activations of the muscles. According to the intermittent control hypothesis, a process of refractory response planning

occurs between sensory analysis and the motor system. The refractory response planner uses current states to plan a time-varying trajectory of muscle activations which are executed without feedback. Refractoriness means this control trajectory is not updated until the next trajectory is planned using updated sensory measurements. This refractory response planner is postulated to reside with the basal ganglia and associated motor decision-making regions of the frontal cortex

of intermittent control is to provide time within the feedback loop for computation using current measured states to inform the next iteration of open loop predictive control. By comparison with continuous control, intermittent control gains adaptability at the expense of bandwidth.

For any task, this hypothesis is falsifiable and can be tested using appropriate experiments and the model-based definition of intermittent control. In the particular case of human balance control, muscle forces should follow trajectories which are determined intermittently by feedback of perceived body position, and events could correspond to body sway exceeding a threshold or to predicted sensory states exceeding a threshold.

Detailed Description

As discussed by Gawthrop et al. (2015), intermittent control has a long history in the physiological literature including Craik (1947), Vince (1948),

Navas and Stark (1968), Neilson et al. (1988), Miall et al. (1993), and Bhushan and Shadmehr (1999). There is strong experimental evidence that some human control systems are intermittent (Craik 1947; Vince 1948; Navas and Stark 1968; Bottaro et al. 2005; Loram et al. 2012; van de Kamp et al. 2013b), and it has been suggested that this intermittency arises in the central nervous system (CNS) (van de Kamp et al. 2013a). For this reason, computational models of intermittent control are important, and, as discussed below, a number of versions with various characteristics have appeared in the literature. Intermittent control has also appeared in various forms in the engineering literature including Ronco et al. (1999), Gawthrop and Wang (2009), and Gawthrop et al. (2015).

As shown in Fig. 1, intermittent control action may be initiated at regular intervals determined by a clock or at irregular intervals determined by events; an event is typically triggered by an error signal crossing a threshold. There is evidence that

human control systems are, in fact, event driven (Navas and Stark 1968; Loram et al. 2012; van de Kamp et al. 2013a; Loram et al. 2014). For this reason, this entry focuses on event-driven control.

Computational Model

A detailed computational model of intermittent control is given by Gawthrop et al. (2011) and refined by Gawthrop et al. (2015) to include occluded sensing and multivariable control. This section summarizes the computational model.

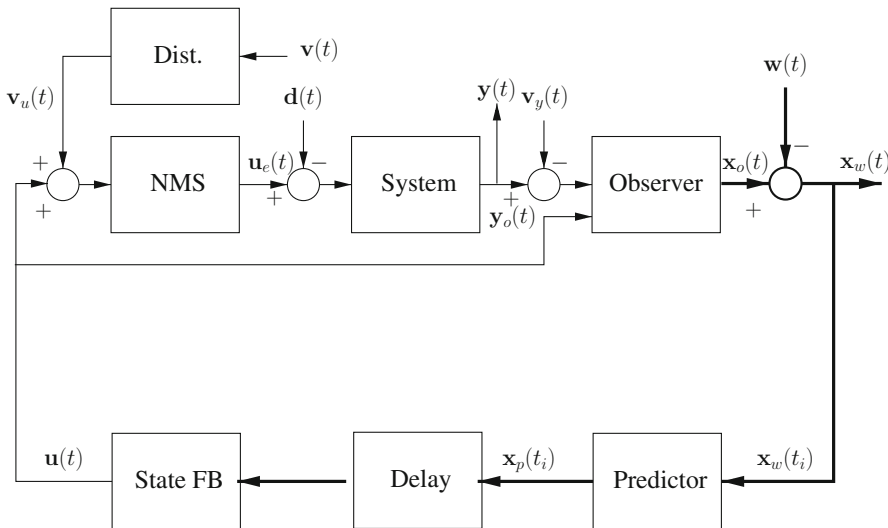
The computational model of intermittent control is based on the *underlying continuous-time design method* of Fig. 2; in particular the classical state-space approach is the basis of the intermittent control of Gawthrop et al. (2011). There are two relevant versions of this approach: state feedback and output feedback. State-feedback control requires that the current system state (e.g., angular position and velocity of an inverted pendulum) is available for feedback. In contrast, output feedback requires a measurement of the system output

(e.g., angular position of an inverted pendulum). The classical approach to output feedback in a state-space context is to use an observer (or the optimal version, a Kalman filter) to deduce the state from the system output.

Human control systems are associated with time delays. In engineering terms, it is well-known that a predictor can be used to overcome time delay. As discussed by many authors (Kleinman et al. 1970; Gawthrop et al. 2011; Loram et al. 2012), it is plausible that physiological control systems have built-in model-based prediction. Thus intermittent control is based on an underlying predictive design.

As explained in detail elsewhere Gawthrop et al. (2011, 2015), intermittent control (Fig. 3) adds three components to the underlying design method of Fig. 2:

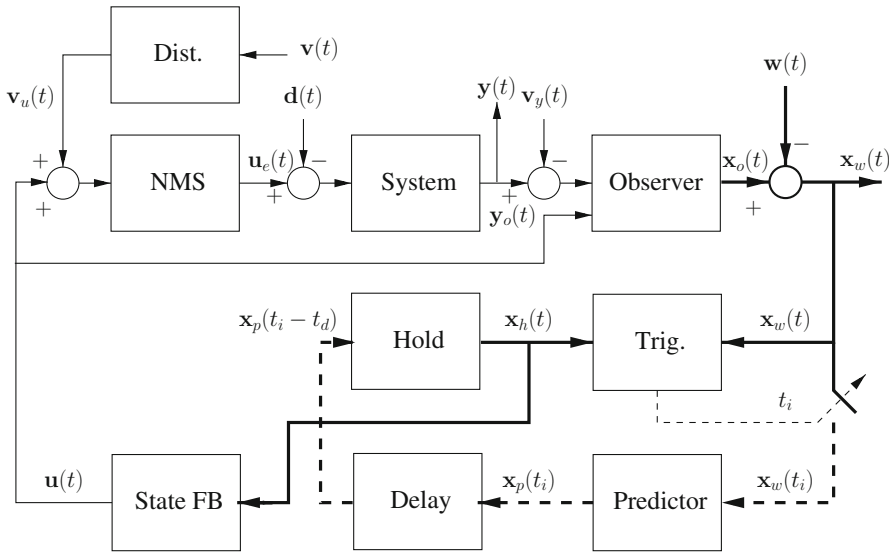
1. A *Hold* device which produces an open-loop state trajectory $\mathbf{x}_h$ based on the most recent intermittent sample at time t_i



Intermittent Control of Movement and Balance, Fig. 2

The Observer, Predictor, State-feedback (OPF) model. The block labelled “NMS” is a linear model of the neuro-muscular dynamics with input $u(t)$; in the engineering context, this would represent actuator dynamics. “System” is the linear external controlled system driven by the externally observed control signal u_e and disturbance d and with output y and associated measurement noise v_y . The input disturbance v_u is modelled as the output of the block labelled “Dist.” and driven by the external signal

v . The block labelled “Delay” is a pure time delay of Δ which accounts for the various delays in the human controller. The block labelled “Observer” gives an estimate $\mathbf{x}_o$ of the state $\mathbf{x}$ of the composite “NMS” and “System” (and, optionally, the “Dist.”) blocks. The predictor provides an estimate of the future state error $\mathbf{x}_p(t)$ the delayed version of which is multiplied by the feedback gain vector $\mathbf{k}$ (block “State FB”) to give the feedback control signal u . (This figure is based on Gawthrop et al. (2011, Fig. 1) which is in turn based on Kleinman (1969, Fig. 2))



Intermittent Control of Movement and Balance, Fig. 3 Intermittent control. This diagram has blocks in common with those of the OPF of Fig. 2: “NMS”, “Dist.”, “System”, “Observer”, “Predictor,” and “State FB” which have the same function; the continuous-time “Predictor” block of Fig. 2 is replaced by the much simpler intermittent version here. There are three new elements: a sampling

element which samples x_w at discrete times the block labelled “Hold”; the system-matched hold, which provides the continuous-time input to the “State FB” block; and the event detector block labelled “Trig.” which provides the trigger for the sampling times t_i . The dashed lines represent sampled signals defined only at the sample instants t_i . This figure is based on Gawthrop et al. (2011, Fig. 2)

2. A trigger device (“Trig.”) which determines when (t_i) intermittent samples are taken
3. A sampling element (represented by a switch symbol) which samples the observed system state at each time t_i

A computational model of intermittent control based on Fig. 3 is given by Gawthrop et al. (2011, 2015).

Explaining Experiments

A number of simulated examples are given by Gawthrop et al. (2011, 2015) to illustrate how the computational model of intermittent control can explain a number of known phenomena associated with human control systems. But as a scientific hypothesis, the computational model of intermittent control must also be compared with real experimental data.

Identifying Intermittent Models

As discussed by Gawthrop et al. (2011), intermittent control can *masquerade* as continuous

control. For this reason experiments must be specifically designed to reveal intermittency. For example, Loram et al. (2012) use a special paired-step set-point sequence; Gollee et al. (2012, 2017) use a special periodic multi-sine input signal.

Moreover, conventional methods for identifying continuous time systems cannot be used. Loram et al. (2012) introduce a novel time-domain approach, and Gollee et al. (2012) introduce a novel frequency domain approach.

Sway

Human balance has a characteristic sway motion. As discussed by Gawthrop et al. (2014), such sway can be explained by the nonlinear behavior of event-driven intermittent control of an inverted pendulum.

Stick Balancing

Balancing a stick on a fingertip is a fourth order unstable control problem which is challenging to humans and is, therefore, an interesting test-bed for computational models of intermittent control.

Gawthrop et al. (2013) present a cascaded form of intermittent control which explains the perceived continuous nature of the control, while the event-driven properties of intermittent control explain experimentally observed variability.

Motor Noise

Although, in some circumstances, the human operator is described adequately by linear translation of sensory input to motor output, such descriptions have a significant *remnant* when compared to experimental data. This remnant has been attributed to sensorimotor noise.

However, Gollee et al. (2017) have shown that remnant can be attributed to aperiodic sampling associated with event-driven intermittent control.

The Neural Substrate of Intermittent Control

The development of intermittent control in the engineering context was driven by the desire to combine continuous time predictive feedback control with intermittent optimization (Ronco et al. 1999). In essence, the intermittency provides the time required for the optimization. It may be that a similar rationale holds for living control systems (van de Kamp et al. 2013a) where the intermittency provides the time for the refractory response planner of Fig. 1.

In human control, the evidence for intermittent control is behavioral and derives from evidence of the psychological refractory period in relation to discrete tasks (Pashler and Johnston 1998) and from visually guided manual tracking and visually guided whole body tracking tasks (van de Kamp et al. 2013a; van de Kamp et al. 2013b; Loram et al. 2012, 2014; Miall et al. 1986). While a neural substrate has not yet been established, from general knowledge of the anatomy and function of neural regions (Loram et al. 2014), it is a current hypothesis that the basal ganglia, and specifically the subthalamic nucleus (STN), are relevant (Boca et al. 2019), and there is also interest in the link between abnormal intermittent control and Parkinson's disease (Perera et al. 2018). For discrete tasks, there is also fMRI evidence for substrates of refractoriness in the frontal and prefrontal cortex (Dux et al. 2006).

Cross-References

- ▶ Basal Ganglia: Bradykinesia Models
- ▶ Basal Ganglia: Decision-Making
- ▶ Basal Ganglia: Globus Pallidus Cellular Models
- ▶ Basal Ganglia: Mechanisms for Action Selection
- ▶ Cerebellum: Overview
- ▶ Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights
- ▶ Neuromechanics of Postural Control
- ▶ Neuromuscular Control Systems, Models of
- ▶ Parkinson's Disease: Deep Brain Stimulation
- ▶ Stochastic Resonance: Balance Control and Cochlear Implants

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Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the

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Synonyms

[Intermittent control](#); [Intermittent delay feedback control](#); [Intermittent feedback control](#)

Definition

The intermittent time-delayed feedback control is a model of neural strategy for stabilizing human upright stance. It exploits two types of instability of the human postural control system. One is the

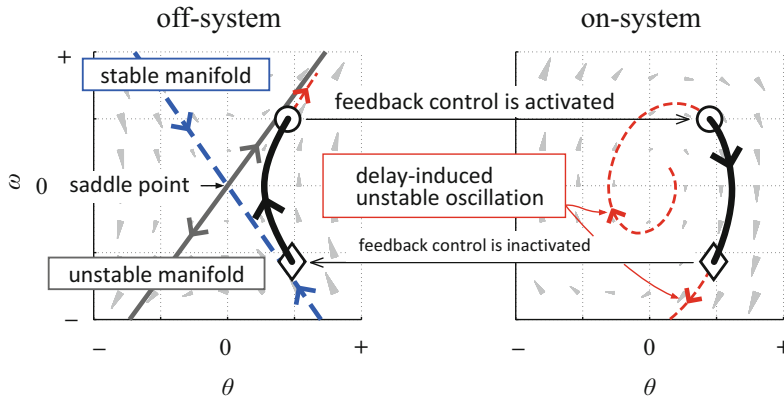
instability of purely mechanical, passive dynamics of the inverted pendulum-like human body in the absence of the active feedback control, due to the fact that intrinsic, i.e., passive, ankle stiffness is insufficient for stabilizing the upright posture, whereby the upright posture is characterized by a saddle-type unstable equilibrium with stable and unstable manifolds. The second is a delay-induced unstable oscillation in the system of the inverted pendulum with an active feedback controller with a large signal transmission delay. In the intermittent control model, the instability is compensated by switching between those two unstable dynamics in an appropriate state-dependent manner, where the switching function is implemented in such a way that the feedback controller is switched off when the state vector is near the stable manifold of the saddle, and it is switched on otherwise.

Detailed Description

Summary of the Intermittent Control Model

The intermittent (time-delayed) feedback is a model of neural motor control strategy for stabilizing human upright stance (Asai et al. 2009; Bottaro et al. 2008; Suzuki et al. 2012). In contrast to the traditional impedance control hypothesis (Maurer and Peterka 2005; Winter et al. 1998), the model assumes that the central nervous system may intermittently *inactivate* the time-delayed active feedback control action, in order to exploit the purely mechanical, passive dynamics of the human body in the absence of the active feedback control. A standing body without active control may be simply modeled by an inverted pendulum, referred to as *the off-system*, whose natural tendency to fall is counteracted but not fully compensated by the passive stiffness of the ankle joint, due to the fact that such stiffness is lower than the growth rate of the gravitational toppling torque (Casadio et al. 2005; Loram and Lakie 2002). Thus, the upright posture of the off-system is a saddle-type unstable equilibrium (*the saddle point*) in the state space. Since the saddle point is accompanied by

stable and unstable manifolds (eigenspaces of stable and unstable eigenmodes) in the state space, the state point can transiently approach the saddle point, if it is near the stable manifold. This would then be followed by a departure from the saddle point along the unstable manifold, determining a fall without feedback intervention (Fig. 1 left panel). In response to an incipient fall, the brain may turn on an active feedback control action, thus switching from the off-system to *the on-system*. Typically, the intermittent control model operates with small feedback gains for the on-system (Asai et al. 2009; Suzuki et al. 2012), namely, gain values that would be incapable to achieve stability even if the feedback controller were persistently activated. Moreover, regardless of the feedback gain values, the persistent feedback control is highly prone to delay-induced instability, leading to a divergent, unstable oscillation around the upright equilibrium point. The rationale of the intermittent control strategy is that the unstable dynamics of the on-system can be exploited, in the sense that the actively driven spiraling out of the state point may provide an opportunity to transverse the stable manifold of the off-system at some time (Fig. 1 right panel): inactivating the active feedback controller at that time (switching from the on-system to the off-system) would trigger another transient behavior approaching the saddle point along or near the stable manifold. In other words, the key feature of the intermittent control model is that, although the off- and on-systems are both unstable, the combination of the two according to the switching mechanism can achieve *bounded stability* (Bottaro et al. 2008) with a limit cycle oscillation that represents a postural sway during quiet stance, even in the absence of motor noise. Another remarkable characteristic of the model is the small joint impedance that originates from the null feedback gains in the off-system and the small feedback gains in the on-system, leading to joint flexibility that induces *power-law-like postural sway* when driven by tiny additive torque noise corresponding to the hemodynamic perturbations during stance (Nomura et al. 2013).



Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the, Fig. 1

The intermittent stabilization strategy of human quiet stance, based on an inverted pendulum model. The left panel illustrates typical dynamics of the pendulum without active feedback control (off-system) in the phase plane (tilt angle θ vs. angular velocity ω), where the upright posture (the origin) is a saddle-type unstable equilibrium point with stable and

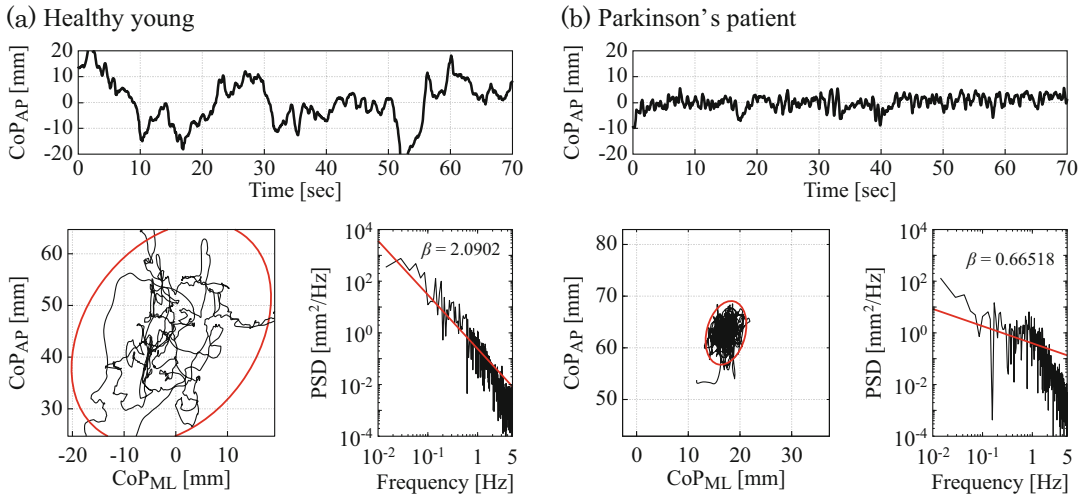
unstable manifolds. The right panel illustrates dynamics of the pendulum with time-delayed feedback control (on-system), where the system shows unstable oscillation due to delay-induced instability. Appropriate state-dependent switchings between these two unstable dynamics make the overall dynamics stable, which are characterized by a bounded stability with a limit cycle oscillation

Physiological and Theoretical Background

Human upright posture during quiet stance, as a mechanical system when no active neural control is provided, is unstable due to insufficient passive stiffness of the ankle joint for overcoming the gravitational toppling torque (Casadio et al. 2005; Loram and Lakie 2002). The central nervous system (CNS) stabilizes the upright posture using neural feedback controllers that generate the active control torques in a robust way, by compensating the danger of instability induced by the large neural feedback transmission delay, which is of the order of 200 ms, while maintaining a level of flexibility that induces the standing body to exhibit stochastic fluctuations, referred to as the *postural sway*.

Postural sway is often measured as a stochastic motion of the center of pressure (CoP) acting on the foot soles during stance. A typical CoP motion in healthy adults is about 0.02–0.04 m of amplitude during quiet stance in both anterior-posterior (AP) and medial-lateral (ML) directions, although the sway size is highly individual dependent (Yamamoto et al. 2015). Collins and De Luca showed that temporal patterns of postural sway for healthy adults exhibit power-law-like behaviors (Collins and De Luca 1994). Specifically, for

the short-term/high-frequency regime (about 0.7–10 Hz), increments of the process behave as those of a positively correlated random walk, corresponding to successive micro-falls due to the gravitational drift. For the long-term/low-frequency regime (about 0.01–0.7 Hz), increments of the CoP motion behave as those of a random walk with slightly negative correlation, corresponding to movements approaching the upright posture, which can be characterized by a power-law-like power spectral density (PSD) function of the following form: $f^{-\beta}$ with $\beta \sim 3/2$ as exemplified in Fig. 2a. Those characteristics are altered in patients with neurological diseases, such as Parkinson's disease, that cause motor dysfunctions, including postural instability (Xiang et al. 2018). Typical patterns of alterations have been reported, including a loss of the $f^{-3/2}$ behavior at the low-frequency regime (Yamamoto et al. 2011) (see Fig. 2b). Thus, the major issue on the study of human postural control is to unveil dynamic mechanisms of how the CNS stabilizes the upright posture in a robust manner and, at the same time, how the power-law-like postural sway pattern is generated. Moreover, clinical challenges are to understand how the upright posture is destabilized in neurological patients and how the



Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the, Fig. 2 Typical fluctuation patterns of CoP (center of pressure) during quiet standing in a healthy subject (a) and a patient with Parkinson's disease (b). For each of them, the sway patterns are illustrated by three graphs: (1) a time series of the

anterior-posterior (AP) component of the CoP oscillation; (2) the CoP trajectory in the AP-ML (mediolateral) plane, with 95% confidence ellipse; (3) the power spectral density (PSD) of the AP component of the CoP, with the linear regression line for the low-frequency regime

power-law-like sway pattern is lost in patients with Parkinson's disease.

In the field of neuroscience of motor control, it has been a common view that the brain stabilizes unstable body dynamics using impedance control, which resists destabilizing motion by regulating co-activation (co-contraction) levels of antagonist muscles (Hogan 1984). In such cases, the CNS would stabilize unstable dynamics by learning optimal impedance, in which optimally selected pairs of antagonist muscles associated with the instability are co-activated in a preprogrammed manner (Burdet et al. 2001). On one hand, such feedforward, nonreactive control strategy decreases the risk of delay-induced instability, but on the other, it forces a trade-off between stability and high muscle activation, as well as a similar trade-off between minimizations of task-related errors and energetic costs. That is, increasing impedance enhances the stability and reduces deviations from the desired goal of a motor task, but co-contraction of muscles increases metabolic cost and, at the same time, decreases joint flexibility. In this sense, the impedance control strategy is rather incompatible with the minimum intervention principle, which is a rational

organizing characteristic for many biological systems (Todorov and Jordan 2002). Since upright stance is a basic motor control function of daily life activity, increases in the energy cost could be critical. Thus, it is very likely that the CNS chooses alternative strategies for achieving the upright stance other than the impedance control strategy.

There are multiple strategies alternative to the impedance control. The use of internal models acquired by the CNS, representing the relationships between motor commands and movements, is one of such strategy. It might be capable of acting as a finite-horizon model predictive controller, i.e., as a feedforward controller, to compensate the destabilizing effect of feedback delay as argued for ballistic voluntary movement (Wolpert and Kawato 1998) and also as a possible strategy used for the postural control (Gawthrop et al. 2011; Morasso et al. 1999). Another way to resolve the trade-off might be to employ optimal feedback controllers, which are often modeled by linear quadratic regulators, including the cases for analyzing human postural control (Kuo 1995). Optimization analysis would often result in gains of feedback

controllers located at the critical edge of stability (Milton et al. 2016), which could often lead to an emergence of power-law-like movement variability (Cabrera and Milton 2002).

A class of nonlinear feedback controllers with time-discontinuous, impulsive actions is an important alternative that can implement the minimum intervention principle for resolving the trade-off problem. An impulsive controller is indeed compatible with the minimum intervention principle, as it acts only during very brief periods of time. Moreover, because impulsive feedback actions are silent most of the time, no deviations from the motor goal are actively opposed, leading to the flexibility of the joint movements. The intermittent controller is a representative of such class of controllers. In recent years, a variety of different versions of the intermittent controllers have been proposed, mostly as computational models of balance control of an inverted pendulum and of postural control during human upright stance. The first version is detailed later in this chapter, which exploits the fact that the state point of the inverted pendulum transiently approaches the upright position along a stable manifold of an unstable saddle-type equilibrium of the off-system as defined above (Asai et al. 2009; Bottaro et al. 2008; Suzuki et al. 2012). The second version assumes anticipatory ballistic bias control (Loram et al. 2011), which has been mathematically modeled with a state predictor for compensating a feedback delay (Gawthrop et al. 2011). In this case, the anticipatory controller operates intermittently, where the intermittency ensures the computational time for the anticipation (Loram et al. 2012). The third version considers open-loop periods (off-periods) representing a sensory dead zone (Eurich and Milton 1996; Insperger and Milton 2014), in which a feedback control during the closed-loop periods (on-periods) with appropriate feedback gains is responsible for stabilizing the pendulum. The fourth version is similar to the third one and has been referred to as the “act-and-wait control,” by which a delay-induced unstable system can be stabilized by an appropriate placement of finite number of poles, if the off-period is larger than the delay time (Insperger and Stepan 2010). The

fifth version may be termed as the “noise-induced stabilization” with a state-dependent multiplicative motor noise (Cabrera and Milton 2002), which arises when the delay-affected system is tuned at, or near, the edge of stability and a critical control parameter is stochastically forced back and forth across the stability boundary.

A Single Inverted Pendulum as a Model of Upright Posture

In this sequel, the intermittent feedback control strategy is described in detail. To this end, we first establish a model of the standing human body simply using an equation of motion of a single inverted pendulum as follows.

$$I\ddot{\theta}(t) = mgh\theta(t) + T(t), \quad (1)$$

where I represents the moment of inertia of the human body around the ankle, θ the tilt angle, g the gravity acceleration, m the body mass, h the distance from the ankle joint to the center of mass of the body, T the total ankle torque, and $mgh\theta$ the linearized gravitational toppling torque for small θ during quiet stance. For the body parameter values, see Asai et al. 2009. For small values of θ and $\dot{\theta}$, it is quite natural, in terms of Taylor expansion of a general torque as a function of θ and $\dot{\theta}$, to consider a model of the ankle joint torque T at time t as follows.

$$T(t) = -K\theta(t) - B\dot{\theta}(t) + T_{\text{act}}(t) + T_{\text{noise}}(t), \quad (2)$$

where the first two terms on the right-hand side represent passive feedback torques generated by the intrinsic mechanical impedance of the ankle joint (K and B are the passive stiffness and viscosity, respectively) with no time delay. The third term T_{act} represents the active neural feedback torque determined by the central nervous system as a function of delay-affected tilt angle $\theta_{\Delta} \equiv \theta(t - \Delta)$ and angular velocity $\omega_{\Delta} \equiv \dot{\theta}(t - \Delta)$ with Δ being the feedback delay time due to the neural signal transmission. The last term T_{noise} is an endogenous, i.e., internal disturbance that is modeled here as a white

Gaussian noise with its standard deviation σ . The state space representation of Eq. 1 is as follows.

$$\frac{d}{dt} \begin{pmatrix} \theta \\ \omega \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ \frac{mgh-K}{I} & -\frac{B}{I} \end{pmatrix} \begin{pmatrix} \theta \\ \omega \end{pmatrix} + \frac{1}{I} \begin{pmatrix} 0 \\ T_{\text{act}} \end{pmatrix} + \frac{1}{I} \begin{pmatrix} 0 \\ T_{\text{noise}} \end{pmatrix} \quad (3)$$

where $\omega \equiv \dot{\theta}$, or formally

$$\frac{dx}{dt} = Ax + u(x_{\Delta}) + d \quad (4)$$

where $x = (\theta, \omega)^T$ and $x_{\Delta} = (\theta_{\Delta}, \omega_{\Delta})^T$. The terms Ax , u , and d define the vector field of the non-actively actuated mechanical system, the active feedback control vector, and the disturbance vector, respectively.

Dynamics of a Non-Actively Controlled Inverted Pendulum

According to the experimental evaluations of the passive ankle viscoelasticity (Casadio et al. 2005; Loram and Lakie 2002), we set as $K = 0.8 \text{ mgh}$ Nm/rad and $B = 4.0 \text{ Nms/rad}$ for passive stiffness and viscosity in Eqs. (2) and (3). Thus, $mgh-K > 0$ and the upright state $x = (0, 0)^T$ is an unstable equilibrium of saddle type (*the saddle point*), with

stable and unstable manifolds when no active control is provided, i.e., $u = 0$ (Asai et al. 2009).

Figure 3 shows the hyperbolic vector field around the saddle point, accompanied with the stable manifold W^s and the unstable manifold W^u . For the body parameter values used here, the stable and unstable manifolds of $dx/dt = Ax$ on the θ - ω plane are given, respectively, by the straight lines passing through the origin.

$$\omega = \lambda^- \theta \sim -1.434\theta \quad (5)$$

and

$$\omega = \lambda^+ \theta \sim 1.367\theta \quad (6)$$

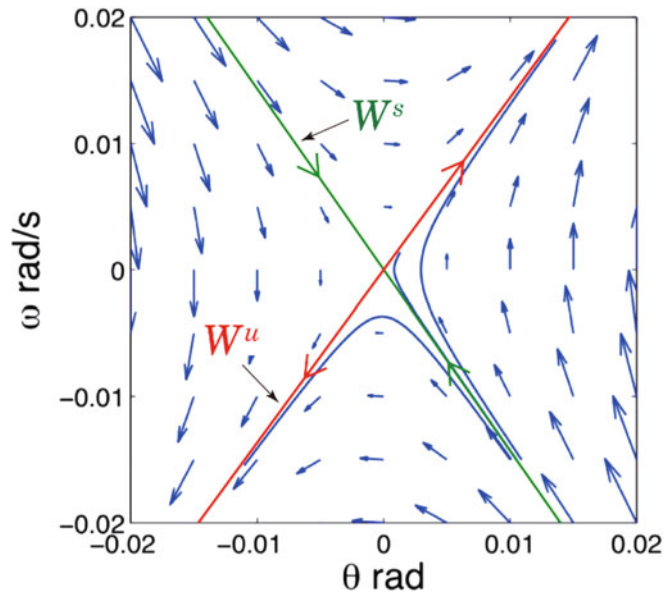
where

$$\lambda^{\pm} = \frac{1}{2} \times \left(-B/I \pm \sqrt{(B/I)^2 + 4(mgh-K)/I} \right), \quad (7)$$

which are the eigenvalues of the system matrix A . Any state point exactly on the stable manifold approaches the saddle point, which takes infinite time, because the vector field becomes null as the

Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the,

Fig. 3 Hyperbolic vector field and sample trajectories of the single inverted pendulum model with no active feedback controllers. The origin is the upright equilibrium of saddle type (*the saddle point*), accompanied with stable manifold W^s and unstable manifold W^u



state point is close to the saddle point. Similarly, any state point near the stable manifold also approaches the saddle point transiently, which would provide convergent dynamics of the intermittent control model as described below. The state point approaching the saddle point, however, moves eventually away from the saddle point along the unstable manifold W^u .

Continuous and Intermittent Feedback Control Models

The traditional impedance control and the intermittent control strategies employ the same conventional proportional (P) and derivative (D) feedback controller (PD controller), but in a strongly different manner. The impedance control model uses the PD feedback control in a conventional manner, i.e., time-continuously, referred to here as the continuous controller. It generates the active feedback torque in Eqs. (2) and (3), denoted by $T_{\text{act}}^{\text{cont}}$ (Maurer and Peterka 2005). In this way, the continuous controller is defined as

$$T_{\text{act}}^{\text{cont}}(t) = -P\theta_{\Delta} - D\omega_{\Delta} \quad (8)$$

where P and D are the P and D gains, respectively.

On the other hand, in the intermittent control model, the PD feedback controller is switched on and off intermittently, depending on the delayed state of the pendulum x_{Δ} (Asai et al. 2009). The corresponding active feedback torque in Eqs. (2) and (3) is denoted by $T_{\text{act}}^{\text{int}}$ as defined later. For both cases, the feedback delay time is set as $\Delta = 0.2$ s according to the experimental evaluation by Peterka (2002).

The Continuous Feedback Control Model and Delay-Induced Instability

As in Eqs. (1), (2), and (8), the equation of motion for the inverted pendulum with the continuous delay feedback controller is rewritten here as

$$I\ddot{\theta}(t) = (mgh - K)\theta(t) - B\dot{\theta}(t) - P\theta(t - \Delta) - D\dot{\theta}(t - \Delta). \quad (9)$$

Taking Laplace transform of both sides with the zero initial condition, we have

$$Is^2\Theta(s) = (mgh - K)\Theta(s) - Bs\Theta(s) - P\Theta(s)\exp(-\Delta s) - Ds\Theta(s)\exp(-\Delta s), \quad (10)$$

where s is the Laplace variable and $\Theta(s) \equiv \mathcal{L}[\theta(t)]$, which yields the following characteristic equation:

$$s^2 + bs - k + ds\exp(-\Delta s) + p\exp(-\Delta s) = 0 \quad (11)$$

where $b = B/I > 0$, $k = (mgh - K)/I > 0$ when K is smaller than the load stiffness mgh , $d = D/I > 0$, and $p = P/I > 0$. This is a transcendental equation that has an infinite number of solutions and difficult to solve analytically. However, we can analyze p and d values, for a given delay Δ , at the critical edge of stability, where the real part of the characteristic roots $s = \sigma + j\omega$ is zero, i.e., $\text{Re}[s] = \sigma = 0$. At such instability points, $s = j\omega$, if ω is non-zero. By substituting this into Eq. (11), we have

$$p \cos(\omega\Delta) + d\omega \sin(\omega\Delta) - \omega^2 - k = 0 \quad (12)$$

$$b\omega - p \sin(\omega\Delta) + d\omega \cos(\omega\Delta) = 0 \quad (13)$$

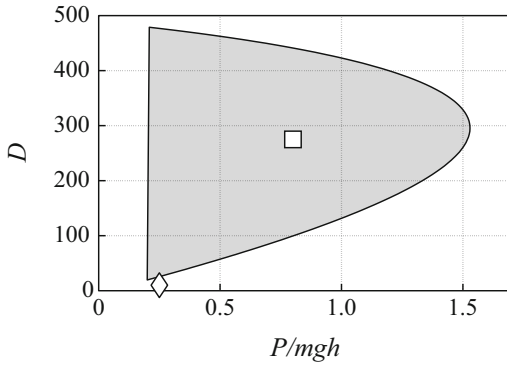
Those equations can be solved for unknowns p and d , which are parameterized by ω , for finding critical feedback gains as follows.

$$\begin{pmatrix} p(\omega) \\ d(\omega) \end{pmatrix} = \begin{pmatrix} (\omega^2 + k) \cos(\omega\Delta) + b\omega \sin(\omega\Delta) \\ (\omega^2 + k) \frac{\sin(\omega\Delta)}{\omega} - b \cos(\omega\Delta) \end{pmatrix} \quad (14)$$

Note that, for $\omega = 0$ at the instability point, the characteristic equation becomes

$$-k + p = 0 \quad (15)$$

meaning that $p = k$ is the stability boundary. Depicting a curve on p - d plane, or indeed P - D plane for varied values of ω , together with $P = mgh/K$ (or $p = k$), we have a stability region of the continuous control model on P - D plane as shown in Fig. 4.



Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the, Fig. 4 Stability region (the gray region) of the continuous PD feedback control model with time delay ($\Delta = 0.2$ s). The open square represents a typical PD gain for the continuous PD feedback controller (the impedance control model). The open diamond is a typical PD gain used for the on-system of the intermittent control model, which is outside of the stability region of the continuous PD feedback control model

Typical gain values that have been estimated by previous studies and also used in this chapter are $P = 471$ Nm/rad, corresponding to 0.8 mgh, and $D = 275$ Nms/rad (Maurer and Peterka 2005). This parameter point $(P, D) = (471, 275)$ is located almost in the middle of a narrow stability

region in the P - D parameter plane. The upright posture $x = 0$ is asymptotically stable of focus type for those values. Maurer and Peterka reported that human postural sway data were best fitted by those values with a given colored torque noise of very large intensity (Maurer and Peterka 2005).

Figure 5a shows dynamics of the continuous control model with two different noise intensities ($\sigma = 0.2$ Nm for small noise case and $\sigma = 2.0$ Nm for large noise case). For the small noise case, the sway amplitude is very small, because the upright posture is rigidly stabilized by the continuous PD controller with the large gains at $(P, D) = (0.8$ mgh, 275). In this case, the tilt angle $\theta(t)$ of the model shows a white-noise-like variation. The sway amplitude becomes large as comparable as human postural sway for the large noise case. However, also in this case, the sway pattern shows a white-noise-like jitter. Indeed, PSDs at the low-frequency regime are almost flat, and the powers decrease steeply for the high-frequency regime, as shown in the bottom panels of Fig. 5.

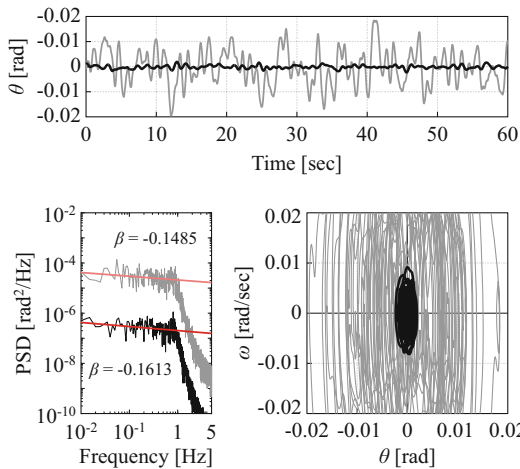
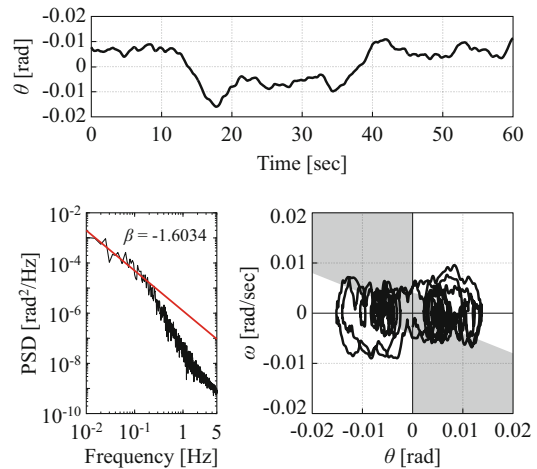
The Intermittent Feedback Control Model

The intermittent feedback controller is defined as follows.

$$T_{\text{act}}^{\text{int}}(t) = \begin{cases} -P\theta_{\Delta} - D\omega_{\Delta}, & \text{if } (\theta_{\Delta}, \omega_{\Delta})^T \in S_{\text{on}}, \\ 0, & \text{otherwise if } (\theta_{\Delta}, \omega_{\Delta})^T \in S_{\text{off}}, \end{cases} \quad (16)$$

where S_{on} and S_{off} define the regions in the θ - ω plane, by which the state-dependent activation and inactivation of the active torque are determined. See Fig. 5b bottom right, in which S_{off} is represented by gray regions and S_{on} by white regions. The parameters P and D are, respectively, the P and D gains of the PD feedback controller when it is activated. The PD feedback controller is activated when the delayed state of the pendulum $x_{\Delta} = (\theta_{\Delta}, \omega_{\Delta})^T$ is located in S_{on} , while it is inactivated when x_{Δ} is in S_{off} . In (Asai et al. 2009), S_{on} and S_{off} are separated by the boundaries defined by $\theta_{\Delta} = 0$, $\dot{\theta}_{\Delta} = a\theta_{\Delta}$ and $\theta_{\Delta}^2 + \dot{\theta}_{\Delta}^2 = r^2$. The parameter r is fixed at 0.004 here, which determines the circular sensory dead zone around

the upright position. The parameter a determines the slope of the on-off boundary line $\dot{\theta}_{\Delta} = a\theta_{\Delta}$ ($a = -0.4$ in Fig. 5b). The parameters P and D of the PD controller, when the PD controller is activated, are set as $P = 147$ Nm/rad corresponding to 0.25 mgh and $D = 10$ Nms/rad in Fig. 5b. Note that the parameter set $(P, D) = (0.25$ mgh, 10) is outside of the stability region of the continuous control model, as indicated by the diamond-shaped symbol in Fig. 4. That is, if the intermittent controller were activated persistently regardless of the location of the state point, the upright equilibrium would be unstable of focus type, due to the delay-induced instability. Note also that these values are much smaller than P - D gains used for

(a) $P = 0.8mgh$, $D = 275$, $\sigma = 0.2$ and 2.0 (b) $P = 0.25mgh$, $D = 10$, $\sigma = 0.2$ 

Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the, Fig. 5 Typical sway dynamics with noise for (a) the traditional continuous control model and (b) the intermittent control model. In each of (a) and (b), top trace: a sample path of the tilt angle

θ for 60 s. Bottom left: power spectral density (PSD), which was estimated by ensemble average of five PSDs. Bottom right: phase portrait. (a) Noise intensities: $\sigma = 0.2$ Nm (black curves) and $\sigma = 2$ Nm (gray curves). (b) Noise intensity: $\sigma = 0.2$ Nm

the impedance controller, which provides a basis of flexibility of the ankle joint by means of the small joint impedance even when the active feedback control is switched on. Despite the fact that upright equilibrium is also unstable of saddle type when the intermittent controller is persistently switched off, it is remarkable that a switching between the activation and the inactivation of the PD feedback controller can establish a bounded stability of the inverted pendulum (Asai et al. 2009).

Figure 5b shows a typical steady-state dynamics of the intermittent control model with small noise ($\sigma = 0.2$ Nm). In contrast to the impedance control model, the sway pattern contains slow oscillatory component with an amplitude as large as human sway even with the small noise. The phase portrait of the model illustrates features of the intermittent control model, in which the state point x in the off-region S_{off} moves slowly along the stable manifold, approaching the saddle point transiently, followed then by the slow fall away from the saddle point along the unstable manifold until the state point goes out the off-region S_{off} . When the PD controller is activated in S_{on} , the delay-induced unstable oscillatory dynamics moves the state point closer to the stable manifold in the off-region, at which the PD controller is

switched off (see Fig. 5b bottom right). Since this scenario works for both right and left halves of the phase plane, the noisy dynamics exhibit transitions between left and right planes, in addition to the on-off transitions, generating a butterfly-shaped trajectory. The PSD for this fluctuation shows the power-law-like behavior at the low-frequency regime (Fig. 5b bottom right), where the regression line, representing the scaling exponent β , is close to $3/2$ as in human postural sway.

Flexibility Versus Rigidity

By comparing Fig. 2 with Fig. 5, the following similarities are evident: similarity between Fig. 2a for a healthy young adult and Fig. 5b for the intermittent control model and similarity between Fig. 2b for a Parkinson's patient and Fig. 5a for the continuous control model. Those similarities suggest that the upright stance of healthy young adults is stabilized flexibly by the intermittent controller, whereas that of a population of patients with Parkinson's disease is stabilized rigidly by the continuous controller. This might be a natural consequence of the selection of strategy for stabilizing the upright stance based on the minimum intervention principle with the trade-off problem regarding the minimization of the deviation from the upright posture and the minimization of the

energetic cost (Michimoto et al. 2016). However, it should be noted that multiple strategies could be adopted by different experimental subjects for a single goal of motor task, probably depending on the criteria used for adapting given tasks and environment (Zenzeri et al. 2014).

Cross-References

- [Dynamic Diseases of the Brain](#)
- [Dynamical Systems: Overview](#)
- [Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights](#)
- [Intermittent Control of Movement and Balance](#)
- [Neuromechanics of Postural Control](#)
- [Stochastic Resonance: Balance Control and Cochlear Implants](#)
- [Time-Delayed Neural Networks: Stability and Oscillations](#)

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Intermittent Delay Feedback Control

- [Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the](#)

Intermittent Feedback control

- [Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the](#)

Internally Coupled Ears

- [Internally Coupled Ears \(ICE\): Biophysical Consequences and Underlying Mechanisms](#)

Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms

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Synonyms

[Internally coupled ears](#); [Pressure-difference receiver](#); [Pressure-gradient receiver](#)

Though the notions of pressure-gradient receiver and pressure-difference receiver have been used widely (van Hemmen et al. 2016, Sect. 2), they are not really synonymous with the “internally coupled ears” or for short ICE that we analyze here because, in contrast to ICE, both are ill-defined or even wrong. The pressure difference between the two eardrums never gives rise to a gradient since, for the terrestrial vertebrates under consideration, the interaural distance L is of the order of cm. A gradient means taking a derivative and, hence, a limit $L \rightarrow 0$ whereas in reality L is fixed and bound to remain finite >0 . Even though L is of the order of a few, usually <2 , cm and hence $\ll \lambda$, with λ as a wavelength relevant to sound localization, a finite L is essential to giving a finite time delay for all nonzero directions. The time delay between left and right eardrums is a cue, though not the only one, to azimuthal sound localization. Furthermore, pressure differences do not single out internally coupled ears since *all* vertebrates, including mammals with independent ears, use pressure differences between the two tympana to azimuthally localize a sound source. Since both terms are either wrong or do not cover the reality they are supposed to describe, it was decided during the international conference *Internally Coupled Ears* at the TUM Institute for Advanced Study, Garching bei München, Germany, June 18–20, 2014, to adopt the new name “Internally Coupled Ears.” For details, see the special issue of *Biological Cybernetics* 110/5–6 (2016) devoted to ICE; in particular, the Editorial (van Hemmen et al. 2016).

Definition

ICE stands for internally coupled ears. Frogs, lizards, crocodilians, and birds, more than half of the land-living vertebrates, possess ICE, where an air-filled internal cavity couples the two eardrums. Though many insects are also equipped with ICE, we will focus here on terrestrial vertebrates. When sound excites the two eardrums, the motion of each of them will induce a pressure wave in the internal or interaural cavity, which then propagates to the other eardrum, and modifies the

response to the incoming sound arriving there. The coupling between the two eardrums is reciprocal and changes the interaural (ITD and ILD) into *internal* time and level difference (iTD and iLD). An animal only perceives the latter. Its neuronal system uses both iTD and iLD for azimuthal sound localization. Hence the effect of ICE is twofold, on both iTD and iLD, and is often profound.

Detailed Description

Before embarking on the underlying mathematical description of ICE, we will review what is currently known about where internally coupled ears have come from through evolution, how widely they are distributed in nature, and what the internal coupling looks like for different groups.

ICE: Phylogeny and Appearance

As Fig. 1 shows, tympana appeared both rather early in evolution, independently in different groups, and the great majority of land-living vertebrates have internally coupled ears. Only mammals, snakes, Sphenodontidae (*Tuataras*), and the Testudines (reptiles commonly known as turtles, tortoises, and terrapins) have independent ears. Living mostly in water with a sound speed of more than four times that in air, they use the otoliths of the vestibular system as inertial masses to localize a sound source, as do fish (Teleosts) (Zeddies et al. 2011). Snakes are equipped with a unique auditory system (Friedel et al. 2008; Young 2003), which makes them feel happy in soil such as sand, with density a 1000 times bigger than that of air, and does not need Eustachian tubes to equilibrate inside and outside pressure. Mammals do need to equilibrate, but their Eustachian tubes are so thin and long that an effective coupling between left and right tympanic cavity does not exist – except for a few exceptions (Mason 2016) of mammals that live underground and by their very existence “prove” the rule.

Azimuthal sound localization is realized neuronally on the basis of what the animal actually hears. In animals with ICE, this is not the

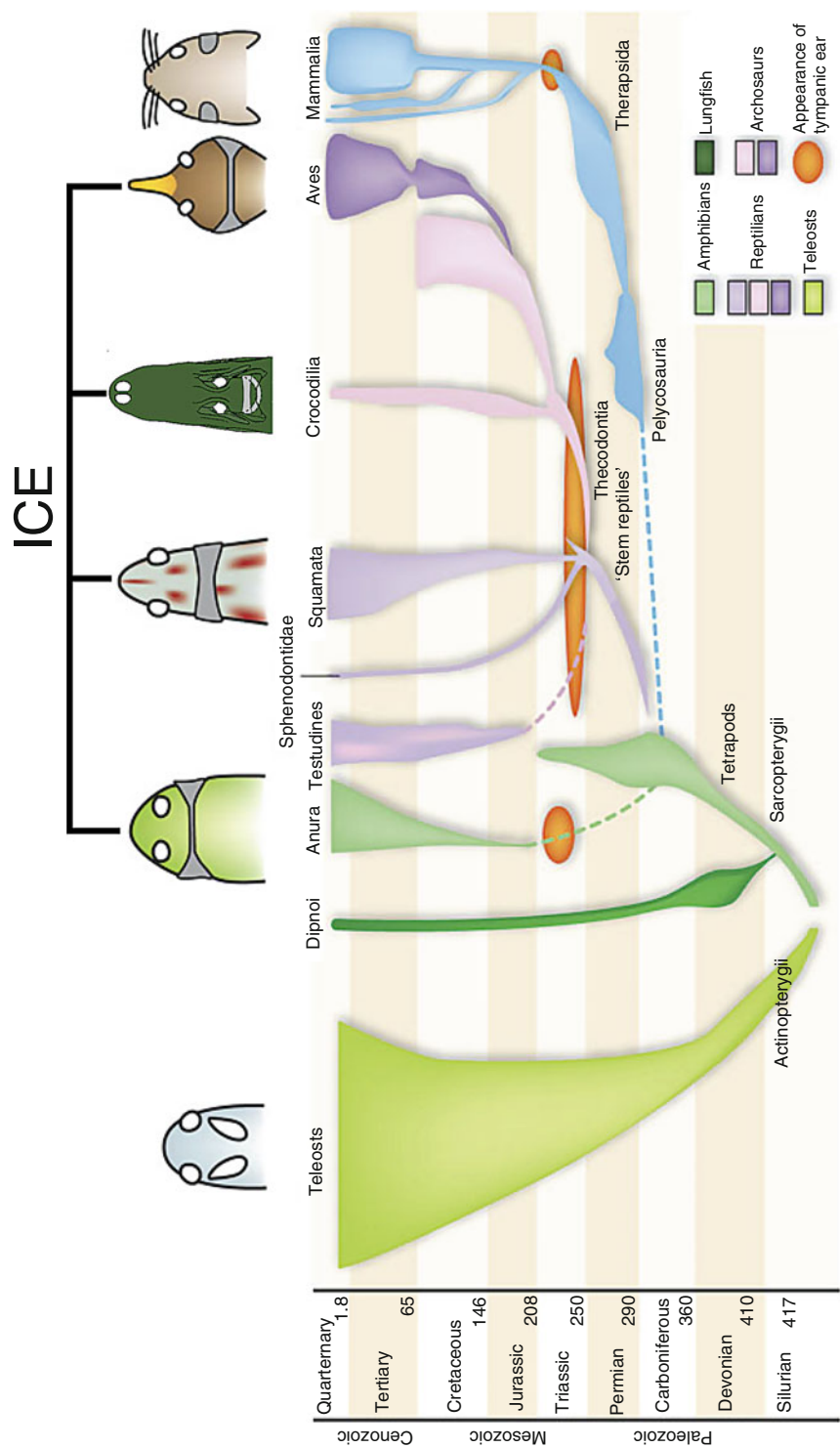
interaural time and level (i.e., intensity) difference, ITD and ILD, generated between the two eardrums by external sound as stimulus, but the *internal* time and level difference, iTD and iLD, which are a consequence of the superpositions of external stimulus p_{ext} at the tympana and the internal, or interaural, cavity pressure p on the inside of the two eardrums that are coupled by the very same p .

Figure 1 already suggests a certain diversity in the geometry of the interaural cavity as present in different orders and this is confirmed by Fig. 2. Since the mere geometry of the cavity determines the resulting iTD and iLD that the animal perceives as superposition of the outside stimulus and the internal pressure at its tympana, we need to focus on the nature of the connective geometry, the essential part of ICE.

Figure 2a shows what the interaural canal looks like in frogs such as the American bullfrog *Rana catesbeiana* or the common frog *Rana temporaria* (Linnaeus, 1758). The pharynx is connected to both the lungs and to the middle ear or tympanic cavities through permanently open, but relatively narrow, Eustachian tubes. Only when croaking do frogs open their mouth and expand their pharynx. When localizing sounds, frogs have their mouth closed and pharynx constricted; their eardrums and middle-ear/tympanic cavities are coupled through their pharynx and Eustachian tubes.

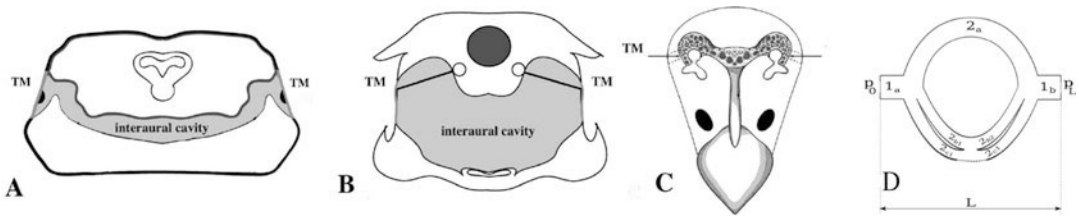
Most frogs are amphibious and exhibit the above setup, but the South-African clawed frog *Xenopus laevis* is fully aquatic, except during rare overland migrations between ponds. We will see later on how the ICE system of *Xenopus* has adapted to this aquatic existence, where the speed of sound is 4.2 times bigger than in air so that iTDs for an interaural distance $L = 2$ cm are reduced to values so small that even ICE cannot make them neuronally manageable; see subsection “[Underwater Hearing and Sound Localization: The Case of *Xenopus*.](#)”

Figure 2b exhibits the pharyngeal cavity, the back part of the lizard’s mouth, which provides ample air, and space, to connect the two eardrums. Lizards are typical representatives of ICE and they have been studied extensively, first experimentally



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 1 Evolutionary origin of audition, with the vertical axis denoting time – top is modern times – and the horizontal direction for indicating natural diversity. Teleosts are fish, Dipnoi are lungfish, and the Anura stand for frogs. Snakes belong to the squamates but have independent ears so that the squamates need to be restricted to the lizards, a gigantic family. The Crocodylia have two, or more, interaural canals connecting the left and right tympanic cavities directly behind the eardrums. Many

birds show a rather intricately shaped interaural cavity with weird looking, supporting, “stalactites” so as to minimize turbulence and give the cavity more stability. Just take it as one canal. Entering the Tertiary the dinosaurs, to the left of the birds (Aves, together with the Crocodylia their relatives, so to say), stopped existing. Tympana appeared in the Triassic and so did ICE. (Figure taken from and modified after van Hemmen et al. (2016))



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 2

Schematic of internally coupled ears (ICE) in terrestrial vertebrates: (a) frogs, (b) lizards, (c) birds, (d) Crocodilians. The realizations are quite different. Frog and lizard are illustrated with coronal slices, as are crocodilians; the bird is shown in a transverse slice as a dorsal view from above. The (colored) tympana are surfaces bounding the air-filled interaural cavity, which physically couples the left and right eardrums. As shown explicitly in

(b), the extracolumella embedded into the eardrum transfers tympanic vibrations through the columella into the cochlea, which is connected to the auditory system, where sound localization is realized neurally. (d) Crocodilians have more than one canal (here one dorsal and two ventral canals, all labeled by 2) connecting the two ear drums, which are flanked by tympanic cavities (1). (Figures (a–c) have been taken from Christensen-Dalsgaard (2005), in a slightly different version due to van Hemmen et al. (2016))

(Christensen-Dalsgaard and Manley 2005, 2008) and then theoretically in terms of mathematical models first for lizards (Vossen et al. 2010), then in far more detail both for lizards (Vedurmudi et al. 2016a) and for nearly all “icy” animals (Vedurmudi et al. 2016b, 2018). The extracolumella is embedded in the eardrum. The columella, which is directly connected to the former and makes a 90° angle with both, then transfers the tympanic motion to the cochlea.

Finally, Fig. 2c, d show the situation in extant archosaurs, viz., birds and crocodilians, the only known survivors of a larger group to which the dinosaurs also belonged. Whereas frogs and lizards exploit a single interaural cavity or canal to connect the left and right eardrums, crocodilians possess two or more canals; generically, a rather robust dorsal one and one or two ventral ones. The latter are connected to the pharyngeal cavity through the median pharyngeal valve and in this way also function as Eustachian tubes that equilibrate interaural and outside pressure, the valve only opening during a short period of time, say, 0.3 s, approximately every 120 s (Young and Bierman 2019). So its opening is sparingly dosed.

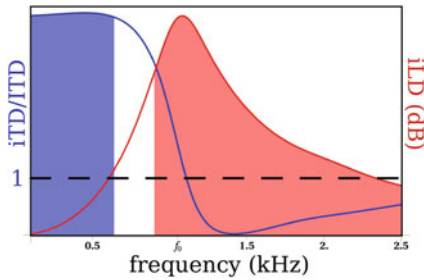
Performance of Internally Coupled Ears (ICE)

Why did nature equip more than half of the terrestrial vertebrates with ICE? Let us analyze the performance of ICE as shown by lizards, a generic case. Sound localization is due to a *neuronal*

evaluation of sound stimuli that arrive at left and right eardrums. As we have seen, the animal does not perceive the interaural but the internal time and level differences, iTD and iLD. Here we focus on azimuthal sound localization, in a horizontal plane at the center of which we imagine the animal. For what follows, a clear definition of both iTD and iLD is crucial. For the iTD things seem, and are, clear. There is, however, an important derived quantity, the *time dilation factor* or for short $TDF = iTD/ITD$. For lizards the TDF is typically of the order of 3 so that their *effective* interaural distance is not L but $3L$.

The outside stimuli arrive at an angle θ with respect to the rostral-caudal axis through the animal so that $\theta = 0$ is straight in front. Once the source is far enough away, the time difference between left and right eardrums is to good approximation $\Delta = (L \sin \theta)/c$ where c is the speed of sound in air. For generic lizards, $L \simeq 1 - 2$ cm. They therefore face a problem: For their neuronal hardware Δ is too small, even for $\theta = 90^\circ$, to get a decent accuracy; say, $10-20^\circ$. It is here that ICE come(s) in to help.

Let us turn to Fig. 3, showing the generic ICE performance. The left vertical axis is for the dimensionless fraction $iTD/ITD = TDF$, the time dilation factor, while the right vertical axis is for the iLD, dimensionless too. Both are shown as a function of the frequency of a pure-tone stimulus, indicated by the horizontal axis. The cochlea



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 3 Performance of ICE, schematic. The time dilation factor $TDF = iTD/ITD$ (left vertical axis, blue) and the internal level difference iLD (right vertical axis, red) are shown as a function of frequency f , plotted along the horizontal axis. Both are shown for stimulus directions $\theta = \pm 90^\circ$. The fundamental frequency f_0 of the eardrum is indicated on the horizontal axis, here slightly beyond 1.0 kHz, and corresponds to that of the Tokay gecko, the second-largest gecko. On the other hand, in the house gecko (*Hemidactylus*) $f_0 \approx 2.8$ kHz. Typically, the TDF exhibits a plateau up to about 3 for $0 \leq f \leq 2f_0/3$, and then drops to 0. TDF values of 4 and more (e.g., for *Crocodylia*) are also known. The frequency interval $[0, 2f_0/3]$ is well within the range of hair-cell phase locking (up to 1.5 kHz) that is needed for neuronally evaluating the iTD obtained from the cochlea. On the other hand, slightly beyond f_0 , say at $1.1 f_0$, the iLD shows a maximum, which may be of the order of 10–20 dB, even though the iLD vanishes. (Figure taken from Vedurmudi et al. (2016a))

makes a frequency decomposition (of a kind we need not discuss here) and tympanic amplitudes are extremely small (in the range of nm; Nature is not a disco) while the velocities are of the order of μ m/s. Linear acoustic theory is therefore applicable (see below) and we can treat the general sound stimulus as a linear superposition of pure tones.

The tympanum is the gate between the outside auditory world and the internal pressure coupling the two eardrums through the interaural cavity. Its fundamental frequency will be called f_0 . To the left of $2f_0/3$ we see in Fig. 3 that the fraction $iTD/ITD \equiv TDF$ exhibits a plateau at a level appreciably bigger than 1. It is typically 3 for lizards but, for instance for *Crocodylia*, it may well assume a value between 4 and 5. Beyond $2f_0/3$, where the $2/3$ is also an estimate that is easy to remember, the TDF drops down to 0 and is worthless for azimuthal sound localization because the hair cells' phase locking is over beyond, typically, 1.5 kHz. The barn owl

(Konishi 1993; Köppl and Carr 2008; van Hemmen 2002) is one of the famous exceptions proving the rule as its phase-locking upper bound is about 9 kHz.

The plateau shown in Fig. 3 is only for the sound-source directions of $\pm 90^\circ$ but the plateau height assumes the same value for all directions (Vedurmudi et al. 2016b, 2018). Hence the neuronal processing ensuing from the cochlea can start, so to speak, with a frequency input that has constant TDF, which makes the ensuing auditory processing workable. For lizards, the plateau value of 3 agrees with experiment (Christensen-Dalsgaard and Manley 2008).

As Fig. 3 shows, when the TDF starts decreasing steeply (to values near 0), the iLD begins to increase and may well assume an appreciable maximum of 10–20 dB. It does so at a frequency slightly beyond f_0 say, at $1.1 f_0$. Most “icy” animals, certainly nearly all lizards, experience a practically vanishing $iLD \approx 0$ because the head does not screen for the wavelengths at stake, with $L \ll \lambda$. Nevertheless, despite a negligibly small external iLD , the accompanying iLD may well become quite large for larger angles, as shown in Fig. 3 for adult animals with sound-source direction of $\pm 90^\circ$ or, equivalently, $\pm \pi/2$.

In summary, through ICE the animal's auditory system obtains two clearly disjoint frequency regimes. First, a low-frequency one, with $0 \leq f \leq 2f_0/3$ where the fraction $TDF = iTD/ITD$ shows a plateau. As noted, here the TDF obtains – for adult lizards – typical values of 3 (but may well become 4–5 in other reptiles). This solves the small-animal problem (Christensen-Dalsgaard and Manley 2014, p. 183) in which the head and, more importantly, the interaural distance L or with θ as direction the $ITD = L \sin \theta$ of most “icy” animals are too small to come up with what one may call a decent value. It can be shown (Vossen 2010, Fig. 3.4) that a TDF of about 3 may give rise to a precision of 10–20°. The argument, however, provides an existence proof but not more than that, because the underlying neuroanatomy is not yet known. Jeffress (Konishi 1993; van Hemmen 2002; Köppl and Carr 2008) sounds plausible but it may be different.

Second, at higher frequencies ICE equips the auditory system with an iLD maximum at about $1.1 f_0$ and, despite $ILD \approx 0$, with iLD values that may well be between 10 and 20 dB; cf. Fig. 3. Turning the head so as to seek the direction of a sound source is quite often observed in animals with ICE, among others in birds. That is, the iLD allows for sound-source detection, though not a fast one.

Finally, and as anatomical confirmation of our discerning iTDs and iLDs, lizards possess a neat split-up of their hair cells (Manley 2000) into low- and high-frequency ones. The former are specialized in timing, the latter in amplitude cues. Following their respective axons, one sees (Szpir et al. 1990; Willis et al. 2014) a bifurcation into disjoint parts of the auditory system, which are functionally consistent with this split-up.

Mathematical Analysis and Explanation

It is now more than timely to show what principles underlie the mathematical analysis of ICE. As a mathematical abstraction we replace the internal cavities of Fig. 3 by cylinders, such as the one in Fig. 4a.

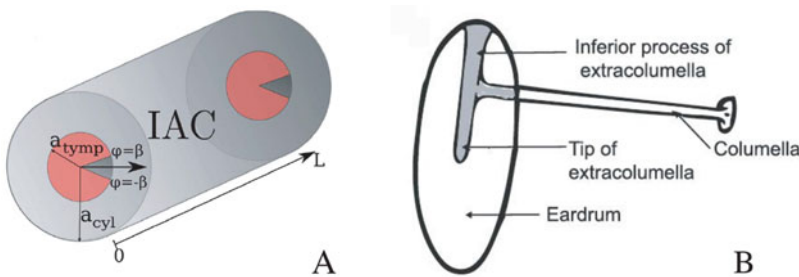
Tympanic membrane Let p be the pressure of the interaural or internal cavity Ω_i , which connects

the two eardrums and, hence, is a three-dimensional bounded domain in $\mathbb{R}^3$, with smooth boundary $\partial\Omega_t$, both Ω_t and its border $\partial\Omega_t$ depending on time t once a stimulus sounds loudly enough to set the eardrum into motion. The tympanic membrane's dynamics is given by a two-dimensional damped wave equation,

$$-\frac{\partial^2 u}{\partial t^2} - 2\alpha \frac{\partial u}{\partial t} + c_M^2 \Delta_{(2)} u = \frac{1}{\rho_m d} [p(x, r, \varphi; t) - p_{\text{ext}}(x, r, \varphi; t)]|_{x=0,L} \quad (1)$$

where $\Delta_{(2)}$ is the two-dimensional Laplacian, u is the membrane's deviation from the equilibrium $u \equiv 0$, measured along the x -axis, α is the damping coefficient, c_M is the membrane's transverse-wave propagation velocity and $[p(x, r, \varphi; t) - p_{\text{ext}}(x, r, \varphi; t)]$ is the total pressure on the eardrum surface driving the membrane at either end $x = 0, L$. Here p_{ext} is the external pressure due to a sound stimulus while p is the internal pressure coupling the tympana. The prefactor $1/\rho_m d$ with ρ_m as the membrane's density and d as its thickness is in fact a dimensional one.

In passing we note that, without external input, that is, with $p_{\text{ext}} = 0$, but with $\alpha > 0$, as in realistic eardrums with damping, the coupled eardrum-air system relaxes to the equilibrium state $u \equiv 0$ &



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 4

(a) Because of the coupling of the eardrums through the internal cavity, an animal equipped with ICE perceives internal rather than interaural time and level differences. The interaural cavity IAC is modeled mathematically as a cylinder of volume V_{cav} and of length L with radius $a_{\text{cav}} \equiv \sqrt{V_{\text{cav}}/\pi L}$; L is also the interaural distance. Cylindrical coordinates are used, with x -axis as cylinder axis parallel to the arrow $(0, L)$ and the polar coordinates $\{r, \varphi\}$ in a plane

orthogonal to it. The smaller (red) circles at either end indicate the eardrums with radius $a_{\text{tymp}} \leq a_{\text{cav}}$. The dark-gray wedge between $\varphi = \pm\beta$ stands for the extracolumella (Vedurmudi et al. 2016b, Fig. 1), which is embedded in the eardrum and is connected with the cochlea through the columella. As indicated in (b), it is practically orthogonal to the extracolumella. (Figures modified after Vedurmudi et al. (2016a) and Christensen-Dalsgaard and Manley (2019), respectively)

$p \equiv 0$. For p there is a three-dimensional wave equation to which we will turn in a minute. Its boundary conditions are governed by Eq. (1) where p appears as source term, a feedback coupling.

Damping as described by Eq. (1) has never been derived as such but is standard and known to be realistic. It leads to an exponential decrease of u as $\exp(-\alpha t)$ where $1/\alpha$ is of the order of one millisecond (ms) so that eardrums are fairly heavily damped, far more heavily than one naively imagines. Since the amplitudes induced by natural sound are in the nm range, with nearly always a maximum of 100 nm, and the eardrum radius a_{tymp} – see Fig. 4a – is in the cm range, tympanic motion can be taken to be purely normal so that only a single degree of freedom remains, viz., u .

In lizards – see for instance Fig. 4 and Vedurmudi et al. (2016b, Fig. 6) – an eardrum can be modeled to fair precision as a circular disk (Manley 1972; Vedurmudi et al. 2016b) with radius a and Dirichlet boundary conditions $u(a_{\text{tymp}}, \varphi) = 0$ at the edge $\{r = a_{\text{tymp}}\}$, including an effectively very heavy cartilaginous sector with boundaries $\varphi = \pm\beta$, which is called extracolumella. The composite system of extracolumella and columella is shown schematically in Fig. 4b. It transports membrane vibrations, which are virtually perpendicular to the eardrum, to the cochlea through the columella, which is practically orthogonal to the extracolumella embedded in the membrane and picking up its vibrations.

Internal cavity The internal pressure p in the cavity Ω describes the dynamics of air. Under normal circumstances the corresponding wave equation for sound has been derived through linear perturbation theory on the basis of the Euler equation (Acheson 1990; Rienstra and Hirschberg 2019; Temkin 1981) so that only the normal derivative $\partial_n p$ at the boundary $\partial\Omega_t$ needs to be specified. Amplitudes of natural sound are nearly always small, that is, in the nm range, while the membrane curvature remains small too, that is, of the order of $10^{-7}/10^{-3} = 10^{-4}$, which is an extremely conservative estimate. Accordingly, during the course of time any normal derivative $\partial p/\partial n$ simply equals $\partial p/\partial x$, and thus $\partial p/\partial n = \partial p/\partial x$ to high precision.

It is here that (linear) acoustics (Acheson 1990; Rienstra and Hirschberg 2019; Temkin 1981) comes in.

Since the boundary $\partial\Omega$ depends on the time t once sound sets the eardrums into motion, we need to say more and must specify boundary conditions for our partial differential equations (3) and (4) below. Now the no-slip boundary condition (Acheson 1990; Rienstra and Hirschberg 2019; Temkin 1981) comes into play in that at the boundary the macroscopic gas velocity and, hence, both normal and tangential components of the velocity vector $\mathbf{v}$ equal those of the (rigid) boundary itself. Experts might grumble that the corresponding wave Eq. (3) below is based on the three-dimensional Euler equation that only takes the normal derivative into account. True, but the no-slip boundary condition has been shown to be universally valid. That is, dropping second-order terms from the Euler equation near/at the boundary, we are left with

$$\frac{\partial p}{\partial x} = -\rho \frac{\partial v}{\partial t} \quad (2)$$

where ρ is the density of air and v is the normal velocity of the tympanic membrane the air sticks to according to the no-slip boundary condition (Acheson 1990), which has been confirmed experimentally since long. From Eq. (1) and its underlying physics we know that $v = \partial u/\partial t$ is the normal derivative to high precision (at least first order) so that the circle is closed.

On the other hand, p satisfies the three-dimensional wave equation

$$\Delta_t p = \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} \quad (3)$$

where c is the speed of sound in air and Δ_t is the three-dimensional Laplacian on Ω_t as the time dependence is in the domain Ω_t . We may rewrite (3) in cylindrical coordinates,

$$\begin{aligned} \frac{1}{c^2} \frac{\partial^2 p(x, r, \phi; t)}{\partial t^2} &= \Delta_{(2)} p(x, r, \phi; t) \\ &+ \frac{\partial^2 p(x, r, \phi; t)}{\partial x^2} \end{aligned} \quad (4)$$

with $\Delta_{(2)} = \partial^2/\partial r^2 + (1/r)\partial/\partial r + (1/r^2)\partial^2/\partial \phi^2$ as the two-dimensional Laplacian in polar coordinates $\{r, \phi\}$; cf. Fig. 4a. The boundary condition (2) of Δ_t lives on $\partial\Omega_t$ and hence depends on the time t , as does the cavity's shape $\partial\Omega_t$ through the fluctuations of the eardrums. As for the rest, “the rest is silence” because most of the boundary is thin skin covering bone, so that the *remaining* part of the boundary is taken to be fixed and we can use Neumann boundary conditions with vanishing normal derivative; viz., $\partial_n p = 0$; see also (2) with $v = 0$.

Systematic perturbation theory Since the amplitudes of eardrum fluctuations are so small (<100 nm $\ll L$), a systematic perturbation theory sounds (van Hemmen 2016), and is (Heider and van Hemmen 2020), reasonable. Here we only analyze its key ideas. We start with the equilibrium configuration Ω_o where $u \equiv 0$ and $p \equiv 0$. Since the eardrum dynamics is (heavily) damped there is no harm in assuming $\Omega_t \subset \Omega_{\max}$, the latter set being only slightly bigger than Ω_o . The mathematical scenery we will meet here can now be imagined to live in the fixed Hilbert space $L^2(\Omega_{\max})$. We therefore proceed without further ado, referring the mathematically interested reader to elsewhere (Heider and van Hemmen 2020).

We write the volume change as $\Omega_t = \Omega_o + \kappa\delta\Omega$ with the $+$ as a formal plus sign for sets, $\delta\Omega$ as the symmetric difference between Ω_t and Ω_o with indicator function $1_{\delta\Omega(t)}$, and κ originating from Ω_t and Ω_o as a clever $\pm$ that makes Ω_t out of Ω_o : If Ω_o is smaller, we add, and if Ω_o is bigger, we subtract; see below. The time-dependent Eq. (3) then reappears in the form

$$\begin{aligned}\partial_t^2 p &= \Delta_t p = [\Delta_o + \kappa(1_{\delta\Omega}\Delta 1_{\delta\Omega})]p \\ &\equiv [\Delta_o + V(t)]p\end{aligned}\quad (5)$$

where the perturbation $V(t)$ directly stems from the volume fluctuation, which induces addition or subtraction of a piece of the Laplacian to or from the “Laplacian cake” based on Ω_o . Moreover, the Δ sandwiched by the $1_{\delta\Omega}$'s in Eq. (5) is the Laplacian as a mere partial-differential operator in our big, fixed, Hilbert space $L^2(\Omega_{\max})$. In other words, in view of Eq. (5) we can also write formally (and a bit more suggestively)

$$\Delta_t = [\Delta_o + \kappa(1_{\delta\Omega}\Delta 1_{\delta\Omega})]. \quad (6)$$

By the way, the operator

$$(1_{\delta\Omega}\Delta 1_{\delta\Omega}) \equiv \Delta|_{\delta\Omega(t)} \quad (7)$$

is the Laplacian restricted to the fluctuating domain $\delta\Omega(t)$, an operator that – despite a slight misuse of language – effectively does what it formally looks like.

Duhamel principle Second derivatives such as $\partial_t^2 = \partial^2/\partial t^2$ in Eq. (5) are nearly always a nuisance but there is an old trick to get rid of them and reduce everything to a single differentiation with respect to time t . To this end we define the two-component vector $\mathbf{p} \equiv (p, \partial_t p)$ so that $\partial_t \mathbf{p} = (\partial_t p, \partial_t^2 p)$. For a two-vector $\mathbf{p}$ we get two equations instead of one and introducing matrix operators carrying a tilde we readily find

$$\partial_t^2 p = \Delta_t p \Rightarrow \partial_t \mathbf{p} = [\tilde{\Delta}_o + \tilde{V}(t)]\mathbf{p} \quad (8)$$

where $\tilde{\Delta}_o$ and $\tilde{V}$ are simple 2×2 matrices containing Δ_o and V in addition to 0 and 1 (zero and unit operators) as matrix elements. In a similar vein, Eq. (4) can be reduced to a first-order equation as well. In this way, we can take into account the physical variation of the cavity domain $\Omega(t)$ as a consequence of the eardrum or whatever membrane variations, which are always very small, and the right-hand side of Eq. (6) then directly leads to the Duhamel principle (Yosida 1980), whose key idea is worth considering.

If $\tilde{V} \equiv 0$, Eq. (8) is easy to solve by means of the semigroup $T_t^o = \exp(t\tilde{\Delta}_o)$ (Engel and Nagel 2006) so as to obtain $\mathbf{p}(t) = \exp(t\tilde{\Delta}_o)\mathbf{p}(t=0)$. Just differentiate. The initial condition $\mathbf{p}(t=0)$ is what we start with. Let us define $\mathbf{f}(t) = \tilde{V}(t)\mathbf{p}(t)$ and rewrite (8) in the form $(\partial_t - \tilde{\Delta}_o)\mathbf{p} = \mathbf{f}$. Once $\tilde{V} \neq 0$ we can still solve (8) formally through the Duhamel formula,

$$\begin{aligned}(\partial_t - \tilde{\Delta}_o)\mathbf{p} &= \mathbf{f} \Rightarrow \mathbf{p}(t) \\ &= T_t^o \mathbf{p}(0) + \int_0^t dt' T_{t-t'}^o \mathbf{f}(t')\end{aligned}\quad (9)$$

It is a straightforward exercise to verify that the expression on the right of Eq. (9) indeed solves the partial differential equation on the left. We simply note that t appears twice in the integral on the right and that the initial condition $\mathbf{p}(0)$ is satisfied by construction. Equation (9) embodies what is often called the Duhamel formula (Yosida 1980, §XIV.5). The semigroup T_t^0 is a continuous one (Engel and Nagel 2006) so that the integral in Eq. (9) is nothing esoteric but can be taken in the sense of Riemann.

One might complain that the solution we are looking for has been hidden in $\mathbf{f}$, which is correct. The idea of Dirac's perturbation theory (Dirac 1958, §§44–46) is to start with a zeroth-order solution we know for sure, for example, $\mathbf{p}(0)$, substitute that into the right-hand side of Eq. (9) so as to obtain $\mathbf{f}(t') = \tilde{V}(t')\mathbf{p}(0)$, and either happily stop or iterate. The “small stuff” is in $\tilde{V}(t)$. Whereas a plethora of books on quantum mechanics, including godfather Dirac's fascinating classic (Dirac 1958), write out everything componentwise in terms of eigenfunctions of $\tilde{\Delta}_0$ – the present author is not aware of any exception – the above representation (9) is far more efficient as it is neatly compact. For details we refer to elsewhere (Heider and van Hemmen 2020, §§2.2–2.4).

The above kind of perturbation theory is called *geometric* perturbation theory because it is based on the mere geometry of the cavity Ω_t as shown for instance in Figs. 2 and 4, and its boundary $\partial\Omega_t$ as it fluctuates during a sound stimulus. The eardrum fluctuations induce slight volume changes and these are taken into account through a series expansion based on Eq. (9). The mathematics as given by Eqs. (1), (2), and (3) then unfolds. It goes without saying that for sound in natural circumstances a single first-order term does the job to satisfying precision (Heider and van Hemmen 2020, §4).

Boundary conditions (2) Partial differential equations such as Eqs. (3) and (4) need side conditions, viz., initial and boundary conditions. When sound starts sounding at $t = 0$, $p(t) = 0$, and $u(t) = 0$ for $t \leq 0$ directly give us initial conditions at $t = 0$ for p and u and whatever (left) derivative.

What, then, are the boundary conditions of Eq. (2)? As background, Shearer and Levy (2015, §6.2.2) provide very useful information through their textbook treatment of an inhomogeneous time-dependent boundary-value problem, including convergence questions associated with the Gibbs phenomenon. This is the modern way where boundary conditions are treated as source terms. The interpretation is ours but the argument below is exactly what is happening there – and at many other places in modern PDE theory.

For whatever $\Omega(t)$, its boundary $\partial\Omega(t)$ is pretty smooth, up to the eardrum's border. The tympanic rim is fixed, hence gives rise to the Dirichlet boundary condition $u = 0$ at the rim, but biological physics dictates that there is no moment transfer either. In other words, the rim is fixed but the tympanum can rotate freely. Hence a discontinuity in the normal derivative may well occur but it does so on a set of (2-dim.) Lebesgue measure zero. So why bother? The two-dimensional manifold $\partial\Omega(t)$ is effectively smooth.

A systematic perturbation theory starts with a zeroth-order term, which is here $p^{(0)} \equiv 0$. To obtain the first, non-zero, contribution $p^{(1)} \equiv p$ we begin with a three-dimensional Laplacian Δ_t with Neumann boundary conditions ($\partial_n p = 0$) and with an extra source term ($\mathbb{F}$ below) that allows for both efficient bookkeeping of the time-dependent boundary conditions (2) and for using the Duhamel expression (9),

$$\frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} - \Delta_t p = \mathbb{F} \quad (10)$$

where $\mathbb{F}$ incorporates the time-dependent boundary conditions stemming from Eq. (2),

$$\mathbb{F} = \rho_0 c^2 [(\partial_t^2 u_0)\delta(\mathbf{x} \in u_0(t, \Gamma_0)) + (\partial_t^2 u_L)\delta(\mathbf{x} \in u_L(t, \Gamma_L))] \quad (11)$$

with Γ_0 and Γ_L denoting the left and right eardrums at $x = 0$ and $x = L$. Moreover, $\delta(\mathbf{x} \in \dots)$ is a Dirac-type delta measure located at the manifold $\Gamma_0 \subset \partial\Omega_0$ and $\Gamma_L \subset \partial\Omega_0$ while the prefactors $(\partial_t^2 u_0)$ and $(\partial_t^2 u_L)$ prescribe the value of p at the tympanic membrane in accordance with the

boundary condition (3). Here we stay in the context of first-order perturbation theory so that we end up with $\partial\Omega_0$. We note that the dynamics is now “stored” solely in the membrane displacements u_0 and u_L and no longer implicitly in the geometry.

Furthermore, in lowest nontrivial order of perturbation theory, with zeroth-order $p^{(0)} \equiv 0$, only the external pressure signal p_{ext} drives the membranes. The lowest-order contribution $u_{0/L}^{(0)}$ to the membrane equations consistent with the previously introduced perturbation theory is now given by (Heider and van Hemmen 2020)

$$\begin{aligned} \frac{\partial^2 u_{0/L}^{(0)}}{\partial t^2} + 2\alpha \frac{\partial u_{0/L}^{(0)}}{\partial t} - c_m^2 \Delta_2 u_{0/L}^{(0)} \\ = \frac{p_{\text{ext}}}{\rho_m d} \Big|_{x=0/L} \quad \text{on } \Gamma_{0/L} \subset \partial\Omega_0. \end{aligned} \quad (12)$$

Together with the wave Eq. (10) for the cavity pressure p , this has the effect of decoupling the ICE equations in lowest-order perturbation theory.

Extensions

We have seen in section “Performance of Internally Coupled Ears (ICE)” that ICE is quite a powerful mechanism in that, among others, it solves the small-animal problem at no cost of energy. It is now time to discuss a few extensions of the formalism that throw new light on the underlying biological physics of the eardrum through underwater hearing of *Xenopus* and on possibilities that have not been analyzed as such yet such as varying the fundamental frequency f_0 at will. As we have seen in Fig. 3, f_0 plays a key role.

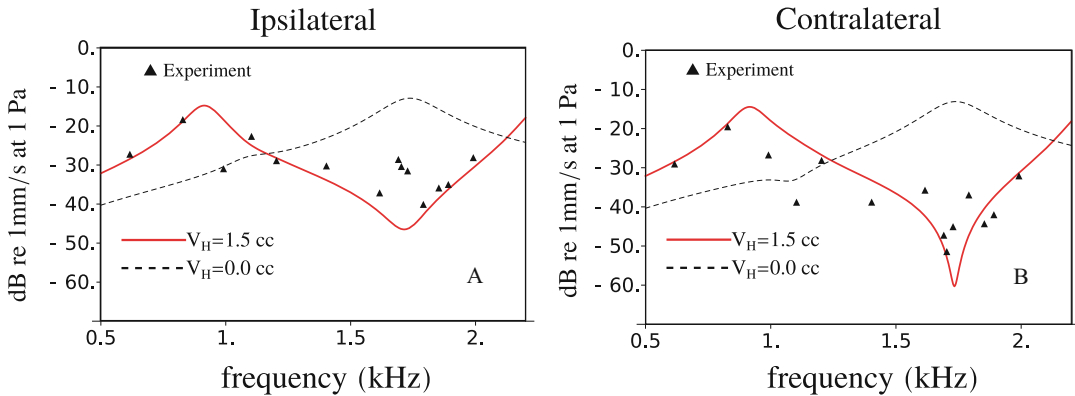
Underwater Hearing and Sound Localization: The Case of *Xenopus*

As noted, tympana of animals with ICE function as gates between the outside auditory world and the internal pressure coupling the two eardrums through the interaural cavity. As Fig. 3 evidences, its fundamental frequency f_0 segregates the low-

frequency iTD plateau from the high-frequency iLD maximum (of course only for angles $\theta \neq 0$). We now focus on the African clawed frog *Xenopus laevis laevis*, which lives in Africa south of the Sahara. Except for rare overland migrations between ponds, the frog is fully aquatic. The speed of sound in water is, however, 1480 m/s (i.e., 4.3 times larger than in air) and *Xenopus*’s interaural distance $L \approx 20$ mm so that iTDs are too small to be determined neuronally. Nevertheless the frog uses its auditory system to localize its sexual partner underwater, that is, for mating. Mating is not a millisecond affair so that iLD determination by quietly rotating the head is possible. In other words, the frog can afford to azimuthally localize the source of a mating call.

There are two big differences between a generic ICE case such as a lizard one and *Xenopus* (Vedurmudi et al. 2018): (i) Instead of a flexible membrane, *Xenopus*’s eardrum is a stiff, cartilaginous, plate suspended in an elastic rim; (ii) the interaural cavity is a narrow Eustachian tube (with radius $a_{\text{ann}} = 0.4$ mm (Vedurmudi et al. 2018, Table I)), in the middle connected to the lungs, which function as a Helmholtz resonator with fundamental frequency of about 1.7 kHz. As underwater animal, *Xenopus* needs a separate, air-filled, interaural tube since under normal circumstances the pharyngeal cavity as part of the mouth is filled with water. The two shallow tympanic cavities have a distinct taper into the much narrower, shared, Eustachian tube. So to speak, *Xenopus* is the opposite of the lizard case depicted in Figs. 2b and 4a.

Lungs as Helmholtz resonator Given the above geometry, we now turn to its performance (Vedurmudi et al. 2018). Figure 5 evidences that inflated lungs that function as Helmholtz resonator (Rienstra and Hirschberg 2019) are essential in explaining the experimental data. The frog has a rich vocal repertoire (Müller and Scheer 1970; Tobias et al. 2011) with two peaks, one at about 1 kHz and another one at 1.7 kHz. Receptive females approach calling males (Picker 1983). Hence they do need sound localization. The peak at about 1 kHz calls the attention of receptive females but, as is evident from Fig. 5, a female cannot localize the calling male since the



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 5 Experimentally measured (filled triangles) and model vibration velocities (solid lines) of the clawed frog *Xenopus* (a) ipsilateral and (b) contralateral eardrum underwater. The eardrum vibration velocities have been measured (Christensen-Dalsgaard and Elepfandt 1995) by using laser vibrometry. The solid (red) line corresponds to inflated lungs with a total volume $V_H = 1.5$ cc and the

dashed (black) line corresponds to the case $V_H = 0$ cc, that is, absent or fully deflated lungs. The sound-source direction is $\theta = 90^\circ$. The contralateral amplitude is significantly lower than the ipsilateral amplitude. As both plots show, the experimental results can be explained only with inflated lungs, whose Helmholtz-resonator function has been analyzed by Vedurmudi et al. (2018) in great detail. (Figure courtesy of Vedurmudi et al. (2018))

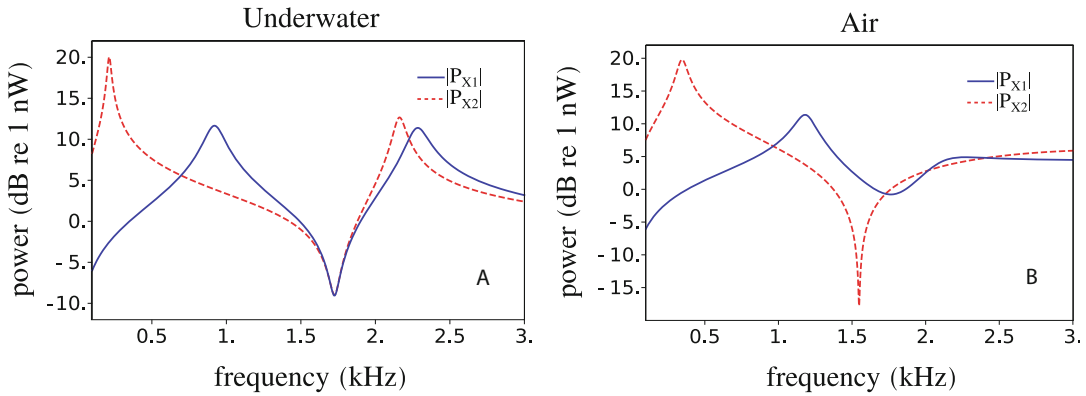
difference between ipsi- and contralateral ear is none. At 1.7 kHz, however, there is an outspoken difference (about 15 dB) and it is due to the inflated lungs (Vedurmudi et al. 2018) that operate as a Helmholtz resonator with fundamental frequency of about 1.7 kHz, whose resonance is fairly sharply peaked. The female can, however, tune in to it by reducing its lung volume from, say, 2 to 1 cc (Vedurmudi et al. 2018, Fig. 10b).

Tympanum as disk instead of flexible drum: *Xenopus2* The 1 kHz regime being eminently important to arousing the female's attention, a natural question is whether and, if so, why a "normal" eardrum would not do the underwater job. To answer this question, a novel frog has been raised (Vedurmudi et al. 2018), *Xenopus2*. It is identical to the normal *Xenopus*, except for having a lizard-like, flexible, eardrum instead of a cartilaginous tympanic disk, as does traditional *Xenopus*. Figure 6 shows *Xenopus2*'s iLD localization performance.

Returning to Fig. 5 we now see that the tympanic disk gives rise to the 1 kHz peak arousing a female *Xenopus*'s attention in a frequency domain that is beyond that (<500 Hz) of ordinary predatory/prey detection but that by itself cannot discern left/right from straight ahead. On the other hand, *Xenopus2* is facing a nasty problem in that

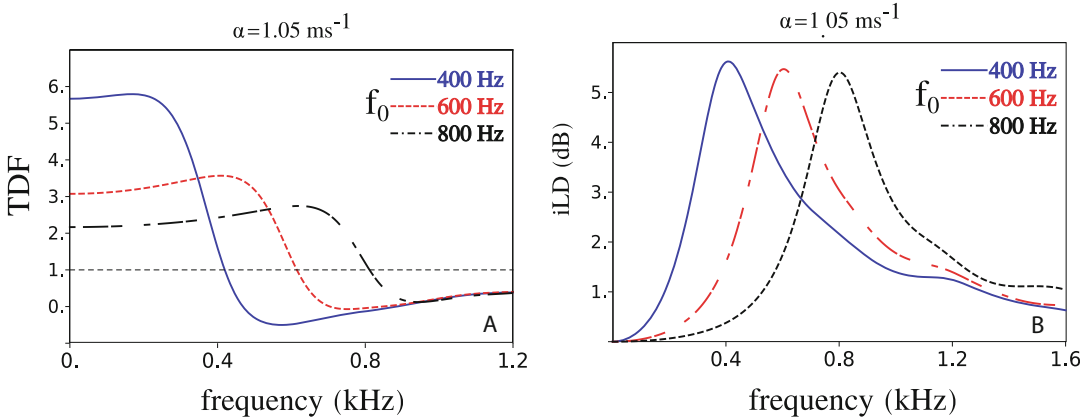
underwater its attentive zone is around 200 Hz (Fig. 6a), which is exactly there where it should not be – except as predators' food. In air, which is what a lizard-like eardrum has been made for, the maximum is at about 350 Hz, but overland trips are only good for seldom, collective, moves from one pond to the next. In passing, *Xenopus*'s foraging time is mainly sunset or sunrise, while it is at the surface of the pond, hunting for insects that have dropped on the water surface and – in vain – struggle for life. In such a case, the frog's lateral-line system performs the prey detection.

Its lungs function as Helmholtz resonator with fundamental frequency of 1.7 kHz, and they equip the clawed frog with a clear difference of about 15 dB between left and right tympanum (for directions $\theta = \pm 90^\circ$) exactly near this 1.7 kHz. Though the frequency window is narrowly spaced, by reducing its lung volume a female *Xenopus* can easily perform a fine-tuning (Vedurmudi et al. 2018, Fig. 10b) so that an a priori perfect fit is not required. Once the access to the lungs is closed or once they have been emptied ($V_H = 0$), Fig. 5 shows that there is only a single maximum with no intensity difference between left and right eardrums. Hence the female *Xenopus* could hear but could not localize the "singing" male, too sad a story to be true.



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 6 Frequency dependence of the power absorption (dB re nW) by the ICE system of *Xenopus* (solid line) and *Xenopus2* (dashed line) for a lung volume $V_H = 1.5$ cc (a) underwater and (b) in air. The solid (blue) line corresponds to *Xenopus* as it exists in nature with rigid-plate eardrums, whereas the dashed (red) line corresponds to the computer-raised *Xenopus2* with thin, flexible, eardrums as

in lizards. Both have the same interaural cavity. Whereas *Xenopus* has a clear underwater maximum at 1 kHz, its companion *Xenopus2* has a peak at about 200 Hz, which is no good for survival since normal underwater predator/prey life happens in the low-frequency regime < 500 Hz. In all cases the sound-source direction is $\theta = \pm 90^\circ$. By varying its lung volume V_H , *Xenopus* can fine-tune the resonances of (a) and (b). (Figure courtesy of Vedurmudi et al. (2018))



Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms, Fig. 7 Variation of (a) time dilation factor ($TDF = iTD/ITD$) and (b) internal level difference (iLD) with the membrane frequency f_0 for an eardrum of the lizard *Varanus* with the damping fixed at $\alpha = 1.05$ (ms^{-1}) Hz. Increasing the fundamental frequency f_0 extends the TDF plateau but at the same time reduces its height. On the other hand, the

iLD peak height decreases only slightly with an increase in the fundamental frequency, whereas the location of the peak shifts linearly with f_0 . Both figures indicate the possibility of tuning the sensitivity to sound localization cues by changing the tension of the eardrum; for instance, by contraction of the tympanus muscle (Vedurmudi et al. 2020)

Tuning the Eardrum's Fundamental Frequency

We now return to “ordinary” animals with ICE such as lizards. Intuitively, the fundamental frequency f_0 of an eardrum increases as $\sqrt{T}$ with increasing

tension T of the tympanic membrane. In fact, one can show (Vedurmudi et al. 2020, Eqs. (3)–(5)),

$$f_0 = \frac{c_M \mu_{11}}{2\pi} = \frac{\mu_{11}}{2\pi} \sqrt{T/\rho_M d_M} \quad (13)$$

where c_M is the propagation speed of waves in the membrane, μ_{11} is a material constant, ρ_M is the membrane's density, and d_M is its thickness. At least a quarter of all “icy” animals possess a so-called tympanus muscle (Vedurmudi et al. 2020, Figs. 1–3) that pulls at the inferior process of the extracolumella, orthogonally to the eardrum's rim (Fig. 4b) and in this way can modify f_0 .

Let us now take a look at Fig. 7, which exhibits the effect of varying the tympanic-membrane tension T on both iTD (left) and iLD (right). Naively one might think that, by contracting the tympanus, T and thus f_0 increase so that the iTD plateau becomes wider, which seems to be advantageous to the animal; cf. Fig. 3. Certainly true but a price is to be paid in that the iTD height and, accordingly, the TDF = iTD/ITD decrease; see Fig. 7a. There is with $\pm 5\%$ error bar something like an equal-area (EA) rule saying that the total area under the TDF curve remains constant while varying f_0 .

As Fig. 7b shows, the iLD behavior is much more regular. The maximum remains practically constant and, as it behooves this maximum, it only shifts with f_0 . Done. An increase of up to 10% of the fundamental frequency is achievable with an applied tension of around 100 mN/m for the Varanus eardrum, a lifelike value. So for $f_0 = 400$ Hz, it is realistic to vary the fundamental frequency up to 440 Hz.

Summary and Conclusions

What have we gained through the novel notion of “internally coupled ears” (ICE)? On the sensory input side, the notion of ICE is a clean one as it describes precisely what the auditory geometry in the animal's head looks like and what, in conjunction with the material properties of the eardrums, the biophysical consequences for iTD and iLD are. Moreover, in the present context the animals are land-living vertebrates. It needs to be constantly borne in mind, though, that many insects also take advantage of ICE and that the notion of ICE – though not the name as such – dates back to the thirties of last century (van Hemmen et al. 2016, Sect. 2). In fact, it was the wart-biter, a bush cricket, that induced the scientific development

leading to what is now called ICE. Nevertheless, the geometry associated with the insects' anatomy is different. Second, the ensuing biological physics is merely based on the geometry of the interaural cavity coupling the two eardrums and their material properties, and nothing more than that. Third, geometric perturbation theory allows for both a systematic treatment and analytical evaluation of iTD and iLD in all desired orders of perturbation theory. Luckily, first order suffices in practically all circumstances.

What internally coupled ears (ICE) do is explained in section “[Performance of Internally Coupled Ears \(ICE\)](#),” notably Fig. 3. How they do this job as seen from a mathematical point of view can be found in section “[Mathematical Analysis and Explanation](#),” while a few enlightening specializations are described in section “[Extensions](#).” Neuronal information processing of the auditory system can be understood *only after* we have gained biophysical and, hence, computational insight into how the biological physics of auditory perception works. That is what has been done here for ICE.

Cross-References

- [Auditory Perceptual Organization](#)
- [Auditory Processing in Insects](#)
- [Auditory Sensing Systems: Overview](#)
- [Cochlear Inner Hair Cell, Model](#)
- [Neuromorphic Sensors, Cochlea](#)
- [Phase-Locking Methods](#)
- [Sound Localization in Mammals and Models](#)
- [Vestibular System: Overview](#)

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Interstitial Space

► [Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery](#)

Interstitial Volume

► [Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery](#)

Intracellular Calcium Signals in Astrocytes, Computational Modeling of

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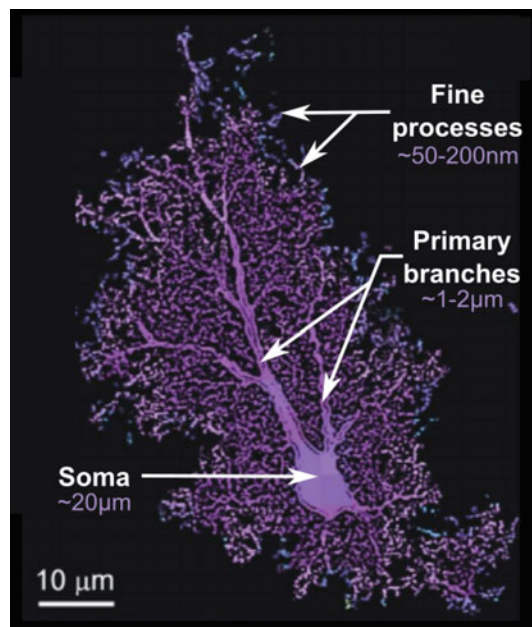
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Definition

Astrocytes are a predominant type of glia in the central nervous system. Although they do not generate electrical signals like neurons, they display a form of excitability characterized by fluctuations in their intracellular Ca^{2+} levels. These Ca^{2+} fluctuations show remarkable spatiotemporal complexity and diversity and further respond to various cellular stimuli. Modeling astrocyte Ca^{2+} dynamics is an essential step toward understanding their physiology and functions within neural circuits. This entry highlights the computational methods and approaches for modeling intracellular Ca^{2+} signals in astrocytes at the single cell level.

Detailed Description

Astrocytes are ubiquitously distributed throughout the central nervous system. Each astrocyte can display a complex morphology characterized by distinct compartments: the soma, primary branches and numerous fine processes, also referred to as branchlets. The latter account for around 75% of the surface of the astrocytic plasma membrane (Bindocci et al. 2017), providing astrocytes a spongiform appearance (see Fig. 1). Some of the fine processes, referred to as perisynaptic processes (PAPs), are in apposition to pre- and post-synaptic neurons, forming tripartite synapses, where they might modulate neuronal communication (see, e.g., Savtchouk and Volterra (2018) for a review). Some astrocytic ramifications, referred to as endfeet, wrap around blood vessels and are involved in neurovascular coupling.



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 1 Astrocytes are characterized by a complex morphology. Confocal image of a dye-filled hippocampal astrocyte, revealing its spongiform structure. Numbers in purple correspond to the approximate diameter of the different cellular compartments observed: the cellular body (soma), primary branches, and fine processes. (Adapted from Shigetomi et al. 2013) with permission from authors and Rockefeller University Press

Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Table 1 Description of terms shown in Figs. 5 and 6

<i>Ca</i> ²⁺ dynamics	
<i>J</i> _{IP3}	<i>Ca</i> ²⁺ influx from the ER to the cytosol through open IP3R
<i>J</i> _{in}	<i>Ca</i> ²⁺ leak from the extracellular space to the cytosol
<i>J</i> _{out}	<i>Ca</i> ²⁺ outflux from the cytosol to the extracellular space
<i>J</i> _{leak}	<i>Ca</i> ²⁺ leak from the ER to the cytosol
<i>J</i> _{pump}	<i>Ca</i> ²⁺ uptake from the cytosol to the ER by SERCA pumps
<i>J</i> _{Glu}	Glutamate-evoked <i>Ca</i> ²⁺ influx
<i>J</i> _{diff}	Cytosolic <i>Ca</i> ²⁺ diffusion
<i>D</i> _{Ca}	<i>Ca</i> ²⁺ coefficient of diffusion
[<i>Ca</i> ²⁺] _c	Cytosolic <i>Ca</i> ²⁺ concentration
[<i>Ca</i> ²⁺] _{ER}	ER <i>Ca</i> ²⁺ concentration
<i>IP</i> ₃ dynamics	
<i>I</i> _{Glu}	Glutamate-evoked <i>IP</i> ₃ production by PLC β
<i>I</i> _{Ca}	<i>Ca</i> ²⁺ -dependent <i>IP</i> ₃ production by PLC δ
<i>I</i> _{deg}	<i>IP</i> ₃ degradation term
<i>I</i> _{Diff}	Cytosolic <i>IP</i> ₃ diffusion
[<i>IP</i> ₃]	Cytosolic <i>IP</i> ₃ concentration
Glutamate dynamics	
ξ _p (<i>t</i>)	Stochastic glutamate source (Poisson process)
τ _{glu}	Synaptic glutamate decay rate constant
<i>G</i> _{Diff}	Glutamate diffusion in the extracellular space
[Glu]	Extracellular glutamate concentration
[<i>Glu</i>] [*]	Extracellular glutamate concentration at steady state
Other parameters	
<i>c</i> ₁	Ratio between ER and cytosolic volumes

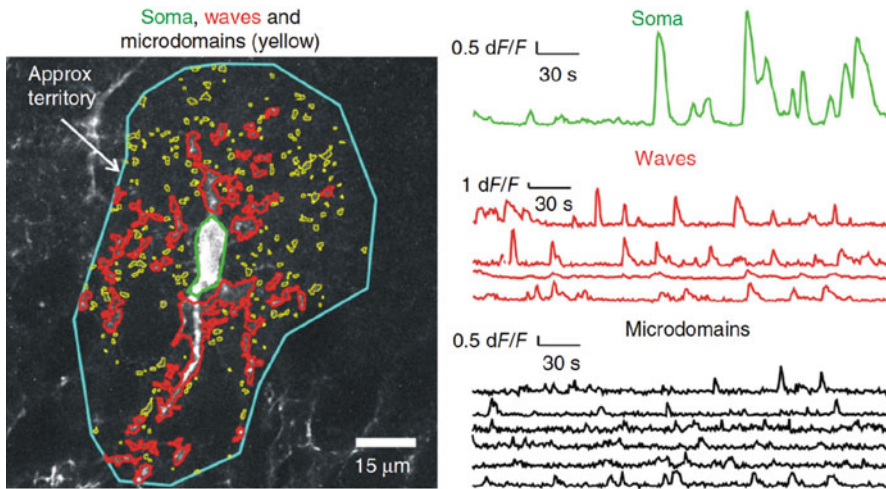
Astrocytes also regulate neuronal excitability by maintaining ionic homeostasis (e.g., *K*⁺ buffering), uptaking neurotransmitters and moderating synaptogenesis (Verkhratsky and Nedergaard 2018).

Diversity of Astrocyte *Ca*²⁺ Signals

Cytosolic *Ca*²⁺ levels in astrocytes show ongoing fluctuations, both *in vitro* and *in vivo* (Verkhratsky and Nedergaard 2018). The amplitude, duration, and frequencies of these so-called *Ca*²⁺ signals/events vary depending on stimuli, such as adenosine triphosphate (ATP) and glutamate. As such,

those *Ca*²⁺ signals are crucial reporters of astrocyte function and are therefore a widely accepted form of astrocyte excitability. Astrocyte *Ca*²⁺ signals can result from diverse mechanisms such as *Ca*²⁺ influx from channels on the membrane of intracellular stores or on the plasma membrane, the spatial distribution of these channels, ATP signaling, and inter-cellular propagation of *Ca*²⁺ via gap junction coupling between astrocytes (Rizzuto and Pozzan 2006). A major pathway that triggers the release of *Ca*²⁺ in astrocytes is initiated by agonists binding to transmembrane G-protein-coupled receptors (GPCRs). This activates the synthesis of an intracellular second messenger, inositol 3-phosphate (*IP*₃). The *IP*₃ molecules bind to *IP*₃ receptor channels (IP3Rs), located on the endoplasmic reticulum (ER) membrane. Binding of *IP*₃ and *Ca*²⁺ to IP3Rs leads to the opening of IP3Rs, resulting in a *Ca*²⁺ influx from the ER into the cytosol. The resulting local increase in *Ca*²⁺ concentration, together with the *IP*₃ molecules, further activates more IP3R channels. This positive feedback loop, referred to as *Ca*²⁺-induced-*Ca*²⁺ release (CICR), can combine with the diffusion of *Ca*²⁺ and *IP*₃ to result in the propagation of *Ca*²⁺ events in the form of waves and of global (whole-cell) events. *Ca*²⁺ diffusion as well as pumps then restore basal cytosolic *Ca*²⁺ levels, thus terminating the signals.

The recent use of super-resolution microscopy and of highly sensitive genetically encoded *Ca*²⁺ indicators (GECIs) have revealed striking spatio-temporal diversity of astrocyte *Ca*²⁺ signals. Notably, there are remarkable differences between signals in the soma and in the peripheral processes (Srinivasan et al. 2015) (see Fig. 2). The latter account for around 80% of the total astrocytic *Ca*²⁺ activity *in vivo* (Bindocci et al. 2017). Those signals are localized in so-called microdomains and display faster kinetics and an order of magnitude smaller amplitudes compared to somatic *Ca*²⁺ signals. Around half of *Ca*²⁺ signals in fine processes persist in the absence of type 2 *IP*₃Rs. The *Ca*²⁺ pathways responsible for the other half of *Ca*²⁺ signals in branchlets are currently unknown and could involve type 1 or 3 *IP*₃Rs, *Ca*²⁺ channels on the plasma membrane or on the membrane of internal stores.



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 2 Diversity of astrocyte intracellular Ca^{2+} signals. *Left:* Astrocyte Ca^{2+} signals in a hippocampal astrocyte reported by GCaMP6f can be detected in discrete cellular compartments. The blue contour demarcates the approximate boundary of the

anatomical domain of the astrocyte. *Right:* The detected signals consist of large amplitude somatic oscillations (green), waves, largely in primary branches (red) and microdomains in fine processes (black traces, corresponding to yellow regions in the left image). (Adapted from Srinivasan et al. 2015 with permission)

A summary of the different spatial patterns of astrocytic Ca^{2+} signals is shown in Fig. 3, and their key features are listed below:

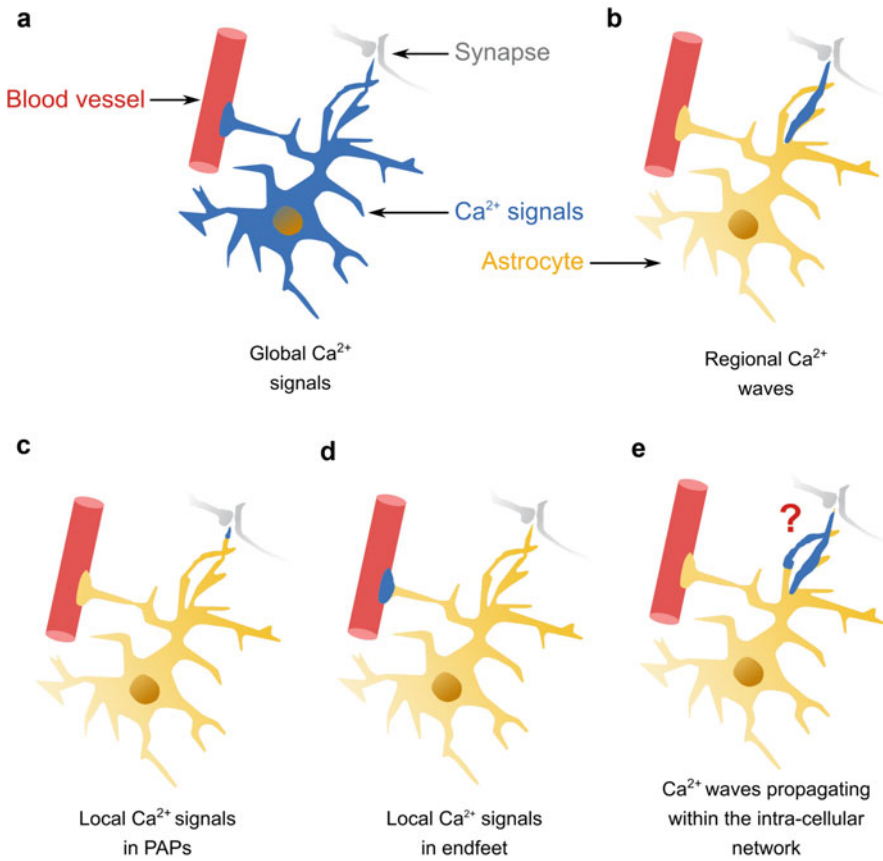
- **Global signals** (Fig. 3a) are IP_3R -dependent Ca^{2+} signals that propagate within the whole astrocyte (Bindocci et al. 2017).
- **Local waves** (Fig. 3b) are observed in branches and sporadically propagate bidirectionally to and from the soma. Ca^{2+} signals could also propagate through gap junction coupling between processes from the same cell (Rohlmann and Wolff 1996) (Fig. 3e), although this has not been reported so far. Note that gap junction coupling also allows for the propagation of intercellular waves, which will not be discussed here as this work focuses on Ca^{2+} signals at the single-cell level (see, e.g., Giaume and Venance 1998 for a review).
- **Spatially restricted microdomains** (Fig. 3c-d) are non-propagating signals characterized by distinct temporal properties (with a signal duration from the order of seconds (Srinivasan et al. 2015) to tens of seconds (Kanemaru et al. 2014)) and can be mediated by tetrodotoxin (TTX)-sensitive (neuronal activity-dependent)

and TTX-resistant mechanisms. Furthermore, these events can occur as IP_3R -independent events, notably in the absence of somatic Ca^{2+} signals (Srinivasan et al. 2015). Those signals are mostly observed in perisynaptic processes (Fig. 3c) or in blood vessel-associated endfeet (Fig. 3d) (Bindocci et al. 2017).

Taken together, the diversity of intracellular astrocyte Ca^{2+} signals concerns their spatial extent (from localized microdomains to whole-cell events), their time scales (order of seconds to tens of seconds), and, arguably, the mechanisms which trigger them. Their physiological roles are not well understood and constitute an active area of research (e.g., see review Verkhratsky and Nedergaard 2018). It is likely that the observed spatiotemporal variability of astrocyte Ca^{2+} signals is associated with the integration of signals in neural circuits coupled to local blood flow changes and metabolic processes to orchestrate integrative physiological functions.

Modeling Astrocyte Ca^{2+} Dynamics

The apparent diversity of intracellular astrocyte Ca^{2+} signals has led to the development of advanced computational tools and approaches to



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 3 Spatial diversity of intracellular Ca^{2+} signals in astrocytes. Ca^{2+} signals in a single astrocyte display various spatial forms. Some signals can propagate within the whole cell, forming a global event (a), propagate via regionalized Ca^{2+} waves (b), or be

localized at the vicinity of synapses (c), in endfeet (d), or might propagate to other processes of the same cell via gap junctions, although such an intracellular propagation via gap junction coupling has not been reported yet (e). PAP, perisynaptic astrocytic process

model astrocyte Ca^{2+} dynamics. A recent and significant advance corresponds to the development of spatially explicit multi-compartment models with realistic 3D morphologies in order to fully reproduce the spatiotemporal diversity of astrocyte Ca^{2+} signals (for a detailed review, see Manninen et al. 2018).

Approaches for Modeling Astrocyte Ca^{2+} Dynamics

In this section, the different approaches that can be used for simulating astrocyte Ca^{2+} signals are presented. Figure 4a summarizes those approaches, the approximations associated to it, as well as the resulting computational cost and accuracy. Briefly, modeling approaches can be

deterministic, i.e., in which all future states can be determined from the current state, or stochastic, i.e., considering each reaction as a probabilistic event. They can also be well-mixed, i.e., considering space as homogeneous and assuming that molecules are equally distributed within the system or spatially explicit. Those methods can be coupled within hybrid models (see, e.g., Winkelmann and Schütte 2017 for a review).

The first models of astrocyte Ca^{2+} signals were deterministic and well-mixed, formulated with ordinary differential equations (ODEs) (Manninen et al. 2018). Those models offered crucial insights on the qualitative and quantitative behaviors of the observed dynamics. However, the probabilistic molecular interactions in

reaction-diffusion systems often necessitate stochastic modeling approaches. Moreover, the spatial complexity of astrocyte morphology and Ca^{2+} signals (see Figs. 1 and 2) has led to the development of spatially explicit models. Figure 4b presents the different geometries that can be used in spatially explicit models of astrocyte Ca^{2+} signals. They can be either realistic or simplified, in 1–3 spatial dimensions. Those models are more realistic, increasing the accuracy of model predictions, however associated with an increased computational cost.

As fine astrocytic processes display complex geometries and have small volumes with low copy number of molecules, models of Ca^{2+} signals at this spatial scale are both stochastic and spatially explicit. The three main spatially explicit stochastic approaches used for simulating reaction-diffusion systems are presented in Fig. 4c, and a brief summary is also provided below. An excellent review of these approaches can be found in Burrage et al. (2011), and ► “Stochastic Simulators” and ► “Particle-Based Stochastic Simulators” detail the available spatially explicit stochastic simulators.

- **Particle-based (or particle-tracking or microscopic) models** (Fig 4c1)

The most straightforward stochastic spatially explicit approach consists of tracking the diffusive path of each individual molecule/ion (referred to as particle) within the spatial domain. Particles are characterized by their individual spheres of interaction/interaction radii. Second-order reactions occur depending on their rates when the reactants are within their interaction radii.

- **Voxel-based (or population-based or mesoscopic) models** (Fig 4c2)

As they are less computationally expensive than particle-based approaches, most intracellular Ca^{2+} models are implemented with the voxel-based stochastic approach. In this approach, the spatial domain is divided into small compartments (voxels) that are assumed well-mixed, and reactions can occur between reactants within the same voxel. Diffusion is modeled as a reaction in which the number of

molecules in the origin compartment is decreased by one, while the number of molecules in the neighboring compartment is increased by one. Accuracy and computational cost decrease with increasing sizes of compartments. (► “Stochastic Simulators”).

- **Hybrid models** (Fig 4c3)

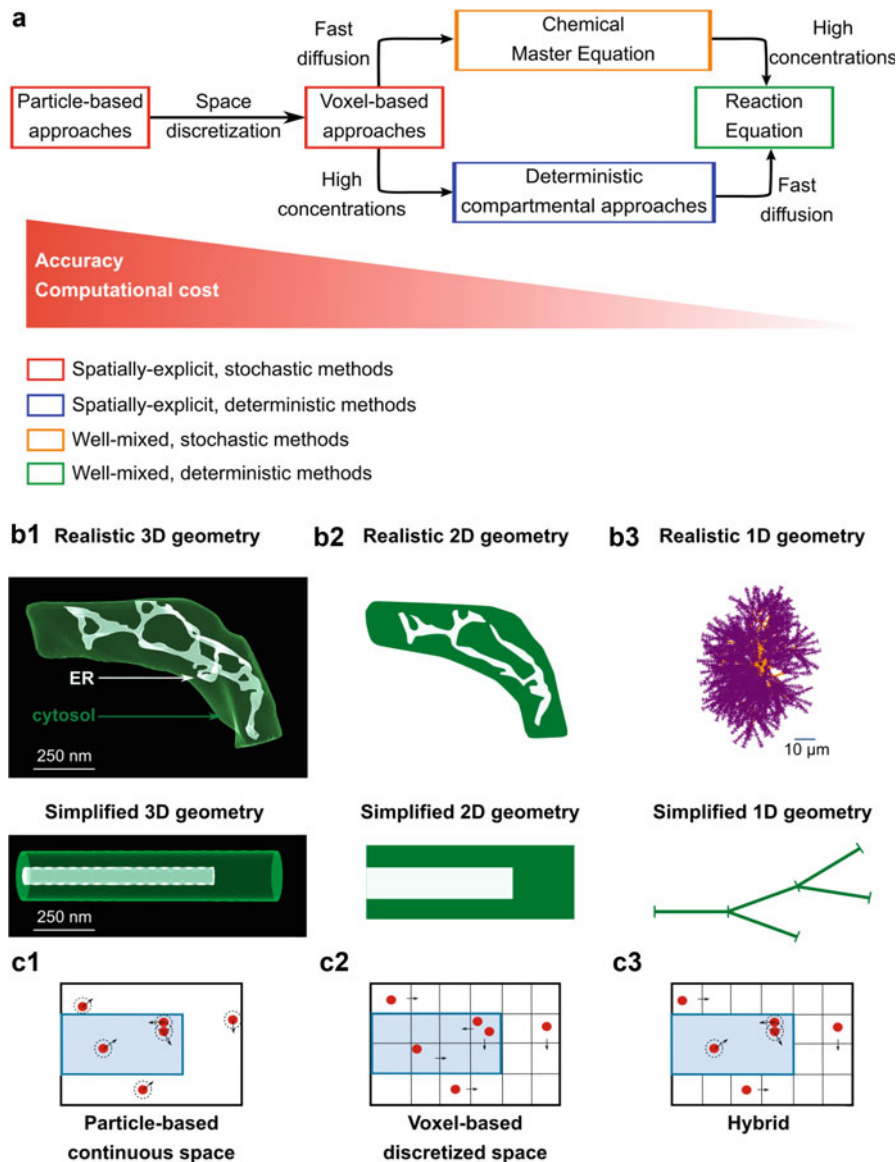
Hybrid methods describe regions of particular interest such as the vicinity of Ca^{2+} channels with microscopic details, while other regions are simulated with a compartment-based approach. Those methods thus offer a trade-off between detailed modeling and computational cost.

Deterministic Models of Ca^{2+} Oscillations in Astrocytes

The early mathematical models of astrocyte Ca^{2+} signals primarily simulated the dynamics of IP_3 -dependent Ca^{2+} release from the ER. These largely consisted of deterministic models based on ODEs. The positive feedback loop of the CICR mechanism consisted of the rate of cytosolic Ca^{2+} influx as a sigmoid or Hill function of IP_3 concentration (see De Pittà et al. 2019 for a review). The termination of the resulting cytosolic Ca^{2+} increase resulted from the reuptake of Ca^{2+} into the ER via the activity of Smooth Endoplasmic Calcium ATPases (SERCA) pumps and from the exponential decay of IP_3 concentration. Together, the CICR and SERCA mechanisms formed the basis for oscillatory models of Ca^{2+} dynamics (see Fig. 5). Influx of Ca^{2+} via transmembrane voltage-gated Ca^{2+} channels was also incorporated using constant rates or realistic conductance-based (Hodgkin-Huxley) formalism.

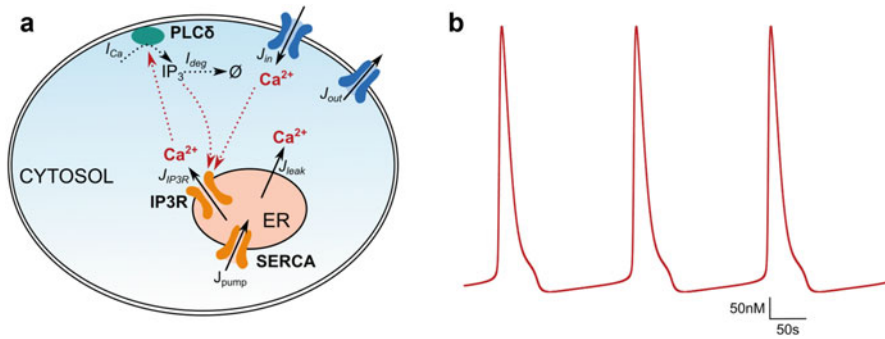
$$\begin{aligned}\frac{d[Ca^{2+}]_c}{dt} &= J_{IP_3} + J_{leak} - J_{pump} + J_{in} - J_{out} \\ \frac{d[Ca^{2+}]_{ER}}{dt} &= \frac{1}{c_1} (J_{pump} - J_{leak} - J_{IP_3}) \\ \frac{d[IP_3]}{dt} &= I_{Ca} - I_{deg}\end{aligned}\quad (1)$$

To segregate the distal (peripheral) Ca^{2+} microdomains from somatic events, deterministic models have incorporated spatial partitioning



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 4 Approaches for modeling intracellular Ca^{2+} signals in astrocytes. (a) The different approaches available for modeling Ca^{2+} signals are presented from high accuracy/high computational cost associated with Brownian dynamics to less accurate but faster models of reactions based on ordinary differential equations. Note that hybrid methods are not represented in this schematic. (b) Depending on the biological question, the astrocytic geometry chosen for simulations can be in 3D (b1), either realistic, extracted from 3D reconstructions of experimental data (top), or simplified (bottom). The mesh in top B1 panel corresponds to a hippocampal astrocytic

process extracted and reconstructed from electron microscopy, provided by C. Cali, BESE Division, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia (Cali et al. 2016). Cytosolic volume is represented in green and ER volume in blue. 2D (b2) or 1D (b3) projections of 3D geometries can also be performed for computational efficiency, although it decreases the accuracy of the model. The top B3 panel was taken from Savtchenko et al. (2018), with permission. Panel C presents the main strategies for performing spatially explicit stochastic simulations: particle-based (c1), voxel-based (c2), and hybrid (c3) approaches



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 5 Classic IP_3 -dependent pathway incorporated in models of intracellular Ca^{2+} oscillations in astrocytes. (a) Plain black arrows correspond to Ca^{2+} fluxes. Dotted black arrows represent IP_3 formation, via Ca^{2+} -dependent PLC activity, and

degradation. Red dotted arrows represent the activation of certain molecules, such as IP_3R and PLC, by IP_3 or Ca^{2+} . (b) A simulated trace of intracellular $[Ca^{2+}]$, displaying $[Ca^{2+}]$ oscillations, based on the model from Lavrentovich and Hemkin (2008)

based on realistic astrocyte morphology. The Brazhe et al. (2018) model, for instance, considered the z-projection of the 3D morphology of a rodent hippocampal astrocyte (see Fig. 6a). Following a spatial discretization, the internal compartments were labeled as belonging either to the perimembrane region (type I) or the deep region (type II), depending on their distance from plasma membrane. In type I regions, glutamate binding at synapses can promote IP_3 production and Ca^{2+} influx. Local Ca^{2+} increases and concomitant IP_3 production were posited to spatially diffuse into the neighboring type II region. The type II region consisted of the classic IP_3R -activated Ca^{2+} release from the ER and the IP_3 - Ca^{2+} CICR, together capable of generating global waves via a positive feedback loop. The two regions were assumed to be coupled by a diffusive Ca^{2+} flux (J_{diff}) and an IP_3 flux (I_{diff}) for which the diffusion coefficients were estimated based on the cell morphology. This approach offers insight into a mechanism by which synaptically driven peripheral Ca^{2+} fluctuations might contribute to the integration and initiation of global events (see Fig. 6b). Additionally, modeling the synaptic input with a noise term (e.g., Poisson process) generated uncorrelated peripheral events representative of realistic Ca^{2+} microdomains. An advantage of this model is that it can be used to study signal propagation within ER-free branchlets.

ODEs for the perimembrane, glutamate uptake-dependent region from the Brazhe et al. (2018) (type I region; see Fig. 6a, blue):

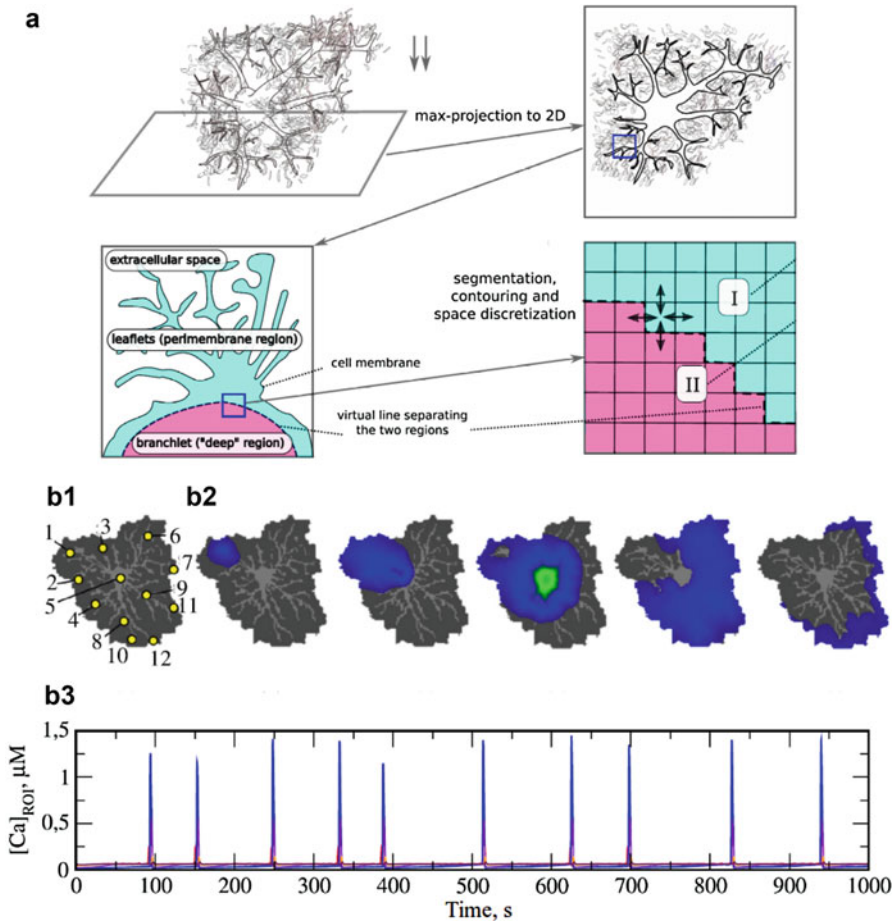
$$\begin{aligned}\frac{d[Ca^{2+}]_c}{dt} &= J_{in} + J_{glu} - J_{out} + J_{diff} \\ \frac{d[Glu]}{dt} &= \frac{[Glu]^* - [Glu]}{\tau_{Glu}} + \xi_p + G_{diff} \\ \frac{d[IP_3]}{dt} &= I_{Glu} + I_{Ca} - I_{deg} + I_{diff}\end{aligned}\quad (2)$$

ODEs for the deep, IP_3R activation-dependent region from the Brazhe et al. model.

Brazhe et al. (2018) (type II region; see Fig. 6a, pink):

$$\begin{aligned}\frac{d[Ca^{2+}]_c}{dt} &= J_{IP_3} + J_{leak} - J_{pump} + J_{diff} \\ \frac{d[Ca^{2+}]_{ER}}{dt} &= -\frac{1}{c_1} (J_{IP_3} + J_{leak} - J_{pump}) \\ \frac{d[IP_3]}{dt} &= I_{diff} - I_{deg}\end{aligned}\quad (3)$$

Recently, detailed 3D reconstructions of astrocyte morphology have been used to generate realistic spatially explicit compartmental models of astrocytes combined with deterministic formulation of Ca^{2+} fluxes within compartments (Savtchenko et al. 2018) (see Fig. 7a). The spatial discretization has captured the

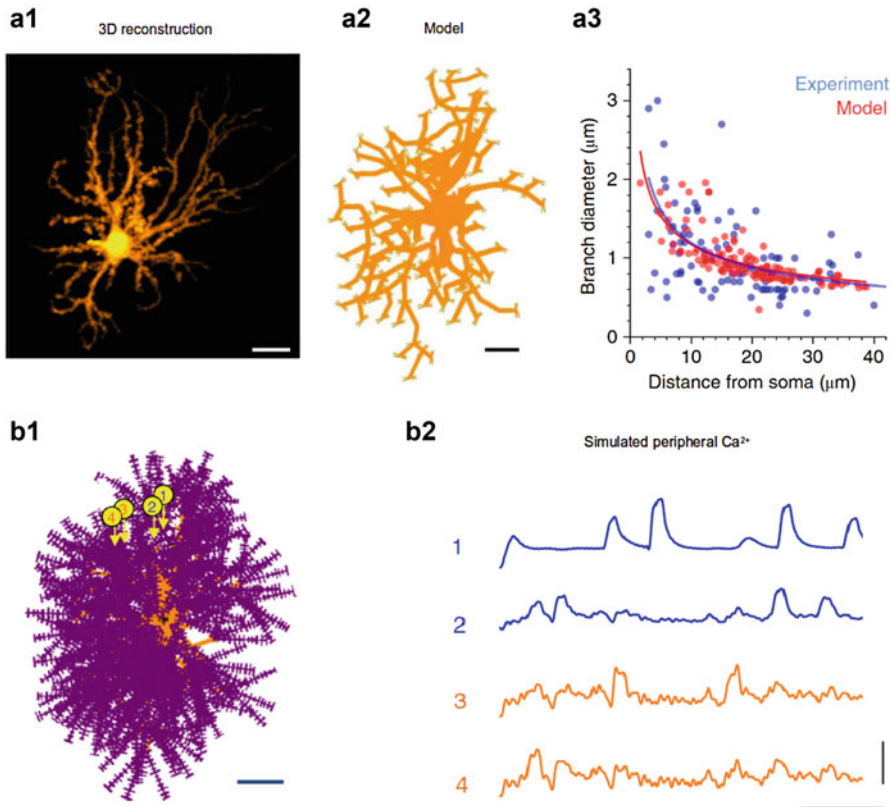


Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 6 Spatially partitioned oscillators. (a) 3D reconstruction from an astrocyte imaged with confocal fluorescent microscopy was projected in 2D and then divided into two types of compartments, perimembrane (blue) or deeper regions (pink), that were then spatially discretized. The ODEs that describe Ca^{2+} and IP_3 dynamics in both compartments are

presented in Eqs. 2 and 3. Terms are described in Table 1. (b1) Image displaying the different regions of interest (ROIs) within the model (numbered 1-12). (b2) Snapshots of a single Ca^{2+} wave originating at ROI 1. (b3) Time series of all the ROIs. For a detailed figure legend, see Brazhe et al. (2018). (Adapted from Brazhe et al. 2018 with permission from authors and AIP Publishing LLC)

spatiotemporal dynamics of diverse Ca^{2+} signals measured experimentally, supporting the usefulness of this approach to further investigate astrocyte physiology in health and disease. However, molecular reactions in small discrete compartments such as microdomains in fine astrocytic processes are inherently probabilistic events. Stochastic modeling approaches offer an attractive alternative when a detailed description of Ca^{2+} signals in microdomains is needed.

Stochastic Approaches for Modeling Intracellular Astrocyte Ca^{2+} Signals
Molecular interactions in spatially restricted compartments such as thin astrocytic processes, which are believed to be the site of neuron-astrocyte communication, occur when molecules are in low copy numbers. Stochastic approaches can describe the associated heterogeneous reaction rates and the inherent stochasticity of biochemical reactions so that they are being used to model astrocyte Ca^{2+} signals in fine processes. Recently,



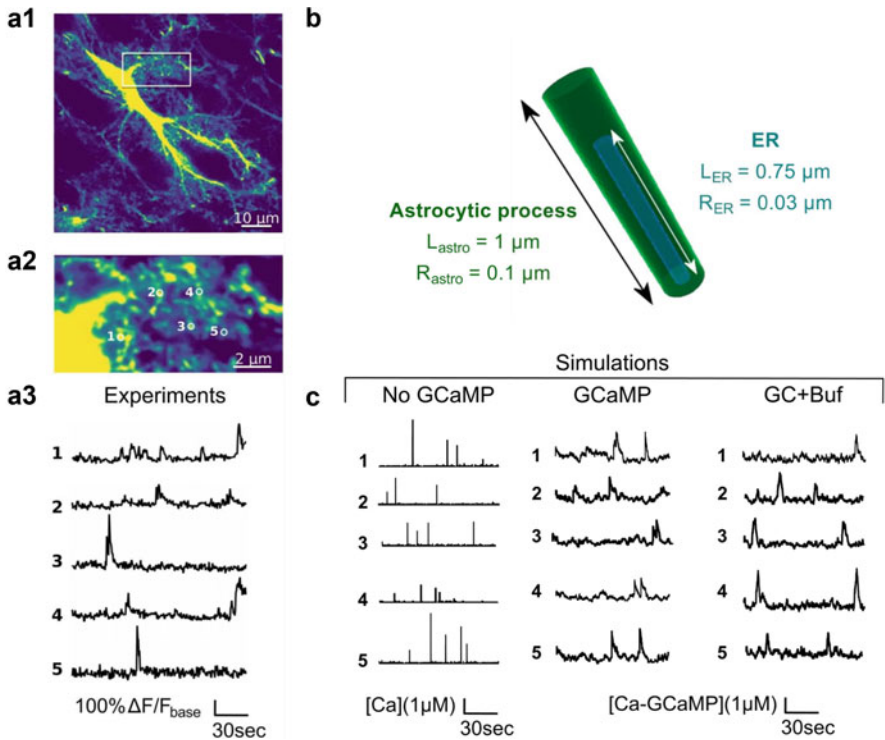
Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 7 Astrocyte model with realistic 3D morphology. (a1) 3D reconstructed stem tree of an astrocyte from the hippocampal CA1 region. Scale bar, 10 μ m. (a2) A typical astrocyte stem tree in NEURON format. Scale bar, 10 μ m. (a3) Comparison of branch diameters in the model (red) and in experiments (blue). Solid lines are best-fit dependence using power law for the corresponding data scatters. (b1) A complete astrocyte morphology model (z-projection) generated in the

NEURON modeling software. The main branches and the nanoscopic processes are depicted in orange and purple, respectively. Scale bar, 10 μ m. (b2) Time series of simulated intracellular Ca^{2+} dynamics in the ROIs labeled 1–4 in the morphology shown on the left panel. Scale bars (v, h): 100% $\Delta F/F$, 20s. See Savtchenko et al. (2018) for detailed figure legends. (Adapted from Savtchenko et al. (2018) with author permission; article with Creative Commons License)

some astrocyte models have started to incorporate noise using hybrid approaches in order to better simulate stochastic components of Ca^{2+} dynamics at the subcellular level. For example, Cresswell-Clay et al. (2018) have developed a whole-cell model of a single astrocyte consisting in a soma with five main branches, all containing ER. Ca^{2+} signals were implemented as a stochastic influx. Their results suggest that both cellular geometry (e.g., somatic volume) and the velocity of diffusing molecules influence the coupling and nature of the Ca^{2+} signals in response to neuronal stimulation. Interestingly, simulations also revealed

complex spatiotemporal characteristics of Ca^{2+} depletion in the somatic ER in response to Ca^{2+} signals in processes, due to intra-ER Ca^{2+} diffusion. For reviews on stochastic models of Ca^{2+} signals, see, e.g., Rüdiger and Shuai (2019) and Manninen et al. (2018) for astrocytes.

As the nanoscale geometry of astrocytic processes can reduce diffusion coefficients due to the tortuosity of the compartment, accurate description of the local variations of the number of Ca^{2+} ions requires spatially explicit models. Spatially explicit stochastic models of Ca^{2+} signaling were first developed to



Intracellular Calcium Signals in Astrocytes, Computational Modeling of, Fig. 8 Simulations of a fully stochastic voxel-based model reproduce experimental measurements of Ca^{2+} signals in fine astrocytic processes. (a1) Spontaneous local Ca^{2+} signals were measured in GCaMP6s-expressing astrocytes from hippocampal organotypic culture. (a2) Magnification of panel A1, presenting the 5 regions of interest (1–5) from which Ca^{2+} traces have been recorded (a3). (b) Geometry used in simulations that represents a simplified region of interest, i.e., a fine process. It consists in a cylinder that is 1 μm long

and 200 nm in diameter. (c) Representative simulations of Ca^{2+} dynamics within the fine process geometry presented in panel B, with the different implementations of the model: “No-GCaMP” (no buffers are present in the model; free Ca^{2+} concentration is monitored), “GCaMP” (GCaMP Ca^{2+} indicators are added to the model; GCaMP-Ca concentration is monitored), and “GC + Buf” (GCaMP and endogenous Ca^{2+} buffers are added to the model; GCaMP-Ca concentration is monitored). (Adapted from Denizot et al. 2019 with permission, article with Creative Commons License)

reproduce local Ca^{2+} dynamics in neural dendrites, characterized by small volumes and low numbers of Ca^{2+} ions (5–6 ions in a half- μm diameter dendritic spine). These studies have demonstrated the influence of dendritic morphology (e.g., dendritic diameter) on the spatiotemporal characteristics of Ca^{2+} signals and their compartmentalization (see CrossRef: [▶ “Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis”](#)). These models highlighted the influence of diffusive noise on intracellular signaling networks, suggesting that noise is an important factor to be considered for accurate description of molecular interactions.

A novel spatially explicit fully stochastic model of Ca^{2+} signals in astrocytes has been proposed by Denizot et al. (2019). The two types of spatially explicit stochastic implementations in the study were:

- A 2D particle-based model to explore the effects of model parameters on the range of Ca^{2+} dynamics that the model can display.
- A 3D voxel-based model in which the geometry of the reaction volume mimicking an astrocytic process consisted of a cylinder of length $L_{\text{astro}} = 1 \mu\text{m}$ and radius $R_{\text{astro}} = 0.1 \mu\text{m}$ (Fig. 8b). Several variations of this model have been implemented to investigate the

effects of multiple mechanisms on astrocyte Ca^{2+} microdomains including (1) clustering of IP₃R channels, (2) endogenous buffers, and (3) GCaMPs (ultrasensitive genetically encoded Ca^{2+} indicators that fluoresce when bound to Ca^{2+}).

Ca^{2+} dynamics in simulations of the model were compared to signals that were measured experimentally in fine processes of hippocampal astrocytes (Fig. 8a). The model successfully reproduced Ca^{2+} peak amplitude, frequency, and duration measured in fine processes and is therefore a valuable tool for investigating intracellular astrocytic Ca^{2+} signals at the subcellular level. Key insights from this model highlight the importance of the spatial distribution of various Ca^{2+} sources within an astrocyte and suggest that local variations of Ca^{2+} indicators might contribute to the spatiotemporal diversity of astrocytic Ca^{2+} excitability.

Conclusion

Understanding astrocytic Ca^{2+} signaling is at the forefront of neuroscience research. The diversity of astrocyte Ca^{2+} excitability may relay spatiotemporally complex code which yet remains to be decoded. Computational modeling of astrocyte physiology and Ca^{2+} dynamics is an essential step toward unraveling the functions of astrocytes in neural circuits. Recent conceptual advances in experimental work have highlighted the spatiotemporal diversity of Ca^{2+} signals at the single-cell level. Parallel advances in tools and methods for modeling astrocytes are beginning to provide novel insights into their physiology. Future work combining neuron-astrocyte models may thus enhance our understanding of the role of astrocytes in neural signal processing in health and disease.

Cross-References

- [Biochemical Signaling Pathways and Diffusion: Overview](#)
- [Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis](#)

- [Calcium Release, Models of](#)
- [Deterministic Reaction-Diffusion Simulators](#)
- [Markov Models of Ion Channels](#)
- [MCell](#)
- [Modeling Ion Concentrations](#)
- [Neuron-Glial Interactions](#)
- [Particle-Based Stochastic Simulators](#)
- [Signaling Pathways, Modeling of](#)
- [Spatial Modeling](#)
- [Stochastic Simulators](#)
- [STEPS: STochastic Engine for Pathway Simulation](#)
- [Stochastic Simulators](#)

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Intracellular Resistivity

- [Resistivity, Axial](#)

Intracortical Microelectrodes for Visual Rehabilitation

- [Visual Prosthesis, Cortical Devices](#)

Intraocular Retinal Prosthesis

- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)

Intraspinal Microstimulation

- [Intraspinal Stimulation](#)

Intraspinal Stimulation

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Synonyms

[Extracellular stimulation](#); [Intraspinal microstimulation](#); [Neuronal activation](#)

Definition

Intraspinal stimulation or microstimulation generally refers to electrical activation of the spinal cord through delivery of electrical current directly into the spinal tissue using microwire electrodes implanted into the white or grey matter of the cord. The term may also be applied for activation of the spinal tissue through iontophoresis (Saltiel et al. 1998) or optogenetics method (Alilain and

Silver 2009). The range of applications includes lower and upper limb movements, bladder and bowel function, and respiration.

Detailed Description

The Spinal Solution to Multi-joint Movement Control and Other Problems

As evidenced in other sections of this encyclopedia (► [“Vertebrate Pattern Generation: Overview”](#)), part of the substantial repertoire of movements observed in vertebrates is programmed at the level of the spinal cord and can function after injury to more rostral levels. Thus, “One of the major challenges facing clinical neurobiologists is how to exploit the untapped reserves of coordinated movement contained in the spinal cord circuits of patients with a functionally isolated spinal cord” (Burke 1992). Selective activation of these spinal cord circuits could lead to enhancements in neuroprostheses for the restoration of movements. While electrical stimulation of paralyzed muscles has been used by various research groups to restore function to the paralyzed neuromuscular system (grasp/release (Handa et al. 1992; Keith et al. 1996)), wrist flexion/extension (Lemay and Crago 1997; Nathan and Ohry 1990), elbow (Grill and Peckham 1998), and arm control (Hincapie et al. 2008; Smith et al. 1996) in individuals with tetraplegia, as well as standing/walking functions in paraplegics (Andrews et al. 1988; Kralj et al. 1983; Marsolais et al. 1991), issues arise as the number of joints to be controlled increases. For multi-joint movements, the number of muscles to be stimulated increases and the task of coordinating those muscles’ activation is greatly complicated by (1) muscle function redundancy, (2) interaction between limb segments through multi-articular muscles and dynamic effects, and (3) other voluntary or reflex actions (Chizeck et al. 1988). Unassisted Functional Neuromuscular Stimulation (FNS) walking requires as many as 48 channels of stimulation and an elaborate tuning of the activation sequence (Marsolais et al. 1991).

The problems posed by multi-joint control are easily addressed by the spinal cord which can

autonomously produce complex movements such as scratching to a target or locomotion. Part of the solution involves modular use of the musculature, as multi-muscle building blocks or primitives that are reused for various movements. This biological solution provides opportunities for stimulation pattern completion strategies based on available voluntary muscles in conventional functional electrical stimulation (FES) as explored by Kirsch and colleagues (Hincapie and Kirsch 2009) and for movement control using intraspinal microstimulation (ISMS). Stimulation of higher-order spinal neurons provides a way of coordinating the activation of the skeletal muscles by recruiting modules or primitives that can be described as feedforward controllers that alleviate the coordination and delay problems of the slow sensory feedback by using the neural circuitry present below the level of the cord injury (Giszter et al. 2000). Presence of low-level spinal reflexes then provides feedback mechanisms that may be able to compensate for fatigue and adapt to changing conditions.

In addition to the circuitry responsible for movements, interneurons involved in bladder (de Groat and Wickens 2013) and respiration (Lane et al. 2009) control are also contained within the cord’s grey matter and can be activated via electrical stimulation or other methodologies as described below.

Intraspinal Stimulation for Movement Applications

Work on intraspinal microstimulation has focused on direct activation of the motoneuronal pools using fine wire microelectrode implanted deep into the lateral ventral horns (Mushahwar and Horch 2000a, b) or into activation of higher-order neurons by stimulation delivered into the intermediate grey matter (Barthelemy et al. 2006; Giszter et al. 1993; Lemay and Grill 2004; Tai 2003; Tresch and Bizzi 1999), or even dorsal columns (Barthelemy et al. 2006). The small volume and proximity between motor pools within the spinal cord allow recruitment of a larger portion of the muscle than traditional intramuscular

electrodes. In addition, the number of electrodes is possibly reduced (proximity of synergistic motor pools to one another would allow coactivation of synergistic muscles), and the electrodes are in a location that suffers less strain, diminishing the risk of electrode breakage (Mushahwar and Horch 1997), although the risk of tissue damage is higher as the electrode is implanted directly into the spinal tissue instead of sitting extradurally to the cord as with epidural stimulation. As demonstrated by modeling (see ► [“Finite Element Modeling for Extracellular Stimulation”](#) in this encyclopedia) and experimental studies (Gustafsson and Jankowska 1976), neuronal activation with intraspinal microstimulation is mostly through transynaptic mechanisms (Gaunt et al. 2006), and recruited fibers of passage lead to a spread of activation to higher-order neurons responsible for the stereotype movements programmed at the level of the interneuronal circuitry. Thus, both approaches (motoneuronal pool or intermediate grey targeting) lead to activation of spinal elements spreading across multiple laminae and segments.

With electrodes implanted in the dorsal, intermediate, or ventral grey of the lumbosacral enlargement, flexion or extension whole limb movement can be obtained through electrical activation with stimuli train in intact or spinal animals (Barthelemy et al. 2006; Boyce and Lemay 2009; Giszter et al. 1993; Saigal et al. 2004; Tresch and Bizzi 1999). Tonic stimulation may even evoke locomotor activity with some reports suggesting that dorsal rostral sites (in dorsal column or dorsal horn around L3/L4 in spinal cats) are more efficacious (Barthelemy et al. 2006), while others report that stimulation of ventral caudal sites (intermediate grey of the L7/S1 region) is more prone to produce bilateral alternating movements in the hindlimb (Guevremont et al. 2006). Flexion responses are typically produced by stimulation in the dorsal horn and may be related to activation of the flexor withdrawal reflex since nociceptive afferent input terminates in the dorsal horns (Barthelemy et al. 2006; Boyce and Lemay 2009; Tresch and Bizzi 1999). Stimulation in more ventral sites tends to produce a greater mix of responses (flexion and extension) (Lemay and

Grill 2004), although a definite somatotopical map of the response type obtained based on electrode location is not apparent.

The responses to stimulation are typically measured either as movements (Barthelemy et al. 2006; Guevremont et al. 2006; Tai 2003) or as isometric force patterns representing the direction and magnitude of the forces produced by activation of a spinal site throughout the limb's workspace (Giszter et al. 1993; Lemay and Grill 2004; Tresch and Bizzi 1999). Forces are plotted as vectors through the workspace with the length of the vector representing force magnitude and vector orientation representing the direction of the force. The responses (movements or forces) obtained with stimulation are stereotypical and similar across individual animals. Across species the responses typically include a pattern of isometric force that would drive the limb toward the body (flexion withdrawal type of response), in caudal or rostral extension, and in some cases in rostral flexion, if free to move. The forces generated and measured under isometric conditions can be generalized to viscoelastic forces incorporating muscle properties for use under dynamic conditions. Indeed computational models of limb movements support this generalization (Giszter and Kargo 2001), and the control theory analysis of the motions produced shows that the force patterns may represent optimal ways of exciting limb dynamics based on analysis of limb mechanics (Berniker et al. 2009). Kinematics measurements of the motion produced by the force pattern measured under isometric conditions (Giszter et al. in the frog (Giszter et al. 1993) and Lemay et al. in the cat (Lemay et al. 2009)) demonstrated that the isometric force patterns were good predictors of the movements obtained by stimulation of the spinal site. The force patterns summate during coactivation of spinal sites, and thus, they can be used as building blocks of movement (Mussa-Ivaldi 1997). The summation property may be limited to the spinal condition (although see results for stimulation in cervical enlargement in the monkey below) as only winner take all (response from one stimulated site dominating during co-stimulation) was observed in decerebrate spinal intact cats (Lemay et al. 2009).

Evidence also suggests that circuits for reaching movements can be activated by intraspinal microstimulation as shown in non-human primates (Moritz et al. 2007; Zimmermann et al. 2011). Movements involving the shoulder, elbow, wrist, and hand were produced through activation of the grey matter or fiber tracts with trains of 3–20 stimulus pulses. Movements were produced through coactivation of multiple muscles, and sites producing arm or hand motions could be simultaneously activated to enable grasp, transport, and release of an object (Zimmermann et al. 2011).

Control of Bladder Function

Intraspinal microstimulation has also been used to produce voiding in spinal cord-injured individuals. Early work by Nashold and colleagues (1981) produced voiding in about 60 % of patients implanted with bilateral penetrating electrode into the conus medullaris. More recent detailed mapping of the sacral segments in cats showed the possibility of generating bladder pressures without increases in urethral pressure by microstimulation (~100 μ A) in the intermediolateral region (lamina VII) and the lateral ventral horn (Lamina VII) of the S1 and S2 sacral segments. Similar effects were observed for stimulation around the central canal (Lamina X) (Grill et al. 1999). Stimulation in those regions was thus effective at producing voiding. On the other hand stimulation in the ventrolateral ventral horn (laminae IX level) produced a concomitant increase in urethral pressure preventing effective voiding (Grill et al. 1999). Stimulation in dorsal horns (laminae II–IV) produced large increases in urethral pressure with minimal increases in bladder pressure; thus, those sites were better for ensuring continence (Tai et al. 2004). Mapping results obtained in spinal intact animals studied under anesthesia were generally similar in chronic spinal animals (Pikov et al. 2007). To date, the voiding obtained with intraspinal microstimulation has not been shown to be consistently superior to the one obtained with anterior sacral root stimulation (and dorsal rhizotomy) (see

► “Methodologies for the Restoration of Bladder and Bowel Functions” in this encyclopedia), and some authors have argued that the methodology is not worth the increased implantation risks (Gaunt and Prochazka 2006).

Control of Respiration

Recent evidence suggests that intraspinal stimulation may also be used to activate/potentiate respiratory spinal circuits, although in this case activation is through light delivery. Through viral gene delivery, it is possible to express Channelrhodopsin-2, a light-activated cation channel, in mammalian neurons. These neurons can then be depolarized by photostimulation to produce action potentials. In a cervical hemisection, it has been shown that phrenic activity ipsilateral to the lesion can be induced with photostimulation and that the activity is maintained for periods after the cessation of light, as it is hypothesized that crossed descending input to the phrenic nucleus is potentiated by the light-induced depolarization (Alilain et al. 2008). The technique could potentially be used in full transection to activate the phrenic nucleus via activation of the phrenic motoneurons or spinal respiratory circuit interneurons.

Future Directions

Examples in locomotor (Boyce and Lemay 2009) and autonomic (Pikov et al. 2007) systems indicate that the responses to intraspinal microstimulation are similar after chronic spinal cord injury although the relative proportions of each response types may alter with rehabilitation (Boyce and Lemay 2009). This suggests that the spinal circuits of interest are preserved when disconnected from supraspinal centers and can still be recruited to restore various functions. The spinal circuitry and its potential topological organization are still rather poorly understood although various efforts are underway to delineate the spinal circuitry responsible for locomotion, micturition, and respiration and their topological

organization (► [“Vertebrate Pattern Generation: Overview”](#)). Clinical applications in humans await development of electrode with mechanical properties suitable for chronic implantation into a soft spinal tissue that is subjected to much greater displacements than the ones observed in the cortex (see ► [“Braided Electrodes”](#) in this encyclopedia).

Cross-References

- [Braided Electrodes](#)
- [Finite Element Modeling for Extracellular Stimulation](#)
- [Methodologies for the Restoration of Bladder and Bowel Functions](#)
- [Vertebrate Pattern Generation: Overview](#)

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Intrathecal Analgesics

► Methodologies for the Treatment of Pain

Intrathecal Drug Delivery

► Methodologies for the Treatment of Pain

Intrinsic Optical Imaging

► Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

Inverse Problems in Neural Population Models

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Definition

Inverse problems are usually based on some *direct* or *forward model*, where the inversion aims to determine either parameter distributions of the model or states of the dynamics. The application and development of inverse techniques to neural population models will be discussed here with a

focus on neural field theory. The goal is the construction and reconstruction of neural connectivity and parameters of neural activity such as the local activation of pulses or spike trains.

Detailed Description

Neural Field Models such as the Cowan-Wilson Model (Wilson and Cowan 1972, 1973; Nunez 1974) or the Amari Neural Field Model (cf. Amari 1975, 1977) establish a field-theoretic approach to the dynamics of neural activity in the brain. The models use excitations and inhibitions over some distance as an effective model of mixed inhibitory and excitatory neurons with typical cortical connectivities, for example, by a simple dynamical equation for the voltage or activity $u(x, t)$ of the form

$$\begin{aligned} \tau \frac{\partial u}{\partial t}(x, t) = & -u(x, t) \\ & + \int_B w(x, y) f(u(y, t) - D(x, y)/v) dy, \end{aligned} \quad (1)$$

$x \in B, t \geq 0$, where initial conditions $u(x, 0) = u_0(x)$, $x \in B$ are given. Here, B is our *brain*, i.e., some domain where the neural activity takes place; f is the local *activation function* or *firing rate function*; w is the *connectivity function* which models the strength of the connectivity or signal propagation from $y \in B$ to the point x ; D is the length of the fiber from x to y ; and v is the propagation speed of the signal.

Inverse problems for such models aim for the determination of either the connectivity kernel $w(x, y)$ or both the connectivity kernel w and parameters of the activation function f . In addition to w and f , inverse neural field problems can also aim to determine the parameter distribution of τ , where either τ is a scalar constant or $\tau = \tau(x)$ is a distributed function.

As a generic problem, for the case $v = \infty$ (such that we can drop the delay term in Eq. 1) and where τ and f are known, assume that the function $u(x, t)$ in Eq. 1 is measured for $x \in B$ and $t \geq 0$. The task to determine $w(x, y)$ from these

data is known as *full field neural inverse problem* (Potthast and beim Graben 2009a,b). Using

$$\begin{aligned} \psi(x, t) := & \tau \frac{\partial u}{\partial t}(x, t) \\ & + u(x, t), \varphi(y, t) := f(u(y, t)) \end{aligned} \quad (2)$$

for $x, y \in B, t \geq 0$, the inverse problem is transformed into a family of *integral equations*

$$\psi(x, t) = \int_B \varphi(y, t) w(x, y) dy, t \geq 0, \quad (3)$$

$x \in B$ (cf. Coombes et al. (2013)). For each $x \in B$, Eq. 3 is an independent integral equation of the *first kind*. It is well known (cf. Kress (1989), Kirsch (1996)) that integral equations of the first kind with continuous or weakly continuous kernel are *ill-posed*, i.e., the calculation of the solution $w(x, \cdot)$ cannot depend stably on the right-hand side. An equation is called *ill-posed* if one or several of the demands of (I) *existence* of a solution for each right-hand side, (II) *uniqueness* of solutions, and (III) *stable dependence* of the solution on the data are violated.

Regularization methods (cf. Kress (1989)) replace the unstable inverse A^{-1} of the operator

$$(Ag)(t) := \int_B \varphi(y, t) g(y) dy, t \in [0, \infty], \quad (4)$$

by a family of bounded operators R_α , such that

$$R_\alpha f^* \rightarrow g^*, \quad \alpha \rightarrow 0, \quad (5)$$

where $Ag^* = f^*$, i.e., g^* is the true solution with true right-hand side f^* . Regularization for the neural field problem as, for example, by *Tikhonov regularization*

$$R_\alpha := (\alpha I + A^* A)^{-1} A^* \quad (6)$$

is worked out in (Potthast and beim Graben 2009a,b); methods for reducing the ill-posedness by *dimensional reduction* have been suggested in (Potthast et al. 2009). The authors also study *transformations* of neural space such that inverse neural problems can be reduced in dimensionality and made independent of the dimension of the

actual neural space in which the task is imbedded. For example, an excitation problem in a space of 10^4 neurons can be reduced to a one-dimensional problem, even though it is distributed over the full original neural space.

Inverse problems for neural field theory have been applied to modeling processes of language generation and language parsing in *dynamic cognitive modeling* (beim Graben and Potthast 2009). The implementation of a *Turing computer* in the framework of neural field architectures has been based on inverse problems techniques in (beim Graben and Potthast 2012b, 2013).

Inverse Problems in NFT and Dynamic Causal Modeling

Dynamic causal modeling was originally developed by (Friston et al. 2003, 2006) to estimate the causal coupling between brain regions from the activity observed by functional magnetic resonance imaging (fMRI) measurements.

More generally, the aim of *dynamic causal modeling* (DCM) (Friston et al. 2006; Friston 2009; Penny et al. 2004; Kiebel et al. 2008) is to determine the causal structure within distributed dynamical systems. In contrast to *inverse problems for dynamical systems*, where the goal is to determine the underlying unknown parameters of the system, *dynamic causal modeling* parameterizes the conditional dependencies by an *effective connectivity*, where DCM employs a simple deterministic model based on ordinary differential equations of neural dynamics in a network or graph.

In this sense, *dynamic causal modeling* can be seen to employ *inverse problems* techniques within a specific setup and application area.

Inverse Problems and Bayes' Theory

Bayes' theory (Berger 1985) estimates some conditional probability distribution $\pi(x|y)$, i.e., the probability of x under the condition of y , when a prior distribution $\pi(x)$ and the conditional distribution $\pi(y|x)$ of y under the condition x are given, using *Bayes' formula*

$$\pi(x|y) = \frac{\pi(x)\pi(y|x)}{\pi(y)} \quad (7)$$

If some prior distribution $\pi(w)$ for the *neural connectivity* w is known, measurements of the *activity fields* u with dynamics Eq. 1 with error distribution $\pi(u|w)$ can be employed to calculate the posterior *neural kernel distribution* $\pi(w|u)$ by Eq. 7, where $\pi(u)$ is determined by the standard probabilistic *norming condition* $\int \pi(w|u) = 1$.

As shown in Freitag and Potthast, Kaipio and Somersalo, for *Gaussian distributions*, the calculation of the *mean* or *maximum likelihood estimator* MAP is identical to the regularization approach Eq. 6. In this case, *regularization theory* of inverse problems and *Bayes' estimation* coincide. The regularization parameter is determined by the covariances of the distribution under consideration.

Advantages of the Approach

Inverse problems appear naturally in many parts of cognitive neuroscience to estimate or determine the connectivity in the brain or parameters of equations which are used to simulate the chemical, physiological, or electrical activity. Thus, the inverse problems approach to neural field theory is a natural and universal approach, which is needed for any system simulating real data.

Limitations

Inverse problems in neural population models are usually strongly underdetermined. It is almost impossible to capture the full complex dynamics which takes place in real systems from limited number and resolution of measurements. Thus, it is common to work with reduced dynamics and particular model systems. But this also strongly limits their applicability in a realistic framework.

Cross-References

- [Amari Model](#)
- [Dynamic Causal Modelling with Neural Population Models](#)

- [Forward and Inverse Problems of MEG/EEG](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Model](#)
- [Neuroimaging, Neural Population Models for](#)
- [Synaptic Connectivity in Neural Population Models](#)

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Inward Rectifier Potassium Channels

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Synonyms

[Anomalous rectifier potassium channels](#); [GIRK channels](#); [K-ATP channels](#); [Kir channels](#)

Definition

Inward rectifier potassium channels, also called Kir channels are potassium channels which, on the contrary of the other potassium channels, let

little potassium ions flow outside of the cell and allow a large inflow of potassium ions inside the cells. In other words, inward rectifier currents present a reduced outward current at membrane potential above the potassium reversal potential and large inward current for membrane potential below the potassium reversal potential.

Detailed Description

First described in skeletal muscle, these channels have been identified in several other cell types: cardiac myocytes, blood cells, osteoclasts, endothelial cells, epithelial cells, oocytes, neurons, and glial cells (for review, see Hibino et al. 2010).

The inward rectifier potassium channels are part of a heterogeneous family of potassium channels named Kir m.n or KCNJ.x. This family can be categorized into four subclasses: transport channels (Kir1.n, Kir4.n, Kir5.n, Kir7.n), regular Kir channels (Kir2.n), G protein-gated channels (Kir3.n), and ATP-sensitive channels (Kir6.n) (Hibino et al. 2010).

These particular channels are not voltage-gated channels due to the lack of S4 voltage sensor, conserved in the different families of voltage-gated channels (Hibino et al. 2010). Despite this lack of voltage dependence, the current flowing through the inward rectifying channels is asymmetric with large inward current and small outward current. This asymmetry is due to the blockade of the permeant pore by intracellular divalent ions (Mg^{2+})/polyamines for depolarized potential.

In experiments realized with various extracellular potassium concentrations, the current-voltage relationship remains asymmetric and is shifted to the new potassium reversal potential (see Fig. 5.14, p. 152, Hille 2001). Similar experiments realized with various intracellular potassium concentrations do not show a similar phenomenon. This demonstrates that inward rectifier channel current activation depends on the difference between the membrane voltage V_m and the impact of extracellular potassium concentration on the potassium reversal potential E_{K+} , given by the quantity $R \cdot T \cdot \ln[K]_o$ (Hille 2001).

How to Model These Channels?

The Kir current-voltage relationship is asymmetric with large inward current for potentials more hyperpolarized than the potassium reversal potential (E_{K+}) and small outward current for potentials more depolarized than E_{K+} (see Fig. 1a, b). This asymmetry can be approximated by Hodgkin and Huxley equations, considering that the activation of the channels is maximal at potentials below E_{K+} and decreasing toward zero for potential more depolarized than E_{K+} (see Fig. 1c).

Several models used this assumption to account for the effects of these particular channels in medium spiny neurons (Gruber et al. 2003; Wolf et al. 2005) or in deep dorsal horn neurons of the spinal cord (Le Franc and Le Masson 2010).

In these different cellular models, the current was modeled as a classical Hodgkin and Huxley current, given by the following equation:

$$i_{Kir} = \bar{g}_{Kir} * m(V) * (V_m - E_{K+})$$

where i_{Kir} is the inward rectifier current, $\bar{g}_{Kir}$ is the maximal conductance of the channels, $m(V)$ is the gating variable representing the voltage-dependent channel activation, V_m is the cell membrane potential, and E_{K+} is the reversal potential of the potassium given by the Nernst equation (see Nernst equation).

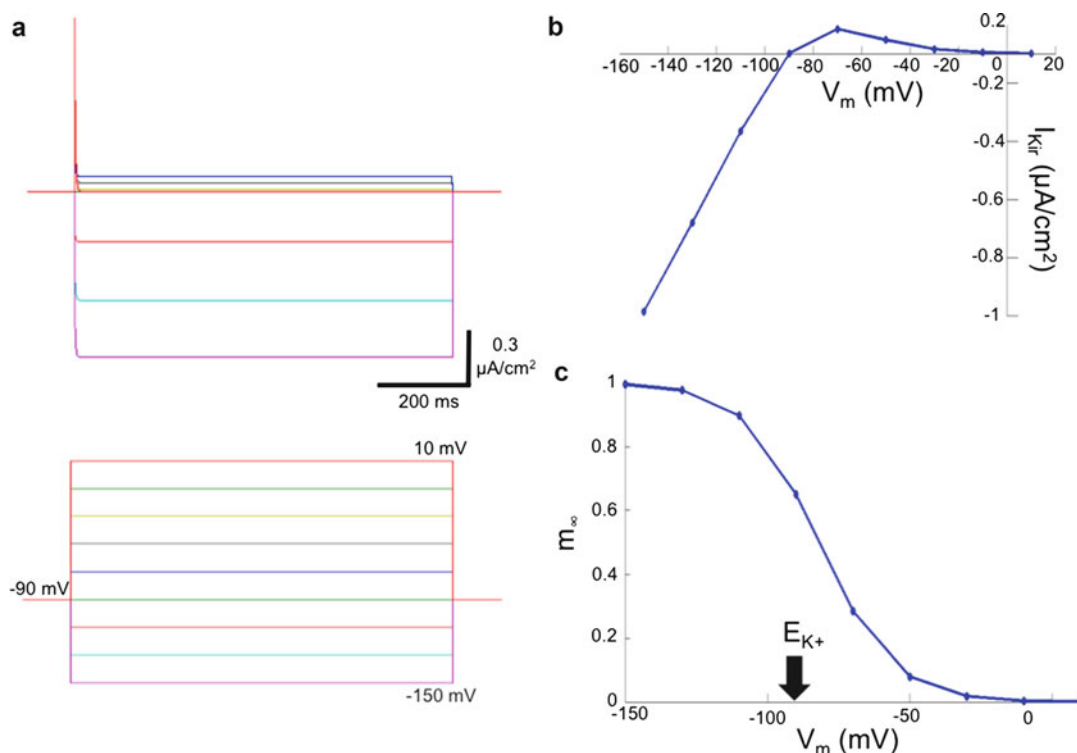
The variation of the activation is given by the following equation:

$$\frac{dm}{dt} = \frac{m_{\infty} - m}{\tau_{Kir}}$$

The steady-state voltage-dependent activation of the channel m_{∞} can be represented by a simple sigmoidal function:

$$m_{\infty}(V) = \frac{1}{1 + \exp((V_{tn} - V_{half})/slope)}$$

Common values for the slope are around 10 mV (13 mV in Wolf et al. 2005; 10 mV in Le Franc and Le Masson 2010; 11 mV in Gruber et al. 2003), while values for the half-activation can be



Inward Rectifier Potassium Channels, Fig. 1 Kir 2.x model. Simulated Kir current based on Wolf (Wolf et al. 2005; ModelDB accession number: 112834). Simulation was run on NEURON 7.2. The current has been inserted in a 10-by-10 μm compartment. The potassium reversal potential E_{K^+} has been set to -90 mV, the Kir maximal

conductance to $150 \mu\text{S}/\text{cm}^2$. The simulation time step was 0.025 ms. $E_{\text{K}^+} = -90$. (a) The simulated Kir current (top) was held at -90 mV and V_m was increased in 20 mV steps (bottom) from -150 mV to $+10$ mV for 800 ms. (b) Steady-state I/V relation for the simulated Kir current. (c) Voltage dependence of the steady-state activation $m_\infty(V)$

more variable (-52 mV in Wolf et al. 2005; -111 mV in Gruber et al. 2003; -65 mV in Le Franc and Le Masson 2010).

This particular model can be used to represent Kir2.x channels (Gruber et al. 2003; Wolf et al. 2005) G protein-gated inward rectifying potassium channels (Kir3.x; Le Franc and Le Masson 2010). However, a recent model has been proposed to account for the activation of Kir current by GABA_B (Sanders et al. 2013).

Functions in the Nervous System

In the nervous system, the different Kir channel types share the same function in physiological conditions: reducing the neuronal excitability by bringing the resting potential near E_{K^+} .

Due to their activation by neuromodulators, the Kir3.x or GIRK (G protein-gated inward rectifier K⁺) channels have been shown to play a crucial role in the nervous system in regulating neuronal excitability at different levels: neuronal self-inhibition, neuron-to-neuron inhibition, or network-level inhibition (for more details, see Lüscher and Slesinger 2010).

Their regulation by metabotropic receptors (glutamate and GABA) has been proposed as a mechanism for bistability contributing to persistent firing in working memory (Sanders et al. 2013) and pain processing (Derjean et al. 2003).

With the large diversity of regulations (Wang et al. 2011), these channels are implicated in multiple disease states including neurological diseases such as epilepsy, Parkinson's disease, Down's syndrome, and drug addiction (Lüscher and Slesinger 2010).

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Ion Channel Mutation

- [Epilepsy: Abnormal Ion Channels](#)

Ionic Currents

- [Modeling Ion Concentrations](#)

Ionic Diffusion

- [Modeling Ion Concentrations](#)

Ionotropic Receptors Dynamics, Conductance Models

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Definition

Ionotropic receptors are an ion channel that opens upon binding of ligand molecules such as neurotransmitters. In addition, receptors may transition into desensitized, nonconducting states. These state transitions can be described with kinetic models, which replicate the time course of the resulting gating and corresponding conductance changes. Such models are particularly useful to simulate the postsynaptic conductance caused by neurotransmitter release during synaptic transmission.

Detailed Description

The temporal dynamics of synaptic transmission strongly depends on the kinetics of postsynaptic neurotransmitter receptors. Binding of transmitter molecules to ionotropic receptors causes a conformational change of the protein that opens an ion channel, which in turn gives rise to a membrane conductance change (Hille 2001). The observation of discrete open and closed states in single-channel recordings has supported the notion that a receptor protein functions by traversing through a succession of conformational state changes (Neher 1992). This motivates the use of kinetic models to describe receptor dynamics. In addition to opening and closing, receptors can also enter long-lived desensitized states, where the ligand is bound but the channel remains closed (Jones and Westbrook 1996).

Alpha Function

A very simple model for the time course of the synaptic conductance change following a presynaptic action potential is the alpha function, first introduced by Rall (1967):

$$g_{\text{syn}}(t) = \frac{t - t_0}{\tau} \exp\left(-\frac{t - t_0}{\tau}\right); t > t_0 \quad (1)$$

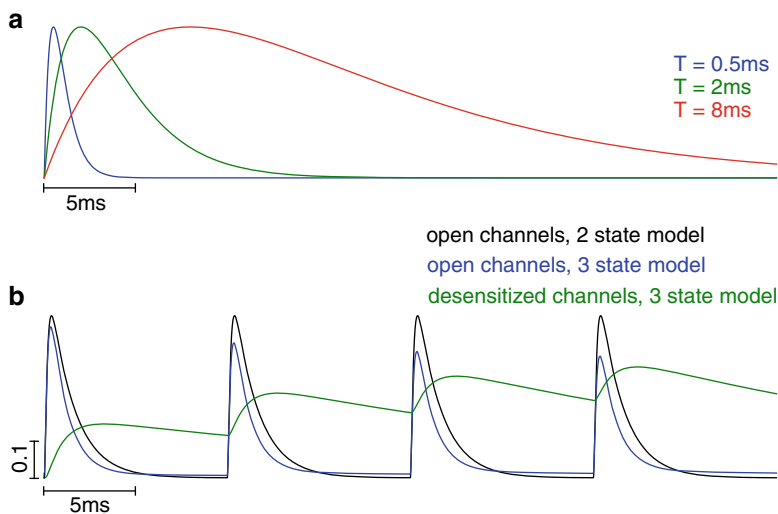
This model describes the postsynaptic conductance $g_{\text{syn}}(t)$ caused by a presynaptic action potential at time t_0 . The single parameter τ determines both the peak time at $t_p = t_0 + \tau$ and the time constant of the exponential decay (Fig. 1a). The parameter can be adjusted to reflect the differences between synapses, such as fast AMPA/kainate receptors ($\tau < 1$ ms) or slower NMDA receptors ($\tau \approx 40$ ms).

This model can be derived as a special case of a second-order kinetic model (see Destexhe et al. 1994, for details), but there is no clear biological interpretation of the parameter. In addition, it fails to reproduce the relatively fast rise times of

synaptic conductances; therefore, extensions such as models with two exponential functions have been proposed (Gerstner and Kistler 2002). In practice even simpler models such as a linear first-order reaction are often used for computational efficacy.

Markov Models

A more comprehensive approach to modelling ionotropic receptors are finite-state models (Destexhe et al. 1994). This involves listing all possible states of the protein as well as the allowed transitions between them. Under the assumption that state transitions only depend on the current state of the protein, these can be formulated as Markov models. The gating dynamics can then be described by a system of ordinary differential equations. This formalism can not only be used to model receptors but the behavior of gated ion channels generally (Colquhoun and Hawkes 1981) and includes the well-known Hodgkin



Ionotropic Receptors Dynamics, Conductance Models, Fig. 1 Examples of simulated receptor responses. (a), The alpha function Eq. 1 with three different time constants. (b), Comparison of the two state Eq. 2 and three state Eq. 4 models of fast AMPA/Kainate receptor, as derived by Destexhe et al. (1994). Brief

neurotransmitter transients with frequency 100 Hz were modeled as alpha functions with $\tau = 0.1$ ms. Each successive response, as indicated by the fraction of open channels, is identical in the two state model. A slow transition into the desensitized state causes the response to decrease in the three state model

Huxley model as a special case (Hodgkin and Huxley 1952).

The simplest, first-order model of a receptor includes one closed (C) and one open (O) state:



The transition into the open state is proportional to the neurotransmitter concentration $T(t)$ and a binding rate constant k_b . From the open bound state, the receptor relaxes back into the closed state with the rate constant k_u .

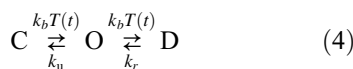
For a system of many identical channels, this model can be written as an ordinary differential equation (ODE) describing the fraction of open channels at time t :

$$\frac{dO(t)}{dt} = \underbrace{k_b T(t)(1 - O(t))}_{\text{binding}} - \underbrace{k_u O(t)}_{\text{unbinding}} \quad (3)$$

Since there are two possible states in this model, the relation $O(t) + C(t) = 1$ has to be fulfilled. When the receptor conductance is independent of other factors such as the membrane voltage, the conductance of the channel population is then given by $g = g_{\max} O(t)$, where $g_{\max}$ is the peak conductance. This model produces kinetics similar to alpha functions but can be adjusted to reflect different rise and decay kinetics (Fig. 1b).

A counterexample is the NMDA receptor, where gating also depends on the membrane voltage and the extracellular Mg^{2+} concentration. This can be modeled with a more complex kinetic model, which in a physiological parameter range simplifies to a factor of $g_{\text{NMDA}}(V) = 1/(1 + \exp(-\gamma V)\eta M)$, where M is the Mg^{2+} concentration (Jahr and Stevens 1990).

Kinetic models can be easily extended to include more states, such as a desensitized state D :



As above, this kinetic scheme can be written as a system of ODEs:

$$\begin{aligned} \frac{dO(t)}{dt} &= k_b T(t)C(t) + k_r D(t) - (k_u + k_d)O(t) \\ 1 &= O(t) + C(t) + D(t) \end{aligned} \quad (5)$$

This model shows how receptor desensitization affects the conductance response time course during transmission of a single synaptic event (Fig. 1b; Trussell et al. 1988). Moreover, desensitization also can lead to suppression of the conductance during fast, repetitive activation of a synapse, suggesting an important physiological role for desensitization (Jones and Westbrook 1996; Wong et al. 2003).

It is important to note that in order to precisely reproduce the kinetics of ionotropic receptors, typically more complex models are required. These may, for instance, also include different conductance states that have been identified in single-channel recordings from AMPA receptors (Robert and Howe 2003; Postlethwaite et al. 2007). In general however, three- or four-state models have been shown to be very effective in describing the main features of the responses of AMPA, NMDA, and GABA_A receptors (Destexhe et al. 1994).

Summary

Kinetic models provide good descriptions of the time course of a range of ionotropic receptor responses and also allow for investigating the underlying dynamics of the receptor protein. This formulation can be directly cast into a set of master equations that describe the probability of the occupancy of the different receptor states (Gillespie 1977). Results from stochastic simulations can then be directly compared to experimental measurements of statistical quantities such as dwell times. A drawback of kinetic models is that they can be computationally costly, which is impractical particularly in larger network simulations. Therefore, often simple exponential or alpha function models are used in such cases.

Cross-References

- [AMPA Glutamate Receptor \(AMPA Receptor\), Conductance Models](#)
- [Gamma-Aminobutyric Acid Type-A \(GABA-A\) Receptors, Kinetic Models](#)
- [Kinetic Models of Postsynaptic Currents](#)
- [Markov Models of Ion Channels](#)
- [Modeling Synapses](#)
- [N-Methyl-D-Aspartate \(NMDA\) Receptors, Conductance Models](#)
- [Synaptic Dynamics: Overview](#)

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Iso-Intensity Response Curves

- [Spectrotemporal Receptive Fields](#)

Izhikevich Model

- [Integrate and Fire Models, Deterministic](#)

Jansen Model

► [Jansen-Rit Model](#)

Jansen-Rit Model

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Synonyms

[Jansen model](#); [Jansen-Zetterberg model](#)

Definition

The Jansen-Rit model is a neural population model of a local cortical circuit. It contains three interconnected neural populations: one for the pyramidal projection neurons and two for excitatory and inhibitory interneurons forming feedback loops. Each neural population is described by a second-order differential operator transforming the mean incoming spike rate to the mean membrane potential and a nonlinear function transforming the mean membrane potential to a mean output spike rate.

Detailed Description

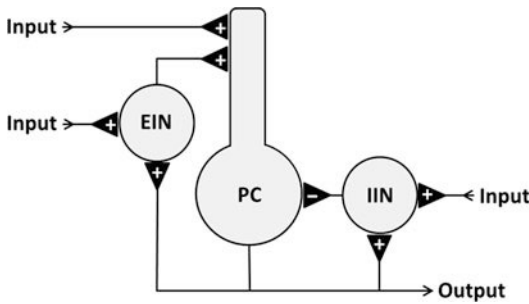
The Jansen-Rit model is a neural population model comprising three interconnected neural populations (see Fig. 1). It has been first described by Jansen and colleagues (Jansen et al. 1993; Jansen and Rit 1995) and goes back to earlier work by Lopes da Silva et al. (1974, 1976).

Mathematical Description

The state variables of the model comprise the mean membrane potentials $V(t)$ and the mean firing rates $m(t)$ of the populations. For each population, a rate-to-potential operator (RPO) describes the dynamics of the synapses and dendritic trees, while the potential-to-rate operator (PRO) describes the output nonlinearity at the axonal hillocks. The RPO can be described as an alpha function, which is a Green's function of a second-order differential equation, where τ is a time constant summarizing passive dendritic cable delays and neurotransmitter kinetics in the synapse, H is the synaptic gain, and c is the connection strength:

$$\left(\frac{\partial^2}{\partial t^2} + \frac{2}{T} \frac{\partial}{\partial t} + \frac{1}{T^2} \right) V(t) = \frac{Hc}{T} m(t). \quad (1)$$

This is equivalent to convolving the incoming spike rate with the alpha function, which has been shown to adequately describe the postsynaptic



Jansen-Rit Model, Fig. 1 Schematic drawing of the Jansen-Rit model of a cortical area. Pyramidal cells (PC) send axons to other areas (output). Collaterals contact excitatory and inhibitory interneurons (EIN, IIN), which in turn form feedback loops onto the PC. Excitatory synapses from other brain areas (input) contact all three neural populations. Black triangles symbolize excitatory (marked “+”) or inhibitory (marked “-”) synaptic contacts

potential in response to a single spike, e.g., by Freeman (1975). The PRO is a sigmoid function, where V_0 is the firing threshold, r is the slope reflecting the variance of firing thresholds within the population, and e_0 is the firing rate at threshold:

$$m(t) = \frac{2e_0}{1 + e^{r(V_0 - V(t))}}. \quad (2)$$

This function can be seen as an approximation of the superposition of many Heaviside functions belonging to individual neurons with normally distributed firing thresholds (Liley et al. 2002).

Full Set of Equation

As shown in Fig. 1, the Jansen-Rit model comprises seven synaptic contacts, each of which can be described by Eqs. 1 and 2. In the original parameterization of Jansen et al. (1993), the PRO parameters are kept constant for all populations ($e_0 = 2.5 \text{ s}^{-1}$; $r = 558.7 \text{ V}^{-1}$; $V_0 = 6 \text{ mV}$), and the remaining parameters are only distinguished between excitatory and inhibitory synapses ($\tau_e = 10 \text{ ms}$; $\tau_i = 20 \text{ ms}$; $H_e = 3.25 \text{ mV}$; $H_i = -22 \text{ mV}$). Equations for synapses with the same postsynaptic and the same type of pre-synaptic (excitatory or inhibitory) populations can be combined, which reduces the number of equations to 4. The following definitions normalize the variables and combine some of the parameters in a convenient way (Spiegler 2011):

- Time: $\kappa = t/\tau_c$ with τ_c being a conveniently chosen reference time constant.
- Time constants: $\beta_e = \tau_c/\tau_e$ and $\beta_i = \tau_c/\tau_i$.
- Potential: $x(\kappa) = r \cdot V(\kappa\tau_c)$.
- Firing rate: $z(\kappa) = m(\kappa\tau_c)/(2e_0)$.
- Coupling $a \rightarrow b$: $\alpha_{ba} = 2e_0rc_{ba}H_{e,i}\tau_{e,i}$ with c_{ba} being the connectivity from population a to population b . Population indices a and b can be 1 for EINs, 2 for IINs, 3 for PCs, and T for external input.
- Sigmoid: $\gamma = \exp(rV_0)$.

With these definitions, the differential operator according to Eq. 1 can be reformulated for excitatory and inhibitory synapses as follows:

$$L_{e,i} = \left(\frac{\partial^2}{\partial \kappa^2} + 2\beta_{e,i} \frac{\partial}{\partial \kappa} + \beta_{e,i}^2 \right). \quad (3)$$

The PRO according to Eq. 2 is described by the following sigmoid function:

$$S(x(\kappa)) = \frac{1}{1 + \gamma e^{-x(\kappa)}}. \quad (4)$$

The state variables are now x_{1e} , x_{2e} , x_{3e} (normalized excitatory postsynaptic potentials for all three populations), and x_{3i} (normalized inhibitory postsynaptic potential in the PCs). The normalized external input firing rates are z_{1T} , z_{2T} , z_{3T} . The state equations can now be written as

$$L_e x_{1e}(\kappa) = \beta_e^2 (\alpha_{13} S(x_{3e}(\kappa) + x_{3i}(\kappa)) + \alpha_{1T} z_{1T}(\kappa)), \quad (5)$$

$$L_e x_{2e}(\kappa) = \beta_e^2 (\alpha_{23} S(x_{3e}(\kappa) + x_{3i}(\kappa)) + \alpha_{2T} z_{2T}(\kappa)), \quad (6)$$

$$L_e x_{3e}(\kappa) = \beta_e^2 (\alpha_{31} S(x_{1e}(\kappa)) + \alpha_{3T} z_{3T}(\kappa)), \quad (7)$$

$$L_i x_{3i}(\kappa) = \beta_i^2 (\alpha_{32} S(x_{2e}(\kappa))). \quad (8)$$

Dynamic Properties

In spite of its apparent simplicity, the Jansen-Rit model is capable of producing a surprisingly rich repertoire of dynamic behaviors, which populate

the parameter space in a very complex way. When the neural populations are exposed to constant external input, thus keeping the system in its equilibrium state, the model can produce constant output, harmonic oscillations, and large-amplitude nonharmonic oscillations. The transitions between these phases are characterized by subcritical and supercritical Andronov-Hopf bifurcations, Shil'nikov's homoclinic bifurcations, and further global bifurcations. Bistability occurs in large parts of the parameter space. While Grimbert and Faugeras (2006) investigated the dynamics of the original parameter configuration proposed by Jansen and Rit, Spiegler et al. (2010) systematically investigated the large parts of the parameter space of the model. When the input to the neural populations is oscillatory, the system also produces complex nonharmonic oscillations as well as quasiperiodic and chaotic behavior, depending in a complex fashion on the amplitude and frequency of the input (Spiegler et al. 2011).

Applications

The Jansen-Rit model has been demonstrated to explain a broad range of phenomena in electric brain activity, including epilepsy-like activity (Wendling et al. 2000; Touboul et al. 2011), narrowband brain oscillations (David and Friston 2003), event-related activity (David et al. 2006), and steady-state responses (Moran et al. 2009). Within the framework of dynamic causal modeling (David et al. 2006), networks of Jansen-Rit models were used to account for the outcomes of neuroscientific experiments (e.g., Garrido et al. 2009).

Advantages and Limitations

The Jansen-Rit model is a very parsimonious model of cortical mean-field activity, which retains a considerable degree of biological realism, as it accounts for the major functional roles of neurons: PCs project to distant areas and, due to their asymmetric appearance and aligned arrangement, form the major source of extracranially detectable electric brain signals; interneurons form local positive and negative feedback loops.

The description of the populations by RPO and PRO is also in principal agreement with cell physiological observations. On the other hand, the circuit represents a significant simplification: in reality, many more distinguishable populations are interconnected in a complex fashion. Therefore, it is difficult to map the parameters of the model directly onto the physical properties of neural populations.

Cross-References

- ▶ [Amari Model](#)
- ▶ [Bifurcations, Neural Population Models and](#)
- ▶ [Chaos, Neural Population Models and](#)
- ▶ [Down Under Neural Population Models](#)
- ▶ [Dynamic Causal Modelling with Neural Population Models](#)
- ▶ [Epilepsy, Neural Population Models of](#)
- ▶ [Neural Population Model](#)
- ▶ [Wilson-Cowan Model](#)

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Jansen-Zetterberg Model

► Jansen-Rit Model

Joint Peri Stimulus Time Histogram (JPSTH)

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Definition

The joint peristimulus time histogram (JPSTH) provides the two-dimensional time-resolved

correlation of two neurons with respect to a trigger event. A specific correction removes the effect of the trigger on the individual neuronal responses and thus highlights the excess correlation between the two neurons.

Detailed Description

The temporal relation between two spike trains is usually studied using the ordinary cross-correlation (see entry ► [“Correlation Analysis of Parallel Spike Trains”](#)) together with the shift or peristimulus time histogram (PSTH)-based (see entry ► [“Estimation of Neuronal Firing Rate”](#)) predictor to partially compensate for firing covariation. These measures are averages over the entire length of data and hence ignore dynamics. This means we can only infer the static average interaction between the neurons. A portion of the dynamics may be associated with the repeated presentation of stimulus, and it is this portion that is delineated by the JPSTH (as an average over the presentations). The JPSTH also gives a better approach to extracting excess correlation than do the traditional shift or PSTH predictors (Aertsen et al. 1989; Palm et al. 1988).

Construction of the JPSTH begins with creation of the scatter diagram shown in Fig. 1. For each presentation of the stimulus, we take the stimulus time as origin and lay off the activity of the two neurons, each along its own axis as indicated. Points are then plotted on the plane at all logical ANDs of the several action potentials on each axis. The process is repeated for subsequent stimuli, building up a scatter of points on the plane. Various features of the neural activity will produce regions of higher point density. If, for example, one neuron responds to the stimulus with a brief increase in firing rate, there will be a bar of high density of points parallel to the appropriate axis at a location corresponding to the response latency. If there is a high probability of near coincidences in the two trains of action potentials, there will be a bar of high density of points parallel to the principal diagonal and at a distance from it that represents the latency of the favored near coincidences. There may be

Deceased – George L. Gerstein passed away on March 28, 2018. Upon his decease, Ad Aertsen agreed to become a Co-Author, taking care of updating this Chapter.

G. L. Gerstein: deceased.

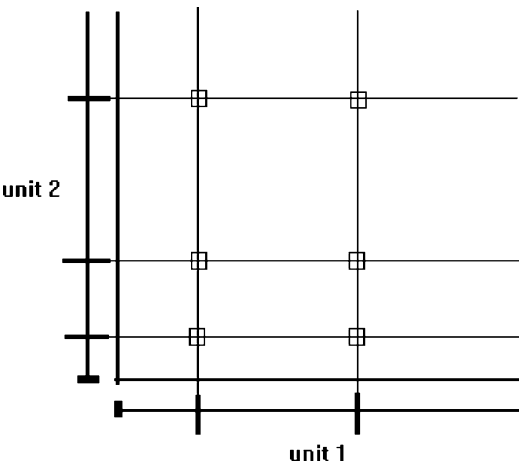
modulations of density along this bar, indicating the averaged stimulus-locked modulations of the probability for the near coincidences.

The scatter diagram described in the previous paragraph is constructed at the maximum temporal resolution available in the data, that is, corresponding to a single clock tick. In order to allow statistical manipulation of the point densities, we need to make coarser bins. The appropriate types of bins are shown in Fig. 2. For the JPSTH matrix, we use square bins at the same values that are used for the ordinary PST histograms of each spike train (Fig. 2a). For the region near the principal diagonal, we use the bins indicated in Fig. 2b, producing the PST coincidence histogram. This measures the averaged stimulus-locked near coincidence probability in the same sense as the ordinary PST histogram measures the

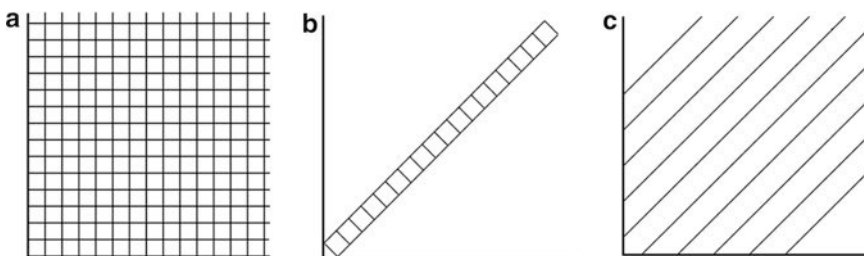
averaged stimulus-locked firing probability of each neuron individually (see entry ► [“Estimation of Neuronal Firing Rate”](#)). Finally, by summing along the para-diagonal bins shown in Fig. 2c, we produce the ordinary cross-correlogram of the two spike trains (see entry ► [“Correlation Analysis of Parallel Spike Trains”](#)). Note that since these bins are not of equal length (and hence area), we must either normalize by the bin length or compute a larger matrix so as to allow making all bins of equal length.

We now apply the JPSTH measurement to a set of spike trains produced by a simulator. The simulated circuit arrangement is shown in Fig. 3. The observed neurons “10” and “12” are each “spontaneously” active because of independent and stationary inputs from networks G10 and G12. In addition, a periodic stimulus input briefly elevates firing probabilities for the observed neurons. Finally, there is an excitatory synaptic connection from neuron “10” to neuron “12” whose strength is itself modulated by the stimulus; this is indicated in Fig. 3 by the small square box in the path. The temporal profile of this modulation is an initial rapid rise followed by a slower decay.

The basic JPSTH analysis of these “raw” data is shown in the left half of Fig. 4. At left and below the JPSTH matrix are the ordinary PST histograms of the two units. The abscissa PSTH (for unit 10) is repeated below the histogram grouping at the right of the matrix. Rising towards the upper right is the PST coincidence histogram and at the extreme right is the ordinary cross-correlogram. The PST histograms show the time course of the stimulus-driven increase in firing. As expected from the descriptions of the scatter diagram



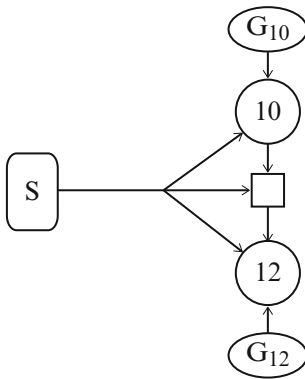
Joint Peri Stimulus Time Histogram (JPSTH), Fig. 1 Construction of JPSTH



Joint Peri Stimulus Time Histogram (JPSTH), Fig. 2 Bin arrangements for (a) JPSTH matrix, (b) peristimulus coincidence histogram, (c) cross-correlogram

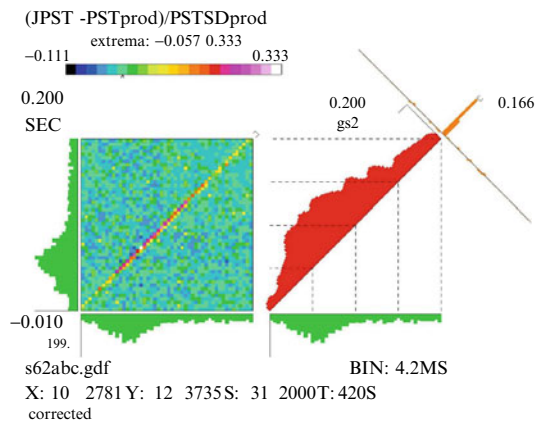
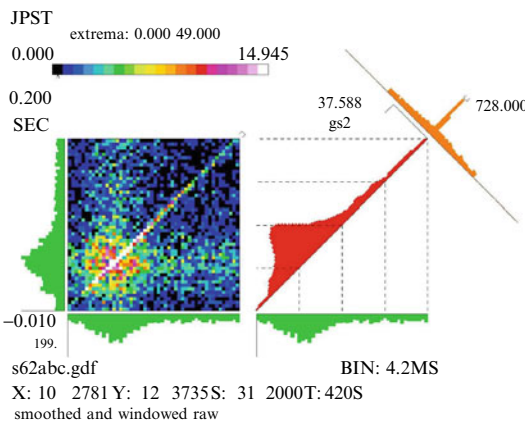
construction and the simulated circuit used to generate the data, the JPSTH matrix shows a hill, a fairly broad stripe parallel to each axis, and a narrow stripe parallel (just above) the principal diagonal. The PST coincidence histogram shows a broad peak at the times when both neurons have stimulus-induced higher firing rates, which is otherwise fairly small. Finally the cross-correlogram shows a narrow peak near the origin riding on a flat background.

Because the observed neurons are being co-modulated by the direct stimulus input, their firing rates increase and decrease in unison, thus creating a large part of the “raw” correlation structure. In order to infer “effective connectivity” or



Joint Peri Stimulus Time Histogram (JPSTH), Fig. 3 Circuit used to generate spike trains with simulator program

organization among our observed neurons, we need to compare the “raw” correlation to that expected for two independent neurons with precisely the observed PST histograms. This is accomplished with the corrected JPSTH as shown in the right half of Fig. 4. Here we subtract the matrix produced by the bin-by-bin product of the two PST histograms (divided by the number of stimuli) from the “raw” JPSTH matrix and then divide, again bin by bin, by the product of the standard deviations in each PST histogram. Each bin in the matrix has now become a correlation coefficient. PST histograms are shown as before, but the derived coincidence histogram and the cross-correlation are now corrected for firing rate changes (see entries ► “Significance Evaluation” and ► “Surrogate Data for Evaluation of Spike Correlation”). Note that the hill and bars parallel to the axes have disappeared from the corrected JPSTH matrix, while the diagonal stripe has persisted. The corrected PST coincidence histogram shows an initial rapid rise and subsequent slow fall, as expected from the stimulus modulation of the synaptic connection in the simulator. The corrected cross-correlogram shows only a central peak, with no “background” correlation. We note that this matrix-based correction of the cross-correlogram is somewhat different but more accurate than correction based on the more usual shift or PSTH-based predictor. Thus, this correction has extracted the (known) stimulus time-



Joint Peri Stimulus Time Histogram (JPSTH), Fig. 4 (Left) Matrix containing the raw spike coincidences (JPSTH) and the PST coincidence histogram (red) to the

right. The cross-correlogram is shown in orange. (Right) Same display as shown on the left but here for the normalized JPST

locked modulation of the “effective correlation” between the two neurons and has removed the direct correlation effects of the stimulus-related co-modulation of firing rates.

It is necessary to establish significance for the features shown in the corrected JPSTH and its associated histograms and also to deal with non-stationarity in the neural activity. Methods for both objectives have been worked out and are discussed in Palm et al. (1988) and Gerstein (1998). In addition it is not necessary to use square time bins in the JPSTH matrix. For example, the bin resolution perpendicular to the main diagonal can be much higher than along it. This produces a stimulus-locked and time-resolved cross-correlation along the main diagonal (see Gerstein 1998; Aertsen 2021) for more detail). Please find an example application of the JPSTH in Vaadia et al. (1995).

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Estimation of Neuronal Firing Rate](#)

- [Significance Evaluation](#)
- [Surrogate Data for Evaluation of Spike Correlation](#)

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K

K-ATP Channels

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Kinetic Analysis for PET/SPECT Imaging

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Kinetic Models for PET/SPECT Imaging

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Synonyms

[Compartment model for nuclear medicine; Kinetic analysis for PET/SPECT imaging](#)

Definition

PET/SPECT is an *in vivo* imaging technique used to quantitate the biodistribution of specific molecules labeled with radioisotopes termed radiotracers, radiopharmaceuticals, or radioligands. A kinetic model is a mathematical expression of the kinetics of radiotracers between compartments, usually defined as the virtual chamber of organs/tissues or as states of the radiotracer. The influx or efflux rate of the radiotracer concentration between compartments is expressed as the product of the

concentration of the radiotracer and the transfer constant and is known as the rate constant. Applying the numerical time course of the radiotracer concentration, arranged by the kinetic model to measure the dynamic PET/SPECT images, the rate constant between compartments, or the combined rate constants can be mathematically estimated as a physiological function. These physiological parameters can be used to diagnose disease and to elucidate the physiology of the brain function.

Detailed Description

What Is a Kinetic Model?

In general, a kinetic model is a mathematical expression regarding the balance of molecules between compartments, which are defined as a virtual chamber for molecules. As shown in Fig. 1, we have assumed a very simple case; the membrane between two compartments A and B and the concentration of the specific molecules, C_A and C_B . If the radioactive molecules are assigned to compartment A at $t = 0$, C_B would

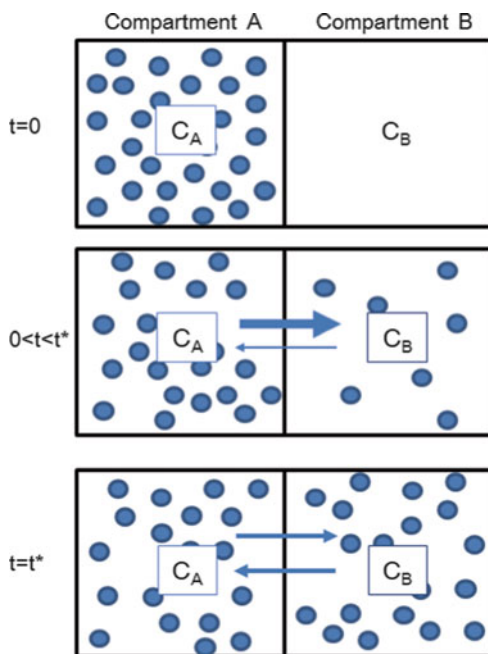
be zero at $t = 0$ and then gradually increase with passive diffusion or facilitated transportation; finally, C_A and C_B would reach an equilibrium condition at $t = t^*$. The influx of molecules into compartment B is given by the product of the concentration of molecules in A and the forward transfer constant k_1 ; the efflux of molecules from compartments B is given by the product of the concentration of molecules in B and the backward transfer constant k_2 , where these constants k_1 and k_2 are called the rate constant (expressed as units of 1/min). The time differentiation of C_B is expressed as the balance between the influx and the efflux as follows:

$$\frac{dC_B(t)}{dt} = k_1 C_A(t) - k_2 C_B(t)$$

This equation can be solved by means of the Laplace transform:

$$C_B(t) = k_1 C_A(t) \otimes \exp(-k_2 t),$$

where $\otimes$ represents the convolution integral. For PET/SPECT, a balance in the concentration of radiotracers between compartments is often assumed in this mathematical model. The compartment A in Fig. 1 is usually regarded as the arterial plasma, which is the supply source of the radiotracer that is taken up into the target organ or tissue. k_1 is often capitalized as K_1 to differentiate it from other rate constants. The unit used for K_1 is $\text{mL} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$. Because the affinities of the radiotracer for compartment A and compartment B are different, K_1 and k_2 are not identical. The ratio of K_1 to k_2 is called a partition coefficient, which suggests a relative distribution volume of the molecule in compartment B as compared with that in compartment A. This partition coefficient becomes an important parameter for the measurement of blood flow using diffusible radiotracers such as ^{133}Xe or H_2^{15}O , as mentioned later. Furthermore, compartment B is subdivided into two or three compartments, between which there is biological uptake/clearance or some other molecular transportation system involved. Then, the entire compartment model would be much more complicated (Phelps et al. 1979). Table 1 shows



Kinetic Models for PET/SPECT Imaging,
Fig. 1 Example of a simple compartment model

Kinetic Models for PET/SPECT Imaging, Table 1 Typical parameters used in the kinetic model for PET/SPECT imaging

Abbreviation	Description	Units
C_t	Concentration of radioactivity in the (target) tissue	$\text{Bq} \cdot \text{mL}^{-1}$
C_T	Measured concentration of radioactivity using PET/SPECT	$\text{Bq} \cdot \text{cm}^{-3}$
C_W	Concentration of radioactivity in the whole blood	$\text{Bq} \cdot \text{mL}^{-1}$
C_p	Concentration of radioactivity in the plasma	$\text{Bq} \cdot \text{mL}^{-1}$
C_a	Arterial input function	$\text{Bq} \cdot \text{mL}^{-1}$
f	Regional blood flow	$\text{mL} \cdot \text{min}^{-1} \cdot \text{cm}^{-3}$
p	Partition coefficient	$\text{mL} \cdot \text{cm}^{-3}$
P	Permeability	$\text{cm} \cdot \text{min}^{-1}$
S	Surface area per unit tissue volume	$\text{cm}^2 \cdot \text{cm}^{-3}$
V_B	Volume fraction of the arterial blood	Unitless
K_1	Rate constant for transfer from the arterial plasma to the tissue	$\text{mL} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$
k_2, k_3, k_4	Rate constants	min^{-1}
V_T	Volume of distribution expressed relative to total plasma ligand concentration C_p	$\text{mL} \cdot \text{cm}^{-3}$
BP	<i>In vitro</i> binding potential	
BP_{ND}	<i>In vivo</i> binding potential against nondisplaceable radiotracer	Unitless
B_{avail}	Density of available target molecule for binding radiotracer <i>in vivo</i> , similar concept as B_{max} <i>in vitro</i>	$\text{nmol} \cdot \text{L}^{-1}$
K_D	Dissociation constant of radiotracer to the molecules	$\text{nmol} \cdot \text{L}^{-1}$

typical parameters that are used in the kinetic model for PET/SPECT imaging.

(Meyer et al. 1984). Constant infusion was initially developed using the continuous inhalation of ^{15}O -labeled gaseous radiotracers (Jones et al. 1976).

Radiotracer Administration

Radiotracers for PET/SPECT studies are administered intravenously or by inhalation, pass through the lung and heart, and are delivered to the target organs by the arterial blood. Gaseous radiotracers (e.g., ^{15}O -labeled gas and ^{133}Xe) are administered by inhalation (Lassen et al. 1981; Jones et al. 1976). These inhaled radiotracers are exchanged by transporting across the alveoli in the lungs and are dissolved in the arterial blood in the lung. Nongaseous radiotracer administration is categorized into two types, namely, bolus injection and constant infusion. Bolus injection involves the administration of a single dose of radiotracer over a short period of time via a blood vessel. Constant infusion, taking into consideration the physical decay of the radioisotope and its biological clearance, achieves a steady-state condition ($dC/dt = 0$) in the target organ

Radiotracer in the Blood

A radiotracer, which will eventually be delivered to the target tissue, distributes in the arterial blood in several ways that include it being (i) freely diffusible between the plasma and blood cells, (ii) mostly soluble in the plasma while partially binding to the blood cells, or (iii) mostly soluble in the plasma while partially binding to the plasma proteins and blood cells. For example, H_2^{15}O freely mixes between the plasma and blood cells. The arterial radiotracer concentration in the whole blood, C_W , corresponds to the arterial input function, C_a (Herscovitch et al. 1983). In the case of a neuroreceptor PET/SPECT study, the administered radiotracer in the plasma is transferred across the blood–brain barrier (BBB) into the brain tissue (Seibyl et al. 1992), and the plasma

radioactivity concentration, C_p , corresponds to the arterial input function, C_a .

Radiotracer in the Tissue

After delivery to the target organ, a radiotracer's uptake or clearance behavior is dependent on its pharmacological or physiological properties. There are several types of uptake mechanisms, such as passive diffusion through the BBB, binding to specific molecules, and metabolic trapping. For example, diffusible radiotracers such as $H_2^{15}O$ exhibit passive diffusion from the artery to the tissue (Raichle et al. 1983). Radiotracers used to target neuroreceptors or for pathological imaging are designed to bind to specific target proteins (e.g., receptor, transporter, and plaque) (Wagner Jr 1986; Bacskai et al. 2002). The most popular radiotracer, ^{18}F -FDG, is metabolically trapped in the tissue by means of a metabolizing enzyme reaction (Reivich et al. 1979), while $[^{11}C]$ raclopride is the most common radiotracer to image dopamine D2/D3 receptors in the brain.

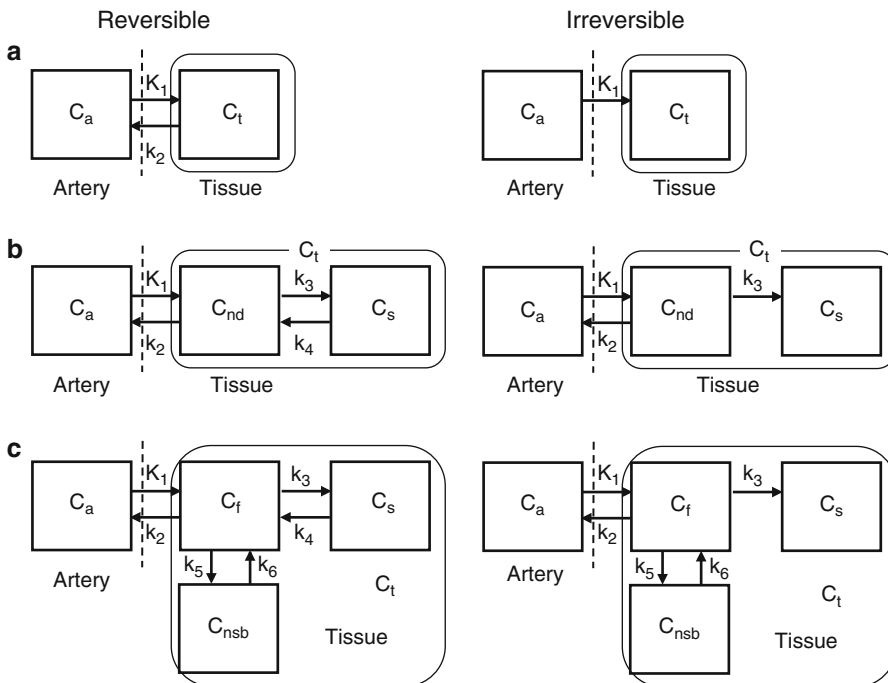
There are several types of clearance such as passive diffusion, unbinding, metabolic (enzyme reactions), and excretion. Furthermore, the property of the radiotracer that is dominant in the target organ during PET/SPECT scans, namely, uptake or clearance, really depends on the design of the compartment model; this includes whether or not the type of kinetics is reversible or irreversible (to the former compartment).

Compartment Models for PET/SPECT

On the assumption that the model can also be simplified in terms of physiological or pharmacological processes, several mathematical compartment models have been proposed and used clinically (Watabe et al. 2006; Schmidt and Turkheimer 2002; Heiss and Herholz 2006).

1-Tissue 2 Compartment Model (1T2CM)

This model, which is shown in Fig. 2a, is the simplest model and involves two parameters; K_1 [$mL \cdot cm^{-3} \cdot min^{-1}$] is a rate constant for the transfer of



Kinetic Models for PET/SPECT Imaging, Fig. 2 Examples of reversible and irreversible compartment models for the human body. (a) 1T2CM, (b) 2T3CM, and (c) 3T4CM

radiotracer from the arterial plasma to the tissue, and k_2 [min^{-1}] is a rate constant for the transfer of radiotracer in the reverse direction. It should be noted that if the model can be regarded as an irreversible type, k_2 can be negligible in the microsphere model (1T2CM) (Kuhl et al. 1982). C_a [$\text{Bq} \cdot \text{ml}^{-1}$] is the so-called arterial input function, and C_t [$\text{Bq} \cdot \text{cm}^{-3}$] is the radioactivity concentration in an organ/tissue. The time differentiation of C_t is expressed as the balance between influx and efflux, and this equation can be solved as mentioned above.

$$\begin{aligned}\frac{dC_t(t)}{dt} &= K_1 C_a(t) - k_2 C_t(t) \\ C_t(t) &= K_1 C_a(t) \otimes \exp(-k_2 t)\end{aligned}$$

The physiological definition of K_1 is often regarded as being “regional blood flow”; however, first-pass extraction, E , of the tracer into the target tissue affects the relationship between the regional blood flow f and K_1 (Ishizu et al. 1996). K_1 is calculated as follows:

$$K_1 = f \cdot E = f \cdot \left(1 - e^{-\frac{PS}{f}}\right),$$

where P is the permeability of the radiotracer across the capillary membrane and S is the capillary surface area per unit volume of the tissue. The equation for the extraction is known as the Renkin-Crone model, in which it is assumed that the capillary is a rigid cylindrical tube (Renkin 1959; Crone 1963). If the product of P and S is large, such as in the case of H_2^{15}O , E becomes almost unity and K_1 can be regarded as f . Furthermore, if the radiotracer only distributes through passive diffusion, the efflux (clearance from the tissue to the blood) would be proportional to the influx divided by the tissue/blood partition coefficient of the radiotracer p :

$$\frac{dC_t(t)}{dt} = K_1 C_a(t) - \frac{K_1}{p} C_t(t)$$

Then, the 1T2CM can be arranged according to the following equation:

$$C_t(t) = K_1 C_a(t) \otimes \exp\left(-\frac{K_1}{p} t\right)$$

If p can be assumed a constant, the above equation has only one parameter of K_1 to be solved.

2-Tissue 3 Compartment Model (2T3CM)

This model has four parameters, namely, K_1 [$\text{mL} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$], k_2 , k_3 , and k_4 [min^{-1}]. If k_4 is negligible in the 2T3CM, the model can be one of the irreversible types as shown in Fig. 2b. Two compartments in the tissue express two different statuses of the radiotracer concentration of the nondisplaceable (C_{nd} [$\text{Bq} \cdot \text{cm}^{-3}$]) and specific compartments (C_s [$\text{Bq} \cdot \text{cm}^{-3}$]). The $C_s(t)$ compartment represents radiotracer that is specifically bound to the target molecules and is usually the compartment of interest to be observed. The $C_{nd}(t)$ compartment includes free and non-specifically bound radiotracer. Exchanges of radiotracer concentration between compartments are governed by simple linear differential equations:

$$\begin{aligned}\frac{dC_{us}(t)}{dt} &= K_1 C_a(t) - (k_2 + k_3) C_{nd}(t) + k_4 C_s(t) \\ \frac{dC_s(t)}{dt} &= k_3 C_{nd}(t) - k_4 C_s(t)\end{aligned}$$

Total radioactivity concentration C_t [$\text{Bq} \cdot \text{cm}^{-3}$] is expressed as the summation of two compartments as follows:

$$\begin{aligned}C_t(t) &= C_{nd}(t) + C_s(t) \\ C_t(t) &= \frac{K_1}{\alpha_1 - \alpha_2} \{(\alpha_1 - k_3 - k_4)e^{-\alpha_1 t} - (\alpha_2 - k_3 - k_4)e^{-\alpha_2 t}\} \otimes C_a(t). \\ \alpha_{1,2} &= \frac{k_2 + k_3 + k_4 \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}}{2}\end{aligned}$$

3-Tissue 4 Compartment Model (3T4CM)

This is a more complicated model involving six parameters, namely, K_1 [$\text{mL} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$], k_2 , k_3 , k_4 , k_5 , and k_6 [min^{-1}]. The combination of these six parameters is very flexible in designing the model, and an example of a 3T4CM is shown in Fig. 2c. In this figure, the nonspecific compartment C_{ns} in the tissue is divided into two statuses, free and nonspecific binding (C_f and C_{nsb} , respectively). Differential equations for each of the concentrations $C_s(t)$, $C_f(t)$, and $C_{nsb}(t)$ are shown below.

$$\begin{aligned}
\frac{dC_s(t)}{dt} &= k_3 C_f(t) - k_4 C_s(t) \\
\frac{dC_f(t)}{dt} &= K_1 C_a(t) + k_6 C_{nsb}(t) + k_4 C_s(t) \\
&\quad - (k_2 + k_3 + k_4) C_f(t) \\
\frac{dC_{usb}(t)}{dt} &= k_5 C_f(t) - k_5 C_{nsb}(t) \\
C_t(t) &= C_f(t) + C_s(t) + C_{nsb}(t)
\end{aligned}$$

There is an analytical solution for the 3T4CM, but its estimates become practically unstable with noisy data. Instead, some simplification, in other words a reduction in the number of compartments by combining relatively similar compartments to each other (e.g., C_f and C_{nsb}), will help in solving the model parameters (refer to the simplified reference tissue model for PET receptor studies (SRTM) developed by Lammertsma and Hume (1996)).

Estimation of Model Parameters

Blood Volume Component

The use of a kinetic model together with the time course of change in the radioactivity concentration $C_t(t)$ allows us to estimate detailed physiological parameters. To measure $C_t(t)$ in the target, PET/SPECT dynamic data sets, which are a series of discrete time-related data points, are acquired for 1–2 h or more in cases where the tracer has a longer biological or physical half-life. Strictly speaking, the measured radioactivity concentration in the corresponding region of the tissue $C_T(t)$ [Bq · cm⁻³] is not equal to the previously defined radio-tracer concentration, $C_t(t)$ [Bq · mL⁻¹], and there is a relationship between $C_T(t)$ and $C_t(t)$:

$$C_T(t) = (1 - V_B)C_t(t) + \rho \cdot V_B C_W(t),$$

where V_B is the fraction of the measured volume occupied by the blood, ρ [mL · cm⁻³] is the density of the tissue, and $C_W(t)$ is the radioactive concentration in the whole arterial blood. Because the brain tissue usually has a small fraction of its volume occupied by the blood (about 5%) (Leenders et al. 1990), the influence of the blood volume parameter is not so large. However, if V_B is large, such as in the renal tissue where it is about

15 % (Kudomi et al. 2009), $C_T(t)$ must be considered to include the V_B parameter.

Nonlinear Least Square Fitting

For estimation of parameters in the model from the measured PET/SPECT dynamic data, the nonlinear least square (NLLS) fitting technique (implemented with a modified Marquardt algorithm (More 1978) or simplex algorithm (Nelder and Mead 1965)) is often used while searching the minimum summed residuals S between measured and modeled time-activity curves (TACs). S is calculated as follows:

$$\begin{aligned}
S &= \sum_t w(t) \{C_T(t) - [(1 - V_B)C_t(t) + \rho V_B C_a(t)]\}^2 \\
(K_1, k_2, \dots, V_B) &= \arg \min (S),
\end{aligned}$$

where $w(t)$ is the weighting factor for the residuals and is often set to 1. However, in the case of a steep TAC or a short half-life radioisotope such as ¹¹C ($T_{1/2} = 20$ min), it is sometimes necessary to adjust the $w(t)$ values such as (frame duration)²/(total counts) (Gunn et al. 1998).

In fitting parameters using the NLLS technique, there are sometimes circumstances in which many solutions for the estimated parameters exist. To avoid convergence to a local minimum (i.e., not the correct estimations), the initial values for the estimated parameters are very important. The estimates obtained from NLLS fitting fluctuate unstably because of statistical noise regarding the measured $C_T(t)$. Therefore, an initial value at a specific $C_T(t)$ is often set to the first $C_T(t)$ estimate for the averaged surrounding regions with less noise than the specific $C_T(t)$. The disadvantage of NLLS fitting is the long computing time required. This disadvantage is significant in the case of voxel-by-voxel estimation, but not in the case of region-of-interest estimation.

Selection of the Compartment Model

In some cases, it is not clear if the 1T2CM or 2T3CM is better adapted to the measured $C_T(t)$. To select which model would be better, statistical tests such as the F test, Akaike's information criterion (AIC), or Schwarz criterion are

performed. AIC (Akaike 1987) is defined as follows:

$$\text{AIC} = n \ln S + 2m,$$

where n is the number of time frames, S is the residual of the fitting procedure, and m is the number of estimates. The preferred model gives the minimum AIC value.

Distribution Volume

In solving the compartment model, the smallest element to be determined is the k parameter. However, if the number of k parameters is increased, the estimated parameters become unstable and variable; in addition, a lengthy calculation time is required for large iterative processes. Therefore, compartment modeling in PET/SPECT often uses combined parameters rather than the individual k parameters themselves.

The distribution volume is one of the most frequently used combined parameters. The basic concept behind it originated from the volume of distribution of the pharmacokinetics, that is, an apparent plasma volume which is equivalent to the administered dose to be evaluated. This concept is widely adopted in the field of *in vivo* radio-tracer imaging. Instead of referring to the total administrated dose in the entire body, the distribution volume (V_T) is expressed as the activity of radiotracer in the tissue as follows:

$$V_T = \frac{C_T}{C_a} = \sum_i V_i = \sum_i \frac{C_{Ti}}{C_a},$$

where C_{Ti} and V_i are the radioactivity concentrations and the distribution volume under specific condition i in the tissue. An important assumption here is that the radioactive concentration in V_T must satisfy the equilibrium condition. However, it is practically difficult to achieve complete equilibrium because of the total loss from an open system, where radiotracer gradually flows out. In the case of exchange between compartments in neuroreceptor studies, the term “transient equilibrium,” where the maximum turning point in radioactivity concentration occurs, is used (Ito et al. 1998; Farde et al. 1989).

Binding Potential

The binding potential (BP) is one of the most frequently used combined parameters. BP represents the ability of a radiotracer to bind to specific target molecules. Binding ability depends on both the density of the available target molecule (B_{avail}) and the affinity of the radiotracer for the molecule ($1/K_D$) (Innis et al. 2007). Instead of estimating and handling B_{avail} and $1/K_D$ individually, it is convenient to use a combined parameter such as BP . For the reversible 2T3CM, BP usually represents BP_{ND} , which is the binding potential regarding a nondisplaceable radiotracer (Innis et al. 2007) and can also be expressed by the ratio of distribution volumes as follows:

$$BP_{\text{ND}} = \frac{V_s}{V_{\text{nd}}} = \frac{(V_1 - V_{\text{nd}})}{V_{\text{nd}}} = \frac{V_T}{V_{\text{nd}}} - 1$$

If the BP_{ND} is high, the radiotracer can be regarded as having a good signal-to-noise property for quantitating/visualizing the target-to-background tissue contrast. The distribution volume of each compartment can be calculated by combining the rate constants. For example, in the reversible 2T3CM, assuming that both C_{nd} and C_s simultaneously reach an equilibrium, differentiations of dC_{nd}/dt and dC_s/dt become zero as follows:

$$\begin{aligned} \frac{dC_{\text{nd}}(t)}{dt} &= K_1 C_a(t) - (k_2 + k_3) C_{\text{nd}}(t) + k_4 C_s(t) \\ &= 0 \\ \frac{dC_s(t)}{dt} &= k_3 C_{\text{nd}}(t) - k_4 C_s(t) = 0 \end{aligned}$$

After arrangement of these equations, the distribution volumes as an expression of the rate constant are as follows:

$$\begin{aligned} V_{\text{nd}} &= \frac{C_{\text{nd}}}{C_a} = \frac{K_1}{k_2} \\ V_s &= \frac{C_s}{C_a} = \frac{K_1}{k_2} \cdot \frac{k_3}{k_4} \\ V_T &= V_{\text{nd}} + V_s = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_3}{k_4}\right) \end{aligned}$$

Therefore, the BP_{ND} can be rewritten as follows:

$$BP_{ND} = \frac{k_3}{k_4}$$

In clinical situation, BP_{ND} is useful outcome measure, and its determination has been investigated for each radiotracer. For imaging of the most common radiotracer in neuroreceptor, [^{11}C] raclopride, it is well known that BP_{ND} is quantitatively estimated using the SRTM (Lammertsma and Hume 1996). However, in some cases (such as translocator protein (TSPO) imaging), kinetic property of the radiotracer is much more complicated than [^{11}C] raclopride due to low specific/nonspecific binding ratio and no apparent reference tissue region, and it is usually difficult how to optimize the estimation (Ikoma et al. 2007).

Graphical Plot

Instead of the estimation of NLLS as one of the alternative estimation processes, graphical analysis or a “graphical plot” is often used to shorten the computing time. This graphical plot is very useful not only because of the rapid calculation time but also because of the stability of the estimates (Yokoi et al. 1993; Patlak et al. 1983; Logan et al. 1990). For example, the time-differential equation in the 1T2CM is integrated from time zero to time t and then divided by the integration of the arterial input function as follows (van den Hoff et al. 1993).

$$\frac{C_t(t)}{\int_0^t C_a(\tau) d\tau} = K_1 - k_2 \frac{\int_0^t C_t(\tau) d\tau}{\int_0^t C_a(\tau) d\tau}$$

The formula can be regarded as $Y = K_1 - k_2 \cdot X$, where X and Y vary with t . So a plot of Y against X should give a straight line with gradient k_2 and intercept K_1 . Once the observed $C_t(t)$ can be adapted to this linearization, both K_1 and k_2 can be uniquely estimated, with a shorter calculation time than that required for the estimation of the NLLS.

Furthermore, in the irreversible 2T3CM, the Gjedde-Patlak plot can be used as a graphical plot. Its formula is as follows (Patlak et al. 1983).

$$\frac{C_T(t)}{C_a(t)} = \frac{K_1 k_3}{k_2 + k_3} \frac{\int_0^t C_a(u) du}{C_a(t)} + bt \geq t^*,$$

where the gradient, $K_1 k_3 / (k_2 + k_3)$, is used to estimate the cerebral metabolic rate of glucose (CMRglu) in the FDG-PET study. CMRglu is calculated as follows:

$$\text{CMRgluc} = \frac{K_1 k_3}{k_2 + k_3} \cdot \frac{C_p}{LC},$$

where C_p is the arterial plasma glucose concentration and LC is the lumped constant, which is used to convert the $K_1 k_3 / (k_2 + k_3)$ of FDG to the glucose concentration. For the 1T2CM or 2T3CM reversible compartment models, Logan graphical analysis (the so-called Logan plot) is often used, and its formula is as follows:

$$\frac{\int_0^t C_T(u) du}{C_T(t)} = V_T \frac{\int_0^t C_a(u) du}{C_T(t)} + bt \geq t^*,$$

where V_T is the distribution volume. Figure 3 also shows a schematic of the Logan plot. Once $C_t(t)$ and $C_a(t)$ (Fig. 3a, b) are converted (Fig. 3c), the slope of the fitted line from $t^* < t$, V_T can be easily estimated.

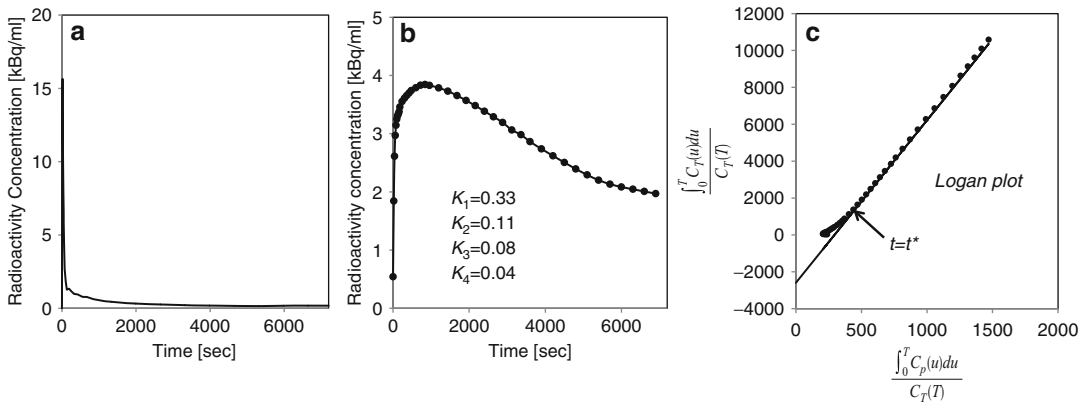
Another approach consists of rearranging the Logan plot equation into a multilinear form to give the following formula (Ichise et al. 2002).

$$C_T(t) = \beta_1 \int_0^t C_a(u) du + \beta_2 \int_0^t C_T(u) du \geq t^*,$$

where $\beta_1 = -V_T/b$ and $\beta_2 = 1/b$ are estimated by linear regression analysis of $t \geq t^*$ and V_T is calculated as $-\beta_1/\beta_2$. This approach is usually called multilinear analysis.

Estimation of Arterial Input Function

In general, a kinetic model requires an arterial input function (C_a). To avoid invasiveness, the arterial input function is derived not only from blood sampling but also from image-based estimation. If the heart cavity (left ventricle) is scanned and imaged simultaneously with the



Kinetic Models for PET/SPECT Imaging, Fig. 3 Examples of graphical analysis of the PET/SPECT data sets. (a) arterial input function (C_a); (b) tissue time-

activity curve (C_T) generated using the 2T3CM model with $K_1 = 0.33$, $k_2 = 0.11$, $k_3 = 0.08$, $k_4 = 0.04$, and $V_B = 0$; (c) implementation of the Logan plot with t^*

target organ/tissue, the arterial input function can be directly derived from dynamic images (Watabe et al. 2005; Iida et al. 1998). Alternatively, the input function can be extracted as a component by means of image processing of dynamic images (Zanotti-Fregonara et al. 2012; Wu et al. 1995; Schain et al. 2013; Qiu et al. 2009; Naganawa et al. 2005, 2008; Jiao et al. 2013). However, in cases where there is a requirement for the separation of the plasma radioactivity concentration $C_p(t)$ from that of the whole blood, it is impossible to extract the input function from PET/SPECT images.

Simplification of the Model

In some applications for receptor studies, the arterial input function can be replaced by a reference tissue devoid of specific binding sites. A typical derivation of such a noninvasive technique is the SRTM (Lammertsma and Hume 1996), reference Logan plot (Logan et al. 1996), and multilinear reference tissue model (MRTM) (Ichise et al. 2003).

The SRTM yields the binding potential value by replacing the arterial input function arithmetically from model equations by TAC for the reference region, where specific bindings are negligible; it is assumed that the distribution volume of the nondisplaceable compartment is equal in the target and reference regions and that a target

region can be described using the reversible one-tissue compartment model.

$$C_T(t) = R_1 \cdot C_R(t) + \left(k_2 - \frac{R_1 k_2}{1 + BP_{ND}} \right) \cdot e \left(- \frac{k_2}{1 + BP_{ND}} t \right) \otimes C_R(t),$$

$$R_1 = K_1 / K_1^r$$

where C_T and C_R are the radioactivity concentrations in the target and reference regions, respectively. The SRTM estimates three parameters, namely, the delivery ratio of the target region to the reference region (R_1), the clearance rate constant for the target region (k_2), and the binding potential referred to as BP_{ND} using the NLLS technique. In the case of a voxel-by-voxel estimation, the basis function method that prepares a considerable number of TACs in advance is often used (Gunn et al. 1997).

The reference Logan plot is a linear regression method that is used for the estimation of the binding potential while using the TAC from a reference region instead of the arterial input function.

$$\frac{\int_0^t C_T(u) du}{C_T(t)} = \text{DVR} \cdot \frac{\int_0^t C_R(u) du}{C_T(t)} + bt \geq t^*,$$

$$\text{DVR} = \frac{V_T}{V_{Tr}} = 1 + BP_{ND}$$

where DVR is the ratio of the distribution volumes in the target (V_T) and the reference region (V_{Tr}).

Because V_{Tr} can be regarded as V_{nd} (described in section "Binding Potential") (DVR-1) would be the estimates of the binding potential.

The MRTM also yields the binding potential value using a TAC from the reference region as follows:

$$C_T(t) = \gamma_1 \int_0^t C_R(u) du + \gamma_2 \int_0^t C_T(u) du - \gamma_3 t \geq t^*$$

$$\gamma_1 = -\frac{V_T}{V_{Tr}b}$$

$$\gamma_2 = \frac{1}{b}$$

$$\gamma_3 = -\frac{V_T}{V_{Tr}k_{2r}b},$$

where k_{2r} is the clearance rate constant for the reference region n and γ_1 , γ_2 , and γ_3 are estimated using linear regression analysis for $t \geq t^*$. BP_{ND} can be calculated from the ratio of the two regression coefficients as $BP_{ND} = -(\gamma_1/\gamma_2 + 1)$. Furthermore, if k_{2r} is fixed in the MRTM (termed the MRTM2), the number of the estimates can be reduced from three to two, and a more robust estimation of BP_{ND} can be obtained.

Although these approaches have several advantages such as noninvasiveness over the method requiring an arterial input function, several assumptions are associated with the simplified technique, and caution is mandatory for its use.

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Kinetic Models of Postsynaptic Currents

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Definition

Modeling synaptic currents and conductances is a central aspect of network simulations. The type of model for synaptic currents depends on the receptor type present in the synapse, as well as if one needs to include mechanisms such as the saturation of successive synaptic events and synaptic depression or facilitation. Kinetic models can provide a way to model these interactions in a compact form and can be analytic in some cases, leading to very fast algorithms to simulate synaptic interactions.

Detailed Description

Introduction

Synaptic currents and conductances represent the most common type of interaction between neurons, and they must be simulated in neuronal networks using the most efficient model as possible. It was shown previously that simplified

two-state kinetic models can be used to simulate postsynaptic currents with a reasonable degree of accuracy (Destexhe et al. 1994a, 1998), as an alternative to the more complex Markov models. This approach is similar in spirit to the classic Hodgkin and Huxley (1952) model of action potentials, in which the voltage-dependent currents are also described by two-state kinetic models (reviewed in Destexhe et al. 1994b). We overview here these kinetic models and their fitting to experimental recordings.

Two-State Kinetic Models

The essential properties of ion channel activation can be captured by simplified kinetic models with just two states. The simplest kinetic models for the gating of different classes of ion channels are illustrated in Table 1. For synaptic currents (Destexhe et al. 1994a, 1998), as for voltage-dependent currents (Destexhe et al. 1994b), simplified kinetic models provide an efficient way to incorporate their basic properties, such as the time course of rise and decay and their summation

Kinetic Models of Postsynaptic Currents, Table 1 Two-state kinetic models of different classes of ion channels. *Voltage-dependent channels*: the channel is assumed to have opened (O) and closed (C) states modulated by voltage-dependent transition rates (α and β). *Calcium-dependent channels*: in this case, the opening of the channel depends on the binding of one or several intracellular Ca^{2+} ions (Ca_i). *Transmitter-gated channels*: molecules of neurotransmitter (T) are released transiently and bind to the channel, leading to its opening. *Second messenger-gated channels*: in this case, the opening of the channel is provided by the binding of one or several intracellular second messengers (G). Kinetic equations allow to describe all these processes, which underlie electrophysiological properties and synaptic interactions, using the same formalism (Destexhe et al. 1994b)

Voltage-dependent gating (Hodgkin-Huxley)	$C \xrightleftharpoons[\beta(V)]{\alpha(V)} O$
Calcium-dependent gating	$C + n \text{Ca}_i \xrightleftharpoons[\beta]{\alpha} O$
Transmitter gating	$C + n T \xrightleftharpoons[\beta]{\alpha} O$
Second messenger gating	$C + n G \xrightleftharpoons[\beta]{\alpha} O$

behavior, in simulations that do not require a great level of detail. Typical examples of this kind are simulations of networks of neurons where the most salient features of ion channel interactions must be represented with maximal computational efficiency.

In synaptic currents, however, one must specify the time course of the transmitter concentration (T in Table 1). The simple model for transmitter time course is a square pulse, based on experiments in excised membrane patches which showed that 1 ms pulses of 1 mM glutamate reproduced PSCs that were quite similar to those recorded in the intact synapse (Hestrin 1992; Colquhoun et al. 1992; Standley et al. 1993). The simplest model is to assume that the transmitter, either glutamate or GABA, is released according to a pulse when an action potential invades the presynaptic terminal. Then, a two-state (open/closed) kinetic scheme (as in Table 1), combined with such a pulse of transmitter, can be solved analytically (Destexhe et al. 1994a). The same approach also yields simplified algorithms for three-state and higher schemes (Destexhe et al. 1994b). As a consequence, extremely fast algorithms can be used to simulate most types of synaptic receptors because no differential equation must be solved for synaptic currents (Destexhe et al. 1994a).

AMPA-Kainate Receptors The simplest model that approximates the kinetics of the fast AMPA/kainate type of glutamate receptors can be represented by the two-state diagram:



where α and β are voltage-independent forward and backward rate constants. If r is defined as the fraction of the receptors in the open state, it is then described by the following first-order kinetic equation:

$$\frac{dr}{dt} = \alpha[T] (1 - r) - \beta r, \quad (2)$$

and the postsynaptic current I_{AMPA} is given by:

$$I_{AMPA} = \dot{g}_{AMPA} r(V - E_{AMPA}), \quad (3)$$

where $\bar{g}_{AMPA}$ is the maximal conductance, E_{AMPA} is the reversal potential, and V is the postsynaptic membrane potential.

The best fit of this kinetic scheme to whole-cell recorded AMPA/kainate currents (Fig. 1a) gave $\alpha = 1.1 \times 10^6 M^{-1}s^{-1}$ and $\beta = 190 s^{-1}$ with $E_{AMPA} = 0 mV$ (Destexhe et al. 1998).

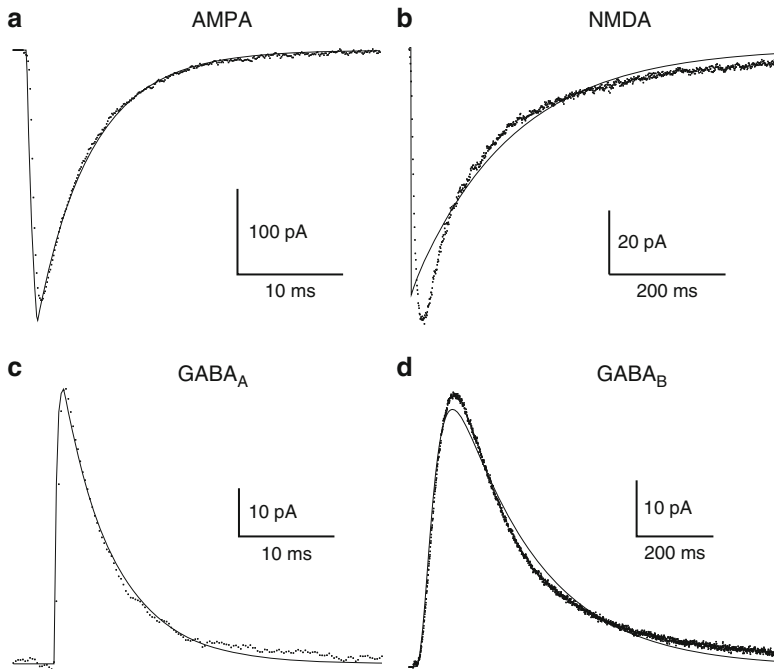
NMDA Receptors A unique property of NMDA receptors is that they are voltage dependent and activate only for depolarized membrane potentials. The activation properties NMDA-mediated postsynaptic currents can be represented with a two-state model similar to AMPA/kainate receptors, with a slower time course and a voltage-dependent term. The voltage dependence of NMDA receptor channels is due to its sensitivity to block by physiological concentrations of Mg^{2+}

(Nowak et al. 1984; Jahr and Stevens 1990a, b). The Mg^{2+} block is voltage dependent, allowing NMDA receptor channels to conduct ions only when depolarized. The necessity of both presynaptic and postsynaptic gating conditions (presynaptic neurotransmitter and postsynaptic depolarization) makes the NMDA receptor a molecular coincidence detector. Furthermore, NMDA currents are carried partly by Ca^{2+} ions, which may also play a role in triggering intracellular biochemical cascades.

Using the same scheme as Eqs. 1 and 2, the postsynaptic current is given by:

$$I_{NMDA} = \dot{g}_{NMDA} B(V) r(V - E_{NMDA}), \quad (4)$$

where $\bar{g}_{NMDA}$ is the maximal conductance, E_{NMDA} is the reversal potential, and $B(V)$ represents the magnesium block of the channel. The magnesium block of the NMDA receptor channel is an



Kinetic Models of Postsynaptic Currents, Fig. 1 Best fits of simplified kinetic models to averaged postsynaptic currents obtained from whole-cell recordings. (a). AMPA/kainate-mediated currents (Obtained from Xiang et al. (1992); recorded at 31 °C). (b). NMDA-mediated currents (Obtained from Hessler et al. (1993); recorded at 22–25 °C in Mg^{2+} -free solution). (c). $GABA_A$ -mediated currents.

(d). $GABA_B$ -mediated currents (c–d recorded at 33–35 °C by Otis et al. 1992, 1993). For all graphs, the averaged recording of the synaptic current (noisy trace) is represented with the best fit obtained using the models (continuous trace). Transmitter time course was a pulse of 1 mM and 1 ms duration in all cases (a–d: Modified from Destexhe et al. (1994b, 1996, 1998))

extremely fast process compared to the other kinetics of the receptor (Jahr and Stevens 1990a, b). The block can therefore be accurately modeled as an instantaneous function of voltage (Jahr and Stevens 1990b):

$$B(V) = \frac{1}{1 + \exp(-0.062 V) [\text{Mg}^{2+}]_o / 3.57}, \quad (5)$$

where $[\text{Mg}^{2+}]_o$ is the external magnesium concentration (1–2 mM in physiological conditions).

The best fit of this kinetic scheme to whole-cell recorded NMDA currents (Fig. 1b) gave $\alpha = 7.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and $\beta = 6.6 \text{ s}^{-1}$ with $E_{\text{NMDA}} = 0 \text{ mV}$ (Destexhe et al. 1998).

GABA_A Receptors GABA_A receptors can also be represented by the scheme in Eqs. 1 and 2, with the postsynaptic current given by:

$$I_{\text{GABA}_A} = \dot{g}_{\text{GABA}_A} r (V - E_{\text{GABA}_A}), \quad (6)$$

where $\dot{g}_{\text{GABA}_A}$ is the maximal conductance and E_{GABA_A} is the reversal potential.

The best fit of this kinetic scheme to whole-cell recorded GABA_A currents (Fig. 1c) gave $\alpha = 5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $\beta = 180 \text{ s}^{-1}$ with $E_{\text{GABA}_A} = -80 \text{ mV}$ (Destexhe et al. 1998).

GABA_B Receptors and Neuromodulators In the three types of synaptic receptors discussed above, the receptor and ion channel are both part of the same protein complex, and these receptors are called “ionotropic.” In contrast, other classes of synaptic response are mediated by an ion channel that is not directly coupled to a receptor but rather is activated (or deactivated) by an intracellular “second messenger” that is produced when neurotransmitter binds to a separate receptor molecule. These so-called “metabotropic” synaptic responses generally affect K^+ channels but can also affect other channels or biochemical processes. This is the case for GABA_B receptors, whose response is mediated by K^+ channels that are activated by G-proteins (Dutar and Nicoll 1988).

One of the fundamental properties of GABA_B receptors is that they are strongly dependent on the pattern of presynaptic spikes. There are no GABA_B-mediated responses for single or isolated presynaptic spikes, but GABA_B responses appear with intense presynaptic activity such as typically with bursts of presynaptic spikes (Dutar and Nicoll 1988; Davies et al. 1990; Kim et al. 1997). It was shown that such properties can be due to nonlinear properties in the activation kinetics of these receptors (Destexhe and Sejnowski 1995), a hypothesis which was later confirmed by paired recordings of neurons connected with GABA_B receptors (Kim et al. 1997; Thomson and Destexhe 1999).

These nonlinear activation properties of GABA_B responses, unfortunately, cannot be handled correctly by a two-state model. The simplest model of GABA_B-mediated currents has two variables and was obtained from a more complex model (Destexhe and Sejnowski 1995) and is given by:

$$\begin{aligned} \frac{dr}{dt} &= K_1 [T] (1 - r) - K_2 r \\ \frac{ds}{dt} &= K_3 r - K_4 s, \\ I_{\text{GABA}_B} &= \dot{g}_{\text{GABA}_B} \frac{s^n}{s^n + K_d} (V - E_K) \end{aligned} \quad (7)$$

where r is the fraction of receptor in the activated (transmitter-bound) state, s is the second messenger (G-protein) concentration, $\dot{g}_{\text{GABA}_B} = 1 \text{ nS}$ is the maximal conductance of K^+ channels, $E_K = -95 \text{ mV}$ is the potassium reversal potential, and $K_1 \dots K_4$ are rate constants. Fitting of this model to whole-cell recorded GABA_B currents (Fig. 1d) gave the following values: $K_d = 100 \text{ } \mu\text{M}^4$, $K_1 = 9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $K_2 = 1.2 \text{ s}^{-1}$, $K_3 = 180 \text{ s}^{-1}$, and $K_4 = 34 \text{ s}^{-1}$ with $n = 4$ binding sites (Destexhe et al. 1998). This model was found to correctly capture the dynamical properties of GABA_B responses in thalamic slices (see Destexhe et al. 1996).

Many other types of neurotransmitters are involved in metabotropic responses on specific receptor types. This is the case for glutamate (through metabotropic receptors), acetylcholine

(through muscarinic receptors), noradrenaline, serotonin, dopamine, histamine, opioids, and others. These neurotransmitter systems have been shown to mediate slow intracellular responses via the intracellular activation of G-proteins, which may affect ionic currents as well as the metabolism of the cell. As with GABA acting on GABA_B receptors, the main electrophysiological target of many neuromodulators is to open or close K⁺ channels (reviewed in McCormick 1992). The model of GABA_B responses outlined above could thus be used to model these currents, with rate constants adjusted to fit the time courses reported for the particular responses (see details in Destexhe et al. 1994b).

Discussion

In this chapter, we reviewed simple models for the main types of synaptic receptors found in the nervous system, namely, the glutamate AMPA and NMDA receptors and the GABAergic GABA_A and GABA_B receptors. It is important to keep in mind that the models shown here are among the simplest models that capture the time course and kinetics of these synaptic receptors, while there exist a wide variety of more complex models (see Destexhe et al. 1998 for an overview of simple and complex models). The main target of simple kinetic models is to be included in network simulations, where computational efficiency is an essential concern. With pulses of transmitted, it is possible to solve these models and obtain an analytic expression for the postsynaptic conductance (Destexhe et al. 1994a). These models are therefore very fast to simulate since no differential equation must be added to model synaptic interactions.

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Further Reading

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Koch C, Segev I (eds) (1988) *Methods in neuronal modeling*, 2nd edn. MIT Press, Cambridge, MA

(Kinetic or Continuum) Electrodiffusion Equation

► [Nernst-Planck Equation](#)

Kinetic Schemes

► [Markov Models of Ion Channels](#)

Kir Channels

► [Inward Rectifier Potassium Channels](#)

K-Set Hierarchy

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Large-Scale Models of the OB

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Large-Scale Models of the Olfactory Bulb

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Synonyms

[Deep short-axon cells](#); [Feedforward inhibition](#); [Glomerular layer](#); [Granule cells](#); [Large-scale models of the OB](#); [Lateral inhibition](#); [Mitral cells](#); [Odor learning](#); [Odor processing](#); [Periglomerular cells](#); [Tufted cells](#)

Definition

The olfactory bulb (OB) is a small, self-contained system that is pivotally involved in generating the

sense of the smell. Large-scale models of the olfactory bulb reconstruct extensive portions of it, including the main neuron populations (i.e., mitral, tufted, and granule cells), along with their connectivity and glomerular organization. Large-scale models of the OB therefore comprise of three components: (i) a model of odor inputs, (ii) cell models of the main neuron classes, and (iii) computational models of feedforward and/or feedback inhibition.

Detailed Description

Analyses of large portions of the olfactory bulb (OB) are the key to understand odor processing. In the OB, odor-specific spatiotemporal patterns characterize odor response (Abraham et al. 2004; Niessing and Friedrich 2010; Vincis et al. 2012), sculpted by long-range inhibitory interactions among mitral and tufted cells (Yokoi et al. 1995; Aungst et al. 2003). In computational terms, these inhibitory interactions can be characterized in feedforward and lateral inhibition (Cavarretta et al. 2016, 2018), mediated via glomerular (GL) and granule cell (GCL) layers, respectively (Cavarretta et al. 2016, 2018). In particular, the lateral inhibition is driven by clusters of odor-responsive mitral and tufted cells (Yokoi et al. 1995), which are organized in glomerular units (GUs) (Migliore et al. 2015; Cavarretta et al. 2016, 2018).

The existing experimental protocols are not the right methods for extensive analyses of the OB. On the one hand, the scope of the electrophysiological studies is limited to small neuron set (Shusterman et al. 2011; Smear et al. 2011). On the other hand, imaging techniques enable the visualization of neuron signals over large areas of the OB but not to identify these signals at the cellular level (Abraham et al. 2004; Niessing and Friedrich 2010; Vincis et al. 2012). In the last decades, the intrinsic limitations of the experimental protocols have been overridden by large-scale computational modeling. Different models of the OB have been developed with different paradigms, reproducing specific aspects of the real system. Here we have discussed the most recent large-scale models of the OB (Yu et al. 2013; Li and Cleland 2013; Polese et al. 2014; Gilra and Bhalla 2015; Cavarretta et al. 2018), with focus on the first three-dimensional large-scale model of the OB (Cavarretta et al. 2018).

The Large-Scale Three-Dimensional Model of the Olfactory Bulb

The three-dimensional model of the OB consists of a digital reconstruction of about 10% of the real system (127 glomeruli) that replicates the physiological properties of the two largest populations of glutamatergic neurons, mitral (MC) and middle-tufted (mTC) cells, and the inhibitory circuitry in GL and GCL, along with their connectivity and glomerular organization (Fig. 1) (Migliore et al. 2014; Cavarretta et al. 2016, 2018).

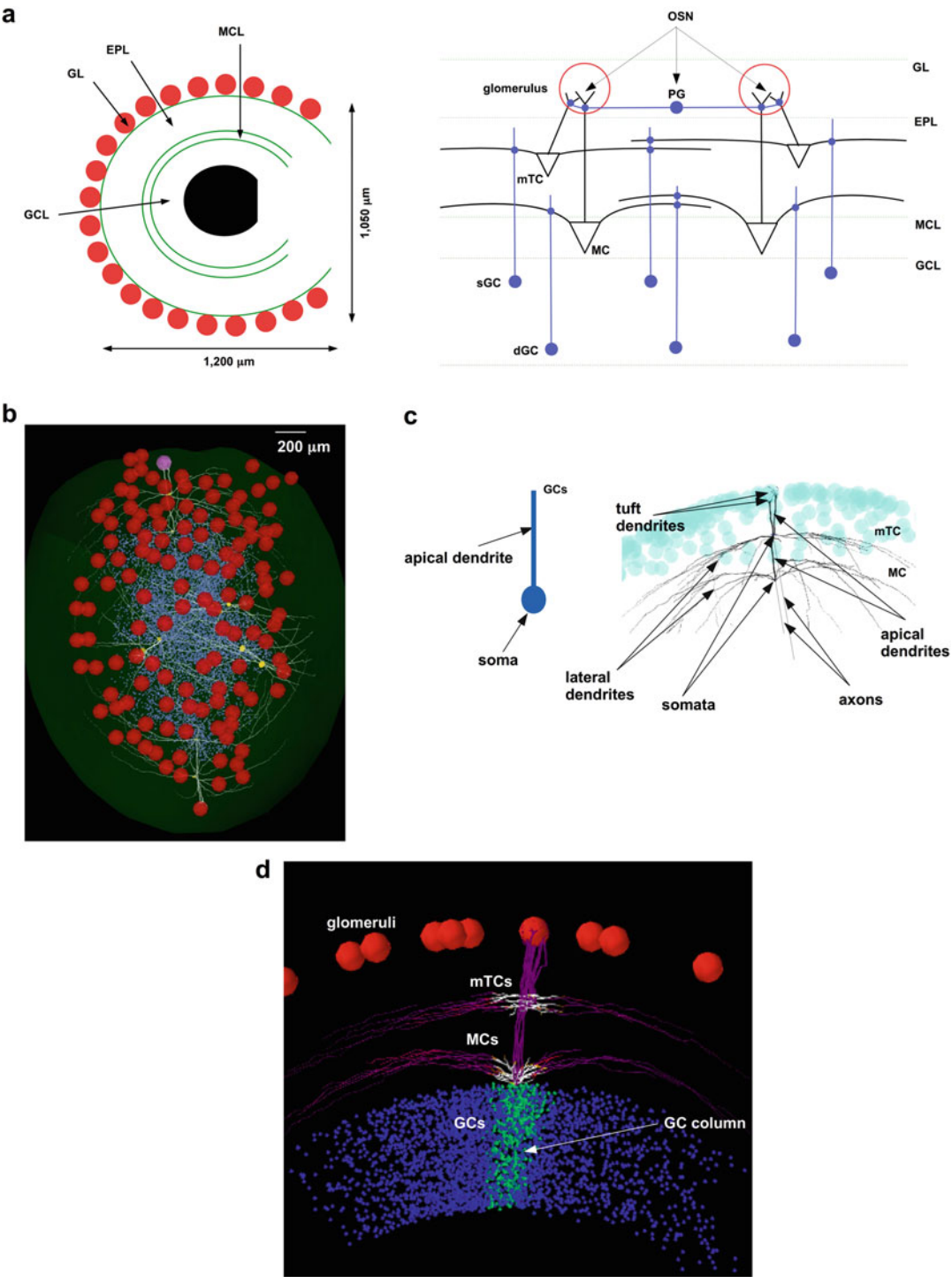
The model recreates the laminar organization of the OB in a virtual three-dimensional space. The OB shape is approximated as an ellipsoid (Fig. 1a, left), where the neuronal elements take place within different laminae (Fig. 1a, right), according to the real positions in the OB. In the dorsal part, 127 glomeruli are positioned on the OB surface (Fig. 1b), replicating a real map of odor-responsive glomeruli obtained experimentally (see Vincis et al. 2012).

Specifically, the reconstruction includes mitral (MC), middle tufted (mTC), granule (GC), and deep short-axon (dSAC) cells. Biophysically detailed models of MCs and mTCs replicate their morpho-electric properties (see “[Morpho-electric Properties of Mitral- and Middle-Tufted Cells](#)”). Their morphologies fully replicate the entire dendritic arborization, in three dimensions, and were generated by a random algorithm (Fig. 1c) (see “[Generation of Realistic Mitral- and Middle-Tufted Cell Morphologies](#)”). Differently, GC and dSAC are represented with biophysically detailed “ball-and-stick” models.

The model connectivity replicates the glomerular organization that characterizes the OB. MCs and mTCs are grouped in glomeruli that receive olfactory inputs from OSNs that belong exclusively to a single genotype (Fig. 1a, right) (see “[Model of Olfactory Sensory Neuron Response](#)”), i.e., expressing the same odor receptor (Shepherd et al. 2004). The size of each glomerulus is reduced to 5 MCs and 10 mTCs. In the external plexiform layer (EPL), MCs/mTCs connect with GCs (Fig. 1a, right), making dendrodendritic reciprocal synapses with separate subsets of GCs, superficial (sGC) and deep (dGC) GCs, respectively (Geramita et al. 2016). For each connection, the MC/mTC makes a glutamatergic synapse on the GC, while this makes a GABAergic synapse on the same MC/mTC (Fig. 1a, right) (for review, see Shepherd et al. 2004). Thus, each MC and mTC in the model connects with ~700 dGCs and ~1250 sGCs, respectively.

Both the synapses in a reciprocal connection incorporate a long-term plasticity rule for odor-learning simulation (for review, see Cavarretta et al. 2016), with the consequent GC column formation and organization in GUs (Fig. 1d) (see “[Summary of Model Predictions](#)”).

Differently, the GL consists of a mathematical microcircuit that computes the net glomerular excitation conveyed onto MC/mTC tuft dendrites, as a result of the excitation conveyed from olfactory sensory neurons (OSN) (see “[Model of Olfactory Sensory Neuron Response](#)”), and inhibition conveyed from juxtaglomerular periglomerular (PG) cells (see “[Glomerular Layer](#)”) (Cavarretta et al. 2016, 2018).



Large-Scale Models of the Olfactory Bulb, Fig. 1 The three-dimensional large-scale model of the olfactory bulb (Cavarretta et al. 2018). (a) *Left*: The laminar organization replicated in the three-dimensional large-scale model of the

olfactory bulb (OB). Laminae: glomerular layer (GL), external plexiform layer (EPL), mitral cell layer (MCL), and granule cell layer (GCL). *Right*: Schematic diagram of the model connectivity in relation to the laminar

Technical Details

The model was implemented in NEURON (Hines and Carnevale 1997) and Python. The cell models comprise of multiple subcellular sections, each subdivided in multiple compartments. Simulations were parallelized with the NEURON Multisplit library (Hines et al. 2008). Synaptic connections were implemented using the NEURON Multisend protocol (Hines et al. 2011).

Morpho-electric Properties of Mitral- and Middle-Tufted Cells

The MC/mTC morphologies are randomly generated with an algorithm designed ad-hoc, which synthesizes an unlimited number of three-dimensional morphologies of MCs/mTCs (Fig. 1c), with realistic levels of morphological complexity as well as cell-to-cell variability (see “Generation of Realistic Mitral- and Middle-Tufted Cell Morphologies”).

The membrane properties are modeled with Hodgkin-Huxley equations (for review, see Hines and Carnevale 1997). In particular, the passive membrane properties are fixed in accord with previous experimental estimates (Burton and Urban 2014, 2015). For all cells, the conductance densities of ion channels are chosen to replicate firing patterns and F-I curves observed experimentally (Burton and Urban 2014; Geramita et al. 2016). In particular, in our model, MCs generate tonic firing in response to current steps (Cavarretta et al. 2016), while mTCs tendentially respond with bursting (Cavarretta et al. 2018). Moreover, the model of mTC suggests that this cell type generates rebound bursts in response to

hyperpolarizing current pulses, confirmed with our subsequent experiments (see Cavarretta et al. 2018).

Generation of Realistic Mitral- and Middle-Tufted Cell Morphologies

The algorithm for MC/mTC morphology generation is:

```
FOR each MC/mTC:
    Generate soma shape and location;
    Generate # of LD and direction of
    first segment of LD and AD;
    Create a list (L) of tip dendrites;
    ITERATE N times AND while L is not
    empty DO:
        FOR each element in L:
            test extension of a dendrite
for M times:
    generate new segment
    (direction and diam);
    IF inside the boundary:
        update L;
        break;
    IF extension fails:
        delete element from L;
    ELSE IF can bifurcate:
        generate new tips and add
to L;
    ELSE IF apical dend. is
within GCL:
        generate first segment of
TDs and add to L;
```

Abbreviations: MC, mitral cell; mTC, middle tufted cell; LD, lateral dendrites; BL, branch length; PL, path length; BO, branch order; AD, apical dendrite; GCL, granule cell layer; TD, tuft dendrites; N = 1000; M = 10.

Notably, during the generation, a driving force bends the lateral dendrites of MCs/mCs as to



Large-Scale Models of the Olfactory Bulb, Fig. 1 (continued) organization. Each lamina contains different neuron classes or neuronal elements: The GL contains periglomerular (PG) cells; the EPL contains granule (GC) cell-apical dendrites, middle-tufted (mTC) and mitral (MC) cells in the superficial and deep parts of EPL, respectively; the MCL contains MC somata; the GCL contains somata of GC and part of their dendrites; and GCs are distinguished in superficial (sGC) and deep (dGC) granule cells. (b) Locations of the 127 glomeruli in the dorsal part of the OB

reconstruction, replicating a real glomerular map obtained experimentally (see Vincis et al. 2012). MC- and mTC-lateral dendrites highly overlap within the EPL. (c) The subcellular sections of GCs (left), MCs (right, bottom half of the lamina), and mTCs (right, top half of the lamina). mTCs comprise of the same types of subcellular sections as MCs but are smaller in size (compare cells in bottom and top halves of the lamina). (d) An example of glomerular unit with GC column in the OB model, generated by odor-learning simulation

follow the shape of the OB surface (Fig. 1b–d), mimicking the characteristic curvature observed in anatomical studies.

The parameters of the algorithm are the distributions of the maximal path-length, branch length, and branching probability, estimated from full morphological reconstructions of MCs and mTCs (see Igarashi et al. 2012). A subset of these morphologies was selected as a test set for validation of the synthetic morphologies, comparing the Sholl plots and the proportions of branches versus order (for MC validation, see Migliore et al. 2014; for mTC validation, see Cavarretta et al. 2018).

Model of Olfactory Sensory Neuron Response

The time course of OSN response $S(t)$ is described with a system of ordinary differential equations:

$$S(t) = O(t)(1 - D(t)) \quad (1)$$

where

$$\begin{cases} \frac{dO}{dt} = K_O(1 - C - O) \\ \frac{dC}{dt} = K_{C_1}OC(1 - C) + K_{C_2}(1 - C) \\ \frac{dD}{dt} = K_{D_1}O(1 - D) + K_{D_2}D(1 - O) \end{cases} \quad \text{with} \\ t \in [0, T]$$

where T indicates the sniffing period (i.e., inverse of the sniffing frequency); O , C , and D are states (initial conditions: $O(0) = 0$, $C(0) = 1$, $D(0) = 0$), corresponding to *open*, *closed*, and *desensitized* states of the olfactory receptor, respectively; $K_O (=0.01 \text{ ms}^{-1})$, $K_{C_1} (=0.01 \text{ ms}^{-1})$, $K_{C_2} (=10^{-4} \text{ ms}^{-1})$, $K_{D_1} (=1.7 \cdot 10^{-4} \text{ ms}^{-1})$, and $K_{D_2} (=0.01 \text{ ms}^{-1})$ are rates.

The aggregate excitatory postsynaptic current induced in MC/mTC tuft dendrites is calculated as

$$I_{ORN}(t) = [\tilde{g} + g_{\max} GL_i(c)S(t)][V_m(t) - E_{\text{AMPA/NMDA}}]$$

where V_m is the membrane potential, $E_{\text{AMPA/NMDA}} (=0 \text{ mV})$ is the reversal potential of the synapse, $g_{\max}$ is the synaptic conductance peak, and $\tilde{g}$ is a random term.

Odor Inputs

Given an odor, $GL_i(c)$ describes the dose-response relationship for an OSN class that expresses exclusively one class of odor receptor, which conveys excitation onto a single glomerulus (for review, see Shepherd et al. 2004). The dose-response relationship depends on the odor affinity of the OSN class, described as function of odor concentration. Specifically, in our model, $GL_i(c)$ describes the peak response of an OSN, i.e., the maximum value of $S(t)$ (see Eq. 1), defined as a Hill function of odor concentration (see Cruz and Lowe 2013):

$$GL_i(c) = \frac{F_{\max}}{1 + \frac{1}{\eta_i} \left(1 + \frac{K_i}{c}\right)^n} \quad (2)$$

where $\frac{F_{\max}}{1+\eta_i}$ defines the maximum OSN response, $F_{\max}$ is the maximum activation across all odor-glomerulus pairs, η_i depends on the odor identity, K_i controls the intercept of the Hill function, and n is the cooperativity exponent.

Furthermore, odors are described as arrays of OSN inputs due to distinct sets of parameters $GL_i(c)$ (Eq. 2), defining the dose-response relationship for an odor-glomerulus pair. For sake of simplicity, $F_{\max}$, K_i , and n are chosen identical for all pairs; the values of η_i were inferred from an experimental data set of 19 natural odors (for review, see Cavarretta et al. 2016), in a way that the dose-response maxima replicate the proportions among the glomerular responses observed in the experiments (see Vincis et al. 2012).

Glomerular Layer

The glomerular microcircuit consisted of a mathematical equation set described in previous works (Cleland and Sethupathy 2006; Cleland and Linster 2012). Under the assumption that PGs modulate OSN excitation, PGs mediate feedforward inhibition on MC/mTC tuft dendrites, implementing *olfactory input normalization* and the *nontopographical contrast enhancement* (see “[Learning-Dependent Processing of Natural Odors](#)”). Given the glomerular excitation $GL_i(c)$ (see Eq. 2), the normalized input $GL_i^{\text{norm}}(c)$ was calculated as

$$GL_i^{\text{norm}}(c) = \begin{cases} GL_i(c) - \bar{GL}_i(c), & \text{if } GL_i(c) - \bar{GL}_i(c) > 0 \\ 0, & \text{otherwise} \end{cases}$$

with $\bar{GL}_i(c) = \frac{1}{N} \sum GL_i(c)$, while contrast-enhanced odor input $GL_i^{\text{CE}}(c)$ was calculated as

$$GL_i^{\text{CE}}(c) = \begin{cases} GL_i^{\text{norm}} - \text{PG}[GL_i^{\text{norm}}(c)] - \bar{GL}_i(c), & \text{if } GL_i^{\text{norm}} - \text{PG}[GL_i^{\text{norm}}(c)] > 0 \\ 0, & \text{otherwise} \end{cases}$$

$$\text{with } \text{PG}(x) = \begin{cases} \frac{0.6}{1 + 0.01 \left(\frac{1}{x} - 1 \right)}, & \text{if } x > 0 \\ 0, & \text{otherwise} \end{cases},$$

$\text{PG}(x)$ describes the intraglomerular. Therefore, $GL_i^{\text{CE}}(c)$ returns the net odor input, i.e., net excitation, conveyed on MC/mTC tuft dendrites.

Summary of Model Predictions

The three-dimensional morphologies of MCs and mTCs constitute a centerpiece of this model of the OB. Their lateral dendrites have anatomically plausible extent so that they likely replicate the breadth of glomerular dendritic fields with physiological levels of overlap. Importantly, the overlap correlates with the number of GCs that are shared between GUs. In our simulations, odor learning generates the sparse and segregated organization in GC columns (Fig. 1d) (see Willhite et al. 2006), with realistic shape, size, and spatial distribution (Cavarretta et al. 2016). Taken together, these features regulate the spatial spreading as well as the strength of lateral inhibition (Cavarretta et al. 2018), and these are a fundamental aspects for the realistic simulation of the lateral interactions between GUs.

Odor Learning, Granule Cell Column Formation, and Organization in Glomerular Unit

The model provides several hints of the dynamics underlying GC column formation (Willhite et al. 2006), which can be summarized in four steps:

- (i) Odors evoke action potentials (APs) in MCs/mTCs that back-propagate along the lateral dendrites.
- (ii) At sufficiently high rate, back-propagating APs activate long-term potentiation in the reciprocal

connections between MCs/mTCs and GCs (MTC-to-GC, GC-to-MTC) (see above).

- (iii) Once the excitatory synapses (MC/mTC-to-GC) are sufficiently potentiated, the APs (back-propagating along MC-/mTC-lateral dendrite) elicit APs in the GCs, activating long-term potentiation in the inhibitory synapses (GC-to-MTC).
- (iv) The inhibitory synapses dampen AP back-propagation in MC-/mTC-lateral dendrites, reducing the firing rate locally, and causing long-term depression in the distal synapses.

Finally, the strongest reciprocal connections remain near the MC/mTC somata, forming cylindrical clusters beneath the odor-responsive glomeruli (Fig. 1a). Therefore, MCs, mTCs, and GCs that are functionally related to a glomerulus form a glomerular unit (GU).

Lateral Interactions Between Glomerular Units During Odor Learning

Under the assumption that GUs interact via GC columns during learning (Migliore et al. 2015), the model suggests that these interactions might promote or hinder GC column formation, affecting breadth and definition (i.e., GC density) of GC columns. The efficacy of these interactions depends on the odor-learning order (i.e., non-commutativity) and decreases with the distance between the interacting glomeruli.

Learning-Dependent Processing of Natural Odors

The model suggests that a learning-dependent dynamic underlies OB processing of natural odors (Cavarretta et al. 2016), showing that it is

optimal after formation of multiple and sparse GC columns (i.e., real anatomical pattern; see Willhite et al. 2006). Specifically, the GL circuit operates sparsely and stabilizes odor representation across different concentrations, decorrelating the spatial representations evoked by different odors, while the effect of lateral inhibition, conveyed via GCL, furthers this decorrelation over time.

Two Parallel Pathways for Odor Signaling Within the Olfactory Bulb

The model makes a functional distinction between the two parallel pathways of the OB due to MCs and mTCs (Cavarretta et al. 2018). In brief, the model suggests that:

- (i) mTCs of different GUs increase their spike synchrony in response to shared GC inputs, while spike rate decreases in MCs with high numbers of GC inputs.
- (ii) MCs and mTCs are controlled by similar computations via GL, while they are functionally separated in GCL, i.e., connecting with different subtypes of GCs.
- (iii) dSAC inhibition organizes GUs into larger entities termed “glomerular unit clusters,” where GC columns mediate inhibition within but not between GU clusters.

Spine Relocation in Adult-Born Granule Cell

Experiments *in vivo* revealed a novel form of fast activity-dependent synaptic plasticity, in which mature spines (3–8%) of adult-born GCs relocate from inactive to active MC dendrites (Breton-Provencher et al. 2016). The model suggested that spine relocations, despite their low percentage (3–6%), increased the synchronization between GUs, thereby resulting in a faster mechanism for fast oscillation generation.

Other Large-Scale Models of the Olfactory Bulb

Polese et al. (2014) developed a model of the OB that included mitral (MC), external tufted (ET),

periglomerular (PG), and superficial short-axon (sSA) cells. The cells were implemented as ball-and-stick models, whose intrinsic properties were described with Izhikevich’s equations. The authors analyzed the effects of feedforward inhibition, on the OB output, and suggested that odor identity and intensity are separately encoded in MCs and ETs, respectively.

Li and Cleland (2013) developed a model including 25 glomeruli, 1 MC per glomerulus, 25 PGs, and 100 GCs. The cells were implemented as oligocompartmental models that included one subcellular section of each type, whose intrinsic properties were described by Hodgkin and Huxley equations (Hodgkin and Huxley 1952). The authors suggested the effects of nicotinic and muscarinic modulations as: (i) Nicotinic modulation, operating in the GL, sharpens the MC-receptive fields, controlling the average firing rate, and decorrelating the representations between similar odors; (ii) muscarinic modulation, operating in the GCL, increases spike synchrony and gamma oscillations in MCs, without affecting the firing rate; and (iii) a combination of nicotinic and muscarinic modulations produces an even sharper odor tuning than either modulation alone.

Gilra and Bhalla (2015) developed a model based on a Multiscale Object Oriented Simulation Environment, Python, and NeuroML. The model included 3 glomeruli, 2 MCs per glomerulus, 1000 PGs, and ~1200 GCs. The cells were implemented as biophysically detailed multicompartmental models, whose intrinsic properties were described by Hodgkin-Huxley equations (Hodgkin and Huxley 1952). The authors studied the effects of lateral inhibition between MCs, under the assumption that intraglomerular lateral inhibition can be conveyed via GCs. However, this contradicts experimental evidence that GCs do not make multiple synapses with MTCs of the same glomerulus (Kim et al. 2011). Together, the model suggested that, over short ranges of odor concentration, MC response to odor mixtures is a linear summation of response profiles evoked by the individual odor components.

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Large-Scale Models of the Visual System

► Hierarchical Models of the Visual System

Large-Scale Neural Networks: Vision

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Synonyms

Excitatory and inhibitory networks; Spike-rate neural networks; Wilson-Cowan equations

Definition

The visual system is the largest single sensory system in the brain, comprising approximately 40% of the entire cerebral cortex. Computational modeling of visual functions accordingly requires large-scale neural networks that are computationally efficient. Such networks invariably provide a mathematical description of neurons at the spike-rate level, as describing neurons at the level of individual spikes or action potentials is too computationally expensive. Despite using spike-rate equations, large-scale neural networks in vision can effectively incorporate effects of modulatory neurotransmitters, spike-rate adaptation, and other processes known to be critical for understanding visual system function.

Detailed Description

Neurons are most accurately described by the Hodgkin-Huxley equations (Hodgkin and Huxley 1952) and their subsequent elaborations. The four Hodgkin-Huxley equations describe the electrical potential across the membrane of a single neuron and accurately reproduce the shape of each spike or action potential. As each action potential is only about 1.0 msec in duration, simulations at this level of detail invariably require very small time steps for their implementation and thus are very computationally expensive. For large-scale network simulations, therefore, neurons are

frequently described at the level of spike rates. This enables each neuron to be described by just one equation rather than four and increases the size of computational time steps by more than an order of magnitude. Thus, for any amount of computational power, a network of spike-rate neurons can be at least 100 times larger than a network of Hodgkin-Huxley neurons (Wilson 1999b). Furthermore, the simplification inherent in spike-rate equations makes them optimal for mathematical analysis.

Before proceeding, it should be acknowledged that there is also an intermediate level of neuronal description that has recently been developed (Izhikevich 2003; Wilson 1999a). These models are simpler and computationally faster than Hodgkin-Huxley, and they also produce individual action potentials. Thus, they are useful for studying networks of neurons exhibiting intrinsic bursting and other complex firing properties. However, further discussion of these models is beyond the scope of this article.

Spike-Rate Equations

One of the first and most popular formulations of spike-rate dynamics are the Wilson-Cowan equations (Wilson and Cowan 1972, 1973). These equations utilize a sigmoid nonlinearity, S , that converts the postsynaptic potential, PSP , into a mean spike rate R :

$$\tau \frac{dR}{dt} = -R + S(PSP - gH) \quad (1)$$

Here τ represents the exponential rate at which R approaches the asymptotic firing rate defined by $S(PSP)$. As τ is related to the time course of postsynaptic potentials spreading along dendrites to the nerve cell body, values in the range of 10–20 msec. are generally appropriate. This represents an enormous improvement in computational efficiency relative to Hodgkin-Huxley simulations. Finally, the variable H represents a hyperpolarizing, self-adaptation function that will be described in the context of binocular rivalry below.

The sigmoid nonlinearity $S(x)$ is simply an S-shaped function such that (a) the slope $dS/dx \geq 0$, (b) there is a single point at which the slope is a maximum, and (c) dS/dx decreases monotonically above and below the point of maximum slope. Frequently used functions satisfying these criteria are:

$$S(x) = \frac{1}{1 + \exp(-a(x - \theta))}$$

$$S(x) = \begin{cases} \frac{(x - \theta)}{1 + (x - \theta)^{0.8}} & x \geq \theta \\ 0 & x < \theta \end{cases} \quad (2)$$

where θ is related to the neuronal threshold. The first of these is the logistic curve, which was used in the original Wilson-Cowan equations (Wilson and Cowan 1972) and is plotted in blue in the figure below. The second (red curve below) is a more recent function with a sharp threshold at $x = \theta$ that was introduced to describe dynamics of binocular rivalry (Wilson 2007). It is related to the Naka-Rushton (Naka and Rushton 1966) function (also called a Hill function), except that it asymptotically approaches $(x - \theta)^{0.2}$ rather than a constant value for large x . The exact shape of $S(x)$ only affects the nonlinear dynamics of large-scale networks quantitatively; the qualitative dynamics remain the same. The key observation is that a sigmoid function can be intersected by a straight line in either one or three points only. These possibilities determine the bifurcation structure of the network dynamics. For example, with three intersections, two asymptotically stable and one unstable, short-term memory states and hysteresis occur. With only one unstable state, limit cycle oscillations arise (Wilson 1999b).

The postsynaptic potential can generally be written as a weighted sum of excitatory inputs from other neurons along with subtractive inhibition:

$$PSP(t) = \sum_k w_k E_k(t) - \sum_m a_m I_m(t) \quad (3)$$

where $E_k(t)$ are firing rates of excitatory neurons with synaptic weights w_k , and $I_m(t)$ are firing rates of inhibitory neurons with synaptic weights a_m .

If appropriate, divisive inhibition can also be included.

Finally, the Wilson-Cowan equations incorporate separate arrays of excitatory and inhibitory neurons, which interact via the postsynaptic potentials in Eq. 3. Recurrent excitation and recurrent inhibition are generally described as Gaussian functions of distance, with inhibition having a wider spatial spread than excitation.

Applications to Vision

The original application of the Wilson-Cowan equations to large-scale visual phenomena consisted of a one-dimensional network comprised of a line of spatially interacting excitatory (E) and inhibitory (I) neurons. With short-range recurrent excitation and longer-range inhibition, multiple dynamic regimes emerged depending on relative excitatory and inhibitory synaptic strengths. Among these was a spatially localized short-term memory that encoded the position of a brief recent stimulus. These dynamics provide a nonlinear instantiation of the more recently introduced concept of a line attractor for eye position memory (Seung 1996). A second dynamic regime with weakened inhibition leads to traveling waves of neural activity, such as those experienced in migraine auras (Wilson and Cowan 1973).

Ermentrout and colleagues have shown that two-dimensional Wilson-Cowan networks can explain the major examples of geometric visual hallucinations induced by drugs (Ermentrout and Cowan 1979). These hallucinations include concentric circles, radial spokes, checkerboards, and spirals. Their network employed two-dimensional Gaussian short-range excitation balanced with longer-range recurrent inhibition. The key to reproducing perceived visual hallucinations was the pattern of asymptotically stable spatial steady states which were transformed into visual coordinates via the retino-cortical complex logarithmic mapping (see ► “Flicker-Induced Phosphenes”). This work was extended to encompass virtually all geometric visual hallucinations by introducing groups of orientation-selective neurons and reciprocal excitatory connectivity between collinear neurons with

the same preferred orientation (Bressloff et al. 2001). The introduction of collinear facilitation makes this large-scale network into a much more accurate model of primate visual cortex.

A further embellishment of Wilson-Cowan dynamics has proved successful at describing many aspects of binocular rivalry (Wilson 2007). The key is the introduction of very slow neuronal fatigue, which is known to occur in excitatory monkey and human cortical neurons as a result of hyperpolarizing Ca^{++} -mediated K^{+} currents with time constants of up to several seconds (Sanchez-Vives et al. 2000). A self-adaptation variable, H , was incorporated into spike-rate dynamics by introducing a simple additional equation for each neuron:

$$\tau_H \frac{dH}{dt} = -H + R \quad (4)$$

where τ_H is in the range 900–1,500 ms. This equation operates in conjunction with Eq. 1 to generate self-adaptation. Two spatial arrays of mutually inhibitory neurons incorporating such self-adaptation can reproduce the oscillations perceived in binocular rivalry. Typically, a noise term is added to the equations to explain the stochastic nature of rivalry. Rivalry has also been shown to generate spreading dominance waves (Wilson et al. 2001), and these waves can be explained by competing spatial arrays of spike-rate neurons with appropriate synaptic connectivity. Mathematical analysis of a continuum version of the Wilson-Cowan equations has elucidated the details of dominance wave propagation and produced estimates of wave speed as a function of network parameters (Bressloff and Webber 2012).

Conclusion

Wilson-Cowan equations are very effective at simulating and analyzing large neural networks for understanding visual and other neural functions. Synaptic connectivity can be specialized based on the anatomy and physiology of different cortical areas, and ion currents with different time courses can be introduced to allow for neural

adaptation. Hebbian learning with symmetric excitatory connections can also be introduced to produce Hopfield networks for long-term associative pattern memory (Hopfield 1984). Finally, temporary synaptic facilitation of network connections can account for short-term perceptual memory in binocular rivalry (Wilson 2007). The only areas in which spike-rate neural networks cannot be used are those in which precision of individual spike timing or spike synchronization is critical. One example would be simulations of auditory localization, in which extremely small differences in the arrival time of spikes from the two ears are crucial.

Cross-References

► [Flicker-Induced Phosphenes](#)

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Lateral Geniculate Nucleus (LGN) Models

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Definition

LGN models refer to mathematical models for the activity of neurons (relay cells and interneurons) in the lateral geniculate nucleus (LGN) of the thalamus. The LGN is positioned between the retina and the primary visual cortex in the early visual pathway in mammals.

Detailed Description

Overview of LGN Circuit

The lateral geniculate nucleus (LGN) acts as a gateway for visual signals to reach cortex. It receives driving input from retinal ganglion cells (RGCs) and modulatory input from the cortex, the thalamic reticular nucleus (TRN), and the brainstem. The principal cells in the LGN, the thalamocortical relay cells (RCs), transmit visual information to the cortex. They constitute about 75–80% of the cells in the

nucleus, while the remaining 20–25% are intrageniculate interneurons (INs). The RCs receive synaptic inputs from a variety of sources: direct *feedforward excitation* from RGCs; indirect *feedforward inhibition* via the INs, which in turn receive excitatory input from RGCs; *feedback inhibition* from the TRN; and *feedback excitation* from primary visual cortex. Both the IN and TRN cells further receive excitatory feedback from the cortex opening up the possibility for *feedback inhibition* of RCs involving the entire thalamocortical loop. For reviews of the neurobiology of LGN, see Ghodrati et al. (2017) and Sherman and Guillery (2001).

LGN models range from biophysically detailed models aiming to explain distinct features of the signaling properties of single neurons to more abstract models aiming to explain the responses of neurons to visual stimuli and the overall function of the LGN circuit.

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types: mechanistic, descriptive, and interpretive (Dayan and Abbott 2001). *Mechanistic* (physics-type) models aim to find out how properties of the system arise from the physical properties of the underlying parts. *Descriptive* (statistical) models are used to summarize experimental data or encapsulate key properties compactly. *Interpretive* (normative) models instead aim to model the functional roles of neural system, for example, relating neuronal responses to the task of processing useful visual information for the animal.

Single Neuron Models

Relay Cells (RCs)

Numerous mechanistic models for RCs based on the cable equation description of neurons have been developed and explored. They differ in the choice of neuronal morphology (single compartment/multicompartment) and included ion conductances. With some right one may distinguish between models tailored to explore specific aspects of RC activity and more general-purpose models that aim to capture a series of RC functions.

Examples of the former type are the investigation of the impact of dendritic morphology on integration of synaptic inputs in models with passive (Bloomfield and Sherman 1989; Briska et al. 2003) and active (Connelly et al. 2016a; Perreault and Raastad 2006) dendrites. Other examples are single-compartment models that explore how a large (~10) number of active (Hodgkin-Huxley style) conductances affect the somatic response properties (McCormick and Huguenard 1992) or control the resting potential and subthreshold dynamics (Amarillo et al. 2014). Many models have focused on the ability of RCs to exhibit two different firing modes (tonic and bursting), a key feature of RCs (Sherman and Guillery 2001). The somatic subthreshold oscillations underlying burst firing in RCs have been studied both in single-compartment (Amarillo et al. 2014; Destexhe et al. 1993; Huguenard and McCormick 1992; Toth and Crunelli 1992; Zeldenrust et al. 2013) and multicompartment models (Destexhe et al. 1998; Wei et al. 2011). Also, different aspects of the suprathreshold bursting/tonic firing properties have been studied both in single-compartment (Broicher et al. 2007; Deleuze et al. 2012) and multicompartment models (Connelly et al. 2015; Destexhe et al. 1998; Zomorodi et al. 2008).

The most comprehensive models are multicompartmental models based on anatomically reconstructed dendritic morphologies and incorporate synaptic input and several active conductances both in the soma and in the dendrites (Antal et al. 1996; Connelly et al. 2015, 2016a; Emri et al. 2000, 2003; Rhodes and Llinas 2005). The perhaps most general of these is a multipurpose model developed to capture a broad range of RC response properties (Rhodes and Llinas 2005). Some of the RC models also explicitly include intracellular calcium dynamics (Connelly et al. 2015, 2016a; Destexhe et al. 1993, 1998; Rhodes and Llinas 2005; Wei et al. 2011; Zomorodi et al. 2008).

Leaky integrate-and-fire (LIF) type models, avoiding the computationally expensive calculation of the action potential generation process itself, are commonly used by computational neuroscientists, and a single-compartment *leaky integrate-and-fire-or-burst* (LIFB) model has been

developed to capture the dual tonic-burst action of RCs (Lesica and Stanley 2004; Smith et al. 2000). Further, descriptive models capturing salient properties of RC neuronal dynamics have been derived by means of techniques from nonlinear dynamics (Rose and Hindmarsh 1985, 1989a, b, c).

Direct fitting of neuron models to in vivo experimental data has been rare. However, the *leaky integrate-and-fire* model has been tuned to model the transmission of spikes at the connection between RGCs and RCs in cat (Casti et al. 2008). Along the same line, a so-called spike response model (Gerstner and Kistler 2002) was fitted to corresponding data from macaque (Carandini et al. 2007). Both models were later found to be well accounted for by simple firing-rate models (Heiberg et al. 2013).

Interneurons (INs)

In addition to the tonic/burst spiking feature also seen in RCs, INs also exhibit dendrodendritic inhibition (on RCs) through specialized triadic synapses (Sherman and Guillery 2001). Despite (or maybe because of) their likely more complicated action, fewer models have been developed for INs than RCs. Some models have investigated signal propagation in the elaborate dendritic structure of INs in the case of passive (Bloomfield and Sherman 1989; Briska et al. 2003) or active (Allken et al. 2014; Casale and McCormick 2011; Perreault and Raastad 2006) dendrites. One simplified model explores the differences in burst firing between INs and RCs (Broicher et al. 2007). A range of IN somatic response properties is captured in two, relatively general, multicompartmental models with realistic morphologies (Halmes et al. 2011; Zhu et al. 1999), and the most comprehensive of these two also includes active dendritic conductances (Halmes et al. 2011). Some of the IN models include intracellular calcium dynamics (Allken et al. 2014; Halmes et al. 2011; Zhu et al. 1999).

Descriptive Models for Response to Visual Stimuli

Starting with the introduction in the 1960s of the *difference-of-Gaussians* (DOG) model (Rodieck 1965) to describe responses in retinal neurons

(RGCs), there has been a long tradition in using descriptive filter models to account for responses to visual stimuli of neurons in the early visual pathway (retina, LGN, primary visual cortex; Chap. 2 in Dayan and Abbott (2001)). In this model the receptive-field function $D(r, t)$ (also called point-spread function) describing the theoretical response of a neuron to a flashing point stimulus (briefly on at time $t = 0$) a distance r from the receptive-field center is assumed (i) spatiotemporally separable, i.e., $D(r, t) = f(t)g(r)$ with (ii) the spatial part given as a difference between two Gaussian functions:

$$g(r) = A_c e^{-r^2/\sigma_c^2} - A_s e^{-r^2/\sigma_s^2}$$

Here the first term is referred to as the *center* contribution, while the second term is referred to as the *surround* contribution.

In applications to RCs in LGN, a generalized receptive-field function where the center and surround terms have different temporal profiles has typically been used (Chap. 2 in Dayan and Abbott (2001)), i.e.:

$$D(r, t) = g_c(r)f_c(t) - g_s(r)f_s(t)$$

Here the spatial functions $g_c(r)$ and $g_s(r)$ have been modeled as Gaussian functions, and the temporal profiles, represented by the functions $f_c(t)$ and $f_s(t)$, have been set to have the surround contribution lagging behind the center contribution (Dawis et al. 1984; Kaplan et al. 1979). While the temporal functions $f_c(t)$ and $f_s(t)$ have been chosen to have the same functional form and to be distinguished only by the choice of function parameters, different choices of biphasic functions have been used to model them (Allen and Freeman 2006; Cai et al. 1997; Dayan and Abbott 2001). Also a variant with a nonlinear suppressive field acting as a response normalization has been used (Bonin et al. 2004).

RC receptive-field functions with $D(r, t)$ given as a sum of three spatiotemporally separable components, two components representing *transient* responses to stimuli onset and one component representing the *sustained* response, have also been developed (Einevoll et al. 2011).

The above receptive-field functions predict time-resolved firing rates suitable for comparison with poststimulus time histograms (PSTHs) (Dayan and Abbott 2001), but such models have also been used to generate spike trains assuming specific spike-train statistics (Gazères et al. 1998). So-called *generalized linear models* (GLMs), determined by fitting such spike-generating descriptive models to experimental data, have also been employed in the analysis of RC data (Babadi et al. 2010).

Mechanistic Network Models

Most mechanistic network models of the early visual pathway have focused on the response of neurons in the primary visual cortex, the station after the LGN. In such models the modification of retinal signals by the LGN has often been neglected altogether or been included in a simplified fashion. Here only models focusing on the response of LGN neurons will be described.

One class of model simulations has considered comprehensive two-dimensional grids of spiking neurons representing a part of the visual field. One class of studies has used simplified LIF model neurons, mostly only explicitly modeling RCs (Connelly et al. 2016b; Kirkland and Gerstein 1998; Köhn and Wörgötter 1996; Wörgötter et al. 1998) but also both RCs and INs (Wielaard and Sajda 2007). In these studies, the network received spike-train inputs from grids of RGCs and sometimes also feedback from cortical cells (Kirkland and Gerstein 1998; Köhn and Wörgötter 1996; Wörgötter et al. 1998). Similar studies have also been performed with firing-rate point-neuron models replacing the spiking neurons (Einevoll and Heggelund 2000; Hayot and Tranchina 2001; Yousif and Denham 2007).

Networks based on single-compartment Hodgkin-Huxley-style models of LGN neurons have also been studied (Behuret et al. 2013; Kosmidis 2002; Rogala et al. 2013). Lately such network models have also incorporated multi-compartment INs exhibiting both axonal and triadic inhibition, both without (Heiberg et al. 2016) and including cortical feedback (Martinez-Canada et al. 2018).

Another line of work has investigated more generic questions about the properties of networks of LIFB neurons representing RC neurons interacting with neurons in the thalamic reticular nucleus (TRN), both a minimal model consisting of a pair of single RC and TRN neurons (Babadi 2005) and a more extended model where each population is represented by one-dimensional grids of LIFBs (Huertas et al. 2005). Such LIFB networks have also been investigated with a *population density approach*, both for a population of RC LIFBs by itself (Casti et al. 2002) and for coupled populations of RCs and TRN LIFBs (Huertas and Smith 2006).

Finally, both neural mass models (Norheim et al. 2012) and neural field models (Einevoll and Plesser 2002, 2012) have been developed to model the processing of visual signals by LGN circuit. In particular, the so-called *extended DOG* (*eDOG*) model combines the descriptive DOG model with a mechanistic model for the effect of cortical feedback to produce a closed-form expression for the spatiotemporal receptive-field function (Einevoll and Plesser 2012; Nirody 2014). A Python simulator, pyLGN, has been implemented for easy exploration of the eDOG model (Mobarhan et al. 2018).

Numerous network models have been developed to investigate the role of thalamocortical oscillations, typically without including sensory input in the model. We do not cover these models here and rather refer the interested reader to Refs. (Barardi et al. 2016; Destexhe and Sejnowski 2001). Also, models of the interactions between the LGN and the TRN, or single-cell models of TRN cells, were not covered here, but see, e.g., Destexhe and Sejnowski (2001) and Willis et al. (2015).

Interpretive Models

Interpretive models for the possible functional role of LGN are fewer. One study showed why both *lagged* and *non-lagged* RCs, which are observed experimentally, could be useful for obtaining efficient visual representations (Dong 1995). Another study in the same vein argued why the observed biphasic temporal response of RCs could reflect *predictive coding* (Jehee and Ballard 2009). A third study showed how the

LGN cells may form a resampled map of visual space to facilitate detection of stimulus position (Martinez et al. 2014).

Resources

- Publicly available RC neuron models with active conductances (Destexhe et al. 1998): <https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=279>
- Publicly available multicompartment RC neuron model with passive dendrites (Briska et al. 2003): <https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=29942>
- Publicly available tutorial for modeling rhythmic activity in an RC neuron model (Meuth et al. 2005): <https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=121600>
- Publicly available rat multicompartment RC neuron (Connelly et al. 2015, 2016a): <https://senselab.med.yale.edu/modeldb/ShowModel.cshhtml?model=223891>
- Publicly available multicompartment IN neuron model with active conductances (Halmes et al. 2011): <https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=140249>
- Publicly available multicompartment IN neuron model with active conductances for exploration of effects of spatial distribution of dendritic calcium conductances (Allken et al. 2014): <https://senselab.med.yale.edu/modeldb/showmodel.cshhtml?model=156039>
- Publicly available neural-mass model exploring temporal effects of feedforward and cortical feedback connections on RC neurons (Norheim et al. 2012): <https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=153092>
- Publicly available open-source tool pyLGN for firing-rate-based modeling (eDOG model (Einevoll and Plesser 2012)) of LGN circuit responses to visual stimuli including cortical feedback connections (Mobarhan et al. 2018): <http://pylgn.rtfid.io>
- Publicly available network model with single-compartment and multicompartment neurons for exploring cortical feedback effects on LGN-cell responses (Martinez-Canada et al. 2018): <https://senselab.med.yale.edu/ModelDB/showmodel.cshhtml?model=239878>

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Lateral Inhibition

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Leaky Integrate and Fire Model

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Leech Local Bend: Neural Coding of Touch Location

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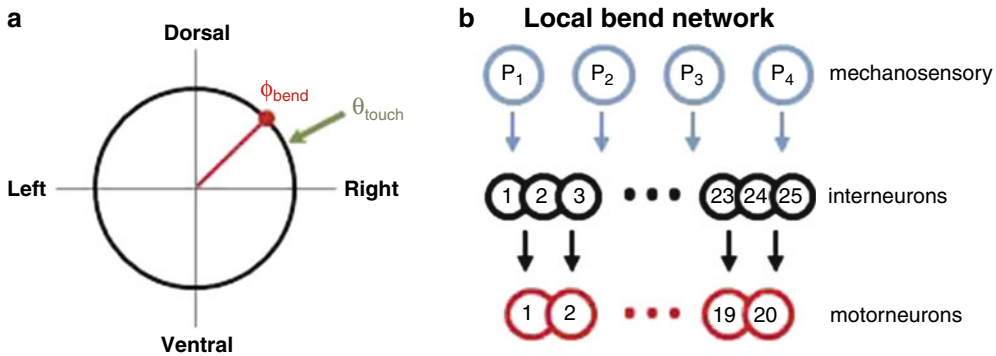
Definition

In response to a light touch, the medicinal leech bends away from the touched site, a behavior called the local bend. Using a three-layer neuronal network comprising mechanosensory neurons, interneurons, and motor neurons, the leech encodes touch location and coordinates muscle contraction to produce the appropriately directed bend.

Detailed Description

Background

Our understanding of neural coding has benefited significantly from the study of well-defined behaviors produced by relatively small nervous systems. In terms of neural underpinnings, more of such behaviors are understood in the medicinal leech than in any other system (Kristan et al. 2005). This is due, in part, to the leech's segmented nervous system, which comprises 21 ganglia connected in series to form a nerve cord, with head and tail ganglia at either end.



Leech Local Bend: Neural Coding of Touch Location, Fig. 1 (a) Schematic of a cross-sectional view of the leech tubular body illustrating the local bend problem. Touching the skin at a location indicated by the green arrow (the

touch angle) produces a bend directed away from the touched site, indicated by the red dot (the bend angle). (b) The local bend network comprising three layers of neurons (see text)

The leech produces “whole-body” behaviors (such as swimming and crawling) that involve coordination between neurons in all ganglia, as well as “local” behaviors (such as local bending) that are generated by neurons in a single ganglion. Other behaviors (such as heartbeat control) involve several ganglia. The leech nervous system is also very amenable to neurophysiological study: the nerve cord (or any number of ganglia) can be isolated in a dish and still produce the motor patterns associated with the different behaviors. In addition, each segmental ganglion contains about 400 neurons, many of them identifiable from animal to animal. So, one can characterize the activity of the same neuron from different ganglia or in different animals to determine how the underlying networks produce each motor pattern and make choices between behaviors (Kristan et al. 2005; Kristan and French 2010).

The Leech Local Bend

A light touch to the skin of a leech results in a local bend, a subtle bending of the body away from the touched site (Kristan et al. 1995; Lewis 1999). The behavior is mediated within a single segment of the leech tubular body. It is convenient to express both the touch location and the bend direction by an angle. In other words, the location

of a touch at some point around the perimeter of the cross section of a single body segment is described by an angle (θ_{touch}) from 0° to 360° (Fig. 1a; green line). Similarly, the bend angle (ϕ_{bend}) can be represented by the point along the body perimeter at which the motor response is maximal (Fig. 1a; red line). In this way, it is clear that the local bend involves a simple directional input–output relationship, with a “perfect” response indicated by $\phi_{\text{bend}} = \theta_{\text{touch}}$.

The local bend network controls this directed behavior. This network contains about 50 neurons organized in three distinct neuronal layers (Fig. 1b). **The first layer** comprises the sensory inputs: four mechanosensory P neurons encode the location of touch on the skin. **The third layer** comprises the motor output: four groups of longitudinal motor neurons (about 20 neurons in total) control the length of longitudinal muscle (shortening near the touch and lengthening opposite the touch produce the appropriate bend). **The second layer** consists of a population of about 25 interneurons, with 17 identified so far (Lockery and Kristan 1990).

To produce the appropriately directed bend, the local bend network must solve a number of problems. First, touch location must be represented in the firing patterns of the P neurons. Second, the layer of interneurons must form a new representation of touch location based on P neuron inputs. Third, this information must be transferred to the

motor neurons, whose relative activity and innervation of the body wall muscle, along with the biomechanics, determine bend direction.

Neuronal Population Coding

Population coding has been implicated in a wide variety of neural systems. In such codes, information is distributed over a population of neurons, rather than in the activity of a single neuron. Coding the intensity of a sensory stimulus (e.g., pressure of a light touch) often involves a single neuron code; the firing rate of the associated receptor neuron increases monotonically with stimulus intensity. On the other hand, the representation of color in the visual system is an example of population coding. Here, color is encoded by the relative activation of different classes of photoreceptors tuned to distinct wavelengths of light (e.g., red, green, and blue). While different photoreceptor classes are tuned to their “preferred” wavelengths, they also respond (albeit to a lesser extent) to a range of wavelengths; this range is large enough that the tuning curves for each class overlap. So for a given wavelength, each class of photoreceptor will be activated to varying levels. Therefore, the activity of a single photoreceptor class does not alone provide sufficient information for the range of color

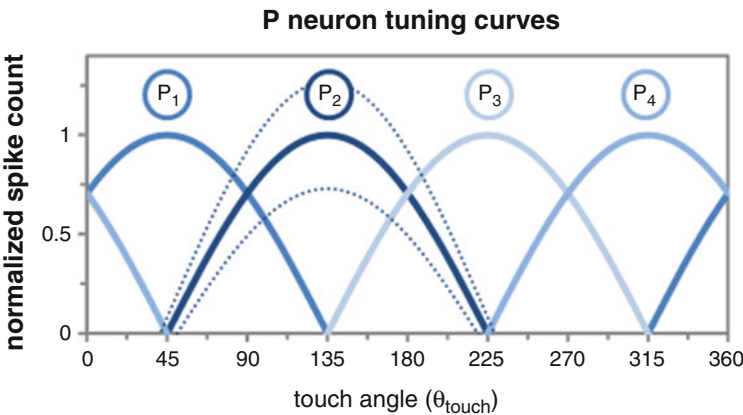
sensitivities. Rather, activity across the population of broadly tuned photoreceptors is necessary. Such broad tuning is one hallmark of population coding.

Neuronal networks can implement a variety of population codes (see ► [“Computation with Population Codes”](#)). To show that a particular population code is implemented in a given system, a number of experimental tests are necessary. First, a measure of population activity that is based on the proposed code should be correlated with the sensory input (or behavioral output). Second, systematic manipulation of the population activity should have an effect that is predicted by that particular code. And third, the network properties required to implement or “read out” the population code must be present.

A Population Code for Touch Location

The local bend network provides a fruitful context in which to evaluate a population code. With only four P neurons, one can record the intracellular activity from all sensory inputs and measure bend direction on a trial-by-trial basis (Lewis and Kristan 1998a).

P neuron responses are characterized by their tuning curves (Fig. 2), which can be quantified by the number of spikes elicited by stimuli at



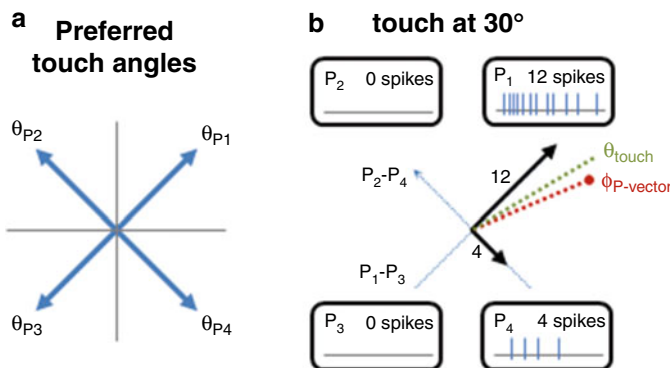
Leech Local Bend: Neural Coding of Touch Location, Fig. 2 The tuning curves for the mechanosensory P neurons. Response is expressed by the total spike count (normalized to maximum) as a function of touch angle. The

mean response is given by a solid blue line (different shade for each of the four P neurons), and for the case of P₂, the dotted lines indicate one standard deviation from the mean

different touch angles, θ_{touch} . The resulting tuning curves are cosine shaped, revealing broad tuning, with the peaks (or preferred touch angles θ_{P_i}) evenly distributed around the body perimeter. This suggests that touch angle is represented in a 2-D coordinate system with two orthogonal axes given by unit vectors pointing in the directions of the preferred touch angles (Fig. 3a). Four neurons are required because the spike count cannot be negative, so a pair of neurons, with preferred angles 180° apart, forms a single axis (i.e., P_1 – P_3 for one axis and P_2 – P_4 for the other). For a given touch angle, two P neurons are usually activated, one associated with each of the two axes (Fig. 3b). This pair of spike counts represents the touch angle just like an (x, y) pair in a Cartesian coordinate system. Such a representation is a 2-D version (four neurons) of the **population vector**, a population code first used to describe the neural coding of **reaching movements**. More generally, the population vector is the vector sum of all neurons' preferred angles, weighted by their respective spike counts; in other words, each spike produced by a given neuron is a “vote” for that neuron's preferred angle (see ► [“Computation with Population Codes”](#)). Figure 3b illustrates a simple example of how the population vector works on a single trial. A touch angle of 30° elicits 12 spikes in P_1 and 4 spikes in P_4 ; P_2

and P_3 are silent (Fig. 3b, insets). The magnitude of the vector in the direction of θ_{P_1} is 12 (P_1 – P_3) and that in the direction of θ_{P_2} is –4 (P_2 – P_4). The red dot shows the point (12, –4) in this coordinate system, with the touch angle predicted by the population vector ($\phi_{P\text{-vector}}$) given by the direction of the resultant vector.

While such cosine-tuning curves are suggestive, their presence does not necessarily indicate that the local bend network uses a population vector code. The next step is to compare the behavioral output (ϕ_{bend}) to the P neuron population vector prediction ($\phi_{P\text{-vector}}$). It is important to consider the variability of P neuron firing: while the mean spike counts of P neurons clearly indicate cosine tuning, the standard deviation of these responses is about 25% of the mean value (Lewis and Kristan 1998b). This is illustrated in Fig. 2 by the dotted lines, showing one standard deviation above and below the mean response of one P neuron. Taking this variability into account, the population vector estimate of touch angle has a root-mean-square error less than 3% (about 11°). If the leech uses a population vector code, then the bend direction cannot be any more accurate than this – the accuracy of the behavior is limited by the variability of the sensory input. While early experiments suggested bending angle to be within about 8% of touch angle (Lewis and Kristan



Leech Local Bend: Neural Coding of Touch Location, Fig. 3 (a) Preferred touch angles for each P neuron (i.e., touch angle of maximum response) are shown in the body coordinates introduced in Fig. 1a. (b) Example trial for a given touch angle (green). P neuron spike trains are

shown schematically in the insets. Each preferred angle is weighted by the associated spike count, and the angle of the resultant vector (P vector in red) is the touch angle predicted by the population vector (see text)

1998c), subsequent studies using more sophisticated measures have revealed behavioral accuracies closer to 4% (Zoccolan et al. 2002; Baca et al. 2005). Even so, a population vector based on P neuron spike counts is still sufficient to explain local bend accuracy, and thus, a more complicated algorithm, for example, involving the details of spike timing, is not necessary.

Further, one can also compare bend angle and P neuron population vector estimates on a trial-by-trial basis. As just discussed, the variability in P neuron firing leads to variability in the P neuron population vector. On a given trial however, one P neuron may fire more than average so that the population vector would be biased towards that neuron's preferred touch angle. Similarly, systematically manipulating the activity of one P neuron (using intracellular current injection) would also bias the population vector estimate. When such experiments were performed, the bend angle was biased in the predicted direction, showing a significant correlation between $\phi_{\text{P-vector}}$ and ϕ_{bend} (Lewis and Kristan 1998a).

These observations suggest that the local bend network uses a population vector code, but do not explain how the computation is performed. For this, we must consider the synaptic connections between network layers. This is no easy task. Although it is possible to use high-throughput techniques to estimate network connectivity, ultimately we need to record from many pairs of neurons. This was possible, although extremely difficult, in the local bend network (Lockery and Kristan 1990). The data showed that the population of local bend interneurons forms a distributed representation of the P neuron inputs. In other words, each interneuron receives inputs from multiple P neurons, but to varying extents. The result is that the interneurons, like the P neurons, are broadly tuned to touch angle, with their preferred angles distributed around the body perimeter (Lewis 1999). More specifically, the synaptic strength from a single P neuron to a given interneuron is related to the cosine of the difference in their preferred angles. This is exactly the type of connectivity that results in the accurate transfer of information encoded in a population vector (Abbott 1998).

Outlook

Despite the extensive support for this population vector strategy in the local bend network, subsequent studies have revealed more complexity at both the sensory and behavioral levels. Although the simple P neuron spike count is sufficient to account for the behavior, the precise timing of the spikes provides additional information. In fact, the relative latency between two P neurons more accurately represents touch angle than does the raw spike count (Thomson and Kristan 2006). It appears that the local bend network uses this information, but to what extent is not clear. Nonetheless, P neuron spike counts are sufficient to explain behavioral accuracy, suggesting that additional information is lost through the network layers. The details of information transfer through the local bend network are also unclear. We know however that the network includes a mechanism for gain control, allowing a robust bending response over a large range of touch intensities. This gain control is mediated by global inhibition that is balanced with the level of sensory excitation (Baca et al. 2008). Additional information loss in the context of local bending may be due to the multifunctional nature of many neurons in the ganglion. The same neurons are commonly used for different behaviors (Briggman and Kristan 2008). Such network-level insight has been achieved by advances in **voltage-sensitive dye imaging** of the whole ganglion. In principle, the entire local bend network can be monitored in parallel. This will lead not only to the identification of any unknown interneurons but also to a better understanding of information transfer (and loss) through population-coding networks.

Cross-References

► [Computation with Population Codes](#)

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Lévy Flights to Improve Balance Control

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LFP

- [Local Field Potentials in Olfaction](#)

LFPy: Multimodal Modeling of Extracellular Neuronal Recordings in Python

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Definition

LFPy is an open-source tool for calculating brain signals such as extracellular potentials and magnetic signals from simulated activity in multi-compartment neuron models, ranging from single cells to large neuronal networks. The tool is provided as a Python package and relies on the NEURON simulation environment.

Detailed Description

Electric extracellular measurements of neuronal activity in brain tissue have been one of the main workhorses in experimental neuroscience for several decades. Although such measurements are relatively easy to carry out, the large number of contributing sources to the measured signals renders the interpretation of the experimental data difficult. On the macroscopic scale, such as for measurements of the electric potential on the scalp, that is, electroencephalography (EEG) (Nunez and Srinivasan 2006), or measurements of magnetic fields outside the head itself, that is, magnetoencephalography (MEG) (Hämäläinen et al. 1993), the interpretation is further complicated by the fact that the measurements are performed some distance from the neural tissue itself. EEG signals are also affected by the different electric

conductivities of tissue between the brain and the electrodes (cerebral spinal fluid – CSF, bone and soft tissues) (Nunez and Srinivasan 2006).

The availability of biophysics-based *forward-modeling* tools is important for hypothesis testing with precisely defined mathematical models, where the experimental system, including neurons and measurement devices, is mimicked in the virtual model and simulated on a computer. Construction and improvements to *inverse* analysis methods applied to experimental data (i.e., inferring underlying neural activity from measurements) also call for improved forward-modeling tools. Inverse methods are required to better understand and analyze the link between measured brain signals and the underlying neural activity. Forward-modeling tools allow for models of measurements with known underlying neural activity, “ground truth”, that inverse methods can be validated against.

LFPy (LFPy.readthedocs.io) implements different established forward models for extracellularly recorded potentials and magnetic fields, stemming from activity in multicompartment neuron models (De Schutter and Van Geit 2009). Extracellular potentials in vicinity of the neurons are computed as distance-weighted sums of contributions from the transmembrane currents of the simulated neurons, while magnetic fields are either calculated from axial currents within the neurons or via the so-called current dipole moment calculated from the associated transmembrane currents. The current dipole moment is also used for EEG predictions. The corresponding electrostatic and magnetostatic forward models are derived using the appropriate volume conductor theory (Hämäläinen et al. 1993; Nunez and Srinivasan 2006; Einevoll et al. 2013).

Application

The first version of LFPy (Lindén et al. 2014, v1.0) incorporated the well-established scheme for extracellular potentials pioneered by Holt and Koch (1999), where transmembrane currents of multicompartment models are first computed using a domain-specific software (NEURON Simulation Environment, Carnevale and Hines (2006)). Then the extracellular potential is

computed as the distance-weighted sum over each current contribution, with weights derived using theory for an infinite homogeneous, isotropic, and ohmic volume conductor model.

This numerical scheme has been applied to predictions of the local field potential (LFP), that is, the low-frequency part of the extracellular potential (Pettersen et al. 2008; Lindén et al. 2010, 2011; Gratiy et al. 2011; Makarova et al. 2011; Schomburg et al. 2012; Łęski et al. 2013; Reimann et al. 2013; Martín-Vázquez et al. 2013, 2015; Głąbska et al. 2014; Mazzoni et al. 2015; Tomsett et al. 2015; Sinha and Narayanan 2015; Taxidis et al. 2015; Hagen et al. 2016, 2017; Głąbska et al. 2016; Ness et al. 2016, 2018; McColgan et al. 2017), as well as extracellular spike waveforms which carry more power at high frequencies (Holt and Koch 1999; Gold et al. 2006, 2007; Pettersen and Einevoll 2008; Pettersen et al. 2008; Franke et al. 2010; Schomburg et al. 2012; Thorbergsson et al. 2012; Reimann et al. 2013; Ness et al. 2015; Hagen et al. 2015; Miceli et al. 2017; Cserpán et al. 2017; Luo et al. 2018; Buccino et al. 2018, 2019).

Since LFPy 2.0 (Hagen et al. 2018), the tool has been extended to also support forward-model predictions accounting for anisotropic media, that is, with different conductivity in different directions (Goto et al. 2010), and discontinuous media where the conductivity is piecewise constant in a single direction. The latter can, for example, be used to mimic in vitro experimental setups using microelectrode arrays (MEAs) (Ness et al. 2015) or to mimic in vivo conditions where a jump in conductivity can be expected such as at the boundary between the brain and CSF. Furthermore, LFPy now incorporates calculations of axial currents across the neuronal morphology for estimating the magnetic field nearby the neuron (Blagoev et al. 2007). Hence, corresponding experiments using magnetic detection devices directly in neural tissue (Barbieri et al. 2016; Caruso et al. 2017) can be mimicked.

LFPy also features calculations of current dipole moments from transmembrane currents (Lindén et al. 2010), which is used for calculation of both EEG and MEG signals. For EEG predictions LFPy incorporates the analytical four-sphere

head model (Nunez and Srinivasan 2006), which was corrected by Næss et al. (2017), to account for the different conductivities of the brain, CSF, skull, and scalp. The computed current dipole moments can also be used with more complex head models (see, e.g., Huang et al. (2016)). MEG signal predictions in a spherically symmetric head model rely on a special form of the magnetostatic Biot-Savart law (ignoring effects of magnetic induction) (Nunez and Srinivasan 2006, Appendix C).

Finally, in contrast to its first release where the tool only supported simulations with a single cell instantiation at the time, LFPy also supports networks of synaptically interconnected neurons. Such network simulations can be executed on a single physical machine, but larger network simulations are better executed in parallel on high-performance computing (HPC) facilities (Hagen et al. 2018).

Architecture

LFPy is a Python package that presently (Hagen et al. 2018) provides different high-level class definitions which represent cells, populations, and networks of cells, synapses, intracellular stimulation devices (current and voltage clamps), and extracellular recording devices (representing both invasive and noninvasive equipment). LFPy's class definitions rely internally on NEURON's Python interface (Hines et al. 2009). As many illustrative LFPy usage examples are provided online (github.com/LFPy/LFPy/examples), we here only briefly summarize the main classes and their intended use and provide a simple use case below. The best way to learn the tool is by going through the various example files. More detailed technical documentation is available online (LFPy.readthedocs.io).

The most basic neuron representation in LFPy is provided by the `LFPy.Cell` class. A `Cell` object is typically instantiated with a chosen morphology, either on the form of a morphology file with instructions NEURON can digest (with file endings “.hoc,” “.asc,” “.swc,” or “.xml”) or a NEURON `SectionList` instance filled with `Section` references. A number of optional arguments can be used to set the passive parameters of

the cell model; additional routines to distribute, for example, active ion channels to different parts of the neuron; rules for spatial discretization of the corresponding cable model; and simulation settings (temporal duration and discretization). After instantiation, the cell object has several public methods that can be used to position and align the cell in space, return indices of different compartments of the model, and run the simulation.

Two additional classes are defined using inheritance from class `Cell`, namely, `TemplateCell` and `NetworkCell`. These can be used with existing “network-ready” single-cell models that use NEURON's *template* definitions which allow for multiple concurrent instantiations of individual neurons. In LFPy, however, the `TemplateCell`'s intended use is still for handling single-neuron simulations (serially), while `NetworkCell` objects are instantiated in neuronal network populations.

After a cell's instantiation, it can be instrumented with synapses by the creation of an arbitrary number of instances of class `LFPy.Synapse`. The main parameters of the `Synapse` class are a reference to the cell object itself, the compartment index where the synapse is located, and synapse type with synapse-specific parameters (time constants, weight, reversal potential, etc.). The synapse current and postsynaptic potential can optionally be recorded during the course of a simulation. The instantiated synapse has public methods to set its activation times, to either explicit values or determined stochastically using NEURON's `NetStim` class.

Intracellular stimulation devices (current and voltage clamps) can be set up using LFPy's `StimIntElectrode` class. The class is instantiated similar to synapses, but the name of point-process type has to be defined as well as its specific parameters. Recording of stimulation current and corresponding compartment membrane voltage can optionally be enabled.

The creation of networks, or simply different populations of concurrent `NetworkCell` instantiations, is in LFPy incorporated through its `Network` class. Its main parameters are the temporal discretization and duration of the simulation, the globally shared initial voltage for

compartments and simulation temperature which affects the active ion-channel dynamics. The network instance contains a public method to create populations of the same cell type (through class `Population`), that is, with the same parameters being passed to the `NetworkCell` instances upon their creation. The network also contains a public method to connect pre- and postsynaptic populations using shared synaptic parameters. Values for connection weights, delays, and synaptic locations can however be drawn randomly from desired function declarations such as `np.random.normal` with corresponding parameters or be set to constant values.

Example Code

Here, we demonstrate how to set up a simple LFPy simulation in Python. We define a simplified neuron representation with an active soma compartment and passive apical dendrite which receives strong synaptic input at the terminating end of the dendrite, with simultaneous calculation of the extracellular potential alongside the neuron. We first create a “ball and stick” morphology file, with a passive dendrite and active soma using NEURON’s HOC syntax from Python:

```
morphology = 'BallAndStick.hoc'
with open(morphology, 'w') as f:
    f.writelines(""" Create sections:
create soma[1]
create apic[1]
// Add 3D information:
soma[0] {
    pt3dadd(0, 0, -15, 30) // x,y,z,d in
um
    pt3dadd(0, 0, 15, 30)
}
apic[0] {
    pt3dadd(0, 0, 15, 3)
    pt3dadd(0, 0, 1015, 3)
}
// Connect section end points:
connect apic[0](0), soma[0](1)
// Set biophysical parameters:
forall {
    Ra = 100. // ohm*cm
    cm = 1. // uF/cm2
}
soma { insert hh }
apic {
```

```
insert pas
g_pas = 0.0002 // S/cm2
e_pas = -65. // mV
}""")
```

We then proceed to set up the simulation of the model, by first importing different classes from LFPy and also other packages we may need:

```
from LFPy import Cell, Synapse,
RecExtElectrode
import numpy as np
import matplotlib.pyplot as plt
```

First we instantiate the cell model, providing the name of the morphology file as well as simulation duration and resolution, and initial voltage for all compartments:

```
cell = Cell(morphology=morphology,
            tstop=100., # ms
            dt=0.05, # ms
            v_init=-65. # mV
            )
```

Next we instantiate the synapse with compartment index information, parameters for the chosen synapse mechanism, and set synaptic activation times:

```
synapse = Synapse(cell=cell,
                  idx=cell.get_idx(section='apic')
                  [-1],
                  syntype='ExpSyn',
                  weight=0.05, # uS
                  tau=5., # ms
                  e=0., # mV
                  record_current=True)
synapse.set_spike_times(np.array([10.,
15., 20., 25., 60.])) # ms
```

Then we instantiate the extracellular recording device, with a chosen value for the homogeneous extracellular conductivity and locations for the electrode contact points in space:

```
z = np.linspace(-100, 1100, 25) # um
electrode = RecExtElectrode
(sigma=0.3, # S/m
 x=np.zeros(z.size)+10,
 y=np.zeros(z.size),
 z=z)
```

Finally, we can simulate the model and predict the resulting extracellular potential:

```
cell.simulate(electrode=electrode)
```

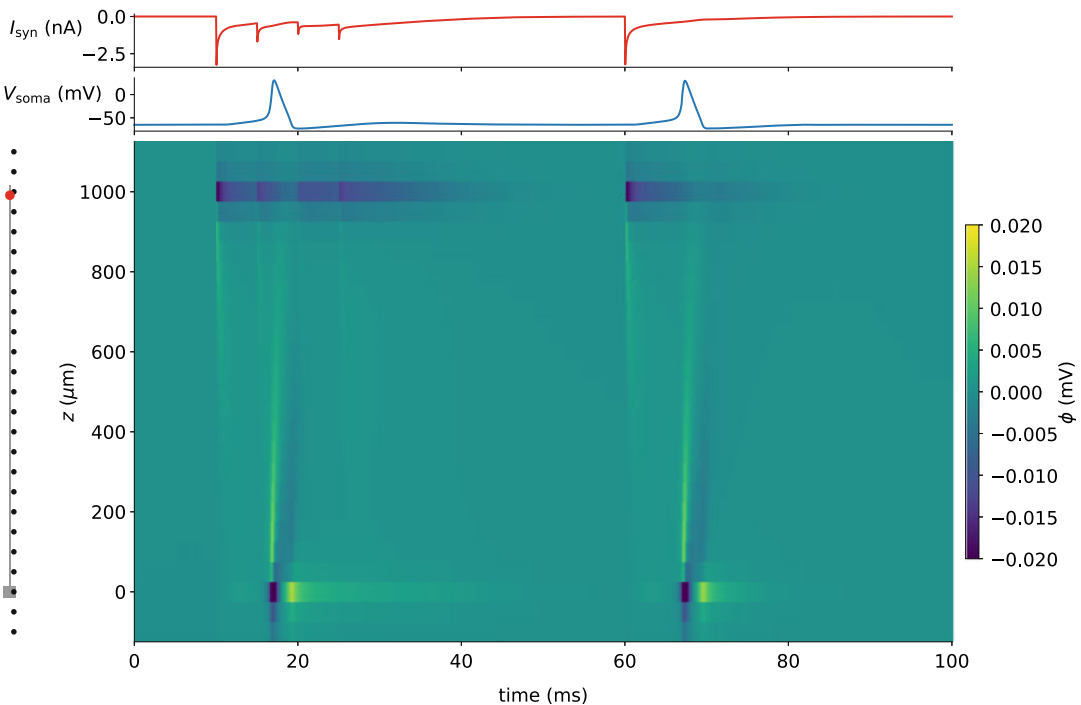
The “simulate” method of the cell does not return any data for storing, visualization, etc. but sets various attributes of the instantiated class objects. For the present example, these are “cell.tvec,” “cell.somav,” “synapse.i,” and “electrode.LFP”. These are all numpy array types which can easily be plotted using matplotlib, for example (see model output in Fig. 1). The membrane depolarizations caused by the synapse current (I_{syn}) result in action potentials at the soma (V_{soma}). Both synaptic input and action potentials result in traveling features in the extracellular potential (image plot), toward the soma for synaptic input and from the soma for action potentials. These

features are governed by the passive dendritic cable properties.

Electrostatic Forward Models

As the different electrostatic and magnetostatic forward models in LFPy are described in detail in Hagen et al. (2018), we here briefly summarize their main assumptions.

The relation between extracellular potentials and transmembrane currents is governed by volume conductor theory (Nunez and Srinivasan 2006; Einevoll et al. 2013). At frequencies relevant for neuronal processes (below 10,000 hertz or so), the derivation of the volume conductor theory from first principles is simplified by application of the so-called quasistatic approximation to Maxwell’s equations (Hämäläinen et al. 1993, p. 426). The extracellular medium is in all cases assumed to be *ohmic*, which implies a linear and



LFPy: Multimodal Modeling of Extracellular Neuronal Recordings in Python, Fig. 1 Single-cell example output. The morphology, synapse site (red dot), and recording locations (black dots) are shown on the left. The

respective synapse current (I_{syn}), soma potential (V_{soma}), and extracellular potential (ϕ) are shown as function of time from top to bottom

frequency-independent relation between currents and electric potentials (Pettersen et al. 2012; Einevoll et al. 2013; Miceli et al. 2017). Then, the simplest possible case is that of an *infinite homogeneous* (same in all locations) and *isotropic* (same in all directions) volume conductor (see, e.g., Hagen et al. (2018, Section 2.2.1)). The medium can then be simply represented by a *scalar* extracellular conductivity, which assumes that local variations throughout the tissue from glia, dendrites, axons, cell bodies, etc. are negligible when estimating the extracellular potential. This assumption of homogeneity appears valid for simulations mimicking recordings in, for instance, cortical gray matter (Goto et al. 2010).

For simple, analytically tractable circumstances, LFPy may also account for both inhomogeneous and anisotropic extracellular media. Inhomogeneities on the macroscopic level may arise at the interface between different tissue types such as white and gray matter or between the gray matter and the conductive CSF on top of cortex. For such cases, LFPy can account for the effects of a discontinuous jump in conductivity by use of the so-called method of images (MoI); see Hagen et al. (2018, Section 2.2.2) for details. Another application of the MoI has been to mimic in vitro experimental setups, where jumps in conductivity occur between the petri dish, the tissue sample, and the saline layer covering the sample (Ness et al. 2015).

LFPy also supports forward-model predictions with homogeneous *and* anisotropic media, meaning that the electric conductivity may depend on direction but not location. This functionality may be utilized to mimic anisotropy in cortex (Goto et al. 2010), assuming that the typical orientation of dendritic and axonal fibers may affect the conductivity. For details on the implementation, see Hagen et al. (2018, Section 2.2.3).

In order to predict EEG signals, LFPy provides the analytically tractable four-sphere head model (Nunez and Srinivasan 2006; Næss et al. 2017). This simplified head representation assumes radial symmetry, and the different electric conductivities of the brain, CSF, skull, and scalp are accounted for by corresponding concentric shells

with homogeneous and isotropic conductivity. Neuronal sources assumed to be some distance away from the measurement site are represented by their *current dipole moment*, computed from the transmembrane currents in the neurons; see Hagen et al. (2018, Section 2.3.1).

The very same current dipole moment is utilized in order to compute distal MEG signals, computed using a special form of the corresponding magnetostatic Biot-Savart law (Nunez and Srinivasan (2006, Appendix C); Hagen et al. (2018, Eq. 16 in Section 2.3.5)). When computing magnetic fields in proximity to the neurons, the axial currents computed from the membrane voltage in each compartment are used instead of the current dipole moment. In both cases, negligible contributions from volume currents to magnetic signals are assumed, that is, axial currents within neurons are the main contributors to magnetic measures of brain activity (Hämäläinen et al. 1993).

Extensions to LFPy

As LFPy is written in Python, a transparent and easy-to-learn programming language, LFPy's areas of application may with relative ease be extended to other measurement modalities or different forward models. Geometrically complicated variations in extracellular conductivity (including those introduced by the electrode device) can be accounted for using finite-element modeling (FEM (Logg et al. 2012; Lempka and McIntyre 2013; Ness et al. 2015; Næss et al. 2017; Buccino et al. 2019)) in order to map transmembrane currents to extracellular signals. In a similar manner, current dipole moments computed using LFPy can be used with detailed head models constructed from MRI data (Bangera et al. 2010; DeMunck et al. 2012; Vorwerk et al. 2014; Huang et al. 2016). Frequency-dependent conductive media may be accounted for by treating each Fourier component of recorded signals independently as pursued in Miceli et al. (2017).

One specific extension of the forward modeling scheme in LFPy is the so-called hybrid scheme for LFP predictions from point-neuron networks (Hagen et al. 2016). There, the

simulation of ongoing spiking activity is first conducted offline using simplified neuron representations. The resulting spikes are used as activation times of synapses distributed onto geometrically detailed multicompartment neuron models, before each individual cell's contribution to the LFP is simulated independently before summing up all contributions. Thus, the prediction of extracellular signals (LFP, EEG, MEG, etc.) of large neuronal networks is simplified by its disentanglement from simulations of recurrent network activity. Furthermore, the arduous effort of fine-tuning parameters of recurrently connected networks of biophysically detailed neuron models is avoided.

Another extension to LFPy is detailed models of extracellular electric stimulation of neurons. LFPy do not include forward models for the effect of electrode stimulation currents onto neurons per se but such can easily be constructed using the same assumptions as discussed above. These models will in fact be closely related to forward models mapping transmembrane current contributions to measured electrode potentials (through reciprocity). Given a prediction of the extracellular potential across the neuron's outer surface, it can already be set as a cable equation boundary condition using the `Cell.insert_v_ext` method, which relies internally on NEURON's extracellular mechanism.

Deployability and Documentation

LFPy is freely available (General Public License v3), runs on most common desktop computer operating systems (Linux, Unix, macOS, and Windows), and is presently tested with multiple versions of Python (2.7, 3.4–3.7). The software is made to run on computers ranging from laptops to HPC facilities. Its main dependencies upon installation are NEURON (neuron.yale.edu) installed with bindings to Python (Hines et al. 2009), NumPy (numpy.org), SciPy (scipy.org), h5py (h5py.org), mpi4py (bitbucket.org/mpi4py/mpi4py), and Cython (cython.org).

Installation

NEURON can usually be installed using pre-compiled installers directly from its homepage

(neuron.yale.edu), but certain systems (e.g., non-standard operating system configurations and HPC systems) may require compilation from source. More detailed instructions for installing both LFPy and NEURON on different common operating systems are provided through LFPy's online documentation (lfp.readthedocs.io).

The easiest way of installing stable releases of LFPy and its dependencies (except NEURON) is from the Python Package Index using the `pip` utility, by issuing in the terminal:

```
pip install LFPy --user
```

An existing installation can be upgraded by issuing:

```
pip install --upgrade --no-deps LFPy
--user
```

Here, the `--no-deps` option disables attempts to update also other installed dependencies. The software can be removed by issuing:

```
pip uninstall LFPy
```

Alternatively, LFPy can be installed from source code hosted at [GitHub.com/LFPy/LFPy](https://github.com/LFPy/LFPy). This repository contains the entire development history of LFPy using Git (<https://git-scm.com>). Installation of LFPy from source can be executed as follows:

```
cd <where to put LFPy sources>
git clone https://github.com/LFPy/LFPy.git
cd LFPy
pip install requirements.txt --user
python setup.py install --user
```

The GitHub homepage also offers the option to directly download compressed (zip or tar.gz) files with the source codes of LFPy.

In addition to the above requirements, also matplotlib (matplotlib.org) and the Jupyter Notebook (jupyter.org) are required to run all the example simulation scripts provided with LFPy. The different example files are provided with the LFPy source codes in the folder named `examples`.

Development and Documentation

Active development and bug/issue tracking related to LFPy are conducted in public at [GitHub.com/LFPy/LFPy](https://github.com/LFPy/LFPy). Fixes and new features are usually handled through Pull Requests, with automated build testing using Travis CI (travis-ci.org/LFPy/LFPy) and test coverage testing using Coveralls (coveralls.io/github/LFPy/LFPy). The full documentation for LFPy is provided at Read the Docs (lfp.readthedocs.io).

Cross-References

- [Cable Theory: Overview](#)
- [Current Source Density \(CSD\) Analysis](#)
- [Forward and Inverse Problems of MEG/EEG](#)
- [Local Field Potentials: LFP](#)
- [NEURON Simulation Environment](#)

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Various individuals who have contributed to LFPy's development are listed at [GitHub.com/LFPy/LFPy/graphs/contributors](https://github.com/LFPy/LFPy/graphs/contributors).

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Liley Model

- [Down Under Neural Population Models](#)

Linear System Kernel

- [Correlation Analysis of Parallel Spike Trains](#)

Linear/Nonlinear Dendritic Integration

- [Dendritic Computation](#)

Liquid Computing

- [Recurrent Network Models, Reservoir Computing](#)

Liquid State Machines

- [Recurrent Network Models, Reservoir Computing](#)

Local Biopotentials

► Local Field Potential and Deep Brain Stimulation (DBS)

Local Field Potential

► Local Field Potential, Relationship to Unit Activity

Local Field Potential and Deep Brain Stimulation (DBS)

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Synonyms

Deep electroencephalography; Local biopotentials; Neuronal population biopotentials

Definition

Local field potentials (LFPs) are biosignals representing the activity of large neuronal populations that can be recorded from intracranial low-impedance electrodes. Electrodes implanted in the human basal ganglia and other subcortical

structures for deep brain stimulation (DBS) therapy in patients with movement and neuropsychiatric disorders can be used to record deep LFPs. The analysis of LFPs in patients after DBS surgery, particularly those with Parkinson's disease, revealed that the basal ganglia information encoding is based on oscillations that respond to movements, behavioral stimuli, cognitive processing, and emotional arousal. The LFP oscillatory code in the last decade helped in clarifying basal ganglia pathophysiology and was regarded as possibly implicated in the still unknown DBS mechanisms of action.

LFPs were hence studied during and after DBS, to understand whether changes in the oscillatory code may reflect the DBS clinical effect of patient's symptoms.

In patients with Parkinson's disease, even though the exact mechanisms remain controversial, ample evidence shows that DBS specifically modulates LFP oscillations. Also in dystonia, pallidal DBS affects some specific oscillations that could be connected with hyperkinesias. The DBS action on LFPs depends on the stimulation voltage, and LFP-specific oscillations can be used to finely tune DBS stimulation frequency.

LFP analysis during DBS, despite providing fundamental insights on basal ganglia pathophysiology in movement disorders, has contributed to a significant advancement on the technology for DBS, being the basis of new adaptive DBS (aDBS) systems that are able to change moment-by-moment DBS stimulation parameters (frequency, voltage, pulse width, etc.) according to the patient's clinical state as reflected by the oscillatory LFP code.

Detailed Description

DBS and Deep Electrophysiological Recordings in Humans

Deep brain stimulation (DBS) is remarkably effective in treating movement disorders such as Parkinson's disease (PD), dystonia, and essential tremor (Benazzouz et al. 1993; Pollak et al. 1993; Moro et al. 1999, 2010; Volkmann 2004; Vidailhet et al. 2005; Nazzaro et al. 2012;

Pizzolato and Mandat 2012). DBS surgery includes a first surgical procedure for stereotactic electrode implantation into specific nuclei of the basal ganglia or other subcortical structures. After that, a secondary surgery is performed to insert the electrical pulse generator in a submuscular pouch under the pectoralis major muscle and to connect it to the electrodes previously positioned.

The location of DBS electrodes depends on the type of neurological disorders and the predominant symptoms of patient. The subthalamic nucleus (STN) is the election target for PD, even though the globus pallidus internus (GPi) is sometimes used to control symptoms (Anderson et al. 2005), as well as the thalamic ventralis intermedius (VIM) (Woods et al. 2001) and pedunculopontine nucleus (PPN) (Tykocki et al. 2012). The GPi is presently the election target for dystonia (Vidailhet et al. 2005), whereas patients with essential tremor are mainly implanted in VIM (Nazzaro et al. 2012). In the past years, encouraging data obtained in patients with severe depression, obsessive-compulsive disorders, and Gilles de la Tourette syndrome have extended DBS therapeutic applications to neuropsychiatric disorders (Mallet et al. 2008; Aouizerate et al. 2009; Porta et al. 2009; Greenberg et al. 2010; Ward et al. 2010; Goodman and Alterman 2012). In these pathologies, the election target structure is still under research and widened the panorama of the structures in which DBS electrodes are implanted, including the nucleus accumbens (Priori et al. 2013) and the hypothalamus (Rosa et al. 2012a).

Although ample evidence, obtained over the past decade, shows that DBS reduces motor disability and improves quality of life of patients with movement disorders, the mechanism underlying the therapeutic action of DBS remains essentially unexplained (Rosa et al. 2012b).

Despite enormous progress achieved by experimental studies and functional models (Wichmann and DeLong 1996), little is known about the signals controlling information processing and integration in the human basal ganglia, “the dark basement of the brain” (Wilson 1925). From a scientific viewpoint, DBS provides a unique window into the human basal ganglia, thus helping to understand the neurophysiological mechanisms

underlying motor functions and cognitive and behavioral information processing. In fact, DBS electrodes offer a unique opportunity to record the electrical activity from the basal ganglia and the other subcortical structures in which electrodes are implanted.

There are two main time windows in which electrodes allow to record electrical activity in the target deep brain structures. During DBS surgery, high-impedance exploratory microelectrodes are used to record the activity of single neurons to optimize the DBS target localization before the final electrodes are definitively implanted. Besides serving clinical purposes, single-unit (SU) recordings also provide a powerful research tool, to correlate anatomical, functional, and electrophysiological information (Levy et al. 2000, 2001; Stefani et al. 2002; Romanelli et al. 2004). After the final DBS electrodes implant and before its leads are connected to the subcutaneous electrical pulse generator, electrodes are accessible for electrophysiological recordings from the target structure. Because the final DBS electrodes have low impedance, they are unsuitable for recording single-neuron activity but are ideal for recording local field potentials (LFPs).

What Are LFPs?

LFPs reflect the synchronous presynaptic and postsynaptic activity in large neuronal populations and can detect focal network rhythms that are not necessarily observable in single neurons or neuron pairs (Levy et al. 2002; Priori et al. 2004; Brown and Williams 2005; Kuhn et al. 2005b; Zaidel et al. 2010; Marceglia et al. 2011).

LFP recordings and analysis demonstrated for the first time the oscillatory nature of basal ganglia (Brown 2003). This was in line with several studies showing that basal ganglia functional processes are mediated not only by firing rates but also and mainly by firing patterns (Bevan et al. 2002; Terman et al. 2002), oscillatory phenomena (Gatev et al. 2006; Uhlhaas and Singer 2006; Wilke et al. 2006), and wave propagation (Rubino et al. 2006).

LFP recordings provide more information than SU recordings, not only because LFPs can detect focal network rhythms but also because, unlike SU, LFPs can be recorded both intraoperatively (Weinberger et al. 2006; Bronte-Stewart et al. 2009) and days after DBS surgery. Researchers can study LFPs at different intervals from DBS electrode implant: acute phase (3–4 days after surgery) (Foffani and Priori 2006; Priori et al. 2006), chronic phase (30 days after surgery) (Rosa et al. 2011), and hyperchronic phase (years after surgery) (Giannicola et al. 2012). Moreover, patients are typically free to move during LFP experimental recordings, and they can be engaged into more complex and ecological tasks than during DBS surgery while SUs are recorded.

The Oscillatory LFP Code

A huge amount of LFP studies in humans revealed in the last 15 years unknown functions of basal ganglia particularly in PD patients during the execution of motor, cognitive, and behavioral tasks showing the existence of a “code” in LFP oscillations corresponding to the clinical condition of patient (Table 1) (Marceglia et al. 2007).

Basal ganglia LFPs oscillate in several frequency bands, ranging from low frequencies (2–7 Hz), to beta frequencies (8–20 Hz, alpha/low beta; 21–35 Hz, high beta), gamma frequencies (60–80 Hz), and very high frequencies (250–350 Hz).

The most studied and debated STN LFP oscillations are in the beta range because they seem to reflect the patient’s motor state. Beta band LFP activity, especially in the lower frequency range (8–20 Hz), and its nonlinear interactions are disrupted by antiparkinsonian medication (Levy et al. 2002; Foffani et al. 2003; Priori et al. 2004; Marceglia et al. 2006; Weinberger et al. 2006; Giannicola et al. 2010, 2013) and correlate with motor symptoms (Kuhn et al. 2004, 2006b, 2008; Ray et al. 2008; Zaidel et al. 2010). Otherwise, STN low frequencies [alpha (4–10 Hz)] correlate with dyskinesias: when the patient experiences dyskinesias, the low-frequency rhythm, particularly around the 8 Hz range, dramatically

increases (Foffani et al. 2005a; Alonso-Frech et al. 2006; Rodriguez-Oroz et al. 2011). Very low-frequency LFPs increase after anti-parkinsonian medication, thus confirming that they correlate with an improvement in the patient’s clinical condition (Priori et al. 2004), even though their overboosting is associated with hyperkinesias (Silberstein et al. 2003; Obeso et al. 2004; Priori et al. 2004). As well as inducing changes in low frequencies, increasing dopaminergic medications also modulates gamma and very high frequencies (Foffani et al. 2003; Brown and Williams 2005; Lopez-Azcarate et al. 2010). Very high-frequency LFP changes may be involved in the mechanism responsible for the therapeutic actions of DBS (Foffani and Priori 2006) on motor symptoms.

Basal ganglia LFP oscillations are also involved in motor execution. STN and PPN LFP beta oscillations correlate with all phases of voluntary movement: preparation, execution, and recovery (Foffani et al. 2005b; Tsang et al. 2010), whereas alpha oscillations in the PPN correlate with gait performance (Thevathasan et al. 2012).

Specific LFP oscillations in the STN might intervene in non-motor processing (Marceglia et al. 2011). In particular beta LFP oscillations correlate with motor representation including action organization and context recognition (Kuhn et al. 2006a; Marceglia et al. 2009) and with response inhibition (Rektor et al. 2009; Ray et al. 2011; Anzak et al. 2012; Alegre et al. 2013); low-frequency LFP oscillations correlate with cognitive information related to decision making (Cavanagh et al. 2011; Fumagalli et al. 2011; Rosa et al. 2013) and alpha/low beta with limbic and emotional information (Kuhn et al. 2005a; Brucke et al. 2007; Huebl et al. 2011; Buot et al. 2013). These observations suggest that LFP oscillations are also markers reflecting changes in patients’ cognitive and behavioral state and that controlling them might prevent post-DBS cognitive and behavioral impairments (Marceglia et al. 2011).

The presence of multiple rhythms at different frequencies differentially modulated by movement and drugs consistently supported the hypothesis that pathological oscillations recorded

Local Field Potential and Deep Brain Stimulation (DBS), Table 1 Local field potential code in movement disorders

	Parkinson's disease				Non-motor processing							Dystonia	Essential tremor
	Rest		Movement										
	Off l-dopa	On l-dopa	Dyskinesia	Tremor	Off l-dopa	On l-dopa	Gait	Motor representation	Response inhibition	Decision	Emotion	Rest	Rest
STN	Low frequency (2–12 Hz)	↓	↑↑	–	≈	≈	–	–		↑	↓	–	↑↑
	Low beta (13–20 Hz)	↑	↓↓	↓	↓	↓	–	↓	↓	–	–	–	↓
	High beta (21–35 Hz)	↑	≈↓	↓	↓	↓	–	↑	–	–	–	–	↑
	Gamma (45–60 Hz)	↓	–	–	–	–	–	–	↑	–	–		
	300 Hz (250–350 Hz)	↓	–	–	↑	↑	–	–	–	–	–	–	–
	Low-beta/high-beta synchronization	↑↑	↓↓	–	–	–	–	–	–	–	–	–	–
	Low-frequency synchronization	↓	↑	↑↑	–	–	–	–	–	–	–	–	–
	EMG-LFP coherence	–	–	–	↓	–	–	–	–	–	–	–	Low frequency
	EMG-LFP cross-bicoherence	–	–	–	–	–	–	–	–	–	–	–	EMG alpha generated by STN + EMG low frequency
Tremor frequency	–	–	–	↓	–	–	–	–	–	–	–	–	

through LFP activity are involved in the physiology of movement disorders and are crucial for understanding the mechanisms of DBS action.

DBS Action on the Oscillatory LFP Code

Mechanisms underlying the remarkable DBS efficacy in reducing motor and non-motor symptoms related to movement disorders remain largely unclear. The study of the interaction between LFPs and DBS was regarded as able to provide insight into this debate. At present, the main results, given the wider number of patients undergoing DBS surgery in the last decade, were obtained for PD, recording LFPs from STN. Only one study recorded LFPs from GPi in patients with dystonia (Table 2).

STN LFPs and DBS in PD

Despite the large spectrum of oscillations characterizing STN LFPs, the beta band (8–30 Hz) and the low-frequency band (2–7 Hz) were mainly investigated provided their consistent and specific response to antiparkinsonian medication and movement (Table 1). Aiming to understand whether DBS may mimic the drug effect and mechanism of action, studies focused on LFP response to DBS first addressed beta and low-frequency modulations. Even though the exact mechanisms remain controversial, ample evidence shows that DBS specifically modulates LFP oscillations in patients with PD.

The main issue to be faced while studying LFP response to DBS is the huge artifact produced by the stimulation pulse (Rossi et al. 2007). The stimulus artifact saturates the recording preamplifier and prevents from LFP recording while DBS is on.

For this reason, as a first step, researchers investigated LFP response immediately after DBS was turned off (Brown et al. 2004; Foffani et al. 2006; Priori et al. 2006; Wingeier et al. 2006; Kuhn et al. 2008; Bronte-Stewart et al. 2009), obtaining controversial results. Whereas some works reported an STN DBS-dependent decrease of beta oscillations in both STN and GPi nucleus (Brown et al. 2004; Wingeier et al. 2006; Kuhn

et al. 2008; Bronte-Stewart et al. 2009), others failed to confirm this result (Foffani et al. 2006). Moreover, the same authors, instead of observing a DBS-dependent beta decrease, reported a consistent increase in the very low-frequency activity that could be observed in all the patients studied and that correlated with the clinical response to DBS ceasing (Priori et al. 2006).

However, this experimental approach had several drawbacks: (i) even though the implanted electrodes were already connected to the recording system when DBS was turned off to start LFP recordings, the amplifier saturation stopped after some seconds, thus preventing from the investigation of the DBS on–off transition; (ii) some rhythms responded to the DBS stimulus almost immediately, and responses were difficult to detect after DBS was turned off because the transition could not be recorded; and (iii) this approach did not guarantee, a priori, that LFP changes observed after turning DBS off reflect LFP changes taking place during DBS.

To overcome such barriers, Rossi et al. (2007) proposed a new technology, called FilterDBS, able to record LFPs while DBS was turned on from the same electrode. FilterDBS is based on a two-stage amplification in which, after a low pre-amplification stage, a low-pass filter is applied to the recording signal cutting the frequency components above 50 Hz, before a second amplification stage. This technology prevented from DBS-dependent amplifier saturation, working on the frequency separation between the LFP oscillatory components and DBS stimulation frequency. The introduction of FilterDBS demonstrated that LFPs can be recorded without turning DBS off, that LFP signals can be continuously recorded and analyzed during DBS therapy, and that LFPs are modulated during DBS, thus opening the window on DBS-induced changes in STN LFP oscillations.

The first studies with LFPs recorded during DBS confirmed some previous results: whereas DBS-induced beta decrease was not observable in all patients, a low-frequency increase of controversial nature was consistently present in all patients (Rossi et al. 2008) (Fig. 1a).

Local Field Potential and Deep Brain Stimulation (DBS), Table 2 Research studies about local field potentials and deep brain stimulation

Patients (n, disease)	LFP from	Time recordings from surgery	After DBS/during DBS	DBS from	DBS		Duration (μs)	Frequency band studied	DBS effect	References
					Frequency (Hz)	Voltage/current				
2 PD	GPI	Intraoperative	After DBS	STN	> 70	2 mA	200	Beta	↓	Brown et al. (2004)
2 PD	STN	Intraoperative	After DBS	STN	185	3 V	90	Beta (11–30 Hz)	↓	Wingeier et al. (2006)
7 PD	STN	2 days	After DBS	STN	130	Range 3.5–7 mA	60	Very low frequency (1–1.5 Hz)	↑	Priori et al. (2006)
7 PD	STN	2–3 days	After DBS	STN	130	Range 1.6–2.9 V	60	Beta (13–20 and 20–35 Hz)	≈	Foffani et al. (2006)
								High frequency (60–90 and 250–350 Hz)	≈	
11 PD	STN	2–5 days	After DBS	STN	130	Range 2–5 V	60	Beta (13–30 Hz)	↓ ^a	Kuhn et al. (2008)
8 PD	STN	2 days	During DBS	STN	130	Stimulation strength of 80% of the threshold for side effects	60	Low frequency (1–7 Hz)	↑	Rossi et al. (2008)
								Low beta (8–20 Hz)	≈	
								High beta (21–35 Hz)	≈	
16 PD	STN	Intraoperative	After DBS	STN	185	3 V	90	Beta (13–35 Hz)	↓	Bronte-Stewart et al. (2009)
9 PD	STN	3 days	During DBS	STN	130	Stimulation strength for clinical effects	60	Individual beta (8–20 Hz)	↓ ^b	Giannicola et al. (2010)
7 PD	STN	Intraoperative; 30 days	During DBS	STN	130	Range 2–3.5 V	60	Individual beta (8–20 Hz)	↓ ^b	Rosa et al. (2011)

(continued)



Local Field Potential and Deep Brain Stimulation (DBS), Table 2 (continued)

Patients (n, disease)	LFP from	Time recordings from surgery	After DBS/during DBS	DBS from	DBS			Frequency band studied	DBS effect	References
					Frequency (Hz)	Voltage/current	Duration (μs)			
16 PD	STN	Few days	During DBS	STN	130	1–3.5 V (step increments of 0.5 or 1 V)	60	Beta (11–30 Hz)	↓ ^c	Eusebio et al. (2011)
19 PD	STN	3 days	During DBS	STN	130	Range 3–5 V	60	Low frequency (2–7 Hz)	↑	Giannicola et al. (2013)
1 secondary Dystonia, 1 DYT3+ dystonia	GPi and GPe	Intraoperative	During DBS	GPi and GPe	185	0.5–1–2–3 V	90	Alpha (4–10 Hz)	↓ ^d	Whitmer et al. (2013)
								Beta (13–35 Hz)	↓ ^d	
27 PD	STN	3 days; 7 years	During DBS	STN	Range 90–190	Range 2.5–3.6 V	60	Low frequency (2–7 Hz)	↑	Giannicola et al. (2012)
								Individual beta (8–20 Hz)	↓ ^c	
8 PD	STN	Intraoperative	During DBS	STN	185	0.25–0.5–1–1.5–2–2.5–3 V		Beta (13–35 Hz)	↓	Whitmer et al. (2012)

Rows are the studies about local field potentials (*LFPs*) and deep brain stimulation (*DBS*). Columns represent details about the studies. Upward arrows indicate an increase; downward arrows indicate a decrease. The symbol $\approx$ means no change. *GPi* globus pallidus internus, *GPe* globus pallidus external, *PD* Parkinson's disease

^aOnly patients that demonstrated a temporary persistence of clinical benefit after cessation of DBS were analyzed

^bOnly in nuclei with significant beta band activity at baseline

^cIn selected patients with a discrete spectral peak in the beta band

^dOnly in patient with DYT3+ dystonia

After that, studies combining pharmacological (levodopa) and electrical (DBS) therapy showed that whereas levodopa produced a specific disruption of the beta oscillation in all patients, DBS-induced decrease in the beta band was limited to those patients having a high beta activity at rest. In addition, in the combined levodopa–DBS therapy administration, which is a common situation in the clinical chronic DBS setting, the levodopa-induced effect predominates (Giannicola et al. 2010) (Fig. 1b).

Conversely, another study using a similar methodology showed that DBS suppressed global beta oscillations in all nuclei selected (Eusebio et al. 2011) (Fig. 1c). Even though this finding seems to contradict the results of Giannicola et al. (2010), it is important to underline that Eusebio and colleagues selected only nuclei that showed significant high beta peak, thus indirectly confirming Giannicola's results. During DBS, a stimulation-dependent low-frequency increase starts when DBS is turned ON and is consistent across patients (Giannicola et al. 2013). This observation agrees with the STN DBS-induced low-frequency band increase observed minutes after DBS is turned off and also corresponds with the persistent STN DBS-induced improvement in the patients' clinical state (Priori et al. 2006; Rossi et al. 2008).

Evidence on the correlation between patient's clinical state and DBS-induced changes in LFPs suffers nevertheless from a major drawback, namely, that all experimental sessions took place within days after brain surgery when a lesion effect and local brain edema remain. To date, only two studies have investigated how DBS influences LFPs recorded more than 1 week after DBS surgery (Rosa et al. 2011; Giannicola et al. 2012). Rosa et al. (2011) investigated STN LFPs recorded in PD patients 30 days after surgery for DBS electrode placement and compared them with those recorded immediately after surgery. To do so, the surgery for electrical pulse generator implant, which usually takes place some days after the surgery for DBS electrode placement, was postponed, ensuring patient's safety, without any adjunctive complication. Thanks to this protocol, it was possible to show that weeks after

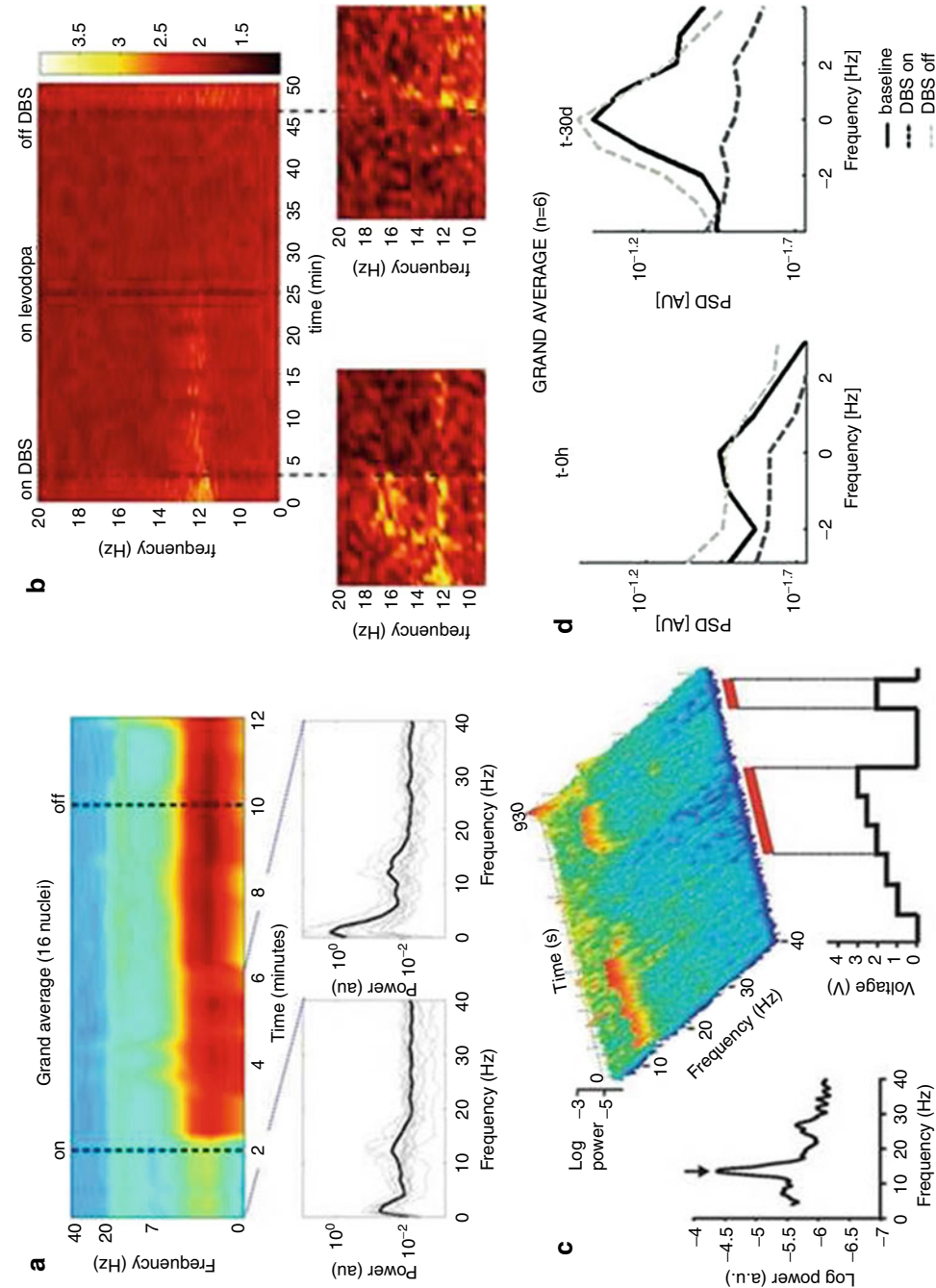
DBS electrode implant, STN LFPs remain stable and that in a subgroup of patients whose recordings showed a strong beta activity at baseline, LFP beta activity recorded during DBS decreased immediately after and 30 days after DBS surgery (Rosa et al. 2011) (Fig. 1d). Moreover, studying LFPs during battery replacement surgery, Giannicola et al. (2012) showed that rest LFP oscillations recorded before DBS were turned on and before levodopa administration a few days after DBS electrode implant remain almost unchanged after patients receive chronic DBS for 7 years. The effect of DBS on LFPs does not change years after DBS electrode implantation and chronic stimulation: whereas in a subgroup of patients, whose LFP recordings showed strong beta activity at baseline, beta activity decreased, and low-frequency activity invariably increased.

Pallidum LFPs and DBS in Dystonia

Only one study investigated LFP activity in the globus pallidus during high-frequency DBS in patients with dystonia (Whitmer et al. 2013). Whitmer et al. recorded LFP from GPi and GPe in a patient with DYT3+ dystonia at rest and during high-frequency DBS showing that alpha (4–10 Hz) and beta (13–35 Hz) bands had visible peak at rest and were attenuated during DBS in both nuclei with immediate and dramatic improvement of patient's symptoms. In the same study alpha and beta bands were not attenuated during DBS in the patient with secondary dystonia, and 6-month follow-up did not show measurable benefit from DBS. Authors speculated that the reduction of LFP activity in specific bands during pallidal DBS would result in an improvement in dystonic symptoms. In particular results showed by Whitmer et al. raise the question whether beta activity now recorded in both primary (Silberstein et al. 2003; Weinberger et al. 2006; Liu et al. 2008) and secondary dystonias may play a pathophysiological role in hyperkinesias.

What Happens if We Change Stimulation Voltage?

Eusebio and colleagues recorded LFPs during continuous increase of voltage of high-frequency



Local Field Potential and Deep Brain Stimulation (DBS), Fig. 1 (continued)

stimulation and showed significant attenuation of the power of beta band during high-frequency DBS at clinically therapeutic voltage levels (≥ 2 V), but not at voltages below 1.5 V (Eusebio et al. 2011) (Fig. 1c).

In a different study, Whitmer et al. tested whether the STN LFPs were attenuated during DBS and, if so, whether the degree of attenuation increased with higher DBS voltages, comparing DBS in two regions of STN: dorsal to and within the STN. The results demonstrated that the beta band was attenuated during high-frequency DBS; the degree of attenuation monotonically increased with DBS voltage in both locations, but this voltage-dependent effect was greater in the central STN than the dorsal STN. In particular DBS dorsal to STN attenuated beta power only at 3 V, whereas DBS within STN attenuated relative beta at voltage >1.5 V (Whitmer et al. 2012). The question as to whether beta and its DBS-induced attenuation correspond to the location of maximally clinically efficacious stimulation remains to be determined.

What Happens if We Change Stimulation Frequency?

In PD, LFP activity in the gamma/high gamma and high frequency range is considered as

fundamental to promote movements and force with specific patterns of the gamma activity observed when patients move (Foffani et al. 2003; Brown and Williams 2005; Anzak et al. 2012; Tan et al. 2012; Alegre et al. 2013). These observations in PD were confirmed by those in dystonia (Brucke et al. 2012). Conversely, the beta activity is considered as “antikinetic,” at least when the beta oscillation is concentrated in its low range.

On this basis, one study addressed the problem of changing DBS stimulation frequency. The authors, after studying the LFP pattern of patients during the levodopa on condition and during movements, compared standard DBS, no DBS, and DBS administered at the low frequency (4–10 Hz), beta frequency (11–30 Hz), and gamma frequency (31–100 Hz). Individual frequencies were obtained measuring the highest decrease in the low-frequency and in the beta band, and the greatest increase in the gamma frequencies when the patient was on medication and during movements. The authors showed that, whereas low-frequency and beta DBS worsen the motor Unified Parkinson’s Disease Rating Scale (UPDRS) scores, the gamma frequency DBS improved it. However, the UPDRS improvement obtained during gamma stimulation did not differ

Local Field Potential and Deep Brain Stimulation (DBS), Fig. 1 Subthalamic local field potentials and deep brain stimulation. (a) Subthalamic local field potential (STN LFP) power spectrum changes during DBS in patients with Parkinson’s disease (PD) (grand average, 16 nuclei). Top: time course of LFP power spectrum changes over 12 min (deep brain stimulation [DBS] for 8 min). DBS begins at the vertical black dashed line on the left and ends at the vertical black dashed line on the right. Bottom: instantaneous power spectra before DBS (baseline) on the left and 4 min after DBS began, on the right. Black lines: the average spectrum; gray lines spectra of individual nuclei. Note that during STN DBS the low-frequency power increases and beta power remains unchanged. (b) Time course of STN LFP in a representative patient with PD. STN LFP time-varying power spectrum in the beta band (8–20 Hz). Top: time–frequency plot over the entire experimental session (50 min total time, 42 min DBS); the black dotted lines, from the left, correspond to turning DBS on, to the clinical effect of levodopa, and to turning DBS off. Bottom: transient states when DBS was turned on (left panel) and off (right panel). Note that

levodopa and DBS both reduced beta oscillations but that the levodopa-induced effect predominates. (c) Effect of DBS on STN LFP in a representative patient with PD. On the right power autospectrum of LFP recorded without stimulation. On the left time–frequency log power LFP spectrum. Bars along the time axis denote ongoing DBS at 2.0 and 3.0 V. Note that DBS at ≥ 2.0 V suppressed the spectral peak, stimulation at 1.5 V transiently increased power peak, and stimulation at 3.0 V delayed its return after stimulation ended. (d) STN LFPs recorded immediately (t-0h) and 30 days (t-30d) after DBS surgery in patients with PD: grand average for nuclei showing significant beta band ($n = 6$ nuclei) power spectral density (PSD) in the three experimental conditions: prestimulation (baseline – black, solid line), during stimulation (DBS on – gray, dashed line), and after stimulation (DBS off – light gray, dashed line). Beta band PSD was aligned on beta peak of each nucleus (0 Hz). Note that beta band power decreases in the on DBS condition in both t-0h and t-30d for nuclei with significant beta band power (Reproduced from Rosa et al. (2012b) with permission from Elsevier)

from that obtained during standard high-frequency stimulation, and UPDRS worsening with low-frequency and beta DBS did not differ from the no DBS condition (Tsang et al. 2012). These results seem in contrast with other studies showing that STN DBS in the gamma range (around 50–60 Hz) did not provide PD motor signs reduction (Rizzone et al. 2001; Moro et al. 2002). However, in these past studies, gamma frequencies were not chosen according to the patient-specific LFP pattern, thus suggesting that DBS specifically interferes with the oscillatory code of the patient in the high frequency range (Foffani and Priori 2006).

LFPs and DBS Mechanisms of Action

The prevalent hypothesis that beta band is a pathological marker of PD motor signs is supported by correlations between improved motor impairments and attenuated beta after medication (Foffani and Priori 2006; Kuhn et al. 2006b, 2008; Weinberger et al. 2006; Ray et al. 2008). The attenuation of beta during high-frequency DBS would lend further evidence in support of this hypothesis because DBS also alleviated PD motor symptoms (Deuschl et al. 2006; Kuhn et al. 2008; Ray et al. 2008) raising the possibility that suppression of pathological activity may mediate the effects of DBS.

Evidence that DBS acts by modulating pathological oscillatory activity towards a pattern that the basal ganglia–cortical system finds more physiological receives strong support from several studies (Silberstein et al. 2005; Kuhn et al. 2006b; Giannicola et al. 2012). STN DBS acts not only by modulating pathological STN activity but also by projecting modulated activity to GPi and SNr (Hammond et al. 2007), the output structures in the basal ganglia. The new STN DBS-driven output might be more palatable to basal ganglia–cortical loops supporting the hypothesis that effective therapies (both medication and DBS) shift overall activity patterns towards a more regular pattern that is better tolerated by the system and manifested by clinical improvement (Kopell et al. 2006).

In particular, in PD, the pathological activity could be the excessive beta synchronization and the efficacy of STN DBS could depend on the regularization of STN activity and suppression of synchronized activity observed in downstream nuclei. Moreover, the stimulation amplitude and frequency dependency of DBS efficacy could stem from whether stimulation is able to effectively suppress and or regularize the pathological oscillations observed in basal ganglia (Cagnan et al. 2009; Hahn and McIntyre 2010).

LFPs for the Future of DBS Therapy: Adaptive DBS Systems

LFP analysis during DBS, despite providing fundamental insights on basal ganglia pathophysiology in movement disorders, has contributed to a significant advancement on the technology for DBS, being the basis of new adaptive DBS (aDBS) systems (Priori et al. 2013).

In fact, present technology provides DBS with constant stimulation settings that are adjusted only during control visits. This stimulation strategy is in contrast with the nature of the pathologies treated with DBS that typically fluctuate over time and, therefore, leaves symptoms partly uncontrolled (Krack et al. 2003; Deuschl et al. 2006; Romito and Albanese 2011). A system able to adapt moment-by-moment stimulation parameters to the patient's clinical condition would hence overcome such limitations. In addition, increasing evidence suggests that several cognitive and behavioral adverse effects, observed years after DBS therapy started, are related to the amount of stimulation delivered (Bronstein et al. 2011; Romito and Albanese 2011).

To obtain a “fine-tuning” of DBS settings (including frequency, amplitude, pulse width, and waveform) in a short time window, an “intelligent” DBS system should detect fluctuations and adverse effects as well as more subtle pathophysiological changes and change settings accordingly without patients waiting until the next control visit for reprogramming (Priori et al. 2005a, b; Marceglia et al. 2007; Burgess et al. 2010; Rosin et al. 2011; Santaniello et al. 2011; Winestone et al. 2012).

aDBS is based on a feedback model that measures and analyzes a control variable related to the patient's clinical condition and changes the stimulation settings of an intelligent stimulator implanted in the chest (Welter et al. 2004; Priori et al. 2005a, b, 2013).

The control variable must be a physiological variable measurable in patients undergoing DBS, without implants other than those patients already carry (electrodes, extensions, and pulse generator), and able to reflect changes in the patient's condition.

For their ability to reflect clinical conditions, neuronal oscillations, measured through LFPs from DBS target structure, can be used as control variable. All the evidence summarized in the previous sections of this entry supports the choice of LFPs as control variable for aDBS: LFPs are recordable without additional implants, they correlate with the patient's clinical condition (Table 1), and they can be recorded during DBS on (Table 2), without artifacts (Rossi et al. 2007), and recorded over time after electrode implant (Rosa et al. 2010) showing DBS-induced modulations similar to those recorded a few days after electrode implant (Rosa et al. 2011).

At present, only external, research-oriented aDBS devices are available. Before the new aDBS systems can be implanted in patients, research should better define the control LFP-based biomarkers that best reflect the patient's clinical state, refine feedback algorithms, develop a prototype device for use in patients, and conduct a clinical study to compare the new aDBS system with the current "reference-standard" DBS system.

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Local Field Potential and Movement Disorders

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Definition

Local field potentials (LFPs) represent the sum of low-frequency electrical activities in the

extracellular medium close to a recording electrode. They predominately reflect field changes related to the flow of electrical current at synapses in the vicinity of the electrode, although other tissue components (neuronal spiking, glia potentials) may also contribute. The amplitude of LFPs is affected by the synchrony of dendritic potentials and by the geometry of dendritic arbors. Most of the electrical events that contribute to LFP signal occur within 200–400 μm of the tip of the electrode (Katzner et al. 2009; Xing et al. 2009).

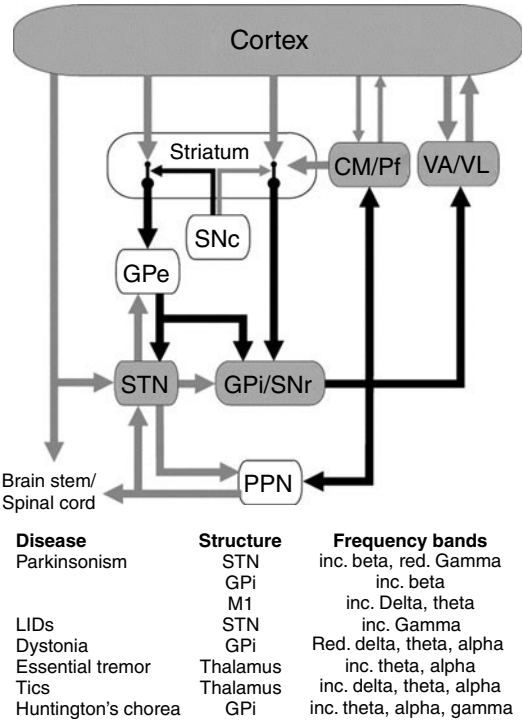
LFPs can be recorded with microelectrodes, usually referenced against an electrode outside of the brain, or with macroelectrodes, usually as differential recordings between two poles of the same electrode. Because most of the spectral power of LFPs is found at relatively low frequencies (<300 Hz), LFP signals are often low-pass filtered (with a filter cutoff of 100 or 300 Hz). Most analyses of LFPs are done with frequency-domain analysis methods, dividing the signal into delta (0–4 Hz), theta (4–7 Hz), alpha (7–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz) components.

Detailed Description

The literature on the role of local field potentials (LFPs) in movement disorders is extensive. In order to keep this review focused, we have chosen to limit our discussion to some representative results of recordings from the basal ganglia and related subcortical structures in human movement disorder patients. Animal studies and the results of cortical recordings are mentioned as appropriate, but are not covered in detail.

Before describing the results of LFP recording studies in movement disorders, we will briefly review the anatomy of the basal ganglia because most movement disorders involved changes of electrical activity patterns in these structures. The basal ganglia are subcortical components of several circuits that also involve the thalamus and cortex. Traditionally, at least four different segregated circuits are distinguished, including circuits involved in motor, oculomotor, associative, and limbic functions (Alexander et al. 1990). As

shown in Fig. 1, the basal ganglia are further divided into the striatum (putamen and caudate in primates), the subthalamic nucleus (STN), the external and internal segments of the globus pallidus (GPe and GPi), and the substantia nigra with its dopaminergic pars compacta (SNc) and the GABAergic pars reticulata (SNr). The STN and striatum receive monosynaptic projections from the frontal cortex (Akkal et al. 2007; Haynes and Haber 2013), while GPi and SNr are the



Local Field Potential and Movement Disorders, Fig. 1 The basal ganglia-thalamocortical motor network. *Black arrows* indicate inhibitory connections and *gray arrows* indicate excitatory connection. Structures marked in *gray* are frequently used for LFP recordings. The table at the *bottom* of the figure summarizes the principal findings in studies of frequency-domain analyses of LFP recordings in the diseases mentioned in the text. Abbreviations: CM centromedian nucleus of the thalamus, *dec.* decreased, *GPe* external segment of the globus pallidus, *GPi* internal part of the globus pallidus, *inc.* increased, *Pf* parafascicular nucleus of the thalamus, *PPN* pedunculopontine, *SNc* substantia nigra pars compacta, *SNr* substantia nigra pars reticulata, *STN* subthalamic nucleus, *VA* ventral anterior nucleus of thalamus, *VL* ventrolateral nucleus of thalamus. (Figure modified from Galvan and Wichmann (2008) and used with permission)

output nuclei of the basal ganglia, projecting to specific nuclei in the thalamus and brain stem.

As the basal ganglia receive excitatory input from the cerebral cortex and send (net inhibitory) output back to the cortex via the intercalated thalamus, the corticobasal ganglia-thalamocortical system is considered to function as an at least partially closed negative feedback loop (Joel and Weiner 1994). Among several other neuromodulators, the release of dopamine in the striatum strongly affects the function(s) of these loops. This neurotransmitter is involved in a variety of specific functions of the basal ganglia such as motor learning, response inhibition, or the facilitation of movement (Do et al. 2012).

Most of the classic movement disorders are associated with abnormal basal ganglia functions, and several involve altered dopaminergic transmission (Albin and Mink 2006). Recordings of LFPs in patients undergoing deep brain stimulation (DBS) surgery or in animal models of these diseases have mostly focused on the nuclei shaded in gray in Fig. 1. Studies in patients and in animal models have their respective advantages and disadvantages. While recordings in patients give direct information on the human disease, it is ethically impossible to obtain true control data from humans, and most patients undergoing surgery have received other therapies previously, which may affect the results of recording studies. LFP recordings in animals are far more controlled and can be obtained at baseline and during a variety of disease states. However, none of the animal models of movement disorders fully replicates the rich phenotype of the corresponding human disorders.

LFP Studies in Brain Diseases

Parkinson's Disease

While Parkinson's disease (PD) involves degeneration of neurons in many brain regions, the defining physical signs of the disease, i.e., tremor, bradykinesia, akinesia, and rigidity, are caused by the loss of dopaminergic cells in the SNc and the resultant degeneration of the dopaminergic projections between the SNc and the striatum and

other basal ganglia nuclei (and potentially cortex). The dopamine loss most severely affects components of the motor circuit of the basal ganglia, although other circuits are also affected. The loss of the dopaminergic innervation in the striatum is thought to lead to abnormal neuronal activity patterns throughout the basal ganglia and related areas in the thalamus and cortex (Galvan and Wichmann 2008).

Studies in human patients with advanced PD have shown that the disease is associated with prominent beta-band oscillations in LFP recordings from the STN (for review see Stein and Bar-Gad 2013), giving rise to the view that synchronized oscillations within the basal ganglia-thalamocortical network of connections are a key feature of PD. This notion is supported by the fact that beta-band oscillations are reduced by antiparkinsonian treatments such as dopaminergic medications or high-frequency stimulation of the STN (Bronte-Stewart et al. 2009; Brown et al. 2001; Kuhn et al. 2008; Levy et al. 2002; Priori et al. 2004; Wingeier et al. 2006). Increased beta-band oscillations have also been described to occur in GPi (Brown et al. 2001; Cassidy et al. 2002), and (presumably) abnormal delta- and theta-band activities have been found in the primary motor cortex of parkinsonian patients (Neufeld et al. 1994; but see Sebban et al. 1999; Serizawa et al. 2008; Soikkeli et al. 1991). Studies in dopamine-depleted (6-hydroxydopamine treated) rats have also documented an increase of the power of beta-band oscillations of LFPs in the basal ganglia (Avila et al. 2009; Mallet et al. 2008; Sharott et al. 2005).

While there is, thus, strong reason to believe that abnormal oscillations occur in the basal ganglia in severely parkinsonian humans or animals, it is less clear whether the oscillations (or the phenomena underlying them) *cause* parkinsonism. There is, in fact, evidence suggesting that beta-band activity in the STN contributes to akinesia (Kuhn et al. 2004; Williams et al. 2005), but other studies in humans failed to demonstrate a strong correlation between clinical impairments and STN beta-band activity (Kuhn et al. 2009; Ray et al. 2008; Weinberger et al. 2006; Zaidel et al. 2010a), and the effects of direct

stimulation of the BG in the beta range of frequencies, designed to mimic the effects of beta-band LFP oscillations, are only subtle (Chen et al. 2007, 2011; Eusebio et al. 2008). Furthermore, studies in parkinsonian monkeys have shown that the animals develop beta-band LFP oscillations only in late stages of parkinsonism, while less severe parkinsonism is not associated with increased beta-band oscillations (Devergnas et al. 2012).

The lack of a clear link between LFP oscillation and parkinsonism underlines that the recorded LFP oscillations are not likely to be pathologic per se but are a proxy for the presence of synchronized oscillatory single-neuron activities. Even if such synchronized single-cell oscillations are a primary pathophysiologic event (which has not been conclusively shown yet), the degree of oscillations and synchrony in the early stages of parkinsonism may simply not lead to recordable LFP oscillations.

Levodopa-Induced Dyskinesia

Choreiform dyskinesias are a side effect of long-term therapy with levodopa in approximately 50% of PD patients within 5 years of commencing levodopa therapy (Del Sorbo and Albanese 2008; Fahn 2000). Levodopa-induced dyskinesias (LID) are a major limitation of levodopa therapy and one of the principal reasons why patients with advanced PD seek surgical treatment, such as DBS applied to GPi or STN. Studies of LFP recordings in such patients showed that beta-band activity is reduced during periods of LIDs, while spectral peaks around 9 and 70 Hz are prominent (Alonso-Frech et al. 2006; Weinberger et al. 2012). The reduction of beta-band activity and the increase in high gamma-band oscillations (around 70 Hz) resemble the levodopa-related responses in non-dyskinetic PD patients, suggesting that these peaks are not specifically related to LIDs (Brown et al. 2001; Williams et al. 2002). However, the 9 Hz peak during LIDs is similar to what was found in the GPi LFP recordings from patients with dystonia (see below) and may, thus, represent an LFP oscillation signature of involuntary movements (Liu et al. 2002). This hypothesis is further supported by a finding of increased coherence at frequencies

below 10 Hz in a patient contralateral to unilateral dyskinesias, compared to the other side (Foffani et al. 2005). As mentioned above, such results do not prove causation; the low-frequency oscillatory activities may simply indicate an altered network state that is conducive to involuntary movement.

Dystonia

Dystonia is characterized by intermittent and sustained muscle contraction, often involving co-contraction of agonist and antagonist, which leads to involuntary abnormal movements and postures. Dystonia is often associated with an increase of low-frequency oscillations (<12 Hz) in LFP recordings from the basal ganglia of patients undergoing DBS lead placement procedures, particularly in the GPi (Chen et al. 2006b; Liu et al. 2002; Silberstein et al. 2003; Weinberger et al. 2012). The LFP oscillations correlate with oscillations found in EMG recordings (Chen et al. 2006a; Liu et al. 2006). Furthermore, a reduction of low-frequency GPi LFP oscillations was found to accompany alleviation of dystonia by use of “sensory tricks” (Tang et al. 2007).

As in the other disease models mentioned, a causal link between oscillations and phenotype is not certain, but, based on the cited observations, it is possible that low-frequency neuronal oscillations in the pallidum drive dystonic muscle contractions or contribute to abnormal processing of afferent information at the pallidal (or striatal) level. Unfortunately, there are few convincing animal models of dystonia, so that a detailed study of the pathophysiologic significance of the oscillatory activity is not possible at the moment. However, in one of the available models, the *dt^{sz}* mutant hamster, increased low-frequency LFP activity in the pallidum was, indeed, identified during and between paroxysms of dystonia (Gernert et al. 1998).

Essential Tremor

Unlike the previous entities in this entry, essential tremor is a movement disorder that does not seem to be directly dependent on abnormal basal ganglia activity or on changes in dopamine release in the basal ganglia. Essential tremor often occurs in families and usually manifests as an asymmetric

action tremor at 4–12 Hz, predominantly involving the hands or head, and not accompanied by major other neurological signs, with the possible exception of mild gait disturbances and some cognitive dysfunctions (Raethjen and Deuschl 2012). Most patients gain satisfactory control of their tremor with medications. Patients with medication-resistant disabling ET benefit from ablative or stimulation treatment, usually directed at the ventral motor nuclei of the thalamus. Although it has proven difficult to convincingly identify a central oscillator that causes the tremor, several lines of evidence have implicated the olivocerebello-thalamic system in its pathophysiology (for review see Raethjen and Deuschl 2012). Studies in this field have shown that the action tremor is associated with excessive theta-alpha activity in the cerebello-thalamocortical network (Air et al. 2012). An early study found LFP oscillations in the cerebellar-receiving nuclei of the thalamus in the 8–27 Hz range in patients with either ET or cerebellar outflow tremor (Marsden et al. 2000). Llinas et al. (1999) suggested that ET movements represent the product of abnormal cross frequency modulation, in which low-frequency thalamic oscillations would influence the generation of pathologic beta or gamma activity (Llinas et al. 1999). A more recent examination of inter-frequency correlation (or modulation) of the LFPs recorded in the motor thalamus of patient with ET corroborated this view (Kane et al. 2009).

Tics

Tics are stereotyped sudden movements, vocalizations, or complex behavioral acts. In marked distinction to other hyperkinetic movement disorders, tics are associated with a premonitory urge and can be temporarily suppressed. While tics are a very common and usually well tolerated, severe tics can significantly interfere with behavior. Additional disability results from the fact that severe tics are frequently associated with obsessive-compulsive symptoms, as is often the case in cases of Tourette syndrome (TS). TS is generally seen as a neurodevelopmental disorder that involves motor and limbic corticobasal ganglia-thalamocortical circuits, specifically networks involving orbitofrontal and prefrontal

dorsolateral cortices (Kalanithi et al. 2005; Worbe et al. 2012).

LFP recordings from the ventralis oralis complex of the thalamus done in TS patients who underwent surgical treatment for their symptoms, and who did not have tics during the recording, showed peaks of oscillatory activity in the 2–13 Hz range (Marceglia et al. 2010). Similarly, a comparison between recordings from a patient with mild tics with recordings from a population of patients with severe tics leads to the suggestion that the amplitude of low-frequency thalamic oscillations may be related to tics (Priori et al. 2013b). Other studies have suggested that the power in the gamma band (30–40 Hz) in LFP recordings from the centromedian thalamic nucleus is positively correlated with tic improvement after high-frequency stimulation (Maling et al. 2012).

LFP changes related to tic-like movements have also been seen in studies in rodent and monkeys (Darbin and Wichmann 2008; Marsden et al. 1975; Muramatsu et al. 1990; Nakamura et al. 1990; Yoshida et al. 1991) in which pharmacologic blockade of striatal GABA receptors resulted in rhythmically recurring stereotypies. These abnormal movements have been variously interpreted as myoclonus, dyskinesias, seizures, or, most recently, as tics (McCairn et al. 2009, 2013; Worbe et al. 2009, 2013). It has been shown that striatal injections of GABAA receptor antagonists lead to high-amplitude LFP activity and burst spiking of interneurons and projection neurons in the striatum (Darbin and Wichmann 2008; Muramatsu et al. 1990; Nakamura et al. 1990; Yoshida et al. 1991), cortex, and cerebellum (Darbin and Wichmann 2008; McCairn et al. 2013). Based on these and other results, it has been hypothesized that tics may result from the sudden regional failure of intra-striatal inhibitory processes (Albin and Mink 2006), leading to local synchronization of striatal activity, local oscillatory activities (detectable in LFP recordings), and the release of unintended movements. Individual patients usually have very stereotypic tics, suggesting that the specific tic phenotype is caused by a regionally specific abnormality in the somatotopically highly organized striatum.

Huntington Disease

Huntington disease (HD) is an autosomal dominantly inherited neurodegenerative disorder that characteristically leads to chorea (defined by jerky, random, and uncontrollable movements) as well as emotional symptoms and cognitive decline. The chorea is thought to result from striatal pathology and disturbances of corticostriatal transmission (Walker 2007). Although a variety of transgenic rodent models exist, most do not replicate the motor phenotype of HD.

LFP studies are very limited in this field. Two studies, utilizing the rapidly progressive R6/2 huntingtin-overexpressing strain of mice, revealed the presence of aberrant striatal LFP oscillation in the delta, theta, and gamma bands. At rest, striatal activity was characterized by prominent gamma band (30–40 Hz) in the “HD” group compared to control animals. With increasing behavioral demands (for instance, during episodes of exploration), the abnormally high corticostriatal coherence in the gamma range of frequencies is normalized (Hong et al. 2012; Miller et al. 2011).

A small number of HD patients with devastating motor symptoms have undergone surgical ablative or stimulation treatments, targeting GPi (Biolsi et al. 2008; Hebb et al. 2006; Moro et al. 2004). In one such study (Groiss et al. 2011), involving a patient with gene-testing-confirmed HD, LFPs in the motor portion of GPi showed strong oscillatory power in the 4–12 Hz and in the 35–45 Hz range close to the effective DBS target site. This preliminary result is in line with the cited data from the HD mouse model, implicating low gamma-band LFP oscillations in the pathologic process. The increase in 4–12 Hz oscillation activity in GPi resembles that in other hyperkinetic disorders (see above and Silberstein et al. (2003)).

Significance and Use of LFP Recordings in Movement Disorder

There remains great uncertainty with regard to the generation of LFPs and their ultimate pathophysiologic relevance in movement disorders. As mentioned above, LFPs strongly reflect postsynaptic

potentials in ensembles of cells. LFPs are therefore often taken as measures of inputs to the brain area from which the LFPs are recorded. The amplitude of LFPs in given brain regions is also a function of the specific cellular arrangements of cells in the studied area. For instance, the regular laminar arrangement of the cerebral cortex favors the generation of large-amplitude LFP signals, while the irregular arrangement of basal ganglia neurons results in smaller LFP amplitudes because electrical field are canceling each other out under these circumstances.

The synchrony or temporal correlation between inputs to the area under study is another factor that determines the amplitude of LFP signals. Synchronous inputs to a given brain area do not only lead, via summation, to larger LFP amplitudes but are also more likely to cause spiking activities than asynchronous inputs. The amplitude of LFPs is therefore not only an indicator of the synchrony of inputs to the recorded brain area but also a measure of correlated activities of the neurons that receive the inputs at the recording site (Goldberg et al. 2004). Other physiologic phenomena that may be related to synaptic activities (for instance, changes in blood flow (Magri et al. 2012)) are also related to LFP amplitudes.

Measurable LFP oscillations may arise if the disease process in question causes abnormal oscillatory activities of ensembles of neurons in the basal ganglia or in structures anatomically linked to them (Bevan et al. 2002; Plenz and Kital 1999). Alternatively, it is possible that an increase in synchrony between neurons affects certain frequency bands more than others, leading to resonance phenomena in these frequency bands. Such changes could occur and could alter LFP oscillations, even if individual neurons do not alter their activity significantly (see, e.g., Terman et al. (2002)).

LFP recordings do not only provide a convenient tool to learn more about the pathophysiology of brain disorders but can also be used to guide and expedite surgical procedures. Currently, electrophysiologically guided neurosurgical procedures rely on lengthy single-cell recordings with microelectrodes which are then

exchanged for the DBS (or lesioning) probes toward the end of the intervention. The use of LFP recordings may be a favorable alternative to the single-cell recordings, shortening the procedure and reducing targeting errors. In fact, some authors have started to explore the use of spectral analysis of intraoperatively recorded LFPs (while advancing DBS electrodes into the brain) to guide electrode placement, particularly in the STN (Chen et al. 2006c; Miyagi et al. 2009). For example, in PD patients, beta-band activity was found to increase progressively during the electrode descent and was maximal at the target (Chen et al. 2006c). This result was confirmed by Miyagi et al. (2009) who found an increase of power in the theta, alpha, and beta bands a few millimeter above the dorsal border of the STN (Miyagi et al. 2009). The spatial resolution of contemporary methods of LFP-based targeting is not fully sufficient, however, and needs to be further improved before it can be recommended as a replacement for microelectrode recording (Zaidel et al. 2010b).

Another exciting application of our emerging knowledge of LFP oscillation patterns is the use of disease-related LFP characteristics to regulate DBS parameters in “closed-loop” feedback regimes. Such adaptive DBS strategies may allow us to better control fluctuating or transient disease manifestations, reduce stimulation-related side effects, and prolong the battery life of the implanted devices (for review see Priori et al. 2013a). Closed-loop modulation of stimulation has already been used in clinical trials for refractory epilepsy (Fridley et al. 2012) where short-term stimulation can be triggered based on analyses of brain activity patterns that predict or signify seizures. Closed-loop control of DBS devices in movement disorder patients is more difficult, because the correlation between the recordable electrical signals and the severity of disease symptoms is generally weak and because DBS in these disorders is usually continuous rather than episodic as in epilepsy patients. It remains challenging to obtain reliable LFP recordings in the face of stimulation artifacts produced by ongoing stimulation. However, the general feasibility of closed-loop approaches in

movement disorder cases has been demonstrated with computational modeling studies (Santaniello et al. 2011) and with experimental studies in which cortical (single neuron) activity patterns were used to trigger STN stimulation in parkinsonian monkeys (Rosin et al. 2011). Very recently, adaptive deep brain stimulation has been used in PD patients, demonstrating greater efficacy and lower power consumption than achievable with conventional open-loop stimulation (Little et al. 2013). The authors of this study used short-term changes in beta-band LFP power (lasting less than 1 s) to trigger the stimulation, based on previous work showing that motor impairments were correlated with beta-band stability in the STN (Little et al. 2012). These results are promising, but the signal analysis and control of the DBS device still required an external computer, and the miniaturization (and *overall* power consumption) of an implantable closed-loop system remains an issue (Starr and Ostrem 2013).

Conclusion

Even if the functional significance of LFP oscillation remains unclear, the ready availability of LFP recordings from both human and animal sources has greatly increased our understanding of movement disorders and other diseases. The discussed disease examples suggest that abnormal basal ganglia oscillations in the delta-alpha range of frequencies are common in patients with hyperkinetic disorders, as well as in animal models of these conditions, while LFP oscillations in the beta band characteristically accompany parkinsonism. Fortunately, even in the absence of unifying pathophysiologic hypotheses to explain the generation of specific LFP patterns, the characteristics of the recorded signals may be empirically used to improve the outcome of surgical interventions. It is important to remember in these efforts that the current focus on frequency-domain features of LFPs is largely driven by the ease with which such characteristics can be analyzed. It may be fruitful to extend the analytical repertoire in the future to also capture feature in the time domain, such as nonlinear characteristics.

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Local Field Potential Decoding

► Decoding Field Potentials

Local Field Potential in the Visual System

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Definition

Low-frequency component of the continuous time-varying electrophysiological signal recorded using intracranial extracellular electrodes placed

inside the visual cortex. It is dominated by local cooperative activity of neural networks occurring in a volume of tissue around the tip of the electrode.

Detailed Description

Biophysical Origin

It is thought that the main contribution to the local field potential (LFP) derives from synchronous activation of neurons in the surrounding cortex. The LFP represents the sum over typically many thousands of local electrical fields that are generated within individual neurons. When a neuron is activated by the arrival of an excitatory postsynaptic potential on its dendrite, charged ions pass through its membrane which normally acts as an electrical insulator (Eccles 1951). An inflow of positive ions is termed current sink by convention, whereas an outflow of positive ions is termed current source. Since inflowing positive ions must be compensated for by an appropriate outflow of positive ions, there must be a current source corresponding to every sink. While current sinks reflect membrane depolarization and neuronal excitation, current sources can, for example, result from hyperpolarization or the action of ionic pumps of the neuron that restore the membrane potential to its equilibrium value. The spatial separation between sources and sinks during neural activation gives rise to an electrical dipole within each neuron, whose magnitude depends on the transmembrane ionic flow. The geometry of neural dendrites determines whether a measurable LFP signal is generated from the dipoles within individual neurons. If all neurons had symmetric “closed-field” dendritic geometry or exhibited randomly oriented dendritic trees, then individual electrical dipoles would tend to cancel each other, and no LFP signal could be measured. However, pyramidal neurons of the cortex exhibit an “open-field geometry,” such that their apical dendrites are all aligned parallel to each other and perpendicular to the cortical layer structure. This causes an alignment of the electrical dipoles in these pyramidal cells when these are synchronously activated, which permits their summation and in turn generates a robust LFP signal.

In addition to synaptic contributions described above, there are a number of additional factors that can influence the LFP. For example, intrinsic properties of the membrane may exhibit resonance such that depolarization or activation of the neuron results in a self-sustaining voltage oscillation (Silva et al. 1991). Other neuronal events have also been shown to contribute to the LFP, including direct electrical communication between neurons via gap junctions (Traub et al. 2004), interactions between neurons and glial cells (Poskanzer and Yuste 2011), and potentially also dendritic calcium spikes. Unlike the action potential, which has a clear functional role as transmitting information from one neuron to another, the LFP is not thought to have a direct role in information processing or transmission. Because of this, it has been sometimes considered to be a mere epiphenomenon. However, in recent years interest in the LFP has accelerated, and it is now widely considered to be a signal that provides useful information about the local processing that occurs in the cortical volume near the electrode tip. In part, this resurgent interest stems from studies that have linked hemodynamic signals, including the functional magnetic resonance imaging (fMRI) signal that is extensively used to study human cognition, to aspects of the LFP (Logothetis 2003; Niessing et al. 2005). An interesting and hitherto largely unexplored issue is whether the LFP itself exerts any ephaptic influence on neural processing, such that the extracellular voltage fluctuations of the LFP might be sensed by local neurons and in turn influence, for example, their excitability. This remains an open issue, but studies using transcranial magnetic stimulation have indeed shown that the electrical gradients of the LFP are within a range that can affect action potential generation and cognitive behavioral performance (Marshall et al. 2006; Ozen et al. 2010).

Characteristics

The LFP often exhibits oscillations, and these are traditionally classified into separate frequency bands on the basis of characteristic behavioral states associated with each band. These bands,

together with the approximate frequency range, are delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–20 Hz), and gamma (20–80 Hz). These bands are also used for analysis of the electroencephalographic (EEG) signal, and the LFP is in fact closely related to the EEG but has superior signal-to-noise ratio and spatial specificity, since it is not subject to the filtering of electrical signals by the skull. The LFP, in similarity to all neurophysiological brain signals, is stochastic, and each repetition of a particular experimental condition yields a distinct time series. During a typical neurophysiological study, about ten repetitions are conducted per experimental condition. Averaging of all repetitions for a given condition yields the visual evoked potential (VEP), which generally consists of a number of positive and negative deflections in a time range between about 30 ms and 400 ms after the presentation of a visual stimulus. The time of the first observable VEP deflection is called visual response latency and represents the time of arrival of visual signals from the eye via the visual pathway. Subsequent VEP deflections are related to local processing of the visual signals within the neural circuits of the visual cortex. To further characterize the VEP, the approach of current source density (CSD) estimation has been introduced (Mitzdorf 1985) and is commonly applied in the analysis of VEP signals. CSD estimation requires VEP signals to be recorded from multiple layers of the cortex, which can be achieved by successively advancing a recording electrode through the layers or by employing a multi-contact depth electrode capable of simultaneous recording of LFP signals from the six layers of the cortex. The CSD of a small-volume element of the cortex can be written as the divergence of the current flow from that surface element under the assumption of an ohmic medium:

$$\text{CSD}(\mathbf{x}, \mathbf{y}, z) = -\nabla(\sigma \nabla \Phi(\mathbf{x}, \mathbf{y}, z)),$$

where σ is the conductivity tensor and $\Phi(\mathbf{x}, \mathbf{y}, z)$ is the field potential.

Under the assumptions of dendrites being elongated in the vertical (z) direction and therefore

current flowing mainly along this dimension, as well as homogenous conductivity medium, this reduces to:

$$\text{CSD} = -\sigma_z \frac{\partial_2 \Phi}{\partial^2 z}$$

Note that homogeneity of conductivity is only approximately true, since the cerebral spinal fluid (CSF) surrounding the brain exhibits about five times higher conductivity than cortical gray matter. This of course means that the above solution is distorted particularly if large reservoirs of CSF are nearby, as is the case in brain structures close to the ventricles.

Using a three point approximation of the second derivative, this results in the following equation for the CSD:

$$\begin{aligned} \text{CSD}(z, t) &\approx \frac{\partial_2 \Phi(z, t)}{\partial^2 z} \\ &\approx \frac{\Phi(z + h, t) - 2\Phi(z, t) + \Phi(z - h, t)}{h^2} \end{aligned}$$

Thus, the CSD value at cortical depth z and time t can be written as a sum of the experimentally determined VEP value Φ at that depth z and at cortical depths above ($z - h$) and below ($z + h$). Under the assumptions described above, the CSD provides information about in which layer of the cortex outward positive ion flow or sources occurs, as well as about the laminar location of extracellular sinks.

The VEP and CSD estimates consider only those portions of the LFP that are time-locked to the onset of a visual stimulus, whereas LFP deflections whose timing varies from one repetition to the next are lost in the averaging process. To faithfully estimate these components, the LFP is first band-pass filtered in an appropriate frequency band, and then the estimates of the power in this band on all repetitions of a particular condition are averaged. LFPs are generally measured against a ground position that is far away from the visual cortex, for example, a metal skull screw over the frontal cortex, and are typically in the range of about $\pm 100 \mu\text{V}$.

Primary Visual Cortex (V1) Visual Evoked Potential (VEP)

The primary visual cortex is the cortical area that receives visual information from the retina via the lateral geniculate nucleus of the thalamus, with most projections arriving in the thalamocortical recipient layer 4 and some also in layer 6. From layer 4, which is often referred to as the granular layer due to the presence of granular cells in this layer, visual signals are sent to the supragranular layers 2 and 3 where they are processed further by cortical circuits (Douglas and Martin 2007). These supragranular layers are the main site of cortico-cortical information exchange and are thus involved both in sending and reception of signals from higher-order cortical areas. In the case of primary visual cortex, strong reciprocal projections exist, for example, with extrastriate visual cortical areas such as V2 or V4. The highly recurrent nature of cortical function generally complicates the interpretation of VEP signals, since these are influenced not just by bottom-up inputs from the ascending visual pathways but also by recurrent feedback from higher visual areas. The earliest VEP deflections are however thought to be determined by the ascending inputs. For example, in macaque monkey V1, the VEP displays a number of features that are related to these anatomical structural characteristics (Schroeder et al. 1998). Accordingly, strongest responses, in terms of VEP deflections and CSD values, occur in thalamo-recipient layer 4 of the cortex, and both layer 4 and layer 2/3 exhibit an initial current sinks consistent with neural activation by the feed-forward pathway. An interesting aspect of the V1 VEP is a prominent reversal of polarity in the early prominent VEP deflection occurring around 50 ms between layer 4 and layers 5/6 that can be used as a marker to estimate the border between granular and infragranular recording sites during neurophysiological experiments. Using the V1 VEP as a measure of response latency in terms of the earliest detectable change of the VEP signal yields values of about 30 ms, considerably larger than corresponding values of about 15 ms observed in the visual thalamus.

Higher Visual Cortex Visual Evoked Potential (VEP)

VEPs invariably accompany spiking activity in response to visually presented stimuli, not only in V1 but also for other brain regions that are part of the visual system, including the extrastriate visual cortex, the inferior temporal and parietal cortices, as well as certain areas of the prefrontal cortex where visual information is used for guiding action. Since synaptic activity is the major determinant of the LFP, this signal provides information about the source of these synaptic inputs. For a cortical neuron, the input source comes mostly from the same cortical column by way of recurrent local connectivity, as well as to a lesser degree from brain regions that send projections to the neuron under study. Conversely, local action potential activity is related mainly to local recurrent processing but also carries the information that is sent from the region under study to distant targets. Following this logic, comparison of timing and task-related information present in LFP and spiking activity can be used to infer the location of neural computations. For example, if task-related signals are present in spiking activity before they are observable in the LFP, this strongly argues for a local computation of this information in the brain region under study (Monosov et al. 2008; Nielsen et al. 2006).

Visual Cortex LFP: Spatial Specificity

A pertinent question related to LFP signals is their spatial specificity, reflecting the degree to which they represent local activation within a region of cortex rather than mirroring activation that actually occurs at a distant site. Electrical signals observed locally may thus be due to transmitted potentials from distant sources, in a process that is termed volume conduction. The degree to which LFP signals in the visual cortex are of local origin is a subject of current debate. On the one hand, various evidences related to EEG recordings suggest that volume conduction can occur and electrical signals can be picked up in scalp recordings from sources that are known to be far away from the recording location (Cobb and Sears 1960; Jewett and Williston 1971). Similarly, LFP recordings in the cortex have also shown that

signals generated in one area of the cortex can spread to regions a centimeter or more away. For example, LFP signals related to auditory stimuli were greatest in amplitude within the primary auditory cortex itself, and the amplitude declined approximately linearly with increasing distance such that 12 mm away a signal of about 5% of the peak magnitude could be picked up (Kajikawa and Schroeder 2011). Notably, the LFP spread in this study was measured in the z-axis, parallel to the apical dendrites and perpendicular to the cortical layer structure. These results were obtained in the auditory cortex, but it is highly likely that similar volume conduction occurs also in the visual cortex but is probably more difficult to observe there due to the close proximity of multiple visual areas in the occipital lobe of the brain that each generates VEPs in response to visual input. Other studies have estimated LFP spread to be up to two orders of magnitude lower, with values between 250 and 600 μm . In one study, a high-resolution map of orientation selectivity of a V1 patch was obtained (Katzner et al. 2009) using voltage-sensitive dye-based optical imaging, by presenting a visual-oriented grating stimuli large enough to activate the entire cortex being imaged in pseudorandom order. The resulting map was then used to predict LFP orientation selectivity at particular grid nodes of the map using different two-dimensional Gaussian spread standard deviation values. When these predicted LFP orientation selectivity values were compared to LFP measurements, the optimal fit occurred for a standard deviation of about 100 μm , which translates to over 95% of the LFP being generated within a radius of 250 μm . In another study, action potential activity, the so-called multiunit activity (MUA), was recorded simultaneously with LFPs in the visual cortex during the presentation of a sparse noise visual stimulus, where small spots of light on a rectangular grid are successively and individually illuminated in a pseudorandom order (Xing et al. 2009). This allows the determination of the spatial spread of both MUA and LFP activities, yielding an average value of 250 μm . Interestingly, spatial spread was lowest for the thalamocortical input layer 4 (150 μm) and relatively highest in the supragranular layer 2/3

(280 μm). Notably, for both cited studies, the LFP spread of 250 μm was estimated in the horizontal (x-y) direction, parallel to the cortical layer structure, which represents a difference compared to the above spread estimate of 1 cm or larger that is based on measurements in the z-direction. Another possible explanation is that LFP integration has been shown to be dependent on the contrast of the stimulus, which is related to the strength of the sensory input. For low-contrast stimuli of relatively weak strength, LFPs tended to be correlated across relatively large distances of 1 mm or more, whereas for high-contrast stimuli, they were more localized (Nauhaus et al. 2009). It is however unclear whether these factors really are the source of the discrepancy in the literature regarding the spatial selectivity of LFP signals. Other potential sources include differences in sensory stimulus characteristics, details concerning data analysis procedures, and experimental data acquisition such as location of the ground or hardware filtering as well as potential capacitive cross talk between channels on multichannel recording probes.

Visual Cortex LFP Oscillations: Locking to External Stimulus

The visual cortical LFP, similar to spiking activity, reflects temporal characteristics of the visual input up to frequencies approaching 90 Hz. Visual displays with deterministic timing characteristics, such as cathode ray tube and some LED displays but not most TFT monitors, can be operated at different refresh rates. For refresh rates up to about 90 Hz, visual LFP signals are highly entrained to this refresh rate and display oscillatory power in the corresponding frequency band during periodic visual stimulation (Veit et al. 2011; Williams et al. 2004). The appearance of the corresponding peaks at the refresh rate and higher harmonics in the LFP spectral analysis is thus not due to intrinsic cortical mechanisms but is driven by the external stimulus and must be interpreted as such. These oscillations are visible in the average VEP only if timing is monitored with millisecond precision which generally requires additional verification using a light-sensitive diode. For refresh rates above 90 Hz, the neural response is no longer

strongly phase locked to the visual display refresh and approximates the response to a real-world object that emits continuous rather than pulsed light.

Visual Cortex LFP Oscillations: Gamma Band

In addition to these oscillations that result from the visual display procedures, the visual LFP also exhibits various oscillations in different frequency bands that are generated intrinsically by the brain and can be linked more or less closely to perceptual or cognitive phenomena. Oscillations in the gamma (20–100 Hz) range occur in the visual cortex during sensory stimulation, as is demonstrated either by enhanced broadband gamma activity or by the appearance of specific spectral peaks in the gamma range when one compares periods of visual activation to spontaneous activity (Eckhorn et al. 1988; Gray et al. 1989). Of the different LFP frequency bands, the gamma band is most closely linked to locally generated action potentials. Elevated spiking is thus often accompanied by the appearance of gamma oscillations in the LFP. Several studies have provided evidence linking gamma oscillations to perceptual processes such as temporal expectation and perceptual grouping (Lima et al. 2010; Lima et al. 2011) which are essential for object vision. Gamma oscillations have also been described in higher-order visual cortices (Grothe et al. 2012; Taylor et al. 2005), generally with an involvement in similar cognitive and perceptual functions as have been associated with V1 gamma. In addition, the phase of the gamma cycle is related to the exact spike timing, such that action potentials tend to appear preferentially during the downward slope and trough of the gamma cycle, with the precise phase relationship varying from neuron to neuron. It has been suggested that this phase locking of spike timing to the gamma cycle may provide a mechanism for optimizing information transmission from primary visual cortex to high visual centers, because spikes arriving simultaneously at postsynaptic targets will generate summing excitatory postsynaptic potentials and thus increase the probability of activating the postsynaptic target neuron compared to a case where inputs arrive uniformly distributed on a gamma

cycle. Indeed, gamma oscillations in extrastriate area V4 have been linked to attention, such that a patch of the cortex that is processing an attended visual stimulus exhibits enhanced gamma oscillations compared to a similar patch of cortex that is processing an identical unattended stimulus (Fries et al. 2001). In the inferior temporal cortex, gamma has also been described and implicated, for example, in perceptual awareness, albeit using recordings from the surface of the cortex (Fisch et al. 2009). Gamma oscillations can thus be considered to be an extremely widespread phenomenon in the visual system and may serve different functions in a brain-region-dependent manner. There is also some evidence suggesting that gamma oscillations may be more strongly coupled to feed-forward processing, i.e., signals sent from primary to extrastriate visual cortex, rather than feedback processing (van Kerkoerle et al. 2014). However, it has also been emphasized that gamma oscillations tend to be highly variable from trial to trial, such that there remains considerable doubt as to the degree to which they serve as a robust encoding mechanism for information processing (Ray and Maunsell 2010; Ray and Maunsell 2015).

Gamma oscillations are thought to originate locally in the cortex through coordinated interaction between excitation and inhibition (Buzsaki and Wang 2012) and generally require thalamocortical activation by a sensory stimulus. Evidence for local generation comes, for example, from the observation that gamma enhancements vary substantially as a function of cortical layer, with the thalamocortical input layer exhibiting much weaker gamma compared to the supragranular layer 2/3 (Xing et al. 2012). The generation of visual cortical gamma oscillations can be influenced by long-range projections from other brain areas that send axons to the visual cortex. One example is the basal forebrain, which provides a source of cholinergic, GABAergic, as well as glutamatergic inputs to the visual cortex. Thus, electrical stimulation of the basal forebrain generates gamma oscillations in V1, and both spectral peaks and broadband enhancements of gamma activity have been observed (Bhattacharyya et al.

2013). While local in nature, gamma oscillations are under the control of nonvisual brain structures, which can thus modulate the transmission of information about the visual environment to higher cortical centers.

While gamma oscillations and action potential spiking activity are closely related, this should not be taken to mean that these signals provide identical information. When spiking and LFP activity are directly compared in terms of their selectivity for orientation, one can observe that single unit as well as multiunit spiking activity at a given site is generally much better tuned for orientation than the gamma-band LFP (Berens et al. 2008). In addition, the orientation preference of gamma activity at a given recording site does not accurately predict the orientation preference of local action potential spiking activity. This observation is generally consistent with the above findings related to the spatial spread of the LFP, because adjacent neurons in the visual cortex can have drastically different orientation.

Visual Cortex LFP Oscillations: Other Bands

There are relatively few reports of beta oscillations in the visual system, and to date no clear functional role in visual processing appears to have emerged for LFP oscillations in this frequency range. In contrast, beta LFP activity plays an important role in the motor cortex and has been linked closely to spiking activity for motor control processes (Witham et al. 2007). Alpha oscillations are classically associated with cortical idling and appear, for example, in the visual cortex when the eyes are closed in the absence of a behavioral task. In contrast, the theta band appears to play an important role in short-term memory and structuring cortical communication over long distances. For example, intermediate extrastriate visual cortical area V4 exhibits characteristic oscillations in the theta frequency band that are linked to short-term memory and thus appear during behavioral tasks that include a delay period during which a previously presented visual stimulus needs to be maintained in memory (Lee et al. 2005; Raghavachari et al. 2006). The phase of the theta – like

gamma – oscillations is related to action potential timing, such that theta can structure information transfer with higher-order visual cortices. Indeed, simultaneous recordings have confirmed that during short-term memory there is in fact enhanced coupling between visual and prefrontal cortices, suggesting an important role of theta oscillations in maintenance of short-term memories (Liebe et al. 2012). At the same time, the role of theta oscillations extends beyond encoding and maintenance aspects of visual information. This has been documented, for example, in the rat, where visual stimulus-induced theta oscillations are closely related to precision and timing of reward-seeking responses (Levy et al. 2017). Theta oscillations in the visual cortex are thus related to long-range coordination of neural activity related to visual information encoding and maintenance, as well as other task-relevant information.

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Local Field Potential, Ephaptic Interactions

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Detailed Description

Charge transfer across the membrane of all structures in brain matter such as neurons, glial cells, etc. induces the so-called extracellular sinks and sources that, in turn, give rise to an extracellular field, i.e., a spatial gradient of the extracellular voltage (V_e) measured in comparison to a distant reference signal. The physics governing such events are described by Maxwell's equations. In their simplest form, Maxwell's equations dictate that V_e depends on the transmembrane current amplitude, the impedance of the extracellular medium, and the distance between the location of the ionic flux and the recording (see also entries ► [“Local Field Potentials: LFP”](#) and ► [“Local Field Potential, Methods of Recording”](#) and (Koch 1999)). V_e signals resulting from the activity of the entire cell populations can therefore be recorded via standard recording techniques and have been used for decades to monitor electric processing in the brain (Buzsaki 2002).

From *in vivo* electrophysiology studies, we know that the hallmark of a living brain is the presence of dynamic extracellular fields giving rise to continuous V_e fluctuations (see entries ► [“Local Field Potential, Relationship to BOLD Signal”](#) and ► [“Electrocorticogram \(ECoG\)”](#)). The strength and frequency content of such V_e fluctuations is highly dependent on a number of features such as the animal's behavior, the brain structure, the V_e bandwidth of interest, and the recording methodology employed (Buzsaki et al. 2012). For example, during various behavioral states such as running, the so-called theta activity gives rise to highly coordinated V_e oscillations observed along rat CA1 pyramidal layer of approx. 0.1–0.3 mV amplitude, while V_e oscillations of larger amplitude and roughly opposite polarity are concurrently recorded in hippocampal

CA1 stratum radiatum (Kamondi et al. 1998). During events related to memory formation such as hippocampal sharp waves, while V_e amplitude in CA1 pyramidal layer remains small (approx. 0.1 mV), V_e amplitude in stratum radiatum can reach 1–2 mV (Ylinen et al. 1995). The strength of electric fields in rat CA1 as measured with high-density silicon probes during theta is approx. 1–5 mV/mm, while during sharp waves, they can reach approx. 30 mV/mm. Finally, during pathological functioning of the brain such as in epileptic seizures, electric fields as strong as hundreds of mV/mm have been measured.

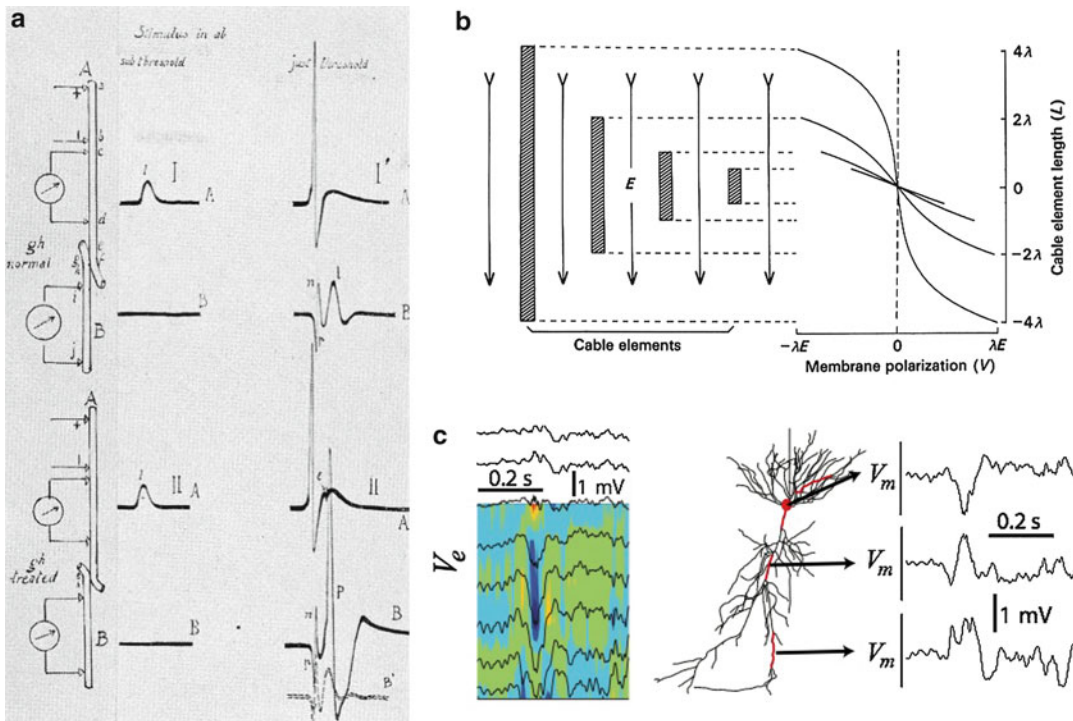
Neuroscientists have typically used V_e recordings to monitor the brain and infer modes of neural circuitry by studying the spatiotemporal features of V_e . This is typically defined as the “feedforward” process (e.g., see entry ► “Local Field Potential in the Visual System”). Yet, the neural membrane is affected by the presence of extracellular fields. A crude example is the strong entrainment of the neural membrane voltage (V_m) and, eventually, spiking observed during and/or immediately after electric stimulation, for instance, in electric microstimulation studies (entraining one or a few neurons (Tehovnik et al. 2006; Histed et al. 2009)) or deep brain stimulation therapy (entraining the entire neural circuits and brain regions (Mayberg et al. 2005; Lozano et al. 2008)). Defined as the difference between the intra- (V_i) and extracellular voltage (V_e) at a given time t and location $\mathbf{x}$, the membrane voltage $V_m(\mathbf{x}, t) = V_i(\mathbf{x}, t) - V_e(\mathbf{x}, t)$ will be affected by changes in $V_e(\mathbf{x}, t)$, i.e., the presence of extracellular fields. In effect, extracellular fields along the cable-like structure of neural morphology act as intracellular current injections at the ends of these cables, leading to alterations in their membrane potential (Ranck 1963a, b; Chan and Nicholson 1986; Chan et al. 1988; Holt and Koch 1998; Anastassiou et al. 2010).

Do dynamic, endogenous electric fields in the brain serve a functional role by altering the functioning of neurons? Can spatiotemporal fluctuations of the extracellular field influence via purely electrostatic, the so-called *ephaptic coupling*, (The term “ephapse” from the Greek word $\varepsilon\varphi\acute{\alpha}\psi\eta$ (i.e., the touch or junction) was coined by

Arvanitaki (1942) to describe electric field interactions occurring between juxtaposed axons. Over the years researchers have used alternative terms such as “electric field effects” to describe the same phenomenon. To date, the most detailed review about ephaptic coupling remains the seminal paper by Jefferys (1995). For a more recent review, see Weiss and Faber (2010)) the activity of individual neurons and neural populations? Such coupling would, thus, be a “feedback” process with electric fields altering the activity of the same neural elements that gave rise to them through an electrostatic mechanism. Addressing whether ephaptic coupling plays a functional role is not straightforward. Intuitively, since extracellular electric fields are always present in the living brain caused by cell functioning, it is challenging to study such functioning in the absence of the field as this would imply a comatose or deceased brain. To understand the impact of fields on neurons, a potentially more tractable question might be the following: which neural components are sensitive to extracellular fields?

As early as the 1940s, it was shown that spatially elongated neural compartments with active membrane processes and aligned within a conductive extracellular medium interact via ephaptic coupling: when inducing an action potential in one of the axons, a deflection in the membrane potential of the second axon was measured in the absence of chemical or electric synapses between the two axons (Katz and Schmitt 1940, 1942; Arvanitaki 1942). The origin of the V_m deflection in the second axon was attributed to volume conduction: the membrane currents induced by the spike along the first axon induced an extracellular field that entrained the nearby axon (Fig. 1). As expected, the features of the V_m deflection along the same axon depended on geometric considerations (distance and alignment of the axons) as well as the electric conductivity of the extracellular medium. Similar observations have been made along dendrites and somata of neurons in a number of non-physiological conditions (Nelson 1966; Dalkara et al. 1986; Turner and Richardson 1991; Anastassiou et al. 2011).

The passive cable theory dictates that the impact the field has on V_m depends on the



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Fig. 1 Ephaptic coupling of the membrane potential. (a) Simultaneous recordings from two individual axons, A and B, for subthreshold (left) and suprathreshold (right) stimulation. When the stimulus into A is subthreshold, only a local response occurs. When the stimulus into A is suprathreshold, a spike propagates along A and induces a deflection in axon B. (b) Simulation of the modulation of a passive cable by an electric field. Finite cable elements sealed at both ends of variable length are subjected to a constant electric field along the cable axis. The membrane polarization (deviation of V_m from rest) is indicated on the

right as a function of cable length. (c) Spatiotemporal V_e fluctuations alter the membrane potential of neurons. Extracellular activity recorded in the behaving rat from CA1 during sharp wave activity (orientation: top, stratum oriens; bottom, stratum lacunosum-moleculare; left panel). Assume a passive neuron, i.e., no active ionic currents and no synaptic input, with realistic morphology (middle panel). The presence of endogenous V_e fluctuations entrains V_m throughout the neural morphology (Reprinted with permission from (a) Arvanitaki (1942), (b) Chan and Nicholson (1986), and (c) Anastassiou et al. (2010))

cable-field alignment as well as on three length constants: the characteristic length of the external field, the cable length, and the electrotonic length (Anastassiou et al. 2010). The range of V_m induced by a spatially inhomogeneous extracellular field can be of the order of the extracellular spatial voltage oscillation. For instance, an external sinusoidal potential profile of amplitude 0.5 mV and spatial frequency 0.5 mm aligned with a cable can give rise to V_m deviations of up to 0.625 mV. For the induced V_m amplitude to become of the order of the amplitude of V_e , two independent conditions must hold: the length of the cable must be larger than the characteristic length of the external field, and the electrotonic

length must be larger than the characteristic length of the external field. If the cable length is considerably smaller than the characteristic length of the field, the V_e gradient along the cable appears insignificant, and thus, V_m remains broadly unaltered. The same applies when the electrotonic length is much smaller than the characteristic field length: for a decreasing cable diameter (i.e., decreasing electrotonic length (Koch 1999)), the impact of the spatially inhomogeneous extracellular V_e on V_m decreases until the amplitude of the V_m deviation along the cable becomes zero. As such, for thin fibers, such as axons, the induced V_m is expected to become very small. Although these effects are derived for stationary cases,

time-dependent cases of spatially inhomogeneous V_e clearly suggest that these events persist for relatively high temporal frequencies (Fig. 2).

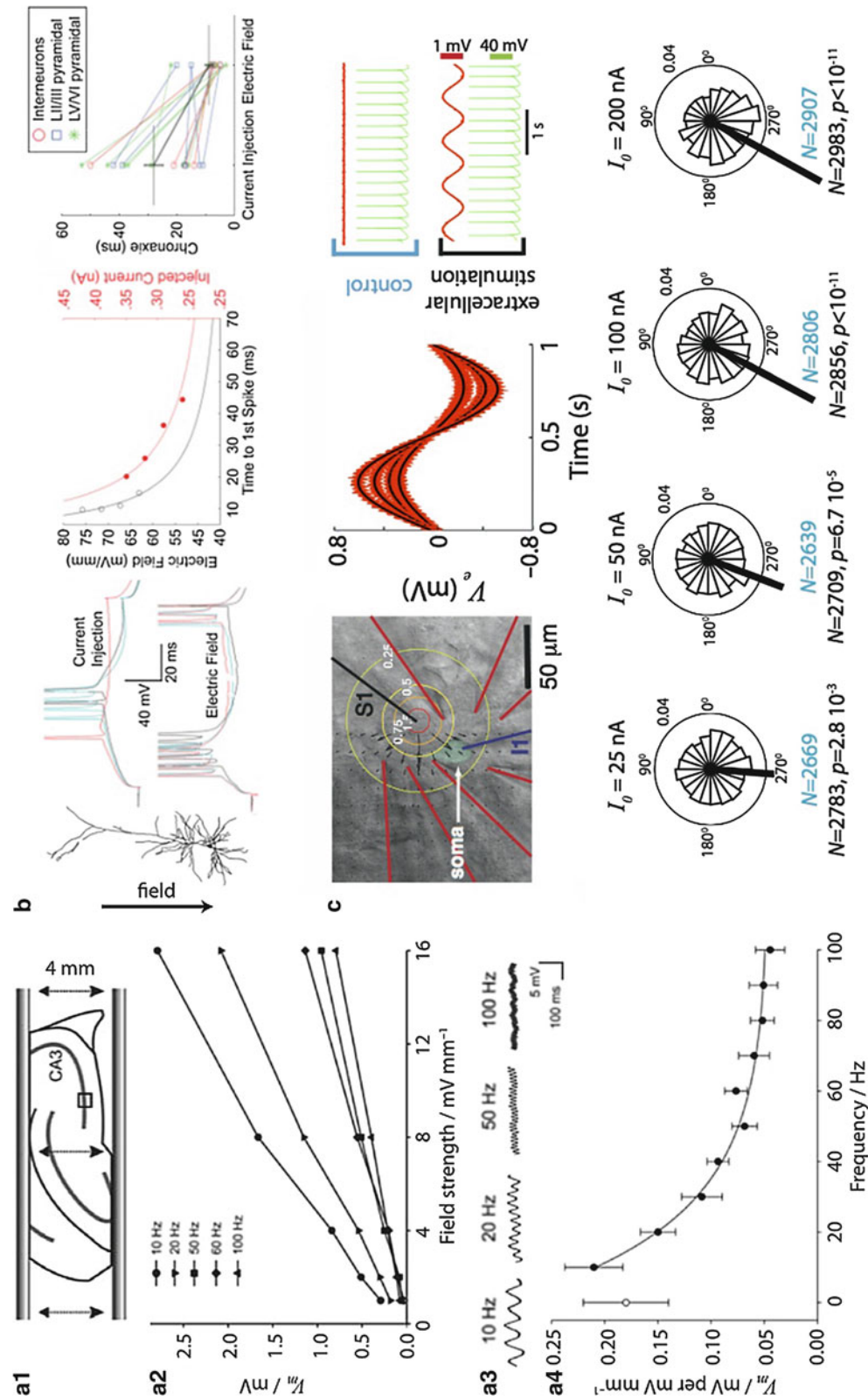
From the aforementioned it follows that V_m along the entire neural morphology is, to some extent, affected by the extracellular field. The specifics of such entrainment depend on the morphological and physiological features of the neuron as well as the characteristics of the extracellular field. This is especially true as active, voltage-dependent conductances are present along all neurons – spatiotemporal changes in V_e have an impact on V_m that, in turn, can also have a nonlinear impact on transmembrane conductances (Koch 1999).

Beyond V_m changes along the neural morphology, electric fields can impact the functioning of synapses. In general, a linear relationship is observed between synaptic current and V_m (with the important exception of the NMDA receptor). In fact, once the reversal potential (E_{rev}) has been accounted for, Ohm's law appears as a satisfactory first-order description of the synaptic current as $I_{syn}(t) = g_{syn}(t)(V_m(t) - E_{rev})$ with I_{syn} being the synaptic current and g_{syn} the synaptic conductance. As observed, I_{syn} depends on V_m , which, in turn, depends on V_e . Thus, changes in V_e influence synaptic currents as well. Moreover, it has been shown that both short-term (Bikson et al. 2004; Radman et al. 2009) and long-term (Fritsch et al. 2010) applications of electric fields can alter the functioning of synapses via elaborate biochemical processes. Finally, as far as an electric field can alter the spiking of neurons, correlations in spiking between two synaptically connected neurons can strongly affect the synaptic strength of their connection by inducing plasticity – this would constitute an indirect impact of ephaptic coupling on synaptic functioning (e.g., Pavlides et al. 1988; Huerta and Lisman 1995; Markram et al. 1997; Poo et al. 1998; Hoelscher et al. 1998; Hyman et al. 2002).

As ephaptic coupling impacts neural functioning at the synaptic and the single-neuron level (influencing V_m , active voltage-dependent conductances, etc.), the fact that it can also affect network-level processing should not come as a surprise (Fig. 3). Purely electrostatic, ephaptic

interaction to endogenous electric activity has been shown to play a role in neural population processing (Ghai et al. 2000; Bikson et al. 2004; Deans et al. 2007; Radman et al. 2007; Frohlich and McCormick 2010) as well as in pathological conditions such as epileptic seizures (for instance, see (Jefferys and Haas 1982); reviewed in (Faber and Korn 1989; Jefferys 1995; Weiss et al. 2013; Zhang et al. 2014)). Data supports that even weak sinusoidal extracellular stimulation during network activity may coordinate and pattern population activity by providing a common, network-wide feedback. On the other hand, *in vivo* field activity rarely exhibits a single, dominant frequency: most commonly, the power of V_e signals scales with frequency (with the exponent typically ranging between 1 and 3). As such, ephaptic feedback occurs at a spectrum of frequencies even if the effect is attenuated for higher ones. And the impact of ephaptic coupling on the network will also depend on the network state (Ozen et al. 2010). From the aforementioned it becomes clear that the functional role of ephaptic coupling of neural networks to endogenous field activity *in vivo* remains enigmatic – this is probably also due to the challenge of characterizing feedback mechanisms within inherently nonlinear networks as well as because ephaptic coupling affects processing at multiple spatiotemporal scales.

Given that extracellular fields are always part of the living, functioning brain and that *in vivo* V_e activity spans across a spectrum of frequencies (Buzsaki 2006; Buzsaki et al. 2012), it may be informative to tease apart ephaptic coupling to extracellular fields with respect to specific bandwidths. Higher V_e bandwidths are typically generated locally with the bandwidth above 500 Hz, being strongly influenced by spiking from neurons proximally located to the recording electrode (see also entry ► “Local Field Potential, Relationship to Unit Activity”). For example, extracellular spike signatures from cortical excitatory and inhibitory neurons decay within a few tens of μm from several hundred μV to zero (Henze et al. 2000; Gold et al. 2006; Anastassiou et al. (unpublished observations)). Thus, ephaptic coupling in higher bandwidths of endogenous extracellular activity is expected to depend on aspects such as local



Local Field Potential, Ephaptic Interactions, Fig. 2 (continued)

cytoarchitecture, neural activity and excitability, as well as local field characteristics (Buzsaki et al. 2012). To date, there have been two clear demonstrations of ephaptic coupling to spikes under physiological conditions: in the Mauthner cell leading to bidirectional inhibition from the Mauthner cell to its inhibitory afferents, and vice versa (Faber and Korn 1980, 1989) and in cerebellar basket cells connecting to Purkinje cells that experience a transient electric hyperpolarization following a Purkinje cell spike (Korn and Axelrad 1980). With respect to the latter, it was recently demonstrated that the pinceau, a structure where the axon initial segment of each Purkinje cell is enclosed by a basket cell, mediates ephaptic inhibition of Purkinje cell spikes at the site of spike initiation (Blot and Barbour 2014). As a result, such axoaxonic ephaptic coupling between pre- and postsynaptic neurons mediates near-instantaneous feedforward and lateral inhibition. Notably, due to the nature of the cellular membrane, ephaptic coupling to such high V_e bandwidths is expected to occur mainly via capacitive currents (Koch 1999).

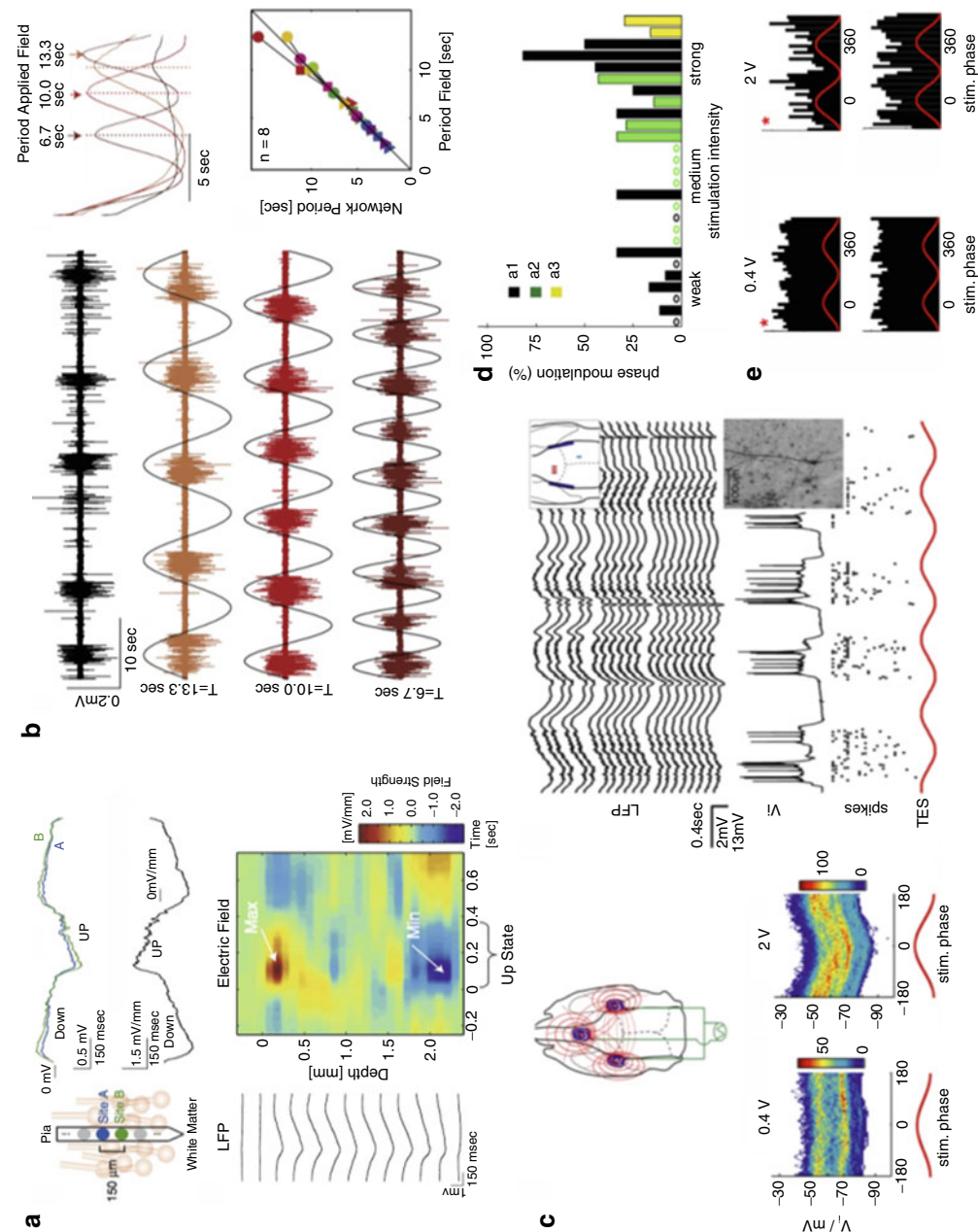
Ephaptic coupling may also become important when considering the entrainment of spiking to slower extracellular fields. The V_e bandwidth below approx. 300 Hz is the so-called local field potential (LFP) which reflects synaptic, passive return but also slower active processing within the entire circuits (Buzsaki et al. 2012; Reimann et al. 2013; Einevoll et al. 2013) (see also entries

► “Local Field Potential: Relationship to Membrane Synaptic Potentials”; ► “Local Field Potential, Relationship to Unit Activity”; and ► “Current Source Density (CSD) Analysis”). It has been shown that LFP activity is spatially considerably more extended compared to the higher bandwidths of V_e . As such, ephaptic coupling to the LFP provides nearly simultaneous feedback to many neurons or even the entire networks. Computer simulations have indicated that ephaptic coupling can alter signaling characteristics within a network (Traub et al. 1985a, b), while experimental studies have suggested that even small-amplitude-slow-frequency LFP activity entrains spiking in neurons and neural assemblies (Jefferys and Haas 1982; Chan and Nicholson 1986; Chan et al. 1988; Bikson et al. 2004; Radman et al. 2007; Anastassiou et al. 2010, 2011; Frohlich and McCormick 2010; Ozen et al. 2010). Due to the nature of the cellular membrane, ephaptic coupling to the LFP, especially the slower part typically of larger amplitude, is expected to occur mainly via resistive currents (Koch 1999). Importantly, there have been reports of the extracellular medium not being purely resistive (for more details, see entry ► “Local Field Potentials: Interaction with the Extracellular Medium”). It follows from the aforementioned that a frequency-dependent impedance of the extracellular medium can result in the alteration of certain V_e characteristics in particular frequency bandwidths due to the physical properties

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Fig. 2 Ephaptic coupling at the single-neuron level. (a1) Setup layout with hippocampal slice positioned between parallel plates used to impose extracellular field activity. The impact of applied sinusoidal fields on hippocampal CA3 pyramidal neurons is shown for variable (a2, a3) field strength (population statistics and for an individual neuron, respectively) and (a4) stimulation frequency. (b) Impact of the electric field on the time to first spike. Notably, the spike response changes from regular spiking to intrinsic bursting in the absence (intracellular stimulation only) versus the presence of an extracellular field. The impact of electric fields on chronaxie, i.e., the duration of stimulation pulse having twice the intensity of the threshold amplitude (rheobase), for intracellular current injection and field stimulation as a function of cell type. In all cases, a statistically significant difference between the absence and the presence of extracellular stimulation was

measured. (c) Impact of sinusoidal electric fields on spike time. Simultaneous intra- and extracellular stimulation and recordings from up to eight pipettes positioned close to the soma of a rat layer 5 pyramidal neuron. Extracellular sinusoidal stimulation is administered from one of the pipettes (red traces: average V_e) concurrently with a supra-threshold intracellular dc stimulation while V_i is monitored (green traces: V_i). While spike frequency remains unchanged in the absence vs. presence of extracellular fields (number of spikes reported; cyan, control; black, field stimulation), the spike phase (the angle of the sinusoidal stimulus at spike time) changes substantially for field strengths even below 0.1 mV/mm (stimulus frequency, 1 Hz). The increasing influence of ephaptic coupling is inferred by the increase in population vector length with field strength (Reprinted with permission from (a) Deans et al. (2007), (b) Radman et al. (2009), and (c) Anastassiou et al. (2011))



Local Field Potential, Ephaptic Interactions, Fig. 3 (continued)

or ongoing processes in that medium, which eventually may lead to frequency-dependent effects in terms of ephaptic coupling.

Even so, whether endogenous electric fields in the brain are merely an epiphenomenon of cellular functioning or whether they serve a functional role via ephaptic coupling remains a mystery. While differences on many levels are observed in the presence versus the absence of electric fields (synapses, cables, neurons, and neural populations), the overall effect is not easily assessed. Part of the difficulty has been the typically subthreshold impact: changes in membrane voltage attributed to ephaptic coupling hardly exceed fractions of a mV or a few mV. Physiologists studying, specifically, changes in membrane voltage and, more generally, input–output relationships at the single-neuron level typically deal with signals of several mV or tens of mV (in the case of intracellular spikes). The role of such subthreshold processing in neural coding is inherently challenging to decipher, especially since the nature and mode of coding and the resulting computation performed are related to many high-level functions. Also, ephaptic coupling has an intrinsically extended spatial nature: it is the spatial gradient of the extracellular voltage spanning along the extended neural morphology that gives rise to such entrainment. Accessing a number of compartments of the same neuron along the field axis to monitor ephaptic coupling is a tremendously tedious task experimentally – especially so *in vivo*. And it is infeasible to abolish

endogenous electric fields *in vivo* and perform control experiments, i.e., study neural functioning in the absence of such fields. These are some of the reasons why the role of ephaptic coupling at the neuron and, especially, the population level remains mysterious.

On the other hand, deciphering the relationship between neural functioning and electric field activity is an active area of research of fundamental importance. This relationship is not limited to biophysics – it is crucially linked to our understanding of neural processes related to behavior. For example, in monkey V4, it has been shown that spike–field coherence in gamma (30–60 Hz) is confined to superficial layers, whereas deep layers show maximal coherence around the alpha range (6–16 Hz) with attention increasing gamma synchrony in superficial layers and reducing alpha synchrony in deep layers (Buffalo et al. 2011). Many similar observations have been made over the past decades for a number of LFP bandwidths and various visual/behavioral paradigms in rodents as well as in humans (Rutishauser et al. 2010) (see also entries ► “Local Field Potential, Relationship to BOLD Signal”, and ► “Local Field Potential in the Visual System”). Clearly, to understand the mapping between neural coding, extracellular field activity, LFPs, and behavior (also) depends on whether we are in position to tease apart input and output and cause and effect. And as experimental and theoretical tools to monitor, emulate, and perturb circuit-wide processing become increasingly sophisticated, the role of

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Fig. 3 Ephaptic coupling during network operation. (a, top) Field stimulation in a similar setup as in Fig. 2a results in changes in V_e as a function of location along the depth axis of the neocortex. (Bottom) LFP and field exhibit spatiotemporal patterns reflecting the oscillatory nature of ongoing network activity. (b, left) Sinusoidal stimulation with three different periods (13.3, 10, and 6.7 s) successfully entrains the ongoing slow neocortical oscillation. (Right) Correlograms exhibit the enhancement of network oscillation at the external stimulation period. (c) Entrainment of subthreshold and suprathreshold neural activity by transcranial sinusoidal electric stimulation in the living rat. Multiple-site recording of unit and LFP activity from prefrontal cortex and simultaneous intracellular recording

from a layer 5 pyramidal cell in somatosensory cortex. Joint probability density counts of V_i and the phase of the stimulation signal are shown for weak (0.4 V) and strong (1.2 V) intensity (red line: stimulation phase). Brain state-dependent Up–Down activity (note bimodal distribution of V_i) in the absence of an extracellular stimulus is substantially smeared during stimulus administration. (d) Percentage of significantly modulated neurons in three chronically implanted rats (a1, a2, a3) as a function of stimulation intensity. (e) Example unit histograms during transcranial stimulation. While no unit was affected by the stimulation during exploration, a fraction of cells were significantly entrained during sleep at all intensities (Reprinted with permission from (a, b) Frohlich and McCormick (2010) and (c–e) Ozen et al. (2010))

such “small” (in amplitude) mechanisms might be shown to play a more prominent role in brain function than hitherto anticipated.

Cross-References

- [Current Source Density \(CSD\) Analysis](#)
- [Electrocorticogram \(ECoG\)](#)
- [Local Field Potential in the Visual System](#)
- [Local Field Potential, Methods of Recording](#)
- [Local Field Potential, Relationship to BOLD Signal](#)
- [Local Field Potential, Relationship to Unit Activity](#)
- [Local Field Potential: Relationship to Membrane Synaptic Potentials](#)
- [Local Field Potentials in Olfaction](#)
- [Local Field Potentials: Interaction with the Extracellular Medium](#)
- [Local Field Potentials: LFP](#)

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Local Field Potential, Methods of Recording

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Definition

The term local field potential (LFP) refers to the electrical field recorded using a small-sized electrode in the extracellular space of brain tissue that is referenced against an electrode recorded either inside or outside that tissue. Such recordings were first made in animals over 130 years ago (Caton 1875) and constitute an increasingly important tool both in neurophysiology and medicine. LFPs can be recorded using a wide variety of electrodes of varied impedance and geometry. In many experimental preparations, the primary purpose of the electrode will be to record action potentials, which are usually filtered above 500 Hz. The field potential represents the slow fluctuations, usually below 300 Hz, that are caused by all ionic process around the electrode (Buzsaki et al. 2012). Fluctuations in the LFP represent spatiotemporally synchronous events in these ionic processes, and LFPs are therefore typically used to measure large population responses to a stimulus or ongoing neuronal oscillations, both of which can cause this local summation. Unlike intracellular or action potentials from a single neuron, the LFP is not a standardized signal but will change depending on methodological details of the experimental preparation (Kajikawa and Schroeder 2011).

Detailed Description

Referencing and Filtering

The position of the reference electrode is crucial for the recording of the LFP. If the reference is distant (e.g., an epidural screw or wire in the skin), the signal is referred to as monopolar. As there is no subtraction of local activity, monopolar signals have low spatial resolution and are vulnerable to volume

conduction: transmission from a distant primary current source to the measurement sensors (Carsten and de Munck 2007). Volume conduction can therefore lead to activity from another brain area being ascribed to the area of the measurement electrode. Such contamination of the signal can be from sources up to millimeters away from the electrode (Kajikawa and Schroeder 2011). If the reference electrode is local (within a few hundred micrometers and often within the same brain structure), the signal is referred to as bipolar. Bipolar recordings can lead to the opposite problem: potentially meaningful components of the signal will be lost if they are recorded by both electrodes. Recording many LFPs, particularly in a spatially organized manner, allows referencing to be carried out offline, which may facilitate an optimal configuration between these extremes. The LFP typically consists of the signal low-pass filtered between 200 and 400 Hz. Irrespective of the configuration, filtering to extract the LFP is increasingly carried out offline on the “wideband” signal, usually sampled at >10 Hz to record action potentials and LFPs.

Recording Electrodes and Configurations

In brain slice preparations, glass electrodes with a low resistance (1–10 M Ω) can be used to record the LFP (Whittington et al. 2001). The reference electrode can be placed either locally or in another brain structure depending on the nature of the signal desired. In vitro, LFP signals have been commonly used in hippocampal slices to record network oscillations that are often induced pharmacologically (Traub et al. 2004). In vivo, a huge variety of electrodes have been used to record LFPs in anesthetized and awake animals. In anesthetized animals, signals from glass electrodes, the primary purpose of which is often to record action potentials, can be filtered to give the LFP and will usually be recorded in a monopolar configuration (Goto and O'Donnell 2001; Magill et al. 2004). In awake animals, standard microelectrodes and tetrodes are commonly used to record LFPs, with or without action potentials. Silicon probes, which have geometrically arranged electrode contacts, have several desirable qualities for recording LFPs. In particular, they

enable the calculation of current source density across laminar structures and flexible offline referencing (Buzsaki 2004). In humans, surgical interventions for epilepsy, Parkinson's disease, dystonia, and essential tremor have enabled LFP recording in the cortex, hippocampus, cerebellum, and basal ganglia (Engel et al. 2005). Such recordings have been made both using microelectrodes to map the implantation area (Weinberger et al. 2006) and using macroelectrodes implanted to deliver deep brain stimulation. Such macroelectrodes typically have four linearly spaced contacts that can be used to record monopolar (with a distant reference) or local bipolar signals (Chen et al. 2006).

Influence of Electrode Type

Despite the intuitive notion that the geometry and impedance of the recording electrode will affect the LFP signal, the issue has rarely been formally addressed (Pesaran 2009; Nelson and Pouget 2010). The issues of geometry and impedance are highly related, as the impedance is mostly a measure of the size of the uninsulated recording site (Nelson and Pouget 2010). Although the impedance of the recording electrode is crucial in determining whether intracellular or action potentials can be recorded, it has relatively little effect on the LFP signal (Nelson and Pouget 2010), at least within the limits of commonly used electrodes. One explanation for this is that the volume of tissue responsible for generating the LFP is far larger than the electrode tip (even for a large recording electrode). Larger electrodes will cause greater physical damage that is likely to affect the electrical activity of the immediate surrounding area. However, because the area generating the LFP is far bigger than the surrounding area, good signals can be recorded even using large electrodes, such as the macroelectrodes implanted for deep brain stimulation in human patients.

Influence of Recording Site and Conditions

The structural properties of the local circuit and the temporal aspects of neuronal activity within

those circuits can greatly affect the LFP signal (Niedermeyer and Lopes da Silva 2005; Buzsaki et al. 2012). The highly regular laminar arrangement of the cerebral cortex is ideal for the superposition and synchronization of dipoles and thus produces the largest LFP of all brain areas (Buzsaki et al. 2012). However, recordings in the cerebellum, which also has a highly ordered laminar structure, generate only small LFPs due to the relatively local processing in cerebellar circuits, unless abnormal population synchrony is introduced (Kandel and Buzsaki 1993; Buzsaki et al. 2012). LFPs can be recorded from the thalamus, basal ganglia, and brain stem, albeit around 1/3 smaller than those seen at the cortex, demonstrating that a strictly laminar arrangement of neuronal processes is not necessary to produce a useful LFP signal (Niedermeyer and Lopes da Silva 2005). This is likely due to these areas receiving highly synchronous input which can summate to produce ongoing fluctuations in local electrical fields. Careful consideration of these factors is therefore necessary when comparing LFPs recorded from different brain structures.

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Local Field Potential, Phase Coding

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Definition

The phase-of-firing code is a neural coding scheme whereby neurons encode information

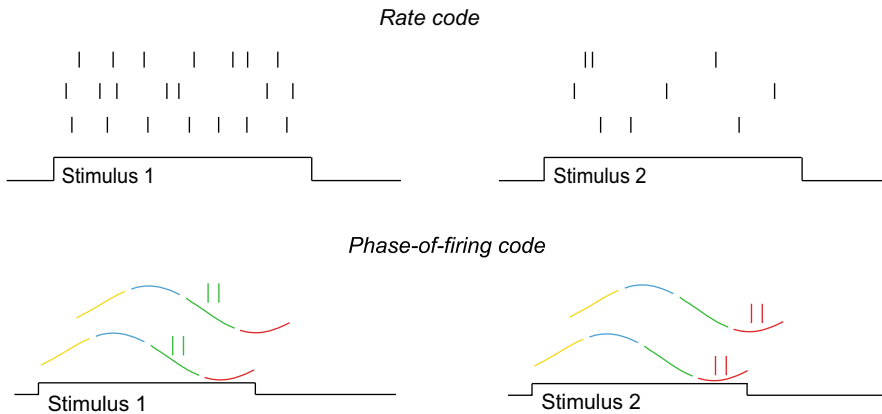
using the time at which they fire spikes within a cycle of the ongoing oscillatory pattern of network activity. This coding scheme may allow neurons to use their temporal pattern of spikes to encode information that is not encoded in their firing rate.

Detailed Description

In this entry, we define phase-of-firing coding, and we outline its properties. We first review early results that suggested the importance of temporal coding, and then we elucidate the insights concerning the central role of phase-of-firing coding in the studies of encoding of spatial variables in the hippocampus and of natural visual stimuli in primary visual and auditory cortices.

The phase-of-firing code is a temporal coding scheme that uses the timing of spikes with respect to network fluctuations to encode information about some variables of interest (such as the identity of an external sensory stimulus) that is not encoded by the firing rates of these neurons (Perkel and Bullock 1968).

Figure 1 shows a schematic representation of both a phase-of-firing code and of a firing-rate code (i.e., a code that uses only the total number of spikes fired by the neuron to transmit information). In the case of firing-rate code (top panel), two hypothetical stimuli can be distinguished from one another based on the neural response because each stimulus evokes a different number of spikes. In the case of phase-of-firing coding (bottom panel) the two hypothetical stimuli elicit neural responses which can be discriminated based on which phase (or part of the cycle) of network oscillations they are fired at, although these two hypothetical stimuli elicit similar spike counts and thus cannot be discriminated using a rate code. Thus, in a phase-of-firing code the time at which spikes are fired, measured with respect to the cycle of network oscillations, carries unique information that cannot be retrieved when ignoring the timing of spikes.



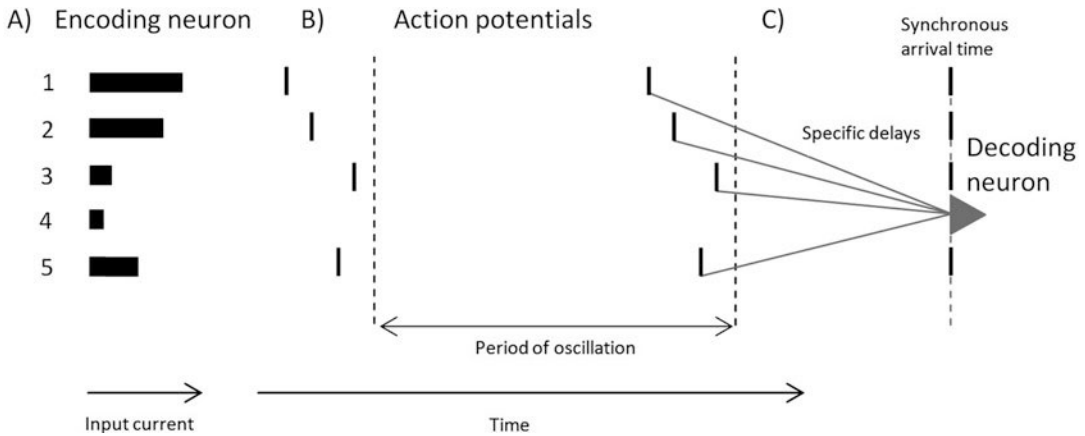
Local Field Potential, Phase Coding, Fig. 1 Schematic cartoon of firing-rate code and phase-of-firing code. In all panels, the x-axis represents peristimulus time, short vertical lines denote spike times, and each row corresponds to a different trial. Top panels show an example of firing-rate code where the two hypothetical stimuli (left, Stimulus 1; right, Stimulus 2) are encoded by the number of spikes fired by the neuron when the stimulus is presented. Bottom panels depict an example phase-of-firing code that carries

information in terms of when spikes occur within a cycle of the ongoing oscillatory network activity. Here, the network oscillation phase is divided in four sectors depending on the phase and each of them is characterized by a different color. In this example, stimulus 1 (left) and stimulus 2 (right) cannot be distinguished by the firing rate, but by their respective phases of firing compared to the underlying oscillation (green vs. red). Redrawn based on ideas presented in Panzeri et al. (2010)

Phase-of-Firing Coding in Hopfield's Analogue Pattern Recognition Model

The computational advantages of coding information by the phase-of-firing were highlighted in a classic model of analogue pattern recognition proposed by Hopfield (1995). Hopfield considered the analogue pattern recognition problem of recognizing the identity of the stimulus or of a mixture of stimuli, whatever their overall intensity. This resembles many important operations that have to be routinely performed by sensory systems, for example, the robust discrimination of the identity of an odor or of a mixture of odors independently of its intensity (Hopfield 1995). Hopfield's model incorporates a set of "encoding" neurons each representing a specific stimulus. Each encoding neuron receives a specific depolarizing input whenever the stimulus it encodes is present (for example, a particular odorant). Crucially, all the encoding neurons also receive a subthreshold oscillatory current common to all of them. In this way it is easy to produce encoding neurons that, whenever the stimulus they encode is present, fire a

spike in advance of the maximum of the intrinsic subthreshold oscillation (Fig. 2a, b). This is a form of phase-of-firing coding of stimulus identity. Under the assumption that the stimulus-specific depolarizing current received by each encoding neuron increases with the stimulus intensity, any stimulus mixture can be easily identified by a downstream neuron with a short membrane time constant (thus implementing coincidence detection) that receives the firing of the encoding neurons with a set of transmission delays. These transmission delays match the relative timing of the firing in the encoding neurons for the considered stimulus mixture to ensure that all such inputs arrive simultaneously to some of the downstream decoding neuron (Fig. 2c). A logarithmic transformation between stimulus strength and input current to the encoding neuron ensures that the times of firing in anticipation of the oscillation maximum of the encoding neurons are all rigidly shifted by the same amount if the overall strength of the stimulus mixture changes. Hopfield's model shows that encoding information by phase-of-firing



Local Field Potential, Phase Coding, Fig. 2 Illustration of Hopfield phase-of-firing model of analogue mixture coding. Panel B shows the action potentials of five different encoding neurons driven with different input current (corresponding to different analogues' signal strengths represented by the length of the black bars in Panel A). Neuron 4 produces no action potential because its input current is too weak to drive that cell above threshold. The other neurons fire just once per oscillation cycle. The time each neuron fire in advance of the maximum of the subthreshold oscillation is larger for neurons driven with a greater input current. Panel C shows a scheme to read out the phase-of-firing coding of the

stimulus mixture. The spikes generated by the encoding neurons reach out the soma of a decoding neuron at the same time because of suitably tuned differences in their conduction delays. The decoding neuron has a short membrane time constant, and thus it fires only when it receives a sufficient number of simultaneous inputs. This only happens when the appropriate analogue stimulus mixture is presented. The logarithmic dependence on each stimulus's strength of the input current to each encoding neurons insure that an overall change of intensity of the analogue stimulus mixture does not change the relative time of arrival to the encoding neuron. Panels A and B adapted from Hopfield (1995)

makes it easy to read out this information in a scale invariant way with a plausible downstream neural system.

Hopfield noted that the scale-invariant analogue matching problem is difficult to solve with a neuron using a firing-rate code. Even a "grand-mother" firing-rate neuron that is tuned only to a specific mixture of stimuli by a set of synaptic weights that boosts a specific stimulus mixture will respond to suboptimal stimulus mixtures provided that they are presented with a large enough intensity.

The phase-of-firing coding idea advanced by Hopfield coding was influential in introducing the notion that some problems that cannot easily be solved by firing-rate based schemes may be more easily solved by spike-timing based neural representations. Another influential aspect of Hopfield's phase-of-firing proposal was that it highlighted the fact that certain possible coding schemes cannot be detected when measuring spikes from single neurons only. However,

whether or not the olfactory system encodes odor information in the way proposed by Hopfield still remains to be experimentally established.

Phase-of-Firing Encoding of Spatial Navigation Variables in the Hippocampus

The activity of hippocampal neurons has long been implicated in the encoding of information of variables important for spatial navigation. In particular, so-called place cells in regions CA1 and CA3 of the rat hippocampal formation have been reported to encode the spatial location of the animal by elevating their firing when the animal is in a small spatial region called the place field of that neuron (O'Keefe 1976).

In a seminal study, O'Keefe and Recce (1993) considered how these cells encoded information. They first noted that, in contrast to the firing rate of place cells, the hippocampal field potential theta pattern of rhythmical waves (7–12 Hz) is better correlated with a class of movements that change the rat's location in an environment. In the

light of this observation, they considered the timing at which place cells fired in relation to the theta cycle. They found that firing consistently began at a particular phase as the rat entered the field but then shifted in a systematic way when traversing the field, moving progressively forward on each theta cycle. The phase-of-firing was highly correlated with spatial location and less well correlated with temporal aspects of behavior, such as the time after place-field entry. They suggested that by using the phase relationship as well as the firing rate, place cells might improve the accuracy of their place coding.

Later and more detailed studies have tried to clarify the exact nature of the information carried by the theta phase-of-firing of hippocampal cells and its relationship with the information carried by firing rates. Single-cell studies using the global statistical relationship between theta phase and spike firing could identify a partial dissociation of phase and firing rate in response to the animal's location and speed of movement (Huxter et al. 2003) but could not determine whether these signals encode complementary information about separate external features. Other studies have also shown that both theta phase and rate reflect the amplitude of the cell's input and might convey redundant spatial information (Mehta et al. 2002; Harris et al. 2002; Harris 2005). However, a population study using decoding techniques (Huxter et al. 2008) demonstrated that the phase-of-firing of hippocampal place cells encodes features related to the animal's spatial navigation that are not encoded by spike rates. Their data suggest that the best position prediction is obtained from spiking in the descending theta-cycle phase, while place cell firing on the ascending slope encodes the direction rats are heading to Huxter et al. (2008). These results imply that considering the theta phase at which hippocampal spikes are fired affords a richness of representation of information about position and heading that would not be possible with the firing-rate information only.

Note that Hafting and colleagues (2008) observed such phase-of-fire coding also in so-called grid cells of the entorhinal cortex, one synapse upstream from the hippocampus. As such

coding was not blocked by inactivation of the hippocampus, it raises the possibility that the phase-of-firing coding for hippocampal place cells is inherited from entorhinal cortex.

Phase-of-Firing Encoding of Natural Stimuli in Primary Sensory Areas

The results discussed above suggest the importance of phase-of-firing coding in the hippocampal formation. However, until recently it has been unclear whether phase coding represents a fundamental currency for cortical information exchange also in primary sensory representation and whether it is a sufficiently robust coding mechanism to represent complex stimuli.

We investigated this question by recording spiking activity and local field potentials (LFPs) from the primary visual cortex of anesthetized macaques while binocularly presenting a color movie (Montemurro et al. 2008). (LFPs are a massed measure of neural activity obtained by low pass filtering of the extracellular potential recorded with intracranial microelectrodes and capturing fluctuations in the input and intracortical processing of the local cortical network, including the overall effect of population synaptic potentials and other types of slow activity, such as spike afterpotentials and voltage-dependent membrane oscillations; see Buzsaki et al. (2012) and Einevoll et al. (2013) for recent reviews.) We found that the presentation of naturalistic color movies elicited reliable responses across trials both for the spikes and for the phase of LFPs in low frequency bands, particularly in the delta (1–4 Hz) and theta (4–8 Hz) band. However, we often found that two different movies scenes elicited very similar firing rates and thus could not be discriminated using a rate code. However, often the spikes elicited in response to scenes with similar rate were fired at a different LFP phase in each scene, thereby suggesting that the phase of firing conveyed information that could not be extracted from spike rate. We investigated this point quantitatively by computing the amount of mutual information about which movie scene was being presented that can be extracted by firing rates and by phase of firing, respectively (mutual information is a principled measure of

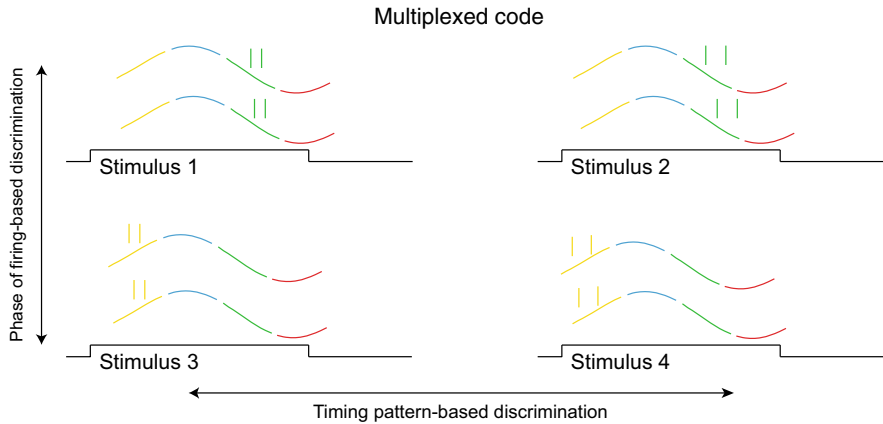
association between variables that is often used in neuroscience to measure the association between sensory stimuli and neural responses; see Quiroga and Panzeri (2009) for a review). The phase-of-firing was indeed found to convey information that was not accessible from the spike rates alone: the overall information about the movie increased by more than 50% when the LFP phase-of-firing was considered. The extra information available in the phase-of-firing was crucial for the disambiguation between stimuli eliciting high spike rates of similar magnitude. Thus, phase coding may allow primary cortical neurons to represent several effective stimuli in an easily decodable format.

We then investigated whether phase-of-firing coding of naturalistic information was present also in auditory cortex of awake macaques during the presentation of natural sounds input (Kayser et al. 2009). We found that also in this case, the phase-of-firing code carried information about the natural sound above and beyond that available in firing rates of auditory cortical neurons, thereby confirming the above results obtained in visual cortex. However, in auditory cortex we also found that an additional type of spike time coding scheme was at work: there were millisecond precise temporal patterns of spikes that too carried information not available in firing rates defined over longer time periods (Kayser et al. 2009). An important question was thus whether millisecond scale spike patterns carry the same or different information than the phase of slow network oscillations at which they are fired. Using again information theoretic measures, we found that information in spike rates and patterns at millisecond timescales was complementary to the information in the phase-of-firing, as sound periods not discernable from spike rates or spike patterns alone could instead be discriminated by also measuring the phase-of-firing. Together, these findings suggest that the timing of spikes measured on a millisecond scale, firing rates on a tens to hundreds of millisecond scale, and timing of spikes measured with respect to network fluctuations operating at

frequencies of a few hertz in sensory cortices constitute largely complementary information channels during naturalistic stimulation, and that these codes can be combined into highly informative codes containing “multiplexed” sensory information.

One way in which a neuron may use multiplexed codes that carry independent information at each time scale is illustrated in the simplified schematic of Fig. 3. This figure shows a cartoon of a neuron that represents information needed to discriminate odd (1 and 3) from even (2 and 4) stimuli with the fine-time scale differences of their temporal firing patterns (very small inter-spike intervals are used for stimuli 1,3 and slightly longer inter-spike intervals are used for stimulus 2,4). This example neuron represents on a much coarser time scale the information needed to discriminate stimuli 1,2 from stimuli 3,4 by using the timing of spikes with respect to the network oscillation (stimuli 1,2 are coded with spikes fired in the descending “green” part of the wave, whereas stimuli 3,4 are coded with spikes fired in the ascending “yellow” part of the wave). This example neuron thus carries all the information needed to discriminate the four stimuli only when putting together the complementary information from these two codes each operating at a different time scale.

As a caveat, it is worth mentioning that the fact that several different neural codes make a complementary contribution to the information encoded in a given brain area does not necessarily imply that all these codes make a complementary contribution to behavioral decisions based on the sensory variables represented by this neural activity. It is possible that, for example, a downstream behavioral readout mechanism is unable to access the information in some of these codes. It is thus of paramount importance that future works test the impact of different components of multiplexed codes on behavioral decisions. A complementary impact on behavior of millisecond spike patterns and firing rates has been recently reported in somatosensory cortex (Zuo et al. 2015). However, a complementary impact of phase-of-firing and



Local Field Potential, Phase Coding, Fig. 3 Schematic cartoon of a multiplexed code. In all panels, the x-axis represents peristimulus time, short vertical lines denote spike times, and waves denote the concurrent network oscillation (measured, e.g., as the Local Field Potential – LFP) recording together with the spikes, and each row corresponds to a different trial. Here, the network oscillation phase is divided in four sectors depending on the phase and each of them is characterized by a different color. In this example, stimulus 1 (left) and stimulus 2 (right) cannot be distinguished by the firing rate, but by their respective phases of firing compared to the underlying oscillation (green vs. yellow). Redrawn from Panzeri et al. (2010). Discrimination between odd (1 and 3) and even (2 and 4)

stimuli is based on fine-precision temporal spike patterns (very small inter-spike intervals are used for stimuli 1,3 and slightly longer inter-spike intervals are used for stimulus 2,4). Discrimination between stimuli 1,2 from stimuli 3,4 is based on a phase-of-firing code based on oscillations at much slower time scales than that used in the temporal spike patterns described above (stimuli 1,2 are coded with spikes fired in the descending “green” part of the wave, whereas stimuli 3,4 are coded with spikes fired in the ascending “yellow” part of the wave). In this cartoon, the example neuron thus uses multiplexing to code this stimulus set: the four stimuli can only be discriminated when putting together the complementary information from these two codes each operating at a different time scale

firing rates on behavioral decisions has yet to be reported, to our knowledge.

Finally, we also used auditory cortex recordings to investigate which kinds of sensory representations are more robust to environmental noise in the sensory input (Kayser et al. 2009). We presented naturalistic sounds either in their original form or mixed with naturalistic environmental noise, which was varied from trial to trial. Although stimulus information decreased with increasing noise for all codes, the information in the phase-of-firing with respect to slow oscillations (hence a multiplexed code) increased relative to the information in spike counts when increasing noise. This suggests that encoding information in spike times using an internal temporal reference frame, such as slow network oscillations, may be central to forming stable sensory representations in unreliable environments.

Cross-References

- [Applications of Information Theory to Analysis of Neural Data](#)
- [Estimation of Neuronal Firing Rate](#)
- [Extracellular Potentials, Forward Modeling of](#)
- [Local Field Potentials: LFP](#)
- [Summary of Information-Theoretic Quantities](#)

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Local Field Potential, Relationship to BOLD Signal

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Definition

Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has rapidly become the leading research tool in cognitive neuroscience. Understanding how BOLD signal relates to activity of neural populations is crucial for constraining the interpretation of any fMRI in humans or animals. Here we review how the mean extracellular field potential (mEFP) recorded with extracellular electrodes samples different components of neural activity and how these components relate to the BOLD fMRI signal.

Detailed Description

In this entry, we first review the properties of the neurophysiological signals recorded with extracellular electrodes, and we then review how neurophysiological measures of neural activity related to the BOLD fMRI signal.

Extracellular Medium and Mean Extracellular Field Potential (mEFP)

The extracellular medium surrounding neurons is a volume conductor with a resistivity (specific impedance) that ranges from 200 to 400 Ωcm depending on neural site (for references, see

Logothetis 2003). This extracellular resistivity, which is higher than that of a saline bath, $\sim 65 \Omega\text{cm}$, in the frequency range of 1 Hz to 10 kHz (Logothetis et al. 2007), is mainly due to limitations on the flow of ions in the extracellular medium compared with saline. For the frequency range of electrophysiological signals (0 to about 7 kHz), inductive, magnetic, and propagative effects can be ignored, and the electric field can be considered homogeneous and purely resistive, obeying Ohm's law. In such a static description, the flow of positive ions (e.g., Na^+) into the active sites of a neuron appears as a current sink (inward current); the injected current flows down the core of the dendrites or axon. Because currents flow in closed loops, a current outflow from distant inactive membrane sites appears as a source (outward current) from which current flows back to the injection site through the extracellular medium. The finite resistance of the latter creates the extracellular field potentials (EFPs) that are measured by electrodes.

The weighted spatiotemporal sum of the sinks and sources from multiple cells is often called the mean extracellular field potential (mEFP). The weighting depends on several factors. Most importantly, the spatial alignment of elongated neural processes establishes an anisotropic conductivity across space and imparts a preferred directionality to the current flow. The directionality complicates the interpretation of the mEFP measurement: Cells whose current flow travels in opposing directions will cancel each other out. There are no practical methods for recovering information about the spatial conductance pattern because such information is rarely available, and there is no widely agreed upon model for interpreting the mEFP with respect to the factors that influence the cellular currents.

The mEFP captures at least three different types of neural activity: single-unit activity (SUA) representing the action potentials of well-isolated neurons next to the electrode tip, multiple unit activity (MUA) reflecting the spiking of small neural populations in a sphere of 100–300 μm radius, and perisynaptic activity of a neural population within 0.5–3 mm of the electrode tip, which is reflected in the variation of the low-

frequency components of the EFP (this is the so-called local field potential – LFP). MUA and LFP can be reliably segregated by frequency band separation. A high-pass filter cutoff of 800–1000 Hz is used in most recordings to obtain the MUA and a low-pass filter cutoff of ca. 500 Hz to obtain LFP. A large number of experiments have presented data indicating that such a band separation does indeed underlie different neural events. In the following we examine the properties of SUA, MUA, and LFP.

Single-Unit Activity (SUA) Recordings

If a microelectrode with a small tip is placed close to the soma or axon of a neuron, then the measured mEFP directly reports the spike traffic of that neuron and frequently that of its immediate neighbors as well. Single-unit spike times are typically obtained by first thresholding the high-frequency part of the mEFP (above approximately 700–800 Hz) to identify spiking events and then by using clustering techniques to sort spikes from different individual neurons.

The firing rate of such well-isolated neurons has been the critical measure for comparing neural activity to sensory processing or behavior ever since the early development of microelectrodes (Adrian and Zotterman 1926), and it has been the mainstay of systems neuroscience for decades.

A great deal has been learned since then, and the single-electrode single-unit recording technique still remains the method of choice in many behavioral experiments with conscious animals. However, it also has the drawback of providing information mainly on single receptive fields, with no access to subthreshold integrative processes or the associational operations taking place at a given site. Moreover, it suffers from an element of bias toward certain cell types (cf. (Stone 1973) and sizes (Towe and Harding 1970). The size bias, which is partially responsible for the cell-type bias as well, is considerable. For equivalent transmembrane action potentials, the discharge of a large neuron generates a substantially greater flow of membrane current and a larger extracellular spike than a small cell, and the

resulting extracellular field remains above recording noise levels over a greater distance. Larger neurons (cells with 20–30 μm diameter or greater) are estimated to generate a potential of 100 μV or more within a 100 μm -diameter sphere with the electrode tip at its center (Rall 1962). The amplitude of this potential decreases rapidly with increasing distance from the electrode tip because of the aforementioned low-pass properties of the extracellular medium. Spikes generated by large neurons will thus remain above the noise level over a greater distance from the cell than spikes from small neurons, so microelectrodes are likely to sample their somas or axons preferentially, a prediction supported by experimental work (Towe and Harding 1970; Humphrey and Corrie 1978). It follows that the measured spikes may actually represent only very small neural populations of large cells, which in cortex are by and large the principal cells (e.g., pyramidal cells in cerebral cortex and Purkinje neurons in cerebellar cortex). Recording from interneurons (e.g., inhibitory cells) is often very difficult both because of their size and because their response is often found to be uncorrelated to the stimulus or behavior state of the animal.

In conclusion, the vast majority of experiments employing single-unit extracellular recordings report on the activity of large principal cells, which represent the output of the cortical area under study. It is the firing rate of these principal neurons that is commonly used to compare the results of animal and human studies.

Multiunit Spiking Activity (MUA)

MUA can be estimated in two ways. The first is estimated by identifying individual spikes by thresholding the high-pass signal (sometimes with the additional step of convolving the resulting spike time series with a temporal kernel), without the additional step of trying to sort and cluster single units. The second is estimated by first high-pass filtering the EFP in the range of more than ~ 700 –800 Hz and then rectifying it. The former method is more suited to sample activity of few neurons, and the latter method is

more suited to sample spiking activity in a larger area of diameter of few hundred microns around the electrode.

The magnitude of EFPs in the high-frequency MUA range was shown to be a function of cell and axon size. Combined physiology-histology experiments demonstrated that the magnitude of MUA is site specific (Buchwald and Grover 1970) and thus also cell-size specific (Nelson 1966), varying considerably from one brain region to another but remaining relatively constant for any particular site (e.g., neocortex vs. hippocampus). Homogeneous populations of large cells were found to systematically occur at sites of large-amplitude fast activity, and vice versa (Grover and Buchwald 1970). Similarly, the magnitude of axonal spikes is directly correlated with the size of the transmitting axon (Gasser and Grundfest 1939; Hunt 1951). All of these experiments show that MUA-range activity reflects the variations in the magnitude of extracellular spike potentials. In other words, large-amplitude signal variations in the MUA range reflect large-amplitude extracellular potentials, and small-amplitude fast activity is correlated with small ones.

The summation range for the fast MUA has also been studied by a number of investigators. Electrodes with exposed tips of approximately 100 μm (impedance from 40 to 120 $\text{k}\Omega$), for example, were estimated to record from a sphere with a radius of 50–350 μm (Grover and Buchwald, Legatt et al. 1980), whereby the activity from each point within the sphere is weighted by a factor depending on the distance of the point from the tip of the electrode (Nicholson and Llinas 1971). Recent tetrode recordings suggest that it is possible to sample individual spikes up to a distance of approximately 140 μm from the electrode tip (Henze et al. 2000). Given the estimated number of neurons contained in a cylindrical region with 140 μm diameter in the hippocampal area CA1 (Boss et al. 1985; Aika et al. 1994), single-electrode recordings could provide information concerning the activity of approximately 1000 neurons (Henze et al. 2000). In the primary visual cortex, which contains about 200,000 neurons beneath 1 mm^2 of cortical surface (Powell and Hendrickson 1981; O’Kusky and Colonnier

1982), this number is likely to be considerably higher.

All in all, depending on the recording site and the electrode properties, the MUA most likely represents a weighted sum of the extracellular action potentials of all neurons within a sphere of approximately 140–300 μm radius, with the electrode at its center. Spikes produced by the synchronous firings of many cells can, in principle, be enhanced by summation and thus detected over a larger distance (Huang and Buchwald 1977; Arezzo et al. 1979).

Local Field Potential (LFP)

The LFP is the low-frequency range of the mEFP signal and is typically computed by low-pass filtering the mEFP below 500 Hz. LFPs represent mostly slow events reflecting cooperative activity in neural populations. Until recently these signals were thought to represent exclusively synaptic events. Evidence for this came from combined electroencephalographic (EEG) and intracortical recordings showing that the slow wave activity in the EEG is largely independent of neuronal spiking (Ajmone-Marsan 1965; Buchwald et al. 1965; Fromm and Bond 1967). These studies showed that, unlike the multiunit activity, the magnitude of the slow field fluctuations is not correlated with cell size, but instead reflects the extent and geometry of dendrites in each recording site. Cells in the so-called open field geometrical arrangement, in which dendrites face in one direction and somata in another, produce strong dendrite-to-soma dipoles when they are activated by synchronous synaptic input. Other cortical neurons are oriented horizontally and contribute less efficiently or not at all to the sum of potentials. The pyramidal cells with their apical dendrites running parallel to each other and perpendicular to the pial surface form an ideal open field arrangement and contribute maximally to both the EEG and LFP.

Evidence concerning the origin of LFPs can also be gathered from current-source density (CSD) analysis and combined field potential and intracellular recordings (for a review of CSD as

well as other types of ensemble recordings, see Mitzdorf 1985, and Nadasdy et al. 1998). Mitzdorf has suggested that LFPs actually reflect a weighted average of synchronized dendrosomatic components of the synaptic signals of a neural population within 0.5–3 mm of the electrode tip (Mitzdorf 1987; Juergens et al. 1999). The upper limits of the spatial extent of LFP summation were indirectly calculated by computing the phase coherence of LFPs as a function of interelectrode distance in experiments with simultaneous multiple-electrode recordings (Juergens et al. 1996) and were also investigated in realistic simulations of networks of multicompartmental neurons that computed the radius around the electrode containing the neural sources that provide most of the LFP amplitude (Linden et al. 2011).

LFPs were initially attributed exclusively to population excitatory or inhibitory postsynaptic potentials that are considerably slower than the spiking activity. Later studies, however, provided evidence of the existence of other types of slow activity unrelated to synaptic events, including voltage-dependent membrane oscillations (Kamondi et al. 1998) and spike afterpotentials. To be more specific, the soma-dendritic spikes in the neurons of the central nervous system are generally followed by afterpotentials, a brief delayed depolarization, the afterdepolarization, and a longer lasting afterhyperpolarization, which are thought to play an important role in the control of excitation-to-frequency transduction (Granit et al. 1963; Harada and Takahashi 1983; Gustafsson 1984). Afterpotentials, which were shown to be generated by calcium-activated potassium currents (Harada and Takahashi 1983; Fulton and Walton 1986; Higashi et al. 1993; Chandler et al. 1994; Kobayashi et al. 1997), have a duration on the order of tens of milliseconds and most likely contribute to the generation of the LFP signals (Buzsaki et al. 1988).

Because multiple neuronal processes contribute to the LFP, the signal is inherently ambiguous and more difficult to interpret than spikes. This ambiguity can, at least in part, be resolved by using computational analysis and modeling to disambiguate the different neural contributions to the LFP (Einevoll et al. 2013).

The simplest, and most traditional, way to separate different contribution to the LFP is to use the frequency domain. Low-frequency signal modulations are classified in a number of specific frequency bands initially introduced in the EEG literature (see, e.g., Elul 1969, and Pedley and Traub 1990). Rhythmic EEG is subdivided into frequency bands known as delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–24 Hz), and gamma (40–100 Hz) that are typically characterized by different amplitudes (Lindsley and Wicke 1974; Steriade and Hobson 1976; Basar 1980; Steriade 1991). The validity of this approach is supported by the strong correlation of each band with a distinct behavioral state, by the largely independent modulation of these bands with sensory inputs (Belitski et al. 2008), and by evidence suggesting that each band is generated by partly different mechanisms. For example, the oscillatory activity in the delta, theta, and alpha bands is associated with the thalamocortical loops and is modulated by the ascending network system and basal forebrain (Steriade 1991; Steriade et al. 1993), while the oscillatory activity in the gamma range is associated with the rhythmic interplay of local inhibition and excitation (Fries et al. 2007). Although the definition of the exact frequency boundaries of each band is often largely arbitrary and based on heuristic criteria that vary substantially between studies, these boundaries can be also determined by rigorous procedures that minimize the overlap both in terms of signal and of noise correlations across different bands (Magri et al. 2012a).

In summary, LFP signals and their different band-limited components (alpha, beta, gamma, etc.) are invaluable help for understanding cortical processing, as they are the only signs of integrative processes in excitation-inhibition networks. In fact, LFP do not, as initially thought, solely reflect population postsynaptic potentials, but also integrative soma-dendritic processes – including voltage-dependent membrane oscillations and afterpotentials following soma-dendritic spikes – that all together represent the local (perisynaptic) activity in a region.

Summary of Components of mEFP

MUA mostly represents the spiking of neurons, with single-unit recordings mainly reporting on the activity of the projection neurons that form the exclusive output of a cortical area. LFPs, on the other hand, represent slow waveforms, including synaptic potentials, afterpotentials of somato-dendritic spikes, and voltage-gated membrane oscillations, that reflect the input of a given cortical areas as well as its local intracortical processing, including the activity of excitatory and inhibitory interneurons. Given the complementarity of these signals, it is apparent that the most useful information will not be derived by one type of signal alone, but rather by the study of relative changes in one signal or the other. Electrophysiological studies examining the individual contributions of different LFP frequency bands, multiple unit activity, and spiking of individual neurons are probably our only realistic chance of gaining insights into the neural mechanisms of hemodynamic responses and their meaning in the context of different cognitive tasks.

Relationship of mEFP to the BOLD fMRI Signal

The relationship of neocortical LFPs and spiking activity to the BOLD signal itself was examined directly in concurrent electrophysiology and fMRI experiments in the visual system of anesthetized (Logothetis et al. 2001) and alert (Goense and Logothetis 2008) monkeys. These studies found that the BOLD responses reflect input and intracortical processing rather than pyramidal cell output activity. At first glance, both LFPs and spiking seemed to be correlated with the BOLD response. However, quantitative analysis indicated that LFPs are significantly better predictors of the BOLD response than multiunit or single-unit spiking. For example, the band-limited power of the gamma band of the LFP carries twice more information about future values of the BOLD than the MUA power does (Magri et al. 2012b).

The decisive finding leading to the conclusion that BOLD responses reflect input and

intracortical processing rather than pyramidal cell output activity, however, is not the degree of correlation between the neural and the fMRI responses or the differential contribution of any type of signal into the BOLD responses (Goense and Logothetis 2008), but rather the striking, undiminished hemodynamic responses in cases where spiking is entirely absent despite a clear and strong stimulus-induced modulation of the field potentials (Logothetis et al. 2001; Goense and Logothetis 2008). Similar dissociations between spikes and cerebral blood flow (CBF) had been demonstrated in a number of studies using other techniques (Mathiesen et al. 1998; Viswanathan and Freeman 2007; Rauch et al. 2008).

The findings are also in close agreement with a number of older autoradiography studies, also showing that regional glucose utilization is directly related to neuronal synaptic activity (Jueptner and Weiller 1995). For example, the greatest uptake of 2- ^{14}C 2 deoxyglucose (an indication of glucose consumption and thus of metabolism) occurs in the neuropil, i.e., in areas rich in synapses, dendrites, and axons, rather than in cell bodies. During orthodromic and antidromic electrical microstimulation, only the first, which involves presynaptic terminals, increases glucose consumption. Similarly, the highest density of cytochrome oxidase (an enzyme of the respiratory chain) is found in somato-dendritic regions that are adjacent to axon terminals. Last but not least, as mentioned earlier, presynaptic activity increases metabolism even when the output is inhibited, i.e., the spiking activity is abolished.

The correlation between BOLD and LFP is strongly frequency dependent. The LFP gamma frequency band carries almost twice more information about the BOLD than any other frequency component of the mEFP (Magri et al. 2012b). Both increases and decreases in BOLD signal follow increases and decreases in LFP gamma power. The reasons of the frequency dependence of the LFP-BOLD relationship are still unknown, although phenomenological models have been proposed (Kilner et al. 2005). Understanding the nature of this relationship is potentially important because it may allow a partial identification of

contributions of different neural pathways to cortical processing using fMRI.

Despite all the above evidence, some discussion still concentrates on the importance of the firing rate of action potentials of projection neurons in the generation of the hemodynamic responses, perhaps stemming from the fact that important early studies of neural correlates of behavior took the mean spiking rate to be the gold standard for quantifying neuronal activation. These discussions, however, often suffer from a certain amount of contention-seeking where none is warranted. In many cases, spikes do indeed correlate with LFPs, and they will also correlate with BOLD. In addition, unusually high correlations between MUA and BOLD (or LFP and MUA) typically reflect excessive averaging due to long image repetition times, i.e., sampling rates of several seconds rather than a fraction of a second (for a detailed discussion, see Goense and Logothetis (2008)).

Can We Predict Neural Activity from the fMRI Signals?

fMRI signals are presumed to result from changes in the activity of the neuronal populations responsible for the functions in question. The psychologist or cognitive neuroscientist who finds a cortical area to be activated by the task at hand implicitly or explicitly assumes an increase in the spiking rate of specialized neurons underlying the subject's behavior. This might well be true in some cases, but not in all. When attempting to interpret the fMRI signal by modeling or when comparing the results of human neuroimaging to those obtained in monkey physiology experiments, it is useful to take the following facts into consideration.

In humans, there are about 100,000 neurons under 1 mm² of cortical surface. This number is relatively constant for all structurally and functionally distinct areas, including the somatosensory, temporal, parietal, frontal, and motor cortical areas (Rockel et al. 1980; Braitenberg and Schuez 1998). An exception is the primary visual cortex of certain primates, including monkey and man,

which has approximately twice as many neurons. The number of neurons is also similar across many species, including mouse, rat, cat, monkey, and human. Neural density is 20,000–30,000 neurons/mm³ (Cragg 1975; Rockel et al. 1980), and synaptic density ranges from 0.4 to 1×10^9 /mm³. It follows that the average voxel size, often about 55 μ L size, contains 5.5 million neurons, $2.2\text{--}5.5 \times 10^{10}$ synapses, 22 km of dendrites, and 220 km of axons! This “large population view” is in sharp contrast to the scope of the traditional microelectrode recordings. In addition, there exists a strong selection bias during extracellular recordings, which is partly due to practical limitations, e.g., injury or simply size bias (Logothetis and Wandell 2004), and partly to the physiological properties of neurons and/or the organizational principles of neural networks. In fact, many different types of electrical and optical measurements provide evidence that a substantial proportion of neurons, including the cortical pyramidal cells, might be silent (Shoham et al. 2006). Their silence might reflect unusually high input selectivity or the existence of decoding schemes relying on infrequent co-spiking of neuronal subsets. Most important for the comparison of neuroimaging and electrophysiology results is the fact that lack of measurable neuronal spiking may not necessarily imply lack of input and subthreshold processing.

A direct analogy between neuronal spiking as measured in animal experiment and the fMRI signal obtained in human recording is thus simply unrealistic and might often lead to wrong conclusions. It is hardly surprising that most studies so far relying purely on BOLD fMRI failed to reveal the actual neural properties of the studied area, at least those properties, e.g., selectivity to various visual features that were previously established in electrophysiological studies. The fMRI signal cannot differentiate between function-specific processing and neuromodulation and between bottom-up and top-down signals, and it may potentially confuse excitation and inhibition. In cortical regions in which stimulus- or task-related perceptual or cognitive capacities are sparsely represented, e.g., instantiated in the activity of a very small number of neurons, volume

transmission which probably underlies the altered states of motivation, attention, learning, and memory may dominate hemodynamic responses and make it impossible to deduce the exact role of the area in the task at hand.

Cross-References

- ▶ [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- ▶ [Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism](#)
- ▶ [Connectivity Analysis in Normal and Pathological Brains](#)
- ▶ [Cortical Columns, Models of](#)
- ▶ [Current Source Density \(CSD\) Analysis](#)
- ▶ [Electrocorticogram \(ECoG\)](#)
- ▶ [Extracellular Potentials, Forward Modeling of](#)
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- ▶ [Local Field Potential, Methods of Recording](#)
- ▶ [Local Field Potential, Relationship to Electroencephalogram \(EEG\) and Magnetoencephalogram \(MEG\)](#)
- ▶ [Local Field Potential, Relationship to Unit Activity](#)
- ▶ [Local Field Potential, Synchrony of](#)
- ▶ [Local Field Potential: Relationship to Membrane Synaptic Potentials](#)
- ▶ [Local Field Potentials in Olfaction](#)
- ▶ [Local Field Potentials: Interaction with the Extracellular Medium](#)
- ▶ [Local Field Potentials: LFP](#)
- ▶ [Neural Coding](#)

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Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG)

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Definition

Electrical currents produced by neural circuits in the brain create both electric fields and magnetic fields. The electrical field activity can be measured close to the neural source with intracranial extracellular microelectrodes and is referred to as the local field potential (LFP). The electric and magnetic fields can also be measured extracranially at a distance from the source on the surface of the head with electroencephalography (EEG) and magnetoencephalography (MEG), respectively.

Detailed Description

Recordings of Different Scales

The LFP is considered a microscopic scale measurement, while MEG and EEG are considered macroscopic scale measurements. A main distinction in microscopic versus macroscopic scale activity is the volume of neural space contributing to the recorded signals and the conductivity profile assumed to impact the measurement, discussed below.

Measurement Devices

Electrical fields in the brain are large enough that they can be measured intracranially with microelectrodes for LFPs and extracranially with macroelectrodes on the scalp for EEG (Buzsaki et al. 2012). Magnetic fields are comparably very small, on the order of $10\text{--}10^3$ femto-Tesla (fT),

but can be measured extracranially with ultra-sensitive detectors known as superconducting quantum interferences devices (SQUIDS) (Fig. 1). MEG devices house the SQUIDS in a dewar that is filled with helium to keep the SQUIDS at superconducting temperatures and MEG is enclosed in a magnetically shielded room to block extraneous magnetic fields in the environment, on the order of 10^8 fT (Hamalainen et al. 1993).

Equations Regulating Relationship Between Electric and Magnetic Fields: The Forward Solution

Given an electrical current in the brain that changes relatively slowly (e.g., <100 Hz), the electric (E) and magnetic fields (B) it produces can be calculated from the quasistatic approximation of Maxwell's Equations:

$$\begin{aligned}\bar{\nabla} \cdot E &= \frac{\rho}{\epsilon} \\ \nabla \times E &= 0 \\ \nabla \cdot B &= 0 \\ \nabla \times B &= \mu_0\end{aligned}$$

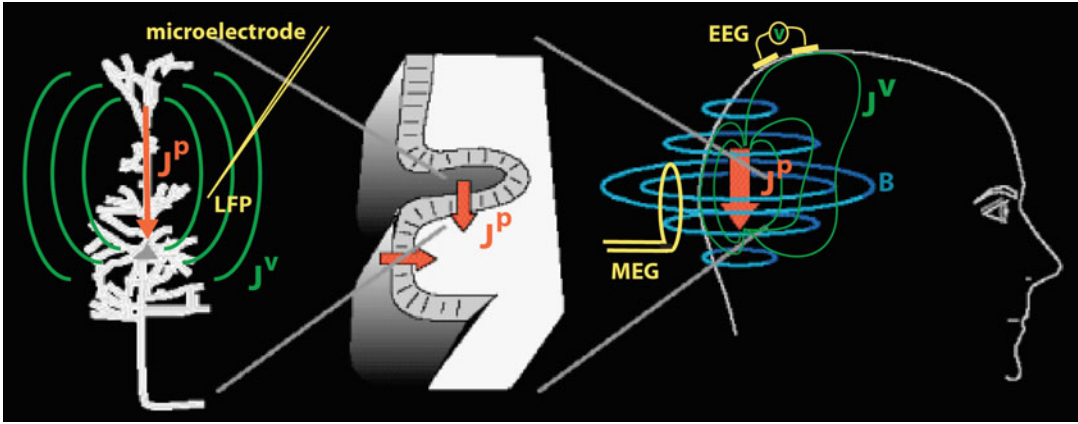
and $\nabla \cdot J = 0$ (conservation of current), where ϵ is the permittivity of the medium, ρ is the charge density, μ_0 is the permeability of free space, and J is the electric current density due to free charges.

The total current density J can be split into two components: the primary current, J^p , which represents the neural current that generates the electric and magnetic fields (see red arrows in Fig. 1), and the extracellular volume or return current, J^v (shown in green in Fig. 1), which is proportional to the conductivity, σ , and the electric field, $J^v = \sigma E$. Thus, the primary current can be represented as

$$J^p = J - \sigma E$$

Since $\nabla \times E = 0$, the electric field can be expressed with a scalar potential, $E = -\nabla V$.

Taking the divergence (bi-domain approximation), we obtain



Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG), Fig. 1 Schematic illustration of the relationship between microscopic local field potentials (LFPs) measured intracranially with microelectrodes and macroscopic electric and magnetic fields measured extracranially with electroencephalography (EEG) and magnetoencephalography

(MEG), respectively. In the neocortex, the primary electrical current sources (J^P) underlying extracranially measured electric (V) and magnetic fields (B), and contributing to local extracellular electric fields (volume currents, J^V), are thought to be generated mainly by the net postsynaptic intracellular current flow in the long and spatially aligned dendrites of pyramidal neurons

$$\begin{aligned}\nabla \cdot J^P &= \nabla \cdot (J - \sigma E) = \nabla \cdot J - \nabla \cdot \sigma E \\ &= \nabla \cdot (\sigma \nabla V)\end{aligned}$$

and arrive at a Poisson Equation for the electric potential

$$\nabla \cdot (\sigma \nabla V) = \nabla \cdot J^P$$

With the proper boundary conditions, and knowledge of σ and J^P , this equation can be solved for V with finite element techniques. Once V is known, the magnetic field, B (blue in Fig. 1), can be computed from Biot-Savart law

$$B(r) = \frac{\mu_0}{4\pi} \int_G J^P(r') \times \frac{R}{R^3} dV$$

where the integration is performed over a volume G containing all active sources and $R = r - r'$ is a vector connecting the location of the source r' to point r where the magnetic field is computed. In an infinite homogeneous volume conduction, the volume currents give no contribution to the electric potential or magnetic field (see (Hamalainen et al. 1993) for derivation). If we assume the volume at which the current flow consists of

homogeneous compartments, both the electric potential and magnetic field can be computed from integral equations involving the value of V on the boundary surface with boundary-element methods (BEM) (Hamalainen and Sarvas 1989).

Further, in a spherical head model, the MEG signals can be calculated directly from the primary current without explicit reference to the structure of the conductor (unlike LFP or EEG). Additionally, radial currents do not produce a magnetic field outside of a spherical conductor model. In contrast, EEG will record fields produced by both radial and tangential current sources, shown in the gyri and sulci, respectively, in Fig. 1. This difference makes the inverse problem easier for MEG than EEG.

While the primary current, J^P , creating the LFP, MEG, and EEG signals can be in principle equivalent, the distance from the current sources over which the electric or magnetic field is calculated necessitates vastly different assumptions on the conductivity profile, σ , and the neural interpretation of the signal can be very different.

LFP: When calculating the forward solution for LFP, a homogeneous extracellular medium is

typically considered with a constant isotropic conductivity profile (Linden et al. 2011). More complicated anisotropic conductivity gradients have been considered (Bedard et al. 2004; Bedard and Destexhe 2009; Anastassiou et al. 2010) and are particularly important for higher frequency signals.

EEG/MEG: When calculating the forward solution for EEG/MEG, a macroscopic scalar measure of conductivity σ with at least 1-mm scale is assumed, and head models with realistic conductor geometries can be determined with structural MRI. For MEG a highly accurate solution can be obtained with BEM by considering only one homogeneous compartment bounded by the inner skull; for EEG at least 3 compartments need to be considered, the scalp, skull, and brain (Hamalainen and Sarvas 1989).

Determining the Current Sources: The Inverse Problem

Estimating the location and temporal evolution of the primary current sources producing the recorded electric or magnetic fields is a problem termed the inverse problem. Inferring the underlying neural level events that create these primary currents is an additional challenge.

LFP: By definition, LFPs are presumed to be local to the current source generators. However, interpreting the exact spatial reach of the recorded activity and the neural level generation is complex and depends on many things including the local cell types, their active membrane properties and morphologies, synaptic arrangements, and the level of neural synchrony (Linden et al. 2011; Reimann et al. 2013). It is generally assumed that low-frequency LFP (<100 Hz) emerges mainly from slower transmembrane postsynaptic events but the geometry of the cells, as well as other non-synaptic events, including glial activity, can greatly influence the extracellular field (Buzsaki et al. 2012). In the neocortex, the synapses on spatially aligned and parallel

orientated pyramidal neuron (PN) dendrites have been hypothesized to dominate the LFP signal, and there is often an agreement between LFP signals and surface EEG signals due to their prominent impact on the extracellular field (Linden et al. 2011; Buzsaki et al. 2012).

EEG/MEG: Estimating the primary current source densities underlying macroscopically measured EEG or MEG signals is an inherently ill-posed problem because the inverse solutions are nonunique (e.g., different spatial-temporal distributions of current sources can give the same forward solution). Additional physiological constraints are used to constrain the problem and simplify the forward solution, including replacement of the actually primary current sources by equivalent generators or point sources referred to as current dipoles, and the assumption that these primary current dipoles are restricted to the cortical surface, which can be accurately modeled with structural MRI. Once a forward solution is determined, a unique solution to the inverse problem can be found by comparing to the recorded data (e.g., least squared fit). There are many alternative approaches to accurately estimate the sources contributing to EEG/MEG measurements, including multi-dipole models and current distribution models, reviewed in Hamalainen et al. (1993).

The neural source of the primary currents estimated with EEG/MEG inverse methods is commonly thought to be the summed postsynaptic longitudinal currents flowing inside the dendrites of the large spatially aligned cortical PNs in a direction perpendicular to the cortical surface (Hamalainen et al. 1993; Okada et al. 1997; Ikeda et al. 2005); see red arrow in Fig. 1. Due to the long length of the deep Layer V PNs apical dendrites, they are thought to dominate the recorded activity (Murakami and Okada 2006; Lee and Jones 2013). The more neurons that participate in synchrony, the bigger the signal will be. Estimates on the size of cortical volume that creates a minimally measurable primary current signal (~ 10 nano-Ampere-meter) are $\sim 10^6$ PNs (Jones et al. 2007).

Computational Modeling

From a computational modeling standpoint, modeling the macroscopic primary current source signals estimated with inverse methods from MEG/EEG with intracellular PN dendritic current flow in multi-compartment neurons, as in Murakami et al. (2002, 2003), Murakami and Okada (2006), Jones et al. (2007, 2009), Ziegler et al. (2010), and Lee and Jones (2013), can be a more tractable problem than modeling the microscopic extracellular LFP or macroscopic EEG signals at the sensors level (i.e., the forward solution). Models of LFP signals need to account for greater details of the local network and extracellular conductivity gradients (Bedard et al. 2004; Bedard and Destexhe 2009; Anastassiou et al. 2010; Linden et al. 2011; Reimann et al. 2013). Models of EEG sensor activity calculated with forward models need to account for folding in the cortical surface and conductivity profiles of the brain tissue, spinal fluid, and skull (Barres et al. 2013). Constructed with proper biophysics, computational neural models can serve as the interpretive link between the different scales of activity.

Cross-References

- ▶ [Cortex: Overview](#)
- ▶ [Extracellular Potentials, Forward Modeling of](#)
- ▶ [Inverse Problems in Neural Population Models](#)
- ▶ [LFP Analysis: Overview](#)
- ▶ [Local Field Potential, Ephaptic Interactions](#)
- ▶ [Local Field Potential, Methods of Recording](#)
- ▶ [Local Field Potentials: Interaction with the Extracellular Medium](#)
- ▶ [Local Field Potentials: LFP](#)
- ▶ [Spike Triggered Average](#)

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Local Field Potential, Relationship to Unit Activity

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Synonyms

Contamination by spikes; Electroencephalogram; Local field potential; Relation to unit activity; Spike contribution; Spike-triggered average

Definition

Unit activity usually refers to timing of spikes elicited by individual neurons (single unit activity, SUA) or local ($r < 140 \mu\text{m}$) population of neurons (multi-unit activity, MUA; Buzsáki 2004). Although local field potential (LFP) reflects both subthreshold and spiking activities that are summed over larger population of neurons ($r < 450 \mu\text{m}$, Berens et al. 2008), usually it does not display discriminable spikes. Nevertheless, the amplitude of high-frequency LFP ($>40 \text{ Hz}$) often correlates with population firing rate,

whereas the phase and amplitude of low-frequency LFP ($<10 \text{ Hz}$) modulates this relationship. The LFP-spike relation is very sensitive to neuronal correlations – at high synchrony levels neurons produce macroscopic spikes visible in the raw LFP signal (“population spikes”).

Detailed Description

The basic physical phenomena involved in generation of LFP are common across all types of neuronal activities, including unit activity (spikes). However, there are several factors that differentiate unit contributions from, for example, synaptic contributions: (1) Their spatial locality leads to rapid decay of their contribution with distance; (2) their short duration hinders the summation of contributions from multiple units; (3) their high-frequency power is cut off by biological medium and hardware filters.

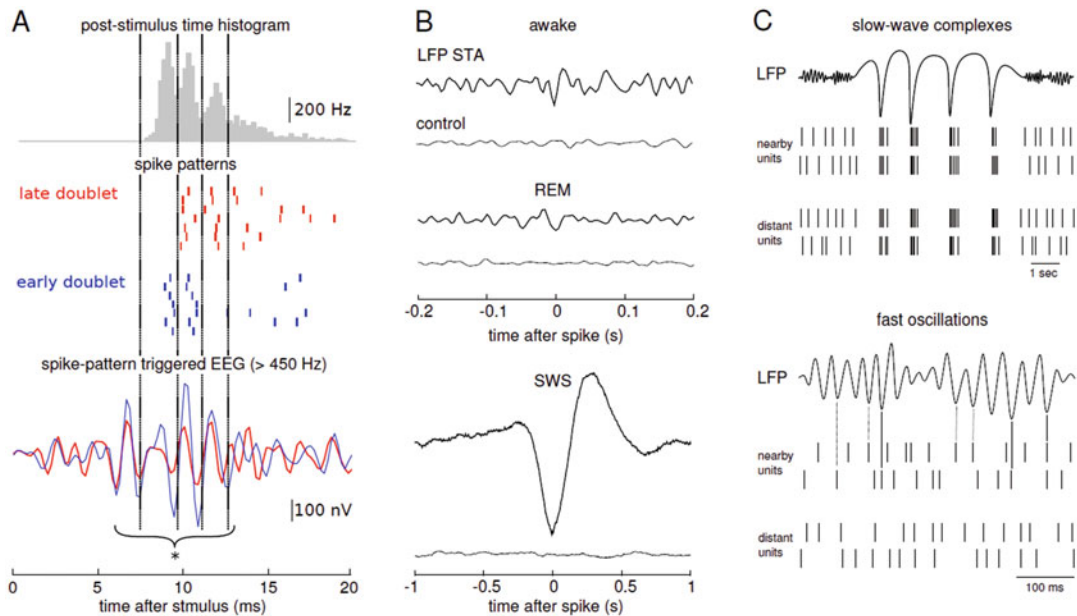
Despite these difficulties some experimental paradigms unveil a substantial spike-related component in the low- and high-frequency LFP signals.

Spike Correlates in High-Frequency LFP ($>40 \text{ Hz}$)

In cat visual cortex, presentation of light bars evokes oscillations at frequencies 35–50 Hz that are tightly correlated with spikes in local neuronal population (MUA; Gray and Singer 1989). These gamma-band oscillations most likely reflect synchronous activation of larger population of cells.

Coupling between LFP and spikes is even stronger at frequencies above 60 Hz: as demonstrated by experiments in visual cortex the power of stimulus-induced high-gamma LFP (60–200 Hz) closely follows the concomitant increase in population firing rate (Ray et al. 2008; Burns et al. 2010). Similar relationship between spontaneous LFP and MUA is also observed in ongoing activity (Destexhe et al. 1999).

Owing to its fine temporal resolution, high-frequency LFP allows to discriminate the timings



Local Field Potential, Relationship to Unit Activity, Fig. 1 Relation of LFP to unit activity in monkeys and cats. **(a)** High-frequency EEG waveforms covary with temporal spike patterns of single units in somatosensory cortex of macaques. Neurons respond to identical stimulation with variable bursts of spikes (top panel: average post-stimulus time histogram in gray, dotted lines – intraburst intervals), which can be classified into one of a few stereotypical spike patterns (raster plot: sample spike trains of two of such patterns). Peaks of high-frequency EEG align to the preferred “spike windows” and their amplitude depends on the spike pattern of simultaneously recorded unit (bottom: average EEG traces coincident with a spike pattern plotted in same color; *significant difference,

$p < 0.05$). (Modified from Telenczuk et al. (2011)). **(b)** LFP-spike correlation depends on the brain state. Spike-triggered LFP average (LFP-STA) calculated in awake state (top) and REM sleep (middle) of cats are shorter in time and smaller in amplitude compared to the slow-wave sleep LFP-STA (SWS, bottom). In all three states randomly shuffling spikes with respect to LFP eliminated the correlations (thin lines below each LFP-STA). **(c)** LFP reflects unit activity that is locally correlated with respect to fast oscillations and globally correlated with respect to slow oscillations. Schematic representation of synchrony of nearby and distant units in relation to troughs of slow (top) and fast oscillations (bottom). **(b)** and **(c)** were modified from Destexhe et al. (1999)

of spikes. When multiple neurons become tightly synchronized, they elicit coincident spikes, which jointly produce discriminable peaks in field potentials (LFP or EEG) even at distant locations (“population spikes,” Andersen et al. 1971). This mechanism, for instance, is involved in generation of macroscopic high-frequency (>200 Hz) bursts in somatosensory cortices of nonhuman primates (Fig. 1a; Baker et al. 2003), rodents (Jones et al. 2000), and frequency-following neurophonic potentials in auditory system of barn owls (Kuokkanen et al. 2010).

Since MUA and LFP are often recorded with the same electrodes, spike waveforms of nearby units may contaminate the LFP, exaggerating the observed correlations. Indeed, low-frequency

band of extracellularly recorded spikes overlaps with gamma/high-gamma band of LFP. However, the subtraction of spike waveforms from LFP affects mainly frequencies above 100 Hz (Belluscio et al. 2012) decreasing but not completely eliminating the correlation between spikes and high-gamma LFP (Zanos et al. 2011).

Relationship Between Low-Frequency LFP (<10 Hz) and Unit Activity

Often the population firing rate may be inferred from the LFP alone, but only when both its low- and high-frequency bands are considered. The most informative features are high-gamma

power (40–90 Hz), and the phase and amplitude of low-frequency oscillations (<10 Hz; Rasch et al. 2008).

Low- and high-frequency LFP bands are inter-related: When awake monkeys are presented with natural movies, the correlation between MUA and gamma-band EEG (which shares many features with LFP) is the highest in the troughs of delta oscillations (2–4 Hz; Whittingstall and Logothetis 2009).

LFP signals in the intermediate frequency bands between 10 and 40 Hz are not clearly related to unit activity (Rasch et al. 2008; Belitski et al. 2008).

Mechanisms of Spike Contribution to LFP

The sources of correlations between LFP and unit-activity are very diverse and it is impossible to single out any particular cause except in few specific scenarios. Nevertheless, two main mechanisms underlie most of the phenomena listed above: (1) contribution through synchronous synaptic release triggered by a spike arriving at axon terminals; (2) direct contribution of ionic currents underlying the spike.

A spike of a single neuron triggers a large number of synaptic potentials in its post-synaptic targets. Despite their small amplitude, post-synaptic potentials can produce large extracellular field (“unitary field potential”) provided that they are spatially and temporally clustered. This occurs at synapses formed by hippocampal interneurons (area CA3), whose spikes generate an LFP bump at monosynaptic latency (Bazelon et al. 2010). It was shown from human and monkey microelectrode recordings that the main spike contribution to LFPs is inhibitory (Telenczuk et al. 2017a), which was recently confirmed by computational models (Telenczuk et al. 2020a). Such features can be used to design methods to calculate LFPs from networks of spiking neurons (Telenczuk et al. 2020b).

The relationship between spikes and LFPs can also be seen in cases where the spiking activity is very tightly timed. For example, fast,

synchronous post-synaptic potentials may underlie bursts of high-frequency LFP oscillations in vivo (Fig. 1a, Telenczuk et al. 2011, 2017b).

Action potentials initiate and propagate due to an interplay between a variety of membrane currents. Axon currents that are involved in propagation of action potentials produce only slight extracellular fields except at both axon ends or while crossing volume conductor boundaries (Jewett et al. 1990). However, action potentials activate also sodium currents in soma and calcium currents in the dendrites, which, in turn, may generate strong contribution to field potentials especially at high frequencies (Murakami et al. 2003). In contrast, slow potassium currents, which hyperpolarize membrane after a spike, can contribute significantly to low-frequency LFP; for example, a slow potassium current shapes the wave component of so-called spike-and-wave complex (Destexhe 1998). Since the extracellular medium is more conductive at low frequencies, it favors these slow currents over faster sodium spikes (Bédard et al. 2004).

Rather than contributing directly to LFP, active ion channels may also modulate low-frequency LFP by shunting synaptic currents (Reimann et al. 2013).

Recent evidence for monopolar effects in LFP generation (Riera et al. 2012) has triggered a discussion about possible physical mechanisms for neuronal monopoles (Destexhe and Bedard 2012; Bedard and Destexhe 2013; Gratiy et al. 2013). If confirmed, such monopolar effects should have strong consequences on the genesis of LFP, even if they occur transiently (Destexhe and Bedard 2012). This possible monopolar contribution should be clarified by future theoretical and experimental studies.

The correlation between low-frequency LFP and unit activity is not always causal, sometimes it results from a common source of variations, such as global changes in the excitability level. For example, in up-and-down states membrane potential switches periodically between depolarized and hyperpolarized states inducing simultaneously slow LFP oscillations (<10 Hz) and alternations in firing rates. Here, modulations in unit activity follow the phase of the slow

oscillations, but they are linked only through an external factor – fluctuations in the membrane potential (Fig. 1b; Destexhe et al. 1999). Similarly, slow shifts in excitability may explain relation between phase of low-frequency LFP and firing rate (discussed above), both of which are under control of sensory inputs and fluctuations in ongoing network activity (Mazzoni et al. 2010).

Effects of Neuronal Correlations on LFP-Spike Relation

LFP amplitude is far more sensitive to correlations between neurons than to the number of active units and their firing rate. For example, simulations show that if cell-to-cell correlations increase just by 2% high-gamma LFP power rises by a factor that would normally require ten-fold increase in firing rate of uncorrelated population (Ray et al. 2008). As discussed above, strong synchrony within the population may produce macroscopic “population spikes,” but even a small neuronal assembly can generate a synchronous event (“unitary event”) that is related to a distinct temporal pattern in LFP (Denker et al. 2011).

One particularly useful technique to investigate field-unit relation is to correlate field potential and single-unit spikes by means of spike-triggered averaging (Fig. 1b). Interestingly, the magnitude and waveform of spike-triggered LFP in low and gamma frequency bands (<20 and 25–75 Hz, respectively) correspond more closely to the dynamics of synchrony between the synaptic inputs rather than to network events associated with spikes (Okun et al. 2010).

Temporal correlations between spikes of single units may also produce small but detectable change in LFP signal. For example, a burst of spikes generated by a single neuron can induce a switch of cortical state and corresponding change in the LFP spectrum (Li et al. 2009). Similarly, sensory-evoked spikes in somatosensory cortex are organized in stereotypical spike burst patterns whose incidence covary with the amplitude of high-frequency EEG burst (>400 Hz, Fig. 1a; Telenczuk et al. 2011, 2017b).

Neuronal correlations are under control of brain states, such as different arousal and attention levels. Consequently, the brain states have large impact on the LFP–unit relation. Specifically, spikes elicited in slow-wave sleep are associated with LFP deflections of longer durations and broader spatial coherence compared to waking and REM sleep (Fig. 1b, c; Destexhe et al. 1999).

Other Factors Influencing LFP-Unit Relation

Neural anatomy and micro-architecture determine the physical aspects of LFP generation. The neuronal morphology (Murakami and Okada 2006), geometry of cortical circuits (Buzsáki et al. 2012), and local circuitry may affect LFP in all frequency bands. In addition, the composition of neural tissue such as presence of neurons of different types, glial cells, and vasculature affects the conductive properties of the medium (Nelson et al. 2013). Therefore, the quantitative and qualitative aspects of LFP relationship with unit activity must be always considered in the context of the specific brain area.

Further, the experimental protocol and recording system are the key features determining the LFP and their relationship to unit and synaptic activity. In particular, the type of stimulation is essential in shaping the spatial and temporal properties of spike-triggered LFP (Nauhaus et al. 2009; Reimann et al. 2013). Other factors include: the type of electrodes, analog and digital filters, tissue preparation, position of signal, and reference electrodes.

Implications for Electrophysiology

Unit-related LFP components offer an excellent opportunity for electrophysiologists to study the output of neuronal computation, the spiking, in anesthetized and behaving animals or even noninvasively in humans. Population firing rate and synchrony are two properties that can be currently assessed by means of LFP and

the list may increase as we learn more about the physical and physiological basis of LFP generation.

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Local Field Potential, Synchrony of

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Synonyms

Coherence of local field potentials; Coupling of local field potentials; Cross-correlation of local field potentials

Definition

The synchrony of local field potentials (LFP) is a neurophysiological property that represents the

correlated activity in simultaneously recorded networks. Its measurement indicates how tightly multiple local networks are coupled. LFP synchrony indicates a potential interaction between the recorded sites and represents a possible mechanism to facilitate synaptic transmission and network-to-network communication.

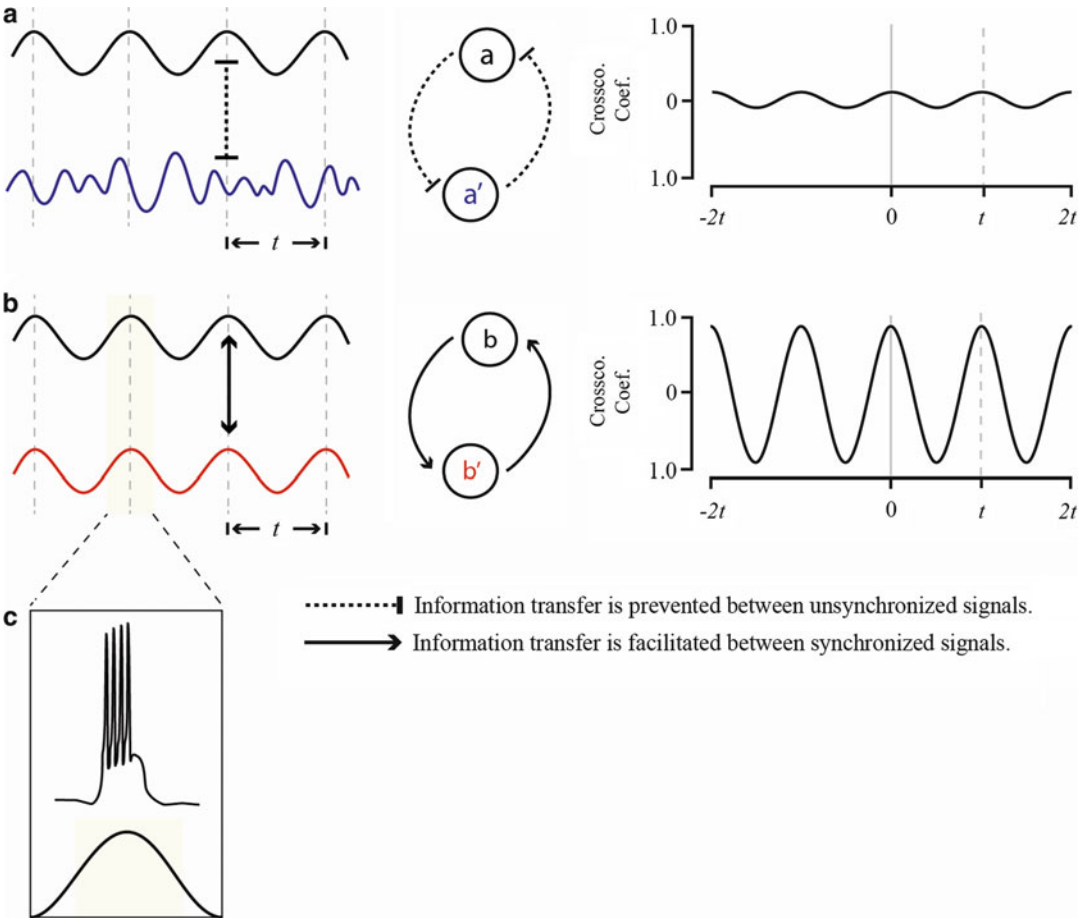
Detailed Description

The Neural Basis of Local Field Potentials

As elaborated in the companion entry (► [“Local Field Potentials: LFP”](#)), local field potentials (LFPs) represent the summed voltage fluctuations among a population of cells within a given field and are measured with electrodes inserted in the extracellular space of brain tissues. Each neuron’s intracellular membrane potential provides an indication of its excitability and its readiness to fire. Under a barrage of constant inputs, these small intracellular synaptic voltage fluctuations from a population of cells combine together into a spatiotemporally integrated signal which is recorded using low-impedance electrodes. Much like electroencephalography (EEG), the LFP thus represents the compound activity from multiple postsynaptic potentials and provides an integrated electrical signal recorded from the local population of neurons. When recording the LFP activity from multiple regions simultaneously, neurophysiologists can compare the changing patterns of activity in time, studying both the presence and characteristics of oscillations within each area and the changes in synchrony between areas.

Local Field Potential Oscillations

Activity of neurons around an electrode can temporally coordinate into a series of alternating membrane potentials, giving rise to LFP oscillations. These oscillations are often classified into distinctive frequency bands, corresponding to different cycle times. Oscillatory activity is mediated by local circuit properties and by large-scale network inputs. Neuronal firing patterns can become phase-locked to the collective rhythm of the LFP, defining a pattern of population activity (Fig. 1c). LFP oscillations can therefore modulate spiking



Local Field Potential, Synchrony of,
Fig. 1 Theoretical mechanism for network-to-network communication between distant areas. (a) An example of an oscillating network a and a desynchronized network a' where information transfer is prevented between the two. The random variability of a' produces a low-amplitude cross-correlation. (b) Perfect signal synchrony from oscillatory activity between distant networks b and

b' . The phase-locking facilitates information transfer and produces a cross-correlation with a maximal amplitude of 1. (c) The LFP oscillations can modulate intracellular activity with high temporal fidelity, and neural firing can become phase-locked to the collective rhythm of the LFP. In this example, we demonstrate a neuron's burst firing around the peak of the oscillation

activity with high temporal fidelity (organizing spike trains between networks), thus providing a structure for sharing information and favoring network-to-network communication. In the study of LFP and EEG signals, specific patterns of stable oscillations have emerged at different time-scales and for many brain areas. These oscillations have been classified into several frequency ranges: slow ($\sim <1$ Hz), delta (0.1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–80 Hz) (Traub and Whittington 2010). LFP oscillations can be related to network

interactions that hold information about cognitive and behavioral states of an animal or individual. As mentioned in companion entries, for example, slower beta oscillations occur in the visual cortex in the absence of stimuli, whereas faster gamma oscillations arise in response to stimuli. In addition, beta oscillations in the motor cortex peak in power just prior to movement onset, possibly representing a critical state of the local network required for processing that motor command. As such, oscillations can be initiated or entrained following external stimuli, or they can be

generated internally and modulated in a brain state-dependent manner, such as with attention.

Oscillations Facilitate Synchrony and Connectivity

The presence of oscillations does not necessarily guarantee synchrony but may facilitate it. In the central nervous system, where information is encoded as fast as on a millisecond scale, a mechanism to control inter-network timing is fundamental as a support for the accurate information transfer. Coherent oscillations could provide such a mechanism and appear especially useful in coordinating the timing of activity and strengthening the functional link between distant areas. For example, in spike-timing-dependent plasticity, the strength of connectivity between two neurons depends on the order of firing and the delay between spikes within each pair. An ideal mechanism for coordinating this interaction is if both cells are entrained by oscillating network activity. On a larger scale, we can infer that if those cells participate in oscillatory networks that are coherent, the connection between the two cells would be strengthened or weakened (Cannon et al. 2014).

Parameters for Synchrony of LFPs

LFP oscillations have been associated with various behavioral operations, such as sensory processing, motor planning, attention, expectancy, and cognition. In each of these situations, oscillations serve an underlying mechanistic purpose, serving to bring neural populations together via optimal timing. Indeed, synchrony between LFPs recorded in two different neuronal populations could tighten the coupling and communication between them (see Fig. 1). The theory that synchrony enables communication has been supported both by computational and experimental studies and most effectively described in the neocortex and hippocampus (Fries 2015; Maris et al. 2016). Computational models representing phase-locked oscillating neural systems quantified this facilitation and showed that more information is transferred between neural populations when they are phase-locked and a faster response is generated from one to the next (Buehlmann and

Deco 2010). This information transfer occurs at a cellular level, where the timing and rate of neuronal firing within the two populations are influenced by the population activity, as recorded with LFPs. If the two populations show similar resonant or oscillatory properties, then the likelihood of synchrony and information transfer is greater.

In single-cell patch-clamp recordings, the influence of the LFP on cell activity is made evident in pyramidal neurons by their increased spike probability to input currents when they are oscillating at subthreshold potentials. These oscillations also provide precise temporal windows when spikes are most likely to occur, during the more depolarized membrane state (Traub and Whittington 2010). This phenomenon has been replicated in vivo, where the timing of afferent inputs, with respect to the phase of the oscillation, is an important predictor of the timing of spike output (Cardin et al. 2009). If synaptic input arrives at the peak of a depolarized state, larger responses, with very short time delays, will be produced. On the other hand, if synaptic input occurs at the hyperpolarized phase, spiking output is less likely or is delayed. Following this principle, in a large-scale network of oscillating neurons, propagation of spike output from one local network to the next will occur faster and more robustly (see ► [“Local Field Potential, Relationship to Unit Activity”](#)).

Some neurons also act like important nodes in establishing network synchrony. This is the case in the visual cortex, where coherence in the gamma range modulates sensory processing. Synaptic connections between the excitatory pyramidal cells and the fast-spiking inhibitory interneurons (basket cells) contribute to the development of gamma (>30 Hz) oscillatory activity in the neocortex and the hippocampus (Cardin et al. 2009). These interneurons often fire in a rhythmic pattern, triggering repeated inhibitory postsynaptic potentials (IPSPs) on their efferent pyramidal cells. This pattern can be modulated by feedback from the pyramidal cells within the local network, which send axon collaterals back to the interneurons. The basket cells are also interconnected through gap junctions, and these can determine

network synchrony through rapid spread of current and enhanced neuron coupling. Gap junctions allow a network of interneurons to temporally correlate their firing, causing the spread of synchronous inhibitory currents, compounding their effect on the local projection neurons. The role of gap junctions is also considered important in contributing to LFP oscillations in other areas such as the cerebellum (Robinson et al. 2017).

As LFP synchrony can provide a measure of coupling and a functional link between networks, lack of synchrony can also indicate how networks can remain independent (Fig. 1a). This population selection could be due to circuit properties that determine predominant resonant frequencies, where networks with similar properties would tend to exchange information. Resonance is a property where a group of neurons have a tendency to remain in oscillation for a period of time, in an amplitude- and frequency-dependent manner. This property allows neurons to selectively react to different patterns of inputs, where a greater response will be generated if the input frequency is close to the intrinsic frequency of the local network. Cellular components that enable circuits to function under preferred resonant frequencies are determined by complex interactions between membrane impedance, leak currents, and the different ionic currents produced when the various postsynaptic neurotransmitter receptors are activated (Hutcheon and Yarom 2000; Buehlmann and Deco 2010). These features can also allow more than one predominant resonant frequency within each circuit (Helfrich et al. 2016).

Functionally, LFP oscillations can act as a mechanism to facilitate information processing and communication between distant networks through synchrony. The synchronization of networks is developed through a combination of intrinsic network properties, such as cell-to-cell interactions and resonant properties. This allows for the possibility of altering communication pathways without affecting the anatomical connections. Since neurons have widespread connections, neural populations may alter their phase relation to synchronize with either the output target or input source for optimal communication.

This theory is supported by long-term potentiation (LTP) mechanisms where synchrony in spiking brings an increase in synaptic strength.

Examples When LFPs Synchronize

Synchrony of local circuits plays a role in sensory processing, motor execution, and cognition. To explore this role, electrophysiologists have simultaneously recorded LFPs within multiple cortical and subcortical sites in an attempt to define synchrony patterns across a variety of tasks. Examples of synchrony during sensory binding and sensorimotor coupling, where the synchrony of LFPs seems to improve information processing, are given below. In general, the communication pathways would be enhanced by the synchronization of LFPs between functionally related networks.

Sensory Binding

Synchrony of LFP oscillations may provide the link between single-cell activity and complex computations. In visual perception, recognition of a particular stimulus relies on the coordinated response of multiple cortical areas. Multiple areas in the visual cortex are required to perceive shape, color, position, and direction in order to create a unified percept of the visual scene. The cell assembly responsible for processing a particular object is thus large and distributed over many areas. In order to distinguish distinct visual features, each population of neurons involved in the complete representation of that feature must fire with a coordinated and discrete temporal coding. LFP oscillations and their synchrony could coordinate the neural populations required for this sensory binding. As the visual stimulus is presented, synchronized oscillations in the gamma range serve to coordinate the local activity from each of the subpopulations of neurons involved in processing that stimulus. This synchronized activity then facilitates the transfer of relevant information upstream for further processing (Engel and Singer 2001).

Internally generated brain states can change the dynamic coupling between brain areas, such as during attentional processing and expectation. Intrinsic network operations related to mental

states and sensory input processing can influence synchronization. These interactions give rise to stronger representations and could subserve conscious perception. For example, a sensory experience becomes more salient as the intensity of the stimulus increases. This is reflected in the brain by an increase in gamma oscillations. Similarly, with increased attention allocated to a stimulus, an observer becomes more aware of it, which is also accompanied with an increase in synchronous gamma oscillations (Engel and Singer 2001). An increase in gamma coherence is also experienced when the individual is expecting a precise stimulus and is attentively waiting for its occurrence. This can be recorded prior to stimulus onset and is believed to improve the flow of information through the cortex. In sum, during sensory processing, the level of synchrony is correlated with the perceived strength of the stimuli. Synchrony may also be involved in the selection of relevant information and in preparing the necessary pathways required for producing the most effective responses as efficiently as possible.

Most perceptual experiences involve multiple sensory modalities, and object recognition can require multisensory integration. For example, we may recognize parchment paper not only by its dry, smooth touch but also by the crisp sounds it makes as we feel it. Holding the paper between our fingers, these two sensations are experienced simultaneously, so we link the sound and touch together into one perceptual experience. This link between sensory modalities impacts sensory processing at the network level. For example, somatosensory stimulation received at exactly the same time as an auditory tone has a greater than additive effect on the primary auditory cortex than either stimulus alone, by increasing both oscillations and neuronal spike rate (Schroeder and Lakatos 2009). Delivered at different phases, somatosensory stimulation also has the ability to reset the phase of oscillations in the auditory cortex, after which neuronal firing is enhanced. When trying to understand a person talking in a noisy room, it is easier if we can see their mouth as they speak; this could be because the combination of sensory inputs, along with our increased attention on the subject, may actually change the way our

neuronal populations are synchronizing, facilitating processing of the sounds. This neuronal population synchrony can be witnessed when measuring EEG or LFP signals, with further fine-grained information coming from the rate and phase of neuronal firing.

Sensorimotor Coupling

Performing complex movements, in a coordinated and precisely timed manner, requires organized firing patterns between multiple brain areas. Sensory information must be optimally integrated, or filtered, so that we can navigate within environmental constraints and meet performance demands as successfully as possible. Sensory integration often combines information from vision, proprioception, and touch to guide the limbs and accurately reach targets. To achieve this, the production of movement requires the integration of information from multiple sensory and motor areas, including the cerebral cortex, basal ganglia, and cerebellum. The coordinated interplay between these areas is likely based on synchronized oscillations.

Simultaneously recording LFP oscillations and evaluating the synchrony between sensory and motor areas during sensorimotor tasks may provide information on the coupling dynamics of different neural populations involved in the production of movements best adapted to the sensory input. These wide-ranging networks can change their dynamics on very short (millisecond) time-scale. For example, in a visuomotor integration task in cats, LFP synchrony between the visual, parietal, and motor cortex is modulated on a fine temporal scale as the coupling between these areas shifts throughout the different phases of the sensorimotor task. This modulation follows the information processing demands of the areas involved in the sharing of information; the underlying neuronal activity coordinates so that the greatest synchronization occurs in cell populations more closely related in function than in spatial vicinity (Roelfsema et al. 1997). Thus, the emphasis is on linking neuronal populations that are exchanging information at a given moment. Examining changes in the coupling between LFP signals, and their oscillations, in

more distant areas may tell us how behaviorally relevant sensory information is integrated to produce coordinated motor output.

In LFPs recorded in primates, oscillations between 10 and 25 Hz are present in sensorimotor areas prior to voluntary arm movement. The strength of these oscillations and their coherence are modulated according to the type of task being performed and throughout different phases within each trial. For example, active expectancy and passive expectancy differentially increase the synchrony across the cerebellum between 10 and 25 Hz. In an active expectancy task, the animal has to press a lever to receive a reward, which increases synchrony in the coronal direction more than in the sagittal direction. This increase in synchrony is not present to the same extent during passive expectancy, when the animal did not have to move to get the reward. Similarly, a lever-press sensorimotor task has been shown to increase coherence between the cerebellum, primary somatosensory cortex, and primary motor cortex prior to movement onset (Fig. 2). This synchrony is present in both the active and passive tasks, which may suggest a coordinating role of attention or a gating of behaviorally relevant information (Courtemanche and Lamarre 2005; Courtemanche et al. 2009).

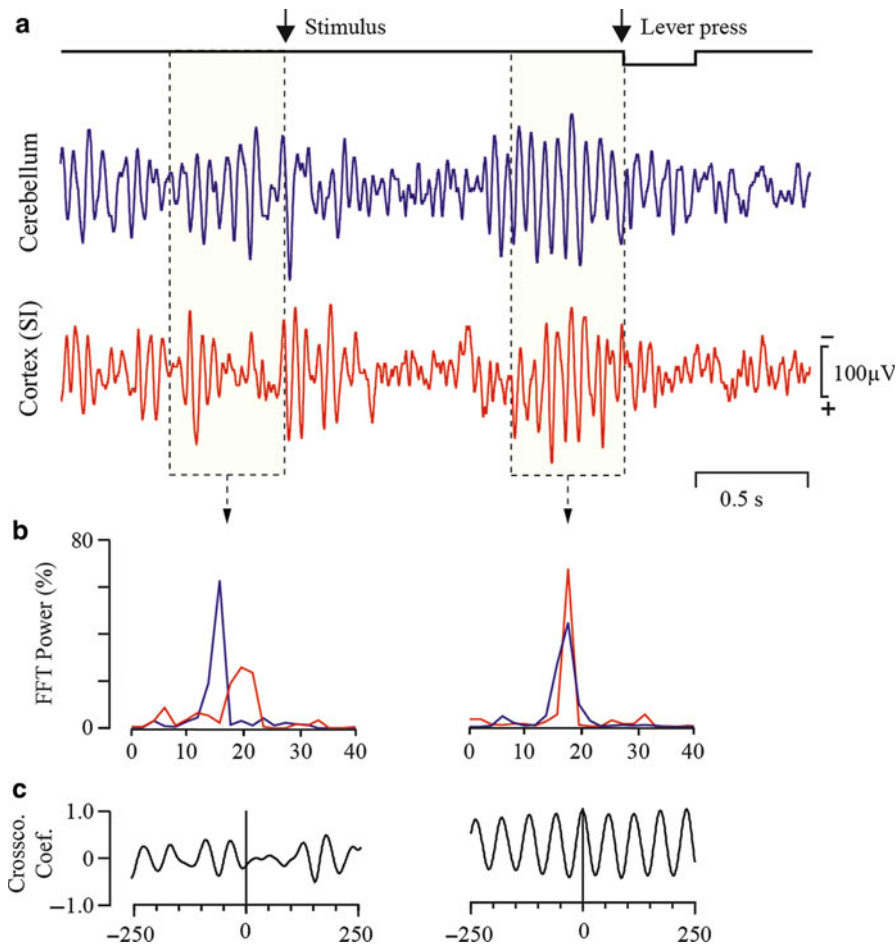
Sensorimotor coupling in humans has been recorded using EEG. This synchrony is modulated in many behavioral conditions, including during learning and memory, and may predict performance. During learning of a bimanual task, such as in a series of finger sequences using both hands, synchrony between the left and right cortices is increased. However, following learning, this synchrony drops to levels similar to tasks requiring only one hand. Similarly, if the cognitive demands of a task are increased, synchrony between sensory and motor areas is enhanced (Hummel and Gerloff 2005). In tasks requiring timed responses, a correlation exists between the speed and accuracy of responses and the level of synchrony between areas involved. This has been demonstrated in both visual- and somatosensory-motor response tasks, where synchrony in beta and gamma range is compared and decreased coupling is associated with slower and less

accurate responses (Womelsdorf et al. 2007). These modulations indicate a specific coordination of task-relevant information requiring multiple brain areas. Synchrony at different frequencies could also determine which operation is taking place, with top-down gathering of information at beta frequencies representing attentional modulation of bottom-up information transfer via synchronous gamma oscillations (Richter et al. 2017).

Measuring Local Field Potentials and Their Synchrony

Local field potentials can be recorded using microelectrode probes of lower impedance (~ 0.3 – 1 M Ω) inserted into the brain tissue and by amplifying the slower frequency bands (e.g., DC–100 Hz). The resulting signal provides a selective window into the slower changes in signal, filtering out the faster changes, such as multiple- or single-unit activity. The sampling frequency should be able to follow millisecond-level changes (1 kHz), especially if fast synchrony changes are to be tracked. With enough bandwidth and sampling frequency, the broadband signal (sub 1 Hz–10 kHz, recorded at 30 kHz) can be initially digitized and stored, permitting off-line extraction of the LFP signal (<100 Hz, decimated) and unit activity (>1 kHz).

LFP signals recorded in close proximity can show a significant amount of similarity across channels throughout various timescales, as can more remote field potentials, though with less probability. This similarity can be noticeable visually but sometimes is difficult to appreciate. Different methods can identify the level of similarity, or level of synchrony of the LFPs, here simplified to the case of two simultaneously recorded LFP signals. One of the first methods, applied in the time domain, is cross-correlation of the two LFP signals. This method identifies the similarity in time between the two signals, with a measure of correlation, at a particular lag time. An example of this is given in Figs. 1 and 2c. Cross-correlation can be normalized to the situation where the two signals are identical, providing a value between -1 and 1 . In this way, the function provides a value of the



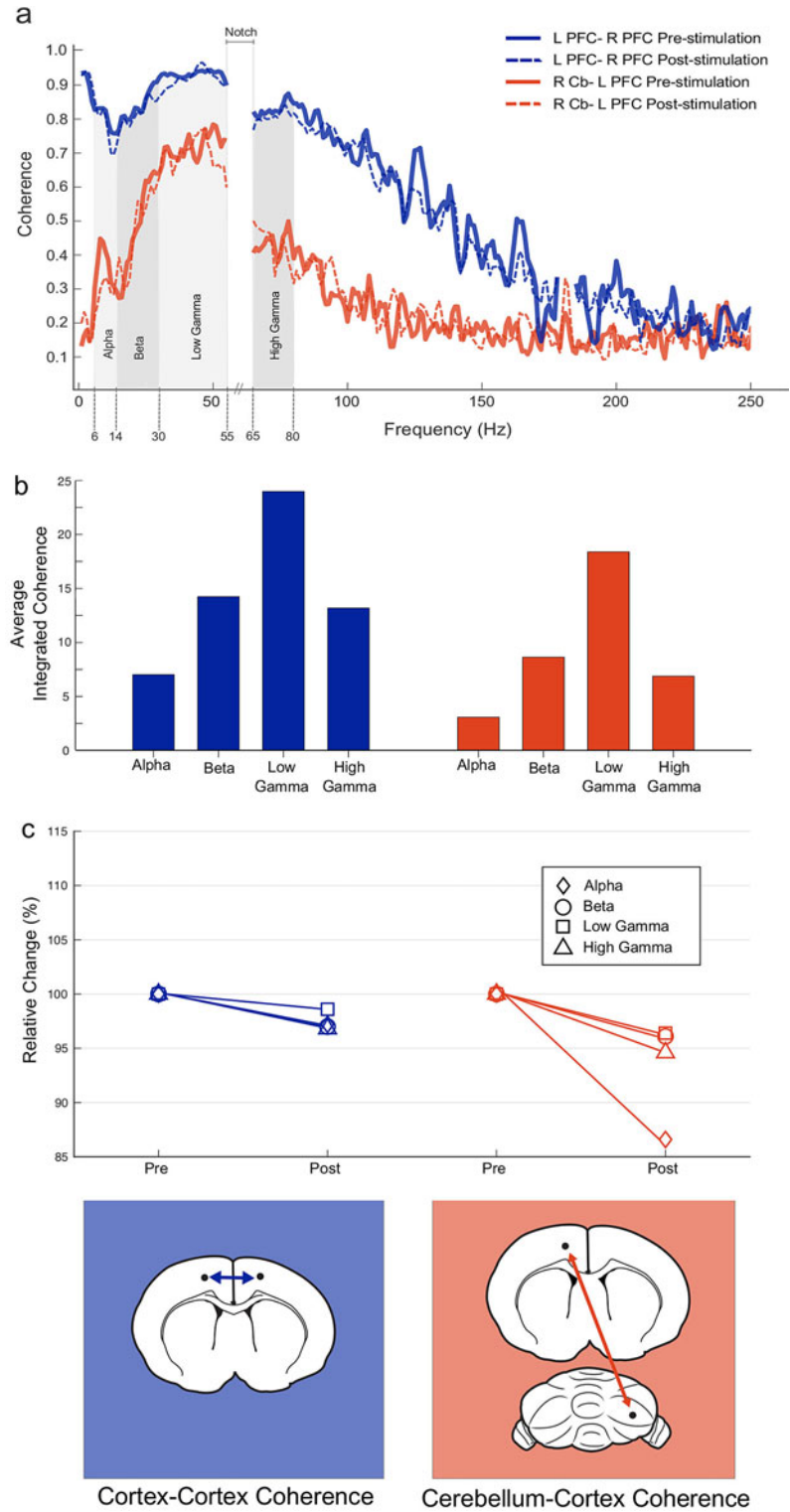
Local Field Potential, Synchrony of, Fig. 2 Example modulation and synchronization between the cerebellum and the cortex during a sensorimotor task. (a) LFP traces recorded simultaneously in the cerebellum and primary sensory cortex (S1), with a timeline showing the appearance of the sound stimulus lasting 1.5 s and movement onset – the lever press (arrows indicate onset). (b) FFTs of the corresponding period highlighted in A. The blue line corresponds to the cerebellar trace and the red line

to the cortical trace. These FFTs highlight a common frequency content at 18 Hz at both sites prior to movement onset. (c) Cross-correlation-coefficient functions corresponding to 250 ms windows pre-stimulus and pre-movement. Note the heightened synchronization that accompanies the 18 Hz oscillations during the pre-movement epoch. (Modified from Courtemanche and Lamarre 2005)

coupling strength of the signals and a delay between them. In many situations, the delay or phase will be at zero, where the changes in signals are happening at exactly the same time. Low correlations are often associated with a variable lag. Cases where the lag is of a stable value other than zero can provide insight into the connectivity between the two sites.

A second method, called coherence, is applied in the frequency domain. This method identifies the commonality between signals across their frequency bands, highlighting the common frequency components in both signals. Coherence is expressed from 0 to 1.0, with higher values for more coherent signals. An example is given in Fig. 3a, which represents the coherence between

Local Field Potential, Synchrony of,
Fig. 3 Example of coherence compared across sites and conditions in the cerebellum and prefrontal cortex in the rat. (a) Coherence between the left and right hemispheres of the prefrontal cortex (blue lines) and between the right cerebellum and left prefrontal cortex (orange lines). Also shown here is the coherence preceding (solid line) and following (dashed line) electrical stimulation of the medial cerebellum. Shaded areas represent pertinent frequency bands. (b) The integrated coherence represents the area under the coherence curves in each frequency band (shaded areas in a). The average of pre- and poststimulation values of integrated coherence is shown in this bar graph. (c) The relative changes (in %) in coherence between pre-stimulation and poststimulation integrated coherence. Comparison sites are illustrated below



left and right prefrontal cortex LFPs, as well as coherence between the cerebellum and the contralateral prefrontal cortex, as a function of frequency, in an anesthetized rat. Coherence is greater intracortically than between the cerebellum and prefrontal cortex LFPs. Coherence can also be compared across different conditions or following experimental manipulations, such as when delivering electrical stimulatory pulses. Integrating the coherence curve between two frequencies provides a way to quantify coherence bands between two LFPs, as shown in Fig. 3b. Coherence decreased slightly in all frequency bands following stimulation but more significantly in the alpha band (nearly 15%) (Fig. 3c).

Finally, a third method that can identify synchrony is directed coherence. An elaborate description of Granger causality methods is given in another entry (► [“Spectral Interdependency Methods”](#)). Briefly, this method has similarities with the basic coherence analysis but also exposes the direction of information flow. This is done by comparing the estimated fraction of the signal around a particular frequency across LFPs but makes different comparisons in time. One LFP is separately compared to the current and previous values of the other LFPs and vice versa, in order to determine if the timing of one precedes the other. This last method allows one to determine which signal potentially drives the other one (Baccala and Sameshima 1999).

Overall, the synchrony of local field potentials is a phenomenon that can provide valuable information about network organization and communication during behavior. The technique has been around for a while, akin to some of the first recordings done in the nervous system. The new electrophysiological techniques that are now available have identified more precisely the microscale network components, from cells to some of their constituent parts. Coupled with those microscale techniques, local field potential synchrony can provide a more complete understanding of network-level organization. Combining those techniques will hopefully lead to a new understanding of brain functions with functional applications in brain-machine interfaces and neuroprosthetics.

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Local Field Potential: Relationship to Membrane Synaptic Potentials

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Definition

The relationship between the somatic membrane potential of an individual neuron and the local field potential signals, assessed by cross-correlation, coherence, or related statistical analysis methods. Typically, correlation between these two signals exists due to synaptic inputs shared by the individual neuron and the entire neuronal population.

Detailed Description

The membrane potential (Vm) of neurons is shaped by transmembrane flow of ions, which

can have both synaptic and intrinsic origins. A net flow of current across the membrane produces, in addition to the change in Vm, a small change in the potential of the extracellular medium outside the cell, which can be picked up by an extracellular microelectrode. The low-frequency (<300 Hz) component of this signal, known as the extracellular local field potential (LFP), is produced by transmembrane currents flowing simultaneously in thousands of neuron and glial cells, superimposed according to the complex spatiotemporal profile of neuronal activity. Thus, unlike Vm, which is determined by processes pertaining to that particular cell, the LFP depends on the morphology of the cells, the spatial distribution of the contributing ion channels, and the temporal coordination of the currents as well as on the spatial organization of the cells.

As both Vm and LFP fluctuations originate in transmembrane electric currents, it is reasonable to find at least some correlation between the sub-threshold (Vm) or the suprathreshold (spiking) activity of individual neurons and the nearby LFP. In cortex, Vm-LFP correlations were indeed observed in pioneering experiments in the 1960s, in which intracellular potential of individual neurons (observed using sharp recording pipettes) and nearby surface LFP (see entry ► [“Electrocorticogram \(ECoG\)”](#)) were simultaneously recorded in the visual and sensorimotor cortices of cats and rabbits (Creutzfeldt et al. 1964, 1966; Klee et al. 1965). These early experiments were performed under deep anesthesia, which strengthens the synchrony in cortical networks and thus in particular increases the correlation between Vm and LFP signals, making Vm-LFP correlation easier to detect.

Since the days of these early experiments, new technologies were developed to monitor the membrane potential of individual neurons and of neuronal populations. These include the whole-cell patch recording and approaches such as voltage-sensitive dye (VSD) or voltage-sensitive fluorescent protein (VSFP) imaging. Whereas a considerable amount of experimental in vivo data was acquired over the years through combined intracellular (sharp or whole-cell) and LFP recordings, in both anesthetized and awake

animals, so far only a few studies combined imaging and LFP recording (e.g., Ferezou et al. 2007; Ayzenshtat et al. 2010). Consequently, here we focus exclusively on electrophysiological intracellular and LFP data. We follow the convention according to which LFP refers to the low-frequency ($<100\text{--}300\text{ Hz}$) portion of the extracellular signal, leaving works studying the Vm origins of the extracellular spike signals (Wehr et al. 1999; Henze et al. 2000; Gold et al. 2006; Chorev and Brecht 2012) outside the scope of this entry.

In brain areas such as the cortex, the volume of tissue in the immediate vicinity of an LFP recording site contains many hundreds of neurons. Therefore, experimentally observed significant correlation between the LFP and the Vm of individual nearby neurons indicates that the Vm of most or possibly even all nearby neurons is correlated with the LFP (suggesting in particular that the Vm of nearby neurons is correlated as well (Lampl et al. 1999)). The LFPs commonly observed in the cortex and hippocampus are on the order of $0.1\text{--}1\text{ mV}$ in amplitude and 3–4 orders of magnitude higher than those produced and observed extracellularly by single synapses (Glickfeld et al. 2009; Lindén et al. 2010), which is consistent with the LFP being a product of synchronized activity of thousands of synapses belonging to a large group of neurons.

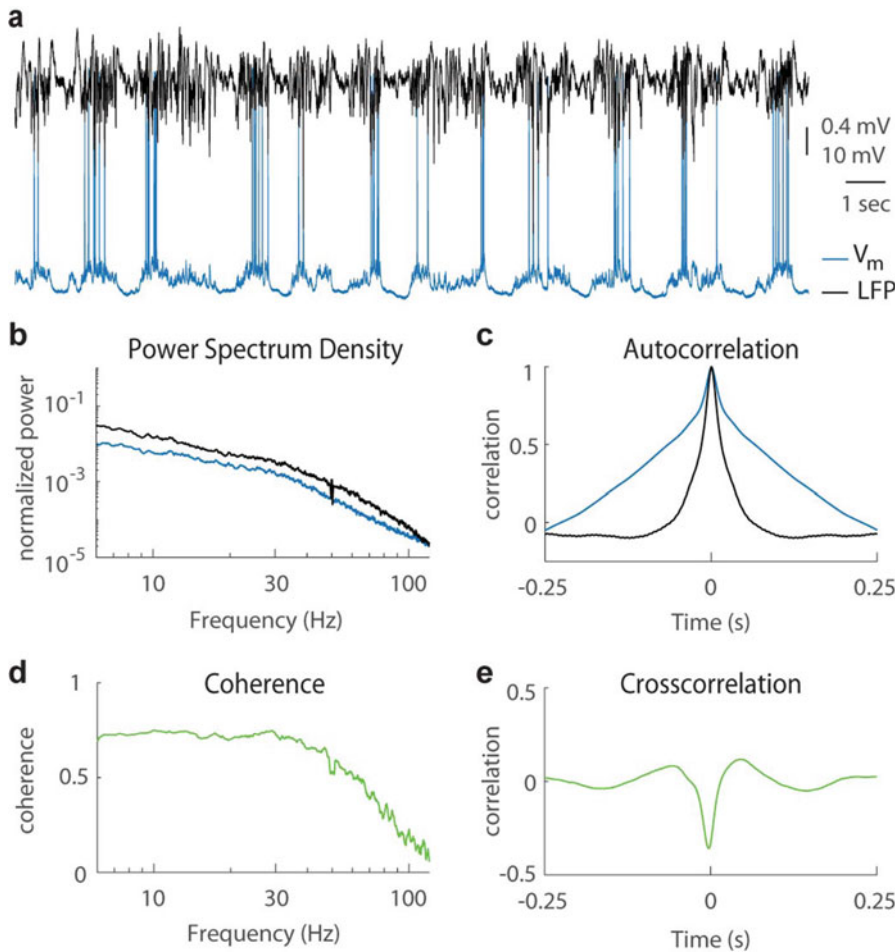
In the simplest scenario, when the paired Vm and LFP recordings are made in the same cortical column and layer, the recorded cell is part of a local ensemble of neurons, all of which simultaneously receive synaptic input barrages. These barrages are seen both as postsynaptic potentials (PSPs) in the Vm and as LFP events reflecting the intracellular PSPs simultaneously happening in the entire ensemble. However, Vm-LFP correlations that are a pure result of such local activity, independent of nearby columns, layers, or areas, are unlikely to exist due to a number of reasons. To begin with, the LFP signal is “contaminated” by volume-conducted events remote from the LFP recording site, e.g., (Kajikawa and Schroeder 2011; Carmichael et al. 2017; Kajikawa et al. 2017; Parabucki and Lampl 2017). Furthermore, the neuronal activity consists not only of localized

barrages received by specific ensembles but also of large waves of synaptic activity that reach the LFP site either simultaneously with reaching the intracellularly recorded neuron (for a standing wave) or with some positive or negative delay (for a propagating wave). In this case, the extracellular LFP fingerprint of the event is a complex combination of the synaptic activity at the LFP recording site with the conducted activity from the surrounding volume. The interpretation of Vm-LFP coupling can be further complicated by the non-synaptic component of both Vm and LFP. One possible way to disentangle some of the different sources contributing to the LFP and thus to Vm-LFP coupling is current source density (CSD) analysis (see entry ► [“Current Source Density \(CSD\) Analysis”](#)), e.g., through recording the LFP at multiple nearby sites with a multi-channel silicon probe. Unfortunately, so far very few studies combined recordings amenable to CSD analysis with simultaneous Vm recordings (one such example is the study of Quilichini et al. (2010) in the entorhinal cortex).

In an entirely different scenario, the Vm and LFP recording sites are far apart, e.g., in different brain structures (specific examples will be mentioned below). In this case, the synapses driving the Vm fluctuations cannot be “felt” by the LFP recording electrode, and vice versa, any synaptic activity driving the LFP is unrelated to the synaptic inputs of the intracellularly recorded neuron. In this case, therefore, any correlation between Vm and LFP is due to temporally synchronized but anatomically distinct synaptic inputs, or alternatively they may be correlated due to volume conductance.

Quantitative Description of Vm-LFP Correlation

Both Vm and LFP are univariate analog signals, so that the most straightforward way to measure the relationship between the two is to compute their cross-correlogram (Fig. 1e). In the cortex, where LFP events are seen as depth-negative bumps, the cross-correlation of nearby Vm and LFP signals (with Vm taken as the reference signal) typically has a unimodal peak pointing downward. The exact shape of the cross-correlogram



Local Field Potential: Relationship to Membrane Synaptic Potentials, Fig. 1 Vm and LFP during synchronized Up-Down activity. (a) 20 s trace of Vm and LFP recorded ~0.3 mm apart in the barrel cortex of

anesthetized rat. (b, c) Power spectrum density and autocorrelation of the Vm and LFP signals. (d, e) Vm-LFP coherence and cross-correlation (Vm was preprocessed by clipping the spikes and high-pass filtering above 5 Hz)

depends on other factors such as the location of the two recording electrodes and the type of activity (see below).

Both the Vm and the LFP have a $1/f$ power spectrum (more precisely $const/f^\alpha$ where the α coefficient need not be the same for the two signals), and most of the power of the signals is in low frequencies, which in particular implies that the Vm-LFP cross-correlation primarily reflects the low-frequency components of the two signals. Coherence analysis (Fig. 1d) is typically used to detect correlation in frequencies higher than 10–20 Hz. More advanced methods (e.g., ►“Spectral Methods in Neural Data Analysis:

Overview” (Haider et al. 2016)) can be applied as well, however will not be reviewed here.

There are several technical caveats one needs to keep in mind when estimating the Vm-LFP relationship in experimental data. First, the LFP signal can often be contaminated by volume conduction, as mentioned above. Second, whereas intracellular amplifiers typically measure the Vm in DC mode, or have a high-pass filter with a rather low cutoff frequency (e.g., 0.01 Hz), extracellular amplifiers used for measuring LFPs typically have high-pass filter with a much higher cutoff frequency, often distorting measurements at frequencies as high as 1–3 Hz (Nelson et al.

2008). If this is not corrected, Vm-LFP and spike-LFP cross-correlation will have a bimodal waveform, with negative value around 0 time lag and positive correlation ensuing 50–500 ms later (Okun 2017).

Vm-LFP Correlation during Synchronized Cortical Activity

Vm and LFP correlation was primarily investigated in the cortex. Here, synchronized Up-Down activity (see entry ► “[Low Frequency Oscillations \(Anesthesia and Sleep\): Overview](#)”) during certain anesthesia regimes, during slow-wave sleep, and during quiet wakefulness (at least in rodents) is the most prominent intracellular activity pattern. Slow oscillations were extensively studied using intracellular, extracellular, and combined recordings. It was established that the cycles are typically 100–1000 ms in duration, with Up states characterized by spiking activity induced by barrages of synaptic inputs causing the Vm of individual neurons to depolarize by 10–20 mV relative to the silent Down baseline. When Up states last for ~300–500 ms and above, the Vm distribution is typically bimodal. In the Up-Down activity mode, large areas of the cortex get activated and deactivated almost simultaneously, so that pairs of intracellularly recorded neurons up to ~1 cm apart exhibit delays of just a few ms (Volgushev et al. 2011), while LFPs separated by 0.5–1 cm are remarkably similar to each other (Destexhe et al. 1999).

The synchronous activity across large areas of the cortex produces very large LFP waves (1–2 mV in the subgranular layers), which at the Up-state onset are positive at the surface and the superficial cortical layer and negative in the deep layers (i.e., a current sink in deep layers and a current source near the cortical surface). Up onsets and offsets are readily seen in both Vm and LFP (Fig. 1a). Due to the synchronization of the Up-Down fluctuations across relatively large distances, the Vm-LFP correlation is dominated by Up and Down transitions. Typically, the Vm-LFP cross-correlation relaxes to its nonsignificant baseline level within several hundreds of milliseconds, reflecting the long time constant of Up-Down activity. Furthermore, it is possible to

predict the onset and offset of the intracellular Up states from the LFP signal (Mukovski et al. 2007; Saleem et al. 2010).

Cortical slow oscillation is correlated across the two hemispheres and with dynamics in other brain structures such as the thalamus (Contreras and Steriade 1995; Rigas and Castro-Alamancos 2007; Hirata and Castro-Alamancos 2010) and the entorhinal-hippocampal circuits. In the hippocampus, there is an interesting difference between the behavior of pyramidal cells and interneurons: whereas pyramidal cells do not exhibit bimodal fluctuations in their Vm, some populations of hippocampal interneurons do participate in the slow oscillation, which was established through experiments that employed simultaneous recordings of cortical LFP and Vm of neurons in hippocampus or entorhinal cortex (Hahn et al. 2006, 2012; Isomura et al. 2006).

Cortical Vm-LFP Correlation During Active Wakefulness and Sensation

Intracellular recordings in the cortex of awake mammals performed together with nearby LFP recording indicate that during active waking, and in particular active sensation, the slow oscillations are replaced by a desynchronized state which to a first approximation resembles a continuous Up state (Destexhe et al. 2007; Poulet and Petersen 2008; Tan et al. 2014). A similar shift is also observed in relatively light anesthesia states. In this “activated” condition, Vm and LFP retain some degree of synchronization, which is lower than for the synchronized state of slow oscillations. This lower correlation reflects the absence of the Up and Down transitions. Interpretation of Vm-LFP correlation in the desynchronized cortex is less straightforward than for Up-Down activity. The Vm of nearby neurons is correlated to some degree even in the active condition (Poulet and Petersen 2008; Volgushev et al. 2011), indicating that some degree of synchrony exists in the activity of synapses in small cortical volumes, which is the most likely cause of the statistically significant Vm-LFP cross-correlation. However, unlike Up-Down activity, where the entire population is entrained, here we do not know which neurons are synchronized, and in fact it is plausible that the

populations (ensembles) of neurons that do synchronize change, possibly many times each second. The nonlocalized spatial origins of single-electrode LFP measurements do not allow answering this question.

Correlation between Vm and LFP activity evoked by discrete sensory inputs was examined in additional studies, carried out in the primary sensory cortical areas of anesthetized and awake rodents (Deweese and Zador 2004; Haider et al. 2016). These studies showed that a large portion of the trial-to-trial variability of the subthreshold sensory response observed in whole-cell recordings is accounted for by variability in the evoked LFP response, consistent with the idea that the sensory evoked PSP in single neurons arises from a network-level response event.

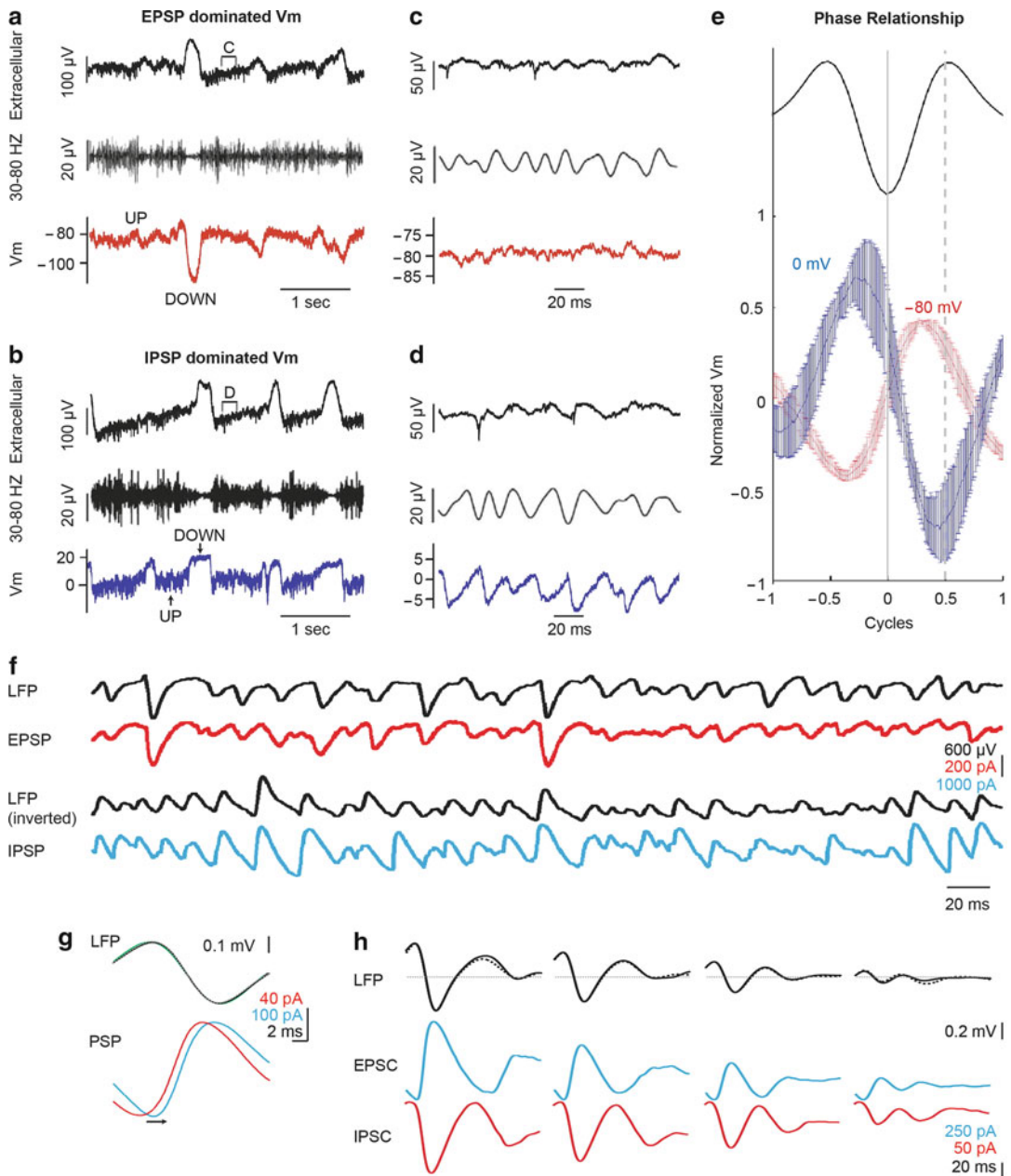
LFP, Spikes, and Excitatory and Inhibitory Synaptic Inputs

Because pyramidal cells are extended in space, whereas interneurons have a compact morphology, LFP is primarily generated by currents in pyramidal cells. Furthermore, under normal physiological conditions, these currents are first and foremost a result of synaptic activity (Buzsáki et al. 2012). The synaptic currents can be either excitatory or inhibitory. In the cortex, the excitatory and inhibitory inputs to individual neurons are to a first approximation balanced in time and strength; therefore, both excitatory and inhibitory currents contribute to the LFP. However, due to a range of factors, the LFP mainly reflects excitatory synaptic currents (in excitatory neurons). To begin with, the resting potential of cortical neurons is much closer to the reversal potential of inhibition; thus, the very same excitatory or inhibitory synaptic conductance produces synaptic currents that are several times bigger for excitation. Moreover, a large proportion of inhibitory inputs (presumably those that originate from fast-spiking neurons) are more proximal to the soma (Kawaguchi and Kondo 2002; Yoshimura and Callaway 2005; Sun et al. 2006), creating only a small dipole. Finally, inhibitory synapses depress significantly more than excitatory synapses (Heiss et al. 2008; Cohen-Kashi Malina et al. 2013) and

thus may contribute significantly less to the LFP signal. A recent study of the correlation of LFP with excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs) found that it is of approximately equal magnitude to LFP correlation with Vm (Haider et al. 2016).

In several studies of correlation between excitation and inhibition in the gamma frequency range, LFP was used as a reference signal. The goal of these studies was to understand the temporal relationship between the excitatory and inhibitory inputs, the problem being that an intracellular recording allows to measure either the EPSCs (when the cell is hyperpolarized) or IPSCs (when the cell is depolarized), but not both of them simultaneously. One approach to tackle this difficulty is to record from pairs of nearby neurons (Okun and Lampl 2008). However, for the purpose of establishing the average relationship between the EPSCs and IPSCs, it is sufficient to correlate each of them separately with a nearby LFP (Fig. 2).

Finally, let us move from the correlation between synaptic inputs to individual neurons and the LFP to briefly describe the relationship between the LFP and neurons' output, i.e., spikes. The correlation between LFP and spikes, typically quantified by the spike-triggered LFP average (stLFP, see entries ► [“Phase-Locking Methods”](#) and ► [“Local Field Potential, Relationship to Unit Activity”](#)), is determined by the Vm dynamics of the neuron. If spiking is considered to be simple threshold crossing detection, then stLFP would be expected to be proportional to Vm-LFP correlation (Boer and Kuyper 1968). Our study comparing stLFP with Vm-LFP correlation in awake rat cortex showed that indeed the stLFP does reflect the underlying Vm-LFP cross-correlation in terms of both its temporal waveform and its magnitude (Okun et al. 2010). These findings provide direct evidence for the commonly held view that the correlation between spikes and LFP reflects synchrony between the synaptic inputs that drive the membrane potential fluctuations of the neuron and the synaptic activity in the local network. Furthermore, the similarity between Vm-LFP cross-correlation and stLFP suggests that the Vm to spike transformation does not alter the



Local Field Potential: Relationship to Membrane Synaptic Potentials, Fig. 2 LFP as a reference signal allowing to resolve the excitatory-inhibitory dynamics. (a, b) Simultaneous LFP (broadband and 30–80 Hz band-pass filter) and Vm recording in prefrontal cortex of an anesthetized ferret. The Vm was recorded in two conditions: a hyperpolarized condition revealing excitatory inputs (a) and a depolarized condition revealing inhibitory inputs (b). (c, d) Part of the traces in (a, b) on an expanded timescale. (e) Average of Vm in hyperpolarized and depolarized conditions, triggered by the trough of the LFP gamma oscillation. This analysis reveals that both excitatory and inhibitory inputs are modulated by gamma

oscillations but have opposing phases. (f) Simultaneous LFP and Vm recording in hippocampal CA3 region of an anesthetized rat. As in (a, b), the Vm was recorded in hyperpolarized and depolarized conditions. (g) Average of Vm in hyperpolarized and depolarized condition, triggered by LFP gamma oscillation, as in (e). The two averages show that excitatory inputs precede the inhibitory inputs by 1–2 ms. (h) EPSC and IPSC averages triggered by LFP events of different magnitudes, showing that bigger events generate stronger excitatory and inhibitory synaptic inputs (Panels a–e reproduced, with permission, from Hasenstaub et al. (2005). Panels f–h adapted, with permission, from Atallah and Scanziani (2009))

underlying subthreshold correlation between single neurons and the LFP.

Cross-References

- ▶ [Current Source Density \(CSD\) Analysis](#)
- ▶ [Electrocorticogram \(ECoG\)](#)
- ▶ [Local Field Potential, Relationship to Unit Activity](#)
- ▶ [Low Frequency Oscillations \(Anesthesia and Sleep\): Overview](#)
- ▶ [Phase-Locking Methods](#)
- ▶ [Spectral Methods in Neural Data Analysis: Overview](#)

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Local Field Potentials in Olfaction

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Synonyms

ECoG; EEG; [Electrocorticogram](#); [Electroencephalogram](#); LFP

Definition

Local field potentials (LFPs) and electroencephalogram (EEG) recordings from many vertebrate and invertebrate olfactory systems show several types of prominent oscillatory features that depend on class, species, learning, and behavioral state. In mammals these oscillations are in three major bands: gamma (30–100 Hz), beta (15–30 Hz), and theta/respiratory (0.5–12 Hz). Modeling efforts are directed at gamma and beta oscillations in the olfactory bulb (OB) and gamma-like oscillations in the insect antennal lobe (AL). In invertebrates and fish, only gamma-like oscillations have been described (20–30 Hz).

Detailed Description

Local field potentials are the summed extracellular voltage fluctuations measured from electrodes placed within an area of the cortex or other brain regions (see entry ► [“Local Field Potentials: LFP”](#)). In cortical systems, with neurons aligned

in parallel, the field is represented by a dipole which reverses at one of the cortical layers. This voltage is often mirrored intracellularly. In non-cortical systems, such as the insect olfactory system, the coherence of the LFP signal across neurons may be poor due to the non-laminar geometry, and the intracellular and extracellular fields may be quite different.

Types of Olfactory LFP Oscillations

When local field potentials are measured in the olfactory system (usually OB and piriform or pyriform cortex (PC) but also including the anterior olfactory nucleus, olfactory tubercle, entorhinal cortex, hippocampus, amygdala, and orbitofrontal cortex), they show robust oscillatory components in several frequency bands. The frequency ranges are variable and depend on the species and behavioral state. The ranges for mammals are listed below, and variances in nonmammalian species are noted where appropriate.

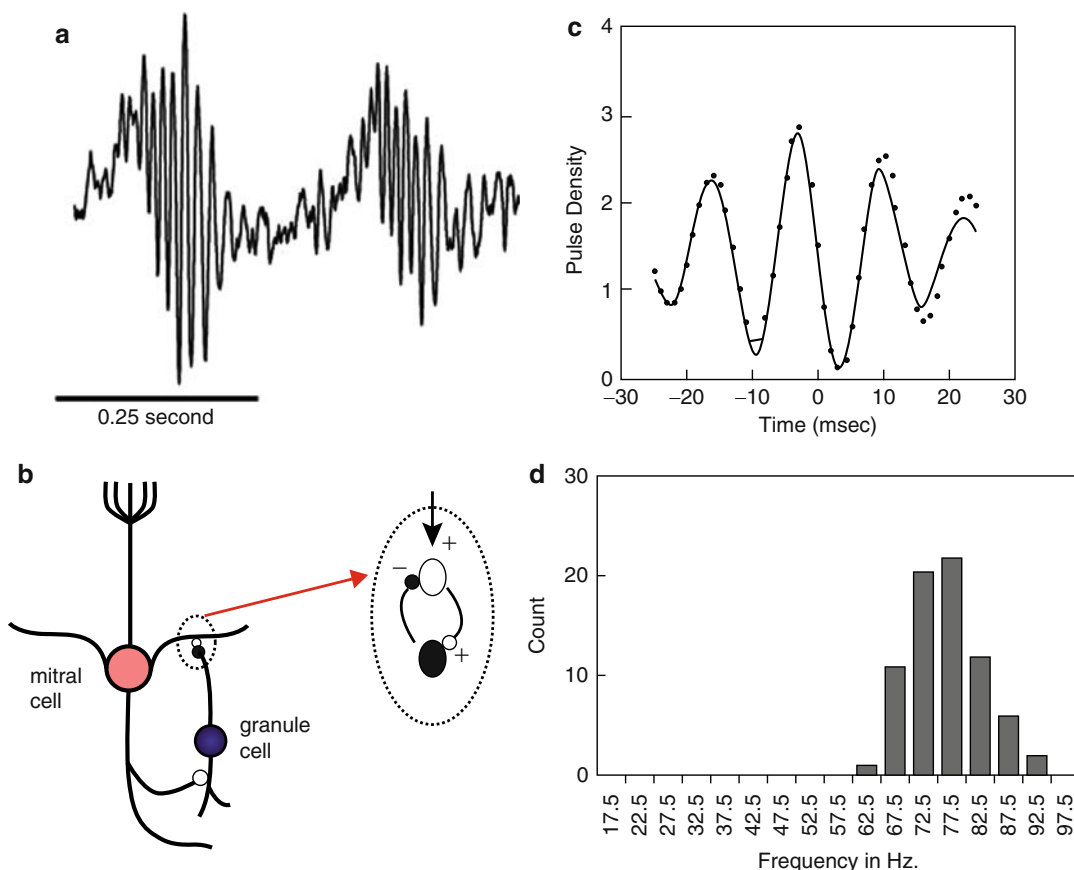
Gamma oscillations (30–100 Hz, depending on the species and behavioral state) were first described in the OB and PC. Two types of olfactory gamma oscillations have been identified. The first, dubbed *gamma1* and also referred to as just “gamma,” is the classic odor-evoked fast oscillation that arises at the transition from inhalation to exhalation (Fig. 1). In the OB, *gamma1* oscillations are generated by the reciprocal dendrodendritic synapse between mitral and granule cells, and mitral/tufted cells’ firing probability over time represents the gamma oscillation (Rojas-Líbano and Kay 2008; Kay et al. 2009). The OB *gamma1* oscillation is one of the most studied brain oscillations, and it is the subject of numerous modeling efforts. Similar oscillations are present in the PC, but less is known about the mechanism. Modeling studies suggest the negative feedback interaction between pyramidal cells and inhibitory interneurons can drive gamma in the PC (Freeman 1975). More recently, the *gamma1* band has been subdivided into high- and low-frequency bands. In rats and mice, these sort out into a higher band centered at about 90 Hz that occurs at the transition from inhalation to exhalation and a lower band centered at about

70 Hz that occurs during early exhalation (Manabe and Mori 2013; Frederick et al. 2016).

Many insects (e.g., locusts, honey bees, *Drosophila*) and nonmammalian vertebrates (e.g., zebra fish and frogs) produce an odor-evoked gamma-like oscillation in the antennal lobe (AL) and OB, respectively, also supported by the reciprocal synapse between principal excitatory neurons and GABAergic inhibitory neurons, but the frequency is 10–30 Hz (Kay and Stopfer 2006; Kay 2015). The oscillation in insects is present intracellularly in projection neurons (PNs). Because the AL is non-laminar, the extracellular LFP recorded from this structure does not show prominent oscillations; LFP recorded from the PN axon terminals in the mushroom body shows robust odor-evoked oscillations.

Lower-frequency gamma oscillations (narrow band ~55 Hz), dubbed *gamma2*, have also been described in rats and mice. These oscillations occur only during periods of low respiratory rates in between breaths and show high coherence with similar oscillations in the PC. There is nothing known about the mechanism or functional relevance of these oscillations, although their absence in mice that lack functional GABA_A receptors on OB granule cells suggests that they may require inhibition of the inhibitory interneurons (Kay 2003).

Theta or respiratory oscillations (0.5–12 Hz, depending on behavioral state and species) match the respiratory rhythm in mammals and produce a slower modulation of the field on which gamma oscillations are superimposed. Small rodents (rats and mice) breathe at several frequencies that depend on behavioral state. Under anesthesia the respiratory rhythm is 0.5–1.5 Hz; at rest the frequency is 2–4 Hz; during exploratory behavior, rats sniff at 5–6 Hz; during stationary active sniffing, the frequency is the highest, 7–12 Hz (Welker 1964; Youngentob et al. 1987; Mainland and Sobel 2006; Rojas-Líbano and Kay 2012; Rojas-Líbano et al. 2014). The mammalian gamma oscillation is initiated at the peak of the inhalation cycle and often lasts through most of the exhalation phase. Glomerular circuitry in the OB is believed to support



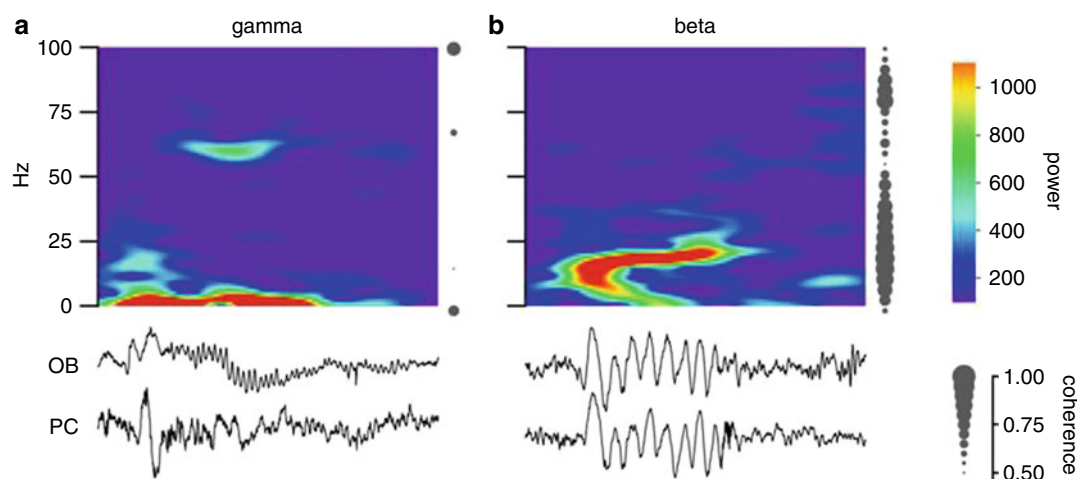
Local Field Potentials in Olfaction, Fig. 1 Gamma oscillations in the olfactory bulb. (a) Example of gamma oscillations from LFP recording. Respiratory frequency was ~ 4 Hz, rat awake but resting. Gamma oscillations arise at the end of inhalation. (b) Basic OB circuit showing a mitral and tufted cell at the dendrodendritic synapse. It is

this synapse that is responsible for gamma oscillations. (c) Pulse probability represents the probability of a mitral cell spiking given that the LFP is recorded locally. (d) Histogram of peak frequencies from pulse probability estimates of many neurons. (Figures c, d from Eeckman and Freeman (1990), with permission from Elsevier)

the respiratory oscillation, and there are neurons in the glomerular layer that burst intrinsically at ~ 2 Hz in OB slices (Hayar et al. 2004). Recent studies have shown theta oscillations coherent with hippocampal theta (see entry ► “[Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)”) within the olfactory bulb in some circumstances and respiratory oscillations driven by the olfactory bulb in the hippocampus in some circumstances (Tort et al. 2018). These oscillations also organize cortical activity in many regions of the cerebrum in humans and rodents (Zelano et al. 2016; Heck et al. 2017).

Beta oscillations (~ 20 Hz; Fig. 2) described in the olfactory system of rats are primarily

associated with specific waking behavioral states. They arise with learning of operant odor associations and are coupled to odor sampling (Martin et al. 2004). Beta oscillations also increase in waking rats upon repeated exposure to highly volatile odors (Lowry and Kay 2007). Gamma oscillations rely on local circuits and increase in amplitude if the OB is isolated from centrifugal input (Gray and Skinner 1988). Beta oscillations depend on the centrifugal input and disappear when this input is temporarily or permanently ablated (Neville and Haberly 2003; Martin et al. 2006). They are highly coherent with simultaneously recorded activity in many parts of the olfactory system, while gamma oscillations are



Local Field Potentials in Olfaction, Fig. 2 Gamma and beta oscillations of the LFP in the OB and PC. Color plots are spectrograms of the OB signal over the 1 s period of the signal displayed below. Gray spots to the right of each plot represent significant coherence between the OB and PC signals at the given frequency, with the size of the spot

representing the magnitude of the coherence. (a) Gamma oscillations elicited during odor sampling show that this oscillatory even is local to the OB, showing very little coherence with the PC. (b) Beta oscillation elicited by an odor shows high coherence between OB and PC. (Figure from Kay et al. 2009, with permission)

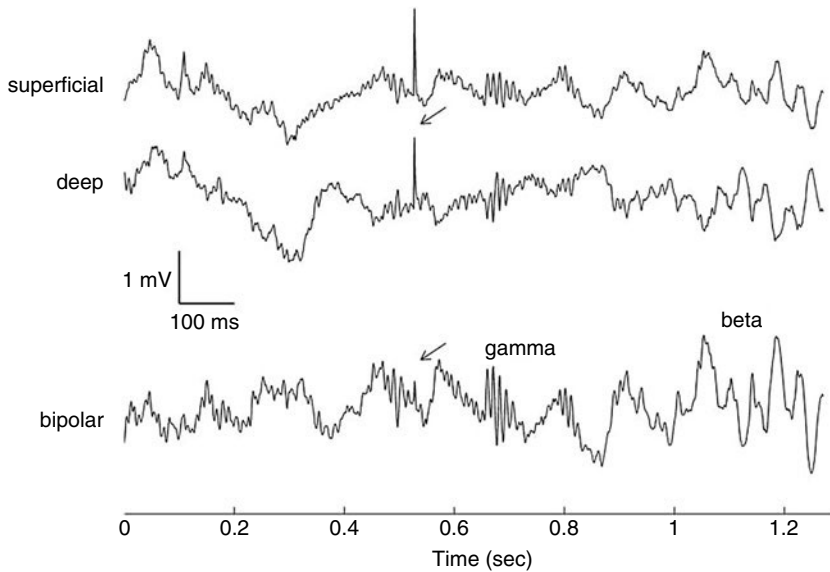
not strongly coherent across areas. Three recent modeling studies have addressed possible mechanisms for beta oscillations, and they all focus on conversion of the gamma circuit supported by the reciprocal dendrodendritic synapse (Fourcaud-Trocmé et al. 2011; David et al. 2015; Osinski and Kay 2016). All of these models rely on the ionic currents at the dendrodendritic synapse that change character depending on excitation of granule cells, but they differ in how the transition to and maintenance of beta is supported.

Recording Mammalian Olfactory LFPs

The LFP is the summed local field produced by neurons in the neighborhood of an electrode. Many factors can affect the LFP, from the electrode size and impedance to the areas in the neighborhood of the recording site. Electrode size can influence the area of the tissue over which the signal is collected; different sized electrodes can lead to different results regarding the coherence of the signal across a cortical area. In the OB larger electrodes produce a more coherent signal, but the coherence also changes with cortical depth (Kay and Lazzara 2010). The curvature of cortical areas can also influence the signal recorded with a

standard LFP electrode (50–100- μ m-diameter stainless steel, tungsten, or other metals). If a cortical sheet curves such that the electrode picks up signals from multiple parts of cortex, then the signal may not be representative of a single group of local neurons. Furthermore, if cortical areas or subcortical and cortical areas are close to each other, then the LFP produced in one area can affect that recorded in the other, for which there are several notable examples (Carmichael et al. 2017; Parabucki and Lampl 2017). It is important to note that much of the OB LFP comes from the granule cells, which are arrayed as a sheet of parallel dipoles. Mitral and other cells in the OB have more radial geometry, which makes for a very poor LFP. While all the cells are participating in the population activity that produces oscillations, the signal received by electrodes represents primarily the granule cells' picture of that population event.

There are techniques that can reduce contamination by nearby areas. First, using bipolar electrodes with a tip separation appropriate to straddle the cortical layer of interest allows placement of the two leads perpendicular to the cortical sheet on opposite sides. (See Freeman (1959) for the first



Local Field Potentials in Olfaction, Fig. 3 Simultaneous recordings of OB LFP using 100- μ m-diameter stainless steel wire. Leads were approximately 1 mm apart in cortical depth. The superficial lead was in the glomerular layer, and the deep lead was in the

granule cell layer. The bipolar trace is the result of subtracting the deep from the superficial wave form. Note the artifact at ~ 0.58 s (arrow) that is nearly eliminated in the bipolar trace. Data were sampled at 2020.2 Hz

description of this technique in the PC.) This is especially easy in mammalian olfactory system recordings. In the OB and PC, the respiratory rhythm reverses across the principal cell layer in the three-layered cortex, so placing the one lead in the superficial layer and the other in the deep layer allows visualization of the mirror-image respiratory wave across the two leads (Fig. 3). If the phase difference is close to 180 degrees, then the leads are perpendicular to the cell layer. Alternatively, antidromic stimulation of OB mitral/tufted cells and orthodromic stimulation of PC pyramidal cells by electrical stimulation of the lateral olfactory tract produces a stereotyped oscillatory evoked potential that can be used to position the bipolar recording electrodes in the OB and PC.

Bipolar recordings can be used in two different ways. First, differential recording across the two leads amplifies the part of the signal that is reversed across them and attenuates any part of the signal that is not reversed, so that signals that come from nearby areas will be removed or

attenuated. Second, specific leads can be selected for analysis to normalize positioning of electrodes across subjects. If monopolar recordings are used, the bipolar traces can be examined to determine whether oscillatory events of interest are reversed across the two leads. This can help resolve questions regarding whether a particular event is generated locally or in a nearby area. Differential recording will not change the frequency of the signals but may shift the phase if the reversal across the two leads is not perfect. This will only be a problem if one is studying phase delays between areas.

Determining the Source of an Oscillation

Many different types of experiments converge to explain the sources of olfactory LFP oscillations. These types of studies involve intracellular recordings in brain slices, pharmacological manipulations, computational modeling, extracellular LFP recordings in many behavioral states, and an extension of LFP recordings known as

current source density (CSD) analysis among many others. CSD analysis takes advantage of cortical geometry. In a laminar cortical system, the spatial derivative along the depth axis perpendicular to the pial surface allows one to estimate the sources and sinks of currents supporting a given LFP event (Mitzdorf 1985). By measuring a given type of event simultaneously at many evenly spaced cortical depths, it is possible to estimate the theoretical current flow between cortical layers. There are many assumptions from the ideal case that are violated in real cortical systems, but current source density remains a powerful tool for examining stereotyped LFP events. CSD has been applied to the olfactory system in a handful of publications. Before the easy availability of multichannel recording, easy and cheap data storage, and fast computers for estimating the current flow across many channels, CSD was done using electrical stimulation of the lateral olfactory tract and analysis of the stereotyped electrically evoked potential in the OB at successive depths recorded one at a time ((Martinez and Freeman 1984); Fig. 4a). Because the evoked potential is very stable, given the correct stimulation parameters, this could be done with good confidence. CSD from simultaneous laminar recordings of spontaneous activity in the OB was done in anesthetized rats and confirms the source of gamma oscillations as an alternating source-sink pair in the external plexiform and internal plexiform layers and beta oscillations generated from slightly deeper sublaminae (Neville and Haberly 2003; Fourcaud-Trocmé et al. 2014; Fig. 4b). There are several different methods to compute the CSD, and these are reviewed along with formulation of a new method (inverse CSD/iCSD) in Pettersen et al. (2006).

Evidence for Functional Relevance of Olfactory Oscillations

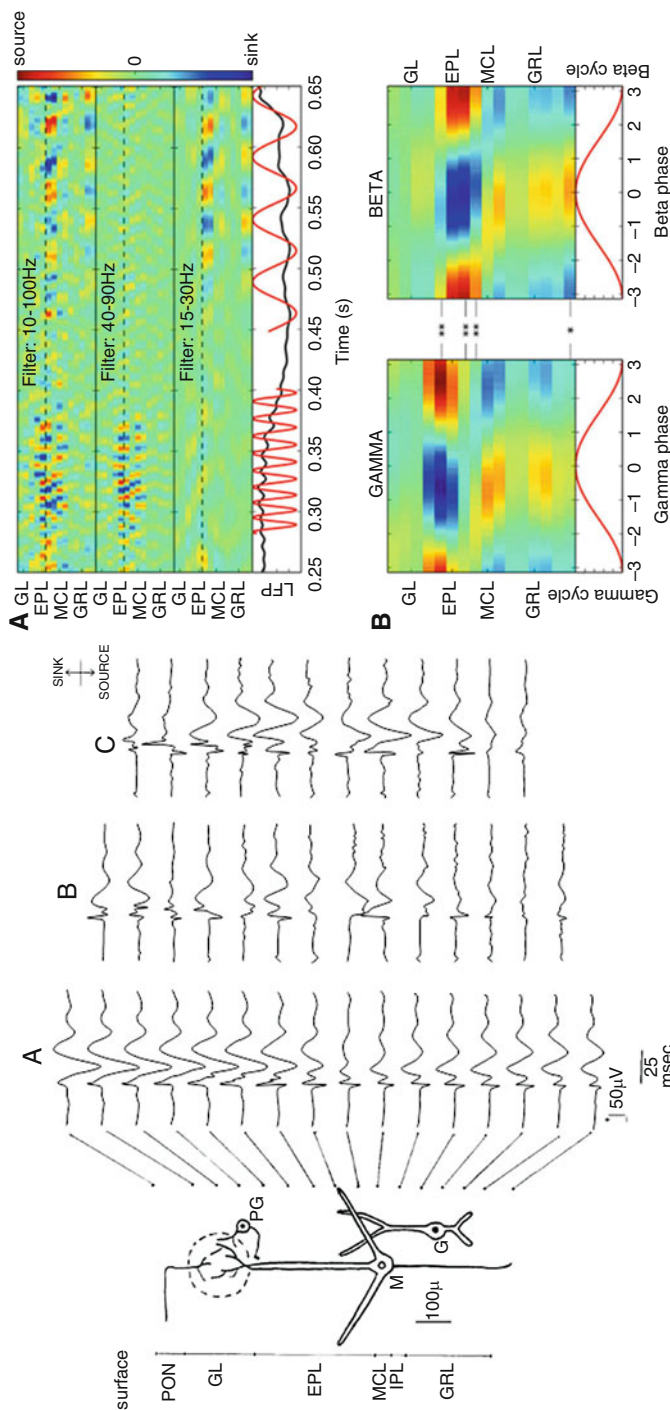
Several studies give converging support for the functional importance of gamma band oscillations in the olfactory bulb. In the honeybee AL, odor-evoked oscillations can be eliminated by application of picrotoxin, which blocks GABA_A

receptors. This takes the inhibitory drive out of the reciprocal synapse between projection neurons and local neurons. Projection neurons still fire in response to odors, but they are not coordinated in a normal oscillation. This does not make the bees anosmic, but it does make it more difficult for them to discriminate chemically similar odors (Stopfer et al. 1997). In beta3 knockout mice, gamma oscillations are artificially enhanced by knocking out inhibition of granule cells (inhibition onto the main inhibitory local neurons). These mice are better than heterozygous controls at discriminating similar odors (Nusser et al. 2001). Rats that are trained to discriminate odors in an operant discrimination task increase gamma oscillations when they have learned to discriminate very similar odors but not when they discriminate more different odors (Beshel et al. 2007). No other olfactory oscillations have been tested in this way, so functional relevance is unknown for olfactory beta, gamma2, and theta or respiratory oscillations. However, there is converging evidence regarding beta oscillations that begin to point at functional roles. Beta oscillations follow a few sniffs associated with gamma oscillations during odor sampling in an operant task, which suggests that they are better related to system-wide interactions associated with decisions or action than with early sensory processing (Frederick et al. 2016) (Fig. 5).

Note that functional relevance does not mean that the LFP is the mechanism of functionality, only that what the LFP represents is associated with the ability to detect fine differences between odors. The LFP gamma (or gamma-like) oscillation represents the coordinated firing of the principal neurons (mitral/tufted cells or projection neurons). This firing is oscillatory at the level of the group average and is represented by intracellular membrane potential oscillations within mitral cells and projection neurons.

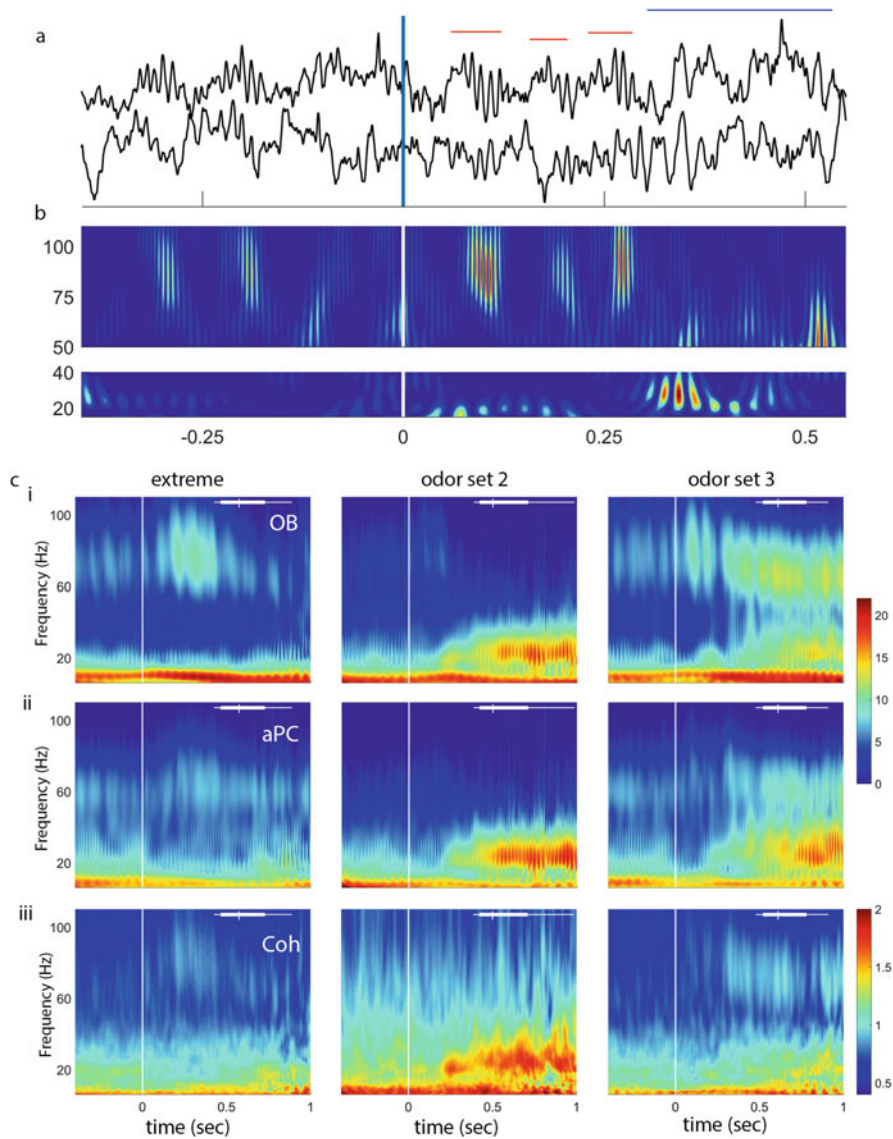
Using the LFP to Infer Neuronal or System Properties

The LFP itself has not been shown to have any causal properties. However, the underlying sets of



Local Field Potentials in Olfaction, Fig. 4 Current source density estimate in the OB. Left: (a) 16 averaged evoked potentials (n=200) recorded from the rabbit olfactory bulb in response to stimulation of the primary olfactory nerve, using a 1×16 electrode array. The recording site for each electrode within the bulbar laminae is indicated by lines drawn to the diagram at left, illustrating the bulbar lamina including the primary olfactory nerve (PON) at the surface, the olfactory glomerulus (dashed circle) with a nearby periglomerular cell (PG), the mitral cell (M), apical dendrite, cell body basal dendrites and axon, and a granule cell (G) interneuron. Abbreviations: GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; IPL, internal plexiform layer; GRL, granule cell layer. (b) Current source density (CSD) values versus time calculated for nearest neighbor electrodes using the averaged evoked potentials from (a). (c) CSD calculations using the second nearest neighbor electrodes. (Left figure and

excerpted caption from Martinez and Freeman (1984), with permission; figure edited to darken evoked potential curves in (a-c)). Right: CSD analysis in the OB of an anesthetized rat. (A) CSD over time (400 ms) showing a gamma oscillation early and a beta oscillation later; gamma on the peak of a slow inhalation and beta in the trough of exhalation. Full-frequency band on the top, with filtered gamma and beta band CSDs below. Gamma and beta oscillatory signals in red and respiratory wave in black at bottom. GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; GRL, granule cell layer. (B) Average CSD map of gamma and beta events. Note that gamma appears to be supported by sink/sources in the superficial EPL and the MCL and superficial GRL, while beta shows a sink in the deeper EPL with source in the GRL. Horizontal axis is phase of each oscillation. (Right set of figures from Fourcaud-Trocmé et al. 2014; use allowed under the Creative Commons Attribution License)



Local Field Potentials in Olfaction, Fig. 5 Gamma and beta oscillations in behaving rats. (a) Sample voltage traces showing gamma (red horizontal bars) and beta (blue horizontal bar) oscillations during a single trial. The vertical line at 0 indicates nosepoke-on, with the estimated arrival of the odor stimulus at approximately 60 ms. OB is the top trace and aPC the bottom trace for the raw data. (b) Gamma (top) and beta (bottom) band wavelet plots showing frequency over time from the data in a. Color represents power with red high. Note the sweep in frequency from higher to lower for the first two gamma bursts and the abrupt transition from gamma to beta just after 250 ms. (c) Sample wavelet time-frequency plots showing three session averages (columns represent three different odor sets). (i) OB power: note strong gamma during early odor sampling for the extreme odor set (two different vials containing the same odor with different trace contaminants), lower power gamma and

strong beta for odor set 2 (easily discriminated high volatility odors), and both gamma and beta power for odor set 3 (easily discriminated odors). (ii) aPC power: note the similarity in beta power between OB and aPC. Gamma power in the aPC is much smaller than in the OB. (c.i and c.ii use the same color scale, which is in dimensionless units after normalization and log transform.). (iii) Coherence between OB and aPC shows a decrease in strength during odor sampling in the lower-frequency bands for the extreme odor set, and coherence overall is primarily limited to the beta band. Coherence is represented as Z-coherence (arctanh of coherence; see methods). Vertical line at time 0 indicates nosepoke-on. White bar at top of each plot shows the distribution of end sampling times for each session. (Figure and caption excerpted from Frederick et al. 2016; shared via Creative Commons Attribution 4.0 International (CC BY 4.0) license)

neurons and their connections and interactions that give rise to these oscillations do cause and are affected by oscillations. The problem of inferring these properties by measuring the LFP is a difficult one. These inferences cannot be made without converging experiments at many levels: intracellular recordings, recording of spiking properties in various behavioral states (awake, anesthetized, during odor discrimination, etc.), current source density, and pharmacological manipulation to name a few. When these studies are done, the LFP can be a powerful tool. In the case of gamma oscillations, many converging studies have shown that increases in gamma power represent better coordination of spikes among mitral/tufted cells.

Cross-References

- [Hippocampal Theta, Gamma, and Theta/Gamma Network Models](#)
- [Local Field Potentials: LFP](#)

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Local Field Potentials: Interaction with the Extracellular Medium

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Definition

The local field potential (LFP) is the electric potential in the extracellular space around neurons. The LFP is generated by electric currents and charges, and is also interacting in several possible ways with the extracellular medium, such as capacitive interactions, polarization, or through ionic diffusion. These types of interaction confer specific frequency dependence of the extracellular electric potential and thus are important for correctly interpreting the LFP, as well as estimating the underlying neuronal sources (inverse problem).

Detailed Description

Introduction

In contrast to the electroencephalogram (EEG) recorded at the surface of the scalp, the local field potential (LFP) is recorded by inserting microelectrodes into neural tissue and is recordable using a variety of electrode systems, such as metal or silicon electrodes, or glass micropipettes. Early studies established that action potentials have a limited participation to EEGs or LFPs (Bremer 1938, 1949; Eccles 1951; Klee et al. 1965; Creutzfeldt et al. 1966a, b). The current view is that EEG and LFPs are generated by synchronized synaptic currents arising on cortical neurons, possibly through the formation of dipoles (Nunez 1981; Niedermeyer and Lopes da Silva 1998). This view applies to

cerebral cortex, hippocampus, or any brain structure where neurons form dipoles arranged in parallel.

The fact that action potentials have little participation to the LFP indicates strong frequency-filtering properties of cortical tissue. High frequencies (greater than ≈ 100 Hz), such as that produced by action potentials, are subject to a severe attenuation and therefore are visible only for electrodes immediately adjacent to the recorded cell. On the other hand, low-frequency events, such as synaptic potentials, attenuate less with distance. These events can therefore propagate over large distances in extracellular space and be recordable as far as on the surface of the brain, where they can participate in the genesis of the EEG. This frequency-dependent behavior is also seen routinely in extracellular unit recordings: the amplitude of extracellularly recorded spikes is very sensitive to the position of the electrode, but slow events show much less sensitivity to electrode position. In contrast, action potentials are recorded only for the cell(s) immediately adjacent to the electrode and are therefore very sensitive to changes in electrode position. This property is fundamental because it allows resolving single units from extracellular recordings.

EEG or LFP measurements also display approximately $1/f$ frequency scaling in their power spectra at low frequencies (Bhattacharya and Petsche 2001; Bédard et al. 2006b; Novikov et al. 1997; Pritchard 1992; Dehghani et al. 2010). The origin of such $1/f$ “noise” is at present unclear. The $1/f$ spectra can result from self-organized critical phenomena (Jensen 1998), suggesting that neuronal activity may be working according to such states (Beggs and Plenz 2003). Alternatively, the $1/f$ scaling may be due to filtering properties of the currents through extracellular media (Bédard et al. 2006b). This conclusion was reached by noting that the global activity reconstructed from multisite unit recordings scales identically as the LFP if a “ $1/f$ filter” is assumed, and without the need to assume self-organized critical states in neural activity.

We review here possible physical bases for such frequency-filtering properties, from the interaction between electrical events (such as membrane currents) and the extracellular space around neurons.

The “Standard Model”

The simplest model for the LFP assumes that the extracellular medium is purely *resistive* or *Ohmic*, with no (or negligible) frequency dependence. In this case, one considers a set of punctual current sources embedded in a homogeneous conductive medium of conductivity σ . The extracellular potential due to a single punctual current source can be deduced simply as follows. Starting from Ohm’s law ($\vec{j} = \sigma \vec{E}$), combined with the law of current conservation ($\vec{j} = \frac{i}{4\pi r^2} \hat{r}$) in spherical symmetry around the source, and by integrating along a straight line from the source to a given point in extracellular space, the extracellular potential at some distance r from the source i is given by:

$$V(r) = \frac{1}{4\pi\sigma} \frac{i}{r}, \quad (1)$$

if we assume that the reference $V(\infty) = 0$. This relation can also be deduced directly from Maxwell-Gauss law ($\nabla \cdot \vec{D} = \rho$) within the quasistatic electric approximation in the electric limit (de Montigny and Rousseaux 2006) a priori. (Note that this “electric limit” quasistatic approximation assumes that the magnetic field is negligible compared to the electric field ($\vec{E} < v_{\text{phase}} \vec{B}$). The other quasistatic approximation (“magnetic limit”) considers that the electromagnetic induction is not negligible.) In the case of a set of n current sources i_j , the superposition principle applies and one can write:

$$V(r) = \frac{1}{4\pi\sigma} \sum_{j=1}^n \frac{i_j}{r_j}, \quad (2)$$

where r_j is the distance from the source i_j to the position r in extracellular space. This expression captures many effects such as dipoles or multipolar configurations (if the distance is large compared to the size of the source). Equation 2 is widely used to model extracellular potentials since early models (Rall and Shepherd 1968) to today’s models of extracellular activity (Protopapas et al. 1998; Destexhe 1998; Nunez

and Srinivasan 2005; Gold et al. 2006; Pettersen and Einevoll 2011).

Microscopic Model of Frequency Filtering

A first possible physical mechanism giving rise to frequency-filtering properties is the fact that the extracellular space around neurons is not homogeneous but is subject to strong variations in conductivity and permittivity. In cerebral cortex, the different cellular processes are densely packed (Peters et al. 1991), and the extracellular space consists of a mixture of membranes of very low conductivity and extracellular highly conductive fluids. To formalize this situation, however, the equations above cannot be used and one must restart from first principles, as done previously (Bédard et al. 2004). To do this, we will consider a “microscopic” model where the electric parameters are subject to spatial variations according to the type of medium (fluid, membranes).

Starting from Maxwell equations, $\nabla \cdot \vec{D} = \rho^f$ (Maxwell-Gauss law), and $\nabla \times \frac{\vec{B}}{\mu} = \vec{j} + \frac{\partial \vec{D}}{\partial t}$ (Ampere-Maxwell law), if we consider a medium with constant magnetic permeability, we obtain:

$$\begin{aligned} \nabla \cdot \vec{D} &= \rho^f \\ \nabla \cdot \vec{j}^f + \frac{\partial \rho^f}{\partial t} &= 0. \end{aligned} \quad (3)$$

where $\vec{D}$, $\vec{j}^f$, and ρ^f are respectively the electric displacement, the free-charge current density, and free-charge charge density in the medium surrounding the sources.

In a linear medium, the equations linking the electric field $\vec{E}$ with electric displacement $\vec{D}$ and with current density $\vec{j}^f$ are given by:

$$\vec{D}(\vec{x}, t) = \int_{-\infty}^{\infty} \varepsilon(\vec{x}, \tau) \vec{E}(\vec{x}, t - \tau) d\tau \quad (4)$$

and

$$\vec{j}(\vec{x}, t) = \int_{-\infty}^{\infty} \sigma(\vec{x}, \tau) \vec{E}(\vec{x}, t - \tau) d\tau. \quad (5)$$

In this model, the electric parameters σ and ε take their “microscopic” values and are assumed to be independent of frequency. Indeed, the electric parameters of the extracellular fluid can be considered constant for frequencies lower than 1000 Hz (Gabriel et al. 1996c). In this case, the Fourier transforms of the above equations are respectively $\vec{D}_\omega = \varepsilon_\omega \vec{E}_\omega = \varepsilon \vec{E}_\omega$ and $\vec{j}_\omega = \sigma_\omega \vec{E}_\omega = \sigma \vec{E}_\omega = \sigma_z \vec{E}_\omega$ (where $\omega = 2\pi f$, where f is the frequency). It is important to note that σ_ω is a real number in this microscopic model, but this is not necessarily the case in a macroscopic model (as in next section).

Given the limited precision of measurements, we can consider $\nabla \times \vec{E} \approx 0$ for frequencies smaller than 1000 Hz. Thus, we can assume that $\vec{E} = -\nabla V$ such that the complex Fourier transform of Eq. 3 can be written as:

$$\nabla \cdot (\varepsilon(\vec{x}) \nabla V_\omega) = -\rho_\omega^f$$

$$\nabla \cdot (\sigma(\vec{x}) \nabla V_\omega) = i\omega \rho_\omega^f$$

Consequently, we have:

$$\nabla \cdot ((\sigma + i\omega\varepsilon) \nabla V_\omega) = 0 \quad (6)$$

This is the main equation to calculate the LFP in nonhomogeneous media, as derived previously (Bédard et al. 2004). It is general enough to calculate the propagation of the extracellular potential in extracellular media which can have a complex or inhomogeneous structure, as well as frequency-dependent electric parameters.

Equation 6 reduces to Laplace equation ($\nabla^2 V_\omega = 0$) when the medium is homogeneous with respect to σ and ε . Thus, Eq. 6 can be seen as a generalization of Laplace equation for media where σ and ε are nonhomogeneous. Except for particular cases where the ratio ε/σ is independent of position, Eq. 6 shows that, in nonhomogeneous media, the extracellular potential will necessarily have a different power spectral structure compared to that of the current sources, because the extracellular potential must be solution of a differential equation with frequency-dependent

coefficients. (Note that in this case, the electric potential does not satisfy Laplace equation ($\nabla^2 V_\omega = 0$), but obeys $\nabla \cdot \sigma(\vec{x}) \nabla V_\omega = 0$ when $\frac{\varepsilon}{\sigma}$ is constant everywhere.)

This “microscopic” model was simulated with different spatial profiles of conductivity and permittivity around neurons (Bédard et al. 2004). It was found that according to the profile of σ and ε , one can have a high-pass or low-pass filter, but in general, when σ is high at short distances and decays with larger distances, a low-pass filter is observed. For example, with an exponentially decaying conductivity, a low-pass filter attenuates more strongly the fast frequencies compared to low frequencies. A simulation of the LFP generated showed that the extracellular waveform of an action potential changes as the distance to the source is increased (Bédard et al. 2004). Thus, this model accounts for basic features of frequency filtering.

In this type of model, one can show that the electric potential is given by:

$$V_\omega = \frac{I_\omega^f}{4\pi\sigma(R)} \int_R^\infty \frac{1}{r'^2} \cdot \frac{\sigma(R) + i\omega\varepsilon(R)}{\sigma(r') + i\omega\varepsilon(r')} dr' \quad (7)$$

for a spherical is potential source embedded in any given medium. Here, I_ω^f is the free-charge current (in Fourier space). Note that the membrane current is the sum of the free-charge current (ion channels) and the capacitive current. Thus, the free-charge current is:

$$I_\omega^f = I_m(\omega) \frac{\sigma(R)}{\sigma(R) + i\omega\varepsilon(R)}$$

where I_m is the membrane current of the source, $\sigma(R)$ is the electrical conductivity, and $\varepsilon(R)$ is the electrical permittivity of the membrane at the source. (This relation is obtained from $\vec{j}_\omega^f = \sigma_\omega \vec{E}_\omega$ and $\vec{j}_\omega^c = i\omega\varepsilon_\omega \vec{E}_\omega$, where $\vec{j}_\omega^c$ is the capacitive current density.) It follows that the PSD of the voltage varies as $I_m(\omega)/\omega^2$ for high frequencies, because in this case, V_ω becomes proportional to $I_m(\omega)/\omega$.

Mean-Field Models of Extracellular Space

In principle, it is sufficient to solve Eq. 6 in the extracellular medium to simulate the LFP in inhomogeneous media. However, if the extracellular medium has a complex spatial structure, it may be tedious to assign the space dependence of the electric parameters σ and ε . One way to solve this problem is to consider a macroscopic or mean-field approach at a larger scale, in which the electric parameters will be considered as constant in space, but are the result of a microscopic mixture of different media such as fluids and membranes.

Note that Maxwell equations are invariant under change of scale if electric parameters are renormalized appropriately (see details in Jackson 1999; Bédard and Destexhe 2011). This approach is further justified by the fact that the values measured experimentally are averaged values, which precision depends on the measurement technique. Ideally, one should have a formalism that can integrate such macroscopic measurements. Thus, we need to design a macroscopic model, in which we take spatial averages of Eq. 6, and make a continuous approximation for the spatial variations of these average values. Such a mean-field model was proposed previously (Bédard and Destexhe 2009, 2011, 2014) and is detailed below.

To this end, we define macroscopic electric parameters, ε^M and σ^M , by taking an average of the “microscopic” electric parameters over some volume V :

$$\varepsilon_\omega^M(\vec{x}) = \langle \varepsilon_\omega(\vec{x}) \rangle_V = f(\vec{x}, \omega)$$

and

$$\sigma_\omega^M(\vec{x}) = \langle \sigma_\omega(\vec{x}) \rangle_V = g(\vec{x}, \omega).$$

We assume that V is of the order of $10^3 \mu m^3$ and is thus much smaller than the cortical volume, so that the mean values will be dependent of the position in cortex.

Because the average values of electric parameters are statistically independent of the mean value of the electric field, the density of

generalized current $\vec{j}^g$ is expressed as (The generalized current must be used in a medium where charge accumulation can occur, because in this case, the free-charge current is not conserved in neurons (Bédard and Destexhe 2013). Note that we assume that there is no charge creation (such as chemical reactions, ionization, etc.)).):

$$\begin{aligned} \langle \vec{j}^g \rangle_{|V}(\vec{x}, t) &= \int_{-\infty}^{\infty} \sigma^M(\tau) \langle \vec{E} \rangle_{|V}(\vec{x}, t - \tau) d\tau \\ &+ \int_{-\infty}^{\infty} \varepsilon^M(\tau) \frac{\partial \langle \vec{E} \rangle_{|V}}{\partial t}(\vec{x}, t - \tau) d\tau, \end{aligned}$$

where the first term in the right hand represents the “dissipative” contribution, and the term represents the “reactive” contribution (reaction from the medium, such as polarization). Here, all physical effects, such as diffusion, resistive, and capacitive phenomena, are integrated into the frequency dependence of σ^M and ε^M . The second term translates the fact that there is an inertia time for polarization (also called Maxwell-Wagner time), because the charges do not move instantaneously. This implies that the electric field will take a characteristic time to settle; this time is given by the Maxwell-Wagner time of the region in which the average is taken (see details in Planck and Brose 1932 and for application to biological membranes, see Bédard et al. 2006a).

The complex Fourier transform of $\langle \vec{j}^g \rangle_{|V}(\vec{x}, t)$ then becomes:

$$\begin{aligned} \langle \vec{j}^g \rangle_{|V} &= (\sigma_{\omega}^M + i\omega\varepsilon_{\omega}^M) \langle \vec{E}_{\omega} \rangle_{|V} \\ &= \gamma_{\omega}^M \langle \vec{E}_{\omega} \rangle_{|V}, \end{aligned} \quad (8)$$

where γ_{ω}^M is the complex macroscopic admittance.

Because $\gamma_{\omega}^M = (\sigma_{\omega}^M + i\omega\varepsilon_{\omega}^M)$ and $\langle \vec{E}_{\omega} \rangle = -\nabla(V_{\omega})$, the expressions above (Eq. 6) can also be written in the form:

$$\nabla \cdot (\gamma_{\omega}^M \nabla \langle V_{\omega} \rangle_{|V}) = 0. \quad (9)$$

by using the conservation of the generalized current.

We note that starting from the continuum model (Bédard et al. 2004), where only spatial variations were considered, and generalizing this model by including frequency-dependent electric parameters, gives the same mathematical form as the original model (compare with Eq. 6; see details in Bédard and Destexhe 2011). This form invariance will allow us to introduce different phenomena, such as surface polarization or ionic diffusion, by including an ad hoc frequency dependence in σ_{ω}^M and ε_{ω}^M . The physical causes of this macroscopic frequency dependence is that the cortical medium is microscopically non-neutral (although the cortical tissue is macroscopically neutral). Such a local non-neutrality was already postulated in a previous model of surface polarization (Bédard et al. 2006a). This situation cannot be accounted by Eq. 6 if σ_{ω}^M and ε_{ω}^M are frequency independent (in which case $\rho_{\omega} = 0$ when $\nabla V_{\omega} = 0$). Thus, including the frequency dependence of these parameters enables the model to capture a much broader range of physical phenomena.

Finally, a fundamental point is that the frequency dependences of the electrical parameters $\sigma_{\omega}^M = \text{Re}(\sigma_{\omega}^M) + i\text{Im}(\sigma_{\omega}^M)$ and $\varepsilon_{\omega}^M = \text{Re}(\varepsilon_{\omega}^M) + i\text{Im}(\varepsilon_{\omega}^M)$ cannot take arbitrary values but are related to each other by the Kramers-Kronig relations which are equivalent to a Hilbert transform (see Kronig 1926; Landau and Lifshitz 1981; Foster and Schwan 1989). It can be shown (Bédard and Destexhe 2018) that:

$$\begin{cases} \Delta \text{Im}(\gamma) = \mathcal{H}[\Delta \text{Re}(\gamma)] & (a) \\ \Delta \text{Re}(\gamma) = -\mathcal{H}[\Delta \text{Im}(\gamma)] & (b) \end{cases} \quad (10)$$

where $\gamma = \text{Re}(\gamma) + i\text{Im}(\gamma)$ and $\Delta\gamma = \gamma(\omega) - \gamma(\infty)$, and $\mathcal{H}$ is the Hilbert transform. $\text{Re}(\gamma)$ and $\text{Im}(\gamma)$ are respectively the real and imaginary part of the admittance γ (for more details, see Bédard and Destexhe 2018).

Note that these equations are valid for any linear medium (i.e., when Eqs. 4 and 5 are linear).

These relations will turn out to be critical to relate models to experiments, as shown previously (Jackson 1999; Bédard and Destexhe 2018).

Conclusions

In this entry, we have overviewed three formalisms to model LFPs. The first formalism, mostly based on Coulomb's law, expresses the potential as resulting from a set of current sources in a homogeneous resistive medium. This simple model is the one used by the majority of studies to simulate the LFP. It is justified by measurements suggesting that the extracellular medium is resistive (Logothetis et al. 2007; Miceli et al. 2017). However, it does not account for other measurements suggesting that the extracellular medium is non-ohmic (Gabriel et al. 1996b; Bédard et al. 2010; Dehghani et al. 2010; Gomes et al. 2016). There is also at present no convincing simulation of the spatial aspect of LFPs and why the spikes from only a few neurons are visible in extracellular recordings. This is why we need to consider other formalisms that allows one to include nonohmic aspects of the extracellular space, such as ionic diffusion or capacitive effects.

A first possibility is to explicitly integrate the strong inhomogeneity of extracellular media, in which the electric parameters σ and ϵ are strongly dependent on position. In this “microscopic” model, one must return to Maxwell equations to derive the correct equations to calculate the extracellular potential. The reason is that in such media, there will be charge accumulation, and the local free-charge conservation law $(\nabla \cdot \vec{j}^f = 0)$ does not apply (one must take into account the displacement current $\nabla \cdot (\nabla \times \vec{H}) = \nabla \cdot \left(\vec{j}^f + \frac{\partial \vec{D}}{\partial t} \right) = \nabla \cdot \vec{j}^f + \frac{\partial \rho}{\partial t}$ (see Bédard et al. 2004). This formalism was derived previously and was shown to simulate the low-pass filtering properties of extracellular space (Bédard et al. 2004). However, this “microscopic” formalism cannot integrate “macroscopic” measurements of σ and ϵ (Gabriel et al. 1996b) nor the

fact that the frequency filter deduced from experimental measurements is of $1/f$ type (Bédard et al. 2006b, 2010).

Thus, another formalism should be derived to include these more global aspects. We derived a “macroscopic” formalism using a mean-field derivation of Maxwell equations. This macroscopic formalism describes the tissue at a larger coarse-graining, and in which the electric parameters will be considered as spatial averages, and independent of position. They are the result of a mixture of different media such as fluids and membranes (Bédard and Destexhe 2009, 2011a, 2014). This mean-field formalism can directly integrate the macroscopic measurements of σ and ϵ , as well as macroscopic impedance measurements (Gomes et al. 2016). Thus, it can be used to simulate a wide variety of physical mechanisms in the extracellular medium. For example, it can be used to simulate the polarization phenomena that the electric field induces on neuronal membranes; it can also be used to integrate capacitive effects or the effect of ionic diffusion in the extracellular space.

This approach was possible because of the scale invariance of the mathematical structure of Maxwell equations. This property allows one to renormalize the electromagnetic parameters such that, even if the microscopic parameters do not depend on frequency, the macroscopic parameters can be frequency dependent in some media (see details in Bédard and Destexhe 2011). This is a consequence of the fact that the Maxwell-Wagner time is non-negligible in such media. Note that the standard model postulates that there is no such frequency dependence, which amounts to neglect the Maxwell-Wagner time and consider that the charges move infinitely fast, which corresponds to the simplest possible model in electromagnetism theory.

Using such formalisms, it was shown that ionic diffusion gives macroscopic electric parameters σ_ω^M and ϵ_ω^M displaying a frequency dependence as $1/\sqrt{\omega}$, which gives a $1/f$ filter in power spectra. Such a $1/f$ filter is consistent with experimental measurements, to relate LFPs with extracellularly recorded units (Bédard et al. 2006b) or LFPs with intracellular recordings (Bédard et al. 2010). It is also consistent with

conductivity measurements showing resistive media (Logothetis et al. 2007), because these measurements were designed to specifically avoid ionic diffusion (see discussion in Logothetis et al. 2007). Thus, if ionic diffusion has dominant effects, and if other effects such as inhomogeneities and polarization are negligible, then all measurements can be reconciled.

Thus, one can conclude that a neuron embedded in a non-resistive medium dominated by ionic diffusion is at present the only possible physical model that can account for all measurements done to date (reviewed in Bedard et al. 2017). A macroscopic model of LFPs (such as Eq. 9) is the most appropriate formalism to model ionic diffusion and was shown to reproduce the frequency-scaling properties of LFPs quantitatively (Bédard and Destexhe 2009). This model is general and includes the standard (resistive) model as a special case.

Finally, it is important to note that capturing the correct frequency dependence of the electric parameters is very important in the so-called “inverse problem” of estimating neuronal sources from measurements of extracellular voltage, such as the current-source density method (Mitzdorf 1985; Nicholson and Freeman 1975). It is evident that such a frequency-dependence, if present, will distort the extracellular electric potential; inversely, starting from the electric potential, the estimation of the source will be different if the frequency dependence is neglected (as in the classic CSD analysis). This problem was addressed recently, and it was shown that generalizing the CSD analysis to frequency-dependent media may lead to large differences in the mathematical estimates of neuronal sources (Bédard and Destexhe 2011).

In conclusion, we have shown that the expressions to calculate the extracellular potential from membrane currents are vastly dependent on the nature of the extracellular medium. If phenomena like inhomogeneities, capacitive effects, polarization or ionic diffusion are taken into account, the medium exerts a strong frequency filtering action on the propagation of the extracellular potentials. As a consequence, if such effects are confirmed, it is imperative to take them into account to correctly

model the extracellular potentials. Similarly, estimating neuronal sources from extracellular measurements also requires to know precisely the nature of the frequency filtering properties of the medium. So far, measurements are contradictory (Gabriel et al. 1996a, b, c; Logothetis et al. 2007; Gomes et al. 2016; Miceli et al. 2017; Bédard and Destexhe 2017). In a recent review paper (Bedard et al. 2017), we overviewed different possible causes for these contradictory measurements and outlined new experiments that should be done to settle the issue.

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Local Field Potentials: LFP

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Definition

The local field potential (LFP) is the electric potential in the extracellular medium around neurons. The LFP is a signal available in many recording configurations, ranging from single-electrode recordings to multi-electrode arrays. The LFP has specific spatial and temporal properties, and also depends on brain state. Different classes of models are used to model the LFP.

Introduction

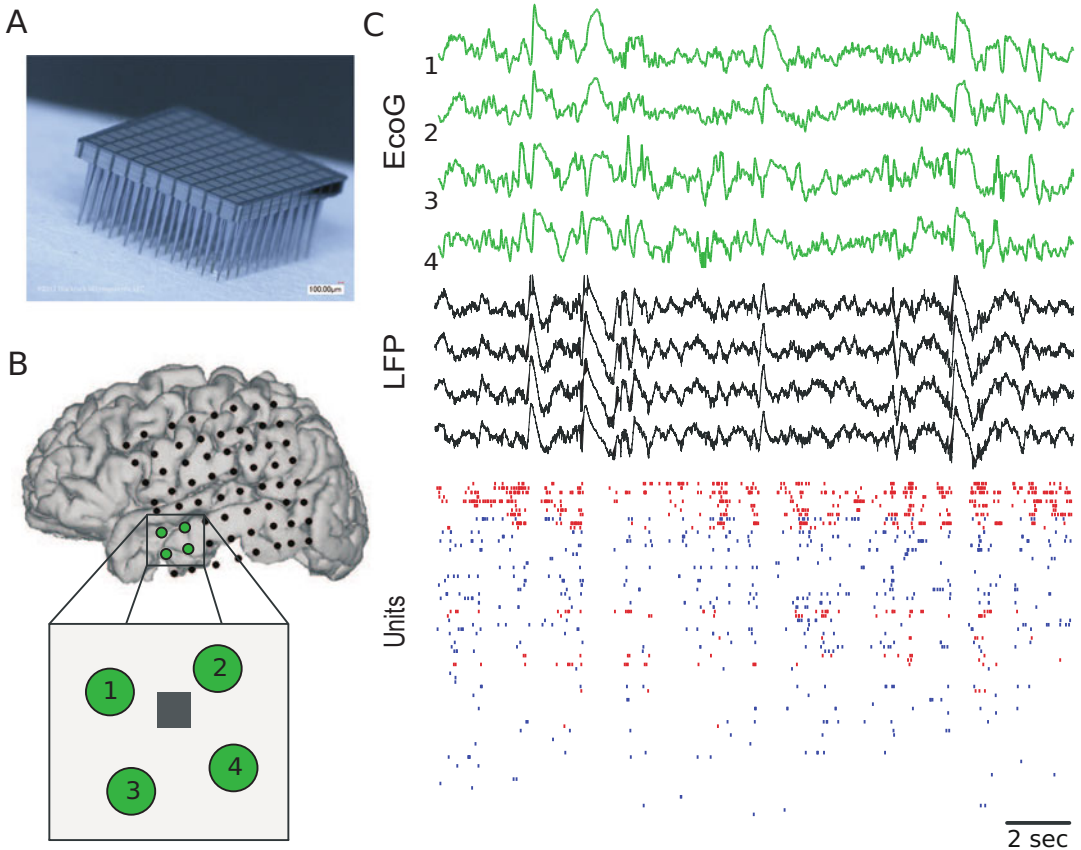
The local field potential (LFP) is the electric potential in the extracellular space around

neurons, and can be recorded using different types of micro-electrodes (metal, silicon, or glass micropipettes). Its characteristics differ from the electroencephalogram (EEG), which is recorded at the surface of the scalp with macro-electrodes. It was shown that the LFP samples relatively localized populations of neurons, as these signals can be very different for electrodes separated by 1 mm (Destexhe et al. 1999) or even by a few hundred microns (Katzner et al. 2009). In contrast, it is thought that the EEG samples large populations of neurons, spanning up to several centimeters (Niedermeyer and Lopes da Silva 1998). Besides these differences, EEG and LFP signals display the same type of oscillations during wake and sleep states (Steriade 2003). These different properties are reviewed here.

Spatial and Temporal Properties of LFPs

In Fig. 1a, human LFP recordings are shown using a very popular extracellular multi-electrode array system, called the “Utah array,” developed at the University of Utah and by BlackRock Microsystems. This 100-electrode array was implanted in human medial temporal cortex together with surface electrodes (Fig. 1b). The surface electrodes record the electrocorticogram (EcoG in Fig. 1), the electric potential at the surface of the cortex (green signals in Fig. 1c). By contrast, the LFP provides a recording of the electric potential from within the brain tissue (black signals in Fig. 1c). In this example, recorded during slow-wave sleep, one can clearly see slow delta waves in both the surface EcoG and depth LFP recordings. A number of discriminated units are also shown and were recorded using the same set of electrodes.

We next illustrate the state-dependence of the LFP signal using LFPs recorded in cat parietal cortex during wake and sleep states (Fig. 2). This figure shows that the LFP displays the same features as classically seen from the EEG: during wakefulness, the LFP was dominated by low-amplitude fast oscillations (Fig. 2a), while during slow-wave sleep, the LFP displayed high-amplitude slow waves (Fig. 2b). During rapid-eye movement (REM) sleep (Fig. 2c), the LFP



Local Field Potentials: LFP, Fig. 1 Local field potentials recorded in humans using a multi-electrode array. (a) Array of 100 silicon electrodes (Utah array, BlackRock systems), with 400 μm inter-electrode distance, and which was inserted into temporal cortex. (b) Plan of implantation of surface electrodes (black dots). Inset: magnified view of the medial temporal lobe, with four surface electrodes (green) and the Utah array (gray square). (c) Recordings obtained with the different electrode systems,

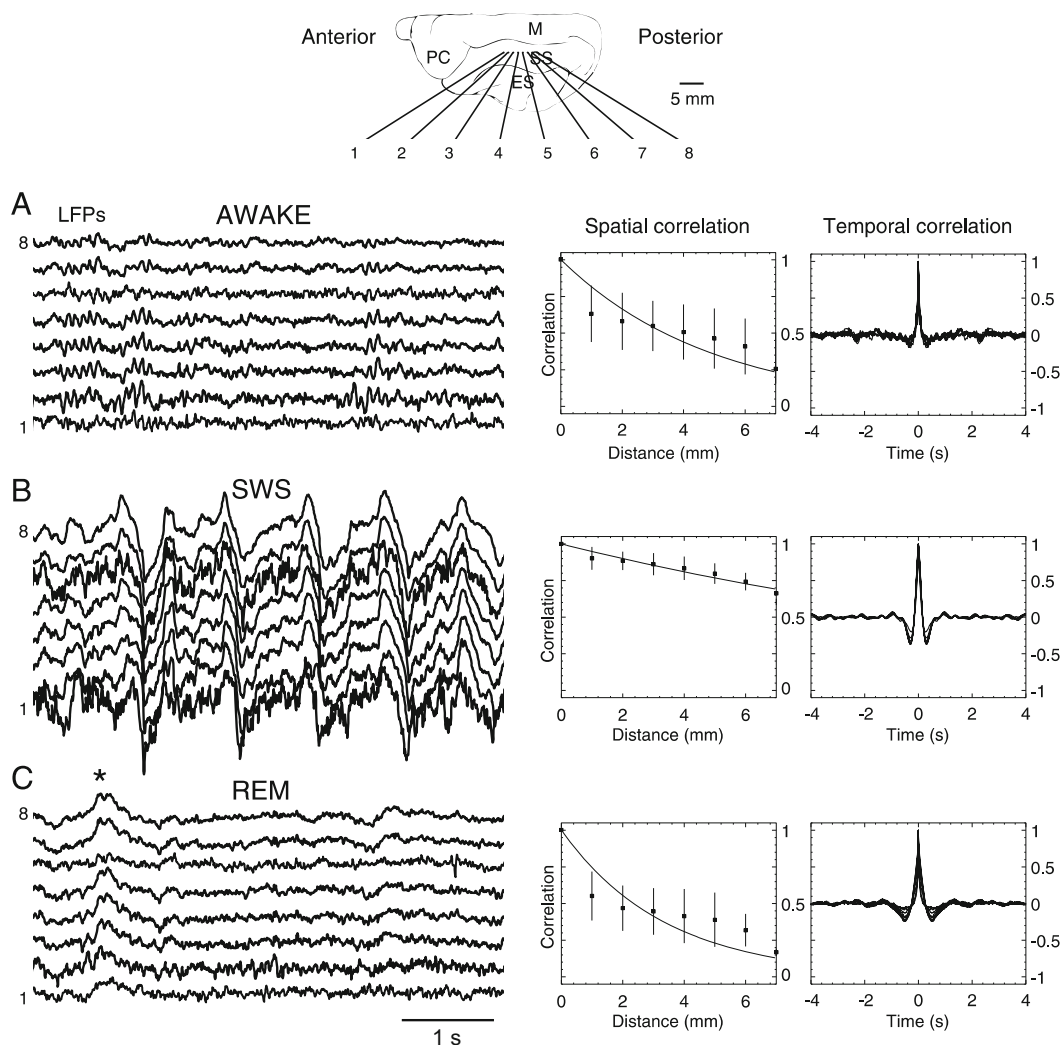
surface electrodes (EcoG, green), local field potentials (LFP), and identified neurons (Units; red = inhibitory, blue = excitatory). The four nearby surface EcoGs are shown (green), while four randomly chosen LFPs were shown among the 100 electrodes available. This example was recorded during slow-wave sleep, and one can see slow delta waves in the surface EcoG and in the LFPs, as well as in the modulation of the firing of units. (Modified from Peyrache et al. 2012; Destexhe and Bedard 2013)

showed nearly identical characteristics as during wakefulness. It was shown that the high similarity between Wake and REM states extends to about everything that can be measured electrophysiologically, such as the spectral content, the correlation dynamics, and the unit activity (Destexhe et al. 1999). On the other hand, slow-wave activity is clearly different, as shown for example by their different pattern of coherence as a function of distance compared to the low coherence of fast activity during Wake and REM states. This difference can be quantified by calculating spatial correlations, and in particular their decay with

distance. As expected from the LFP signals, the correlations remained high for larger distances only during slow-wave sleep (Fig. 2, middle panels). In contrast, the temporal correlations displayed similar profiles between different brain states (Fig. 2, right panels).

Relation Between LFP and Neuronal Activity

Figure 3 illustrates that the relationship between LFP and the firing of neurons highly depends on

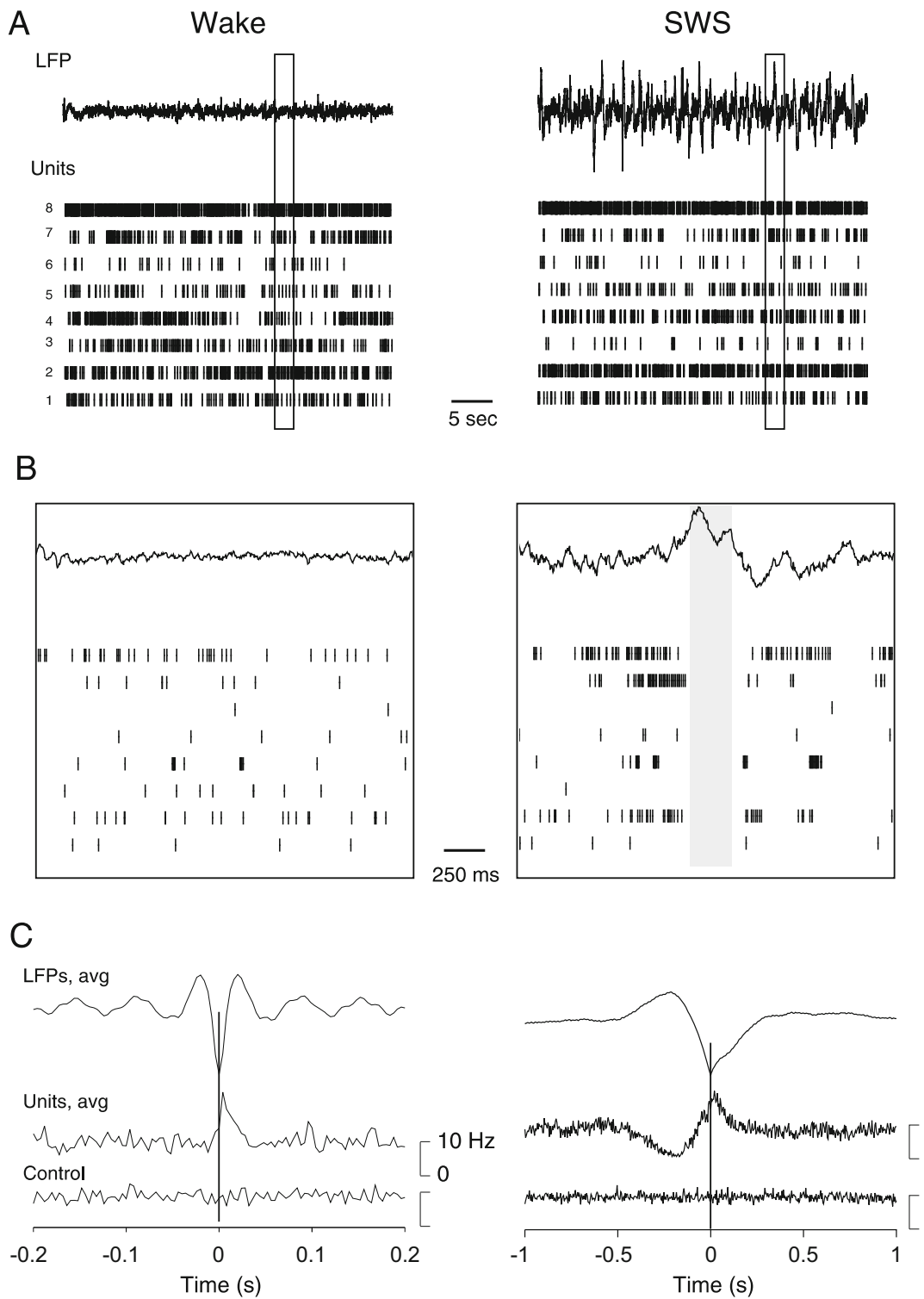


Local Field Potentials: LFP, Fig. 2 Local field potential recordings in cat parietal cortex during wake and sleep states. Eight bipolar tungsten electrodes (inter-electrode distance of 1 mm) were inserted into the depth (1 mm) of areas 5–7 of cat parietal cortex (suprasylvian gyrus, area 5–7; see top scheme for arrangement of electrodes). Local field potentials (LFPs) are shown (left panels) together with a representation of the correlations as a function of distance (Spatial correlations; middle panels) and time (Temporal correlations; right panels). (a) When the animal

was awake, LFPs were characterized by low-amplitude fast activities in the beta/gamma frequency range (15–75 Hz). Correlations decayed steeply with distance and time. (b) During slow-wave sleep, the LFPs were dominated by large-amplitude slow-wave complexes recurring at a low frequency (<1 Hz; up to 4 Hz). Correlations stayed high for large distances. (c) During episodes of REM sleep, LFPs and correlations had similar characteristics as during wake periods (* indicates a PGO wave). (Modified from Destexhe et al. 1999)

the brain state. During wakefulness, the low-amplitude fast-frequency LFP was associated with sustained irregular firing activity in the units (Fig. 3a, b, Wake). There was no apparent relation between units and LFP by visual

inspection. However, a statistical analysis revealed that the depth-negative deflections were on average related to an increase of firing activity in the units (Fig. 3c, Wake; see details in Destexhe et al. 1999). During slow-wave sleep, the



Local Field Potentials: LFP, Fig. 3 (continued)

ensemble activity tended to be more bursty (Fig. 3a, SWS). At closer scrutiny (Fig. 3b), it appears that synchronous “silences” in all the units occur systematically and simultaneously with the depth-positive part of the slow wave (Fig. 3b, SWS; blue shaded area). This type of synchronized silence is often referred as “Down-state,” and was also visible in the human recordings (see Fig. 1c). This modulation of firing by the slow wave also appears in the statistical relation between units and slow waves (Fig. 3c, SWS). This relation between slow waves and Up and Down states in single neurons was demonstrated using intracellular recordings in natural slow-wave sleep in cats (Steriade et al. 2001; reviewed in Steriade 2003). We therefore conclude that the human and cat recordings display very similar features of the relation between LFPs and neuronal units.

In a more recent study in human and monkey (Telenczuk et al. 2017), it was shown that the LFP is more tightly related to inhibitory activity. This conclusion was reached by analyzing datasets where excitatory and inhibitory cells could be distinguished, and the relation could be determined separately. In particular, the so-called unitary LFP (uLFP) results from the synchronous release of synapses belonging to a single axon. The uLFP of inhibitory cells is much more powerful than that of excitatory cells (Telenczuk et al. 2017), a conclusion also reached by detailed computational models (Telenczuk et al. 2020a). uLFPs can constitute the basis of a “kernel method” to calculate LFPs from point neurons (see details in Telenczuk et al. 2020b; see also the *Modeling LFPs* section below).

Power Spectra and Frequency Scaling of LFPs

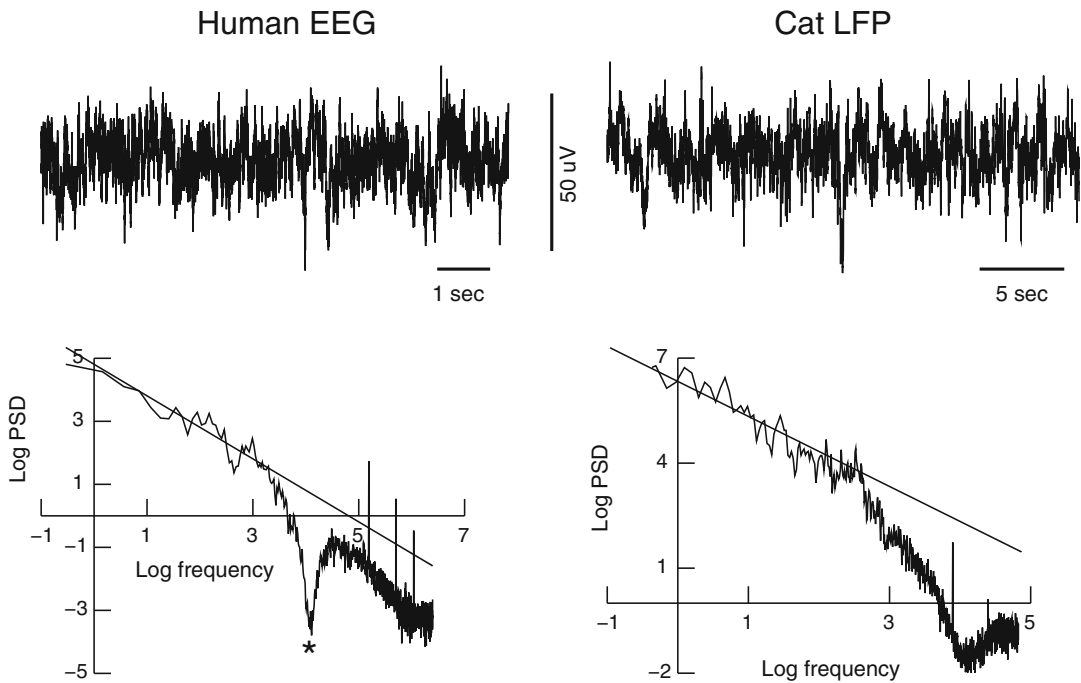
Another characteristic of EEG and LFP signals is that their power-spectrum exhibits $1/f$ frequency scaling at low frequencies, as shown by a number of studies (Pritchard 1992; Novikov et al. 1997; Bhattacharya and Petsche 2001; Bedard et al. 2006a; Dehghani et al. 2010). Figure 4 illustrates such scaling in the human EEG and in the LFP recorded with tungsten electrodes in cat parietal cortex, both when the subject was awake and attentive. In these conditions, the low-frequency end of the PSD scales as $1/f$. A more detailed study showed that the scaling exponent of the EEG signals varies from 1 to 2 according to the brain region considered (Dehghani et al. 2010).

Such $1/f$ “noise” may have different origins. First, $1/f$ spectra can result from self-organized critical phenomena (Jensen 1998), suggesting that neuronal activity may be working according to such states (Beggs and Plenz 2003), but this subject is controverted (Bedard et al. 2006a; Dehghani et al. 2012). The morphology of the neuron may also be responsible for filtering in the $1/f$ to $1/f^2$ range (Pettersen and Einevoll 2008), but this scaling applies only to high frequencies and does not explain the $1/f$ scaling at low frequencies. Finally, the $1/f$ scaling may be due to filtering properties of the currents through extracellular media (Bedard et al. 2006a). This conclusion was reached by noting that the global activity reconstructed from multisite unit recordings does not reproduce the power spectra found for LFPs (Fig. 5). This failure to reconstruct LFPs spectra from unit activity applies in particular to the $1/f$ scaling at low frequencies. Interestingly, a $1/f$ component was miss-



Local Field Potentials: LFP, Fig. 3 Relation between LFP and unit activity in different brain states. (a) *Left*: During wakefulness, the low-amplitude fast-frequency LFP activity is associated with highly irregular firing activity of the 8 multi-units recorded simultaneously (same experimental setup as in Fig. 2). *Right*: During slow-wave sleep (SWS), the activity is similar as wakefulness, except that synchronized “silences” of firing activity occur in all cells simultaneously, and in relation to the slow waves. (b) Same activity as in A at 20 times higher

temporal resolution. The blue shaded area indicates the synchronized silence (“Down state”) simultaneous in all cells, and occurring in parallel with slow waves. (c) Wave-triggered averages of spiking activity. During wakefulness, the LFP negative peaks were correlated with an increased firing activity in the units. During SWS, the negative peak of the slow wave was correlated with a strong decrease of firing in the units (Down state), followed by a rebound a sustained activity (Up state). (Modified from Destexhe et al. 1999)



Local Field Potentials: LFP, Fig. 4 $1/f$ scaling of EEG and LFP signals. The top traces show examples of human EEG recordings (left, vertex EEG) and LFP recording from cat parietal cortex (right) during awake and attentive states. The corresponding power spectra (lower panels) display approximate $1/f$ scaling at low frequencies. The straight

lines (red) indicate a slope of -1 in this log-log representation. The signals were not filtered, except for a notch filter at 60 Hz (*) for the EEG, and the data acquisition filters at high frequencies (not visible at this scale). (Modified from Bedard and Destexhe 2012)

ing for all frequency bands (compare Fig. 5b and d), suggesting that a “ $1/f$ filter” could explain the LFP spectra, without the need to assume self-organized critical states in neural activity (Bedard et al. 2006a). We will see below that ionic diffusion may explain such a $1/f$ filter.

Modeling LFPs

In this section, we review different approaches that have been proposed to model LFPs (see also the chapter by Bedard and Destexhe, ► “Local Field Potentials: Interaction with the Extracellular Medium” in this volume).

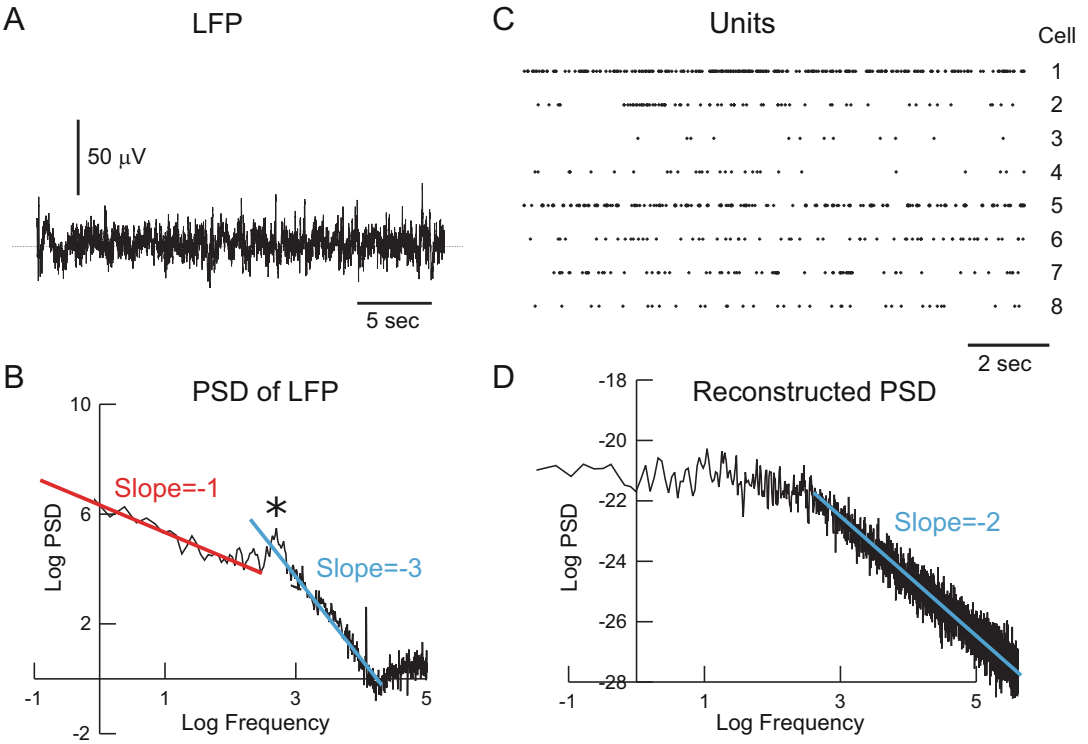
Standard model: The first model that was proposed for the genesis of LFPs, which we call here the “standard model,” assumes that the LFP is generated by a set of current sources in a homogeneous and resistive extracellular

medium. According to this model, the extracellular potential V at a position r in extracellular space resulting from a set of n current sources i_j is given by:

$$V(r) = \frac{1}{4\pi\sigma} \sum_{j=1}^n \frac{i_j}{r_j}, \quad (1)$$

where σ is the electric conductivity, r_j is the distance from the source i_j to the position r in extracellular space. Equation 1 is widely used to model extracellular potentials, since early models (Rall and Shepherd 1968) to today’s models of LFPs (Protopapas et al. 1998; Destexhe 1998; Nunez and Srinivasan 2005; Gold et al. 2006; Pettersen and Einevoll 2008).

General model: A more general model of the LFP must explicitly consider the inhomogeneities of conductivity in the extracellular space around neurons. In such a case, one cannot use the



Local Field Potentials: LFP, Fig. 5 Failure to reconstruct LFP power spectra from unit activity. (a) LFP recording in awake cat parietal cortex (same recording as in Fig. 4, left). (b) Power spectral density (PSD) of the LFP, showing two scaling regions, $1/f$ at low frequencies (red line, slope = -1), and $1/f^3$ at high frequencies (blue line; slope = -3). (c) Unit activity from the same experiment.

(d) Attempt to reconstruct the LFP signal from the unit activity. The low-frequency end of the PSD was constant (zero slope), while the high-frequency end scaled as $1/f^2$ (blue line, slope = -2). An exponent of -1 is missing to reproduce the LFP scaling. (Modified from Bedard et al. 2006a)

equation above, and must start from first principles (Maxwell equations) and derive the equations that govern the extracellular potential V . This was done previously (Bedard et al. 2004), and the main result is that, in a non-homogeneous medium, the extracellular potential obeys the following equation (written in Fourier space):

$$\nabla \cdot ((\sigma + i\omega\epsilon)\nabla V_\omega) = 0. \quad (2)$$

This equation gives the evolution of the ω -frequency component of the extracellular potential, V_ω , as a function of the electric conductivity σ and permittivity ϵ , which are both allowed to vary in space. This equation is general enough to calculate the propagation of the extracellular potential in

extracellular media which can have a complex or inhomogeneous structure. If σ and ϵ are constant, this model recovers the standard model, and is therefore a generalization of this model. This approach was used to show that inhomogeneities of conductivity can lead to a low-pass filtering of the extracellular medium, which generates more realistic patterns of extracellular potentials (Bedard et al. 2004) and CSD profiles (Bazhenov et al. 2011).

Mean-field model: A third type of model considers the LFP as generated at more macroscopic scales. In this case, the same approach as above is followed but using a mean-field formalism (Bedard and Destexhe 2009, 2011). Instead of considering that σ and ϵ vary in space, one defines

macroscopic electric parameters, ϵ^M and σ^M , by taking an average of the “microscopic” electric parameters over some volume Vol :

$$\epsilon_{\omega}^M(\vec{x}) = \langle \epsilon_{\omega}(\vec{x}) \rangle_{|Vol}$$

and

$$\sigma_{\omega}^M(\vec{x}) = \langle \sigma_{\omega}(\vec{x}) \rangle_{|Vol}.$$

It must be emphasized that these macroscopic electric parameters are in general frequency dependent. This frequency dependence arises from the renormalization process, and is necessary for the macroscopic equations to be consistent. It can be shown that different physical processes will result in different frequency dependence of these parameters. A perfectly resistive and homogeneous medium will result in no frequency dependence of σ^M and ϵ^M , while processes such as polarization, capacitive effects, and ionic diffusion will all lead to specific frequency-dependent profiles of σ^M and ϵ^M . For example, for a diffusive medium we have $\sigma^M + i\epsilon^M = k\sqrt{\omega}$ (where k is a complex number; see details in Bedard and Destexhe 2009).

Defining similarly a macroscopic extracellular potential $\langle V_{\omega} \rangle_{|Vol}$ by averaging V_{ω} over a volume Vol leads to the following mean-field equation for V :

$$\nabla \cdot ((\sigma_{\omega}^M + i\omega\epsilon_{\omega}^M)\nabla \langle V_{\omega} \rangle_{|Vol}) = 0. \quad (3)$$

This equation generalizes Eqs. 1 and 2 at macroscopic scales. Solving this equation will give access to the macroscopic variations of V .

Kernel model: Finally, a more recent approach has been proposed where the LFP is generated using a “kernel method” (Telenczuk et al. 2020b). In this model, the LFP is calculated from the sole knowledge of the spiking activity of neurons. The spiking activity is convolved with kernels specific to each neuron type:

$$V(r) = \sum_k K_e(r, t - t_{e,k}) + \sum_l K_i(r, t - t_{i,l}), \quad (4)$$

where $K_e(r, t - \tau)$ are $K_i(r, t - \tau)$ the excitatory and inhibitory uLFP kernels, while $\{t_{e,k}\}$ and $\{t_{i,l}\}$ are the spike times of excitatory and inhibitory neurons, respectively.

The kernels typically have the form:

$$K(r, t) = A(r) \Theta(t) \exp \left[-(t - t_p)^2 / 2\sigma^2 \right], \quad (5)$$

where A is an amplitude constant (which can be negative), Θ is the Heaviside step function, σ is the standard deviation in time, and t_p is the peak time of the kernel. The latter is given by

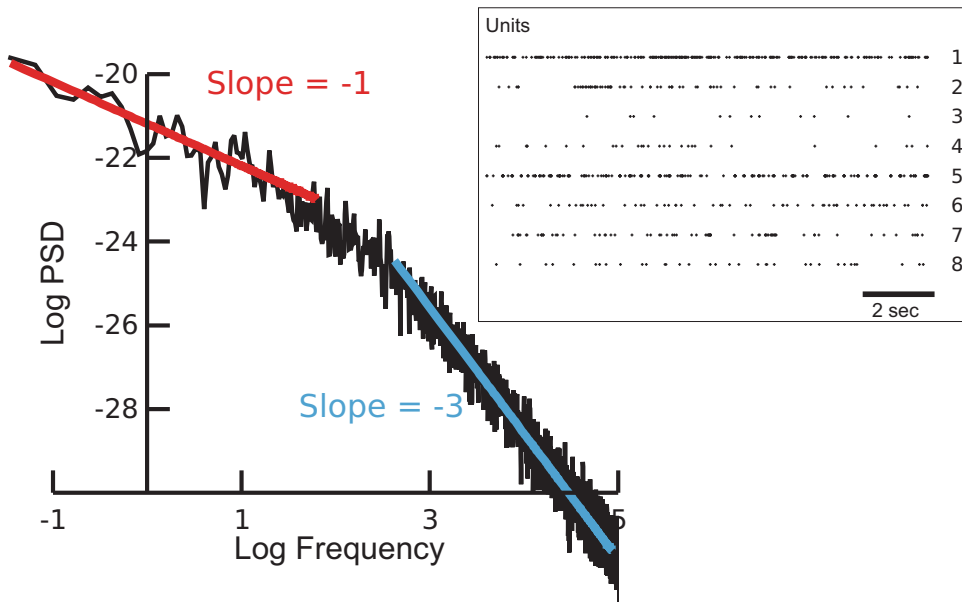
$$t_p = t_0 + d + |r - r_0| / v_a, \quad (6)$$

where t_0 is the time of the spike of the cell, $|r - r_0|$ is the distance between cell and electrode, d is a constant delay, and v_a is the axonal speed.

This method was tested on various neural networks using kernels estimated from human microelectrode recordings, and it was shown that the kernel LFP provides a low-pass version of the LFP calculated with the standard model (see details in Telenczuk et al. 2020b).

Reconstructing the Spectral Structure of LFPs from Unit Activity

To reconstruct the correct frequency-scaling properties of LFPs, as measured experimentally (Fig. 5b), we showed above that the standard model was unable to account for this frequency scaling (Fig. 5d). To determine if the non-resistive properties of the extracellular medium can lead to the correct scaling behavior, one can use the mean-field LFP model described above. Using Eq. 3 with $\sigma^M + i\epsilon^M = k\sqrt{\omega}$ derived from extracellular ionic diffusion (Bedard and Destexhe 2009), it was possible to reconstruct LFPs with frequency scaling in qualitative agreement with experimental data (Fig. 6). With ionic diffusion, it is therefore possible to reconstruct the correct frequency scaling properties of LFPs from unit activity, for all frequencies, which is presently not possible with any other model. Ionic diffusion



Local Field Potentials: LFP, Fig. 6 Successful reconstruction of LFP power spectra from unit activity when ionic diffusion is taken into account. The PSD of the LFP was reconstructed from the units (inset; same as in Fig. 5c),

taking into account ionic diffusion. The reconstructed LFP displays the same frequency scaling as the real LFP (compare with Fig. 5b). (Modified from Bedard and Destexhe 2009)

appears, therefore, as a plausible physical mechanism to fully explain the spectral structure of LFPs (Bedard and Destexhe 2009).

Conclusions

In this contribution, we have illustrated the main spatial and temporal (or frequency) properties of LFPs. It is important to emphasize that spatial (correlations with distance) and temporal properties (frequency scaling, frequency content) of LFPs are highly dependent on brain state. In the awake brain, the LFPs scales as $1/f$ at low frequencies, a property which was also found at the level of the EEG (Pritchard 1992; Novikov et al. 1997; Bhattacharya and Petsche 2001; Bedard et al. 2006a; Dehghani et al. 2010).

To model the LFP, a first type of approach, the simplest conceptually, postulates that the LFP is generated by a set of current sources embedded in a homogeneous and resistive medium. This approach leads to a very simple relation between the extracellular potential and the current sources

(Eq. 1). This formalism is used in the vast majority of studies modeling the LFP. It provides an acceptable simulation of the LFP in many cases (e.g., Rall and Shepherd 1968; Protopapas et al. 1998; Destexhe 1998; Holt and Koch 1999; Nunez and Srinivasan 2005; Gold et al. 2006; Milstein and Koch 2008; Pettersen and Einevoll 2008; Linden et al. 2011). The procedures to implement this standard model are now available in popular simulators such as NEURON, or python scripts such as LFPy (Linden et al. 2014) or NeuronEAP (Telenczuk and Telenczuk 2016).

Although resistive extracellular media are justified by some measurements (Logothetis et al. 2007; Miceli et al. 2017), other measurements suggest that the extracellular medium is non-ohmic (Gabriel et al. 1996; Bedard et al. 2010; Dehghani et al. 2010; Wagner et al. 2014; Gomes et al. 2016). But most importantly, the microstructure of extracellular space shows that it is far from being uniform, and rather consists of an aggregate of highly conductive fluids with low-conductive and capacitive membranes. There is therefore a serious possibility that the medium is more

complex than a simple resistor, although this issue is still unclear today.

To account for such inhomogeneities, a specific formalism must be derived, starting from Maxwell equations and integrate electric parameters that depend on the spatial position in extracellular space. Such a formalism revealed that the inhomogeneities of conductivity can give rise to strong filtering properties of LFPs (Bedard et al. 2004). Such a model should be used if one needs to account in detail for the attenuation of LFPs with distance. It was also shown that this model accounts for the characteristics of the current-source density (CSD) analysis of the slow oscillation in cerebral cortex (Bazhenov et al. 2011). A caveat of this model is that it is complex to apply in principle, because it requires to know in detail the 3D arrangement of fluids and membranes in the extracellular space around each neuron.

Another formalism, easier to implement in practice, is a mean-field approach that describes the tissue at a larger coarse-graining. In this case, the extracellular potential is considered as an average over some volume of space. This mean-field model of LFPs (Bedard and Destexhe 2009, 2011) also presents the advantage that it can directly incorporate macroscopic measurements of σ and ϵ in brain tissue (Gabriel et al. 1996; Gomes et al. 2016). This approach can integrate various physical mechanisms, such as the polarization of the extracellular medium (Bedard et al. 2006b) or ionic diffusion (Bedard and Destexhe 2009). Ionic diffusion turns out to be the mechanism that best explains various measurements including the $1/f$ scaling properties of LFPs at low frequencies (Fig. 6). This mean-field approach can also be applied to generalize the CSD analysis (which is only valid in resistive media) to extracellular media with arbitrarily complex electrical properties (Bedard and Destexhe 2011).

Finally, a recent approach, more phenomenological, consists of reconstructing the LFP from kernels estimated from the relation between units and LFPs extracted from experimental data (Telenczuk et al. 2020b). This method has the advantage of simplicity, because it only requires the knowledge of the spike times of neurons,

while biophysical models require all membrane currents, which is considerably more complex. The kernel method is also very fast to compute in comparison to biophysical models. The kernel LFP method was shown to provide good estimates of surface and depth LFPs from networks of spiking neurons (Telenczuk et al. 2020b). NEURON and python scripts have been published to use the kernel-based method (Telenczuk et al. 2020c). Interestingly, the kernel LFP appears as a low-pass version of the LFP generated by the standard model, which may also indicate low-pass filtering properties of the extracellular medium. This relation should be investigated in future studies.

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Locomotor Central Pattern Generator

► Locomotor Pattern Generation in the Rodent Spinal Cord

Locomotor Pattern Generation in the Rodent Spinal Cord

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Synonyms

CPG; Locomotor central pattern generator; Spinal locomotor network

Definition

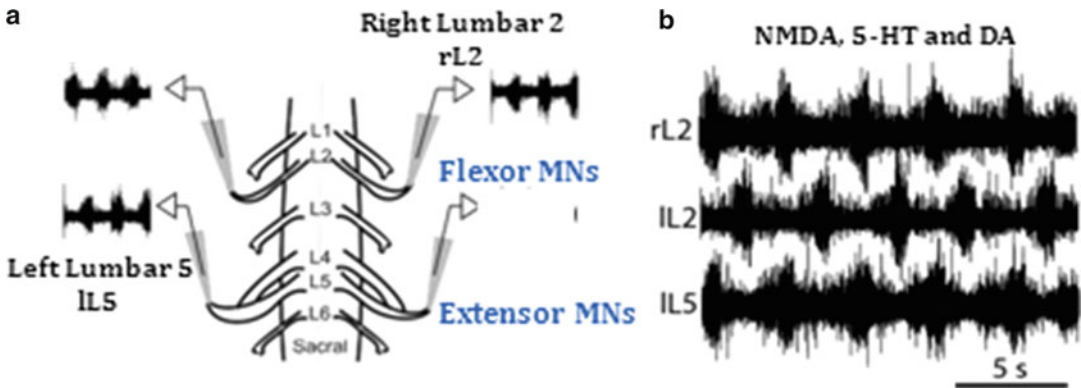
The locomotor central pattern generator is a neural network in the spinal cord that can generate the basic motor pattern for locomotion in the absence of sensory feedback or rhythmic input from the brain. Most research in rodents has focused on hind limb movements: the hind limb CPG is located in lower thoracic and lumbar segments of the spinal cord. This network generates both the locomotor rhythm (cycle frequency) and the detailed phasing of motoneuron activation during the cycle, including alternation of left and right limb movements and alternation of ipsilateral flexor and extensor activity.

Detailed Description

A central pattern generator (CPG) is a limited neural network that can produce an organized rhythmic motor output in the absence of sensory or descending inputs from other parts of the nervous system (Marder and Calabrese 1996). CPGs drive behaviors such as locomotion, respiration, mastication, and digestion (Gossard et al. 2010). The CPG for vertebrate locomotion is located in the spinal cord. This entry will focus on the organization of the rodent hind limb locomotor CPG, which directs rhythmic movements of the left and right hind limbs of rats and mice. Under normal circumstances, in the intact animal, locomotor CPGs are strongly affected by sensory feedback, which can, for example, determine the timing of the swing phase initiation during walking, by descending inputs from the brain, which normally provide tonic drive to activate the locomotor CPG, and by modulatory inputs which shape CPG output and prepare it for activation.

The rodent spinal cord is particularly useful for studies of CPG function because the locomotor CPG can be activated in the isolated spinal cord (Smith and Feldman 1987). Motor output is monitored with extracellular recordings of motoneuron activity from the ventral roots (VRs); higher lumbar VRs (L1–2) contain axons predominantly from flexor motoneurons (MNs), while lower lumbar VRs (L4–5) predominantly contain axons of extensor MNs (Fig. 1a). The CPG can be activated by a number of methods which non-specifically excite the isolated spinal cord. These include pharmacological manipulation (typically with a combination of *N*-methyl-d-aspartate (NMDA) and serotonin), sensory stimulation by tonic activation of dorsal roots, and tonic stimulation of the brainstem or specific activation of brainstem regions such as the parapyramidal region (Jordan 1998; Jordan et al. 2008). The elicited motor output shows alternation of left and right segmental VRs (e.g., left and right L2) combined with alternation of ipsilateral flexor (L2) and extensor (L5) MN activity (Fig. 1b). This is the fictive equivalent of walking.

Lesion studies have shown that the rodent CPG is distributed continuously along the lower



Locomotor Pattern Generation in the Rodent Spinal Cord, Fig. 1 Fictive locomotion in the isolated rodent spinal cord. (a) Experimental preparation, with extracellular recordings from the right and left L2 (flexor-dominated) and L5 (extensor-dominated) ventral roots of the lumbar spinal cord. Recordings from identified interneurons have been mostly performed in the rostral region.

(b) simultaneous extracellular recordings from left and right flexor (L2) and the left extensor (L5) ventral roots during fictive locomotion evoked by bath application of NMDA, serotonin (5-HT), and dopamine (DA). Alternation across the cord (IL2 and rL2) and between ipsilateral flexors and extensors (IL2 and IL5) are seen

thoracic and lumbar segments of the spinal cord (Kudo and Yamada 1987b; Kjaerulff and Kiehn 1996; Cowley and Schmidt 1997). Each segment, and even each hemisegment, is capable of generating a rhythmic output with appropriate MN phasing, showing that both the “clock,” or rhythm-generating component of the CPG, and the pattern-organizing network, which determines the phasing of MN activation, are widely and redundantly distributed over many spinal segments. Coordination of this distributed network requires ascending and descending interneuron coordinating pathways, which have not yet been identified in rodents.

Identified Interneurons in the Mouse Spinal Locomotor CPG

Recent studies of the developmental determination of spinal interneurons in mice have provided important tools to identify interneurons that may be components of the hind limb locomotor CPG (Stepien and Arber 2008; Goulding 2009; Gosgnach 2011; Kiehn 2011). These interneurons are identified by selective expression of defining transcription factors during development, which drives differentiation of the interneuron subtypes

from common precursors. Modern genetic techniques allow visualization of these neurons as well as manipulation of their activity and selective elimination. The major interneuron types implicated in locomotor CPG function are described below.

V0 Interneurons

This is a heterogeneous class of interneurons, defined by embryonic expression of *Dbx1*. Almost all of the V0 interneurons are commissural, sending their axons to synapse on neurons on the opposite side of the spinal cord. As expected, they play a role in left-right hind limb coordination. The V0 group has been subdivided into four subgroups based on subsequent transcription factor expression and location of origin (Gosgnach 2011; Kiehn 2011). All of these groups are rhythmically active during fictive locomotion in the neonatal mouse spinal cord, suggesting that they may participate in the locomotor CPG. V0_D interneurons comprise 70% of the V0 class; they are predominantly inhibitory, contralaterally projecting commissural interneurons (CINs). The V0_V class represents the majority of the remaining V0 neurons; they express *Evx1/2* and are excitatory glutamatergic CINs. The V0_C group (5% of the class) expresses *Evx1/2* and *Pitx2* and

generates cholinergic interneurons that have either commissural or ipsilaterally directed axons; these neurons are the source of the cholinergic C-boutons found on predominantly ipsilateral MNs (Zagoraïou et al. 2009). There is also a small group of $V0_G$ neurons which are glutamatergic, $V0_V$ -derived, Pitx2-positive neurons (Zagoraïou et al. 2009). Ablation of the $V0_V$, $V0_C$, and $V0_G$ groups in *Evx1* mutant mice did not affect fictive locomotion (Lanuza et al. 2004); selective loss of cholinergic function in the $V0_C$ group does not affect behavioral locomotion but may selectively reduce extensor muscle activity during swimming behavior (Zagoraïou et al. 2009). Ablation of the entire $V0$ population in *Dbx1* mutant mice leads to a disruption of left-right alternation, with drift between the two sides during neonatal fictive locomotion (Lanuza et al. 2004), and may enhance a hopping behavior in intact mice (Kiehn 2011). This emphasizes the major role of the commissural $V0$ interneurons in coordinating the networks on the left and right sides of the spinal cord.

V1 Interneurons

The $V1$ class is characterized by expression of *En1* and encodes ipsilaterally projecting inhibitory GABAergic/glycinergic interneurons. Only about 30% of these neurons have been physiologically characterized. Renshaw cells are detected by their selective expression of *En1* and calbindin. They are activated by motoneuron collateral axons and provide a negative feedback to inhibit the motoneurons that excite them. They are rhythmically active, in phase with either ipsilateral flexor or extensor motoneurons during fictive locomotion, and may help terminate MN activity in each cycle (Nishimaru et al. 2006). They receive rhythmic excitatory drive from MNs, which release both ACh and glutamate in the neonate (Nishimaru et al. 2005), and ipsilateral and contralateral rhythmic inhibition to shape their output. Another set of $V1$ neurons differentiates into Ia inhibitory interneurons; these are activated by muscle spindle afferents and monosynaptically inhibit antagonist muscles. Flexor- and extensor-related Ia inhibitory interneurons are mutually inhibitory. These neurons are

rhythmically active during the inhibitory phase of the antagonist MNs. Deletion or acute silencing of the entire $V1$ population causes a dramatic slowing of the motor pattern and prolongation of motoneuron firing during the cycle, with little effect on the motoneuron phasing (Gosgnach et al. 2006). This suggests that the $V1$ population has input to the rhythm-generating components of the locomotor CPG, though how this is effected is unknown; presumably this is one function of the 70% of $V1$ interneurons that are not yet identified.

V2 Interneurons

The $V2$ class is derived from progenitors that express *Lhx3* and contains several different subtypes. The $V2a$ class expresses *Chx10* and forms glutamatergic, excitatory ipsilaterally projecting interneurons. $V2a$ neurons have been shown to synapse onto *Evx1*-expressing $V0_V$ commissural interneurons and appear to play a role in regulation of left-right alternation (Crone et al. 2008). Some $V2a$ neurons also synapse onto ipsilateral motoneurons. Genetic deletion of $V2a$ interneurons has little motor phenotype at low locomotor frequencies, but as the frequency of walking increases, left-right alternation is much more variable than usual, and at high frequencies, a synchronous left-right bounding gait is observed which is never seen in control mice (Crone et al. 2008, 2009). A similar frequency-dependent effect is seen in the isolated spinal cord during fictive locomotion. $V2a$ interneurons are only weakly active at low frequencies but are increasingly active and recruited as the cycle frequency increases (Zhong et al. 2010). Thus, these neurons seem to play a major role to prevent a gait change to bounding at high cycle frequencies. Recent studies of the consequences of spontaneous motor deletions during fictive locomotion (described below) suggest that the $V2a$ interneurons can be split into two subgroups, one of which is related to the rhythm generator network in the CPG and drives CINs, while the other is an output path from the pattern formation networks of the CPG and provides some of the drive to ipsilateral motoneurons (Zhong et al. 2012). The $V2b$ class of interneurons expresses *GATA2/3* and forms ipsilaterally projecting inhibitory interneurons.

Little is known about this class, though it may form a small subset of the Ia inhibitory interneurons which are mostly generated from the V1 class (Kiehn 2011). A new class of V2c interneurons has recently been identified which are derived from the GATA3-expressing V2b lineage and express Sox1 (Panayi et al. 2010). At present, nothing is known of their roles in the locomotor CPG.

V3 Interneurons

The V3 class is derived from progenitors that express Sim1 (Zhang et al. 2008). These interneurons are excitatory and glutamatergic; most of them are commissural, though about 15% have ipsilateral axons. These neurons form synapses onto contralateral and ipsilateral motoneurons, Renshaw cells, and Ia interneurons. Selective silencing of V3 neurons caused a marked degeneration in the regularity of the fictive locomotor rhythm both in vivo and in the isolated neonatal spinal cord: there were marked variability in the duration of ventral root bursts and asymmetry in left and right bursting (Zhang et al. 2008). However, the basic rhythmic alternating motor pattern was conserved. Thus, V3 interneurons appear to be important in retaining the regularity of the motor rhythm, especially by coordinating left and right sides of the cord.

Hb9 Interneurons

The Hb9 transcription factor is predominantly expressed in motoneurons, but it is also expressed in a small set of interneurons located adjacent to the central canal in the ventral cord. These interneurons are rhythmically active during fictive locomotion and show endogenous oscillator activity when excited by NMDA and serotonin. This has led to suggestions that the Hb9 interneurons may be components of the rhythmogenic kernel of the locomotor CPG (Hinckley et al. 2005; Wilson et al. 2005; Brownstone and Wilson 2008; Brocard et al. 2010). However, during locomotor activity, their onset of firing lags behind that of ipsilateral motoneurons; during electrically stimulated fictive locomotion, they are only weakly active or silent after the first few cycles, despite continued strong rhythmic motoneuron

firing (Kwan et al. 2009). These results suggest that they may not be the sole rhythmic drive for locomotion, but they could participate in mediating the rhythm generator network's drive of lower-level interneurons and motoneurons.

dl6 Interneurons

This mixed class of commissural and ipsilaterally projecting interneurons arises from Lbx1-expressing progenitors in the dorsal embryonic spinal cord and migrates ventromedially to laminae VII/VIII, where the locomotor CPG is localized. Transmitter labeling suggests that these are a mixture of excitatory and inhibitory interneurons. They have been proposed to express Wt1 (Goulding 2009); an inhibitory subpopulation expresses Dmrt3 (Vallstedt and Kullander 2013), which may help identify them in future experiments. Physiological analysis of dl6 neurons (Dyck et al. 2012) showed that the majority are rhythmically active during fictive locomotion. Physiologically, they divide into two populations: one population possesses endogenous rhythmic capability, while the other fires rhythmically due to synaptic stimulation. Dyck et al. propose that the endogenously rhythmic neurons may be components of the rhythm-generating kernel of the CPG, along with other interneurons. Mutants lacking Dmrt3 show relatively normal fictive locomotion at low speeds but increasing lack of coordination both of left-right and ipsilateral flexor-extensor phasing at higher speeds; Vallstedt and Kullander (2013) propose that they may act as phase-lock neurons to control and secure a robust gait.

Organization of the Segmental CPG for Locomotion in Rodents

In preparation for a computational model of the neonatal rodent locomotor CPG, it is useful to try to place the identified interneurons into a context where they drive selected components of the motor pattern, including the mechanisms for rhythmogenesis, left-right hind limb coordination, and flexor-extensor alternation within a limb. Although these components have not been studied

in detail using mathematical models, schematics have been developed which could serve as templates for future modeling efforts.

Rhythmogenesis

As described in detail below, studies of the consequences of locomotor deletions during fictive locomotion have implicated the existence of a separate rhythm-generating network within the locomotor CPG, which provides the rhythmic drive for locomotion in the isolated spinal cord. The neuronal composition of the rhythm-generating kernel remains unknown, despite considerable work. Blockade of inhibitory synapses with a combination of GABA and glycine antagonists (Cowley and Schmidt 1995), or targeted deletion of the V1 inhibitory interneurons (Gosgnach et al. 2006), does not eliminate rhythmogenesis, though it can slow the rhythm frequency. A number of results suggest that ipsilaterally projecting glutamatergic neurons are essential for normal rhythmogenesis (Kiehn 2011); rhythmic activity can be generated by an isolated left or right hemicord and even an isolated hemisegment (Kudo and Yamada 1987a; Zhong et al. 2012). Blockade of glutamatergic synapses eliminates the rhythm, and optogenetic excitation of glutamatergic neurons is sufficient to activate locomotor activity (Hagglund et al. 2010). However, the identity of these glutamatergic neurons is not known. Elimination of either of the known glutamatergic interneurons, V2a and V3, affects the locomotor pattern but does not eliminate the rhythm (Crone et al. 2008; Zhang et al. 2008; Crone et al. 2009); neither of these neurons has intrinsic rhythmogenic properties. The Hb9 interneurons show endogenous rhythmicity and are rhythmically active during fictive locomotion; however, their weak and delayed activation during the locomotor cycle (trailing behind the ipsilateral motoneurons they are supposed to drive) suggests that they receive drive from other rhythmogenic neurons (Kwan et al. 2009). The dl6 interneurons contain a subpopulation which is endogenously rhythmic and shows loosely coupled rhythmic firing beginning before the onset of ipsilateral MN activity (Dyck et al. 2012). Dyck et al. propose that these interneurons

may participate in the rhythmic kernel of the locomotor CPG; selective inactivation of these neurons has not yet been accomplished. The rhythmogenic kernel could activate rhythmic firing due to endogenous bursting properties of the kernel interneurons (Brocard et al. 2010), which may only become manifest during activity-dependent changes in extracellular ion concentrations (Brocard et al. 2013). Alternatively, a network of mutually excitatory interneurons with spike frequency adaptation could form the kernel (Kiehn 2011). This network could arise from the combined interactions among several of the currently identified groups (none of which is essential) or an entirely new group that has not yet been specified.

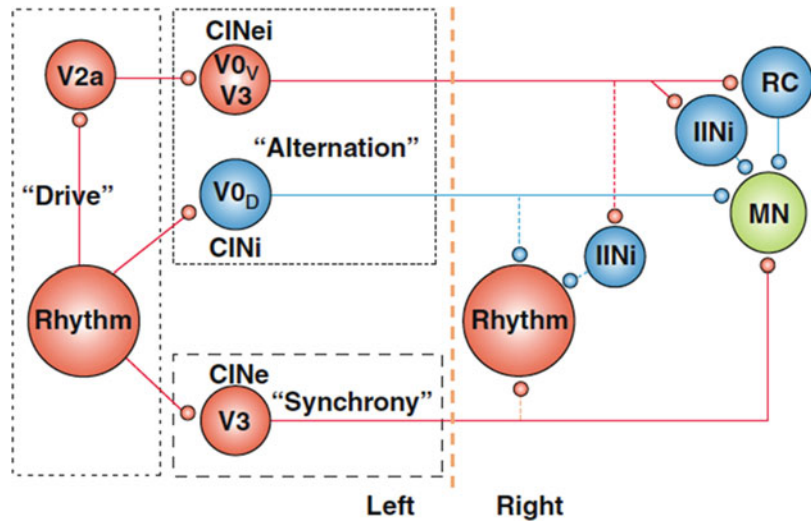
Left-Right Hind Limb Coordination

Through their detailed studies of the commissural interneurons (CINs), Kiehn and colleagues have generated the most sophisticated model for the coordination of left-right limb movements (Fig. 2; Kiehn 2011). Electrophysiological measurements demonstrated the existence of three separate commissural pathways to contralateral motoneurons (Butt and Kiehn 2003). A direct inhibitory pathway uses glycinergic CINs to monosynaptically inhibit contralateral MNs. A disynaptic inhibitory pathway uses glutamatergic CINs to drive contralateral GABAergic and/or glycinergic interneurons which inhibit MNs (Butt and Kiehn 2003; Quinlan and Kiehn 2007). This dual inhibitory commissural pathway could serve to maintain contralateral flexor (or extensor) MNs out of phase with ipsilateral flexor (or extensor) activity. A third pathway uses glutamatergic CINs to directly excite contralateral MNs. These could serve to couple activity of flexors with contralateral extensors; they also appear to coordinate synchronous left-right activity, as seen after blockade of glycinergic synapses with strychnine (Cowley and Schmidt 1995), or in mutants that reduce crossed inhibitory commissural projections (Kullander et al. 2003; Rabe et al. 2009).

In Fig. 2, the direct inhibitory pathway is proposed to be mediated by the V0_D class of inhibitory CINs, while the indirect inhibitory pathway is

Locomotor Pattern Generation in the Rodent Spinal Cord, Fig. 2

Schematic of organization of the commissural system that coordinates left and right limb movements. Excitatory interneurons and synapses are shown in red, while inhibitory interneurons and synapses are shown in blue. Only one half of the network is shown, with identified neurons on the left making synapses onto neurons on the right. See text for details (From Kiehn 2011)



thought to be mediated by the excitatory $V0_v$ and $V3$ commissural interneurons synapsing onto contralateral $V1$ interneurons, including Renshaw cells, Ia inhibitory interneurons, and other unidentified $V1$ neurons (Kiehn 2011). The monosynaptic excitatory pathway is proposed to be mediated by the $V3$ interneurons; in mutant $\text{Netrin-1}^{-/-}$ mice, the $V3$ interneurons are the major surviving commissural pathway, and the motor pattern is synchronous across the cord (Rabe et al. 2009). The $V3$ pathway could also help maintain alternation under normal conditions, as the flexor center on one side could use them to excite the contralateral extensor MNs (Butt and Kiehn 2003). The rhythmic drive to these CINs has not been fully elucidated. However, a subset of the excitatory $V2a$ interneurons form synapses onto members of the $V0_v$ neurons and could help drive the indirect inhibitory commissural pathway (Crone et al. 2008). This is not the only drive to this pathway, as locomotor behavior and fictive locomotion are essentially normal at low frequencies in mutants lacking these neurons; only at higher frequencies is left-right coordination disrupted, suggesting that other unidentified inputs provide the predominant drive to $V0_v$ CINs at lower speeds (Crone et al. 2009). Based on detailed studies of the spinal locomotor CPG in aquatic organisms, CINs are very likely to synapse on neurons in the rhythm-generating kernel of the CPG, as well as other interneurons in the

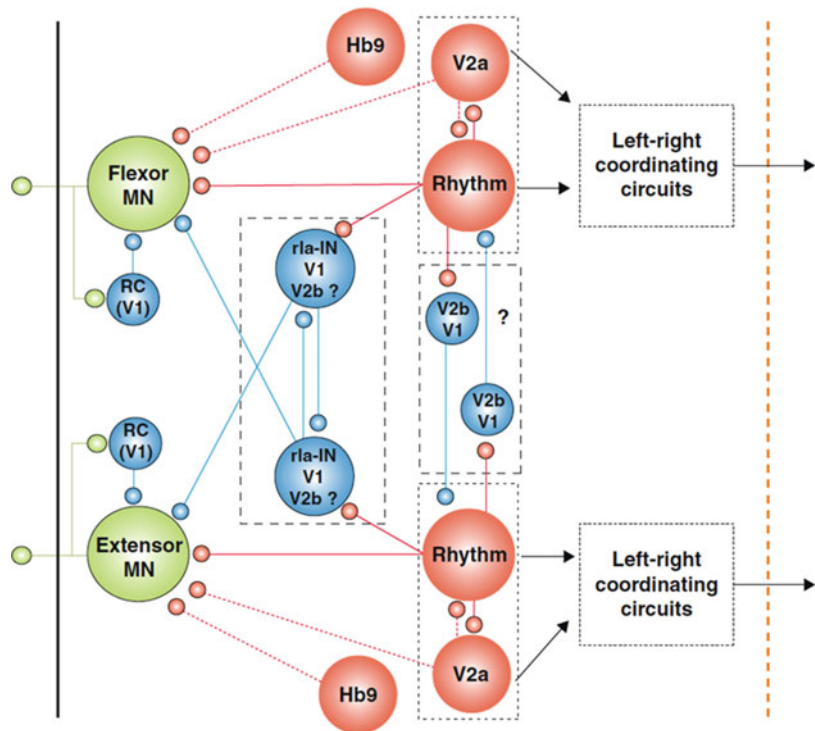
network. This is indicated in Fig. 2 by the dotted lines to the rhythm center on the right side.

Flexor-Extensor Alternation

The third component of the locomotor pattern is alternation between ipsilateral flexor (F) and extensor (E) motoneurons (Fig. 3; Kiehn 2011). F-E alternation is preserved in isolated hemicord preparations, suggesting that contralateral input, while it may support F-E alternation, is not essential (Kudo and Yamada 1987a; Zhong et al. 2012). Identified ipsilaterally projecting inhibitory interneurons include the heterogeneous $V1$ population and the $V2b$ neurons. In the $V1$ population, the Renshaw cells mainly provide recurrent inhibition to motoneurons (Alvarez et al. 2013). The Ia inhibitory interneurons mediate sensory crossed reflexes that can support F-E alternation: flexor-related Ia-INs inhibit extensor-related Ia-INs and MNs, and vice versa. Both Renshaw cells and IA-INs are rhythmically active during fictive locomotion (Nishimaru et al. 2006). Over 70% of the $V1$ population remains unidentified. Genetic deletion of the entire $V1$ population does not abolish F-E alternation, and some reciprocal inhibition is still detected in the absence of the IA-INs (Gosgnach et al. 2006). The inhibitory GATA 2/3-expressing $V2b$ interneurons could also participate in F-E phasing (Kiehn 2011). Finally, in the intact cord, CINs from the opposite side of the cord could help coordinate ipsilateral flexor-

Locomotor Pattern Generation in the Rodent Spinal Cord, Fig. 3

Schematic organization of the network ensuring flexor-extensor alternation during fictive locomotion. Excitatory interneurons are shown in red, while inhibitory interneurons are shown in blue. Only one side of the spinal cord is shown. See text for details (From Kiehn 2011)



extensor alternation by both excitatory inputs (which could couple contralateral flexors and extensors) and inhibitory inputs (which could simultaneously block contralateral homologs) (Butt and Kiehn 2003). These possible connections are shown in the schematic in Fig. 3.

Computational Models of the Rodent Locomotor CPG

While experimental data have generated many schematics of how the rodent locomotor CPG might be organized, there are few fully realized computational models that allow testing of hypotheses. Sherwood et al. (2011) presented an abstract model of the rodent locomotor CPG, based on interactions between coupled oscillators following the unit burst generator (UBG) approach of Grillner (1981). This model is described in detail in the entry by Sherwood in this volume, so will be only superficially described here. This model explores the consequences of variable levels and patterns of

excitatory and inhibitory connections between intrinsically oscillatory neurons, ranging from a half-center of two neurons with mutual excitation or inhibition to a 12-neuron network with bilateral flexor and extensor oscillators, commissural interneurons, and motoneurons. The neuron models are adapted from a conductance-based model of the respiratory network in the pre-Bötzinger complex (Butera et al. 1999); oscillatory neurons have an appropriate balance of persistent sodium currents (I_{NaP}) and leak currents and show spike frequency adaptation. The full 12-neuron model required significant tuning of synaptic weights and cellular properties to generate stable alternation. A more detailed analysis was made of smaller 2- and 4-neuron networks coupled with variable excitatory and inhibitory synapses. Of the 4-cell models, most rapid convergence to the locomotor pattern was obtained with strong inhibition between ipsilateral flexors and extensors, and different levels of inhibition between flexors (and extensors) on opposing sides of the cord, along with moderately strong excitatory connections between contralateral extensors and flexors;

however, the strength of the synapses had to be very high for significant convergence to the locomotor pattern. This model showed the strong dependence of the locomotor output on the ratios of strengths of synaptic connections between the components of the CPG network.

Rybak and colleagues explored a different set of models of the locomotor CPG, based on experimental studies of spontaneous deletions in locomotor activity during fictive locomotion. First studied in turtles (Stein 2008) and cats (Duysens 1977; Lafreniere-Roula and McCrea 2005; Duysens 2006) and more recently in mice (Zhong et al. 2012), deletions occur when one or more motor roots remain silent when they should fire a rhythmic burst of action potentials; for example, the flexor nerves innervating a limb may fall silent while the extensor nerves fire tonically. In cats, about two-third of these deletions resume activity an integer number of locomotor cycles later and are named “non-resetting” deletions; in neonatal mice, almost all of the deletions are non-resetting. This implies that a “clock” continues to tick during the deletion, when there is sometimes no rhythmic motoneuron output at all. The remaining deletions reset the phase of the next cycle, presumably through resetting the “clock.”

Rybak et al. (Rybak et al. 2006; McCrea and Rybak 2007) formulated a two-layer model of the cat locomotor CPG that could explain the origin of resetting and non-resetting deletions by positing two functional levels in the CPG: a half-center rhythm generator (RG), performing a “clock” function, and determining the rhythmic output of the system, and pattern formation (PF) networks that are driven by rhythmic input from the RG and coordinate the phasing and intensity of the different motoneuron groups to drive locomotion. This model is described in detail by Shevstova in this volume, so is only briefly described here. In this model, the RG is symmetrical, with a half-center organization of mutually inhibitory rhythmogenic flexor and extensor modules: these drive respective interneurons in the flexor and extensor PF networks (which are also mutually inhibitory) which in turn drive their motoneurons to generate the behavior. Resetting deletions,

which do not resume an integer number of cycles later, arise from errors in the RG network, while non-resetting deletions, which do resume an integer number of cycles later, arise from errors in the PF network. Only one limb was modeled, as the cat electrophysiological data were obtained only from one side of the animal.

Zhong et al. (2012) carried out a parallel physiological analysis of spontaneous locomotor deletions during transmitter-evoked fictive locomotion in the isolated neonatal mouse spinal cord. This preparation allowed simultaneous recordings from flexor and extensor ventral roots on both sides of the cord. The general outlines of the cat results were affirmed, but with some significant differences. First, nearly all (over 90%) of deletions were non-resetting, suggesting the stability of the RG network in this preparation. Second, the consequences of flexor and extensor deletions were quite different, suggesting a basic asymmetry in the CPG network organization. During a flexor ventral root deletion, extensor motoneurons fired continuously throughout the period that the flexors were silent. In contrast, during an extensor ventral root deletion, the flexor motoneurons continued to fire rhythmically at the same cycle frequency seen before the deletion. This suggests that the CPG has an asymmetric flexor-dominated architecture, as suggested initially by Pearson and Duysens (1976). Third, virtually all of the non-resetting deletions affected only one side of the cord: flexor and extensor bursts on the opposite side continued with no disturbance. Such uninterrupted contralateral bursting is not required for continuation of the ipsilateral rhythm during non-resetting deletions, however: non-resetting deletions could be observed with an isolated left or right hemicord, and even from a single isolated hemisegment.

The isolated neonatal mouse spinal cord also allowed recordings from identified spinal neurons from the L2 segment during non-resetting flexor deletions (Zhong et al. 2012). Ipsilateral motoneurons lost their rhythmic excitatory synaptic drive and fell silent during a flexor deletion; it appeared that neurons upstream of the motoneurons were falling silent during the deletion. Commissural interneurons, in contrast, continued to receive

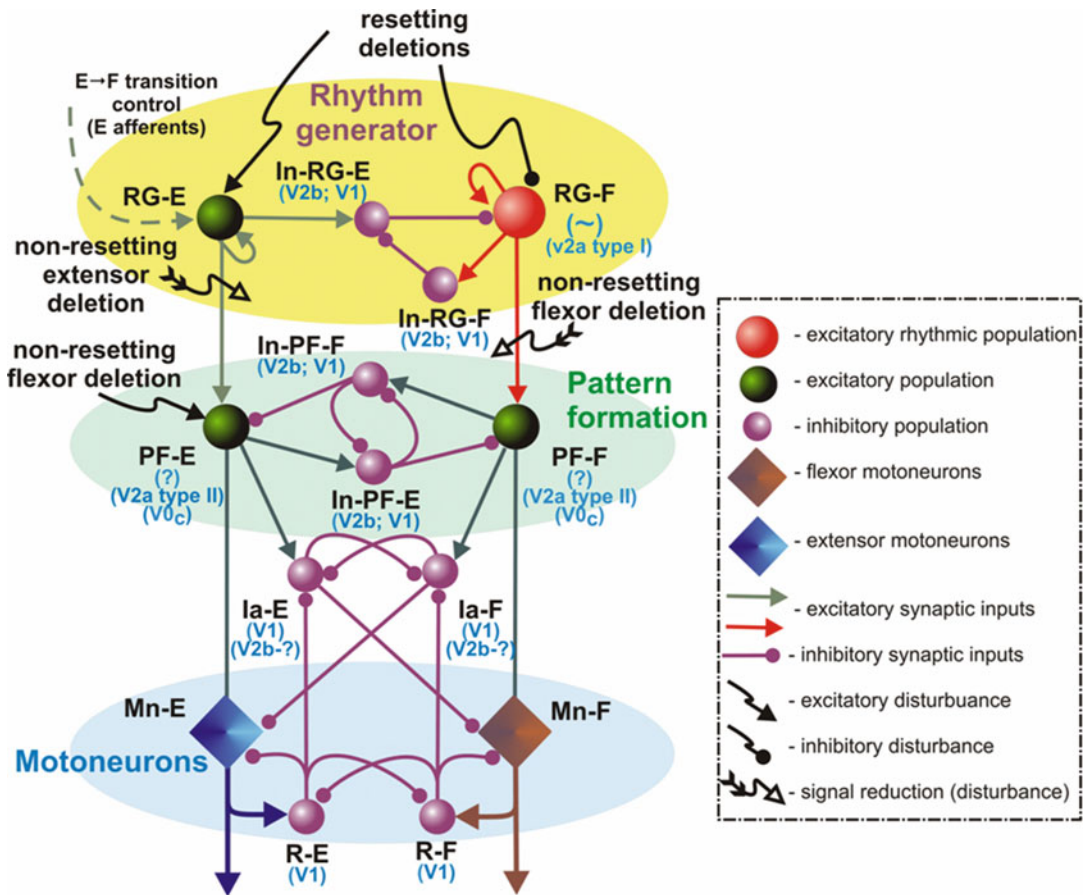
rhythmic synaptic drive and fired rhythmically during an ipsilateral motor deletion. The ipsilaterally projecting V2a interneurons fell into two distinct classes during ipsilateral flexor deletions. Type I V2a interneurons continued to receive rhythmic excitatory synaptic drive and fired rhythmically during the deletions. In contrast, the type II V2a interneurons acted like motoneurons: these V2a interneurons lost their synaptic drive and fell silent during the ipsilateral flexor deletion. The strength of synaptic drive to this class was significantly correlated with the strength of the motoneuron bursts. Zhong et al. (2012) hypothesize that the type I V2a INs synapse onto CINs (Fig. 2) and drive CIN activity, especially at higher frequencies; these neurons appear to continue to receive RG-related synaptic drive during non-resetting deletions and may thus be included in the RG network. The type II V2a INs appear to be outside the RG network as they lose rhythmic synaptic drive during non-resetting deletions; these may be output neurons that synapse on and help to drive motoneuron activity.

Rybak and colleagues revised their earlier model to incorporate these new data to generate a model of the rodent CPG (Zhong et al. 2012). In this model, the neurons are modeled by Hodgkin-Huxley-style differential equations for the soma and the dendrite compartments, with different distributions of active currents and their parameters in each compartment, following the methods of Booth et al. (1997). Synaptic interactions are modeled by a time-dependent conductance and the driving force. Each type of neuron is represented by a population of neurons (between 50 and 200 for each type), with variable initial parameters and synaptic strengths.

Initially, Rybak and colleagues modeled the CPG on only one side of the cord (Fig. 4). As with the cat model, this model has two layers, a rhythmogenic RG layer and an organizing PF layer. However, the organization of the RG layer is asymmetrical, to explain the asymmetric consequences of flexor versus extensor deletions in the mouse spinal cord. In the RG layer, only the flexor group (RG-F) neurons show intrinsic rhythmic activity, produced by an I_{NaP} -dependent mechanism with mutual synaptic excitation among

members of the group. The extensor group (RG-E) does not have sufficiently large I_{NaP} to be endogenously rhythmic and fires tonically. These groups drive major populations in the PF network (PF-F and PF-E) which drive locomotor activity in flexor and extensor motoneuron populations, respectively. These reciprocally inhibit one another through inhibitory interneurons. The PF-F group receives rhythmic drive from the rhythmogenic RG-F pacemakers, while the PF-E group is tonically excited by the RG-E group and fires rhythmically due to rhythmic inhibition from the PF-F group. This model can produce robust locomotor-like activity at each level of the network.

The model was then extended to include both sides of the spinal cord, with left and right RG networks connected by inhibitory commissural interneuron pathways between the flexor RG half-centers, excitatory commissural pathways between flexor centers, and contralateral extensor centers, as well as weaker flexor-flexor and extensor-extensor pathways that could maintain synchrony in the absence of inhibition (Fig. 5). Exploration of this model showed that it could reproduce the experimental deletion results (Zhong et al. 2012). For example, hemisection of the cord (modeled by elimination of commissural pathways) slows the cycle frequency by half while maintaining flexor-extensor phasing; analysis showed that the slowing arose primarily from loss of excitatory drive from the contralateral RG-E populations to the rhythmogenic ipsilateral RG-F populations. The model could reproduce the asymmetrical effects of deletions described above. For example, non-resetting flexor deletions resulted in ipsilateral tonic extensor activity but unchanged contralateral activity; this could be obtained by simulated suppression of excitatory input from the ipsilateral RG-F population to the ipsilateral PF-F population; this relieved the PF-E population from rhythmic inhibition to allow it to tonically drive the extensor motoneurons. Simulated loss of tonic input from the nonrhythmic RG-E population silenced the PF-E and extensor motoneuron populations with no effect on rhythmic drive from the RG-F population to the PF-F and flexor motoneurons. These deletion results



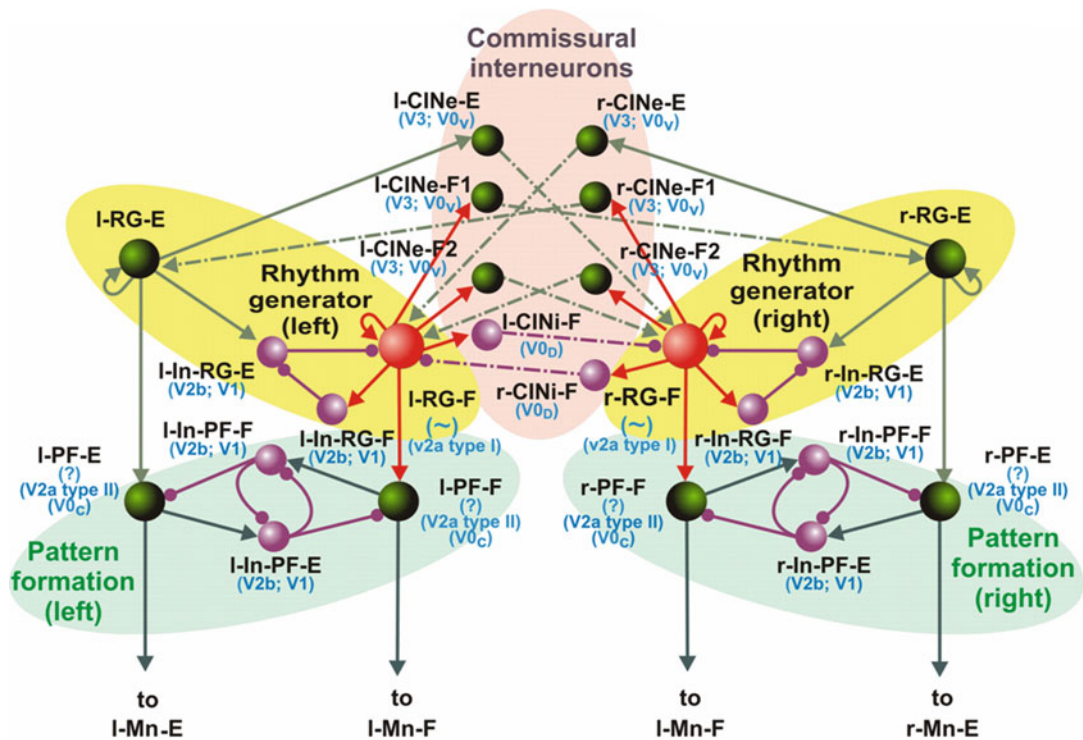
Locomotor Pattern Generation in the Rodent Spinal Cord, Fig. 4 Two-layer computational model of the rodent CPG for one hind limb. The *RG* rhythm generator layer is shown in *yellow*, while the *PF* pattern

formation layer is shown in *blue*. Arrows show excitatory synapses, while *circles* show inhibitory synapses. See text for details (Modified from Zhong et al. 2012)

could also be obtained by loss of synaptic drive at other points in the network. Resetting deletions, which are rare in mice, could be simulated by perturbations at the RG level, for example, temporary inhibition of the rhythmic RG-F population; this is predicted to affect the contralateral population as well.

Preliminary attempts have been made to place the identified interneuron classes within the formal organization of the asymmetric locomotor CPG model. Type I V2a interneurons, which continue to oscillate during non-resetting deletions, are modeled to act within the RG network, though since they do not have rhythmogenic properties they are probably driven by other neuronal

populations. Type II V2a interneurons, which lose synaptic drive and fall silent during non-resetting deletions, are modeled to be among the output paths from the PF network to motoneurons, though they are not the only population of neurons to do so. As described above, many of the other defined interneuron classes are heterogeneous and will require additional molecular analysis to subdivide them into single classes. However, among the neurons that could act within the RG network are the endogenously rhythmic subset of dI6 interneurons and a subset of Hb9 interneurons. Among outputs to motoneurons are another subset of Hb9 interneurons. V1 and V2b interneurons form the Renshaw cells and Ia inhibitory INs in the output



Locomotor Pattern Generation in the Rodent Spinal Cord, Fig. 5 Two-layer bilateral model of the rodent CPG for locomotion. The RM rhythm generator layer is shown in yellow, the PF pattern formation layer is

shown in blue, and the commissural network is in pink. Arrows show excitatory synapses, while circles show inhibitory synapses. See text for details (Modified from Zhong et al. 2012)

layer from the PF network; they could also form the inhibitory interneurons that are modeled in the PF and RG networks. Finally the commissural pathways are composed of inhibitory V0 and excitatory V3 interneurons. The model provides predictions of the patterns of synaptic drive that interneurons at different points in the network will receive, both under normal conditions and during deletions of various kinds. Much further work will need to be done to measure these synaptic interactions and verify or correct these predictions.

Future work on models of the rodent spinal locomotor CPG will be able to generate hypotheses for the roles of the various subsets of the cardinal identified interneuron classes and of their synaptic interactions. At present, our knowledge of the interneurons, and the existence and properties of synapses between them, is fragmentary but is the focus of much concerted experimental effort. The interaction of modeling with

experimental work should rapidly push forward our understanding of the rodent locomotor CPG, which can serve as a model for other, more complex neural networks in the nervous system.

Cross-References

- [Computational Analysis of Rodent Spinal CPG](#)
- [Two-Level Model of Mammalian Locomotor CPG](#)

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Long Term Depression in the Granule Cell-Purkinje Cell Synapse

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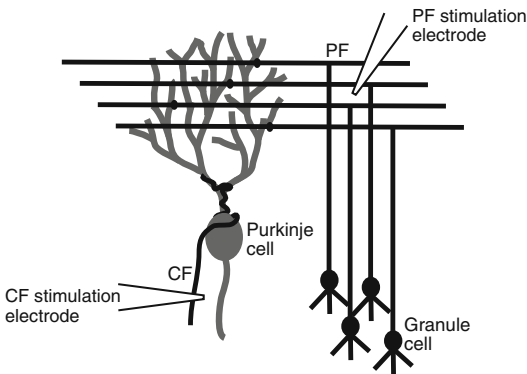
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Synonyms

[Cerebellar long term depression](#); [Cerebellar LTD](#); [Long term synaptic depression at the parallel fiber-Purkinje cell synapse](#)

Definition

Long-term depression (LTD) in the granule cell-Purkinje cell synapse is a reduction of synaptic transmission efficacy, which lasts for hours or longer. The synaptic transmission at this synapse is mediated via α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), a member of the ionotropic glutamate receptors, and the direct cause of LTD is a reduction in the numbers of postsynaptic AMPARs. The traditional stimulation to trigger LTD is simultaneous and repeated activation of two excitatory inputs onto Purkinje cells, parallel fibers (PFs) and climbing fibers (CFs), which are neuronal projections originated from granule cells and neurons in inferior olivary nucleus, respectively.



Long Term Depression in the Granule Cell-Purkinje Cell Synapse, Fig. 1 A schematic illustration of two excitatory inputs onto Purkinje cells, CF and PF. Traditional stimulation to induce LTD is simultaneous and repeated stimulation of CF and PF through glass electrodes

Detailed Description

The LTD at synapses between PFs, axons of granule cells, and Purkinje cells (Fig. 1) was first discovered in the 1980s, and the observations of LTD have led to the Marr-Albus-Ito theory (Marr 1969; Albus 1971; Ito 1986), in which some forms of cerebellum-dependent motor learning depend on long-term changes in synaptic transmission at these synapses. Long-term changes, reduction (LTD) or potentiation (LTP), in synaptic transmission efficacy, which is so-called long-term synaptic plasticity, have been observed in a variety of synapses in the brain. Indeed, the synapses between PFs and Purkinje cells could undergo not only LTD but also LTP (Lev-Ram et al. 2002). Such individual forms of long-term synaptic plasticity in several brain areas have their own molecular mechanisms or characteristic features, even though the final outcomes are either reduction or potentiation in synaptic transmission efficacy. Roles of long-term synaptic plasticity are further complicated, although they are mainly thought to be related to learning and memory. Therefore, it is important to know details of individual forms of long-term synaptic plasticity.

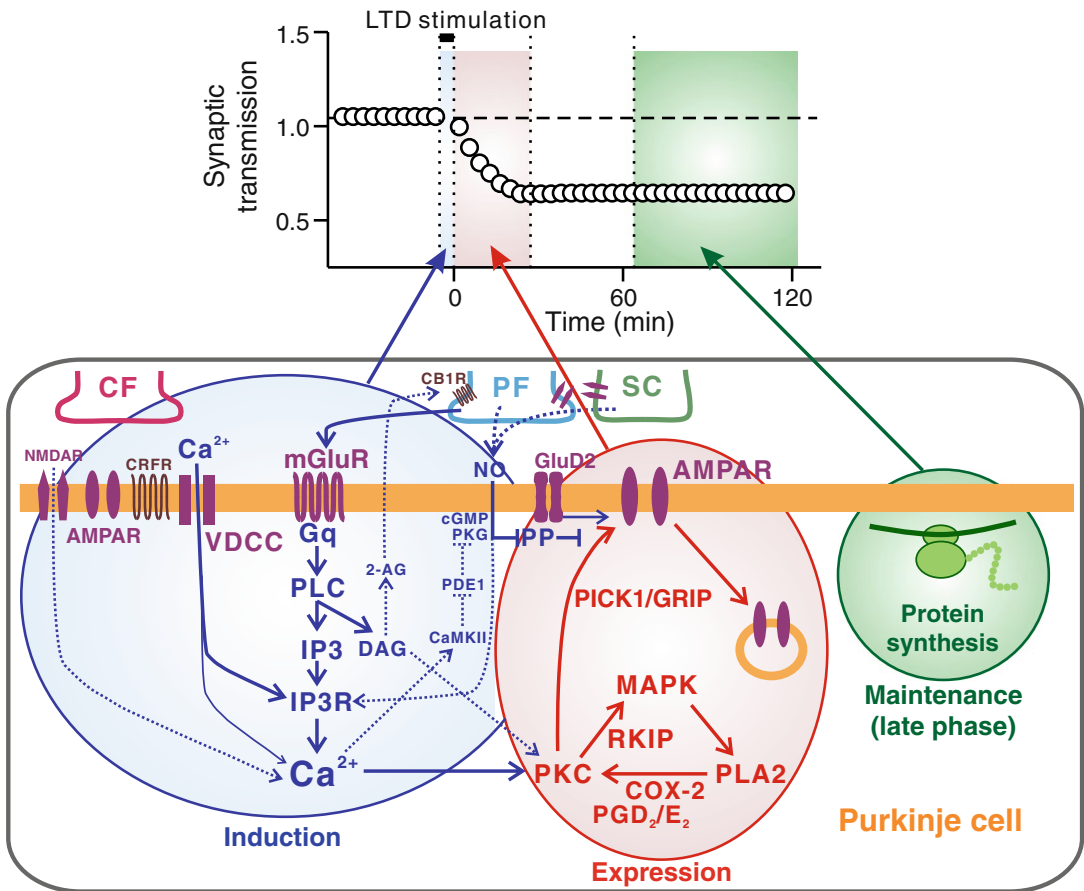
There are several ways to describe details of LTD in the granule cell-Purkinje cell synapse, such as history of LTD, mathematical description of LTD, or argument regarding the behavioral

functions of LTD. In this description, LTD will be explained mainly from a standpoint of signaling mechanisms and molecules related to the LTD (Fig. 2).

Stimuli to Trigger LTD

Based on a theory of Albus and Marr (Marr 1969; Albus 1971), who postulated that CFs, another excitatory input onto Purkinje cells (Fig. 1), provide a teaching signal that induces long-term changes in the efficacy of PF-Purkinje cell synapses, stimulation to induce synaptic plasticity at these synapses was explored. Then it was discovered that LTD can be induced when simultaneous and repeated stimulations of PFs and a CF were applied in vivo or in cerebellar slice preparations. In most cases, these stimulations are applied electrically via glass electrodes (Fig. 1). Optimal conditions of such stimulation were also explored. Karachot et al. tested several conditions of stimulation in slice preparations, and they found that simultaneous stimulation of PF and CF at 1 Hz with 300 pulses most effectively induced LTD in terms of amounts and probability of depression (Karachot et al. 1994). Interestingly, similar stimulation with more pulses (500 pulses) is much less effective than 300 pulses. Further, timing between PF and CF stimulation seems to be critical, although precise interval is varied depending on other parameters of stimulation. Specifically, three studies have shown that LTD was effectively induced when PF stimulation preceded CF stimulation with approximately 100 ms, but LTD is not observed by opposite order of stimulation (Chen and Thompson 1995; Wang et al. 2000a; Safo and Regehr 2008). It should be noted that PF stimulation paired with CF stimulation to induce LTD is composed of one pulse in some cases but of a few pulses in other cases. Considering the existence of optimal conditions, the temporally and quantitatively precise regulation of signaling mechanisms seems to be important for triggering LTD.

The LTD described here is a long-term reduction of synaptic transmission at PF-Purkinje cell synapses, so that synaptic transmission has to be measured for the LTD study. At synapses between

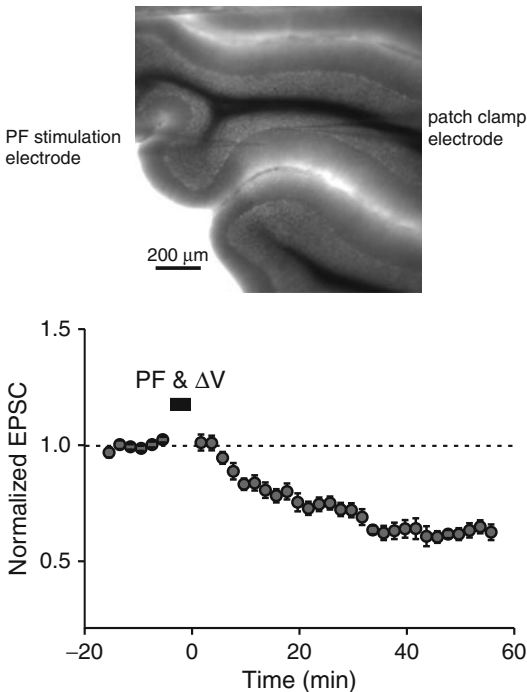


Long Term Depression in the Granule Cell-Purkinje Cell Synapse, Fig. 2 A schematic illustration of time course of LTD and signaling mechanisms of LTD induction, expression, and maintenance. See text for abbreviations

PF and Purkinje cells, AMPARs mediate synaptic transmission. Since AMPARs are nonselective cation channels, excitatory postsynaptic potential or current (EPSP or EPSC) can be recorded when AMPARs are activated by glutamate released from PFs. Usually, EPSP or EPSC is recorded by electrophysiological methods, such as extracellular recordings or patch clamp recordings.

Even though paired stimulation of PFs and CFs has been the traditional stimulation that triggers LTD, as understanding of signaling mechanisms of LTD progressed, other stimulations, which can bypass several pathways or directly activate signaling molecules, have been used to induce LTD. For example, depolarizing pulses of Purkinje cells through patch clamp pipette can be used instead of

CF stimulation (Fig. 3; Crépel and Jaillard 1991; Konnerth et al. 1992), because CF stimulation actually results in the depolarization of Purkinje cells that is necessary for LTD. In addition to in vivo or in slice preparations, LTD was observed in cultured Purkinje cells, where there are no longer intact synaptic connections. In order to trigger LTD in cultured Purkinje cells, glutamate receptor agonists were applied while depolarizing Purkinje cells, probably on the idea that the agonists could mimic PF stimulation (Linden et al. 1991). Glutamate has been also utilized to apply LTD stimulation onto whole cerebellar slices, when more tissue samples are required for analyses, such as biochemical, histological, or molecular biological analyses. In these experiments,



Long Term Depression in the Granule Cell-Purkinje Cell Synapse, Fig. 3 An image of cerebellar slice showing the position of patch clamp electrode onto a Purkinje cell and the PF stimulation electrode (*top*), and time course of cerebellar LTD triggered by PF stimulation paired with Purkinje cell depolarization at 1 Hz for 5 min (*bottom*)

slices are treated with glutamate in high-potassium solutions, and such treatment, which can be called chemical LTD stimulation, indeed triggers LTD (Tanaka and Augustine 2008). Moreover, direct increase or activation of signaling molecules, such as increase in intracellular calcium (Ca^{2+}) concentrations or activation of protein kinase C (PKC), could induce LTD (Linden and Connor 1991; Lev-Ram et al. 1997a; Kondo et al. 2005; Tanaka et al. 2007). These alternative stimulations are convenient for certain experimental conditions, effective to show the importance of a specific signaling molecule, or useful to determine the interactions of molecules working for LTD. However, results obtained in different conditions or by different stimulations are sometimes inconsistent. In order to reconcile discrepancy and to fully understand LTD, we may need to consider whether the observations in

certain conditions can be generalized in more physiological conditions.

Time Course of LTD

Long-term synaptic plasticity, including cerebellar LTD, is generally composed of three temporal phases: induction, expression, and maintenance. The synaptic stimulation that triggers LTD usually lasts for a few to several minutes. During this period, the stimulation elevates or activates many signaling molecules, and this period of triggering LTD can be defined as the induction phase. The signaling molecules, which are elevated or activated during the stimulation, sequentially activate downstream molecules and finally cause the reduction of AMPAR numbers at synapses. This period when depression is in process is defined as the expression phase. The time course of expression varies according to stimulus conditions or preparations. In some cases, expression is rapid, so that depression reaches maximum level in a few minutes after the end of stimulation. In other cases, slow and gradual expression, which lasts for 20–60 min, can be observed. Mechanisms that determine the time course of LTD expression are not yet understood. Once depression reaches a maximum level, the depressed level is maintained for a few hours or even longer. The maintenance phase is often divided into early and late phases, latter of which is thought to depend on newly protein synthesis. It is not known whether the depression is terminated and synaptic transmission is returned to the original level after a certain period.

Fast Signals Required for the Induction of LTD

The well-studied and important signals required for the induction of cerebellar LTD are increases in postsynaptic Ca^{2+} concentrations ($[\text{Ca}^{2+}]_i$). The importance of $[\text{Ca}^{2+}]_i$ increase is first demonstrated in the experiments, where Ca^{2+} chelators, EGTA or BAPTA, were introduced into postsynaptic Purkinje cells (Sakurai 1990; Shibuki and

Okada 1992; Konnerth et al. 1992). Such introduction of Ca^{2+} chelators blocks LTD. As mentioned above, the traditional stimulation that triggers LTD at least in cerebellar slice preparations can be the simultaneous and repeated stimulation of CFs and PFs. The stimulation of CFs or PFs causes increases in $[\text{Ca}^{2+}]_i$ in Purkinje cells (Konnerth et al. 1992; Eilers et al. 1997; Wang et al. 2000a). One Purkinje cell receives synaptic inputs from only one CF, but a pair of CF and Purkinje cell makes a few hundreds of synaptic connections. Thus, stimulation of CF activates many AMPARs at the CF and Purkinje cell synapses, so that the CF stimulation strongly depolarizes the innervated Purkinje cell, which in turn activates voltage-dependent Ca^{2+} channels (VDCCs) and induces Ca^{2+} entry through these channels (Ross and Werman 1987; Miyakawa et al. 1992; Konnerth et al. 1992). In contrast, one PF makes only one synapse onto one Purkinje cell, while about 150,000 PFs innervate a single Purkinje cell. At synapses between PFs and Purkinje cells, metabotropic glutamate receptor 1 (mGluR1) exists (Nusser et al. 1994; Baude et al. 1993; Petralia et al. 1998; López-Bendito et al. 2001) and is required for triggering LTD (Aiba et al. 1994; Conquet et al. 1994; Ichise et al. 2000). The mGluR1 is a type of receptor that is coupled with Gq-proteins, whose activation produces inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) via phospholipase C (PLC). The IP3 produced by PF activity binds and activates IP3 receptors on the endoplasmic reticulum, which is an intracellular Ca^{2+} store, so that $[\text{Ca}^{2+}]_i$ is increased by Ca^{2+} release through IP3 receptors. Such Ca^{2+} release from IP3 receptors is required for LTD (Khodakhah and Armstrong 1997; Inoue et al. 1998; Finch and Augustine 1998; Miyata et al. 2001). Although these pathways of $[\text{Ca}^{2+}]_i$ increase by PF and CF stimulation are superficially distinct, they also cooperate to induce larger $[\text{Ca}^{2+}]_i$ increase. Because paired stimulation of CFs and PFs, but not the stimulation of only CFs or PFs, induces LTD, it has been studied how the coincidence activation of two synaptic inputs is detected. One of the coincidence detection mechanisms is synergistic activation of IP3 receptors by IP3 and

Ca^{2+} (Wang et al. 2000a; Doi et al. 2005; Sarkisov and Wang 2008), which are produced by PF stimulation and are entered through VDCCs after CF stimulation, respectively. Thus, it seems that $[\text{Ca}^{2+}]_i$ increase can reach to the level that is enough for LTD induction, when stimulations of PFs and CFs are paired.

The question was how large $[\text{Ca}^{2+}]_i$ increase is required for LTD. Because $[\text{Ca}^{2+}]_i$ increase triggered by synaptic stimulation is temporally complex and other signaling pathways activated by such stimulation may affect LTD, it is difficult to define the precise $[\text{Ca}^{2+}]_i$ increase required for LTD. Nevertheless, several efforts have been made to know the $[\text{Ca}^{2+}]_i$ increase by PF or CF stimulation. $[\text{Ca}^{2+}]_i$ increase evoked by CF stimulation is reaching around several hundred nanomolar in a wide area of dendrites (Wang et al. 2000a; Schmidt et al. 2003; Sarkisov and Wang 2008). Although $[\text{Ca}^{2+}]_i$ increase evoked by PF stimulation vary depending on the number and frequency of stimulation, $[\text{Ca}^{2+}]_i$ increase produced by a single or a few pulses of PF stimulation, which is often used to induce LTD, could also reach several hundred nanomolar in a part of dendrites where stimulated PF innervates (Finch and Augustine 1998; Wang et al. 2000a). In contrast, paired stimulation of CF and PF produces supralinear $[\text{Ca}^{2+}]_i$ increase, reaching a few micromolar to 10 μM (Wang et al. 2000a; Brenowitz and Regehr 2005), which is higher than the sum of $[\text{Ca}^{2+}]_i$ increase produced by PF and CF stimulation alone. Even though the $[\text{Ca}^{2+}]_i$ increase evoked by single paired stimulation is transient, presumably a few hundred milliseconds, repetitive stimulation could also produces gradually elevated $[\text{Ca}^{2+}]_i$ plateau (Eilers et al. 1995, 1996; Takechi et al. 1998; Finch and Augustine 1998; Wang et al. 2000a), so that repetitive and transient $[\text{Ca}^{2+}]_i$ increase is superimposed on such $[\text{Ca}^{2+}]_i$ plateau.

In order to define precise $[\text{Ca}^{2+}]_i$ required for triggering LTD, relationships between $[\text{Ca}^{2+}]_i$ increase and LTD were determined by using caged Ca^{2+} , which can release Ca^{2+} when photolysis is applied (Tanaka et al. 2007). The monotonic increase in $[\text{Ca}^{2+}]_i$ was produced by the photolysis of caged Ca^{2+} introduced into

Purkinje cells, and the resultant LTD was measured. The relationships can be described by Hill equation with Hill coefficient of around 5, so that there is a threshold of $[Ca^{2+}]_i$ for triggering LTD. Further, in this series of experiments, several durations of $[Ca^{2+}]_i$ increase were tested. It was found that the $[Ca^{2+}]_i$ threshold of peak amplitude is higher when shorter duration of $[Ca^{2+}]_i$ increase is applied. In case that 0.5, 1, 15, or 30 s duration of photolysis was applied, $[Ca^{2+}]_i$ threshold is 2.8, 1.8, 1.1, or 0.9 μ M, respectively. This suggests that peak $[Ca^{2+}]_i$ is not an absolute determinant for LTD. In contrast, more integrated $[Ca^{2+}]_i$ is necessary when longer duration of $[Ca^{2+}]_i$ increase is applied. The relationship between the threshold level of integrated $[Ca^{2+}]_i$ for LTD and duration of $[Ca^{2+}]_i$ increase fits to the leaky integrator property, similar to the “leaky integrate and fire” concept used in models of neuronal electrical signaling (Knight 1972; Fohlmeister et al. 1977). The leaky integrator for Ca^{2+} -triggered LTD can be expressed by an equation:

$$\tau \frac{dx}{dt} = -x + a[Ca^{2+}]_i(t)$$

where τ is the time constant of the integration, x is the amount of a hypothetical downstream signal that transduces Ca^{2+} into LTD, and a is a scaling factor representing the efficacy of the integrator in converting Ca^{2+} into x . This suggests that, while $[Ca^{2+}]_i$ increase activates molecules that positively work for LTD, negative regulators seem to gradually become active during longer duration of $[Ca^{2+}]_i$ increase. The leaky integrator property of LTD triggering may be the reason why 500 pulses of paired stimulation of PF and CF are less effective than 300 pulses (Karachot et al. 1994). Thus, the analysis using caged Ca^{2+} defined $[Ca^{2+}]_i$ required for LTD, which depends on the duration of $[Ca^{2+}]_i$ increase.

In addition to Ca^{2+} -related signals described above, the stimulation of PF and CF could elevate or activate other signals that are superficially independent to these Ca^{2+} signals. PF stimulation can trigger the release of nitric oxide (NO) from PF terminals or stellate cells (Shibuki and Okada

1991; Lev-Ram et al. 1997b; Namiki et al. 2005), the latter of which are interneurons in the molecular layer. Several studies demonstrated that NO is involved in LTD (Ito and Karachot 1990; Cr  pel and Jaillard 1990; Shibuki and Okada 1991; Daniel et al. 1993; Lev-Ram et al. 1995; Reynolds and Hartell 2001). Although NO cannot induce LTD by itself, NO cooperates with sub-threshold level of Ca^{2+} , which is not sufficient to induce LTD (Lev-Ram et al. 1995, 1997a), so that NO is considered to play a permissive role for LTD. Considering that NO is generally known to activate guanylate cyclase (GC) (Jaffrey and Snyder 1995; Calabrese et al. 2007), the roles of NO for LTD are thought to be as follows. NO released from PF or stellate cells diffuses into Purkinje cells and activates GC, which produces cyclic guanosine monophosphate (cGMP). The cGMP activates cGMP-dependent protein kinase (PKG), which reduces protein phosphatase 2A (PP2A) activities. Phosphorylation of molecules, such as AMPARs, is necessary for LTD, so that the reduction of PP2A activities positively works for LTD. In fact, inhibition of GC or PKG blocked LTD, and inhibition of PP2A itself could induce synaptic depression (Ito and Karachot 1990; Hartell 1994; Reynolds and Hartell 2001; Endo et al. 2003; Launey et al. 2004). These results suggest that this NO-mediated pathway is likely one mechanism working for LTD induction. Further, because it is reported in other types of cells that cGMP facilitates Ca^{2+} release from IP3 receptors via PKG activation (Guihard et al. 1996; Rooney et al. 1996; Wagner et al. 2003) and the IP3-dependent Ca^{2+} release is critical for cerebellar LTD (Khodakhah and Armstrong 1997; Inoue et al. 1998; Finch and Augustine 1998; Miyata et al. 2001), a pathway of NO, cGMP, and PKG may also contribute to induce higher $[Ca^{2+}]_i$ increase. Thus, NO may have dual roles for LTD induction.

Another molecule released upon the PF stimulation is endocannabinoid, which is known as a retrograde messenger. In the cerebellar cortex, 2-arachidonoyl glycerol (2-AG) is released from Purkinje cells (Maejima et al. 2005). Because local $[Ca^{2+}]_i$ increase due to AMPAR-mediated depolarization and mGluR1

activation cooperatively produce endocannabinoid (Maejima et al. 2001; Brown et al. 2003; Marcaggi and Attwell 2005), relatively strong PF stimulation, such as a brief burst of PF stimulation, seems to trigger the release of 2-AG. 2-AG is produced by diacylglycerol lipase from DAG (Sugiura et al. 2006), which is produced by PLC after the activation of mGluR1 and Gq-protein. Because the PLC, specifically PLC β 4, is also sensitive to Ca²⁺, strong PF stimulation activates PLC β 4 via Gq-protein and Ca²⁺ and in turn leads to 2-AG release via DAG production (Maejima et al. 2005). The function of endocannabinoid as a retrograde messenger has been well studied to explain the mechanism of short-term synaptic depression at PF and Purkinje cell synapses (Maejima et al. 2001; Brown et al. 2003; Marcaggi and Attwell 2005), which depends on the reduction of glutamate release via presynaptic cannabinoid receptor type 1 (CB1R) (Yoshida et al. 2002). Endocannabinoid signaling is also involved in cerebellar LTD, because LTD was impaired in the presence of a CB1R antagonist or a diacylglycerol lipase inhibitor or in CB1R knockout mice (Safo and Regehr 2005). Further, LTD was not observed even in mice lacking CB1Rs selectively in cerebellar granule cells (Carey et al. 2011). It is known that LTD is postsynaptically induced, so that it remains elucidated how retrograde endocannabinoid signaling and presynaptic CB1Rs affect postsynaptically induced LTD.

Corticotropin-releasing factor (CRF) exists in the CF (Palkovits et al. 1987; Sakanaka et al. 1987; Cummings et al. 1994), so that CRF can be released from CF terminals. On the other hand, mRNA of CRF receptors is detected in Purkinje cells (Chang et al. 1993; Potter et al. 1994). A study demonstrated that antagonists of CRF receptors blocked not only LTD induced by conjunctive stimulation of PF and CF but also LTD induced by the pairing of PF stimulation with Purkinje cell depolarization (Miyata et al. 1999). Further, LTD was not observed in animals, whose CF was chronically destructed, but it was restored by CRF replenishment (Miyata et al. 1999). According to these results, it is

thought that spontaneously released CRF from CF, rather than CRF released by CF stimulation during LTD induction, plays a permissive role in LTD.

As described above, DAG is produced via mGluR activation. Although there has been no direct evidence showing that DAG produced by mGluR activation is truly required for LTD, DAG may cooperate with Ca²⁺ to activate downstream molecules, such as PKC, or may contribute to produce 2-AG.

Mechanisms Required for Expression of LTD

The expression of LTD correlates with a reduction in the number of synaptic AMPARs, and the reduction is due to the enhancement of AMPAR internalization by clathrin-mediated endocytosis (Wang and Linden 2000). The enhancement of AMPAR internalization is triggered by PKC-dependent phosphorylation of GluR2, an AMPAR subunit, at serine 880 (Ser880) (Matsuda et al. 2000; Xia et al. 2000; Chung et al. 2003). While dephosphorylated GluR2 interacts with glutamate receptor-interacting protein/AMPA receptor-binding protein (GRIP/ABP), which is the postsynaptic density-95/discs-large/zonula occludens-1 (PDZ) domain-containing protein, via PDZ-binding motif of GluR2, such interaction is prevented by the PKC-dependent phosphorylation of GluR2 (Matsuda et al. 2000; Xia et al. 2000). The unbinding of GRIP/ABP itself or the following interaction of phosphorylated GluR2 with another PDZ domain-containing protein, PICK1, leads to the endocytosis of AMPARs (Steinberg et al. 2006).

Among several subtypes of PKC, PKC α has been shown to be responsible for the LTD, because knockdown of PKC α blocked LTD (Leitges et al. 2004). Given that PKC α is a Ca²⁺-dependent form of PKC, it is likely that PKC α is activated by Ca²⁺. However, even though such a Ca²⁺-dependent PKC α activation might be sufficient for the AMPAR internalization during rapid expression of LTD, it cannot explain the gradual expression of LTD, which is often observed,

because $[Ca^{2+}]_i$ increase is transient (Konnerth et al. 1992; Eilers et al. 1997; Tanaka et al. 2007). To fill the temporal gap, a positive feedback kinase loop is shown to be responsible for the prolonged PKC activation and consequently gradual expression of LTD (Kuroda et al. 2001; Tanaka and Augustine 2008). This loop includes several molecules. PKC phosphorylated Raf-kinase inhibitory protein (RKIP). RKIP usually binds and inhibits Raf1 and MEK, which are upstream kinases of mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/Erk), but phosphorylated RKIP dissociates from these molecules, so that the Raf1-MEK-MAPK pathway can be activated (Yamamoto et al. 2012). MAPK directly phosphorylates and activates phospholipase A2 (PLA2), and PLA2 produces arachidonic acid, which can activate PKC directly or indirectly via cyclooxygenase-2 and prostaglandin D₂ or E₂ (Le et al. 2010). Thus this loop can extend the timing of PKC activation, so that LTD is gradually expressed.

As described above, it is well known that PKC-dependent phosphorylation of GluR2 AMPARs is important for LTD. However, it is not known whether other molecules in the positive feedback loop have roles in LTD, except for working as components of this loop. Specifically, since MAPK generally has many target molecules and is involved in several cellular events, it is interesting to elucidate another function of MAPK in LTD.

Involvement of this positive feedback loop fits well to the time course of gradual expression of LTD. Although it is not clear whether this loop is also required for LTD with rapid expression, this loop and similar regenerative system may be generally attractive mechanisms for long-term synaptic plasticity. One of the important aspects of long-term synaptic plasticity is that such plasticity is generally triggered by transient synaptic stimulation but lasts for a long time, so that some mechanisms seem to work for the temporal conversion from transient stimulation to long-term signaling activities. The positive feedback loop working for the cerebellar LTD is likely one example of such mechanisms.

Mechanisms Required for Maintenance of LTD

Compared with the induction and expression, considerably less is known about mechanisms required for LTD maintenance. Nevertheless, studies using cultured Purkinje cells demonstrated the requirements for transcriptional and translational cellular events in the late phase of LTD, which is defined as a phase beginning 60 min after induction. Activity-driven transcriptional regulators, the cyclic AMP (cAMP)-responsive element-binding protein (CREB) and the Ca^{2+} -/calmodulin-dependent protein kinase type IV (CaMKIV), were implicated in this phase (Ahn et al. 1999), although it is not clear which transcripts are regulated by these transcriptional regulators. Another transcriptional regulator, serum response factor (SRF), was also implicated in the late phase of LTD. In case of SRF, a target transcript is also shown. SRF binds to the SRE 6.9 site in the promoter region of the synaptic protein Arc, so that Arc is expressed in an SRF-dependent manner (Smith-Hicks et al. 2010). Further, the late phase of LTD is reported to require persistent dynamin-mediated endocytosis, which may also depend on Arc expression (Linden 2012).

These studies using cultured Purkinje cells have advanced our understanding of the maintenance mechanisms of LTD. However, there are still some questions to be addressed. The first question is whether the abovementioned signaling molecules are also involved in late-phase LTD in slice preparations or in vivo. In fact, it is not clear whether or when newly synthesized protein-dependent late-phase LTD is initiated in slice preparations, because bath application of translational inhibitors already blocks its induction (Karachot et al. 2001). Even if we assume that similar mechanisms observed in cultured Purkinje neurons account for the maintenance of the late phase of LTD in intact cerebellar networks, it still has to be elucidated how early maintenance between the expression phase and late phase is achieved. A conceptual model and an analysis of experimental results suggest that another type of bistable switch, which shows threshold behavior, works after the positive feedback loop described

above (Kawato et al. 2011; Kim and Tanaka-Yamamoto 2013).

Spatial Aspects of LTD

Spatial aspects of long-term synaptic plasticity can be represented by homosynaptic and heterosynaptic plasticity. Long-term synaptic plasticity is typically input-specific, meaning that long-term changes in synaptic transmission occur only in synapses, where synaptic plasticity-inducing activities are applied. This is called homosynaptic plasticity. In contrast, when synaptic plasticity is triggered at synapses, where activities are not applied, this is called heterosynaptic plasticity. While cerebellar LTD appears to be homosynaptic when LTD is induced by pairing weak PF activity with CF activity (Wang et al. 2000a), it has also been shown that cerebellar LTD induced by pairing stronger PF activity with CF activity can spread to nearby inactive PF synapses (Wang et al. 2000b; Reynolds and Hartell 2000). Mechanisms of this heterosynaptic LTD are not understood. One suggestion arose from experiments of LTD induced by uncaged Ca^{2+} . The uncaged Ca^{2+} -induced LTD does not spread beyond the area of $[\text{Ca}^{2+}]_i$ increase (Tanaka et al. 2007), so that downstream signals of Ca^{2+} are unlikely key factors for spreading LTD, although they may cooperate with other molecules, such as IP3 or lower concentration of $[\text{Ca}^{2+}]_i$. Since NO is a gas messenger, NO was thought to be a candidate of spreading molecules (Reynolds and Hartell 2001), yet it was demonstrated that NO released by PF stimulation did not spread as expected (Namiki et al. 2005).

Other Signaling Mechanisms Involved in LTD

Although many molecules are already discussed in this description, there are still several other molecules that have been shown to be involved in LTD. Some of them are introduced below.

A member of ionotropic glutamate receptor, $\delta 2$ glutamate receptor (GluD2 or GluR $\delta 2$), is

predominantly expressed on the postsynaptic sites of synapses between PFs and Purkinje cells (Landsend et al. 1997; Zhao et al. 1998). In GluD2-null mice, the numbers of PF-Purkinje cell synapses are severely reduced (Kurihara et al. 1997; Lalouette et al. 2001) and LTD is impaired (Kashiwabuchi et al. 1995; Motohashi et al. 2007), so that GluD2 has two functions on PF-Purkinje cell synapses. These two functions are distinct, because expression of mutant GluD2, which lacks a PDZ ligand domain at C-terminus, rescued the morphological abnormality, but not the impairment of LTD (Uemura et al. 2007; Kakegawa et al. 2008). Unlike other ionotropic glutamate receptors, such as AMPARs, GluD2 does not normally function as an ion channel for LTD (Kakegawa et al. 2007), even though GluD2 is included as a member of ionotropic glutamate receptor. Instead, the C-terminal PDZ ligand domain of GluD2 has functions to regulate intracellular signaling. It is indeed demonstrated that GluD2 interacts with the tyrosine phosphatase PTPMEG via the PDZ ligand domain and regulates phosphorylation of GluR2 AMPARs at tyrosine 876 (Tyr876) (Kohda et al. 2013). The dephosphorylation of Tyr876 of GluR2 via GluD2 and PTPMEG allows GluR2 to be phosphorylated at Ser880, which is required for LTD. Thus, GluD2 gates the LTD by coordinating interactions between two phosphorylation sites of GluR2.

Another type of ionotropic glutamate receptor, *N*-methyl-D-aspartate receptor (NMDAR), is critical in many forms of synaptic plasticity. However, NMDAR was originally excluded from mechanisms of cerebellar LTD, because it was believed that NMDAR was not expressed in Purkinje cells, based on studies using young animals (Perkel et al. 1990; Llano et al. 1991). On the other hand, when adult animals were used, the expression of NMDAR was detected at postsynaptic sites of CF-Purkinje cell synapses (Piochon et al. 2007; Renzi et al. 2007). Then, it is demonstrated that NMDAR at CF-Purkinje cell synapses contributes to the CF-dependent $[\text{Ca}^{2+}]_i$ increase and LTD in adult animals (Piochon et al. 2010). In addition, NMDAR at presynaptic sites of PF terminals or stellate cells are also shown to be

involved in LTD (Casado et al. 2002; Shin and Linden 2005).

For the hippocampal LTP, calcium-/calmodulin-dependent protein kinase II (CaMKII) has been intensively studied, and it is indeed demonstrated that CaMKII is an important mediator for LTP (Lisman et al. 2012). The involvement of CaMKII in cerebellar LTD was not investigated for a long time, probably because other kinases, specifically PKC, have been already shown to be critical for LTD. Yet it was demonstrated that α CaMKII knockout mice show impairment of LTD or even show LTP upon the stimulation that usually triggers LTD in wild-type mice (Hansel et al. 2006). Further, β CaMKII knockout mice show opposite direction of synaptic plasticity: LTP is triggered by a stimulation that usually triggers LTD in wild-type mice, while LTD is triggered by a stimulation that usually triggers LTP in wild-type mice (van Woerden et al. 2009). Detailed mechanisms of these phenomena were not fully understood. However, a combined study of computational model and experiments using cultured Purkinje cells proposed that CaMKII gates LTD by reducing PP2A activities via several steps (Kawaguchi and Hirano 2013). In their model, CaMKII negatively regulate phosphodiesterase1 (PDE1), which degrades cGMP and consequently reduces PKG activities. Thus, negative regulation of PDE1 by CaMKII leads to PKG activation, which in turn reduces PP2A activities. The pathway of cGMP-dependent PKG activation is triggered by NO, as mentioned above, so that NO seems to be capable of compensating the lack of CaMKII activities.

Kinetic Model of LTD

Mathematical description is not a focus of this description, so that details of computational model are not described here. However, it is probably worth to mention the contribution of computational models of kinetic simulations. As described here, signaling mechanisms of LTD are complex and many molecules are implicated in LTD. To systematically understand the

interaction of molecules and characteristic aspects produced by these signaling mechanisms, a computational model of kinetic simulation has been effective. A kinetic model indeed first incorporated the positive feedback loop of PKC and MAPK as a mechanism to expand the timing of PKC and MAPK activation as well as AMPAR phosphorylation (Kuroda et al. 2001). This model also succeeded to reproduce the permissive role of NO. A slightly modified version of this model was then used to explain the relationship between $[Ca^{2+}]_i$ and LTD (Tanaka et al. 2007). Then the model suggested that the sigmoidal relationship arose at least in part from the positive feedback loop. Although this model reproduces most of features in the relationship, there is one feature that the model predicts differently from experimental results. The slope of sigmoidal curve for the relationship is steeper in the model than that in the experimental results. In other words, the model predicts all-or-none induction of LTD, while intermediate level of LTD is observed in experiments. However, if the distribution and noise of $[Ca^{2+}]_i$ increase are considered, a similar curve could be obtained. In contrast, another computational study considered stochastic features of signaling in LTD by taking into account only a few tens of molecules being involved in the LTD process within a confined region like a dendritic spine (Antunes and De Schutter 2012). This stochastic model actually reproduces experimental relationship between $[Ca^{2+}]_i$ and LTD without including the effects of distribution and noise of $[Ca^{2+}]_i$ increase. Thus, it may be interesting to directly test such stochastic features by experiments.

Postsynaptic LTD and LTP

In addition to LTD, two forms of LTP can be also triggered at the PF-Purkinje cell synapses. One is presynaptic LTP, which is induced by a few minutes of PF stimulation at 4 Hz. This presynaptic LTP is mediated by cAMP and protein kinase A (PKA) and relies on the potentiation of glutamate release (Salin et al. 1996). Because LTD is postsynaptically induced and expressed, it was believed that there should be postsynaptic LTP

as a mechanism of resetting LTD. Indeed, another form of LTP is postsynaptic LTP (Lev-Ram et al. 2002), which seems to depend on GluR2 trafficking (Kakegawa and Yuzaki 2005). The LTP is induced by 5 min of PF stimulation at 1 Hz and requires NO, but not cAMP, PKA, cGMP, or PKG. In clear contrast to LTD, this LTP requires the activation of protein phosphatases (PPs), PP1, PP2A, and PP2B (Belmeguenai and Hansel 2005). As expected, LTD can be canceled, when this LTP protocol is applied after LTD is saturated. Oppositely, when LTD protocol is applied after LTP is saturated, LTP can be canceled (Lev-Ram et al. 2003; Coesmans et al. 2004). Thus the postsynaptic LTD and LTP reset each other.

The postsynaptic LTD can be triggered by 5 min of PF stimulation at 1 Hz with concomitant CF stimulation, while the postsynaptic LTP can be triggered by the same PF stimulation without concomitant CF stimulation. It has been discussed regarding the signaling mechanisms to distinct LTP and LTD. Because CF stimulation is the difference between stimulation causing LTD and LTP, one idea is that Ca^{2+} concentration during stimulation may determine the direction of synaptic plasticity. Relatively higher concentrations of $[\text{Ca}^{2+}]_i$ increase is required and is even sufficient for LTD. In contrast, LTP is blocked by 15–30 mM BAPTA, a Ca^{2+} chelator, but not by 5 mM BAPTA (Coesmans et al. 2004). This indicates that lower concentration of Ca^{2+} seems to be necessary for LTP, although it is not clear whether $[\text{Ca}^{2+}]_i$ increase is required or basal level of $[\text{Ca}^{2+}]_i$ is enough for LTP. Based on these results, “inverse BCM rule” has been proposed (Coesmans et al. 2004). BCM stands for Bienenstock, Cooper, and Munro, who originally proposed the “BCM rule,” which is a theory to describe how the threshold of synaptic plasticity is determined (Bienenstock et al. 1982). Based on the BCM rule, lower and higher $[\text{Ca}^{2+}]_i$ increases are associated with the induction of LTD and LTP, respectively. In case of PF-Purkinje cell synapses, the requirement of $[\text{Ca}^{2+}]_i$ for LTD and LTP is opposite, so that “inverse BCM rule” was proposed. However, because LTD, but not LTP, was observed by $[\text{Ca}^{2+}]_i$ increase upon uncaging Ca^{2+} ,

the amplitude of $[\text{Ca}^{2+}]_i$ may not be a sole factor to determine the direction of synaptic plasticity in PF-Purkinje cell synapses. Probably, the combination of Ca^{2+} signals with other signals, such as NO, balances the activities of protein phosphatases and kinases and consequently triggers either LTD or LTP (Lee 2006).

Roles of LTD

Even though LTD was originally found as a cellular basis of motor learning, the relationship between LTD and motor learning is still controversial. In many studies using genetically modified animals, in which signaling molecules required for LTD are modified, it has been demonstrated that motor learning is impaired in these animals (Yuzaki 2013). These studies support the idea that LTD is important for motor learning. In contrast, there are also reports showing discrepancy between cerebellar LTD and motor learning. For example, in mice that do not show LTD due to the genetic modification causing inhibition of AMPAR internalization in Purkinje cells, several types of motor learning were intact (Schonewille et al. 2011). Thus, the relationship between LTD and motor learning has to be further elucidated. However, if LTD would not play a role in motor learning, the question is what would be the roles of LTD. Given that LTD is induced by the conjunctive stimulation of two excitatory inputs and is precisely regulated by many signaling molecules, it is difficult to imagine that LTD does not have any functions. LTD seems to have at least an impact on the function of cerebellar neural networks, because it was reported that the pause of simple spikes in Purkinje cells, which is seen after burst stimulation of PFs, is modified by the induction of LTD (Steuber et al. 2007).

Cross-References

- Nitric Oxide Neuromodulation
- Protein Kinase A, Models of
- Protein Kinase C, Models of

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Long Term Synaptic Depression at the Parallel Fiber-Purkinje Cell Synapse

► [Long Term Depression in the Granule Cell-Purkinje Cell Synapse](#)

Long-Term Plasticity, Biophysical Models

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Definition

Connections between neurons are called synapses. Their strength is defined as the voltage amplitude, or slope, of a postsynaptic neuron response to a presynaptic action potential. The synapses can change in strength, i.e., they are plastic, and these changes can operate on different time scales. Long-term plasticity denotes the synaptic changes that last more than 20–30 min (see Fig. 1). This is opposed to short-term plasticity that lasts hundreds of milliseconds.

Models of synaptic plasticity describe mathematically how synapses change under which factors. They are often formulated as differential equations. Biophysical models describe how biophysical quantities, such as spike timing, voltage, calcium, and Ca^{2+} /calmodulin-dependent protein kinases (CaMKII), influence changes in synaptic strength. These latter models can also be called bottom-up. If the variables of the model are only a few biophysical quantities (e.g., only spike timing) or are abstract quantities, they are called phenomenological models (although there is no sharp distinction). Biophysical models are opposed to optimal or top-down models, designed to optimally fulfill a function (see Fig. 2).

Detailed Description

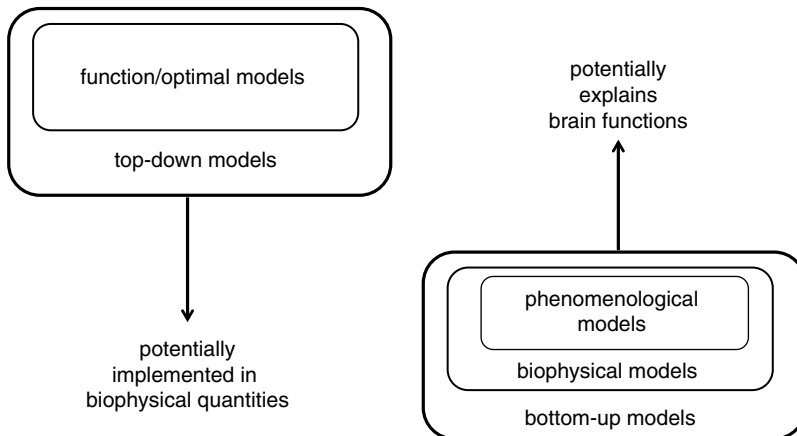
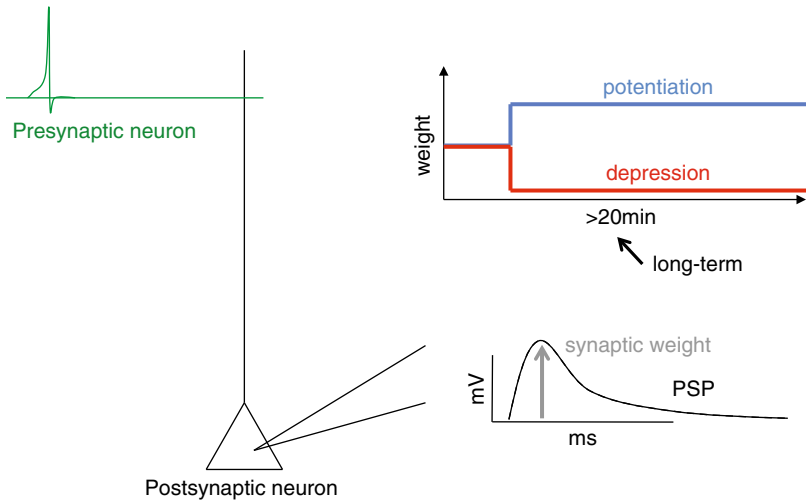
This entry is first describing the basic mechanism of synaptic plasticity and presenting the different experimental evidence of long-term plasticity, before describing the different models of long-term plasticity, from the most simple ones to the most detailed ones.

Synaptic Plasticity

Two neurons can be connected via chemical and/or electrical (gap junction) synapses. A chemical synapse is placed between the axon of a presynaptic neuron and a dendrite of the postsynaptic neuron forming a unidirectional connection. The classical view of the synaptic communication mechanism is as follows: when a presynaptic spike arrives at the presynaptic terminal, neurotransmitters, typically glutamate for excitatory synapses, are released. They can bind on the postsynaptic side to receptors, such as N-methyl-d-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptors then open and let sodium ions flow into the cell, resulting in a depolarization of the postsynaptic membrane potential. The NMDA receptor opens only if at the same time (a) the glutamate binds to the receptors and (b) the postsynaptic cell is depolarized, freeing the magnesium block (see Fig. 3). This depolarization of the postsynaptic cell typically comes from back-propagating action potentials. The NMDA receptor is therefore seen as a coincidence detector between presynaptic and postsynaptic activities. The opening of these receptors allows calcium to enter the synapse. Despite the detailed description of the mechanisms that allow synaptic communication (Lisman and Zhabotinsky 2001; Rubin et al. 2005), the mechanism that leads to changes in the synaptic strength is not completely clear. Calcium plays an important role for further cascade signaling, which acts on AMPA receptor activation through kinases and phosphatases (Lisman et al. 2002). Moreover retrograde messengers like endocannabinoids can influence plasticity, in particular for depression of the synapses (Nevian and Sakmann 2006; Piomelli 2003; Sjöström et al. 2003, 2004).

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Fig. 1 Cartoon of long-term plasticity. The synaptic strength is defined as the height, or the slope, of the postsynaptic voltage response (postsynaptic potential [PSP]) to a presynaptic spike. If the weight is increased, it is called potentiation, and if it is decreased, it is called depression. Long-term plasticity denotes the changes that last more than 20 min



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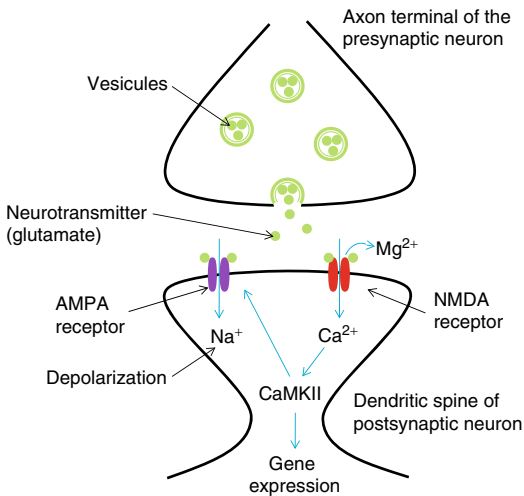
Fig. 2 Models of synaptic plasticity. Biophysical models denote models that take into account biophysical quantities in order to explain synaptic plasticity. If the biophysical quantities are restricted or abstract, the models are called phenomenological. These models are also called bottom-up, since they are based on biophysical quantities but

ultimately can be used to describe brain functions (bottom for biophysical quantities and up for brain functions). This is opposed to functional or optimal models, designed to optimize a function. These models can then be related to biophysical qualities and are thus also called top-down models (top for function and down for biophysical implementation)

Experimental Evidence of Long-Term Plasticity

The typical measurement of synaptic strength is the amplitude or the slope of the excitatory postsynaptic potential (EPSP), i.e., the potential response to a single (or a group of coincident) presynaptic spike(s). Synaptic plasticity can be separated by two different time scales: short-term plasticity, where changes persist during a

few hundred milliseconds, and long-term plasticity that lasts more than 20 min. Short-term plasticity is believed to be presynaptically expressed (Gupta et al. 2000; Markram et al. 1998) and is partly caused by the limited number of neurotransmitters at the synapse. It is well modeled by a reservoir that partially empties at the presynaptic spike time (with a certain probability) and recovers with a certain time constant (Abbott



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Fig. 3 Cartoon of a glutamatergic synapse. When a pre-synaptic spike arrives at the synapse, neurotransmitters are released in the synaptic cleft. They can bind to the NMDA receptor, and if at the same time the postsynaptic cell is depolarized, the channel opens. Calcium enters the cell, which induces a molecular cascade that phosphorylates the Ca^{2+} /calmodulin-dependent protein kinases (CaMKII), which in turn acts on the AMPA receptor activation. Neurotransmitters can also directly bind to AMPA receptor, opening the channel, allowing sodium to enter, and leading to a depolarization called excitatory postsynaptic potential (EPSP)

et al. 1997; Markram and Tsodyks 1996). Here the focus is on long-term plasticity, which can be induced by different types of protocols.

- (i) Simultaneous voltage clamp and presynaptic stimulations (Ling et al. 2002; Ngezahayo et al. 2000; Fig. 4a). If the cell is slightly depolarized while receiving presynaptic inputs, the synaptic weight is depressed, whereas if the cell is highly depolarized, the synapse is potentiated.
- (ii) Extracellular presynaptic stimulations at different frequencies (Dudek and Bear 1993; Kelso et al. 1986; O'Connor et al. 2005; Fig. 4b). Low-frequency stimulation leads to depression, whereas high frequency leads to potentiation.
- (iii) Pairing of presynaptic and postsynaptic spikes at different time lags (Fig. 4c). In pyramidal cells pre-post pairing typically results in

potentiation, whereas post-pre results in depression (Bi and Poo 1998; Markram et al. 1997) (although it depends on the system (Bell et al. 1997; Egger et al. 1999; Lu et al. 2007; Tzounopoulos et al. 2004)).

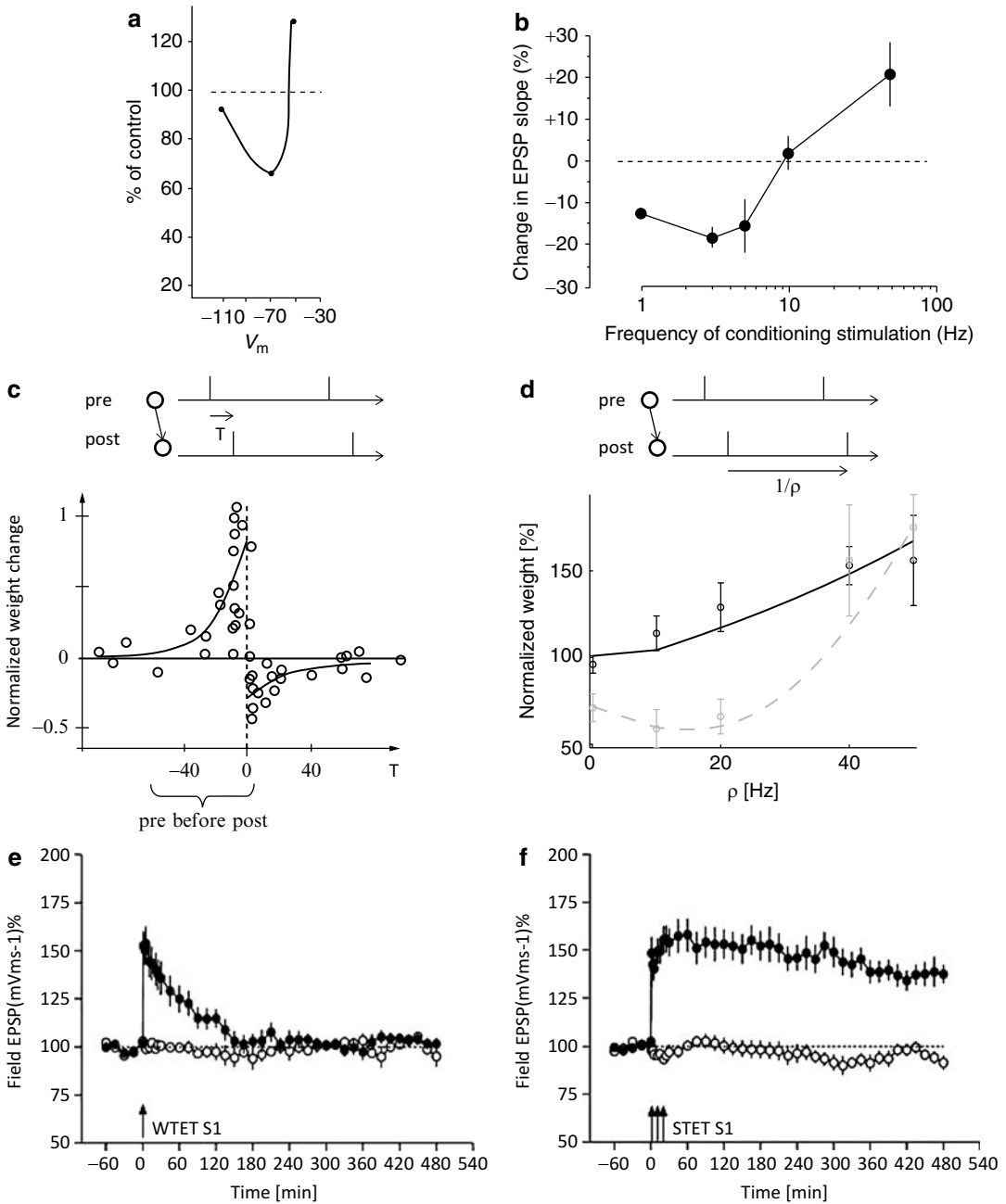
- (iv) Pairing at different frequencies (Markram et al. 1997; Sjöström et al. 2001; Fig. 4d). Pre-post pairing at low frequency does not change the synaptic weight; increasing the frequency leads to potentiation.
- (v) Induction of various spike patterns. Synaptic plasticity can also be induced with different patterns, such as triplets of spikes (Froemke and Dan 2002), bursts (Gustafsson et al. 1987; Nevian and Sakmann 2006), quadruplets (Wang et al. 2005), or natural spike trains (Froemke and Dan 2002). The resulting plasticity depends on the protocol: in particular it depends if presynaptic stimulation is extracellular (many inputs at the same time, slices more active) (Froemke and Dan 2002) or intracellular (Sjöström et al. 2001).
- (vi) Synaptic tagging experiments (Frey and Morris 1997). These experiments provide evidence for another separation of time scales of long-term plasticity. The early phase of long-term plasticity lasts 2–3 h and can be induced by tetanic stimulation for potentiation (Fig. 4e). The late phase, or consolidation phase, lasts more than 10 h (i.e., the time of those experiments) and can be induced by a stronger extracellular tetanus that also stimulates dopaminergic fibers (Fig. 4f). Neuromodulation is therefore critical in the process of consolidation (Pawlak et al. 2010; Reymann and Frey 2007).

Models

This section is describing the different models of long-term plasticity, from the most simple ones to the most detailed ones, starting from firing rate models all the way to detailed biophysical models.

Models Based on Firing Rates

The first models of synaptic plasticity in line with Hebb's principle ("Who fires together wires



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Fig. 4 Different experimental protocols. (a) Voltage clamp experiment. The postsynaptic voltage is clamped at the soma during extracellular presynaptic stimulation. If the voltage is hyperpolarized, no weight change is recorded; for slight depolarization, depression is observed; for strong depolarization, potentiation occurs (Figure redrawn from Artola et al. (1990)). (b) Presynaptic frequency dependence. Extracellular presynaptic spike trains at different frequencies are induced.

Low-frequency stimulation yields depression, whereas high-frequency stimulation results in potentiation. (Figure redrawn from Dudek and Bear 1993). (c) STDP experiment. Pairs of presynaptic and postsynaptic spikes are elicited, while the lag between the presynaptic spike and the postsynaptic spike varies. Pre-post pairing induces long-term potentiation (LTP), whereas post-pre leads to long-term depression (LTD). (Figure redrawn from Bi and Poo 1998). (d) Pairing frequency experiment. Here the lag between the pre- and

together”) (Hebb 1949) depend on the correlation of the pre- and postsynaptic firing rates. The subsequent models subtracted a baseline so that the weight can also be depressed (covariance rule (Sejnowski and Tesauro 1989)), added weight dependency (hard or soft bounds), and added normalization to induce competition between weights (Miller and MacKay 1994). Multiplicative normalization was introduced in Oja’s rule (Oja 1982), which performs principle component analysis (PCA). At the same time, the Bienenstock-Cooper-Munro (BCM) rule (Bienenstock et al. 1982) was designed with a nonlinearity in the postsynaptic firing rate and a sliding threshold, as a homeostatic mechanism. The BCM model also exhibits properties of selectivity in the inputs.

Models Based on Spike Timing

Spike-timing-dependent plasticity (STDP) models (Gerstner et al. 1996; Gütiğ et al. 2003; Karmarkar and Buonomano 2002; Kempster et al. 1999; Rubin et al. 2001; Senn et al. 2001; Song et al. 2000; van Rossum et al. 2000) depend on the precise timing of the pre- and postsynaptic spike.

Standard Pair-Based Models

For the LTD part, standard pair-based models assume that presynaptic spike arrival, at synapse i , induces depression of the synaptic weight w_i by an amount that is proportional to $\bar{y}$, an exponential low-pass-filtered version of the postsynaptic spike train $Y(t)$ with a time constant τ_- (see Fig. 5b, trace post):

$$\tau_- \frac{d}{dt} \bar{y}(t) = -\bar{y}(t) + Y(t),$$

where $Y(t)$ is expressed as the series of short pulses at time t^n , with n being a spike index, $Y(t) = \sum_n \delta(t - t^n)$. The variable $\bar{y}$ is an abstract

variable which could, for instance, reflect the level of calcium concentration (Lisman 1989), the release of endocannabinoids (Sjöström et al. 2004), or the back-propagating action potential, although such an interpretation is not necessary for this type of phenomenological rules. Similarly, the presynaptic spike train is described as a series of short pulses at time t_i^n with i being the index of the synapse, $X_i(t) = \sum_n \delta(t - t_i^n)$. The depression is then modeled as the following equation (see Fig. 5b):

$$\frac{d}{dt} w_i^- = -A_{\text{LTD}}(w_i^-) X_i(t) \bar{y}(t), \quad (1)$$

where A_{LTD} is the amplitude for depression.

For the LTP part, the temporal evolution of the presynaptic low-pass filter $\bar{x}_i(t)$ is described by (see Fig. 5a, trace pre):

$$\tau_+ \frac{d}{dt} \bar{x}_i(t) = -\bar{x}_i(t) + X_i(t),$$

where X_i is the spike train defined above. The quantity $\bar{x}_i(t)$ could, for example, represent the amount of glutamate bound to postsynaptic receptors (Karmarkar and Buonomano 2002; Pfister and Gerstner 2006) or the number of NMDA receptors in an activated state (Senn et al. 2001). The potentiation is then described by the following equation (see Fig. 5a):

$$\frac{d}{dt} w_i^+ = +A_{\text{LTP}}(w_i^+) Y(t) \bar{x}_i(t). \quad (2)$$

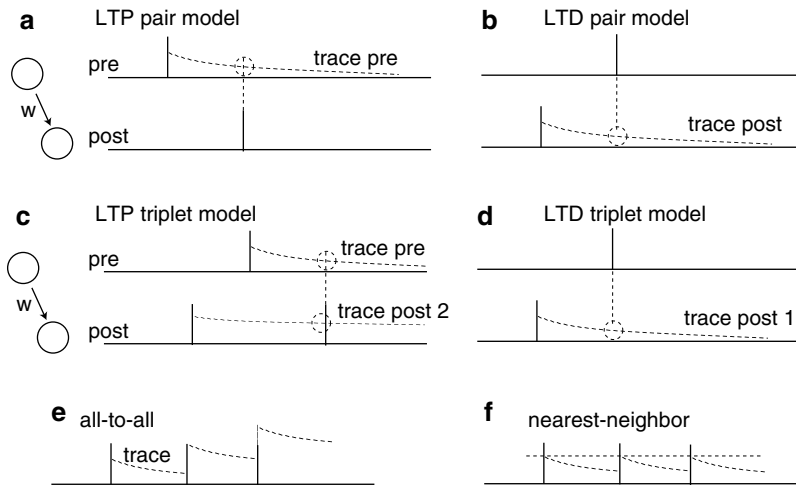
where A_{LTP} is the amplitude for potentiation.

There are several implementations of pair-based STDP models. For example, the pre- and postsynaptic traces can consider either all the spikes, i.e., all-to-all interactions (Fig. 5e), or only the nearest neighbor spike (Fig. 5f). Since

Long-Term Plasticity, Biophysical Models, Fig. 4

(continued) postsynaptic spike is constant (pre-post (black), post-pre (gray)), but the frequency of the pairings varies. Pre-post at low frequency does not lead to any weight change, whereas increasing frequency allows for potentiation. (Figure redrawn from Sjöström et al. 2001).

(e) Weak tetanus stimulation. Few extracellular high-frequency trains stimulated presynaptic yield LTP that lasts 2–3 h. (f) Strong tetanus stimulation. If longer high-frequency trains are induced, the potentiation is stable for longer than 10 h. (Figure redrawn from Sajikumar and Frey 2004a)



Long-Term Plasticity, Biophysical Models, Fig. 5 Different types of models. (a) LTP with standard STDP model. The synaptic weight is potentiated at the time of the postsynaptic spike by an amount corresponding to the presynaptic trace. (b) LTD with standard STDP model. The synaptic weight is depressed at the time of the presynaptic spike by an amount corresponding to the postsynaptic trace. (c) LTP with the minimal triplet rule (Pfister and Gerstner 2006). The synaptic weight is potentiated at the

time of the postsynaptic spike by an amount corresponding to the product of a presynaptic and a postsynaptic trace. (d) LTD with triplet rule. Same as standard STDP model. (e) All-to-all interaction of spikes. The trace jumps by a fixed amount when a spike occurs and decays otherwise, leading to cumulative effect from all the previous spikes. (f) Nearest-neighbor interaction of spikes. The trace jumps to a fixed value when a spike occurs and decays otherwise. Only the last spike affects the trace

the synaptic weight cannot grow indefinitely, STDP models add bounds. Additive STDP has hard bounds, i.e., there is a hard cutoff at a minimal and maximal weight value. Multiplicative STDP has soft bounds, and therefore the amount of plasticity depends on the actual synaptic strength (Gütig et al. 2003; Kistler and Leo van Hemmen 2000; Rubin et al. 2001; van Rossum et al. 2000) (see experimental findings on weight dependence (Bi and Poo 1998; Turrigiano and Nelson 2004)). Models of STDP also can take into account homeostasis (Clopath et al. 2010; Kempster et al. 1999; Pfister and Gerstner 2006; van Rossum et al. 2000) (see Turrigiano and Nelson 2004 for experiments).

These types of models can reproduce the spike-timing-dependent learning window (see Fig. 4c), but not the pairing frequency dependence (see Fig. 4d) nor the voltage clamp experiment (see Fig. 4a; Markram et al. 1997; Sjöström et al. 2001). Therefore, nonlinear models were developed to describe those experiments, where triplet interaction of spikes (Clopath et al. 2008, 2010;

Pfister and Gerstner 2006; Senn et al. 2001) (see below) or discount factors on the “efficacy” of successive spikes are considered, similar to including a model of short-term plasticity (Froemke and Dan 2002, model based on extracellular inductions of triplets of spikes).

Triplet Model

The minimal triplet model (Pfister and Gerstner 2006) describes depression the same way as the standard pair-based models. However, potentiation takes into account triplet interactions of spike, two postsynaptic spikes and one presynaptic spike (see Fig. 5c). The model defines a second type of postsynaptic trace $\bar{y}_2$ that decays with a time constant τ_2 , typically on the order of 100 ms. This second trace might represent calcium concentration at the synapse. The synapse is potentiated at the postsynaptic spike time by an amount that is proportional to the product of the presynaptic spike trace $\bar{x}_i(t)$ (see Fig. 5c, trace pre) and the second postsynaptic spike trace $\bar{y}_2$ (see Fig. 5c, trace post 2). The potentiation is written:

$$\frac{d}{dt}w_i^+ = +A_{\text{LTP}}(w_i^+)Y(t)\bar{x}_i(t)\bar{y}_2(t), \quad (3)$$

where A_{LTP} is the amplitude for potentiation.

This model is able to reproduce the frequency experiment (see Fig. 4d), but not the voltage clamp experiment (see Fig. 4a), since it only depends on the spike timing, and not on the postsynaptic membrane potential.

Models Based on Spike Timing and Postsynaptic Voltage

Voltage-based models (Abarbanel et al. 2002; Brader et al. 2007; Clopath et al. 2010) typically depend on the presynaptic spike time and on the postsynaptic voltage. We describe here one voltage-based model in more detail.

Voltage-Triplet Model

The voltage-based-triplet model (Clopath and Gerstner 2010; Clopath et al. 2008, 2010) is designed to reproduce the frequency experiment (see Fig. 4d) and the voltage clamp experiment (see Fig. 4a; Clopath et al. 2008). The rule is written as.

$$\begin{aligned} \frac{d}{dt}w_i = & -A_{\text{LTD}}X_i(t)[\bar{u}_-(t) - \theta_-]_+ \\ & + A_{\text{LTP}}[u(t) - \theta_+]_+\bar{x}_i(t)[\bar{u}_+(t) - \theta_+]_+, \end{aligned} \quad (4)$$

where u is the postsynaptic voltage, $\bar{u}_{+/-}$ are postsynaptic voltage low-pass filters with two different time constants, $\theta_{+/-}$ are thresholds, and $[x]_+$ is x when $x > 0$ and 0 otherwise. It was shown to reproduce a large part of the experimental literature on long-term plasticity (Clopath and Gerstner 2010), such as spike-timing pair, burst, triplet and quadruplet experiments (Bi and Poo 1998; Froemke and Dan 2002; Markram et al. 1997; Nevian and Sakmann 2006; Wang et al. 2005), frequency dependence (Dudek and Bear 1992; Markram et al. 1997; Sjöström et al. 2001), voltage clamp experiments (Artola et al. 1990; Ngezahayo et al. 2000), and dendritic dependency (Sjöström and Häusser 2006). This model has very different functional implications in networks than pair-based rules (Clopath et al. 2010).

Models Based on Receptor Dynamics

Those models describe typically glutamate binding, AMPA receptors (Saudargiene et al. 2003), or NMDA receptors (Gamble and Koch 1987; Holmes and Levy 1990; Senn et al. 2001; Zador et al. 1990).

Senn-Tsodyks-Markram Model

The Senn-Tsodyks-Markram (STM) model (Senn et al. 2001) takes into account the dynamics of the NMDA receptor. The receptors can be in three different states: rest, up, or down. In the absence of spikes, NMDA receptors are in the rest state, but they can be upregulated when a presynaptic spike occurs or downregulated at the postsynaptic spike time. A notion of two types of second messengers is introduced in the model, so that when a postsynaptic spike occurs, second messenger type 1 can be upregulated only if the NMDA receptors are in the up states already. Conversely, the second messenger type 2 can be downregulated if there is a presynaptic spike and if the NMDA receptors are already in the down state. Finally, LTP is elicited when there is a postsynaptic spike and the second messenger type 1 is in the up state; LTD occurs at the time of a presynaptic spike if the second messenger type 2 is downregulated. This model takes into account pair interaction of spikes and triplet interactions of spikes, i.e., one presynaptic spike, two postsynaptic ones for potentiation, and two presynaptic and one postsynaptic spike for depression.

It reproduces frequency dependence experiment (see Fig. 4d), as well as STDP experiment (see Fig. 4c), but not the voltage clamp experiment (see Fig. 4a). It can be mapped to the BCM rule although the depression term is not linear in the presynaptic term.

Models Based on Calcium

There are several models depending on calcium concentration (Abarbanel et al. 2003; Badoual et al. 2006; Cai et al. 2007; Froemke et al. 2005; Karmarkar and Buonomano 2002; Karmarkar et al. 2002; Lisman 1989; Rubin et al. 2005; Shouval et al. 2002); two are described here in more detail.

Shouval Model

The calcium model of Shouval et al. (2002) takes the concentration of calcium in the postsynaptic cell as a measure for plasticity. Low calcium concentration is not affecting the synapse, intermediate concentration leads to LTD, and high concentration leads to LTP. The model describes the calcium changes at the synapse: the calcium current flows through the NMDA receptors only if the presynaptic spike is paired with a back-propagating action potential.

It reproduces the voltage clamp experiment (see Fig. 4a), presynaptic stimulation frequency experiment (see Fig. 4b), and the STDP experiments (see Fig. 4c). However, it predicts a LTD part in the pre-post side of the STDP curve due to the shape of the back-propagating action potential. Refinements of this model are proposed in Shouval and Kalantzis (2005).

Graupner Model

In the calcium model of Graupner and Brunel (2012), potentiation and depression are activated by calcium thresholds, where presynaptic and postsynaptic action potentials elicit calcium transients. The synapses are considered to be bistable. The model gives rise to a multiple of learning curves and reproduces the frequency dependence (see Fig. 4d). This model is a simplified version of a more detailed biophysical model (Graupner 2008).

Models Based on CaMKII

Bistable Models

Bistable models (Lisman 1985) were introduced as a solution to the following paradox: since the molecular turnover is fast, on the order of minutes to hours, how can the synapses keep their strength for much longer? The idea was that the CaMKII can switch between a phosphorylated and unphosphorylated state (Lisman 1985, 1989; Okamoto and Ichikawa 2000; Zhabotinsky 2000). Mathematical models of CaMKII phosphorylation and dephosphorylation show a bistability regime (see, e.g., (Lisman and Zhabotinsky 2001; Miller et al. 2005; Zhabotinsky 2000), although some don't find bistability mathematically (Kubota and Bower

2001) and in the experiments (Bradshaw et al. 2003)). These models have a number of limitations concerning the number of molecules involved (Miller et al. 2005) and CaMKII trafficking (Hayer and Bhalla 2005). Finally, although the importance of CaMKII for the induction of plasticity is clearly demonstrated, some experimental studies suggest that CaMKII is not involved for the maintenance of plasticity (late-phase consolidation) (Malinow et al. 1989; Othmakhov et al. 1997).

There are alternative models for the maintenance of plasticity, such as a bistability of translational switch (Blitzer et al. 2005), a cluster model of AMPA receptors (Shouval 2005), and memory reactivation model (Smolen 2007; Wittenberg et al. 2002). For models of kinases and phosphates, refer to (Abarbanel et al. 2003; Ajay and Bhalla 2004; Castellani et al. 2005).

Bistable Biophysical Models and Spike Timing

These models (Graupner and Brunel 2007; Urakubo et al. 2008) describe how precise spike timing induces a calcium transient. The resulting calcium concentration influences the CaMKII bistable system: at low concentration, up and down states are stable; at medium concentration, only the down state is stable; and at high calcium concentration, only the up state is stable. The model reproduces the different spike-timing-dependent plasticity experiments, and the bistable CaMKII system allows stable synapses.

Consolidation Models

Synaptic tagging experiments (Frey and Morris 1997) reveal two phases of long-term synaptic plasticity: the early phase, which induces a change that lasts 2–3 h (Fig. 4e), and the late phase, which lasts more than 10 h (Fig. 4f). Standard STDP models and detailed biophysical models don't discriminate and only describe the induction of plasticity, assuming the changes to be long lasting. Below, models of synaptic consolidation are explained in detail.

Cascade Model

The cascade model (Fusi et al. 2005) is designed to optimize the memory lifetime. It proposes a bistable synapse that can either take a weak or a strong value.

For each value, the synapse can be in different plastic states, called “metastates.” For example, if the synapse is already weak and undergoes a LTD protocol, it will keep the same weak value but will go to a lower metastate, where the synaptic weight is harder to change, i.e., less plastic.

Models of Synaptic Tagging

There are currently two models describing the late phase of long-term plasticity.

The TagTriC model (Clopath et al. 2008) is separated into three processes:

1. **Tagging:** The synapse strength is the sum of two parts, the weight of the early phase and the weight of the late phase. The early weight is a stochastic three-state variable (O’Connor et al. 2005; Petersen et al. 1998); it can be in neutral state, high state, or low state. If the early weight is in the high or low state, it is automatically tagged. The state of the early weight switches from neutral to high or low with a probability given by a Hebbian rule for the induction of plasticity (Clopath et al. 2008, 2010). It decays back to neutral with a certain transition probability.
2. **Trigger:** If the number of tags exceeds a threshold, plasticity-related proteins are synthesized. The threshold depends on the dopamine level, such that if dopamine is high, the threshold is lowered. Extracellular stimulation also stimulates dopaminergic fibers, lowering the threshold.
3. **Consolidation:** The late weight of the synapse is a continuous variable with two stable states. If plasticity-related proteins are available and if the synapse is tagged, the late weight can switch to a different stable state, thus allowing for consolidation.

This model can reproduce the synaptic tagging experiment (Fig. 4e, f), as well as several pharmacological experiments (Frey and Morris 1997; Sajikumar and Frey 2004a).

The consolidation model of Barrett et al. (2009) is very similar to TagTriC (Clopath et al. 2008), with some differences in its implementation. A synapse has one of two states (weak or low),

but each state additionally has one of three meta-states: early phase, tagged, or consolidated. As in TagTriC, synapses are stochastic, and their synaptic weight is a compound of several synapses. The transitions between states are a function of the protocol (weak tetanus or strong tetanus). Thus, induction of plasticity is not modeled explicitly nor is a mechanism of plasticity-related proteins synthesis designed, in contrast to the TagTriC model. However, the model dissociates the tag state from early-phase state, which is supported by the experiments where tags are reset (Sajikumar and Frey 2004b), experiments that are not directly captured by the TagTriC model.

Sources and Further Readings

This text is based on the introduction of Clopath (2009, 2012). For further readings, refer to the reviews on biophysical models (Graupner and Brunel 2010) (and the Chap. 2.7.2–4 of Graupner 2008), on phenomenological models of STDP (Morrison et al. 2008), on models and experiments of STDP (Feldman 2012), and synaptic consolidation (Clopath 2012), as well as the Scholarpedia articles (Shouval 2007, 2009; Sjoestrom and Gerstner 2010).

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Low-Voltage-Activated Calcium Channels

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Synonyms

[α1G](#); [α1H](#); [α1I](#); [Cav3](#); [T-type calcium channel](#)

Definition

Low-voltage-activated (LVA) calcium channels are a class of voltage-gated calcium (Ca^{2+}) channels that exhibit a high probability of opening at hyperpolarized membrane voltages (negative to -50 mV). LVA channels consist of a Cav3 family, of which there are three isoforms (Cav3.1 ([α1G](#)), 3.2 ([α1H](#)), 3.3 ([α1I](#))). Cav3 channels exhibit a low single-channel conductance and rapid inactivation, resulting in “tiny” and “transient” currents, often termed T-type current or I_T . T-type calcium channels were first recognized for their contribution to burst depolarizations and pacemaker activity in specific neurons but are now known to influence a wide range of cell outputs (Huguenard [1996](#); Perez-Reyes [2003](#); Yunker and McEnery [2003](#)).

Detailed Description

Several families of Ca^{2+} channels are expressed in neurons, which can be broadly classified in two groups based on voltage dependence. High-voltage-activated (HVA) Ca^{2+} channels show significant activation at potentials positive to -30 mV and include the L-type (Cav1), P-/Q-type (Cav2.1), N-type (Cav2.2), and R-type

(Cav2.3) channels. Low-voltage-activated (LVA) Ca^{2+} channels are activated at hyperpolarized potentials 20–30 mV more negative than HVA channels and are comprised solely of the Cav3 family of channels (although some L-type isoforms (Cav1.3, Cav1.4) do exhibit relatively low-voltage dependence). Cav3 channels have a small single-channel conductance of only ~ 1.7 pS in 2 mM $[\text{Ca}^{2+}]_o$ and 9 pS in 10 mM $[\text{Ba}^{2+}]_o$ (Weber et al. 2010).

Distribution of LVA Ca^{2+} Channels

To date, three Cav3 isoforms (Cav3.1–Cav3.3) have been discovered and all are prominently but differentially expressed throughout the CNS, including the cortex, hippocampus, thalamus, and cerebellum (Craig et al. 1999; Talley et al. 1999; McKay et al. 2006). Each isoform can be expressed as a variety of splice variants, increasing the variation of expression of Cav3 channels.

Quantification of Voltage Dependence

All Cav3 channel isoforms and splice variants exhibit significant activation at hyperpolarized voltages that can be detected below threshold for spike discharge in neurons, with half-activation voltages ranging from -40 to -75 mV (although Cav3 channels do show activation from as low as -90 mV (Engbers et al. 2012)) (Fig. 1). Cav3 channels also exhibit rapid inactivation upon depolarization with a half-inactivation voltage ranging from -90 to -60 mV (Fig. 1). The inactivation time constant decreases with increased depolarization (Fig. 1a), but unlike Cav1 channels that exhibit Ca^{2+} -dependent inactivation via binding of calmodulin, T-type inactivation is inherent to the channel and Ca^{2+} independent.

A unique aspect of Cav3 channels is an overlap of activation and inactivation curves that provides a “window” current between -70 and -20 mV, where a small percentage of channels remains in the active state (Fig. 1b). This window current provides continual Ca^{2+} influx at subthreshold potentials and may comprise only 2% of total

available current yet is sufficient to markedly affect neuronal firing (Huguenard 1996; Perez-Reyes 2006; Engbers et al. 2012). The size of the window current depends critically on the extent of overlap of Cav3 voltage for activation and inactivation, with a resulting cell-to-cell variation depending on the biophysical properties of Cav3 channels (Dreyfus et al. 2010). The role for Cav3 window current in controlling membrane excitability must then be assessed carefully in individual cell classes.

Modeling LVA Calcium Channels

T-type channel kinetics can be modeled using the Hodgkin-Huxley formalism with both activation and inactivation variables being described by Boltzmann functions (Fig. 1b). Steady-state voltage relationships are then described by the equation:

$$m_{\infty} = \frac{1}{1 + e^{\frac{-(V - V_a)}{k}}}$$

where m is the gating variable, V_a is the half-(in) activation voltage that satisfies $m_{\infty}(V_a) = 0.5$, and k is the slope factor which is positive for activation and negative for inactivation. The gating variables move toward the steady-state values as $t \rightarrow \infty$ according to the differential equation:

$$\frac{dm}{dt} = \frac{m_{\infty} - m}{\tau_m}$$

where τ_m is the gating time constant. Parameters for half-activation and inactivation voltages, as well as slope factors and time constants, have been determined experimentally and tabulated previously (Huguenard 1996; Ifinca et al. 2006). T-type channel gating can also be modeled with Markov state models (Chen and Hess 1990; Burgess et al. 2002).

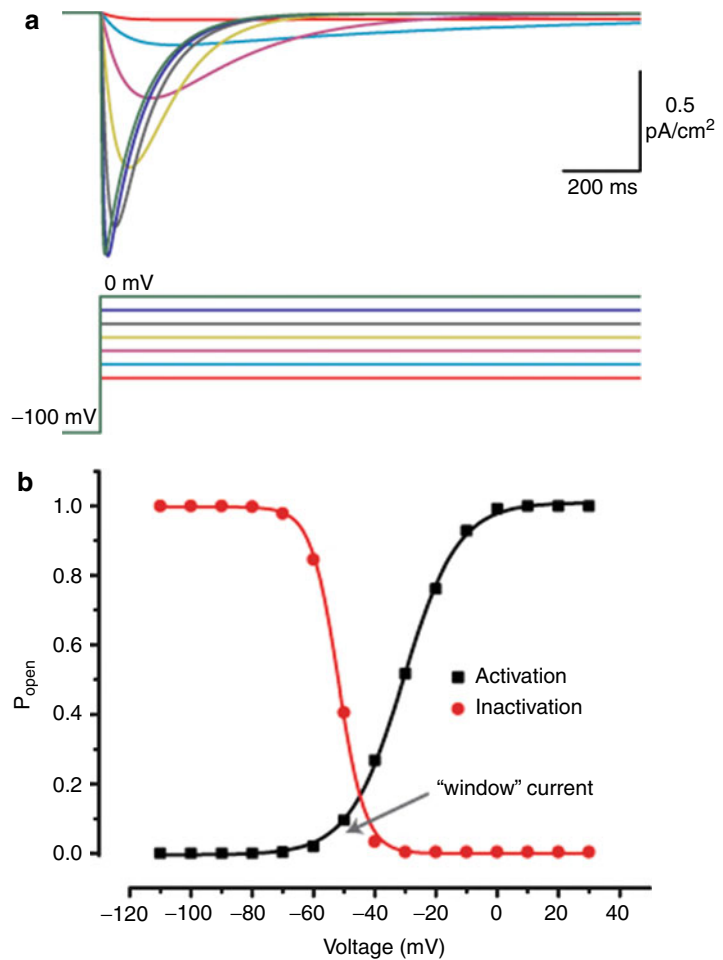
Once a model with suitable parameters has been chosen, LVA Ca^{2+} current (I_{CaT}) is described by the equation:

$$I_{CaT} = g_{CaT} \cdot m \cdot h \cdot (V - E_{Ca})$$

Low-Voltage-Activated Calcium Channels,

Fig. 1 Illustration of Cav3 activation and inactivation properties.

(a) Simulated LVA Ca^{2+} current based on a published model (Chen and Hess 1990). The model was held at -100 mV and voltage was increased in 10 mV steps (bottom). Currents are detected by -60 mV (red), with increased depolarization resulting in larger currents and faster inactivation, resulting in a transient current that exhibits a “crossover” at higher levels of depolarization due to the voltage dependence of inactivation. (b) Activation (black) and inactivation (red) plots of Cav3 channels exhibit an overlap to create a “window” current that straddles resting potential and spike threshold where Cav3 channels are constitutively active



where g_{CaT} is the conductance density of Cav3 channel, m and h are activation and inactivation gating variables, respectively, and E_{Ca} is the reversal potential for Ca^{2+} . It is important to note that differential permeabilities to Ca^{2+} and K^{+} ions cause the reversal potential for T-type current to deviate from the predicted Nernst potential of ~ 130 mV to a less polarized value of ~ 40 mV. Moreover, it is becoming increasingly common to model Ca^{2+} currents using Goldman-Hodgkin-Katz current equations; in this case the conductance density has to be replaced by a permeability.

Functions of LVA Calcium Channels

LVA current can generate a “low threshold spike” which leads to burst generation, such as that seen

in thalamic (Jahnsen and Llinas 1984) and cerebellar nuclear neurons (Jahnsen 1986; Molineux et al. 2006). Through interplay with other subthreshold currents, such as hyperpolarization-activated current (I_{H}), LVA current can generate pacemaker activity in neurons. The voltage-dependent inactivation of Cav3 channels can also give rise to multiple spiking modes, as seen for thalamocortical neurons, where tonic firing is observed at depolarized potentials that inactivate Cav3 channels and a burst firing mode at hyperpolarized potentials that deinactivate Cav3 channels.

Subthreshold activation allows Cav3 channels to affect synaptic integration, such as amplifying subthreshold excitatory postsynaptic potentials (Magee and Johnston 1995). While long believed to function in isolation, recent work indicates that

Cav3 channels can associate with both Ca^{2+} - and voltage-gated K^{+} channels to regulate cell output (Turner et al. 2011; Engbers et al. 2012; Rehak et al. 2013; Anderson et al. 2010). For reviews on LVA channel function, see the “References” section.

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Lumbar Spine Pain

- [Biomechanical Model of Low Back Pain](#)

M

Macaque Axonal Projection Matrix

► [Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)

Macaque Brain Wiring Diagram

► [Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)

Macrocolumn and Neural Population Models

► [Mesoscopic Anatomy and Neural Population Models](#)

Magnetic Paravertebral Stimulation

► [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Magnetic Spinal Stimulation

► [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Mammalian Motor Nerve Fibers, Models of

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Synonyms

[Cable model\(s\)](#); [Nerve fiber model\(s\)](#); [Neuron model\(s\)](#)

Definition

A model of a mammalian motor nerve fiber is a mathematical description of the electrochemical events taking place during the initiation and propagation of an action potential in a peripheral nerve fiber. This description accounts for the movement

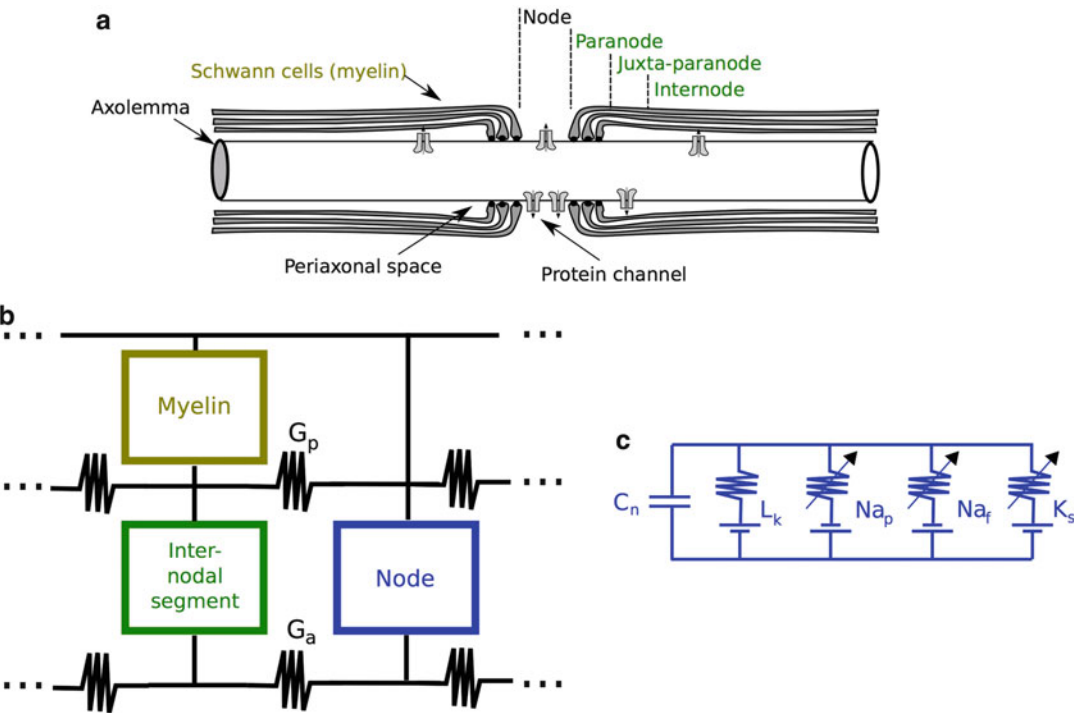
of ions through protein channels (conductances) embedded in the axon membrane. These channels are differentially distributed along different regions of the nerve fiber (e.g., node of Ranvier vs. internode) and have different conduction properties (e.g., fast sodium, persistent sodium, or slow potassium conductances).

Detailed Description

Anatomical Considerations

The cell body of a mammalian motor fiber resides in the ventral grey matter of the spinal cord or in the brainstem and projects its axon through a peripheral or cranial nerve that innervates its final target: the muscle fiber. The axonal

diameter of a mammalian α -motor neuron that innervates extrafusal muscle fibers typically falls between 9 and 20 μm (Eccles and Sherrington 1930). Additionally, its conduction velocity (speed at which it propagates an action potential) is approximately 6 m/s per μm of diameter (Hursh 1939). The axon of a motor fiber is predominantly covered by Schwann cells, which form a myelin sheath (Fig. 1a). At regular intervals of about 100 times the fiber diameter, however, the underlying axonal membrane is exposed at the nodes of Ranvier. These nodes exhibit a high concentration of certain ionic channels, particularly channels that conduct sodium in the mammalian fiber, and therefore most of the active conduction occurs at the nodes (saltatory propagation).



Mammalian Motor Nerve Fibers, Models of, Fig. 1 Modeling a mammalian motor fiber. (a) Diagram of a myelinated fiber showing the myelin sheath, mostly covering the axon except at the nodes of Ranvier, and protein channels embedded in the axolemma (axon membrane). The distinct segments of the fiber are also illustrated: node, paranode, juxta-paranode, and internode. (b) Double cable model of a mammalian myelinated fiber

showing a node connected to an internodal segment through an axoplasmic conductance (G_a) and to a myelin segment through a periaxonal conductance (G_p). (c) Electrical circuit equivalent model of the node of Ranvier used in McIntyre et al. (2002), including a linear leakage (L_k), fast (Na_f) and persistent (Na_p) sodium, and slow potassium (K_s) conductances, in parallel with the membrane capacitance (C_n)

Cable Model

The flow of ions (charges) involved in the initiation and propagation of an action potential can be calculated with electrical circuit equivalent models that account for the membrane capacitance (phospholipid bilayer) and the resistance or conductance of individual ionic channels (Fig. 1b, c). A short length or “patch” of nerve fiber membrane constitutes a compartment, which can be assembled in series with other compartments to represent a section or an entire fiber. In a myelinated fiber, each node of Ranvier can be represented as a single nodal compartment. In addition, if myelin acts as an electrical insulator, then consecutive nodal compartments can be coupled with single resistors. These resistors represent the intracellular conduction between nodes along the length of axon under the myelin. However, more comprehensive representations include a finite impedance myelin sheath attached to internodal compartments (Halter and Clark 1991). Furthermore, since the fiber morphology appears to play an important role in the threshold fluctuations following an action potential (recovery cycle), specific segments including the belt of myelin attachment and the paranodal region can be explicitly represented. Hence, a double cable model has been proposed in which the internodal segments are composed of the myelin sheath and the internodal axolemma (Fig. 1b) (Stephanova and Bostock 1995; Richardson et al. 2000; McIntyre et al. 2002).

Membrane Dynamics

Each compartment of the cable model represents the electrochemical properties of the associated membrane patch. First, since the phospholipid bilayer membrane acts as a dielectric separating two conductive media, it can be modeled as a capacitor. Secondly, the differences in concentrations of each ion between the intracellular and extracellular spaces (i.e., across the membrane) give rise to a transmembrane voltage difference that can be modeled with batteries representing the Nernst potential of each of the contributing ions. Finally, the protein channels embedded in

the membrane that allow passage of ions can be modeled with resistors. Under low-amplitude stimulation (below threshold), the ionic conductances (resistors) are represented with linear models. In this case, the membrane passively conducts current and no action potential occurs. However, larger stimuli (above threshold) can drive the membrane to conduct actively ionic currents. In this situation, the ionic conductances are better described by nonlinear models. According to the Hodgkin and Huxley (1952) formulation, the conductance of an ionic channel equals the maximum conductance multiplied by one or more gating variables. It follows that each gating variable, u , evolves according to the differential equation $du/dt = \alpha(1 - u) - \beta u$, where the parameters α and β are estimated empirically and usually vary with the transmembrane voltage.

In mammalian peripheral fibers, different types of sodium channels as well as slow voltage-gated potassium channels tend to concentrate in the node of Ranvier, whereas other potassium channels, cation channels, and calcium channels, as well as certain pumps and exchangers, concentrate in the paranode and internode (Krishnan et al. 2009). Consequently, models of mammalian motor fibers have represented the nodal compartments with fast (Na_f) and persistent (Na_p) sodium and slow potassium (K_s) conductances (e.g., Schwarz et al. 1995; McIntyre et al. 2002; Howells et al. 2012, who also added a fast potassium conductance), although models with a single sodium conductance have also been proposed (e.g., Chiu et al. 1979; Sweeney et al. 1987).

Recovery Cycle

Following an action potential, axons exhibit absolute and relative refractory periods, where they are less susceptible to re-excitation, followed by periods of decreased (supernormality) and increased (subnormality) thresholds that are associated with oscillations in the transmembrane voltage, termed depolarizing (DAP) and hyperpolarizing (AHP) afterpotentials, respectively. This sequence of changes in excitability following an action potential constitutes the recovery cycle

of axons. Models of motor fibers have illuminated the mechanism of the recovery cycle by incorporating more accurate geometrical and electrical descriptions of the axon. For instance, the double cable model of McIntyre et al. (2002) suggested that both persistent sodium current and passive discharge through the paranodal seal resistance contributed to the DAP, whereas AHP was mediated by slow potassium channels.

Difference with Sensory Fibers

Motor and sensory fibers differ in action potential shape, recovery cycle, and excitability properties (Howells et al. 2012). The mechanisms underlying these differences may be determined using fiber-type-specific models. For example, McIntyre et al. (2002) argued that the smaller supernormality of sensory fibers could be attributed to the kinetics of the sodium conductances rather than the density of these channels in the node. Specifically, they found that slowing the fast sodium channels resulted in reduced supernormality, which is consistent with experimental findings in sensory fibers. Similarly, both the duration and amplitude of the supernormal period decreased with faster sodium channel inactivation. Moreover, Howells et al. (2012) proposed that an increased expression of the fast isoform of the hyperpolarization-activated cyclic-nucleotide gated (HCN) channel could participate in limiting hyperpolarization in sensory fibers. Additionally, their model suggested that a reduced expression of slow potassium channels in the node of sensory fibers and the concomitant depolarization of resting membrane potential could be responsible for the broader action potential in these fibers. Taken together, these findings emphasize that dynamical and structural considerations can lead to more accurate models of functionally distinct fibers.

Cross-References

- [Axon, Modeling](#)
- [Cable Theory: Overview](#)
- [Hodgkin-Huxley Model](#)

- [Peripheral Nerve Models](#)
- [Resistivity, Axial](#)
- [Sodium Channels](#)

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Manual Parameter Tuning

► Neuronal Model Hand-Tuning

MAPK1, 2

► Extracellular Signal-Regulated Kinases, Models of

Markov Chains

► Markov Models of Ion Channels

Markov Models of Ion Channels

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Synonyms

Kinetic schemes; Markov chains

Definition

A Markov model is a simplified phenomenological representation of (bio)physical, chemical, or biological process dynamics, described quantitatively as a set of discrete states and by the ease of transition through time from one state to another.

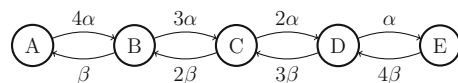
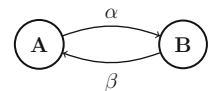
In chemistry, for instance, a complex reaction can be represented as a kinetic scheme, although ultimately it occurs from the rearrangement of

electrons in the bonds between atoms, according to the laws of quantum physics. Nonetheless, for most practical purposes, the changes of the reactants' concentration and their equilibria can be effectively predicted by a reduced kinetic description, involving simple concepts such as affinity, valence, and reaction rates.

In the context of modeling the ionic permeability of a protein channel and the activation of a (synaptic) membrane receptor, of a transporter, of a second messenger, or of the activity-dependent short-term synaptic plasticity (Destexhe et al. 1998; Yamada et al. 1998; Tsodyks et al. 1998), Markov models are widely used and defined as a weighted directed graph, such as those in Figs. 1 and 2. Individual nodes of the graph represent the discrete conformational states that the proteins tertiary or quaternary structure may assume at a given time, while the edges represent the possible transitions between states. In addition, a positive (kinetic) coefficient is associated with each edge, representing the frequency (or rate) of occurrence of the corresponding transition in time.

Of course, ion permeation across an excitable biological membrane ultimately depends on a variety of molecular properties, chemical interactions, and electrostatic effects (Johnston and Wu 1994; Hille 2001), including the primary structure of protein channels, their subunits' composition, the charge distribution across their domains, the electrostatic and geometrical properties of their

Markov Models of Ion Channels, Fig. 1 Markov model of a single ion channel, with two possible states: **A** and **B**. In the graph, the transition probabilities between states per unit of time are indicated by α and β , above each edge



Markov Models of Ion Channels, Fig. 2 Markov model of the Hodgkin-Huxley delayed rectifier potassium channel

selectivity filter, their phosphorylation binding sites, the local electric field, and so on. However, reduced phenomenological descriptions by Markov models allow one to understand and predict the evolution in time and the equilibrium of each membrane ionic conductance. For such reasons, Markov models are a versatile tool for modeling the ionic basis of cellular excitability.

We also remark that their description, based on a directed graph, captures an important feature of many – but not all – (bio)physical systems, the Markovian property (Cox and Miller 1965): the occurrence of a transition from a state to another depends only on the currently occupied state and on the transition rates of the edges originating from it, but not on the states occupancy history of the system.

Detailed Description

The most widespread application of Markov models, in the field of computational neuroscience, is the deterministic description of ionic membrane currents across an excitable cell membrane patch (Sterrat et al. 2011). Since these macroscopic currents emerge from the superposition of a large number of microscopic contributions across individual ion channels, we discuss first the dynamics of a single ion channel (Clay and DeFelice 1983; Hille 2001; Colquhoun and Hawkes 2009a). We then introduce the ionic permeability arising from a large population of identical and independent channels, discussing deterministic models of the macroscopic membrane currents. We then briefly discuss numerical methods for the simulation of both stochastic and deterministic versions of Markov models.

Stochastic Description: Single-Channel Dynamics

Let us consider the simplest ion channel: a membrane protein whose three-dimensional conformation has only two possible stable configurations. Therefore, at any given time, the channel can be found only in one of the two states (Fig. 1). We

completely neglect the molecular details underlying those stable configurations, as well as the mechanisms of state transition: we phenomenologically describe the system by naming its states with two abstract labels, **A** and **B**. We also assign to each possible transition its corresponding frequency of occurrence: these are assumed to be known from electrophysiological experiments (Conti and Wanke 1975; Colquhoun and Sigworth 2009; Milesu et al. 2008; Menon et al. 2009), and they have been indicated as α and β in Fig. 1 and have the unit of the inverse of a time.

The weighted graph summarizes the ion channel dynamics by implying a key underlying hypothesis: the transitions from **A** to **B** or from **B** to **A** occur randomly in time as Poisson point processes (Cox and Miller 1965), with parameters α and β , respectively. This can be rephrased equivalently by specifying the unpredictable character of the intervals between two successive random transitions: these intervals, known as the occupancy lifetimes T , are realizations of continuous random variables, with an exponential probability distribution density $f_T(T)$ (Papoulis and Pillail 2002; Colquhoun and Hawkes 2009a):

$$\begin{aligned} f_{T_A}(T) &= \alpha \exp(-\alpha T), & f_{T_B}(T) \\ &= \beta \exp(-\beta T) \end{aligned} \quad (1)$$

We reconcile our intuition with the style of (graphically) placing α and β above each edge in Fig. 1, by deriving the instantaneous transition probabilities. By definition of probability density, and by evaluating Eq. 1 over a very small interval $T = \Delta t$, it follows that

$$\begin{aligned} \text{Prob}\{\mathbf{A} \rightarrow \mathbf{B} \text{ in}[t; t + \Delta t)\} &= f_{T_A}(\Delta t)\Delta t \approx \alpha\Delta t \\ \text{Prob}\{\mathbf{B} \rightarrow \mathbf{A} \text{ in}[t; t + \Delta t)\} &= f_{T_B}(\Delta t)\Delta t \approx \beta\Delta t \end{aligned}$$

where higher-order infinitesimal terms (e.g., Δt^2 , Δt^3) have been ignored in the Taylor series expansion around $T = 0$, for each exponential function.

These transition probabilities, together with the initial occupancy (probability) conditions, fully describe the dynamics of the ion channel during both transients and steady state. In fact, the time-varying marginal probabilities of occupancy of

each state at time t , $P_A(t)$ and $P_B(t)$, can be readily computed from α and β and from the above hypotheses. To this aim, we consider an infinitesimal interval $[t; t + dt)$ and express the probability of observing the ion channel in a state (e.g., **A**) at $t + dt$, in terms of the same probability at t . This is equivalent to the conjunction and disjunction of four independent events, expressed by the known quantities: observing the ion channel in **A** at t and having no transition **A** $\rightarrow$ **B** during $[t; t + dt)$ or observing the ion channel in **B** at t and having a transition **B** $\rightarrow$ **A** during the same time interval. Formally, we can write two equations,

$$\begin{aligned} P_A(t + dt) &= P_A(t)(1 - \alpha dt) + P_B(t)\beta dt \\ P_B(t + dt) &= P_B(t)(1 - \beta dt) + P_A(t)\alpha dt \end{aligned}$$

which, in the limit $dt \rightarrow 0$, become a homogeneous system of linear ordinary differential equations, known as the Kolmogorov equations:

$$\begin{aligned} \frac{d}{dt}P_A(t) &= -\alpha P_A(t) + \beta P_B(t) \\ \frac{d}{dt}P_B(t) &= \alpha P_A(t) - \beta P_B(t) \end{aligned}$$

By matrix notation, these equations can be rewritten in compact form as

$$\frac{d}{dt}\mathbf{P} = \mathbf{Q}\mathbf{P} \quad (2)$$

by defining the (column) probability vector $\mathbf{P}$ and the (square) matrix $\mathbf{Q}$, known as *generator* matrix of the Markov model:

$$\mathbf{P} = \begin{pmatrix} P_A \\ P_B \end{pmatrix}, \quad \mathbf{Q} = \begin{pmatrix} -\alpha & \beta \\ \alpha & -\beta \end{pmatrix}$$

Solving Eq. 2 by analytical or numerical methods (see section “[Deterministic Simulations: Numerical Methods](#)”) gives a complete description of the system, as $\mathbf{P}(t)$ fully reveals statistically its state occupancies at any time t .

Of course, in most cases, a simple two-state kinetic scheme as that of Fig. 1 is not sufficient to model the dynamics of a generic ion channel. Nevertheless, Eq. 2 is a general formulation of the temporal evolution of the statistical occupancy of any Markov model. For kinetic schemes of arbitrary complexity with n states, the probabilities of occupancy at time t are still the solution of the system of n equations, formally Eq. 2, with an appropriate $n \times n$ generator matrix.

For instance, the voltage-gated delayed rectifier potassium channel (Hille 2001) of the Hodgkin-Huxley description of the squid giant axon excitability (Hodgkin and Huxley 1952) is best described by $n = 5$ states and 8 transitions, out of the $n(n - 1) = 20$ theoretically possible (Fig. 2). In this case, the scheme of Fig. 2 has a probability vector $\mathbf{P}$ and a generator matrix $\mathbf{Q}$, can be defined and derived as in the two-state model, and is given by

$$\mathbf{P} = \begin{pmatrix} P_A \\ P_B \\ P_C \\ P_D \\ P_E \end{pmatrix}, \quad \mathbf{Q} = \begin{pmatrix} -4\alpha & \beta & 0 & 0 & 0 \\ 4\alpha & -(3\alpha + \beta) & 2\beta & 0 & 0 \\ 0 & 3\alpha & -(2\alpha + 2\beta) & 3\beta & 0 \\ 0 & 0 & 2\alpha & -(\alpha + 3\beta) & 4\beta \\ 0 & 0 & 0 & \alpha & -4\beta \end{pmatrix}$$

We further remark that the transition rates, combined together as elements of $\mathbf{Q}$, can be in general positive functions of time or of any external variable that controls the channel dynamics (e.g., the membrane potential for voltage-gated ion channels or the concentration of a ligand for

ligand-gated ion channels). In this case, a closed-form analytical solution of Eq. 2 may not be available. We also note that, by definition, the occupancy probabilities sum to 1 (e.g., $P_A + P_B + \dots + P_E = 1$), so that given a kinetic scheme with n states, only $n - 1$ equations of Eq. 2 are

independent. Equivalently, the generator matrix $\mathbf{Q}$ always has at least one null eigenvalue.

We conclude this subsection by adding that no assumption has been made on the reversibility of the transition between any connected pair of states. At the thermodynamical equilibrium, it might be argued that the molecular mechanisms underlying the state transitions must obey a microscopic reversibility principle (Colquhoun and Hawkes 2009a). For the purpose of this review, Markov models have been considered as phenomenological abstract descriptions without accounting for any further microscopic details of channel gating. For instance, strongly asymmetric Markov models may still occur when the microscopic mechanisms are coupled to a source of energy (Colquhoun and Hawkes 2009a). Nonetheless, in the context of experimental identification of the parameters of a Markov model (Conti and Wanke 1975; Colquhoun and Sigworth 2009; Milesu et al. 2008; Menon et al. 2009), imposing constraints for the scheme reversibility might of course be advantageous as it reduces the number of free parameters (Colquhoun and Sigworth 2009).

Stochastic Description: Single-Channel Currents

Relating the ionic currents through a cell membrane patch to single-channel configurations is now mathematically straightforward. For simplicity, we discuss the case in which only one *open* state exists, among the n states of its kinetic scheme. Such a conformational state is the only one to have a nonzero electrical conductance, and we refer to such a value as γ (with typical values ≈ 1 –50 pS). We conventionally rename this state as **O** (e.g., corresponding to the state **B** in Fig. 1 or to the state **E** in Fig. 2), and we associate a (Bernoulli) random variable ξ to it, taking at time t the value 1 with probability $P_{\mathbf{O}}(t)$ or 0 with probability $1 - P_{\mathbf{O}}(t)$: $\xi(t)$ is then a stochastic process of time, with discrete (i.e., binary) values.

We note that, in the context of the matrix notation introduced earlier, $P_{\mathbf{O}}(t)$ can be concisely referred to the solution of Eq. 2, as $P_{\mathbf{O}}(t) = \mathbf{R}\mathbf{P}$, by the definition of an ad hoc (row) vector $\mathbf{R}$. This

vector has the same number of elements as $\mathbf{P}$, but all of them are identically zero except for the entry in the position corresponding to the **O** state, which is set to 1. For instance, referring to **O** as the state **B** in the scheme of Fig. 1 implies defining $\mathbf{R} = [0 \ 1]$, while as the state **E** in Fig. 2 implies defining $\mathbf{R} = [0 \ 0 \ 0 \ 0 \ 1]$.

Then, the ionic conductance of a single channel is also a Bernoulli random variable for each time t , $g_1(t) = \chi\xi(t)$, which can take either the value 0 or γ . When N identical and independent ion channels operate in parallel within the same membrane patch, we describe each channel by an identical Markov model and we associate to each of them an independent variable $\xi_k(t)$, $k = 1, 2, 3, \dots, N$, as defined before. The resulting overall conductance of the membrane patch is assumed to be the linear superposition of individual contributions, $g_N(t)$ is a stochastic process taking discrete random values γ , or 2γ , or 3γ , ..., or up to a maximal value $\bar{g} = N\gamma$, following a binomial probability distribution (Papoulis and Pillai 2002).

Under the common *ohmic* approximation (Sterrat et al. 2011), the ionic currents of a single channel $I_1(t)$ or of a population of N identical channels $I(t)$ are given by

$$\begin{aligned} I_1(t) &= g_1(t)(E_x - V_m(t)) \\ I(t) &= g_N(t)(E_x - V_m(t)) \end{aligned} \quad (3)$$

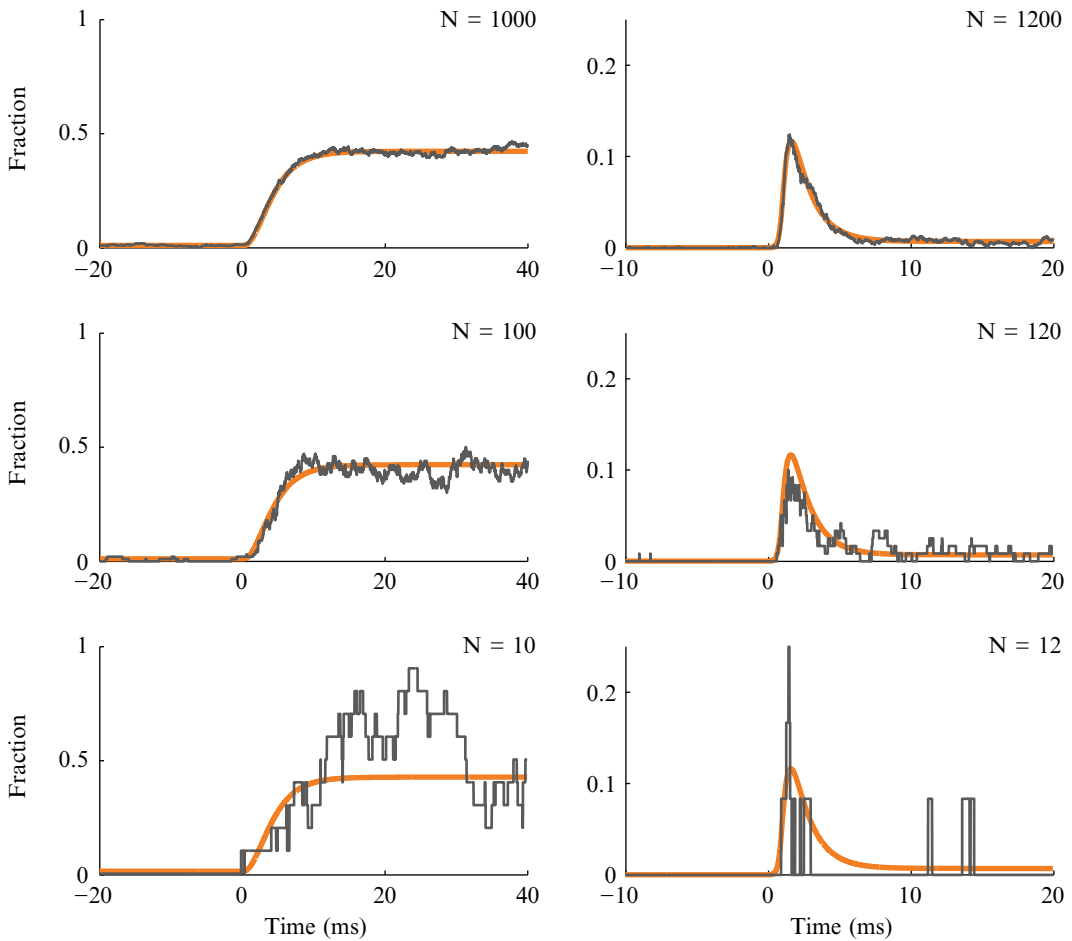
where E_x is the Nernst-Planck equilibrium potential for the ionic species x the channels are selectively permeable to (e.g., $x \in \{Na^+, K^+, Cl^-, Ca^{2+}\}$). Finally, $V_m(t)$ represents the transmembrane electrical potential of the membrane patch.

Introducing a precise motivation for the deterministic formulation of Markov models, discussed next for large populations of identical channels, we report below the ensemble mean and variance of $g_N(t)$ (Conti and Wanke 1975), indicating by $E\{\cdot\}$ the expected value:

$$E\{g_N(t)\} = \bar{g}P_{\mathbf{O}}(t) \quad (4)$$

$$\text{Var}\{g_N(t)\} = N^{-1}\bar{g}P_{\mathbf{O}}(t)(1 - P_{\mathbf{O}}(t)) \quad (5)$$

We observe that the variance decreases for increasing values of N . Therefore, by the law of



Markov Models of Ion Channels, Fig. 3 Numerical stochastic simulations of a step change in the transition rates of potassium (*left column*) and sodium (*right column*) Hodgkin-Huxley voltage-gated channels, obtained for increasing number of identical channels within the same membrane patch. The step is applied as a voltage step,

occurring at time $t = 0$ and ranging from -65 to -25 mV. The *black lines* are realizations of the stochastic process underlying channel dynamics (Eq. 3), while the *orange trace* is obtained as Eq. 4, solving numerically Eq. 2

large numbers (Papoulis and Pillail 2002), one may replace the stochastic temporal evolution of $g_N(t)$ by its ensemble mean $E\{g_N(t)\}$ for large N (e.g., in the hundreds or thousands), effectively ignoring the random fluctuations which are intrinsically associated to single-channel permeability. To better clarify this important point, we report the numerical simulations of the open-state dynamics of a population of N Hodgkin-Huxley fast-inactivating sodium ion channels or delayed rectifier potassium ion channels (as in Fig. 2) (Hodgkin and Huxley 1952). Both channel types are described by Markov models, with

kinetic rates that change as a function of V_m (Sterrat et al. 2011; Hille 2001). Figure 3 displays as black traces the realizations of the process $g_N(t)$, normalized to its maximal possible value $\bar{g}$. Such a normalization implies that the fraction of channels in the **O** state, out of the total N , is the quantity displayed. These realizations are compared to each others, upon increasing N , ranging from 10 to 1000 for potassium and from 12 to 1200 for sodium channels. The thick orange lines in each panel represent instead the expected value of $g_N(t)$ (see Eq. 4) under the same normalization. The generally good

agreement between fluctuating realizations and their ensemble averages, for large N (Colquhoun and Hawkes 2009a), illustrates that $E\{g_N(t)\}$ is a good representation of the collective behavior of the channel population, fully disregarding its stochastic properties.

We also remark that from the estimate of the variance of ion currents, recorded experimentally, the number N of channels underlying those currents can be also inferred (Conti and Wanke 1975).

Deterministic Description: Macroscopic Membrane Currents

The previous discussion illustrates that if the fluctuations arising from single-channel (stochastic) dynamics can be neglected (i.e., large N , in the hundreds or thousands), kinetic models and their mathematical formulation by Eq. 2 can still be employed. Equation 4 and Fig. 3 convincingly illustrate the relationship between stochastic and deterministic interpretations, which also corresponds to replacing the probability of an event in a single channel with the relative frequency of its occurrence in a population. In the last case however, the solution of Eq. 2 has a different meaning than the occupancy probabilities: it represents the fractions of state occupancies, across the channels of the population. Conceptually, this implies reinterpreting the Markov models (e.g., Figs. 1 and 2) as first-order kinetic descriptions of the fractions of channels in a given state.

Let us, for instance, consider again the two-state scheme of Fig. 1 and apply the law of mass action: the rate of a transition is proportional to the occupancy fractions of the participating states. This means that the changes in time of the fraction of channels in the state **A** and in the state **B** obey first-order kinetics. Indicating by $a(t)$ and $b(t)$ the fraction of channels in the states **A** and **B**, respectively (i.e., $a(t) + b(t) = 1$), the rate of decrease of $a(t)$ is proportional, via α , to $a(t)$ itself, while the rate of its increase is proportional, via β , to $b(t)$. Formally, this can be written as

$$\begin{aligned}\frac{d}{dt}a(t) &= -\alpha a(t) + \beta b(t) \\ \frac{d}{dt}b(t) &= \alpha a(t) - \beta b(t)\end{aligned}$$

As expected, these equations coincide with the differential equations derived for P_A and P_B : they describe in time the evolution of the ensemble average, i.e., $b(t) \approx E\{g_N(t)/\bar{g}\}$. For the same reason, the evolution of the occupancy fractions in a generic Markov model with n states is given by the solution of the homogeneous system of linear differential equations we already presented:

$$\frac{d}{dt}\mathbf{X}(t) = \mathbf{Q}\mathbf{X}(t) \quad (6)$$

where $\mathbf{X}(t)$ corresponds to $\mathbf{P}(t)$, under the relative frequency interpretation of the probabilities (i.e., as fractions). For the (deterministic) two-state model, the state vector and transition matrices take the form

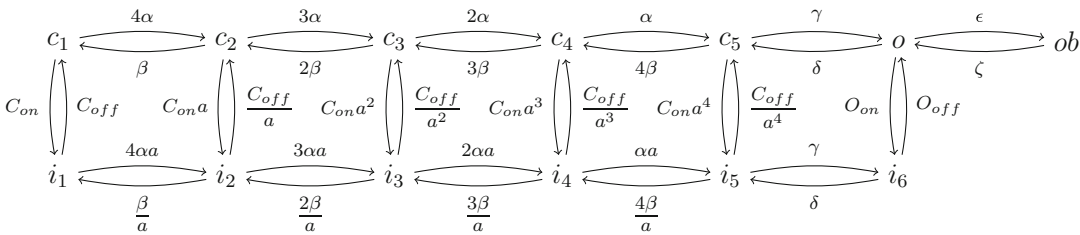
$$\mathbf{X}(t) = \begin{pmatrix} a \\ b \end{pmatrix} \quad \mathbf{Q} = \begin{pmatrix} -\alpha & \beta \\ \alpha & -\beta \end{pmatrix}$$

Regardless of the conceptual differences, Eqs. 6 and 2 are formally identical and share the exact same generator matrix $\mathbf{Q}$. As done before, assuming that only one *open* state exists and referring to the fraction of channels in such a state as $o(t)$, the macroscopic membrane current is given by

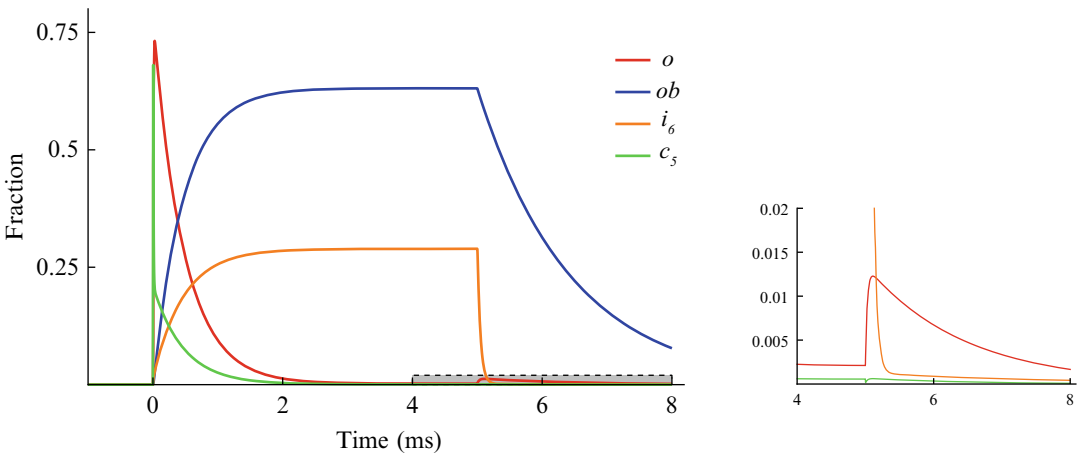
$$I(t) = \bar{g}o(t)(E_x - V_m(t)), \quad o(t) = \mathbf{R}\mathbf{X}(t)$$

We conclude this section by presenting an example of a “realistic” model, employed in real application to describe deterministically macroscopic membrane currents in neuron models: a Markov model of resurgent sodium channels. This model was originally identified in a series of electrophysiological experiments (Raman and Bean 2001; Khaliq et al. 2003) and is described by the kinetic scheme of Fig. 4, with $n = 13$ states and 34 transitions.

The peculiarity of this kinetic scheme is the presence of a “blocked” state **ob**, to which ion



Markov Models of Ion Channels, Fig. 4 Kinetic scheme for a resurgent sodium channel



Markov Models of Ion Channels, Fig. 5 Time course of a subset of the state occupation fractions, in the resurgent sodium kinetic scheme of Fig. 4, upon a step change

of the membrane potential from -80 to 40 mV applied at time $t = 0$ and lasting for 5 ms. The *dashed box* is expanded in the right inset

channels quickly transition from the open state. Channels in the **ob** state need to transition again through the open state **o** in order to either inactivate (e.g., **i₆**) or close (e.g., **c₅**), which leads to the resurgent behavior typical of these ion channels. We further note that not all the rate coefficients in Fig. 4 are voltage dependent and that their large diversity gives rise to a variety of time scales, both fast and slow, in the evolution of the state occupancy fractions over time. Figure 5 shows the behavior of a subset of the state variables in response to a step of voltage from -80 to 40 mV and back. The presence of multiple time scales is clearly visible, for instance, in the dynamics of the **i₆** and **c₅** states, while the open state **o** displays the typical inactivation dynamics of the sodium channels responsible for action potential generation. The inset on the right is an expanded view around

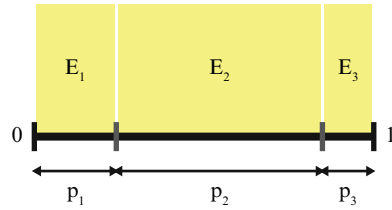
the time of the reset of the voltage to -80 mV: the transient increase in the fraction of channels in the open state (red trace) reflects the temporary “flow” of channels occupancies out of the blocked state (blue trace in the main panel) and it gives rise to an additional tail current component.

Stochastic Simulations: Exact Methods

The generation of pseudorandom numbers (Press et al. 2007) is the most important tool for computer simulating random transitions. These routines are today available in any programming language, computing environment, or neural simulator and enable the quick simulation of a variety of deviates (e.g., uniform, Gaussian, binomial, exponential, Bernoulli). For instance, generating

a realization of a uniform deviate r in the interval $[0, 1]$ is all that is needed to generate a Bernoulli deviate (e.g., ξ , as introduced earlier). In fact, when repeatedly generating several realizations of r , the number of times its values are below a desired parameter p (e.g., 0.74) is given by p 100% (e.g., 74%). It follows that simulating the occurrence of an event with probability, e.g., $P_O(t)$, is as easy as drawing a realization of r and using it within an *if-then* construct, to test for the condition $r \leq P_O(t)$:

- The first simulation method for a Markov model of a single ion channel, implied above, consists in solving (at any time step) Eq. 2 and then refers to its solution $P_O(t) = \mathbf{R}\mathbf{P}(t)$, in order to generate Bernoulli (i.e., $g_1(t)$) or binomial (i.e., $g_N(t)$) deviates (Press et al. 2007), needed to update Eq. 3.
- When solving Eq. 2 is computationally intensive, other methods known as Monte Carlo methods can be employed (Mino et al. 2002). The method known as *brute-force* requires to keep track of the current occupied state (for each channel) in the computer memory and consists in simulating the random occurrence of transitions from one state to another of the Markov model, solving no differential equations. This must be performed for each channel and at each time step, updating the current state as the result of the occurrence of a simulated random event. These events are related to the actual transitions of the Markov model, whose probabilities are of course contained in the generator matrix $\mathbf{Q}$. In fact, a uniform deviate allows one to simulate the random occurrence of a discrete event out of many possible outcomes (e.g., $\{E_1, E_2, E_3\}$), where each has its own probability (e.g., p_1, p_2, p_3). As those probabilities sum to 1, one can graphically arrange these probabilities as (unequal) segments one next to the other, covering the range $[0,1]$ of r , as in Fig. 6. Upon drawing a realization of r , one can test by multiple *if-then-else* constructs in which of the (three, in this example) intervals the current value of r is located. The equivalent simulated random event that has just been generated is the one corresponding to such an interval, e.g., event



Markov Models of Ion Channels, Fig. 6 The random occurrence of an event out of more than two possibilities ($\{E_1, E_2, E_3\}$ in this example), such as the random transitions to one out of more possible target states in a Markov model, can be computer simulated employing a uniform pseudorandom number and testing the interval its realization falls into

E_2 when $p_1 \leq r \leq p_1 + p_2$. For example, considering a single channel described by Fig. 2 and assuming that the currently occupied state is $\mathbf{D}$, the algorithm must simulate the occurrence of a discrete event out of three possible outcomes: $\mathbf{D} \rightarrow \mathbf{E}$, $\mathbf{D} \rightarrow \mathbf{C}$, or *stay in D*. All the transition probabilities from $\mathbf{D}$ must then be listed, $p_1 = \alpha dt$, $p_2 = \beta \beta dt$, $p_3 = 1 - (\alpha + \beta \beta)dt$, and conceptually arranged in the range $[0,1]$ as in Fig. 6. Drawing a realization of r , and computing in which interval r fell, reveals which of the three events occurred and indicates whether and how the currently occupied state has to be updated. Finally, the occupancy of the open state(s) $\mathbf{O}$ is the link to the actual simulation of the ion current (Eq. 3).

- The *brute-force* method must of course be repeated for each channel and at each time step. For such a reason, it is computationally intensive for moderate to large number of channels N . Most importantly, it requires a large number of deviates to be generated. A more conservative approach is the one of an alternative method that enjoys great popularity: the Gillespie's algorithm (Gillespie 1977). This method involves *event-driven* state occupancy updates, rather than repeating the update procedure at each time step of the simulation. Let us consider a single channel: an exponential deviate T is first generated, simulating the occupancy lifetime of the current state (e.g., as in Eq. 1), with parameter λ . This parameter is the unsigned element on the diagonal of the generator matrix $\mathbf{Q}$, corresponding

to the current state. The time of the simulation is then asynchronously advanced by T , as opposed to dt . Next, the update of the (newly) occupied state is performed, by drawing again a uniform deviate r and simulating the (conditional) random occurrence of a transition (i.e., excluding by the definition of lifetime the persistence in the current state). For instance, in the example of Fig. 2 and for the currently occupied state **D**, one first obtains a realization of T_D , distributed according to\

$$f_{T_D}(T) = \lambda \exp(-\lambda T) \quad \lambda = (\alpha + 3\beta)$$

by equivalently transforming a uniform deviate r as $T = -\log \frac{r}{\lambda}$ (Papoulis and Pillail 2002; Press et al. 2007). Next, another realization of r is drawn and used to randomly simulate the occurrence of one event with two possible outcomes **D** $\rightarrow$ **E** or **D** $\rightarrow$ **C**, each occurring with (conditional) probabilities $p_1 = \alpha(\alpha + 3\beta)^{-1}dt$ and $p_2 = 3\beta(\alpha + 3\beta)^{-1}dt$. Finally, the occupancy of the open state (s) **O** is the link to the actual simulation of the ion current (Eq. 3). Gillespie's algorithm is still computationally intensive, as the time of occurrence of transitions is inversely proportional to the number of channels. Thus, when a high number of channels are considered, this algorithm takes very small time steps, which often lead to prohibitive simulation times. On the other hand, for small enough number of channels, these algorithms are very appealing, since they provide an exact simulation of the Markov stochastic kinetics.

This algorithm can be generalized and improved, for simulating a population of channels (Skaugen and Walløe 1979; Chow and White 1996): instead of tracking the state of a single channel, one can describe and simulate how the number of channels in one state must be (randomly) updated by the end of a simulated occupancy lifetime.

Stochastic Simulations: Approximate Methods

An alternative class of algorithms have also been proposed, approximating the discrete-valued

stochastic process appearing in Eq. 3 (i.e., $g_N(t)$) as a continuous *diffusion* process (Fox and Yn 1994; Fox 1997; Linaro et al. 2011; Goldwin and Shea-Brown 2011). These algorithms are collectively known as *Langevin methods*, reminiscent of the equation in statistical mechanics describing the random movement of a particle in an aqueous medium, due to collisions with the molecules of the medium (i.e., Brownian motion). Instead of keeping track of the (microscopic) random collisions with every single molecule of the medium, such an equation approximates them by an effective (macroscopic) Gaussian distributed stochastic process, modeled as an external force field in the equation of motion of the particle.

While we point the reader to the cited references for an extended discussion of this approach, we note that in the previous subsections, $g_N(t)$ has been characterized as a binomial distributed stochastic process of time. Under some circumstances (e.g., empirically as $P_{ON} > 30$), a Gaussian deviate well approximates a binomial deviate (Papoulis and Pillail 2002), so that on a first approximation, it should be apparent that $g_N(t)$ in Eq. 3 might be replaced with an ad hoc designed stochastic process with correct mean (Eq. 4) and variance (Eq. 5), among other higher-order statistical properties (Linaro et al. 2011).

This approximation, which in the limit of an infinite number of channels N must coincide with the (deterministic) solution of Eq. 6, has a lower computational load than Monte Carlo methods, and the load is independent on the number of channels, making it most appropriate for moderate to large number of channels and in multi-compartmental neuron models.

Deterministic Simulations: Numerical Methods

When the transition rates, and thus the $n \times n$ elements of **Q**, are varying in time, the solution of Eq. 6 (and Eq. 2) can only be obtained numerically, for instance, by employing Runge-Kutta method (Press et al. 2007). The update of **X**(t) in time occurs by iterating few algebraic equations at each time step of the simulation. However, if

$\mathbf{Q}$ has constant elements, at least during each small integration interval dt , a variation of the explicit Euler forward method can be employed,

$$\mathbf{X}(t + dt) \approx e^{\mathbf{Q}(t)dt} \mathbf{X}(t) \quad o(t) = \mathbf{R}\mathbf{X}(t)$$

If the transition rates are constant in time (i.e., or even piecewise constant), the exact solution can also be obtained:

$$\mathbf{x}(t) = \mathbf{X}(0)e^{\mathbf{Q}t} \quad o(t) = \mathbf{R}\mathbf{X}(t)$$

where $\mathbf{X}(0)$ is the known occupancy fraction at the initial time $t = 0$.

The exponential of a matrix appearing in both equations above can be expressed using the spectral expansion $e^{\mathbf{Q}t} = \mathbf{A}^{(1)}e^{s_1t} + \mathbf{A}^{(2)}e^{s_2t} + \dots + \mathbf{A}^{(n)}e^{s_nt}$ (Colquhoun and Hawkes 2009b). The spectral matrices $\mathbf{A}^{(i)}$ are obtained by multiplying the i th column of the matrix $\mathbf{M}$ by the i th row of the inverse matrix $\mathbf{M}^{-1}$, where $\mathbf{M}$ is the matrix that contains, column-wise, all the eigenvectors of $\mathbf{Q}$ corresponding to the eigenvalue s_i . The parameters s_i , $i = 1 \dots n$, are in fact the eigenvalues of $\mathbf{Q}$ and are the roots of a polynomial of degree n , by definition obtained as the determinant of the matrix $\mathbf{Q} - s\mathbf{I}$, where $\mathbf{I}$ is the identity matrix. For Markov models of ion channels, these roots are in general real and positive and, for simplicity, we also assume that they are all distinct. We also note that as $\mathbf{Q}$ is singular, one eigenvalue is zero and we refer to it as s_1 .

From these considerations, $o(t)$ can be expressed as a simple weighted sum of exponential terms:

$$o(t) = o_\infty + h_2e^{s_2t} + h_3e^{s_3t} + h_4e^{s_4t} + \dots + h_ne^{s_nt}$$

In the previous expression, we have indicated by $O_\infty = \mathbf{R}\mathbf{X}_\infty$ the element corresponding to the open state $\mathbf{O}$, within the steady-state state vector $\mathbf{X}_\infty$ of Eq. 6. This can be obtained by linear algebraic methods as a solution of the equation $\mathbf{Q}\mathbf{X}_\infty = 0$ or more efficiently as

$$o_\infty = \mathbf{u}(\mathbf{S}^T\mathbf{S})^{-1}\mathbf{R}^T$$

where the matrix $\mathbf{S}$ and its transpose $\mathbf{S}^T$ have been obtained from $\mathbf{Q}$ by addition of an extra (rightmost) column composed of n identical unitary elements, while $\mathbf{u}$ is a (row) vector of n identical unitary elements (Colquhoun and Hawkes 2009b).

Finally, the coefficients $h_2, h_3, \dots, h_n$ are found as the (k th) row in the matrix $\mathbf{W}$ that corresponds to the open state $\mathbf{O}$ within $\mathbf{X}$ (i.e., $\mathbf{O}$ is the k th element of $\mathbf{X}$). The elements of $\mathbf{W}$ are computed as

$$w_{ij} = \sum_{r=1}^n \mathbf{x}_r(0)\mathbf{a}_{rj}^{(i)}$$

where $\mathbf{x}_r(0)$ is the r th element of $\mathbf{X}(0)$ and $\mathbf{a}_{rj}^{(i)}$ is the generic element of the spectral matrix $\mathbf{A}^{(i)}$.

Independent, Multiple Subunits' Markov Models

We have introduced and described so far a Markov model by means of a single-weighted directed graph. In some cases however, heuristic, experimental, or biophysical considerations may suggest symmetries and constraints on the geometrical arrangement and on the values of the rate coefficients (e.g., compare the scheme of Fig. 2 with the one of Fig. 4). Under these circumstances, a model with several states can be equivalently formulated as a set of Markov models, where each of them has an active and an inactive state (as in Fig. 1). Individual subsystems may not necessarily share identical transition rates and, as a whole, the entire system is said to be in the open state when all its parts are simultaneously activated.

The ionic permeability through a single channel is often attributed to the activation of multiple, independent, protein subunits, which together form the ionic pore through the membrane (Hille 2001). In these cases, following the approach originally proposed by Hodgkin and Huxley (1952), the dynamics of activation of each subunit may be

described as a 2-state Markov model, and the resulting membrane permeability is referred to the activations of all subunits at the same time. The single-channel conductance is then readily obtained as a new Bernoulli random variable η , $g_1(t) = \gamma \eta$ obtained multiplying together the elementary independent Bernoulli variables, each associated with a distinct subunit, e.g., $\eta = \xi^{(1)}(t)\xi^{(2)}(t)\xi^{(3)}(t)\xi^{(4)}(t)$, where each $\xi^{(k)}$ takes the value 1 with probability $P_{\mathbf{B}}(t)$ of the corresponding subunit graph. In the previous example, four independent subunits have been considered, and the channel is in the open state when all four are in an activate state (i.e., all in **B**). By describing each subunit by the same kinetic model of Fig. 1 (i.e., same α and β for all four subunits), it is easy to prove that this new description and the one of Fig. 2 are statistically equivalent.

It is possible to rewrite Eq. 3 for the stochastic description of single-channel currents as

$$I_1(t) = \gamma \eta (E_x - V_m(t))$$

$$I(t) = \gamma (\eta_1 + \eta_2 + \dots + \eta_k + \dots + \eta_N) (E_x - V_m(t))$$

and for the deterministic description of macroscopic membrane currents as

$$I(t) = \bar{g} \quad b(t)^4 (E_x - V_m(t))$$

The experimental identification and simulation of these channels is simpler than the full models discussed so far. This is apparent by inspecting the way the analytical expressions of the transient and steady-state solutions of Eq. 2 (and Eq. 6) reduce for multiple subunits, under the hypotheses of time invariance of the rate coefficients already mentioned earlier:

$$P_{A\infty} = a_{\infty} = \frac{\beta}{\alpha + \beta} \quad P_{B\infty} = b_{\infty} = \frac{\alpha}{\alpha + \beta}$$

and

$$P_A(t) = (P_A(0) - P_{A\infty})e^{-(\alpha+\beta)t} + P_{A\infty}$$

$$P_B(t) = (P_B(0) - P_{B\infty})e^{-(\alpha+\beta)t} + P_{B\infty}$$

$$a(t) = (a(0) - a_{\infty})e^{-(\alpha+\beta)t} + a_{\infty}$$

$$b(t) = (b(0) - b_{\infty})e^{-(\alpha+\beta)t} + b_{\infty}$$

Limitations

One of the main assumptions underlying the application of Markov models is the independence of the ion channels in a population. It has been proposed that this assumption may not be always accurate (Undrovinas et al. 1992; Marx et al. 2001) and that coupled gating, i.e., *cooperativity* in transition probabilities, should be instead considered. This was more recently suggested to be hypothesized, at least in specific compartments of neuronal morphologies, such as the axon initial segment, to explain experimental observations. As a consequence, a single-compartmental model has been proposed (Naundorf et al. 2006) that incorporates cooperativity among (groups of) sodium ion channels, where the rate coefficients of each channel depend on the occupancy state of neighboring channels. It was then shown that cooperativity explains some dynamical feature of action potential initiation in cortical neurons, in particular the steep slope of the membrane potential observed both *in vitro* and *in vivo* at the onset of the action potential.

However, it is important to note that analogous results have been obtained by employing independent sodium ion channels in a multi-compartmental neuron model (Yu et al. 2008).

Another fundamental assumption is that there exists a discrete set of stable configurations (i.e., states) in which an ion channel can reside. An alternative description has been introduced (Liebovitch and Tóth 1990), in which fractals are used to analyze single-channel data, leading to the introduction of a continuum of states, instead of the discrete set commonly used. This makes the transition probabilities depend on time, making the analysis, identification, and simulation more elaborate.

It is not however clear whether either of these alternative formulations realistically captures the biophysics of membrane permeability (Colquhoun and Hawkes 2009a).

Cross-References

- [Hodgkin-Huxley Model](#)
- [Nernst-Planck Equation](#)
- [Sodium Channels](#)

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Masking and Masking Release

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Definition

Masking has a technical definition of “the process ... and the amount by which the threshold of hearing for one sound is raised by the presence of another (masking) sound” (ANSI 2013). Masking release does not have such an established definition but refers to both the process and the amount by which masking is decreased by some manipulation of the masking or target sound.

Detailed Description

Masking is the process by which the presence of one sound makes another sound more difficult to hear. We all encounter masking in our everyday lives, when we fail to hear the phone ring while we are having a shower or when we struggle to follow a conversation in a noisy restaurant. In general, a more intense sound will mask a less intense sound, but masking also depends on the time and frequency relations between the sounds. In fact, much of the masking we encounter in everyday life can be explained in terms of processes that occur in the ear itself.

Origins of Masking

When sound enters the ear, it sets in motion a complex chain of events that results in the movement of the basilar membrane within the cochlea. The cochlea acts something like an acoustic prism, splitting sound up into its constituent frequency components. Each frequency within a sound sets up a traveling wave along the basilar membrane, which peaks at a point along the basilar membrane that is related to its frequency: high frequencies reach a peak closer to the base of

the cochlea, whereas low frequencies travel further along the basilar membrane, reaching a peak nearer to the apex of the cochlea. Von Békésy was awarded the 1960 Nobel Prize in Physiology and Medicine for his discovery of the traveling wave within the cochleae of human cadavers (von Békésy 1960).

Masking is often based on the extent to which the pattern of motion on the basilar membrane produced by the masking sound (the masker) interferes with the pattern of motion produced by the target sound (the maskee). Because of the way that filtering in the cochlea functions, low frequencies are more likely to mask high frequencies than vice versa, particularly at high sound intensities. This asymmetric aspect of masking at high intensities is known as the “upward spread of masking” (Egan and Hake 1950). Recent studies have found that behavioral and physiological measures produce very similar estimates of filter sharpness and shape (Shera et al. 2002; Sumner et al. 2018), strengthening the argument that many aspects of perceptual masking can be explained in terms of cochlear processing. The loss of sharp cochlear tuning that often accompanies cochlear damage leads to broader filtering and more masking – a physiological phenomenon that is likely to contribute to the difficulties experienced by people with hearing loss in noisy environments (Moore 2007).

Nonsimultaneous Masking

Most masking occurs when the masker and target overlap in time. This situation is known as simultaneous masking. In contrast to the visual system, the auditory system is relatively fast, so, unless the masker is loud enough to cause temporary or permanent hearing loss, the effects of a masker do not extend far beyond the end of the masker in time. However, if a very brief target occurs within 100–200 ms of the end of a masker, some “forward masking” will occur. “Backward masking” occurs when the audibility of a target is reduced by a masker that follows the target in time. However, the effect is generally small, extends for only a few milliseconds, and can

become almost negligible after extended practice (Oxenham and Moore 1995). It remains unclear where in the auditory system nonsimultaneous masking occurs. Cortical processes are suggested by the long learning period associated with backward masking, and even forward masking seems likely to be governed by processes higher than the auditory nerve (Relkin and Turner 1988; Oxenham 2001).

Informational Masking

Masking based on interactions within the cochlea is often termed “energetic masking.” There are other forms of simultaneous masking that can occur even when interactions within the cochlea are unlikely. These other types of masking come in different forms but have often been categorized together under the term “informational masking” (Watson 1987; Durlach et al. 2003). Relatively little is known about the causes of informational masking, although most forms can be ascribed to a perceptual “fusion” of the masker and target sounds and/or “confusion” of the target with elements of the masker. Relatively little is also known about the neural loci of informational masking, except that at least some forms seem to originate in the auditory cortex and not before (Gutschalk et al. 2008).

Speech Masking

One of the most important examples of masking is when speech is rendered difficult to understand by competing sounds in noisy environments. In a background of quasi-stationary noise, such as air-conditioning or heavy traffic, masking seems to be dominated by energetic masking, and speech intelligibility can often be well predicted by considering just the power spectrum of the speech and the noise (ANSI 1997). In more complicated, fluctuating maskers, such as someone else talking, masking appears to be a combination of energetic and informational masking.

Practical Applications

Quantitative models of auditory masking date back at least to the power spectrum model of Fletcher (1940) and more recently incorporate nonlinear aspects associated with

cochlear mechanics and auditory-nerve responses (Lopez-Poveda and Meddis 2001; Zilany and Bruce 2006). Even relatively simple models of masking, based on the spread of excitation within the cochlea, can produce reasonably accurate predictions of how audible a given target will be in the presence of a given masker; thus, our knowledge of auditory masking has practical implications for the design of acoustic signals and auditory warnings, such as ambulance sirens (Patterson and Mayfield 1990).

Although masking has disadvantages, such as making speech or warning signals more difficult to understand in noisy environments, it can also be used to advantage in some situations. For instance, low bit-rate digital coding of speech and music, using formats such as MP3, relies on auditory masking (Brandenburg 1999). Reducing the resolution of the digital code to save space results in a noisier recording, but the coding algorithm ensures that the additional noise is masked by the music or speech itself, so that there is little or no perceptual degradation of the signal.

Masking Release

The term masking release refers to a reduction in masking produced by a change in either the masker or the target. The most commonly studied forms of masking release involve changes to the spatial relations between the masker and target. For instance, if the maskers and target are both located in front of the listener and the maskers are then moved to the left and right of the target, some masking release may occur, because the binaural system can now take advantage of differences between the ears to extract more information about the target (Gallun et al. 2005). Differences in other features, such as pitch or vocal tract length, between the target and maskers can also lead to masking release (Darwin et al. 2003). Another form of masking release involves introducing amplitude modulation to the masker. The amplitude modulation introduces momentary improvements in the target-to-masker ratio, which can lead to improved audibility of both speech and non-speech targets (Gregan et al. 2013). Hearing loss often leads to reduced masking release (Marrone et al. 2008) for reasons

that may include reduced audibility, poorer peripheral encoding of suprathreshold sounds, and impaired binaural processing.

Cross-References

- [Anatomy and Physiology of the Mammalian Auditory System](#)
- [Auditory Perceptual Organization](#)
- [Neural Coding of Speech Sounds](#)
- [Spectrotemporal Receptive Fields](#)

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Master Stability Function for Globally Synchronized Systems

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Definition

One of the most common structures of dynamical systems in a network is the basic situation of

having all the network nodes being identical oscillators or other dynamical systems and the edges being different couplings between the nodes and oscillators. A basic question in this case is whether all the oscillators can synchronize with each other creating an emergent, extremely coherent state and, if this motion is possible, under what circumstances is it stable. We show here that the case of identical synchronization (all oscillators are executing identical dynamical motions at the same time) permits the solution of the stability equations in a very simple form which decomposes the perturbation dynamics into synchronized and unsynchronized perturbations, greatly reduces the computations, and allows generalizations about the synchronization conditions and system parameters to be made.

Detailed Description

The General Dynamical Equations

Synchronized behavior is a collective phenomenon and its occurrence indicates a cooperative or constrained action. It is a pattern of dynamics that greatly simplifies motion in what could be a complex network of systems. Such behavior might model many systems in physics, chemistry, or biology. A few examples are networks of magnetic spins, chaotic chemical reactions, flocking or schooling of animals, and firing of neurons. Given such applications, it would be useful if we could say some general things about such dynamics and, especially, find ways to simplify the analysis of many networks of oscillators. To do this, we need to set up the structure of such a system and identify the right questions to ask.

The mathematical questions are the following. Given a set of identical or nearly identical oscillators in a network, under what conditions can they sustain synchronized behavior? Here by synchronized we mean that they are all doing the same dynamics (or nearly so) at the same time. If the answer is yes, then an additional important question is, for what parameter values (e.g., coupling strength) is the synchronized state stable?

The first question will put constraints on the equations of motion. Here we use ordinary differential equations (ODE) although most of what is presented here generalizes to other situations, e.g., iterated maps. We will start with simple models and generalize.

Since we want the oscillators in the network to be identical, we can start with a network where each node is an oscillator whose isolated dynamics is given by a differential equation

$$\frac{dx}{dt} = \mathbf{F}(\mathbf{x}). \quad (1)$$

Here $\mathbf{x}$ and $\mathbf{F}$ are n -dimensional vectors. The simplest way to connect them in a network is to label each node's vector by its number in a subscript on the vector and write the general ODE for each node as

$$\frac{d\mathbf{x}_i}{dt} = \mathbf{F}(\mathbf{x}_i) + \sigma \sum_{j=1}^N C_{ij} \mathbf{x}_j, \quad (2)$$

where there are N nodes in the network and σ is the overall coupling strength. If any two nodes are not coupled, we set the coupling matrix $C_{ij} = 0$. Note that each node has the same vector field. However, we still have to check that synchronized dynamics is possible. If we put the network in a synchronized state, we have $\mathbf{x}_i = \mathbf{s}$ for all nodes, where $\mathbf{s}$ is any n -dimensional vector. The constraint $\mathbf{x}_i = \mathbf{s}$ defines a subspace that is a submanifold of the whole space where all the components of the dynamical node vectors are equal. This is often called the **synchronization manifold**, and it is the n -dimensional analog of the 45° diagonal in two dimensions where “ $x = y$.” It is easy to see that if we do this in Eq. 2, the motion will not stay in a synchronous state in general, i.e., the system will generally evolve to a state where the $\mathbf{x}_i$ are not all equal. If we substitute $\mathbf{x}_i = \mathbf{s}$ into Eq. 2, we get

$$\begin{aligned} \frac{ds}{dt} &= \mathbf{F}(\mathbf{s}) + \sigma \sum_{j=1}^N C_{ij} \mathbf{s} \\ &= \mathbf{F}(\mathbf{x}_i) + \sigma \left(\sum_{j=1}^N C_{ij} \right) \mathbf{s} \text{ for node } i. \end{aligned} \quad (3)$$

The only way all nodes have the same behavior is to have the sum, $\sum_{j=1}^N C_{ij}$, be the same for all i . Hence, our first restriction to get complete, identical synchronization is that the row sums of the coupling matrix must be the same for all rows. Very often, the row sum is taken to be zero. This means the motion for all coupling strengths σ is the same as given by Eq. 1; otherwise, the synchronized motion changes as coupling-strength changes. When the row sum is zero, the coupling is often described as being in a **Laplacian** form which is a term from graph theory, the mathematics of networks and their structure. A constant row sum means that if the motion is started in a synchronized state, it remains in a synchronized state. Mathematically, it is said that the synchronized state is **flow invariant**. This is a requirement to have synchronized motion.

We can rewrite the equations of motion so that the coupling has zero row sum by defining a new vector field $F'_i(x_i) = F(x_i) + \left(\sigma \sum_{j=1}^N C_{ij} \right) x_i$ so that the equations of motion become

$$\frac{dx_i}{dt} = F'_i(x_i) + \sigma \sum \left[C_{ik} - \left(\sum_{j=1}^N C_{ij} \right) \delta_{ik} \right] x_j, \quad (4)$$

where the new coupling matrix has zero row sum. We must remember that this case has different dynamics than the Laplacian form. In the Laplacian case, the synchronized motion is the same for all coupling strengths σ , but in Eq. 4 the synchronized dynamics depends on σ because of the extra term in F'_i .

We can generalize the above situation by using an output function $\mathbf{H}$ from each node's oscillators instead of just the dynamical variable. $\mathbf{H}$ is the same for all oscillators. The equations of motion would then look like

$$\frac{dx_i}{dt} = F(x_i) + \sigma \sum_{j=1}^N C_{ij} H(x_j). \quad (5)$$

It is easy to show that the requirement for the existence of a synchronized state is again that all row sums of the coupling matrix C_{ij} are equal. Equation 5 is much more general than Eq. 3. It includes the case of coupling through only a few components of each node rather than all of them and various nonlinear functions of each node's components.

Finally, we consider a very general case which is useful to think about since it forces us to think more deeply about the phenomenon of synchronization. Let the vector $\mathbf{x}$ be the collection of all the N node dynamical vectors $\mathbf{x}_i$, that is, we can write $\mathbf{x} = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N)^T$. From here on, we assume all the vectors are actually column vectors, but we will suppress the transpose T in the notation. Now we write the network's equation of motion as

$$\frac{d\mathbf{x}}{dt} = \mathbf{G}(\mathbf{x}), \quad (6)$$

where $\mathbf{G}$ is a vector of functions $\mathbf{G} = (\mathbf{G}_1, \mathbf{G}_2, \dots, \mathbf{G}_N)$ so that the equation of motion for each node is $\frac{dx_i}{dt} = G_i(\mathbf{x})$. That is, each node has dynamics that is tailored for it. For example, using the above, we would have $G_i(\mathbf{x}) = F(x_i) + \sigma \sum_{j=1}^N C_{ij} x_j$,

although we are now allowing much more general functional forms. As before, we need to constrain the dynamic functions to ensure total synchronization of the nodes. This means we want the synchronized state to be flow invariant, so that if we start in a synchronized state $\mathbf{S} = (\mathbf{s}, \mathbf{s}, \dots, \mathbf{s})$, we stay in a synchronized state, i.e., we stay on the synchronization manifold. This requires

$$G_i(\mathbf{S}) = G_j(\mathbf{S}) \forall i, j. \quad (7)$$

Note: this equality only need hold on the synchronization manifold. We can't say much beyond this, but in the next section, we will make some simplifying assumptions that will enable the analysis to continue for the most general case.

Stability of the Synchronized State

If our system obeys the synchronization constraints of the previous section, it will support

synchronized motion. This leads to an important question: will the synchronized motion be stable? In most experiments and real systems, if synchronized motion is not stable, we will never see it. Any small perturbation will grow and the dynamics will move away from synchronization to some other dynamical behavior. Here we will examine the criteria for linear stability, that is, that small perturbations to the dynamical variables $\{\mathbf{x}_i\}$ will generally die out and the system will return to its synchronized state where $\mathbf{x}_i = \mathbf{s} \forall i$. We will be able to derive some very general results using linear stability, but the reader should be aware that there are other criteria for synchronization such as Lyapunov functions (Guckenheimer and Holmes 1983). These are stronger conditions for synchronization, but much harder to prove and generalize.

Suppose our system is synchronized and we perturb it so that each node is, in general, slightly “away” from the synchronized motion. As before, let $\mathbf{s}(t)$ represent the synchronized motion. We want to consider what happens when we replace each node’s dynamics with dynamics slightly different from the synchronized state. Let ξ_i be a small perturbation of the i th node so that after the perturbation, $\mathbf{x}_i = \mathbf{s} + \xi_i$. We can now derive an equation of motion for the small perturbations which will tell us if they will grow or shrink, that is, if the synchronized state is unstable or stable, respectively.

We’ll start with the simplest form of dynamics, Eq. 2. The perturbed equations are

$$\frac{d(\mathbf{s} + \xi_i)}{dt} = \mathbf{F}(\mathbf{s} + \xi_i) + \sigma \sum_{j=1}^N C_{ij}(\mathbf{s} + \xi_j)$$

If we subtract the equations of motion from the above, we get

$$\frac{d\xi_i}{dt} = \mathbf{F}(\mathbf{s} + \xi_i) - \mathbf{F}(\mathbf{s}) + \sigma \sum_{j=1}^N C_{ij}\xi_j$$

Now we use Taylor’s theorem and expand $\mathbf{F}(\mathbf{s} + \xi_i)$ to first order (since ξ_i is small) to get

$$\begin{aligned} \mathbf{F}(\mathbf{s} + \xi_i) &\approx \mathbf{F}(\mathbf{s}) + \left. \frac{\partial \mathbf{F}}{\partial \mathbf{x}} \right|_{\mathbf{x}=\mathbf{s}} \cdot \xi_i \\ &\equiv \mathbf{F}(\mathbf{s}) + D\mathbf{F}(\mathbf{s}) \cdot \xi_i \end{aligned}$$

where we have defined the Jacobian $D\mathbf{F}$ evaluated on the synchronized state. $D\mathbf{F}$ is a matrix which multiplies the perturbation ξ_i . Combining the last two equations, we get the equation of motion for the perturbations also called the **variational equations** of the dynamics

$$\begin{aligned} \frac{d\xi_i}{dt} &= D\mathbf{F}(\mathbf{s}) \cdot \xi_i + \sigma \sum_{j=1}^N C_{ij}\xi_j \\ &= \sum_{j=1}^N [\delta_{ij} D\mathbf{F}(\mathbf{s}) + \sigma C_{ij} \mathbf{1}_n] \cdot \xi_j \end{aligned} \quad (8)$$

where δ_{ij} is the Kronecker delta and $\mathbf{1}_n$ is the $n \times n$ **identity matrix**. Equation 8 is the equation of motion for the evolution of the perturbations ξ_i . Note that it is time dependent (through $\mathbf{s}(t)$) and linear.

We can write Eq. 8 more compactly using direct or tensor product notation which is very handy when manipulating linear matrix equations of this form. Given two matrices, $\mathbf{A}$ being $m_1 \times n_1$ in dimension and $\mathbf{B}$ being $m_2 \times n_2$ in dimension, we define the $(m_1 + m_2) \times (n_1 + n_2)$ matrix $\mathbf{C}$ by the direct product

$$\begin{aligned} \mathbf{C} &= \begin{pmatrix} A_{11}\mathbf{B} & A_{11}\mathbf{B} & \cdots & A_{11}\mathbf{B} \\ A_{21}\mathbf{B} & A_{22}\mathbf{B} & \cdots & A_{2n_1}\mathbf{B} \\ \vdots & \vdots & \vdots & \vdots \\ A_{m_1 1}\mathbf{B} & A_{m_1 1}\mathbf{B} & \cdots & A_{m_1 n_1}\mathbf{B} \end{pmatrix} \\ &\equiv \mathbf{A} \otimes \mathbf{B}, \end{aligned}$$

where, for example, the upper left-hand block $A_{11}\mathbf{B}$ is $m_2 \times n_2$ and consists of A_{11} times the matrix $\mathbf{B}$. The advantage of this notation is that one can operate on the first and second factors of the direct product separately, namely, $\mathbf{A} \otimes \mathbf{B} \cdot \mathbf{D} \otimes \mathbf{E} = (\mathbf{A} \cdot \mathbf{D}) \otimes (\mathbf{B} \cdot \mathbf{E})$, assuming the dimensions of the matrices are properly matched. Using this notation, we write

$$\frac{d\tilde{\xi}}{dt} = \left[\mathbf{1}_N \otimes DF(s) + \sigma C \otimes \mathbf{1}_n \right] \cdot \tilde{\xi}, \quad (9)$$

where $\tilde{\xi} = (\xi_1, \xi_2, \dots, \xi_N)$ and $\mathbf{1}_N$ is the $N \times N$ identity matrix.

Solutions of Eq. 9 yield perturbations which will (very roughly speaking) grow or shrink exponentially. Thus (abusing the notation), $\xi_i e^{\mu_i t}$. The exponents μ_i tell us if the perturbation grows ($\mu_i > 0$) or shrinks ($\mu_i < 0$), the former indicating a direction that is unstable and the latter a stable direction. In order for the synchronized state to be stable, all exponents must be negative. There are standard ways to calculate the exponents. When the behavior is periodic, one calculates **Floquet multipliers** or **exponents** (Guckenheimer and Holmes 1983), and when the behavior is chaotic, one calculates **Lyapunov exponents** (Guckenheimer and Holmes 1983).

However, there are two problems with Eq. 9: one is structural and the other problematic in efficiency. The structural problem arises because we don't want to consider all perturbations. One way to cover all possible perturbations is to take all components of perturbations and run them through the variational equation to get all stability exponents. This means we replace the single column vector of perturbations $\tilde{\xi}$ with a matrix of perturbations in all components

$$\begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix} \delta,$$

where δ is a small n -dimensional vector. We can evolve the above identity matrix and calculate all exponents, in principle. The problem comes in that we have not separated the synchronous perturbations from the nonsynchronous perturbations. The synchronous perturbations simply add the same perturbation to all nodes keeping them synchronized. This tells us the exponents of the synchronous dynamics which will tell us nothing about whether the nonsynchronous perturbations die out or grow. The latter tells us if the

synchronous state is stable. We have to find a way to get the synchronous perturbations separated from the nonsynchronous (transverse) perturbations.

The second problem is efficiency of the calculations. We only need the largest exponents (Floquet or Lyapunov) to tell us about the stability of the transverse perturbations. But we are calculating nN exponents. If we have 100 nodes each with a three-dimensional oscillator, we have $nN = 300$ dynamical perturbation variables.

We can solve both the structural and efficiency problem with one transformation of the variational equations. If we look at Eq. 9 and concentrate on the first matrix in each term, we see that the first term is diagonal ($\mathbf{1}_N$), but the second is not. However, we can diagonalize the σC factor, and this will not affect the first term since $\mathbf{1}_N$ commutes with the diagonalizing transformation matrices. This leaves us with variational equations which are diagonal in the node coordinates and are now uncoupled and individually look like

$$\frac{d\zeta_k}{dt} = [DF(s) + \sigma \lambda_k \mathbf{1}_n] \cdot \zeta_k \quad (10)$$

where λ_k is an eigenvalue associated with the eigenvector direction of ζ_k of the network given by C .

We can now make an important observation. All the eigenvalue perturbation equations are of the same form. Only the eigenvalue is different in each. If we take the general form of the variational equation (Eq. 10) to be

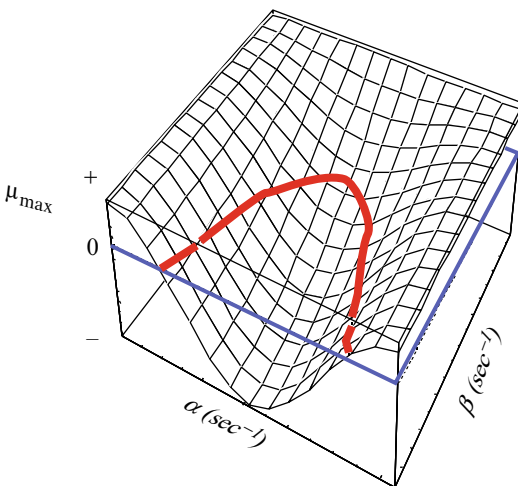
$$\frac{d\zeta}{dt} = [DF(s) + \sigma z \mathbf{1}_n] \cdot \zeta, \quad (11)$$

where z is a complex number (in general, the eigenvalues of C are complex since C is not necessarily symmetric). Now if we calculate the maximum exponent of Eq. 11 on a fine grid over the complex plane sufficiently large to encompass all eigenvalue $\times$ coupling strength products of Eq. 10, then for any network of this particular oscillator with the coupling we chose above, we can quickly find the stability of all the possible

eigen-directions by looking up the value of the product $\sigma\lambda_k$ on the grid and reading its stability exponent. If that exponent is negative, the eigenmode is stable, and if positive, the eigenmode is unstable. It is easy to show that the eigenvector associated with the synchronization manifold is given by $\zeta_0 = (1, 1, \dots, 1)$. Hence, we look at the exponents associated with all other eigenvalues and those are the transverse (nonsynchronous) perturbations.

We have reduced the number of computations by this eigenvalue transformation, decoupled the transverse and synchronous perturbations, and provided once and for all a function on a grid in the complex plane which gives the stability of the transverse modes for any network $\mathbf{C}$ that we choose for this oscillator. This function is called the **master stability function**. The master stability function (MSF) is a function on $\mathbb{C} \rightarrow \mathbb{R}$. If the network is symmetric, then the eigenvalues are real and the MSF is a function on the real line, $\mathbb{R} \rightarrow \mathbb{R}$. Once the MSF is known for an oscillator and coupling type, then the stability of the synchronous state for any network of that oscillator is just an eigenvalue calculation for the coupling matrix $\mathbf{C}$.

Figure 1 shows a schematic of one type of an MSF ($\mu_{\max}$) as a function of $z = \alpha + i\beta$. Inside the red boundary is the stable zone. If all coupling $\times$



Master Stability Function for Globally Synchronized Systems, Fig. 1 The MSF $\mu_{\max}(\alpha, \beta)$ for a fictional oscillator shown just to acquaint the reader with the concept

eigenvalue products for a network of identical oscillators fall inside the red boundary, then the synchronization state is stable. If even one product falls outside the stable zone, then that eigenmode is unstable and the synchronization state is unstable. In fact the first instability the synchronization state will display as it goes unstable will the spatial pattern of the eigenvector associated with the unstable mode. This is shown in more detail in Pecora (1998).

Using the same formulation as above, it is easy to show that the perturbation equation for the MSF for the more general coupling case (Eq. 5) is

$$\frac{d\zeta}{dt} = [DF(s) + \sigma z DH(s)] \cdot \zeta, \quad (12)$$

where we now have the Jacobian of the coupling or output function $\mathbf{H}$. Now the MSF will depend on the coupling function, too. But, again, for the same vector field and coupling function, we can calculate the stability of the synchronized state once and then easily determine the stability of any network with those oscillators and coupling.

Finally, we can produce an MSF for the more general case Eq. 6 if we make some simplifying assumptions about the Jacobians of the general vector field for the whole system $\mathbf{G}(\mathbf{x})$. Starting with the general variational equation, we separate out the diagonal terms in the Jacobian ($D_i \mathbf{G}_j = j$) from the off-diagonal terms ($D_i \mathbf{G}_j \neq j$),

$$\frac{d\zeta_i}{dt} = \left[D_i \mathbf{G}_i(s) + \sum_{i \neq j} D_i \mathbf{G}_j(s) \right] \cdot \zeta_i$$

Since we are using identical oscillators, the diagonal terms are all the same function form, and we set them equal to $D_i \mathbf{G}_i(s) = DF(s)$. And since we expect the coupling functional forms to be the same for all nodes in the network, we set $D_i \mathbf{G}_j$ proportional to the same function of s , namely, $D_i \mathbf{G}_j(s) = C_{ij} \mathbf{H}(s)$, and we note these simplifications only need hold on the synchronization manifold. Hence, even a very general case may possibly have a variational form that permits the calculation of an MSF from an ODE form like Eq. 12.

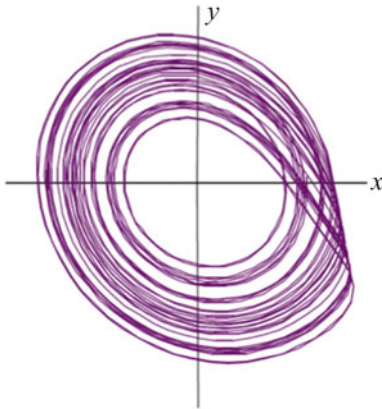
Calculated Examples of MSFs

Here we show contour plots of the MSF for a Rössler-like oscillator for two different coupling functions $\mathbf{H}$. If we let x_i^j be the j th component of the i th node's dynamical variable, the nodes are assumed to have oscillators which obey the equations

$$\begin{aligned}\frac{dx_i^1}{dt} &= -k(ax + by + cz) \\ \frac{dx_i^2}{dt} &= -k(x + fy) \\ \frac{dx_i^3}{dt} &= -k(-g(x_i^1) + x_i^3) \\ \text{with } g(x_i^1) &= \begin{cases} 0, & \text{if } x_i^1 \leq 3 \\ h, & \text{if } x_i^1 > 3 \end{cases}\end{aligned}\quad (13)$$

where $a = 0.05$, $b = 0.5$, $c = 1.0$, $f = 0.133$, and $h = 15$. The constant k is simply a time-scaling factor, which for our system is 104 s^{-1} . An isolated node produces an attractor that is similar to the original Rössler system as shown in Fig. 2. The Jacobian of Eq. 13 is

$$DF(x_i) = \begin{pmatrix} -kax_i^1 & -kbx_i^2 & -kcx_i^3 \\ -kx_i^1 & -fx_i^1 & 0 \\ -k\frac{dg}{dx}|_{x_i^1} & 0 & -kx_i^3 \end{pmatrix}$$



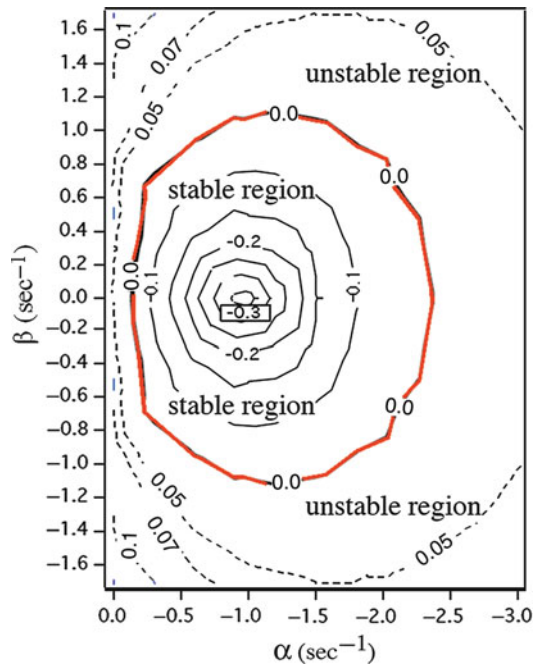
Master Stability Function for Globally Synchronized Systems, Fig. 2 The attractor of the Rössler-like oscillator

We choose our first coupling function to be

$$\mathbf{H}(x_i) = \begin{pmatrix} x_i^1 \\ 0 \\ 0 \end{pmatrix} = D\mathbf{H}(x_i).$$

In other words, we are coupling all the oscillators in our network through only the first component. Now we can use Eq. 12 with the above substitutions to generate the MSF for this oscillator in a network with the given coupling above. This is shown in Fig. 3.

The MSF for the x_i^1 -coupled case has a finite, single minimum stability region. Networks of this oscillator will only synchronize if the coupling-strength-eigenvalue products all fall into the stability island. For some networks, it is not possible to get all products in the stable region, and it is possible to cause desynchronization if the



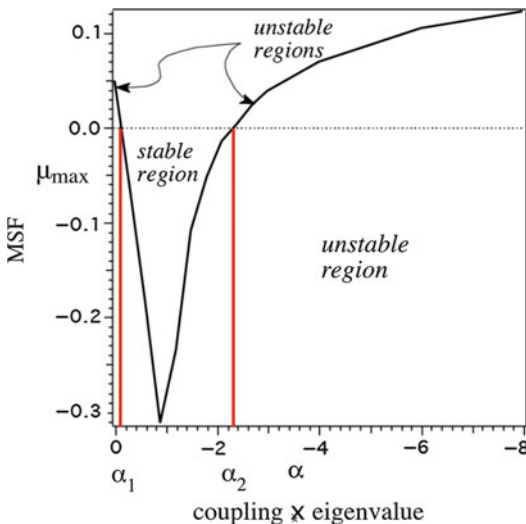
Master Stability Function for Globally Synchronized Systems, Fig. 3 The MSF for the x_i^1 -coupled Rössler-like system in the complex plane, $z = \alpha + i\beta$. Note that when the real part of the coupling goes near zero, the synchronized state is not stable. This is the result of the fact that the attractor for each node is chaotic, and without dissipative coupling, the nodes will naturally diverge from a synchronized state when slightly perturbed

coupling becomes too large. We explain more about this next when we examine the symmetric coupling case.

In the symmetric coupling case, the eigenvalues of the coupling matrix are real so that we have an MSF that is a mapping $\mathbb{R} \rightarrow \mathbb{R}$. Figure 4 shows this for the Rössler-like oscillator with coupling through the first component as above. We see that there is an unstable region (the MSF is > 0) from a coupling of $\alpha = 0$ to α_1 , a stable region (the MSF is < 0) from α_1 to α_2 , and an unstable region from α_2 to ∞ . Having a limited coupling region for stability (α_1, α_2) leads to some interesting phenomena. Suppose we have N oscillators coupled in a ring through nearest neighbor coupling only (see inset, Fig. 4), then the eigenvalues of the coupling matrix are

$$\lambda_k = 4\sigma \sin^2\left(\frac{\pi k}{N}\right). \quad (14)$$

The $k = 0$ eigenvalue belongs to the synchronization manifold so we do not use it for stability calculations of the transverse perturbations. The smallest eigenvalue is $\lambda_1 = 4\sigma \sin^2(\pi/N)$ which becomes very small as N increases, but we can always keep $\lambda_1 > \alpha_1$ by



Master Stability Function for Globally Synchronized Systems, Fig. 4 The MSF for a symmetrically coupling array of Rössler-like oscillators. The stability range of coupling $\times$ eigenvalues is limited to a finite region

increasing the coupling σ . However, the largest eigenvalue is $\lambda_{N/2} = 4\sigma$ (assuming for now that N is even). Thus, increasing the coupling will eventually cause the largest eigenvalue to become greater than α_2 . This has two consequences.

One is that there will be rings of oscillators which have limited stability ranges of coupling $\times$ eigenvalue for which adding more oscillators to the ring will cause the synchronized state to become unstable and be impossible to stabilize by varying the overall coupling, i.e., there will be a “size effect,” beyond which rings (or other suitable networks) cannot be enlarged or stability will be lost. Another interesting effect is that increasing the coupling when there is an upper bound on the stability region can cause the synchronized state to destabilize. This is somewhat counterintuitive and causes the highest mode to go unstable rather than the lowest (just above $\alpha = 0$) to go unstable. For a ring, the highest mode is the one with the highest spatial frequency. Such instabilities are often called short-wavelength bifurcations (Heagy et al. 1995).

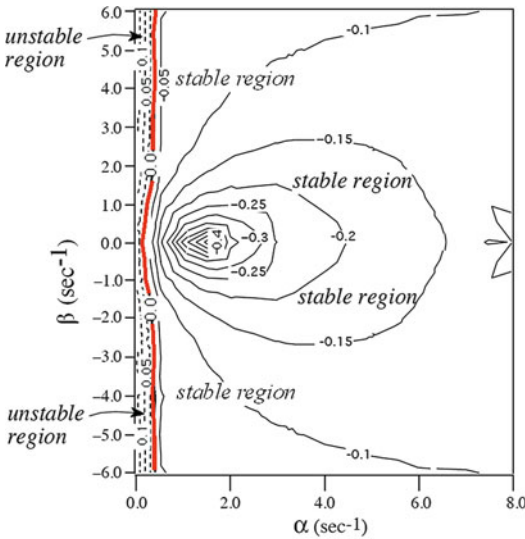
We can compare the limited stability range above with the infinite stability range of the same oscillators, but with different coupling function **H**. Here we let the coupling be through the second component of the oscillators

$$H(x_i) = \begin{pmatrix} 0 \\ x_i^2 \\ 0 \end{pmatrix} = DH(x_i).$$

Figure 5 shows the MSF for this case. There remains a “gap” of instability near $\alpha = 0$, but then there is an infinite stability region beyond that. In this system there are no side effects or short-wavelength bifurcations.

Experimental Determination of MSFs

So far we have focused on the calculation of MSFs, but an important question is, is there any experimental way to access the shape or values of the MSFs? The answer is “yes,” and here we show one way a simple experimental setup can determine the shape of the stable region of the MSF.



Master Stability Function for Globally Synchronized Systems, Fig. 5 The MSF for Rössler-like oscillators using coupling through the second component

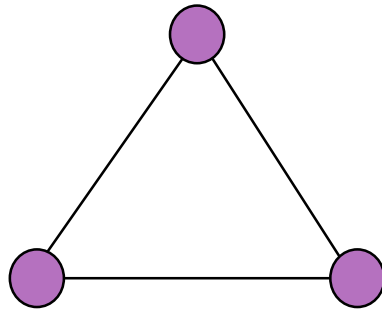
This depends on the ability to experimentally control the coupling between oscillators in a simple network. This is certainly possible in electronic circuits and may be possible in other systems (e.g., some using chemical oscillators or neurons where certain chemicals might enhance or diminish coupling strength).

To see how to do this, let's take the simple three-oscillator system shown in Fig. 6.

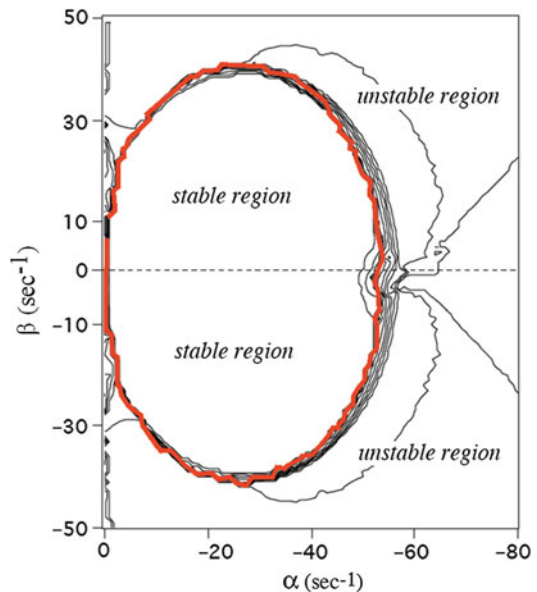
The coupling matrix (C) is given by

$$C = \begin{pmatrix} -2\frac{\alpha}{3} & \frac{\alpha}{3} + \frac{\beta}{3} & \frac{\alpha}{3} - \frac{\beta}{3} \\ \frac{\alpha}{3} - \frac{\beta}{3} & -2\frac{\alpha}{3} & \frac{\alpha}{3} + \frac{\beta}{3} \\ \frac{\alpha}{3} + \frac{\beta}{3} & \frac{\alpha}{3} - \frac{\beta}{3} & -2\frac{\alpha}{3} \end{pmatrix}. \quad (15)$$

This may look unnecessarily complicated, but viewing the eigenvalues of C associated with the transverse perturbation directions, we see something interesting. The eigenvalues are $\lambda_1 = \alpha + i\beta$ and $\lambda_2 = \alpha - i\beta$. We can now vary α and β and run the experiment starting each time in the synchronous state. We note values of α and β where the synchronization is stable and unstable and in that way map out the stable and unstable regions of the MSF. Figures 7 and 8 show this for an



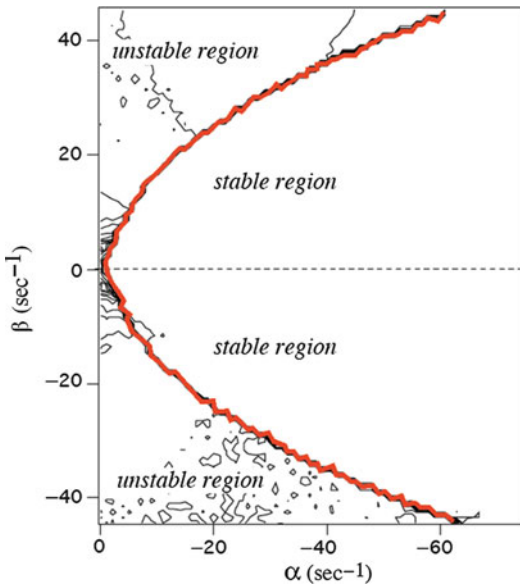
Master Stability Function for Globally Synchronized Systems, Fig. 6 A three-oscillator system for determining the shape of the stability region for particular oscillator (F) and coupling function (H) types



Master Stability Function for Globally Synchronized Systems, Fig. 7 Contour plot of experimental probe of the MSF (x coupling). Compare to Fig. 3 (units are different, but shapes are correct)

experimental implementation of the Rössler-like oscillator circuit. You can see that the general shapes agree well with the calculations (Figs. 3 and 5, respectfully).

It turns out that although the three-oscillator network works well and has an obvious symmetry, it is only necessary to use a two-oscillator system. This was shown in the paper by Wu



Master Stability Function for Globally Synchronized Systems, Fig. 8 Experimental probe of the MSF (y coupling). Compare to Fig. 5 (units are different, but shapes are correct)

(2002). Hence, with two oscillators in an experiment and control over the coupling strengths, one can probe the MSF whose form will hold for any size and shape of network of those same oscillators and coupling functions. This is a rather remarkable result. Not much advantage has been taken of this development, but it should eventually find applications as more sophisticated, computerized experiments come online in many areas of network dynamics.

Conclusions and Remarks

Much of this review was based on results in the paper by Fink et al. (2000). There we showed that all the machineries developed here carry over to iterated maps in networks, too. One should also see the papers by Gade et al. (1995), Gade (1996), Hu et al. (1998), Boccaletti et al. (2002), Nishikawa et al. (2003), Belykh et al. (2004a, b), Chavez et al. (2005), Motter et al. (2005a, b), Belykh et al. (2006), Boccaletti et al. (2006), Zhou et al. (2006), and Belykh et al. (2008)

whose work also showed that such generalizations as the MSF might be possible in papers published at the time of our original paper on the MSF topic (Pecora and Carroll 1998). With the emphasis on network mathematics and physics starting in the late 1990s on up to today, many papers have been published that show various applications of the MSF to many different types of networks. This began with an analysis of small-world networks and synchronization (Barahona and Pecora 2002; Pecora and Barahona 2005) and continued on to analysis of synchronization under many different conditions. The topic became popular in the 2000s and continues to today.

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MCell

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Definition

MCell (Monte Carlo Cell) is a program for simulating spatially resolved cell models using particle-based Monte Carlo algorithms.

Detailed Description

Biological processes at the cell level take place in small and often complex geometries and frequently involve only a small number of molecular players (tens to thousands). A prime example of a process in which this “microphysiology” plays a central role is neurotransmission at chemical synapses in the brain and in the peripheral nervous system (Stiles et al. 2001; Stiles and Bartol 2001). At such small subcellular scales, the familiar macroscopic concept of concentration breaks down and stochastic behavior dominates. MCell uses optimized Monte Carlo algorithms to track discrete molecules in space and time as they diffuse and interact with other effector molecules such as membrane channels, receptors, transporters, or enzymes (Bartol et al. 1991; Stiles and Bartol 2001; Kerr et al. 2008).

The first version of MCell, released in 1995, was developed collaboratively by Tom Bartol at the Salk Institute and Joel Stiles at Cornell University for modeling chemical signaling, diffusion, and reaction of discrete neurotransmitter molecules in synaptic spaces. Version 1 of MCell supported only basic planar surfaces that represented shapes of

synaptic membranes (Stiles et al. 1996). MCell version 2, released in 1997, employed arbitrary triangulated meshes to better represent the complex geometries inherent to systems but lacked the capability to simulate diffusion on surfaces or reactions in volumes (Stiles and Bartol 2001). MCell3, the current version of MCell, was released in 2006 and is a general-purpose reaction-diffusion simulator that handles surface and volume diffusion as well as surface-surface, surface-volume, and volume-volume reactions (Kerr et al. 2008). MCell is developed and maintained by the National Center for Multiscale Modeling of Biological Systems (<http://mmbios.org>).

MCell is widely used for simulating cellular microphysiology and has been employed for computational studies of neurophysiological (e.g., Beenhakker and Huguenard 2010; Coggan et al. 2005; Nadkarni et al. 2010, 2012; Scimemi and Diamond 2012; Dittrich et al. 2013) and other cellular systems (Kerr et al. 2006; Rappel and Levine 2008). So far, more than 40 studies have been published that utilized MCell in an integral way. An up-to-date list of publications using MCell can be found on (www.mcell.org).

Software

MCell is open-source software released under a GPLv2 license and is available in both source code and binary format for the Windows, Mac, and Linux operating systems. CellBlender provides an open-source, cross-platform graphical user interface for MCell that enables a user to build, visualize, simulate, and analyze models and is available as an add-on for the open-source 3D content creation tool (<http://blender.org>). In particular, CellBlender allows the rapid creation and refinement of complex biological structures without the need for image segmentation, which can be time consuming.

Model Syntax and Components

MCell models are described using Model Description Language (MDL), which provides

grammar for defining model components (Kerr et al. 2008). These are:

1. *Initialization*: global time step, iteration number, and other user-specified model parameters.
2. *Molecule definitions*: list of participating chemical species (e.g., ions, molecules), along with their diffusion constants.
3. *Reaction definitions*: description of the biochemical interactions between the chemical species as a chemical reaction network along with reaction rate constants.
4. *Meshes*: triangulated surface meshes representing the membranes and scaffolds of a 3D cellular/subcellular domain. Meshes, which are specified using boundary representation (B-rep), can be generated in a number of ways: (i) from simple geometric primitives available in MDL, (ii) via CellBlender (or CAD tools), (iii) algorithmically by a script, and (iv) via reconstruction from electron or optical microscopy images or real tissue samples.
5. *Molecule placement*: distribution of molecules, specified in terms of densities or absolute numbers, within or on defined volume or surface domains, respectively.
6. *Output description*: counts of molecules in specified spatial domains, counts of reaction occurrences in specified spatial domains, and molecule coordinates at user-specified times over the simulation time course.

MDL also provides syntax for several advanced simulation features such as:

1. Functions for release of molecules that vary in time and space
2. Reaction-driven activation of molecule release events
3. Simulation checkpointing

The required parameters for species concentrations and reaction rates typically come from the literature, community databases, or bench experiments. Complex models can be split across any number of MDL files, which are then included from a single runnable main MDL file. The

CellBlender graphical interface allows users to build, generate, and run models without explicitly writing MDL.

Simulation

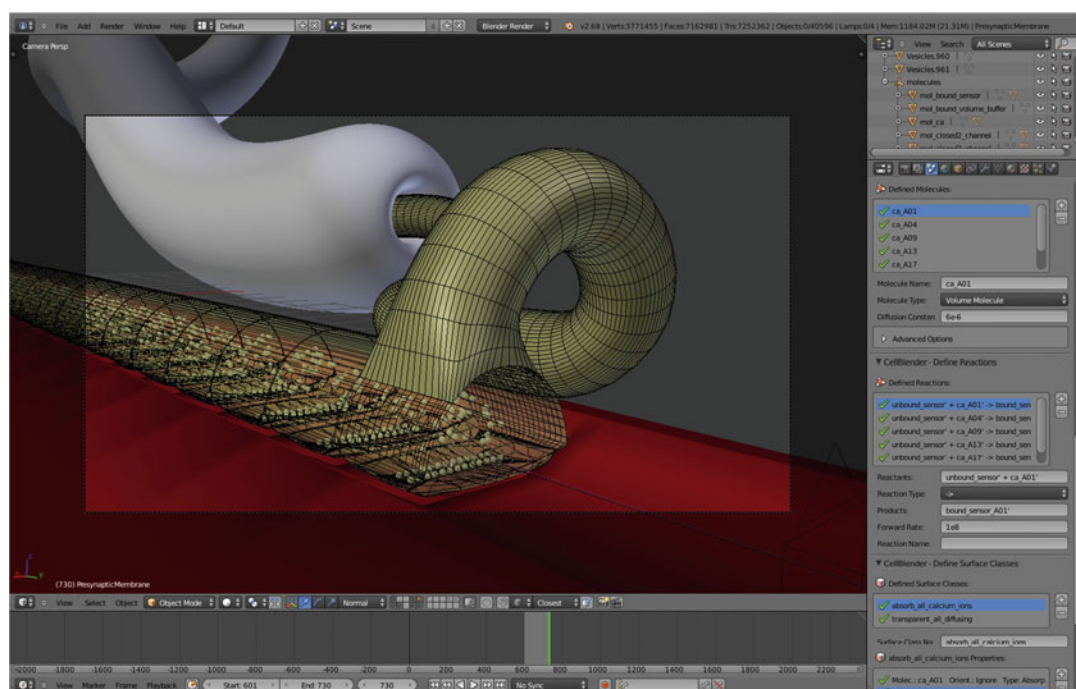
The MCell simulation kernel can be run from the command line or from within CellBlender. On start-up, MCell parses and error-checks the model description, sets the initial state of the simulation according to the user's specification, and then proceeds with the simulation. MCell provides two types of simulation output: *visualization output* contains time series of positions of molecules and meshes that can be visualized in CellBlender (see Fig. 1); *reaction data* output contains time series of molecule or reaction counts or fluxes within or on defined spatial regions of the model. Individual simulations can be stopped and restarted using MCell's checkpointing facility. An example of the visualization and video production capabilities provided by the CellBlender-MCell interface can be

seen at <http://www.youtube.com/watch?v=FZT6c0V8fW4>.

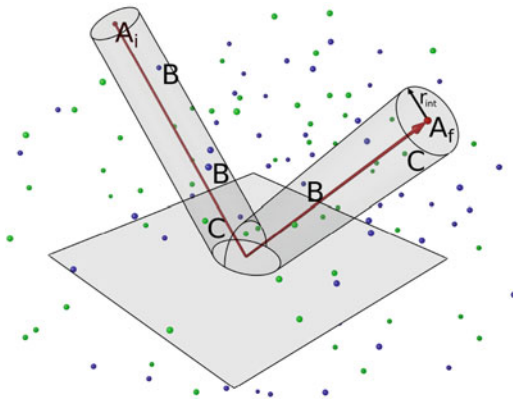
Simulation Algorithms

MCell uses optimized and validated Monte Carlo algorithms for simulating the diffusion and interaction of individual particles in 3D volumes and on 2D surfaces (see Kerr et al. 2008 for a complete description). An event-driven scheduler with adaptive time stepping handles the reaction-diffusion events as the simulation evolves in time. A particle diffusion event consists of spatial movement according to the particle's diffusion constant and the user-specified time step. The diffusion step length is computed by Monte Carlo sampling of the probability distribution function for 2D or 3D diffusion. A particle trajectory is tracked through space by ray-tracing/ray-marching algorithms, which detect collisions with membrane or scaffold surfaces and with other particles (Fig. 2). Bimolecular reaction events are driven by collisions between reactive pairs of

M



MCell, Fig. 1 Visualization of an MCell model of the frog neuromuscular junction using the CellBlender interface



MCell, Fig. 2 Particle movement and collision detection in MCell. Ray-tracing algorithms are used to detect collisions between a diffusing particle along its direction of motion and other particles or surfaces. Ray marching is used to propagate rays following collisions, such as those involving a reflective surface as illustrated here. Molecules within the shaded tube of radius r_{int} around the trajectory (and on the near side of the surface) are collision partners, which are checked in sequence of encounter to determine whether a reaction occurs. For further details, see Kerr et al. (2008)

particles. The bimolecular reaction rate constants specified by the user are converted to per collision reaction probabilities, and a random number generator is used to determine whether a given collision results in a reaction in accordance with this probability. Unimolecular reaction events are scheduled by sampling the exponential distribution of particle state lifetime corresponding to the rate constant of the unimolecular reaction.

Future Developments

The MCell development team is currently actively working on several advanced new simulation features, which will be made available in future MCell releases. These include import/export of SBML models, import of rule-based models, parallelization, dynamic model geometries, and space-filling particle diffusion approaches.

Acknowledgments We gratefully acknowledge the funding from NIH/NIGMS grant P41GM103712. In addition we thank Jacob Czech for his help with the figure preparation; the members of the MCell development team, including Dipak Barua, Jacob Czech, Leonard Harris, Bob Kuczewski, and Jose Juan Tapia, for the helpful discussions;

and Terry Sejnowski for the support and inspiration. We dedicate this entry to the memory of Joel R. Stiles.

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Mean Field Model

► Population Density Model

Mechanisms of Excitability

► Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation

Mechanotransduction, Models

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Synonyms

[Models of mechanoreceptive afferents](#)

Definition

Computational models of mechanotransduction describe how somatosensory receptors respond to stimuli applied to the skin. There are two distinct approaches to this problem: (1) modeling skin mechanics and transduction and (2) modeling single neuron spike generation. The first type of model describes how the skin is deformed by a tactile stimulus and how this deformation leads to a neuronal response. These models of skin mechanics and transduction can be further divided into two distinct subcategories: those based on continuum mechanics and those based on finite element analysis. The second type of model focuses on the biophysics of spike generation in single neurons. It usually consists of two stages: a transduction stage and an integrate-

and-fire (IF) stage. The transduction stage describes the conversion from skin deformation into a current injection into the neuron, while the IF stage simulates the generation of action potentials. Under some circumstances, these models can predict the precise temporal structure of the spiking activity with millisecond-level precision.

Combined skin mechanics models and biophysical spike-generation models can account for the gamut of spatiotemporal transformations that occur at the somatosensory periphery including the spatial filtering properties of the skin and the nonlinearities and dynamics of transduction and spike generation.

Detailed Description

Tactile Sensation

Tactile sensation and the haptic manipulation of objects begin with the activation of mechanoreceptors embedded in the skin. The skin itself is composed of viscoelastic media and deformed by contact with external stimuli (Lanir 1987). Forces applied to the skin elicit the flow of electrical currents into mechanoreceptors. Three types of mechanoreceptors innervate primate glabrous skin: slowly adapting type 1 (SA), rapidly adapting (RA), and Pacinian (PC) afferents (Gescheider et al. 2004; Hsiao and Bensmaia 2008; Johansson 1978; Johnson 2001; Pare et al. 2002; Talbot et al. 1968). These afferents respond to different aspects of skin deformation. SA afferents are sensitive to static indentations and to low-frequency skin vibrations. These afferents encode the shape of an object grasped in the hand. RA afferents are most responsive to skin vibrations at the flutter frequencies (10–40 Hz), commonly generated when an object moves across the skin or slips from one's grasp (Johansson and Westling 1987; Srinivasan et al. 1990). These afferents also produce a robust transient response at the onset and offset of contact with an object. PC afferents mainly respond to high-frequency vibrations generated, for example, during scanning of textured surfaces. Importantly, mechanoreceptive responses of all three types are highly repeatable and precise, and this millisecond-precision spike

timing shapes the way stimuli are perceived (Johansson and Birznieks 2004; Mackevicius et al. 2012).

Classes of Models

Mechanotransduction models were developed to better understand the biophysics of touch. As mentioned above, there are two general classes of models: (1) models of skin mechanics and (2) biophysical receptor models. Models of skin mechanics are based on continuum mechanics (Oomens et al. 1987; Phillips and Johnson 1981; Sripati et al. 2006) or finite element analysis (Dandekar et al. 2003; Gerling and Thomas 2008; Larrabee Jr and Galt 1986; Wu et al. 2004) and are intended to estimate the impact of skin deformations on mechanoreceptors. On the other hand, biophysical receptor models provide a simplified representation of the transduction and spike-generation process (Dong et al. 2012; Freeman and Johnson 1982; Kim et al. 2010, 2012;). Here, we describe a representative skin mechanics model based on continuum mechanics (Sripati et al. 2006) and a receptor model based on integrate-and-fire mechanism (Dong et al. 2012). Finally, we will show how these models can be combined for other applications.

A Model of Skin Mechanics

The skin mechanics model summarized here (Sripati et al. 2006) is based on continuum mechanics. The purpose is to estimate 3D stress/strain profiles produced by a stimulus and to then predict the response of mechanoreceptive afferents based on these profiles. The model includes two computational steps. First, the forces exerted by the stimulus on the skin are computed from the spatial profile of the stimulus (Phillips and Johnson 1981). Second, the stresses and strains experienced by the receptors in the skin are computed from the skin deformation profile.

To determine how the skin is displaced by the stimulus, the model begins with the assumption that the skin touches the entire surface of stimulus. In reality, some parts of the stimulus do not touch the skin (imagine a toy rubber stamp on your finger). To determine which parts of the stimulus do not touch the skin, an algorithm (see Eq. 1 below) identifies parts of the stimulus that yield negative forces. In other words, this skin area would need to be pulled towards these regions of the stimulus in order for the skin to conform to them (thus the negative forces). Hence, this area is simply removed from further consideration. The force calculation and exclusion of areas with negative force is computed iteratively until the resulting stimulus yields no negative forces (see Sripati et al. 2006 for more details).

The forces exerted on the skin, are given by solving the following equation for (Phillips and Johnson 1981):

$$S = CP \quad (1)$$

where S is a vector describing the skin deformation pattern or, equivalently, the stimulus pattern. C is a matrix providing a mapping between force and displacement: element (i, j) represents the displacement at position i when a unit force is applied at location j :

$$C_{ij} = \frac{(1 - \nu^2)}{\pi E r_{ij}} \quad (2)$$

where E is the modulus of elasticity, ν is Poisson's ratio (set to 0.4; cf. Wu et al. 2004), and r_{ij} is the distance between locations i and j (Timoshenko and Goodier 1969). As described above, if any elements of P are negative, corresponding elements of Eq. 1 are excluded from subsequent calculations.

In the second step, the stress tensor with six components (three normal forces and three shear forces in 3D space) can be easily computed for a given three-dimensional point in the skin (Timoshenko and Goodier 1969):

$$\sigma = \begin{bmatrix} \sigma_r & \sigma_{r\theta} & \sigma_{rz} \\ \sigma_{r\theta} & \sigma_\theta & \sigma_{\theta z} \\ \sigma_{rz} & \sigma_{\theta z} & \sigma_z \end{bmatrix} = \frac{P}{2\pi} \begin{bmatrix} \frac{3r^2 z}{R^5} - \frac{1-2\nu}{R^2 + zR} & 0 & \frac{3rz^2}{R^5} \\ 0 & (1-2\nu)\left(\frac{1}{r^2} - \frac{z}{r^2 R} - \frac{z}{r^3}\right) & 0 \\ \frac{3rz^2}{R^5} & 0 & \frac{3z^2}{R^5} \end{bmatrix} \quad (3)$$

where, in Cartesian coordinates, $r = \sqrt{x^2 + y^2}$, $R = \sqrt{r^2 + z^2}$, and z are the axes perpendicular to the skin surface. The stress profile is then computed, in Cartesian coordinates, and summed

across all deformed skin positions, using the coordinate transformation method (Timoshenko and Goodier 1969):

$$\begin{bmatrix} \sigma_x & \sigma_{xy} & \sigma_{xz} \\ \sigma_{xy} & \sigma_y & \sigma_{yz} \\ \sigma_{xz} & \sigma_{yz} & \sigma_z \end{bmatrix} = \begin{bmatrix} \cos \theta & -\sin \theta & 0 \\ \sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \sigma_r & \sigma_{r\theta} & \sigma_{rz} \\ \sigma_{r\theta} & \sigma_\theta & \sigma_{\theta z} \\ \sigma_{rz} & \sigma_{\theta z} & \sigma_z \end{bmatrix} \begin{bmatrix} \cos \theta & \sin \theta & 0 \\ -\sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad (4)$$

Finally, the strain tensor (ϵ) can be then obtained using Hooke's law:

$$\epsilon_{ij} = \frac{1+\nu}{E} \sigma_{ij} - \frac{\nu}{E} (\sigma_x + \sigma_y + \sigma_z) \delta_{ij} \quad (5)$$

where δ_{ij} is the Kronecker delta function.

A Biophysical Model of Transduction

Given the importance of spike timing in somatosensory processing (Johansson and Birznieks 2004; Mackevicius et al. 2012), a mechanoreceptor model must reproduce neural activity with great temporal accuracy. Early attempts to model mechanoreceptive afferents using an integrate-and-fire model showed that some key features of the fine temporal structure of afferent responses (in addition to the strength of their response) can be captured using such a modeling framework (Freeman and Johnson 1982). Recent models incorporated known properties of mechanoreceptors to make them more versatile:

1. All three afferents have been shown to rectify or partially rectify time-varying stimuli (Bolanowski Jr and Zwislocki 1984; Whitsel et al. 2000). For example, some afferents

respond only to the indentation phase of a sinusoidal skin vibration, while others respond to both the indentation and retraction phase.

2. All three afferents are differentially sensitive to indentation depth and/or its derivatives (velocity and acceleration) (Kim et al. 2010; Loewenstein and Skalak 1966; Pubols Jr 1980).
3. Afferent responses saturate when stimulated at high intensities (Johnson 2001).
4. Different mechanoreceptive afferents exhibit differential sensitivity to stimulus frequency (Freeman and Johnson 1982; Muniak et al. 2007; Talbot et al. 1968).

The model summarized here (Dong et al. 2012) involves two stages (Fig. 1). In the first stage, the stimulus and its derivatives are rectified and summed with different weights. In the second stage, the output of the first stage is passed through a saturation filter and fed into a generalized integrate-and-fire model (Mihalas and Niebur 2009), which generates spikes. The transduction stage is described as

$$s(t) = \sum_{i=0}^2 w_i^+ s_i^+(t) + w_i^- s_i^-(t) \quad (6)$$

$$I(t) = \frac{I_0 s(t)}{I_0 + |s(t)|} \quad (7)$$

where $s_i^+(t)$ and $s_i^-(t)$ are the rectified positive and negative components of the i th derivative of the skin deformation depth (with s_o the depth itself), respectively, and w_i^+ and w_i^- are free parameters (see Fig. 1). I_0 is a free parameter that determines the degree of saturation. In total, there are seven free parameters in the transduction stage. Then, the integrate-and-fire model stage is governed by the following equation:

$$V'(t) = -\frac{1}{\tau}(V(t) - V_{rest}) + \frac{I(t) + I_{ind}(t)}{C} \quad (8)$$

$$\Theta'(t) = a(V(t) - V_{rest}) - (\Theta(t) - \Theta_\infty)/b \quad (9)$$

where C , V_{rest} , Θ_∞ , and b represent capacitance, resting membrane potential, equilibrium threshold, and threshold rebound time constant (that allows for long-term adaptation), respectively. Equation 8 describes the leaky integration of the injected current, and Eq. 9 computes the time-varying threshold of the neuron. For some of these variables, we used fixed values: $C = 150$ pF, $V_{rest} = -70$ mV, $\Theta_\infty = -30$ mV, and $b = 0.1$ s derived from the literature. The free parameters of the model include ς and τ , the threshold adaptation constant for short-term

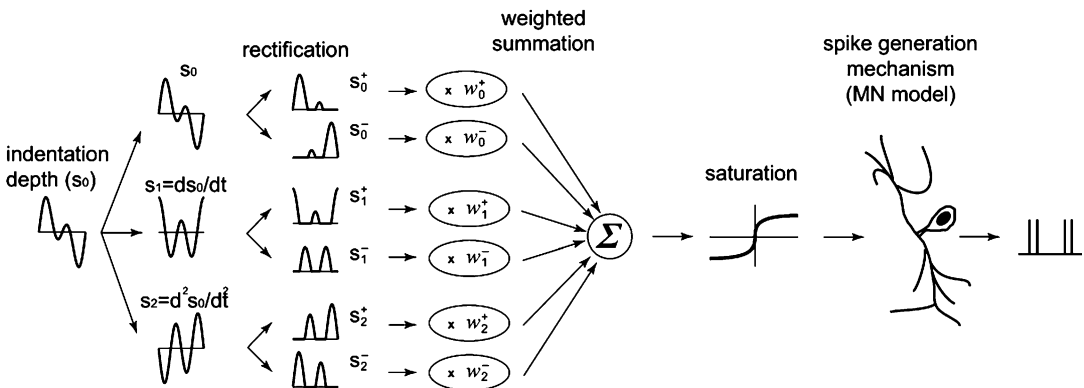
adaptation and the membrane time constant, respectively. A spike-induced current, $I_{ind}(t)$, accounts for refractoriness and consists of two types of inhibitory ion channels (i_0 and i_1) with different decay time constants, $\tau_0 = 5$ ms and $\tau_1 = 50$ ms:

$$\begin{aligned} I_{ind} &= i_0 + i_1 \\ \frac{di_0}{dt} &= -\frac{i_0}{\tau_0} \\ \frac{di_1}{dt} &= -\frac{i_1}{\tau_1} \end{aligned} \quad (10)$$

When $V(t)$ reaches $\Theta(t)$, the membrane voltage and the threshold are reset to V_{reset} and $\max(\theta(t), \Theta_\infty)$, respectively, and a spike is generated, which, in turn, induces currents through two ion channels:

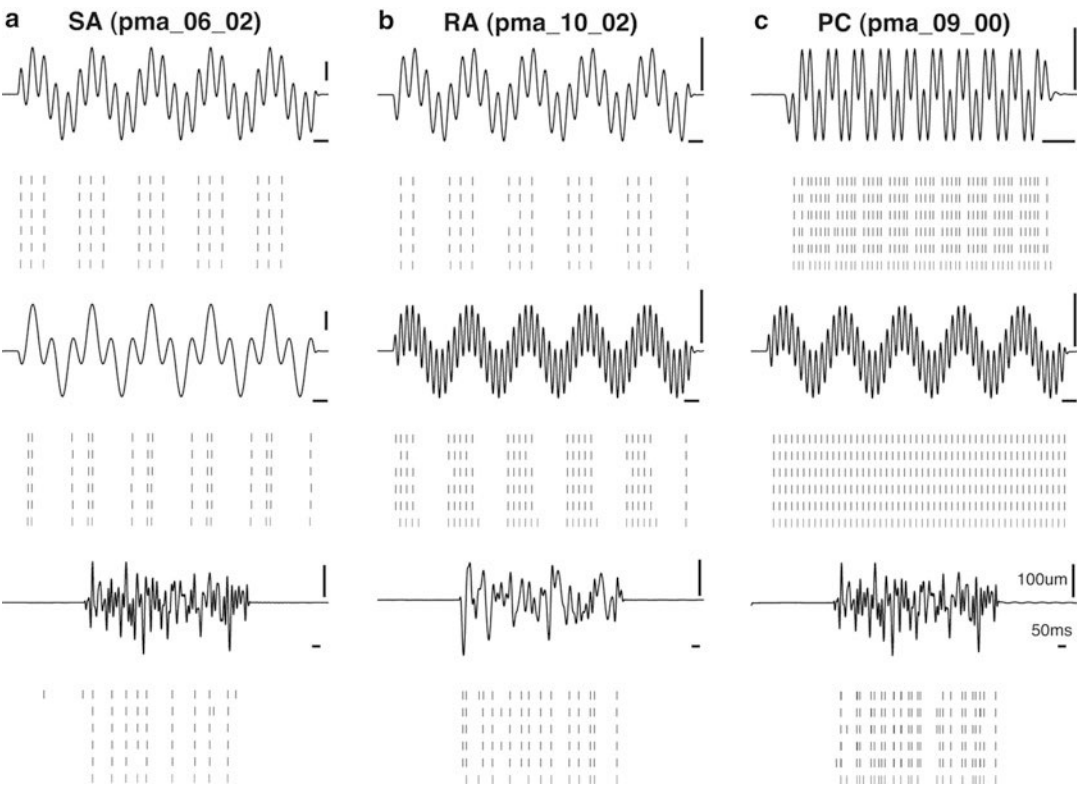
$$\begin{aligned} i_0 &\leftarrow i_0 + A_0 \\ i_1 &\leftarrow i_1 + A_1 \end{aligned} \quad (11)$$

where A_0 , A_1 are free parameters representing the initial amplitudes of the spike-induced currents, which decay away with time constants, τ_0 and τ_1 . Finally, the transduction delay is the last additional free parameter, resulting in a total of 12 free parameters in the model. The small number of parameters (compared to hundreds in an older model proposed by Kim et al. 2010) yields a model that generalizes well. That is,



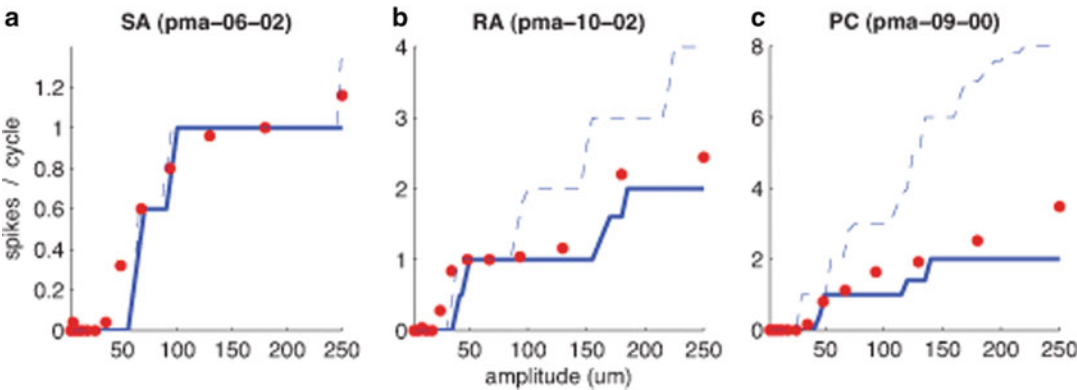
Mechanotransduction, Models, Fig. 1 Model of mechanotransduction. The time-varying skin indentation and its derivatives are computed in real time. The weighted

sum of rectified signals is fed into the MN model (Mihalas and Niebur 2009) through a saturating filter



Mechanotransduction, Models, Fig. 2 Responses of a typical SA, RA, and PC afferents to complex time-varying skin deformations and corresponding model predictions. *Black* rasters show the measured spiking responses to five repeated presentations of each stimulus, and the *red* rasters

show the predicted responses. The first and second rows show response to diharmonic stimuli used to fit the model. The third row shows responses to band-passed noise stimuli that were not used to train the model



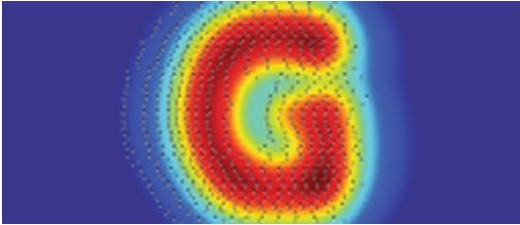
Mechanotransduction, Models, Fig. 3 Measured and predicted rate-intensity functions in response to sinusoids for an SA, RA, and PC afferent. *Red dots* represent the average number of spikes evoked on each stimulus cycle.

Solid blue lines show the predicted response rate, and the *dashed blue lines* show the model prediction without the saturation filter

good performance of the model on the training data generally leads to good performance on novel stimuli.

The model can be efficiently fit to observed physiological neural activity by minimizing a cost function defined by

$$F = \sum_i 1 - e - \log (T_{\tau n}^i / T^i)^2 \quad (12)$$



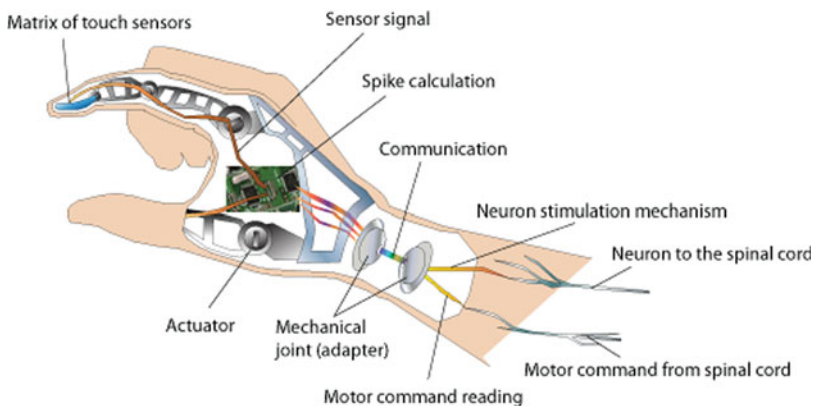
Mechanotransduction, Models, Fig. 4 Simulated response to a letter scanned across the skin. The displacement profile of the letter “G” is first converted into a strain profile using a skin mechanics model (*heat map*). Each row of this profile represents a single scan across the skin (scanning is from *left to right*). The time-varying strain is then fed into the mechanotransduction model, which generates spikes, shown as rasters superimposed on the strain profile. These model-predicted spiking responses are almost identical to their measured counterparts (Kim et al. 2010; Phillips et al. 1988)

where T^i is the i th observed spike time interval and T_m^i is the corresponding spike interval of the model (see Dong et al. (2011) for details).

Figure 2 shows an example of each afferent type responding to two diharmonic and noise stimuli. Note that diharmonic stimuli were used to train the model, whereas noise stimuli were used to test it. For these stimuli, the model predictions were matched with the observed response with millisecond-level accuracy. The model also captures the characteristic piecewise linear rate-intensity function to sinusoidal stimuli (Freeman and Johnson 1982; Johnson 1974; Muniak et al. 2007; Fig. 3). Finally, the model captures the response saturation property, most prominent in PC afferents.

Application

Given its ability to predict afferent response to novel stimuli with millisecond precision, the model can be used in a variety of applications (Kim et al. 2009, 2010; Russell et al. 2009). In scientific applications, the model can be used to simulate neural responses and thus obviate the need to perform neurophysiological studies, which are time consuming and require the sacrifice of animals. Skin mechanics models can be integrated with integrate-and-fire models to simulate the afferent responses to



Mechanotransduction, Models, Fig. 5 An example of a neuroprosthesis with a peripheral nerve interface. The motor command from the brain is delivered to the actuators via the spinal cord. Then a matrix of touch sensors embedded in the artificial skin detects the contact with objects.

This signal is transformed into spike timings using embedded computer. Finally, the residual nerve of the patient is stimulated electrically or through optogenetics

arbitrarily complex spatiotemporal patterns of skin deformation. First, the skin mechanics model generates a skin strain profile at each time step based on the indentation profile, which in turn can be used as input to the biophysical model described. For example, the well-documented response of a population of SA afferents to a letter scanned across the skin can be reproduced using this approach (Fig. 4; Kim et al. 2010).

For a more medically oriented application, these models can be used to convey sensory feedback in upper-limb neuroprostheses. Specifically, they can be used to convert the output of force sensors embedded in upper-arm neuroprostheses into naturalistic patterns of activation (Fig. 5; Kim et al. 2009), effected in the nerve through electrical (or perhaps someday optogenetic) stimulation. The model itself can be implemented in a semiconductor chip in a computationally effective way because of its small number of parameters and simple structure to allow for real-time artificial transduction. Even analog silicon chips could be used for maximum integration (Indiveri et al. 2011). Furthermore, if the integration time window of upstream structures is long enough (>25 ms), a single canonical parameter set for each afferent type can be used for all embedded sensors, which vastly simplifies device production (Kim et al. 2011).

Cross-References

- [Neural Coding](#)
- [Peripheral Nerve Interface Applications, Sensory Restoration](#)
- [Peripheral Nerve Models](#)
- [Peripheral Nerve Signal Processing, Source Localization](#)
- [Somatosensory Neurons: Spike-Timing](#)

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Medial and Lateral Efferents

► Physiology and Function of Cochlear Efferents

Memory Decoding Model

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Synonyms

[Hippocampal memory decoding model](#)

Definition

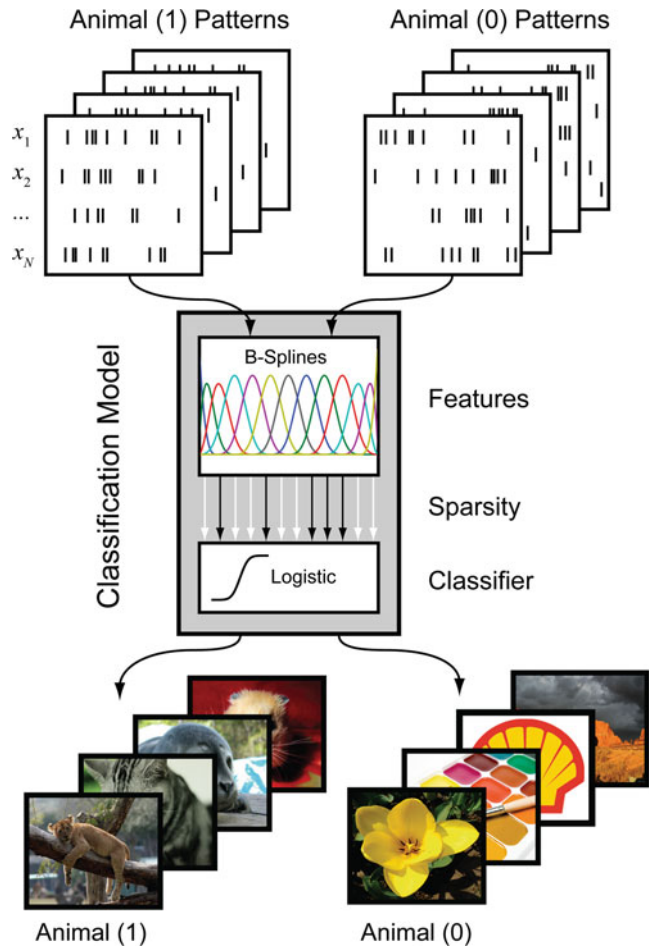
Memory decoding model is a computational model that maps neural signals to memories (Fig. 1). It can be used to investigate memory encoding and retrieval processes in the brain.

Detailed Description

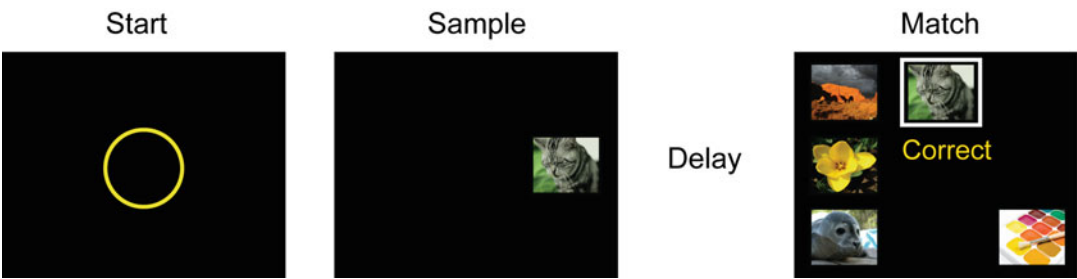
Memory decoding models can take many different forms. In a human hippocampal memory decoding model, hippocampal CA3 and CA1 spike trains are recorded from human subjects performing a delayed match-to-sample (DMS) task (Fig. 2), in which subjects are required to remember sample images after a delay. Within the DMS task, memory encoding is defined as

Memory Decoding

Model, Fig. 1 Structure of the hippocampal memory decoding model. Model inputs are spatio-temporal patterns of hippocampal spikes. Model outputs are memory labels related to features and categories of sample images. Neural activity features are extracted with B-spline basis functions. The classifier takes the form of a sparse logistic regression classifier



M



Memory Decoding Model, Fig. 2 Delayed match-to-sample (DMS) task. A DMS trial starts with a circle cue presented on the touchscreen. In the Sample Phase, the patient touches an image presented in a specific position

of the screen. In the Match Phase, the patient needs to choose and touch the correct image that he has seen in the Sample Phase among distractors to generate a correct response

the mapping from sample images to hippocampal spike trains, while memory decoding becomes the prediction of sample images from hippocampal spike trains (Song et al. 2014, 2016, 2017). The

modeling task is formulated as building a classifier that predicts categories and features of sample images based on spatio-temporal patterns of hippocampal spike trains (Fig. 1).

B-spline basis functions are used to extract neural activity features from spatio-temporal patterns of spikes (Song et al. 2013, 2014). B-splines are piecewise polynomial functions with smooth transitions between adjacent pieces at a set of interior *knot* points. The number of knots J , controls the temporal resolution of B-splines. Given a B-spline basis B , spike trains x are projected to the B-spline feature space via an inner product to yield feature vectors z as

$$z^{(n)}(j) = \sum_{\tau_1}^{\tau_2} B_j(\tau) x_n(\tau) \quad (1)$$

Interval $[\tau_1 \tau_2]$ is the time window for the inner product, which is chosen to be from -2 s to $+2$ s of the Sample Response events. Variable x_n is the n th neuron of the N neurons included in the analysis. J is the number of B-spline basis functions.

Images presented in the sample phase are labeled by normal human subjects with 29 non-mutually exclusive categories and features: Cartoon, Photo, Black & White, Color, Red, Orange, Yellow, Green, Blue, Activity, Animal, Artifact, Building, Geometric Shape, Human, Landscape, Plant, Tool, and Vehicle. This procedure provides the target signal for the classification model. Therefore, the model output is simplified as a binary variable β . The classification model based on logistic regression can be expressed as

$$P(\beta = 1|x) = \left[1 + \exp \left\{ -w_0 - \sum_{n=1}^N \sum_{j=1}^J w^{(n)}(j) z^{(n)}(j) \right\} \right]^{-1} \quad (2)$$

$$P(\beta = 0|x) = 1 - P(\beta = 1|x) \quad (3)$$

Variable w are the sought classification model coefficients; 1 and 0 represent positive and negative labels, respectively. The linear classification rule becomes

$$\beta = \begin{cases} 1 & \text{if } \left\{ -w_0 - \sum_{n=1}^N \sum_{j=1}^J w^{(n)}(j) z^{(n)}(j) \right\} < 0 \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

This classification model often suffers from a serious overfitting problem due to the super high-dimensional input and the relatively small number of data points. $L1$ regularization (Lasso) is applied to achieve sparse model estimation and avoid overfitting as (Song et al. 2013, 2014)

$$S(w) = -l(w) + \lambda \left(\sum_{n=1}^N \sum_{j=1}^J \|w^{(n)}(j)\|_2^1 \right) \quad (5)$$

$-l(w)$ and λ are the negative log likelihood function and the tuning parameter, respectively. By minimizing S with a n -fold cross-validation method, λ is optimized and w is estimated.

For a given B-spline knot sequence, the sparse classification function matrix (SCFM) F can be reconstructed with w and B as

$$F^{(n)}(\tau) = \sum_{j=1}^J B_j(\tau) w^{(n)}(j) \quad (6)$$

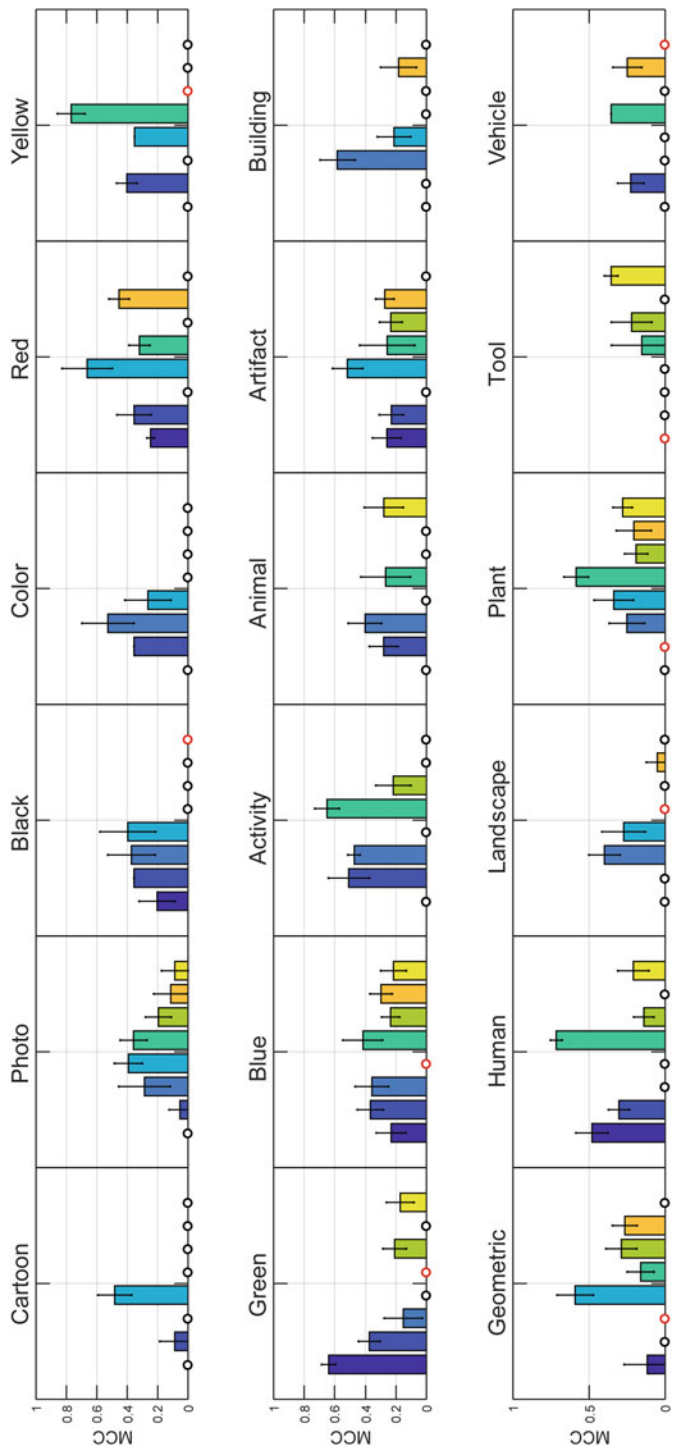
F can be directly used to calculate the conditional probability of the modeled label with the input spatio-temporal pattern x as

$$P(\beta = 1|x) = \left[1 + \exp \left\{ -w_0 - \sum_{n=1}^N \sum_{t=1}^M F^{(n)}(\tau) x^{(n)}(t) \right\} \right]^{-1} \quad (7)$$

The performance of each model is evaluated with the Matthews correlation coefficients (MCCs). MCC is robust to unbalanced data and can be calculated from the confusion matrix as

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}} \quad (8)$$

TP , TN , FP , and FN are the numbers of true positives, true negatives, false positives, and false negatives, respectively. The MCC value is between -1 and 1 . MCCs of 1 , 0 , and -1 represent perfect prediction, no better than random prediction, and completely opposite prediction, respectively.



Memory Decoding Model, Fig. 3 Decoding memory features and categories from hippocampal spike trains using the memory decoding model. Each color represents one patient ($n = 8$)

Applications

The memory model can be used as a computational tool to investigate memory encoding and retrieval processes in brain regions such as the hippocampus. Furthermore, it can also be used to design stimulation patterns for testing the effectiveness of neural code-based electrical stimulation in facilitating memory formations (Song et al. 2017). Such experiments have crucial implications for the development of hippocampal memory prostheses for restoring and enhancing memory functions (Hampson et al. 2018; Song et al. 2007, 2014, 2018).

Human studies have shown that multiple memory features and categories can be decoded from hippocampal CA3 and CA1 spike trains (Fig. 3). These memory decoding results support the hypothesis that episodic memories are formed in the hippocampus and encoded in the hippocampal activities.

Cross-References

► [Hippocampal Memory Prosthesis](#)

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Memristive Hardware Artificial Neural Networks

► [Neuromorphic Technologies, Memristors](#)

Mesosopic Anatomy and Neural Population Models

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Synonyms

[Cortical columns and neural population models](#);
[Macrocolumn and neural population models](#);
[Microcolumns and neural population models](#)

Definition

For the purposes of constructing biologically plausible neural population and field models of cortical activity, it is necessary to take into account the anatomical and histological

organization of the cortex that is intermediate in scale between that of the single neuron and the whole brain. The anatomy of the intermediate, or mesoscopic, level of cortical organization is defined by the variety of neuronal and non-neuronal cellular components, their spatial disposition and organization, and the structural features of their bulk connectivity.

Detailed Description

The thin outer rind of the mammalian brain, the neocortex, is generally thought to be the principal structure responsible for the generation and elaboration of purposeful activity. For a structure that is between 1 and 5 mm thick and has a surface area of only $\sim 0.19 \text{ m}^2$ (Van Essen 2005) in humans, it has an unparalleled degree of structural complexity with the $\sim 2 \cdot 10^{10}$ neurons (Pakkenberg and Gundersen 1997) broadly divided into six horizontal layers and with at least a dozen major neuronal subtypes (Markram et al. 2004), interacting with each other via synaptic connections with other neurons (Tang et al. 2001), synapses that utilize an array of chemical messengers and can be individually modified. Fortunately, the mammalian cerebral cortex is sufficiently well organized over a number of relatively distinct spatial scales to enable the meaningful construction of neural population models.

Cellular Composition of the Neocortex

The cortex is comprised of neuronal and non-neuronal components with the neurons being broadly classified as belonging to two types: pyramidal and non-pyramidal cells. The nonneuronal components of cortical tissue can be divided into the neuroglia and the cells of the perforating blood vessels. The neuroglia are comprised of astrocytes, microglia, oligodendrocytes, and ependymal cells.

Pyramidal cells are the most numerous neuronal class making up somewhere between 60% and 85% (Braitenberg and Schüz 1998; Nieuwenhuys et al. 2008) of all cortical neurons. A typical

pyramidal neuron is composed of a cell body from which a single axon descends and branches intracortically before exiting the cortex to travel subcortically, as the cortico-cortical fibersystem, to terminate in distant cortical areas. The dendritic tree is composed of two main branching structures: an apical dendritic tree composed of a trunk ascending in the direction of the pial surface and a basal dendritic tree composed of multiple trunks giving rise to a cloud of local dendritic branches about the cell body. Both dendritic structures are typically extensively covered with small excrescences called spines where synapses form (Spruston 2008). Cylindrical groupings of the apical dendrites of 50 or so pyramidal neurons constitute a core component of the hypothesized *minicolumn*: a barrel-shaped region representing the basic modular unit of the neocortex (Rockland and Ichinohe 2004). While pyramidal neurons generally show a fair degree of morphological variability, the only atypical variant is the spiny stellate cell, an excitatory interneuron which lacks the characteristic ascending apical dendritic tree and descending axon. Pyramidal neurons constitute a functionally homogeneous group as they all exclusively release the excitatory monoamine glutamate from their axonal terminals.

Non-pyramidal cells are a morphologically much more differentiated class of cortical neuron that have a number of features in common (Nieuwenhuys et al. 2008): their dendrites are often spine-free, their axons do not leave cortex (hence often called *local circuit* or *interneurons*), most release the inhibitory neurotransmitter γ -amino butyric acid (GABA), and a certain fraction (25–30%) also express one or more neuropeptides such as vasoactive intestinal polypeptide (VIP) or cholecystokinin, and various subpopulations show differential immunoreactivity to one or more intracellular calcium-binding proteins which can be used as subpopulation-specific markers. It has been estimated that a dozen or so non-pyramidal cell subtypes can be identified morphologically (Markram et al. 2004), the most numerous of which are basket cells. Other notable non-pyramidal cells include the chandelier, bipolar, and double-bouquet cells.

Laminar Organization of the Neocortex

The cerebral cortex can be divided into vertically stacked cellular laminae extending through the thickness of the cortex. The number, size, and organization of these layers show substantial regional/areal variation. Developmentally two broad structural forms of the cerebral cortex can be identified – homogenetic and heterogenetic cortices.

Homogenetic cortex, commonly referred to as neocortex or isocortex, makes up the bulk of the cerebral cortex and either consists of six reasonably well-defined cellular laminae (homotypical cortex) or began as a well-defined six-layered cortex, but during development the addition or elimination of layers occurred (heterotypical cortex). Heterogenetic cortex (also known as allocortex) is divided into primitive (or paleo-) cortex, in which there is no clear laminar cellular organization (e.g., olfactory bulb), and rudimentary (or archi-) cortex, in which there are only the crude beginnings of lamination (e.g., hippocampus).

The six neocortical layers, typically labeled I–VI (superficial–deep), are characterized by variations in cellular densities, types, and morphologies as well as the patterns of termination and generation of cortical and subcortical afferents and efferents. Non-pyramidal cells occur in all layers and pyramidal cells in layers II to VI. Layer IV of sensory cortices is notable for the large numbers of tightly packed spiny stellate neurons, which are only found there, and the termination of sensory thalamocortical afferents on these neurons and the dendrites of other neurons passing through this layer (Thomson and Bannister 2003). In contrast it has been observed that associational and callosal cortico-cortical efferents arising from layer II and III pyramidal neurons preferentially terminate in layer IV, whereas layer V/VI pyramidal neuron long-range axons preferentially terminate in layers I and VI (Rockland and Pandya 1979).

A variety of attempts have been made to systematically classify variations in the cellular architecture of the various neocortical laminae (cytoarchitectonics) over the whole cerebrum. The most important of these is the architectonic

parcellation scheme of Brodmann (Brodmann and Garey 2006).

Modular Organization of the Neocortex

Commencing with the work of Lorente de No, who first proposed that a small radially oriented cylinder of cells extending through the full extent of the cortex with a single thalamocortical axon as its axis defined an *elementary unit* of neocortical organization, the intervening years have seen a variety of attempts to define a *basic modular unit* of cortical organization.

Amongst the most well known are the micro-, mini-, macro-, and cortico-cortical columns. Micro- and minicolumns typically refer to radially organized chords of ≈ 10 –200 cells that span layers II to VI, arranged as horizontal mosaics with periodicities of the order of 15–80 μm (Jones 2000; Buxhoeveden and Casanova 2002; Rockland and Ichinohe 2004; Nieuwenhuys et al. 2008).

Macrocolumns, first hypothesized by Mountcastle (1957) on the basis of electrophysiological evidence, are thought to be anatomically comprised of aggregations of several 100 minicolumns bound together by short-range horizontal excitatory and inhibitory connections (Mountcastle 1997). Cortico-cortical columns (also referred to as neocortical columns) are typically defined in terms of the cylindrical aborization volumes of either a single afferent cortico-cortical fiber or closely packed bundles of such fibers (Jones et al. 1975; Goldman and Nauta 1977; Szentágothai 1983). Estimates of the radial extent of such columns vary from 200 to 800 μm .

While some areas of cortex have a greater claim to displaying some form of columnar organization than others, visual and somatosensory in particular, cortical columns of any form or variety have not been substantiated by unequivocal anatomical evidence and therefore remain hypothetical. Neocortical columns (Markram 2008), intensely studied in barrel cortex (Petersen 2007; Lübke and Feldmeyer 2007), are perhaps closest to being established.

Mesoscopic Anatomy and Neural Population Models, Table 1 Major structural units of organization in mammalian neocortex and their approximate

characteristics, see text. For neuronal groupings the diameter of a disk with equivalent cortical surface area is given as scale

	Unit	Neurons per unit	No. of units ^b	Scale
Micro	Neuron (soma)	1	$2 \cdot 10^{10}$	15 μm
	Microcolumn ^a	20	10^9	15 μm
	Minicolumn	100	$2 \cdot 10^8$	35 μm
Meso	Dendritic tree	–	–	0.15 mm
	Cortico-cortical column	10^4	$2 \cdot 10^6$	0.35 mm
	Intracortical axonal tree	–	–	0.5 mm
	Macrocolumn	$2 \cdot 10^5$	10^5	1.5 mm
	Martinotti axonal tree	–	–	2 mm
Macro	Architectonic area	$2 \cdot 10^8$	100	5 cm ^b
	Cortico-cortical axon	–	–	10 cm ^b
	Brain region	$2 \cdot 10^9$	10	15 cm ^b
	Neocortex	$2 \cdot 10^{10}$	1	50 cm ^b

Table reproduced from Liley et al. (2012)

^aThe term “microcolumn” is sometimes used to refer to our “minicolumn”

^bFigures are given for the human neocortex

The neocortex consists of populations of vertically well-connected cellular elements interacting horizontally over a range of spatial scales. In general it is the lateral intra- and cortico-cortical axonal ramifications of neocortical pyramidal neurons that define the spatial scales of horizontal connectivity within the neocortex. The lateral axonal ramifications of certain interneurons (e.g., layer II/III double-bouquet cells, Martinotti cells) provide additional characteristic scales for the horizontal organization of the cerebral cortex.

Table 1 summarizes the various scales of cortical organization that have been identified or proposed on the basis of anatomical evidence.

Cross-References

- [Neural Field Model, Continuum](#)
- [Neural Mass Action](#)
- [Neural Population Model](#)

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Meta-analysis in Neuroimaging

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Definition

Meta-analysis is the post hoc combination of experimental results from independently performed neuroimaging studies to better estimate a parameter of interest.

Detailed Description

Meta-analysis

The advent of neuroimaging has resulted with an abundance of data localizing the neural effects of specific mental processes in both healthy and clinical populations. To ease the burden of interpretation and consistency across studies, standards of spatial normalization and the reporting of peak activation locations in stereotactic coordinates based upon a standardized atlas space have been

accepted community-wide. As an alternative to image-based databases, mining coordinate-based data has also yielded new insight into functional connectivity in the human brain (Toro et al. 2008; Smith et al. 2009; Laird et al. 2011). In the context of coordinate-based archives, the 3D stereotactic coordinates of significant functional activations can be archived along with metadata describing subjects, task or paradigm, including behavioral conditions, and standard brain template. The two largest and most commonly known coordinate-based databases are the BrainMap database (brainmap.org; Fox and Lancaster 2002; Laird et al. 2005a; Fox et al. 2005) and Neurosynth (Neurosynth.org; Yarkoni et al. 2011).

The BrainMap database separates functional and anatomical articles into two separate databases. Each paper is manually coded and reviewed by faculty to maintain accuracy and consistency of the entries. Information that is coded along with the coordinates provides a description of how the activations were derived from the subjects. This metadata is based on an expert-generated taxonomy that has been refined over the past 15 years and is the basis for the Cognitive Paradigm Ontology (Turner and Laird 2011). In contrast, *the Neurosynth database* provides an automated annotation of the literature. Because of the automated labeling of experimental results, Neurosynth combines functional and anatomical experiment coordinates and tags each paper with a set of terms that frequently occur within the text.

Both the BrainMap database and the Neurosynth database have been shown to be extremely useful for meta-analysis in which sets of coordinates are pooled to search for spatially consistent regions of brain activity (Niendam et al. 2012; Zald et al. 2012; Turkeltaub et al. 2002). In general, the term “meta-analysis” often refers to a variety of methods focused on combining the post hoc results from independently performed studies to better estimate a parameter of interest (Fox et al. 1998). In the field of neuroscience, localized neural activity is the parameter of interest, and quantitative, coordinate-based meta-analytic methods are often preferred over the historically qualitative literature review. These reviews can be quite time consuming, are substantially less precise, and often are susceptible to sampling bias.

Coordinate-based meta-analysis algorithms, on the other hand, have been statistically refined and enhanced for the last ten years and are now widely accepted within the neuroimaging community. One of the most common algorithms for coordinate-based meta-analyses is activation likelihood estimation (ALE; Turkeltaub et al. 2002; Laird et al. 2005b; Eickhoff et al. 2009) which treats reported foci as not as points but as spatial probability distributions centered at the given coordinates. This method is supported by the BrainMap project and can be applied to a set of activation foci using the GingerALE application (brainmap.org/ale). Other commonly used coordinate-based meta-analysis algorithms in neuroimaging include the *kernel density analysis* (KDA; Wager et al. 2004), *multilevel kernel density analysis* (MKDA; Wager et al. 2007), and signed differential mapping (Radua et al. 2012).

Cross-References

- [BrainMap](#)
- [Human Connectome Project](#)

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Metabotropic Receptors (G Protein Coupled Receptors)

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Synonyms

7TM receptors; Computational modeling;
Dynamic models; G protein linked receptors;

[Heptahelical receptors](#); [Mathematical modeling](#); [Serpentine receptors](#); [Seven-transmembrane domain receptors](#); [Spatial modeling](#); [Systems biology](#); [Time-dependent modeling](#)

Definition

G protein-coupled receptors (GPCRs) are a large and important class of eukaryotic membrane receptors that bind extracellular ligands (molecules as diverse as odorants, hormones, pheromones, photons, neurotransmitters, and small molecule drugs) and transmit those cues to networks of intracellular signaling molecules ultimately driving and modulating cellular response. Mathematical modeling of GPCR signaling provides a platform to elucidate the mechanisms by which GPCR signaling carries out normal cellular function and, in disease states, what aspects of the system are perturbed.

Detailed Description

The wide variety of GPCR receptor species (>800 genes (Venter et al. 2001; Howard et al. 2001)), their diverse cellular responses, and their location at the cell membrane make GPCRs an ideal target for pharmacological intervention in disease states. In fact 30–40% of all current pharmaceuticals target GPCRs (Overington et al. 2006; Howard et al. 2001). GPCRs activate membrane-associated heterotrimeric G proteins, which then initiate signaling of the phosphatidylinositol (IP) and cyclic adenosine monophosphate (cAMP) pathways. GPCRs also participate in non-G protein-associated signaling through G protein-coupled receptor kinases (GRKs), Src kinases, arrestin binding, and PDZ domain-containing proteins (Magalhaes et al. 2012; Romero et al. 2011; Shenoy and Lefkowitz 2011). In addition, the dynamics of GPCR-mediated cellular responses are modulated by multiple ligand-dependent and cellular-dependent phenomena including ligand affinity, efficacy, receptor oligomerization, receptor trafficking (internalization and recycling, localization into

lipid rafts), receptor desensitization by phosphorylation and arrestin binding, and nonlinear feedback and cross talk events within the signaling network. Taken together it is difficult, if not impossible, to intuit the contribution of so many kinetic processes to GPCR-dependent cellular behavior. Mathematical modeling offers a tool by which these mechanisms can be examined, parsed, and understood.

As with all modeling efforts, the techniques employed to investigate different aspects of GPCR signaling vary in their specificity and complexity, from techniques that are meant to focus on network topology and connections (principal component analysis, directed graphs, Bayesian networks, and fuzzy logic) to deterministic models that include regulatory mechanisms, rates of change in concentration, and spatial location of biochemical species (ordinary and partial differential equations) to models tracking the movement of individual biomolecules (probabilistic agent-based and stochastic models). In constructing a computational model of a system, the details that are included depend on the questions being asked, the level of details known, the timescale involved, and a variety of other assumptions about the system under study (for more details on GPCR models, see (Linderman 2009)).

A critical aspect of computational modeling is model validation. Models are built on simplifying assumptions and parameters that are not always known or that have significant uncertainty. Therefore, it is important to validate the assumptions and parameters by:

- Experimentation and measurement
- Extensive literature searches
- Parameter fitting

Expanding the analysis by running simulations under varying assumptions and initial conditions builds intuition about how parameters of the system interact to determine system behavior. Developing models with the goal of making experimentally testable predictions serves to consolidate information, test hypotheses, and provide insight into previously held notions about signaling mechanisms.

While specific models of GPCR systems in neuroscience are sparse, the ubiquity of GPCRs across cell and tissue types allows researchers to adapt previously published models to particular neuro-systems of interest. The next sections discuss general classes of modeling techniques that have been used with great effect in understanding different aspects of GPCR signaling and function not necessarily restricted to traditional neuronal systems.

Equilibrium models describe how perturbations of a system change the distribution of the states of model species, for example, how addition of a ligand changes the distribution of receptor states. They are built using algebraic equations and assume that dynamic changes in redistribution are rapid relative to the timescale of interest. The dynamics of the redistribution itself is not under investigation. They have limited use in describing the inherent dynamic behavior of intracellular signal transduction but have been applied with great utility to describe pharmacological phenomena of ligand efficacy, allosteric modulation, and receptor states observed in GPCR systems (Kenakin 2002; Monod et al. 1965).

Kinetic models of GPCR signaling are used to examine the mechanisms that drive the dynamic behavior of GPCR activation, downstream protein-protein interactions, and receptor regulatory mechanisms (phosphorylation, desensitization, and receptor endocytosis and recycling). In these models, signaling events are described by systems of differential equations in which protein-protein interactions are governed by binding and dissociation rate constants (“ k_{on} ” and “ k_{off} ”), and concentrations of molecular species are tracked over time (ordinary differential equations (ODEs)) or time and space (partial differential equations (PDEs)). Depending on the timescale and level of model abstraction, the activity of enzymes (for GPCR systems, mostly GTPases, adenylyl cyclases, phosphodiesterases, kinases, and phosphatases) can be modeled using quasi-equilibrium Michaelis-Menten kinetics. Alternatively, enzyme-substrate binding and product formation kinetics can be explicitly included.

In just one example of the many systems relevant to neuroscience, several recent modeling efforts have used ODEs to investigate dopaminergic and glutamatergic signaling in the striatum and hippocampus. It has been shown that cross talk between GPCR receptor-activated networks and Ca^{2+} -activated networks (coming from the opening of NMDA receptors) modulates the strengthening and weakening of synapses (Kim et al. 2010; Fernandez et al. 2006; Nakano et al. 2010).

Compartmental models of biochemical signaling segregate relevant signaling domains into sub-cellular compartments, but do not explicitly consider the spatial movement of molecular species or the shape of a cell. Signaling molecules are assigned to compartments, and movement between compartments is typically defined such that the rate is dependent on species concentration. Within each compartment the system is assumed to be well mixed (fast diffusion), such that the model is still written in terms of ODEs.

Molecular diffusion and scaffolding are important processes that set up signaling sub-domains in the cell. They are of particular interest in neuroscience where cell shape is especially important; diffusion may not be assumed to be rapid due to molecular crowding, scaffolding proteins may act to increase local concentrations of signaling molecules, and spatial gradients of second messenger molecules (Ca^{2+} and cAMP in particular) are emergent properties of the system. When these processes are important considerations PDEs are employed to track concentrations of molecular species in both time and space. For some recent reviews of considerations in setting up compartmental and PDE models see Cowan et al. (2012), Neves and Iyengar (2009), and Blackwell et al. (2013). Examples in which PDEs have been employed to study neuronal GPCR function include: (1) a model of β_2 -adrenergic signaling in realistic neuronal volumes, where cell shape and negative biochemical regulation work together to form localized signaling domains (Neves et al. 2008), and (2) a study by Lenkei and colleagues showing that activation-dependent receptor endocytosis and endocytosis-dependent targeting of recycled receptors to the axon lead to

distinct differences in the axonal versus somatodendritic localization of CB1R cannabinoid and SSTR2 somatostatin receptors (Simon et al. 2013).

Stochastic models describe signaling events in terms of probabilities. In contrast to the deterministic models described above, stochastic equations are most useful when considering the spatial and/or temporal function of a small number of individual molecules. These considerations regularly arise in neuroscience due to the small volume and small number of molecules found in structures such as dendritic spines and spiny neurons and in the leading edge of axonal growth cones.

The challenge in employing stochastic models is that they are much more computationally intensive to solve and must be run multiple times in order to accurately calculate the probabilities of possible signaling outcomes. Readily available simulation environments to build and run stochastic simulations include MCell, Virtual Cell, Smoldyn, GENESIS and its associated packages (KinetiKit), and NeuroRD (Cowan et al. 2012; Vayttaden and Bhalla 2004; Oliveira et al. 2010; Andrews et al. 2010; Andrews 2012; Stiles and Bartol 2001; Kerr et al. 2008). See Blackwell (2013) for a recent review of these methods and simulation packages.

Despite the challenges and due to the increasing availability of computational power, reliable stochastic algorithms, and simulation packages, many researchers have used stochastic simulation to study GPCR mechanisms. These include studies to elucidate the complex interactions between ligands, receptors, and lipids at the membrane surface (Woolf and Linderman 2003; Brinkerhoff et al. 2004; Fallahi-Sichani and Linderman 2009), identify the role that RGS proteins may play in localizing and specifying GPCR signals (Zhong et al. 2003), and investigate the temporal and spatial effects of kinase activity downstream of GPCR signaling (Oliveira et al. 2012; Kim et al. 2013; Blackwell et al. 2013; Bhalla 2004a, b).

Other mathematical techniques provide relevant information. Data-driven modeling is used

for network reconstruction and analysis (Benedict and Lauffenburger 2013; Janes and Yaffe 2006). Sensitivity analysis identifies and classifies important model parameters (Zheng and Rundell 2006; Zi et al. 2008; Kinzer-Ursem and Linderman 2007). Molecular dynamics simulations provide insight into GPCR structure, oligomerization, and membrane interactions (Simpson et al. 2010; Selent and Kaczor 2011; Grossfield 2011; Filizola and Weinstein 2005). All these plus new methods to allow the incorporation of qualitative data from *in vivo* and *in vitro* experiments into quantitative models (Pargett and Umulis 2013) and model-based experiment design (recently reviewed by Chakrabarty et al. 2013) represent exciting directions for future work using computational models to elucidate complex phenomena in GPCR signaling.

There is little doubt that computational modeling will increasingly serve as a useful tool for understanding and elucidating mechanisms of GPCR and other complex biochemical networks. Indeed, simply examining the assumptions that one must make in order to mathematically describe a signaling network increases one's understanding of the system. Computational modeling can be applied to help interpret seemingly conflicting observations and offer new explanations of mechanisms underlying network behavior, provide insight into the role of distinct yet simultaneous signaling pathways in an observed behavior, identify potential new targets for therapeutic intervention, design maximally informative experiments, and much more.

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Metabotropic Receptors Dynamics, Conductance Models

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Definition

A metabotropic receptor is a receptor, usually located on the surface of a cell, that when activated by the binding of transmitter leads to the activation of a secondary messenger system inside the cell. This in turn can induce a conformational change in ion channels in the cell membrane, thus modifying their conductance properties. In many cases, this secondary messenger system involves G-proteins, and thus the term “G-protein-coupled receptor” is often used instead of metabotropic receptor.

Detailed Description

A salient feature of metabotropic receptors is that they act on a much longer timescale (seconds to minutes) than directly gated (ionotropic) receptors, the latter typically acting on a timescale of a few milliseconds. Also, ionotropic receptors act only locally, whereas because of the secondary messenger system, metabotropic receptors can affect the behavior of ion channels in other parts of the cell. Another property is the amplification feature, in that one activated receptor molecule can activate hundreds to thousands of G-protein molecules and thus influence many ion channels in the cell. Examples of metabotropic receptors are muscarinic acetylcholine receptors, metabotropic glutamate receptors, GABA_B receptors, and beta-adrenergic receptors (Kandel et al. 1991). A number of these receptors either excite or inhibit neurons by either closing or opening K⁺ channels (Hille 1992).

A Simple Phenomenological Model

The basic signaling mechanism is shown in Fig. 1.

Let $c(t)$ be the concentration of transmitter at the receptor site. The receptor activation $a(t)$ can be described by a Michaelis-Menten-type formula:

$$p(t) = \frac{rc(t)}{k + c(t)},$$

where r is the receptor availability and k is a constant. Ignoring all details of the secondary messenger system, the activation $a(t)$ of the ion channel satisfies

$$\frac{da}{dt} = \frac{p(t)}{\tau_a} - \frac{a(t)}{\tau_i}.$$

The significant quantities here are the time constants τ_a and τ_i of activation and inactivation, respectively, and these can be chosen to give the desired time course (cf Postnova et al. 2010). The current through the ion channel is then

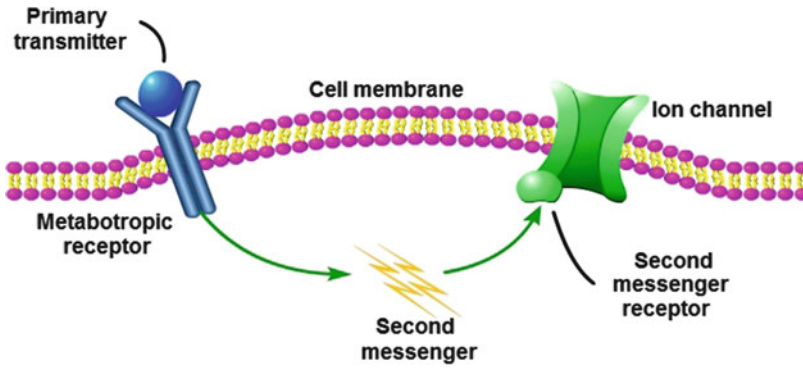
$$i(t) = ga(t)(V - E_R)$$

where g is the channel conductance, V is the membrane potential, and E_R is the reversal potential.

As a simple example, suppose transmitter is applied at a constant rate in the time interval $0 < t < t_0$. Then the above equations give a scaled activity $\bar{a}(t) = 1 - \exp(-t/\tau_i)$ for $t < t_0$ and $\bar{a}(t) = (\exp(t_0/\tau_i) - 1) \exp(-t/\tau_i)$ for $t > t_0$. By choosing a suitable value for τ_i , one can mimic the long time course of a metabotropic receptor.

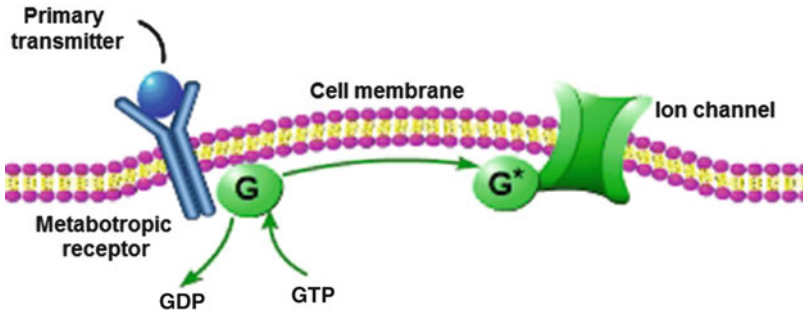
A Model Incorporating G-Protein Coupling

Some metabotropic receptors may operate with a G-protein as the sole secondary messenger, as shown in Fig. 2 (Hille 1992).



Metabotropic Receptors Dynamics, Conductance Models, Fig. 1 Schematic diagram showing the basic mode of operation of a metabotropic receptor. The receptor is activated by the binding of a primary transmitter in the

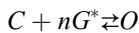
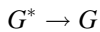
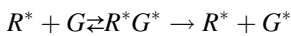
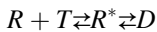
extracellular space. This leads to the activation of a secondary messenger that diffuses inside the cell and binds to receptors on an ion channel, causing a change in the channel conductance



Metabotropic Receptors Dynamics, Conductance Models, Fig. 2 G-protein as the secondary messenger. Activation of the receptor causes the G-protein to bind to the intracellular domain of the receptor leading to GTP

replacing GDP in the G-protein, thus transforming it to the activated form G^* . This remains in the membrane and can interact directly with an ion channel

This process can be represented by the following equations (Destexhe et al. 1998; see also Destexhe et al. 1994).



T is transmitter, R is receptor, G is G-protein, C is the closed state, and O is the open state of the ion channel; the transition between these states is governed by the binding of activated G-protein molecules to n independent binding sites on this channel. Asterisks denote activated forms. The scheme also allows the receptors to go to a desensitized form, D . Kinetic equations can be

written for the concentration of substances in these reactions. These can be simplified by setting $d[R^*G^*]/dt = 0$ ("quasi-steady-state approximation") and assuming that G is present in excess, so $[G] \gg [G^*]$ ($[]$ denotes concentration). Also, R acts only as a catalyst, so $[R] + [R^*] + [D]$ is constant. This leads to the following equations (Destexhe et al. 1998).

$$\frac{d[R]}{dt} = K_1[T](1 - [R^*]) - K_2[R^*] + K_3[D]$$

$$\frac{d[D]}{dt} = K_4[R^*] - K_3[D]$$

$$\frac{d[G]}{dt} = K_5[R^*] - K_6[G^*],$$

where $[R^*]$ is the fraction of activated receptors, $[D]$ is the fraction of desensitized receptors, and

$[G^*]$ is the concentration of activated G-protein per receptor molecule. Assuming equilibrium between open and closed channels gives the fraction of open channels as $[G^*]^n/([G^*]^n + K_d)$, where K_d is the dissociation constant, and thus the current through a channel is

$$I = g \frac{[G^*]^n}{[G^*]^n + K_d} (V - E_R)$$

where g is the channel conductance, V is the membrane potential, and E_R the reversal potential. Destexhe et al. (1998) have applied the above method to the GABA_B receptor, where the ion channel is a K⁺ channel.

The above equations can be simplified by removing the desensitized state, D (Destexhe et al. 1998). Making the additional assumption that the activated receptor concentration changes slowly gives

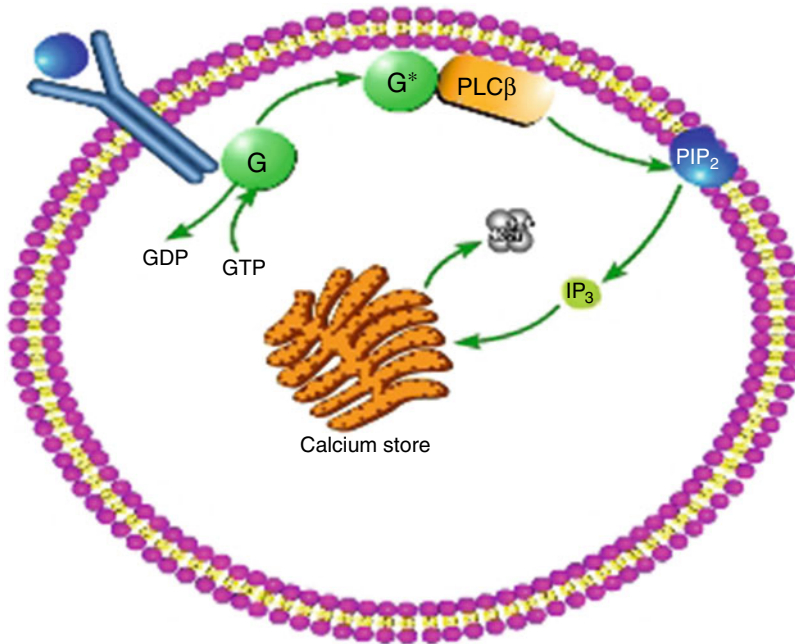
$$[R^*] = \frac{[T]}{[T] + K_2/K_1}$$

It will be seen that this simplified version relates to the phenomenological model given above.

More Elaborate Models

In most cases the activated G-protein does not act directly on the ion channel, as in the above model, but sets off a cascade of events that involve substances such as adenylyl cyclase, cyclic AMP (cAMP), inositol 1,4,5-trisphosphate (IP₃), etc. (Kandel et al. 1991). One possible chain of events is shown in Fig. 3, where Ca²⁺ is released from internal stores.

This model has been developed in detail in Lemon et al. (2003). If it is assumed that there is



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Metabotropic Receptors Dynamics, Conductance Models, Fig. 3 Release of Ca²⁺ from internal stores. The G-protein activation is as for Fig. 2, but rather than acting directly on an ion channel, G* binds to a site on phospholipase C-β (PLC) and this activated unit initiates an interaction with membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP₂) leading to the hydrogenation of

PIP₂ and the production of IP₃. This diffuses into the cytosol where it opens IP₃-sensitive channels in the calcium store (endoplasmic reticulum, ER) allowing the release of Ca²⁺ into the cytosol. This Ca²⁺ can now have further effects, for example, increasing the current through Ca-dependent K⁺ channels (not shown)

no depletion of PIP_2 , then the production of IP_3 can be described by

$$\frac{d[\text{IP}_3]}{dt} = r_h^*[G^*] - k_{deg}[\text{IP}_3]$$

where r_h^* and k_{deg} are constants, and the release of Ca^{2+} by

$$\frac{d[\text{Ca}^{2+}]}{dt} = \beta(J_{\text{IP}_3} - J_{\text{pump}} + J_{\text{leak}})$$

where $[\text{Ca}^{2+}]$ is the cytosolic Ca^{2+} concentration; J_{IP_3} , J_{pump} , and J_{leak} are the rates of Ca^{2+} change due to release through IP_3 receptor channels on the ER, pump uptake into the ER and leaks from the ER, respectively; and β is a factor describing Ca^{2+} buffering. Expressions for these quantities can be found in Lemon et al. (2003). This formalism has been used in other applications, in particular, in modeling Ca^{2+} waves in arrays of astrocytes, where the slow action of metabotropic purinergic receptors is essential for obtaining the observed speeds of the waves (Bennett et al. 2005).

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Methodologies for the Restoration of Bladder and Bowel Functions

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Synonyms

[Neural control of bladder and bowel functions](#); [Neuromodulation for bladder and bowel](#); [Treatment of lower urinary tract dysfunction](#)

Definition

Bladder and bowel dysfunctions are frequently caused by neurological disease or injury such as spinal cord injury (SCI). With an annual incidence of 15–40 cases per million worldwide (Sekhon and Fehlings 2001), SCI results in neurogenic bladder or bowel dysfunction in a substantial percentage of cases (Levi et al. 1995). Surveys of quality-of-life measures in those with SCI show that the participants' highest priorities were restoration of bladder/bowel function, restoration of sexual function, restoration of sensation, and elimination of chronic pain (Anderson 2004). In an earlier study, subjects with SCI indicated that bowel and bladder dysfunctions have a significant effect on their lives, ranking neurogenic bladder and bowel dysfunction as one of their major life-limiting problems (Hanson and Franklin 1976). Electrical stimulation of the nervous system is an approach to restore bladder and bowel functions following neurological disease or injury.

Detailed Description

Normal Control of Bladder Function: Anatomy and Neurophysiology

The lower urinary tract (LUT), which includes the urinary bladder and urethra, serves two important roles: continence (the storage of urine in the bladder) and micturition (efficient voiding of urine from the bladder at an appropriate time). Under normal conditions, both of these functions are controlled by neural circuits in the spinal cord and brain. Neural signals encoding bladder control are transmitted to and from the bladder, urethra, and periurethral skeletal muscle via peripheral nerves that innervate the LUT.

The bladder and urethral sphincter are controlled in a reciprocal manner to accomplish continence and micturition. During storage, the smooth muscle of the bladder is relaxed and the urethral sphincter is contracted enabling low-pressure urine storage, while during voiding, the bladder muscle contracts and the urethral sphincter relaxes, allowing urine to leave the bladder (Beckel and Holstege 2011b).

The reflexes that facilitate urine storage and voiding are mediated through coordinated sympathetic, parasympathetic, and somatic neural activity. Sensory fibers in the hypogastric (sympathetic), pelvic (parasympathetic), and pudendal (somatic) nerves provide information from the bladder and urethra to the lumbar and sacral levels of the spinal cord. These sensory fibers enter the dorsal horn, projecting to local interneurons and projection neurons making ascending connections to the periaqueductal gray (PAG) and pontine micturition center (PMC) (Benarroch 2010). Descending modulation from these areas innervates the sacral parasympathetic nucleus (SPN) and somatic Onuf's nucleus. Originating from the SPN, pelvic nerve efferents are responsible for contraction of the bladder. The output of Onuf's nucleus, the pudendal nerve, controls the contraction or relaxation of the external urethral sphincter (EUS) and provides sensory input about flow in the urethra to the sacral spinal cord, which can act as important feedback during micturition (Shafik et al. 2003).

During bladder filling, the pelvic afferents carry signals from stretch receptors in the bladder wall and signal bladder distention to the spinal cord (Fowler et al. 2008). To maintain storage, the sympathetic pathway is activated and tonic output to Onuf's nucleus is increased (Benarroch 2010), which results in relaxation of the bladder and contraction of the EUS, respectively.

The higher level control of micturition is complex, involves multiple brain areas, and relies on ascending information from spinal circuits and sensory peripheral nerve inputs. The PMC plays a critical role and may act as the efferent switch between storage and voiding phases, although higher brain areas provide inputs which determine when it is on or off (Beckel and Holstege 2011a). When the PMC is excited, descending pathways are activated, resulting in urethral relaxation and an increase in SPN activity, which, via the pelvic nerve, causes a contraction of the bladder (Fowler et al. 2008). The synchronized activation of the SPN and the inhibition of the somatic Onuf's nucleus induce a coordinated contraction of the bladder and relaxation of the EUS, which results in efficient bladder emptying (Kinder et al. 1995).

Disorders Affecting Bladder and Bowel Function

Neurological diseases and injuries such as SCI or trauma, multiple sclerosis, transverse myelitis, spina bifida, tumors of the brain or spinal cord, dementia, and pelvic surgical injuries can disturb normal bladder or bowel function. Bladder dysfunction can cause urinary incontinence, the involuntary leakage of urine; urinary retention, the lack of the ability to urinate; and detrusor-sphincter dyssynergia (DSD), bladder contractions concurrent with an involuntary contraction of the urethral musculature. The location and severity of the injury affect the degree of dysfunction, which could include interrupting communication between the sacral spinal cord and pontine micturition centers or directly damaging part of the sacral spinal circuits that control detrusor and sphincter functions (Benevento and Sipski 2002).

Additionally, bladder conditions and dysfunction may change over the course of an injury and recovery as a result of neuronal plasticity, making bladder management a persistent challenge.

Treatments of Bladder Dysfunction

Treatment of bladder dysfunction commonly includes pharmacological intervention and urethral catheterization, although these may be accompanied by drug side effects and frequent urinary tract infections. In cases of bladder dysfunction such as DSD, the goal of treatment is to provide bladder emptying while maintaining low bladder pressures during both storage and voiding. Anticholinergic medications, e.g., oxybutynin, may be used to suppress detrusor contractions and combined with intermittent catheterization to empty the bladder. Blockers of alpha-adrenergic receptors, e.g., tamsulosin, can be prescribed to reduce internal urethral sphincter or bladder neck resistance in males, and other types of medications, e.g., baclofen, may be used to decrease muscle spasticity in the pelvic floor (Burns et al. 2001).

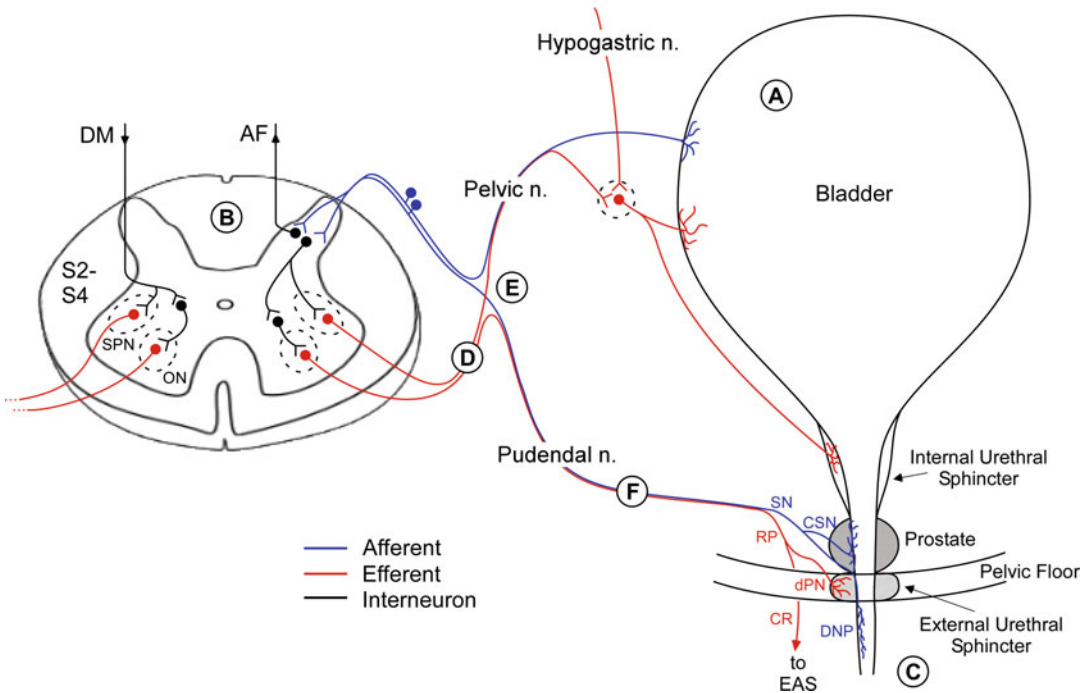
More aggressive interventions are often necessary if these pharmacological treatments fail to restore continence or allow for micturition. In some cases, surgical interventions, such as a transurethral sphincterotomy or the placement of a urethral stent, may be used to prevent DSD or decrease outlet resistance. In cases of detrusor hyperreflexia, where the bladder is hyperexcitable, treatment with intravesical capsaicin or botulinum A toxin may be performed to paralyze the bladder and prevent incontinence.

Functional electrical stimulation with the goal of emptying the bladder at a desired time to produce low residual volumes has been increasingly used when more conservative treatments are unsuccessful or intolerable. Many different stimulation locations have been investigated for the application of electrical stimulation to restore functional bladder control, with varying degrees of success (Fig. 1).

There are five locations where electrical stimulation electrodes could be placed in an attempt to

control bladder function in SCI: the bladder, skin, peripheral nerve, sacral roots, and spinal cord (Gaunt and Prochazka 2006). There has been limited clinical success with direct bladder wall stimulation due to problems with concomitant sphincter activation, pain, or device failure (Bradley et al. 1963; Hald et al. 1967; Stenberg et al. 1967). Spinal cord stimulation for bladder control has not been well received either, as it does not provide benefits over sacral root stimulation, it is very invasive, and it had high complication rates (Nashold et al. 1981). Transcutaneous electrical stimulation for bladder control, e.g., dorsal penile nerve surface stimulation to inhibit bladder activity, targets peripheral nerves through a less invasive manner. However, skin stimulation is less common than more invasive approaches to stimulate peripheral nerves due to discomfort in persons with incomplete SCI (Previnaire et al. 1998) and practical challenges of chronic stimulation with surface electrodes. Peripheral nerve and sacral root stimulations have proved to be the leading candidates for effective restoration of bladder function with electrical stimulation.

Neuromodulation with sacral anterior root stimulation, Finetech-Brindley SARS, can produce efficient voiding in those with SCI (Brindley et al. 1982). However, implantation requires a concomitant surgical transection of the sacral dorsal roots (posterior rhizotomy), which limits detrusor-sphincter dyssynergia but irreversibly eliminates reflex erection, reflex micturition, and any remaining sensation. Sacral nerve stimulation with InterStim[®] (Medtronic Inc., Minneapolis, MN, USA) has been shown to treat effectively overactive bladder by reducing bladder hyperreflexia and increasing cystometric capacity (Vodusek et al. 1986; Ishigooka et al. 1998), although it has not been effective at restoring bladder function in those with SCI, as it rarely produces on-demand voiding (Chartier-Kastler et al. 2001; De Ridder et al. 2007). Success with InterStim[®] is highly dependent on etiology, and while it has been generally effective for overactive bladder, it has not been as effective in producing efficient voiding in a majority of patients with bladder retention.



Methodologies for the Restoration of Bladder and Bowel Functions, Fig. 1 Neuroanatomy of the lower urinary tract and locations targeted for restoration of bladder control using electrical stimulation. Afferents from the bladder and pelvic floor enter the spinal cord, where they send information to local interneurons and ascending fibers (AF). Descending modulation (DM) relays signals from the pontine micturition center that control the outputs of the sacral parasympathetic nucleus (SPN) and Onuf's nucleus

(ON). Locations where electrical stimulation has been tested for restoration of bladder function are shown, including (A) bladder, (B) spinal cord, (C) skin, (D) sacral anterior roots, (E) sacral nerve, and (F) pudendal nerve. Abbreviations: CR caudal rectal, CSN cranial sensory nerve, dPN deep perineal nerve, DNP dorsal nerve of penis, PN pudendal nerve, RP rectal perineal, SN sensory nerve

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Peripheral nerves provide multiple locations for the application of electrical stimulation for control of bladder function. Pelvic nerve stimulation was shown to produce bladder contractions in dogs but also resulted in undesirable co-activation of urethral sphincters (Holmquist and Olin 1968). Tibial and pudendal nerve stimulations are currently being investigated and may be effective targets for control of bladder function. Uniquely, electrical stimulation of the pudendal nerve is capable of producing both excitation of the bladder and voiding, in addition to bladder inhibition and continence, in cats (Boggs et al. 2006; Tai et al. 2007) and rats (Peng et al. 2008). Importantly, these inhibitory and excitatory reflexes have also been demonstrated in persons with SCI (Kirkham et al. 2001; Gustafson et al. 2004; Yoo et al. 2007).

Treatments of Bowel Dysfunction

The goals of managing bowel dysfunction include continence of stool, willful and independent defecation, and the prevention of additional gastrointestinal complications (Stiens et al. 1997). Bowel programs, including individualized treatment plans of scheduled bowel evacuations and careful dietary planning, are often used to prevent incontinence and achieve effective colonic evacuation (Stiens et al. 1997). In cases of areflexic bowel, bowel programs must be performed more frequently and manual evacuation may be required. Medications used to manage neurogenic bowel dysfunction include stool softeners, laxatives, prokinetic agents, and fiber. Surgical treatments of bowel dysfunction include antegrade colonic enema with an appendicostomy or

colostomy formation (Glickman and Kamm 1996). Sacral anterior root stimulation (SARS), which has been used to treat neurogenic bladder dysfunction, may also improve bowel function. SARS significantly increased bowel movement frequency, reduced the number of methods needed to evacuate bowel, and reduced constipation in a study of patients with SCI (Vallès et al. 2009).

Cross-References

- [Peripheral Nerve Interfaces: Overview](#)
- [Peripheral Nerves, Anatomy and Physiology of](#)

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Further Reading

- Furlan JC, Urbach DR, Fehlings MG (2007) Optimal treatment for severe neurogenic bowel dysfunction after chronic spinal cord injury: a decision analysis. *Br J Surg* 94(9):1139–1150

Methodologies for the Treatment of Pain

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Synonyms

[Intrathecal analgesics](#); [Intrathecal drug delivery](#);
[Spinal cord stimulation](#)

Definition

Invasive techniques to interface with the spinal cord are often selected for patients suffering pain conditions that are refractory to conventional medical management. These spinal interfaces for the treatment of pain can include epidural electrical stimulation and intrathecal drug delivery.

Detailed Description

Introduction

A significant number of patients suffering chronic pain do not respond well to standard pharmacological therapies. For these patients, more invasive therapies are often considered. One standard therapy is electrical stimulation of the spinal cord with electrode arrays implanted in the epidural space dorsal to the spinal cord. Another common treatment option is the delivery of analgesics by insertion of a catheter system inside the intrathecal space of the spine. Due to the invasive nature of these therapies, they are typically selected as a last resort for pain management.

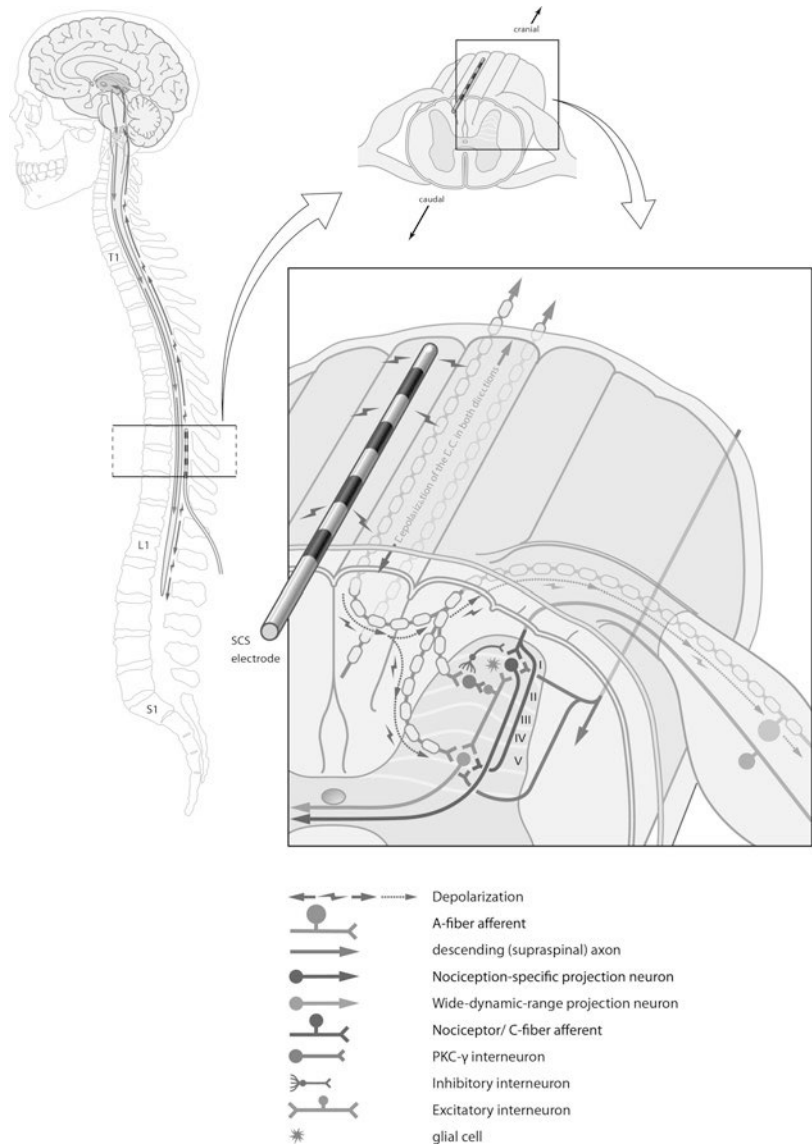
Spinal Cord Stimulation

Spinal cord stimulation (SCS) is a pain management therapy for patients suffering from specific types of chronic pain conditions that are refractory to conventional medical management (CMM) (e.g., pharmacological treatments). SCS was first tested in patients in 1967 and is now considered a routine surgical option (Shealy et al. 1967). It is estimated that approximately 15,000 SCS systems are implanted yearly in the USA alone at a cost of more than one billion US dollars (Linderroth and Meyerson 2002). Although SCS has a high initial cost, studies have shown its long-term potential cost-effectiveness relative to other treatment options (Linderroth and Meyerson 2009; North and Linderroth 2010).

SCS is typically considered for neuropathic limb pain that is refractory to CMM, including conditions such as failed back surgery syndrome (FBSS) and chronic regional pain syndrome (CRPS). SCS has also been indicated in visceral abdominal pain as well as ischemic pain resulting from peripheral vascular disease or stable coronary insufficiency (Linderroth and Meyerson 2009). Studies have shown a higher rate of success and improved patient quality of life with SCS in combination with CMM relative to CMM alone (Linderroth and Meyerson 2009). SCS-induced pain relief of 50% or more is typically considered a satisfactory outcome.

Methodologies for the Treatment of Pain,

Fig. 1 Possible mechanisms of spinal cord stimulation (SCS). In SCS, an electrode array is inserted into the epidural space dorsal to the spinal cord. Electrical pulses are applied through the electrode(s) in an attempt to excite the large-diameter myelinated fibers in the dorsal column (DC) resulting in both orthodromic and antidromic action potential propagation. According to the gate-control theory, antidromic propagation is believed to activate inhibitory interneurons that attenuate the transmission of pain signals to the brain by projection neurons (i.e., close the “gate”). Orthodromic activation of the DC fibers can produce activation of supraspinal areas and possible modulation of descending inputs to the spinal cord. (Figure reproduced from Smits et al. (2013) with permission from Wiley)



SCS involves implantation of a multielectrode array in the epidural space dorsal to the spinal cord a few levels above the affected spinal segments (Fig. 1). Electrical pulses are typically applied at a moderate frequency (e.g., 50–60 Hz) with the goal of exciting the large-diameter ($A\beta$) sensory afferents in the dorsal columns (DC) to create paresthesias (i.e., tingling) over the painful areas. According to the gate-control theory, some of the $A\beta$ fibers have collaterals that project to the affected spinal levels. SCS results in antidromic

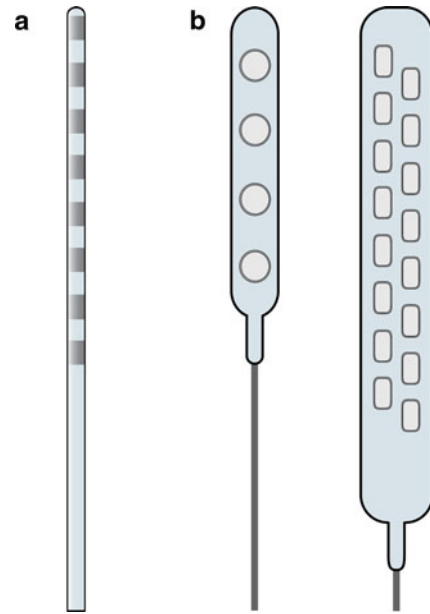
activation of the $A\beta$ fibers that in turn (via their collaterals) lead to inhibition of nociceptive-specific or wide dynamic range projection neurons in the dorsal horn. In neuropathic pain conditions, excessive nociceptive inputs are believed to produce hyperexcitability in these projection neurons (i.e., central sensitization). One of the possible mechanisms underlying the effects of SCS is antidromic activation of $A\beta$ fibers, inhibiting output from these projection neurons largely through the activation of inhibitory

interneurons that help close the “gate” and prevent the transmission of pain signals to the brain (Guan 2012).

Although the effects of SCS may be mediated by spinal or segmental mechanisms as described above, multiple supraspinal mechanisms have also been implicated in SCS-induced analgesia. Orthodromic activation of DC fibers during SCS is relayed through the DC nuclei and transmitted from the brainstem to the sensory thalamus and to the cortex. SCS has also been shown to modulate evoked potentials in both the thalamus and cortex (Linderth and Meyerson 2002). Descending pathways have also been shown to play a role in the development and maintenance of neuropathic pain, and experimental evidence suggests SCS may lead to activation of descending inputs to the spinal cord (Guan 2012). Although SCS has been implemented clinically for several decades, the therapeutic mechanisms of SCS are still poorly understood. Several references are available discussing its potential mechanisms of action (Linderth and Meyerson 2002; Linderth et al. 2009; North and Linderth 2010; Guan 2012).

Two types of electrode arrays are common in SCS: cylindrical or paddle leads (Fig. 2). Cylindrical leads have multiple electrodes (e.g., 4–8) on the distal end and can be implanted in the epidural space with minimally invasive percutaneous techniques. The lead location is guided with fluoroscopy and intraoperative stimulation is often used to determine the final lead location in which stimulation produces maximal paresthesia coverage over the painful area. The most common complication of SCS with cylindrical electrodes is lead migration that results in a loss of therapeutic efficacy (de Oliveira and Machado 2012).

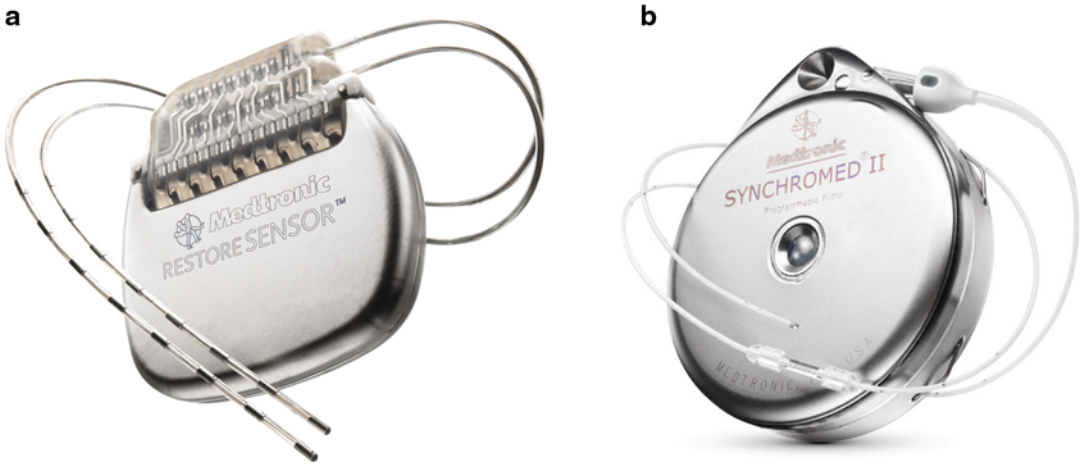
Paddle leads are a second option that can be considered for SCS (Sears et al. 2011). Paddle leads can often be directly anchored to spinal elements and thus have a lower risk of migration relative to cylindrical leads. The geometry of paddle leads improves stimulation efficiency (North et al. 2002), and modern paddle leads typically have a large number of electrodes (e.g., 8–16) that increase programming options in an attempt to



Methodologies for the Treatment of Pain, Fig. 2 Electrode arrays for spinal cord stimulation (SCS). (a) An example of an eight-contact cylindrical electrode array that can be implanted in the epidural space with minimally invasive percutaneous techniques using a needle. (b) Two different geometries of paddle electrodes used for SCS. These electrode arrays must be surgically implanted by removing a portion of the vertebral bone called the lamina. The electrode on the left has four contacts, while the electrode on the right has two columns of staggered electrodes (16 electrodes total)

improve therapeutic outcomes. The main drawback of paddle leads is that implantation requires a laminectomy or laminotomy, which is an open surgery with removal of a small portion of the lamina in order to pass the paddle lead.

Before an SCS system is permanently implanted, a short trial period (e.g., 5–10 days) with the electrode wires externalized is often utilized to assess the efficacy of stimulation. If the therapy is deemed effective (e.g., pain relief $\geq 50\%$), the patient may then undergo a second procedure for implantation of a fully internal (implantable) system with percutaneous or paddle leads (Fig. 3a). Detailed descriptions of the equipment, surgical procedures, and complications of SCS are available (Linderth and Meyerson 2009; North and Linderth 2010; Rauck et al. 2012; Feler 2012).



Methodologies for the Treatment of Pain, Fig. 3 (a) Example of an SCS system with two percutaneous eight-electrode arrays connected to an implantable electrical

pulse generator. (b) Example of an implantable drug delivery pump and catheter system (Images courtesy of Medtronic, Inc., Minneapolis, MN)

Infusional Therapies

Intrathecal infusion can be accomplished via externalized catheters or implanted systems (Slavin 2002). Externalized infusion is typically utilized for acute pain management of in-hospital patients, including postsurgical pain management. Externalized infusion can also be utilized to test the effects and side effects of intrathecal infusion of opioid and non-opioid medications to inform the patient's candidacy for a fully implanted system (Levy 2002; Osenbach 2010). The implantable medical devices for intrathecal infusion consist of a combination of an implantable pump and catheter system (Fig. 3b) (Slavin 2002). The pumps can be programmable or nonprogrammable. The main advantage of programmable pumps is that the daily dose of medications can be adjusted via telemetry, without changing the concentration of the medication. Nonprogrammable pumps infuse only at one set rate, and to change the daily dose, it is necessary to drain the medication from the pump and reload it with a new concentration. The pumps are typically implanted in the abdominal area, but other surgical sites are also possible.

The surgical procedure for implantation of these devices can be explained in three steps (Slavin 2002; Osenbach 2010). The first step is insertion of the catheter, typically through a lumbar tap with a Tuohy needle. The catheter is typically advanced to the thoracolumbar transition under fluoroscopy. The second step is to tunnel the intrathecal catheter or a second, more resistant, catheter from the low back to the abdominal area. The third step is to implant the pump in a subcutaneous abdominal pocket and connect to the catheter system.

While intrathecal infusion remains a viable and commonly utilized alternative for pain management, its use has declined significantly over the past decades mostly due to concerns related to limited long-term efficacy, side effects, and complications. Intrathecal pumps serve as an alternative route for delivery of pharmacological agents that allows for maximal analgesia with lower effective doses and subsequent reduced side effects. However, chronic intrathecal infusion can be associated with cognitive and behavioral changes as well as other complications associated with chronic use of opioid medications (Osenbach 2010; de Oliveira and Machado 2012). New, non-opioid, medications are currently being evaluated for intrathecal infusion and may significantly

boost the future utilization of these devices (Reig et al. 2009). As for all surgical procedures, there are possible complications associated with implantable intrathecal systems (Slavin 2002; Osenbach 2010; de Oliveira and Machado 2012). Some of the most common complications are related to the catheters, which can migrate, plug, kink, or break. These complications can be evaluated via imaging studies and surgical revision is required to correct them. Although malfunction of the pump mechanisms have been reported, they are uncommon. In recent years, formation of granulomas in the tip of the intrathecal catheters has been reported as a cause of malfunction and neurological deficits. Unlike patients with spinal cord stimulation, patients with intrathecal pumps can have magnetic resonance imaging of the body and imaging studies are ordered when catheter tip granuloma is suspected. Future improvements of this technology for pain management depend not only on device miniaturization (pumps remain much larger than neurostimulators) but also combined development of new drugs and delivery systems.

Cross-References

- Neuromodulation: Overview
- Paraspinal Magnetic and Transcutaneous Electrical Stimulation
- Peripheral Nerve Interface Applications, Neuropathic Pain
- Spinal Interfaces: Overview

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Methods for Optimizing Stimulus Waveforms for Electroceutical Control

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Definition

The increasing interest in and use of bioelectronic devices, also known as electroceuticals, as a medical therapeutic is necessitating the use of optimized stimulus waveforms in order to minimize adverse effects and maximize battery life. This entry examines how these optimized stimulus waveforms can be found including both traditional model-dependent approaches and some of the newer model-independent techniques.

Detailed Definition

Recent advances in a variety of disciplines, ranging from electrode technology to anatomical and functional mapping of the nervous system to digital waveform generators, have ushered in a new age of electrical stimulation, or electroceutical, therapies. While the use of electrical shocks as a therapeutic modality is not new, the ability to precisely target fine structures in brain and nerves is allowing for an unprecedented level of control over the nervous system. These technologies are being explored and studied to treat medical conditions including Parkinsonian tremors, epilepsy, inflammatory and autoimmune disorders, and heart failure (Majid 2017).

One of the challenges associated with the development of any new therapy is determining the optimal dosing protocol. Historically, dosing

of current stimulation was limited to the strength and the duration of stimulation. Modern digital waveform generators can construct arbitrary waveforms on the fly, opening up a completely new world of potential waveform shapes. Even though this technology exists today, the majority of electroceutical devices on the market still use standard waveform shapes, rectangular or sinusoidal, allowing clinicians only a limited number of parameters to adjust.

It is important to note that there are many ways to define optimality. Studies have shown that excessive electrical stimulation can cause damage to tissue (Merrill et al. 2005), and, thus, it is important to minimize the amount of stimulation so as to prevent such damage. Yet, even with this definition of optimality, there are different metrics by which to measure “excessive” stimulation, and most of this is application-dependent. In some situations, one may want to minimize total charge delivered in order to minimize tissue damage due to inappropriate electrical gradients imposed on the cells or charge deposition within cellular structures, while in other scenarios, one may want to minimize time to effect of the stimulus, sacrificing charge optimization for more expedient effects, for instance, in cardioversion. For the purposes of the rest of this entry, energy efficiency will be used as the default primary optimization objective, though most of the methods discussed can be easily adapted for other objectives as well.

Given a particular optimization metric, the challenge is how to find these optimal stimulus waveform shapes. A handful of studies exist that have questioned the use of the traditional rectangular waveform shape using a set of alternative shapes including linear ramps, exponential ramps, and Gaussian and sinusoidal waveforms. Using a predefined waveform shape is easier because the number of tunable parameters becomes manageable. Both computational and experimental studies have shown that non-rectangular waveforms are actually more optimal. The problem is that searching across arbitrary waveform shapes is nearly impossible due to the infinite number of possibilities that exist. All search methods can be broken down into roughly two categories: model-dependent methods that leverage the prior

knowledge of the system, usually in the form of mathematical equations, and model-independent methods, which treat the system like a black box.

Model-Dependent Approaches

The challenge with using predetermined alternative waveforms is that the optimized waveform found is biased to the constrained solution space. Model-dependent approaches leverage existing knowledge of a system, in the form of a mathematical model, in order to calculate optimality.

The use of calculus of variations (Gelfand et al. 2000) as a tool to solve for optimal stimulus waveforms was utilized first by Offner (1946) and later by Jezernik and Morari (2005), as well as Forger et al. (Forger and Paydarfar 2004; Forger et al. 2011). Using relatively simple neuronal models, they were able to analytically solve for a system of equations defining optimality. Mathematically, the biological system is represented as

$$\dot{x} = f[x(t), u(t)], \quad (1)$$

where $x(t)$ describes an m -dimensional system and $u(t)$ describes an n -dimensional external stimulus acting on the system. The goal of this approach is to find an optimal $u^*(t)$ such that a performance metric, $J[u]$, is minimized. The performance metric can be defined as

$$J[u] = \int L[x(t), u(t), t] dt, \quad (2)$$

where $L[x(t), u(t), t]$ represents the performance metric. In the case of optimizing energetics, most studies use the L^2 -norm of the stimulus:

$$L[x(t), u(t), t] = u^2. \quad (3)$$

Once the problem is defined, calculus of variations or Pontryagin's Maximum Principle (Pontryagin et al. 1962) is used to develop a set of additional equations defining the optimal function. Whereas traditional calculus often seeks to find the maxima or minima of functions, setting the derivative to zero, calculus of variations seeks to find the maxima or minima of functionals,

functions of functions. This is done by setting the functional derivative to zero. Given Eqs. 1 and 2, the fundamental lemma of calculus of variations states that

$$\frac{\partial L}{\partial f} - \frac{d}{dx} \frac{\partial L}{\partial f'} = 0. \quad (4)$$

This is known as the Euler-Lagrange equation. In the case of both Offner's and Jezernik's work, the computational models were simple enough that a closed form solution could be generated using variational approaches. In Forger et al., a closed form solution was not possible due to the complexity of the system of equations being solved, and so the shooting method was used to numerically compute the optimal waveform. In order to accomplish this, Forger et al. used Lagrange multipliers to combine the equations governing the system with the optimization metrics to form a new $J[u]$:

$$J[u] = \int L[x(t), u(t), t] + \lambda (f[x(t), u(t)] - \dot{x}) dt, \quad (5)$$

Applying the Euler-Lagrange equations results in a set of new differential equations on top of the original differential equations governing the system. These new differential equations govern the Lagrange multipliers, and using numerical methods like the shooting method or Newton's Method, a numerical approximation can be constructed. A full derivation and explanation can be found in Forger and Paydarfar's work (Forger and Paydarfar 2004). This class of techniques that use Lagrange multipliers to create an intermediate set of equations defining optimality is known as indirect methods. While they produce equations that define optimality, solving for the numerical approximation is a difficult task as the initial conditions for the lambda values must be guessed. Guessing these values incorrectly can lead the numerical approximation to diverge toward infinity.

Because of the challenges, a set of direct methods has also been formulated, built also on

calculus of variations. Instead of first computing a new set of constraining equations that define optimality using indirect methods, direct methods iteratively progress toward more optimal solutions from a starting seed using calculated gradients. By not adding a new set of constraining equations to the system, these methods allow for a larger region of convergence from the initial estimate. Both Betts and Rao provide useful reviews on these numerical methods for optimal control (Betts 1998; Rao 2009). Through such direct methods, models like the Hodgkin-Huxley can be solved to compute an optimal stimulus waveform to elicit an action potential as seen in Fig. 1 (Chang and Paydarfar 2014). It is interesting to note that the optimal stimulus waveform as computed through calculus of variations is not rectangular and in fact outperforms the best rectangular pulse waveform.

It is important to note that even with direct methods, as the systems become more complex and the number of equations grows, calculating even first-order gradients becomes difficult. Solving these complex systems of equations becomes nearly intractable. Some researchers have sought to simplify the system of equations using phase reduction techniques, representing oscillatory systems by their phases (Moehlis et al. 2006; Danzl et al. 2010; Nabi and Moehlis 2012). By simplifying these systems to a more

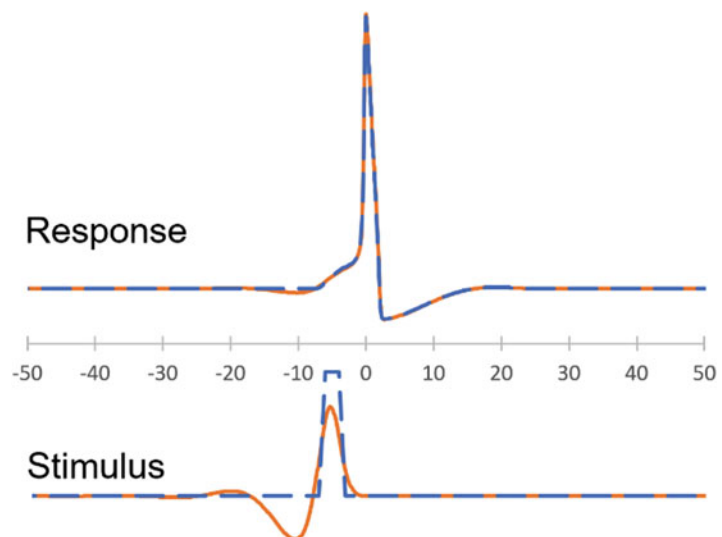
manageable and analytically tractable problem, insights can be gained, and more useful design-based control solutions can be computed (Monga et al. 2019). Monga et al. provide an excellent in-depth tutorial on phase reduction and phase-based optimal control. The challenge with these methods are that they still require (1) a mathematical model of the oscillatory behavior of the system and (2) they collapse a complex mathematical model to a single state, the phase, potentially losing out on other key insights gained from the other state variables. Furthermore, the use of models will always require a trade-off between the complexity of the mathematical framework and its accuracy. At the end of the day, no model is as accurate as the actual biological system.

Model-Independent Approaches

In all of the above approaches, a mathematical model is required to begin applying calculus of variations or other optimal control methods. In some cases, these models are nonexistent, or they are very large and complicated and thus not amenable to phase reduction or pseudospectral techniques. A class of methods born out from computer science called stochastic search approaches were developed to find optimality in systems where a model does not exist, so called “black box” systems.

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Fig. 1 System response (top) to optimized stimuli (bottom). Stimulus determined by calculus of variation (orange) outperforms the optimal rectangular stimulus (blue)



One of these stochastic approaches, genetic algorithms, constructs a “population” of solutions, represented as vectors or “chromosomes.” Genetic algorithms, inspired from biological evolution, manipulate these chromosomes through an iterative process of mutation, cross-over, and selection. For an overview of this process, we refer readers to Forrest’s work (Forrest 1993). A few different research groups have sought to use genetic algorithms to find optimal stimulus parameters and shapes including Wongsarnpigoon and Grill who optimized action potential stimulation in a peripheral mammalian axon (Wongsarnpigoon and Grill 2010), Yip et al. who studied electrical stimulation of the cochlear nerve (Yip et al. 2017), and Feng et al. who examined suppression of Parkinsonian behavior in a computational subthalamopallidal model (Feng et al. 2007).

In each of these cases, the number of stimuli necessary to test was very large due to both the size of each population and the number of generations required for convergence. This large iteration count is fairly common in stochastic search approaches. Bellman introduced the phrase, “curse of dimensionality” in 1957 (Bellman 1957). He noted that the addition of extra dimensions in a search space resulted in an exponential increase in the solution space. In most of the applications examining the optimization of stimulus shape, the stimulus is represented as a vector containing the stimulus intensities at a specific resolution. Thus, a 30-ms stimulus sampled at 0.1-ms resolution would be contained with a 300-unit vector. For every increase in either resolution or stimulus duration, the search space becomes exponentially large, resulting in extremely large iteration numbers.

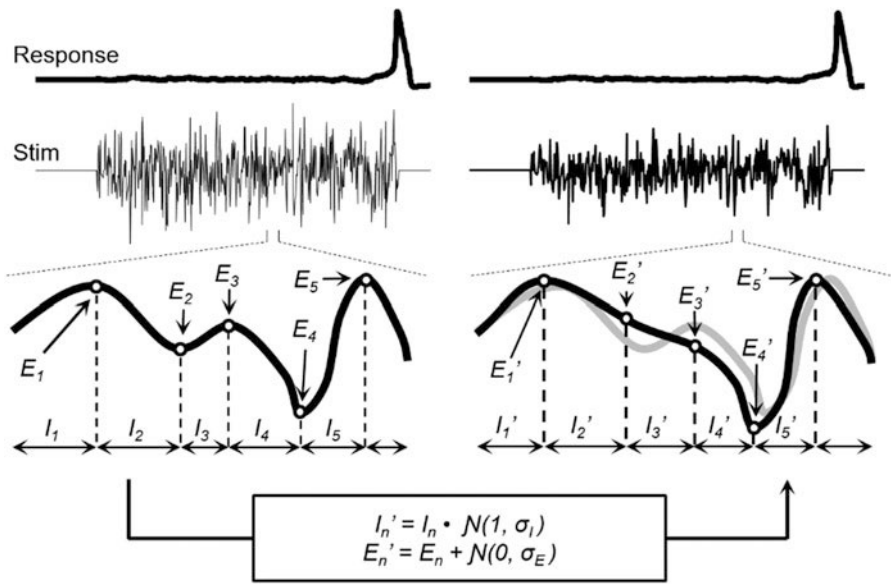
In order to address this “curse of dimensionality,” Chang and Paydarfar leveraged the idea of focusing on extrema features (Chang and Paydarfar 2018a). The use of extrema features has been prevalent in signal analysis and pattern recognition, acknowledging the idea that the extrema features often hold the most information about the signal itself. Instead of treating the stimulus intensity at every time step as a unique

dimension, focusing solely on the extrema reduced the dimensionality of the problem and allowed for more efficient, model-independent searching. Chang and Paydarfar tested this concept using a simpler approach called stochastic hill climbing. In this method, a randomly generated stimulus is used as an initial seed. Neighboring solutions are examined around that initial seed, and the best is chosen to be the initial seed of the next generation. This iterative process continues until the program converges. Normally neighboring solutions are determined by adding noise to each of the stimulus intensities at every time point. By focusing on extrema, noise was added to the amplitude of the extrema and the intervals between the extrema. The intermediate signal was reconstructed using a linear translation of the original stimulus with new extrema as seen in Fig. 2.

An outline of the algorithm is as follows:

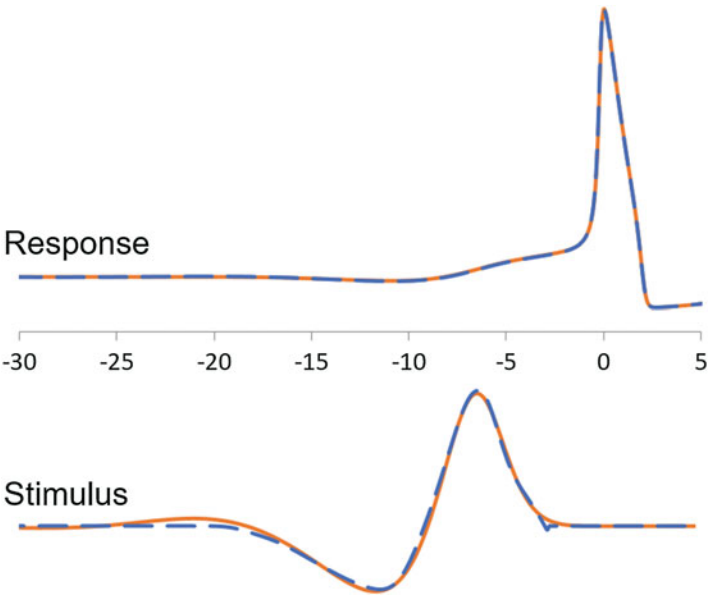
1. Choose an initial randomly generated stimulus.
2. Identify the extrema of the stimulus.
3. Add noise to the amplitudes of each of the extrema while multiplying the interval between extremas by a random value.
4. Calculate the performance metric of the resulting stimulus, penalizing the metric if the stimulus does not successfully cause the desired transition (e.g., an action potential or a state switch).
5. Repeat steps 2–4 ten times to produce ten neighboring solutions based on the initial stimulus.
6. Identify the stimulus that performs the best.
7. Repeat steps 2–6 for a predetermined number of iterations or until the performance metric has converged, using the best stimulus found thus far as the initial stimulus for the next iteration.

It is important to note that by chance, extrema may move in such a way that they are no longer extrema in the next iteration. As seen in Fig. 2, extrema E_2 and E_3 move in such a way that in the next iteration they would no longer be considered extrema. This phenomenon also helps to reduce the dimensionality of the problem as the



Methods for Optimizing Stimulus Waveforms for Electroceutical Control, Fig. 2 Use of extrema features to reduce dimensionality in optimizing stimulus waveform shapes

Methods for Optimizing Stimulus Waveforms for Electroceutical Control, Fig. 3 Optimal stimulus as computed by extrema-driven stochastic search (blue) matches very closely with calculus of variations (orange)



search process continues. As more and more of the unnecessary extrema are weeded out, the search becomes more efficient. As can be seen in Fig. 3, the result from this process matches very closely to results computed using calculus of variations.

Future Directions

As one can see from this review, there are still plenty of opportunities to further refine these methods to finding optimal control in electroceutical systems. Chang and Paydarfar provide a

more in-depth review of these techniques (Chang and Paydarfar 2018b). As the clinical applications continue to grow and more researchers explore the potential of electrical stimulation as a medical therapy, the need to find ways to optimize these waveforms becomes ever more important. Moreover, the use of these methods may help reveal unique mechanisms in our understanding of neurological processes. Clay et al. demonstrated this with their analysis of the optimal stimulus waveform for single neurons modeled by the Hodgkin-Huxley equations (Clay et al. 2012). The optimal stimulus waveform for the Hodgkin-Huxley model is composed of a relatively long and shallow hyperpolarizing phase followed by a rapid depolarizing component. By analyzing this optimal stimulus waveform and the state variable responses, they recognized that the hyperpolarizing component was removing sodium channel inactivation, allowing the depolarizing component to fire the neuron more efficiently. Their results showed how optimized stimulus waveforms relate to the ionic dynamics and can be used to gain insight into how nature structures energy efficiency in neural excitation.

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Metric Space Analysis of Neural Information Flow

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Definition

In the metric-space approach to spike train analysis, spike trains are regarded as points in a metric space, that is, a space with a distance defined between any pair of points.

Detailed Description

Spike Train Metrics

The Victor-Purpura metric (Victor and Purpura 1996) is one common way to define a metric distance between spike trains. The Victor-Purpura metric considers a fictional total cost for transforming one spike train into another using three basic operations: spike insertion, spike deletion, and spike movement. Each basic operation is given an individual cost, one for inserting or deleting a spike and $q|\delta t|$ for moving a spike a temporal distance δt . The cost-per-time, q , is a parameter, with the timescale $2/q$ thought of as corresponding to the temporal precision of spike times in the metric. The distance between the two spike trains is then defined as the cost of the cheapest transformation of one to the other. In other words, the distance between spike trains x and y is given by

$$d(x, y) = \min_{\gamma \in \Gamma} c(\gamma) \quad (1)$$

where γ is a sequence of basic operations transforming x to y , Γ is the set of all such sequences, and $c(\gamma)$ is the cost of γ , that is, the sum of the individual costs of the basic operations that make up γ . This is not the only spike-train metric: there is also the van Rossum metric (van Rossum 2001) which is part of a kernelization approach to spike trains (Paiva et al. 2009), and there are more recent metrics like the synapse metric (Houghton 2009) and the ISI-distance (Kreuz et al. 2007). These are reviewed and compared in, for example, Victor (2005), Houghton and Victor (2012), and Houghton and Kreuz (2013). There are also multi-neuron metrics (Aronov et al. 2003; Houghton and Sen 2008), which allow metric-based methods to be applied to multiunit data.

In a metric-space approach to analyzing a collection of spike trains, the data is reduced from a set of complicated objects, spike trains, to a much simpler object, the matrix of distances between the trains. When applied to neural information, the information contained in this matrix is used to estimate information theory quantities for the corresponding spike train data; typically the

quantity of interest is the mutual information between a sensory stimuli and a spiking response. Of course, this reduction of the data to the distance matrix is a simplification and it is likely that the metric will not be sensitive to all the information-carry features of the spike trains. This means that the information contained in the distance matrix will underestimate the true mutual information. However, it is hoped that metric-based methods will be less prone to bias on small data sets than traditional approaches like the direct method described in Strong et al. (1998). There are sophisticated bias-reduction techniques developed for the direct method (Nemenman et al. 2007; Paninski 2003; Panzeri et al. 2007), and it is unclear as yet whether bias is a substantial enough problem to warrant consideration of metric-based methods.

The Transmitted Information

The transmitted information applies to situations when the spiking data represents multi-trial responses to a set of distinct data. In this case, the spike trains can be clustered by stimulus and the transmitted information estimates the mutual information between this “true clustering” and metric-based clustering. The transmitted information is written in terms of a matching or confusion matrix N . If the stimuli are labeled by $s = 1, \dots, S$ and the responses are grouped into clusters labeled $c = 1, \dots, C$, then N is an $S \times C$ matrix whose element n_{sc} is the number of responses to stimulus s placed in cluster c . This means that the probability that a response to stimulus s is placed in cluster c is estimated as $p(s, c) \approx n_{sc}/n$, where $n = \sum_{s=1}^S \sum_{c=1}^C n_{sc}$ is the total number of responses. The transmitted information, h , measured in nats, is derived by substituting this into the usual definition of the mutual information:

$$h = \frac{1}{n} \left(\sum_{s=1}^S \sum_{c=1}^C n_{sc} \ln n_{sc} - \sum_{s=1}^S n_s \ln n_s - \sum_{c=1}^C n_c \ln n_c - n \ln n \right) \quad (2)$$

where, in an abuse of notation, $n_c = \sum_{s=1}^S n_{sc}$ and $n_s = \sum_{c=1}^C n_{sc}$ denote the row and column sums.

Although the transmitted information is straightforward to calculate once the data have been clustered, it does rely on a clustering algorithm as well as a metric, and, in practice, the transmitted information will substantially underestimate the mutual information. In fact, the confusion matrix is often calculated by clustering the data by stimulus, removing individual data points one-by-one and deciding which cluster the test point is closest to. This is not an unsupervised clustering, and this transmitted information does not measure the actual mutual information, it is used as a comparative quantity, for example, it was originally introduced in Victor and Purpura (1996) as a way to determine the optimal value of the parameter q in the Victor-Purpura metric.

A Kozachenko-Leonenko Estimate

In Kraskov et al. (2004) the mutual information is estimated using the Kozachenko-Leonenko k -nearest-neighbors estimator (Kozachenko and Leonenko 1987). This approach is developed in the case where the stimuli are also points in a metric space, rather than points in a discrete case, as was considered for the transmitted information above. The Kozachenko-Leonenko estimator requires the calculation of the rate of change of the probability of finding a data point as a sphere increases; in Kraskov et al. (2004) this rate of change is calculated using the coordinate-based measure and it is assumed the stimulus and response spaces both have a well-defined dimension. These assumptions do not hold in the case of the space of spike trains. However, different k s are used in the stimulus and response spaces. This is done to allow biases in the entropies $H(R)$, $H(S)$, and $H(R, S)$ to cancel, but, fortuitously, this is done in such a way that all the terms that depend on the dimension of the two spaces, or on the volumes of spheres in those spaces, also cancel. This leads to a formula which can be applied to spike trains; in fact, it is possible to derive a Kozachenko-Leonenko estimator for the mutual information directly for metric spaces (Houghton 2015).

Let R be the random variable corresponding to the spiking response and S the random variable corresponding to the stimulus. S is now a

continuous random variable and could correspond to a continuous stimulus, such as the position of a foraging rat, or to another spike train. It is assumed that there are metrics on both spaces; this in turn induces a metric on the space of stimulus-response pairs:

$$d[(s_1, r_1), (s_2, r_2)] = \max [d(s_1, s_2), d(r_1, r_2)] \quad (3)$$

Now, for a given set of experiments the data consists of a set of stimulus-response pairs: $\{(s_1, r_1), (s_2, r_2), \dots, (s_n, r_n)\}$. As a k th nearest neighbor approach the estimate relies on a choice of a positive integer k . Let $d(i; k)$ be the distance from (r_i, s_i) to the k th nearest data-point, so $d(i; k)$ is the smallest distance such that

$$\begin{aligned} |\{(s_j, r_j) | d[(s_i, r_i), (s_j, r_j)] \leq d(i; k)\}| \\ = k + 1 \end{aligned} \quad (4)$$

where the set has size $k + 1$ rather than k because it includes the point (s_i, r_i) itself. Now let

$$C_S(i) = |\{(s_j | d(s_i, s_j) \leq d(i; k)\}| \quad (5)$$

and

$$C_R(i) = |\{(r_j | d(r_i, r_j) \leq d(i; k)\}| \quad (6)$$

Thus $C_S(i)$ is the number of stimuli with any response within $d(i; k)$ of s_i ; this will, of course, include the k data points counted when defining $d(i; k)$, but it may also include points (s_j, r_j) where $d(s_i, s_j) \leq d(i; k)$ but $d(r_i, r_j) > d(i; k)$. Hence $C_S(i) \geq k$. The same sort of observation applies to $C_R(i)$. Roughly speaking, a separate k -nearest neighbor estimate is calculated for $H(R)$, $H(S)$ and $H(R, S)$ with $C_R(i) - 1$ and $C_S(i) - 1$ playing the role of k for $H(R)$ and $H(S)$. Now, the estimate of the mutual information is

$$\begin{aligned} I(R; S) = & \psi(k) + \psi(n) - \frac{1}{n} \sum \psi[C_S(i)] \\ & - \frac{1}{n} \sum \psi[C_R(i)] \end{aligned} \quad (7)$$

where $\psi(x)$ is the digamma function of x .

If the stimulus space is discrete, the same approach can still give an estimate of the mutual information (Tobin and Houghton 2013). If there are n_s stimuli and each is presented n_t times, the mutual information is

$$I(R; S) = \psi(k) + \psi(n_s n_t) - \psi(n_t) - \frac{1}{n} \times \sum \psi(C_R(i)) \quad (8)$$

In Tobin and Houghton (2013) a similar formula is derived using a kernel-density-estimate based approach. An alternative Kozachenko-Leonenko estimate of the mutual information between a discrete stimulus set and spiking responses is given in Victor (2002).

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Metrical Structure

► Rhythm Perception: Pulse and Meter

Microcolumns and Neural Population Models

► Mesoscopic Anatomy and Neural Population Models

Microglia Modeling

► Neuron-Glia Interactions

Microphotodiode Arrays (MPDA)

► Visual Prosthesis, Subretinal Devices

Micro-Wires

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Definition

Microwires consist of a cylindrical conductor with a diameter on the order of micrometers and, generally, have an insulating sheath. They are commonly used for recording of neural signals or electrical stimulation of nervous tissue.

Detailed Description

Microwires can range anywhere from roughly five to a few hundred microns without insulation. They consist of a conductive material such as pure metals (e.g. gold, Tungsten or stainless steel) or metal alloys (e.g. Pt/Ir or Nichrome). Most pure metals have the advantage of being biologically inert, whereas metal alloys are often favored for their lower cost and better physical properties such as higher flexibility and strength. Typical materials used to electrically insulate the wires from their surroundings are Teflon, Parylene, Formvar, Isonel, polyimide or polyurethane. The insulating layer adds at least 3–7 μm to the wire thickness.

Microwires are available on a spool as single wires or multi-stranded wires where two or more wires are twisted together into a single larger strand. Twisting can be done with either insulated or bare wires depending on the application.

The advantage of microwires for neurophysiological use is that they are relatively inexpensive and can be adapted for use in many different applications. The smaller-diameter, highly flexible microwires also tend to cause less tissue reaction when implanted chronically compared to stiff electrodes and electrode arrays (Bae et al. 2008; Winslow and Tresco 2010; Karumbaiah et al.

2013). This makes them particularly useful in applications like the spinal cord where the tissue not only undergoes micromotion as a result of breathing and heart pulsations but also stretches, contracts and moves significantly within the spinal column when the subject moves.

Stimulation of Neural Tissue

Microwires have been used for intraspinal stimulation for studying spinal networks and the restoration of bladder and movement control (for a review see Bamford and Mushahwar 2011) as well as the stimulation of peripheral nerves (Yoshida and Horch 1993; Lago et al. 2007; Micera and Navarro 2009) and the cortex (Otto et al. 2005; Bretzner and Drew 2005; Nelson et al. 2011).

Recording Use

Single Wires

Depending on their diameter, material and insulation material, single microwires can be stiff enough to be inserted into neural tissue like a needle or they have to be inserted using a guide (Westby and Wang 1997; Tseng et al. 2011). They also have been used in peripheral nerves (Lawrence et al. 2004), spinal cord (Prasad and Sahin 2011) and in cortex (Chang et al. 1988) but the use of arrays of microwires is more common nowadays.

Tetrodes

To improve the isolation of recorded single and multi unit activity, first stereotrodes (McNaughton et al. 1983) with two microwires in close proximity have been developed and then tetrodes (Wilson and McNaughton 1993). For tetrodes, four wires are bundled together in a know pattern and distance from each other. More recently, multiple tetrodes have been mounted in a microdrive assembly where each tetrode can be precisely placed in the neural tissue to further improve recording success (Gray et al. 1995; Nguyen et al. 2009; Santos et al. 2012).

Microwire Arrays

While tetrodes mostly aim to improve recording quality, single wires can also be combined into an electrode array to provide recordings from multiple locations. These arrays are either custom-built or commercially available (Thomas Recording, Tucker-Davis Technologies, Micro-Probes, Alpha-Omega Engineering, Nan Instruments, Neuralynx). One form of multiwire array that allows both tetrode-like and independent single-unit recordings are electrode braids (Kim et al. 2013) in which fine, flexible wires are braided around a stiff, removable core like a sleeve.

There are two types of microwire arrays, one where all wires are spatially arranged and fixed in place before insertion in the tissue (Williams et al. 1999; Rennaker et al. 2005; Zhou et al. 2012) and one where the wires are mounted in an apparatus that allows the movement of individual wires during the experiment (Baker et al. 1999; Kralik et al. 2001; Nicolelis et al. 2003; Jackson and Fetz 2007; Lehew and Nicolelis 2008).

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Migraines and Cortical Spreading Depression

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Synonyms

Spreading depolarizations

Definition

Migraine is a headache disorder characterized by recurrent episodes of head pain, often throbbing and unilateral, sometimes preceded by neurological symptoms called aura. The known pathophysiologic mechanism suggest that this disorder should be considered as a neurovascular

headache. Migraine is a highly disabling disorder according to the World Health Organization – the seventh most disabling in the world and the fourth most disabling among women.

Spreading depression (SD) is essentially a slow (about 3 mm/min = 50 μ m/s) reaction–diffusion wave in gray matter tissue during which ion concentrations inside and outside the cells change by over one order of magnitude to a nearly complete elimination of transmembrane chemical gradients, i.e., a nearly complete release of Gibbs free energy with depressed neuronal activity. SD is accompanied by a pronounced hemodynamic response of increased regional cerebral blood flow (hyperemia) for about 2 min and a long-lasting, ~2 h, decrease (oligemia).

Detailed Description

Clinical and Pathophysiological Background

In migraine without aura (MO), attacks are usually associated with nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia), and attacks are worsened by movement. Migraine with aura (MA) involves in addition nonpainful neurological symptoms (called aura) (Olesen 2013). Migraine aura symptoms are most often visual field disturbances but affect also other sensory modalities or cognitive functions (Vincent and Hadjikhani 2007). Aura symptoms are caused by a wave of cortical spreading depression. Whether this wave also contributes to the headache phase in migraine is currently debated (Karatas et al. 2013, Dalkara and Moskowitz 2017). Epidemiological studies suggest that MA and MO share the same headache phase; however, on average the pain seems to be less severe and shorter lasting in MA than in MO (Rasmussen and Olesen 1992).

The aura phase and pain phase constitute the central part of the attack. Moreover, migraine symptoms can vary across two framing stages, namely, the prodrome and postdrome. Together with the attack-free interval, five phases comprise the migraine cycle with associated severe disabilities and reduced quality of life even between attacks (Brandes 2008). **Aura:** all kinds of fully reversible sensory disturbances, visual is most

frequent. Each individual aura symptom can last 5–60 min. They occur in about 30% of the reported cases. **Headache:** often unilateral and throbbing (though this seems to be not related to blood pulsation). It lasts 4–72 h and occurs in about 95% of the cases. **Prodrome:** feeling tired and weary, difficulty concentrating, yawning, polyuria, sweating, and fatigue are some typical features (Giffin et al. 2003). It lasts up to 1 day and occurs in about 60% of the reported cases. **Post-drome:** tiredness, difficulty concentrating, weakness, dizziness, persistence of sensitivity to light and noise, lethargy, and fatigue together often described as “headache hangover.” It lasts a few days and occurs in about 70% of the reported cases. **Attack-free interval:** In the attack-free migraine, patients exhibit a generalized pressure pain hypersensitivity in the head as compared to healthy controls (Barón et al. 2017).

Before the advent of noninvasive imaging, blood flow changes were thought to be at the origin of the headache phase in migraine. In the 1980s and into the mid-1990s, it became clear by studies of the clinical features of migraine and its physiological mechanisms that there is no clear correlation between blood flow changes and the headache, but instead imaging studies suggested (Weiller et al. 1995) that upstream events in the brainstem named “migraine generator” (MG) (Welch et al. 2001) lead to the cascade activating trigeminal nerve endings leading to migraine pain perception. Furthermore, in migraine with aura, the neural phenomenon of cortical spreading depression was shown by functional imaging to be the neural correlate of migraine aura (Olesen et al. 1981; Hadjikhani et al. 2001).

Migraine Theories

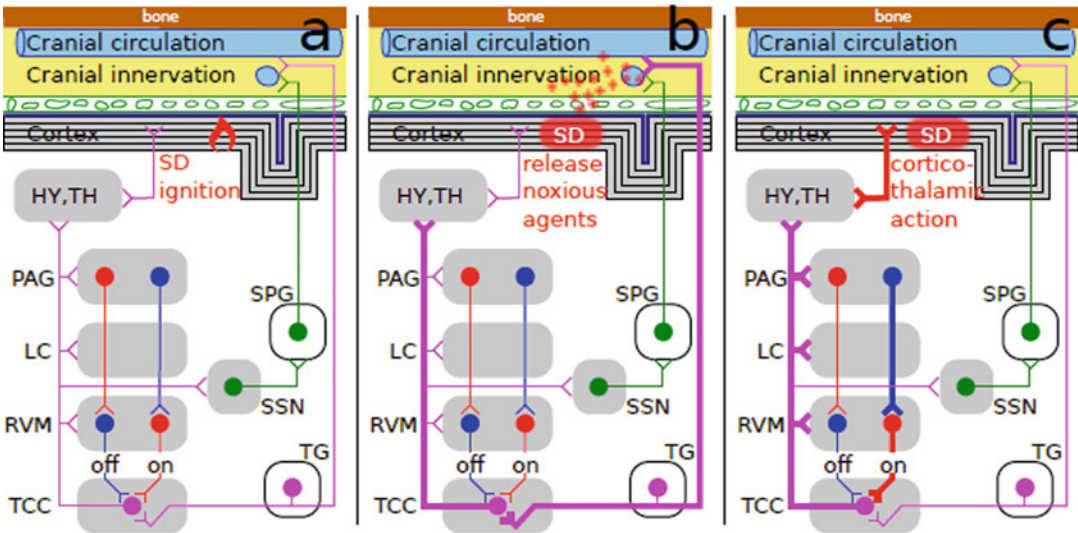
The migraine generator theory states that a dysfunction of the brainstem causes the pain and via further connections (directly and indirectly) the brainstem is also responsible for the neurological changes before the headache phase including symptoms in the prodromal phase and the aura phase, that is, the MG is causing SD via a failure of vasomotor control (Fig. 1a).

The spreading depression theory of migraine assumes that this cortical wave causes the

neurological systems (aura) (Lauritzen 1994) and it can also cause the pain in the headache phase, which usually occurs after the aura phase but cf. Hansen et al. (2012). Two independent pathways are suggested, a peripheral and a central pathway. The headache pain can be triggered by a local release of noxious substances during the hyperemic phase of SD (Karatas et al. 2013). These substances are thought to be transmitted outward in the direction perpendicular to the cortical layers into the pain-sensitive meninges (peripheral pathway, Fig. 1b). This results in an activation of pain receptors (nociceptors) and local inflammation, which triggers the migraine headache. An alternative explanation that could lead to headache induced by SD is a corticothalamic feedback that affects sensory processing by third-order neurons arising within the sensory thalamus. This is supported by the efficacy of calcitonin gene-related peptide receptor antagonists at the level of these neurons in migraine therapy (Summ et al. 2010) (central pathway, Fig. 1c).

The cause of events during migraine cycle are rather complex; in particular, SD drives complex vasomotor effects on cerebral vasculature and may in response be modulated and also initially be caused by cerebral vasculature events (Ayata 2013). Migraine as a chronic disorder with recurrent episodic manifestations should therefore be considered as an inherently dynamical disease to which a simple course of downstream events following on upstream events within a linear arrangement of the involved brain nuclei would not do justice. It rather is a complicated network (see Fig. 1), and sufficient evidence speaks to the fact that both the MG and SD theory of migraine can be validly maintained and that they need to be unified in a network theory.

To this end, a simple dynamically regulated control system was schematically identified and further reduced to a network of the major centers in the brain, including a subnetwork of brainstem nuclei; the trigeminal nerve, which innervates the cranial circulation; parasympathetic vasomotor efferents; and the cortex. This extends the idea of a migraine generator region in the brainstem to a larger network and is still simple



Migraines and Cortical Spreading Depression, Fig. 1 Schematic reduction of the migraine generator network and the effect of cortical spreading depression in migraine. (a) The cranial circulation is connected by first-order perivascular pain-sensitive neurons via the trigeminal ganglion (TG) to the trigeminocervical complex (TCC) and receives also parasympathetic input from vasomotor efferents that may cause SD directly or indirectly via the sphenopalatine ganglion (SPG) and its second-order pre-ganglionic neurons in the superior salivatory nucleus (SSN). (b) Further structures in the brainstem build a

descending modulatory subnetwork that may enhance pain traffic caused by the release of noxious and amatory substances during SD: the rostral ventromedial medulla (RVM), locus coeruleus (LC), periaqueductal gray (PAG). (c) Furthermore, a role of the third-order corticothalamic interactions during SD that might sensitize the central nervous system to react on normal sensory input from cranial circulation with pain (allodynia). This would highlight the role of the thalamus (TH) and also hypothalamus (HY) in migraine

M

and explicit enough to open up possibilities for mathematical modeling, in particular, understanding the complex interactions of cortical SD within other relevant brain structures in migraine (Ayata 2013; Noseda et al. 2010; Akerman et al. 2011; Dahlem 2013). Currently, however, computational models exist only for the cortical event of SD, which are reviewed in the remainder of this entry.

Computational Models of Cortical Spreading Depression

Computational models of spreading depression date back to the mid-1970s. A simple rule-based cellular automata model was used to mimic the two-dimensional spread on the cortical surface, including spiral-shaped SD waves reentering around a functional block (Reshodko and Bures 1975). Partial differential equations were used later to describe the detailed

physiological cellular events (Tuckwell and Miura 1978). There are detailed reviews of computational modeling SD propagation (Miura et al. 2007; Zandt et al. 2015). In this encyclopedia entry, only the very basic approaches that currently are followed can be covered, with a focus on ordinary differential equation for the microscopic local cellular events on a millisecond to second scale and partial differential equations for the macroscopic tissue events that occur on a temporal scale of up to 1 h, that is, the scale of the migraine aura phase.

Cellular Events Caused by SD

The focus in computational models of the cellular mechanisms of SD is on transmembrane events that can be observed, for example, in in vitro experiments without the complex vasomotor feedback involved in SD (Ayata 2013). This in vivo dynamical feedback can be fixed in vitro

by studying, for example, normoxic versus hypoxic spreading depression-like transmembrane cell depolarizations (Somjen 2001). With this focus set, SD is a massive but temporary perturbation of ion homeostasis. The ion concentrations are usually kept within a narrow range of acceptable limits, and their gradient across the cell membrane is treated in traditional computational models of Hodgkin–Huxley (HH) type as a constant battery, the reversal potential or Nernst potential (Hodgkin and Huxley 1952). During SD, however, ion concentrations can change by over one order of magnitude, so that the original HH approach to describe the potential changes across the excitable membrane must be extended. For instance, the extracellular potassium concentration raises from 3 mM within a few seconds to peak values around 55 mM, plateaus at this level for about 30 s, and recovers to the physiological range within 1–2 min (Lauritzen 1994). Furthermore, neuronal activity is depressed due to the nearly complete depletion of the transmembrane ion gradients. This depleted and depressed state can spread through gray matter tissue by electrodiffusion due to newly formed ion gradient along the membranes in the neuronal and glial syncytium and the interstitial volume.

To model local cellular events, we start with Kirchhoff's current law that was introduced as an equivalent membrane circuit by Hodgkin and Huxley (1952):

$$\frac{dV}{dt} = -\frac{1}{C_m} (I_{Na^+} + I_{K^+} + I_{Cl^-} + I_{pump} - I_{app}). \quad (1)$$

The variable V is the potential difference or voltage across the membrane relative to the grounded extracellular side. The cell membrane has a capacitance C_m . The currents I_{ion} are the transmembrane currents with the index $ion \in \{Na^+, K^+, Cl^-\}$. I_{app} is an externally applied current.

In the original HH framework, an unspecified leak current was modeled but not a chloride current. The major extension, however, is the pump current I_{pump} , which can be modeled, for example, as (Cressman et al. 2009):

$$I_{pump}(Na_i, K_e) = \rho \left(1 + \exp \left(\frac{25 - Na_i}{3} \right) \right)^{-1} (1 + \exp(5.5 - K_e))^{-1}. \quad (2)$$

The pump current I_{pump} describes the ATP-driven exchange of intracellular sodium ions with extracellular potassium at a 3:2 ratio.

The ion concentrations ($[ion]$) change due to fluxes proportional to the ion currents. The additional rate equations for intracellular ion concentrations are:

$$\frac{d[ion]}{dt} = -\frac{\gamma}{\omega} (I_{ion} + \alpha I_p), \quad (3)$$

with α being 3, 2, and 0 for Na^+ , K^+ , and Cl^- , respectively. The parameter γ converts currents to ion fluxes and depends on the membrane surface area A_m and Faraday's constant F , $\gamma = A_m/F$. The parameter ω is the volume of the intracellular space (ICS).

In addition, also dynamical gating variables n , h , and m have to be introduced, as in the original HH model. The potassium activator, sodium activator, and sodium inactivator are defined by the voltage-dependent gating dynamical variables n , m , and h , respectively. These are given by $p \in \{n, m, h\}$:

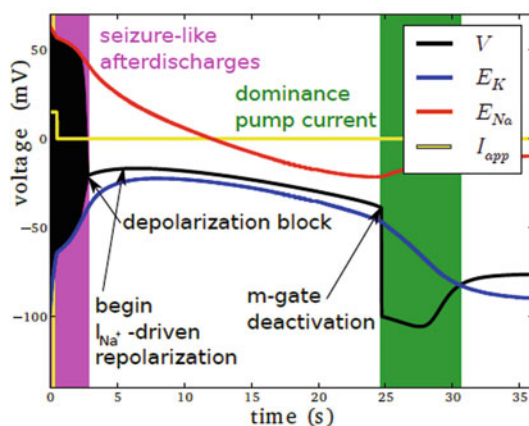
$$\frac{dp}{dt} = \frac{1}{\tau_p} (p_\infty - p) \quad (4)$$

For the detail of the voltage-gating mechanism, see the article of the HH model. The HH model is sometimes also called a conductance-based model, while, in contrast, neural mass models are called rate based or activity based. In each case, the model is named after the respective dependent dynamical variables other than the transmembrane potential V . In this terminology, the second-generation HH models described by Eqs. 1, 2, 3, and 4 are ion-conductance-based models.

With a minimal ion-conductance-based model of a total of only four dynamical variables, the main features of SD across the cell membrane can

be modeled. Using electroneutrality and further symmetry constraints, ion-conductance-based models can be reduced. However, more physiological detailed models of SD are given by ion-conductance-based models with 9–29 dynamical variables in various (~ 200 , which effectively multiplies the number of dependent dynamical variables) electrically coupled neural compartments (Miura et al. 2007; Kager et al. 2000; Shapiro 2001).

Although in the minimal ion-conductance-based model, the time course of the dynamical variables can be lightly distorted as compared to more realistic models (Miura et al. 2007; Kager et al. 2000; Shapiro 2001; Somjen et al. 2008); the main features of SD are revealed. In Fig. 2, the nine dynamical variables are the membrane potential, two gating variables, and six ion concentrations. During the course of SD (Fig. 2), two phases and three points stand out because of their significant mechanistic meaning in SD as an excitation phenomenon: the seizure-like afterdischarges, the subsequent excitation block, the beginning of an I_{Na} -driven transient repolarization, and the m-gate deactivation that finally initiates a phase where the pump current I_{pump} can become dominant.



Migraines and Cortical Spreading Depression, Fig. 2 Time course of transmembrane potential (black) and Nernst reversal potential for Na^+ (red) and K^+ (blue) in a minimal ion-conductance-based second-generation Hodgkin-Huxley model following a brief (0.5 s) stimulation (gray). For further details, see text

In hypoxic conditions, these phases can be quite different; in particular the point of the m-gate deactivation can be missed resulting in tissue infarct. However, only the normoxic migraine condition and their corresponding electrophysiological mechanism of ignition and recovery in SD can be described here. For more details, the reader is referred to the review by Miura et al. (2007).

Of all these events highlighted in Fig. 2, maybe the most notably is the recovery phase of SD at around ~ 24.5 min. According to the computational models, recovery is due to a deactivation of the sodium activator m driven by a dominate sodium current I_{Na} that actually repolarizes V a few seconds after the seizure-like firing stops due to a depolarization block. After the deactivation of sodium activator m, the pump current I_{pump} drives the membrane potential for several seconds outside the window of the two reversal potentials of Na^+ and K^+ , red and blue curves, respectively. The ignition of SD is due to a torus bifurcation (not shown) of the tonic seizure-like firing. The seizure-like firing is caused by the initial stimulation phase. However, after the offset of the stimulation at 0.5 s, the state of the dynamical system is already behind a canard-like sharp threshold trajectory causing firstly a brief phase of sustained (2–3 s) afterdischarges. Only then a long-lasting (~ 0.5 h) recovery phase begins during which the system is refractory.

Before we consider large-scale tissue events caused by SD, it is worth noting that cellular models often do not include lateral space, except for the original work by Tuckwell and Miura (1978) and some modern approaches from the group of Miura (Yao et al. 2011) and an isolated work by Shapiro (2001) considering osmotic forces and gap junctions. The compartments mentioned before extend in the vertical direction to model the apical dendritic tree of pyramidal cells in the cortex (Kager et al. 2000; Somjen et al. 2008). But the very detailed models by Kager, Wadman, and Somjen are not spatially extended to describe the lateral extension, that is, they describe SD not as an excitable phenomenon in a spatially extended system, called excitable media.

The lateral extension of cellular SD models is far from straightforward. Naively adding diffusion to the extracellular dynamical ion concentrations yields some insights, but it does not reflect the necessary detail that needs to be considered to take the spatial continuum limit. Neural field models, for example, describe this limit for rate- or activity-based neural models (Bressloff 2012). The problem is that the neural tissue is heterogeneous. A bottom-up approach toward an ion-conductance-based medium model that lacks the support of an effective medium theory cannot expand from membrane to tissue level in a canonical way and therefore loses its advantage over the simpler top-down approaches. Likewise, a coarse graining in time from individual spiking to rate- or activity-based dynamics in simulated cell populations is needed for the relevant time scales in migraine.

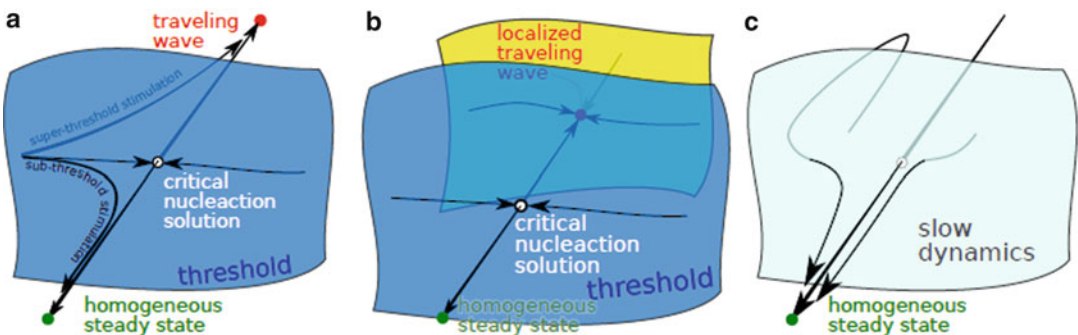
Tissue Events Caused by SD

In accordance with noninvasively imaged SD progression using high-field functional magnetic resonance imaging (Hadjikhani et al. 2001) and reported visual field defects (Dahlem and Hadjikhani 2009), a macroscopic computational model of SD was proposed in which in each episodic migraine attack with aura, a particular spatiotemporal SD pattern is formed (Dahlem and Isele 2013). Such heterogeneous propagation

of SD has later been also discovered in the lissencephalic and gyrencephalic brain (Santos et al. 2017).

In the proposed macroscopic computational model of SD, the wave front takes the shape of a discontinuous wave segment that spreads out only in one direction. These heterogeneous propagation patterns are the tissue events that are of clinical importance for migraine. Note that reentrant SD waves are of clinical relevance under conditions of stroke, where repeated SD waves are believed to have the potential to worsen outcome in incremental steps with each wave circling near the infarct core (anatomical block) but could also have some beneficial component by stimulating blood flow in the penumbra zone far from the infarct tissue (Dahlem et al. 2010). A major advantage of generic, i.e., low-dimensional, reaction–diffusion models lies in the fact that they provide insight in the phase-space structure of the whole class of models they represent. Various pattern-forming mechanisms can be understood in terms of phase-space structures that describe the migraine aura-ischemic stroke continuum as transitions from two-dimensional wave pattern in SD, from retracting (migraine) via reentrant (stroke) to stationary waves (persistent migraine aura without infarct); see for retracting SD waves Fig. 3.

To simulate the clinically observed patterns in migraine (Hadjikhani et al. 2001; Dahlem and



Migraines and Cortical Spreading Depression, Fig. 3 Schematic sketch of phase spaces: (a) excitable media support traveling wave solutions (red point) that are separated from the stable homogeneous steady state (green point) by the stable manifold (blue surface) of critical nucleation solutions (white point, saddle); (b) in excitable media with mean field control of a threshold

parameter (cf. β in Eq. 6), the control can be adjusted such that the branch (using β as a bifurcation parameter) of the nucleation solution folds and is partly stabilized; and (c) the medium with mean field control and control parameters such that the system is beyond the fold point, that is, there exists a ghost of the saddle-node bifurcation still influencing the dynamics by a critical slowing down

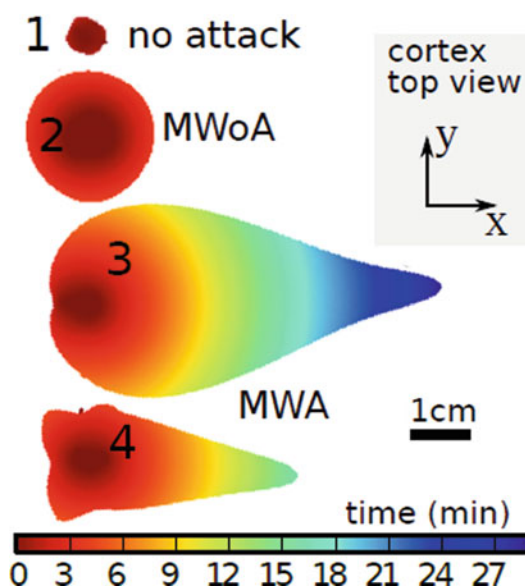
Hadjikhani 2009), a generic reaction–diffusion mechanism can be described in abstract terms of activator–inhibitor kinetics of just two variables u and v , respectively. In fact, simple activator kinetics of u date back to a mechanism of SD described in 1963 by Grafstein, Hodgkin, and Huxley GHH (Grafstein 1963). The GHH model assumed that $u = [K^+]_e$, i.e., the extracellular potassium ion concentration, is the activator u in SD. We extended this scheme in the following way (for details of the full model, see Dahlem and Isele (2013)):

$$\varepsilon \frac{\partial u}{\partial t} = u - \frac{1}{3}u^3 - v + \nabla^2 u, \quad (5)$$

$$\frac{\partial v}{\partial t} = u + \beta + K \int H(u) dx dy, \quad (6)$$

with H being the Heaviside step function. Both activator u and inhibitor v are lump variables. Unlike in the original GHH model, it is not necessary or even possible to identify particular physiological quantities, like $[K^+]_e$, with them. Instead, the activator u should be viewed as the bistable energy state. One stable fixed point corresponds to the maintenance of homeostasis far from thermodynamic equilibrium and the other stable fixed point to the state where the cellular Nernst reversal potentials are depleted (thermodynamic equilibrium). In the presence of an inhibitor v , which was not included in the GHH model, the second stable fixed point becomes a transient state. In other words, the inhibitor v is a recovery variable. It is related to ion buffering and ion pumps (Hübel et al. 2014, Hübel and Dahlem 2014) that drive the tissue far from thermodynamic equilibrium and (re)charge Nernst reversal potentials. We set the parameter as follows: the time scale separation, $\varepsilon = 0.04$; the threshold, $\beta = 1.32$; and the mean field coupling, $K = 0.003$, to obtain the patterns shown in Fig. 4.

To summarize, the reaction–diffusion patterns simulated by Eqs. 5 and 6 (Fig. 4) are macroscopic manifestations of SD, which is on a microscopic cellular level described by electrophysiological ionic events simulated by Eqs. 1–5. The pathological state in migraine arises from complex



Migraines and Cortical Spreading Depression, Fig. 4 Spatiotemporal signatures of SD as obtained from a generic reaction–diffusion model with mean field coupling, Eqs. 5 and 6. There are two cases where the SD front does not break open: (1) subthreshold, SD dies out quickly without initial spread; (2) superthreshold perturbation, SD dies out after less than 5 min at the propagation boundary δP (see text), corresponding according to the diagnostic criteria of headache to migraine without aura (MO). Two examples where SD front does break open, corresponding to migraine without aura (MA): (3)–(4) suprathreshold perturbation, SD propagates for up to 25 min in (3) and ~15 min in (4) possibly with less or no severe pain experience (migraine with typical aura without headache)

processes that interact over these large-range spatial and temporal scales and from interaction with subcortical central brain structures and peripheral innervation of the cranial circulation. We still lack a thorough theoretical framework to interpret these events to fully realize the potential of computational models in migraine. The challenge in the future will be to integrate these into a tractable migraine model.

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MIIND: A Population-Level Neural Simulator Incorporating Stochastic Point Neuron Models

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Definition

MIIND (Multiple Interacting Instantiations of Neural Dynamics) is a neural simulator that allows the creation of large-scale neuronal networks at the population level. Populations of neurons are considered to be homogeneous and comprised of point model neurons. MIIND does not simulate individual neurons but considers their distribution over the model neuron's state space in terms of a density function and models the evolution of this density function in response to input from other neural populations or external input. From the density function, other quantities can be calculated, such as the population's firing rate. This rate, in turn, can influence other

populations. Because populations interact through firing rates rather than individual spikes, the simulation of networks of spiking neurons becomes easier as no events need to be buffered. Using an XML format, it is easy to configure large-scale network simulations. MIIND is implemented as a C++ package but has a Python interface so that simulations can be driven and results can be analyzed in Python. It has been used in the simulation of networks of language representation and spinal cord circuits.

Detailed Description

MIIND (de Kamps et al. 2008) is a simulation package that can be driven from Python through an XML file. It can simulate complex circuits of neural populations. It stands out from other simulation packages in that it (i) models directly at the population level; (ii) uses population density techniques (PDTs) to model the state and firing rate response of the population; and (iii) offers the capability to incorporate existing and novel two-dimensional (2D) point model neurons into its framework.

Most population-level simulations described in the literature use rate-based modeling: a population is characterized by a single variable, such as firing rate or average membrane potential. A network simulation based on these methods usually results from the solution of a coupled set of first-order ordinary differential equations. A prominent example of such a system are the Wilson-Cowan equations (Wilson and Cowan 1972). There are efficient solution methods for large coupled networks, and their use is appropriate when considering quantities that are only indirectly related to the neural substrate, for example, in modeling imaging techniques where they have found widespread application.

Sometimes reducing the state of a population to a single variable is too restrictive and leads to the wrong simulation results (Montbrió et al. 2015). One option is to perform spike-based simulations, using neural simulators such as NEST or BRIAN (we will not discuss compartmental modeling here).

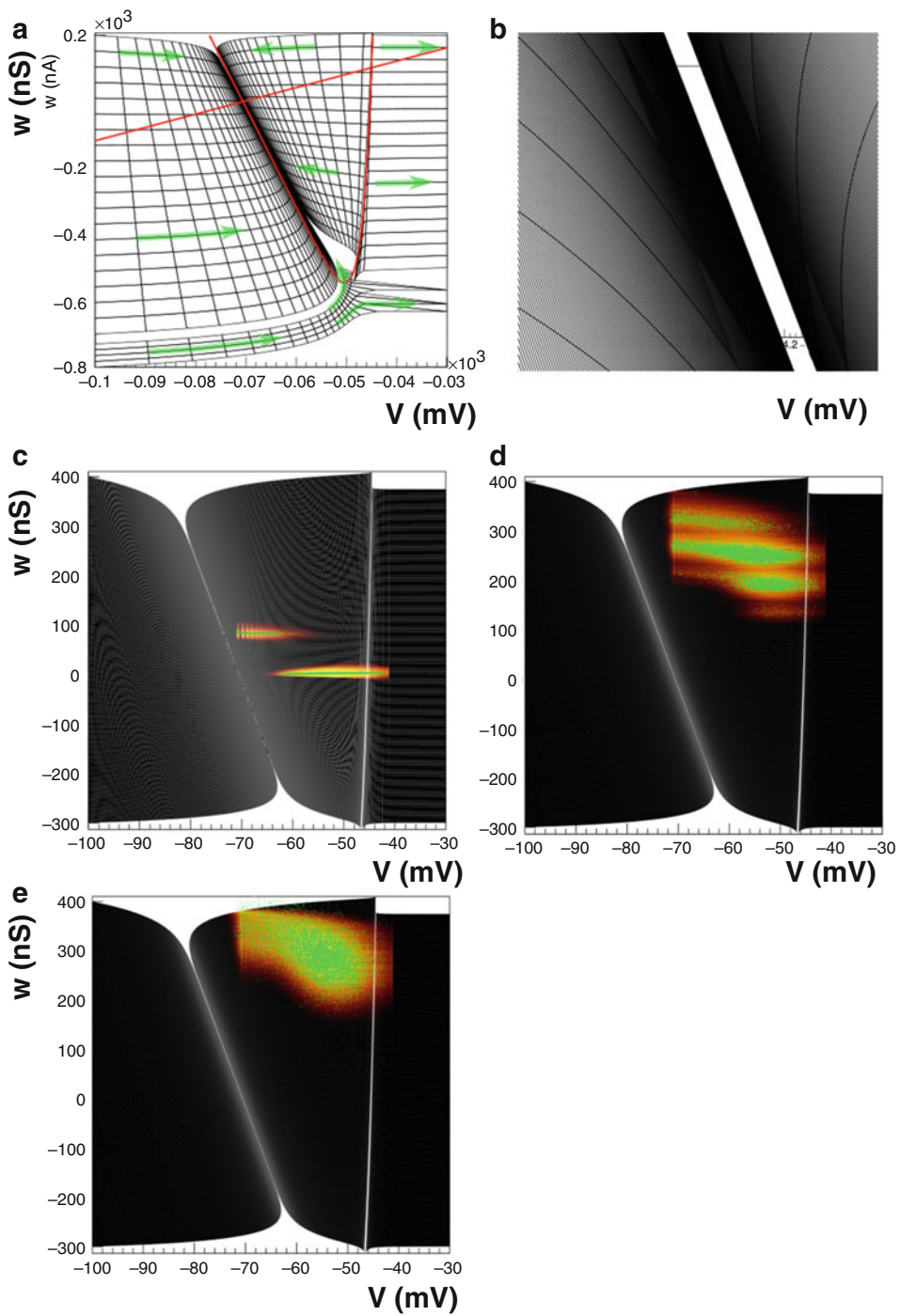
When applied to large-scale networks, these simulations can become unwieldy, in terms of the number of parameters required or resources (CPU, memory) consumed. A good compromise is to use *population density techniques* (PDTs). PDTs are based on point model neurons, such as leaky integrate-and-fire (LIF), which are one dimensional as the only variable characterizing their state is the membrane potential. Richer models usually have more variables defining the neuronal state, e.g., the FitzHugh-Nagumo model has two and is therefore referred to as 2D, and so does the adaptive-exponential-integrate-and fire (AdExp), while the Hodgkin-Huxley model has 4. In a detailed NEST simulation, it would be possible to follow individual neurons as they move through state space, driven by their own dynamics, as well as by the effects of incoming spikes from other neurons. A large population can then be imagined as a cloud of points in the state space of the model neuron if this population is assumed to be homogeneous – and the neurons have the same state space. An example is given in Fig. 1, which tracks the state of individual AdExp neurons over time. Although the individual neurons, represented by green points, are kicked around state space by incoming spikes and their state is unpredictable as these incoming spikes are modeled as random events, the behavior of the entire cloud of neurons is far more predictable, so much so that one can define a density function that represents the probability of finding a given neuron in state space. Using statistical techniques, one can model the evolution of this density function directly, without the need for keeping track of individual neurons, purely based on the dynamics of the point model neuron and the characteristics of the statistics governing spike trains that arrive at the neuron. A good introduction to PDTs can be found in Omurtag et al. (2000).

A major advantage of PDTs is that they represent the neuronal state of the population faithfully, something that cannot be said of rate-based models. In some cases, this leads to radically different predictions for the same network connectivity. A disadvantage of PDTs is that they are computationally more expensive than rate-based

models. They tend to be more efficient than direct simulations however, both for one- and two-dimensional models. For higher dimensional models, like Hodgkin-Huxley, PDTs are still computationally inefficient, as they suffer from the curse of dimensionality, although a more intelligent representation of state space may make them viable in the future. At the moment, there is a trend in computational neuroscience to reduce complex neuronal dynamics, described by high-dimensional systems to two-dimensional ones, as these retain the essence of the higher dimensional ones but are easier to visualize and analyze. 2D PDTs appear a good compromise between computational efficiency and expressivity of the neural model. Recently, we have made considerable progress in the solution of network equations for 2D PDTs (de Kamps et al. 2019).

MIIND and DIPDE (Allen Institute for Brain Science n.d.) are the only simulators, to our knowledge, that are based on PDTs. Where DIPDE is restricted to one-dimensional model (LIF), MIIND can use 2D point model neurons, as well as 1D models, such as leaky integrate-and-fire, quadratic integrate-and-fire, and others, which in the MIIND framework emerge as specializations of 2D models. The introduction of a new model MIIND is very easy: it requires a representation of the flow field of the model in terms of an ASCII file in a predefined model but does not require programming. As such it is a great tool for studying noise in 2D dynamical systems, not just neurons.

We have performed comparison studies and found that large networks of 1D neurons, such as LIF and QIF, can be simulated much faster than by simulating spikes individually. For 2D models, the run times are similar to NEST, but memory use is at least an order of magnitude lower than when simulating individual neurons. We have provided a CUDA implementation, which means that a network comprised over thousands of populations can be run on a single PC, equipped with GPU, rather than on an HPC cluster. MIIND is available at: miind.sf.net, where the code and training materials can be found.



MIIND: A Population-Level Neural Simulator Incorporating Stochastic Point Neuron Models, Fig. 1 (a) The state space of AdExp neurons. (b) A detail. (c–e) The evolution of a group of AdExp neurons (green dots), as well as the density function. The density function accurately tracks the individual neurons, which were modeled by a NEST simulation. (Figure adapted from de Kamps et al. 2019)

Cross-References

- [Brain-Scale Networks: Overview](#)
- [Dynamical Systems: Overview](#)
- [Software Tools for Modeling in Computational Neuroscience: Overview](#)

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Mitral Cells

- [Large-Scale Models of the Olfactory Bulb](#)

Mixed-Mode Oscillations in Single Neurons

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Definition

Mixed-mode oscillations (MMOs) in neuronal systems are oscillatory patterns of activity

consisting of subthreshold (or membrane potential) oscillations interspersed with action potentials (or spikes).

Detailed Description

Introduction

Rhythmic oscillations in the theta (4–12 Hz) and gamma (30–100 Hz) frequency bands have been recorded in the hippocampus and the entorhinal cortex and have been implicated in cognitive processes including memory, spatial navigation, and sleep (Buzsáki 2002, 2006; Kahana et al. 1999; O’Keefe and Recce 1993; Traub and Whittington 2010; Buzsáki and Wang 2010; Engel et al. 2003; Fries 2009; Singer and Gray 1995; Bragin et al. 1995; Montgomery and Buzsáki 2007). These network oscillations emerge from the cooperative activity of the participating neurons and network connectivity.

Intrinsic subthreshold (membrane potential) oscillations (STOs) and MMOs at theta and gamma frequencies have been observed in various neuron types (Alonso and Llinás 1989; Chapman and Lacaille 1999; Dickson et al. 2000a, b; Leung and Yim 1991; Fransén et al. 2004; Schmitz et al. 1998; Yoshida and Alonso 2007; Bourdeau et al. 2007; García Muñoz et al. 1993; Llinás et al. 1991). MMOs have been most notably investigated in stellate cells in layer II of the medial entorhinal cortex (Fransén et al. 1998; Fernandez and White 2008; Giocomo et al. 2007; Yoshida and Alonso 2007).

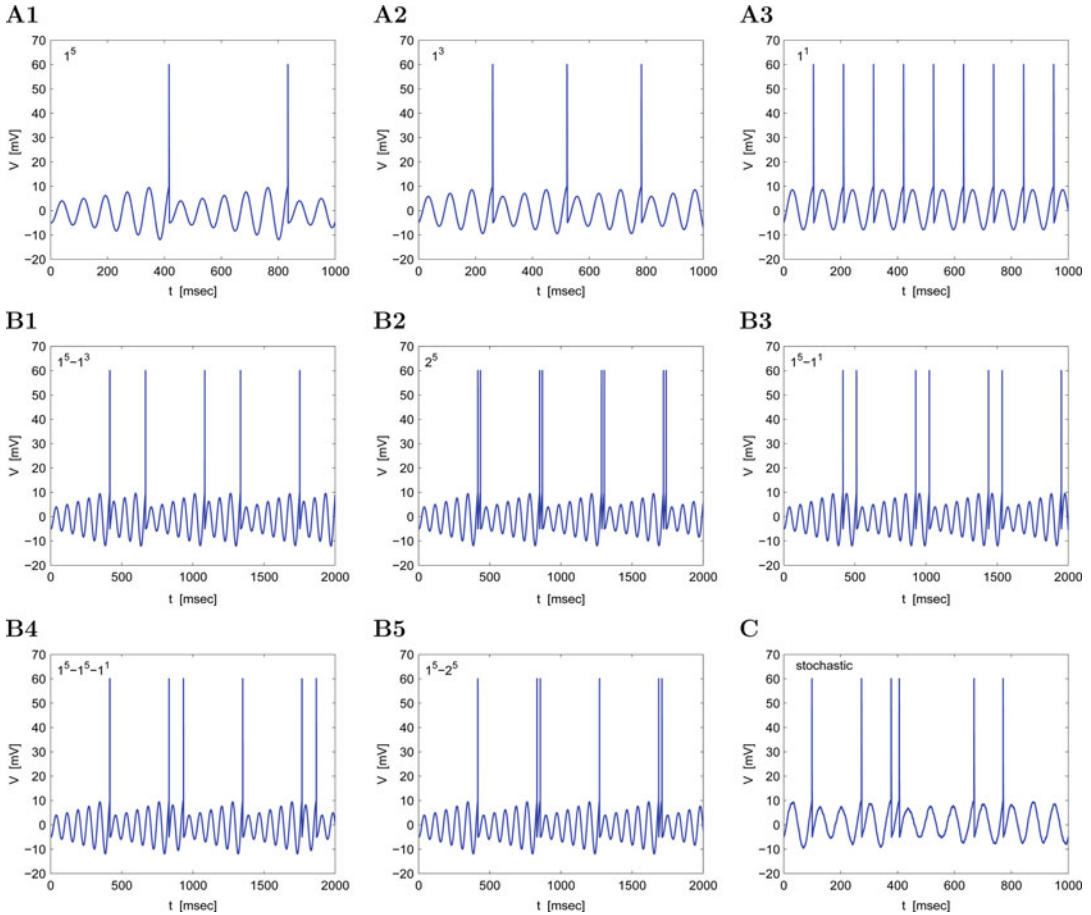
Several models have been used to investigate MMOs (Wang 2002; White et al. 1998; Fransén et al. 2004; Acker et al. 2003; Rotstein et al. 2006, 2008; Jalics et al. 2010; Medvedev and Cisternas 2004; Dorval and White 2005; Brøns et al. 2008; Desroches et al. 2012; Morin et al. 2010). These models focus on the role of the ionic currents in shaping the MMO patterns (generation of STOs and the onset of spikes) or the dynamic mechanisms that give rise to MMOs.

The functionality of MMOs is still a matter of discussion. STOs have been argued to function as a timing device (Lampl and Yarom 1993) and to play a role in spatial navigation (Giocomo et al.

2007). While action potentials (or spikes) are the basic neuronal signaling mechanism (Johnston and Wu 1995; Koch 1999; Dayan and Abbott 2001; Ermentrout and Terman 2010), the interspersed STOs in the MMO patterns (Figs. 1 and 2) may help create a time scale at which information is effectively communicated among neurons.

The Structure of MMO Patterns

Typically, a basic MMO cycle consists of s small amplitude oscillations followed by L spikes (or vice versa). The notation L^s is customarily used to describe these patterns (Desroches et al. 2012; Bröns et al. 2008) (and papers therein).



Mixed-Mode Oscillations in Single Neurons,

Fig. 1 MMO patterns in a 2D STO-F model with linear subthreshold dynamics (see also resonate-and-fire models (Izhikevich 2001)). The subthreshold dynamics are governed by the following two equations describing the dynamics of the rescaled voltage V (mV) and gating variable w (mV) (see (Richardson et al. 2003)): (i) $CdV/dt = -g_L V - gw + I_{app}$ and (ii) $\tau dw/dt = v - w$. Spikes are added manually when V reaches V_{th} , and V and w are reset to V_{rst} and w_{rst} respectively. (a) The reset values V_{rst} and w_{rst} are constant and independent of the number of spikes. (A1) $I_{app} = -0.2$. (A2) $I_{app} = 0$. (A3) $I_{app} = 0.2$. We used the following parameter values: $C = 1$, $g_L = -0.03$, $g = 0.3$, $\tau = 40$, $V_{th} = 10$, $V_{rst} = -5$, $w_{rst} = -1$. Units are as in

(Richardson et al. 2003; Rotstein 2013). (b) The reset value w_{rst} changes as a function of the number of consecutive spikes (N) according to the following rule: when $N = N_{max}$, w_{rst} is decreased by an amount Δw_{rst} . (The reset value V_{rst} is constant and independent of the number of spikes). (B1) $N_{max} = 2$ and $\Delta w_{rst} = 1.5$. (B2) $N_{max} = 2$ and $\Delta w_{rst} = 2.5$. (B3) $N_{max} = 2$ and $\Delta w_{rst} = 3$. (B4) $N_{max} = 3$ and $\Delta w_{rst} = 2.1$. (B5) $N_{max} = 3$ and $\Delta w_{rst} = 2.7$. (c) The reset values V_{rst} and w_{rst} are constant and independent of the number of spikes (as in A). $I_{app} = -0.2 + \sqrt{2D} \eta(t)$ where the last term is white noise (delta correlated) with zero mean and standard deviation D . We used $D = 0.2$. Other parameter values are as in A

MMO patterns can be regular (Figs. 1a, b) or irregular (Fig. 1c). In turn, regular MMO patterns can be uniform, where the sequence L^s describes the MMO patterns in their entirety (Fig. 1a), or nonuniform, where MMO cycles consist of sub-cycles described by sequences of the form $L_1^{s_1} - L_2^{s_2} - \dots - L_N^{s_N}$ (for some integer N) (Fig. 1b). Irregular MMO patterns can be either stochastic (Fig. 1c) or chaotic (not shown).

The occurrence of L^0 cycles (for $L > 1$) embedded in MMO patterns, with two or more consecutive spikes with no interspersed STOs (Figs. 1B2, B5, C), is customarily referred to as spike clustering (Fransén et al. 2004; Alonso and Klink 1993; White et al. 1998; Serafin et al. 1996; Desmaisons et al. 1999; Wang 2002; Muratov and Vanden-Eijnden 2008; Kuske and Borowski 2009). The inter- and intra-spike frequency may belong in the same frequency range or not depending on the neuronal type and other parameter values.

Dynamic Mechanisms of Generation of MMOs

The generation of MMO patterns requires the coordinated action of various mechanisms: (i) a mechanism for the generation of STOs; (ii) a spiking mechanism, including the onset of spikes and the description of the spiking dynamics; and (iii) a return mechanism from the spiking regime back to the subthreshold regime.

The minimal models able to generate intrinsic oscillatory behavior are 2D and involve the dynamics of the voltage v and a recovery variable (w) (Rinzel and Ermentrout 1998; Rinzel 1985; Ermentrout and Terman 2010; Ermentrout and Kopell 1998; FitzHugh 1961; Nagumo et al. 1962). These models may generate either STOs (Fig. 3a) or spikes (Fig. 3b) but not MMOs. MMO patterns require an additional mechanism that describes the dynamic transition between these two regimes. This mechanism may be provided by an external input (non-autonomous system), such as in certain cases of the slow passage through a Hopf bifurcation (Holden and Erneux 1993; Baer et al. 1989) and the patterns resulting

from oscillatory forcing (Barnes and Grimshaw 1997; Shimizu et al. 2012), or by an additional dependent variable (autonomous system) (Fig. 3c) as in the 3D canard phenomenon (Wechselberger 2005; Brøns et al. 2006).

The minimal models that are able to generate intrinsic MMOs are nonlinear, 3D, and involve multiple time scales. The prototypical example is the 3D extended version of the FitzHugh-Nagumo (FHN) model (FitzHugh 1961; Nagumo et al. 1962) (Fig. 3) describing the dynamics of the voltage v and two gating variables (w and z) with linear dynamics. Models of FHN type are caricature models, but they capture the basic dynamic properties observed in detailed biophysical (conductance-based) models.

In the example presented in Fig. 3, all the MMO mechanisms are described by the same model. The generation of STOs (Fig. 3A3) and the onset of spikes (Fig. 3B3) are governed by the locally parabolic portion of the v -nullcline, near its minimum. The spiking dynamics and the return mechanisms are primarily governed by the right and left branches of the v -nullcline respectively (Fig. 3A2). The abrupt transition from STOs to spikes is due to the 2D (Figs. 3a, b) and 3D canard phenomena (Figs. 3c) (Krupa and Szmolyan 2001; Wechselberger 2005; Brøns et al. 2006). The locally parabolic nonlinearity at the minimum of the v -nullcline and the time scale separation between v and the remaining dependent variables are key for these mechanisms.

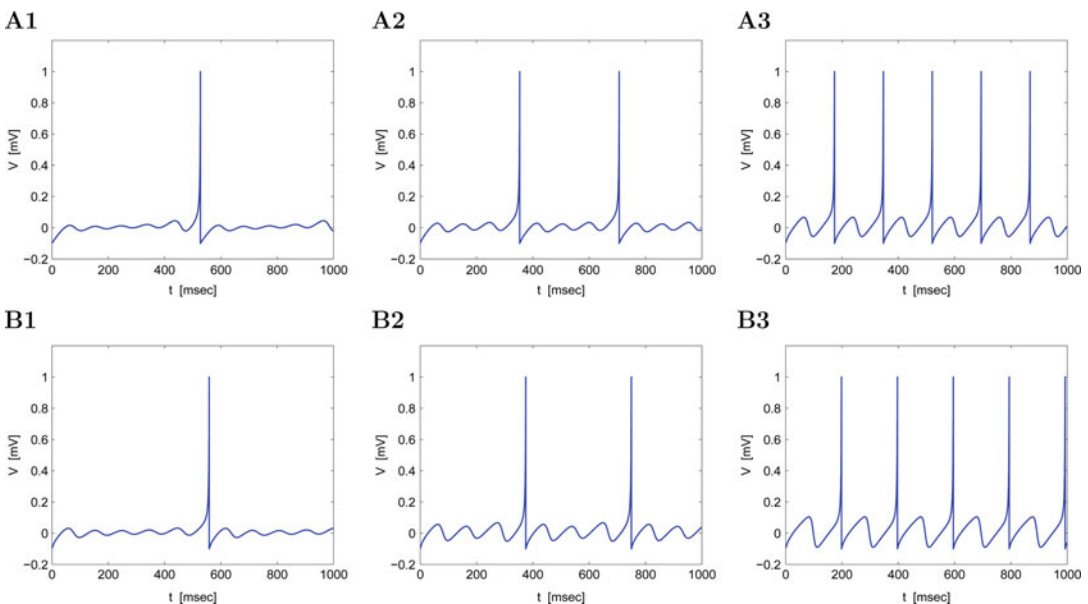
Higher-dimensional models provide the necessary flexibility for the generation of more complex MMO patterns. Typically, in these models each mechanism (e.g., STOs, spikes) is described by a different, lower-dimensional regime (Rotstein et al. 2006).

Generalizations of the integrate-and-fire model to include 2D linear subthreshold dynamics (Izhikevich 2001; Richardson et al. 2003; Rotstein 2013) are able to produce MMOs provided that the fixed-point of the underlying (subthreshold) 2D linear system is an unstable focus (Rotstein 2013). (Stable foci are possible in the stochastic case). These models are referred to as STO-F models (STO-and-fire models)

(Rotstein 2013). The mechanism of spike generation consists of a voltage threshold (V_{th}) and “artificial spikes”: spikes are added manually when the voltage V crosses V_{th} . The return mechanism consists on the manual reset of V and w to predetermined values V_{rst} and w_{rst} after a spike has occurred. STO-F models with constant values of w_{rst} generate regular uniform 1st MMO patterns (Fig. 1a) where the number of STOs per cycle depends on the model parameters. The generation of regular nonuniform MMO patterns requires a return mechanism where at least one reset value (either V_{rst} or w_{rst}) is not constant and depends, for instance, on the number of consecutive spikes within some range (Fig. 1b).

Generalizations of the integrate-and-fire model to include 2D or 3D nonlinear subthreshold dynamics, such as the reduced medial entorhinal cortex layer II stellate cell model (Rotstein et al. 2006) and extensions of the quadratic-integrate-

and-fire models (Izhikevich 2001, 2006; Rotstein et al. 2006, 2008; Jalics et al. 2010), typically have a parabolic-like voltage nullcline in the subthreshold regime, and the gating variables have either linear or sigmoidal nullclines (Izhikevich 2001, 2010; Rotstein et al. 2006). These models are able to generate STOs provided the fixed-point in the subthreshold regime is a focus. In addition, these models describe the onset of spikes, but not the spiking dynamics. The voltage threshold V_{th} indicates the occurrence of spikes, which are added manually. (Note that V_{th} is not a part of the spiking generation mechanism). The voltage and possibly the gating variables are reset after a spike has occurred (return mechanism). In principle, MMOs are possible when the subthreshold dynamics are 2D provided the reset point (V_{rst} , w_{rst}) is close enough to the fixed-point and the latter is unstable, thus generating a spiraling out solution. However, for biophysically plausible



Mixed-Mode Oscillations in Single Neurons, Fig. 2 MMO patterns in 3D parabolic STO-F models with a parabolic nonlinearity in the voltage equation. The subthreshold dynamics is governed by the following three equations describing the dynamics of the rescaled voltage V and gating variables w and z : (i) $dV/dt = V^2 - w + I_{app}$, (ii) $\tau dw/dt = 0.5 * V - w$, and (iii) $\tau dz/dt = \eta$ (panels A) and $\tau dz/dt = \eta (0.5 V + 0.02 - z)$ (panels B). The onset of spikes is described by the equations describing the

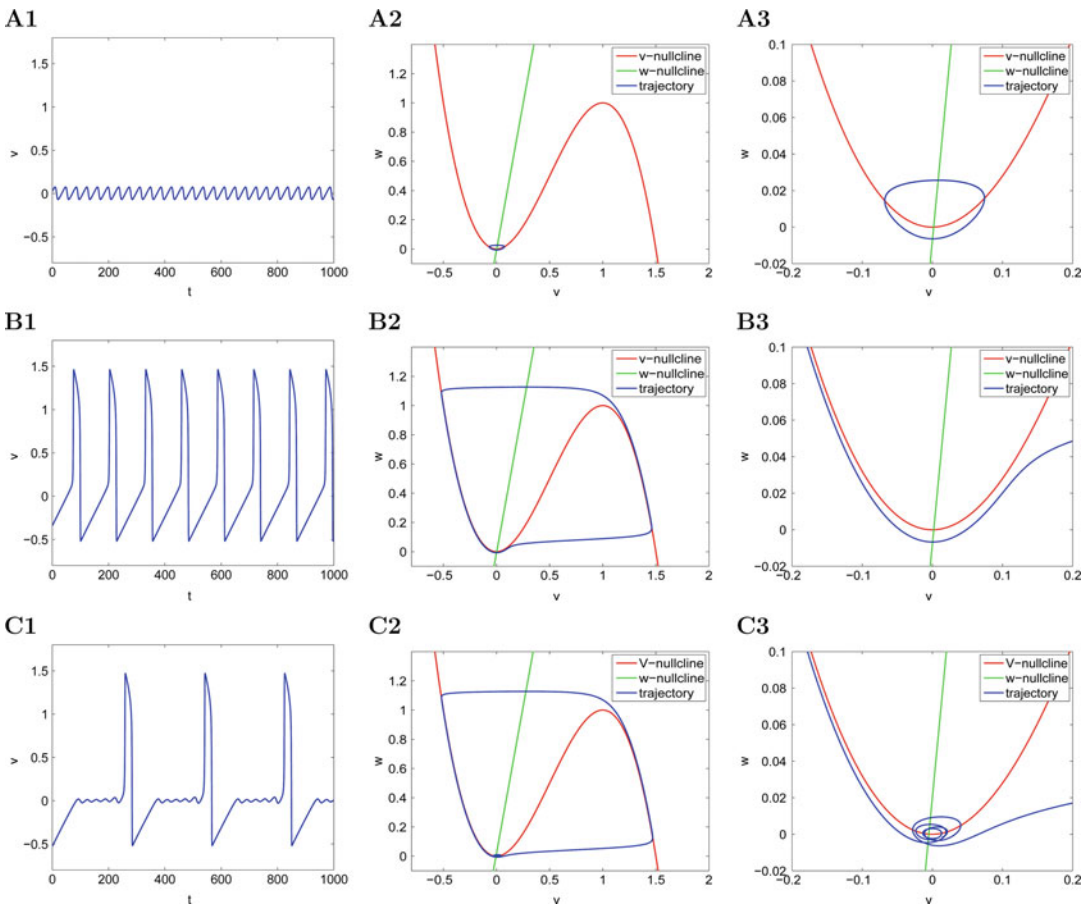
subthreshold dynamics. The occurrence of spikes is indicated when V reaches V_{th} , and V , w , and z are reset to V_{rst} , w_{rst} , and z_{rst} respectively. For $\eta = 0$, the corresponding 2D systems display damped STOs. (A1) $I_{app} = -0.008$. (A2) $I_{app} = -0.006$. (A3) $I_{app} = -0.004$. (B1) $I_{app} = -0.004$. (B2) $I_{app} = -0.003$. (B3) $I_{app} = -0.0027$. We used the following parameter values: $\tau = 100$, $V_{th} = 1$, $V_{rst} = -0.1$, $w_{rst} = V_{rst}^2 + I_{app} - 0.001$, $z_{rst} = 0$, $\eta = 0.0003$ (A), and $\eta = 0.1$ (B).

situations, this condition is not satisfied, and an additional subthreshold variable (z) is required to govern the dynamic transition from STOs to spikes (Fig. 2). The slow component of the h-current plays this role in the stellate cell model mentioned above (Rotstein et al. 2006, 2008), while a persistent sodium and the fast component of the h-current are enough to generate STOs.

The mechanisms of generation of MMOs in conductance-based models when different sets of ionic currents govern the dynamics of the subthreshold and spiking regimes are more difficult to analyze due to their high dimensionality. There

are circumstances where the dynamics for different regimes can be treated separately by using reduction of dimensions methods (Rotstein et al. 2006).

The mechanism of generation of MMOs crucially depends on the mechanism of transition from STOs to spikes. Several mechanisms have been described in the literature (Guckenheimer et al. 1997; Wechselberger 2005; Guckenheimer 2008a, b; Krupa and Wechselberger 2010; Koper 1995; Larter and Steinmetz 1991) in addition to the canard phenomenon (Szmolyan and Wechselberger 2001; Wechselberger 2005;



Mixed-Mode Oscillations in Single Neurons, Fig. 3 STOs, spiking, and MMOs in models of FitzHugh-Nagumo type. (a) STOs ($\lambda = 0.0075$) and (b) spiking ($\lambda = 0.008$) for the 2D FHN model described by the following equations: (i) $dv/dt = -2v^3 + 3v^2 - w$, (ii) $dw/dt = 0.01(4v - \lambda - w)$. (c) MMOs for the extended, 3D FHN model described by the following equations:

(i) $dv/dt = -2v^3 + 3v^2 - w$, (ii) $dw/dt = 0.01(4v + 0.02 - z - w)$, (iii) $dz/dt = 0.0005(4v + 0.9 - z)$. *Left panels:* voltage time courses. *Middle and right panels:* phase planes. The *right panels* are magnifications of the *middle ones*. Panel C3 corresponds to the projection of the phase-space (for the variables v , w , and z) onto the v - w plane

Brøns et al. 2006; Rotstein et al. 2006) and the slow passage through a Hopf bifurcation (Larter et al. 1988; Holden and Erneux 1993; Baer et al. 1989). These mechanisms are reviewed in (Desroches et al. 2012).

We note that MMOs have also been observed in other fields of science including chemistry and biology (Petrov et al. 1992; Aguda et al. 1989; Hauser and Olsen 1996; Strizhak et al. 2002; Baba and Krischer 2008). In these cases MMOs consist of an alternation of small amplitude oscillations (SAOs) and large amplitude oscillations (LAOs) where the amplitude between SAOs and LAOs differs roughly by an order of magnitude.

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Further Reading

- Focus Issue on Mixed-Mode Oscillations, *Chaos* (2008) Brøns et al. (2008)
- SIAM Review Desroches et al. (2012)

9ML

- [NineML](#)

Model Repository

- [BioModels Database: A Public Repository for Sharing Models of Biological Processes](#)

Model Systems for Spine Pain

- [Biomechanical Model of Low Back Pain](#)

ModelDB

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Definition

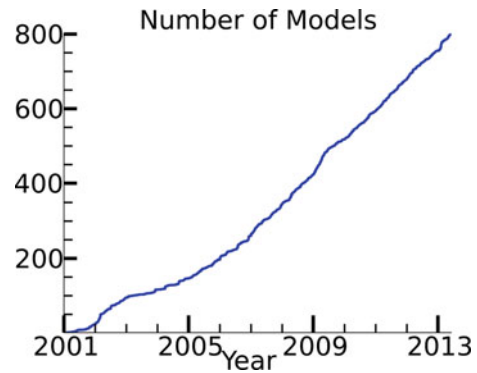
ModelDB is a database that supports the development of the field of computational neuroscience by storing and making available the computer code for publications that contain biophysical models of neurons and microcircuits. The focus is on models of biologically realistic neurons and circuits, but the spatial scales also range from molecules (ion channels and receptors) through behavior (dynamical systems, including an organism and its environment). The complexity of these mathematical models makes it challenging to recreate the simulations described in the papers from scratch, due to incomplete or ambiguous information in the paper or to errors introduced in attempting to recreate the model. Having the author's original code or a third-party contribution available for download is invaluable for recreating a model for verification, extending the model, and reusing the model as a template or building block for new research projects.

Detailed Description

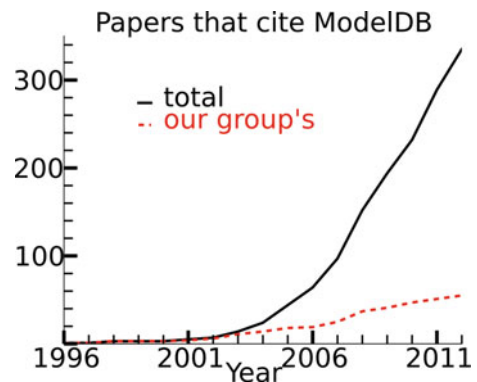
ModelDB began in the Shepherd lab at Yale University in 1995 (Peterson et al. 1996) with the goal of supporting the development of computational neuroscience by sharing simulation computer code. The importance of computational models for integrating neuroscience data was envisaged in the original Human Brain Project (see Pechura and Martin 1991). ModelDB has been supported under the original Human Brain Project, which provided crucial early support for the development of neuroinformatics tools in support of neuroscience research, including the integration of neuroscience data into computational models.

Many of the model entries of channels and receptors are descendants of the original Hodgkin–Huxley model (Hodgkin and Huxley 1952) of the sodium, potassium, and leak currents which generate the squid axon action potential. The modeling methods that extended studies of neuronal electrical activity from “point” neurons to passive and active dendrites and axons (represented as tapering cylindrical cables) were introduced in neuroscience by Wilfrid Rall, with the first applications to brain neurons in the olfactory bulb (Rall and Shepherd 1968). Initially built to store and share models of neurons in the olfactory system, the main topic of research in the Shepherd lab, ModelDB was quickly broadened to include investigators who contributed their published model computer code of neurons in many other regions of the nervous system.

These broadened contributions have rapidly expanded the database as can be seen in Fig. 1; from a modest number in 2001, the inventory of models has risen steadily over 12 years at an annual rate of about 70. The first method was for the curator to solicit authors of articles containing the models, and this method continues. However, in recent years there has been a steady increase in unsolicited submission of models by the authors themselves, who then work with the curator to insure accurate incorporation into the database. In parallel with this rise has been a rise in the citations of ModelDB in the literature (currently over 360, see Fig. 2) as a place where code was obtained, or deposited, or is mentioned in a



ModelDB, Fig. 1 Total number of models in ModelDB



ModelDB, Fig. 2 Total number of papers that cite ModelDB. In red are the portion of papers published by the ModelDB group

neuroinformatics context. These two trends indicate the growing recognition of the critical role that models are playing in modern neuroscience.

ModelDB contains functionality that enhances the value of the database by providing search tools for different purposes. As can be seen on the home page (Fig. 3), the user can search on, for example, neuronal type, brain regions, receptors and channels, and a wide variety of topics, which include plasticity, depolarization block, synchronization, and magnetoencephalography among many. These tools are under continual development to assist users in finding models of interest. Within the topics, “microcircuits” has undergone a particularly robust development in recent years (see Handbook of Brain Microcircuits, Shepherd and Grillner 2010), so that a new database



ModelDB provides an accessible location for storing and efficiently retrieving computational neuroscience models. ModelDB is tightly coupled with [NeuronDB](#). Models can be coded in any language for any environment. Model code can be viewed before downloading and browsers can be set to auto-launch the models. For further information, see [model sharing in general](#) and [ModelDB in particular](#).

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Search for SenseLab models using Google

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Combine ModelDB curated keywords with a Google search: [ModelSearch](#)

ModelDB, Fig. 3 ModelDB home page

(MicrocircuitDB) on this topic alone has been created and now contains over 180 models.

Another type of search tool enables the user to find models by different model environments, which currently total over 70 different applications. The most numerous is NEURON (398) (Hines and Carnevale 2013) whose authors are key members of the SenseLab group. Also numerous are MATLAB (185), C or C++ (88), XPP (73), GENESIS (31), and Python (23). The extraordinary variety of modeling environments is evidenced by the fact that there are a large number of model entries created by only one or two applications (46).

A significant barrier to effective model sharing is the effort that a user must invest to decide whether a particular model is applicable. It is one thing for a model author to say “this program creates a model of a pyramidal cell” and quite another to know exactly what anatomical and biophysical properties are represented in that model. Source code is essential but can be difficult to analyze, and variables may have values at run

time different from the first values indicated in the top of the code. A new web-based “ModelView” tool that provides ModelDB users with a browsable graphical and textual summary of the anatomical and biophysical attributes of a model is being developed. ModelDB’s ModelView does this without requiring the user to install a simulator or other specialized software and even without having to download model source code from ModelDB; the only prerequisite is a web browser and Internet access. This helps modelers develop a conceptual understanding of a model much faster and with far less effort than required to understand code.

This tool was inspired by, and makes use of, the NEURON simulation environment’s own ModelView tool. The prototype implementation was used to generate pilot data from three models in ModelDB, available through a “Model View” link for these models (McDougal et al. 2013); for example, click on Model View in <http://senselab.med.yale.edu/ModelDB/ShowModel.asp?model=87284>.

Another problem commonly faced by modelers is how to identify ion channels that are appropriate for their own modeling projects. The proliferation of data on membrane ion channels enables models of channels and their contributions to neural function to be increasingly accurate. By the same token, it presents serious challenges in the form of multiplicity of channel subtypes, duplication of subtypes in different models, and searchability for specific model subtypes for a given type of neuron model of interest. To solve this problem, ModelDB has begun using a direct comparison of file contents to identify duplicate files. This method allows tagging filenames with an asterisk suffix in the model-viewing page, ShowModel.asp, which have been found to be duplicated (present in other entries in ModelDB). Identification of reused ion channels and receptors in different models in ModelDB will help investigators assess channel mechanisms in their larger context of (sometimes widespread) use in different types of cells.

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Modeling Cerebellar Learning: Input Minimization

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Definition

Input minimization (InMin) is a learning algorithm that can be used to train neural networks to accomplish time-varying input–output transformations. InMin is also a plausible model of cerebellar learning. The model represents the major cerebellar cell types and connections: Purkinje cells, stellate cells, granule cells, mossy fibers, parallel fibers, climbing fibers, and deep cerebellar or vestibular nuclei neurons. InMin uses a combination of two learning mechanisms to train connection weights in the cerebellar network: the parallel-Purkinje weights are trained using the self-organizing map algorithm, while the stellate-Purkinje or Purkinje-nuclear weights are trained using a form of reinforcement learning. Through these mechanisms the Purkinje cells each learn to specialize for their own segment of the time-varying input and to adjust the strength of their contribution in order to reduce both error and effort in accomplishing the input–output transformation. Unlike almost all other models of cerebellar learning, climbing fibers in InMin do *not* carry error signals. Instead, error signals are carried along with sensory and efference copy signals by parallel fibers, while the climbing fiber spikes, which are random and infrequent, provide pulses that serve to synchronize the learning process. The unique feature of InMin is that it uses total parallel fiber input as a negative reinforcement signal and it learns to reduce both the error and the effort associated with any input–output transformation by minimizing its total parallel fiber input (hence the name). InMin successfully trains neural system models to simulate the kinds of motor control exhibited by the real cerebellum, and the neural elements representing Purkinje cells in trained models have properties that resemble those of real Purkinje cells.

Detailed Description

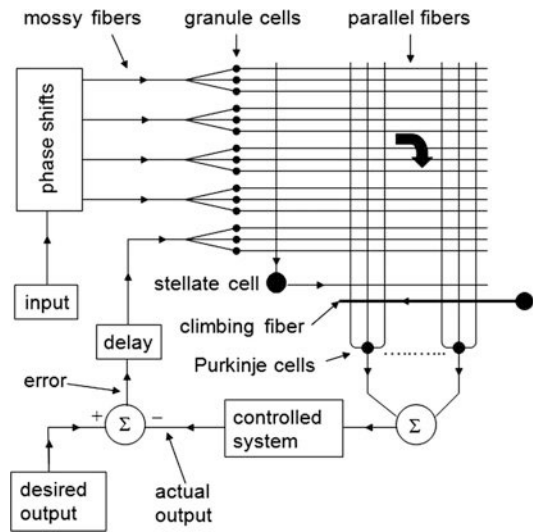
The Marr/Albus Paradigm

In 1969 David Marr published a highly influential paper describing a model of cerebellar learning (Marr 1969). This model was elaborated by James Albus (Albus 1971), and ever since the Marr/Albus paradigm has provided the framework for almost all models of learning in the cerebellum. Although the cerebellum is involved in many neurological processes, it is most closely associated with motor control, and because eye movements can be studied relatively easily and precisely, many neural systems models of cerebellar learning have been considered in the context of adaptive oculomotor control. Almost all of these models are based on the Marr/Albus paradigm (e.g., Fujita 1982; Ito 2000; Yamamoto et al. 2002). Input minimization (InMin) represents a departure from this tradition.

The Marr/Albus paradigm treats cerebellar learning as perceptron learning. In this framework, the weights of the connections from parallel fibers onto Purkinje cells are trained in a supervised, error-driven fashion using precise error signals provided to Purkinje cells by climbing fibers. This is an elegant and effective scheme, but the evidence that climbing fibers carry error signals is inconclusive (Gibson et al. 2004; Kitazawa and Wolpert 2005). Climbing fibers fire spikes at a low average rate of about 1 Hz; modulations of this low rate are difficult to discern and the interspike intervals are random (Keating and Thach 1995). Available data certainly leave open the possibility that the climbing fiber input to Purkinje cells serves a purpose other than error signaling.

InMin Models of Cerebellar Function

InMin is used to train neural system models that are based on the neuroanatomy of the cerebellum (Eccles et al. 1967; Llinás and Walton 1990). A generic scheme for modeling cerebellar adaptation of motor control is shown in Fig. 1. In this scheme, Purkinje and stellate cells are modeled as



Modeling Cerebellar Learning: Input Minimization, Fig. 1 Schematic diagram of the input minimization (InMin) model of cerebellar learning

summing units while granule cells and climbing fibers are binary (for clarity of description, all units are referred to using the names of the actual cell types they represent). Purkinje cells receive excitatory input from parallel and climbing fibers and inhibitory input from stellate cells. Each parallel fiber arises from a separate granule cell. Subsets of granule cells receive the same mossy fiber, and each mossy fiber carries a differently phase-shifted version of the input. Phase dispersion is a characteristic of visual, vestibular, and other oculomotor-related mossy fiber signals (e.g., Miles et al. 1980; Mustari et al. 1988). Mossy fibers encode sensory and efference copy signals. Each granule cell in a subset has its own unique threshold, so each provides its own distinctly phase-shifted and threshold-limited version of the input to Purkinje cells. Depending on the application, granule cells outnumber Purkinje cells by one or two orders of magnitude, and together the mossy fibers and granule cells produce an expansive recoding of the input. InMin is compatible with any sort of expansive recoding of mossy fiber signals at the granular layer, including the nonlinear combinations of the kind used in support vector machines.

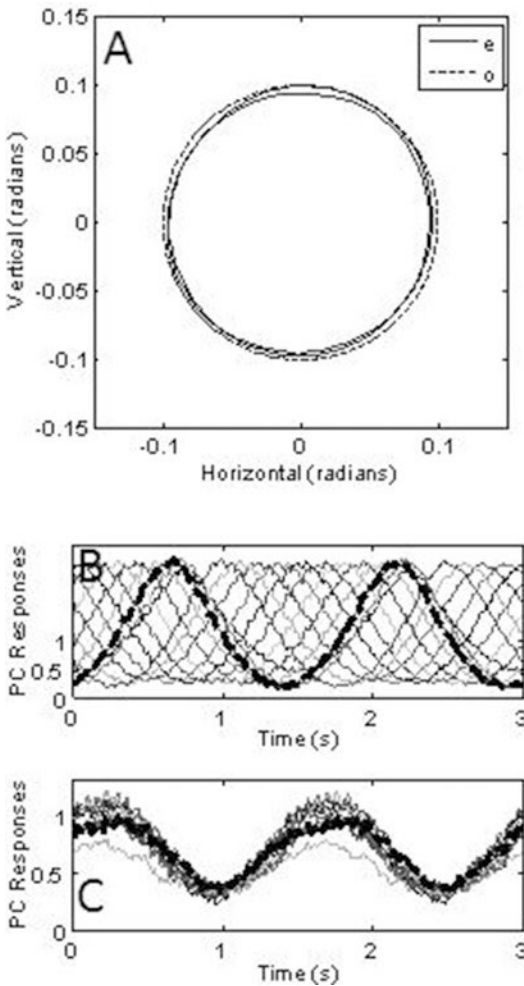
Each Purkinje and stellate cell computes the weighted sum of its parallel fiber inputs. Stellate cells inhibit Purkinje cells, and in some InMin applications this is modeled as a shunting inhibition which lowers Purkinje cell sensitivity. The weighted sum of the Purkinje cell responses is then used as a signal to adjust an ongoing sensorimotor process; oculomotor examples include vestibuloocular image stabilization or smooth pursuit tracking. The difference between a desired output and the output of the cerebellar-adjusted process forms an error signal which is delayed, expansively recoded, and presented as additional parallel fiber signals to Purkinje and stellate cells. The climbing fiber produces spikes at random times with an average interspike interval of 1 s. These synchronize learning in the model.

Each climbing fiber spike initiates one cycle of standard self-organizing feature map training (Kohonen 1997). Briefly, the Purkinje cell with the strongest response is determined, and it and its neighbors are made more sensitive to the current pattern of parallel fiber input, by adding a scaled version of the parallel fiber input vector to the parallel-Purkinje weight vectors of the Purkinje cells in the training neighborhood and normalizing. Each climbing fiber spike also initiates one cycle of perturbative reinforcement training, the form of which is based on the directed-drift algorithm (Venkatesh 1993). Briefly, some parameter that determines the magnitude of the Purkinje cell adjustment of the controlled process is transiently perturbed, and the effect of this perturbation on total parallel fiber input is assessed. The assessment is based either on delayed or integrated parallel fiber signals in order to account for the delay inherent in the error-related component of the total parallel fiber signal. Perturbed parameters can include the amount of stellate shunting inhibition or the Purkinje cell output weight, and the perturbation can be applied to a single (generally the most strongly responding) Purkinje cell or to any subset of Purkinje cells. If the total parallel fiber input is decreased by the perturbation, then it is reinstated. Otherwise the parameter is kept at its pre-perturbation value.

InMin has been applied in modeling cerebellar learning in the context of adaptation of the vestibuloocular reflex (Anastasio 2001a) and

smooth pursuit (Rothganger and Anastasio 2009). Retinal error signals are produced whenever either the vestibuloocular or the pursuit systems operate imperfectly, and saccadic eye movements can be triggered during imperfect pursuit to momentarily reduce the error. As stated above, signals such as retinal error and saccade command efference copy are carried by parallel fibers, along with visual, vestibular, and other signals. By minimizing overall parallel fiber input, InMin reduces both retinal error and saccade efference copy signals, making the controlled system more accurate and, in the pursuit case, more efficient.

InMin trains Purkinje cells to act as feedforward pattern correlators that each respond best to a unique pattern of parallel fiber activity and make an adjustment that improves the performance of the controlled system (e.g., vestibuloocular or pursuit). In this regard cerebellar models trained by InMin are similar to Marr/Albus models (see also Anastasio 2001b). However, the properties of the Purkinje cells in InMin models, which resemble those of real Purkinje cells, differ in a critical respect from those in Marr/Albus models. This is illustrated in Fig. 2. Panel A shows simulated eye position following InMin training on a circular pursuit task. Model output closely matches the desired output. Panel B shows the responses of all of the Purkinje cells that control the horizontal component of the movement (those controlling the vertical component are similar). The responses are roughly sinusoidal because the production of a circular 2D trajectory requires sinusoidal horizontal and vertical components. The responses appear jagged because their parallel fiber inputs come from binary granule cells. Crucially, all of these Purkinje cells are from the same model microzone. A microzone is defined as all of the Purkinje cells that are innervated by the same climbing fiber (Oscarsson 1979). Note that all of the Purkinje cell responses in Panel B have distinct phases. The same model was then trained under the Marr/Albus, error-driven learning paradigm. Overall model behavior was very similar to that shown following InMin training in Panel A. The Purkinje cell responses following Marr/Albus training, shown in Panel C, all have the same phase, because they are all correlated with the same error signal as supplied, according to the



Modeling Cerebellar Learning: Input Minimization, Fig. 2 Using InMin to simulate pursuit learning. Panel A shows the output of the model after training on a circular pursuit task. Panel B shows the responses following InMin training of the Purkinje cells controlling the horizontal eye movement component (those controlling the vertical component are similar). Panel C shows the horizontal Purkinje cell responses following Marr/Albus training on the circular pursuit task (model performance following Marr/Albus training was similar to that following InMin training, which is shown in panel A)

Marr/Albus paradigm, by their common climbing fiber. These results stand as a prediction. If the Marr/Albus paradigm is correct, then all Purkinje cells in a microzone following vestibular or pursuit training should have the same phase. If they are not, then an alternative account, such as InMin, should be considered instead.

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Modeling Intracellular Ionic Concentrations

► Modeling Ion Concentrations

Modeling Intracranial Electroencephalography (iEEG) Signals

► [Electrocorticogram \(ECoG\)](#)

Modeling Ion Concentrations

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Synonyms

[Ionic currents](#); [Ionic diffusion](#); [Modeling intracellular ionic concentrations](#)

Definition

Realistic models for ionic concentration changes should capture essential aspects of ionic dynamics which are relevant for neuronal function. Ionic concentration changes affect many ionic channels and thereby also the membrane voltage. In addition, ionic concentration changes (e.g., calcium concentration changes) influence also intracellular biochemical signaling cascades. Ionic dynamics is an important determinant of neuronal inhibition, excitability, and synaptic plasticity. We will first introduce how to model intracellular ionic dynamics in general and then describe briefly some details relevant for modeling calcium and chloride dynamics.

Detailed Description

Ion Influx

Ions enter the neuron via ion channels in the cell membrane. This influx can be modeled as a **linear ohmic current**:

$$I_{\text{ion}} = g_{\text{ion}} (V - E_{\text{ion}})$$

where V is the membrane potential, g_{ion} is the membrane ionic conductance (which can be voltage or ligand gated), and E_{ion} is the reversal potential which is given by the **Nernst equation**. However, if ionic currents are rectifying and show strong deviations from ohmic behavior (as in the case of calcium currents), one should use a more accurate **nonlinear** formalism such as the **Goldman–Hodgkin–Katz equation** (GHK):

$$I_{\text{ion}} = P_{\text{ion}} z^2 F^2 V / RT \frac{[\text{Ion}]_i - [\text{Ion}]_o \exp(-zFV/RT)}{1 - \exp(-zFV/RT)}$$

where P_{ion} is the total ion permeability, z is the valence of the ion, F is the Faraday constant, V is the membrane voltage, R is the gas constant, T is the absolute temperature, and $[\text{Ion}]_o$ and $[\text{Ion}]_i$ are the extra- and intracellular ion concentrations, respectively. To calculate the total ion permeability, one can multiply the maximum ion permeability by the time-varying fraction of open channels (e.g., given by Hodgkin–Huxley-like gating variables). The contribution of the ion influx (I_{ion}) to the ion concentration change inside a cellular compartment can be calculated as follows:

$$\frac{d[\text{Ion}]_i}{dt} = -\frac{I_{\text{ion}}}{zF\text{volume}}$$

where z is the valence of the ion, F is the Faraday constant, volume is the volume into which the ions flow, and t is time.

Ion Removal

Ions can be removed by various pumps and exchangers which are present on the cell

membrane and on the membrane of intracellular organelles. These ion removal mechanisms can be represented by simple **phenomenological** models with low number of parameters or by complex **biophysical** models including many buffers and pumps. A commonly used phenomenological model of ion influx and removal is the **exponentially decaying pool model** of ion concentration:

$$\frac{d[\text{Ion}]_i}{dt} = -\frac{I_{\text{ion}}}{zF\text{volume}} + \frac{[\text{Ion}]_i^{\text{rest}} - [\text{Ion}]_i}{\tau_{\text{ion}}}$$

The equation represents ion accumulation due to ion influx (see previous equation) with exponential recovery (decay time constant τ_{ion}) to the resting level of intracellular ion concentration $[\text{Ion}]_i^{\text{rest}}$. The decay time constant determines the ion removal rate and approximates the removal effects of buffers and pumps. If the simplification of the ion removal to a single time constant is not sufficient to capture observed ion dynamics, one should use more realistic biophysical models of ion transport and buffering. A simple **biophysical** model for ion removal mediated by a pump is a **Hill equation**:

$$\frac{d[\text{Ion}]_i}{dt} = -v_{\text{max}} \frac{[\text{Ion}]_i^n}{K_d + [\text{Ion}]_i^n}$$

where v_{max} is the maximum rate of ion transport, K_d is the dissociation constant (neuronal $[\text{Ion}]_i$ at which the extrusion rate is half maximal), and n is the Hill coefficient (describes the cooperativity of ion binding). If $n = 1$ (noncooperative ion binding), the Hill equation reduces to **Michaelis-Menten kinetics**. This pump model represents an outward transport mechanism and may drive intracellular ion concentration below its resting level. Therefore, in practice, a small leak influx (from extracellular space or intracellular organelles) is often included in the model to achieve steady-state resting ion concentration:

$$\frac{d[\text{Ion}]_i}{dt} = -\frac{I_{\text{ion}}}{zF\text{volume}} + \text{leak} - v_{\text{max}} \frac{[\text{Ion}]_i^n}{K_d + [\text{Ion}]_i^n}$$

Ion Diffusion

In neuronal models with multiple compartments, it is often necessary to implement diffusion of ions between compartments and within compartments.

Simplified **one-dimensional diffusion** modeling (De Schutter and Smolen 1998) can be employed if highly local (nano- and micro-domain) ionic changes can be neglected. Ion diffusion can be formalized using **Fick's first law** according to which the net flow of ions (J , i.e., the diffusion flux or the amount of ions per unit time) is equal to the product of the coefficient of diffusion (D_{ion}), the spatial concentration gradient ($d[\text{Ion}]/dx$), and the area across which the ions diffuse (A):

$$J = -D_{\text{ion}} \frac{d[\text{Ion}]}{dx} A$$

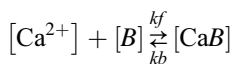
The direction of the ionic flux (between compartments or subcompartments) is opposite to the concentration gradient, and thus the gradient gets smaller over time. **Longitudinal diffusion** (along the length of the dendrite) can be modeled in one dimension as an exchange of ions between adjacent compartments described by the Fick's law. For one-dimensional **radial diffusion** (perpendicular to the axis of the dendrite), the volume of a single compartment can be discretized into a series of **concentric shells** around a cylindrical core (De Schutter and Smolen 1998). Again, the ion flux between neighboring shells can be described by the Fick's law: $-D_{\text{ion}} \Delta[\text{Ion}]/\Delta r A$, where D_{ion} is the diffusion coefficient, $\Delta[\text{Ion}]$ is the concentration difference between shells, Δr is the distance between the shell centers, and A is the area of the boundary between neighboring shells (Hines and Carnevale 2000).

One-dimensional diffusion models are computationally fast. However, for the realistic modeling of highly local ionic dynamics, full **three-dimensional diffusion models** including stochastic diffusion might be necessary (for details, see Smith 2001; Bhalla and Wils 2010; De Schutter 2010). Furthermore, using "pure" (Fickian) diffusion to model ionic dynamics assumes that ionic movement is driven to a much larger extent by concentration gradients than by electrical

potential gradients. This simplification can be removed by using the **Nernst–Planck electrodiffusion equation** (e.g., Qian and Sejnowski 1989; Lopreore et al. 2008). It is a matter of current debate under which physiologically relevant conditions the electrodiffusion equation is more accurate than the classical cable equation combined with “pure” diffusion equations (De Schutter and Smolen 1998; De Schutter 2010; see also entry ► “Diffusion Equation” and the references therein). Recent computer modeling showed that large-scale diffusion of charged ions in extracellular space is able to affect local field potentials (Halmes et al. 2016, 2017). These simulations were based on an electrodiffusive (Kirchhoff–Nernst–Planck) formalism (Halmes et al. 2016).

Modeling Intracellular Calcium Dynamics

Calcium modeling is very often used in neuronal models. The reason is that neuronal electrical activity depends on multiple calcium-gated channels and also many other important neuronal phenomena (e.g., synaptic plasticity) are calcium dependent. The details of calcium modeling approaches can be found in several reviews (e.g., De Schutter and Smolen 1998; Smith 2001; Holcman et al. 2005; De Schutter 2010; Blackwell 2013; see also Chap. 6 in Sterrat et al. 2011). Briefly, **calcium influx**, **calcium removal**, and **calcium diffusion** can be modeled using general approaches for simulating ionic dynamics which we described above. **Calcium buffering** can be formalized using the following kinetic reaction for the interaction between calcium (Ca^{2+}) and a buffer B:



where $[\text{B}]$ and $[\text{CaB}]$ are free and bound buffer concentration, respectively, and kf and kb are the rate constants for the forward and backward reactions, respectively (De Schutter 2010). Most buffers are mobile and therefore their diffusion should be also included in calcium buffering models. Thus, four parameters are needed to fully characterize each buffer: kf , kb , diffusion coefficient, and total buffer concentration

(De Schutter 2010). In some cases (e.g., in models of synaptic plasticity), **calcium release** from internal stores (endoplasmic reticulum) needs to be simulated (Jedlicka and Deller 2017). Calcium release (through IP3 receptors or through ryanodine receptors) can be modeled as a gated flux along the concentration gradient:

$$\frac{d[\text{Ca}^{2+}]_i}{dt} = V_R f_0 \left([\text{Ca}^{2+}]_s - [\text{Ca}^{2+}]_i \right)$$

with V_R as the maximum rate of release, f_0 as the fraction of open channels, and $[\text{Ca}^{2+}]_s$ as the calcium concentration in the stores (De Schutter 2010). The Hill function (see above) can be used to compute f_0 from ligand concentrations (e.g., IP3 and calcium are ligands for the IP3 receptors).

The choice of the best approach to modeling calcium depends on the properties of the phenomenon that one wants to simulate. For detailed guidelines on how to choose the proper level of simplification in the calcium model, see De Schutter (2010). In compartmental models, it is often sufficient to compute calcium concentration only in the submembrane region to activate calcium-dependent channels in the cell membrane. In such case, the **exponentially decaying calcium model** (see above) can be used to implement calcium influx and removal. In this simple phenomenological model, the calcium influx contributes to calcium concentration changes only in a thin **submembrane shell** with small volume and thus can be used to open a calcium-activated (e.g., potassium BK) channel. If multiple calcium-dependent channel types or other calcium-dependent mechanisms need to be used in a compartment model, then biophysical models for calcium buffers and pumps should be included. Realistic modeling of highly local calcium concentration changes in **micro-** or **nano-domains** usually requires highly detailed three-dimensional morphology models; detailed biophysical models of calcium channels, pumps, and buffers; and determinist or stochastic **three-dimensional reaction–diffusion** modeling approaches (e.g., voxel-based **finite-volume** methods or **continuous random walk/ Monte Carlo** methods; Stiles and Bartol 2001; Bhalla and Wils 2010).

Modeling Intracellular Chloride Dynamics

Although chloride plays a crucial role in synaptic transmission and neuronal excitability (De Koninck 2007), so far, chloride modeling has not been extensively used in computational neuroscience. In fact, most models keep chloride concentration constant in spite of experimental evidence that it can change rapidly. Only recently, computational models for chloride influx, removal, and diffusion in large neuronal morphologies became available (Jedlicka et al. 2011; Doyon et al. 2011; Lewin et al. 2012; Mohapatra et al. 2016). These models were used to study activity-dependent changes of intracellular chloride concentration and their impact on synaptic inhibition. Similar to calcium, **chloride influx**, **chloride removal**, and **chloride diffusion** can be modeled using general approaches for simulating ionic dynamics which we described above. An important difference to calcium modeling is that **chloride buffering** can be neglected since chloride is thought to diffuse freely (Kuner and Augustine 2000). Chloride extrusion can be approximated by the exponentially decaying chloride model (Jedlicka et al. 2011). If complex interactions of chloride with other ion species (e.g., K^+ , Na^+ , H^+) need to be simulated, detailed biophysical models for chloride pumps and transporters such as K^+/Cl^- cotransporter (KCC2), $Na^+/K^+/Cl^-$ cotransporter (NKCC1), or Cl^-/HCO_3^- exchanger should be used as described in Doyon et al. (2011) and Lewin et al. (2012). Notice that current chloride dynamics models use determinist one-dimensional diffusion (Jedlicka et al. 2011; Lewin et al. 2012) or electrodiffusion (Doyon et al. 2011). Thus, they neglect potential effects of stochastic three-dimensional chloride diffusion. It remains to be tested whether three-dimensional diffusion or electrodiffusion (Lopreore et al. 2008) is needed for correct simulations of highly local chloride changes. Recent stochastic simulations showed that dendritic spines were able to slow down longitudinal chloride diffusion along dendrites (Mohapatra et al. 2016). Such effects may alter short-term ionic plasticity of inhibitory synapses (Mohapatra et al. 2016). However, since similar results were observed also in deterministic simulations,

potential advantages of stochastic three-dimensional diffusion or electrodiffusion still need to be explored.

Cross-References

- [Cable Theory: Overview](#)
- [Calcium Release, Models of](#)
- [Calcium-Dependent Potassium Channels](#)
- [Deterministic Reaction-Diffusion Simulators](#)
- [Diffusion Equation](#)
- [MCell](#)
- [Nernst Equation](#)
- [STEPS: STochastic Engine for Pathway Simulation](#)

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Modeling of Slow Waves in the Stomach

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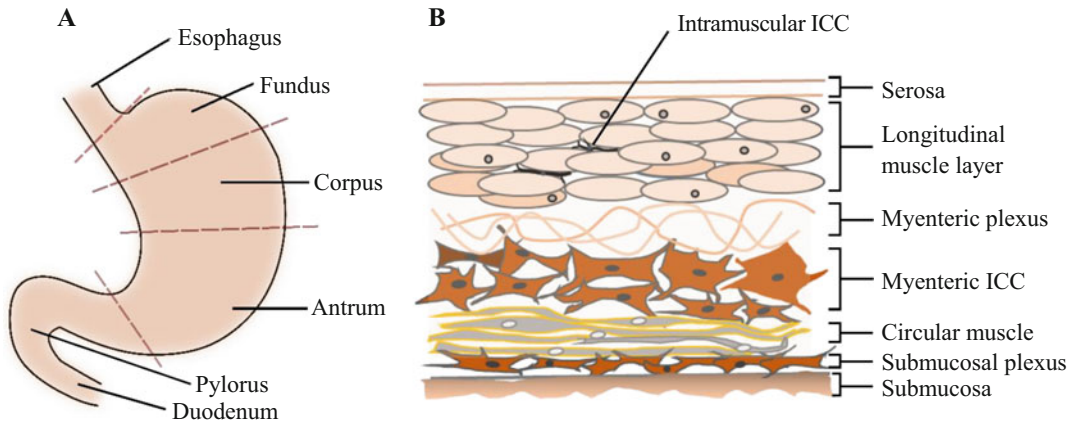
Definition

Within the gastrointestinal (GI) tract, the stomach generates and propagates an omnipresent rhythmic electrical activity known as the gastric slow-wave. The interstitial cells of Cajal (ICCs) are now widely regarded as the pacemaker cells that generate the slow waves that propagate to neighboring ICCs and smooth muscle cells (SMC). Thus, a multicellular network of ICC and SMC can represent the behavior of slow waves in the stomach.

Detailed Description

Essential Anatomy

The human stomach is divided into three central regions; the rostral region is called the fundus, the caudal region is the antrum, and the region in between is known as the corpus (Mandal et al. 2016). The junction between the stomach and the small intestine is known as the pylorus (Fig. 1a). The stomach wall consists of different layers from outside to inside (Fig. 1b). The outermost layer is serosal. Two muscle layers are underneath it: a longitudinal muscle layer and a circular muscle layer. A neural layer called the myenteric plexus resides between these two muscle layers. Two main types of ICC have been identified in the stomach (Camborová et al. 2003). There is a dense cellular network of pacemaker ICC in the myenteric plexus (ICC_MY), whereas intramuscular ICCs (ICC_IM) are interspersed between muscle cells, mainly in the circular layer, from the oral end (fundus) to the anal end (antrum) of the stomach.



Modeling of Slow Waves in the Stomach, Fig. 1 (a) Anatomy of the stomach based on Mandal et al. 2016. (b) Schematic representation of different layers in the gut based on Camborová et al. 2003

Slow Waves in the Stomach

Slow waves originate from dominant pacemaker ICCs within the stomach wall along the greater curvature in the mid-corpus and spread aborally through the antrum to the pyloric sphincter. Although, the ICC_MY are widely believed to be responsible for the regular electrical slow-wave activity in the stomach (Hirst and Edwards 2001); ICC_IM may also play a role (Hirst et al. 2006). There have been substantial efforts to understand the generation and propagation of the slow-wave and the change in slow-wave characteristics in a dysfunctional stomach. Despite these efforts, the physiology behind the aberrant slow-wave in a dysfunctional stomach is not understood. There have been several efforts to simulate the slow waves in a multicellular model of the stomach. Since ICC may be responsible for the generation and propagation of slow waves, and slow-wave recordings are usually obtained from SMC, computational models of these two layers of cells can be used to analyze aspects of the functional behavior of the stomach. Modeling of single ICC and single SMC has been done by various groups (Youm et al. 2006; Corrias and Buist 2007, 2008; Faville et al. 2009; Du et al. 2010; Lees-Green et al. 2014), and this effort offers a basis for multicellular modeling of the slow-wave in the stomach.

Models of Single ICC

Several computational models for a single ICC of the GI tract (consisting of the stomach, small

intestine, and colon) have been developed. In a single cell model of an intestinal ICC, the role of several ion channels that are believed to participate in the generation and development of the slow-wave have been described (Youm et al. 2006). The model includes an inward rectifier K^+ current (I_K), an L-type Ca^{2+} current (I_{L-type}), a voltage-dependent and dihydropyridine-resistant Ca^{2+} current (I_{VDDR}), an autonomous inward current (I_{AI}), a Na^+/Ca^{2+} pump current (I_{NaCa}), a Na^+/K^+ pump current (I_{NaK}), and a plasmalemmal Ca^{2+} pump current (I_{PMCA}). Time-dependent change in the membrane potential is described by the following equation:

$$\frac{dV}{dt} = \frac{-(I_{tot} + I_{ext})}{C_m}, \quad (1)$$

where I_{ext} is the external current applied, C_m is the cell membrane capacitance, and

$$I_{tot} = I_K + I_{CaL} + I_{VDDR} + I_{AI} + I_{NaCa} + I_{NaK} + I_{PMCA}, \quad (2)$$

$$I_K = G_K \left(\frac{[K^+]_0}{5.4} \right)^{0.62} (V - E_K) n f_U, \quad (2.1)$$

$$I_{CaL} = P_{CaL} Ca_{CF} m h, \quad (2.2)$$

$$I_{VDDR} = P_{VDDR} Ca_{CF} m h, \quad (2.3)$$

$$I_{AI} = P_{AI}(Ca_{CF} + 0.36K_{CF} + 0.4Na_{CF})p(AI), \quad (2.4)$$

$$I_{NaCa} = P_{NaCa}(k_1p(E_1Na)y - k_2p(E_2Na)(1 - y)), \quad (2.5)$$

$$I_{NaK} = \frac{P_{NaK}}{1 + \left(\frac{Km_{Na}}{[Na^+]_i}\right)^{1.36}} \frac{1 - ((V + 50)/250)^2}{1 + \frac{Km_{Ko}}{[K^+]_o}}, \quad (2.6)$$

$$I_{PMCA} = \frac{P_{PMCA}}{1 + \left(\frac{Km_{Cai}}{[Ca^{2+}]_i}\right)^2}, \quad (2.7)$$

where G_X denotes conductance of ion channel X, E_X denotes reversal potential of ion channel X, $[X]_o$ denotes the extracellular concentration of ion X, $[X]_i$ denotes the intracellular concentration of ion X, f_U denotes the fraction of unblocked channels, P_X denotes conversion factor for ion channel X, X_{CF} denotes constant field equation of ion channel X, m and n denote activation gate variable, h denotes inactivation gate variable, p (X) denotes the probability of state X, and y denotes gate variable in the reduced two-state model (Powell et al. 1993). Km_{Na} , Km_{Ko} , and Km_{Cai} are empirical constants.

In this model, the L-type Ca^{2+} channel in an ICC supposedly activates in response to the depolarization of the previous ICC. However, the channel is represented by a two-state model for the single ICC. The K^+ current repolarizes the pacemaker potential, the I_{VDDR} contributes to slow-wave propagation in the GI tract, the I_{AI} works as the pacemaker current generating the spontaneous depolarization of ICC without an electrical stimulus, the Na^+/Ca^{2+} pump extrudes single calcium ion in exchange for three sodium ions, the Na^+/K^+ pump extrudes three Na^+ ions in exchange for two K^+ ions generating a net outward current. The model also includes inositol 1,4,5-trisphosphate (IP_3) production and IP_3 -mediated Ca^{2+} release activity from the endoplasmic reticulum (ER). The model produces a spontaneous slow-wave whose frequency is 20 cycles per minute (cpm), and resting potential is -78 mV, which are close

to in vitro recordings from the murine small intestine (Goto et al. 2004). However, the role of the mitochondria in the generation of the slow-wave is not taken into account despite experimental evidence of the cessation of slow waves under the presence of mitochondrial uncouplers and inhibitors of the mitochondrial Na^+/Ca^{2+} exchanger (Magnus and Keizer 1997).

Another biophysical model of the single ICC was developed by Corrias and Buist for the stomach (Corrias and Buist 2008). This model is based on the hypothesis that Ca^{2+} shuttling between mitochondria and ER is responsible for the pace-making capabilities of ICC. The model includes several ion channel currents such as the I_{VDDR} and I_{L-type} , voltage-dependent K^+ channel (encoded by the $Kv1.1$ gene) current ($I_{kv1.1}$), Ether-a-go-go (ERG) K^+ channel current (I_{ERG}), calcium-dependent K^+ current (I_{CaK}) and background K^+ current (I_{kb}), a Na^+ channel current (I_{Na}), a chloride channel current (I_{Cl}), and a nonselective cation channel current (I_{NSCC}). The change in membrane potential is given by the following equation:

$$\frac{dV}{dt} = \frac{-I_{ion}}{C_m}, \quad (3)$$

where

$$I_{ion} = I_{VDDR} + I_{L-type} + I_{kv1.1} + I_{ERG} + I_{CaK} + I_{kb} + I_{Na} + I_{Cl} + I_{NSCC}, \quad (4)$$

$$I_{VDDR} = G_{VDDR}d_{VDDR}f_{VDDR}(V - E_{Ca}), \quad (4.1)$$

$$I_{L-type} = G_{L-type}d_{L-type}f_{L-type}f_{Ca}(V - E_{Ca}), \quad (4.2)$$

$$I_{kv1.1} = G_{kv1.1}d_{kv1.1}f_{kv1.1}(V - E_K), \quad (4.3)$$

$$I_{ERG} = G_{ERG}d_{ERG}(V - E_K), \quad (4.4)$$

$$I_{CaK} = G_{CaK}P_{CaK}(V - E_K), \quad (4.5)$$

$$I_{kb} = G_{kb}(V - E_K), \quad (4.6)$$

$$I_{Na} = G_{Na}d_{Na}f_{Na}(V - E_{Na}), \quad (4.7)$$

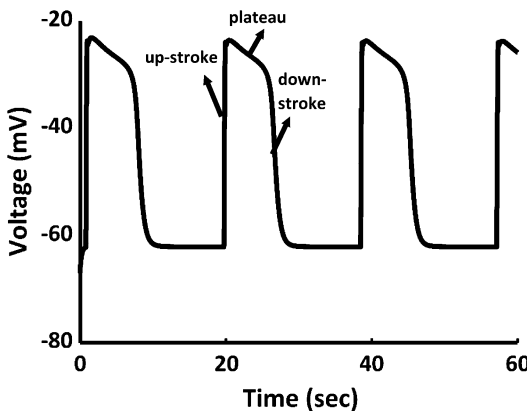
$$I_{Cl} = G_{Cl}d_{Cl}(V - E_{Cl}), \quad (4.8)$$

$$I_{NSCC} = G_{NSCC}P_{NSCC}(V - E_{NSCC}), \quad (4.9)$$

where G_X represents conductance of ion channel X, d_X and f_X represent activation and inactivation gating variables for ion channel X, f_{Ca} represents Ca^{2+} -dependent inactivation, E_X represents the Nernst potential of ion X, and P_X represents the open probability of ion channel X.

Here the nonselective cation channels (NSCC) are the primary pacemaker channels that allow ionic flux into the submembrane space between mitochondria and ER. Along with I_{NSCC} , the I_{VDDR} and I_{Na} contribute to the upstroke phase of the slow-wave. The I_{L-type} current is primarily responsible for the plateau phase of the slow-wave. The K^+ channel currents contribute to the down-stroke phase of the slow-wave. The model generates slow waves from a single ICC (Fig. 2) whose pacemaking frequency is 3.02 cpm, and resting potential is -67.6 mV, both of which are in agreement with recordings from the ICC of the guinea-pig gastric antrum in an in vitro preparation (Hirst and Edwards 2001).

Peng Du et al. (2010) modified the Corrias and Buist model for the single ICC by addition of a voltage-dependent, IP_3 -related mechanism based on previously published equations (Imtiaz et al. 2002):



Modeling of Slow Waves in the Stomach, Fig. 2 Different phases of the membrane potential of an ICC simulated using the Corrias and Buist (2008)

$$\begin{aligned} \frac{d[IP_3]}{dt} = & \beta - \eta[IP_3] - V_{m4} \frac{[IP_3]^4}{k_4^4 + [IP_3]^4} \\ & + P_{MV} \left(1 - \frac{V_m^8}{k_v^8 + V_m^8} \right), \end{aligned} \quad (5)$$

where β is an external stimulus, η is the rate constant for linear IP_3 degradation, V_{m4} is maximal value for the nonlinear IP_3 degradation, K_4 is half-saturation constant for the nonlinear IP_3 degradation, P_{MV} is maximal rate of voltage-dependent IP_3 synthesis, and K_v is half-saturation constant for voltage-dependent IP_3 synthesis. Voltage-induced IP_3 synthesis is suggested responsible for slow-wave entrainment (Du et al. 2010). The outward current flux from ER depends on IP_3 concentration, which eventually determines the shuttling interval of Ca^{2+} between ER and mitochondria, that is, the frequency of the slow-wave.

While the Corrias and Buist model for the single ICC does not produce any phase change in response to an external current stimulus, the Peng Du model responds to pulse stimuli by phase advancing the intrinsic activity of the ICC while maintaining the same intrinsic frequency. The Peng Du model is thus capable of altering the slow-wave in response to an extracellular current input. Another model of the single ICC was developed incorporating the same mechanisms for the generation of the slow-wave as in the Corrias and Buist model (Faville et al. 2009). The primary difference is that in the Faville model, multiple pacemaker units are incorporated in a single intestinal ICC, and the I_{L-type} current is omitted. The model produces slow-wave depolarizations with an amplitude of 65 mV at a frequency of 17.4 cpm, matching with in vitro recordings from the myenteric ICC of the guinea-pig small intestine (Kito and Suzuki 2003).

Still another model for small intestinal ICC features the calcium-activated chloride channel, anoctamin1 (Lees-Green et al. 2014). This model assumes a store-operated calcium (SOC) channel that responds to the depletion of calcium levels in the ER. Anoctamin1 channels co-localized with

SOC channels are activated by the local rise in Ca^{2+} in microdomains, resulting in depolarization of the ICC. Other than the calcium-activated chloride current (I_{CaCl}), the model includes a T-type Ca^{2+} current (I_{CaT}), background Na^+ current (I_{Na}), I_{Kb} , and voltage or Ca^{2+} -activated non-selective currents or Na^+ current (I_{X}). The change in membrane potential is expressed by Eq. (3), whereas

$$I_{\text{ion}} = I_{\text{SOC}} + I_{\text{CaCl}} + I_{\text{CaT}} + I_{\text{Kb}} + I_{\text{Na}} + I_{\text{X}}, \quad (6)$$

$$I_{\text{SOC}} = G_{\text{SOC}} O_{\text{SOC}} (V - E_{\text{Ca}}), \quad (6.1)$$

$$I_{\text{CaCl}} = G_{\text{CaCl}} O_{\text{CaCl}} (V - E_{\text{Cl}}), \quad (6.2)$$

$$I_{\text{Na}} = G_{\text{Na}} (V - E_{\text{Na}}). \quad (6.3)$$

Here, O_{X} represents the open probability of ion channel X, and as before, G_{X} represents conductance of ion channel X, and E_{X} represents the Nernst potential of ion X. The I_{CaT} is modeled using the I_{VDDR} model from Corrias and Buist (2008), and I_{Kb} is modeled using Eq. (4.6). The I_{CaCl} acts as the pacemaker current. Voltage or Ca^{2+} -activated nonselective channels or Na^+ channels are plausible candidates for generating the plateau current. Although the model simulates the voltage-clamp experiments done earlier (Xiao et al. 2011), and the expression for anoctamin1 has been observed experimentally (Hwang et al. 2009), the type of SOC channel that might be present in the ICC is yet unknown.

Models of Single SMC

Unlike the multiple computational models available for the single ICC, there are relatively few computational models for a single smooth muscle cell of the GI tract. One attempt was made by the same group that modeled the ICC biophysically (Corrias and Buist 2007). The model for the single SMC lacks the pacemaking mechanism like the ICC. The depolarizations are, however, due to several ion channel currents and a stimulus current supplied by the ICC network. The ion channel currents described in the model are: $I_{\text{L-type}}$, low voltage-activated calcium current (I_{LVA}), delayed

rectifier potassium channel current (I_{Kr}), A-type potassium channel current (I_{KA}), calcium-activated potassium current (I_{CaK}), I_{kb} , I_{Na} , and I_{NSCC} . The rate change in the membrane potential of SMC is given by the following equation:

$$\frac{dV}{dt} = \frac{-(I_{\text{ion}} + I_{\text{stim}})}{C_{\text{m}}}, \quad (7)$$

where I_{stim} is the incoming current from ICC, C_{m} is SMC capacitance, and

$$I_{\text{ion}} = I_{\text{L-type}} + I_{\text{LVA}} + I_{\text{Kr}} + I_{\text{KA}} + I_{\text{CaK}} + I_{\text{kb}} + I_{\text{Na}} + I_{\text{NSCC}}, \quad (8)$$

The equations for $I_{\text{L-type}}$, I_{CaK} , I_{kb} , and I_{Na} are the same as Eqs. (4.2), (4.5), (4.6), and (4.7). The equations for other ion channel currents are as follows:

$$I_{\text{LVA}} = G_{\text{LVA}} d_{\text{LVA}} f_{\text{LVA}} (V - E_{\text{Ca}}), \quad (8.1)$$

$$I_{\text{Kr}} = G_{\text{Kr}} x_{r1} x_{r2} (V - E_{\text{K}}), \quad (8.2)$$

$$I_{\text{KA}} = G_{\text{KA}} x_{A1} x_{A2} (V - E_{\text{K}}), \quad (8.3)$$

$$I_{\text{NSCC}} = G_{\text{NSCC}} m_{\text{NSCC}} r_{\text{lig}} h_{\text{Ca}} (V - E_{\text{NSCC}}). \quad (8.4)$$

As before, G_{X} represents conductance of ion channel X, d_{X} and f_{X} represent activation and inactivation gating variables for ion channel X, and E_{X} represents the Nernst potential of ion X. Other than that, x_{r1} and x_{A1} are Hodgkin-Huxley type activation gating variables for delayed rectifier and A-type potassium channels, x_{r2} and x_{A2} are Hodgkin-Huxley type inactivation gating variables for the respective potassium channels, m_{NSCC} represents the voltage dependency of the activation kinetics of the NSCC channel, r_{lig} represents the fact that NSCC channels are activated by muscarinic ligands, and h_{Ca} facilitates the effect that intracellular Ca^{2+} has on I_{NSCC} .

A phenomenological description of intracellular Ca^{2+} dynamics is included because of its primary importance in regulating several cellular

processes. In terms of shape, duration, and amplitude, the resulting simulated smooth muscle depolarizations are in good agreement with in vitro recordings from the canine antrum SMC in control and altered (while ion channels are blocked) conditions (Ward et al. 2004).

The Corrias and Buist model for the SMC was used to simulate the response of rat smooth muscle cells to electrical stimuli (Du et al. 2009). Computational models for smooth muscle cells of the small intestine (Poh et al. 2012) and colon (Yeoh et al. 2017) have also been published.

Models of a Multicellular Network of the GI Tract

There have been several approaches to model slow waves using a multicellular network of the GI tract. Some have employed continuum field models, while others have employed explicit multicellular models. A continuum nonlinear dual cable model is notable where the ICCs and SMC are spatially distributed (Buist et al. 2010). The distribution is described by the following equations:

$$\sigma_{ICC} \frac{\partial^2 V_{(ICC)}}{\partial x^2} = A_{m(ICC)} \left(C_{m(ICC)} \frac{\partial V_{(ICC)}}{\partial t} + (I_{ion(ICC)} - I_{coup}) \right), \quad (9)$$

$$\sigma_{SMC} \frac{\partial^2 V_{(SMC)}}{\partial x^2} = A_{m(SMC)} \left(C_{m(SMC)} \frac{\partial V_{(SMC)}}{\partial t} + (I_{ion(SMC)} + I_{coup}) \right), \quad (10)$$

$$I_{coup} = g_{coup} \eta_{ICC} (V_{(ICC)} - V_{(SMC)}). \quad (11)$$

Here, with the appropriate subscripts differentiating ICC and SMC parameters, V , C_m , and I_{ion} represent the definitions provided earlier in the “Models of Single ICC” section, σ is the axial conductivity, x is a spatial coordinate along the axis of the fiber, A_m is the surface-to-volume ratio, and g_{coup} is the electrical conductance between ICC and SMC.

The result was a 337 mm long cable discretized at a 1-mm resolution representing a stomach from the fundus to the antrum. A linear IP_3 concentration gradient is included in the model to yield an entrained pacing frequency of 3.1 cpm across the

length of the model which matches with the in vitro recordings from smooth muscle cells of the guinea-pig antrum (Hirst and Edwards 2001), but does not match with the in vitro recordings from smooth muscle cells of the guinea-pig corpus (Hirst et al. 2006). Additionally, the model includes a hypothesized ionic channel current formulated by directing a small percentage of the whole-cell voltage-dependent dihydropyridine-resistant current into the aggregate ICC pacemaker submembrane space in order to reproduce entrainment. The existence of this channel current has not yet been verified experimentally.

Among the multicellular models, some have been phenomenological, whereas others have been biophysical with a detailed description of ion channels and intra- and intercellular mechanisms. A phenomenological model simulates the intestinal slow-wave (Aliev et al. 2000) using a one-dimensional array of 300 coupled cells. The model conceptually distinguishes slow waves as two interconnected electrical events generated from the ICCs and a longitudinal muscle layer. The primary expression of the model comprises two first-order ordinary differential equations to describe the electrical activity in each tissue layer:

$$u_t = ku(u - a)(1 - u)v + D_{ii/l} \nabla_u^2 + \alpha D_{ii}(u_l - u_i), \quad (12)$$

$$v_t = \varepsilon(\gamma(u - \beta) - v), \quad (13)$$

where u and v stand for the transmembrane potential and slow currents, respectively, u_t and v_t are their first derivatives with respect to time, ε is proportional to the frequency of oscillations in the ICC layer, α describes the symmetry of coupling between the two layers, and D represents the coupling coefficient with subscripts i and l which stand for ICC and longitudinal muscle cell, respectively. The parameters used in these equations are adjusted to fit the model's output to experimental data (Sarna et al. 1971). This model can reproduce the basic properties of electrical activity in the intestine such as the spatial variation of the frequency of oscillation along the gut (19.7 cpm proximally and 17.8 cpm distally), synchronization across short distances and

desynchronization across long distances, and a reduction in propagation length and time toward the distal part. However, the frequency becomes irregular toward the distal part and the membrane potential shapes are deformed compared to those measured in the canine intestine in vitro (Sarna et al. 1971).

An electrical phenomenological description of the generation and propagation of slow waves was provided for the guinea-pig gastric antrum (Edwards and Hirst 2006). In this electrical model, three distinct sets of electrical cables (each consisting of series circuits of resistances and source potentials) are linked. One cable is made of chains of longitudinal muscle compartments; a second is made of a chain of ICC_MY, with the third being a chain containing a mixture of circular smooth muscle cells and ICC_IM orientated at right angles to the longitudinal muscle chain. ICC_MY are connected to both muscle layers resistively. Each tissue layer represents a length of 2 mm as a series connection of 20 iso-potential compartments, each 100 μ m long. The values of the communicating conductance between the three compartments were taken from in vitro experiments in the guinea-pig gastric antrum (Cousins et al. 2003). The model reproduces the longitudinal and circumferential propagation of the slow-wave in an in vitro preparation of the guinea-pig gastric antrum. However, the predictive power of the model is limited by the accuracy of the kinetic models used for the primary and plateau components of the pacemaker potential in the myenteric ICC network and the regenerative potential in circular muscle compartments.

Some groups have tried to incorporate a biophysical approach to represent the slow-wave in the stomach. A multicompartment model of the colon comprised of ICCs, SMC, and enteric neurons is one such effort (Barth et al. 2017). The model was designed to recreate peristalsis, where enteric neurons (a network of sensory neurons, motor neurons, and interneurons) integrate sensory feedback to control smooth muscle contraction. Enteric neurons are modeled biophysically as Connor-Stevens neurons where the neurons have a leak channel current (I_{leak}), voltage-gated

sodium current, potassium current, and a transient potassium current (Connor and Stevens 1971). ICCs are modeled phenomenologically as resistive cables (Edwards and Hirst 2006), and smooth muscle cells are defined by a conductance model with ionic membrane currents (I_{leak} , I_K , and I_{CaL}) and synaptic currents. Synaptic currents include excitatory junction potentials (I_{EJP}), inhibitory junction potentials (I_{IJP}), and gap junctions (I_{gap}). The smooth muscle cells in this model are connected to ICCs by gap junctions and motor neurons by neuromuscular junctions. Sensory neurons are connected to local ascending and descending interneurons by excitatory synapses. Ascending interneurons innervate neighboring excitatory circular motor neurons orally, and descending interneurons innervate neighboring inhibitory circular motor neurons anally. The group also assessed rat colon transit time experimentally, and compared the results to the ones from their in silico model. Although the model provides a reasonable estimate of the colonic transit time, its applicability is limited due to its non-biophysical approach of modeling pacemaker cells.

In Peng Du's multicellular model of the stomach (Du et al. 2010), simulations have been conducted over a linear one-dimensional chain of ICCs arranged as a single geometric element of length 2 mm, at 0.2-mm spatial discretization. The equations used in this model to simulate propagation of slow-wave are as following:

$$\nabla \times ((\sigma_i + \sigma_e)\nabla\varphi_e) = -\nabla \times (\sigma_i\nabla V), \quad (14)$$

$$\begin{aligned} &\nabla \times (\sigma_i\nabla V) + \nabla \times (\sigma_i\nabla\varphi_e) \\ &= A_m \left(C_m \frac{\partial V}{\partial t} + I_{ion} \right), \end{aligned} \quad (15)$$

where V and C_m represent the meanings provided earlier, I_{ion} is the same as I_{tot} in Eq. (2), φ_e represents the extracellular potential, and the σ terms represent tissue conductivity tensors, where the subscripts i and e represent the intracellular and extracellular domains, respectively. Although the equations are for a continuum field model, since the model represents a specific number of cells in

a specified space, essentially the equations represent a multicellular model.

A linear gradient of intrinsic frequencies is assigned to the one-dimensional model by varying the chemical stimulus agent parameter linearly over the chain length to obtain an intrinsic frequency gradient between 3.0 and 2.8 cpm. The model has not been extended to intrinsic frequencies higher or lower than the specified range. A 1-D model of 60 mm in length with 1 mm spatial resolution is described in a subsequent manuscript where an intrinsic frequency range of 4.9–4.0 cpm is produced by changing linear degradation of the IP_3 parameter (Du et al. 2014). In another version, a scaling factor is used to reproduce intestinal slow-wave frequencies as high as 15 cpm (Du et al. 2017).

Unlike other models, a model of slow-wave in the guinea-pig gastric pylorus (van Helden and Imtiaz 2003) includes cells not only electrically interconnected by gap junctions but also chemically. The model includes a one-dimensional array of representative pacemaker cells, with each cell considered to have a length of 100 μ m. Along with the electrical current across the resistive gap junctions, Ca^{2+} and IP_3 are considered to traverse between the pacemaker cells. The model assumes the same voltage-dependent IP_3 synthesis mechanism like Peng Du, but unlike Peng Du, the ionic channels in the pacemaker cells are lumped into a Ca^{2+} channel and a leak current channel. The model produces an accurate representation of the emergence of the slow-wave, although the frequency of the simulated slow-wave is not measurable due to a lack of proper scaling.

There has been substantial progress in mathematical modeling of the slow-wave in the stomach. Phenomenological and biophysical both kinds of models simulate a functional stomach's behavior within a limited capacity. However, a comprehensive model would help us understand the stomach in its functional as well as diseased states, in particular the pathologies related to gastric motility such as tachygastritis and delay in gastric emptying or gastroparesis. A comprehensive model would include detailed intracellular mechanisms, intercellular connection

mechanisms through gap junctions, a long enough representation of the stomach, and a comparison of the model simulation results with previously published experimental recordings from different locations of the stomach. A 2-D, perhaps a 3-D network model of the stomach, may realize all these requirements and improve our understanding of the GI tract. This enhanced understanding will enable us to determine the physiological reasons that may underlie aberrant slow waves and their effect on pathological conditions such as functional uncoupling in the stomach prevalent in diabetes mellitus (Jebbink et al. 1994) and other GI diseases such as functional dyspepsia (Lin and Chen 2001).

Cross-References

- Calcium Release, Models of
- Gap Junctions, Neural Population Models and
- Goldman-Hodgkin-Katz Equations
- Low-Voltage-Activated Calcium Channels
- Modeling Ion Concentrations
- Pre-Botzinger Complex Rhythm Generation

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Modeling Synapses

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Definition

Modeling a synapse usually entails a mathematical description of the transformation of a presynaptic action potential into a postsynaptic response, such as an ionic current. The mathematical description is often phenomenological, treating the synapse as a black box that takes the presynaptic action potential as input, and produces as output a change in the postsynaptic membrane; no explicit modeling of the cascade of biophysical events underlying synaptic transmission is implemented. However, that said, modeling a synapse can also entail a more biophysical than phenomenological approach, describing one or more of the biophysical events underlying synaptic transmission. Such biophysical models might describe, for example, the gating of presynaptic voltage-sensitive Ca^{2+} channels, the diffusion of Ca^{2+} within the presynaptic terminal, the binding of Ca^{2+} to buffers and Ca^{2+} sensors such as synaptotagmin, the binding and fusion of synaptic vesicles at an active zone, the diffusion of neurotransmitter across the synaptic cleft, the gating of postsynaptic neurotransmitter receptors, or the movement of neurotransmitter receptors within the postsynaptic membrane. In some instances, modeling a synapse might entail a mathematical description of an electrical synapse (i.e., a gap junction) between the presynaptic and postsynaptic membrane, rather than the more common chemical synapse which uses neurotransmitter to propagate and transform the presynaptic electrical signal.

Detailed Description

Background

Synapses (Bennett 1999; Palay 1956) are specialized connections that allow signals from a presynaptic membrane to be transmitted to a postsynaptic

membrane. The presynaptic signal is usually an action potential, but can be a simple depolarization away from the resting membrane potential, for example, in some somatic sensory neurons. The postsynaptic response is usually an excitatory postsynaptic current (EPSC) or inhibitory postsynaptic current (IPSC), but can also be a nonelectrical response such as the phosphorylation of proteins. Most synapses occur between neurons but can also occur between neurons and muscle cells, also known as the neuromuscular junction.

Synapses are categorized into two main types: electrical and chemical. Electrical synapses create a direct electrical connection between the presynaptic and postsynaptic membrane via interlinking ion channels (connexins) spanning both membranes. Because of the direct connection, electrical synapses are fast and pass signals bidirectionally. Electrical synapses are also known as gap junctions.

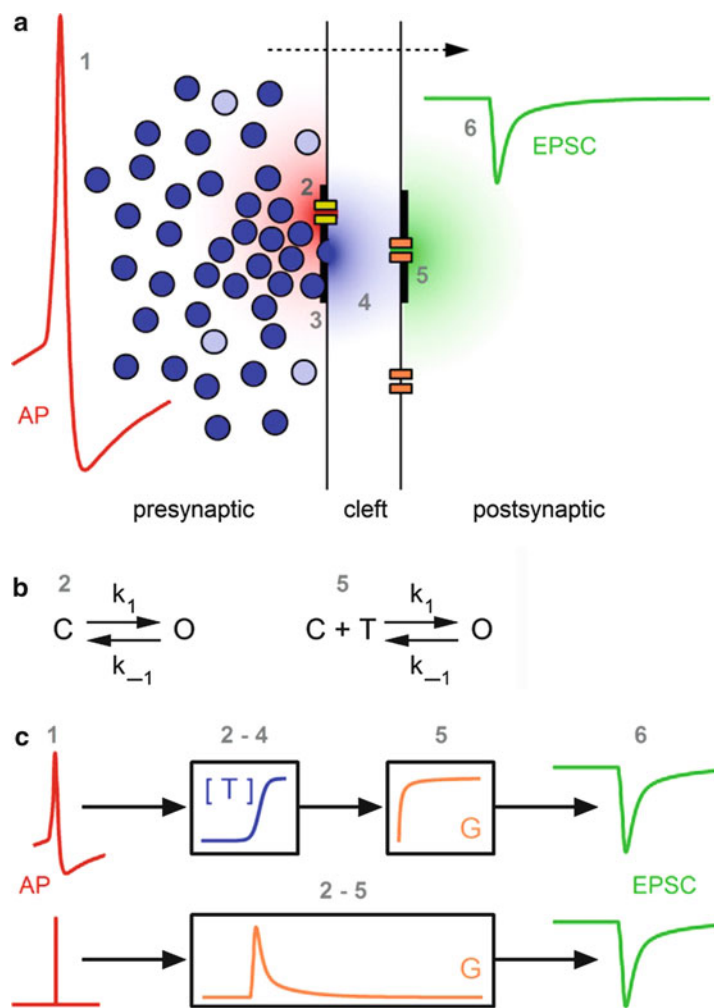
Chemical synapses, in contrast, do not create a direct electrical connection between the presynaptic and postsynaptic membrane, but rather use neurotransmitter as a secondary messenger to convey the presynaptic signal. The introduction of a secondary messenger allows a wealth of computational power not readily achieved by a simple electrical synapse, such as various forms of gain control, plasticity, and inhibitory shunting (Abbott and Regehr 2004; Silver 2010). This higher computational power of chemical synapses is reflected in a large diversity of molecular components, including a range of neurotransmitters (glutamate, glycine, GABA, acetylcholine, dopamine, serotonin, etc.), postsynaptic receptors (ionotropic and metabotropic receptors), as well as presynaptic receptors. There is also a large diversity in the structural aspects of chemical synapses, including the number of presynaptic vesicles (the quantal units that store and deliver neurotransmitter), the number and size of active zones and postsynaptic densities, and the number and location of postsynaptic receptors. The structural arrangement of nearby glia can also influence the computational power of chemical synapses by regulating the concentration of extracellular neurotransmitter (Haydon 2001).

Much of what we know about chemical synapses dates back to 1951, when Fatt and Katz (1951) made the first intracellular recordings of the postsynaptic response at the neuromuscular junction. From these intracellular recordings, Fatt and Katz were able to infer how acetylcholine reacts with its receptor to give rise to the postsynaptic end-plate potential. From then on the technique of intracellular recording moved on to synapses of the central nervous system, and some 50 years later our level of understanding of synaptic transmission has greatly unfolded. Today, we know the basics of chemical synaptic transmission can be summarized in the following cascade of events (see Fig. 1a):

- Step 1: An action potential invades the presynaptic terminal and depolarizes the membrane.
- Step 2: The brief depolarization causes voltage-dependent Ca^{2+} channels to open, leading to a transient increase in the intracellular Ca^{2+} concentration, $[\text{Ca}]_i$.
- Step 3: The increase in $[\text{Ca}]_i$ leads to an increase in probability of one or more synaptic vesicles fusing with the presynaptic membrane, thereby releasing neurotransmitter into the synaptic cleft.
- Step 4: The neurotransmitter diffuses across the synaptic cleft.
- Step 5: The neurotransmitter binds to postsynaptic receptors, causing a conformational change in the receptors.
- Step 6: For ionotropic receptors, the conformational change leads to the opening of their internal ion channel, thereby allowing ionic current to flow, producing an EPSC or IPSC. For metabotropic receptors, the conformational change leads to a chain of intracellular reactions that produce some desired end effect, like phosphorylation of an enzyme or upregulation of a particular receptor subunit.

Modeling any one of the steps 1–6 can be challenging. Hodgkin–Huxley-type models

(Hodgkin and Huxley 1952) of the presynaptic membrane (step 1) or the postsynaptic membrane (step 6) can include several types of ionic conductances, including Na^+ , K^+ , Cl^- , and Ca^{2+} , all of which can vary in density and kinetics between different types of neurons. Markov models of Ca^{2+} channel gating (step 2) or neurotransmitter receptor binding (step 5) can entail complicated pathways between open, closed, blocked, and/or desensitized states, with numerous kinetic parameters (Destexhe et al. 1998). Monte Carlo models of Ca^{2+} diffusion in the presynaptic terminal (step 2) or the postsynaptic dendrite or soma (step 5) usually include several types of Ca^{2+} buffers, each having their own diffusion coefficient and binding/unbinding kinetic reaction. As research progresses, these models are often modified to include more and more biophysical realism with increasing complexity. However, with the increased complexity comes an increase in computational costs. For large-scale neural networks, the increased costs can make simulations intractable. Hence, for neural network simulations simple phenomenological models are usually the rule. These phenomenological models might include one or more kinetic reactions that have only two states, for example, a closed and open receptor channels (Fig. 1b) and/or black boxes that lump together two or more of the steps 1–6, where the input–output relationship of each box is described by a simple mathematical equation (Fig. 1c, top). By far the most computationally efficient approach is to lump steps 2–5 into one black box (Fig. 1c, bottom). This approach coincides with a growing wealth of experimental data obtained from voltage-clamp experiments where a presynaptic action potential is triggered by a stimulating electrode (step 1) while the resulting postsynaptic current (step 6) is simultaneously recorded using an intracellular patch pipette. With little effort such experimental data can be manipulated to provide a transform function for the black box shown at the bottom of Fig. 1c. It is this latter approach that is described here. Except for the final section on electrical synapses, the description focuses entirely on chemical synapses; in these sections “synapse” therefore refers to a chemical synapse.



Modeling Synapses, Fig. 1 Modeling synaptic transmission. (a) Cartoon of a chemical synapse between two neurons showing a presynaptic action potential (AP), vesicles filled with neurotransmitter (dark blue circles), empty vesicles (light blue circles), an active zone (thick black line, left) containing vesicle release sites and voltage-activated Ca²⁺ channels (yellow), a postsynaptic density (thick black line, right) containing neurotransmitter receptors (orange), and an excitatory postsynaptic current (EPSC). Gray numbers denote the six basic steps described in the text. (b) Simple kinetic scheme representing the gating of a presynaptic voltage-activated Ca²⁺ channel with forward and

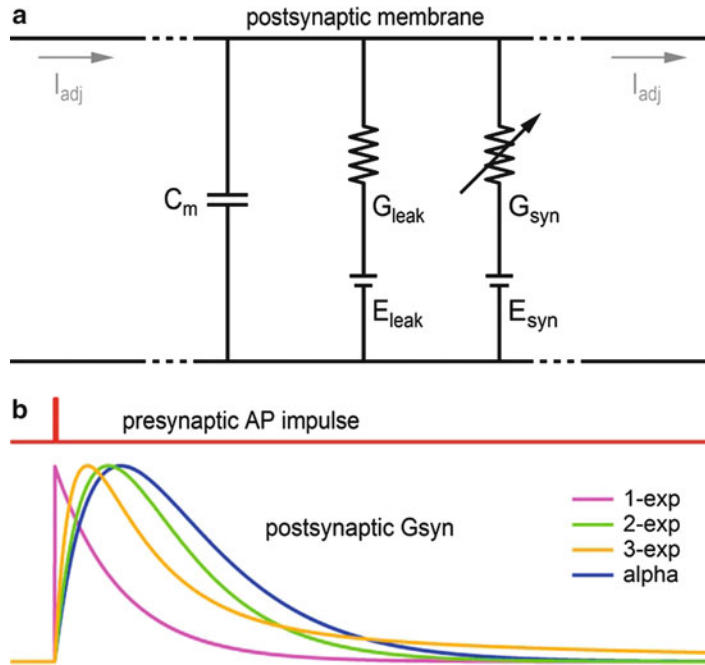
backward rate constants k_1 and k_{-1} (left). The channel is either closed (C) or open (O). A similar kinetic scheme (right) represents the gating of a postsynaptic receptor binding neurotransmitter (T). (c) Black boxes depicting the signal transformation between the presynaptic action potential and EPSC. In one approach, two transfer functions are used in sequence (top). The simplest approach, however, is to use a single transfer function that takes the time of the presynaptic action potential as its input and produces an EPSC in response (bottom); this is the approach described in the text

Modeling Synaptic Currents/Conductances

A synapse is usually simulated within a single postsynaptic compartment on a dendritic tree or the cell body using a simple electrical circuit as

shown in Fig. 2a. In this circuit, the voltage across the membrane (V_m) can be described by the following differential equation:

$$C_m \cdot dV_m/dt = -G_{leak}(V_m - E_{leak}) + \Sigma I_{adj} + \Sigma I_{syn} \tag{1}$$



Modeling Synapses, Fig. 2 Modeling a postsynaptic conductance. **(a)** Simple electric circuit diagram of a neuron's membrane containing a variable postsynaptic conductance (G_{syn}) with reversal potential E_{syn} , a constant leak conductance (G_{leak}) with reversal potential E_{leak} , and a capacitor (C_m). The circuit includes optional currents from adjacent compartments (I_{adj}). The membrane potential (V_m) is measured across C_m . **(b)** Functions often used to describe the time course of G_{syn} (bottom; see $a(t)$ in Eq. 3) include the single-exponential (1-exp, Eq. 4; $\tau_d = 0.3$ ms),

double-exponential (2-exp, Eq. 5; $\tau_r = 0.2$ ms, $\tau_d = 0.3$ ms), multi-exponential (3-exp, Eq. 6; $n = 2$, $\tau_r = 0.2$ ms, $a_1 = 0.9$, $\tau_{d1} = 0.3$ ms, $a_2 = 0.1$, $\tau_{d2} = 2.0$ ms), and the alpha functions (Eq. 7; $\tau_\alpha = 0.3$ ms). Peak amplitudes were normalized to 1. *Top red trace* shows the arrival time of the presynaptic action potential. There was no delay between the action potential and the generation of G_{syn} , but a delay is sometimes added when modeling synapses

where t is time, C_m is the membrane capacitance, I_{adj} is the flow of current from adjacent electrical compartments, and I_{syn} is the synaptic current, the current of interest for modeling synapses. The circuit could also contain voltage-dependent ion currents, such as Na^+ , K^+ , and Ca^{2+} currents, but for simplicity we assume here a purely passive postsynaptic membrane, in which case the resting membrane potential and resistance are primarily determined by the leak reversal potential (E_{leak}) and conductance (G_{leak}).

In Eq. 1, I_{syn} , the postsynaptic current of interest, is generated at the time of a presynaptic action potential and usually takes the form of the following equation:

$$I_{\text{syn}} = G_{\text{syn}}(t, V_m) \cdot (V_m - E_{\text{syn}}) \quad (2)$$

Here, E_{syn} is the reversal potential of the synaptic conductance and determines whether the synapse tends to depolarize the membrane toward the threshold of action potential generation (e.g., when $E_{\text{syn}} = 0$ mV), in which case the synapse is excitatory, or tends to hyperpolarize the membrane away from the threshold of action potential generation (e.g., when $E_{\text{syn}} = -75$ mV), in which case the synapse is inhibitory. G_{syn} is usually zero under resting conditions, but then becomes positive on arrival of a presynaptic action potential. The amplitude of this positive deflection will be a function of time, but can also be a function of V_m . In most synaptic models, the time and voltage dependencies are usually separated into multiple components, such as in the following expression:

$$G_{\text{syn}} = (t, V_m) = G_{\text{max}} \cdot a(t) \cdot b(V_m) \quad (3)$$

where G_{max} determines the maximum conductance, $a(t)$ determines the rise and decay time course, and $b(V_m)$ determines the amount of voltage-dependent nonlinearity of G_{syn} . Both $a(t)$ and $b(V_m)$ are normalized between 0 and 1 so as to allow G_{max} to determine the maximum value of G_{syn} . If the synaptic conductance is tonically active, then $a(t)$ can be omitted from Eq. 3, or if the synaptic conductance is linear with respect to voltage, then $b(V_m)$ can be omitted. Equation 3 can also be expanded to include time-dependent scale factors for synaptic depression and facilitation described further below.

In Eq. 3, the time course of G_{syn} is determined by $a(t)$. Common expressions for $a(t)$ are 1- and 2-exponential functions such as the following (see Fig. 2b):

$$a(t) = \exp(-(t - t_s)/\tau_d) \quad t \geq t_s \quad (4)$$

$$a(t) = [\exp(-(t - t_s)/\tau_d) - \exp(-(t - t_s)/\tau_r)] / a_{\text{norm}} t \geq t_s \quad (5)$$

where t_s is the time of the presynaptic action potential (with perhaps an added delay to simulate the delay between presynaptic action potential and EPSC), τ_r and τ_d are the rise and decay time constants, $a(t) = 0$ for $t < t_s$, and a_{norm} is a normalization factor that ensures the peak amplitude of $a(t)$ equals 1. The advantage of the 1-exponential function is that it contains only 2 free parameters. The disadvantage is that it ignores the finite rise time of the synaptic conductance, rising instantaneously from 0 to 1 at $t = t_s$. Hence, the 2-exponential function is technically better since it contains a finite rise time. Because the decay of synaptic conductances often contains multiple time constants, such as the NMDA (N-methyl-D-aspartic acid) receptor conductance, Eqs. 4 and 5 are sometimes extended to include multiple decay components, possibly using a notation for the time constants such as τ_{d1} , τ_{d2} , τ_{d3} , etc. Still, Eqs. 4 and 5 may be inadequate in describing a synaptic conductance that exhibits sigmoidal activation, such as the fast AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor conductance. In this case, the following multi-exponential function is sometimes used (Bekkers and Stevens 1996):

$$a(t) = [1 - \exp(-(t - t_s)/\tau_r)]^n \cdot [a_1 \cdot \exp(-(t - t_s)/\tau_{d1}) + a_2 \cdot \exp(-(t - t_s)/\tau_{d2}) + \dots] / a_{\text{norm}} \quad t \geq t_s \quad (6)$$

In this equation, the first term in square brackets determines the rise time course; if the power $n > 1$, then the rise time course exhibits sigmoidal activation. The second term in square brackets determines the exponential decay and can contain one or more time constants as is necessary. Again, a_{norm} is a normalization factor that ensures the peak amplitude of $a(t)$ equals 1 and can be computed numerically by computing the product of the expressions in square brackets at high temporal resolution and setting a_{norm} equal to the peak of the resulting waveform. The disadvantage of Eq. 6 is that it is more computationally expensive than Eqs. 4 and 5, which could have a significant impact on the simulation time,

especially when simulating neural networks. Tricks exist, however, to avoid such computational costs, such as using lookup tables. Yet another popular expression for $a(t)$ is the following equation, also known as the alpha function:

$$a(t) = [(t - t_s)/\tau_\alpha] \cdot \exp(1 - (t - t_s)/\tau_\alpha) \quad t \geq t_s \quad (7)$$

where τ_α sets the time of the waveform's peak. While this function is computationally inexpensive to use, since it contains only 2 free parameters, its rise time is constrained to equal its decay time, since $\tau_r = \tau_d = \tau_\alpha$. Hence, the alpha function

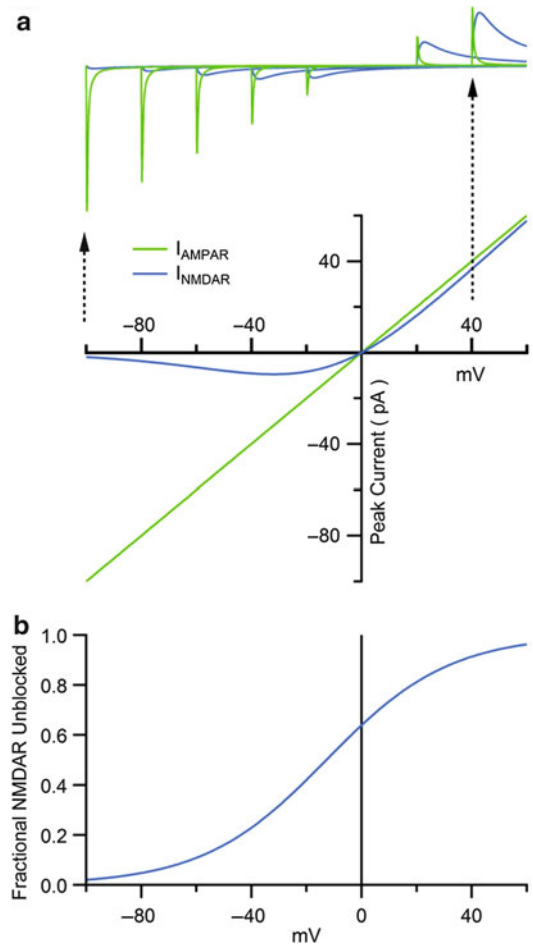
adequately describes only those synaptic conductances where $\tau_r \approx \tau_d$.

Excitatory AMPA and NMDA Receptor Currents

The vast majority of excitatory synapses in the brain use glutamate as their transmitter. At these synapses, glutamate is released from the presynaptic membrane into the synaptic cleft. The released glutamate then diffuses across the synaptic cleft and binds to postsynaptic transmembrane receptors which can be either metabotropic (e.g., mGluRs) or ionotropic. The ionotropic receptors are responsible for generating all or most of the EPSC and are therefore the basis of many synaptic models. The most common of these ionotropic receptors are the AMPA receptors (AMPARs), which mediate the fast component of the EPSC, and the NMDA receptors (NMDARs), which mediate a slower component of the EPSC and can also mediate synaptic plasticity as NMDARs pass Ca^{2+} ions. While a biophysical description of AMPARs and NMDARs can be quite challenging, as these receptors exist in multiple states, including open, closed, desensitized, and blocked states, simple phenomenological models have been quite successful in describing the macroscopic current that passes through these receptors. The voltage dependence of the AMPAR current (I_{AMPAR}), for example, can be adequately described by the following simple ohmic relation derived from Eqs. 2 and 3 (see Fig. 3a, red):

$$I_{\text{AMPAR}} = G_{\text{AMPAR}} \cdot a(t) \cdot (V_m - E_{\text{AMPAR}}) \quad (8)$$

where G_{AMPAR} is the peak AMPAR conductance and E_{AMPAR} is the AMPAR current's reversal potential, typically 0 mV. Because the voltage dependence of I_{AMPAR} is primarily linear, $b(V_m)$ is normally omitted from Eq. 8. Depending on the size of the synaptic connection, which may include more than one active zone, the value of G_{AMPAR} can vary widely, from a few pico-siemens at small bouton synapses to tens of



Modeling Synapses, Fig. 3 Modeling AMPAR and NMDAR currents. (a) Current versus voltage (IV) relation (bottom) of the peak I_{AMPAR} and I_{NMDAR} . Traces at top show overlaid examples of simulated I_{AMPAR} and I_{NMDAR} computed via Eqs. 8 and 9 for holding potentials -100 to $+60$ mV, shifted in time to match the voltage scale of the IV relation (arrows). (b) Boltzmann function describing Mg^{2+} unblock of the NMDAR as a function of voltage (Eq. 10; $V_{0.5} = -12.8$ mV, $k = 22.4$ mV) used to compute I_{NMDAR} in (a)

nano-siemens at large calyx-type synapses. The value of G_{AMPAR} will also vary with temperature. Expressions used to describe $a(t)$ include those defined in Eqs. 4, 5, 6, and 7. Sometimes there are additional slow components of $a(t)$ due to extrasynaptic receptors.

Similar to I_{AMPAR} , the voltage dependence of the NMDAR current (I_{NMDAR}) can be adequately described by the simple current-voltage relation defined by Eqs. 2 and 3. However, because

I_{NMDAR} shows a strong nonlinearity with respect to voltage due to Mg^{2+} block of the NMDAR (see Fig. 3a, blue), I_{NMDAR} as a rule is modeled with the nonlinearity parameter $b(V_m)$ included:

$$I_{\text{NMDAR}} = G_{\text{NMDAR}} \cdot a(t) \cdot b(V_m) \cdot (V_m - E_{\text{NMDAR}}) \quad (9)$$

Like E_{AMPA} , E_{NMDAR} is usually 0 mV, and the value of G_{NMDAR} can vary widely. Again, expressions used to describe $a(t)$ include those defined in Eqs. 4, 5, 6, and 7.

The most commonly used expression for $b(V_m)$, which simulates the Mg^{2+} block of the NMDAR, is a simple Boltzmann function (Dubois et al. 2009) of the following form (Fig. 3b):

$$b(V_m) = 1/[1 + \exp(-(V_m - V_{0.5})/k)] \quad (10)$$

where $V_{0.5}$ sets the potential at which half of the NMDAR channels are blocked and k sets the steepness of the voltage dependence. Because $b(V_m)$ moves from values near 0 at hyperpolarized potentials to values near 1 at depolarized potentials, $b(V_m)$ describes the fraction of NMDARs that are *unblocked* rather than blocked. Another common expression of $b(V_m)$ is what is known as the Woodhull formalism (Woodhull 1973) which uses a kinetic model to describe the blocking action of an ion species from either inside or outside an ion channel (a 2-state model) or from both sides of the ion channel (a 3-state model). A 2-state model of Mg^{2+} blocking from the external side of the NMDAR channel, for example, can be described by the following equation:

$$b(V_m) = \frac{k_{-1}}{(k_{-1} + k_1)} = 1/(1 + k_1/k_{-1}) \quad (11)$$

where the Mg^{2+} binding rate $k_1 = [\text{Mg}^{2+}]_o K_1 \exp(-\delta_o \phi V_m/2)$, the unbinding rate $k_{-1} = K_{-1} \exp(-\delta_o \phi V_m/2)$, $[\text{Mg}^{2+}]_o$ is the external Mg^{2+} concentration, δ_o is the fraction of V_m that Mg^{2+} experiences at the blocking site, $\phi = zF/RT$, and z , F , R , and T have their usual meaning.

Substituting and rearranging terms, Eq. 11 reduces to the following equation:

$$b(V_m) = 1/(1 + [\text{Mg}^{2+}]_o/K_D) \quad (12)$$

where $K_D = K_{D0} \cdot \exp(\delta_o \phi V_m)$ and $K_{D0} = K_{-1}/K_1$. Equation 12 has two free variables, K_{D0} and δ_o , and is mathematically equivalent to the Boltzmann function in Eq. 10. The advantage of using Eq. 12 over Eq. 10 is that parameters K_{D0} and δ_o have a more physiological meaning than $V_{0.5}$ and k : K_{D0} is the Mg^{2+} dissociation constant at 0 mV and δ_o predicts the location of the Mg^{2+} binding site from the extracellular face of the NMDAR channel. A more complicated 3-state model can also be used to describe Mg^{2+} block of the NMDAR. For example, a 3-state model that includes Mg^{2+} permeation through the NMDAR channel has been used to simulate the incomplete Mg^{2+} block of the NMDAR in cerebellar granule cells (Schwartz et al. 2012). This particular 3-state model is described by the following equation:

$$b(V_m) = (k_{-1} + k_2)/(k_{-1} + k_1 + k_2) \quad (13)$$

where k_1 and k_{-1} are defined above, the rate of Mg^{2+} permeation $k_2 = K_2 \exp(-\delta_i \phi V_m/2)$, and δ_i predicts the location of the Mg^{2+} binding site from the intracellular face of the NMDAR channel. In the original Woodhull formalism, it was assumed $\delta_i = 1 - \delta_o$ (Woodhull 1973). Besides the experimental evidence that indicates Mg^{2+} permeates through the NMDAR channel, there is experimental evidence of two Mg^{2+} binding sites within the NMDAR channel, one that binds external Mg^{2+} and one that binds internal Mg^{2+} (Johnson and Ascher 1990). Hence, a 3-state model such as that described by Eq. 13, or the original 3-state Woodhull formalism that includes four rate constants, k_1 , k_{-1} , k_2 , and k_{-2} , may be necessary to adequately describe I_{NMDAR} .

Because Ca^{2+} is known to play an important role in intracellular signalling, including long-term modifications of synaptic strength, it is sometimes necessary to include Ca^{2+} dynamics in a synaptic model. For the I_{NMDAR} model described above, this is somewhat problematic

since it lumps together its underlying Ca^{2+} current with its other cationic currents, K^+ and Na^+ . This might also be true of the I_{AMPA} model since some AMPARs (those lacking a GluR2 subunit) pass Ca^{2+} ions. One of the simpler solutions to this problem is to simultaneously compute a Ca^{2+} current (I_{Ca}) that corresponds to I_{NMDAR} or I_{AMPA} , using the same parameters for $a(t)$ and $b(V_m)$. I_{Ca} for the NMDAR, for example, can be defined as follows:

$$I_{\text{Ca_NMDAR}} = G_{\text{Ca}} \cdot a(t) \cdot b(V_m) \cdot (V_m - E_{\text{Ca}}) \quad (14)$$

To use this equation, one needs to know the peak Ca^{2+} conductance (G_{Ca}) passing through the NMDARs. The value of the Ca^{2+} reversal potential (E_{Ca}) is often set to ~ 150 mV or might be described by the Goldman–Hodgkin–Katz equation (Hille 1992). Note that $I_{\text{Ca_NMDAR}}$ is not added to the electrical circuit defined by Eq. 1 since this current is already included in the circuit, via I_{NMDAR} . $I_{\text{Ca_NMDAR}}$ is only added to the part of the synaptic model that simulates $[\text{Ca}^{2+}]_i$ dynamics, which might also include contributions from voltage-dependent Ca^{2+} channels, Ca^{2+} buffers, Ca^{2+} stores, and Ca^{2+} pumps (DeSchutter and Smolen 1998; Sterratt et al. 2011).

Inhibitory GABA Receptor Currents

Most inhibitory synapses in the brain use either GABA (gamma-aminobutyric acid) or glycine as their neurotransmitter, and some use GABA and glycine together (Bowery and Smart 2006). Inhibitory synapses that use GABA make up a significant fraction of all synapses in the brain. At these synapses, GABA is released from the presynaptic membrane into the synaptic cleft. The released GABA then diffuses across the synaptic cleft and binds to postsynaptic transmembrane receptors which can be either metabotropic or ionotropic. The ionotropic receptors, also known as GABA_A receptors, are responsible for generating all or most of the IPSC and are therefore the basis of most

GABAergic synaptic models. For GABA_A receptors, binding of GABA triggers opening of their Cl^- -selective pore. The increased Cl^- conductance drives the local membrane potential toward the reversal potential of Cl^- , about -65 to -80 mV, thereby inhibiting the generation of action potentials.

The synaptic current generated by GABA_A receptors (I_{GABAR}) is classified as being either phasic or tonic. Phasic I_{GABAR} has a comparatively fast time course, with no residual component, and is mediated by receptors situated within or near the postsynaptic density (i.e., intrasynaptic receptors). Tonic I_{GABAR} , on the other hand, is a persistent current mediated by receptors outside the synapse (i.e., extrasynaptic receptors). Tonic I_{GABAR} is thought to be important for shunting inhibition and gain control of neuronal excitability (Farrant and Nusser 2005).

A typical model of phasic I_{GABAR} is as follows:

$$I_{\text{GABAR}} = G_{\text{GABAR}} \cdot a(t) \cdot (V_m - E_{\text{GABAR}}) \quad (15)$$

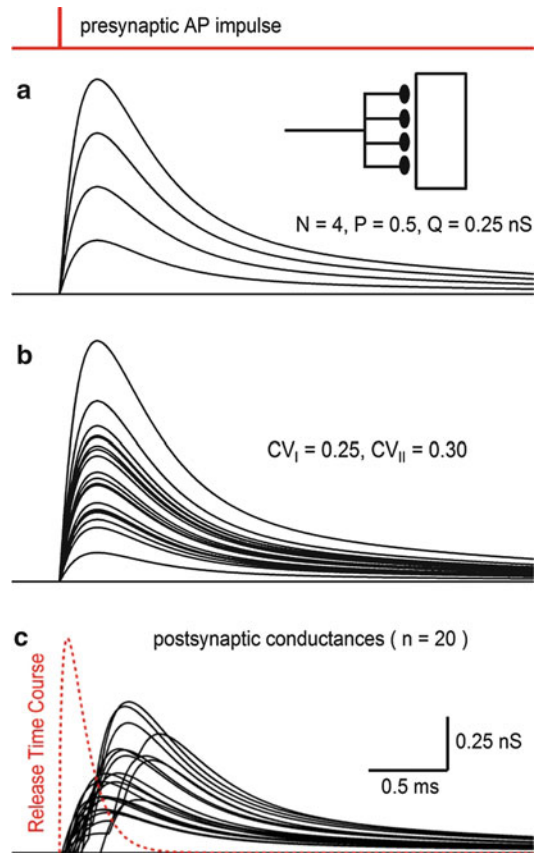
where G_{GABAR} is the peak GABAR conductance, E_{GABAR} is the Cl^- reversal potential, and $a(t)$ can be described by one of the Eqs. 4, 5, 6, and 7. Equation 15 can also be used to describe tonic I_{GABAR} by simply removing $a(t)$ from the expression.

Stochasticity

Up until now the description of synaptic models has been completely deterministic: on arrival of a presynaptic action potential, the model's postsynaptic response is identical in size and shape under basal conditions. However, it has long been known that real synapses show trial-to-trial variability due to the stochastic nature at every level of the synaptic signal cascade outlined in steps 1–6 above. For central synapses, the variability can be significant, in which case the addition of stochasticity to a synaptic model may be necessary.

A main source of synaptic variability arises from the stochastic nature of vesicle release. The

analysis of such variability at the neuromuscular junction led to the quantum hypothesis by Katz and colleagues (Katz 1969) which states that presynaptic action potentials are transmitted by the release of discrete packets of neurotransmitter, or quanta, into the synaptic cleft; moreover, the release of the quanta is not 100% reliable but probabilistic. For central synapses, a binomial model is often used to simulate stochastic quantal release, the simplest model being one that assumes a uniform quantal release probability (P) and uniform postsynaptic quantal response (Q) across a fixed number of quantal release sites (N_T). In this case, the success of quantal release (i.e., vesicular release) at a given release site is computed by drawing a random number u from the interval $[0, 1]$. If $u < P$, then quantal release is a success at that site and a postsynaptic response with amplitude Q is generated. Summing all successes across the N_T release sites results in the final postsynaptic response of the synapse. Figure 4a shows an example of such a simple binomial model, where $N_T = 4$, $P = 0.5$ and $Q = 0.25$ nS. Here, 20 repetitions resulted in a series of postsynaptic conductances (G_{syn} ; Eq. 3) with five discrete amplitudes (G_{max}) between 0 and 1 nS, due to the five possible combinations of Q , including 0 for the case of failures at all release sites. A more complicated binomial model of quantal release might assume a nonuniform Q at individual release sites (i.e., intrasite variability) and a nonuniform Q between release sites (i.e., intersite variability) (Silver 2003). Figure 4b shows an example of such a model, where both types of nonuniform Q were generated from two different Gaussian distributions. Here, 20 repetitions resulted in a series of postsynaptic conductances each with a unique amplitude between 0 and 1.1 nS. An even more complicated binomial model of quantal release might include variability in the vesicle release time course by adding a time delay between the arrival of the presynaptic action potential and the onset of the postsynaptic conductance response. Such a model is shown in Fig. 4c. Here, the delay in release sometimes reveals the quantal release events in isolation.



Modeling Synapses, Fig. 4 Binomial model of a synapse containing four independent release sites (N_T), each with a vesicle release probability of 0.5 (P) and peak postsynaptic receptor conductance of 0.25 nS (Q). (a) Overlaid G_{syn} of the binomial model for 20 repetitions in response to a presynaptic action potential (top red trace). **Inset** shows schematic of a presynaptic neuron with four release sites (left) making a synaptic contact with a postsynaptic neuron (right). (b) Same as (a) but now with added intrasite variability of Q (Gaussian distribution with a coefficient of variation $CV_{\text{QS}} = 0.25$) and intersite variability of Q (Gaussian distribution with $CV_{\text{QII}} = 0.30$). (c) Same as (b) but now with added variability in the release time at each release site. Dashed red line defines the release time course function used to generate the latencies

Synaptic Depression and Facilitation

Besides the variability of the synaptic strength under basal conditions discussed in the previous section (i.e., the variability in Q), there is also a use-dependent modulation of synaptic strength on short time scales (Eccles et al. 1941; Zucker and

Regehr 2002). During trains of closely spaced action potentials, for example, some synapses show a decrease, or depression, in the EPSC amplitude (typically at synapses with a high release probability), whereas other synapses show an increase, or facilitation, in the EPSC amplitude (typically at synapses with a low release probability), and some show signs of both during the same train (see, e.g., Dittman et al. 2000). In all likelihood, synapses probably exhibit both depression and facilitation together, but because one predominates both are not readily apparent.

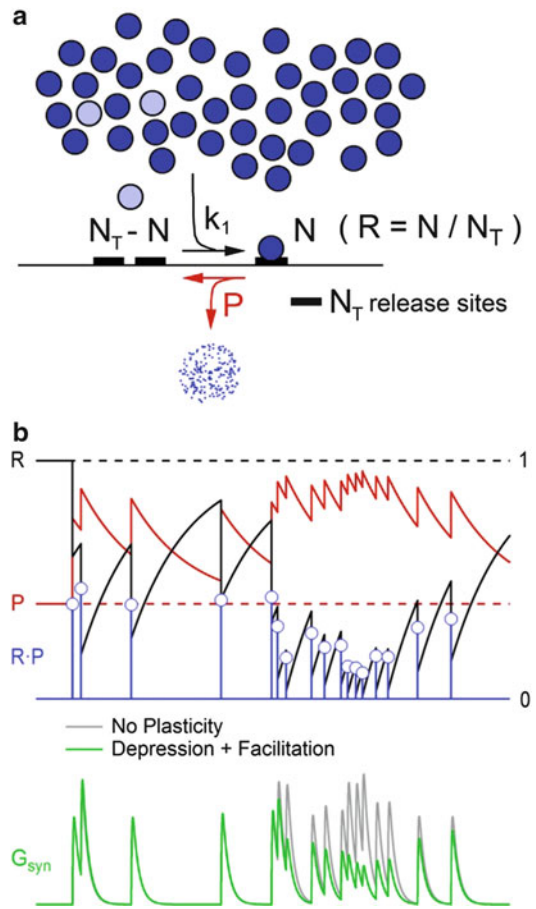
Although the source of synaptic depression can vary, the main source is thought to be the finite time it takes to clear and replenish emptied release sites. A common model used to describe such a process is known as the depletion model, first described by Liley and North (1953). In a modern version of the Liley and North model (Fig. 5a), a fixed number of release sites (N_T) is supplied by a large pool of vesicles (assumed to be large enough so that it never empties) at a rate k_1 . Once a vesicle docks at a release site, it stays docked until the arrival of an action potential (although some models might simulate undocking at a slow rate defined by k_{-1}). If the number of release sites filled with a vesicle at any given time is defined by N , then the number of empty release sites equals $N_T - N$. At the arrival of an action potential, say at time t_s , a fraction (P) of N is released into the synaptic cleft, thereby triggering a postsynaptic response in proportion to $N \cdot P$. The change of N with respect to time after release is then described by the following differential equation:

$$dN/dt = k_1(N_T - N) \quad (16)$$

If one assumes all sites are filled under steady-state conditions, Eq. 16 has the following solution:

$$N = N_T + (N_{s+} - N_T) \cdot \exp(-(t - t_s)/\tau_r) \quad (17)$$

where $\tau_r = 1/k_1$ and N_{s+} is the value of N immediately after vesicle release at time t_s . However,



Modeling Synapses, Fig. 5 Modeling synaptic short-term depression and facilitation. (a) Cartoon of a vesicle depletion model containing a large pool of vesicles (blue circles) and a fixed number of vesicle release sites (N_T , black), N of which are filled with a readily releasable vesicle (the number of free release sites is therefore $N_T - N$). The arrival of an action potential triggers a fraction of the readily releasable vesicles to be released ($N \cdot P$), increasing the number of empty release sites. Empty release sites are refilled with a vesicle at a rate k_1 . The normalized resource variable $R = N/N_T$. (b) Example simulation of the depletion model in (a) using Eqs. 22, 23, 24, 25, and 26 ($\tau_r = 20$ ms, $P_\infty = 0.4$, $\Delta_p = 0.6$, $\tau_f = 20$ ms). The time evolutions of R , P , and $R \cdot P$ are shown at top and the resulting G_{syn} at bottom (green line) for a 100 Hz train of action potentials with random time intervals. Gray line shows G_{syn} in the absence of depression and facilitation

most depletion models express Eqs. 16 and 17 with respect to the fraction of release sites filled with a vesicle (i.e., N/N_T), also known as site occupancy. In this case, Eqs. 16 and 17 become

$$dR/dt = k_1(1 - R) \quad (18)$$

$$R = 1 + (R_{s+} - 1) \cdot \exp(-(t - t_s)/\tau_r) \quad (19)$$

At the arrival of an action potential, $R \cdot P$ is now released into the synaptic cleft. The value $R \cdot P$ is then used to scale the postsynaptic response (e.g., $G_{\max}$ in Eq. 3).

Unlike synaptic depression, synaptic facilitation is thought to arise from a single source, that source being the accumulation of intracellular Ca^{2+} near vesicle release sites (Katz and Miledi 1968; Zucker and Regehr 2002). This explanation of facilitation is known as the residual Ca^{2+} hypothesis. Since Ca^{2+} plays an integral part of synaptic transmission (Fig. 1a, step 2), facilitation is thought to be a universal characteristic of synapses. However, facilitation has not always been apparent at some synapse types, most likely due to the presence of strong depression or strong intracellular Ca^{2+} buffering. A typical model implementation of synaptic facilitation is similar to that of depletion and goes as follows: at the arrival of an action potential at t_s , the probability of release, P , is instantaneously increased by a scale factor Δ_p , after which P decays back to its steady-state value P_{∞} . The change of P with respect to time after the action potential is then described by the following differential equation:

$$dP/dt = (P_{\infty} - P)/\tau_f \quad (20)$$

which has the following solution:

$$P = P_{\infty} + (P_{s+} - P_{\infty}) \cdot \exp(-(t - t_s)/\tau_f) \quad (21)$$

where τ_f is the time constant for recovery from facilitation and P_{s+} is the value of P immediately after an action potential at time t_s . Note that this type of facilitation model does not explicitly model intracellular Ca^{2+} ; rather, Ca^{2+} entry and the effect of Ca^{2+} on P are combined into the same instantaneous event, i.e., the instantaneous increase in P . More complicated facilitation models will explicitly simulate intracellular Ca^{2+}

dynamics, possibly including Ca^{2+} buffering and extrusion, and equate P with $[\text{Ca}^{2+}]_i$.

An example of a simple simulation of a depletion model that includes both synaptic depression and facilitation is shown in Fig. 5b. Here, a random train of action potentials arrived at times t_s , where $s = 1, 2, 3, \dots$, and values for R and P at t_s were computed via the following equations (derived from Eqs. 19 and 21):

$$R_s = 1 + (R_{s-1} - 1) \cdot \exp(-(\Delta t_s)/\tau_r) \quad (22)$$

$$P_s = P_{\infty} + (P_{s-1} - P_{\infty}) \cdot \exp(-(\Delta t_s)/\tau_f) \quad (23)$$

where s denotes the current spike stimulus, $s - 1$ the previous spike stimulus, and Δt_s the interstimulus time ($\Delta t_s = t_s - t_{s-1}$). Values for R_s and P_s were then used to scale the postsynaptic conductance via the following equation:

$$G_{\max} = Q \cdot N_T \cdot R_s \cdot P_s \quad (24)$$

where Q is the quantal conductance (see $G_{\max}$ in Eq. 3). Finally, new values for R and P at t_s were computed via the following equations:

$$R_s = R_s(1 - P_s) \quad (25)$$

$$P_s = P_s + \Delta_p(1 - P_s) \quad (26)$$

These values for R_s and P_s then became R_{s-1} and P_{s-1} in Eqs. 22 and 23 on arrival of the next action potential, creating a recursive algorithm. Note that for the first action potential (i.e., $s = 1$), $R_{s-1} = 1$ and $P_{s-1} = P_{\infty}$.

The story of synaptic depression and facilitation can be more complicated than just described. Besides presynaptic depression due to the depletion of vesicles, some synapses exhibit depression due to desensitization of postsynaptic neurotransmitter receptors (Jones and Westbrook 1996). Other synapses show signs of use-dependent vesicle replenishment rates (i.e., τ_r). Longer lasting forms of depression and facilitation also occur, including long-term depression and potentiation. With a few adjustments, however, these additional

forms of depression and facilitation can be incorporated into the simple depletion model just described (Hennig 2013).

Electrical Synapses: Gap Junctions

As stated above, gap junctions create a direct electrical connection between the presynaptic and postsynaptic membrane via interlinking ion channels (connexins) spanning both membranes. Because of the direct connection, gap junctions are fast and pass signals bidirectionally. However, the signals tend to be highly low-pass filtered (Galarreta and Hestrin 1999). Most neurons connected via gap junctions are GABAergic, and those connected tend to be of the same neuronal type (McCracken and Roberts 2006). Gap junctions are important for generating neural synchronization (Bennett 1997).

The easiest way to simulate a gap junction in a Hodgkin–Huxley-type model is to place a resistor between the presynaptic and postsynaptic membrane. The current flowing into the postsynaptic membrane compartment is then described by the following equation:

$$I_{\text{gap}} = G_{\text{gap}}(V_{\text{m}} - V_{\text{pre}})$$

where G_{gap} is the gap junction conductance and V_{pre} is the presynaptic membrane potential. In most models, G_{gap} is a constant; however, G_{gap} can also be a function of V_{m} , as this conductance can show voltage dependence. In some instances a more complicated representation of a gap junction is implemented with a resistor in parallel with a capacitor.

Cross-References

► [Hebbian Learning](#)

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MOOSE, the Multiscale Object-Oriented Simulation Environment

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Definition

MOOSE (Multiscale Object-Oriented Simulation Environment) is a general-purpose biological simulator with an emphasis on systems biology and computational neuroscience.

Detailed Description

Introduction

Mathematical modeling and computer simulations constitute an increasingly important approach for understanding complex biological systems. MOOSE is a modern, free, and open-source software designed for the modeling and simulation of a wide range of detailed biological phenomena spanning many spatial and temporal scales. MOOSE uses standard C++ with a variety of open-source libraries and currently runs on laptops, workstations, and large parallel machines that support Linux.

This section explains the basic features of MOOSE by examining the terms in its acronym: Multiscale Object-Oriented Simulation Environment.

MOOSE is a **multiscale** simulator. This means that it can simulate processes at many levels of detail and at many timescales. This

includes the movement and interactions of individual molecules, large reaction pathways, entire cells, and even large networks of neurons. The typical timescales range from microseconds for some neuronal phenomena to hours or even days for some biochemical reactions.

Not only can MOOSE handle each of the above phenomena separately, it also supports “true” multiscale calculations where processes belonging to many spatial and temporal scales are coupled together in a single, large simulation. For example, it has been used for models involving detailed and mutually interacting models of electrical and chemical signaling events in neurons.

MOOSE is **object-oriented**. Fundamental biological entities like molecules, reactions, synapses, and dendritic segments are represented as “objects.” Objects have “fields” which represent properties. For example, a `Molecule` object may have a field which holds its concentration value. The user can monitor state variables by inspecting these fields and specify model parameters by modifying these fields.

Objects serve as building blocks of models, and the user can compose a model by connecting objects together. Each of the connections is called a “message.” Messages serve not only as a way to represent relationships in a model but also as conduits through which information can flow during a simulation. In this way, objects and messages allow for flexible model building and present an intuitive interface for user interaction.

Finally, MOOSE is not just a simulator, but is also a **simulation environment**. Existing simulators (Bower and Beeman 1998; Carnevale and Hines 2006; Bergmann et al. 2011) excel within limited domains of computational biology. While they implement fast algorithms for handling certain biological processes, these implementations tend to be tightly coupled with the rest of the simulator. This tight coupling makes it very difficult to extend the capability of such a simulator. In MOOSE, new algorithm implementation is facilitated by an infrastructure that supports seamless and transparent mapping between specialized numerical engines and the object-oriented

specification of the model. MOOSE thus separates the process of algorithm development from the much larger infrastructure that a full-fledged simulator requires.

In MOOSE, one can introduce new biological concepts simply by adding new object types. Newer object types can talk to existing ones using the clean and well-defined interface of fields and messages. New objects automatically plug into the infrastructure provided by MOOSE, such as scripting and model description languages, file I/O, and parallelization.

MOOSE is a free and an open-source software and is licensed under the Lesser GNU Public License, version 2. The basic infrastructure and numerics are written in C++ for speed, and Python bindings allow for scripting and access to a host of Python-based libraries and simulators. MOOSE also has a graphical user interface, with model inspection, plotting, and 3D graphics for spatial models. All these communicate with MOOSE through the Python interface, thus insulating interface development from the underlying C++ core. MOOSE can run on a range of hardware: from laptops to supercomputing clusters. The MOOSE project is based at <http://moose.ncbs.res.in/>.

Architecture

Numerics

As mentioned above, MOOSE objects are used to represent biological concepts. In addition to this, most objects can perform calculations to advance their state variables. The exponential Euler numerical scheme is used for these calculations, because it is object local and is simple to implement.

For almost all domains, specialized, higher-order numerical methods exist which are faster, more robust, and more accurate. They are faster because they contain domain-specific optimizations and, being higher-order methods, can afford much longer time steps for the same accuracy. In addition to being algorithmically faster, they are faster also because they make much more efficient use of computer resources. While these advanced numerical schemes are great for speed and

accuracy, they do not offer the intuitive interface that objects and messages do. MOOSE achieves the best of both worlds by retaining objects and messages for the user to interact with, but transferring their computational responsibilities to solvers. A single solver typically takes over calculations of a large number of objects, and any requests or messages meant for an object are transparently rerouted to the corresponding solver. This avoids the overhead of message-passing and allows excellent use of fast cache memory.

MOOSE makes it easy to incorporate new numerical methods via these solvers. A host of specialized numerical engines have already been implemented. A neuronal solver has been implemented based on the Hines algorithm (Mascagni and Sherman 1998), which is a fast numerical scheme for simulating the electrical activity in branched neurons and their networks. Similarly, reaction-diffusion computations of large biochemical pathways can utilize a range of numerical algorithms supported by the GNU scientific library. The default engine for reaction systems uses an adaptive time-step Runge-Kutta-Fehlberg (RKF45) method provided by the GNU scientific library, and a custom backward Euler implicit method is being prototyped for diffusion in branched neurons. For chemical reactions in sufficiently small volumes, stochastic effects become important and are handled by an implementation of the Gillespie algorithm. For even smaller volumes, it is important to simulate each individual molecule separately. For this, the SMOLDYN Monte Carlo simulator (Andrews et al. 2010) has been adapted to run as an engine inside MOOSE. Finally, a steady-state solver allows for the prediction of a steady state of biochemical reactions using analytical methods.

Scheduling

MOOSE has a sophisticated scheduling system that cleanly handles the varied timescales that exist in a multiscale simulation. Different parts of a simulation can be running at completely different and arbitrary time steps, and all the calculations will take place at the right time and in the right order.

Parallelism

MOOSE can run in parallel on large supercomputing clusters. It supports completely transparent parallelism. This means that the user can write a simulation script in the normal, serial, fashion, and MOOSE will handle the partitioning, communication, and load balancing. The user, and to a large extent even the MOOSE developer, can interact with objects directly without needing to know where on a cluster they reside.

Interfaces and Interoperability

Python Interface

MOOSE offers Python bindings which allow full access to all MOOSE capabilities. Python is a well-supported high-level language with an emphasis on clarity, maintainability, and rapid development. The user also has access to a large trove of in-built Python utilities and third-party tools for analysis, plotting, graphics, etc. This allows the user to carry out simulation and post-processing in a single script, using their favorite Python libraries. For these reasons Python has steadily gained popularity in scientific computing over the last decade. Since many other simulators also have Python bindings, this opens up the possibility of multiple simulators being used synergistically in a single, large, simulation (Ray and Bhalla 2008).

Graphical Interface

MOOSE has a fully-featured graphical user interface (GUI) built using the Qt framework, as supported by Python. Using the GUI, the user can load models, run simulations, and view results as plots and graphical representations. OpenGL-based 3D graphics allow one to visualize spatial models (e.g., networks of branched neurons) and their state during a simulation. Models can also be inspected and edited using generic widgets in the GUI. In addition, domain-specific graphical toolkits allow for more advanced model interaction. For example, Kinetikit is a powerful toolkit for editing, inspecting, and visualizing the structure and runtime state of chemical kinetic models. Similarly, Neurokit, a toolkit allowing similar interactions with neuronal models, is under development.

In addition to the above general tools, a host of graphical educational tutorials have also been included. Each tutorial is a self-contained graphical program illustrating important concepts in computational neuroscience, like Hodgkin-Huxley channels, Izhikevich spiking neurons, etc. All graphical libraries used in making the GUI (Qt, OpenGL, matplotlib) are multi-platform libraries, allowing the GUI to run on all the major operating systems.

Interoperability and Standards

A major problem in the field of computational biology has been that each simulator has its own custom file formats for representing models and simulations. Any researcher wishing to run the same simulation in a different simulator would have to deal not only with porting models from one language to another but also with a host of simulator-specific idiosyncrasies. This always turns out to be a highly arduous and error-prone process. To overcome these problems, the community has standardized XML-based model description languages which are being adopted by many simulators. MOOSE already supports the major modeling languages: SBML (Systems Biology Markup Language) and NeuroML (Hucka et al. 2010; Gleeson et al. 2010). SBML is a mature specification which covers a large number of aspects of modeling of biochemical pathways. NeuroML is a language used to describe highly detailed models of neurons and their networks. In addition, MOOSE aims to support the Network Interchange format for NEuroscience (NineML) as the specification matures. Finally, MOOSE is one of the first simulators with multi-scale capability, and it provides a key test bed for implementations of multiscale model definition standards.

Developers and Support

MOOSE has been under development for over 5 years, and the principal architect is Dr. U.-S. Bhalla. The core development team includes Subhasis Ray, Niraj Dudani, Harsha Rani, and Aditya Gilra. Several other developers have participated, and there has been valuable community

feedback for the MOOSE project. The MOOSE project receives continuing core support from the National Centre for Biological Sciences. It has also been supported by several grants including NIH/NIGMS SBCNY (SBCNY6637) and the Department of Biotechnology, India.

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Morphoelectrotonic Transform

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Definition

A morphoelectrotonic transform is a graphical mapping from morphological into electrotonic

space where the physical length of each dendritic section is replaced by a distance measure, keeping diameter and morphological orientation constant, to provide a direct, intuitive, and functional measure of intracellular signaling.

Detailed Description

From cable theory, the steady-state decay of voltage with distance along a semi-infinite cable is given by $V(x) = V_0 \exp(-x/\lambda)$ where x is physical distance and λ is the space constant. While this solution is useful for describing passive voltage decay in axons, it is not appropriate for estimating voltage decay in dendrites whose electrotonic lengths ($L = \ell/\lambda$) are not infinite and in fact are often less than 1.0. As shown by Rall and Rinzel (1973), voltage attenuation in dendritic trees depends strongly on boundary conditions and is asymmetric in that attenuation *out* from the soma is typically very different from attenuation *in* to the soma. Electrotonic transforms and morphoelectrotonic transforms have been developed to express voltage attenuation in dendritic trees in an intuitive and quantitative manner to gain an understanding of the dependence of intracellular signaling on morphology.

In morphoelectrotonic transforms, the physical length of each neurite is replaced by a distance measure while keeping diameter and morphological orientation constant. Several distance measures are possible. For example, physical distance can be transformed to electrotonic distance $X = x/\lambda$. However, this transform does not provide a direct measure of voltage attenuation except for the case of an infinite cylinder. A transform that has been found to be useful for dendritic trees is the log attenuation L_{ij} defined as the natural log of the voltage attenuation spreading from point i to point j or $\log(A_{ij}) = \log(V_i/V_j)$. Here the length of each dendritic section is replaced by the log attenuation between the ends of the section, i and j , in the direction of interest. This transform has a number of useful properties (Tsai et al. 1994; Zador et al. 1995) including asymmetry ($L_{ij} \neq L_{ji}$) and additivity ($L_{ik} = L_{ij} + L_{jk}$ for j on the path between i and k). The asymmetry property reflects the fact that voltage

attenuation from dendritic tip *in* toward the soma is much greater than voltage attenuation from the soma *out* to dendritic tips. The additive property allows this transform to provide a direct, straightforward logarithmic relationship to describe attenuation between any two points in a dendritic tree, e.g., $L_{ij} = 1$ means that there is an e-fold drop in voltage from point i to point j .

Given the asymmetry, morphoelectrotonic transforms are computed separately for voltage attenuation *in* toward the soma and *out* from the soma to dendrites and also separately for DC and AC inputs. The simulator NEURON provides several impedance tools, one of which can be used to display the log-attenuation morphoelectrotonic transforms of a neuron for a given input frequency and given points of reference in the neuron.

Another morphoelectrotonic transform, entirely analogous to the log-attenuation transform, depicts the cell morphology in terms of propagation delay of synaptic signals through the dendritic tree (Agmon-Snir and Segev 1993). The delay is defined as the difference in centroids or the average or center of gravity of the signal. Both the log-attenuation transform and the propagation delay transform have been computed for a number of different cell types, and some dramatic differences have been noted (Zador et al. 1995; Tsai et al. 1994), suggesting morphology plays different roles in signaling in different cells.

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Morphogenetic Algorithm

► Synthetic Neuronal Morphology

Morphologically Detailed Cellular and Pool Motoneuron Models

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Definition

Morphologically detailed motoneuron models refer to a class of motoneuron (MN) models that are developed using experimentally derived, three-dimensional digital reconstructions of MN morphology (Fig. 1, left panel). In contrast to models with reduced morphological detail (Fig. 1, right panel), these models offer more accurate spatial resolution and allow realistic distribution of electrical properties.

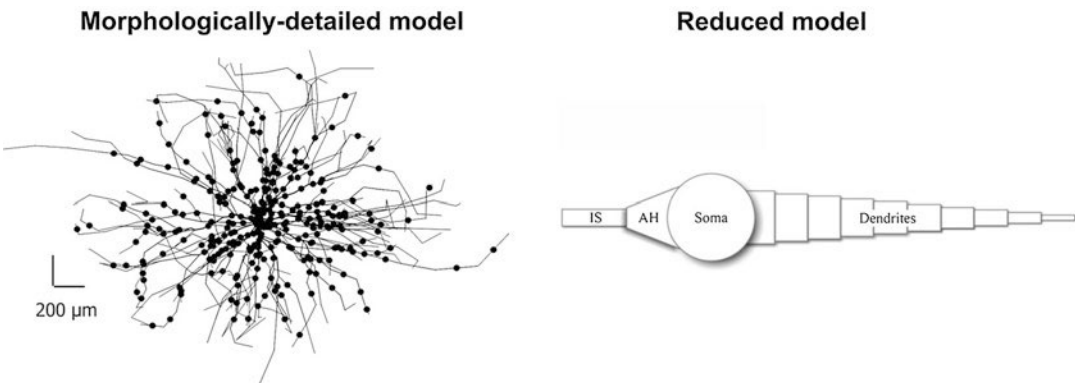
Detailed Description

In a computer simulation, each part of the membrane is represented by an isopotential (i.e., fixed potential) compartment governed by a system of differential equations (see ► [“Compartmental Models of Spinal Motoneurons”](#)). These equations calculate the membrane electrical properties and ion channel behaviors/kinetics. Therefore, in order to have accurate spatial resolution, each compartment should be very small in length ($<0.1\lambda$, λ is the space constant) (Fleshman et al. 1988; Clements and Redman 1989). Because of the intricacy of a MN's structure, a morphologically detailed computer model would typically have thousands of compartments to fully represent the MN. Simplified computer models (also known as “equivalent cable models” or “reduced models”), on the other hand, represent the dendritic morphology with a single unbranched cable which contains membrane surface area equivalent to all real dendrites combined – thus “equivalent cable.” This cable usually comprises 10–50 compartments (but might sometimes only contain one).

M

Development of Computer Models with Realistic Morphology

The first step in constructing a morphologically detailed computer model is importing the three-dimensional morphology of the cell, which is



Morphologically Detailed Cellular and Pool Motoneuron Models, Fig. 1 A morphologically detailed model (left) versus its reduced counterpart for the same MN [cell 43c5, originally published in Cullheim et al. 1987]

usually obtained from the reconstruction of intracellularly stained or retrograde-labeled MNs. Examples of reconstructed morphologies are available through the online database NeuroMorpho. Org (<http://neuromorpho.org/neuroMorpho/index.jsp>). The second step in model development is matching the passive electrical properties of the model cell to experimental data. This step involves setting the passive membrane parameters [e.g., specific transmembrane resistance (R_m), specific axial membrane resistance (R_a), and specific membrane capacitance (C_m)] of each compartment of the model cell to replicate those electrical properties in which active conductances have little or no contribution (e.g., MN input resistance, time constants, electrotonic length). The third step is matching the active electrical properties of the model cell to experimental data. This is the point at which decisions are made on what active conductances need to be included and what their spatial distributions on various cell structures should be (soma, initial segment, and dendrites). The ionic current, I_{ion} , mediated through each active conductance can be described by the following general expression:

$$I_{ion} = g_{ion} \times (V_m - E_{ion}) \quad (1)$$

$$g_{ion} = \bar{g}_{ion} \times m^n \times h^l \quad (2)$$

in which g_{ion} is the varying conductance of the ion channel; $\bar{g}_{ion}$ is the maximum conductance of the ion channel; m and h are the activation and inactivation state variables, respectively; and n and l are the order of activation and inactivation, respectively.

For each membrane state variable (η), the time and voltage dependence are given by

$$d\eta/dt = \alpha_\eta(1 - \eta) - \beta_\eta\eta \quad (3)$$

$$\tau_\eta = 1/(\alpha_\eta + \beta_\eta) \quad (4)$$

The spatial distribution, densities ($\bar{g}_{ion}$), and activation and inactivation kinetics (α_η , β_η , τ_η) of individual active conductances are then adjusted to produce comparable firing behaviors to

experimental data (see ► [“Compartmental Models of Spinal Motoneurons,”](#) for examples on how calcium channels are distributed in order to replicate plateau potentials successfully). A computer model would be validated if it matches multiple sets of experimental data (passive and active) under various experimental conditions (current clamp and voltage clamp). To test the robustness and validity of model results, sensitivity analysis is usually required on critical model parameters. In this process, model parameters that greatly impact the simulation results are first identified. Then, their values are varied within the range observed in experimental recordings in order to assess the dependence of output model behaviors on the variation in those parameters.

Utility of Morphologically Detailed MN Models

Simplified MN models were developed as a necessary means to make simulations computationally efficient, an issue which is being resolved by increasing computational power. Morphologically detailed computer models are now more feasible and offer numerous attractive features. First, they can be used to investigate both the passive and active properties of MNs. In contrast, the dendritic reduction of reduced models is unable to accurately reproduce active conditions (Rall 1962; Holmes et al. 1992). Second, the incorporation of full MN morphology allows these detailed models to simulate MN firing behaviors more accurately, whereas reduced models are unable to simulate some MN firing behaviors (Jackson and Cauler 1997; Hendrickson et al. 2011). This is because the equivalent membrane surface area, even when optimized to match a real MN's electrical properties, is not the only factor which affects active conductances: The morphology of dendrites – the number of branches and the direction of branching – also affects dendritic active conductances. Third, morphologically detailed models contain enough anatomical data to produce unique solutions to questions about passive properties –

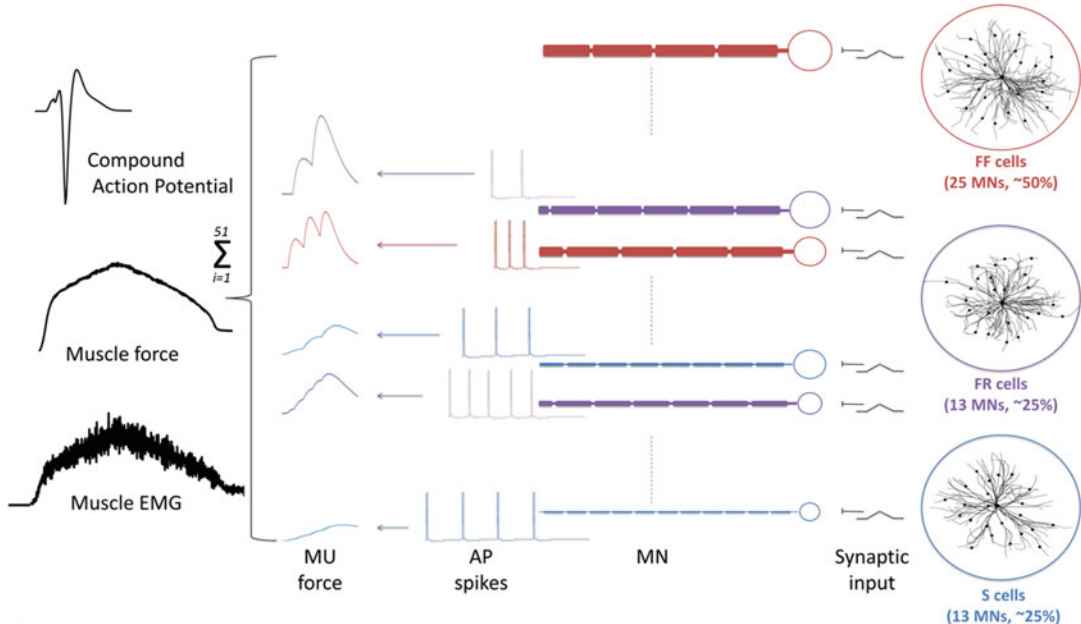
that is, a single scenario or a single set of model parameters can account for all aspects of empirical data (Holmes and Rall 1992; Holmes et al. 1992). This is in contrast to reduced models, which suffer great *redundancy* of model parameters – that is, they produce too many potential solutions to a question or too many candidate mechanisms to feasibly test in experiments (Holmes and Rall 1992; Holmes et al. 1992). Fourth, morphologically detailed models allow investigation of scientific questions impacted by the specific spatial distribution of various cellular properties (e.g., spatial distribution of dendritic ion channels and synaptic inputs), which are not faithfully represented in reduced models (Elbasiouny et al. 2005). Finally, in neurological conditions, such as spinal cord injury or amyotrophic lateral sclerosis, the MN experiences massive pathological changes in dendritic morphology (Kitzman 2005; Amendola and Durand 2008). Because accurate modeling of changes in dendritic structure is critical for accurate simulation of these

pathologies, morphologically detailed models would be more appropriate to use in such neurological conditions, as opposed to reduced models which lack dendritic morphological detail.

Simulations of Pool Models Formed from Morphologically Detailed MN Models

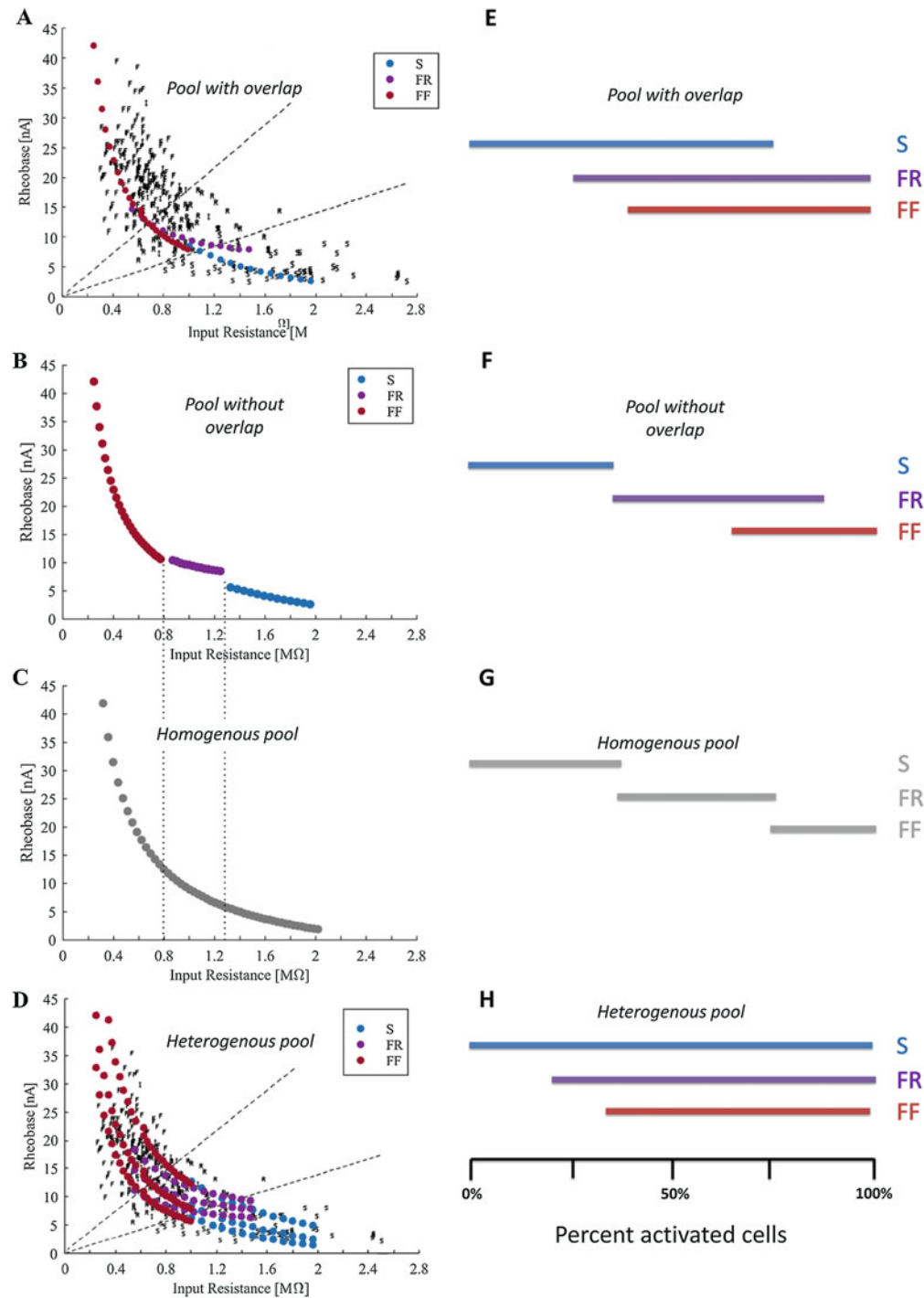
Although morphologically detailed cell models are useful for studying MN behaviors at the cellular level, muscle and network behaviors require highly detailed pool models in which a number of MNs are included to represent the pool of spinal neurons innervating the muscle of interest (Jiang et al. 2015; Allen and Elbasiouny 2018). These pool models (Fig. 2) could then be used to examine the neuronal drive to the muscle, the recruitment pattern of MNs, and the total as well as individual forces and EMG signals generated by the different fiber types comprising the muscle. For example,

M



Morphologically Detailed Cellular and Pool Motoneuron Models, Fig. 2 Example of a MN pool model, from right to left: a morphologically detailed MN model is activated by triangular synaptic commands. Somatic action potentials are generated; these can then be used to calculate

the force and EMG signals of each motor unit and the compound action potential, total force, and EMG from the whole pool. (Adapted from Allen and Elbasiouny (2018) with permission)



Morphologically Detailed Cellular and Pool Motoneuron Models, Fig. 3 Rheobase versus input resistance for pool models of different design features. (a) Pool model with overlap in MN-type cellular properties. (b) Pool model with discrete ranges of MN-type properties (i.e., no overlap). (c) Homogenous pool model in which MN

types are modeled using generic cell templates with varied electrical properties. (d) Pool model which simulates heterogeneity in individual MN properties within MN types. (e, f) The recruitment range of MN types in each pool model. (Adapted from Allen and Elbasiouny (2018) with permission)

Fig. 2 shows an example of a motor pool from Allen and Elbasiouny (2018): 51 morphologically detailed cells were incorporated into a pool model in order to simulate the motor nerve's neural activity, as well as the resulting compound action potentials, muscle EMG, and force from individual MN spikes. With such a pool, muscle and individual motor unit behaviors could be examined under different conditions and in response to different synaptic inputs.

Despite the advantages of 3D morphologically detailed pool models, there are challenges in their operation and development. Operation of a pool model formed of morphologically detailed cells requires high computational power and involves long run times. Computational resources such as parallel supercomputer hardware [e.g., the Neuroscience Gateway (Sivagnanam et al. 2013)] are therefore critical for such simulations. In these simulations, the run time is determined by the complexity of individual model cells, the architecture of the pool model, and how cells communicate with each other. Accordingly, the run time will be governed by the slowest and most complex cell in the pool model.

Challenges in the development of pool models include consideration of several key design choices. Importantly, several design considerations were shown to have a strong impact on simulation predictions made by morphologically detailed MN pool models (Allen and Elbasiouny 2018). The features tested included (1) the number of model cells to include in the pool; (2) whether MN types were explicitly represented (slow-twitch vs. fatigue-resistant vs. fast-twitch); (3) whether MN types were modeled using generic templates versus those developed with distinct electrical and morphological properties; (4) whether different MN types were modeled with overlapping cellular properties or with discrete property ranges; (5) whether biological heterogeneity in cellular properties within MN types was simulated; and (6) whether comprehensive experimental data were available for model verification. Specifically, MN recruitment pattern, firing rates, and force data were shown to be affected by these design choices. Figure 3 illustrates four examples of possible design choices for the pool

model. Figure 3a shows a pool model with overlap in the properties of the different MN types. Figure 3b shows a pool model with discrete ranges (i.e., no overlap) in the properties of MN types. In Fig. 3a, b, MN types were modeled using discrete templates. Figure 3c, on the other hand, shows a pool model in which MN types were represented by generic templates and without overlap in properties. Finally, Fig. 3d shows a pool model which simulates biological heterogeneity in individual MNs within each type. As shown in panels e–h, the recruitment pattern of MNs was affected significantly by these design choices. In various scenarios, mixed or reverse recruitment patterns could be suppressed or exaggerated. In sum, incorporating high levels of detail into pool simulations requires careful consideration of the scientific question being investigated and of the cost vs. benefit of each feature, in order to choose the most relevant pool model design features. However, the effort is justified by the high fidelity of these simulations to the observed experimental data.

Cross-References

► Compartmental Models of Spinal Motoneurons

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Morris–Lecar Model

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Definition

The Morris–Lecar model usually refers to a reduced two-variable model of action potential

generation, originally formulated by Morris and Lecar (1981) in their study of barnacle muscle electrical activity (for historical perspective see Lecar 2007). It was later popularized as a reduced model for neuronal excitability (Rinzel and Ermentrout 1998). The Morris–Lecar model is formulated in the Hodgkin–Huxley framework, with biophysically meaningful parameters and structure. It incorporates a slower hyperpolarizing potassium current and a fast non-inactivating calcium current (depolarizing and regenerative, like the Hodgkin–Huxley sodium current). In the simplest two-dimensional formulation, the activation of Ca^{2+} is assumed to be so fast that it is modeled as instantaneous. The model equations are

$$C \frac{dV}{dt} = -I_{ion}(V, w) + I_{app},$$

$$\frac{dw}{dt} = \phi [w_{\infty}(V) - w] / \tau_w(V),$$

where $I_{ion} = \bar{g}_{Ca} m_{\infty}(V)(V - \bar{V}_{Ca}) + \bar{g}_K w(V - \bar{V}_K) + \bar{g}_L(V - \bar{V}_L)$. The activation variable w is the fraction of open potassium channels and provides the slow voltage-dependent negative feedback as required for excitability, $\bar{g}_{Ca}$ and $\bar{g}_K$ are the maximal conductances of Ca^{2+} and K^+ , and $\bar{V}_{Ca}$ and $\bar{V}_K$ are the corresponding reversal potentials. Activation functions m_{∞} and w_{∞} are given by

$$m_{\infty}(V) = .5(1 + \tanh((V - V_1)/V_2)),$$

$$w_{\infty}(V) = .5(1 + \tanh((V - V_3)/V_4)).$$

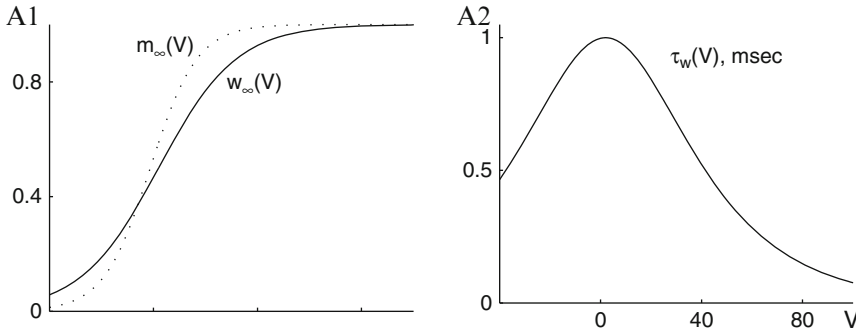
and are shown in Fig. 1 together with voltage-dependent activation “time constant”

$$\tau_w(V) = 1 / \cosh((V - V_3)/(2V_4))$$

for a choice of parameter values, as summarized in the figure caption. The temperature factor ϕ speeds up the activation rate for increasing temperature:

$$\phi = 3^{(Temp-6.3)/10}.$$

As a two-dimensional dynamical system, the Morris–Lecar model, on one hand, readily lends



Morris–Lecar Model, Fig. 1 Time constants and the steady-state functions for the Morris–Lecar model. **(a1)** $m_{\infty}(V) = 0.5(1 + \tanh((V - V_1)/V_2))$ (dotted), $w_{\infty}(V) = 0.5(1 + \tanh((V - V_3)/V_4))$ (solid); **(a2)** $\tau_w(V) = 1/\cosh((V - V_3)/(2V_4))$, where $V_1 = -1.2$, $V_2 = 18$, $V_3 = 2$, $V_4 =$

30 , $\phi = 0.04$. Other parameters: $C = 20 \mu\text{F}/\text{cm}^2$, $\dot{g}_{Ca} = 4$, $V_{Ca} = 120$, $\dot{g}_K = 8$, $V_K = -84$, $\dot{g}_L = 2$, $V_L = -60$. (Reproduced with permission from Borisyyuk and Rinzel 2005)

itself to the use of the full strength of geometrical phase plane and bifurcation analysis. At the same time, it exhibits a diverse repertoire of interesting dynamical regimes and its parameters have direct biophysical interpretation.

The Morris–Lecar model has been used in many single-cell and network studies requiring a model, which is reduced (e.g., as a 2D projection of a higher dimensional model), amenable to analysis, yet biophysically interpretable. Many of the results from these studies are summarized and detailed in textbooks, e.g., Borisyyuk and Rinzel (2005), Ermentrout and Terman (2010), Izhikevich (2007), and Rinzel and Ermentrout (1998).

w -nullcline is simply the activation curve $w = w_{\infty}(V)$. Above this curve w decreases and below w increases (Fig. 2a).

The steady-state solution $(\bar{V}, \dots, \bar{w})$ of the system is the point where the nullclines intersect. It must satisfy $I_{ss}(\bar{V}) = I_{app}$, where $I_{ss}(V)$ is the steady-state $I - V$ relation of the model given by

$$I_{ss}(V) = I_{ion}(V, w_{\infty}(V)).$$

If I_{ss} is N-shaped, then there can be three steady states for some range of I_{app} . However, if I_{ss} is monotone (as is the case for the parameters in Fig. 1), then there is a unique steady state, for any I_{app} .

Detailed Description

Phase Plane Basics

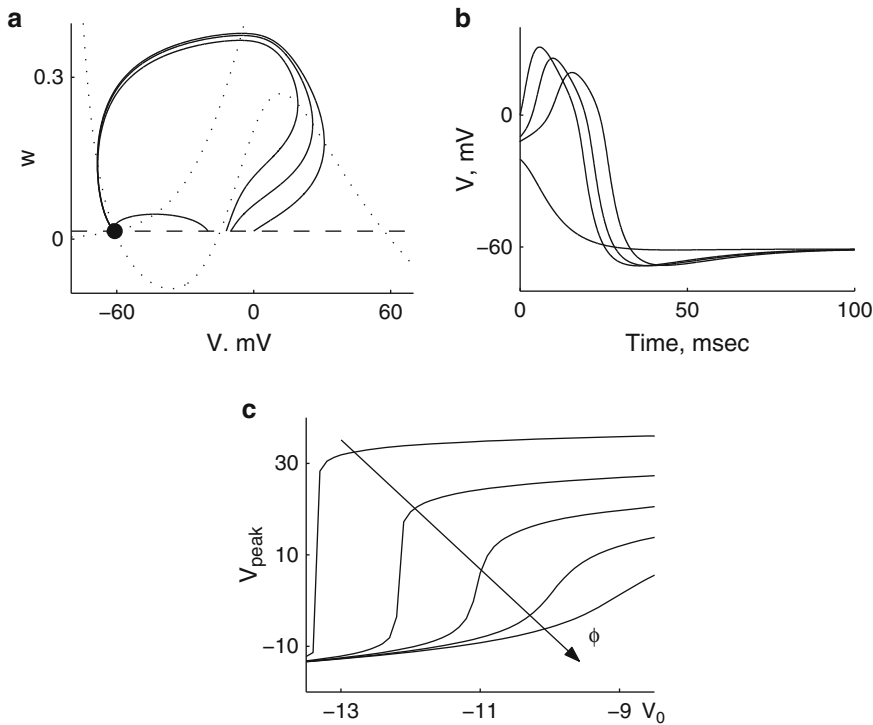
This two-variable system's behaviors can be fully revealed in the phase plane. We start by finding the nullclines – the two curves defined by setting dV/dt and dw/dt individually equal to zero. The V -nullcline is defined by

$$-I_{ion}(V, w) + I_{app} = 0$$

and has a cubic-like shape. Below the V -nullcline in the $V - w$ plane $dV/dt > 0$, i.e., V is increasing, while above the nullcline V is decreasing. The

Excitable Regime

A system is said to be excitable when it has one stable steady state and the action potential (large voltage excursion) is evoked by a large enough brief stimulation. Figure 2a, b shows the responses to brief I_{app} pulses of different amplitude. After a small (subthreshold) pulse, the solution returns directly back to rest. If the pulse is large enough, Ca^{2+} current gets sufficiently activated, leading to even more depolarization and more Ca^{2+} influx. The solution trajectory heads rightward toward the right



Morris–Lecar Model, Fig. 2 Excitability in Morris–Lecar model. **(a)** Phase plane for excitable case (same parameter values as in Fig. 1). *Dotted lines* show V - and w -nullclines, and *solid lines* show solution trajectories with initial conditions $w_0 = 0.014173$, $V_0 = -20, -12, -10$, and 0 mV. **(b)** V Time courses for the same solutions as in

(a). **(c)** The peak value of the action potential V_{peak} versus initial value V_0 . Different curves correspond to different values of ϕ : from *top to bottom* ϕ increases (marked with an *arrow*) from 0.02 to 0.1 in 0.02 increments. (Reproduced with permission from Borisyuk and Rinzel 2005)

branch of the V -nullcline (upstroke) and follows the right branch upward (corresponding to the opening of K^+ channels). When the solution passes the knee (i.e., enough K^+ accumulates), it heads leftward (downstroke). The number of K^+ channels open reaches a maximum during the downstroke, as the w -nullcline is crossed. Then the trajectory follows V -nullcline's left branch (minimum of V) downward (K^+ channels close) and returns to rest.

Notice that if w is much slower than V (e.g., because ϕ is very small), the solution trajectories in the phase plane will be nearly horizontal during the upstroke and downstroke phases of the action potential. At these low temperatures, the trajectory of the action potential looks like a relaxation oscillation with very fast upstroke and downstroke, pronounced “plateau” near the maximum of the action potential and middle branch of the

V -nullcline serving as a threshold. However, at higher temperatures (larger ϕ), the flow in the phase plane is less horizontal and the shape and the maximum value of the spike are sensitive to the pulse size. If we plot the maximum voltage value during an action potential versus the size of the pulse that elicited that spike or initial condition V_0 , we get a continuous curve (Fig. 2c). The steepness of this curve depends on ϕ . This observation suggested that action potentials that look like stereotypical all-or-none events may have variable amplitudes at higher temperatures, which was later confirmed experimentally (Cole et al. 1970).

An action potential in the Morris–Lecar model can also be produced upon release from a prolonged hyperpolarizing stimulus. This phenomenon is termed post-inhibitory rebound. It occurs because K^+ channels that are normally open at rest

are closed by hyperpolarization, and thus the negative feedback near resting values of voltage is removed (see ► “[Postinhibitory Rebound and Facilitation](#)”).

Onset of Repetitive Firing

In the excitable regime resting steady state is stable. As applied current I_{app} is varied, the transition to periodic firing can happen when that steady state is destabilized. Stability of the steady state in the Morris–Lecar model is determined by the eigenvalues λ_1 and λ_2 of the Jacobian matrix J , evaluated at the steady state:

$$J = \left(\begin{array}{cc} -\frac{1}{C} \frac{\partial I_{inst}}{\partial V} & -\frac{1}{C} \frac{\partial I_{inst}}{\partial w} \\ \phi \frac{w'_{\infty}}{\tau_w} & -\phi \frac{1}{\tau_w} \end{array} \right) \bigg|_{(\bar{V}, \bar{w})}$$

The steady state is stable if and only if the real parts of both eigenvalues of the Jacobian matrix are negative. There are two main scenarios for the onset of oscillations.

First scenario (Andronov–Hopf bifurcation): a pair of complex conjugate eigenvalues crosses the imaginary axis moving from left to right. As a result the steady state becomes unstable and stable oscillations (a stable limit cycle) of small amplitude appear near the steady state. This is Andronov–Hopf bifurcation. At the bifurcation parameter value I_{bif} , we have $Re(\lambda_{1,2}) = 0$, and near bifurcation the amplitude of oscillations is proportional to $\sqrt{|I_{app} - I_{bif}|}$.

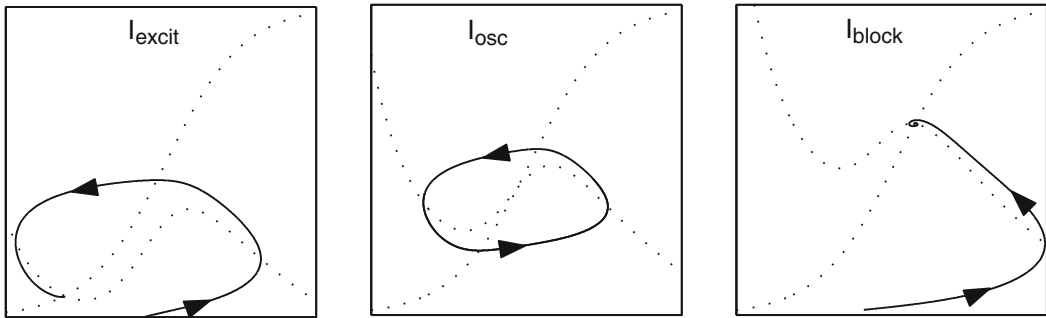
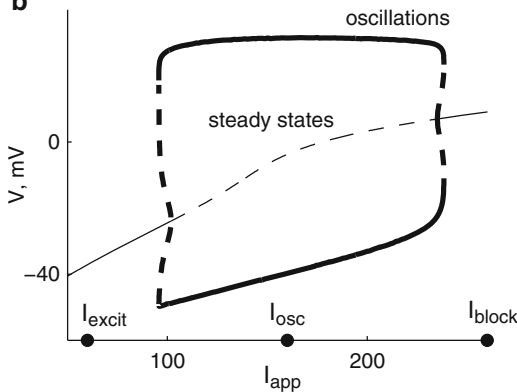
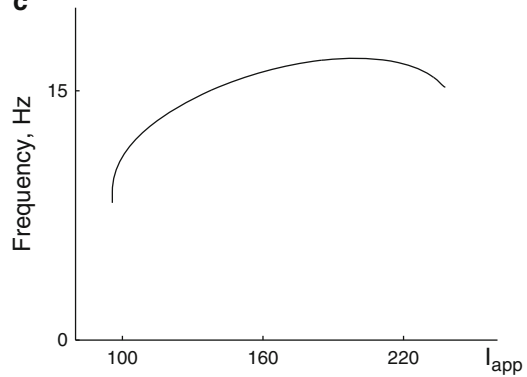
The scenario for the Andronov–Hopf bifurcation can also be viewed in terms of the trace of the Jacobian matrix: the negative trace corresponds to the stable steady state and at the bifurcation the trace becomes positive. For the Morris–Lecar model condition $tr(J) > 0$ means:

$$-\frac{1}{C} \frac{\partial I_{inst}}{\partial V} > \frac{\phi}{\tau_w} \quad (1)$$

Condition 1 can be interpreted as the rate of depolarization being faster than the negative

feedback’s rate (in particular, for negative feedback (represented by w) to be slow, the temperature cannot be too high). When this condition is met, periodic solution arises via Andronov–Hopf bifurcation, resulting in ongoing spiking activity. This periodic solution has a nonzero frequency associated with it, which is proportional to the $Im(\lambda_{1,2})$ – the imaginary part of the eigenvalues at the bifurcation parameter value – i.e., the repetitive firing emerges with nonzero frequency. Figure 3a shows snapshots of the nullcline positions and solution trajectories at different values of I_{app} (marked I_{excit} , I_{osc} , and I_{block} in Fig. 3b). Figure 3b, c shows the bifurcation diagram and the f – I relation, respectively. This is an example of the so-called Hodgkin type II spiking onset (see ► “[Excitability: Types I, II, and III](#)”).

The second scenario for onset of periodic spiking corresponds to the saddle–node on an invariant circle (SNIC) bifurcation. This can happen, for example, at increased values of $\dot{V}_K$ (corresponding physiologically to increased extracellular K^+ concentration). Parameters can then be chosen to result in three steady states: one on the left branch of cubic and the other two on the middle branch. If, additionally, ϕ is very small, then both middle and upper steady states can be unstable. Figure 4a1 shows nullclines and a schematic of stable and unstable manifolds of the middle fixed point, which is a saddle. As I_{app} is increased, the V –nullcline moves up and the saddle and the stable fixed point (node) coalesce and disappear (see Fig. 4a2, middle and right panels) leaving behind a periodic trajectory (a repetitive spiking solution). Exactly at the bifurcation value of parameter $I_{app} = I_1$, two coalescing points form a complex steady state, called saddle–node on an invariant circle (SNIC), and one eigenvalue becomes zero. For parameter values just above the bifurcation, the frequency of oscillations is proportional to $\sqrt{I_{app} - I_1}$, i.e., the periodic spiking emerges initially with zero frequency (or very large spiking period; see example in Fig. 4b). This bifurcation scenario is typical for Hodgkin type I excitability (see [Excitability: Types I, II, and III](#)). Figure 4c, d

a**b****c**

Morris–Lecar Model, Fig. 3 Onset of repetitive firing with one steady state (type II). **(a)** Phase planes for different values of I_{app} (60, 160, and 260 $\mu\text{A}/\text{cm}^2$), corresponding to excitable, oscillatory, and nerve-block states of the system. **(b, c)** Bifurcation diagram **(b)** and $f-I$ curve **(c)**. **(b)** Thin solid curves, stable steady state;

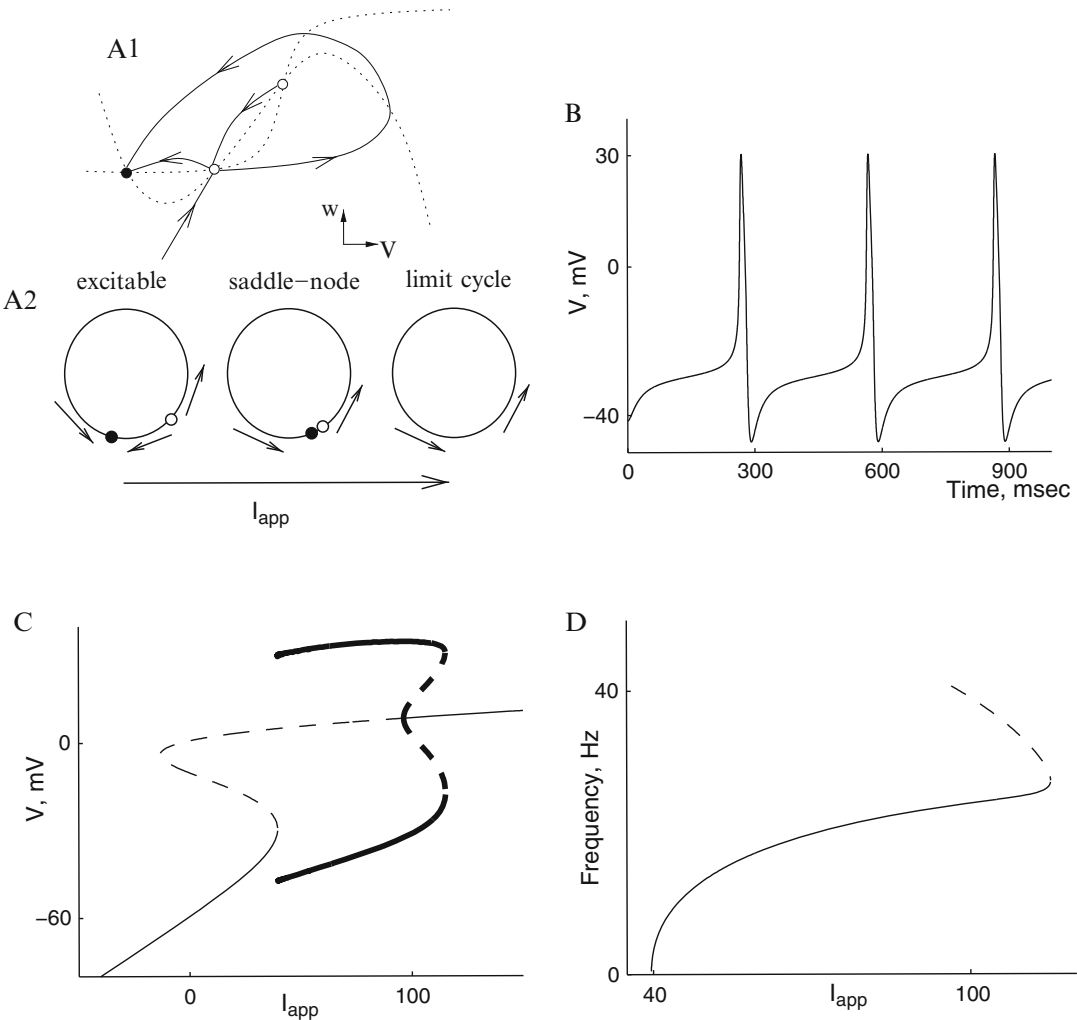
thin-dashed curves, unstable steady state; thick solid curves, maximum and minimum V of the stable limit cycle; thick-dashed curves, maximum and minimum V of the unstable limit cycle. Parameter values are the same as in Fig. 1. (Reproduced with permission from Borisjuk and Rinzel 2005)

shows bifurcation diagram and $f-I$ curve for this case.

Bistability

There are many parameter combinations at which bistability is observed in the Morris–Lecar model. Bistability means that there are two stable structures (steady states or periodic orbits) coexisting at the same parameter values. Depending on initial condition, the solution will converge to one or the other attractor. A brief perturbation (of appropriate direction

and timing) can switch the solution between the attractors. For example, starting with the phase plane with three steady states, as in Fig. 4, different kinds of bistability can be observed by varying ϕ . At large values of ϕ , the middle steady state is unstable and the upper and lower ones are stable. The voltage can be switched from one constant level to the other by brief pulses. At intermediate values of ϕ , both middle and upper steady states can be unstable, but the upper steady state is surrounded by a stable periodic orbit. In this case there is bistability between the low-voltage resting state and depolarized repetitive firing. This example in



Morris–Lecar Model, Fig. 4 Type I excitability in Morris–Lecar model. Parameters are the same as in Fig. 1, except $V_3 = 12$ mV, $V_4 = 17$ mV, $\phi = 0.06666667$. (a) Schematics of phase plane. (a1) Schematic of phase plane for $I_{app} = 0 \mu A/cm^2$. The curves are slightly modified from the actual computed ones for easier viewing; in particular, actual trajectories would not have extrema away from nullclines. (a2) Schematic of change in phase plane with

change of I_{app} . (b) Time course of voltage for $I_{app} = 40 \mu A/cm^2$. (c) Bifurcation diagram. *Thin solid curves*, stable steady state; *thin-dashed curves*, unstable steady state; *thick solid curves*, maximum and minimum V of the stable limit cycle; *thick-dashed curves*, maximum and minimum V of the unstable limit cycle. (d) $f-I$ curve. *Dashed portion* corresponds to unstable periodic orbit. (Reproduced with permission from Borisjuk and Rinzel 2005)

which a stable rest state coexists with a depolarized limit cycle provides the basis for square wave bursting.

Another example of bistability, in a situation when only one steady state exists can be seen in Fig. 3b. There, close to Andronov–Hopf bifurcations, there is bistability between a stable steady state and a periodic orbit for narrow ranges of I_{app} .

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Motion Energy Model

- [Spatiotemporal Energy Models](#)

Motion Parallax

- [Optic Flow Processing](#)

Motion vision

- [Visual Motion Detection in *Drosophila*](#)

Motor Control

- [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Motor Intention

- [Decision-Making, Motor Planning](#)

Motor Learning

- [Eye-Blink Conditioning](#)
- [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Motor Preparation

- [Decision-Making, Motor Planning](#)

Motor Set

- [Decision-Making, Motor Planning](#)

Multi-array Nerve Electrode

- [Peripheral Nerve Signal Processing, Multipole Cuff Methods](#)

Multi-contact Nerve Electrode

- [Peripheral Nerve Signal Processing, Multipole Cuff Methods](#)

Multielectrode Array

- [Peripheral Nerve Signal Processing, Multipole Cuff Methods](#)

Multimodal Neural Population Models

- [Neuroimaging, Neural Population Models for](#)

Multimodal Neuroimaging, Neural Population Models for

- [Neuroimaging, Neural Population Models for](#)

Multi-objective Evolutionary Algorithms

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Synonyms

Multi-objective evolutionary optimizations;
Multi-objective genetic algorithms

Definition

Multi-objective evolutionary algorithms (MOEAs) are any of the paradigms of evolutionary computing (e.g., genetic algorithms, evolutionary strategies, etc.) used to solve problems requiring optimization of two or more potentially conflicting objectives, without resorting to the reduction of the objectives to a single objective by the means of a weighted sum.

Detailed Description

The main ideas of evolutionary algorithms (EAs) are derived from the principles of variation and selection that are the foundation of Darwinian evolution (Beyer 2001). An evolutionary algorithm operates on a population of individuals, every one of which represents a candidate solution to a given optimization problem. Each individual is assigned a fitness value, which represents the “quality” of that potential solution. Solutions evolve by replication and become increasingly better, based on the mechanisms of natural selection and the two so-called genetic operators: crossover (recombination) and mutation.

Multi-objective evolutionary algorithms (MOEAs) form a special group of evolutionary algorithms that are specifically designed to deal with multiple, potentially conflicting objectives that need to be fulfilled in the process of

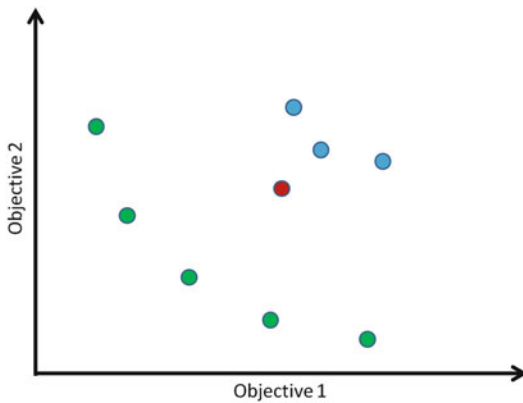
EA-driven optimization. Since rarely in multi-objective optimization (MOO) does there exist a single, optimal solution and, instead, one can usually expect a set of trade-off solutions, MOEAs, which by definition operate on entire populations of potential solutions, are well suited for MOO (Deb 2001).

The core concept in MOO is that of dominance relation. Formally, dominance is defined as follows (Deb 2001):

Let us assume that there are M objective functions, and the optimization goal is to minimize all of those objective functions (the same logic will apply to maximization and combined minimization/maximization, albeit with different signs). A solution x_1 is said to dominate the other solution x_2 , if both conditions 1 and 2 are true:

1. The solution x_1 is no larger (“worse”) than x_2 in all objectives, or $f_j(x_1) \leq f_j(x_2)$ for all $j = 1, 2, \dots, M$.
2. The solution x_1 is strictly smaller (“better”) than x_2 in at least one objective, or $f_j(x_1) < f_j(x_2)$ for at least one $j \in \{1, 2, \dots, M\}$.

The majority of MOEAs approach multi-objective optimization problems by targeting the so-called Pareto-optimal set of solutions. The set comprises all of the solutions from the entire population of solutions that do not dominate one another and are not dominated by any of the remaining solutions in the population. This means that within the set, one solution might be better than another solution in light of one of the objectives, but worse in some other objective, and vice versa. Therefore, there is no single “best” solution in the set. At the same time, for every solution outside of this set, one can always find a solution in this set which will dominate the former. Consequently, the Pareto-optimal set has the property of dominating all of the solutions that do not belong to this set, and thus all of its members can be considered better than the rest of the general population of solutions. The figure below illustrates a hypothetical example of a minimization problem in terms of two objectives. The solution represented by a red dot clearly dominates the three blue solutions, which are non-dominating



Multi-objective Evolutionary Algorithms,
Fig. 1 Illustration of the concepts of dominance and Pareto-optimality

with respect to each other. The green dots correspond to the Pareto-optimal front and as such dominate the rest of the population of solutions (Fig. 1).

Most contemporary multi-objective evolutionary algorithms apply various Pareto-based ranking schemes, which assign some kind of ranking to all the potential solutions in a given iteration, depending on to which Pareto-optima front (i.e., locally Pareto-optimal set) they belong. Examples of such evolutionary algorithms include the Non-dominated Sorting Genetic Algorithm-II (NSGA-II; Deb et al. 2002) and Strength Pareto Evolutionary Algorithm 2 (SPEA-2; Zitzler et al. 2001), which have become the standard approaches in multi-objective evolutionary optimization and are often utilized as benchmarks for other algorithms.

Applications

Multi-objective evolutionary algorithms have found applications in many areas of science, engineering, economics, business, and logistics. Since building neuronal models is basically a multi-objective optimization problem, where many goals are to be reached simultaneously (e.g., various aspects of the electrical activity must be matched, the cell morphology must be preserved,

the maximum complexity of the model must not be exceeded, etc.), MOEAs lend themselves perfectly to this application, as well. This is especially true in light of recent discoveries suggesting that the same functional neuronal activity can be produced by nerve cells of widely varying properties (e.g., Marder and Goaillard 2006), which has also been observed in modeling studies (e.g., Prinz et al. 2003). While most applications of multi-objective evolutionary algorithms in computational neuroscience pertain to parameter tuning of neuronal models (e.g., Druckmann et al. 2007; Smolinski and Prinz 2009), other applications such as classificatory decomposition of cortical evoked potentials (e.g., Smolinski et al. 2006) also exist.

Advantages and Disadvantages of MOEAs

One of the most significant advantages of multi-objective evolutionary algorithms is the straightforward generation of multiple trade-off solutions in a single run and the feasibility of utilization on large parameter search spaces, where most “brute-force” or manual approaches often fail. Another advantage – pertaining specifically to the problem of construction and/or tuning of neuronal models – is the ease of visualization of the parameter values in the form of scatterplots, which allows for a better comparison to biological data, as well as easier identification of relationships between parameters. This is possible due to the fact that the parameter search space explored by an MOEA is usually much more finely defined than competitive grid-based, “brute-force” approaches. In other words, while the range in the “brute-force” approach may reflect a three- to four-fold variation in the parameter values, and the granularity may allow for 5–10 possible values, incorporating up to 20-fold variation with hundreds of possible values for each parameter is not unheard of in an MOEA.

The biggest disadvantage of multi-objective evolutionary algorithms is the fact that the arrival at the global Pareto-optimal set is not guaranteed. Another disadvantage – as compared to

“brute-force” approaches to tuning of parameters of neuronal models – is the risk of missing large “chunks” of the parameter search space, if the space is not properly defined and/or premature convergence of the algorithm takes place. Finally, as the number of objectives being optimized increases, so does the computational complexity of the implementation.

Related Approaches

Several other nature-inspired computational intelligence approaches have been utilized in related applications. Those include particle swarm optimization (PSO) and simulated annealing (SA).

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Multi-objective Evolutionary Optimizations

- [Multi-objective Evolutionary Algorithms](#)

Multi-objective Genetic Algorithms

- [Multi-objective Evolutionary Algorithms](#)

Multiscale Brain Connectivity

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Definition

Multiscale brain connectivity refers to physical and functional connection patterns between a set of brain units on multiple levels of spatial extent. For large, complex systems such as the human brain, units may be defined as, e.g., single neurons (MRI, EEG/MEG), voxels, or brain areas on a microscopic, mesoscopic, or macroscopic scale, respectively. Connectivity between these units may be measured in terms of anatomical/structural connectivity (SC; Hagmann et al. 2010), the statistical relations between their functional states (functional connectivity, FC), or their inferred causal interactions (effective connectivity, EC; Friston 1994). Brain connectivity underlies signal propagation in neural networks and is thus crucial to understanding cognition and the brain’s information and activity flow in health and disease.

Detailed Description

Aspects of Brain Connectivity

In general, the term “connectivity” may refer to related but distinct concepts. In principle, all interactions in the brain are physical at the basic level, but they can be distinguished by their time scales and dynamics: SC represents the anatomical links between units, that is, by synapses or fiber bundles. FC is used to measure the bidirectional statistical interdependencies (correlations or synchronizations) of the functional states between units, independent of their structural connectedness (van den Heuvel and Hulshoff Pol 2010). Both SC and FC may change over time, but SC changes are typically much slower (from the order of minutes for synaptic plasticity) than for FC patterns. The latter are much more variable and span several time scales, because they depend on the dynamical evolution of the network units’ functional states and the temporal connectivity structure. Finally, EC refers to the “influence one neuronal system exerts over another” (Friston 1994). EC can be extracted from time series by statistical analysis of information flow (such as Granger causality, Ding et al. 2006), or dynamic causal modeling (Friston et al. 2003), and may further be constrained by knowledge about structural links. However, although these terms designate different concepts of brain connectivity, their distinction and precise definitions are not perfectly well defined and subject of discussion (Horwitz 2003; Fingelkurts et al. 2005).

In all cases, the connectivity is determined by all existing weighted or binary links between network units, and the number of links rises quickly with network size. In order to summarize, describe, and classify brain connectivity of complex networks, graph theory can be used and is an important tool in the study of brain connectivity (Bullmore and Sporns 2009). Graphs represent networks in an abstract form by vertices/nodes that are connected by edges and can be constructed for all types of connectivity. This way, it is possible to characterize brain networks in terms of various global and

local measures, such as network clustering coefficient, path length (the average number of nodes that have to be passed through to travel between two random nodes in the graph), or node centrality (the importance of a certain node in the graph). With graph theory, key brain regions can be identified, as well as network properties such as small worldness and subnetworks.

Connectivity at Multiple Scales

While it is possible and meaningful to describe the whole neuronal connectome in terms of synapses in simple organisms with only hundreds of neurons, more complex brains necessitate some levels of abstraction. In all brains, at the microscale, neurons form microcircuits through characteristic connection patterns, such as the characteristic connectivity patterns between neurons of different cortical layers. Here, single synapses and axons form the links between neurons. In larger brains, at the mesoscale, populations of similar neurons or microcircuits, e.g., in cortical columns, have been identified as functional units of encoding. These units may encode features or sets of features of our environment, such as locations in visual space in the visual cortex (Mountcastle et al. 1955). At this level, the units are defined functionally, and connectivity between units may be diffuse or patchy, depending on area and layer. Finally, brain areas based on Brodmann areas, cytoarchitectonic features and landmarks, and their white matter fiber tracts or functional relations are investigated to study large-scale brain networks and communications. Large-scale and multiscale networks and brain connectivity is a field of study that has been quickly growing since around the turn of the millennium and that has made major advances in beginning to reveal the principles of brain architecture (Craddock et al. 2013; Sporns 2010). At the same time, efforts are being made to map and model the whole human brain connectivity at multiple scales (Sporns et al. 2005; Markram 2006).

Connectivity in Large-Scale Network Models

In the study of the spontaneous activity of brain networks, large-scale brain network models are used to study the relationship between structural, functional, and effective connectivity. Typically, the models consist of nodes, connected by edges where indicated by empirically derived SC matrices from invasive tracing (CoCoMac) or (functional) diffusion (tensor/spectrum) magnetic resonance imaging (DTI/DSI). The interaction of the nodes depends on both the large-scale connectivity structure and the local node dynamics, which may be represented as single units, or by pools of smaller, interacting subunits, giving rise to multiscale dynamics in the models (Deco et al. 2011). Computational models have identified the importance of the underlying (spatiotemporal) structural connectivity matrix and its interaction with local dynamics in shaping FC patterns (Nakagawa et al. 2013), and in the future, they can potentially be used to study the effects of changes in dynamical properties and connectivity at multiple scales in different cognitive state or between healthy and diseased brains.

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Further Reading

More information on current developments of the two large European and U.S. research project on mapping and simulating the whole human brain as completely as possible, down to single-neuron scales, can be obtained from the projects websites of the Human Connectome Project, and the Human Brain Project. Additionally, a brain connectivity workshop (<http://brain-connectivity-workshop.org/>) is held annually to discuss major progresses in the field

Multiscale Modeling of Purkinje Cells

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Definition

The Purkinje cell is one of the most extensively modeled neurons in computational neuroscience. Purkinje cells have large dendritic trees that contain more than 150,000 dendritic spines. While

dendritic spines are femto-liter cytosolic volumes with lengths of less than 2 μm , the dendritic tree can have a total length of hundreds of microns and thousands of femto-liters in volume. Thus, biochemical and electrical interactions take place over three orders of magnitude in space. Similarly, the time constant of activation of the different dendritic and somatic active conductances ranges from sub-milliseconds to almost 1 s (four orders of magnitude). Therefore, a comprehensive computational study of the Purkinje cell has to be done using multi-scale models and modeling techniques.

Detailed Description

Models of Purkinje cells range from perceptrons to detailed biochemical models of single synapses to biophysical models that take into account the intricate dendritic structure.

Passive Compartmental Models

The Purkinje cell is one of the first neurons to be modeled with a compartmental technique. These models consisted in digitizing the dendritic arbor and dividing it in finite elements where the passive properties (membrane resistance, membrane capacitance, and axial resistance) were fitted to replicate experimental measurements. These models were mainly used to study electrotonic decay and synaptic signal filtering.

Active Dendritic Models

The first compartmental model of a Purkinje cell with active conductances was developed by Pellionisz and Llinás (1977). A more detailed model was later developed by De Schutter and Bower (1994a, b). Ten different types of channels were added to the soma and dendrite. The model also included a calcium concentration calculation using a radial diffusion model within each compartment. The calcium concentration was used to activate calcium-activated potassium channels. The model was able to replicate the in vivo and

anesthetized in vivo firing rate statistics of Purkinje cells. This model has been modified and updated to study dendritic integration under multiple different experimental conditions.

Synaptic Plasticity Models

Long-term depression (LTD) of the parallel fiber to Purkinje cell synapse is a type of synaptic plasticity believed to be the cellular substrate of learning and memory in the cerebellum. Kuroda et al. (2001) developed a mass-action well-mixed model of a synapse undergoing LTD. This model has helped in determining that the biochemical network that underlies LTD is a type detector of intracellular calcium ion concentrations. The threshold to express LTD depends not only on the concentration of calcium ions but also on the temporal dynamics, which is better described as a leaky integrator of the calcium concentration signal. This mass-action model has been translated to a stochastic environment to study the reliability of LTD expression. The model has also been used to study short-term facilitation and depression.

Simplified Models

It has been proposed that the function of dendritic excitability is to compensate for the electrotonic decay of synaptic signals along the complex dendritic tree. In as such, the entire Purkinje cell can be collapsed into a single somatic compartment with a nonlinear integration function and a threshold. Furthermore, experimental and computation work suggests that the Purkinje cell can be treated as a perceptron, further simplifying the processing of synaptic input.

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Multistability Arising from Synaptic Dynamics

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Definition

The strength of a synapse imparted by a presynaptic neuron onto its postsynaptic target can change as a function of the activity of the presynaptic neuron. This change is referred to as short-term synaptic plasticity. Networks of neurons connected with plastic synapses have the potential ability to display multiple stable solutions either at different parameter values or for the same set of parameters. This latter property is known as multistability. Self-consistency between the network frequency and the level of plasticity is needed to ensure multistability.

Detailed Description

The central nervous system (CNS) controls a vast array of behaviors that include both basic functions such as processing of sensory input (Sharp et al. 1990), regulating circadian rhythms (Piggins and Guldin 2011), coordinating motor output (Marder and Calabrese 1996), and more complex functions such as spatial navigation (O’Keefe 1991), decision making, and memory formation

(Treves and Rolls 1994). Although the CNS includes a large number of neurons and an even larger number of synaptic connections, these constitute a finite number of networks and few compared to the seemingly limitless number of behavioral tasks. This disparity strongly indicates that the networks of the CNS can reorganize to produce multiple outputs.

The output of a neuronal network can be quantified in a number of ways. The firing rate of the network neurons, for example, may encode information or, alternatively, the output may be coded in the pattern of activity of sub-networks of neurons. The specific timing of spikes or bursting events is also a way in which networks direct their output. In many contexts, to be useful to downstream targets, the neuronal output must be stable, resistant to perturbations or noise. From a mathematical viewpoint, this implies that the output is likely to be a stable periodic solution of a set of underlying equations that govern the network activity.

In order to have multiple functional roles, a network must have the ability to exhibit multiple stable outputs. There are two obvious ways in which this ability may arise. One is through neuromodulation, where different stable solutions exist for different parameter values or for different inputs to the network. The role of the modulator is to change parameter values between these states depending on the task to be completed. A second way is through multistability where more than one stable solution exists for the same set of parameter values. Which stable state ends up being the attracting solution depends on the initial conditions, i.e., the state at which the network becomes employed.

Short-term synaptic plasticity (STSP) refers to the ability of a synapse to change its synaptic strength depending on the frequency at which it is being activated by a presynaptic neuron. Facilitation refers to case where the strength is an increasing function of frequency and depression when it is a decreasing function. Significant research has been conducted to understand the mechanisms underlying plasticity. How STSP can shape the output of a neuronal network is also a central focus of investigation.

Just as there are synaptic rise and decay rates associated with different neurotransmitter receptor types, there are also different rates associated with facilitation or depression of a synapse. STSP acts at short timescales and, as a form of synaptic plasticity, is distinct from plasticity forms that act at long timescales: long-term potentiation and depression (LTP and LTD) and spike timing-dependent plasticity (STDP). LTP, LTD, and STDP last for very long time durations on the order of hours to weeks and are mainly associated with changes in synaptic strength due to the relative timing of firing in pre- and post-synaptic pairs. Timescales associated with STSP are on the order of several milliseconds to seconds, the same order as the rise and decay of excitatory, inhibitory, and typical voltage-gated ionic currents.

Below, we discuss a few basic models of STSP and provide some examples of how multiple stable solutions are created in small neuronal networks that involve STSP. Synapses that exhibit STSP have different steady-state amplitudes for different presynaptic firing rates. Multistability arises when the components of the network can be organized to access different values of these steady-state behaviors. This can occur through “fine-tuning” in predominantly feed-forward networks or through “self-consistency” in feedback settings. The role that STSP plays in creating these opportunities for multistability will be discussed below.

Mathematical Models of Short-Term Synaptic Depression

Three phenomenological models of short-term synaptic plasticity are reviewed. The first two, the AVSN model of Abbott et al. (1997) and the TM model (Tsodyks and Markram 1997), are the most popular and are generally used in conjunction with networks of spiking neurons. The third model, BMN (Bose et al. 2001), is relevant to neurons, such as bursters, that display slow oscillations and has the added feature that it separates the dynamics of synaptic plasticity from those of synaptic rise and decay.

For simplicity, we focus on models that only involve synaptic depression. In the Abbott et al. model, synaptic depression is based on the assumption that when a presynaptic spike results in transmission, the synaptic strength is decremented by some fraction f . Between spikes, the synapse recovers from depression. If $A(t)$ denotes the synaptic strength at time t and t_i denotes a sequence of spike times, then at each spike time

$$A(t_i^+) = fA(t_i^-),$$

where the superscript $+$ denotes limit from above and $-$ from below. Between spikes, the variable is allowed to recover according to

$$A' = (1 - A)/\tau_A$$

for time constant τ_A . If a set of presynaptic spikes arrives periodically with rate r , then the steady-state synaptic amplitude $A(r)$ can be calculated as

$$A(r) = \frac{1 - e^{-1/r\tau_A}}{1 - f e^{-1/r\tau_A}}. \quad (1)$$

In this model, the dynamics of depression and those of synaptic efficacy are both modeled by a single variable A .

The TM model describes synaptic plasticity by partitioning synaptic resources into three states: effective (E), inactive (I), and recovered (R), with $E + R + I = 1$. Each presynaptic spike at $t = t_{AP}$ utilizes a fraction U_{SE} of recovered resources transferring them to the effective pool. Resources in this group decay with time constant τ_{inact} to the inactive pool. From here, resources reenter the recovered pool with time constant τ_{rec} .

$$\begin{aligned} R' &= \frac{1}{\tau_{rec}} - U_{SE}R\delta(t - t_{AP}) \\ E' &= -\frac{E}{\tau_{inact}} + U_{SE}R\delta(t - t_{AP}). \end{aligned}$$

If action potentials arrive with interval Δt and if this time is large compared to τ_{inact} , then the postsynaptic current at each action potential can be calculated from

$$\begin{aligned} PSC_{n+1} &= PSC_n(1 - U_{SE})e^{-\Delta t/\tau_{rec}} \\ &+ A_{SE}U_{SE}\left(1 - e^{-\Delta t/\tau_{rec}}\right), \end{aligned} \quad (2)$$

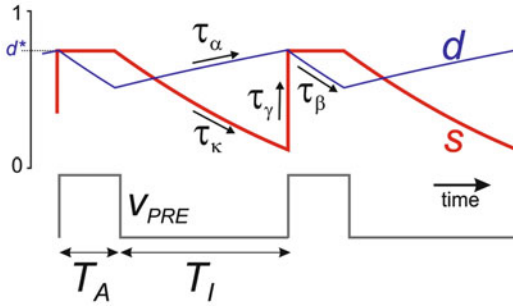
where A_{SE} is the maximal PSC that can be produced if all resources immediately go from R to E . As with the AVSN model, the efficacy and time-scales associated with the synaptic current are modeled by the same set of variables that describe depression.

The BMN model is different than the above models in two ways. First, it dissociates the dynamics of plasticity from those of synaptic efficacy. Second, it is designed to model the effect of slow wave or bursting oscillations, not just spiking neurons. A variable d keeps track of the level of depression of the synapse, while the variable s transmits the synaptic efficacy. These variables are linked at $t = t_{sp}$ defined by the moment when the presynaptic voltage v increases through a threshold v_θ . Both are governed by first-order equations:

$$d' = \frac{1 - d}{\tau_a} H(v_\theta - v) - \frac{d}{\tau_\beta} H(v - v_\theta) \quad (3)$$

$$s' = \frac{d(t_{sp}) - s}{\tau_\gamma} H(v - v_\theta) - \frac{s}{\tau_\kappa} H(v_\theta - v), \quad (4)$$

where $H(x)$ is the Heaviside function equal to one when $x \geq 0$ and zero otherwise. The postsynaptic current generated by this model is simply $I_{syn} = \dot{g}_{syn}s(v - E_{syn})$ where $\dot{g}_{syn}$ and E_{syn} are the maximal conductance and reversal potential of the synapse. Figure 1 shows an example of how the s and d variables interact in the BMN model. Equations 3 and 4 are coupled only when the presynaptic neuron crosses v_θ at which point the value of s is allowed to evolve towards the value $d(t_{sp})$. If τ_γ is small, then this effectively serves as an instantaneous reset. Note that the dynamics of s then remains uncoupled from those of d until the next moment that v increases through threshold. In particular, when the presynaptic neuron is below threshold, the synaptic current decays with time constant τ_κ that is independent of the recovery of synaptic resources which is



Multistability Arising from Synaptic Dynamics, Fig. 1 The time trace of the d and s variables for the BMN model plotted in response to the presynaptic activity V_{pre} . The time constants that control depression (τ_β), recovery (τ_α) and decay (τ_κ) of the synapse are shown. s approaches the value of d at the onset of activity (d^* at steady state) with a fast time constant (τ_γ)

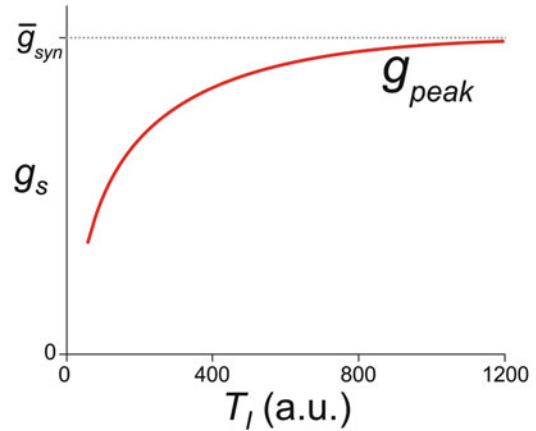
dependent on τ_α . If $A(t)$ from the AVSN model and the R variable from the TM model were plotted, they would qualitatively resemble the d variable of the BMN model (Fig. 1), except that, in the former two models, the variables would instantaneously be decremented at the time of a spike and recover between spikes, as opposed to the gradual decline over the time T_A in the BMN model. If a periodic train of presynaptic spikes or bursts with active time given by T_A and inactive time given by T_I drives Eqs. 3 and 4, then the steady-state amplitude for the synaptic resources, called d^* , measured at the time that v increases through v_θ is

$$d^* = \frac{1 - e^{-T_I/\tau_\alpha}}{1 - e^{-T_A/\tau_\beta} e^{-T_I/\tau_\alpha}}. \quad (5)$$

The peak synaptic strength g_{peak} can be calculated as the product of d^* with the maximal synaptic conductance

$$g_{peak} = \bar{g}_{syn} d^* \quad (6)$$

Note that for fixed T_A the expression for d^* is equivalent to that of $A(r)$ given in Eq. 1 in the AVSN model. Further, $T_I \rightarrow \infty$, $d^* \rightarrow 1$, monotonically showing that the level of available synaptic resources recovers back to a maximal value as the inactive time increases (equivalently as the frequency tends to 0).



Multistability Arising from Synaptic Dynamics, Fig. 2 For a depressing synapse, the peak synaptic strength is an increasing function of the presynaptic silent duration T_I as derived from Eqs. 5 and 6

All three models describe the short-term dynamics of a synapse when the presynaptic neuron is intrinsically rhythmic. In this case, the parameters r in the AVSN model, T_{AP} in the TM model, and T_I and T_A in the BMN model can be adjusted to achieve a specific synaptic strength. In particular, in a feed-forward or driven network, the level of plasticity can be finely tuned by controlling the frequency of the drive. In the case of a depressing synapse, strong drive leads to higher frequencies of synaptic usage, leading to weaker synapses. The opposite is true for lower-frequency driving. Figure 2 shows how the peak synaptic strength g_{peak} increases as a function of increasing T_I (T_A is kept fixed) for the BMN model. A qualitatively equivalent graph arises using Eq. 1 by plotting $A(r)$ versus $1/r$ or by using Eq. 2 to plot the steady-state PSC versus Δt . As the period increases (frequency decreases), the peak synaptic strength increases to the maximal level $\bar{g}_{syn}$.

In a feedback network containing many synapses with STSP, the quantities r , T_{AP} , T_I , and T_A do not necessarily remain parameters. Instead they can be affected by the synaptic inputs that the neuron receives. Thus to obtain periodic solutions, the plasticity variables must satisfy a consistency condition. Namely, network period is a function of synaptic strength and, alternatively, peak synaptic strength is a function of network

period. When these two are self-consistent, a periodic solution can occur. Multistability results when this consistency condition can be satisfied in different ways at different network periods.

Fine-Tuning Synaptic Strength in Feed-Forward Networks

In many central pattern-generating networks, the constituent neurons maintain a constant relative phase with respect to the network cycle even as the period of oscillations varies. To examine the role of STSP in such phase constancy, consider a network of two neurons O and F in which O is an oscillatory pacemaker neuron (with period P) which inhibits F and F rebounds from this inhibition to fire. After each inhibitory input to F , the time Δt that F takes to reach threshold can be determined. This defines a phase $\phi = \Delta t/P$ as the phase at which F fires. Manor et al. (2003) showed how synaptic depression could help the O – F network maintain phase. Namely, if O has small period, its synapse to F is depressed and thus weak. There is little effect on the timing Δt of F firing. In this case, there is a periodic solution in which the time to F firing is basically constant and controlled by parameters that are intrinsic to F . Alternatively, when the period of O is increased by increasing T_I , then its synapse to F has a chance to recover and become stronger. Now the firing time Δt depends more strongly on g_{peak} and the decay rate of inhibition τ_κ . This represents another stable solution where the phase of firing is controlled by the interplay of parameters associated with the O synapse and those intrinsic to F . In Manor et al. 2003, it is shown that Δt satisfies an equation of the form

$$c_1 e^{-\Delta t/\tau_w} + c_2 g_{\text{peak}} e^{-\Delta t/\tau_\kappa} = c_3. \quad (7)$$

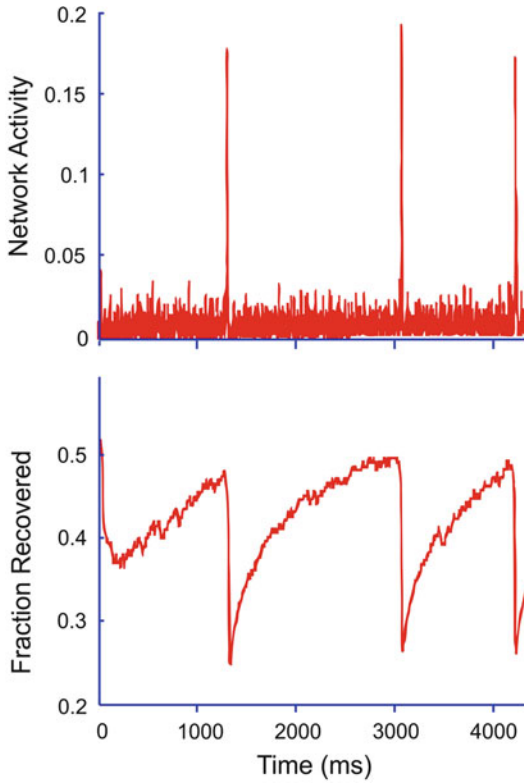
for $c_1, c_2 > c_3 > 0$ and τ_w being a time constant associated with a potassium current in F . At small periods, g_{peak} is small and the first term in Eq. 7 dominates. As can be seen, Δt is independent of T_I , and therefore, $\phi = \Delta t/P \sim 1/P$. At larger periods, g_{peak} given in Eq. 6 increases with T_I and the second term dominates. In this case Δt

changes with P leading to a complicated dependence of phase with P [see (Manor et al. 2003) for the full details].

The main point to convey here is that, in a feed-forward network, if the peak synaptic strength is controlled by the pacemaker, then it can be effectively treated as a parameter. In particular, by controlling the period of the pacemaker, g_{peak} can be fine-tuned to any desired value leading to different kinds of solutions. Also see Carver et al. (2008) and Lewis and Maler (2002) where similar ideas are employed in a feed-forward context.

Self-Consistency in Feedback Networks

In Tsodyks et al. (2000), Tsodyks et al. showed how synaptic depression can be used to obtain population bursts in cortical excitatory-inhibitory (E – I) networks. Tabak et al. (2000) showed a similar result in a model of development of the chick spinal cord using a rate model that only involved excitation. Both models operate using similar principals. In the Tsodyks et al. study, a network of 400 E cells was mutually and randomly coupled to a set of 100 I cells. All synapses display both synaptic facilitation and depression of varying degrees. The effect of synaptic depression was more relevant, as facilitation plays less of a role in creating the population burst. Focusing solely on synaptic depression, if the E cells have a high firing rate, then their synapses weaken and have less effect on their postsynaptic targets. At lower frequencies, their synapses have a chance to recover so that, when they fire, they can strongly recruit other E and I cells into the population activity. In effect, the model utilizes the two distinct stable states (strong versus weak synapses) that are present in the feed-forward network described in the previous section, but now finds a way to internally toggle between the two. Figure 3 is from Tsodyks et al. (2000) in which the top panel shows the fraction of neurons that are active in a specified time bin and the bottom panel the time course of synaptic resource recovery from depression, averaged over all E cells. As the top panel shows, there are bursts of network activity where larger numbers of neurons are



Multistability Arising from Synaptic Dynamics, Fig. 3 Population bursts in a network model of E and I neurons coupled with dynamic synapses. *Top panel* shows network population activity. *Bottom panel* depicts the average synaptic resources for each E cell. (Modified from Tsodyks et al. 2000)

coactive. Correspondingly, associated with each burst is a rapid drop in the average synaptic resources, followed by recovery on a longer time-scale. Note that the recovery dynamics shown in the bottom panel corresponds to the trace of the d variable in Fig. 2 of the BMN model for the case where T_A is very short.

A critical reason that population bursts exist in the Tsodyks et al. model is the heterogeneity in the basal firing rates of the individual E cells. The network is tuned so that some fractions of E cells have high spontaneous firing rates. It is the firing of this group that initiates recruitment of other E cells that form the burst. Self-consistency then dictates that the level of available synaptic resources is sufficient to continue the recruitment of enough cells to form the burst. This will occur

only if the recruitment occurs after a suitably (and self-consistently) long inter-burst interval. See Tsodyks et al. (2000) for further details including how the existence of the burst depends on the maximal synaptic conductance.

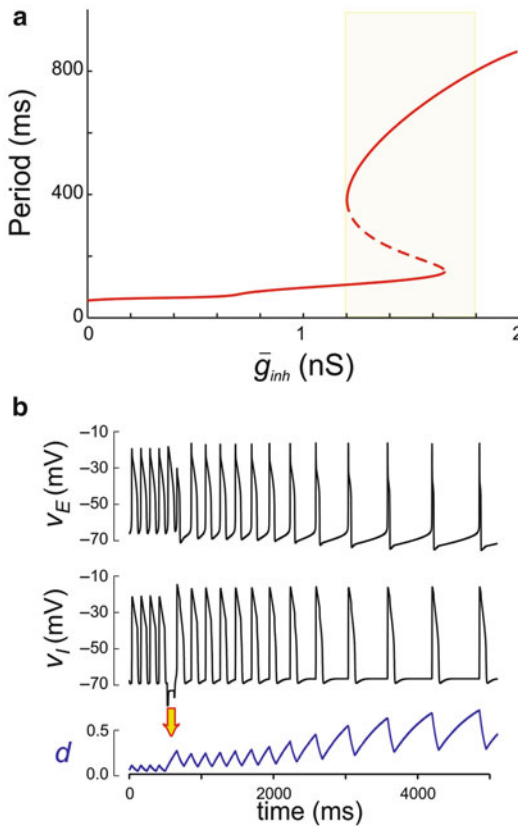
In Bose et al. (2001), a simpler deterministic system consisting of just one E – I pair with depression in the I to E synapse is considered. Here, it is possible to mathematically analyze the self-consistency condition. In this model, the activity of I is slaved to that of E . A map $\Pi(d)$ is derived that measures the value of the depression variable each time E fires. This map is easily obtained by solving Eq. 3 over one complete cycle of a typically E oscillation. Namely, solve $d' = -d/\tau_\beta$ with initial condition $d(0)$ for a time T_A corresponding to how long E is active. Then solve $d' = (1 - d)/\tau_\alpha$ with initial condition $d(T_A)$ for a time T_I to find $d_{n+1} = \Pi(d_n)$ given by

$$d_{n+1} = 1 - \left(1 - d_n e^{-T_A/\tau_\beta}\right) e^{-T_I/\tau_\alpha}. \quad (8)$$

Consider the case where T_A is fixed, but T_I varies as a function of the synaptic strength of the I to E synapse. Because this synapse is frequency dependent, T_I is an unknown in Eq. 8. However, T_I can be determined at each cycle using an equation similar to Eq. 7 given by

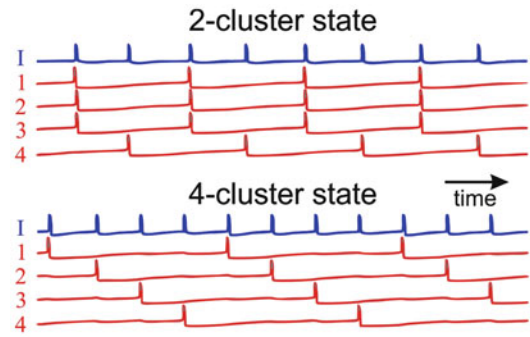
$$c_1 e^{-T_I/\tau_w} + c_2 \bar{g}_{\text{inh}} d_n e^{-T_I/\tau_k} = c_3, \quad (9)$$

where $\bar{g}_{\text{inh}}$ is the maximal inhibitory conductance. A fixed point of the map Π corresponds to a periodic solution of the E – I network. The value of d at the fixed point, denoted d^* , determines the overall level of depression associated with that solution and correspondingly determines the network period. Note that d^* is still given by Eq. 5 and it represents the situation where there is a self-consistency between the network period ($T_I + T_A$) and synaptic strength (g_{peak}). As $\bar{g}_{\text{inh}}$ changes the fixed points of Π undergo two different saddle-node bifurcations leading to range of values over which there are two stable solutions shown in Fig. 4a. Along the lower stable branch of fixed points, the maximal synaptic strength is small and the ensuing I to E synapse never becomes strong



Multistability Arising from Synaptic Dynamics, Fig. 4 Bistability of a two-cell $E-I$ network where the I to E synapse is depressing. (a) The bifurcation diagram of network period versus the maximal conductance of the depressing synapse. Shaded region shows the bistable range. Solid lines are stable, dashed lines unstable. (b) Voltage traces of the two cells and the depression variable shown for a value of $\bar{g}_{inh}$ in the bistable range. A brief hyperpolarizing pulse in the I cell (arrow) results in a transition from the fast period oscillations [lower solid branch of (a)] to slow period oscillations [higher solid branch of (a)]. (Modified from Bose et al. 2001)

enough to slow the high-frequency intrinsic oscillations of E . Here, T_i is small and the value of the fixed point is small. On the upper branch, $\bar{g}_{inh}$ is large enough so that when I fires, it forces E to remain inactive for a longer time. This makes T_i become larger through Eq. 9, which through Eq. 5 forces d^* to become large. This leads to a low-frequency solution. In Bose et al. (2001), it is shown that both solutions can coexist leading to bistability. Figure 4b illustrates the bistability showing a voltage trace of an $E-I$ pair along



Multistability Arising from Synaptic Dynamics, Fig. 5 Two of multiple stable solutions in a network of one I neuron reciprocally coupled to four E neurons. The I to E synapse is depressing. (Modified from Chandrasekaran et al. 2009)

with the corresponding trace for d . At the beginning of the trace, $E-I$ oscillates at a high frequency in which the I to E synapse is depressed. Transient hyperpolarization of I allows its synapse to recover so that when it again fires, it can strongly inhibit E . The transition to longer periods then ensues. The transition back to high-frequency oscillations could occur, for example, by transiently driving E to higher frequencies (not shown). Thus, there are two coexistent stable solutions, and transient inputs can make the network transition between them.

In Chandrasekaran et al. (2009), the two-cell network is generalized to a globally inhibitory network consisting of a single I cell that is reciprocally coupled to a network of E cells. The E cells have no direct synaptic connections to one another. Each of the I cell synapses exhibits short-term depression. Similar to the previous example, I fires whenever any E cell fires. If the E cells are all synchronized, the I cell's firing rate will be low in comparison to when the E cells are clustered into different groups. As a result, the firing rate of I can be used as a proxy for determining how many clusters the E cells have broken into; see Fig. 5. The different firing rates of I yield different levels of depression which in turn can only exist if there is self-consistency with the exact number of clusters needed to produce the specific amount of depression. The generalization of equations and Eq. 9 to handle this case led to a

2-dimensional map for which there are multiple coexistent fixed points. Each fixed point corresponds to a solution with a different number of clusters of E cells. Full details are in Chandrasekaran et al. (2009), where it is shown that the firing rate of I has a one-to-one increasing relationship with the number of clusters. See also Bose and Booth (2011), which considers the role of synaptic depression in phase locking of two heterogeneous I cells.

General Observations Regarding Networks and Short-Term Synaptic Plasticity

Short-term synaptic plasticity has been suggested to be of importance for many functions in the nervous system. It has been proposed to play a role in cortical gain control (Abbott et al. 1997), population rhythm generation (Tabak et al. 2000; Tsodyks et al. 2000), and direction selectivity (Carver et al. 2008). In addition, temporal coding in cortical processing such as novelty detection, coincidence detection (Thomson 2000), sound localization (Cook et al. 2003), and phase maintenance (Manor et al. 2003) may be attributed to depression. In experimental (Manor and Nadim 2001) studies of invertebrate central pattern generators, synaptic depression has been shown to introduce bistability of firing patterns. In Izhikevich et al. (2003), it is proposed that STSP creates a synaptic resonance whereby networks align themselves to operate at frequencies where there is a balance between synaptic facilitation and depression. That work suggests that by operating at resonant frequencies, networks increase the reliability of synaptic transmission and provide a novel mechanism for selective communication between neurons.

A specific proposed role of synaptic plasticity is that it gives rise to multistability or the existence of multiple different stable states. Multistability is defined as the coexistence of different stable states for the same parameter values. Alternatively, networks can have different stable states as a result of changing of parameter values due to neuromodulation or external drives to the

network. These two situations give rise to distinct types of networks, predominantly feedback versus feed-forward. Furthermore, they lead to different kinds of mathematical questions and challenges.

In studying networks involving STSP, the underlying intrinsic dynamics of individual neurons are relevant, but often only in how they affect the synapses. Indeed, an important point to note is that there are effects of plasticity that are independent of the properties of the postsynaptic cell. This is especially true in feed-forward networks where the level of plasticity, as argued above, can be fine-tuned. One can then assess how the level of fine-tuning affects different kinds of model cells. The fine-tuning itself is just a synaptic property. Where the interplay between synapse and cell model can become important is in feedback networks, where the postsynaptic cell has to transform the synaptic input it receives into a synaptic output. If the outgoing synapse itself exhibits plasticity, then how the intrinsic properties of the cell interact with the incoming synaptic properties would quantitatively affect the output of the system. However, the qualitative behavior of the network, including the existence of multistability, would be less affected by these intrinsic properties.

There are several mathematical challenges that arise in assessing whether multistability arises due to synaptic plasticity. In the absence of plasticity, when the synaptic coupling is not frequency dependent, then it is often possible to derive a 1-dimensional map to assess the existence and stability of solutions. Further, when the coupling between neurons is weak, then averaging can be used to derive a simplified 1-dimensional equation based on phase differences to assess these questions (Ermentrout and Kopell 1991). Synaptic plasticity, by its nature, does not lead to weak coupling. The maps in this case are typically 2 dimensional or higher. While the analysis of these higher-dimensional maps poses significant mathematical challenges, it also affords the opportunity to derive new mathematical techniques for their analysis that can be generalized to other scenarios.

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Multistability in Perception Dynamics

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Synonyms

[Ambiguous stimuli](#); [Binocular/monocular rivalry](#); [Multistable perception](#); [Perceptual alternations](#); [Perceptual bistability/tristability](#); [Perceptual rivalry](#); [Perceptual switching](#); [Visual rivalry](#)

Definition

Multistability in Perception Dynamics is the phenomenon of spontaneous switching in the subject’s perception between different interpretations of an ambiguous sensory stimulus.

Detailed Description

When subjects are confronted with an ambiguous sensory stimulus for an extended time, instead of experiencing a fixed percept, they report spontaneous switching between the different interpretations, a phenomenon known as perceptual multistability.

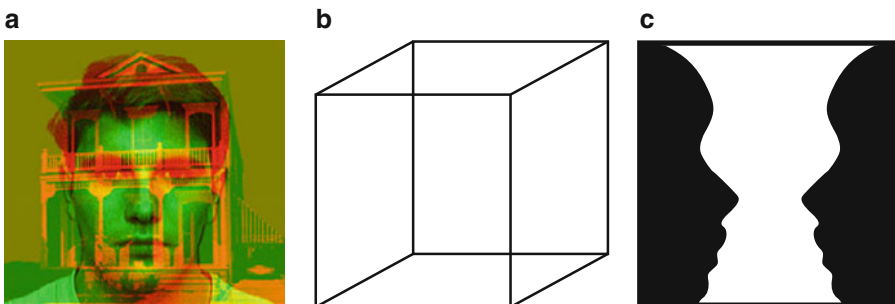
In perceptual multistability, while the subject is aware of one percept, the others appear suppressed from consciousness. Moreover, the subject experiences constant switches from being aware to being unaware of a given percept. This phenomenon is thought to provide a powerful method to search for neural correlates of conscious awareness, since it allows to disentangle the neural response related to the physical properties of the stimulus, which is continuously present, from that related to the conscious percept (Rees et al. 2002; Sterzer et al. 2009).

Perceptual multistability, and especially perceptual bistability (two interpretations), has been extensively studied in the visual modality (see Leopold and Logothetis 1999; Blake and Logothetis 2002; Tong et al. 2006 for reviews). The paradigmatic example of perceptual multistability in the visual system is the so-called binocular rivalry, for which there exists a vast literature (see, for instance, Blake 1989; Tong and Engel 2001). In binocular rivalry two drastically different images (face and house, for instance; see Fig. 1a) are presented to the two eyes simultaneously, and perception alternates between these two images. Other examples of perceptual bistability in the visual system include the Necker cube (alternation of two depth organizations; Fig. 1b), Rubin's vase-face (alternation of two figure-ground organizations; Fig. 1c), bistable apparent motion (alternation of two

arrangements of moving objects, Wallach 1935; Hupé and Rubin 2003; Rubin and Hupé 2004; see http://cerco.ups-tlse.fr/~hupe/plaid_demo/demo_plaids.html for a demonstration), etc.

Typically associated to the visual system, multistable perception has been reported in other sensory systems: auditory (Deutsch 1974; Pressnitzer and Hupé 2006; Bregman 1990), olfactory (Zhou and Chen 2009), and tactile (Carter et al. 2008). Recent studies suggest some common characteristics of perceptual multistability (Leopold and Logothetis 1999) across sensory modalities (Pressnitzer and Hupé 2006; see also Schwartz et al. 2012; Denham et al. 2012), namely:

- **Exclusivity.** Conflicting visual representations are not simultaneously present.
- **Inevitability.** Given sufficient time, switching will ultimately occur. Some factors such as attention (van Ee et al. 2005; Meng and Tong 2004) and strong intrinsic or extrinsic biases towards one of the percepts (Lack 1978; Moreno-Bote et al. 2010) can slow switching down but do not eliminate it.
- **Randomness.** Durations of perceptual bouts follow log-normal (or gamma) distributions (Levelt 1968; Lehky 1995; Logothetis et al. 1996; Brascamp et al. 2005). Correlations between durations of successive perceptual bouts are absent or insignificant (Lehky 1995; Logothetis et al. 1996; Pastukhov and Braun 2011).



Multistability in Perception Dynamics, Fig. 1 Examples of visually ambiguous patterns (a) Face-house rival image created by Frank Tong and used in his fMRI study of binocular rivalry (reproduced from Tong et al. 1998 with permission from Elsevier); when viewed with *green-red* 3D glasses, perception alternates

between a house and a face. (b) Necker cube; it can be perceived as a cube with the *lower-left* face or the *upper-right* face in front. (c) Rubin's face-vase; it can be perceived as a white vase or the silhouette of two black faces. Figures (b) and (c) from wikimedia commons

Since alternations occur not only when the inputs to the competing percepts are equal but also when they are largely unbalanced, one can study how changes in the stimulus' parameters affect perceptual dominance durations. For the domain of binocular rivalry, Levelt introduced a set of four "propositions" that summarize the effects of stimulus contrast of the monocular images on the switching dynamics (Levelt 1968). These properties, which are based on experimental observations, have been object of study in several works on perceptual bistability. Based on the existing literature, there is a general agreement on the reformulation of the second proposition. Thus, Levelt's updated set of binocular rivalry propositions state that:

- (I) Increasing the stimulus strength in one eye will increase the predominance of the stimulus.
- (II) Increasing the stimulus strength in one eye will affect the mean dominance duration of the eye with highest contrast (Brascamp et al. 2006; Boxtel et al. 2007; Klink et al. 2008; Moreno-Bote et al. 2010).
- (III) Increasing the stimulus strength in one eye will increase the alternation rate.
- (IV) Increasing the stimulus strength in both eyes will increase the alternation rate.

Although these propositions were originally described for the domain of binocular rivalry, dynamic properties for some stimulus manipulations in other bistable paradigms also satisfy them (Rubin and Hupé 2004; van Ee 2005; Klink et al. 2008; Moreno-Bote et al. 2010).

Neural Correlates of Perception

Experimental results in the visual system for subjects experiencing rivalry – imaging in humans and electrophysiology in awake, behaving monkeys – have revealed traces of neural activity that correlates with subject's perception at anatomically lower areas of visual processing (Tong and Engel 2001; Polonsky et al. 2000; Parkkonen et al. 2008), higher areas of visual processing (Leopold

and Logothetis 1996; Tong et al. 1998; Leopold and Logothetis 1999; Sheinberg and Logothetis 1997), as well as nonvisual parietal and frontal areas (Sterzer and Kleinschmidt 2007). Moreover, monkey electrophysiology (Leopold and Logothetis 1996) revealed that the proportion of neurons firing in time with perception increases along the visual pathway. Thus, while evidence of alternations is seen in different brain areas, the origin, which may involve interacting multiple areas, is still unknown.

Perceptual Multistability in Different Sensory Modalities: Auditory Streaming

Perceptual multistability has been extensively studied in the visual system. However, multistable perception has been reported in other sensory systems, in particular in the auditory system (see Schwartz et al. 2012 for a short review). Examples of multistability in the auditory system are found in binaural rivalry (Deutsch 1974), in the verbal transformation effect observed during word repetition (Warren and Gregory 1958; Warren 1961) and, especially, in the *auditory streaming* paradigm (Pressnitzer and Hupé 2006; Schnupp et al. 2010).

For the auditory streaming paradigm, the stimulus consists of a high-frequency tone A and a low-frequency tone B that are played alternately (AB-AB pattern) or in triplets (ABA-ABA pattern). For a slow presentation rate, the melody is perceived as a single stream that resembles a galloping (for the triplet pattern). However, if the presentation rate is fast enough and the frequency separation between the two tones is large enough, the melody is perceived as two separate streams (A-A-A-A and B-B-B-B). For intermediate values, there is ambiguity between coherence (a single stream) and segregation (two streams). These perceptual states were first reported by van Noorden in the so-called van Noorden diagram (van Noorden 1975). See Fig. 2. Later, experiments with long presentations reported alternations between these two states in the ambiguous region (Pressnitzer and Hupé 2006). Visit <http://auditoryneuroscience.com/topics/streaming-galloping-rhythm-paradigm>

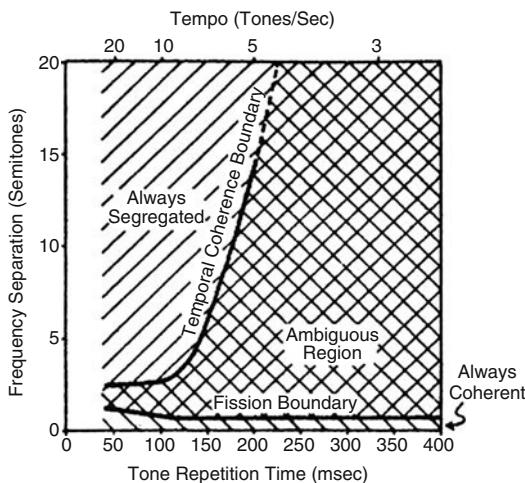
and <http://auditoryneuroscience.com/topics/streaming-alternating-tones> for a demonstration that illustrates auditory streaming.

As in visual multistability, perceptual correlations of neural activity have been observed in different brain areas. Recent studies indicate that perceptual auditory object formation, or “streaming,” may be based on neural activity within the auditory cortex and beyond (Cusack 2005; Micheyl et al. 2005), as well as in early stages of the auditory pathway, such as the cochlear nucleus (Pressnitzer et al. 2008).

Some models have been developed for the auditory streaming paradigm (Almonte et al. 2005; Wang and Chang 2008; Mill et al. 2013). However, most of them try to account for the van Noorden diagram (see Fig. 2), rather than the dynamics of perceptual switches reported for parameters in the ambiguous region of the diagram (Pressnitzer and Hupé 2006).

Computational Models for Perceptual Switches

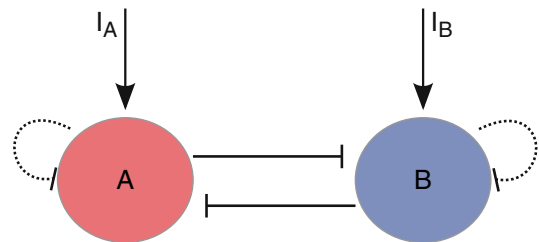
Current models of perceptual multistability are mainly phenomenological and try to explain the



Multistability in Perception Dynamics, Fig. 2 Van Noorden diagram for the auditory streaming paradigm. (Reproduced from McAdams and Bregman 1979 and adapted from Van Noorden (1975) with permission from the author)

dynamics of perceptual switching with simple computational mechanisms. They mainly focus on visual bistable stimuli (just two competing interpretations) and especially on binocular rivalry. Among representative firing rate models, we find Lehky (1988); Mueller (1990); Wilson (2003); Laing and Chow (2002); Moreno-Bote, Rinzel, and Rubin (2007); and Kilpatrick and Bressloff (2010). While details vary among models, the mechanism underlying the alternating rhythmic behavior is similar. It involves competition between two neural populations coding for the competing percepts via reciprocal inhibition (the neurons generating the dominant percept inhibit the neurons coding the suppressed percept) and slow negative feedback in the form of spike-frequency adaptation and/or synaptic depression (over time the system fatigues allowing the suppressed percept to become dominant). See Fig. 3. Noise is added to the system to account for the irregular oscillations and, in some cases, to drive the switches, causing adaptation to play a secondary role (Kim et al. 2006; Brascamp et al. 2006; Moreno-Bote et al. 2007). These models do not usually specify the site at which these competing neural populations are located.

This framework (competition with mutual inhibition and adaptation) is, in principle, that of the half-center oscillator in models for central pattern generators, networks that drive opposing muscles for locomotion, respiration, swallowing, etc. (Hooper 2001; Brown 1914).



Multistability in Perception Dynamics, Fig. 3 Schematic representation of the network architecture consisting of two mutually inhibitory populations that code for the two competing percepts. In addition to the mutual inhibitory connections (represented by *solid lines*), neural populations receive excitatory synaptic input of strength I_i associated to the external stimuli and undergo self-adaptation (indicated by the *dashed* connections)

Mathematical Formulation

The firing rate models developed for perceptual multistability try to capture the qualitative aspects of the behavioral data with idealized models that avoid the overhead of detailed cell-based models. They assume that the relevant information is captured by the firing rate of each neural population. The mathematical formulation for the firing rate or activation dynamics r_i of the i -population (responsive to percept i) can be described by

$$\begin{aligned}\tau \frac{dr_i}{dt} &= -r_i + f_i \left(\sum_j w_{ij} s_j r_j - \gamma a_i + I_i + n_i \right) \\ \tau_a \frac{da_i}{dt} &= -a_i + r_i \\ \tau_s \frac{ds_i}{dt} &= 1 - s_i + \phi s_i r_i\end{aligned}\quad (1)$$

where I_i is the direct stimulus input, w_{ij} is the strength of the synaptic currents to population i generated by the rates r_j of the other competing populations j , a_i is the spike-frequency adaptation of population i (subtractive negative feedback), and s_j is the variable controlling synaptic depression of the synapses from population j (divisive negative feedback). The parameters γ and ϕ control the strength of spike-frequency adaptation and synaptic depression, respectively. The time scales for the slow self-adaptation τ_a (subtractive) and τ_s (divisive) are much larger than the time scale τ for the activation dynamics r_i of population i . Population's gain function f_i describes the steady-state output firing rate for constant input. It is usually assumed to be non-negative and monotonically increasing, typically taken to be a Heaviside, piecewise linear, or sigmoid function. Gaussian white noise or colored noise n_i is added to the differential equations for the neural responses r_i .

Parameters are tuned so that the models account for many features of the empirical data of the alternations (distributions of dominance durations, lack of correlations, etc.) and satisfy to some extent Levelt's propositions for stimulus parameter variations corresponding to binocular rivalry and other bistable phenomena.

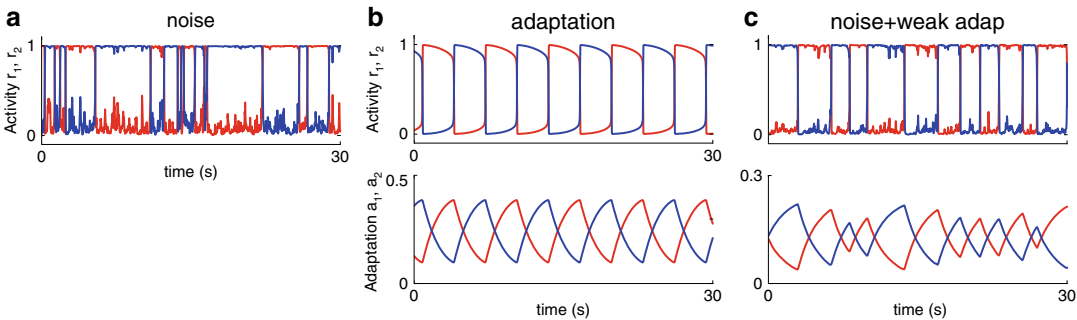
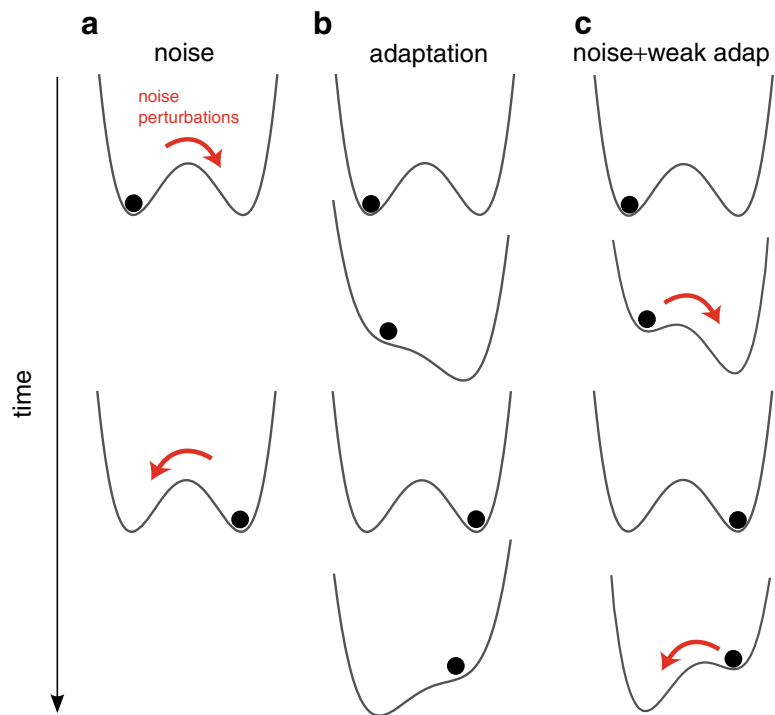
What Drives the Switches? Adaptation Versus Noise; Oscillatory Versus Winner-Take-All Models

Schematically, the dynamics of switches for model Eq. 1 can be represented by a double-well-potential-type architecture coupled with noise (Brascamp et al. 2006; Kim et al. 2006; Moreno-Bote et al. 2007). The two perceptual states are represented by two wells and the current state is represented by the position of a ball within these wells (see Fig. 4). The ball initially settles into one of these wells. If adaptation is not present in the system, the depth of the wells will remain unchanged and the noise fluctuations will eventually kick the ball from the occupied well to the other one. See Fig. 4a. In Fig. 5a we show the time course of the activity of the two populations. But if adaptation is present, the wells will slowly change, depth decreasing for the well where the ball is located and then recovering when the ball is absent. If adaptation is strong enough, it will eventually destroy the energy minimum and form a single well potential; the ball will roll towards the other well. See Fig. 4b. In Fig. 5b we show for the time course of the population activity and the adaptation. However, if adaptation is weak, it will only reduce the depth of the well but without destroying the local minimum. As in the adaptation-free case, the noise will be the ultimate responsible of kicking the ball to the other well. See Fig. 4c. In Fig. 5c we show the time course of the population activity and the adaptation.

Thus, one can distinguish between *oscillatory models* (slow adaptation causes alternations by itself) and *noise-driven attractor models* (noise drives switches in a winner-take-all framework). For noise-driven attractor models, the deterministic system (without noise) has two stable fixed points (attractors) (Figs. 4a and 5a). Such a system may incorporate adaptation, as long as it is weak enough so that it does not destroy the stable fixed points (Figs. 4c and 5c). For those models, if noise is removed, the system will remain indefinitely in one of the attractors. For oscillatory models the deterministic system does not have stable fixed

Multistability in Perception Dynamics, Fig. 4

Double well potential landscape for three models of perceptual bistability: (b), (a) noise-driven model without adaptation, adaptation-driven model, and (c) noise-driven model with weak adaptation. The position of the ball represents the perceptual state at a given moment. Adaptation slowly modulates the potential landscape



Multistability in Perception Dynamics, Fig. 5 Time courses of activity and adaptation for the two populations coding for two different percepts for (b), (a) noise-driven

model without adaptation, adaptation-driven model (c), and noise-driven model with weak adaptation

points but a stable limit cycle, with most of the time spent in the wells (Figs. 4b and 5b). For such a system, noise can be incorporated (e.g., to account for the variability in the dominance durations) as long as it does not destroy the limit cycle. To assess the role of noise and adaptation, the models try to conform to experimental data on dominance durations (averages, histograms' shape, correlations

between successive durations, etc.) and Levelt's propositions. Several studies suggest that models should operate in the noise-driven regime but not far from the boundary of being adaptation driven (Moreno-Bote et al. 2007; Shpiro et al. 2009; Pastukhov et al. 2013; Huguet et al. 2014).

Indeed, for white noise-driven attractor models, the residence times in each state will be

exponentially distributed; switching is a Poisson process, described by Kramer's rate theory (Kramers 1940). For adaptation-driven oscillator models, the residence times are regular, and adding noise will only perturb them around the mean; the distributions will look symmetrical around the mean. If adaptation is weakened, effectively giving more strength to noise, the histogram gradually evolves into a skewed one (log-normal or gamma as observed in the experiments). Thus, noise-driven models provide more variability and weak adaptation precludes short perceptual durations. In the double-well framework, the ball must wait for adaptation to adequately reduce the barrier before leaving the well, thus preventing the ball from leaving immediately after settling into the well.

Noise and adaptation should be set within some appropriate range so that correlations between successive perceptual durations are weak or absent, consistent with the experimental data. Indeed, if adaptation is too strong, during a long phase of dominance, the active population recruits a lot of adaptation, and when this population becomes suppressed, a long phase of recovery will be necessary before the next switch can occur. In the double-well case, if the ball jumps from one well after a long residence time, it falls into the other, now very deep, well; the barrier between wells is very high and the ball must wait a long time before it can switch back. These relations between successive durations lead to strong positive correlations.

Finally, for mutual inhibition models (irrespective of being noise or adaptation driven), one can distinguish two mechanisms for which transitions may take place: escape and release. For the release mechanism, the dominant population weakens (due to the slow self-adaptation) allowing the suppressed one to take over. However, for the escape mechanism, the suppressed population takes over after recovering from self-adaptation, suppressing the active population. In Shpiro, Curtu, Rinzel, and Rubin (2007), the authors identified these two mechanisms in different parameter regions for the models in Laing and Chow (2002) and Wilson (2003) as well as other models based on mutual inhibition. They found

that these models only satisfy Levelt's IV proposition when set in an escape mechanism. In Seely and Chow (2011), various biophysically plausible modifications to mutual inhibition models are proposed to resolve this issue.

Other Models of Perceptual Bistability

Centralized Mechanism of Perceptual Decision

Pettigrew and colleagues (Carter and Pettigrew 2003; Sheppard and Pettigrew 2006; Miller et al. 2000) conjectured the existence of a single oscillator external to the level of sensory representation that drives the switches, based on their results showing strong correlations of switch rates across subjects for different visual bistable stimuli. They proposed that oscillatory activity in the brainstem/subcortical area may generate rhythmic fluctuations in activity across the two cortical hemispheres. This would lead one to expect similar dynamics for bistable perception in different modalities. However, some studies reported absence of correlation across modalities for subject-specific biases (Pressnitzer and Hupé 2006; Carter et al. 2008).

Winnerless Competition Models

Winnerless competition models propose a mechanism for perceptual dynamics based on deterministic trajectories moving along heteroclinic orbits that connect saddle points in the phase space (Rabinovich et al. 2001). The saddles correspond to the activity of specific neurons or group of neurons and the heteroclinic orbits connecting the saddles correspond to the switches between different states. Winnerless competition models are not multistable; states are represented by transient trajectories close to the saddles rather than attractors of the noiseless system. The models can account for properties such as distribution of dominance times and Levelt's propositions (Ashwin and Lavric 2010).

Models of Percept Formation

Most models focus on the dynamics of perceptual alternations assuming that the percepts and their neuronal representations are given. Other models have been developed to account for the form of the generated percepts. Diekmann, Golubitsky, and Wang (2013) presented an algorithmic-like model based on Wilson's networks to account for interocular grouping percepts in binocular rivalry (Kovacs et al. 1996; Suzuki and Grabowecky 2002). These percepts are new images generated from features extracted from the images presented to the left and right eyes. The model considers neural populations that code for a particular image feature (such as color, orientation, motion direction, position, etc.). Neural populations that code for features of the presented images have excitatory connections. The model then looks for bifurcations from a fused state to an oscillatory state, in which several competing percepts alternate. They can also predict the form of the conflicting percepts, which in the case of interocular grouping contains features from both presented images.

In the auditory domain, Mill et al. (2013) proposed a model that looks for predictable patterns from the ongoing sequence of tones. These patterns are then strengthened or weakened based on their predictive success. The ones that are strengthened and thus maintained compete with other representations, creating perceptual multistability.

Perceptual Multistability with More Than Two Interpretations

Results on ambiguous sensory stimuli with more than two interpretations are still scarce in the literature. However, more than two percepts allow us to go beyond the temporal dynamics and explore transitions to different states. Recent results suggest that switches are not totally random but there is some dependence on perceptual history and/or trapping (Suzuki and Grabowecky 2002; Naber et al. 2010; Wallis and Ringelhan 2013; Huguet et al. 2014).

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Further Reading

- Binocular rivalry: http://www.scholarpedia.org/article/Binocular_rivalry
- Gestalt psychology: http://en.wikipedia.org/wiki/Gestalt_psychology
- Multistable perception: http://en.wikipedia.org/wiki/Multistable_perception

Multistability in Seizure Dynamics

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Definition

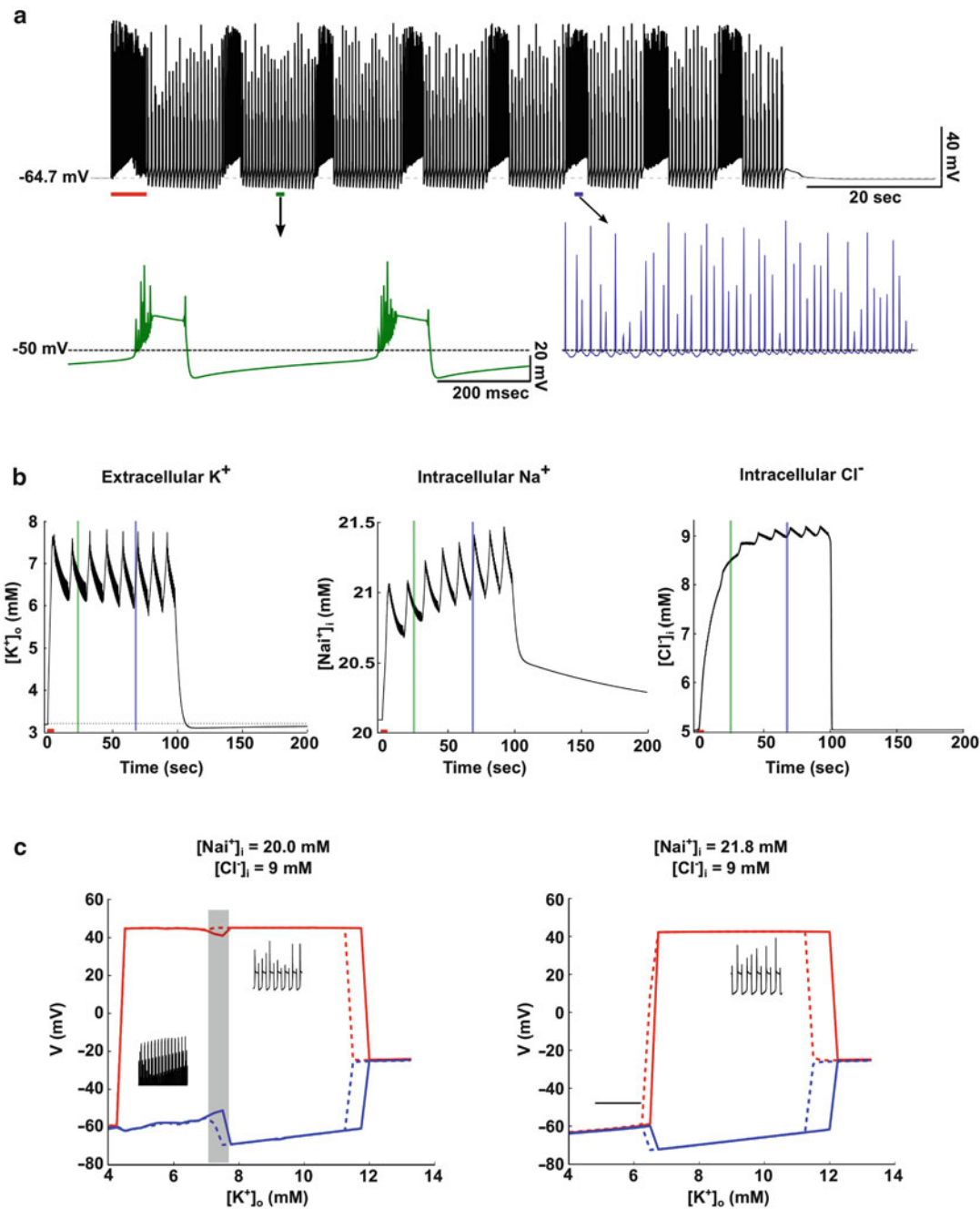
Several types of seizures manifest themselves in stereotyped patterns of electrical activity

characterized by large-amplitude periodic fluctuations of the local field potential (LFP), alternations of the spike/polyspike and wave (SW/PSW) EEG discharges, and fast runs of EEG spikes. Alternations between different types of activity over the course of a seizure may be explained by transitions between different states of the multistable dynamical system describing the brain network in the pathological epileptic condition. Furthermore, the epileptic state itself may represent one of many dynamical states, including a healthy state, which coexist in the same brain network. Thus, understanding the role of multistability is of tremendous importance for identifying the mechanisms and driving factors of epileptic seizures.

Detailed Description

Many types of epileptic seizures, including absence seizures, Lennox-Gastaut syndrome, West syndrome, and posttraumatic epilepsy (Niedermeyer 2005), are associated with spike/polyspike and wave (SW/PSW) complexes recurring at 2–3 Hz and/or fast runs at 10–15 Hz. The fast runs (or tonic state) and slow SW/PSW activity (or bursting state) commonly occur several times during seizure with spontaneous transitions between states (Fig. 1a). One duration estimate in animal models of a typical spike-wave seizure episode includes approximately 80% bursting activity and 20% of tonic spiking (Boucetta et al. 2008). Recordings from humans during epileptic seizures show evidence of multiple state transitions in self-terminating seizures (Schiff et al. 2005; Kramer et al. 2012).

Ionic concentrations may fluctuate significantly during seizure. Indeed, substantial fluctuations of extracellular K^+ concentration ($[K^+]_o$) were found during electrically or pharmacologically induced paroxysmal activity (Heinemann and Lux 1977). Extracellular Na^+ concentration ($[Na^+]_o$) decreases during epileptiform activity (Somjen 2002), which likely corresponds to increase of $[Na^+]_i$. Depolarizing effects of GABA-A receptor activation during seizure suggest elevated levels of intracellular Cl^- concentration ($[Cl^-]_i$) (Timofeev et al.



Multistability in Seizure Dynamics, Fig. 1 (a) Following transient (red line) DC stimulation, membrane voltage of a single pyramidal neuron from the network revealed several state transitions between tonic (fast runs) and clonic (bursting) periods before spontaneous termination. Bottom plots in (a) show activity of a pyramidal neuron for 2 s during bursting (green) and tonic periods (blue) (b) $[K^+]_o$, $[Na^+]_i$, and $[Cl^-]_i$ of one pyramidal neuron increased during tonic states and

decreased during bursting (c) Left, bifurcation diagram as a function of $[K^+]_o$ (minimum and maximum values of membrane voltage plotted as a function of parameter $[K^+]_o$). Solid lines indicate increasing $[K^+]_o$ and dashed lines for decreasing $[K^+]_o$. Insets show sample voltage traces for two values of $[K^+]_o$ (6.1 and 9.5 mM). Each plot was obtained for progressively increasing (left) and then decreasing (right) values of $[K^+]_o$. Gray region indicates existence of both tonic and bursting state or

2002). These changes in ion concentrations are observed experimentally and were also simulated in computer models (Fig. 1b). The ion changes may have profound effects on the network dynamics and may be responsible for the characteristic patterns of electrical activity observed during seizures.

Extracellular potassium concentration oscillates during seizure (Somjen 2002), a characteristic of the variable that determines state transitions. Application of dynamical system analysis to the study the role of $[K^+]_o$ in generating electrical patterns of activity during epileptic seizures revealed (1) the existence of four distinct activity patterns as a function of $[K^+]_o$, i.e., silence, tonic firing, bursting, and depolarization block, and (2) bistability with hysteresis between tonic firing and bursting for elevated $[K^+]_o$ levels (Frohlich and Bazhenov 2006; Frohlich et al. 2006, 2008). This bistability found by open-loop analysis of the models explains the occurrence of transitions between tonic firing and bursting (Fig. 1c, left). Specifically, neurons remained in tonic-firing mode, while $[K^+]_o$ increased up to the level where they were forced to switch to bursting mode (upper endpoint of hysteresis). Conversely, neurons remained in bursting mode, while $[K^+]_o$ decreased until the lower endpoint of the hysteresis was reached where they were forced to switch back to tonic-firing mode and the next cycle began. These modeling results show the alternating occurrence of positive (during tonic firing) and negative (during bursting) feedback. It suggests that transitions between tonic firing and bursting observed during many types of seizure may arise from the slow alternations between two metastable states, tonic firing and bursting states, mediated by $[K^+]_o$ dynamics.

In a network of neurons, bistability becomes critical in maintaining a stable seizure-like

state. However, in realistic conditions seizures spontaneously terminate within a few minutes. This can be explained by taking into account dynamics of other ion concentrations. Intracellular sodium ($[Na^+]_i$) progressively increases during a seizure episode due to spiking activity and the slow nature of Na^+ removal processes (Fig. 1b). This leads to a reduction of the resting membrane potential and increase in activity of the Na^+/K^+ exchange pump, which is electrogenic and mediates outward hyperpolarizing current. Both of these processes result in hyperpolarization of the membrane potential leading to termination of the seizure and start of the postictal depression state (Fig. 1a; Krishnan and Bazhenov 2011).

In terms of dynamical systems analysis, the slow increase of $[Na^+]_i$ during seizure leads to the disappearance of bistability which is required for self-sustained periodic transitions between tonic spiking and bursting, causing termination of the paroxysmal activity (Fig. 1c, right). Other studies have also reported transitions between different dynamical states due to change in ion concentrations in various classes of the model neurons (Cressman et al. 2009; Barreto and Cressman 2011).

Multistability between various seizure states can be mediated by other neuronal variables. Analysis of a leech neuron shows bistability exists between different tonic states (Cymbalyuk and Shilnikov 2005), tonic spiking and bursting states (Shilnikov et al. 2005), and between silence and bursting states (Malashchenko et al. 2011). In these studies, bistability was observed as a function of the reversal potential of potassium currents or external inputs. Detailed analysis of these models further revealed that bistability arises from the coexistence of stable periodic orbits (Cymbalyuk and Shilnikov 2005) or due to various bifurcation of periodic orbits (Shilnikov et al. 2005).

Multistability in Seizure Dynamics, Fig. 1 (continued) the bistable region. The tonic/bursting bistable region disappeared for sufficiently large values of $[Na^+]_i$. *Right*,

the same bifurcation diagram for slightly elevated $[Na^+]_i$. Note the disappearance of bistability

Ion concentration dynamics might explain not only transitions between different seizure states but also occurrence of the epileptic state itself (Frohlich et al. 2010). According to this hypothesis, the network can be in either the physiological or the pathological activity state. The relative size of the domain of attraction of the physiological state defines the resistance to seizure initiation. On the other hand, the relative size of the domain of attraction of the seizure state may define the intensity and duration of the individual seizures. These two domains of attractions will thus define if and how severely a brain will develop epileptic seizures. Patients suffering from epilepsy would have a reduced basin of attraction for the stable physiological state such that random input fluctuations can more easily cause a transition into the seizure state.

Experimental studies suggest that the balance of excitation and inhibition may change during the course of a seizure (Ziburkus et al. 2006, 2013), causing the basin of attraction of different dynamical states to change or even eliminate/create bistability. Existence of bistability due to the changes of excitation and/or inhibition has been shown in various types of neural mass models. In these studies, populations of neurons were reduced to a single equation (Lopes da Silva et al. 2003), and “normal” and “epileptic states” coexisted for the same sets of parameters. External inputs or internal random perturbations of the system determined the transition between normal and epileptic states.

In summary, the emergence of the network bistability proposes a fundamentally different viewpoint on how brain circuits can exhibit different activity states. In contrast to the commonly used approach of “parameter-mediated dynamic repertoire”, the dynamical richness of the neuronal circuit is not necessarily mediated by external, modulating factors but may be a direct consequence of dynamical mechanisms endogenous to the network.

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Multistability of Coupled Neuronal Oscillators

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Definition

The phase resetting curve (PRC) tabulates the transient changes in the firing period of an isolated neuron (*open-loop*) subject to an external stimulus identical to the one received when the neuron is part of a neural network (*closed loop*). The PRC is similar to a lookup table that gives the new firing period of a neuron in response to a specified perturbation applied at a given phase during the regenerative firing cycle. As such, the PRC contains all information needed to predict the response of a neural oscillator to a particular external perturbation. Under certain circumstances, networks of neural oscillators can develop stationary firing patterns called phase-locked modes. With appropriate external perturbations, a network can exhibit multistability and switch between different phase-locked modes. Memory storage and information processing are important examples of phase-locking processes that take place in neural networks. PRCs were used for the purpose of predicting the effects of

periodic stimuli to oscillating heart cells (Glass and Mackey 1988) and also for analyzing synchronization in systems of oscillators with pulsatile coupling (Winfree 1980; Glass and Mackey 1988; Reyes and Fetz 1993; Strogatz 2001; Pikovsky et al. 2003). The shape of the PRC determines the phase-locked modes and their sensitivity to noise and network heterogeneities (Tass 2007; Schultheiss et al. 2011).

Detailed Description

Among the techniques that are often used for predicting the activity of a neural network with the aid of a simplified model of individual neuron is the phase resetting curve (Tass 2007; Schultheiss et al. 2011). Both the phase resetting curve (PRC) and the spike time resetting curve (STRC) techniques reduce the complexity of a neuron to a black box whose output is a train of regular brief action potentials, or spikes, sensitive to the timing, or phase, of the external perturbations such as injected currents, presynaptic inputs, or neuromodulators (Oprisana and Boutan 2008; Oprisana 2009, 2010, 2014). The generality of both the PRC and STRC techniques stems from the fact that they can be applied to heterogeneous networks and are not limited to small amplitude (Rinzel and Ermentrout 1998; Ermentrout 2002; Preyer and Butera 2005) or short duration (pulsatile, or instantaneous) couplings among neurons (Oprisana et al. 2004; Netoff et al. 2005). Moreover, the PRC and STRC methods can be used to predict phase-locked modes in neural networks even when explicit mathematical models of component neurons are not available (Oprisana et al. 2003; Kralemann et al. 2013).

Neural Excitability Classes and PRC Types

Neural excitability refers to the capability of a neuron to produce repetitive action potentials in response to an externally applied current. In their seminal work on a giant squid axon, Hodgkin and Huxley (Hodgkin and Huxley 1952a, b, c, d;

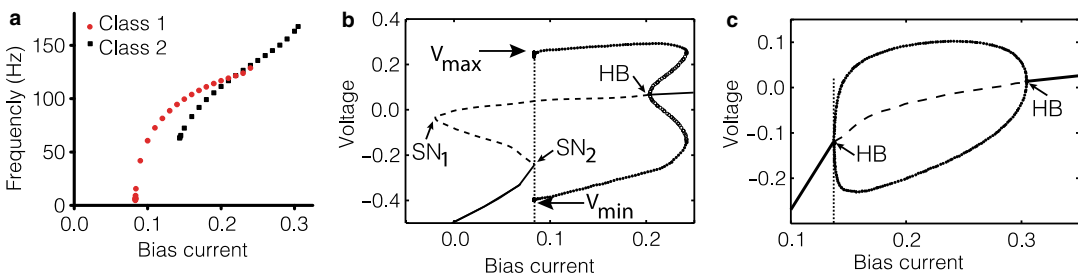
Hodgkin et al. 1952) experimentally identified three classes of axonal excitability: class 1, for which the repetitive firing is controlled by the intensity of an external stimulus and firing begins at arbitrarily low frequencies and increases as current increases; class 2, for which the repetitive firing starts at higher frequency range and the firing frequency change only marginally with increasing current; and class 3, for which there are no endogenous firing regardless of stimulus intensity or duration. The model neuron used in this entry is represented by the dimensionless equations of Morris-Lecar (ML) model neuron given at the end of the entry (Morris and Lecar 1981; Ermentrout 1996).

The class of membrane excitability is related to the mechanism underlying the transition from silence to oscillations. A gradual increase of a control parameter, such as the strength of an external bias current, could lead to a qualitative transition, or bifurcation, in the activity of the neuron (Ermentrout and Terman 2010). For example, a ML model neuron for which the bias current is between 0.02073 (SN₁ point in Fig. 1b) and 0.08326 (SN₂ point in Fig. 1b) has three steady states, of which only the lower fixed point (thick continuous line) is stable. At a bias current of 0.08326, marked by the vertical dashed line in Fig. 1b, i.e., the bifurcation point SN₂, the membrane potential suddenly starts large-amplitude oscillations, i.e., spiking between the $V_{\min}$ and

$V_{\max}$. At this bifurcation point, at least one eigenvalue of the linearized model neuron near the critical (bifurcation) point becomes positive with all the other eigenvalues being real and negative. Such a bifurcation is called a saddle node and is traditionally associated with class 1 excitability (see Fig. 1b). The peak-to-peak amplitude of the stable limit cycle that emerges at SN₂ is represented by one solid circle on the lower ($V_{\min}$) branch and a corresponding solid circle on the upper ($V_{\max}$) branch of the bifurcation diagram shown in Fig. 1b. The stable limit cycle (solid circles) collides with the unstable limit cycle (open circles) that emerges from a subcritical Hopf (HB) for a current of 0.2038. At the Hopf bifurcation point, a pair of the eigenvalues of the linearized model neuron assumes pure imaginary values with all other eigenvalues being real and negative (see Fig. 1c). A supercritical Hopf bifurcation leads to stable limit cycle oscillations and is traditionally associated with class 2 excitability (Hoppensteadt and Izhikevich 1997; Izhikevich 2007).

As a rule of thumb, the neural oscillators that are near a saddle node on an invariant circle (SNIC) bifurcation (see Fig. 1b) produce unimodal, or type 1, PRCs (see Fig. 2b). When oscillations arise from a Hopf bifurcation (see Fig. 1c), the PRCs tend to be bimodal, or type 2 (see Fig. 2c). The above rule has its exceptions, e.g., a modified Poincaré model of an abstract

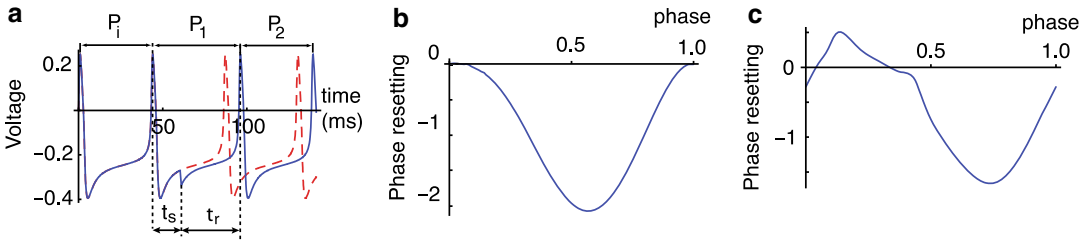
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Multistability of Coupled Neuronal Oscillators,

Fig. 1 The frequency versus bias current curve for class 1 (solid circles) starts at arbitrarily small frequency, whereas for class 2 excitability (solid squares), the oscillations start at a nonzero frequency (a). The bifurcations diagram of a class 1 excitable ML model has a SNIC bifurcation point at SN₂ for a current of 0.08326 (b). The continuous/dashed lines represent stable/unstable steady

states. Stable limit cycle oscillations have peak-to-peak amplitude between pairs of solid circles on lower ($V_{\min}$) and upper ($V_{\max}$) branches of the bifurcation diagram. Unstable limit cycle oscillations emerge from a subcritical Hopf bifurcation (HB) for a current of 0.2038. Stable oscillations of a class 2 excitable ML model emerge via supercritical HB (c)



Multistability of Coupled Neuronal Oscillators, Fig. 2 Repetitive firing of a model neuron (*dashed line*) is briefly perturbed at stimulus time t_s (*continuous line*), and the firing period changes from the intrinsic value P_i to P_1 during the current cycle that includes the perturbation (a). The stimulus time, t_s , represents the time elapsed between an arbitrarily phase reference and the activation of the

external stimulus. Alternatively, a stimulus phase variable could be used $\varphi = t_s/P_i$. The recovery time, t_r , is the elapsed between the stimulus activation and the next crossing of the phase reference. The first-order PRC is the normalized change in the firing period, i.e., $F^1(\varphi) = (P_1 - P_i)/P_i$, and can have unimodal shape for type 1 PRCs (b) or bimodal shape for type 2 PRCs (c)

oscillator near a SNIC bifurcation that can produce bimodal PRCs (Schultheiss et al. 2011; Ermentrout et al. 2012; Oprisan 2013).

Mathematical Definition of the PRC and the STRC

The intrinsic, or free-running, period P_i of a neural oscillator is the time interval between two successive crossings of an arbitrary membrane voltage threshold with the same slope in the absence of any external perturbation (Fig. 2a). External stimuli induce transient changes in the firing period that could be captured by the PRCs (Tass 2007; Schultheiss et al. 2011) or the STRCs (Kopell and Ermentrout 1988; Oprisan and Boutan 2008; Oprisan 2010, 2014). The largest change in the transient period of oscillation occurs during the current cycle, P_1 , i.e., the cycle that includes the perturbation, and is measured by the first-order PRC (Fig. 2a). Long-lasting transient changes of the intrinsic firing period, P_i , can be captured by measuring the interspike intervals of the subsequent cycles, P_2 , P_3 , etc. The stimulus time, t_s , represents the time elapsed between an arbitrarily phase reference and the activation of the external stimulus. The stimulus phase is the normalized stimulus time $\varphi = t_s/P_i$. The stimulus time is the duration between the most recent crossing of an arbitrary voltage threshold with positive slope, i.e., phase reference, and the onset of the stimulus. In this entry, the phase reference was set by a

crossing of $V_{thr} = 0$ mV voltage threshold with a positive slope (Fig. 2a). For example, the first-order transient PRC is defined by

$$F^1(\varphi) = P_1/P_i - 1, \quad (1)$$

where P_1 is the transiently modified firing period of the current cycle and $F^1(\varphi)$ measures the relative advance, if $F^1(\varphi) < 0$, or delay, if $F^1(\varphi) > 0$, of the subsequent spike due to a perturbation applied at phase φ during the current cycle.

The STRC keeps track of the recovery time t_r , i.e., how long it takes the neuron to recover from the most recent external input and fire again, and conveniently plots it versus the stimulus time t_s (Fig. 3a, b; Kopell and Ermentrout 1988; Galan et al. 2005; Oprisan and Boutan 2008; Oprisan 2010):

$$t_r = f(t_s) \quad (2)$$

The first-order PRC and the STRC are mathematically related. Indeed, from Fig. 2a, it results that $P_1 = t_s + t_r$, which, leads to

$$t_r = P_1 - t_s = P_1 - \varphi P_i \quad (3)$$

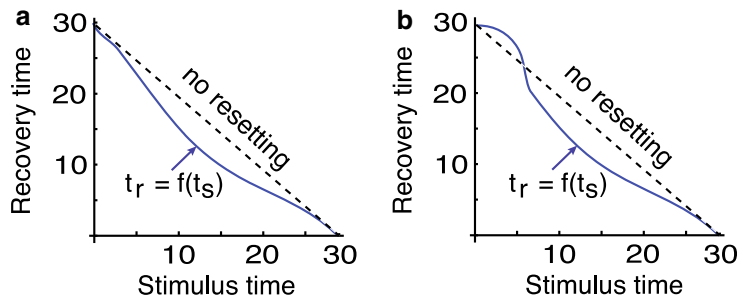
By substituting the definition Eq. 1 of the PRC, $P_1 = (1 + F^1(\varphi))P_i$, into Eq. 3,

$$t_r = P_i(1 - \varphi + F^1(\varphi)) = f(t_s), \quad (4)$$

which explicitly describes the relationship between the first-order PRC, $F^1(\varphi)$, and the

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Fig. 3 The STRC of type 1 (a) and type 2 (b) with the intrinsic period of 30 ms (continuous curve). The dashed line represents the curve of no phase resetting, i.e., $t_r = P_i - t_s$



corresponding STRC, $f(t_s)$. Therefore, all mathematical criteria for the existence and stability of phase-locked modes using the first-order PRC can be immediately expressed in terms of the STRC. Higher-order PRCs break the equivalence between the two approaches (Schultheiss et al. 2011). If there is no resetting, i.e., $F^1(\varphi) = 0$, then the STRC curve becomes $f(\varphi) = P_i(1 - \varphi)$, which is the dashed line of no resetting shown in Fig. 3.

Notation

The PRC order is always shown as an upper numerical index, e.g., F^1 is the first-order PRC. The corresponding neuronal oscillator is identified by a lower numerical index, e.g., t_{s1} refers to the stimulus time t_s of the input received by neuron “1” and P_{12} refers to the transiently modified period of the current cycle P_1 for the neuron labeled “2.” Open brackets () are reserved for functional arguments, as in $F(\varphi)$ or $f(t)$, whereas closed brackets [] label the firing cycle counted from an arbitrary reference.

Assumptions and Limitations of PRC Method

Shape Invariance

Both the PRC and the STRC methods predict the phase-locked firing patterns of neural networks using the response of an isolated neuron, i.e., open-loop setup, to an injected stimulus identical to the one received by the same neuron when it is fully connected, i.e., closed-loop setup. However, the actual shape of a presynaptic input is determined by both neuron’s intrinsic dynamics and its

environment. As a result, stylized shapes of the presynaptic inputs such as infinitesimally short pulsatile currents and rectangular- or triangular-shaped presynaptic inputs are often used (Gerstner and Kistler 2002; Ermentrout and Terman 2010; Schultheiss et al. 2011).

Attractive Limit Cycles

In practice, a neuron receives a stimulus at a given phase, and its response is recorded in order to determine the PRC. After 4–5 cycles, another perturbation is applied at a different phase and the response is recorded again and so on. The 4–5 cycles between successive perturbations allow the neuron to return to its unperturbed free-running state (Cui et al. 2009; Netoff et al. 2012). However, when using the PRC for the purpose of predicting the phase-locked modes of the network, the neuron receives one (or more) presynaptic input(s) every cycle. As a result, there is an implicit assumption that neural oscillators return to the unperturbed state in one cycle, i.e., the limit cycle strongly attracts any state space trajectory. This assumption can be relaxed by considering the effect of higher-order PRCs.

Instantaneous Resetting

Somewhat related to the high convergence rate of state space trajectories to the unperturbed limit cycle is the assumption that the effect of a stimulus is only captured by the (first-order) PRC, i.e., the resetting happens instantaneously. This assumption is problematic for perturbation that has a finite duration, especially when the perturbation is applied toward the end of the

cycle and spans two cycles. The issue can be alleviated by considering higher-order PRCs (Oprisan 2010; Schultheiss et al. 2011).

Single Input per Cycle

Finally, depending on the topology of the network, some neurons may receive multiple inputs per cycle, which are handled by a special form of the PRC (Oprisan and Canavier 2003, Oprisan 2012b), which is outside of the scope of this entry. Rings with neurons with appropriate periods of oscillations of individual oscillators allow only one input per cycle and can be solved with the traditional PRC technique described in this entry. Such networks were extensively studied as model neural circuits mimicking central pattern generators controlling legged locomotion (Pavlidis 1973; Golubitsky et al. 1998, 1999; Buono 2001; Nakanishi et al. 2004; Tass 2007; Proctor and Holmes 2010; Proctor et al. 2010; Schultheiss et al. 2011).

Phase-Locked Modes in Half-Centers

Although the PRCs and STRCs can be used to study arbitrarily large ring networks, we only refer here to two-neuron networks, or half-centers, due to their biological relevance. *Half-centers* are reciprocally inhibitory functional antagonists leading to an alternating activity pattern (Brown 1914). Half-centers rely on tonic external stimuli to trigger oscillations or to set the appropriate frequency of the rhythm, or they rely on exogenous rhythmic input, as in the case of pyloric network of the lobster stomatogastric nervous system (Harris-Warrick et al. 1992; Chow et al. 2005). Other well-studied half-centers control the leech's heartbeat (Calabrese et al. 1995; Efimov 2011), crab's stomatogastric (STG) nervous system (Bartos et al. 1999; Thuma et al. 2003), and lobster's STG (Harris-Warrick et al. 1992; Marder and Bucher 2001; Hooper and DiCaprio 2004; Marder and Bucher 2007). In addition, larger networks often can be divided into loosely connected half-centers (Skinner et al. 1994; Marder and Bucher 2001). Therefore, predicting firing patterns of half-

centers based on the intrinsic properties of individual oscillators and their connections is biologically relevant.

Throughout this entry, we will use a biophysically relevant, yet low-dimensional, neural oscillator model developed by Morris and Lecar (ML) to mimic the action potentials in barnacle muscle (Morris and Lecar 1981; Ermentrout 1996). In addition, ML model has the advantage that it can switch from class 1 to class 2 excitability by changing the values of only a few control parameters (see the "Model section for a detailed mathematical model").

Coupling spiking neurons through fast synapses produces brief synaptic currents that induce soft resetting. Such brief synaptic inputs change the firing period of the postsynaptic neuron, and their effect can be captured entirely by the first-order PRC or, equivalently, by the STRC. The advantage of the STRC-based prediction of phase-locked modes over the first-order PRC method consists of a straightforward geometric interpretation.

In a two-neuron network of reciprocally coupled spiking neurons, the recovery time of one neuron is the same as the stimulus time of the other neuron (Fig. 5):

$$t_{s1}[n] = t_{r2}[n-1] \& t_{s2}[n] = t_{r1}[n] \quad (5)$$

Using the STRC definitions from Eq. 2, the recovery time can be written in terms of the stimulus time for the same neuron, i.e., $t_{r2}[n-1] = f_2(t_{s2}[n-1])$ and $t_{r1}[n] = f_1(t_{s1}[n])$. By substituting these definitions into Eq. 5, one finds

$$t_{s1}[n] = f_2(t_{s2}[n-1]) \& t_{s2}[n] = f_1(t_{s1}[n]), \quad (6)$$

which after substituting the second equation of Eq. 6 into the first one gives the *recursive existence criterion for 1:1 phase-locked modes*:

$$t_{s1}[n] = f_2(f_1(t_{s1}[n-1])), \quad (7)$$

which determines the n th cycle's stimulus time based on its value during the previous cycle. The fixed points of Eq. 7 determine the phase-locked stimulus time:

$$t_{s1}^* = f_2(f_1(t_{s1}^*)) \quad (8)$$

The geometrical interpretation of the existence criterion given by Eq. 8 is as follows. Normally, the STRC, i.e., $t_r = f(t_s)$, is represented with the recovery time, t_r , along the vertical axis and the corresponding stimulus time, t_s , along the horizontal axis (see Fig. 3). However, in order to fulfill the mathematical condition for phase-locked modes, i.e., the stimulus time of one neuron must be equal to the recovery time of the other neuron (see Eq. 5), the axes of the STRC of the second neuron are flipped (Schultheiss et al. 2011; Oprisan 2012a, b). Indeed, in Fig. 5a we plotted the STRC of neuron “1” (continuous line) with the recovery time on the vertical axis and the stimulus time along the horizontal axis. The STRC of neuron “2” was plotted with the axes flipped, i.e., the recovery time along the horizontal axis and the stimulus time along the vertical. Therefore, the crossing point of the two STRCs satisfies the condition that $t_{s1} = t_{r2}$, which is the phase-locked existence criterion given by Eq. 5. In Fig. 5 we used an asymmetric coupling of two identical type 1 ML model neurons with synaptic couplings $g_{2 \rightarrow 1} = 0.010$ a.u., $g_{1 \rightarrow 2} = 0.015$ a.u. The predicted 1:1 phase-locked mode is $t_{s1}^* = 8.5$ ms and $t_{s2}^* = 23.5$ ms (Fig. 5a).

According to the STRC-based existence criterion given by Eq. 8, it is possible to have multiple intersections of the two STRCs of which some will be stable and other unstable. To determine the stability of a phase-locked mode to small perturbations, let us assume small deviations, $\delta t_{s1}[n]$, of the stimulus time from its steady-state (phase-locked) value, t_{s1}^* , predicted by the existence criterion (see Eq. 8). First, let us estimate the effect of small perturbation on $f_1(t_{s1}[n-1])$ and then use the result to determine how that perturbation propagates to the next recursion cycle that determines the existence of phase-locked modes according to Eq. 7, i.e., $t_{s1}[n] = f_2(f_1(t_{s1}[n-1]))$. For small perturbations, i.e., $|\delta t_{s1}[n]| \ll t_{s1}^*$, the Taylor's expansion around t_{s1}^* is

$$\begin{aligned} f_1(t_{s1}[n-1]) &= f_1(t_{s1}^* + \delta t_{s1}[n-1]) \\ &= f_1(t_{s1}^*) + \partial f_1 / \partial t_{s1}^* \delta t_{s1}[n-1] \\ &\quad + o(\delta t_{s1}[n-1]^2) \\ &\approx t_{s2}^* + n_1 \delta t_{s1}[n-1] \end{aligned} \quad (9)$$

where n_1 is the slope of the STRC of the first neuron at steady state. By substituting Eq. 9 into Eq. 7, one gets

$$\begin{aligned} t_{s1}[n] &= f_2(f_1(t_{s1}[n-1])) \\ &\approx f_2(t_{s2}^* + n_1 \delta t_{s1}[n-1]) \\ &= f_2(t_{s2}^*) + \partial f_2 / \partial t_{s1}^* n_1 \delta t_{s1}[n-1] \\ &\quad + O(\delta t_{s1}[n-1]^2) \approx t_{s1}^* \\ &\quad + n_2 n_1 \delta t_{s1}[n-1] \end{aligned} \quad (10)$$

Based on the linear stability analysis above, the error on the stimulus time during the n th cycle, $\delta t_{s1}[n]$, is related to its error during the previous cycle by

$$\begin{aligned} \delta t_{s1}[n] &= n_2 n_1 \delta t_{s1}[n-1] \\ &= \lambda_{\text{STRC}} \delta t_{s1}[n-1], \end{aligned} \quad (11)$$

which is the *STRC-based recursive stability criterion*. The solution of Eq. 11 is $\delta t_{s1}[n] = \lambda_{\text{STRC}}^n \delta t_{s1}[0]$ and describes the evolution of a small perturbation $\delta t_{s1}[0]$ from the steady-state t_{s1}^* , which is the phase-locked mode, over n cycles. The 1:1 phase-locked mode is stable if the stability index $|\lambda_{\text{STRC}}| = |n_2 n_1| < 1$.

The above STRC-based existence and stability criteria for phase-locked modes can be also expressed using PRC and Eq. 4, i.e., $P_i(1 - \varphi + F^1(\varphi)) = f(t_s)$. For example, Eq. 6 becomes

$$\begin{aligned} (\varphi_2[n-1]P_{i2}) &= P_{i2}(1 - \varphi_2[n-1] + F_2^1(\varphi_2[n-1])), \\ \varphi_1[n]P_{i1} &= P_{i1}(1 - \varphi_1[n] + F_1^1(\varphi_1[n])), \end{aligned} \quad (12)$$

which can be solved as before by substituting the second Eq. 12 into the first one. Based on Eq. 12, the phase-locked mode for identical oscillators, i.e., $P_{i1} = P_{i2}$, becomes

$$\begin{aligned}\varphi_1^* &= 1 - \varphi_2^* + F_2^1(\varphi_2^*), & \& \\ \varphi_2^* &= 1 - \varphi_1^* + F_1^1(\varphi_1^*),\end{aligned}$$

which can be written as

$$\varphi_1^* + \varphi_2^* - 1 = F_2^1(\varphi_2^*) = F_1^1(\varphi_1^*) \quad (13)$$

The geometric interpretation of the PRC-based existence criterion for identical neurons given by Eq. 13 involves finding all pairs $(\varphi_1^*, \varphi_2^*)$ that satisfy $F_2^1(\varphi_2^*) = F_1^1(\varphi_1^*) = F^*$ (see the horizontal dashed line in Fig. 5b) and only retaining those for which $\varphi_1^* + \varphi_2^* - 1 = F^*$. In the abovementioned asymmetrically coupling of two neurons with synaptic couplings $g_{2 \rightarrow 1} = 0.010$ a.u., $g_{1 \rightarrow 2} = 0.015$ a.u. gives the steady-state phases $\varphi_1^* = 0.82$, which corresponds to $t_{s1}^* = \varphi_1^* P_{i1} = 0.82 * 28.8 \text{ ms} = 23.6 \text{ ms}$, and $\varphi_2^* = 0.27$, which corresponds to $t_{s2}^* = \varphi_2^* P_{i2} = 0.27 * 28.8 \text{ ms} = 7.8 \text{ ms}$.

The PRC-based stability criterion can be immediately determined based on the STRC-based stability criterion Eq. 11 and the relationship between the PRC and STRC (see Eq. 4). Indeed, from Eq. 4 it results that the relationship between the slopes of PRCs and STRCs is

$$\begin{aligned}d(1 - \varphi + F^1(\varphi))/d\varphi &= d(f(t_s))/dt_s \\ \Leftrightarrow m - 1 &= n,\end{aligned} \quad (14)$$

which when substituted into Eq. 11 leads to

$$\begin{aligned}\delta\varphi_1[n] &= (m_2^1 - 1)(m_1^1 - 1)\delta\varphi_1[n-1] \\ &= \lambda_{\text{PRC}}\delta\varphi_1[n-1],\end{aligned} \quad (15)$$

where the stability index is $\lambda_{\text{PRC}} = (1 - m_1^1)(1 - m_2^1)$ and m_k^1 is the slope of the first-order PRC for neuron k . The phase-locked mode is stable to small perturbations if the PRC-based stability index $|\lambda_{\text{PRC}}| = |(1 - m_1^1)(1 - m_2^1)| < 1$. For identical neurons, the PRC-based stability criterion is $(1 - m)^2 < 1$, which leads to $0 < m < 2$ (Schultheiss et al. 2011).

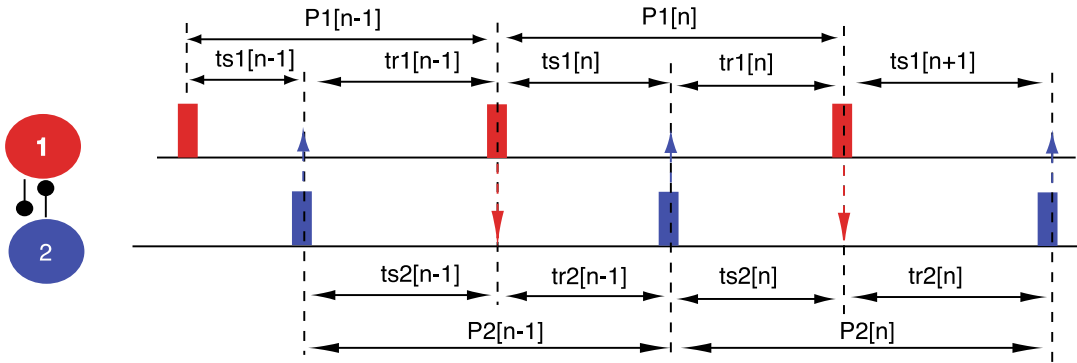
The above predictions based on the STRC (see Fig. 5a) gave us steady spike times $t_{s1}^* = 8.5 \text{ ms}$ and $t_{s2}^* = 23.5 \text{ ms}$. Similarly, using the PRC

method (see Fig. 5b), we predicted for the same half-center the steady phase that $\varphi_1^* = 0.82$, which corresponds to $t_{s1}^* = \varphi_1^* P_{i1} = 0.82 * 28.8 \text{ ms} = 23.6 \text{ ms}$, and $\varphi_2^* = 0.27$, which corresponds to $t_{s2}^* = \varphi_2^* P_{i2} = 0.27 * 28.8 \text{ ms} = 7.8 \text{ ms}$.

The above predictions were made in open-loop setup, and we also tested the phase-locked mode in closed loop. For this purpose, we coupled two identical type 1 ML model neurons with an instantaneous synaptic current $I_{\text{syn}} = g_{\text{syn}}(V_{\text{pre}} - E_{\text{syn}})$, where V_{pre} is the membrane potential of the presynaptic neuron and E_{syn} is the reversal potential of the synapse (Oprisan and Boutan 2008; Oprisan 2010; Schultheiss et al. 2011). All open-loop predictions were in very good agreement with closed-loop numerical simulations. For example, Fig. 5c shows the firing pattern of the half-center in closed loop with a stable stimulus time $t_{s1} = 21 \text{ ms}$ and a recovery time $t_{r1} = 12 \text{ ms}$.

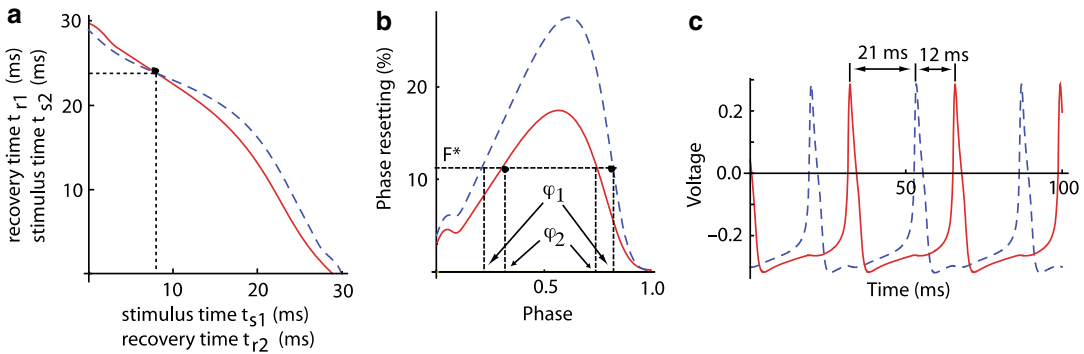
Multistability in Half-Centers with Phase Resetting Curve

Coupled oscillators often develop more complex phase-locked modes, such as $m:n$ firing, which is a stable firing pattern that repeats after the first neuron completed m cycles and the second neuron completed n cycles. Prominent examples of $m:n$ phase-locked modes include the 4:1 phase-locked mode between the heart beats and the respiratory cycle (Seidel and Herzog 1998; Schafer et al. 1998), motor patterns (von Holst 1939), and voice modulation (Mergell et al. 2000). The existence and stability criteria developed in the previous sections can be used to predict the circumstances that can force a half-center to change its firing pattern, for example, from 1:1 to 1:2. Although the PRC can be used to investigate multistability and phase-locked mode instabilities for more general network architectures, we will only give the highlights of the application to entrainment, i.e., the case when one neuron, such as neuron “2” in Fig. 4, only drives a second neuron, such as neuron “1,” and the feedback loop is absent. Based on the definition given in Eq. 4, the recovery time of the driven neuron is.



Multistability of Coupled Neuronal Oscillators, Fig. 4 A schematic representation of a half-center network with two reciprocally inhibiting neurons, labeled “1” and “2” (left panel). Temporal evolution of a 1:1 firing pattern (right panel). The action potential generated by each neuron is marked by vertical thick rectangle and the

solid vertical arrows marks the moment the presynaptic neuron generates an action potential and sends an inhibition to its postsynaptic neuron. The recovery interval for the postsynaptic neuron t_r is the same as the stimulus time t_s of the presynaptic neuron



Multistability of Coupled Neuronal Oscillators, Fig. 5 Phase-locked mode prediction using STRC and PRC methods. (a) The STRC plot, i.e., t_{r1} versus t_{s1} , of the first neuron (continuous line) overlapped with the STRC plot of the second neuron (long dashed line) with the axes flipped, i.e., t_{s2} versus t_{r2} . The crossing point of the two STRCs is the fixed point of the recursive existence criterion given by Eq. 8 and represents the phase-locked mode of the network. (b) For each acceptable value F^*

(horizontal dashed line) of the phase resetting, there are two pairs of phases (φ_1, φ_2) that satisfy the existence criterion $F^* = F_2^1(\varphi_2^*) = F_1^1(\varphi_1^*)$. One pair of phases (φ_1, φ_2) would determine a stable phase-locked mode (solid circles), and the other leads to an unstable solution. (c) Actual recordings of membrane voltage traces of the two coupled neurons confirm that predicted phase difference with both STRC (a) and PRC (b) methods

$$t_{r1} = P_{i1}(1 - \varphi + F^1(\varphi)) \quad (16)$$

In general, for 1:1 entrainment (see Fig. 4), the driven neuron, i.e., “1,” should recover from the inhibition induced by the driving neuron “2” before it receives another input from the driving neuron. Mathematically, the above condition for 1:1 entrainment means that $t_{r1} \leq P_{i2}$. If $t_{r1} \geq P_{i2}$, then the driven neuron “1” receives two inputs

from the driving neuron “2” during the same cycle and the network switched to 1:2 entrainment. The marginal stability condition for 1:1 entrainment is

$$t_{r1} = P_{i1}(1 - \varphi + F^1(\varphi)) = P_{i2} \quad (17)$$

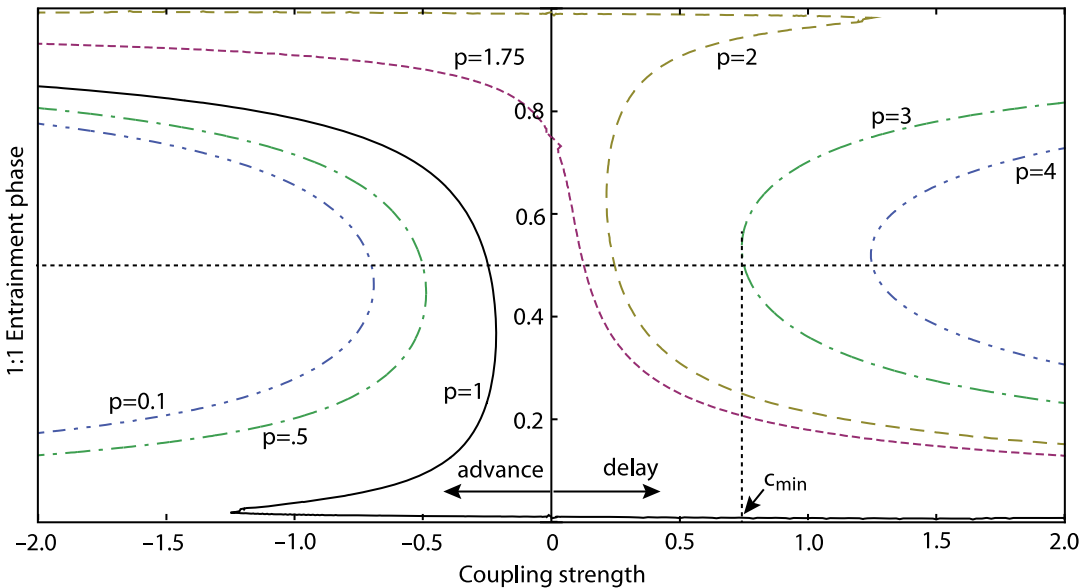
The above stability condition can be solved numerically to find the entrainment phase φ at

which the network develops multistability and switches from 1:1 to 1:2 modes. Alternatively, we could use an analytical expression for the PRC, if known, and solve Eq. 17. For example, in case of a SNIC bifurcation that is characteristic for class 1 excitability and that is usually associated with a unimodal PRC (see Fig. 2b), the analytic approximation for the infinitesimal PRC is (Izhikevich 2007; Ermentrout and Terman 2010; Schultheiss et al. 2011)

$$(F^1(\varphi)) = c (1 - \cos(\varphi)), \quad (18)$$

where c is a parameter that depends on the strength of the perturbation and the intrinsic firing period of the neuron receiving the perturbation. Additionally, if $c > 0$ the PRC is positive, which means that the subsequent spike is delayed by a perturbation, otherwise the spike is advances. By substituting Eq. 18 into Eq. 17,

the marginally stable phase of 1:1 entrainment can be determined for any given coupling strength, c , and intrinsic period ratio $p = P_{2i}/P_{1i}$ (see Fig. 6). For example, if the driving neuron has an intrinsic period P_{2i} three times as large as the driven neuron, i.e., $p = P_{2i}/P_{1i} = 3$ (dashed-dotted line in Fig. 6), then entrainment is only possible if the coupling strength is larger than a minimum, $c_{\min}$, required value able of forcing the follower to delay its next spike in order to match the driving neuron's intrinsic period. We also noticed that for each coupling strength that is able to produce a 1:1 entrainment, there are two possible values of the entrainment phase, which are almost symmetric with respect to the perfectly antiphase mode, i.e., phase = 0.5. In the case the driving neuron with intrinsic period P_{2i} is faster than the follower, i.e., $p = P_{2i}/P_{1i} < 1$, the 1:1 entrainment is only possible if the follower



Multistability of Coupled Neuronal Oscillators, Fig. 6 The 1:1 entrainment phase of a SNIC oscillator for which period ratio $p = P_{2i}/P_{1i}$ between the driving neuron (intrinsic period P_{2i}) and the follower (intrinsic period P_{1i}) is between 1 and 2 smoothly changes with the strength of the coupling and there is no bistability. A positive coupling constant means a positive PRC, i.e., a delay in the subsequent spike. For very dissimilar firing

periods, e.g., $p = 3$, a minimum coupling strength, $c_{\min}$, is necessary in order to delay the follower until it matches the driving neuron's intrinsic period. In this case, for each coupling strength, $c > c_{\min}$, there are two possible 1:1 phase-locked phases, i.e., the network shows bistability. Perturbations of the marginal 1:1 phase-locked modes can immediately lead to transitions from 1:1 to 1:2 firing patterns

can be advanced, i.e., the PRC is negative (see Fig. 6). For period ratios between 1 (continuous line in Fig. 6) and 2 (long dashed line in Fig. 6), there is only one possible entrainment (no multistability), and the phase difference between driving and follower linearly smoothly changes with the coupling strength. In conclusion, multistability emerges when the firing periods are very dissimilar ($p = P_{2i}/P_{1i} > 2$), and small perturbations at the marginal phases computed here can lead the neurons to switch from 1:1 to 1:2 phase-locked modes.

Conclusions

The bifurcation structure of a single cell (see Fig. 1) is the foundation for network-level multistability. We showed that, depending on the single-cell bifurcation structure, the response of a cell when it is part of a network, i.e., its phase response curve (see Fig. 2), has different degrees of bimodality. Type 1 PRCs are unimodal and allow only advance or delay of the subsequent action potential in response to a presynaptic input. Type 2 PRCs are bimodal and allow neurons to fine-tune their response until they “resonate” with a stable firing pattern of the network. While a PRC tabulates the response of a neuron in terms of phase of oscillation, the STRC (see Fig. 3) contains similar information in terms of stimulus and response times. The PRC is a powerful and versatile method that allows us to predict both the existence and the stability of phase-locked modes in neural networks. PRC- and STRC-based stability criteria for phase-locked modes allow us to predict when a firing pattern changes its stability and leads to multistability. For half-centers (see Fig. 4), both PRC and STRC methods give accurate and identical predictions, although the STRC-based method is slightly easier to apply and has a simpler geometrical interpretation (see Fig. 5). We also showed that the multistability of half-centers is controlled by both the intrinsic properties of the coupled neurons, such as their intrinsic firing periods, and the synaptic coupling strengths (see Fig. 6).

Appendix: Morris-Lecar Model

All numerical simulations were carried out with a conductance-based model that mimics the model giant barnacle muscle fiber (Morris and Lecar 1981). The model’s equations are

$$\begin{aligned}CdV/dt &= -g_{Ca}m_0(V - V_{Ca}) - g_Kw(V - V_K) \\ &\quad - g_L(V - V_L) + I, \\ dw/dt &= \phi(w_0 - w)/\tau_w,\end{aligned}$$

where the steady state values for Ca^{++} , i.e., $m_0 = (1 + \tan h((V - V_1)/V_2))/2$, and K^+ , i.e., $w_0 = (1 + \tanh((x - V_3)/V_4))/2$, are given by sigmoidal functions, and $\tau_w = 1/\cosh((V - V_3)/(2V_4))$ (Table 1).

All voltages are normalized by $V_0 = 120$ mV. The reversal potentials are $V_K = -0.7$, $V_L = -0.5$, and $V_{Ca} = 1.0$. The model’s constants are $V_1 = -0.01$ and $V_2 = 0.15$. The normalization constant for the conductances is $g_0 = 4$ mS/cm², and for the currents it is $V_0g_0 = 480$ μ A/cm².

The Mathematica code that implements the above ML model is the following:

```
Remove["Global`*"];
Clear[V1, V2, V3, V4, VK, VCa, VL, gK,
gL, gCa, I0, phi, m0, x, y, lambda0, w0,
f1, f2, Vthreshold, gsyn, Vsyn,
workingdata, workingfig, tmin,
ttransient, tmax, Vinit, winit, work];
(***** Model
parameters
*****)
V1 = -0.01; V2 = 0.15; V3 = 0.1; V4 =
0.145; VK = -0.7; VL = -0.5; VCa =
1.0; gCa = 1.33; gK = 2.0; gL = 0.5;
phi = 0.6; I0 = 0.0725;
```

Multistability of Coupled Neuronal Oscillators, Table 1 Morris-Lecar model parameters from class 1 and, respectively, class 2 excitability

	Class 1	Class 2
V_3	0.1	0.017
V_4	0.145	0.25
g_{Ca}	1.33	2.2
g_K	2.0	4.0
g_L	0.5	1.0
ϕ	0.6	0.417
I	0.0725	0.4

```
(***** Model
equations
*****)
f1[x_, y_] := - gCa*m0[x]*(x-VCa) -
gK*y*(x-VK) -gL*(x-VL);
f2[x_, y_] := lambda0[x]*(w0[x]-y);
(*****
Auxiliary functions and current
definitions
*****)
m0[x_] := (1 + Tanh[(x-V1)/V2])/2;
lambda0[x_] := Cosh[(x-V3)/V4]/2;
w0[x_] := (1 + Tanh[(x-V3)/V4])/2;
(* Zero phase threshold *)
Vthreshold = 0.26;
(*****
Numerical integration parameters
*****)
tmin = 0; ttransient = 1,000; tmax =
5,000;
(*****)
Clear[crossingsPlus, crossingsMinus,
solution];
(* Integrate with random initial
conditions to remove the transient
oscillations *)
Vinit = RandomReal[{-0.2, 0.2}](Netoff
et al. 2005a, b)]; winit = RandomReal
[{0.0, 0.2}];
solution = Reap[NDSolve[{V'[t] == f1[V
[t], w[t]] + I0, w'[t] == phi*f2[V[t], w
[t]], V[tmin] == Vinit, w[tmin] ==
winit}, {V, w}, {t, tmin, ttransient},
PrecisionGoal -> Infinity, MaxSteps -
> Infinity, Method -
> "StiffnessSwitching"]];
(*Integrate again with the last initial
conditions for a stable oscillation *)
Vinit = Evaluate[V[ttransient]/.
solution][[1, 1]]; winit = Evaluate[w
[ttransient]/. solution][[1, 1]];
crossingsPlus = {}; crossingsMinus =
{};
(* Use EventLocator to detect positive
and negative lope crossings of a
voltage threshold *)
solution = Reap[NDSolve[{V'[t] == f1[V
[t], w[t]] + I0, w'[t] == phi*f2[V[t], w
[t]], V[tmin] == Vinit, w[tmin] ==
winit}, {V, w}, {t, tmin, tmax},
PrecisionGoal -> Infinity, MaxSteps -
> Infinity, Method -> {EventLocator,
"Event" -> {V[t]-Vthreshold, V[t]-
Vthreshold}, "Direction" -> {1, -1},
"EventAction" -> {AppendTo
[crossingsPlus, t], AppendTo
[crossingsMinus, t]}}, Method -
> "StiffnessSwitching"]];
(* Determine the period of oscillation
and spike duration from voltage
crossing times *)
```

```
crossA = Table[crossingsPlus[[i + 1]] -
crossingsPlus[[i]], {i, 1, Length
[crossingsPlus]-1}]; If[crossingsMinus
[[1]] < crossingsPlus[[1]],
crossingsMinus = Drop[crossingsMinus,
1]];
crossB = Table[crossingsMinus[[i]] -
crossingsPlus[[i]], {i, 1, Length
[crossingsMinus]-1}];
burst = Mean[crossB]; period = Mean
[crossA];
sdperiod = StandardDeviation[crossA];
sdburst = StandardDeviation[crossB];
Print["period = ", period, " +/- ",
sdperiod, " ms; burst = ", burst, " +/-
", sdburst, " ms."];
```

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Definition

Dynamical systems describe orbits or trajectories as they evolve in time-space. The brain is a dynamical system whose macroscopic behavior may be couched in terms of normal (e.g., waking, attentive, etc.) or abnormal (e.g., coma, seizure or post-seizure, etc.) states. Brain stability may be defined as the proneness of a trajectory or orbit to remain in its “neighborhood” in the presence of perturbations. The terms bistability and multistability denote the coexistence of more than one simultaneously “stable” states in a system.

Epilepsy is a disorder characterized by the aperiodic emergence of unprovoked seizures that in 20–40% of sufferers are uncontrollable by medications. Behaviorally, seizures are characterized by one or more of involuntary movements, sensations, perceptions, and loss of awareness or of consciousness. Electrically, seizures manifest as aberrant increases in power of neuronal oscillations at certain frequencies. Subjects with pharmaco-resistant seizures require special forms of therapy such as resection of epileptogenic brain tissue or electrical stimulation delivered to the said tissue. Electrical stimulation for seizure blockage has been traditionally delivered in pulse trains lasting for at least 1 s at frequencies rarely below 50 Hz (Lesser et al. 1999; Osorio et al. 2005). Seizure blockage using a single electrical pulse or at most a handful (e.g., up to 6) of pulses was attempted in vivo.

Multistability: Stopping Events with Single Pulses

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Synonyms

Bistability; Flip-flop; Systems with two or more phase-spaces

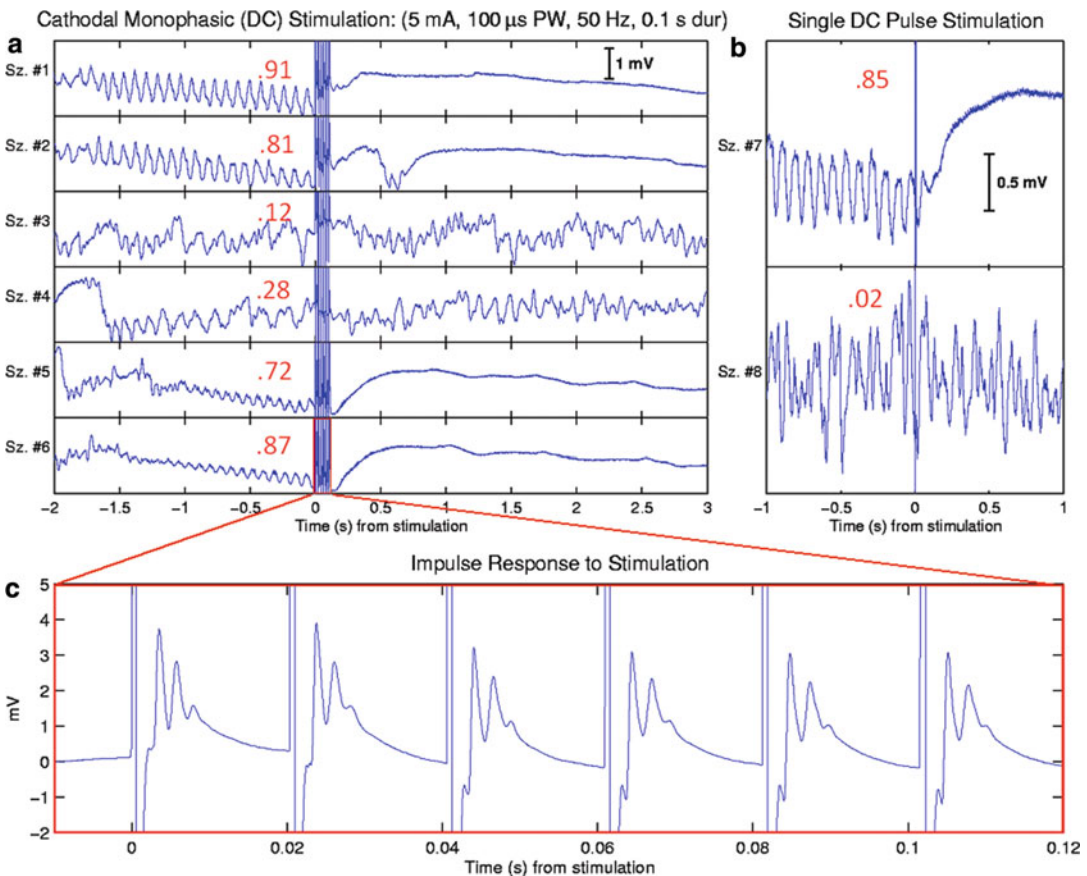
Detailed Description

Seizure blockage using exogenous means such as a *single* electrical pulses is feasible only if neuronal oscillators behaving pathologically possess and may be forced into a “non-seizure well.” The existence of “non-seizure wells” or of non-seizure phase spaces for pathological neuronal oscillations (e.g., epileptic seizures) and the dynamics of the seizure (ictus) to non-seizure (postictal) transition were studied in animals whose brains (in whole or in part) had been rendered seizure prone with systemically or topically administered compounds (Osorio and Frei 2009).

Seizure blockage (or induction) was attempted with either single (or with up to 6) monophasic (DC) square wave pulses whose blocking (or triggering) efficacy was optimized by varying their intensity and polarity.

Single or few (up to 6) DC pulses (1.0–8.0 V; width: 100–200 μ s; electrode impedances: $\sim$ 1 K Ω) were delivered manually or automatically to (a) generalized tonic-clonic seizures, induced in rats with 3-mercaptopropionic acid, a GABA synthesis inhibitor, or (b) to a small region of

disinhibited (by topical application of penicillin, a GABA receptor antagonist) rabbit's cortex. Treatment outcome (blocked vs. non-blocked seizures) was investigated using the degree of morphological similarity among waves ("rhythmicity index"), an indirect measure of neuronal synchrony level. Blockage using single or brief (0.1 s) DC pulses was consistently achieved for seizures with a rhythmicity index >0.7 , while seizures with levels <0.6 were largely unperturbed (Fig. 1).



Multistability: Stopping Events with Single Pulses, Fig. 1 (a) Top left-hand panels depict six seizures recorded from one (representative) rat using subdural electrodes (activity from only one contact is shown) each treated with a total of 6 monophasic (cathodal) pulses delivered through the electrodes adjacent to those used for recording. (b) Top right-hand panels depict two seizures treated with single monophasic (cathodal) pulses (5 mA, 100 μ s) also delivered adjacent to the recording electrodes (same rat). The numbers on top of each tracing

to the left of the stimulation artifacts in each panel correspond to the "rhythmicity index," a measure of similarity between successive signal waveforms, computed using software developed by these investigators. (c) Magnified view of 6 tissue impulse responses to each of the 6 monophasic pulses delivered over 0.12 s to seizure #6. The probability of seizure blockage is clearly a function of rhythmicity index value. The impulse responses to cathodal stimulations show subtle phase changes (resetting) on their "way to the 'null space'"

The capacity of a single electrical pulse to either block (Figs. 1 and 2) or trigger (figure not shown) epileptic seizures may be construed as evidence of multistable dynamics in rodents' and lagomorphs' brains and by inference in those of humans with epilepsy. The dependence of probability of blockage on neuronal synchronization level is indicative of its importance for treatment outcome.

Three observations in this study (Osorio and Frei 2009) of interstate transitions in the mammalian brain merit deliberation:

1. Seizures were blocked by more than one pulse (e.g., up to 6 monophasic pulses) (Fig. 1), but by a much lesser number of pulses than conventionally used (e.g., 50–300) (Lesser et al. 1999; Osorio et al. 2005); that a handful (e.g., up to 6) instead of a single electrical pulse may under certain conditions be required to block seizures (Fig. 1) hints at the state-dependent existence of multiple “well potentials” between the ictal and postictal states.
2. Seizure blockage is dependent on pulse polarity; changing the polarity from positive to negative (or vice versa) may lead to failure

of blockage, an observation that insinuates that these phase-spaces have distinct “spatial orientations.”

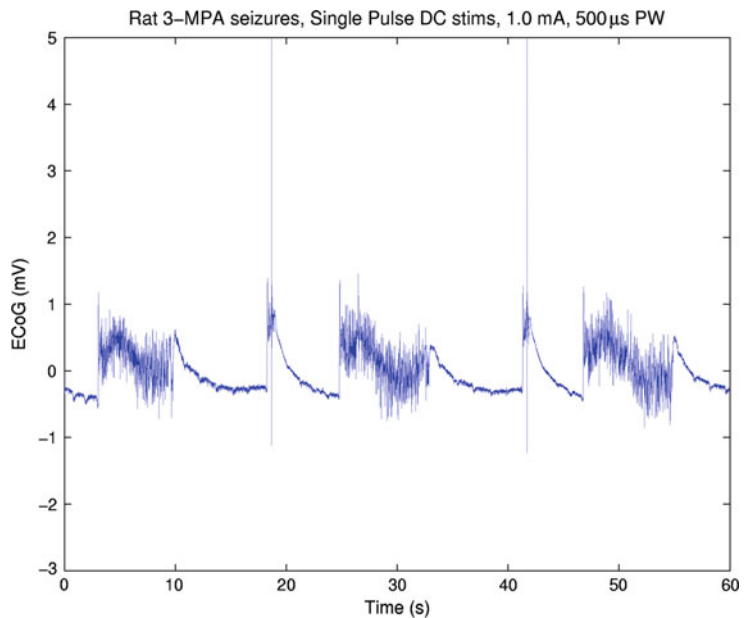
3. The transition associated with seizure blockage is to another *abnormal* state, the so-called post-ictal, and not to the normal or interictal phase-space; exogenous or spontaneous termination of seizures does not immediately restore functional normalcy to the brain or more specifically to the networks engulfed by paroxysmal electrical activity as evidenced using spectral and clinical analyses.

A sudden highly desirable transition from an ictal to an interictal/normal space seems elusive, an indication that the dynamics of this transition are qualitatively different from that of the interictal to interictal phase-space or “well.”

While premature transitions (as required for clinical usefulness) from the ictal to the postictal “well” require some form of exogenous energy to violate the laws (Osorio et al. 2009, 2010) governing the intensity, duration, and extent of spread of pharmaco-resistant seizures, this transition occurs spontaneously, that is, in the absence of identifiable exogenous energy. The proclivity

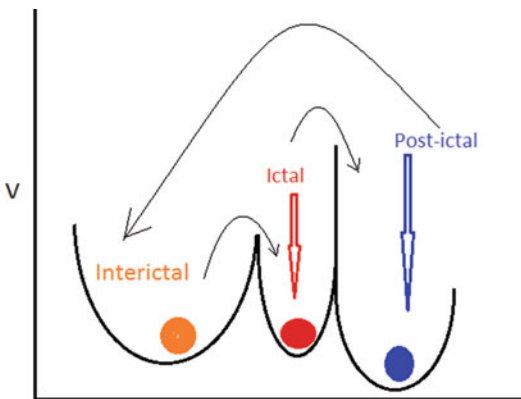
Multistability: Stopping Events with Single Pulses, Fig. 2

To investigate if single DC pulses (1.0 ma; 500 us) were annihilating seizures, they were delivered to every other seizure, during a period when their morphology and duration were quite similar. Seizures are annihilated by single monophasic pulses



of the brain to transition between and within normal and abnormal phase-spaces without large energy expenditures may be observed in systems near the edge of stability.

For simplicity and for the sake of didactics, the epileptic brain may be conceptualized by resorting to the standard “double-well” potential (interictal and ictal) model (Fig. 3). In this model, the two minima (or “wells”) are stable phase-spaces, and only the maximum (e.g., the energy “barrier” between the 2 “wells”) is deemed unstable. The accepted dynamical description of a “double-well” potential is that, for example, stochastic perturbations force a “particle” that performs a “random walk” constrained by the well’s geometry toward the maximum; whether or not the “particle” returns to its original “well” (interictal) or is “forced” into the ictal (Fig. 3) depends on factors such as the magnitude, type, and timing of the perturbation, the height of the inter-well maxima, etc. While exogenous seizure blockage or generation (energy is required to “push” the particle out a well into another) may be adequately



Multistability: Stopping Events with Single Pulses, Fig. 3 Representation of three brain states (interictal, ictal, postictal) as “wells.” Transitions between states (e.g., from interictal to ictal) are indicated by arrows. The height of the inter-well separatrices (corresponding to voltage (V) barriers) varies as a function of level of consciousness, level and type of cognitive activity, time of day, stochastic factors (e.g., luminance level), etc., shaping interstate transition probabilities. Note that the transition from ictal to interictal requires passage through the post-ictal “well”

described by the two-well model, *spontaneous* interictal to ictal and ictal to postictal transitions in the epileptic brain may occur differently, and the epileptic brain may be better described by a *multi-* than a bistable paradigm as inferred from experimental observations by the group of Lopes da Silva. Indeed, the epileptic brain may be more aptly regarded as “multi-unstable” (e.g., far from stability).

Seizure blockage with a single (or a handful) of electrical pulses is not only a valuable therapeutic strategy but also a useful experimental tool that informs the scantily understood dynamics of the epileptic brain. Exploitation of “multistability” for therapeutic purposes is not modern; Pelops from Alexandria, the teacher of Galen, implemented this concept as early as 150 AD, using mechanical means (Siegel 1976).

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Multistable Perception

- [Multistability in Perception Dynamics](#)

Multivariate Spectral Analysis

- [Spectral Interdependency Methods](#)

Muscle

- [Hill's Model for Muscle Physiology and Biomechanics](#)

Music Processing in the Brain

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Definition

Music perception involves acoustic analysis, auditory memory, auditory scene analysis, processing of interval relations and of musical syntax and semantics, and activation of (pre)motor representations of actions. Moreover, music perception potentially elicits emotions, thus giving rise to the modulation of emotional effector systems such as the autonomic nervous system, the hormonal system, and the immune system. EEG and fMRI studies inform us about the time course of the processes underlying music perception, as well as about where in the brain these processes might be located.

Detailed Description

Introduction

Music has been proven to be a valuable tool for the understanding of human cognition, human emotion, and their underlying brain mechanisms. Music is part of the human nature: It appears that throughout human history, in every human culture, people have played and enjoyed music. The oldest musical instruments discovered so far are around 30,000–40,000 years old (Conard et al. 2009), but it is likely that already the first individuals belonging to the species *homo sapiens* made music (about 100,000–200,000 years ago). Only humans learn to play musical instruments, and only humans play instruments cooperatively together in groups. It is assumed by some that human musical abilities played a key phylogenetical role in the evolution of language (Wallin et al. 2000) and that music-making behavior engaged and promoted evolutionarily important social functions (Cross and Morley 2008; Koelsch 2014). Ontogenetically, newborns (who do not yet understand the syntax and semantics of words) are able to decode acoustic features of voices and prosodic features of languages (Moon et al. 1993), and it appears that infants' first steps into language are based in part on prosodic information (Jusczyk 1999). Moreover, musical communication in early childhood (such as parental singing) plays a major role in the emotional, presumably also in the cognitive and social development of children (Trehub 2003). Making music in a group is a tremendously demanding task for the human brain that elicits a large array of cognitive (and affective) processes, including perception, multimodal integration, learning, memory, action, social cognition, syntactic processing, and processing of meaning information. This richness makes music an ideal tool to investigate the workings of the human brain.

Auditory Feature Extraction

Music perception begins with the decoding of acoustic information. Acoustic information is translated into neural activity in the cochlea and progressively transformed in the auditory brainstem, as indicated by different neural

response properties for the periodicity of sounds, timbre (including roughness, or consonance/dissonance), sound intensity, and interaural disparities in the superior olivary complex and the inferior colliculus (Sinex et al. 2003; Langner and Ochse 2006; Pickles 2008; Geisler 1998). Already the dorsal cochlear nucleus projects into the reticular formation (Koch et al. 1992), and the vestibular nerve also contains numerous acoustically sensitive nerve fibers (Todd et al. 2014). Moreover, both the vestibular nuclei and cochlear nuclei project to the reticular formation, and the vestibular nucleus also projects to the parabrachial nucleus, a convergence site for vestibular, visceral, and autonomic processing. Such projections initiate and support movements and contribute to the arousing effects of music. Thus, subcortical processing of sounds gives rise not only to auditory sensations but also to muscular and autonomic responses, and the stimulation of motor neurons and autonomic neurons by low-frequency beats might contribute to the human impetus to “move to the beat.”

Further up in the auditory pathway, the inferior colliculi can initiate flight and defensive behavior in response to threatening stimuli (Lamprea et al. 2002; Cardoso et al. 1994). From the thalamus (particularly over the medial geniculate body), neural impulses are mainly projected into the auditory cortex (Kaas et al. 1999; LeDoux 2000; Öngür and Price 2000). Importantly, The auditory pathway does not only consist of bottom-up, but also of top-down projections; nuclei such as the dorsal nucleus of the inferior colliculus presumably receive even more descending than ascending projections from diverse auditory cortical fields (Huffman and Henson 1990).

During the last years, a number of studies investigated decoding of frequency information in the auditory brainstem using the frequency-following response (FFR). The FFR can be elicited preattentively and is thought to originate mainly from the inferior colliculus (but note also that it is likely that the auditory cortex is at least partly involved in shaping the FFRs, e.g., by virtue of top-down projections to the inferior colliculus). Using FFRs, Wong et al. (2007) measured brainstem responses to three Mandarin

tones that differed only in their (f_0) pitch contours. Participants were amateur musicians and nonmusicians, and results revealed that musicians had more accurate encoding of the pitch contour of the phonemes (as reflected in the FFRs) than nonmusicians. This finding indicates that the auditory brainstem is involved in the encoding of pitch contours of speech information (vowels) and that the correlation between the FFRs and the properties of the acoustic information is modulated by musical training. Similar training effects on FFRs elicited by syllables with a dipping pitch contour have also been observed in native English speakers (nonmusicians) after a training period of 14 days (Song et al. 2008). The latter results show the contribution of the brainstem in language learning and its neural plasticity in adulthood.

A study by Strait et al. (2009) also reported musical training effects on the decoding of the acoustic features of an affective vocalization (an infant’s unhappy cry), as reflected in auditory brainstem potentials. This suggests (a) that the auditory brainstem is involved in the auditory processing of communicated states of emotion (which substantially contributes to the decoding and understanding of *affective prosody*) and (b) that musical training can lead to a finer tuning of such (subcortical) processing.

Acoustical Equivalency of “Timbre” and “Phoneme”

With regard to a comparison between music and speech, it is worth mentioning that, in terms of acoustics, there is *no* difference between a phoneme and the timbre of a musical sound (and it is only a matter of convention that some phoneticians rather use terms such as “vowel quality” or “vowel color,” instead of “timbre”). Both are characterized by the two physical correlates of timbre: spectrum envelope (i.e., differences in the relative amplitudes of the individual harmonics) and amplitude envelope (also sometimes called the amplitude contour or energy contour of the sound wave, i.e., the way that the loudness of a sound changes, particularly with regard to the onset and offset of a sound). Aperiodic sounds can also differ in spectrum envelope (see, e.g.,

the difference between /f/ and /s/), and timbre differences related to amplitude envelope play a role in speech, e.g., in the shape of the attack for /b/ vs. /w/ and /f/ vs. /t/.

Auditory Feature Extraction in the Auditory Cortex
As mentioned above, auditory information is projected mainly via the subdivisions of the medial geniculate body into the primary auditory cortex (PAC, corresponding to Brodmann's area 41) and adjacent secondary auditory fields (corresponding to Brodmann's areas 42 and 52). These auditory areas perform that a more fine-grained, and more specific, analysis of acoustic features compared to the auditory brainstem. For example, Tramo et al. (2002) reported that a patient with bilateral lesion of the PAC (a) had normal detection thresholds for sounds (i.e., the patient could say whether there was a tone or not), but (b) had elevated thresholds for determining whether two tones had the same pitch or not (i.e., the patient had difficulties to detect fine-grained frequency differences between two subsequent tones) and (c) had markedly increased thresholds for determining the pitch direction (i.e., the patient had great difficulties in saying whether the second tone was higher or lower in pitch than the first tone, *even though* he could tell that both tones differed). Note that the auditory cortex is also involved in a number of other functions, such as auditory sensory memory, extraction of inter-sound relationships, discrimination and organization of sounds as well as sound patterns, stream segregation, automatic change detection, and multisensory integration (Hackett and Kaas 2004; Winkler 2007).

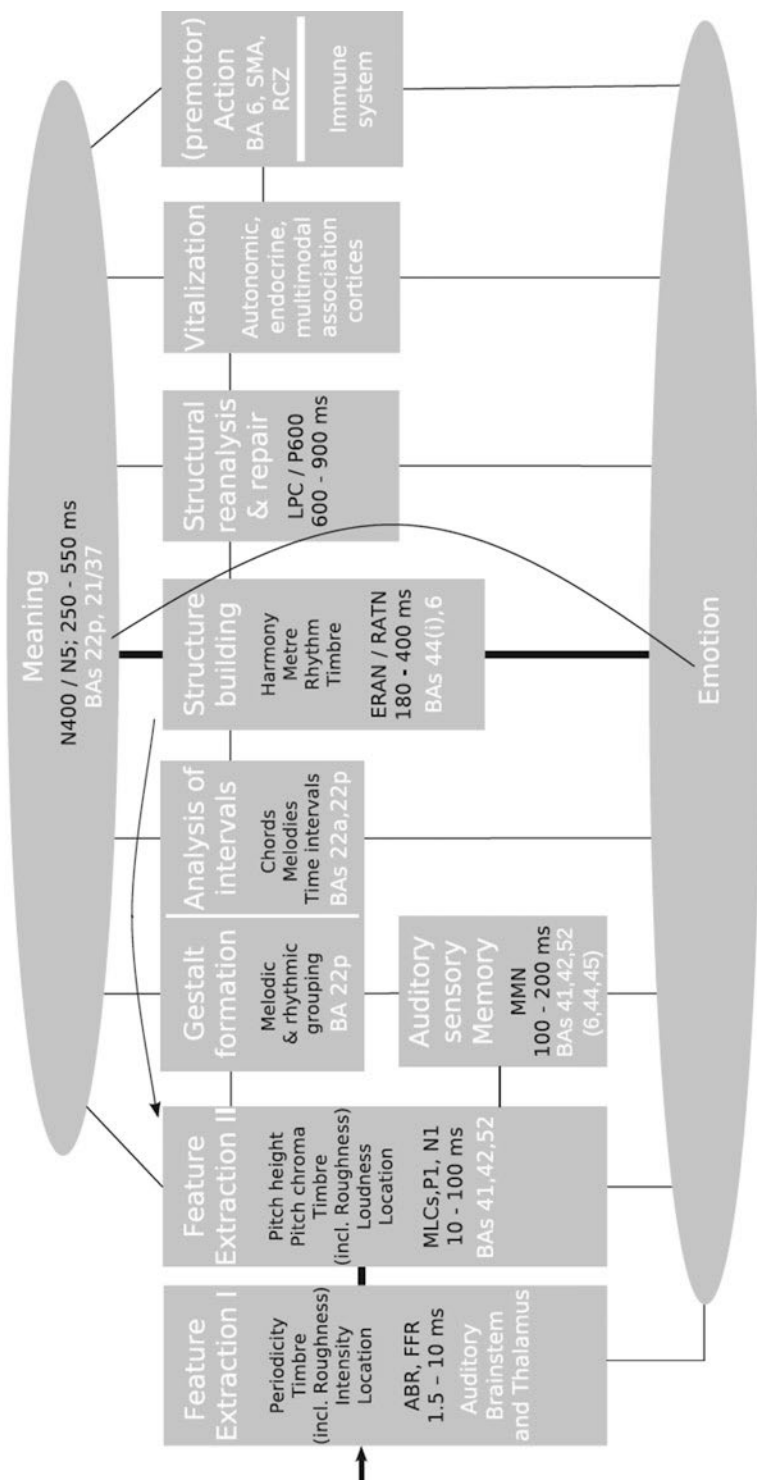
Moreover, the (primary) auditory cortex is involved in the transformation of acoustic features (such as frequency information) into percepts (such as pitch height and pitch chroma): Lesions of the (right) PAC result in a loss of the ability to perceive residue pitch in both animals (Whitfield 1980) and humans (Zatorre 1988), and neurons in the anterolateral region of the PAC show responses to a missing fundamental frequency (Bendor and Wang 2005). Moreover, magnetoencephalographic data indicate that response properties in the PAC depend on whether or not a missing fundamental of a complex tone is

perceived (Patel and Balaban 2001). Note, however, that combination tones emerge already in the cochlea and that the periodicity of complex tones is coded in the spike pattern of auditory brainstem neurons; therefore, different mechanisms contribute to the perception of residue pitch on at least three different levels (basilar membrane, brainstem, and auditory cortex). However, the studies by Zatorre (1988) and Whitfield (1980) suggest that, compared to the brainstem or the basilar membrane, the auditory cortex plays the more prominent role for the transformation of acoustic features into auditory percepts (such as the transformation of information about the frequencies of a complex sound, as well as about the periodicity of a sound, into a pitch percept).

Warren et al. (2003) report that changes in pitch chroma involve auditory regions anterior of the PAC (covering parts of the planum polare) more strongly than changes in pitch height. Conversely, changes in pitch height appear to involve auditory regions posterior of the PAC (covering parts of the planum temporale) more strongly than changes in pitch chroma (Warren et al. 2003). Moreover, with regard to functional differences between the left and the right PAC, as well as neighboring auditory association cortex, several studies suggest that the left auditory cortex (AC) has a higher resolution of temporal information than the right AC and that the right AC has a higher spectral resolution than the left AC (Zatorre et al. 2002; Hyde et al. 2008; Perani et al. 2010).

Finally, the auditory cortex also prepares acoustic information for further conceptual and conscious processing. For example, with regard to the meaning of sounds, just a short single tone can sound, for example, "bright," "rough," or "dull." That is, single tones are already capable of conveying meaning information (this is indicated by the line connecting the module "Feature Extraction II" and "Meaning" in Fig. 1; processing of musical meaning will be dealt with further below).

Operations within the (primary and adjacent) auditory cortex related to auditory feature analysis are reflected in electrophysiological recordings in ERP components that have latencies of about



Music Processing in the Brain, Fig. 1 Neurocognitive model of music perception. mid-latency component, *MMN* mismatch negativity, *RATN* right anterior temporal *ABR* auditory brainstem response, *B4* Brodmann's area, *ERAN* early right anterior negativity, *RCZ* rostral cingulate zone, *SMA* supplementary motor area. *MLC* indicates peak latencies of scalp-recorded evoked potentials

10–100 ms, particularly middle-latency responses, including the P1, and the later “exogenous” N1 component (Pantev et al. 2001).

Echoic Memory and Gestalt Formation

While auditory features are extracted, the acoustic information enters the auditory sensory memory (or “echoic memory”), and representations of auditory Gestalten (Griffiths and Warren 2004) are formed (Fig. 1). Operations of the auditory sensory memory are at least partly reflected electrically in the mismatch negativity (Näätänen et al. 2001). The MMN has a peak latency of about 100–200 ms and most presumably receives its main contributions from neural sources located in the PAC and adjacent auditory (belt) fields, with additional (but smaller) contributions from the frontal cortical areas (for a review see Deouell 2007). These frontal areas appear to include (ventral) the premotor cortex (Brodmann’s area [BA] 6), the dorsolateral prefrontal cortex near and within the inferior frontal sulcus, and the posterior part of the inferior frontal gyrus (BAs 45 and 44). The frontal areas are possibly involved due to their role in attentional processes, sequencing, and working memory processes (Schonwiesner et al. 2007). Auditory sensory memory operations are indispensable for music perception; therefore, practically all MMN studies are inherently related to, and relevant for, the understanding of the neural correlates of music processing. As will be outlined below, numerous MMN studies have contributed to this issue (a) by investigating different response properties of the auditory sensory memory to musical and speech stimuli, (b) by using melodic and rhythmic patterns to investigate auditory Gestalt formation, and/or (c) by studying effects of long- and short-term musical training on processes underlying auditory sensory memory operations. Especially the latter studies have contributed substantially to our understanding of neuroplasticity and thus to our understanding of the neural basis of learning (for reviews, see Tervaniemi and Huotilainen 2003; Tervaniemi 2009). For example, MMN studies showed effects of long-term musical

training on the pitch discrimination of chords (Koelsch et al. 1999), on temporal acuity (Rammsayer and Altenmüller 2006), on the temporal window of integration (Rüsseler et al. 2001), on sound localization changes (Tervaniemi et al. 2006a), and on the detection of spatially peripheral sounds (Rüsseler et al. 2001). Moreover, using MEG, an MMN study from Menning et al. (2000) showed effects of a 3-week auditory musical training on the pitch discrimination of tones.

Auditory oddball paradigms were also used to investigate processes of melodic and rhythmic grouping of tones occurring in tone patterns (Sussman 2007), as well as effects of musical long-term training on these processes. These studies showed effects of musical training (a) on the processing of melodic patterns (e.g., Zuijen et al. 2004), (b) on the encoding of the number of elements in a tone pattern (Zuijen et al. 2005), and (c) on the processing of patterns consisting of two voices (Fujioka et al. 2005).

Finally, several MMN studies investigated differences between the processing of musical and speech information. These studies report larger right-hemispheric responses to chord deviants than to phoneme deviants (e.g., Tervaniemi et al. 2000); similar results have also been shown for the processing of complex tones compared to phonemes (e.g., Tervaniemi et al. 2009). These lateralization effects are presumably due to the different requirements of spectral and temporal processing posed by the chords and the phonemes used as stimuli in that study.

The formation of auditory Gestalten entails processes of perceptual separation, as well as processes of melodic, rhythmic, timbral, and spatial grouping. Such processes have been summarized under the concepts of *auditory scene analysis* and *auditory stream segregation* (Bregman 1994). Grouping of acoustic events follows Gestalt principles such as similarity, proximity, and continuity (e.g., Darwin 2008). In everyday life, such operations are important not only for music processing, but also, for instance, for separating a speaker’s voice during a conversation from other sound sources in the environment. That is, these operations are important because their function is to recognize and to

follow acoustic objects and to establish a cognitive representation of the acoustic environment. Knowledge about neural mechanisms of auditory stream segregation, auditory scene analysis, and auditory grouping is still relatively sparse (e.g., Shinn-Cunningham 2008; Winkler et al. 2009). However, it appears that the planum temporale (which is part of the auditory association cortex) is a crucial structure for auditory scene analysis and stream segregation (Griffiths and Warren 2002), particularly due to its role for the processing of pitch intervals and sound sequences (e.g., Patterson et al. 2002).

Analysis of Intervals

Presumably closely linked to the stage of auditory Gestalt formation is a stage of a more fine-grained analysis of intervals, which includes (i) a more detailed processing of the pitch relations between the tones of a chord (required to determine whether a chord with a specific root is a major or minor chord, played in root position, inversion, etc.; see also below) or between the tones of a melody and possibly (ii) a more detailed processing of temporal intervals. With regard to chords, such an analysis is required to specify the “chord form,” that is, whether a chord is a major or a minor chord and whether a chord is played in root position or in an inversion; note that chords with the same root can occur in several versions (e.g., all of the following chords have the root c: c–e–g, c–e-flat–g, e–g–c, g–c–e, c–e–g–b-flat, e–g–b-flat–c, etc.). The neural correlates of such processes are not known, but it is likely that both temporal and (inferior) prefrontal regions contribute to such processing; with regard to the processing of melodies, lesion data suggest that the analysis of the contour of a melody (which is part of the auditory Gestalt formation) particularly relies on the posterior part of the right superior temporal gyrus (STG), whereas the processing of more detailed interval information appears to involve both posterior and anterior areas of the supratemporal cortex bilaterally (Peretz and Zatorre 2005; Liegeois-Chauvel et al. 1998; Patterson et al. 2002).

Melodic and temporal intervals appear to be processed independently, as suggested by the observation that brain damage can interfere with the discrimination of pitch relations but spare the accurate interpretation of time relations, and vice versa (Peretz and Zatorre 2005; Di Pietro et al. 2004). However, these different types of interval processing have so far not been dissociated in functional neuroimaging studies.

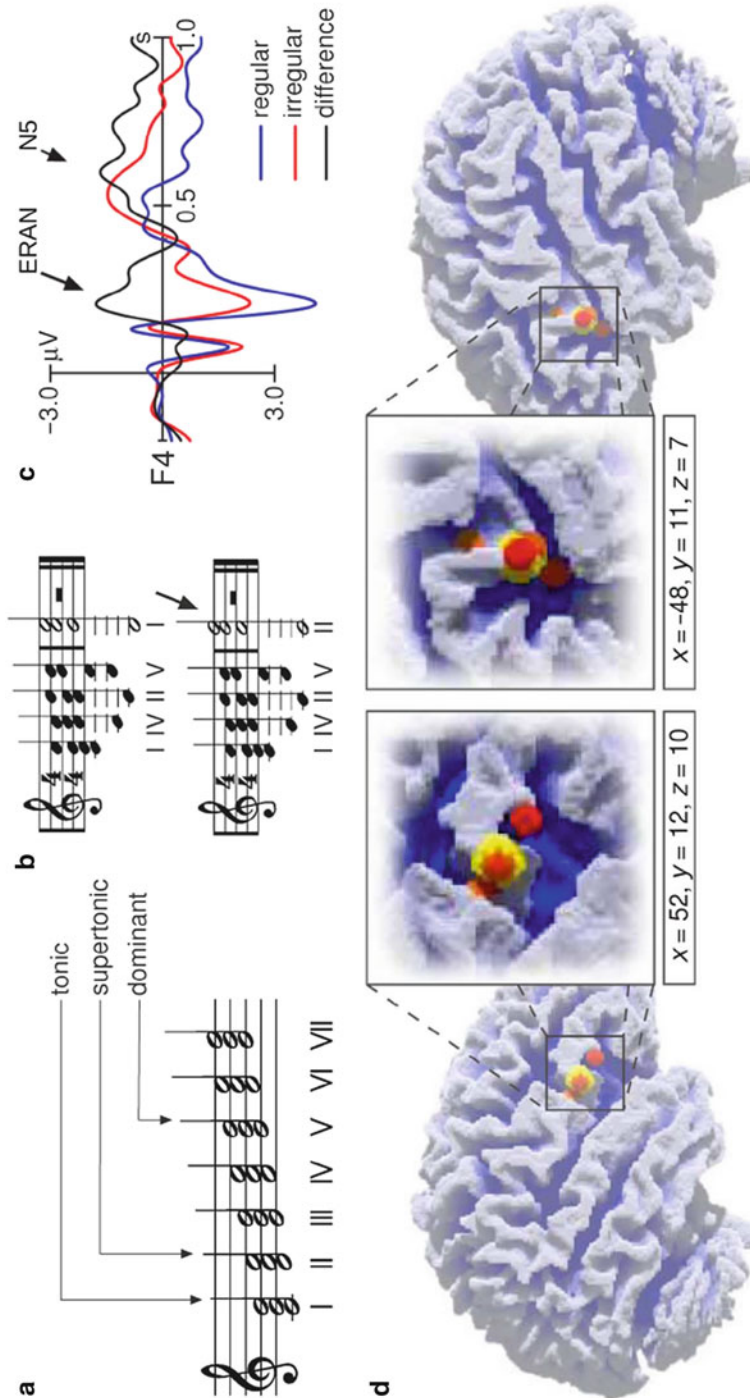
When Intelligence Comes into Play: Processing Musical Syntax

The following section deals with the processing of major–minor tonal syntax, particularly with regard to chord functions (i.e., with regard to harmony; for explanation of chord functions see Fig. 2a). Other aspects of tonal syntax are rhythm, meter, melody (including voice leading), and timbre (including intensity, instrumentation, and texture).

Formal Descriptions of Musical Syntax

Before describing neural correlates of music-syntactic processing, a theoretical basis of musical syntax will be outlined briefly. One possible theoretical description of the syntax of major–minor tonal music is the classical theory of harmony as formulated, e.g., by Jean-Philippe Rameau, Hugo Riemann, Arnold Schönberg, and Walter Piston. These descriptions primarily deal with the derivation of chord functions, less so with how chord functions are chained into longer sequences. Also, these approaches are best suited to describe local dependencies between harmonies.

Heinrich Schenker was the first theorist to deal systematically with the principles underlying non-local dependencies; this included his thoughts on the *Ursatz*, which implicitly assumes (a) a hierarchical structure (such as the large-scale tonic–dominant–tonic structure of the sonata form), (b) that (only) certain chord functions can be omitted, and (c) recursion (e.g., a sequence in one key which is embedded in another sequence in a different key, which is embedded in yet another sequence with yet another different key, etc.). Schenker’s thoughts were formalized by the



Music Processing in the Brain, Fig. 2 (a) Examples of chord functions: The chord built on the first scale tone is denoted as the tonic, the chord on the second tone as the supertonic, and the chord on the fifth tone as the dominant. (b) The dominant-tonic progression represents a regular ending of a harmonic sequence (*top*) and the dominant-tonic progression is less regular and unacceptable as a marker of the end of a harmonic progression (*bottom* sequence, the *arrow* indicates the less regular chord). (c) ERPs elicited in a passive listening condition by the final chords of the two sequence types shown in (b). Both sequence types were presented in pseudorandom order equiprobably in all 12 major keys. Brain responses to irregular chords clearly differ from those to regular chords (best to be seen in the black difference wave, regular

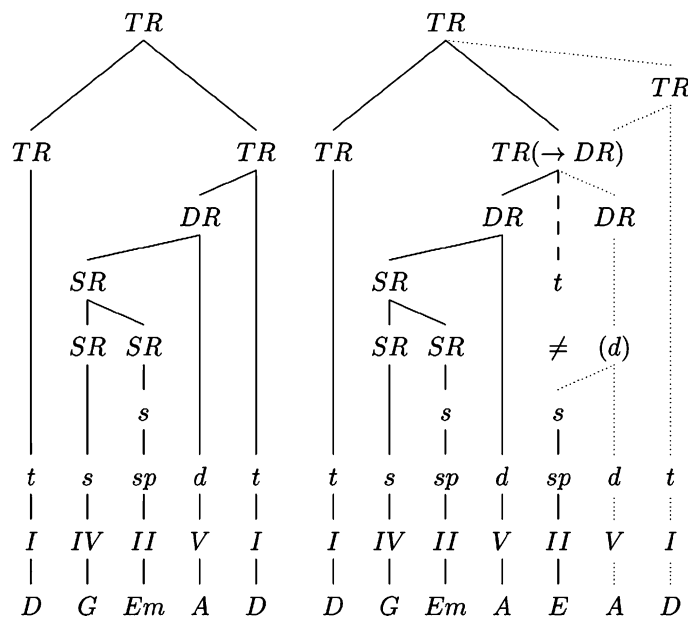
subtracted from irregular chords). The first difference between the two waveforms is maximal around 200 ms after the onset of the fifth chord (ERAN, indicated by the *long arrow*) and taken to reflect processes of music-syntactic analysis. The ERAN is followed by an N5 taken to reflect processes of harmonic integration (*short arrow*). (d) Activation foci (*small spheres*) reported by functional imaging studies on music-syntactic processing using chord sequence paradigms (Koelsch et al. 2002, 2005a; Maess et al. 2001; Tillmann et al. 2003) and melodies (Janata et al. 2002a). *Large yellow spheres* show the mean coordinates of foci (averaged for each hemisphere across studies, coordinates refer to standard stereotaxic space) (Reprinted from Koelsch and Siebel 2005)

approaches of the “Generative Theory of Tonal Music”(GTTM) by Lerdahl and Jackendoff (1999), which, however, does not provide generative rules (in contrast to what its name says). Nevertheless, the advance of the GTTM lies in the description of Schenker’s *Urlinie* as a tree structure (in this regard, GTTM uses terms such as *time-span reduction* and *prolongation*). These tree structures also parallel the description of linguistic syntax using tree structures (Patel (2008)), although Lerdahl and Jackendoff’s GTTM at least implicitly implies that musical and linguistic syntax have only little to do with each other (except perhaps with regard to certain prosodic aspects).

Up to now, only one neurophysiological investigation has tested whether individuals perceive music cognitively according to tree structures (Koelsch et al. 2013), and behavioral studies on this topic are also extremely scarce (Cook 1987; Bigand et al. 1996; Lerdahl and Krumhansl 2007). Note that GTTM is an analytical (not a generative)

model; Lerdahl’s Tonal Pitch Space theory (Lerdahl 2001) attempts to provide algorithms for this analytical approach (but the algorithms are often not sharp and precise). However, TPS provides the very interesting approach to model tension–resolution patterns from tree structures (Lerdahl and Krumhansl 2007).

A more recent approach to model tonal harmony with explicit generative rules according to tree structures is the *Generative Syntax Model* (GSM) by Martin Rohrmeier (2007, 2011). Rohrmeier’s GSM distinguishes between four structural levels with increasing abstraction: a level with the surface structure (in terms of the naming of the chords, e.g., C, G, C), a scale-degree structure level (e.g., I, V, I), a functional–structural level (e.g., t, d, t), and a phrase-structure level specifying tonic regions, dominant regions, and subdominant regions (see also Fig. 3). Each of these levels is described with generative rules of a phrase-structure grammar, the generation beginning on the highest (phrase-structure) level and



Music Processing in the Brain, Fig. 3 Tree structures (according to the GSM) for the sequences shown in Fig. 2b, ending on a regular tonic (*left*) and on a supertonic (*right*). Dashed line, expected structure (≠: the tonic chord is expected, but a supertonic is presented); dotted lines, a possible solution for the integration of the supertonic. TR (→DR) indicates that the supertonic can still be integrated,

e.g., if the expected tonic region is restructured into the dominant region. TR tonic region, DR dominant region, SR subdominant region. Lowercase letters indicate chord functions (functional–structural level), Roman numerals indicate the scale-degree structure, and the *bottom row* indicates the surface structure in terms of the naming of the chords

propagating information (in the process of derivation) through the subordinate levels. This opens the possibility for the recursive derivation of complex sequences on both a functional and a scale-degree structural level (e.g., “dominant of the dominant of the dominant”). The actual tonality of a tree is propagated from the head (“knot”) into the subordinate branches. The tree structure reflects (a) the formal arrangement of the piece, (b) the phrase structure, (c) the functional aspects of partial phrases and chords, (d) the relation of key regions, and (e) the degree of relative stability (which is determined by the subordination rules between the branches).

The GSM combines three principles:

1. Given (a) that musical elements (e.g., a tone or a chord) always occur in relation to other musical elements (and not alone) and (b) that each element (or each group of elements) has a functional relation either to a preceding or to a subsequent element, the simplest way of representing these relations is a tree structure. This implies that relations of elements that are functionally related, but not adjacent, can be represented by a tree structure. For example, in a sequence which consists of several chords and which begins and ends on a tonic chord, the first and the last tonic are not adjacent (because there are other chord functions between them), but the last tonic picks up (and “prolongates”) the first tonic; this can be represented in a tree structure in a way that the first and the last tonic chords build beginning points and endpoints of the tree and that the relations of the other chord functions can be represented by dendritic ramification (“prolongating” chords can extend the tonal region and “progressing” chords determine the progression of tonal functions). This also implies that adjacent elements do not necessarily have a direct structural relation (e.g., an initial tonic chord can be followed by a secondary dominant to the next chord; the secondary dominant then has a direct relation to the next chord, but not to the preceding tonic chord). It is not possible that a chord does not have a functional relation to a preceding nor to a subsequent
2. The tree structure indicates which elements can successively be omitted in a way that the sequence still sounds correct. For example, secondary dominants can be omitted or all chords between first and last tonic chord can be omitted, and a sequence still sounds correct. In a less trivial case, there is a dominant in a local phrase between two tonic chords; the tree structure then indicates that on the next higher level, all chords except the two tonic and the dominant chords can be omitted. This principle is a consequence of the “headedness,” in which each knot in the syntax tree dominates subordinate branches. That is, the tree structure provides a weighting of the elements, leading to an objectively derivable deep structure (another advantage compared to the classical theory of harmony).
3. Chord functions are a result of their position within the branches of the tree. For example, a predominant is the subordinate branch preceding a dominant, or there are stable and instable dominants which can be differentiated based on how deeply they are located in the syntax tree. Similarly, a half-cadence is a case in which a dominant is reached as stable local endpoint of a phrase, which must be followed by a phrase that ends on a tonic, thus resolving the open dominant (with regard to the deep structure).

As mentioned before, the GSM is relatively new, and due to the lack of usable tree models, most studies investigating neurophysiological correlates of music-syntactic processing have so far simply utilized the classical theory of harmony as a syntactic rule system (for an exception see Koelsch et al. 2013): According to the classical

theory of harmony, chord functions are arranged within harmonic sequences according to certain regularities (Riemann 1877/1971). Ity-based arrangement implies long-distance dependencies involving hierarchical organization (also referred to as phrase-structure grammar). However, it cannot be excluded that “irregular” chord functions such as the final supertonic in Fig. 2b are detected as irregular based on a finite state grammar (according to which the tonic is the most regular chord after a I–IV–II–V progression); as will be illustrated below, processing of such chord functions presumably involves processing of both finite state and phrase-structure grammar.

Neural Correlates of Music-Syntactic Processing

Neurophysiological studies using EEG and MEG showed that music-syntactically irregular chord functions (such as the final supertonic shown in Fig. 2b) elicit brain potentials with negative polarity that are maximal at around 150–350 ms after the onset of an irregular chord and have a frontal/frontotemporal scalp distribution, often with right-hemispheric weighting (see also Fig. 2c). In experiments with isochronous, repetitive stimulation, this effect is maximal at around 150–200 ms over right anterior electrodes and denoted as early right anterior negativity or ERAN (Koelsch 2009a). In experiments in which the position of irregular chords within a sequence is not known (and thus unpredictable), the negativity often has a longer latency and a more anterior–temporal distribution (Patel et al. 1998; Koelsch and Mulder 2002). The ERAN elicited by irregular tones of melodies has a shorter peak latency than the ERAN elicited by irregular chord functions (Koelsch and Jentschke 2010).

Functional neuroimaging studies using chord sequence paradigms or melodies suggest that music-syntactic processing involves the pars opercularis of the inferior frontal gyrus (corresponding to BA 44) bilaterally, but with right-hemispheric weighting (see yellow spheres in Fig. 2d). It seems likely that the involvement of (inferior) BA 44 in music-syntactic processing is due to the hierarchical processing of (syntactic)

information: This part of Broca’s area is involved in the hierarchical processing of syntax in language (Friederici et al. 2006; Makuuchi et al. 2009), in the hierarchical processing of action sequences (Koechlin and Jubault 2006; Fazio et al. 2009), and possibly also in the processing of hierarchically organized mathematical formulas and termini (Friedrich and Friederici 2009). These findings suggest that at least some cognitive operations of music-syntactic and language-syntactic processing (and neural populations mediating such operations) overlap and are shared with the syntactic processing of actions, mathematical formulas, and other structures based on long-distance dependencies involving hierarchical organization (phrase-structure grammar).

However, it appears that inferior BA 44 is not the only structure involved in music-syntactic processing: Additional structures include the superior part of the pars opercularis (Koelsch et al. 2002), the anterior portion of the STG (Koelsch et al. 2002, 2005a), and ventral premotor cortex (Janata et al. 2002a, b; Koelsch et al. 2002, 2005a; Parsons 2001). The PMCV probably contributes to the processing of music-syntactic information based on finite state grammar: Activations of PMCV have been reported in a variety of functional imaging studies on auditory processing using musical stimuli, linguistic stimuli, auditory oddball paradigms, pitch discrimination tasks, and serial prediction tasks, underlining the importance of these structures for the sequencing of structural information, the recognition of structure, and the prediction of sequential information (Janata and Grafton 2003). With regard to language, Friederici (2004) reported that activation foci of functional neuroimaging studies on the processing of long-distance hierarchies and transformations are located in the posterior IFG (in the inferior pars opercularis), whereas activation foci of functional neuroimaging studies on the processing of local structural violations are located in the PMCV (Friederici et al. 2006; Makuuchi et al. 2009; Opitz and Kotz 2012). Moreover, patients with lesion in the PMCV show disruption of the processing of finite state, but not phrase-structure grammar (Opitz and Kotz 2012).

That is, in the abovementioned experiments that used chord sequence paradigms to investigate the processing of harmonic structure, the music-syntactic processing of the chord functions probably involved processing of both finite state and phrase-structure grammar. The music-syntactic analysis involved a computation of the harmonic relation between a chord function and the context of preceding chord functions (phrase-structure grammar). Such a computation is more difficult (and less common) for irregular than for regular chord functions (as illustrated by the branch with the dashed line in the right panel of Fig. 3), and this increased difficulty is presumably reflected in a stronger activation of (inferior) BA 44 in response to irregular chords. In addition, the local transition probability from the penultimate to the final chord is lower for the dominant–super-tonic progression than for the dominant–tonic progression (finite state grammar), and the computation of the (less predicted) lower-probability progression is presumably reflected in a stronger activation of PMCV in response to irregular chords. The stronger activation of both BA 44 and PMCV appears to correlate with the perception of a music-syntactically irregular chord as “unexpected.”

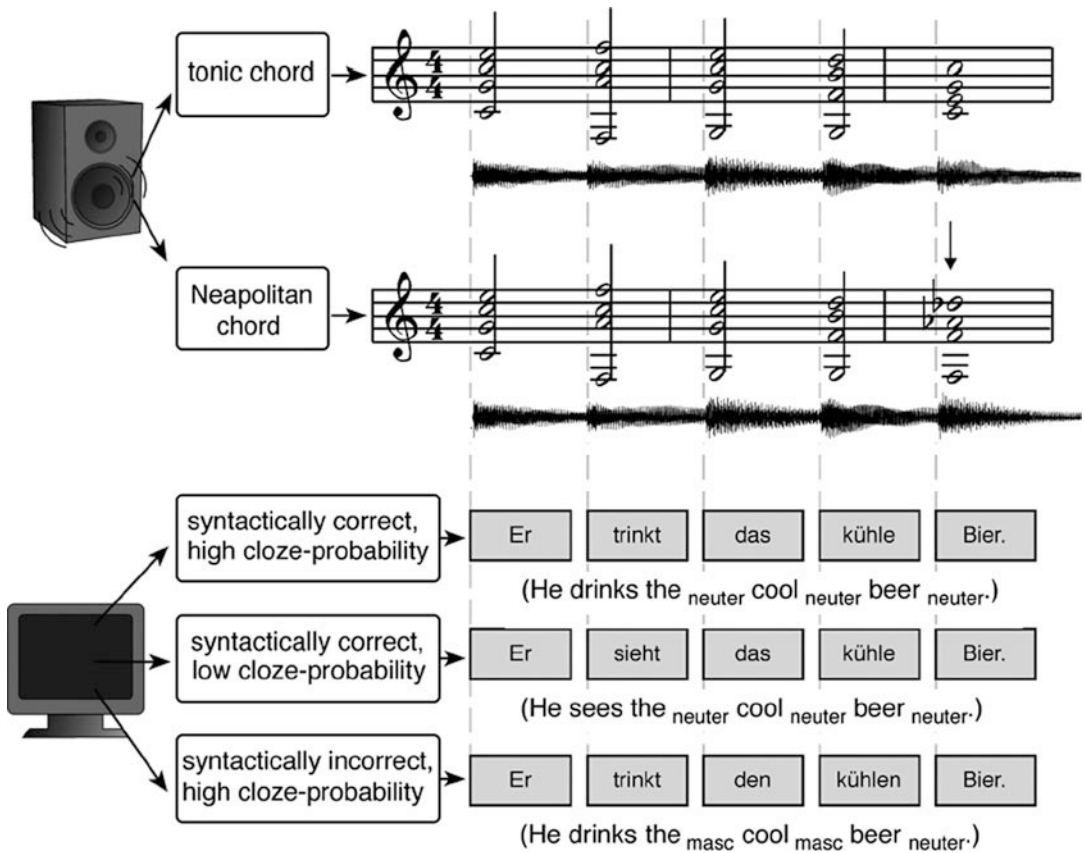
Note that the ability to process phrase-structure grammar is available to humans, whereas non-human primates are apparently not able to master such grammars (Fitch and Hauser 2004). Thus, it is highly likely that only humans can adequately process music-syntactic information at the phrase-structure level. It is also worth noting that numerous studies showed that even “nonmusicians” (i.e., individuals who have not received formal musical training) have a highly sophisticated (implicit) knowledge about musical syntax (Rohrmeier and Rebuschat 2012). Such knowledge is presumably acquired during listening experiences in everyday life.

Interactions Between Language- and Music-Syntactic Processing

As mentioned above, hierarchical processing of syntactic information from different domains (such as music and language) requires contributions from neural populations located in BA 44.

However, it is still possible that, although such neural populations are located in the same brain area, entirely different (nonoverlapping) neural populations serve the syntactic processing of music and language *within the same area*. That is, perhaps the neural populations mediating language-syntactic processing in BA 44 are different from neural populations mediating music-syntactic processing in the same area. Therefore, the strongest evidence for shared neural resources for the syntactic processing of music and language stems from experiments that revealed interactions between music-syntactic and language-syntactic processing (Koelsch et al. 2005b; Steinbeis and Koelsch 2008b; Slevc et al. 2009; Fedorenko et al. 2009). In these studies, chord sequences were presented simultaneously with visually presented sentences (for an example see Fig. 4). Two of these studies (Koelsch et al. 2005b; Steinbeis and Koelsch 2008b) used EEG and three different sentence types. The first type was a syntactically correct sentence in which the occurrence of the final noun was semantically highly probable. The other two sentence types were modified versions of the first sentence type: firstly, a sentence with a gender disagreement between the last word (noun) on the one hand and the prenominal adjective as well as the definite article that preceded the adjective on the other (such gender disagreements elicit a left anterior negativity; Gunter et al. 2000) and, secondly, a sentence in which the final noun was semantically less probable – such “low-cloze probability” words elicit an N400 reflecting the semantic processing of words (see also section on musical semantics below). Each chord sequence consisted of five chords (and each chord was presented together with a word, see Fig. 4), one chord sequence type ending on a music-syntactically regular and the other type ending on an incorrect chord function.

Both studies (Koelsch et al. 2005b; Steinbeis and Koelsch 2008b) showed that the ERAN elicited by irregular chords interacted with the left anterior negativity (LAN) elicited by linguistic (morpho-syntactic) violations (Koelsch et al. 2005b; Steinbeis and Koelsch 2008b): The LAN elicited by words was reduced when the syntactically irregular word was presented simultaneously



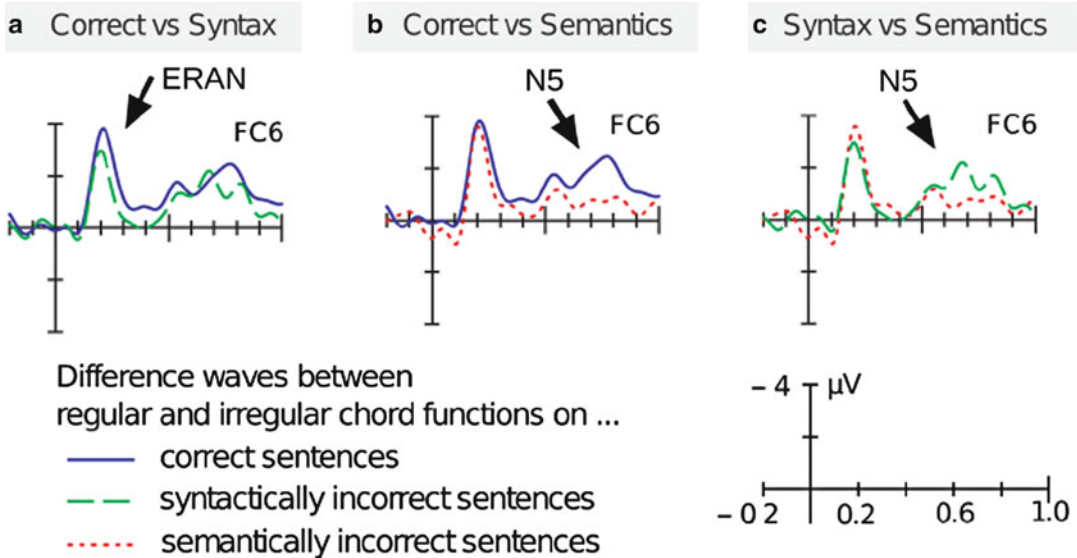
Music Processing in the Brain, Fig. 4 Examples of experimental stimuli used in the studies by Koelsch et al. (2005b) and Steinbeis and Koelsch (2008b). *Top*: examples of two chord sequences in C major, ending on a regular (*upper row*) and an irregular chord (*lower row*, the irregular

chord is indicated by the *arrow*). *Bottom*: examples of the three different sentence types. Onsets of chords (presented auditorily) and words (presented visually) were synchronous. (Reprinted from Steinbeis and Koelsch 2008b)

with a music-syntactically irregular chord (compared to when the irregular word was presented with a regular chord). In the study by Koelsch et al. (2005b), a control experiment was conducted in which the same sentences were presented simultaneously with sequences of single tones. The tone sequences ended either on a standard tone or on a frequency deviant. The physical mismatch negativity (phMMN) elicited by the frequency deviants did not interact with the LAN (in contrast to the ERAN), indicating that the processing of auditory oddballs (as reflected in the phMMN) does not consume resources related to syntactic processing. In addition, the study by Steinbeis and Koelsch (2008b) also showed that the amplitude of the ERAN was reduced when

participants processed a syntactically wrong word (Fig. 5a). Notably, the ERAN was not affected when words were semantically incongruous (Fig. 5b), showing that the interaction between ERAN and LAN is specific for syntactic processing.

The findings of these EEG studies were corroborated by two behavioral studies (Slevc et al. 2009; Fedorenko et al. 2009), as well as by a patient study by Patel et al. (2008). The latter study showed that individuals with Broca's aphasia also show impaired music-syntactic processing in response to out-of-key chords occurring in harmonic progressions (note that all patients had Broca's aphasia, but only some of them had a lesion that included Broca's area).



Music Processing in the Brain, Fig. 5 Grand-average ERPs elicited by the stimuli shown in Fig. 4. Participants monitored whether the sentences were (syntactically and semantically) correct or incorrect; in addition, they had to attend to the timbre of the chord sequences and to detect infrequently occurring timbre deviants. ERPs were recorded on the final chords/words and are shown for the different word conditions (note that only difference waves are shown). (a) The solid (blue) difference wave shows ERAN (indicated by the arrow) and N5 elicited on syntactically and semantically correct words. The dashed (green) difference wave shows ERAN and N5, elicited when chords are presented on morpho-syntactically incorrect (but semantically correct) words. Under the latter condition, the ERAN (but not the N5) is reduced. (b) The solid (blue) difference wave is identical to the solid difference

wave of (a), showing the ERAN and the N5 (indicated by the arrow) elicited on syntactically and semantically correct words. The dotted (red) difference wave shows ERAN and N5, elicited when chords are presented on semantically incorrect (but morpho-syntactically correct words). Under the latter condition, the N5 (but not the ERAN) is reduced. (c) shows the direct comparison of the difference waves in which words were syntactically incorrect (dashed, green line) or semantically incorrect (dotted, red line). These ERPs show that the ERAN is influenced by the morpho-syntactic processing of words, but not by the semantic processing of words. By contrast, the N5 is influenced by the semantic processing of words, but not by the morpho-syntactic processing of words. (Data from Steinbeis and Koelsch 2008b)

It is also interesting to note that there are hints for an interaction between the ERAN and the *early left anterior negativity* (Friederici 2002): In a study by Maidhof and Koelsch (2011), participants were presented simultaneously with spoken sentences and chord sequences. Thus, the experiment was similar to the studies by Koelsch et al. (2005b) and Steinbeis and Koelsch (2008b), except (a) that sentences were presented auditorily, (b) that syntactic violations were phrase-structure violations (not morpho-syntactic violations), and (c) that the attention of listeners was directed to either the speech or the music. In that study, the amplitude of the ERAN was slightly smaller when elicited during the presentation of phrase-structure violations occurring in sentences

(compared to when elicited during correct sentences); this effect was, however, only marginally significant. Thus, it appears that music-syntactic processing of an irregular chord function (as reflected in the ERAN) also interacts with the processing of the phrase structure of a sentence, although this interaction seems less obvious than the interaction between ERAN and LAN (i.e., between music-syntactic processing of chord functions and the processing of morpho-syntactic information in language).

In summary, neurophysiological studies show that music- and language-syntactic processes engage overlapping resources (presumably located in the inferior fronto-lateral cortex), and evidence showing that these resources underlie

music- and language-syntactic processing is provided by experiments showing interactions between ERP components reflecting music- and language-syntactic processing (in particular LAN and ERAN). Importantly, such interactions are observed in the absence of interactions between LAN and MMN, i.e., in the absence between language-syntactic and acoustic deviance processing (reflected in the MMN) and in the absence of interactions between the ERAN and the N400 (i.e., in the absence of music-syntactic and language-semantic processing). Therefore, the reported interactions between LAN and ERAN are syntax-specific and cannot be observed in response to any kind of irregularity.

Processing of Phrase Boundaries

During auditory music or language perception, the recognition of phrase boundaries helps to decode the syntactic (phrase) structure of a musical phrase, as well as of a sentence (the melodic and rhythmic features that mark a phrase boundary in a spoken sentence are part of the *speech prosody*). The processing of phrase boundaries is reflected in a *Closure Positive Shift* (CPS), during both the processing of musical phrase boundaries (Knösche et al. 2005) and the processing of international phrase boundaries during speech perception (Steinhauer et al. 1999). The first study on the perception of musical phrase boundaries by Knösche et al. (2005) investigated musicians only, and a subsequent study also reported a CPS in nonmusicians (Neuhaus et al. 2006). The latter study also reported larger CPS amplitudes for longer pauses as well as longer boundary tones (which make the phrase boundary more salient). Both studies (Knösche et al. 2005; Neuhaus et al. 2006) used EEG as well as MEG, showing that the CPS can be observed with both methods. In a third study, Chinese and German musicians performed a categorization task with Chinese and Western music (Nan et al. 2006). Both groups showed CPS responses to both types of music (with no significant difference between groups). The exact contributions of the processes reflected in the CPS to syntactic processing remain to be specified.

Using fMRI, a study by Meyer et al. (2004) suggests that the processing of the prosodic

aspects of the sentences used in the study by Steinhauer et al. (1999) involves the premotor cortex of the (right) Rolandic operculum, (right) the auditory cortex located in the planum temporale, as well as the anterior insula (or perhaps deep frontal operculum) and the striatum bilaterally.

A very similar activation pattern was also observed for the processing of the melodic contour of spoken main clauses (Meyer et al. 2002). That is, similar to the right-hemispheric weighting of activations observed in functional neuroimaging studies on music perception, a right-hemispheric weighting of (neocortical) activations is also observed for the processing of speech melody.

Structural Reanalysis and Repair

Following a syntactic anomaly (or an unexpected syntactic structure), processes of structural reanalysis and repair may be engaged. It appears that these processes are reflected in the ERP as positive potentials that are maximal around 600–900 ms (Besson and Schön 2001).

The P600/LPC can be elicited by irregular melody tones (Besson and Macar 1986; Besson and Faita 1995; Verleger 1990; Paller et al. 1992; Besson and Faita 1995; Besson et al. 1998; Miranda and Ullman 2007; Peretz et al. 2009), as well as by irregular chords (Patel et al. 1998). It seems that the P600/LPC can only be elicited when individuals attend to the musical stimulus and that the LPC is partly connected to processes of the conscious detection of music-structural incongruities. In an experiment by Besson and Faita (1995), in which incongruous melody endings had to be detected, the LPCs had a greater amplitude, and a shorter latency, in musicians compared to “nonmusicians,” presumably because musicians were more familiar with the melodies than nonmusicians (thus, musicians could detect the irregular events more easily). Moreover, the LPC had a larger amplitude for familiar melodies than for novel melodies (presumably because incongruous endings of familiar phrases were easier to detect) and for

non-diatonic than for diatonic endings. Diatonic incongruities terminating unfamiliar melodies did not elicit an LPC (presumably because they are hardly to detect), whereas non-diatonic incongruities did (they were detectable for participants by the application of tonal rules).

It is remarkable that in *all* of the mentioned studies on melodies (Besson and Macar 1986; Verleger 1990; Paller et al. 1992; Besson and Faita 1995; Besson et al. 1998; Miranda and Ullman 2007; Brattico et al. 2006; Peretz et al. 2009), the unexpected tones also elicited an early frontal negative ERP (emerging around the N1 peak, i.e., around 100 ms after stimulus onset). This ERP effect resembles the ERAN (Koelsch and Jentschke 2010), although it presumably overlapped in part with a subsequent N2b due to the detection of irregular or unexpected tones. That is, earlier processes underlying the detection of structural irregularities (as partly reflected in the ERAN) are followed by later processes of structural reanalysis (as reflected in the P600/LPC) when individuals attend to the musical stimulus and detect structural incongruities. It remains to be specified whether the P600/LPC is a late P3 and how the processes of structural reanalysis and repair are possibly related to context-updating (Donchin and Coles 1998; Polich 2007).

Using sentences and chord sequences, Patel et al. (1998) compared ERPs elicited by “syntactic incongruities” in language and music within subjects (harmonic incongruities were taken as grammatical incongruity in music). Task-relevant (target) chords within homophonic musical phrases were manipulated, so that the targets were either within the key of a phrase or out of key (from a “nearby” or a “distant” key). Both musical and linguistic structural incongruities elicited P600/LPC potentials which were maximal at posterior sites and statistically indistinguishable. Moreover, the degree of a structural anomaly (moderate or high) was reflected in the amplitude of the elicited positivities. Therefore, the results indicated that the P600 reflects more general knowledge-based structural (re-)integration (and/or reanalysis) during the perception of rule-governed sequences. The intersection between the processes of music-syntactic and language-

syntactic (re)integration and repair is referred to as the *Shared Syntactic Integration Resource Hypothesis* (SSIRH), which states that music and language rely on shared, limited processing resources that activate separable syntactic representations (Patel 2003). The SSIRH also states that whereas the linguistic and musical knowledge systems may be independent, the system used for online structural integration may be shared between language and music (Fedorenko et al. 2009). This system might be involved in the integration of incoming elements (words in language and tones/chords in music) into evolving structures (sentences in language, harmonic sequences in music). Beyond the SSIRH, however, the previous section on music-syntactic processing also showed early interactions (between the ERAN and LAN), indicating that processing of music- and language-syntactic information intersects also at levels of morpho-syntactic processing, phrase-structure processing, and possibly word-category information. The overlap of cognitive resources (and their neural correlates) for the early and late processing of syntactic information in music, language, actions, mathematical formulas, etc. has been referred to as the *Syntactic Equivalence Hypothesis* (Koelsch 2012).

Processing Meaning in Music

Music is a means of communication, and during music listening, meaning emerges through the interpretation of (musical) information. Previous accounts on musical meaning can be summarized with regard to three fundamentally different classes of meaning emerging from musical information: extramusical meaning, intra-musical meaning, and musicogenic meaning (Koelsch 2011). Extramusical meaning refers to meaning emerging from reference to the extramusical world (Meyer 1956). This class of meaning comprises three dimensions: musical meaning due to iconic, indexical, and symbolic sign qualities (Karbusicky 1986).

- (a) Iconic musical meaning emerges from common patterns or forms, such as musical sound

patterns that resemble sounds of objects or qualities of objects. For example, acoustic events may sound “warm,” “round,” “sharp,” or “colorful,” and a musical passage may sound, e.g., “like a bird” or “like a thunderstorm.” In linguistics, this sign quality is also referred to as *onomatopoeic*.

- (b) Indexical musical meaning emerges from action-related patterns (such as movements and prosody) that index the presence of a psychological state, for example, an emotion or an intention. Juslin and Laukka (2003) compared in a meta-analysis the acoustical signs of emotional expression in music and speech, finding that the acoustic properties that code emotional expression in speech are highly similar to those coding these expressions in music. With regard to intentions, an fMRI study by Steinbeis and Koelsch (2008c) showed that listeners automatically engage social cognition during listening to music, in an attempt to decode the intentions of the composer or performer (as indicated by activations of the cortical *theory-of-mind* network). That study also reported activations of posterior temporal regions implicated in semantic processing (Lau et al. 2008), presumably because the decoding of intentions has meaning quality. Ian Cross (2008) refers to this dimension of musical meaning as “motivational–structural” due to the relationship between affective–motivational states of individuals on the one side and the structural–acoustical characteristics of (species-specific) vocalizations on the other.
- (c) Symbolic musical meaning emerges from explicit (or conventional) extramusical associations (e.g., any national anthem). Note that the meaning of the majority of words is due to symbolic meaning. Cross and Morley (2008) refers to this dimension of musical meaning as “culturally enactive,” emphasizing that symbolic qualities of musical practice are shaped by (and shape) culture.

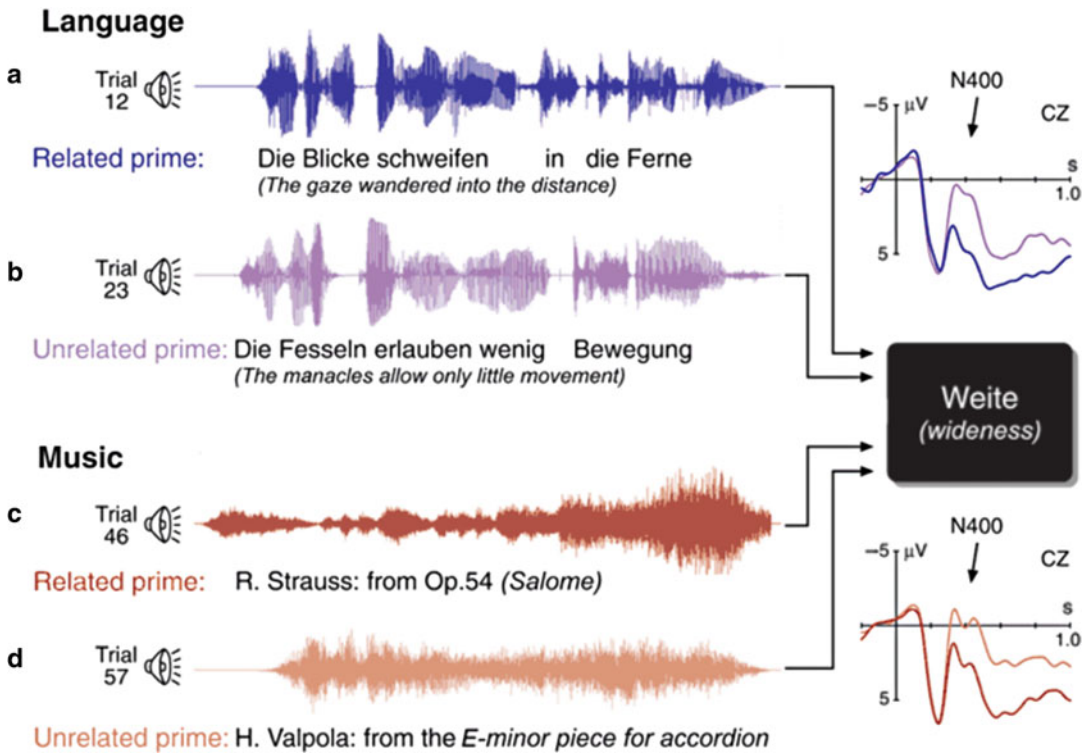
Musical semantics, notably, extends beyond the relations between concepts and the (extramusical) world in that musical meaning

also emerges from the reference of one musical element to another musical element, that is, from intra-musical combinations of formal structures. The term “intra-musical” was also used by Malcolm Budd (1996); other theorists have used the terms “formal meaning” (Alpersen 1994), “formal significance” (Davies 1994), or “embodied meaning” (Meyer 1956). Similar distinctions as the one drawn here between extra- and intra-musical meaning have been made by several theorists (Koopman and Davies 2001).

Processing of musical meaning information is reflected in (at least) two negative ERP components: the N400 and the N5. The N400 reflects processing of meaning in both language and music; the N5 has so far only been observed for the processing of musical information. In the following I will present evidence showing that, with regard to the processing of musical meaning, the N400 reflects processing of extramusical meaning and the N5 processing of intra-musical meaning.

The N400 has been used to investigate processing of musical meaning (or “musical semantics”) in semantic priming paradigms (Koelsch et al. 2004; Steinbeis and Koelsch 2008a; Daltrozzo and Schön 2009a; Steinbeis and Koelsch 2011; Grieser-Painter and Koelsch 2011). In an initial study (Koelsch et al. 2004), sentences and musical excerpts were presented as prime stimuli. The prime stimuli were semantically either related or unrelated to a target word that followed the prime stimulus (see top of Fig. 6). For example, the sentence “The gaze wandered into the distance” primes the word “wideness” (semantically related), rather than the word “narrowness” (semantically unrelated). Analogously, certain musical passages, for example, from a symphony by Mozart, prime the word “angel,” rather than the word “scallywag.”

In the language condition (i.e., when target words followed the presentation of sentences), unrelated words elicited a clear N400 effect (this is a classical semantic priming effect). This semantic priming effect was also observed when target words followed musical excerpts. That is, target words that were semantically unrelated to a preceding musical excerpt also elicited a clear



Music Processing in the Brain, Fig. 6 Left: examples of the four experimental conditions preceding a visually presented target word. *Top panel:* prime sentence semantically related to (a) and unrelated to (b) the target word *wideness*. The diagram on the right shows grand-average ERPs elicited by target words after the presentation of semantically related (solid line) and unrelated prime sentences (dotted line), recorded from a central electrode. Unprimed target words elicited a clear N400 component in the ERP (compared to the primed target words). *Bottom panel:* musical semantically related to (c) and unrelated to (d) the same target word. The diagram on the right shows

grand-average ERPs elicited by target words after the presentation of semantically related (solid line) and unrelated prime sentence (dotted line). As after the presentation of sentences, unprimed target words elicited a clear N400 component (compared to primed target words). Each trial was presented once; conditions were distributed in random order, but counterbalanced across the experiment. Note that the same target word was used for the four different conditions. Thus, condition-dependent ERP effects elicited by the target words can only be due to the different preceding contexts. (Reprinted from Koelsch et al. 2004)

N400. The N400 effects did not differ between the language condition (in which the target words followed sentences) and the music condition (in which the target words followed musical excerpts), neither with respect to amplitude nor with respect to latency or scalp distribution. A source analysis localized the main sources of the N400 effects, in both conditions, in the posterior part of the medial temporal gyrus bilaterally (BA 21/37), in proximity to the superior temporal sulcus. These regions have been implicated in the processing of semantic information during language processing (Lau et al. 2008).

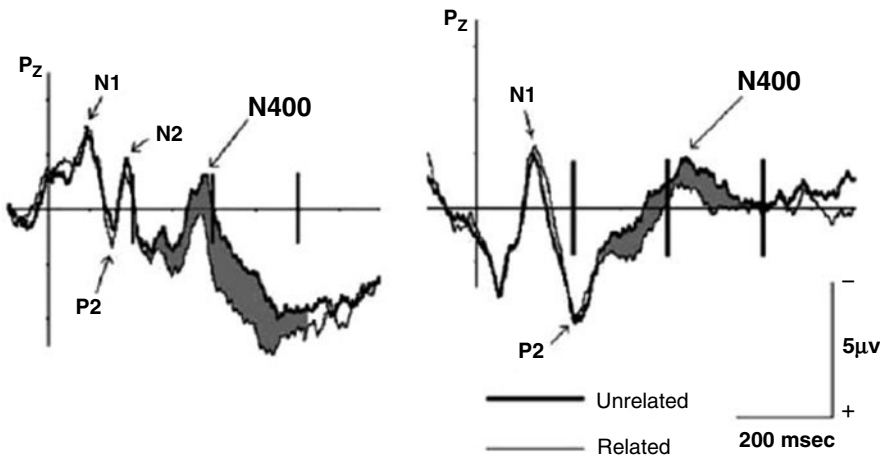
The N400 effect in the music condition demonstrates that musical information can have a systematic influence on the semantic processing of words. The N400 effects did not differ between the music and the language condition, indicating that musical and linguistic priming can have the same effects on the semantic processing of words. That is, the data demonstrated that music can activate representations of meaningful concepts (and that, thus, music is capable of transferring considerably more meaningful information than previously believed) and that the cognitive operations that decode meaningful information while

listening to music can be identical to those that serve semantic processing during language perception. The N400 effect was observed for both abstract and concrete words, showing that music can convey both abstract and concrete semantic information. Moreover, effects were also observed when emotional relationships between prime and target words were balanced, indicating that music does not only transfer emotional information.

The priming of meaning by the musical information was due to (a) iconic sign qualities, i.e., common patterns or forms (such as succeeding interval steps priming the word staircase); (b) indexical sign quality, such as the suggestion of a particular emotion due to the resemblance to movements and prosody typical for that emotion (e.g., saxophone tones sounding like derisive laughter); or (c) symbolic sign quality due to meaning inferred by explicit extramusical associations (e.g., a church anthem priming the word devotion). Unfortunately, it was not investigated in that study whether N400 responses differed between these dimensions of musical meaning (and, so far, no subsequent study has investigated this). However, the results still allow to conclude

that processing of extramusical meaning is associated with N400 effects.

Due to the length of musical excerpts (~10 s), musical information could not be used as target stimulus; thus, only words were used as target stimuli (and the N400 was only elicited on words, not on musical information). Hence, a question emerging from that study was whether musical information can also elicit N400 responses. One study addressing this issue (Daltrozzo and Schön 2009a) used short musical excerpts (duration was ~1 s) that could be used either as primes (in combination with word targets) or as targets (in combination with word primes). Figure 7 shows that when the musical excerpts were used as primes, meaningfully unrelated target words elicited an N400 (Koelsch et al. 2004). Importantly, when musical excerpts were used as target stimuli (and words as primes), an N400 was observed in response to excerpts that the participants rated as meaningfully unrelated to the preceding target word (compared to excerpts that were rated as related to the preceding word). This was the first evidence that musical information can also elicit N400 responses. Note that the musical excerpts were composed for the



Music Processing in the Brain, Fig. 7 Data from the experiments by Daltrozzo and Schön (2009a). The *left* panel shows ERPs elicited by target words (primed by short musical excerpts); the *right* panel shows ERPs elicited by musical excerpts (primed by target words). The thick line represents ERPs elicited by unrelated

stimuli; the *thin* line represents ERPs elicited by related stimuli. Note that the difference in N1 and P2 components is due to the fact that words were presented visually and musical excerpts auditorily. Both meaningfully unrelated words and meaningfully unrelated musical excerpts elicited N400 potentials

experiment and thus not known by the participants. Therefore, musical meaning was not due to symbolic meaning, but due to indexical (e.g., “happy”) and iconic (e.g., “light”) meaning. In the data analysis used in that study (Daltrozzo and Schön 2009a), the relatedness of prime-target pairs was based on the relatedness judgments of participants. Another study (Daltrozzo and Schön 2009b) showed that even if the data are analyzed based on the un-/relatedness of prime-target pairs as predefined by the experimenters, a significant N400 was elicited (in the latter study a lexical decision task was used, whereas in the former study participants were asked to judge the conceptual relatedness of prime and targets). Further studies investigated the processing of musical meaning using only single chords (Steinbeis and Koelsch 2008a; Steinbeis and Koelsch 2011) or single tones (Grieser-Painter and Koelsch 2011). These studies showed that even single chords and tones can prime the meaning of words (in both musicians and nonmusicians) and that even chords (in musicians) and tones (in nonmusicians and therefore presumably also in musicians) can elicit N400 effects.

Intra-musical Meaning and the N5

The previous section dealt with the N400 and extramusical meaning. However, musical meaning can also emerge from intra-musical references, that is, from the reference of one musical element to at least one other musical element (e.g., a *G* major chord is usually perceived as the tonic in *G* major, as the dominant in *C* major, and – in its first inversion – possibly as a Neapolitan sixth chord in *F#* minor). This section will review empirical evidence for this hypothesis and describe an electrophysiological correlate of the processing of intra-musical meaning (the so-called N5, or N500). The N5 was described first in reports of experiments using chord sequence paradigms with music-syntactically regular and irregular chord functions (Koelsch 2000), in which the ERAN was usually followed by a late negativity, the N5 (see also Fig. 2c). Initially (Koelsch 2000) the N5 was proposed to reflect processes of harmonic integration, reminiscent of the N400 reflecting semantic integration of words,

and therefore proposed to be related to the processing of musical meaning, or musical semantics, although the type of musical meaning had remained unclear.

One reason for this proposition was a remarkable resemblance between N5 and N400: *Firstly*, similar to the N400 elicited by open-class words, which declines towards the end of sentences (Van Petten and Kutas 1990), the amplitude of the N5 (elicited by regular chords) declined towards the end of a chord sequence (Koelsch 2000). That is, during sentence processing, a semantically correct final open-class word usually elicits a rather small N400, whereas the open-class words preceding this word elicit larger N400 potentials. This is due to the semantic expectedness of words, which is rather unspecific at the beginning of a sentence, and which becomes more and more specific towards the end of the sentence (where people already have a hunch of what the last word will actually be). Thus, a smaller amount of semantic integration is required at the end of a sentence, reflected in a smaller N400. If the last word is semantically unexpected, then a large amount of semantics is required, which is reflected in a larger amplitude of the N400. Similarly, the N5 is elicited not only by irregular chords but also by regular chords, and the amplitude of the N5 decreases with each progressing chord of the chord sequence. A small N5 elicited by the (expected) final chord of a chord sequence presumably reflects that only a small amount of harmonic integration is required at this position of a chord sequence.

Secondly, at the same position within a chord sequence (or a sentence) the N5 (or the N400) is modulated by the degree of fit with regard to the previous harmonic (or semantic) context. A wealth of studies has shown that irregular chords (Koelsch 2004, 2009a) and irregular tones of melodies (Miranda and Ullman 2007; Koelsch and Jentschke 2010) evoke larger N5 potentials than regular ones (see also Fig. 2c). As mentioned above, the ERAN is related to syntactic processing. In addition, the experiment from Steinbeis and Koelsch 2008b also showed that the N5 reflects processing of meaning information: In that study, the N5 interacted with the N400

elicited by words with low semantic cloze probability. The N5 was smaller when elicited on words that were semantically less probable (“He sees the cold beer”) compared to when elicited on words that were semantically highly probable (“He drinks the cold beer”; see Fig. 5b). Importantly, the N5 did not interact with the LAN (i.e., the N5 did not interact with the syntactic processing of words), indicating that the N5 is not simply modulated by any type of deviance, or incongruency, but that the N5 is specifically modulated by neural mechanisms underlying semantic information processing. That is, the N5 potential can be modulated by semantic processes, namely, by the activation of lexical representations of words with different semantic fit to a previous context. This modulation indicates that the N5 is related to the processing of meaning. Note that the harmonic relation between the chord functions of a harmonic sequence is an intra-musical reference (i.e., a reference of one musical element to another musical element and not a reference to anything belonging to the extramusical world). Therefore, we have reason to believe that the N5 reflects the processing of intra-musical meaning.

The neural generators of the N5 have remained elusive. This is in part due to the difficulty that in most experiments the N5 follows the ERAN (but see also Poulin-Charronnat et al. 2006), making it difficult to differentiate the neural correlates of N5 and ERAN in experiments using functional magnetic resonance imaging. The N5 usually has a clear frontal scalp distribution; thus, the scalp distribution of the N5 is more anterior than that of the N400, suggesting at least partly different neural correlates. Perhaps the N5 originates from combined sources in the temporal lobe (possibly overlapping with those of the N400 in BAs 21/37) and the frontal lobe (possibly in the posterior part of the inferior frontal gyrus). This needs to be specified, for example, using EEG source localization in a study that compares an auditory N4 with an auditory N5 within subjects.

The third class of musical meaning (musicogenic meaning) emerges from individual responses to musical information, particularly movement, emotional responses, and self-related memory associations. This dimension of musical meaning, as well

as details about the extra- and intra-musical dimensions of musical meaning, is discussed in more detail elsewhere (Koelsch 2011).

How the Body Reacts to Music

The present model of music perception also takes the potential “vitalization” of an individual into account: Vitalization entails activity of the autonomic nervous system (i.e., regulation of sympathetic and parasympathetic activity) along with the cognitive integration of musical and non-musical information. Nonmusical information comprises associations evoked by the music, as well as emotional (e.g., happy) and bodily reactions (e.g., tensioned or relaxed). The *subjective feeling* (Scherer 2005) requires conscious awareness and therefore presumably involves multimodal association cortices such as parietal association cortices in the region of BA 7 (Block 2005). Effects of music perception on activity of the autonomic nervous system have mainly been investigated by measuring electrodermal activity and heart rate, as well as the number and intensity of reported “shivers” and “chills” (Khalfa et al. 2002; Blood and Zatorre 2001; Panksepp and Bernatzky 2002; Sloboda 1991; Grewe et al. 2007a, b; Lundqvist et al. 2009; Orini et al. 2010).

Vitalizing processes can, in turn, have an influence on processes within the immune system. Effects of music processing on the immune system have been assessed by measuring variations of (salivary) immunoglobulin A concentrations (Hucklebridge et al. 2000; McCraty et al. 1996; Kreutz et al. 2004). Interestingly, effects on the immune system have been suggested to be tied to motor activity such as singing (Kreutz et al. 2004) or dancing (Quiroga Murcia et al. 2009). With regard to music perception, it is important to note that there might be overlap between neural activities of the late stages of perception and those related to the early stages of action (Rizzolatti and Craighero 2004; Janata et al. 2002b).

Music perception can interfere with action planning in musicians (Drost et al. 2005a, b), and premotor activity can be observed during the perception of music (a) in pianists listening to

piano pieces (Haueisen and Knösche 2001), (b) in nonmusicians listening to song (Callan et al. 2006), and (c) in nonmusicians who received 1 week of piano training and listened to the trained piano melody (Lahav et al. (2007)). For neuroscience studies related to music production, see, e.g., Bangert and Altenmüller (2003), Katahira et al. (2008), Maidhof et al. (2009), Kamiyama et al. (2010), and Maidhof et al. (2010).

Movement induction by music perception in the way of dancing, singing, tapping, hopping, swaying, head-nodding, etc. along with music is a very common experience (Panksepp and Bernatzky 2002); such movements also serve social functions, because synchronized movements of different individuals represent coordinated social activity. Notably, humans have a need to engage in social activities; emotional effects of such engagement include fun, joy, and happiness, whereas exclusion from this engagement represents an emotional stressor and has deleterious effects on health. Humans making music is an activity involving several social functions (summarized as the “Seven Cs”; Koelsch 2014): (1) When we make music, we make *contact* with other individuals (preventing from social isolation). (2) Music automatically engages *social cognition* (Steinbeis and Koelsch 2008c). (3) Music engages *co-pathy* (the social function of empathy) in the sense that interindividual emotional states become more homogenous (e.g., reducing anger in one individual and depression or anxiety in another), thus promoting interindividual understanding and decrease of conflicts. (4) Music involves *communication* (Fitch 2006; Trehub 2003). (5) Music making also involves coordination of movements (Overy and Molnar-Szakacs 2009; Patel et al. 2009; Kirschner and Tomasello 2009). The coordination of movements in a group of individuals appears to be associated with pleasure (e.g., when dancing together), even in the absence of an explicit shared goal (apart from deriving pleasure from concerted movements). (6) Performing music also requires *cooperation* (involving a shared goal and increasing interindividual trust); notably, engaging in cooperative behavior is an

important potential source of pleasure (Rilling et al. 2002). (7) As an effect, music leads to increased *social cohesion* of a group (Cross and Morley 2008), fulfilling the “need to belong” (Baumeister and Leary 1995), and the motivation to form and maintain interpersonal attachments. Social cohesion also strengthens the confidence in reciprocal care (Trehub 2003), and the confidence that opportunities to engage with others in the mentioned social functions will also emerge in the future. Social cohesion has aesthetic quality because it can be experienced as beautiful.

Music seems to be capable of engaging all of the “Seven Cs” at the same time, which can lead to “aesthetic emotions” such as transcendence and spirituality. These evolutionarily advantageous social aspects of music-making behavior represent one origin for the evolution of music-making behavior in humans.

Action induction by music perception is accompanied by neural impulses in the reticular formation (in the brainstem; e.g., for the release of energy to move during joyful excitement). It is highly likely that connections also exist between the reticular formation and structures of the auditory brainstem (Levitt and Moore 1979) and that the neural activity of the reticular formation therefore also influences the processing of (new) incoming acoustic information.

Music Perception and Memory

The modules presented in Fig. 1 are associated with a variety of memory functions (Jäncke 2008). For example, the auditory sensory memory (along with Gestalt formation) is connected with both working memory (Berti and Schröger 2003) and long-term memory (Näätänen et al. 2001). Structure building requires working memory as well as a long-term store for syntactic regularities, and processing of meaning information is presumably tied to a mental “lexicon” (containing conceptual–semantic knowledge), as well as to a musical “lexicon” containing knowledge about timbres, melodic contours, phrases, and musical pieces (Peretz and Coltheart 2003). However, the

details about interconnections between the different modules and different memory functions remain to be specified.

Neuroimaging studies suggest that the phonological loop of verbal working memory (WM) and the “tonal loop” of working memory for pitch strongly overlap in nonmusicians (Hickok et al. 2003; Koelsch et al. 2009; Schulze et al. 2011a), involving the ventral premotor cortex (encroaching Broca’s area), dorsal premotor cortex, planum temporale, inferior parietal lobe, anterior insula, subcortical structures (basal ganglia and thalamus), as well as cerebellum. A study by Schulze et al. (2011b) showed that, in contrast to nonmusicians, musicians use specific neural sub-components of WM only during verbal (right insular cortex) or only during tonal WM (right globus pallidus, right caudate nucleus, and left cerebellum). These results revealed the existence of two WM systems in musicians: a phonological loop supporting rehearsal of phonological information and a tonal loop supporting rehearsal of tonal information. Note that differences between nonmusicians and musicians for tonal WM (and between verbal and tonal WM within musicians) were mainly related to structures involved in controlling, programming, and planning of actions, thus presumably reflecting differences in action-related sensorimotor coding of verbal and tonal information. That is, verbal and tonal WM rely strongly on action-related coding (Schulze et al. 2011a).

The knowledge about musical long-term memory is still rather limited. Functional neuroimaging data suggest that access to musical semantic memory involves the (left) middle temporal gyrus and that musical semantic representations (i.e., parts of a musical lexicon) are stored in (left) anterior temporal areas (Groussard et al. 2009, 2010). In addition, Watanabe et al. (2008) reported that retrieval of musical information involves the hippocampal formation and the inferior frontal gyrus. Further systematic research in these areas is needed to differentiate memory operations from operations of the modules described in Fig. 1; it is important to bear in mind that, especially in functional imaging experiments, both types of operations usually co-occur.

Music and Language

The previous sections provided a number of examples for cognitive processes (and their neural correlates) underlying the processing of music as well as of (spoken) language. Decoding of both music and speech information requires a fine-grained analysis of the spectral and temporal features of acoustic information (boxes “Feature Extraction I and II” in Fig. 1). The section on auditory feature extraction mentioned the acoustic equivalence of timbre and phoneme, and the *identification* of “phonemes” in language is thus presumably paralleled by the identification of “timbres” in music. However, the segmentation of phonemic information during language perception usually requires a higher temporal resolution compared to the music (because timbral information in music usually does not change as rapidly as phonemic information in language). This probably leads to the left-hemispheric weighting for the segmentation of phonemes during language perception, whereas segmentation of spectral information such as melodic information of speech prosody or musical melodies engages the right auditory cortex more strongly than the left auditory cortex.

Adequate processing of both music and speech also requires auditory sensory memory and auditory scene analysis/auditory stream segregation (see boxes “Auditory sensory memory” and “Gestalt formation” in Fig. 1), particularly in noisy environments (which are more common than the quiet auditory environments typical for experiments on language or music perception). The processes mediating the identification of chords (e.g., whether a chord is a major or a minor chord, whether a chord is presented in root position or in inversion, etc.; see box “Analysis of intervals” in Fig. 1) perhaps parallel those underlying the identification of word form (due to both words and chords having a stem or “root” from which different versions emerge); however, this remains to be specified.

The section on music-syntactic processing (see also box “Syntactic structure building” in Fig. 1) presented evidence for interactions between the processing of music- and language-syntactic

information at levels of morpho-syntactic processing, phrase-structure processing, and possibly word-category information (see the evidence for the interaction between the ERAN and LAN and the provisional evidence for an interaction between ERAN and ELAN). Beyond these early interactions between music- and language-syntactic processes, it appears that cognitive and neural resources are also shared during later stages of syntactic integration (see box “Structural reanalysis and repair” in Fig. 1; see also the *Shared Syntactic Integration Resource Hypothesis* and the *Syntactic Equivalence Hypothesis* described above).

Both speech and music perception involve premotor coding (Liberman and Mattingly 1985; Koelsch 2009b), and both music and language give rise to affective processes: With regard to language, the perception of affective prosody (Ethofer et al. 2009; Wittfoth et al. 2010) as well as the affective contents of words (Vö et al. 2009; Herbert et al. 2009) can elicit emotional responses; for a review of the neural correlates of music-evoked emotions, see Koelsch 2014.

Finally, the section on musical meaning illustrated that communication of meaning is not exclusively a linguistic domain, but that music can also convey meaningful information: The interpretation of extramusical sign qualities of musical information can prime representations of meaningful concepts, and such priming can emerge from different cognitive levels (e.g., from auditory feature extraction or from a more fine-grained analysis of intervals, see also Fig. 1). Moreover, structural relations give rise to intramusical meaning (suggested to be reflected in the N500).

Corresponding to these shared processes, there is considerable resemblance, overlap, and interaction between ERP components (and their neural generators) elicited during the perception of music or language: Processing of musical as well as of speech information evokes (a) FFRs originating from the auditory brainstem; (b) P1, N1, and P2 potentials originating from the auditory cortex; (c) MMN potentials originating from temporal and frontal cortical areas; (d) potentials of early

syntactic processing that interact with each other (ERAN/LAN) and receive main contributions from the (inferior) pars opercularis (BA 44i); (e) potentials of syntactic (re)integration/reanalysis and repair (P600); and (f) N400 effects reflecting semantic processing (probably originating from posterior temporal and inferior frontal cortex).

The illustrated overlaps between music and language show that “language” and “music” are different aspects of the same domain, or two poles of a rather continuous dimension, rather than being two strictly separate domains (the *music–language continuum*; Koelsch 2012). Spoken language has rhythm, melody, and timbre, and the illusory transformation from speech to song described by Diana Deutsch (Deutsch et al. 2011) shows that humans can perceive spoken language also as song (although individuals often do not realize this in everyday life). Once an individual puts emphasis in his/her utterances, the speech becomes more song-like, and many art forms, such as rap music or recitatives, are both song and speech. In addition, music is often structured according to a syntactic system, and during music listening, meaning emerges from the interpretation of musical information. Therefore, any clear-cut distinction between music and language (and thus also any pair of separate definitions for language and music) is likely to be inadequate or incomplete.

As mentioned already above, even individuals without formal musical training show sophisticated abilities with regard to the decoding of musical information, the acquisition of knowledge about musical syntax, the processing of musical information according to that knowledge, and the understanding of music. This finding supports the notion that musicality is a natural ability of the human brain. Such musical abilities are important for the acquisition and the processing of language: Infants acquire information about word and phrase boundaries (possibly even about word meaning) in part through different types of prosodic cues. Moreover, tonal languages rely on a meticulous decoding of pitch information, and both tonal and nontonal languages require an accurate analysis of speech prosody to

decode structure and meaning of speech. The assumption of an intimate connection between music and speech is corroborated by the reviewed findings of overlapping and shared neural resources for music and language processing in both adults and children. These findings suggest that the human brain, particularly at an early age, does not treat language and music as strictly separate domains, but rather treats language as “a special case of music” (Koelsch and Siebel 2005).

Cross-References

- [Acoustic Timbre Recognition](#)
- [Auditory Event-Related Potentials](#)
- [Auditory Perceptual Organization](#)
- [Pitch Perception, Models](#)

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Musical Tones

► Pulse-Resonance Sounds

n:m Phase-Locking

► [Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)

Na⁺ Channels

► [Sodium Channels](#)

NDVis–Neuro

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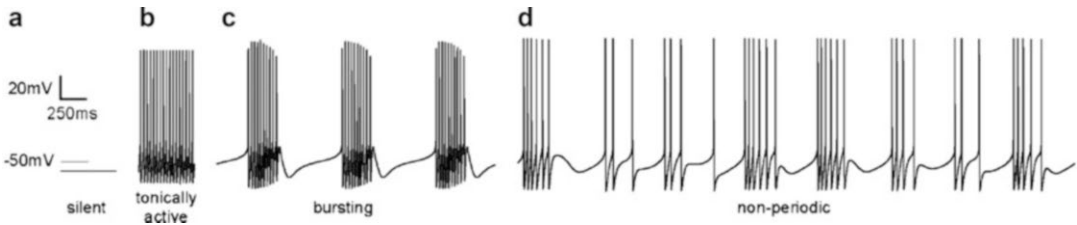
Definition

NDVis–neuro is a Java application that enables visualization and analysis of model neuron simulation databases. It is open source and available at <http://ndvis.sourceforge.net/>. The tool was originally created to visualize the database described in “Alternative to hand-tuning conductance-based models: construction and analysis of databases of model neurons” (Prinz et al. 2003). It has now been used with a number of different databases generated by simulating neuron models with various input parameters.

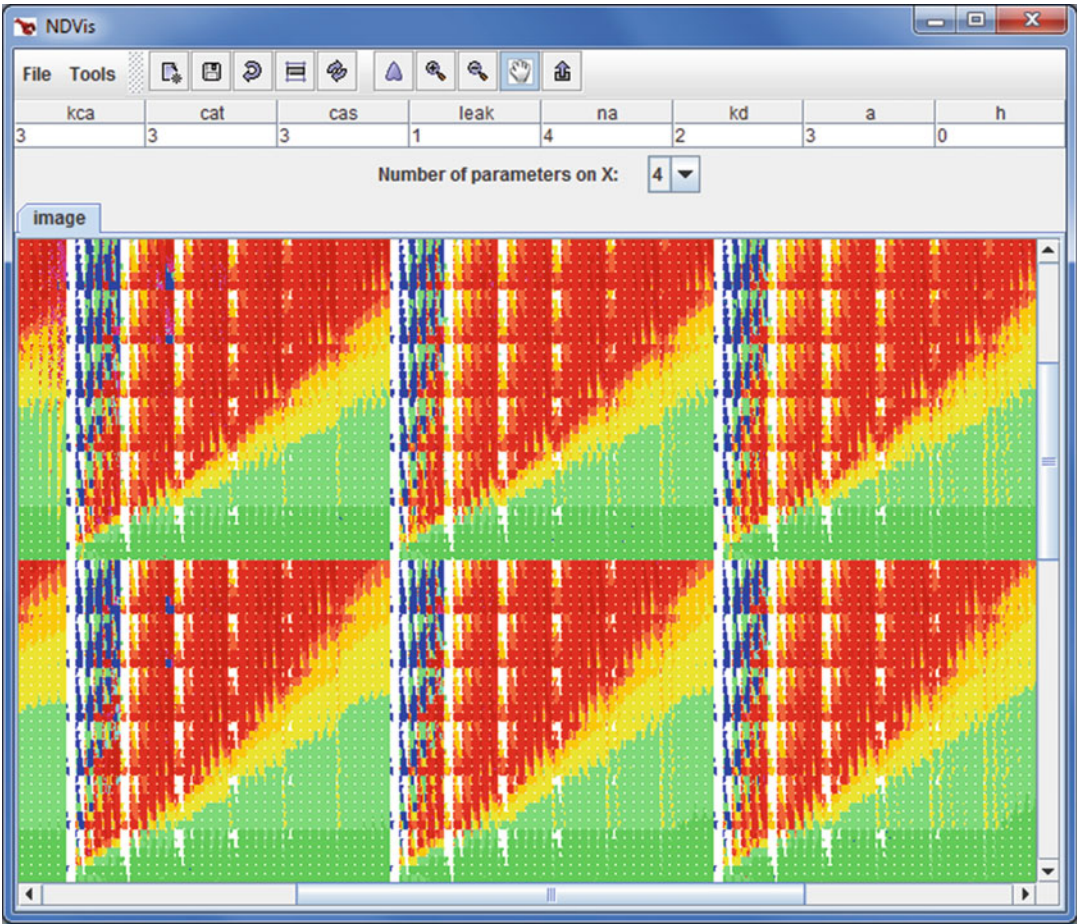
Detailed Description

The examples and visualizations shown here are based on the Prinz database referenced above. The neuron model used to create the database contained eight conductance parameters: Na, CaT, CaS, A, KCa, Kd, H, and leak. Each parameter had six possible starting values. A simulation was run for every possible combination of the eight parameter values, yielding 6^8 or 1,679,616 simulations. For each simulation, the conductance parameters served as inputs and represented the initial state of the neuron model. Each simulation ran until neuron activity reached a steady state, or some time threshold was reached. Various attributes of the simulation output were measured and recorded in a database. This process included classifying models based on activity patterns in the simulation output. Figure 1 shows examples of four activity patterns labeled as follows: (A) silent, (B) tonically active or “spiking,” (C) bursting, and (D) nonperiodic (meaning there is no clear repetition of specific behavior).

Figure 2 shows a screenshot of NDVis–neuro visualizing the Prinz database. The visualizations combine two techniques: pixelization and dimensional stacking. Pixelization maps each data point (or simulation) to a single pixel. Dimensional stacking projects multiple dimensions onto the axes of a two-dimensional display (as labeled in Fig. 4). The goal is not to detect detail in a single pixel but to discover patterns and relationships across the data. For instance, a visualization can



NDVis-Neuro, Fig. 1 Four types of neuron activity



NDVis-Neuro, Fig. 2 NDVis-neuro visualizing model neuron simulation output classified according to activity type as defined in Fig. 1. Each pixel corresponds to one simulation and is colored as follows: bursting models are

blue, silent models are green, and a range of tonically active models range from light yellow to dark red to show the range in spike frequency

reveal boundaries between neuron activity types and reveal the conductance parameter values that create them. The tool can connect to any Structured Query Language (SQL)-compatible

database with any number of tables. It expects each row to represent one simulation and requires columns for the input parameters. Additional columns may contain measurements taken on

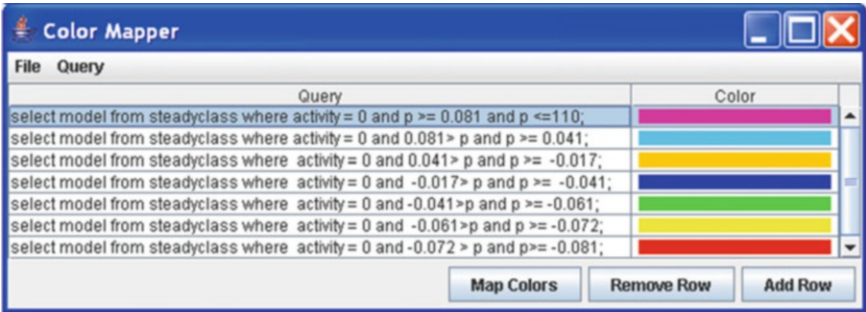
simulation output such as the duration of bursts in bursting neurons as shown in Fig. 1.

In Fig. 2, every pixel corresponds to one neuron model simulation and the color is mapped to some measure on the simulation output (e.g., classification of the neuron activity pattern). The mapping from data to pixel color is controlled through NDVis’ ColorMapper tool, as shown in Fig. 3. The user can specify an SQL query of arbitrary complexity and map the results to a discrete color or a color gradient. In the first row of the table in Fig. 3, the user selects models with spiking output (i.e., output that is classified as “activity = 0”), but only if it has a period (“p”) or spike frequency within a certain range. The user has assigned the color pink which will be mapped to pixels that represent models returned by the query. The rest of the rows have almost the same query but select different values for the range of “p”. This query set essentially uses color to show changes in spike frequency based on parameter values. Only discrete colors are assigned in Fig. 3. However, scalar values can also be mapped into a color gradient by picking two colors in the second column. For instance, the user could have simply selected “p” in the query without specifying a range. They would then pick two colors in the second column which represent the beginning and ending hues of a color gradient. NDVis-neuro normalizes scalar values and maps them into a gradient between the two color selections.

User queries in the ColorMapper tool are not limited to selecting values from the database.

They can perform any SQL function on the data and map the return value into the visualization. For instance, a common use is to take the log of certain values so that they better fit within a color gradient representation.

NDVis maps multiple parameters to the axes of a two-dimensional visualization using a technique called dimensional stacking (LeBlanc et al. 1990). Figure 4 shows an example with clearly labeled axes. On the X-axis, the visualization is first segmented according to the six values CaS can take on. Each of those segments is then segmented according to the six values that A can take on. Each A segment is segmented for the six values that Na can take on, and each of those segments contains every value for H (at the pixel level). The same general structure is repeated for the Y-axis. There is no need for every parameter to have the same number of possible values (as is the case in this example). NDVis was engineered to support models with different numbers of parameters and possible values. Mixed radix computation is used to mathematically map from parameter values to pixel coordinates and vice versa. Each parameter is treated as one digit in the value for either the X or Y coordinate. In our example we have eight parameters that can each take on six possible values. To derive a value for the X coordinate, we can concatenate four parameters and treat them as a four-digit, base six number. We convert the base six number to base ten to get the coordinate value. The Y coordinate can be computed in the same way from the remaining



NDVis-Neuro, Fig. 3 ColorMapper used to define apping from data to visualization

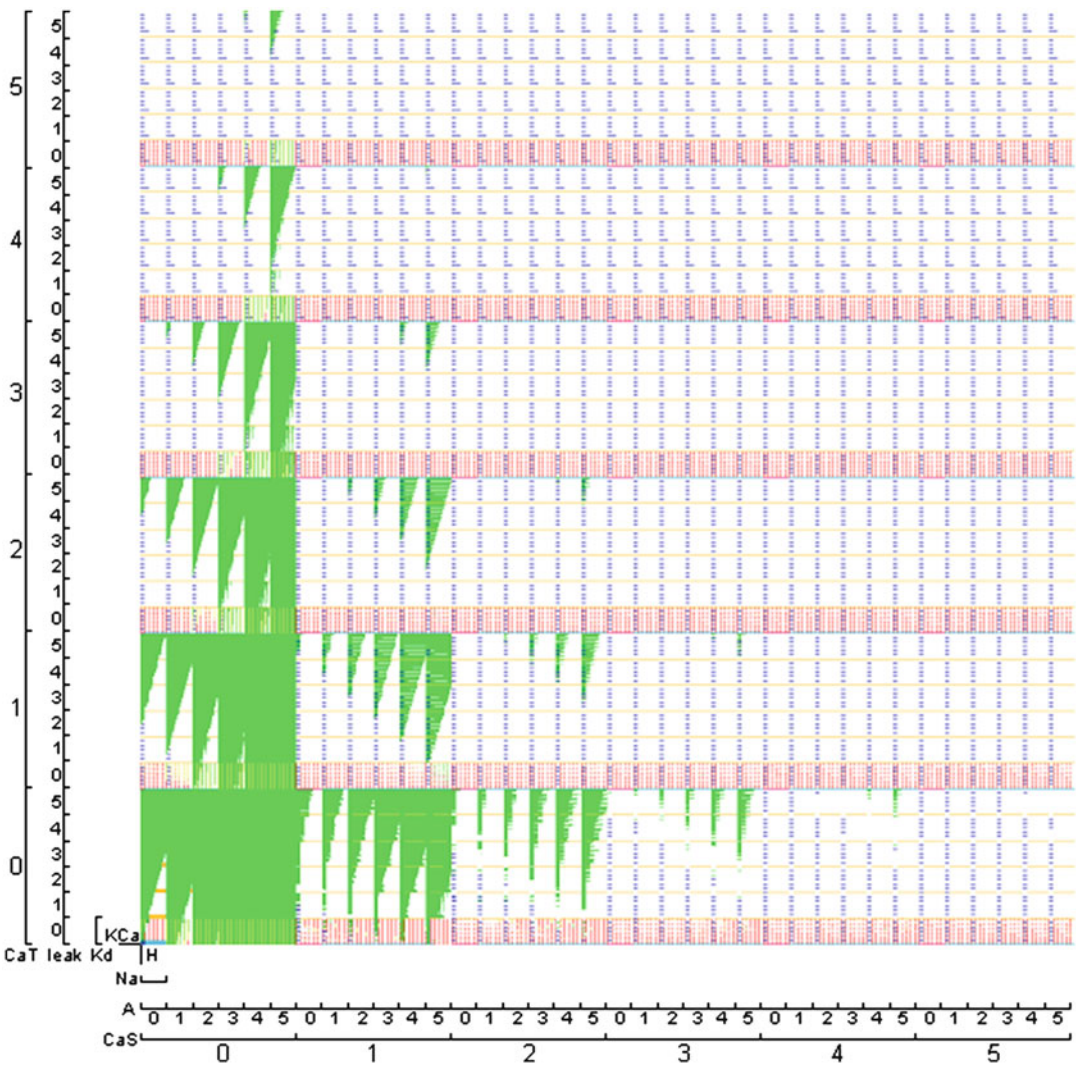
four parameters. An example of this computation using the parameter order in Fig. 4 is as follows:

$$X = \text{CaS?}6^3 + \text{A?}6^2 + \text{Na?}6^1 + \text{H?}6^0$$

$$Y = \text{CaT?}6^3 + \text{leak?}6^2 + \text{Kd?}6^1 + \text{KCa?}6^0$$

Note that parameter order does matter and can dramatically change the visualization. Different orders can reveal different insights. There is no optimal parameter order; however, certain parameter orders can reveal more or less information than others. NDVis-neuro enables users to change

the parameter order and refresh the visualization. This is done using the one-row table at the top of Fig. 2. The first four columns of the table represent parameters that are mapped to the X-axis, while the last four columns represent parameters that are mapped to the Y-axis. The user can drag and drop the columns of the table to reorder dimensions then refresh the visualization. Some versions of the tool have machine learning algorithms for finding informative parameter orders. For instance, genetic algorithms can be used along with image analysis which computes entropy (i.e., information content) as a fitness function



NDVis-Neuro, Fig. 4 NDVis image projecting eight parameters into two dimensions

based on color variation across the visualization. The general idea is that an image that clusters similarly colored pixels will reveal information. However, within dimensional stacking, a cluster can also appear as repeating patterns rather than a solid block of color.

NDVis–neuron is no longer supported actively; however, it is open source and anyone may use or contribute its code.

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Further Reading

- Taylor AL, Hickey TJ, Prinz AA, Marder E (2006) Structure and visualization of high-dimensional conductance spaces. *J Neurophysiol* 96(2):891–905

Nernst Equation

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Synonyms

[Equilibrium potential](#)

Definition

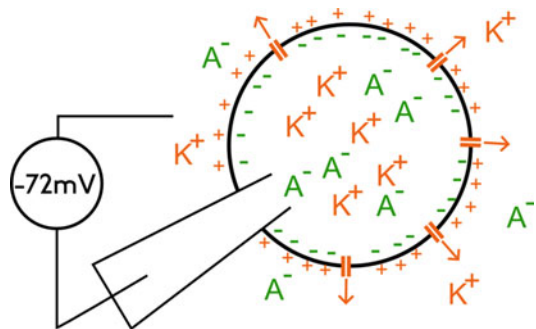
The Nernst equation describes how the equilibrium potential for an ion species (also known as its Nernst potential) is related to the concentrations of that ion species on either side of a membrane permeable to the ion.

Detailed Description

Physical Basis of the Equilibrium Potential

The membrane potential is the electric potential difference that exists across a membrane which is permeable to an ionic species and which separates solutions of the ionic species at differing concentrations. For example, cell membranes are often permeable to potassium, and the concentration of potassium inside the cell is greater than the concentration outside the cell. Negatively charged anions balance out the positive charge of potassium ions so that the charge inside and outside the cell is neutral, and the membrane is assumed to be impermeable to the anions (Fig. 1).

In this situation, potassium ions from the more concentrated solution inside the cell will tend to diffuse through the membrane to the lower-concentration solution outside. Because potassium ions are positively charged, this will cause a build-up of positive charge on the outside of the cell membrane and an equal and opposite build-up of negative charge on the inside. Thus, the electric potential outside the cell is greater than that inside, and the membrane potential, by convention defined as the potential inside minus the potential outside, will be negative. This potential difference corresponds to an electric field that exerts an inward force on the potassium ions, thus opposing their diffusion down the concentration gradient



Nernst Equation, Fig. 1 A cell containing high, balanced concentrations of potassium ions and anions inside and low, balanced concentrations of the same ions outside. The membrane is permeable to the potassium ions but not the anions. At equilibrium, the outside of the membrane is positively charged relative to the inside, which gives rise to the equilibrium membrane potential

from inside to outside. The potential difference at which the electric and diffusive influences on the ions balance out is known as the equilibrium potential or the Nernst potential. At this potential, there is no net flow of the ion species through the membrane.

The Nernst Equation

In a cell, the Nernst equation (Nernst 1888) relates the equilibrium potential E_X for an ion of type X with valency z_X to the concentrations $[X]_{\text{out}}$ and $[X]_{\text{in}}$ of the ion outside and inside the cell:

$$E_X = V_{\text{in}} - V_{\text{out}} = \frac{RT}{z_X F} \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$$

where F is Faraday's constant, R is the molar gas constant, and T is the temperature in kelvins.

Examples

1. The intracellular and extracellular concentrations of potassium ions in squid giant axon are $[K^+]_{\text{in}} = 400 \text{ mM}$ and $[K^+]_{\text{out}} = 20 \text{ mM}$, respectively. Since potassium ions carry a single positive charge, the valency $z_K = 1$, and using the values of $R = 8.314 \text{ J K}^{-1} \text{ mol}^{-1}$ and $F = 9.648 \times 10^4 \text{ C mol}^{-1}$, the equilibrium potential for potassium at 6.3°C (279.3 K) is obtained by substituting these values into the Nernst equation:

$$E_K = \frac{8.314 \times 279.3}{+1 \times 9.648 \times 10^4} \ln \frac{20}{400} = -72 \text{ mV}$$

2. The intracellular and extracellular concentrations of chloride ions in squid giant axon are $[Cl^-]_{\text{in}} = 40 \text{ mM}$ and $[Cl^-]_{\text{out}} = 560 \text{ mM}$, respectively. Since chloride ions carry a single negative charge, the valency $z_{Cl} = -1$, and the equilibrium potential for chloride at 6.3°C is

$$E_{Cl} = \frac{8.314 \times 279.3}{-1 \times 9.648 \times 10^4} \ln \frac{560}{40} = -64 \text{ mV}$$

Derivation

The Nernst equation can be derived from the Nernst-Planck equation of electrodiffusion (Johnston and Wu 1995; Hille 2001; Sterratt et al. 2011). Diffusion is assumed in one dimension (labeled x), through the membrane. At equilibrium, no current flows, so the flux in the Nernst-Planck equation is set to zero to give: $\frac{1}{[X]} \frac{d[X]}{dx} = -\frac{z_X F}{RT} \frac{dV}{dx}$. This equation can be rearranged and integrated: $\int_{V_{\text{in}}}^{V_{\text{out}}} -dV = \int_{[X]_{\text{in}}}^{[X]_{\text{out}}} \frac{RT}{z_X F [X]} d[X]$. The Nernst equation results from evaluating this integral.

Alternatively, the Nernst equation can be derived from thermodynamic principles (Hille 2001).

Cross-References

► [Goldman-Hodgkin-Katz Equations](#)

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Nernst-Planck Equation

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Synonyms

[Drift-diffusion equation](#); [\(Kinetic or continuum\) electrodiffusion equation](#)

Definition

The Nernst-Planck equation is a physical reformulation of Fick's macroscale diffusion law, extended to the motion of charged particles. The equation was established and experimentally underpinned by Nernst, and theoretically elaborated by Planck, and acquired growing significance when it was recognized that essential processes of life, such as cellular excitation and mitochondrial energy metabolism, depend on electrodiffusion.

Detailed Description

Derivation of the Steady-State Nernst-Planck Equation

Nernst (1888) started from van't Hoff's (1887) insight that solute particles generate, in a solvent, an osmotic pressure that obeys the gas laws, and from the observation that they move, under the influence of a constant force, at constant mean velocity owing to the enormous friction forces generated by collisions with solvent molecules.

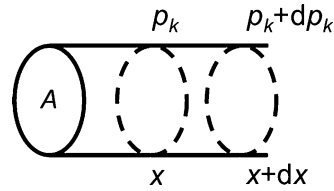
Let the mobility μ of a particle be the velocity v it acquires under the influence of a unit force F (Benedek and Villars 2000):

$$\mu = \frac{v}{F}$$

(in units of time/mass). Then the flow density or flux J (the number of particles passing through a surface perpendicular to the direction of particle motion, during a time interval dt , in units of moles $\text{m}^{-2} \text{s}^{-1}$) will be proportional to the speed v and concentration c :

$$J_k = v_k c_k$$

Clearly, on a slice of cylinder centered at x and of width dx and area A , the particles of species k generate a diffusion force dp_k , which is the difference in osmotic pressure p_k measured over the distance dx (Fig. 1). Given that the number of particles of species k in the slice equals $c_k N dx$, where N is Avogadro's number and c_k the particle concentration, the force per particle is



Nernst-Planck Equation, Fig. 1 Diffusion cylinder of cross-sectional area A , indicating the osmotic pressure gradient for ion species k at position x

$$-\frac{A dp_k}{A c_k N dx},$$

and the velocity

$$v_k = -\mu_k \frac{1}{N c_k} \frac{dp_k}{dx}$$

Hence, the flux

$$J_k = -\mu_k \frac{1}{N} \frac{dp_k}{dx},$$

or, using the ideal gas law,

$$J_k = -\mu_k \frac{RT}{N} \frac{dc_k}{dx}$$

(R being the gas constant and T the absolute temperature in kelvins).

From Fick's law, one also concludes that the diffusion coefficient D_k relates to μ_k as $D_k = \mu_k \frac{KT}{N} = \mu_k k_B T$, k_B being Boltzmann's constant.

Nernst then postulated that when a compound dissolves and dissociates into ions, the difference in diffusion coefficient between the ions must induce an electric field $E(x)$ that enhances the speed of the slower ion and slows down the faster, so as to make both ions diffuse at the same speed. More particularly, in an electric field $E = -\frac{d\phi}{dx}$, a positively charged particle of valency z_k is acted on by a force $z_k e E$, where e represents the unit charge. Hence, the particle's velocity is $\mu_k z_k e E$, and its flux $\mu_k z_k e E c_k$.

Taken together, the flow densities or fluxes J_i^+ and J_j^- for each positively charged ion i and each negatively charged ion j are

$$J_i^+(x) = -\mu_i^+ \left(k_B T \frac{dc_i^+}{dx} + z_i^+ e c_i^+ \frac{d\phi}{dx} \right)$$

$$\frac{\partial c_i^+}{\partial t} = \mu_i^+ \left(k_B T \frac{\partial^2 c_i^+}{\partial x^2} + z_i^+ e \frac{\partial}{\partial x} \left(c_i^+ \frac{\partial \phi}{\partial x} \right) \right)$$

$$J_j^-(x) = -\mu_j^- \left(k_B T \frac{dc_j^-}{dx} - z_j^- e c_j^- \frac{d\phi}{dx} \right)$$

$$\frac{\partial c_j^-}{\partial t} = \mu_j^- \left(k_B T \frac{\partial^2 c_j^-}{\partial x^2} + z_j^- e \frac{\partial}{\partial x} \left(c_j^- \frac{\partial \phi}{\partial x} \right) \right)$$

An equivalent formulation, using the above relationship between D_k and μ_k , and the identity $\frac{RT}{F} = \frac{k_B T}{e}$, reads

$$J_k(x) = -D_k \left(\frac{dq}{dx} + \frac{F z_k}{RT} c_k \frac{d\phi}{dx} \right),$$

where the valency z_k now takes negative integer values for anions and positive values for cations.

To obtain the steady-state ion current density I_k , the flux J_k must be multiplied by $z_k F$.

As noted by Nernst (1888), other flux terms can be added, representing gravitational, centrifugal, or magnetic forces. Planck (1890a) extended Nernst's equation to three spatial dimensions (Modeling Ion Concentrations). He also added Poisson's equation, which is a reformulation of Coulomb's law, to quantify the charge involved in generating the electrostatic field E :

$$\begin{aligned} \nabla^2 \phi(x) &= \nabla \cdot \text{grad}(\phi(x)) = \nabla \cdot E(x) = -\frac{\rho(x)}{k\epsilon_0} \\ &= -\frac{F}{k\epsilon_0} \sum_k z_k c_k(x) \end{aligned}$$

where ϵ_0 is the permittivity of free space and κ the dielectric constant of the solvent (assuming a homogeneous medium).

The Time-Dependent Nernst-Planck Equations

Planck (1890a) formulated the time-dependent equation (equivalent to Fick's second law). From the continuity constraint

$$\frac{\partial c_k}{\partial t} = -\frac{\partial J_k}{\partial x}$$

one derives

The electric current $I(x,t)$ must now be supplemented with the displacement current (Cohen and Cooley 1965):

$$I_D = \kappa \epsilon_0 \frac{\partial E}{\partial x}$$

Solutions of the Nernst-Planck Equations

Solving the full Nernst-Planck equations requires solving for each ion species separately, along with Poisson's equation. Note that the coupled set of equations is very nonlinear, due to the product of the ionic concentration with the strength of the electric field, which itself is determined by the distribution of charges. The system can be solved numerically after expressing the equations in integral form (Cohen and Cooley 1965; Arndt and Roper 1972). For many applications, however, reasonable assumptions can be made, such as zero or steady-state current, the presence of only monovalent ions, symmetries in the ionic compositions of the separated solutions, electro-neutrality, linear concentration gradients, constant electric field, etc. These assumptions enable analytic solutions to be obtained that have proven to be in close agreement with both experimental observations and numerical simulations.

For instance, Planck (and Nernst), instead of solving Poisson's equation, assumed electro-neutrality everywhere:

$$c_1^+ + c_2^+ + \dots = c_1 + c_2 + \dots$$

Note that this approximation still allows finite potentials to be obtained, provided the permittivity in the right-hand side of Poisson's equation vanishes as well (which is equivalent to assuming an infinite speed of light). Planck (1935) argued that the electrostatic field establishes so fast, and

involves the separation of so little charge over so little distance, that the resulting effects on concentration, and hence on the calculation of the field, are negligible. In contrast to this, on a macroscale, diffusion is a very slow process (on a microscale it can be extremely fast!) – Nernst used units of days and centimeters.

Nernst's Diffusion Potential

Nernst (1888, 1889) calculated the field E that establishes in a solvent across the concentration gradient $c(x)$ of a compound dissociating into ions having different diffusion coefficients (a generalization of Fick's first law to charged particles). For the dissociation into a univalent anion and cation, zero electric current ($J^+ = J^-$) requires

$$k_B T (\mu^+ - \mu^-) \frac{dc}{dx} = -e(\mu^+ + \mu^-) c(x) \frac{d\phi}{dx}$$

and hence,

$$\frac{d\phi}{dx} = -\frac{k_B T}{e} \left(\frac{\mu^+ - \mu^-}{\mu^+ + \mu^-} \right) \frac{1}{c} \frac{dc}{dx}$$

Nernst's diffusion potential generalizes, for arbitrary distributions of monovalent ions, to

$$\frac{\partial \phi}{\partial x} = -\frac{k_B T}{e} \frac{\frac{\partial(U-V)}{\partial x}}{U+V}$$

where

$$U = \mu_1^+ c_1^+ + \mu_2^+ c_2^+ + \dots$$

$$V = \mu_1^- c_1^- + \mu_2^- c_2^- + \dots$$

The Nernst Potential

The electric potential needed to cancel for a particular ion species k the flux generated by its concentration gradient is called the Nernst potential E_k and can be derived by solving for $J_k = 0$. The equation for the Nernst potential is just a restatement of the Maxwell-Boltzmann equation:

$$c_k(x) \propto e^{-\frac{z_k e \phi(x)}{k_B T}}$$

confirming that at equilibrium, the distribution of particles satisfies the distribution of energies due to thermal agitation.

Planck's Solution for the Diffusion Potential

In order to obtain the potential difference $\Delta\phi$ between two locations, the electric field E between them must be integrated, which generates a problem when two different ionic solutions have a planar interface where the derivative of concentration with respect to space becomes infinite. This discontinuity can be removed by assuming the presence of a transition zone, but Planck (1890b) recognized that $\Delta\phi$ now depends on the exact shape of the concentration gradient $\varphi(x)$, and hence the field $E(x)$, within the transition zone.

Planck obtained the exact solution for solutions of monovalent ions at thermodynamic equilibrium $\frac{\partial c_k}{\partial t} = 0$, for each ion species k . However, Planck's solution may require solving a transcendental equation.

Henderson's Solution for the Diffusion Potential

Henderson obtained a simpler solution, for the constraint that at each given position of the junctional zone, all ions form identical mixtures of their concentrations across the boundary (the simplest case being each species varying linearly, but the solution is not limited to this). Henderson's formula reads for the interface between a c_1 molar NaCl solution and a c_2 molar KCl solution as (Benedek and Villars 2000)

$$\Delta\phi = -\frac{k_B T}{e} \frac{(\mu_{K^+} - \mu_{Cl^-})c_2 - (\mu_{Na^+} - \mu_{Cl^-})c_1}{(\mu_{K^+} + \mu_{Cl^-})c_2 - (\mu_{Na^+} + \mu_{Cl^-})c_1}$$

$$\ln \frac{(\mu_{K^+} + \mu_{Cl^-})c_2}{(\mu_{Na^+} + \mu_{Cl^-})c_1}$$

For the general case of solutions of monovalent ions, Henderson's formula is

$$\Delta\phi = -\frac{k_B T}{e} \frac{(U_1 - U_2) - (V_1 - V_2)}{(U_1 - U_2) + (V_1 - V_2)} \ln \frac{U_2 + V_2}{U_1 + V_1}$$

Although Henderson's solution is different from Planck's equilibrium solution, it is often closer to experiment, because convection currents (not taken

into account in the Nernst-Planck equation) affect the ionic composition of the transition zone.

Goldman's Constant-Field Equation

Goldman (1943) applied in his study of rectifying membranes techniques used by Mott (1939) for semiconductors. Herein the stronger constraint is adopted that the electric potential $\varphi(x)$ within the transition zone varies linearly with position x . Although Planck's general solution generates a constant field E only under limited conditions, involving symmetries in the ionic compositions across the membrane ($[K^+]_{\text{inside}} = [Na^+]_{\text{outside}}$), Goldman's approximate solution offers the benefits of easier integration, as each Nernst-Planck equation now becomes linear and uncoupled.

A Note on the Hodgkin-Huxley Model

In the Hodgkin-Huxley model, the Nernst-Planck steady-state current for each ion species, say K^+ ,

$$I_{K^+} = -\mu_{K^+} F \left(k_B T \frac{dc_{K^+}}{dx} + ec_{K^+} + \frac{d\phi}{dx} \right)$$

is rewritten as

$$V = -\int_0^d \phi dx = \frac{k_B T}{e} \int_0^d \frac{d(\ln c_{K^+})}{dx} dx \\ + I_{K^+} \int_0^d \frac{dx}{\mu_{K^+} e F c_{K^+}}$$

The first term is the Nernst potential, and the current I_{K^+} could be taken out of the second integral because at steady state all current is position independent; hence, formally, this reduces to

$$I_{K^+} = g_{K^+} (V - E_{K^+})$$

with

$$(g_{K^+})^{-1} = \int_0^d \frac{dx}{\mu_{K^+} e F c_{K^+}}$$

To conclude, the Hodgkin-Huxley formalism replaces the diffusion term by its electric equivalent but loses the concentration dependency of the drift term. Some will therefore argue that its use

has become obsolete and that Goldman's equation is a better substitute.

Electrodiffusion Through Ion Channels

How well the Nernst-Planck equations can predict, at the microscale, electrodiffusion through ionic channels, is still being investigated. Even though it has been argued that at all biologically relevant time scales steady state can be assumed (Cole 1968), the size of the current will depend, as stated above, on the exact shape of the electric field and hence on the spatial distribution of charges within the channel. Fixed charges on channel proteins and on the membrane surface may impose boundary conditions, and as the thermal agitation of mobile charges will prevent their being completely shielded, the Poisson-Boltzmann equations may need to be simultaneously solved (Benedek and Villars 2000). The field within the channel will also depend on the concentration of the permeating ions within the pore and on the polarization charges they induce in the channel's wall (Eisenberg 1996). One recent technique is first to explore these parameters with Brownian motion simulations, before importing them into the Nernst-Planck equations (Song and Corry 2011).

Physical Constants

R , gas constant (pressure of N particles in 1 m^3 volume at 1 K): $8.3145 \text{ J mol}^{-1} \text{ K}^{-1}$.

F , Faraday's constant (the charge of N particles of unit charge): 96485 C mol^{-1} .

k_B , Boltzmann's constant: $1.3807 \cdot 10^{-23} \text{ J K}^{-1}$,

e , unit charge: $1.6022 \cdot 10^{-19} \text{ }^\circ\text{C}$,

N , Avogadro's number (number of particle in 1 g mole): $6.0221 \cdot 10^{23}$.

ϵ_0 , permittivity of vacuum: $8.85 \cdot 10^{-12} \text{ }^\circ\text{C V}^{-1} \text{ m}^{-1}$.

Cross-References

- [Diffusion Equation](#)
- [Goldman-Hodgkin-Katz Equations](#)
- [Hodgkin-Huxley Model](#)
- [Modeling Ion Concentrations](#)
- [Nernst Equation](#)

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Nerve Cuff Electrode

- [Peripheral Nerve Interface, Epineural Electrode](#)

Nerve Fiber Model(s)

- [Mammalian Motor Nerve Fibers, Models of](#)

Nerve Pain

- [Peripheral Nerve Interface Applications, Neuropathic Pain](#)

NEST

- [NEST: The Neural Simulation Tool](#)

NEST: The Neural Simulation Tool

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Synonyms

NEST; Neural Simulation Tool; SYNOD

Definition

NEST, the *Neural Simulation Tool*, is optimized for large networks of spiking model neurons. NEST

includes a wide range of neuron and synapse models and provides high-level commands to create spatially structured networks. NEST is controlled through a Python-based interface and supports parallel simulation. NEST is available from www.nest-simulator.org under a GNU Public License.

Detailed Description

NEST is optimized for networks of neurons whose subthreshold dynamics can be described by a small number of differential equations. By default, NEST simulations operate on a fixed time grid. However, NEST also supports precisely timed spikes (Morrison et al. 2007b; Krishnan et al. 2018), combining the precision of event-driven simulators (Henker et al. 2012) with the efficiency of grid-based simulation. Furthermore, NEST allows the simulation of neurons coupled by gap junctions (Hahne et al. 2015) and of networks of rate-based neurons (Hahne et al. 2017).

NEST supports hybrid parallelization combining MPI processes with OpenMP threads, permitting lightweight thread-only parallelization for small simulations on laptops as well as brain-scale simulations with nearly two billion neurons and eleven trillion synapses on supercomputers (Kunkel et al. 2014) and is ready for exascale supercomputers (Jordan et al. 2018).

PyNEST is the most widely used user interface for NEST (Eppler et al. 2008; Zaytsev and Morrison 2014), integrating NEST simulations with scripting and data analysis in Python. NEST can be controlled through PyNN (Davison et al. 2008) and can interact at run-time with other simulators through MUSIC (Djurfeldt et al. 2010).

New models can be added to NEST by writing an extension module in C++ which are dynamically loaded into a running NEST instance.

For an introduction to NEST usage, see Gewaltig et al. (2012).

Implementation

The core of NEST is a C++-application managing neurons, connections, and spike exchange. Each neuron model specifies an appropriate solver for its dynamics: linear models are solved using exact

integration (Rotter and Diesmann 1999), whereas the integration of nonlinear models is usually delegated to external solvers.

Parallel simulation of large networks is based on the concept of *virtual processes* (VP). VPs can be divided between MPI-processes and threads to optimally exploit the capabilities of the underlying hardware; NEST ensures identical results if the number of VPs is fixed (Plesser et al. 2007).

History, Development, and Applications

NEST started out as a student project by Markus Diesmann and Marc-Oliver Gewaltig called SYNOD (Diesmann et al. 1995). The simulator was renamed NEST in 2001 and was first released to the public in 2004. As of October 2012, NEST is available under a GNU Public License from www.nest-simulator.org, and since 2015 code development is hosted on Github (<https://github.com/nest/nestsimulator>). NEST development is driven by specific research needs (Kunkel et al. 2010), generating a steady evolution of simulator capabilities, including parallelization (Morrison et al. 2005), precise spike timing (Morrison et al. 2007b; Krishnan et al. 2018), spiketime-dependent (Morrison et al. 2007a) and neuro-modulated plasticity (Potjans et al. 2010), and spatially structured networks (Plesser and Enger 2013).

To ensure software quality, NEST source code has been version-controlled since 1996, checked against an automated testsuite since 2008 (Eppler et al. 2009), and subject to continuous integration testing since 2012 (Zaytsev and Morrison 2013), and mandatory code review since 2015.

NEST has been taught at numerous summer schools around the world and is a key simulation tool in the European Human Brain Project. Since 2015, the NEST community meets annually at the NEST Conference. NEST is used today for a wide range of applications in computational and theoretical neuroscience, brain modeling, and neurorobotics.

Cross-References

- [Brian Spiking Neural Network Simulator](#)
- [GENESIS, the GEneral NEural SIMulation System](#)

- ▶ [MOOSE, the Multiscale Object-Oriented Simulation Environment](#)
- ▶ [NEURON Simulation Environment](#)
- ▶ [PyNN: A Python API for Neural Network Modelling](#)

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Network Disorders

► Neuropathologies and Networks

Network Models of Contextual Effects

► Center-Surround Processing, Network Models of

Network Science

► Connectivity Analysis in Normal and Pathological Brains

Network Theory in Neuroscience

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Synonyms

Complex network theory in neuroscience; Graph theory in neuroscience

Definition

Network theory is a branch of mathematics concerned with the analysis of the structure of graphs, the mathematical abstraction of networks. Since the beginning of the twenty-first century, it has become an applied discipline due to the availability of large datasets for social,

technological, and biological systems. Although network theory was initially restricted to topological analysis, it has soon become a tool for understanding the emergence, functioning, and evolution of networks and the dynamical processes occurring on them. The application of network theory to neuroscience and, more specifically, to the analysis of brain structure and function represents a qualitatively different view of brain activity and brain-behavior mapping, shifting from a computerlike to a complex system vision of the brain, where networks are endowed with properties which stem in a non-trivial way from those of their constituent nodes. The network approach allows addressing an entirely new set of issues, such as detection and description of modularity and hierarchical structure, evaluation of efficiency and vulnerability, and structure-function relationships in healthy brains and disease.

Detailed Description

Background

The brain can be understood as a network of cells forming a massively parallel system, organized to carry out three major functions: computation, information transport, and communication among computational structures.

Brain tissue can be separated into gray matter (neurons) and white matter fibers connecting neurons (axons and dendrites). The human brain consists of roughly 10^{10} – 10^{11} neurons. Each neuron has approximately 10^4 synapses, which directly connect it to other neurons. The total wiring in the human cortical gray matter is of the order of 10^5 – 10^6 km, resulting in an overall neuronal potential bandwidth of the order of the terabit/second. Furthermore, the brain performs an estimated 10^{15} synaptic operations per second, but only consumes around 12 W, thus achieving an operation/joule ratio several orders of magnitude higher than the fastest available microprocessors (Sarpeshkar 1997).

On the other hand, powering the human adult brain accounts for ~20% of resting energy consumption (~60% in infants). Neuronal signal

transmission through axons and synapses accounts for about 50% of the brain's overall consumption (Laughlin and Sejnowski 2003), and due to the dense interconnected structure of its axons and synapses, the cortical gray matter uses more than 75% of total energy consumption for signaling. The energy supply limits both the total size and the amount of information that can be transmitted within the brain at a time.

The brain achieves these impressively high levels of computational efficiency by adopting energy-efficient architectures, involving trimming of superfluous signals and the representation of information with energy-efficient codes, resulting in appropriate distribution of the signal in space and time (Laughlin and Sejnowski 2003).

Brain Anatomy and Functional Activity

Human brain anatomy is characterized by networks of coupled neural systems across many spatial scales. Vertical structures divide the cortex into six main layers, within which basic computational units can somehow heuristically be defined as *minicolumns*, consisting of dense local interconnections between excitatory cells and inhibitory interneurons. Couplings between these local regions arise through sparse long-range excitatory projections, such as cortico-cortical fibers. These couplings facilitate large-scale integrative processes involving coordination between specialized networks.

Functional brain activity consists of transient episodes of synchronized/desynchronized activity between different parts of the brain (Breakspear 2002). Synchronization may facilitate integrative functions, by transiently binding together spatially distributed neural populations in parallel networks during sensory perception and information processing (Singer 1995; Miltner et al. 1999). Desynchronization may allow the brain to flexibly switch from one coherent state to another (Rodriguez et al. 1999). Asynchronous (nonlinear) couplings may also play an important role in functional integration, facilitating the creation of transient context-sensitive coherent neural assemblies between distant brain regions (Friston 2000).

Brain Connectivity

A network representation arises naturally both for the brain's anatomy and its functional activity. Brain networks can be defined at different scales, from the micrometer scale to the millimeter or centimeter scale of system-level neural assemblies, corresponding to the spatial resolution of the brain imaging technique used to define them.

For anatomical brain networks, it is straightforward to identify nodes as neurons or cortical areas and edges with axons or fiber tracts. On the other hand, when considering *functional connectivity*, networks are defined where edges correspond to correlated activity at different brain regions. Finally, *effective connectivity* can be associated to networks with directed edges whenever activity at one node modulates activity at another node (Sporns et al. 2004).

The classical approach to brain connectivity reflects the two basic ingredients of early neuropsychology: localization of cognitive function into specialized brain modules and the role of connection fibers in the integration of various modules. Thus, the emphasis is on the *identity* of the particular nodes and links forming the networks, under the covert hypothesis that each node and each link provide a unique contribution to the structure and function of the brain. The general model is that of a computerlike box-and-arrow one: by and large, computations are carried out within nodes, with links essentially working as pipes in a hydraulic system. Connectivity analysis is typically used to validate simple models of a given aspect of brain activity, and networks with only a few nodes and links are considered. The overall meaning of a given network can be traced back to the sum of its parts: an interpretation of a given connectivity pattern is in general proposed based upon the precise identity of its constituents' properties and on their known properties.

The Complex Network Approach

Over the last decade, brain structure and function have started been investigated using *complex network theory* (Boccaletti et al. 2006; Newman 2010), a statistical physics approach to an old branch of pure mathematics: graph theory.

Graph theory studies the properties of the formal mathematical structures called graphs, which are representations of a set of objects where some pairs of objects are connected by links. Complex network theory focuses on how *real* networks are organized and aims at identifying the guiding rules behind observed structures and dynamics of observed networks. For instance, nodes and links can both be endowed with dynamical properties and resulting collective behaviors such as synchronization can be investigated. It is also possible to study processes using the network as their support.

The way nodes and links are connected is associated with a great number of topological and dynamical properties at all scales, from that of the node to that of the whole network, which eventually allow neuroscientists to address many hitherto unaddressed issues.

Behavioral dynamics and its transitions are naturally described in terms of rewiring processes and the evolution of quantifiable network properties. Thus, network theory endows brain scientists with a potentially very high number of associated metrics of brain structure and activity, and brain *organization* receives a quantitative characterization. Moreover, it allows finding similarities and differences in the organization of neural networks, in spite of considerable variability in size and surface shape of individual brains.

The complex network approach represents a *qualitatively* different view of brain activity and brain-behavior mapping. The brain is understood as a complex system, where relationships between a *great number* of constituent parts give rise to collective behaviors. The spirit of the statistical physics approach hinges on an understanding of observed network properties as macroscopic phenomena resulting from microscopic interactions among a great number of individual components. Thus, in this approach, the identity of nodes and links is somehow lost. The network, rather than well-specified nodes or links, is endowed with specific properties. In general, these network properties are not easily traced to their single nodes and links; rather, they *emerge* from the *statistical properties* of their components.

With respect to prior connectivity methods, the complex network approach presents a range of distinctive *advantages*: first, it affords a *multi-scale* characterization of the brain's organization. Not only does network theory provide a description of network properties at microscopic, mesoscopic, and macroscopic scales, but it also naturally describes the *relationship across these scales*. Second, it allows handling complex relationships between brain structure, dynamics, and function. Third, it allows studying the brain as a biophysical machine and investigating a wide range of aspects of mechanistic brain functioning, including efficiency, resistance to failure, and synchronizability, which could not directly be addressed with connectivity techniques alone. Not only does network theory afford a quantitative description of directly observed states, but it also allows appraising the functional potential of healthy brains and the extent of the damage of those suffering from neurological or psychiatric pathologies.

Complex network theory therefore achieves three main *objectives*:

1. Singling out important anatomical and functional brain components
2. Characterizing general organizational principles of brain structure and function and as a consequence validating models of anatomical and functional brain organization, development, and pathology, as well as of cognitive function
3. Characterizing the brain, both anatomically and functionally, as a complex biophysical system whose constructive rules are subject to energetic constraints

Tools

What Is a Complex Network

A network consists of a group of N nodes (or vertices) connected through a set of L links (or edges). *Graph theory* focuses on the statistical properties of networks, mainly from a theoretical perspective. *Complex network theory* describes the analysis of real networks and the ways

topological structure determines the dynamical processes occurring in networks. Most real networks have an organization that is neither regular nor random. Complex network theory studies the laws that govern network topology and dynamics, the rules that lead to the formation of these non-random patterns, how topology influences the dynamics on top of the network, and the interplay between dynamics and the evolution of the network structure (Boccaletti et al. 2006; Newman 2010).

Building a Brain Network

The projection of experimental data onto a network is one of the most delicate steps in the application of network theory to the analysis of biological data. Both the nature (anatomical or functional) and the scale of observation constrain the way networks are reconstructed. The experimental technique used to record brain activity determines the size of the network and, ultimately, the information that can be extracted from it. Important methodological aspects of brain network reconstruction and possible pitfalls are still a subject of debate (Bialonski 2012; Zanin et al. 2012).

Brain networks can be classified into three main types: **anatomical, functional, and effective networks**.

Anatomical networks refer to the physical connections between neuronal elements, ranging from synapses between neurons to the grid of bundles between regions of interest (ROIs). We can define an anatomical network of connections at the scale we are interested in (or the scale given by experimental limitations): neurons, cortical columns, ROIs, or any parcellation of the brain with significant meaning. There exist different experimental techniques to trace the anatomical network of connections, which rely on both the scale and the organism being studied. For example, electron microscopy allowed extraction of the complete set of connections between neurons of the nematode *C. elegans* (White et al. 1986), the only living system whose nervous system has been fully mapped (Varshney et al. 2011). More recently, micro-optical sectioning tomography (MOST) has also revealed the connectivity of a mouse brain (Li et al. 2010). Both the anatomical

networks of the cat (Scannell et al. 1999) and the macaque (Felleman and van Essen 1991) cortex have been extensively studied thanks to the data obtained from different histological studies, leading to a complete cortico-cortical network of $N = 53$ cortical regions and $L = 650$ connections in the cat (Scannell et al. 1999) and the reconstruction of the macaque visual area ($N = 32$ and $L = 305$) (Felleman and van Essen 1991). Diffusion tensor imaging (DTI) (Iturria-Medina et al. 2007; Gong et al. 2009) allowed reconstruction of the human brain anatomical network, with the limitation of inferring the fiber bundle orientation. The use of diffusion spectrum imaging (DSI) has overcome this constraint (Hagmann et al. 2008) allowing an anatomical reconstruction of the human brain anatomical network formed by up to $N \sim 1,000$ nodes and $L \sim 100,000$ links (Hagmann et al. 2007).

Although the anatomical networks provide a substrate for the dynamical processes occurring on them, they are not necessarily linked to the functional activity occurring between different brain regions. Anatomical and functional networks may differ depending on the specific cognitive process that an individual is carrying out: while at short time scales the anatomical network is essentially static, the functional network associated with the execution of a cognitive task is inherently dynamical.

Functional networks account for the neurodynamical interactions between neural regions. Functional connectivity measures statistical interdependence between the dynamics of all pairs of the network nodes without taking into account causal effects. The more correlated the activity between two regions, the higher the weight of the functional connections between them. Note that despite the fact that functional connectivity requires the existence of an underlying anatomical connection, both functional and anatomical networks do not necessarily need to resemble each other (as the map of road connections does not necessarily reveal the traffic moving through them). As we will see, functional networks share common features between them, despite the fact that each network is task dependent.

There are different ways of measuring brain dynamics in order to later extract a functional

network. Electroencephalography (EEG) and magnetoencephalography (MEG) measure, respectively, the electric and magnetic fields created by the neuronal activity. Despite high temporal resolution (in the order of milliseconds) in both techniques, the spatial resolution is low (several centimeters) which leads to a poor reconstruction of the real dynamics of the brain. In addition, recordings are extracranial in both methodologies, which leads to problems of volume conduction in the case of EEG and common sources in MEG. Functional magnetic resonance imaging (fMRI) on the contrary, which monitors the brain activity by measuring the blood oxygenation, leads to a high spatial resolution ($\sim$ millimeters) paying the price of temporal resolution in the order of seconds.

Nevertheless, one of the main drawbacks of functional networks is the lack of directionality of their links. The fact that correlation does not imply causality leads to the necessity of defining an additional kind of brain networks. **Effective networks**, which are constructed from the analysis of the dynamical response of different brain sites, assign directionality to the links based on causality analysis (Büchel and Friston 2000). This kind of networks is the most mathematically demanding (Stephan and Friston 2007) but also the most accurate approximation to evaluate the real relations between brain sites.

Definitions and Notations

Tables 1 and 2 summarize the main node and network parameters, together with their mathematical definitions and the underlying concepts. Table 1 contains those parameters that concern to the node, although averaging over the whole network would lead to the extension of the parameter to the network level. Table 2 contains those parameters that only apply to network as a whole.

Important Parts of the Network

Degree and Strength Distributions

The degree k of a node simply accounts for the number of connections a node has. The degree distribution $p(k)$ of a network refers to the

probability of finding a node i with a certain number of connections k . When links are directed, the degree distribution is split into two: the in-degree (incoming links) and the out-degree (outgoing links) distributions. If links have a certain weight, then the degree distribution is transformed into the strength distribution $s(i)$, being the strength of a node, the sum of its links' weights. The degree distribution is a delta function in the case of regular networks and a Poissonian distribution when networks are completely random. Nevertheless, real networks show a diversity of degree distributions, with the majority of them being broad, with long tails. Additionally, in many cases, they can be described with a power-law decay ($p(k) \sim k^{-\gamma}$) (Newman 2003). In the case of the brain, different kinds of distribution have been reported depending on the spatial scale at which the system is analyzed, since the scale determines the number of nodes N and links L of the network which, in turn, constrains the width of the degree distribution. In cultured neural networks, the fact that neurons primarily connect through a random process leads to exponential distributions (Shefi et al. 2002). This kind of distribution is also reported in the in-degree and the out-degree of the anatomical connections of *C. elegans* nematode, the only living system with a whole reconstruction of its neural network (Amaral et al. 2000).

In human brain networks, the degree distribution strongly depends on the experimental technique used to acquire the data, the scale at which the system is observed, and the nature of the network that it is being analyzed (anatomical, functional, or effective). Hagmann et al. (2007) showed, by means of diffusion MRI, that a reconstruction of the anatomical brain network into 66 ROIs led to a degree distribution with an exponential decay. Later results (Hagmann et al. 2008) showed that though not having a power-law decay, a small group of hubs exists in both the degree and strength distributions. These functional hubs have high betweenness centrality and act as connectors between the main structural modules.

If we take a look at functional networks, the diversity of degree distributions increases.

Network Theory in Neuroscience, Table 1 Mathematical definition of the most significant node parameters

Node parameter	Mathematical definition	Underlying concept
Degree $k(i)$ and strength $s(i)$	$k(i) = \sum_{j \in N} a_{ij}$ $s(i) = \sum_{j \in N} w_{ij}$ where $a_{ij} = 1$ if nodes i and j are connected and $a_{ij} = 0$ otherwise. w_{ij} corresponds to the weights of the links in case they are considered	The degree accounts for number of links a node has. The strength is the sum of weights w_{ij} of the links arriving at a certain node (Amaral et al. 2000; Newman 2003)
Outreach $o(i)$	$o(i) = \sum_{j \in N} l_{ij} w_{ij}$ where l_{ij} is the length of the link between nodes i and j	Sum of the link's weight w_{ij} multiplied by the link's Euclidean length l_{ij} (Buldú et al. 2011)
Eigenvector centrality $e_c(i)$	$e_c(i) = \sum_{j \in V(i)} e_c(j)$ $V(i)$ being the set of neighbors of node i	A measure of node importance that takes into account the importance of the node's neighbor. It is equivalent to the eigenvector associated with the largest eigenvalue of the connectivity matrix (Newman 2010)
Shortest path d	Given two nodes i and j , the shortest path d_{ij} is the minimum number of nodes to be visited when going from i to j	Computes the minimum number of steps to go from one node to another (Newman 2010)
Clustering $C(i)$	$C(i) = \frac{2L_i}{k_i(k_i - 1)}$ where L_i is the number of links between neighbors of node i	It is related to the percentage of neighbors of a certain node that, in turn, are neighbors between them (Watts and Strogatz 1998). There exist other metrics that quantify the node clustering (Newman 2010)
Node betweenness $b(i)$	$b(i) = \sum_{j \neq k} \frac{n_{jk}(i)}{n_{jk}}$ where n_{jk} is the number of the shortest paths between nodes j and k and $n_{jk}(i)$ is the number of these paths that go through node i	Accounts for the number of the shortest paths between any node j and k of the network that cross node i (Newman 2010)
Within-module degree $z(i)$	$z(i) = \frac{k_i(m_i) - k(m_i)}{\sigma_{k(m_i)}}$ where $k_i(m_i)$ is the degree of node i inside its community and $k(m_i)$ and $\sigma_{k(m_i)}$ are, respectively, the average and the standard deviation of the degree inside the community	Measures the importance of a node inside its community (Guimerà and Amaral 2005)
Participation coefficient $p(i)$	$p(i) = 1 - \sum_m \left(\frac{k_i(m)}{k_i} \right)^2$ where $k_i(m)$ is the degree of node i inside community m	Evaluates the percentage of links that a node has to other communities (Guimerà and Amaral 2005)
Local efficiency $E_l(i)$	Computed as the global efficiency of the subnetwork $V(i)$ containing all neighbors of node i (see definition of Global Efficiency in Table 2)	Accounts for the inverse of the shortest path of the neighborhood of a node i when node i has been deleted. It is a measure of local resilience (Latora and Marchiori 2001)

It is possible to translate the majority of these metrics to the network level by simply averaging over the all nodes of the network. See (Rubinov and Sporns 2010) for the adaptation of these parameters to weighted networks

Eguíluz et al. showed that functional brain networks obtained from fMRI data show scale-free distributions for different tasks (Eguíluz et al. 2005) which could be related to their resistance to failure, facility of synchronization, and fast signal processing (Lago-Fernandez et al. 2000). Van den

Heuvel et al. (2008) also reported a scale-free distribution. Nevertheless, other results showed some discrepancies at the tail of the degree distribution, which was better fitted with an exponential decay leading to a power-law, exponentially truncated distribution (Achard et al. 2006a).

Network Theory in Neuroscience, Table 2 Mathematical definition of the most extended network parameters

Network parameter	Mathematical definition	Underlying concept
Assortativity r	$r = \frac{L^{-1} \sum_i j_i k_i - [L^{-1} \sum_i \frac{1}{2} (j_i + k_i)]^2}{L^{-1} \sum_i \frac{1}{2} (j_i^2 + k_i^2) - [L^{-1} \sum_i \frac{1}{2} (j_i + k_i)]^2}$ where $-1 \leq r \leq 1$ and j_i and k_i are the degrees of the nodes at the end of the i_{th} link, with $i = 1 \dots L$	Quantifies the degree correlation of the whole network. Assortative (disassortative) networks are those with positive (negative) degree correlations (Newman 2002)
Small-worldness S	$S = \frac{C/C_{ran}}{d/d_{ran}}$ being $C(d)$ and $C_{ran}(d_{ran})$, respectively, the clustering (shortest path) of the network and its randomized version	It evaluates the ratio between the normalized network clustering and the normalized shortest path. The highest the S , the more “small world” the network is (Humphries and Gurney 2008)
Synchronizability r and λ_2	$r = \frac{\lambda_N}{\lambda_2}$ (class III) λ_2 (class II) where λ_2 and λ_N are, respectively, the second smallest and the largest eigenvalues of the Laplacian matrix $L = K - A$, with K being a diagonal matrix containing the degree of the nodes and A the adjacency matrix	It is related to the stability of the synchronized state of the network. The dynamical system and the kind of coupling determine the class (I, II, or III), which is related to the ability of the system to synchronize (Boccaletti et al. 2006)
Global efficiency E_g	$E_g = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{d_{ij}}$ where d_{ij} is the shortest path between nodes i and j	Measures the harmonic mean of the inverse of the shortest paths between all nodes of the network (Latora and Marchiori 2001)
Modularity Q	$Q = \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - \left(\frac{d_s}{2L} \right)^2 \right]$ where l_s and d_s are, respectively, the number of links inside community s and the average degree of the community. N_M is the total number of communities inside the network	Evaluates how good is a given partition of the network into communities by comparing the density of links inside each community with that obtained in an equivalent random network (Newman 2006)

These parameters only have a meaning when analyzing the network as a whole. There exists a translation of all of them to weighted networks (Rubinov and Sporns 2010)

Altogether, no unique function seems to describe the degree distribution of brain networks. The number of nodes and links of the network strongly constrains the width of the distribution, together with the experimental technique used to obtain the data and the task performed during the recordings.

Network Hubs and the Rich Club

Network hubs are those nodes with higher importance in the network structure. Different measures have been proposed to quantify the relevance of a node within a network. At a local scale, the node degree (or strength if the network is weighted) is a good approach for identifying hubs. If we take into account the global structure of the network, the *betweenness* and the *eigenvector centralities* are the most widely used indicators (Newman

2010). The former is related to the number of shortest paths that crosses a given node, while the second takes into account not only the number of connections but also the importance of the neighbors.

The existence of hubs in both anatomical and functional brain networks has been related to a reduction of the wiring cost of the network, since hubs behave as integrators and distributors of information through the network when combined with a few long-range connections to other brain modules. Several studies have focused on the identification of these hubs and their role inside their respective community (i.e., among the nodes tightly connected to them) and as connectors between different brain modules (Hagmann et al. 2008). The tracking of hub connectivity during aging has

shown an alteration of both its importance within its community and its participation in other network modules (Meunier et al. 2009b). Interestingly, hub failure, quantified in terms of loss of connectivity, has been associated with the emergence of different brain diseases (Bassett et al. 2008).

A number of recent studies investigated the interconnections *between brain hubs* as a potential substrate for central integrative processes. In both the human and the macaque cerebral cortices, a largely consistent set of brain regions termed the *rich club* turns out to be more densely interconnected than expected based on comparisons to degree-preserving null models, with a large number of short communication paths connecting two or more rich club regions to each other (Colizza et al. 2006; Harriger et al. 2012; Van den Heuvel et al. 2012). In the human brain, the rich club spans regions including the superior parietal cortex, the precuneus, both the posterior and anterior cingulate cortices, and the insula (Van den Heuvel et al. 2012). The brain's rich club appears as a "super hub" where information converges from and is broadcast back to segregated communities and networks, allowing for integrated processing, offering a potential network substrate for the "global neuronal workspace" proposed in recent influential theories of cognition (Shanahan 2012).

General Organizing Principles

Complex systems, of which the brain is an example *par excellence*, are typically characterized by structure at and within multiple scales and by a correspondence between topology and dynamical processes taking place on them. In the brain, it is clear that both topology and dynamics control function. In turn, function retroacts, possibly at much longer time scales, to optimize network topology and brain dynamics, producing topological communities corresponding to functional subdivisions in the brain. Complex network theory is ideally suited to extract the general rules governing these sophisticated spatiotemporal multiscale relationships.

Assortativity/Disassortativity

Assortativity is a measure of the degree-degree correlations within a complex network. First introduced by Newman in the context of complex networks (Newman 2002), the assortativity parameter r (see Table 2 for a mathematical definition) computes the Pearson correlation coefficient for the nodes of the same degree. In assortative (*disassortative*) networks, nodes of the same (different) degree are prone to be connected, often leading to the appearance of a *rich club* where nodes of higher degree have connections to each other. Hagmann et al. (2008) also reported assortative mixing in the anatomical network of the human brain, showing that hubs are prone to connect to each other. Functional brain networks obtained from fMRI recordings during music listening and finger tapping were shown to be assortative (Eguiluz et al. 2005). Interestingly, the majority of biological networks seem to be disassortative, with clusters organized around local hubs (Newman 2010).

Motifs

Motifs are structural organizations of small size (typically less than 10 nodes) that are overrepresented inside the topological structure of a complex network. Milo et al. (2002) showed that biological networks have certain building blocks, which they called motifs, which emerge as a consequence of an underlying function. The existence of motifs in brain networks reveals the existence of nonrandom rules for creating local connections, and the diversity of network motifs has been related to the enhancement of the processing capacities at the local level (Sporns and Kötter 2004; Sporns et al. 2007).

Modularity and Hierarchy

The modularity of a network accounts for the existence of densely connected groups of nodes that lead to the formation of network communities. The detection of network communities has several difficulties (e.g., the absence of a perfect network partition, the overlap between communities, the coexistence of modules of different size) and has been a field of intense research during the last years (Fortunato 2010). In addition, it is common to observe a hierarchy in the modular

organization which indicates that, at different scales, there exist different network partitions that, in turn, have hierarchical dependencies between them (Sales-Pardo et al. 2007; Meunier et al. 2010). Detecting and evaluating the modular structure of a brain network is a complex task, but it is mandatory since, first, it gives information about the well-known segregated activity of the brain and, second, part of the complexity of the dynamical processes occurring in the brain relies on the existence of network modules (Pan et al. 2010). Interestingly, anatomical networks exhibit a modular (Hilgetag et al. 2000) and hierarchical organization (Zamora-Lopez et al. 2010). Different community partition algorithms of anatomical networks have shown high correlations of the obtained communities with known functional localized areas in the human brain (Chen et al. 2008) and also allow identification of those regions that make the structural core of the network (Hagmann et al. 2008). But the wealth of this kind of analysis is increased when analyzing functional networks. A series of studies have tracked the modular structure of resting-state functional networks at different ages, showing an alteration of the connections between communities as a consequence of the aging process (Meunier et al. 2009b). A hierarchical organization of functional communities has also been reported in the human brain (Meunier et al. 2009a), and it seems to indicate that the hierarchically modular structures facilitate the embedding of complex topologies into low-dimensional physical space (Bassett et al. 2010).

Integration/Segregation

Consistent experimental and computational evidence shows that cognitive function requires an optimal balance between *global* integrative and *local* functionally specialized processes (Tononi et al. 1994, 1998; van Putten and Stam 2001). Cooperation between local and global processing was shown to be the basis of cooperative phenomena such as feature binding in gestalt-like perception, in which the emergence of a coherent percept from spatially distant stimuli is associated with synchronous responses of distant neuronal assemblies (Singer 1995).

An appropriate balance between these two tendencies has been shown to be necessary for efficient functioning, particularly in neural systems (Tononi et al. 1994); in fact, exceedingly segregated or integrated brains have been associated with various pathological conditions, e.g., autism (Just et al. 2004) or schizophrenia (Fletcher et al. 1999; Tononi et al. 1998).

It appears then that the functional organization of the human brain presents an essential trade-off: on the one hand, modules should be sufficiently independent to guarantee functional specialization and parallel computing. On the other hand, modules should be sufficiently connected to bind multiple sources of information to promote coordinated activity or coherent percepts.

Small Worlds and Fractal Networks

Small-World Property

Small-world structure, a particular topology combining high local clustering and short path length, has been suggested to represent a solution to the trade-off between module independence and specialization. The small-world property refers to a very small distance in a network's path length, as compared to the total number of network nodes. The idea of a small world appeared in 1929, in a short story by the Hungarian author Frigyes Karinthy called *Láncszemek* (*Chains*), and later made famous by Stanley Milgram's *six degrees of separation* experiment (Milgram 1967). Milgram's experiments showed that the average number of successive acquaintances (i.e., the distance) between any two individuals in a population of the order of billions is just six.

Small-world networks show a high local density of connections together with a short number of steps to go from one node to any other (Watts and Strogatz 1998). They are characterized by (i) a high clustering coefficient C , which measures the percentage of the first neighbors of one node that are, in turn, connected with each other, and (ii) by the existence of long-range connections that create shortcuts between distant regions of the network. On the other hand, scale-free networks are associated with a power-law degree distribution $P(k) \sim k^{-\gamma}$, where γ is the degree exponent; the

average distance $\bar{d}$ scales logarithmically with the network size as $\bar{d} \sim \ln N$. The scale-free nature of functional networks implies that there are always a small number of brain sites functionally connected to most other brain regions and that the number of these nodes is comparatively much larger in these networks than in randomly connected ones.

It has consistently been shown that brain anatomical networks have characteristically small-world properties of dense or clustered local connectivity with relatively few long-range connections mediating a short path length between any pair of neurons or regions in the network (Sporns et al. 2004; He et al. 2007; Hagmann et al. 2007). Similarly, human brain functional networks of coherent activity associated with the execution of cognitive tasks have also been associated with power-law or truncated power-law degree distributions (Eguíluz et al. 2005; Salvador et al. 2005; Achard et al. 2006b; Bassett et al. 2006; Achard and Bullmore 2007).

The small-world structure seems to be pervasive both across scales of brain activity and across species. Such a structure also characterizes functional cortical neuronal circuits in mammals (Song et al. 2005; Yu et al. 2008) and been identified in nervous systems as simple as that of the nematode *C. elegans* (Watts and Strogatz 1998).

The modifications of small-world structure in disease (Stam et al. 2007), in normal aging, and by pharmacological blockade of dopamine neurotransmission (Achard and Bullmore 2007) may be functionally interpreted in the light of theoretical studies showing that small-world architecture optimizes information processing (Strogatz 2001), facilitates synchronization (Bucolo et al. 2003) and rapid response and emergence of coherent oscillations (Lago-Fernandez et al. 2000), and confers resilience against pathological attack.

Fractal Networks

Because complex systems typically exhibit structure at many scales, it is extremely interesting to understand the behavior of a complex network under a scale transformation and see the degree of similarity across scales. Fractality in a complex network can be identified in a manner similar to

that of ordinary fractals, which are objects consisting of self-similar copies at all scales. In this process, the network is first covered with boxes. After optimally covering a network with boxes of a given diameter l_B , a renormalization transformation is applied where each box is replaced by a single node and the links of the original network are transferred to the renormalized one, so that original links between nodes belonging to different boxes constitute links between these boxes.

Under general conditions, the required number of boxes N_B scales with the box diameter l_B as $N_B \sim l_B^{-\gamma_B}$ and γ_B is the fractal dimension of the network. Thus, fractality indicates a power-law scaling of the distances with network size, which is very different from the logarithmic dependence of small-world structures.

The dependence of N_B on l_B highlights two main families of networks: fractal networks, displaying power-law scaling with a finite-valued exponent γ_B , and non-fractal networks with a sharp exponential decay of N_B with l_B and an infinite fractal dimension $\gamma_B \rightarrow \infty$. Several experimental studies have shown that brain networks show hierarchical, fractal structures (Meunier et al. 2010; Bassett et al. 2010).

In fractal networks hubs tend to connect to small degree nodes and not to each other. In other words, hubs tend to stay away from each other. As a result, centrality is weakly correlated with degree: due to the repulsion between hubs, small degree nodes appear at all parts of the fractal network. Thus, their centralities can have both small and large values, and their average centrality is significantly larger, resulting in transport properties that are different from those of networks with different topological organizations. Fractality is closely related with modularity: the isolation of hubs allows considering that each box is built around a local hub, so that boxes ultimately roughly correspond to a module. By comparison to scale-free networks, fractal networks should be more stable to hub damage. The isolation of hubs from each other may provide an explanation of why most biological networks evolved toward a fractal behavior.

Solving the Integration-Segregation Trade-Off: The Role of Weak Ties

Shortcuts generating small worlds and the persistence of modularity, a global property unrelated to local clustering, are intrinsically conflicting mechanisms. Clustering is a local quantity related to the immediate neighborhood of a node, while modularity is a global network property (Girvan and Newman 2002; Meunier et al. 2010; Fortunato 2010). Furthermore, the short distances of a small-world network are generally incompatible with strong modularity, which typically presents the properties of a “large world” (Song et al. 2005, 2006; Radicchi et al. 2008; Rozenfeld et al. 2010) characterized by long distances.

Gallos et al. (2012) presented a possible solution to the seeming trade-off between integration and segregation: while strong ties within the brain are hierarchically organized into modules with “large-world” self-similar properties, the addition of weak ties overcomes the repulsion between hubs, rendering the network non-fractal and small world (Watts and Strogatz 1998). Remarkably, weak ties are organized in a way that maximizes information transfer with minimal wiring cost, suggesting a natural solution to the paradox of efficient information flow in the highly modular structure of the brain (Gallos et al. 2012).

Topology and Dynamics

Topological aspects of brain anatomy and the dynamical processes taking place on them are mutually intertwined.

On the one hand, the topology of structural (anatomical) networks influences the dynamical processes (namely, synchronization) taking place within them (Boccaletti et al. 2006). The topology of brain connectivity was shown to be a control parameter guiding global brain dynamics through series of phase transitions corresponding to different observable patterns, so that a wide range of different behaviors can be accessed by varying coupling strengths (Jirsa and Kelso 2000). For instance, changes in the topology or synaptic strengths in the relevant networks can cause transitions between various regimes of activity

(i.e., from normal to seizing to bursting) in models of epilepsy (Netoff et al. 2004). This has important implications for neural networks, where synaptic coupling strengths can change at all temporal and spatial scales due to learning processes and plasticity.

On the other hand, the synchronization process unveils the emergence of hierarchical neural communities at different time scales (Arenas et al. 2006). Simulations showed that brain dynamics exhibits a modular hierarchical organization, where clusters coincide with the topological community structure of anatomical networks (Zhou et al. 2006). It was also shown that in the presence of (neurophysiologically plausible) weak synchronization between distant brain regions, dynamical clusters of brain activity closely reflect topological communities of brain anatomy, as areas that are important for long-range information integration; neuroanatomical connectivity patterns are univocally associated with given functional complexity levels; and networks capable of producing highly complex functional dynamics share common structural motifs (Sporns et al. 2000, 2002).

Synchronizability

Synchronization is one of the emerging dynamical processes, the understanding of which has benefited the most from network theory. The spectral analysis of the *adjacency* and *Laplacian* matrices of a network allows evaluation of the synchronization properties of the whole network and quantification of the stability of the synchronized state (Boccaletti et al. 2006; Arenas et al. 2008). The analysis of the eigenratio $r = \lambda_N/\lambda_2$ (see section “Tools”) of the *Laplacian matrix* showed that functional networks obtained for brain activity at rest and during the execution of a finger tapping task have a synchronizability parameter indicating that brain activity lies at a critical point separating the coherent/incoherent state of the whole network (Bassett et al. 2006). Interestingly, pathological dynamics, such as those reported during epileptic seizures, lead to an alteration of the network synchronizability, which recovers its adequate value just after the epileptic episode (Schindler et al. 2008).

Mechanical Principles of Brain Organization

When considered as a biophysical system, it is clear that the brain faces harsh energetic constraints limiting its computational capabilities (Laughlin and Sejnowski 2003), and that is influenced by its interactions with the environment and a range of potential sources of damage (as a result of trauma or degenerative damage). Correspondingly, it is interesting to understand how the brain faces its inherent trade-off between its information processing and transmission functions and the huge energetic costs that these suppose and how it prospers, withstands, or collapses in response to exogenous and endogenous events.

While understanding the general organizational principles of brain structure and function goes a long way into explaining the strategies that the brain uses to manage its economic dilemma in an optimal way (Bullmore and Sporns 2012), network theory provides valuable tools that allow for directly and quantitatively addressing this issue and through which insight as to how the brain would respond to various sources of attack can be gathered.

Efficiency

In the general context of complex networks, the concept of efficiency has been related to the ability of traveling through a network with the minimum number of steps. Latora and Marchiori introduced a parameter called *global efficiency* corresponding to the inverse of the shortest paths between any pair of nodes of the network (Latora and Marchiori 2001).

The concept of efficiency of a brain network relies both on the cost of creating and maintaining the network and the performance in executing a given task. It is important to see that such a metric is essentially tantamount to a topological distance, so that, when used in the context of brain networks, it would be wrong to interpret it as a quantifier of biological efficiency and of the ability of a given anatomical or functional network to perform a certain task.

Studies on the anatomical network of the *C. elegans* showed that the sparse structure of

connections between neurons (only 5% of the total number of possible links) leads to a reasonably high global efficiency, resulting in a high-performance background for information transfer (Latora and Marchiori 2001). Different studies have shown that, in brain anatomical networks, both the number of steps between any pair of nodes in the network (Kaiser and Hilgetag 2006) and the physical cost of their placement in a three-dimensional space (Bassett et al. 2010) are reasonably close to their optimal value.

Interestingly, the dynamical nature of functional networks allows them to adapt the trade-off between cost and efficiency during cognitive processes. Functional networks can enhance their efficiency during a demanding cognitive process, paying the price of an extra cost and recovering the initial (and more “economical”) state after finalizing the task (Kitzbichler et al. 2011).

Another fact that reinforces the hypothesis of the existence of a cost-efficiency balance in the brain is the analysis of impaired networks. The emergence of brain diseases appears to shift the whole network either to regimes with much higher costs, as is the case in schizophrenia (Lynall et al. 2010), or to organizations with low efficiency, for instance in Alzheimer’s disease (Stam et al. 2007).

Robustness

The robustness of a network is related to the impact of node/link deletion in the topological structure of the network (Cohen and Havlin 2010) and is classically quantified by measuring the deviations of the network parameters resulting from these deletions. The specific topology of a network determines its robustness. For example, scale-free networks maintain fairly well their structural properties when random failures are introduced in the network but turn out to be extremely fragile when hubs are the object of an attack (Albert et al. 2000). Anatomical networks of the cat and macaque showed a robustness similar to that of scale-free networks (Kaiser et al. 2007) due to the existence of hubs and the omnipresent modular structure of brain networks (Kaiser and Hilgetag 2004). Counterintuitively,

an increase in the network robustness is not necessarily associated with better performance of a brain network. For example, in the case of childhood-onset schizophrenia, the analysis of resting-state functional networks showed a decrease in the modular behavior of the network resulting in a more integrated structure and as a consequence an increased robustness to targeted attacks (Alexander-Bloch et al. 2010).

Modulating Network Properties

Temporal Evolution

The fact that brain networks are in continuous evolution demands that different analyses from those performed on static network properties be used. Specifically, what is needed is a perspective that would focus not only on the topology of the network but also on how it evolves in time. Interestingly, even in the absence of external stimulation, brain activity shows significant fluctuations in the network connectivity (Hutchison et al. 2012) with corresponding consequences in the topology of the functional network. At the fastest scales, functional networks emerge, evolve, and disappear according to the specific requirements of a given cognitive process. Several works have dealt with the evolution of functional brain networks (De Vico Fallani et al. 2008; Dimitriadis et al. 2010) showing that new information can be obtained when looking at the temporal evolution of functional networks. For example, Valencia and colleagues showed that during visual stimulation, the functional network maintains its small-world configuration, while, at the same time, functional connectivity is varying in time and frequency; network reconfiguration is also reported at larger time scales (Valencia et al. 2008). Bassett et al. followed the structure of functional networks during a learning process and demonstrated that the flexibility of the network topology is strongly correlated with the amount of learning in future sessions (Bassett et al. 2011). If we consider aging as the largest time scale that can be analyzed in the brain, again clear signs of reorganization are reported. While childhood is related to more disordered functional networks with progressive increase in

small-worldness (Boersma et al. 2011), a subsequent evolution toward a hierarchical modular structure has been reported, which seems to be optimized in maturity. Nevertheless, as aging advances the modular structure and its hierarchy are lost (Meunier et al. 2009b), showing the importance of this particular kind of configuration in the optimal functioning of brain networks.

Brain Diseases

Graph theoretical measures have proven to represent good indicators of the emergence and evolution of a series of brain diseases, an aspect that renders them of enormous practical application. The emergence of brain dysfunction can be quantified using network metrics, which are altered in a disease-specific way (Stam and van Straaten 2012). For example, during epileptic seizures, functional brain networks become more regular, modifying their degree distribution and losing part of their modular structure (Ponten et al. 2007; Kaiser and Hilgetag 2010). On the contrary, functional networks of schizophrenic patients become more random, with a consequent decrease of both the normalized clustering coefficient and shortest path (Micheliyannis et al. 2006). Mild cognitive impairment, a condition which sometimes evolves into Alzheimer's dementia, also shows increased functional network randomness, but in this case it is associated with increased network synchronization and a propensity to enhance long-range connections (Buldú et al. 2011). Network analysis of Alzheimer's disease indicates a disconnection syndrome leading to an increased shortest path and decreased network clustering, both leading to a severe impairment of the desirable properties afforded by small-world networks (Stam et al. 2009).

Future Lines of Investigation

Complex network theory has undoubtedly started opening new avenues on the understanding of brain networks. Still, some aspects of this methodology have yet more to offer as new lines of investigation open in the coming years. Four main lines seem to have a particularly promising future:

Quantitative Modeling of the Fundamental Principles of System-Level Brain Functioning

One of the merits of network theory is its ability to relate the topological structure of real networks to the processes occurring in them. It is possible to implement different network models which reproduce experimental observations or test new hypotheses with the aim of investigating the guiding rules behind the emergence, functioning, and evolution of anatomical and functional brain networks (Vértes et al. 2012). These models cannot be directly borrowed from other technological or biological fields and should contain the particular constraints of brain networks.

Predicting the Behavior and Evolution of Brain Networks

The fact that both anatomical and functional networks are in continuous evolution leads to the conclusion that we should pay attention not only to the observed network but also its future stages. Models that predict the evolution of a network would provide a fundamental contribution of complex network theory to the understanding of brain functioning.

Controlling and Targeting the State of the Network

Control and targeting of complex technological networks are two well-studied issues (Liu et al. 2011). Nevertheless, the application of these concepts to biological systems is a pristine field. Identification of those nodes that guide the behavior (or evolution) of a network and drive its dynamics would be of great interest in pathologies such as epilepsy.

Classification of Brain Networks

There is now some evidence showing that network metrics are robust enough quantifiers of brain activity to be used as features capable of distinguishing healthy from pathological behavior (Zanin et al. 2012). Ultimately, network theory should help in the identification of the signatures of pathology in a selective way and in the comparison and classification of anatomical and functional networks, thus lending a hand in the early

detection of brain neurodegenerative diseases or in the monitoring of a healthy aging.

Cross-References

- [Brain Imaging: Overview](#)
- [Connectivity Analysis in Normal and Pathological Brains](#)
- [Information Theory: Overview](#)

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Neural Coding

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Definition

Neural coding encapsulates the concept that neurons act as information-processing channels that

take incoming information, integrate it, and produce a signal that contains information encoded in the neuronal (Akil and Lewis 1993) electrical activity pattern.

Detailed Description

The brain can be regarded as an information-processing machine. It takes sensory information from both the external world and our internal state, compares it with stored representations, be they genetically encoded or learned, and produces directed behavior. The basic units for information processing are single neurons. Single neurons act as information channels, taking inputs impinging upon them from other neurons (or sensory organs at the periphery), integrating those inputs, and emitting a response. The step from input to output, both in single neurons and across populations, gives rise to what has been called the neural code, where a code is a signal that carries an abstract representation of some signal or process of interest. For example, neurons in the visual system carry information about some aspect of the visual scene. The code can be directly related to the signal being encoded such as the intensity of the neural response could be directly related to the intensity of the light in the visual scene. In almost all cases, however, the code is not that simply related to the signal being encoded, or if it is, we do not recognize the link. The ultimate goal of studying neural coding is to understand what information is taken in, how it is encoded, and how it is integrated across populations of neurons to give rise to coherent behavior.

The spike train, which is a series of narrow pulses (see ► [“Spike Train”](#)), is a code of great interest because it is the means by which information is transmitted over distances beyond a maximum of a hundred microns or so, and even at short distances, it is often the response of interest. This pulse train arises from sampling the fluctuations across the neuronal cell membrane; whenever the potential reaches a threshold value, a self-propagating pulse, an action potential that travels down the axon, is emitted. When the pulse reaches the axonal terminus, it often leads to the release of

neurotransmitter packets, the number of which is variable from pulse to pulse. These packets in turn influence the membrane potential of the target neuron, making the target more (excitatory) or less likely (inhibitory) to emit a pulse of its own. The sequence of these spikes is related to the pattern of fluctuations in the membrane potentials. In reduced systems such as tissue culture or tissue slice and in invertebrates, the membrane potential can be recorded directly. However, recording the membrane potential itself requires touching the neuron, a procedure so difficult that it can only be done under exceptional circumstances in vertebrates where the brain moves due to pulsations from blood entering and leaving with each heartbeat. Thus, in vertebrates the best look at neural codes is to examine the sequence of spikes. When the set of packets impinging on a target arise from some coherent input signals, for example, a particular visual stimulus, the sequence of spikes that follow can be treated as a code related to the input. Thus, spike trains of encoded information cascade through the nervous system, with the integration of these trains on target neurons giving rise to spike trains representing some complex integration of the incoming signals.

In the cerebral cortex, each neuron is thought to receive inputs from up to 10,000 other neurons, although these may have far different amounts of influence or weight on the targets. Spike trains have a great deal of variability to the point where the individual members in sets of emitted spike trains are seldom if ever identical. One issue of continuing debate is whether to consider the variability as true noise or whether it is unexplained variability with the possibility that it might someday be explained. At this time, if there is an explanation for the variability, it is beyond the resolution of our current techniques to describe in other than statistical terms, so it is in large part treated as noise. As a qualification, there are examples especially in early sensory processing where the variability can be small under conditions of strong, rapidly varying input, that is, when the membrane potential is being jerked quickly and hard.

For investigation of neuronal codes, the sequence of pulses is often considered to arise as a point process, that is, a series of equivalent

impulses without width. In this context the issue is whether the encoded information can be read out from the pattern of pulses. Because of the variability, this becomes a problem in statistical pattern recognition (Richmond 2009). The tools that have been most useful to date come from statistics, information theory, signal processing, and statistical pattern recognition. It is clear from inspection and easily confirmed quantitatively that the number of spikes being emitted encodes information (Optican and Richmond 1987). In general, the number of spikes (see ► [“Estimation of Neuronal Firing Rate”](#)) is the most robust aspect of the neural code.

There are several issues to consider when confronting neural codes. First, the spectrum of information that is encoded must be hypothesized or known – what does the information represent? Second, the representation in the neuronal spike train must be hypothesized – what is the code? Finally, there must be some hypothesis about how the signals are related within the population, that is, what is the population code? Defining the spectrum of information and the code is an interactive process. The experimental conditions are varied, and the neuronal spike train is examined to determine whether there are related changes – these changes are the neural code. For example, in the visual system, changes in the visual scene are related to the changes in the neuron’s activity (Hubel and Wiesel 1962), and in other brain systems such as the orbitofrontal cortex, changes in what is provided as a reward lead to changes in neuronal activity (Kobayashi et al. 2010).

Critical to identifying the neural code is to learn what aspect of the neuronal activity changes, that is, what is the code? It is obvious and universally agreed that the number of spikes changes. For example, for one neuron in the primary visual cortex, presentation of a vertical bar of light might elicit a lot of spikes while the stimulus is on, whereas a horizontal bar will only elicit a few, if any, spikes. In orbitofrontal cortex, delivering grape juice as a reward might elicit a lot of spikes from one neuron and orange juice only a few. Defining the spectrum of stimuli, whether easily parameterized like the orientation of a bar of light or difficult to parameterize like grape vs. orange juice, is referred to as measuring the “tuning.”

If the number of spikes were the only aspect of the response making up the code, understanding the code would reduce to the problem of knowing how long to observe the spike train to get a good estimate of its rate and know how variable it is. This hypothesis is essentially that the response is a fixed stochastic point process, something closely related to a Poisson process (spike trains have never been found to be strictly Poisson). However, again it is easy to observe that the pattern of spikes varies, also. There are two ways to consider the pattern. The first is that the pattern might represent a time-varying underlying signal and that the number of spikes is following that time-varying signal. This hypothesis is that the response is essentially a time-varying point process similar to a time-varying Poisson process. Both of these codes, the rate and the time-varying rate, account for a substantial proportion of the power in neural codes (Wiener and Richmond 2003). The final possibility is that the timing of some or all of the individual spikes is under tighter control than either of the first two possibilities, that is, there are spike patterns at some level of detail, an elegant speculation that arises from theoretical considerations of neural networks as synfire chains (Abeles 1991) (see ► [“Spatial Temporal Spike Pattern Analysis”](#)). This last possibility is under debate. The transmission of such a code presumably requires carefully placed targeting of axons onto target neurons to take advantage of these patterns, something that is hypothesized by some, but difficult to prove (Staude et al. 2008).

Decoding requires a hypothesis about what has been encoded such as the orientation of a bar of light in the primary visual cortex and a guess as to what aspects of the neural responses carry information. Finally, there must be data. Frequently when there is no explicit model of the transformation from input to output, codes are tested using a Bayesian decoder. The experimenter measures the responses to several inputs, say bars of light with different orientations. The joint probability distribution, $p(s, r)$, is calculated. What is to be identified is $p(s|r)$, the posterior probability of each input given the neural response, $p(s|r) = p(s, r)/p(r)$. r can be a vector, allowing estimation of decoding assuming multidimensional response

codes (see ► [“Generalized Linear Models for Point Process Analyses of Neural Spiking Activity”](#)). This procedure, as straightforward as it is theoretically, is fraught with difficulties in practice. Gathering enough examples to estimate the probability functions is difficult, and there is a substantial literature (see ► [“Population Encoding/Decoding”](#)) about how to deal with the problem.

Population codes, which can be conceptualized as multidimensional codes, remain a frontier. The problem for estimation of probability distributions is magnified. To really learn how population codes work will almost certainly require knowing the circuit in detail with the dynamics of how signals pass through groups of neurons. Currently, population codes assume simple averaging of some sort, e.g., the vector codes that scale responses according to the weights on their tuning curves are common (see ► [“Neuronal Population Vector”](#)). Although there have been some quite spectacular results in invertebrates, matching those results in vertebrates seems out of reach, although new techniques such as molecular tools and new high-resolution imaging techniques are likely to improve this situation. So, unfortunately, there is little direct evidence in vertebrates about how encoded signals are combined within populations.

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Brian Spiking Neural Network Simulator](#)
- [Computation with Population Codes](#)
- [Estimation of Neuronal Firing Rate](#)
- [Generalized Linear Models for Point Process Analyses of Neural Spiking Activity](#)
- [Hierarchical Models of the Visual System](#)
- [Information Theory: Overview](#)
- [Neural Decoding](#)
- [Neuronal Population Vector](#)
- [Physiology and Function of Cochlear Efferents](#)
- [Population Encoding/Decoding](#)
- [Sensory Coding, Efficiency](#)
- [Spatial Temporal Spike Pattern Analysis](#)
- [Spike Train](#)
- [Spike Train Analysis: Overview](#)
- [Stimulus-Specific Information](#)

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Neural Coding of Speech Sounds

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Synonyms

Cortical representation of speech sounds; Distributed speech processing; Neural processing of speech; Neural representation of speech sounds

Definition

Speech sounds are composed of both rapid spectrotemporal changes and slow steady-state portions. The neural coding of speech sounds involves the representation of precise action potential timing across many cortical areas. Behavioral speech sound discrimination accuracy is well predicted by quantifying the similarity between the spatiotemporal response patterns evoked by two sounds.

Detailed Description

Speech Sounds

Speech sounds, like all sounds, evoke patterns of activity in the auditory nerve that are transmitted to the central nervous system. The brain must accurately identify speech sounds despite large amounts of acoustic variability. For example, it is possible to perceive the word “dad” regardless of who is speaking (a male, female, or child), in various types of degradation (at a cocktail party or a concert), or at various intensities (when the sound is whispered or shouted). Speech sounds are incredibly robust and highly redundant. While there are many acoustic cues that can be used to identify an individual sound, no one cue is necessary for sound identification. Voice onset time (VOT) is the amount of time between the onset of a consonant and the onset of voicing. The words “dad” and “tad” differ in their VOT and can often be categorized using this cue alone, but in the absence of this cue, other cues, such as burst intensities, pitch contours, or formant transition durations, can also be used to accurately categorize the two sounds.

Speech sounds are composed of both rapid spectrotemporal changes and slow steady-state portions. Imaging studies performed in humans do not have the level of spectral and temporal precision needed to study speech processing. Because it is rare to have the opportunity to record the responses to speech sounds in human auditory cortex, most speech processing studies are conducted in animals. Numerous studies have

documented the ability of animals to discriminate speech sounds as accurately as humans. Chinchillas can easily categorize words by VOT and have the same category boundary as humans (Kuhl and Miller 1975). In addition to being able to discriminate sounds by VOT, other animal studies have shown that animal performance matches human performance on consonant (Reed et al. 2003; Engineer et al. 2008) and vowel discrimination tasks (Kluender et al. 1987; Perez et al. 2013), speech in noise discrimination tasks (Shetake et al. 2011), and speech discrimination tasks using spectrally and temporally degraded stimuli to simulate cochlear implants (Ranasinghe et al. 2012).

Primary Auditory Cortex Coding of Speech Sounds

Cortical responses to speech sounds in animals resemble the responses to speech sounds recorded in human auditory cortex (Steinschneider et al. 1999, 2005). The acoustic features a speech sound is composed of can be derived from auditory cortex responses (Schreiner et al. 2006; Mesgarani et al. 2008). In both humans and animals, sounds differing in their VOT evoke unique temporal activity patterns. Sounds with a short VOT evoke a single peak of activity in response to the consonant onset, while sounds with a long VOT evoke a second peak of activity in response to the onset of voicing (Steinschneider et al. 2003, 2005; Wong and Schreiner 2003). Likewise, consonants differing in their place of articulation (POA) evoke unique spatial activity patterns. For example, the consonant /b/ evokes the strongest response at low-frequency recording sites, /g/ evokes the strongest response at mid-frequency recording sites, and /d/ evokes the strongest response at high-frequency recording sites (Steinschneider et al. 1995; Engineer et al. 2008).

Although the neural responses reflect differences along single acoustic cue dimensions, these differences do not always correctly reflect how the sound is perceived (Sharma et al. 2000). This suggests that the cortical responses to

multiple acoustic cues need to be integrated in order to accurately identify a sound. The primary auditory cortex spatiotemporal response pattern to speech sounds strongly predicts consonant discrimination performance. Sounds that evoke similar cortical activity patterns (/m/ and /n/) are difficult for rats to discriminate, while sounds that evoke more distinct cortical activity patterns (/d/ and /s/) are easy for rats to discriminate (Engineer et al. 2008). Neural similarity is quantified using Euclidean distance where the ED between the spatiotemporal response pattern to sound x and the spatiotemporal response pattern to sound y is the square root of the sum of the squared differences between the firing rates in each temporal bin (j) at each recording site (i):

$$\text{Euclidean distance} = \sqrt{\sum_{i=1}^{\text{\#sites}} \sum_{j=1}^{\text{\#bins}} (x_{ij} - y_{ij})^2}$$

Neural similarity using the primary auditory cortex spatiotemporal response pattern strongly predicts consonant discrimination performance in quiet, background noise and when the sounds are spectrally or temporally degraded (Engineer et al. 2008; Shetake et al. 2011; Ranasinghe et al. 2012). Consonant discrimination performance is well predicted when the temporal activity pattern is preserved using 1–10 ms bin sizes but is not well predicted when the temporal activity pattern is eliminated. In a primary auditory cortex study of vocalization stimuli, the amount of information present in the neural response pattern remains high with bin sizes less than 40 ms (Schnupp et al. 2006, 2010). Information is quantified using mutual information in bits, where $p(x, y)$ is the joint probability distribution function of x (sound identity) and y (sound classification) and $p(x)$ and $p(y)$ are the marginal probability distribution functions of x and y , respectively:

$$MI = \sum_{xy} p(x, y) \cdot \log_2 \left(\frac{p(x, y)}{p(x) \cdot p(y)} \right)$$

Interestingly, consonant sounds and vowel sounds are not represented on the same timescale in primary auditory cortex. Behavioral

discrimination accuracy of vowel sounds, which are steady-state sounds without rapid transitions, is well predicted when the temporal activity pattern is eliminated but is not well predicted when the temporal activity pattern is preserved (Ranasinghe et al. 2012; Perez et al. 2013). This finding of differential coding of consonants and vowels is consistent with the asymmetric sampling in time (AST) hypothesis that speech sounds are extracted using multiple temporal integration windows (Poeppel 2003). Sparse mathematical representations of speech that minimize the number of active model neurons needed to represent typical speech sounds have receptive fields that are similar to neurons in inferior colliculus, thalamus, and auditory cortex (Carlson et al. 2012).

Non-primary Auditory Cortex Coding of Speech Sounds

Speech sound processing takes place along a hierarchy in auditory cortex. Like the visual system, the auditory system is thought to be divided into separate processing pathways: an anteroventral pathway used to identify a sound and a posterodorsal pathway used for auditory spatial discrimination (Rauschecker and Scott 2009). Neurons in the superior temporal gyrus (STG) and the ventrolateral prefrontal cortex (vPFC), both further along the nonspatial hierarchy compared to primary auditory cortex, accurately identify vocalizations with rapid spectrotemporal transitions when the temporal activity pattern is preserved (Russ et al. 2008). However, pairs of neurons in the vPFC are less redundant (i.e., code more complex or orthogonal properties of a vocalization) compared to pairs of neurons in the STG (Miller and Cohen 2010) and more accurately encode the speech sound category decision than the actual speech sound category (Lee et al. 2009), demonstrating the hierarchical processing between the two areas. Stimulus reconstruction using a nonlinear modulation model and a linear spectrogram model can identify speech sounds using non-primary auditory cortex population responses (Pasley et al. 2012).

Cross-References

- [Brain Imaging: Overview.](#)
- [Pitch Perception, Models](#)

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Neural Control of Bladder and Bowel Functions

- [Methodologies for the Restoration of Bladder and Bowel Functions](#)

Neural Decoding

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Abbreviations

AP	Action Potential
CLDA	Closed-Loop Decoder Adaptation
HMM	Hidden Markov Models
LDA	Linear Discriminant Analysis
LFP	Local Field Potential
MAP	Maximum a Posteriori
ML	Maximum Likelihood
MUA	Multi-Unit Activity
NMP	Neuromotor Prosthesis
OLE	Optimal Linear Estimator
PVA	Population Vector Algorithm
SUA	Single-Unit Activity
SVM	Support Vector Machines

Definition

Neural decoding refers to the process of transforming measured neural activity from its original, usually high-dimensional, domain of representation to a new domain that is typically of much lower dimension.

Detailed Description

Overview

In information theory, “decoding” means reversing an “encoding” process that was used to encrypt a set of information-bearing signals in a new domain, usually of lower dimension, where the information is fully preserved. In neuroscience, “encoding” is concerned with the neural representation of behavioral covariates (e.g., sensory inputs, motor outputs, or other cognitive processes). As such, neural decoding is concerned with the process of *off-line* extraction of information about these behavioral covariates from the measured neural activity (Dayan and Abbott 2005; Wallisch et al. 2008).

The definition of neural decoding, however, has evolved since the introduction of neuromotor prosthesis (NMP) in which neural activity is measured and instantaneously used, through neural decoders, to effect the state of an external device (Fetz 1969; Chapin et al. 1999; Serruya et al. 2002; Taylor et al. 2002). Because the state of that device becomes observable to the subject who modulates the neural activity, changes in the encoding process as the subject learns to control the device become quite significant. Neural decoding in such setting refers to the *online* transformation of the measured neural activity. Consequently, a critical difference between online and off-line neural decoders is that the former has to deal with continuously varying representation of information in the neural activity based on the user’s motor intent within the NMP context, whereas the latter does not.

Because neural decoders are critical to NMP performance, a large body of studies has been devoted to explore ways to optimize their design. Historically, neural decoders were derived through a mathematical inversion of some “encoding model” of movement variables such as directional tuning (Schwartz et al. 2001). More recently, it was demonstrated that arbitrary mathematical mappings can also act as neural decoders, effectively creating a novel way to

engage learning and adaptation by the subject (Fetz 2007; Orsborn and Carmena 2013).

Electrical neural activity from a wide range of signals can be used for decoding. Depending on the level of invasiveness, electroencephalograms (EEGs), electrocorticograms (ECoGs), and extracellular recordings of action potentials (APs) and local field potentials (LFPs) have been used as signal sources in NMP applications. Nonelectrical sources can also be used, such as functional magnetic resonance imaging and functional near-infrared spectroscopy, though portability, affordability, and practicality are major impediments to using such signal modalities (Thakor 2013). As such, we focus here on online neural decoding algorithms that make use of extracellular recordings. These algorithms are also applicable to minimally invasive (ECoGs) and noninvasive (EEG) decoding as well as to decoding signals from the peripheral nervous system such as electromyograms (EMGs).

We first provide a brief overview of the types of signals and features used in decoding, then we follow by a description of the most commonly used online decoding algorithms. While these algorithms have been used for both off-line and online decoding, the emphasis is on the online decoding aspects. We conclude with a discussion of further algorithmic innovations that pertain to online closed-loop decoding.

Extracellular Recordings

Spikes, the most common term for AP waveforms, and LFPs can be acquired using microelectrodes implanted in close proximity to individual neurons or clusters of cell bodies (Nicollelis 2001; Dayan and Abbott 2005; Buzsáki 2004). This includes single-unit activity (SUA) and multi-unit activity (MUA) – the aggregate activity of a small group of neurons (Schwartz 2004; Millán and Carmena 2010; Becedas 2012). Based on off-line neural decoding studies, these signals usually contain affluent information about movement parameters, such as direction, velocity, acceleration, among others (Georgopoulos et al. 1986; Schwartz et al. 1988, 2001; Schwartz 2004). As such, they are also believed to contain similar information during online decoding. One caveat

of using these signals in online decoders is that the process of implanting penetrating electrodes in the brain usually elicits neuroprotective mechanisms that result in gliosis with subsequent degradation in signal quality. On the other hand, LFP signal quality often persists over longer periods of time compared to spikes in chronic implants (Becedas 2012; Lee et al. 2013; Flint et al. 2013).

Spike Times and Firing Rates

It is critical to derive continuous-time signals for online neural decoders to ensure smooth control of the actuated device. As such, neuronal APs are first extracted from extracellular recordings by high-pass filtering above 300 Hz, where such signals typically exist in the high-frequency band of 300–6000 Hz (Brockmeier and Príncipe 2013). A sequence of occurrences of APs can be simply characterized by a list of spike times, i.e., a *spike train*. Spike trains can then be mathematically represented as infinitesimally narrow spikes idealized in the form of Dirac δ functions (Dayan and Abbott 2005):

$$\rho(t) = \sum_{i=1}^n \delta(t - t_i) \quad (1)$$

Spike counts from SUA or MUA are then calculated as the integration of spike trains in time windows (bins) of a predetermined width Δ . These spike counts are approximate estimates of the firing rates in the specified time bins (Dayan and Abbott 2005), up to a scaling factor of Δ , as

$$r[k] = \frac{1}{\Delta} \int_{(k-1)\Delta}^{k\Delta} \rho(\tau) d\tau \quad (2)$$

In practice, the scaling factor $\frac{1}{\Delta}$ can be dropped with proper rescaling of the decoder coefficients, and the firing rate estimates are commonly known as binned spike counts. The discrete-time signal $r[k]$ is derived from a continuous-time signal $\rho(t)$ with a sampling period of Δ . However, the use of rectangular (boxcar) window in binned spike counts usually results in noisy estimates of instantaneous firing rates $r[k]$. As such, a smoothing window (kernel) is sometimes used to estimate the instantaneous firing rates (Brockmeier and Príncipe 2013).

Local Field Potentials

Unlike SUA, LFPs represent an aggregate sum of neuronal activity of hundreds to thousands of cells within the vicinity of the recording electrode tip (Andersen et al. 2004; Buzsáki et al. 2012; Lee et al. 2013). LFPs are in the lower frequency band (0.5–300 Hz) of extracellular recordings (Brockmeier and Príncipe 2013). LFPs can be separately used in online decoding, or in combination with SUA, for neural decoding with comparable or better performance to SUA. Recent work has shown that better decoding performance may result compared to only SUA decoding (Andersen et al. 2004; Lee et al. 2013). Signal powers in different frequency bands in the LFP (e.g., beta, 13–30 Hz, and gamma, 30–70 Hz) have been typically used as features for decoding.

Continuous Decoding Approaches

In continuous decoding, a control signal is decoded from neural activity at progressive time samples, thereby forming a decoded “trajectory.” Since the features being decoded vary continuously over time, system identification methods can be used to identify the relationship between the inputs and the outputs (Brockmeier and Príncipe 2013).

Continuous decoding has been used to estimate kinematic and kinetic parameters from cortical

extracellular recordings in NMPs (Hatsopoulos and Donoghue 2009; Homer et al. 2013).

Linear Decoding

Linear decoding assumes a linear transformation between the features extracted from neural activity and the output control signal (e.g., velocity of the actuated device). Despite its simplicity, linear decoding has been proven to be very useful both in online and off-line decoding contexts and is one of the most commonly used decoding approaches in NMPs (Schwartz et al. 2001; Homer et al. 2013). Linear decoding involves linear regression and its commonly used extensions.

Linear Regression Without loss of generality, the input to the decoder is assumed to be the discrete-time signal $r[k]$ that represents estimated neuronal firing rates (following the definition in Eq. 2). Let $\{r_i[k]\}_{i=1,\dots,C}$ denote the instantaneous firing rates of C neurons being decoded. The decoded output can be expressed as (Bishop 2006)

$$v[k] = w_0 + w_1 \cdot r_1[k] + \dots + w_C \cdot r_C[k] \quad (3)$$

For decoding multiple time bins $k = 0, \dots, T-1$, we use the matrix form

$$\begin{bmatrix} v[0] \\ v[1] \\ \vdots \\ v[T-1] \end{bmatrix}_{T \times 1} = \begin{bmatrix} 1 & r_1[0] & r_2[0] & \dots & r_C[0] \\ 1 & r_1[1] & r_2[1] & \dots & r_C[1] \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & r_1[T-1] & r_2[T-1] & \dots & r_C[T-1] \end{bmatrix}_{T \times C+1} \begin{bmatrix} w_0 \\ w_1 \\ w_2 \\ w_3 \\ \vdots \\ w_C \end{bmatrix}_{C+1 \times 1} \quad (4)$$

If we assume that both the input $r[k]$ and the output $v[k]$ are zero centered, then the bias weight w_0 and the extra column of ones can be eliminated, and we can write

$$\mathbf{y} = \mathbf{R} \times \mathbf{w} \quad (5)$$

where $\mathbf{v} \in \mathbb{R}^T$ is the vector of output samples, $\mathbf{R} \in \mathbb{R}^{T \times C}$ is a matrix with entries from zero-

centered neuronal firing rates, and $\mathbf{w} \in \mathbb{R}^C$ is a vector of decoder coefficients (weights). Zero-centering of the neuronal firing rates can be done by subtracting the average (baseline) firing rate for each neuron.

In the biomimetic approach to neural decoding, a set of input samples (e.g., neural firing rates) and output samples (e.g., kinematics) are typically

measured during a decoder training session where subjects passively observe the action to be performed, or imagine making movements with their limbs (Hatsopoulos and Donoghue 2009). In the current linear regression problem, the vector of decoder coefficients $\mathbf{w}^*$ that minimizes the squared error $\|\mathbf{v} - \mathbf{R} \times \mathbf{w}^*\|^2$ satisfies the *normal equation*

$$\mathbf{R}^T \mathbf{R} \times \mathbf{W}^* = \mathbf{R}^T \times \mathbf{V} \quad (6)$$

which gives

$$\mathbf{w}^* = (\mathbf{R}^T \mathbf{R})^{-1} \mathbf{R}^T \times \mathbf{V} \quad (7)$$

where $\mathbf{R}^\dagger = (\mathbf{R}^T \mathbf{R})^{-1} \mathbf{R}^T$ is known as the Moore–Penrose pseudo-inverse of the matrix $\mathbf{R}$, and the solution $\mathbf{w}^*$ is known as the *least-squares* solution (Bishop 2006).

Once the decoder coefficients are calculated from the *training set*, the linear regression decoder can be used online by applying Eq. 4 at each time bin k .

Population Vector Algorithm The population vector algorithm (PVA) was developed in the 1980s by Georgopoulos et al. using multiple single-cell recording sessions in monkeys performing a center-out reach task (Georgopoulos et al. 1986; Schwartz et al. 1988). The idea is to represent movement kinematics at every time bin as a 3-dimensional velocity vector $\mathbf{v}[k] = [v_x[k], v_y[k], v_z[k]]^T$, where the vector $\mathbf{v}[k] \in \mathbb{R}^3$ is of unit length, i.e., $\|\mathbf{v}[k]\| = 1$. This velocity vector always points in the current direction of movement. As such, the PVA assumes an *encoding model* of neural firing that linearly correlates with the direction of movement (Schwartz et al. 2001; Schwartz 2004). This model is a linear (cosine tuning) regression model (compare to Eq. 4) for the neural firing rates, namely,

$$r_i[k] - b_i = s_i (p_{xi} v_x[k] + p_{yi} v_y[k] + p_{zi} v_z[k]) \quad (8)$$

which can be written as an inner product between two unit vectors $\mathbf{v}[k]$ and $\mathbf{p}_i = [p_{xi}, p_{yi}, p_{zi}]^T$ as

$$\begin{aligned} r_i[k] - b_i &= s_i \times \mathbf{p}_i \cdot \mathbf{v}[k] \\ &= s_i \times \cos(\theta_{p_i - v_k}) \end{aligned}$$

where b_i is the baseline neural firing rate, s_i is the standard deviation of the SUA firing rate that scales the unit velocity vector $\mathbf{v}[k]$, and $\theta_{p_i - v_k}$ is the angle between the current unit velocity vector $\mathbf{v}[k]$ and the neuron's *preferred direction* $\mathbf{p}_i$. As can be seen, the model assumes a static preferred direction for each neuron at which the neuron fires maximally, i.e., when $\mathbf{v}[k]$ points in the same direction as $\mathbf{p}_i$, the angle between them is *zero* and the neuron fires maximally at a rate of $r_i[k] = b_i + s_i$. On the other hand, when the current movement direction, $\mathbf{v}[k]$, is opposite to the neuron's preferred direction, the neuron fires minimally (below its baseline) at a rate of $r_i[k] = b_i - s_i$, with a saturation at $r_i[k] = 0$ if $b_i < s_i$ (Georgopoulos et al. 1986). Both $\mathbf{v}[k]$, $\mathbf{p}_i \in \mathbb{R}^d$, where $d = 3$ in the current formulation (3-D space). However, the PVA can be extended to some arbitrary dimension d .

Using this encoding model, the PVA can *decode* movement direction from population firing rates $\{r_i[k]\}$ $i = 1, \dots, C$ using a *voting* scheme where each neuron votes according to its preferred direction with some weight w_i :

$$\mathbf{v}[k] = \sum_{i=1}^C w_i \mathbf{p}_i \quad (9)$$

where different weighting formulae have been explored (Schwartz et al. 2001; Georgopoulos et al. 1988). One such formula is

$$\frac{r_i[k] - b_i}{s_i} \quad (10)$$

In matrix form

$$\begin{aligned} &[v_x[k] v_y[k] v_z[k]] \\ &= \begin{bmatrix} \frac{r_1[k] - b_1}{s_1} & \dots & \frac{r_c[k] - b_c}{s_c} \end{bmatrix} \begin{bmatrix} p_{x1} & p_{y1} & p_{z1} \\ \vdots & \vdots & \vdots \\ p_{xc} & p_{yc} & p_{zc} \end{bmatrix} \end{aligned} \quad (11)$$

and by transposing

$$\mathbf{v}[k] = \mathbf{P}^T \mathbf{q}[k], \quad (12)$$

where $q_i[k] = \frac{r_i[k] - b_i}{s_i}$ are normalized firing rates.

Comparing this formulation to Eq. 3, we see that neural decoding using PVA assumes a linear regression model between the input firing rates and output velocity vectors. Further, PVA normalizes the firing rates to mean zero and variance one (where the parameter s_j would be equal to the standard deviation of the neuron's firing rate).

Unlike standard linear regression, PVA does not fit the model parameters $[p_{xi}, p_{yi}, p_{zi}, s_j, b_i]^T$ using the *normal equation*. Instead, PVA uses multiple linear regression analysis to fit these parameters using a linear encoding model (Schwartz et al. 1988).

Optimal Linear Estimator The PVA approach to neural decoding makes strong assumptions about the nature of encoding by primary motor cortex neurons (cosine tuned) and their preferred directions (uniformly distributed). Under these assumptions, the encoding model of the PVA is equivalent to a least-squares (also known as maximum likelihood) estimation (Schwartz et al. 2001). In practice, however, the uniform (spherical) distribution of preferred directions is rarely encountered, and the quality of tuning can vary greatly within the measured sample (Schwartz et al. 2001), particularly when recruitment properties differ when an entire ensemble, rather than an individual cell, is used in the decoder design.

Optimal linear estimator (OLE) models overcome these limitations by defining the neuron's preferred direction as the "center of mass" of the tuning function (Salinas and Abbott 1994).

OLEs find the decoder output $\mathbf{v}[k]$ as the least-squares estimator with minimum variance: (Koyama et al. 2010)

$$\mathbf{v}[k] = (\mathbf{P}^T \mathbf{P})^{-1} \mathbf{P}^T \mathbf{q}[k], \quad (13)$$

Under the assumption that the preferred directions are uniformly distributed within a unit sphere, $\mathbf{P}^T \mathbf{P}$ would be a diagonal matrix and OLE will reduce to PVA (Koyama et al. 2010; Brockmeier and Príncipe 2013). (Compare to Eq. 12.)

In the presence of correlations in the neural firing rates $\mathbf{q}[k]$ – which is often the case – OLEs are given by a weighted least-squares solution, where the inverse covariance matrix Σ^{-1} of the neural firing rates is used as the weights matrix (Koyama et al. 2010; Brockmeier and Príncipe 2013):

$$\mathbf{v}[k] = (\mathbf{P}^T \Sigma^{-1} \mathbf{P})^{-1} \mathbf{P}^T \Sigma^{-1} \mathbf{q}[k]. \quad (14)$$

In online decoding, Δ is typically chosen between 0.01 and 0.1 s, and the estimated firing rates $r_i[k]$ are typically noisy. PVA and OLE require a preprocessing step to smooth these firing rate "trajectories" using a rectangular (boxcar) window (Koyama et al. 2010). Additionally, the time lag between natural arm movement and the neural activity of about 150–200 ms needs to be estimated by optimizing some objective function to ensure the firing rates can be optimally combined (Moran and Schwartz 1999; Koyama et al. 2010).

Wiener Filters A limitation of PVA and OLE is that they do not take into account the characteristics of a changing noise variance. Some elements of this noise may be correlated with the signal (e.g., neural noise), while others may not (e.g., instrumentation noise). A Wiener filter provides an optimal solution to this problem, both off-line (Warland et al. 1997) and online (Paninski et al. 2004; Hochberg et al. 2006). It is equivalent to the linear regression formulation in Eq. 3 but extends to N time lags in the past. As such it includes a history of neural firing, where N is the length of a single-neuron filter, i.e., (assuming zero-centered inputs and output)

$$\begin{aligned} v[k] = & \sum_{j=k-N+1}^k \\ & \times \sum_{i=1}^C r_i[j] w_i[j - k + N - 1] \end{aligned} \quad (15)$$

In matrix form

$$\begin{bmatrix} v[N-1] \\ v[N] \\ \vdots \\ v[T-1] \end{bmatrix} = \begin{bmatrix} r_1[0] & \cdots & r_1[N-1] & \cdots & r_c[0] & \cdots & r_c[N-1] \\ r_1[1] & \cdots & r_1[N] & \cdots & r_c[1] & \cdots & r_c[N] \\ \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots \\ r_1[T-N] & \cdots & r_1[T-1] & \cdots & r_c[T-N] & \cdots & r_c[T-1] \end{bmatrix} \begin{bmatrix} w_1[0] \\ \vdots \\ w_1[N-1] \\ w_2[0] \\ \vdots \\ w_2[N-1] \\ \vdots \\ w_c[0] \\ \vdots \\ w_c[N-1] \end{bmatrix}, \quad (16)$$

e.g.,

$$\mathbf{y} = \mathbf{R} \times \mathbf{w} \quad (17)$$

where $\mathbf{v} \in \mathbb{R}^{T-N+1}$ is the vector of output samples, $\mathbf{R} \in \mathbb{R}^{(T-N+1) \times NC}$ is a matrix with entries from zero-centered neuronal firing rates, and $\mathbf{w} \in \mathbb{R}^{NC}$ is a vector of decoder coefficients (weights). Zero-centering of the neuronal firing rates can be done by subtracting the average (baseline) firing rate for each neuron. Analogous to linear regression, the optimal decoder coefficients can be found by solving the normal equation using the pseudo-inverse of the neural response matrix $\mathbf{R}$ (Warland et al. 1997; Paninski et al. 2004):

$$\mathbf{w}^* = \mathbf{R}^\dagger \mathbf{v} = (\mathbf{R}^T \mathbf{R})^{-1} \mathbf{R}^T \mathbf{v} \quad (18)$$

Despite the fact that both PVA/OLE and Wiener filtering give rise to the same matrix equation for decoding, namely, $\mathbf{v} = \mathbf{R} \times \mathbf{w}$, it should be noted that there exist two fundamental differences between the two approaches:

1. PVA/OLE assumes an explicit encoding model. This model is fit to the training data first, and then a decoder is derived essentially by inverting the encoding model (Koyama

et al. 2010). In contrast, the Wiener decoder is fit directly to the training data (Warland et al. 1997; Paninski et al. 2004).

2. PVA/OLE relates the inputs to the outputs at a single time lag. The noisy decoded output that results from this approach is remedied by averaging the input samples over multiple lags (Koyama et al. 2010). This averaging (filtering) operation is implicit, whereas it is explicit in the Wiener approach, allowing the latter to take the temporal characteristics of the input signals into account (Schwartz et al. 2001). In essence, decoders that take account for correlation dynamics may be exploiting some inherent temporal coding strategies used by the brain (Andersen et al. 2010).

Ridge Regression Ridge regression is commonly used with linear decoding (PVA/OLE and Wiener filtering) of both SUA/MUA and LFPs (Suminski et al. 2010; Flint et al. 2012; Collinger et al. 2013; Flint et al. 2013). It overcomes the limitation of the pseudo-inverse solution to the normal equation, where the pseudo-inverse solution would typically overfit the noise inherent in the data yielding poorer generalization performance (Bishop 2006). Ridge regression introduces a *regularization parameter*, λ , which trades off the bias

and the variance of linear estimators (Marquardt 1970; Bishop 2006). This is a remedy for the case when the matrix $\mathbf{R}^T \mathbf{R}$ is ill conditioned, due to linear correlations between the inputs, in which case finding the inverse of this matrix becomes problematic (Marquardt 1970).

The ridge regression solution is given by

$$\mathbf{w}^* = (\mathbf{R}^T \mathbf{R} + \lambda \mathbf{I})^{-1} \mathbf{R}^T \mathbf{v}, \quad (19)$$

where $\mathbf{I}$ is identity matrix of appropriate dimensions.

Recursive Bayesian Decoding

Linear filters and OLEs, as solutions to the normal equations, bear a probabilistic interpretation: they are maximum likelihood linear estimators under a stationary Gaussian noise model (Bishop 2006). Recursive Bayesian decoders go a few steps further by assuming a *trajectory model* for the decoded output as it relates to the neural activity through a probabilistic *observation model* (Yu et al. 2010). This enables this class of decoders to incorporate two important features: time varying and stochastic behavior of the input and output variables.

The most commonly used recursive Bayesian decoder is the Kalman filter (Wu et al. 2006; Yu et al. 2010). The Kalman filter assumes the decoder output kinematics $\mathbf{x}[k] \in \mathbb{R}^d$ (which can include, e.g., position, velocity, and acceleration) evolve according to a trajectory model

$$\mathbf{x}[k+1] = \mathbf{A}\mathbf{x}[k] + \mathbf{w}[k] \quad (20)$$

where $\mathbf{w}[k] \sim \mathcal{N}(0, \mathbf{W})$ is the Gaussian noise term with the covariance matrix $\mathbf{W} \in \mathbb{R}^{d \times d}$. This model is equivalent to a linear Gaussian model (Wu et al. 2006; Yu et al. 2010):

$$\mathbf{x}[k] | \mathbf{x}[k-1] \sim \mathcal{N}(\mathbf{A}\mathbf{x}[k-1], \mathbf{W}). \quad (21)$$

The observation model is given by

$$r[k] = \mathbf{C}\mathbf{x}[k] + \mathbf{q}[k] \quad (22)$$

where $\mathbf{r}[k] \in \mathbb{R}^C$ is the vector of instantaneous firing rates for the ensemble of neurons, $\mathbf{C} \in \mathbb{R}^{C \times d}$ is a linear encoding model that relates firing rates to kinematics (compare to Eq. 8), and $\mathbf{q}[k] \sim \mathcal{N}(0, \mathbf{Q})$ is the Gaussian noise term with covariance matrix $\mathbf{Q} \in \mathbb{R}^{C \times C}$. This is also equivalent to a linear Gaussian model (Wu et al. 2006; Yu et al. 2010)

$$\mathbf{r}[k] | \mathbf{x}[k] \sim \mathcal{N}(\mathbf{C}\mathbf{x}[k], \mathbf{Q}) \quad (23)$$

Given a training data set with synchronized kinematic and neural data, the parameters of the Kalman filters (covariance matrices, priors, and linear matrices) can be fit to the data using a maximum likelihood approach (see Maximum Likelihood under section “Discrete Decoding Approaches”). Additionally, the optimum time lags between $\mathbf{r}[k]$ and $\mathbf{x}[k]$ can be estimated (Wu et al. 2006).

Given a trajectory model (Eq. 20) and an observation model (Eq. 22), the Kalman filter is an optimal state observer (i.e., it can optimally estimate the kinematic state from the observed firing rates) that minimizes the mean-squared reconstruction error $\sum_{k=0}^{T-1} \|\hat{\mathbf{x}}[k] - \mathbf{x}[k]\|_2^2$ (Wu et al. 2006). The Kalman filter algorithm is a recursive algorithm that implements the following steps:

1. Given the last state estimate $\hat{\mathbf{x}}[k-1]$, use the trajectory model to predict the current state estimate

$$\hat{\mathbf{x}}_-[k] = \mathbf{A}\hat{\mathbf{x}}[k-1] \quad (24)$$

2. Compute the increase in uncertainty over the state, expressed by the error covariance matrix:

$$\mathbf{V}_-[k] = \mathbf{A}\mathbf{V}[k-1]\mathbf{A}^T + \mathbf{W} \quad (25)$$

3. Use the observation model to calculate a prediction of the firing rates which should be $\hat{\mathbf{r}}[k] = \mathbf{C}\hat{\mathbf{x}}_-[k]$. Compare this prediction to the actual firing rates $\mathbf{r}[k]$, and use the difference to update the current state estimate through the *Kalman gain* $\mathbf{K}[k]$:

$$\hat{\mathbf{x}}[k] = \hat{\mathbf{x}}_-[k] + \mathbf{K}[k](\mathbf{r}[k] - \hat{\mathbf{r}}[k]) \quad (26)$$

$$\mathbf{K}[k] = \mathbf{V}_-[k]\mathbf{C}^T(\mathbf{C}\mathbf{V}_-[k]\mathbf{C}^T + \mathbf{Q})^{-1} \quad (27)$$

4. Finally, update the uncertainty over the current state by updating

$$\mathbf{V}[k] = (\mathbf{I} - \mathbf{K}[k]\mathbf{C})\mathbf{V}_-[k] \quad (28)$$

Comparing the Kalman filter implementation to the linear filter, it can be seen that:

1. The Kalman filter is recursive, which means it takes into account *all* past neural activity (with decaying exponential weights) rather than just N lags (Wu et al. 2006; Yu et al. 2010).
2. The uncertainty about each state estimate is given in the form of error covariance matrices at each time step, from which one can draw confidence intervals (Bishop 2006; Yu et al. 2010).

The Kalman filter assumes a parametric model. Another popular recursive Bayesian decoder that is nonparametric is the *particle filtering* approach (Brockwell et al. 2004). The parameterization is traded off with added computational expense in the latter approach.

Nonlinear Decoding

Artificial Neural Networks Artificial neural networks have origins in the early attempts to mathematically represent the computational aspects of biological systems. Their power comes from their ability to model arbitrary nonlinear mappings. They can be used for continuous decoding (i.e., regression) as well as for discrete decoding (i.e., classification – see section “[Discrete Decoding Approaches](#)” below) (Bishop 2006). They have been used for real-time prediction of hand trajectories from neural ensembles in M1 (Wessberg et al. 2000). The three Cartesian coordinates were assumed to be independent each with a separate output layer. The network outputs were successfully used to drive a robotic hand.

Volterra Series Volterra series is a nonlinear nonparametric model that is frequently used in system identification. It is the generalization of Taylor series to systems with memory, where the output of the nonlinear system can depend on the input at all previous time lags (Paiva et al. 2010; Song and Berger 2010).

A model with parametric and nonparametric components was developed for hippocampal prostheses. The overall model structure is parameterized to be “neuron-like,” while the input–output relationships of the model subcomponents are captured with the nonparametric Volterra series. This model is a neural decoder that transforms input neural signals from one brain region into output signals that activate another nervous system region (Hsiao et al. 2013). It has been successfully applied to predict the hippocampal CA3-CA1 population dynamics (Berger et al. 2005; Song and Berger 2010).

Discrete Decoding Approaches

Discrete decoding is used in applications in which knowledge of discrete end effector states is needed. A typical example is communication prostheses, in which subjects are instructed to choose between two or more discrete targets, with examples ranging from a simple click/no-click choice to spelling entire words. In this regard, communication prostheses are more concerned with “information throughput” from the subject to the outside world. One important distinction between continuous decoding and discrete decoding is that in the latter a target can be immediately chosen once it is decoded from neural activity, without the need to follow a specific trajectory to reach that target. For example, in spelling applications, the spatial locations of letters displayed on a screen keyboard that the user intends to strike are decoded, and a cursor is instantaneously moved to strike that letter. In this context, multiple classification techniques from pattern recognition are successfully used based on neural activity recorded during motor planning (Yu et al. 2010; McFarland and Wolpaw 2011; Gilja et al. 2011). Discrete decoding, however, is

not limited to communication prostheses applications. Indeed, a grasp/no-grasp state decoder was utilized in NMPs for people with tetraplegia (Hochberg et al. 2012), and it was shown that NMPs can benefit from discrete decoders whenever the “intended target(s)” can be decoded efficiently in goal-directed movements (Yu et al. 2010; Shanechi et al. 2012).

Linear Discriminant Analysis Linear discriminant analysis (LDA) is an approach to discrete classification of measured variables. LDA, particularly Fisher’s linear discriminant, is one of the most popular approaches to discrete neural decoding, specially in the noninvasive brain–computer interfaces (McFarland and Wolpaw 2011) as well as peripheral neural interfaces (Micera et al. 2010). LDA utilizes *discriminant functions* for decoding, where a discriminant function is a function that takes an input vector $\mathbf{r}$ and assigns it to one of K classes directly. A linear discriminant makes use of a linear function: $y_k(\mathbf{r}) = \mathbf{w}_k^T \mathbf{r}$, such that class k is chosen for input $\mathbf{r}$ if $y_k(\mathbf{r}) \geq 0$ (assuming no bias) (Bishop 2006).

Briefly, Fisher’s linear discriminant is defined in terms of a projection onto a lower dimensional subspace. For a simple two-class problem (Bishop 2006), let the input vectors $\mathbf{r}_i, i = 1, \dots, N_1$ be members of class C_1 and the input vectors $\mathbf{r}_i, i = 1, \dots, N_2$ be members of class C_2 , where $\mathbf{r}_i \in \mathbb{R}^D$. Let the means of the vectors belonging to both classes be $\mathbf{m}_1$ and $\mathbf{m}_2$, respectively. Let $\mathbf{w}$ be a vector that projects the input vectors, and their means, to a one-dimensional subspace (a line). The D -dimensional means $\mathbf{m}_1$ and $\mathbf{m}_2$ are projected to the points m_1 and m_2 , respectively. Choosing a unit vector $\mathbf{w}$ to maximize the *separation* between the projected means, $|m_1 - m_2|$, allows separating the projected vectors from the two classes using a simple threshold in the one-dimensional subspace. The choice of $\mathbf{w}$ corresponds to a vector that is parallel to the vector connecting the two means $\mathbf{m}_1$ and $\mathbf{m}_2$. When features from input vectors are not statistically independent, the classes may significantly overlap in the projection subspace. This overlap can be quantified in terms of the *within-class variance* of the input vectors after projection,

i.e., $s_k^2 = \sum_{i=1}^{N_k} (x_i - m_k)^2$, where $\mathbf{x}_i = \mathbf{W}^T \mathbf{x}_i$ is the projection of an input vector $\mathbf{x}_i$. Fisher’s linear discriminant approach chooses $\mathbf{w}$ such that the ratio of the between-class separability to the within-class variance is maximized. This criterion can be expressed as

$$J = \frac{(m_2 - m_1)^2}{s_1^2 + s_2^2}, \quad (29)$$

which can be written explicitly in terms of the original input vectors and $\mathbf{w}$ as

$$J(\mathbf{w}) = \frac{\mathbf{w}^T \mathbf{S}_B \mathbf{w}}{\mathbf{w}^T \mathbf{S}_W \mathbf{w}}, \quad (30)$$

where $\mathbf{S}_B$ is the *between-class* covariance matrix defined in terms of the means and $\mathbf{S}_W$ is the *within-class* covariance matrix defined as the sum of original input vectors covariance matrices. The optimal projection vector $\mathbf{w}$ that maximizes J is in the same direction as $\mathbf{S}_W^{-1}(\mathbf{m}_2 - \mathbf{m}_1)$. After projecting all input vectors into this low-dimensional subspace, we can discriminate between the classes using simple linear discriminants, which could be a single threshold in case of one-dimensional subspaces. Fisher’s linear discriminant can be generalized to multiple classes (Bishop 2006) and even extended to handle nonlinear decision boundaries using the *kernel trick* (Paiva et al. 2010).

Support Vector Machines Support vector machines (SVM) are also popular in discrete neural decoding (Micera et al. 2010; McFarland and Wolpaw 2011). They can be thought of as *maximum margin classifiers*, where a margin is defined as the smallest distance between the decision boundary and any of the training feature vectors. SVMs can be trained efficiently by solving a quadratic programming problem (i.e., an optimization problem with a quadratic cost function subject to linear constraints). Once trained, the training feature vectors are discarded, except for a few vectors that reside on the maximum margin, known as *support vectors*. Similar to LDA, the *kernel trick* (Paiva et al. 2010) can be used to extend SVMs to handle nonlinear decision boundaries (Bishop 2006).

Maximum Likelihood Two of the most commonly used probabilistic discrete decoding approaches are maximum likelihood (ML) and maximum a posteriori (MAP) classifiers. The link between these two approaches is Bayes' theorem. Let a particular behavioral variable of interest be denoted by s , and the vector of features (e.g., neural firing rates) be denoted by $\mathbf{r}$, then Bayes' theorem relates the probabilities for s and $\mathbf{r}$ as

$$\mathbb{P}(s | \mathbf{r}) = \frac{\mathbb{P}(\mathbf{r} | s)\mathbb{P}(s)}{\mathbb{P}(\mathbf{r})}, \quad (31)$$

where $\mathbb{P}(s)$ is the prior probability of observing a value for s , $\mathbb{P}(\mathbf{r})$ is the probability of observing a feature vector $\mathbf{r}$, $\mathbb{P}(\mathbf{r}|s)$ is the conditional probability of how likely it is to observe the feature vector $\mathbf{r}$ given that a specific value for s was observed for the behavioral variable, and $\mathbb{P}(s|\mathbf{r})$ is the posterior probability of the behavioral variable taking on a value s given the observed feature vector $\mathbf{r}$ (Dayan and Abbott 2005; Quian and Panzeri 2009). In communication prostheses, the variable s is the most likely target (Yu et al. 2010).

The ML approach makes direct use of the *likelihood function* $f(s) := \mathbb{P}(\mathbf{r} | s)$ (Bishop 2006). ML decoders select the value for s that maximizes the likelihood function for the observed feature vector $\mathbf{r}$, i.e.,

$$s_{\text{ML}} := \arg_s \max \mathbb{P}(\mathbf{r} | s) \quad (32)$$

On the other hand, MAP selects the value for s that maximizes the *posterior probability*:

$$s_{\text{MAP}} := \arg_s \max \mathbb{P}(s | \mathbf{r}) \quad (33)$$

As such, when all targets are equally likely, the MAP essentially reduces to the ML (Bishop 2006; Quian and Panzeri 2009).

In both approaches, it is critical to model the probability distributions involved in Bayes' theorem, with the conditionally independent multivariate Gaussian and Poisson models being most commonly used, where conditional independence is assumed between the different variables (components) of $\mathbf{r}$. The conditional independence

assumption is used largely for practical reasons (e.g., to simplify the model and avoid overfitting) (Yu et al. 2010), but it ignores the potentially synergistic information encoded in the spike trains of different neurons (Paiva et al. 2010). The Gaussian distribution is more suited for variables that can take on positive and negative values, while the Poisson distribution more accurately models binned spike counts. It is also possible to square-root transform the binned spike counts and then use a Gaussian model (Yu et al. 2010).

Hidden Markov Models Hidden Markov models (HMMs) are conceptually similar to the state space model assumed by the Kalman filter, with the distinction being that the "states" in the HMMs are discrete valued. As such, the state space model becomes a finite-state machine in which the transition between the finite set of states is governed by the state *transition* probabilities. Similar to the Kalman filter, the "states" are *hidden* and not observed. Instead, an observation model is described by the *emission* probabilities, i.e., the conditional probabilities of observing a particular outcome given that the system is in a particular state (Bishop 2006).

HMMs have been used in noninvasive brain-computer interface and peripheral neural interface applications (Micera et al. 2010; Brockmeier and Principe 2013), as well as to detect neural state transitions in motor cortical prostheses (Kemere et al. 2008).

Online Closed-Loop Decoding

Decoder Initialization

A critical step in all neural decoding methods is decoder initialization. In the biomimetic approach, the initialization is done using a concurrently measured set of neural activity and kinematics during motor imagery or action observation (Hatsopoulos and Donoghue 2009). Recent studies, however, have shown that this is not a stringent requirement, as subjects can learn arbitrary mapping between their volitionally controlled neural activity and variables in the task space (Carmena 2013). The closed-loop nature of online NMPs enables subjects to establish a

causal link between the volitionally controlled neural activity and the change in state of the actuated device through an arbitrary mapping (Orsborn and Carmena 2013). Rooted in the pioneering work of Fetz 1969, this mapping can be used to operantly condition subjects to increase the likelihood of specific firing patterns of recorded neurons when coupled to reward. This arbitrary mapping thus constitutes an unsupervised decoder initialization step that is tailored to the observed population without the need for synchronized behavioral covariates. This approach has been extended to other NMP studies (Moritz et al. 2008; Koralek et al. 2012; Badreldin et al. 2013).

Closed-Loop Decoder Adaptation and Calibration

A critical aspect in neural decoding is the extent to which neural decoders need to be adapted and the time scale over which this adaptation needs to take place. When subjects are trained to use a fixed decoder, the experimenter effectively relegates the learning to the subjects. In some cases, the learning process can saturate, and the control performance may not continue to improve with increasing task demands. As such, closed-loop decoder adaptation (CLDA) algorithms attempt to adaptively change the decoder parameters, using adaptive control algorithms, during closed-loop operation in order to accelerate learning and improve performance. Examples include the recursive least-squares (RLS) adaptation (Gage et al. 2005), the Bayesian parameter updates and Kalman smoother (Li et al. 2011), the ReFIT Kalman filter algorithm (Gilja et al. 2012), the SmoothBatch algorithm (Orsborn et al. 2012), the unsupervised and error-based adaptation (Gürel and Mehring 2012), and the reinforcement learning (Pohlmeyer et al. 2014). While there is no consensus on the best strategy for decoder update rules, some points to consider are to determine the following: (i) the decoder parameters that should adapt, (ii) the adaptation rule, and (iii) the frequency of adaptation. Because the mechanisms by which the brain learns to adapt to a particular

decoder are largely unknown, this subject remains a topic of intensive research (Carmena 2013). A temporary, less optimal solution is to limit decoder adaptation to early blocks of closed-loop trials until performance asymptotes and then fix the decoder for the remainder of the session.

Cross-References

- [Cortical Motor Prosthesis](#)
- [Decoding Field Potentials](#)
- [Hippocampal Memory Prosthesis](#)
- [Noninvasive Brain-Computer Interfaces](#)
- [Recurrent Brain-Computer Interfaces](#)

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Neural Development

► Receptive Field Modeling

Neural Field Model, Continuum

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Synonyms

Cortical field theory

Definition

Neural field models describe the spatiotemporal evolution of mean neural activity in neural populations. The neural population is embedded in a continuous spatial domain (mean-field approximation), while its activity is assumed to be coarse grained in space and time. The spatial “grains” are not visible in the mathematical description, but reflect the physiological interpretation that the field is built by tiny hyper-columns.

The temporal “grain” is also not visible in the equations but results from the interpretation of a temporal average over a short time interval, while the field evolves on a larger time scale. Hence, neural fields describe neural population activity averaged over small spatial and temporal structures.

Detailed Description

Physiological Motivation

To deal with the functional complexity and hierarchy of the brain, it is necessary to find the functional relationships between the network activity based on single neurons and neural population activity on a higher hierarchical level. In the 1960s, Hubel and Wiesel had studied in detail the response properties of single neurons and spatially extended populations in the visual cortex and have found the existence of functional neural columns, i.e., populations, in which neurons respond similarly to external stimuli (Rockland 2010). These so-called hyper-columns (or cortical module or macro-column) represent functional self-organized subunits in the brain resulting from the nonlinear interaction of single neurons (DeFelipe et al. 2012). Several experimental and theoretical studies have revealed the importance of spatially extended neural population dynamics in brain functions (Deco et al. 2008), such as hallucinations in the visual cortex (Bressloff et al. 2002), epilepsy (Milton and Jung 2003), or anesthesia and sleep (Hutt 2011).

Standard Derivation of Model Equations

In order to understand the experimental data obtained in neural populations, a promising approach considers theoretical models that elucidate the importance of physiological properties such as synaptic strength or the topology of the underlying neural network. The class of neural field models provides a powerful mathematical description of neural activity. Their major model components reflect dynamic features of single neurons and their interactions. These features are (1) the nonlinear dynamics of the neuron discharge (action potentials or spikes), (2) the temporal neural response to activity changes (at a

certain time scale), (3) the existence of excitation and inhibition, and (4) the spatial connectivity in the case of neural fields. Additional physiological properties (5) render the model more realistic.

The subsequent paragraphs will sketch these model features in some detail.

Population Firing Rate

Single neurons generate action potentials if their membrane potential exceeds a threshold. In a neural population, the number of neurons that fire in a certain short time interval at a certain time is called the population firing rate P . Since it relates the dendritic activity of the neurons U (as input) to the firing rate (as output), $P(U)$ is also called transfer function. The standard derivation of the transfer function (Amit 1989) considers an ensemble of neurons with different firing thresholds U_{th} and a distribution of membrane potentials $d(U - \bar{U})$ with mean potential $\bar{U}$. Then the number of firing neurons in a short time interval Δt is

$$P(U(t)) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Theta(U - U_{th}) F(U_{th} - U_{th}) d(U - U(t)) dU dU_{th}$$

where F is the number of neurons in the short time interval Δt with threshold U_{th} that are ready to fire, i.e., which have left their refractory period and would fire if their membrane potential exceeds the threshold. The parameter $\bar{U}_{th}$ is the mean firing threshold in the population and $\Theta(x)$ is the Heaviside function with $\Theta(x) = 0$ for $x < 0$ and $\Theta(x) = 1$ for $x \geq 0$. In general, one can show that unimodal statistical distributions F and d lead to a sigmoidal shape of $P(\bar{U})$. The most typical choice for the transfer function is the logistic function

$$P(\bar{U}(t)) = \frac{S_{ra}}{1 + e^{-c(\bar{U}(t) - \bar{U}_{th})}}$$

with the steepness parameter $c > 0$ that is large for narrow firing threshold distributions F .

Temporal Mean Synaptic Response

The membrane dynamics of a single neuron obeys the differential equation

$$CdV(t)/dt = -g_l(V(t) - E_l) - g_s(t)(V(t) - E_s)$$

assuming a single synaptic receptor with conductance $g(t)$ and reversal potential E . The parameters C , g_l , and E_l are the capacitance, constant conductance, and leakage reversal potential of the membrane, respectively. In the absence of the synaptic receptor, the resting potential of such a membrane is $V_r = E_l$. In the absence of any arriving action potentials at the synapse, $g(t) = 0$, while the synaptic receptor channel opens if an action potential arrives at the synapses leading to a conductance change $g(t) > 0$. Typically, excitatory ionotropic receptors respond with a conductance change slower (~ 5 to 200 ms) than the membrane time scale g_l/C of few milliseconds. Assuming this time-scale separation, voltage changes induced by arriving action potentials (so-called postsynaptic potentials, PSPs) decay fast to the resting potential V_r and hence $V(t) \approx E$ on the larger time scale of synaptic receptor response. Following this line of argumentation, the membrane current induced by arriving action potentials at synaptic receptors is $I_s(t) \approx g_s(t)(V_r - E)$.

Now considering a large number of receptors on a single neuron and a large number of neurons, the induced mean synaptic current of a specific receptor type in a population is $\bar{I}(t) \sim h(t)$ where the function $h(t)$ resembles in shape the temporal response function $g(t)$ but taking into account average time scales. These time scales reflect both the heterogeneity of time scales of single receptors and the propagation delay time of PSP along the dendritic tree to the neuron soma. Hence, there is no precise derivation of the mean dendritic response function in the neural mass models but an approximative description based on the single-receptor response. A typical response functions has the bi-exponential form

$$h_2(t) = \frac{\alpha_1 \alpha_2}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \Theta(t), \quad \alpha_2 > \alpha_1$$

with the Heaviside function $\Theta(t)$. The parameters α_2 and α_1 are the rise and decay rate of the response function, respectively. For $\alpha_2 = \alpha_1 = \alpha$, one obtains Rall's alpha function $h_2(t) = \alpha t e^{-\alpha t}$. A simple but still physiologically reasonable

model function has the exponential form $h_1(t) = \alpha e^{-\alpha t} \Theta(t)$ which assumes an instantaneous rise and considers the decay phase with time constant $1/\alpha$ only. Now considering the response of neurons in a population to incoming action potentials, the extracellular potential in the population reads

$$\begin{aligned} U(t) &= a \sum_{i=1}^T s_i \int_{-\infty}^t h(t - \tau) \delta(\tau - \tau_i) d\tau \\ &= a \int_0^\infty h(\tau) s(t - \tau) d\tau \end{aligned}$$

where a is the synaptic strength, the action potentials are approximated by delta-function-shaped spikes, τ_i are the spike arrival times at the receptors, s_i are the synaptic weights of the spikes, T is the number of spikes arrived until time t , and $s(t) = \sum_i s_i \delta(t - t_i)$ is the population spike train. Then averaging over a short time interval Δt of few milliseconds, the mean population potential reads

$$\bar{U} = \int_0^\infty h(\tau) P(t - \tau) d\tau$$

where $P(t) = \int_t^{t+\Delta t} s(\tau) d\tau / \Delta t = n(t) / \Delta t$ is the number of incoming spikes in the population in the time interval Δt , i.e., the time-dependent population firing rate.

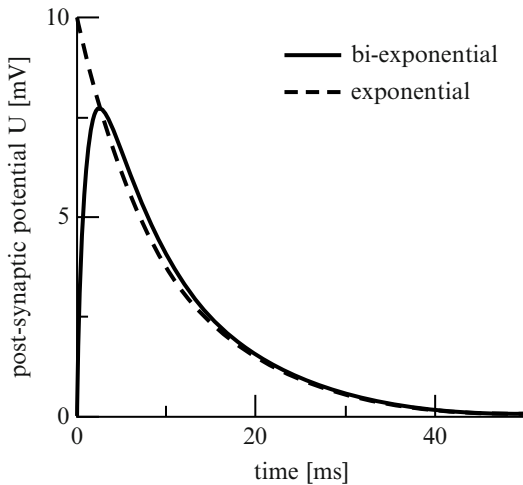
In most studies, the latter expressions are rewritten as

$$\begin{aligned} \bar{U} &= \int_0^\infty h_{1,2}(\tau) P(t - \tau) d\tau \leftrightarrow \hat{L}_{1,2}(d/dt) \bar{U}(t) \\ &= P(t) \end{aligned}$$

with

$$\begin{aligned} \hat{L}_2 &= \frac{1}{\alpha_1 \alpha_2 dt^2} \frac{d^2}{dt^2} + \left(\frac{1}{\alpha_1} + \frac{1}{\alpha_2} \right) \frac{d}{dt} + 1, \hat{L}_1 \\ &= \frac{1}{\alpha} \frac{d}{dt} + 1 \end{aligned}$$

for the bi-exponential function and exponential function $h_{1,2}(t)$, respectively (Fig. 1).



Neural Field Model, Continuum, Fig. 1 The model postsynaptic potential for two approximations of receptor dynamics

Excitation and Inhibition

Different types of synapses respond differently to incoming action potentials. The most important ionotropic synaptic receptors respond by excitatory (glutamate receptors) and inhibitory (GABA receptors) PSPs. In addition, these synaptic receptors may be axonal terminals of different neuron types, such as pyramidal cells or interneurons. Since both pyramidal cells and interneurons may excite or inhibit postsynaptic neurons, various combinations of cells and synapses are realistic. A typical way to implement synaptic excitation and inhibition is through their sum of their dendritic activity, i.e., the mean dendritic membrane potential that generates the action potential if exceeding a threshold is $U(t) = U_e(t) - U_i(t)$ where the mean excitatory and inhibitory PSP $U_e(t)$ and U_i obey the response dynamics given in the previous paragraph on section “Temporal Mean Synaptic Response”.

Spatial Connectivity

Axonal fiber branches connect neurons, and their spatial range may be short in connections in the same neural structure and long in connections between different neural structures. In addition, short-range axonal branches may project different neuron types onto excitatory and inhibitory

synapses, whereas most long-range axonal fibers originate from excitatory neurons and excite far-distant postsynaptic neurons. Various types of these different connections may be present in the same neural structure, and their combination results in diverse spatial topologies of excitation and inhibition. Neural fields extend point-like neural mass models by a spatial dimension, i.e., $\bar{U}(t) \rightarrow \bar{U}(x, t)$, with spatial location $x \in \Omega$ and hence embed the neural population in the spatial domain Ω . This extension allows one to model spatially extended neural populations as found in real neural tissue.

Mathematically, the spatial interaction is taken into account by an integral over the space of the population introducing a spatial interaction kernel $K(x, y) = \sum_j a_j K_j(x, y)$. The summand K_j is the

probability density function for finding axonal connections of type j between neurons in the hyper-columns at spatial locations x and y , and a_j are weights of the different interactions. The connection type may be excitatory or inhibitory.

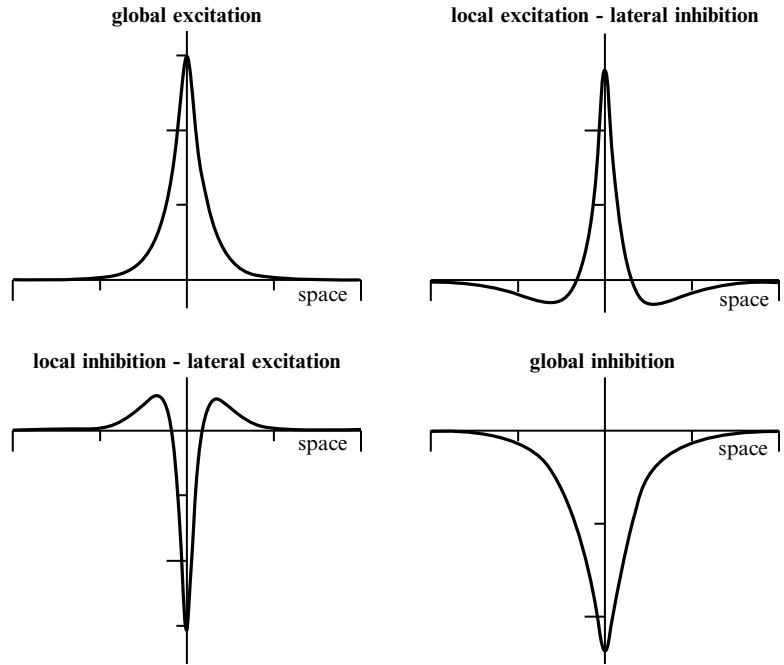
If the connectivity in the neural field just depends on the distance between two spatial locations and hence is independent of the spatial location itself, i.e., $K_j(x, y) = K_j(|x - y|)$, then the field is called homogeneous (Jirsa 2009). Typical homogeneous kernels (Deco et al. 2008) consider excitation and inhibition and decay at infinity, e.g., in one spatial dimension $K(|x|) = a_e w(|x|) - a_i w(|x|) r$, and $w(x)$ is typically chosen as an exponential function or a Gaussian function. Figure 2 shows $K(|x|)$ for the most important connection kernel functions.

For instance, in one spatial dimension, the population firing rate arriving at spatial location x reads

$$P(x, t) = \int_{\Omega} K(|x - y|) S(\bar{U}(y, t)) dy$$

This mathematical implementation by an integral is not the only way to consider spatial interaction. Under certain conditions on the kernel function K , one finds the inverse of the spatial integral operator which is a partial differential operator (see, e.g., Jirsa (2009) and references therein)

Neural Field Model, Continuum, Fig. 2 Most important synaptic interaction kernel functions $K(|x|)$



$$D(\partial/\partial x)P(x, t) = S(\bar{U}(x, t))$$

Additional Physiological Elements

Putting elements (1–4) together leads to the standard neural field model with the properties that fit best to the real structure under study. To extend this standard model and render it more realistic, recent models add dynamic features:

Finite Axonal Transmission Speed

Action potentials propagate along axonal branches with a finite transmission speed leading to a delayed interaction between two spatial locations x and y . Assuming a single axonal transmission speed c , the population firing rate is (Coombes 2005; Jirsa 2009)

$$P(x, t) = \int_{\Omega} K(|x - y|) S\left(\bar{U}\left(y, t - \frac{|x - y|}{c}\right)\right) dy.$$

Heterogeneous Spatial Interaction

If the axonal connectivity depends on the spatial location and not just on the distance between two spatial locations, the neural field is not homogeneous. Previous studies have investigated the existence of both homogeneous and heterogeneous

axonal interactions $K(x, y) = K_{hom}(|x - y|) + K_{het}(x, y)$ yielding

$$P(x, t) = \int_{\Omega} K_{hom}(|x - y|) S(\bar{U}(y, t)) dy + Q(x, t)$$

with the additional nonlinear function

$$Q(x, t) = \int_{\Omega} K_{het}(x, y) S(\bar{U}(y, t)) dy$$

Spike Frequency Adaption

Metabolic processes modulate synaptic currents by a feedback mechanism dependent on the neural population activity, e.g., in visual perception (Bressloff 2012). In neural field models, considering these mechanism results into the so-called spike frequency adaptation which adds a current in the presence of high population activity (Coombes 2005; Bressloff 2012)

$$\begin{aligned} P(x, t) &= \int_{\Omega} K_{hom}(|x - y|) S(\bar{U}(y, t)) dy \\ &\quad - \int_{\Omega} f(|x - y|) a(y, t) dy \\ \hat{L}_a(d/dt)a(x, t) &= S(\bar{U}(x, t)) \end{aligned}$$

with the differential operator $\widehat{L}_a$, the recovery variable $a(x, t)$, and the spatial homogeneous interaction kernel of the feedback $a(x, t)$.

Synaptic Depression

It is well established that action potentials terminating at synapses may facilitate or depress synaptic action. In the case of synaptic depression in neural populations, the larger the population firing rate is, the smaller the synaptic gain $q(x, t)$ (Bressloff 2012):

$$P(x, t) = \int_{\Omega} K(|x - y|) q(y, t) S(\overline{U}(y, t)) dy,$$

$$\frac{\partial q(x, t)}{\partial t} = \frac{1 - q(x, t)}{\tau} - q(x, t) S(\overline{U}(x, t))$$

with the depression time constant τ .

Examples of Neural Field Models

The previous paragraphs have detailed the fundamental building blocks of neural field models involving various mathematical formulations, such as integral or differential description of synaptic responses or spatial axonal connectivity. By virtue of the diversity of these mathematical descriptions, in recent years research groups have derived and studied different neural field models. Historically, the first developed neural field equations are integral-differential equation of the types (Ermentrout 1998; Coombes 2005; Ermentrout and Terman 2010; Bressloff 2012)

$$\begin{aligned} \frac{\partial F(x, t)}{\partial t} = & -F(x, t) + S \left[\int_{\Omega} K(x - y) F(y, t) dy \right] \\ & + I(x, t), \end{aligned}$$

$$\begin{aligned} \frac{\partial V(x, t)}{\partial t} = & -V(x, t) + \int_{\Omega} K(x - y) S(V(y, t)) dy \\ & + I(x, t) \end{aligned}$$

with the external input variable $I(x, t)$. The first equation type describes the evolution of the population firing $F(x, t)$ and considers the spatial

interaction as argument of the transfer function (Wilson and Cowan 1973), whereas the second equation describes the evolution of the mean population voltage $V(x, t)$ implementing the transfer function under the spatial integral (Amari 1977). Both model types describe the evolution of different population activity variables but are equivalent and even may be transformed into each other. The combination of these equations allows to describe different neural structures (Bressloff 2012).

Certain spatial interaction kernels permit to inverse the spatial integral yielding a partial differential equation as described in the previous section. For instance, a typical model of this type describes the spatiotemporal evolution of the mean population potential by (Deco et al. 2008)

$$\begin{aligned} \left(\frac{1}{\gamma^2} \frac{\partial^2}{\partial t^2} + \frac{2}{\gamma} \frac{\partial}{\partial t} + 1 - r^2 \frac{\partial^2}{\partial x^2} \right) \phi(x, t) \\ = S(\overline{U}(x, t)) + I(x, t) \end{aligned}$$

$$\left(\frac{1}{\alpha\beta} \frac{\partial^2}{\partial t^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta} \right) \frac{\partial}{\partial t} + 1 \right) \overline{U}(x, t) = g\phi(x, t)$$

in one spatial dimension. Here $\phi(x, t)$ is the pulse activity obeying a damped traveling wave equation with time scale $1/\gamma$ and spatial range r , and $I(x, t)$ is the external input. The pulses induce dendritic currents with time constants $1/\alpha$ and $1/\beta$ and synaptic gain g . As for the integral model, combinations of these coupled equations allow to derive a large family of different models adapted to real neural structures (Deco et al. 2008).

More recent studies have taken up the task to re-derive neural field equations considering the random nature of single neuron dynamics and networks. Such studies (see Sect. 6 in Bressloff 2012) reveal that the dynamics of the mean population activity depends strongly on the temporal or ensemble variance of the mean activity whose temporal evolution in turn depends on the mean activity. This strongly nonlinear interaction of mean and variance originates naturally from the presence of a large number of neurons (mean-field limit) and hence is supposed to reflect realistic neural behavior.

Spatiotemporal Dynamics

Neural field equations describe the spatiotemporal dynamics of neural populations. Both types of model equations shown in the previous section are nonlinear in the field variable: the integral model is nonlocal in space due to the general interaction kernel, whereas the partial differential equation model describes activity diffusion and is local in space.

Global Structures

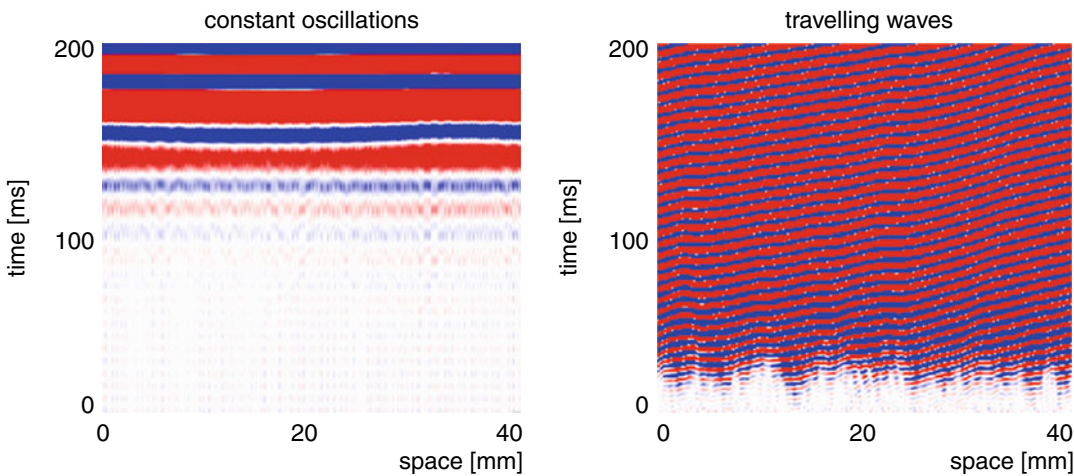
Such structures emerge on the full domain. Figure 3 shows the emergence of spatiotemporal oscillations from a constant stationary state losing stability toward a spatially constant (Fig. 3a) and a spatially periodic (Fig. 3b) structure.

Another example of a global structure is propagating fronts which may emerge from the stimulation of a localized spatial patch. If the activated

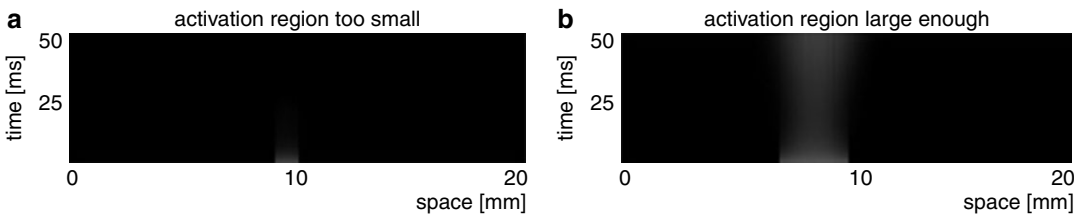
region is too small (Fig. 4a), then the initial global activity structure is unstable and the system returns to the inactive state. If the initial center region is large enough (Fig. 4b), then the initial spatial structures broaden in size. The existence of the activation threshold (critical size of activated region) reflects the excitability of neural systems: too small perturbations from a stable stationary state relax to the stationary state, whereas perturbations large enough generate a strongly different activity pattern. This shows that the excitability known for single neurons translates to neural field on a population level (Hutt 2009).

Localized Structures

In addition to global structures, two stable stationary states may allow for localized structures, such as standing or propagating bumps, which are supposed to reflect the way how memory is stored in



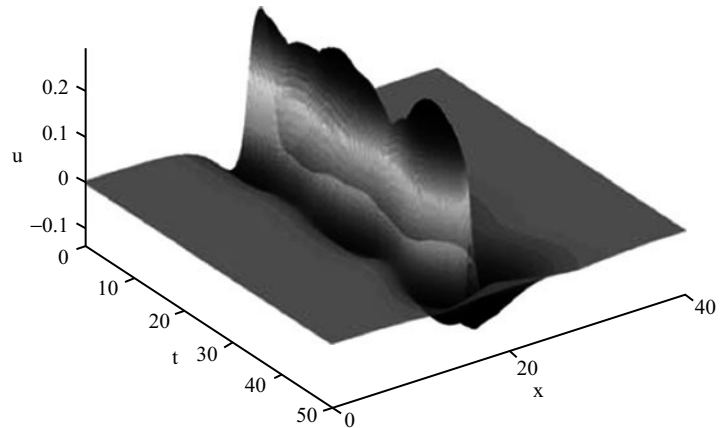
Neural Field Model, Continuum, Fig. 3 Constant oscillations (left) and traveling waves (right) in a neural field



Neural Field Model, Continuum, Fig. 4 Generation of spreading activity representing two overlapping traveling fronts

Neural Field Model, Continuum,

Fig. 5 Unstable bump vanishes. (Taken from Fig. 7 in Coombes (2005) with permission)



the brain (Ermentrout 1998; Coombes 2005; Bressloff 2012). These structures may be stable or unstable subjected to physiological parameters. Figure 5 shows a localized unstable stationary standing bump over a stable constant stationary state. The bump is perturbed by small external fluctuations, starts to oscillate, and vanishes after some time. For large times, the constant stationary state remains the only state.

Cross-References

- [Amari Model](#)
- [Cortical Columns, Models of](#)
- [Down Under Neural Population Models](#)
- [Neural Mass Action](#)
- [Neural Population Model](#)
- [Neuroimaging, Neural Population Models for](#)
- [Pattern Formation in Neural Population Models](#)
- [Population Density Model](#)
- [Propagator, Axonal](#)
- [Stochastic Neural Field Theory](#)
- [Synaptic Connectivity in Neural Population Models](#)
- [Wilson-Cowan Model](#)

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Neural Interface

- [Visual Prosthesis, Optic Nerve Approaches](#)

Neural Map Formation

- [Retinotopic Development, Models of](#)

Neural Mass Action

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Synonyms

[K-set hierarchy](#)

Definition

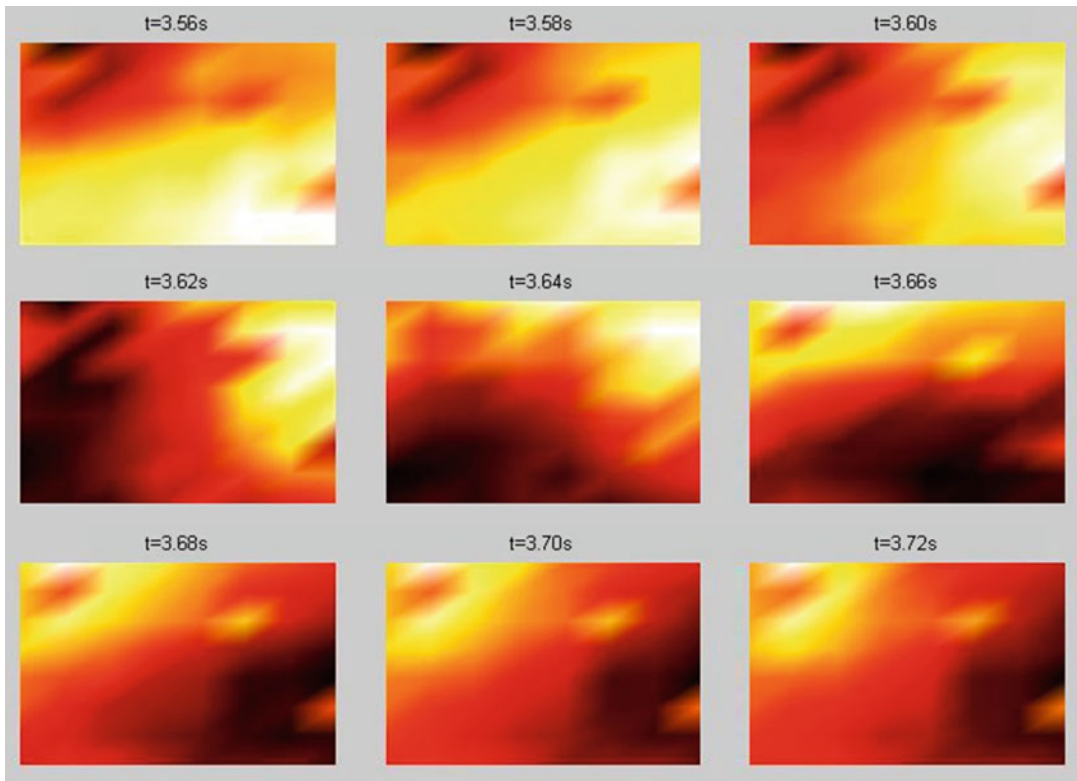
Neural mass action is a field of synchronized axonal pulse firings that cortical neurons create and impose on themselves and others by distributed synaptic interactions. Neural mass action combines sensory representations with memories and binds them into percepts.

Basic Features of Mass Action in Neural Populations

Freeman described mass action (FMA) in the nervous system based on electrocorticogram (ECoG) measurements with electrodes implanted on the cortical surface of animals and in human subjects with their consent during epilepsy surgery (Freeman 1975; Barrie et al. 1996; Freeman et al. 2003; Freeman and Kozma 2010). FMA self-organizes the spontaneous cortical background activity at criticality by continuous mutual excitation (positive feedback) among pyramidal cells at intensities related to the degree of arousal. FMA activity is segmented into wave packets by beats in narrowband oscillations that are sustained by inhibition from interneurons (negative feedback). FMA converts a sensory representation of a stimulus, which is expressed in microscopic trains of pulses, into a percept of the stimulus, which is expressed in a mesoscopic spatial pattern of amplitude modulation (AM) of a narrowband carrier wave.

FMA is measured indirectly by recording potential fields, which are formed by the flow of dendritic current across the resistance of brain and scalp tissues. The sequence of metastable AM patterns can be viewed as frames in a movie, separated by the collapse of AM patterns (null spike), analogous to the shutter (Freeman and Kozma 2010; Kozma and Freeman 2009). Extraction of the forms of FMA that define the wave packet and modeling the neural mechanism of perception require both broad fields of view and high resolution in the spectral, temporal, and spatial domains of measurement, straining the limits of contemporary neuroscience technology and theory (Freeman et al. 2003; Ruiz et al. 2010).

Examples of AM patterns in the theta band are displayed in Fig. 1, as they evolve in time between time instance 3.56 and 3.72 s. In these experiments, the electrical activity of the primary visual cortex in rabbits was measured using an 8×8 array of chronically implanted electrodes (Barrie et al. 1996). The space between the electrodes is 0.79 mm covering an area of 5.6×5.6 mm. Data were collected during 6 s using a 500 Hz sampling frequency. In Fig. 1, dark and light tones indicate low and high amplitudes,



Neural Mass Action, Fig. 1 Temporal evolution of spatial amplitude-modulation (*AM*) patterns. There is an apparent rotation in the vortex counterclockwise from $t = 3.56$ – 3.72 s. (After Rodriguez and Kozma 2007)

respectively. One can observe practically a complete rotation during the given sequence of amplitude frames of duration 0.26 s. These results show that the synchrony is not completely lost during the transitional period at the null spike; rather it is represented by sequentially appearing semi-localized mesoscopic vortex structures.

Hierarchical Neural Population Models to Describe Neural Mass Action

The cortical fields created by FMA are much larger than the synapses and neurons supporting them, and the frequency components are much slower than those of action potentials, so mesoscopic measurements can be modeled as continuous variables. The pulse frequencies of incoming trains of pulses determine the dendritic current amplitude. The current amplitude controls the output pulse frequencies. The wave amplitude

summed from a local neighborhood (a wave density) is correlated in time and space with the pulse density of neurons in the same neighborhood. The statistical relation of pulse density on axons to wave density on dendrites is characterized by an asymmetric sigmoid function, which is used as a basic component of Freeman K models (Freeman and Erwin 2008). A hierarchical approach to neural dynamics from microscopic to mesoscopic and macroscopic populations is summarized as the ten building blocks of neurodynamics (Freeman 1975; Skarda and Freeman 1987; Freeman 2001):

1. State transitions of an excitatory population from a point attractor with zero activity to a nonzero point attractor with steady-state activity by positive feedback
2. Emergence of oscillations through negative feedback between excitatory and inhibitory neural populations

3. State transitions from a point attractor to a limit cycle attractor that regulates steady-state oscillation of a mixed excitatory-inhibitory cortical population
4. Genesis of chaos as background activity by combined negative and positive feedback among three or more mixed excitatory-inhibitory populations
5. Distributed wave of chaotic activity that carries a spatial pattern of amplitude modulation made by the local heights of the wave
6. The increase of nonlinear feedback gain that is driven by input to mixed population, which results in construction of an amplitude-modulation pattern as the first step in perception
7. The embodiment of meaning in amplitude-modulation patterns of neural activity, which are shaped by synaptic interactions that have been modified through learning
8. Attenuation of microscopic sensory-driven noise and enhancement of macroscopic amplitude-modulation patterns by divergent-convergent cortical projections
9. Gestalt formation and pre-afference through the convergence of external and internal sensory signals leading to the activation of the attractor landscapes and leading to intentional action
10. The formation of a sequence of global amplitude-modulation patterns of chaotic activity that integrates and directs the intentional state of an entire hemisphere

Various components of these principles have been implemented in computational models. For example, the Freeman Katchalsky K models use a set of ordinary differential equations (ODEs) with distributed parameters to describe the hierarchy of neural populations starting from micro-columns to the hemispheres (Kozma and Freeman 2001, 2009). Recent advances include neuropercolation implementations of K sets using random graph theory (Kozma 2008; Kozma and Puljic 2013).

Cross-References

- Bifurcations, Neural Population Models and
- Chaos, Neural Population Models and

- Electrocorticogram (ECoG)
- Embodied Cognition, Dynamic Field Theory of
- Extracellular Potentials, Forward Modeling of
- Network Theory in Neuroscience
- Neural Population Model
- Neuroimaging, Neural Population Models for
- Neuropercolation and Neural Population Models

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Neural Mass Model

- Neural Population Model

Neural Oscillation

► [Rhythm Perception: Pulse and Meter](#)

Neural Population Model

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Synonyms

[Neural mass model](#); [Neural population models of the alpha rhythm](#)

Definition

Neuronal population models refer to a class of models that describe the temporal evolution of one or more statistical moments that characterize the dynamical state of interconnected populations of neurons. Existing neuronal population models, for mathematical tractability and direct connection with experiment, are generally restricted to the temporal evolution of mean quantities such as the mean firing rate or mean (soma) membrane potential over an appropriately defined neural ensemble. Such an ensemble is typically defined in terms of the physical domain over which the activity of functionally identical neurons can be, statistically speaking, assumed spatially homogeneous.

Detailed Description

History

By postulating that, in analogy to the collective phenomena of atomic interaction underpinning ferromagnetism, neurons acted cooperatively, Cragg and Temperley (1954) provided the first clear rationale for modeling the collective

behavior of populations of neurons. They argued that dense functional interactions between neurons would lead to the emergence of large-scale (compared to the dimensions of the individual neuron) domains of coordinated activity having features that could not be understood by appealing to the behavior of the single neuron. While often regarded as the basis for Ising-based models of networks of enumerable neurons (see entry ► [“Hopfield Network”](#)), it also stimulated efforts to understand the collective properties of neurons based on more specific and relevant anatomical and physiological predicates.

Early Mathematical Developments

While McCulloch and Pitts (1943), Ashby (1950) and Rapoport (1950), among others, had made a variety of abstract attempts to mathematically formalize the interactions between populations of neuron-like elements and to characterize their collective properties, it was Beurle (1956) who is generally acknowledged for developing the first dynamical description of a mass of neurons. In this theory, the dynamics of continuously distributed populations of excitatory neurons, having a fixed firing threshold, were studied. This formulation was central to the subsequent development of neuronal population models because of the explicit mathematical definitions of population neuronal activity, bulk (population) synaptic feedback and synaptic delay, and mean integrated excitation.

The first attempt to account for a physiologically measurable phenomena (prepyriform EEG) in terms of the modeled properties of populations of neurons may be attributed to Freeman (1964). This model aimed to account for the oscillatory prepyriform average evoked potential in terms of a distributed population of cortical pyramidal (excitatory) neurons, receiving an impulse-driving input and interacting with each other via recurrent inhibition. Pyramidal neurons received input from the lateral olfactory tract which was then dispersed in time due to the distributed delay effected by the cable properties of the pyramidal cell dendrites and convolved with a simple exponential function corresponding to the unitary excitatory postsynaptic potential (EPSP). The

resulting postsynaptic activity was then linearly transduced into efferent pulse activity to excite a feedback interneuron population, the activity again dispersed in time due to an undefined combination of conduction, synaptic, and electrotonic delays. Mathematically this sequence of neuronal population events was formulated as a linear transfer function containing transcendental terms corresponding to the various distributed delays. This *cortical transfer function* (see entry ► [“Transfer Function, Electro cortical”](#)), subsequently approximated by a rational function for empirical comparison and parameter evaluation, introduced a number of concepts central to the development of almost all future population neural models – feedback between functionally distinct neuronal populations, the dynamics of population averaged postsynaptic potentials, the transduction of averaged integrated postsynaptic activity to a continuously defined average pulse (spike) rate (subsequently referred to as “wave-to-pulse” conversion), and the transformation of incoming population pulse (spike) trains to postsynaptic potentials (later to be designated “pulse-to-wave” conversion). This lumped negative feedback model of cortical dynamics was later further elaborated to include positive feedback loops for mutual excitation and inhibition in the respective inhibitory and excitatory neuronal populations and to include an amplitude-dependent, and hence nonlinear, neuronal population feedback gain – the precursor of the static sigmoid nonlinearity (Freeman 1967). This lumped configuration of neuronal populations not only encapsulated the topology of synaptic interactions in mature neuropil but also introduced the main features of the K-set hierarchy of neural population interactedness (see below) – a schema that was to exert a prominent influence in the development of later neuronal population models.

Commencing in the early 1970s, a number of approaches were developed to modeling populations of neurons that were to introduce a range of conceptual innovations that would have a commanding influence on all ensuing approaches. Particularly notable were the works of Wilson and Cowan (1972) and Lopes da Silva et al. (1974).

Wilson and Cowan derived a pair of coupled nonlinear ordinary differential equations describing the short-time averaged dynamics of the spatial mean ring rates of interacting excitatory and inhibitory neuronal populations. Of crucial significance was their introduction of the *sigmoidal firing rate function* and an explicit cortical mesocircuit quantitatively defined by population (synaptic) connectivity coefficients. Because mean ring rates characterized neuronal population dynamics, this, and similarly formulated models, was developed in terms of the *activity* of a neuronal population. Arguably Grossberg (1967) had mathematically anticipated this formulation by deriving an “additive STM (short-term memory) equation”; however, the inspiration for such a formulation was principally psychological (Hebbian) and as such its domain of application was that of enumerable networks of neurons rather than populations or masses.

In contrast to, but inspired by, this model, Lopes da Silva et al. (1974) subsequently presented a population model of the ventro-posterolateral thalamus, in which they dynamically characterized the *average membrane potential* of reciprocally connected populations of excitatory thalamocortical relay cells and inhibitory interneurons. Novel to this approach was the formal inclusion of average unitary excitatory and inhibitory postsynaptic potentials (PSPs) described by weighted bi-exponentials.

Physiological and Anatomical Representations

Two essential premises distinguish neural population models from biological recurrent neural networks: firstly, that individual neurons in a circumscribed area (e.g., a cortical macrocolumn; see entry ► [“Mesoscopic Anatomy and Neural Population Models”](#)) need not be enumerated and secondly, that in this circumscribed area, the connectivity between neurons is random and non-specific to the extent that the inner circuitry cannot, or need not, be meaningfully specified. The consequence of this is that for each bounded neural population, the spatial and temporal microstructure, or microstates, of neural activity can be disregarded in favor of characterizing the

population's dynamical state in terms of certain average (or higher order) properties or macrostates. In this way the dense and complex interactions between individual neurons can be replaced by effective averages – the mean fields – between populations of neurons.

In general the contention of a population macrostate is expected to remain valid as long as interneuronal propagation delays are negligible compared to local synaptic and dendritic cable delays (see below), and there is no characteristic spatial structure to population neuronal connectivity. However, in modeling spatially extended neural populations, such as the neocortical sheet, neuronal connectivity typically exhibits a substantial degree of spatial organization (see entry ► [“Mesoscopic Anatomy and Neural Population Models”](#)) with the corresponding propagation delays no longer negligible. Thus, spatially extended formulations of neural population models have to be implemented by either constructing networks of neural populations (see entry ► [“Neuroimaging, Neural Population Models for”](#)) or by assuming that the neural populations, continuously distributed in space, interact via spatially dependent connectivity functions (see entry ► [“Neural Field Model, Continuum”](#)).

Most neural population models can be understood in terms of a sequence of serial physiological transformations between synaptic input and axonal output in terms of a mean neuron. The mathematical definition of a mean neuron is easily motivated by spatially averaging (or coarse-graining) a discrete set of functionally homogeneous neurons over a physical domain corresponding to the length scales of the random/nonspecific interneuronal connections and by assuming that membrane potential fluctuations due to spiking are uncorrelated. The serial physiological transformations generally include synaptic delays, transduction of postsynaptic potentials, neuronal cable delays/passive electrotonic processes, and action potential generation.

Neuronal Populations, Hierarchies, and Connectivity

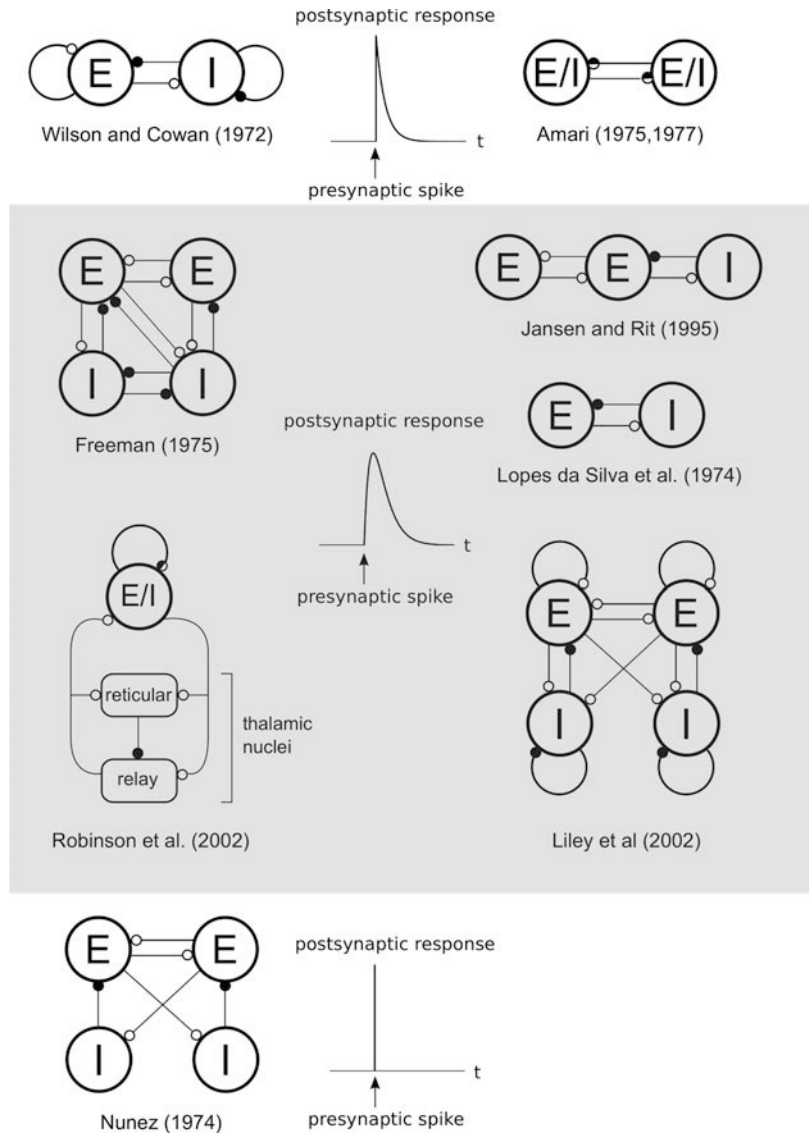
A typical starting point for the formulation of neuronal population models requires the

specification of functionally homogeneous neural populations and the topology of their interactions, driven by histological considerations of the cellular composition and anatomical organization of neural tissue. Because all neurological processes of any complexity depend on the interaction of excitatory and inhibitory neurons, anatomically circumscribed populations of these respective populations form the basis of, with certain weak exceptions (see, e.g., Amari 1975, 1977), all neuronal population models. Figure 1 schematically represents the circuit topologies for all the major neuronal population models (see also entry ► [“Neural Field Model, Continuum”](#)).

Based on the histological properties of the mammalian olfactory bulb and prepyriform cortex, Freeman (1975) defined a hierarchical scheme of interaction in which populations of excitatory and inhibitory neurons interact over progressively larger physical scales. The schema, referred to as the K-set hierarchy (in honor of the biophysical chemist Aharon Katchalsky), commences with the simplest type of neural population referred to as the *KO* set (or noninteractive K set). This set, or neural population, is defined as a population of 10^3 – 10^8 neurons having a common source of input, a common sign of output, and no functional interaction. The K-set hierarchy is then next extended to the case where there exist dense, but random and nonspecific, interactions between neurons of any given *KO* set. This defines the so-called *KI* set or interactive *KO* set, of which there are two types: the *KI_e* set, consisting of mutually excitatory neurons, and the *KI_i* set, comprised of mutually inhibitory neurons. Dense functional interactions between two *KI* sets, *KI_j* and *KI_k*, define the interactive *KII* set such that $KII_{jk} \equiv KII_{kj}$. The K-set hierarchy can then be extended in a straightforward manner to *KIII* and *KIV* sets. While the exact topology of these sets ultimately depends on certain peculiarities of Freeman's mass action approach, it is nevertheless capable of serving as a general schema for characterizing neuronal population architectures. For example, in terms of neocortex, *KI_e* can be identified with populations of pyramidal neurons densely interacting via recurrent axonal collaterals (see entry ► [“Mesoscopic Anatomy and Neural Population Models”](#)) and

Neural Population

Model, Fig. 1 Schematic representation of the principle neural population model circuit topologies segregated by the form of the postsynaptic response. All approaches consider functionally differentiated excitatory (E) and inhibitory (I) neuronal populations. *Open circles* represent excitatory connections, *filled circles* inhibitory ones, and *half-filled circles* both. (Figure adapted from Liley et al. 2012)



KI_i could correspond to one or more local inhibitory interneuron populations, KII_{ie} the resulting macrocolumn and $KIII$ and KIV , respectively, the cortical area and region/lobe. However, care has to be taken in defining neural sets. For example, the fact that the apical dendrite of a single pyramidal (excitatory) neuron can extend across multiple neocortical layers means that cortical lamination represents an insufficient anatomical basis on which to define a KO neural population.

While it is often assumed that the functional interactions between neurons are exclusively axosynaptic, there is no requirement that this restriction need be observed in the construction

of neural population models or in order to justify their physiological utility. It is now known that the functional structure of mammalian cortical tissue extends well beyond neurons and their axosynaptic interactions. For example, neurogliaform cells, rather than solely providing structural and biochemical support for the neuronal parenchyma as previously thought, have been shown to regulate neuronal activity through a complex involving astrocytes and neuronal pre- and postsynaptic terminals (see entry ► [“Tripartite Synapse \(Neuron–Astrocyte Interactions\), Conductance Models”](#); Giaume et al. 2010). Further other forms of neuronal interaction have

either been suggested (ephaptic or local field; Terzuolo and Bullock 1956) or demonstrated (gap junction/dendrodendritic, axo-myelinic, axo-axonic, volume/extrasynaptic; Sohl et al. 2005; Stys 2011; De-Miguel and Fuxe 2012; Mozzachiodi and Byrne 2010). The addition of such biological complexity, rather than undermining a neural population modeling approach, arguably serves to further justify abandoning the idea of articulating neuronal microstates in favor of a population macrostate.

Neuronal Structure and Dendritic Filtering

Neural population models generally take a parsimonious approach to describing the electrical properties of populations of neurons. The most basic approach is to simply assume that the average neuron behaves as a summing junction for induced postsynaptic potentials

$$V_i = \sum_j \text{PSP}_{ij}(t), \quad (1)$$

where V is the mean neuronal membrane potential or mean soma membrane potential (to emphasize the membrane potential locus that regulates neuronal firing) and $\text{PSP}_{ij}(t)$ represents the magnitude of the average induced postsynaptic potentials of type j at time t on neurons of type i .

A better approach is to consider the extended electrotonic neuron collapsed down to a point parallel-resistive circuit, representing the neuronal membrane, into which all synaptically induced activity terminates. In this case the temporal evolution of $V(t)$ is simply described by a *current-based neuron*

$$\tau dV_i/dt = -V + \sum_j \text{PSP}_{ij}(t), \quad (2)$$

where τ defines a mean membrane time constant. However, because the magnitude of any induced postsynaptic activity depends upon the state of the postsynaptic membrane, given that presynaptically released neurotransmitters regulate postsynaptic ionic conductances, the evolution of $V(t)$ may be described in terms of the alteration of a

mean equivalent conductance. On this basis a *mean conductance-based neuron* is defined as

$$\tau dV_i/dt = -V + \sum_j \psi_j(V_i) \text{PSP}_{ij}(t), \quad (3)$$

where $\psi_j(V_i)$ represents a dimensionless ionic driving force.

Synaptic Activity

From a physiological perspective, the time course of the postsynaptic potential felt at the neuronal soma represents a combination of the kinetics of neurotransmitter action and neuronal cable delays. In the simplest case, these effects can be ignored such that the unitary population postsynaptic potential (or population postsynaptic impulse response) $\alpha_{ij}(t)$ is

$$\alpha_{ij}(t) = A_{ij} \delta(t), \quad (4)$$

where A_{ij} is the peak amplitude (positive for excitatory postsynaptic potentials, negative for inhibitory postsynaptic potentials) and $\delta(t)$ the Dirac delta function corresponding to the arrival of a single presynaptic action potential. However, given the extended nature of the neuronal dendritic tree and the temporal variations in postsynaptic potentials of various types, such delays can generally not be ignored. On this basis, following Rall (1967), the unitary postsynaptic impulse response, $\alpha_{ij}(t)$, is better described by a function that rises to a peak and then decays away:

$$\alpha_{ij}(t) = A_{ij} a_{ij} t \exp [1 - a_{ij} t] \Theta(t), \quad (5)$$

where $\alpha_{ij}(t = 1/a_{ij}) = A_{ij}$ is the peak amplitude and $\Theta(t)$ the Heaviside step function. While it is often assumed that $a_{ij} \equiv a_i$ depends only on the postsynaptic population, there is mounting physiological evidence to suggest that the configuration of postsynaptic ionic channels depends upon certain properties of the presynaptic neurons. Other normalizations of this function, for example, to fixed area, are also possible. Because $F_j(t') dt'$ action potentials arriving at t' about t would be expected to contribute $d\text{PSP}_{ij}(t) = \alpha_{ij}(t-t') F_j(t') dt'$ to the population postsynaptic potential we find, assuming additivity of response,

$$\text{PSP}_{ij}(t) = \int_{-\infty}^t \alpha_{ij}(t-t') F_j(t') dt'. \quad (6)$$

In neural population models, it is found convenient to reformulate this convolution in terms of a critically damped oscillator driven by $F(t)$:

$$(d/dt + a_{ij})^2 \text{PSP}_{ij}(t) = A_{ij} a_{ij} \exp(1) \cdot F_j(t). \quad (7)$$

The form of this, and similar differential equations, is easily established by finding a linear differential operator L such that $L\alpha(t) = \delta(t)$. As is similarly done in Green's function formulations of integral continuum neural field equations (see entry ► “[Neural Field Model, Continuum](#)”) to obtain partial differential equation representations, such differential equations are most simply found by taking either the Fourier or Laplace transforms of α_{ij} with respect to t and identifying $s = i\omega \leftarrow d/dt$. It is often found desirable to have more flexibility in specifying the shape of the population postsynaptic response, and therefore, bi-exponential generalizations of the alpha function can be utilized (Fig. 2). Two such formulations that have been found particularly useful are

$$\begin{aligned} [d/dt + a(\epsilon)][d/dt + \tilde{a}(\epsilon)] \text{PSP}(t) \\ = A\tilde{a}(\epsilon) e^{a(\epsilon)/a_0} \cdot F(t), \end{aligned} \quad (8)$$

$$\begin{aligned} a(\epsilon) &= \epsilon a_0 / (e^\epsilon - 1), \tilde{a} = a(\epsilon) e^\epsilon; \\ \epsilon &\geq 0, \end{aligned} \quad (9)$$

and

$$\begin{aligned} (d/dt + a)(d/dt + b) \text{PSP}(t) \\ = A(b - a)/k \cdot F(t), \end{aligned} \quad (10)$$

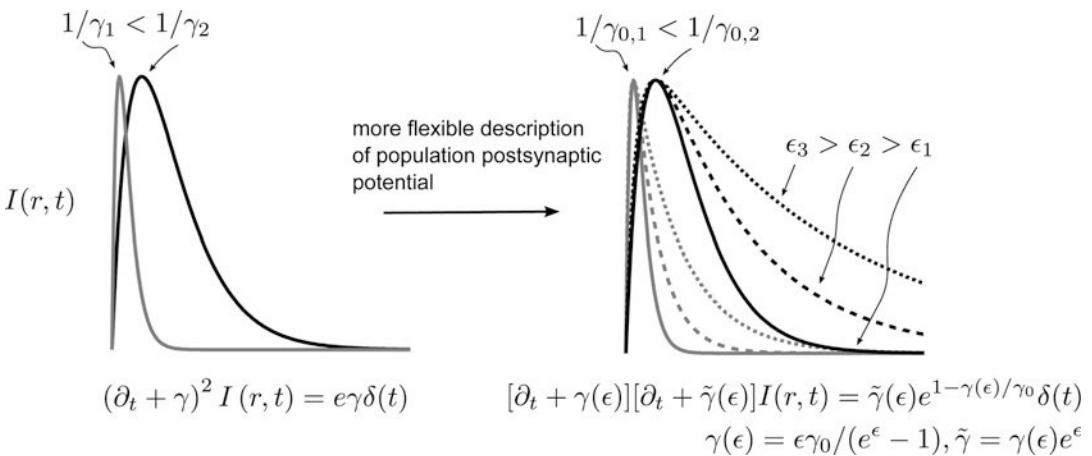
$$k = (a/b)^{a/(b-a)} - (a/b)^{b/(b-a)}; a < b, \quad (11)$$

where the subscripts specifying the type of postsynaptic potential have been dropped for clarity. The first of these is useful if the independent parametric regulation of rise and decay times is necessary, as, for example, in modeling the effects of anesthetics on postsynaptic kinetics (see below). The effects of bulk synaptic plasticity can be modeled by assuming that a_{ij} and A_{ij} are activity-dependent functions of population activities F_i and F_j .

Pulse Generation

The closure of equations defining neural population models depends on formally specifying the

N



Neural Population Model, Fig. 2 Illustration of the forms of postsynaptic potentials utilized in neural population models and their corresponding differential structure. The modeled postsynaptic potential on the left corresponds

to the well-known alpha function introduced by Rall (1967). The modeled postsynaptic potentials on the right illustrate a parametric form that allows the independent specification of the rise and fall phases

relationship between mean (soma) neuronal population membrane potential and the generation of axonal spikes. While the generation of the post-synaptic response depends on innovating axonal spikes, because of the assumption of dense and random intrapopulation connectivity, the timing of individual spikes is not defined. For this reason, neural population models define axonal activity in terms of the total number of spikes $F_j(t)dt$ generated in the interval $[t, t + dt]$ via a time-dependent firing rate function $F_j(t)$. The simplest approach to the construction of such a firing rate function is to assume that it is an instantaneous bounded monotonic function (logistic) of the mean population (soma) membrane potential,

$$F_j(t) \equiv F_j(V_j[t]) = F_j^{\max} / \{1 + \exp[-c_j(V_j - \theta_j)]\}, \quad (12)$$

i.e., a sigmoid or squash function having maximal slope $c_j F_j^{\max}/4$ at $V_j = \theta_j$. θ_j nominally defines a neuronal population threshold. This and similar sigmoids (e.g., error function, arctangent, etc.) are often described as being symmetric because $dF/dV|_V = dF/dV|_{2\theta - V}$. Asymmetric sigmoid functions can also be defined, for example,

$$F_j(V_j) = F_j^{\max} - F_j^{\max} \{1 + \exp[-c_j(V_j - \theta_j)]\}^{-k}; \quad c_j, k > 0, \quad (13)$$

$$F_j(V_j) = F_j^{\max} \{1 - \exp[-c_j \exp(V_j - \theta_j)]\}; \quad c_j > 0, \quad (14)$$

the latter of which has been used in modeling the neuronal population dynamics of mammalian olfactory bulb (Freeman 1979). Firing rate functions can also be motivated by considering the unimodal distribution of firing thresholds in a population of neurons having a fixed absolute refractory period. For example, following Beurle (1956), Wilson and Cowan (1972, 1973) described neural population activity $F_j(t)$ in

terms of the fraction of neurons that receive at least a threshold level of excitation per unit time that are able to fire (i.e., not refractory) on the assumption that there is no correlation between the suprathreshold and refractory fractions, i.e.,

$$F_j(t + \tau)dt = R_j(t) \cdot S_j(V_j)dt, \quad (15)$$

$$= \left\{ 1 - \int_{t-r_{\text{abs}}}^t F_j(t')dt' \right\} \cdot \int_{-\infty}^{V_j} f_V(v)dvdt, \quad (16)$$

where $R_j(t)$ is the fraction of neurons of type j that are able to fire at time t , $S_j(V_j)$ the fraction of neurons per unit time that receive at least a threshold level of activation V_j , r_{abs} the spike refractory period, $f_V(\cdot)$ a unimodal neuronal firing threshold distribution function, and τ a nominal synaptic operating delay. By assuming that τ and r_{abs} are small compared to the time scale of variations in $F_j(t)$, it can be easily shown that $0 \leq F_j(t) < 1/(1 + r_{\text{abs}}) \equiv F_j^{\max}$.

Canonical Formulations

Among the most important and influential neural population models is that developed by Wilson and Cowan (1972, 1973). Based on the topological structure of mature neuropil suggested by Freeman (1967), they developed a set of planar nonlinear differential equations describing the activity of coupled, spatially lumped, populations of excitatory and inhibitory neurons. As originally formulated, they made use of the concept of temporal coarse-graining, first applied to problems in statistical physics, to derive equations of motion for the respective time averaged neuronal population firing rates. For pedagogical purposes, these equations can be easily, though not rigorously, derived. By assuming postsynaptic potentials are described by Dirac delta functions (Eq. 4) and linearly sum (Eq. 1), we find from Eq. 15 that

$$F_E(t + \tau) = \left\{ 1 - \int_{t-r_E}^t F_E(t')dt' \right\} \cdot S_E[A_{EE}F_E(t) + A_{EI}F_I(t)], \quad (17)$$

$$F_I(t + \tau) = \left\{ 1 - \int_{t-r_I}^t F_I(t') dt' \right\} \cdot S_I[A_{IE}F_E(t) + A_{II}F_I(t)], \quad (18)$$

with $E, I = \text{excitatory, inhibitory}$.

By reinterpreting $\tau_{E,I} \ll r_{E,I} (\equiv r_{\text{abs}})$ as the combined characteristic time scale for uniform synaptic, cable, and axonal delays, we obtain, after first-order expansion in t and the addition of external inputs $Q(t)$ and $P(t)$,

$$\tau_E \frac{dF_E(t)}{dt} = -F_E(t) + \{1 - r_E F_E(t)\} \cdot S_E[A_{EE}F_E(t) + A_{EI}F_I(t) + P(t)], \quad (19)$$

$$\tau_I \frac{dF_I(t)}{dt} = -F_I(t) + \{1 - r_I F_I(t)\} \cdot S_I[A_{IE}F_E(t) + A_{II}F_I(t) + Q(t)], \quad (20)$$

This coupled pair of nonlinear ordinary differential equations represents the well-known spatially lumped Wilson and Cowan equations. The equations, and subsequent extensions and modifications, are widely used in the modeling of coupled neuronal population activity. These equations represent an example of an *activity-based* neuronal population model (see below). Extensions to continuously distributed populations of interacting excitatory and inhibitory neurons in planar sheets are easily formulated (see entries ► “[Neural Field Model, Continuum](#)” and ► “[Wilson-Cowan Model](#)”).

An alternative approach to formulating a neuronal population model is to develop equations of motion in terms of the mean (soma) membrane potential of the respective neural masses. A particular advantage to this approach is that the mean soma membrane potential can be more naturally linked to meso- and macroscopic physiological measurements such as the local field potential (LFP), the EEG, and the electrocorticogram (ECoG). An important basis for this approach was the lumped neuronal population

model developed by Lopes da Silva et al. (1974) to explain the rhythmic origins of the mammalian alpha rhythm. In this model, a “feedforward” population of excitatory neurons receives external excitatory input and inhibitory feedback from inhibitory interneurons. Originally formulated as a model of thalamic tissue, a modified form is now widely used to model cortical neuronal population dynamics (see entry ► “[Jansen-Rit Model](#)”). The equations describing the model of Lopes da Silva et al. (1974), which can be seen to follow in a fairly straightforward manner from Eqs. 1 and 10, are

$$\begin{aligned} & \left(\frac{d}{dt} + a_E^1 \right) \left(\frac{d}{dt} + a_E^2 \right) V_I(t) \\ &= A_E (a_E^2 - a_E^1) \cdot C_{IE} F_E \underbrace{[\text{PSP}_{EP}(t) - \text{PSP}_{EI}(t)]}_{\equiv V_E(t)}, \end{aligned} \quad (21)$$

$$\begin{aligned} & \left(\frac{d}{dt} + a_I^1 \right) \left(\frac{d}{dt} + a_I^2 \right) \text{PSP}_{EI}(t) \\ &= A_I (a_I^2 - a_I^1) \cdot C_{EI} F_I [V_I(t)], \end{aligned} \quad (22)$$

$$\begin{aligned} & \left(\frac{d}{dt} + a_E^1 \right) \left(\frac{d}{dt} + a_E^2 \right) \text{PSP}_{EP}(t) \\ &= A_E (a_E^2 - a_E^1) \cdot P(t), \end{aligned} \quad (23)$$

where $P(t)$ is an external excitatory pulse input and $C_{IE,EI}$ are defined as the average number of axosynaptic contacts that an excitatory neuron makes on an inhibitory interneuron and an inhibitory interneuron makes on an excitatory neuron, respectively. All other symbols have been defined previously. These equations are an exemplar of a *voltage-based* neuronal population model (see below).

Contemporary neural population models, in order to best approximate known physiology, utilize features of both of these canonical modeling approaches (Deco et al. 2008). An example of such a model is the spatially lumped approximation that can be obtained from Liley et al. (2002) by ignoring long-range axonal connectivity. The resulting model equations, developed on the basis of the *mean conductance-based* neuron, can be written as

$$\tau_i \frac{dV_i(t)}{dt} = -V_i(t) + \sum_j \frac{V_{ij}^R - V_i(t)}{|V_{ij}^R|} \text{PSP}_{ij}(t), \quad (24)$$

$$\left(\frac{d}{dt} + a_{ij} \right)^2 \text{PSP}_{ij}(t) = a_{ij} A_{ij} \exp(1) \{F_j[V_j(t)] + P_{ij}(t)\}, \quad (25)$$

where a normalized ionic driving force has been explicitly defined in terms of the synaptic reversal potential V_{ij}^R and $P_{ij}(t)$ represents an external pulse input. Such a formulation is typically restricted to single distinct excitatory and inhibitory neural populations.

Voltage Versus Activity-Based Models

A number of authors (Bressloff 2012; Ermentrout 1998) have made a distinction between neuronal population models in terms of whether they are *activity based* or *voltage based*. To see this distinction, consider the following generalized representation of a population model involving multiple coupled populations:

$$L_i V_i = \sum_j \text{PSP}_{ij}(t), \quad (26)$$

$$\hat{L}_{ij} \text{PSP}_{ij}(t) = k_{ij} F_j[V_j(t)], \quad (27)$$

where L_i and $\hat{L}_{ij}$ represent linear differential operators. If the derivatives in L_i vanish (i.e., the time scales of postsynaptic potentials dominate), then we have

$$\hat{L}_{ij} \text{PSP}_{ij}(t) = F_j \left[\sum_i k_{ji} \text{PSP}_{ji}(t) \right], \quad (28)$$

where we have redefined $\text{PSP}_{ij} \rightarrow k_{ij} \text{PSP}_{ij}$. This is said to define an *activity-based* model.

If instead the derivatives in $\hat{L}_{ij}$ vanish (i.e., the time scales of passive electrotonic properties dominate), then we have

$$L_i V_i = \sum_j k_{ij} F_j[V_j(t)], \quad (29)$$

then we have a *voltage-based* model. In practice, however, the distinction between activity- and voltage-based models is not that important as physiologically the time scales of synaptic kinetics and passive neuron properties are of the same order of magnitude such that neither of these limits will be applicable.

Solutions of Deterministic Neuronal Population Equations

The properties of neural population models can be established using all the standard mathematical and computational methods that are typically used to investigate the dynamics of coupled non-linear systems such as phase-plane analysis and numerical bifurcation methods. However, it is also useful to explicitly consider linearizations of the defining equations, as it assists in determining whether the structure of the population model accords with the physiological measurements of the system being modeled. This is particularly the case in attempts to account for rhythmic EEG activity in terms of the activity of recurrently connected populations of cortical and thalamic neurons. For example, Lopes da Silva et al. (1974), by assuming a stable steady state (V_E^*, V_I^*) about which a linearization could be performed, were able to rewrite their model's defining equations in transfer function form as

$$V_E(f) = \frac{A_E(a_E^2 - a_E^1)(2\pi if + a_I^1)(2\pi if + a_I^2)}{(2\pi if + a_E^1)(2\pi if + a_E^2)(2\pi if + a_I^1)(2\pi if + a_I^2) + K} P(f), \quad (30)$$

$$K = C_E C_I A_E A_I (a_E^2 - a_E^1)(a_I^2 - a_I^1) dF_E/dV_E|_{V_E^*} dF_I/dV_I|_{V_I^*} \quad (31)$$

where f is frequency and G_E , particularly in the context of neural population models of the EEG, is typically referred to as the *electrocortical transfer function* (see entry ► “[Transfer Function, Electrocortical](#)”) and enables the determination of a theoretical power spectrum $|V_E(f)|^2 = |G_E(f)|^2 |P(f)|^2$. If it is further assumed that $|P(f)|^2$ is flat (i.e., mean external ring rates can be described by a Gaussian white noise process) then the poles of $G_E(f)$ will determine the dominant spectral components (or resonances) of the power spectrum. This approach is exploited by a number of neural population models of the EEG (Liley et al. 2002, 2003; Robinson et al. 2002; Steyn-Ross et al. 1999) in order to facilitate comparison with experimental recordings.

While the dynamics of planar formulations of neural population models are restricted to hysteresis and limit-cycle activity, higher order population models are capable of exhibiting substantial dynamical complexity, such as multistability, bursting, and chaos, as well as complex, and potentially novel, bifurcation scenarios due to the large number of irreducible model parameters. For example, the spatially homogeneous Liley equations (Liley et al. 2002) (see entry ► “[Down Under Neural Population Models](#)”) can spawn chaos (see entry ► “[Chaos, Neural Population Models and](#)”) through a co-dimension of one homoclinic Shil’nikov saddle-node bifurcation (not to be conflated with a saddle node on an invariant circle bifurcation) (van Veen and Liley 2006).

Stochastic Models

At the level of the single neuron, there are many sources of noise – noise generated by thermally induced fluctuations in the state of ion channels and the noise generated due to the probabilistic vesicular release of neurotransmitter being among the most important (Longtin 2013). The effects of such noise are assumed to contribute to the stochastic variability of neuronal activity, such as the near Poisson pulse trains that are characteristic of many cortical neurons (Softky and Koch 1993). However, it is neither straightforward nor obvious how noise at the single neuron level translates into noise and fluctuations in activity at the neuronal

population level and therefore how the addition of this noise qualitatively shapes the dynamical activity of the neural mass. For this reason, a variety of theoretical attempts have been developed in an attempt to address this issue systematically. One important approach has been to conceive the dynamics of populations of spiking neurons in terms of the temporal evolution of the probability density of the soma membrane potentials. The resulting formulations, typically referred to as *population density methods* (see entry ► “[Population Density Model](#)”), typically assume a highly simplified model of a neuron (generally the leaky-integrate-and-fire) and either fully or sparsely connected neuronal networks. Nevertheless no rigorous approach has yet emerged to derive neural population models that take proper account of noise-induced fluctuations or the statistical correlations between neurons. Further complicating such attempts is the absence of any clear framework for how to deal with the reported effects that non-neuronal components may have. For this reason, stochastic extensions to deterministic neural population models are largely phenomenologically motivated. The general phenomenological approach can be illustrated by considering the indefinite voltage-based population model evolving according to a Langevin (stochastic differential) equation of the form

$$\tau_i dV_i(t) = \left\{ -V_i(t) + \sum_j k_{ij} F_j[V_j(t)] \right\} dt + dW_i(t), \quad (32)$$

where $dW_i(t)$ is a Wiener process. In the case that the modeled source of noise arises from fluctuations about an asynchronous state due to finite (network) size effects, then the population Wiener noise processes will be spatially correlated, i.e., $\langle dW_i(t) dW_j(t) \rangle = \nu > 0$ for all i, j . In the case that the source of noise is due to membrane potential fluctuations, then $F_j[V_j(t)]$ will be redefined as the expectation $\mathbb{E}(F_j[V_j(t)])$ such that a fully implicit set of stochastic differential equations result (Bressloff 2012).

Applications and Relationship to Physiological Measurement

Despite their sometimes phenomenological construction, the importance of neuronal population models lies in their ability to serve as a framework for understanding the physiological genesis of a range of macroscopic scale neurophysiological phenomena, such as spontaneous and evoked EEG, and the relationships of such activity to other bulk measures of brain function such as BOLD (blood oxygen level-dependent) MRI. For this reason, neural population models are often characterized as “mesoscopic bridges” – in that phenomenological descriptions of molecular/cellular level activity can be linked with large-scale activity through an intermediate (mesoscopic) bridging theory (Foster et al. 2008). Examples of phenomena that are particularly amenable to a neural population model description are the mammalian alpha rhythm and the various sensory (visual, auditory, somatosensory)-evoked potentials.

Spontaneous and Evoked EEG

Scalp-recordable electrical activity exhibits a number of dynamical phenomena that can be and have been characterized by neural population models. Among the most important of these is the mammalian alpha rhythm. The 8–13 Hz alpha rhythm is arguably the most ubiquitous rhythmic phenomena seen in scalp EEG. First discovered by Hans Berger in the late 1920s, it has subsequently played a central role in characterizing electroencephalographic activity observed in cognition and behavior. To date two broad explanatory approaches have emerged to account for this electrocortical phenomenon: (1) the direct (feedforward) oscillatory pacing of cortex from either thalamus or endogenously oscillatory populations of cortical neurons and (2) emergence through reverberant activity generated by the reciprocal (feedforward and feedback) interaction of populations of cortical and thalamic neurons. While representations of both approaches can be achieved by the computational modeling of individual populations of spike-based neurons, the latter approach when conceived using a coupled population-based method results

in mathematically compact formulations that are able to retain significant physiological detail.

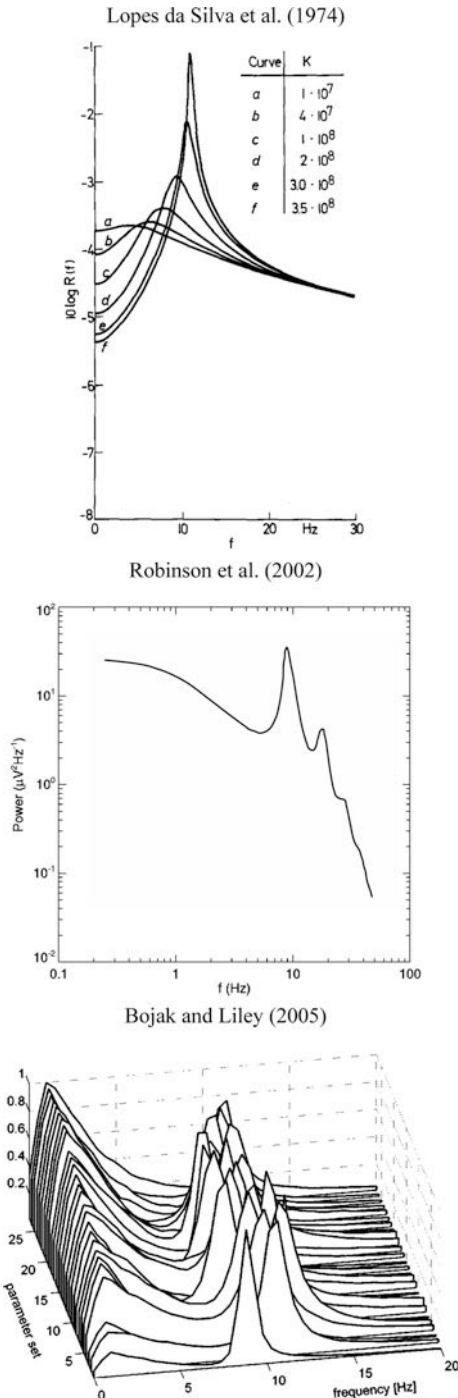
As previously mentioned, Lopes da Silva et al. (1974) developed a population-based model of the alpha rhythm on the basis of the reciprocal coupling of excitatory and inhibitory neuronal populations. In the linearized model, by parameterizing the respective postsynaptic potentials according to the “fast” synaptic kinetics of inhibitory GABA and excitatory AMPA/kainate ionotropic receptor activity, alpha band resonances (damped poles of the electrocortical transfer function) emerged. Thus, in response to an impulse input $P(t) = \delta(t)$, damped sinusoidal behavior would result, thereby serving as a model for time-locked evoked electrocortical activity. In response to broadband white noise driving $|P(f)|^2$ is constant and a peaked power spectrum, for physiologically plausible values of the population coupling strength K , is obtained. This model was subsequently extended by Jansen and Rit (1995), by the addition of a feedback population of excitatory neurons, in order to account for the visual evoked potential.

In contrast to this approach, a number of neural population models have been developed that produce deterministic and noise-driven alpha band activity by the coupling of populations of thalamocortical (Robinson et al. 2002) and cortical inhibitory neurons (Bojak and Liley 2005; Liley et al. 2002). Figure 3 illustrates the linearized noise spectra of three important neural population models that have been developed to explain resting alpha band EEG activity.

Epilepsy, Anesthesia, Sleep, and Inferential Neuroimaging

Because neural population models aim to describe macroscopic level properties, they are consequently well placed to describe macroscopic level perturbations that attend alterations in brain function as occurring during sleep, anesthesia, and disease states such as epilepsy.

Epilepsy is characterized by the sudden occurrence of hyper-synchronous firing activity within relatively large populations of neurons and is thus amenable to being dynamically described by state changes in appropriately constructed neural



Neural Population Model, Fig. 3 White noise fluctuation spectra of three prominent neural population models that produce alpha (8–13 Hz) band model electroencephalographic activity. *Top* – model of Lopes da Silva et al. (1974) for various values of K (see Eq. 30). *Middle* – model of Robinson et al. (2002) fitted to a single subject’s eyes-

population models (see entry ► “Epilepsy, Neural Population Models of”). A typical approach is to consider coupled populations of excitatory and inhibitory neurons and to systematically investigate the onset of limit-cycle oscillations through either physiologically motivated parametric perturbations (bifurcations), noise-driven transitions between stable attractors that correspond to normal and seizure states (multistability), or a combination of the two. On this basis it has been hypothesized that variations in the shape of the boundary between normal and seizure states and the magnitude of noise-driven resting fluctuations may account for many of the dynamical features seen in focal and generalized epilepsies (Lytton 2008).

During the progression to deep anesthesia, the EEG undergoes a sequence of reasonably well-defined quantitative changes. The majority of clinically used anesthetic agents, at increasing concentrations, progressively decrease the median EEG frequency until the onset of burst suppression – quasiperiodic alternations of high-amplitude and isoelectric EEG activity. Modeling the large-scale electrophysiological effects of anesthetic agents using a neural population formalism, based on the parametric incorporation of empirically identified cellular and molecular targets, may provide an important mesoscopic explanatory bridge linking the microscopic sites of drug action with their large-scale macroscopic effects (Foster et al. 2008). On this basis a range of neural population models have been developed to account for the effects of anesthetics on the EEG (see entry ► “Anesthesia, Neural Population Models of”) by assuming that they selectively prolong the decay phase of the unitary inhibitory postsynaptic potential (see Fig. 2).

Sleep and anesthesia share a number of important features. Both are associated with unconsciousness and reduced cerebral metabolism and, at modest anesthetic levels, share similar EEG

◀ **Neural Population Model, Fig. 3** (continued) closed resting EEG. *Bottom* – model of Liley et al. (2002) for a range of parameter sets exhibiting spectrally plausible eyes-closed EEG. (All figures reproduced with permission)

patterns such as spindles, K-complexes, and delta waves. However, there appear to be important differences, particularly in the role that subcortical neuromodulatory systems have in modulating cortical activity. Neural population models of sleep have therefore been developed in an attempt to resolve the mechanistic differences between natural sleep and anesthesia (see entry ► [“Sleep, Neural Population Models of”](#)). To date two broad approaches have emerged (Sleigh et al. 2011). In the first it is assumed that brain stem neuromodulatory control is preeminent with cortical responses “slaved” to the output of the subcortical systems. In the second approach, subcortical neuromodulatory systems are not explicitly modeled, but instead their effects are incorporated as parametric modifications of a cortical or thalamocortical level neural population model.

An emerging application of neural population models is in inferencing from neuroimaging data to functional connectivity. Important in this regard is the Bayesian-based fitting of the Jansen and Rit model to stimulus-evoked EEG, known as dynamic causal modeling (DCM) (Moran et al. 2009; see entry ► [“Dynamic Causal Modelling with Neural Population Models”](#)). In this approach a set of competing hypotheses are formulated regarding the architecture of connectivity between neural populations. Model comparison and selection depends on a Bayesian evaluation of how well a given model m explains the observed data y , i.e., $p(y|m)$ is defined as the probability of observing data y given model topology m .

Cross-References

- [Anesthesia, Neural Population Models of](#)
- [Bifurcations, Neural Population Models and](#)
- [Chaos, Neural Population Models and](#)
- [Down Under Neural Population Models](#)
- [Dynamic Causal Modelling with Neural Population Models](#)
- [Electrocorticogram \(ECoG\)](#)
- [Epilepsy, Neural Population Models of](#)
- [Gamma Rhythm, Neural Population Models of the](#)

- [Jansen-Rit Model](#)
- [Mesoscopic Anatomy and Neural Population Models](#)
- [Neural Field Model, Continuum](#)
- [Neural Mass Action](#)
- [Neuroimaging, Neural Population Models for](#)
- [Sleep, Neural Population Models of](#)
- [Synaptic Connectivity in Neural Population Models](#)

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Neural Population Models for

- [Embodied Cognition, Dynamic Field Theory of](#)

Neural Population Models of the Alpha Rhythm

- [Neural Population Model](#)

Neural Processing of Speech

- [Neural Coding of Speech Sounds](#)

Neural Prosthetics

- [Brain-Machine Interface and Neuroimaging](#)

Neural Representation of Speech Sounds

- [Neural Coding of Speech Sounds](#)

Neural Resonance

- [Rhythm Perception: Pulse and Meter](#)

Neural Simulation Tool

► [NEST: The Neural Simulation Tool](#)

Neuralgia

► [Peripheral Nerve Interface Applications, Neuropathic Pain](#)

neuroConstruct

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Definition

neuroConstruct (<http://www.neuroConstruct.org>, Gleeson et al. 2007) is a software application designed to facilitate the creation of complex networks of biophysically detailed neurons in 3D through a graphical user interface. It automatically generates scripts for a number of popular neuronal simulators, allowing the modeler to concentrate on incorporating and analyzing the anatomical and physiological aspects of the model, rather than learning a simulator specific programming language.

Detailed Description

Key Features

Generation of 3D Networks of Cells neuroConstruct was initially developed to allow generation of complex networks of anatomically detailed cells, to help understand the functioning of intricately connected microcircuits in brain regions such as the cerebellum and cerebral cortex. Prototype cells can be created for the neurons known to be present, with 3D representations of

dendrites and axons. Populations of these cells can be placed in regions in space, reflecting known cell densities and anatomical arrangements. Synaptic connectivity can then be generated based on rules for numbers of connections between pairs of cells, specific subregions of the cells to target, and the dynamical models to use for synaptic connections.

Simulator-Independent Specification of Multi-compartmental Spiking Cell Models

Cell models incorporating realistic morphologies along with known distributions of active membrane currents are important tools in helping to understand the physiological basis for cell spiking properties as well as synaptic integration in complex neurons. Multiple simulators (e.g., NEURON, GENESIS) support these types of cell models but normally have their own ways to specify the structure and biophysical properties of the cells. neuroConstruct allows users to create such cell models through the graphical interface which can then be mapped onto multiple simulator specific formats for executing the model. This is achieved through support for cross simulator standards (such as NeuroML, see below) and the ability to import various model elements, such as reconstructed neuronal morphologies (e.g., traced with Neurolucida) into neuroConstruct's internal format.

Automated Code Generation for Multiple Simulators

Neuronal simulators like NEURON, GENESIS, MOOSE, and PSICS have their own native formats for describing the structure of cells, ion channel, and synapse models, for controlling simulations and plotting/saving the generated data. Learning these simulator specific languages can be a big barrier to use of such simulators. neuroConstruct can translate its internal representation of cells and networks into scripts specific for a number of simulators, including the above named ones, as well as generating scripts for PyNN, a Python-based, cross simulator format which is currently supported by NEURON, NEST, and Brian. Note that not every type of model supported by neuroConstruct can be run across all simulators, see table below for more details.

Simulators supported by neuroConstruct

Simulator	Types of models supported
NEURON	Multicompartmental, conductance-based neurons and networks
GENESIS	Multicompartmental, conductance-based neurons and networks
MOOSE	Multicompartmental, conductance-based neurons and networks
PSICS	Single (multicompartmental, conductance-based) neuron models
PyNN	Large-scale networks of abstract/single compartment cells

Visualization and Analysis of Network Activity

When a simulation is run on one of the above platforms supported by neuroConstruct, the data generated is saved in a common format across simulators (either in simple text files or a standard binary format, HDF5). This simulation data can be loaded back into neuroConstruct along with the generated network structure. The cell spiking behavior can be visualized, and there are various options available through the graphical interface for analyzing cells and network activity, including plotting of single cell membrane potential traces, raster plots, population activity histograms, etc.

Import and Export of NeuroML neuroConstruct was created in parallel with the development of NeuroML, a simulator-independent language for describing biophysically detailed neuronal and network models (Gleeson et al. 2010). There are a number of options in neuroConstruct for importing model elements (morphologies, ion channels, synapses, or network structure) in NeuroML format, and all networks generated by neuroConstruct can be exported in NeuroML format (both the stable, widely used 1.8.1 version and the 2.0 version which is in active development, see below).

Recent Work

Python Interface Interacting with a model through a graphical interface is useful for model construction and testing, but once the model is ready to be used for addressing a research question, it is often the case that many simulations will need to be run, usually with a small modification

to the model between each simulation. For this purpose a Python scripting interface has been added to neuroConstruct, allowing full access to all features of the application (loading projects, changing any parameters, and generating networks and simulation code) from a script file. This allows neuroConstruct to be integrated into a larger toolchain using Python for model construction, refinement, validation, and analysis.

Support for Parallel Simulations NEURON has recently added support for running simulations across multiple processors, from a single machine with multiple cores up to parallel supercomputing clusters. neuroConstruct has added features to specify the target parallel computing environment and generate the appropriate NEURON scripts for execution either on the local machine or on a remote computing resource.

Interaction with NeuroML 2 The latest version of NeuroML, v2.0, is based on a new language for describing the behavior of dynamical models in a hierarchical manner (LEMS, the Low Entropy Model Specification language), allowing greater extensibility in the types of models which are supported by NeuroML. neuroConstruct supports cells and channel/synapses specified in this format. The machine readable nature of LEMS also facilitates mapping to and from other structured formats (e.g., SBML, which is widely used in the Systems Biology community) and so will help to widen the range of model types supported by neuroConstruct and the types of simulators on which the models can be executed.

Availability

neuroConstruct is written in Java, allowing it to be used across multiple operating systems. The application is freely available for download from <http://www.neuroconstruct.org/download>, and there are binary installers available for Windows, Linux, and Mac OS. The source code for neuroConstruct is also available under the GNU General Public License. It is currently being developed on GitHub at <https://github.com/NeuralEnsemble/neuroConstruct>.

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Neurodynia

- [Peripheral Nerve Interface Applications, Neuropathic Pain](#)

Neuroelectro

- [NeuroElectro Project](#)

NeuroElectro Project

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Synonyms

[Neuroelectro](#); [neuroelectro.org](#)

Definition

The NeuroElectro Project is an effort to curate data about the electrophysiological properties of neurons. It contains experimental data extracted from the literature about dozens of basic properties (such as resting membrane potential, action

potential width, etc.) for hundreds of distinct types of neurons. It can be browsed online at <http://neuroelectro.org>.

Detailed Description

Computational neuroscientists have argued that the electrophysiological properties of neurons determine their computational roles. Furthermore, models containing or concerning neurons can be constrained or validated in part using empirical data on single-cell electrophysiology. However, compared with imaging or genetic data, these data are infrequently published in a format that permits them to be easily discovered in the literature. The NeuroElectro Project (<http://neuroelectro.org>, Tripathy et al. 2014) solves this problem by providing a database on the electrophysiological diversity of mammalian neuron types.

Implementation

This database is populated primarily using automated text extraction from tables of journal articles using Python. A subset of records have been manually validated against the primary literature. Neuron types are identified using the listing of neuron types provided by NeuroLex ((Larson and Martone 2013; Hamilton et al. 2012), <http://neurolex.org>); electrophysiological property types are identified using a custom ontology which formalizes existing community standards (Ascoli et al. 2008).

Data Provenance

While NeuroElectro contains information about 27 distinct electrophysiological properties, those most heavily represented include resting membrane potential, input resistance, action potential height and width, etc. The list of journals containing the source information includes those from the Elsevier, HighWire, Wiley, and Oxford family of journals, including The Journal of Neuroscience, The Journal of Physiology, and The Journal of Neurophysiology, among others.

NeuroElectro also contains details on each study experimental condition (like species or electrode-type used), the so-called metadata, obtained using similar text extraction techniques applied to article methods sections.

Participation

The NeuroElectro web interface (<http://neuroelectro.org>) also invites users to contribute to the database content. For example, users can suggest relevant articles on a specific neuron type as well as validate content that has been extracted via the automated algorithms. Furthermore, users can elect to become “content experts” on a specific neuron type and can then modify the database content directly.

Scientific Goals

NeuroElectro also contains analyses of the resulting database, yielding novel relationships on the electrophysiological similarity of different neuron types throughout the brain. Among these are hierarchical classifications of neuron types based on similarity of electrophysiological properties. The project maintainers are also aiming to relate gene expression patterns in specific cell types to those cells’ electrophysiological properties, using expression data obtained through the Allen Brain Atlas ((Lein et al. 2007), <http://brain-map.org>).

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Neurofitter

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Definition

Neurofitter is a software tool developed to enable computational neuroscientists to tune the parameters of a neuron model. The constraints on the

model are given in the form of intracellular voltage traces recorded during stimulus protocols. The parameters are in general the maximal conductances of the ion channels in the model. Neurofitter uses global optimization methods to find the parameter values that minimize the differences in the phase-plane trajectory density plot between the target voltage traces and the voltage traces generated by the neuron model.

Detailed Description

Background

Due to improvements in experimental techniques and computational power available to neuroscientists, over the years, neuron models have become more and more complex. One manifestation of this complexity is the number of parameters used in these models. Unfortunately, it is not always possible to experimentally determine exact values for all these parameters. Especially, the maximal conductances of all the ion channels in a complex morphology tend to be unknown factors.

Traditionally, neuroscientists tried to overcome this limitation by tuning these unknown model parameters by hand. This can however be a tedious task and has the risk of introducing biases. To automate the fitting of parameters, software tools have been developed by several research groups. Neurofitter (Van Geit et al. 2007) was originally designed to help with the development of a cerebellar Purkinje cell model. The complex morphology of the dendrites of this type of cell, together with its elaborate calcium dynamics, makes it difficult to tune its parameters.

Method

When solving an optimization problem, one important aspect is the choice of the fitness function that evaluates for every parameter set how good or bad the solution is. For the problem Neurofitter tries to solve, the fitness function has to compare the similarity between two voltage traces. A naïve implementation would calculate the root-mean-square (RMS) error between the two voltage traces. Unfortunately, when neurons are repeatedly stimulated with the same protocol, their responses mostly do

not overlap exactly. Using the RMS error would punish a small time shift between traces with a very bad fitness value, which is undesirable. To overcome this problem, Neurofitter makes use of the phase-plane trajectory density method (LeMasson and Maex 2001). The data is plotted as voltage against the time derivative of the voltage and binned by a two-dimensional grid (Fig. 1).

The method then compares the number of points in every bin between the two voltage traces to calculate an error value:

$$\text{Error} = \sqrt{\sum_{i=1}^{N_x} \sum_{j=1}^{N_y} \left(\frac{\text{Target}_{ij}}{N_{\text{target}}} - \frac{\text{Model}_{ij}}{N_{\text{model}}} \right)^2}$$

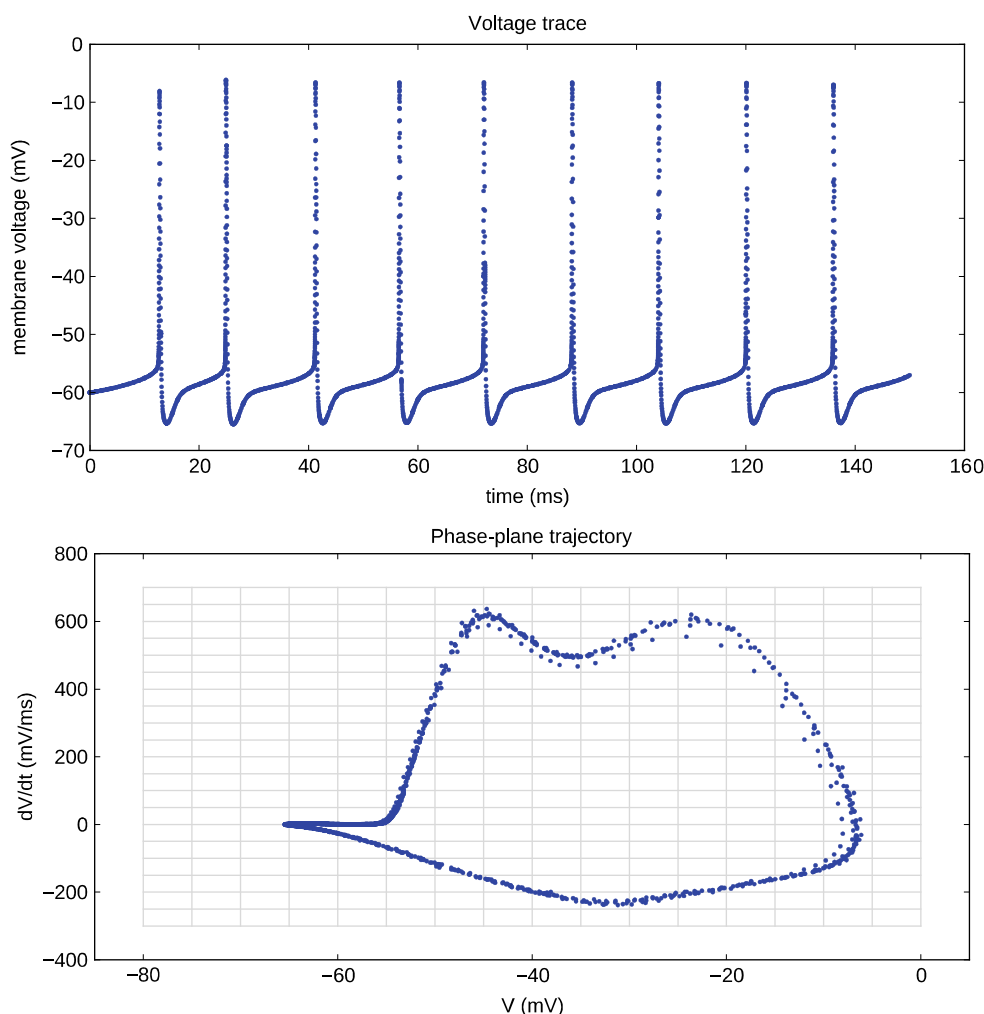
with Target_{ij} and Model_{ij} being the number of points in a bin in the V - dV/dt plot of the target and model voltage traces, respectively. N_x and N_y are the number of bins of the grid in the x and y direction. The error measures of several traces can be combined by calculating a weighted sum or, in case multi-objective optimization methods are used, the error value of every trace can be defined as a separate objective.

By comparing in this way the different traces generated by the model and the target data, Neurofitter can generate a fitness value for every parameter set that determines how good the model, using these parameter values, is able to replicate the target data. Global optimization techniques, like, e.g., evolutionary algorithms, are then used by the software to find the set of parameter values that maximizes the fitness function.

Although the nature of this error measure puts a lot of emphasis on the shape of the action potential, studies like Achard and De Schutter 2006, show that the method can create models that also match firing frequencies, resting membrane potentials, etc.

Software Implementation

The software is written in C++. It interacts with neuron simulators using a file-based protocol, which allows the user to choose between a wide range of simulators like, e.g., Neuron (Hines and Carnevale 1997) and Genesis (Bower and Beeman 1998). Since fitness evaluations in the optimization algorithms are in general



Neurofitter, Fig. 1 Voltage trace recorded from a Purkinje cell model and the corresponding phase-plane trajectory plot (grid bins in *grey*)

embarrassingly parallel, Neurofitter has the ability to farm out these evaluations on cluster computers using the Message Passing Interface (Nagle 2005). Because the code does not have many external dependencies, it should run on most Unix-like operating systems that have an MPI package and neuron simulator installed.

Some global optimization techniques like evolutionary algorithms, particle swarm optimization, random search, etc., are already built into Neurofitter, but the user can easily link to external libraries or self-implemented search algorithms.

The software is configured using an XML file. In this file, the user can specify which

optimization algorithm to use, the number of parameters, the parameter ranges, etc.

The code is available at <http://neurofitter.sourceforge.net> and <http://github.com/tclose/NeuroFitter>.

Applications

The Neurofitter method was used in several studies including a parameter analysis of a Purkinje cell model (Achard and De Schutter 2006), the fitting of a two-dimensional pattern generator model (Van Geit et al. 2007) and to find the parameters of a calcium model (Anwar et al. 2012).

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Neuroimaging, Neural Population Models for

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Synonyms

EEG, neural population models of; fMRI BOLD, neural population models of; Functional magnetic resonance imaging (fMRI), neural population models of; Multimodal neural population models; Multimodal neuroimaging, neural population models for; Voltage sensitive dye (VSD) imaging, neural population models of

Definition

Neuroimaging denotes measurements of the brain with sufficient spatial resolution to construct maps of anatomy (structural neuroimaging) and activity (functional neuroimaging), respectively. Where a functional neuroimaging modality can capture spatial snapshots at sufficient speed, its data can be used to infer spatiotemporal brain dynamics. The spatial resolution of noninvasive functional neuroimaging in humans is limited to about one millimeter and requires the coherent activity of a large number of neurons to generate a signal that exceeds the noise floor. This is an ideal match for neural population models (NPMs), which are designed to capture the mass activity of neural groupings at mesoscopic scales and above. However, in order to compare NPM predictions to neuroimaging data, one also has to include signal expression – a measurement function – that maps the NPM-generated activity onto the sensor recordings. For most popular neuroimaging modalities, including multimodal approaches, such forward modelling “pipelines” are now available and have been used to predict and analyze data.

Detailed Description

Functional neuroimaging encompasses a wide variety of methods to detect and quantify brain activity (Bandettini 2009; Friston 2002; Horwitz et al. 2000). The most popular methods today are perhaps electro- and magnetoencephalography (EEG and MEG) (Hansen et al. 2010; Michel and Murray 2012; Niedermeyer and Lopes da Silva 2005; Salmelin and Baillet 2009) and functional magnetic resonance imaging (fMRI) (Buxton 2009; Huettel et al. 2008; Logothetis 2008; Ramsey et al. 2002), respectively. A wide variety of other methods exist, for example, positron-emission tomography (PET) (Bailey et al. 2005; Valk et al. 2006), voltage-sensitive dye imaging (VSDi) (Chemla and Chavane 2010; Grinvald and Hildesheim 2004), and functional near-infrared spectroscopy (fNIRS) (Bunce

et al. 2006; Ferrari and Quaresima 2012; Villringer et al. 1993). One can make a conceptual distinction between neuroimaging and methods that directly record the activity of individual neurons, like patch clamping. However, this boundary is somewhat fluid, raising, for example, the question of whether measurements obtained with a multielectrode array (MEA) (Bakker et al. 2009; Buzsaki 2004; Taketani and Baudry 2006) belong to the category of neuroimaging or electrophysiology. Here we take the view that the “imaging” aspect indicates an ability to map out, at least in principle, spatially distributed activity. This almost invariably requires processing of the recorded raw data before an actual spatial image can be constructed for visualization, i.e., even fNIRS, which uses light, does not literally take a picture of brain activity. Inference from such data usually relies on statistical maps of signal variance, not on the signals themselves (Friston et al. 1991). It is also true that often the spatial aspect does not play a role in neuroimaging applications, e.g., research might concentrate merely on the temporal EEG patterns recorded from a single EEG electrode. However, we will consider a method to be “neuroimaging” if it easily allows and/or is commonly used for spatial activity mapping.

A further distinction can be made between invasive and noninvasive methods. We will focus here on noninvasive methods, simply because for ethical reasons these are typically the only ones available for the study of human brain activity. Invasive neuroimaging of humans primarily occurs during surgical treatment of epilepsy, where electrocorticograms (ECoG) can be recorded (Foster et al. 2012; Jerbi et al. 2009; Lee et al. 2013). The ECoG is, however, sufficiently similar to EEG to not require a separate discussion here. Furthermore, we will focus on discussing EEG/MEG and fMRI. On one hand, this reflects the preference of current studies, both experimental and theoretical. On the other hand, these methods can be considered as representative of two distinct classes of neuroimaging: EEG/MEG reflects electrophysiological activity. In contrast, fMRI is sensitive to metabolic and hemodynamic

responses to neural activity (Aquino et al. 2012; Shibasaki 2008). Other methods can be classified accordingly, for example, VSDI is an electrophysiological measurement whereas PET is a metabolic-hemodynamic one. In consequence, modelling concepts and methods developed for the leading modalities EEG/MEG and fMRI usually translate straightforwardly to other neuroimaging techniques of the same respective class. Furthermore, EEG and fMRI can be recorded concurrently (Huster et al. 2012; Laufs et al. 2008; Mulert and Lemieux 2010; Ullsperger and Debener 2010). This is particularly attractive for the currently very active field of multimodal neuroimaging (Biessmann et al. 2011; Blinowska et al. 2009; Freeman et al. 2009; Mulert et al. 2008; Stufflebeam and Rosen 2007), since simultaneous recordings avoid the problem of potentially different brain states in spite of the same external setting (e.g., executing the same task). Once more we can expect that modelling and data analysis methods now being developed for the EEG and fMRI case of (Nguyen et al. 2013) will become the basis for the integration of other neuroimaging modalities. Finally, EEG/MEG and fMRI are naturally complementary, as detailed in Table 1. This makes them attractive from both a modelling and a data analysis perspective as extreme test cases for a unified description. In the following we will hence focus on EEG/MEG

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Table 1 Comparison of EEG/MEG and fMRI

	EEG/MEG	fMRI
Spatial resolution	>1 cm	>0.5 mm
Temporal resolution	~1 ms	>1 s
Brain coverage	Gyri/sulci	All
Source to signal	Direct, electrophysiological	Indirect, metabolic-hemodynamic
Signal type	Surface measure	Volume measure
Signal generation	Unclear	Unclear
Costs	Cheap/expensive	Expensive

and fMRI, although the same principles apply to other functional neuroimaging modalities.

Spatial Resolution of Neuroimaging and Coherent Activity

NPMs do not describe the activity of individual neurons but the collective activity of many. We can connect this kind of description directly to the experimental constraints of neuroimaging if we assume that the population of neurons we describe with such models is *localized*. Thus, the individual neurons that make up the population are not spatially dispersed across the brain, as they could be, but rather are located in a circumscribed region of the brain. Furthermore, we assume that this localization is compact, i.e., ideally all individual neurons within the population's region are in fact part of it, and none outside are.

The spatial resolution of a functional neuroimaging modality indicates to what extent we can separate the signal generated by different circumscribed regions of the brain. Basically, the actual spatial geometry of the brain gets parcelled into “source regions” expressing distinct outputs: it is from these that we form an “image” of brain activity. For example, fMRI acquires data from “voxels,” cuboids parcellating the brain volume. If the NPM describes the neural sources of this signal and if we assign populations according to the spatial separation of signals in the neuroimaging modality or at even smaller scales (Breakspear and Terry 2002), then the NPM can predict the recorded neuroimage. However, in practice this simple picture becomes more complicated. For example, experimentally there is signal distortion between different fMRI voxels (Jezzard and Clare 1999; Weiskopf et al. 2006), compromising the idea of a clean separation into signal regions. Or on the theoretical side, the NPM might be based upon a continuum approximation (Coombes 2010; Liley et al. 2012), in which case the predicted signal could derive from an average over the designated source region, with the underlying field values possibly being quite inhomogeneous across this region. Nevertheless, it remains

useful to connect the spatial resolution of a neuroimaging modality to a conceptual “population size” of the NPM if one uses the NPM as model for the recorded signals. More detailed technical considerations of continuum versus discrete NPMs are provided in other entries; here, we concern ourselves primarily with their practical use in providing generative models of functional neuroimaging data.

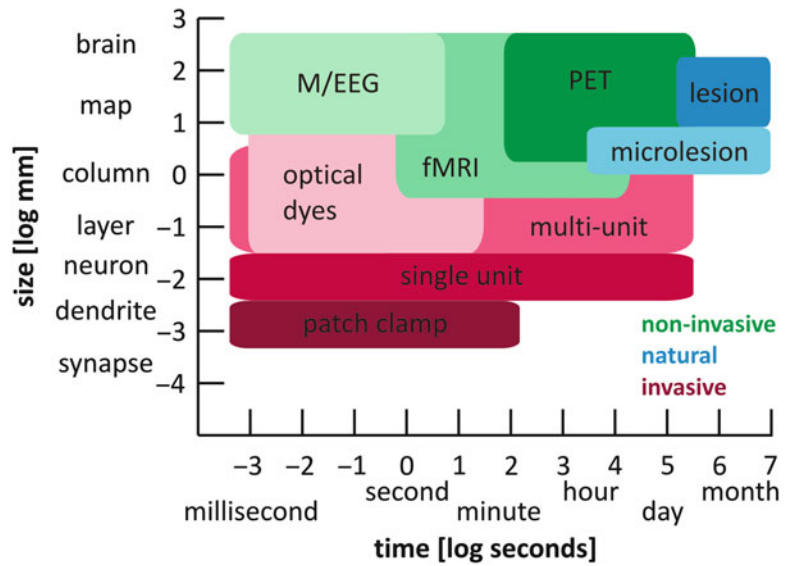
The maximum spatial resolution of current functional neuroimaging is about 0.1 mm; cf. Fig. 1. For noninvasive techniques it is about 1 mm. At the anatomical level, this scale corresponds roughly to the lateral extent of a macrocolumn (0.5–3 mm) and the vertical depth of a few layers (6 canonical layers in 2–5 mm cortical thickness). The actual number of neurons that actively contribute to each part of a maximally resolved neuroimage is difficult to determine. However, if we take the total number of neurons in the mentioned anatomical structures as a proxy, then the number of neurons participating directly (as sources) or indirectly (influencing the sources) in the signal generation will be in the hundreds of thousands for fMRI and in the order of millions for EEG. It is these large numbers that make a description in terms of NPMs, rather than individual cell models, attractive.

There is a second consideration that motivates the use of NPMs as a model for neuroimaging signals, namely, that of coherent activity. We know from theoretical studies that strongly coupled neural systems typically start to exhibit coherent activity, i.e., the neurons start to align their activity patterns and fire together (Breakspear et al. 2003). We also know that the neurons are strongly connected at the anatomical size levels discussed above. For example, the lateral extent of a macrocolumn is given by the reach of horizontal short-range connectivity (Mountcastle 1997). It is hence reasonable to expect coherent activity in the millimeter range, and this has been confirmed experimentally (Bullock et al. 1995).

We can now make a conceptual argument: assume N sources that produce an oscillatory signal $S_i = A_i \sin(\omega t + \varphi_i)$, where for simplicity all of them have the same frequency. Then the sum of all

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Fig. 1 Temporal and spatial scales of various neuroimaging modalities and other techniques for recording neural activity



these signals $S \equiv \sum_{i=1}^N S_i = A \sin(\omega t + \varphi)$, and the amplitude is given by $A^2 = \sum_{i=1}^N A_i^2 + 2 \sum_{i=1}^N \sum_{j>i}^N A_i A_j \cos(\varphi_i - \varphi_j)$. If all phases are equal, then the cosine becomes one and we have $A = \sqrt{\left(\sum_{i=1}^N A_i\right)^2}$. But if the phases are random with uniform distribution on $(0, 2\pi)$, then the expected value will be $E[A] = \sqrt{\sum_{i=1}^N A_i^2}$, since the expected value of the cosine becomes zero. The difference becomes obvious if we consider the case where all $A_i = A_0$, then for coherent activity $A = N A_0$, but for random activity $E[A] = \sqrt{N} A_0$. Thus, in essence the signal of coherent activity grows linearly with the number of sources but the signal of entirely incoherent (random) activity only with the square root of the number of sources (Nunez and Srinivasan 2006). In consequence, a thousand coherently active neurons can produce a signal that rivals the expected signal of a million incoherently active neurons.

We have seen that NPMs created for describing neuroimaging describe regions of the brain parcelled out by the modality that contains a large number of neurons and that strong anatomical connections between these lead to coherent activity in these regions that is both theoretically expected and experimentally observed. We can

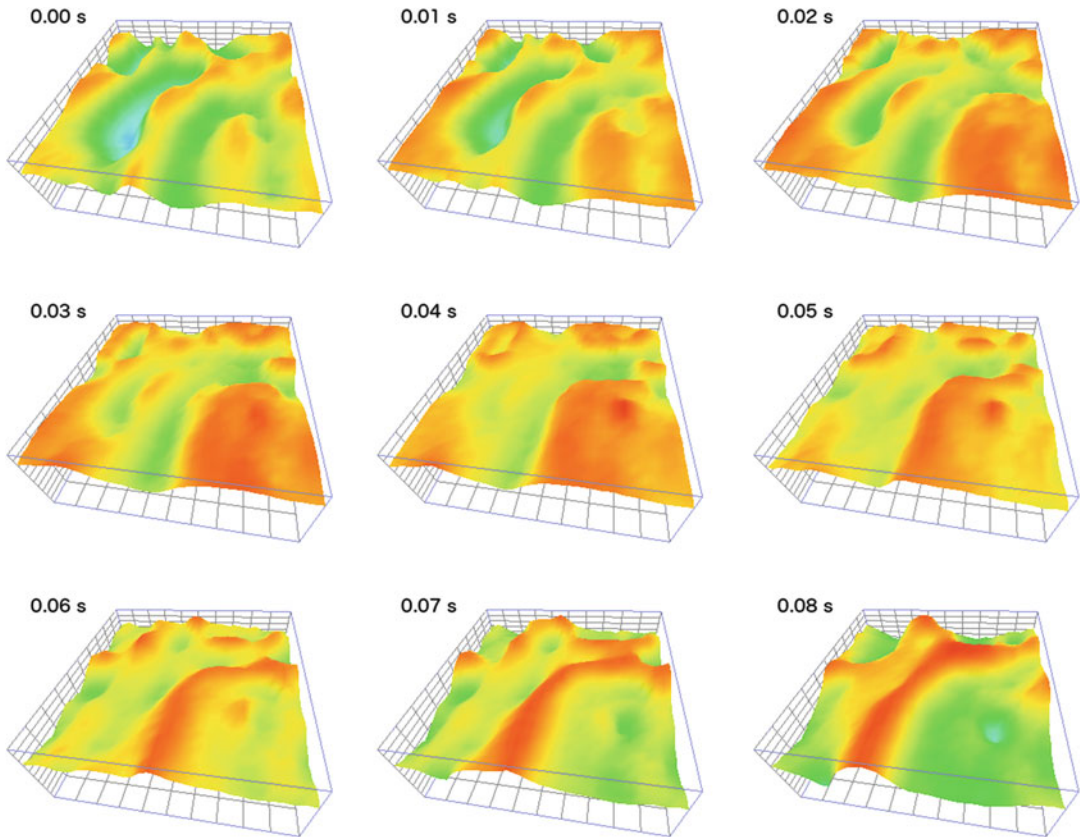
hence conclude that NPMs primarily (and as spatial resolution decreases, exclusively) model the *coherent* signal generation within the regions parcelled out by the functional imaging modality. Hence, the neural populations in such models should be understood as effectively representing not *all* neurons (of a specific type), but rather only those directly or indirectly involved in generating coherent activity. This point is not always appreciated in the literature. For example, if an NPM predicts very little activity for a population of pyramidal neurons involved in generating a neuroimaging signal, then patch-clamp measurements of individual neurons showing high firing rates do not necessarily contradict this. Rather one would have to check whether such firing is also coherent across the entire region. If it is incoherent, then it simply does not feature dominantly in the NPM. Finally, we note that the mathematical approach of deriving NPMs from individual cell models by keeping only the first few moments of a population density (Brunel and Wang 2001) neatly parallels our argument above from signal strength. Essentially the mean captures the expected signal intensity, whereas the variance captures the dispersion of those states, which also plays an important role in shaping NPMs (Marreiros et al. 2008).

Head Geometry, Brain Connectivity, and Signal Expression

There are essentially three levels of modelling the anatomical and physiological substrate of the NPMs in neuroimaging. At the most basic level, one focuses on a single neural population, or perhaps on a few that are connected, but without mapping out the location of the sources or employing a spatial representation of the brain connectivity. A typical example for this is the Jansen-Rit model (Jansen and Rit 1995). This kind of model is suitable for investigating basic intrinsic dynamics and studying gross extrinsic influences that either act to some extent indiscriminately across the brain (e.g., psychoactive drugs) or where a localized description is sufficient (e.g., a seizure confined predominantly to one region). At an intermediate level, the spatial distribution of sources and brain connectivity can be introduced in a simplified manner that represents a trade-off between tractable mathematics and biological realism. Since the cortical gray matter is sheet-like (in humans 2–5 mm radial depth but with 0.2 m² horizontal area), usually a representation as two-dimensional surface is chosen. Often this surface is realized as a square grid to accommodate numerical computation. Most authors also limit brain connectivity to the “background connectivity” (Hellwig 2000; Kaiser et al. 2009; Liley and Wright 1994; Robinson et al. 1997) of the brain, which is compatible with assumptions of homogeneity and isotropy. In this case one can simulate the spread of activity with a partial differential equation (PDE), which is convenient both for analytical and for numerical reasons (Griffith 1963, 1965; Jirsa and Haken 1996; Liley et al. 2002; Robinson et al. 1997). Finally, the signal expression is typically simplistic. Usually the measured signal is considered to be directly proportional to some model variable, perhaps including some averaging over a region to represent the spatial resolution of the neuroimaging modality (Bojak and Liley 2005).

Models making these simplifications can be used to describe certain spatial features of brain activity, e.g., various features of “brain waves” (Bojak and Liley 2007; Robinson et al. 2002;

Wu et al. 2008) or power spectra predictions taking spatial effects into account (Bojak et al. 2004; Bojak and Liley 2005; Robinson et al. 2001), as illustrated in Fig. 2. At the cost of greater numerical effort, it is also possible to describe anisotropic connectivity with the convenient PDE approach, which is, for example, important in the visual cortex (Bojak and Liley 2010; Coombes et al. 2007; Pinotsis et al. 2013; Robinson 2006). Furthermore, we have so far focused our discussion on the cortex. However, the potential importance of (reciprocal) connectivity between the cortex and the subcortical structures cannot be overstated. Models that only include the cortex de facto subsume the influence of the subcortical structures into an effective description of the cortical neural population, much as, for example, the omission of an explicit model for the glia in the cortex does not indicate a denial of their potential influence on the neural dynamics. However, for certain brain phenomena, it will doubtlessly be the case that explicit modelling of the subcortical structures is required. Some authors argue that the corticothalamic feedback is crucial even for the common alpha rhythm, while others see it as a cortical resonance merely excited by the thalamus (Freyer et al. 2011, 2012; Liley et al. 2002, 2010; Robinson et al. 2001). It is difficult to decide between such competing theoretical models if direct experimental evidence is ambiguous and the models are complex enough to fit available data. Here we need to keep Einstein’s razor in mind: “Everything should be made as simple as possible, but no simpler.” The mere existence of further anatomical and physiological detail does not mean that it has to be included. In practice it may be better to simplify the model if the task at hand does not require that detail. However, if either the data speak to this detail or the need to interpret the model meaningfully requires it, then we should include it. For example, it cannot be doubted that a proper description of Parkinsonism requires the inclusion of the basal ganglia and the thalamus (van Albada and Robinson 2009; van Albada et al. 2009). Furthermore, in principle one would always wish to find a unifying, single model that can fit and predict multiple phenomena (Breakspear et al. 2006).



Neuroimaging, Neural Population Models for, Fig. 2 Excitatory mean soma membrane potential h_e of a Liley model evaluated on a 512×512 grid representing $(51.2 \text{ cm})^2$ of flattened-out cortex; variations by about 3 mV peak to trough are shown by height and color. The EEG was assumed to be linearly proportional to h_e . Nine

consecutive system states are shown with relative timings as indicated. The calculation is described in more detail in Bojak et al. (2004). Shown here is the case with a 7 m/s conduction velocity in the process of spontaneously developing an α -rhythm of 10.7 Hz with a radial wavelength of 17.1 cm

N

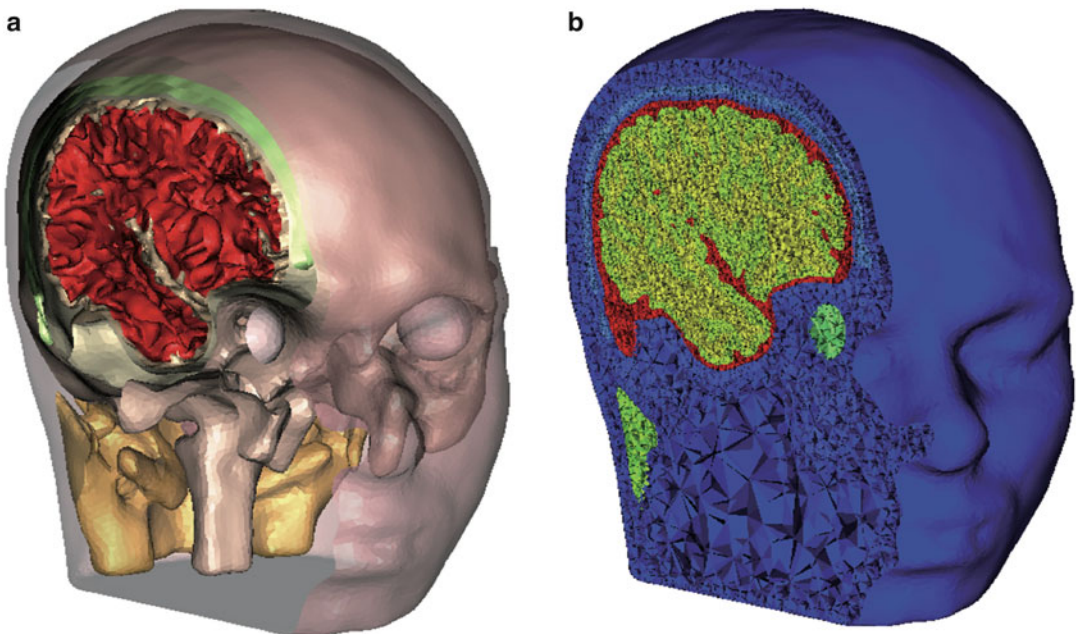
A third level of modelling employs anatomically and physiologically accurate representations of the cortex, potentially of the subcortical structures, and of the surrounding head structure as needed for realistic signal expression (Bojak et al. 2011; Jirsa et al. 2002; Riera et al. 2005, 2013; Sotero et al. 2007). The first step here is to obtain structural MRI data, which can be used to distinguish different tissue types. If one is interested purely in metabolic-hemodynamic signals like fMRI, then it is sufficient to model the system parcellated into these voxels, e.g., by assigning neural populations to gray matter voxels. However, as we will discuss modelling of electrophysiological signals like EEG/MEG relies on spatially oriented dipole sources. Their

orientation is essentially perpendicular to the pial surface, hence one must add to the voxels an estimate of surface normals. Furthermore, electromagnetic signals suffer from volume conduction effects as the signal passes through tissues with different conductivities. For magnetic signals (e.g., MEG), the resulting distortions and spreading of the signal can be approximated well with a simple spherical model (Huang et al. 1999). However, for electrical signals the structure and conductivity of the head volume play a significant role. Hence, to realistically express electrophysiological signals, one must further process the structural MRI data suitably for orienting the sources and computing volume conduction. Volume conduction can be calculated in the

quasi-static approximation of Maxwell's equations (Sarvas 1987). The so-called boundary element method (BEM) assumes compartments wherein the conductivity is constant and isotropic (de Munck 1992; Oostendorp and van Oosterom 1989; Oostendorp et al. 2000) and requires the discretization of their surfaces, typically as a triangular mesh. The so-called finite element method (FEM) does not require such assumptions (Drechsler et al. 2009; Wagner et al. 2014; Yan et al. 1991), but requires the discretization of the entire volume, typically as a tetrahedral or hexahedral mesh. Figure 3 gives an impression of such mesh discretizations. While these methods are technically complex, their final result is usually delivered in a simple transfer matrix form: $\vec{\varphi}(t) = \mathbf{T} \cdot \vec{d}(t)$, where $\vec{d}$ is an N -dimensional vector of N sources, for example, N -oriented dipoles derived from NPM activity in a source region; $\vec{\varphi}$ is an M -dimensional vector of M recorded signals, for example, the potentials measured by M scalp electrodes; and $\mathbf{T}$ is an $M \times N$ -dimensional transfer matrix for the volume

conduction. Note that $\mathbf{T}$ is considered to be time-independent at least for the duration of the recording, i.e., structural changes that significantly impact signal expression typically require more time than is being recorded.

A growing number of open-source and commercial software tools exist for automatic MRI tissue segmentation, including FreeSurfer (Dale et al. 1999; Fischl et al. 1999), BrainSuite (Shattuck and Leahy 2002), BrainVISA (Rivière et al. 2003), FSL (Smith et al. 2004), SPM8 "New Segmentation" (Ashburner and Friston 2005; Weiskopf et al. 2011), CIVET (Kim et al. 2005), ITK-SNAP (Yushkevich et al. 2006), NFT (Acar and Makeig 2010), Atropos (Avants et al. 2011), FieldTrip (Oostenveld et al. 2011), ASA Pro (ANT Neuro BV, Enschede, Netherlands), CURRY Scan 7 (Compumedics NeuroScan, Charlotte, NC, USA), and BESA MRI 2.0/Research 6.0 (BESA GmbH, Gräfelfing, Germany). Mesh generation is included as well in some of the packages already mentioned, but can likewise be achieved with a variety of free and



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Fig. 3 Mesh discretization of the head obtained from structural MRI. (a) Triangular surface meshes as appropriate for BEM. (b) Tetrahedral volume meshes as

appropriate for FEM. (Picture courtesy of Tom F. Oostendorp and Arno Janssen, Radboud University Nijmegen, the Netherlands)

proprietary software tools including DellIso (Dey and Levine 2008), Gmsh (Geuzaine and Remacle 2009), iso2mesh (Fang and Boas 2009), SimBio-Vgrid (Berti 2004), Abaqus/CAE (Dassault Systèmes, Vélizy-Villacoublay, France), COMSOL Multiphysics (COMSOL Ltd., Cambridge, UK), GiD (CIMNE, Barcelona, Spain), and ScanIP (Simpleware Ltd., Exeter, UK). One also needs electromagnetic forward solvers, which again are included in several of the initially mentioned packages. In addition we mention tools like Brainstorm (Tadel et al. 2011), MNE (Gramfort et al. 2014), OpenMEEG (Gramfort et al. 2010, 2011), and SimBio-NeuroFEM (Wolters et al. 2002). There also exists a complete open-source software pipeline for all these steps provided by ImageVis3D, Seg3D, BioMesh3D, and SCIRun (MacLeod et al. 2009).

In terms of connecting an NPM description to an obtained cortical surface, two basic numerical approaches are possible: on one hand, one can use simpler geometries for computation, e.g., representing each brain hemisphere by a sphere, and then deform these to obtain a prediction for the actual cortical surface (Jirsa et al. 2002). The simpler geometry will be covered with a regular mesh, and vertices there represent surrounding regular areas, which are then mapped to the convoluted cortical surface. However, this deformation will be nonconformal, thus changing relative distances between vertices on the cortical surface as compared to the simple geometry. Effectively, this leads to uncontrolled changes of the conduction velocity between vertices. On the other hand, one can directly use the extracted cortical surface and consider the mesh vertices as representing the surrounding neural tissue (Bojak et al. 2010, 2011). This does not distort the conduction velocity but is more complicated numerically since the vertices are not placed in a regular manner. The latter approach also can be used to connect gray matter voxels, if one does not extract a cortical surface first (Sotero and Trujillo-Barreto 2008).

Given any such spatial discretization of the cortex (or of the brain more generally), one can assign one NPM per vertex to represent the local dynamics. The total brain dynamics are then determined by potentially thousands of NPMs at

the vertices, which are, however, typically coupled. Since the NPM at one specific vertex represents the dynamics of the surrounding neural tissue, the NPM should describe any brain connectivity contained in this tissue. For a typical discretization with tightly spaced vertices, perhaps a few millimeters apart, this would mean inhibitory and “intrinsic” (superficial layer) excitatory connectivity within the gray matter. Conduction delays at this range are typically neglected in the NPM, although temporal filtering in the synaptic compartment can introduce an effective time delay. One can also introduce explicit couplings between the NPMs at different vertices. These would be representative of mid- to long-range connections through the white matter and, hence, should be exclusively excitatory. Figure 4a demonstrates the principle. Here the different colors of the vertices are supposed to indicate parts of the same cortical mesh with large spatial separation, i.e., different brain regions. Clearly the entire connectome of the brain can now be specified through four numbers per connection (blue arrows): number of the source vertex (colored red), number of the target vertex (colored green), delay until a signal arrives (thus fiber length is divided by conduction velocity), and coupling weight (some measure of the strength of synaptic impact at target). In addition, however, one likely has to distinguish different types of connections, e.g., there might be two identical fiber specifications but one attached to the inhibitory and one to the excitatory subgroup of the target NPM.

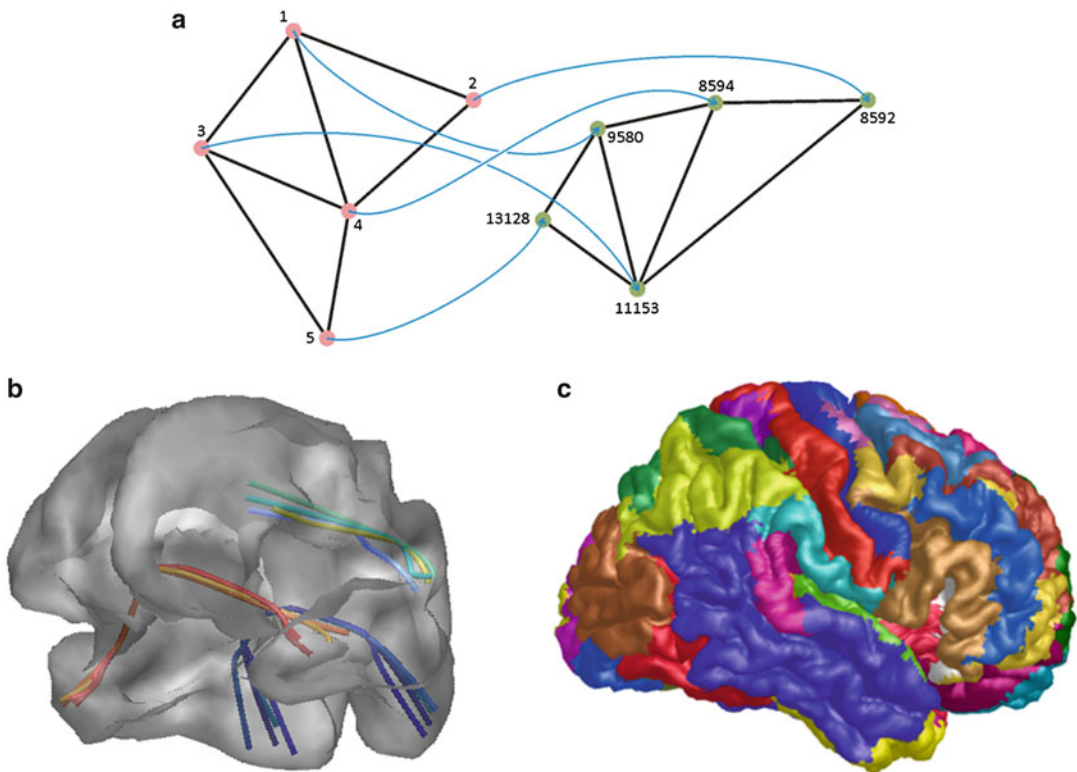
The late Rolf Kötter pioneered the usage of tracer-derived connectivity data from macaque monkey contained in the CoCoMac database (Bakker et al. 2012; Blumenfeld et al. 2013; Stephan et al. 2001) for these kinds of simulations (Deco et al. 2011; Honey et al. 2007). The necessary cross-species mapping was first performed coordinate-free with the so-called Regional Map (Kötter and Wanke 2005) but has been associated with a specific parcellation of the cortex (Bezdin et al. 2012); cf. Fig. 4c. The main rationale was that tractography based on diffusion MRI in humans (Johansen-Berg and Rushworth 2009), while in most ways equal or even superior to the

tracer studies in animals, can only show the existence of a connection between two brain regions but not in which direction the signal will flow. In spite of the uncertainties of cross-species mapping, which includes some insuperable mismatches (e.g., concerning the brain regions for speech), the resulting differences in causal influences basically mandate going beyond just diffusion MRI for modelling purposes. Rough estimates of fiber tracts and, hence, their length can be obtained from a white matter surface by estimating the minimal path through the volume as shown in Fig. 4b (Bojak et al. 2011). As noted above, connectivity modelling requires simply the delay of signal conduction between two spatial points. Given the considerable uncertainties that remain concerning the actual conduction velocity of specific fibers in the brain (Liley et al. 2010), such a rough estimate of fiber length may well be

sufficient in a practical sense. Finally, it should be noted that any brain region like the ones in Fig. 4c will typically comprise many vertices, but connectivity matrices are typically given only at the brain region level. Hence, modellers need to specify by what scheme they actually match the vertices in one region to those in the other region, given that they only have the overall information for connectivity between regions. The issue of calibrating all the various assumptions that flow into connectivity models remains in our opinion unresolved (Bojak et al. 2011).

Electrophysiological Signals: EEG, MEG, and VSDi

The genesis of EEG and MEG is comparatively well understood. We will first discuss the EEG



Neuroimaging, Neural Population Models for,
Fig. 4 (a) Illustration of the coupling between different mesh vertices representing different brain regions. (b) Examples of minimal path estimates of long-range fiber

lengths. (Bojak et al. 2011). (c) An example of parcellating the cortex into different brain regions with the Regional Map. (Bezgin et al. 2012; Kötter and Wanke 2005)

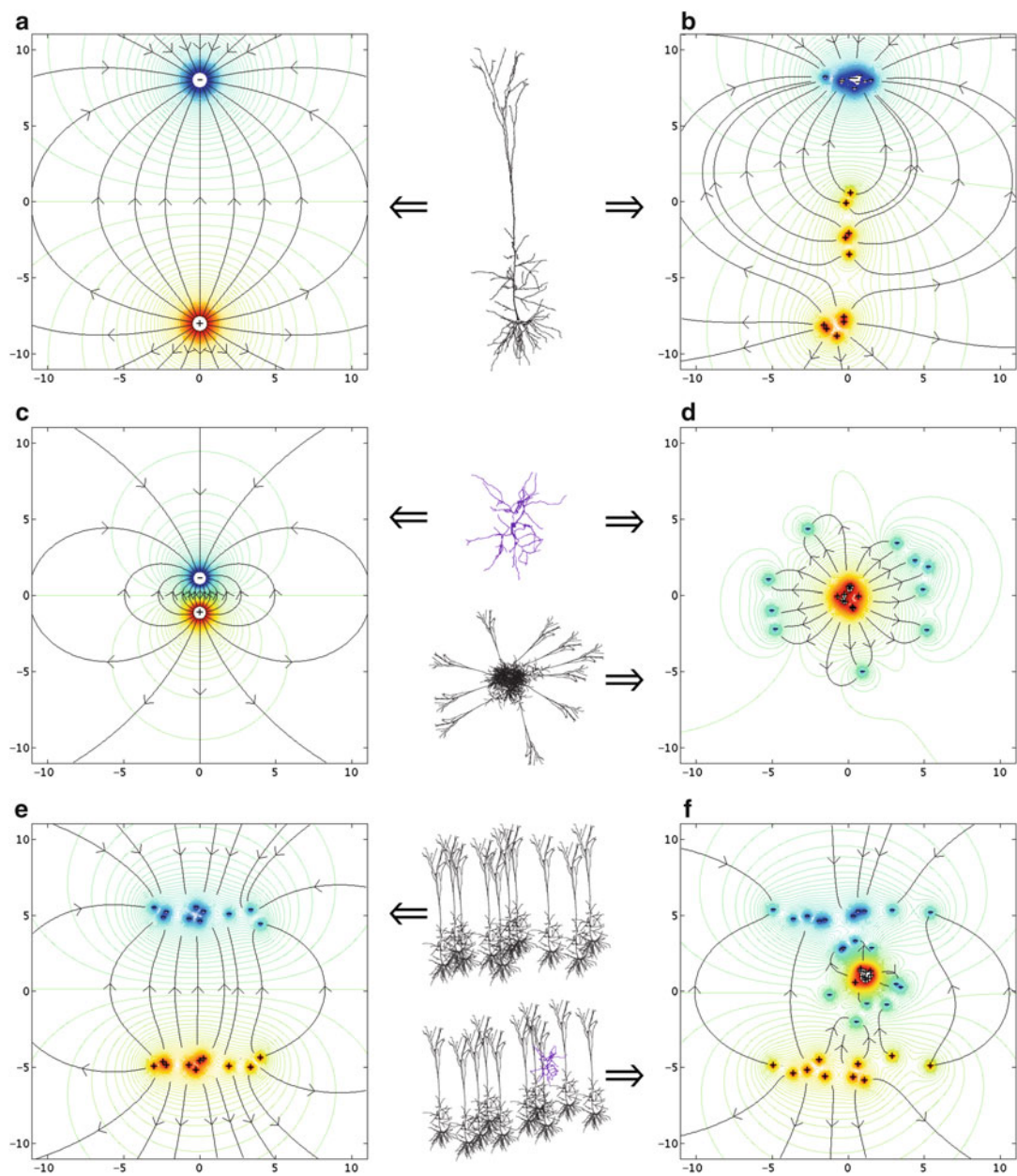
and then comment briefly on the differences between EEG and MEG. Furthermore, in the following we mean by EEG recordings with electrodes placed on the scalp, as opposed to similar recordings with subdural electrodes resting on the surface of the cortex (ECoG) or by microelectrodes inside the brain (local field potentials, LFPs). A key observation is that while the most prominent activity of neurons is the production of action potentials, short “spikes” of activity traveling along their axons, such spikes do not make an appreciable contribution to the EEG (or indeed the ECoG). Instead the EEG shows “waves” of activity with the vast bulk of EEG activity occurring at frequencies below about 100 Hz. Originally it was thought that EEG/ECoG waves arise as temporal envelope of spiking activity (Adrian and Matthews 1934). This hypothesis can be tested with differential recordings using two microelectrodes, which localize the source of the activity to the space between the microelectrodes. LFPs indeed show both spike and wave contributions. However, the wave signals remain present up to cellular distances of 30 μm (Elul 1962, 1971), indicating that the wave contribution stems directly from neurons.

In the meantime it has become clear that the wave contribution to LFPs, and thus the EEG, arises from synaptic activity (Buzsaki et al. 2012; Nunez and Srinivasan 2006). For example, an excitatory synaptic input in the apical dendrites leads to a local influx from the extracellular space of cations, a localized “sink.” This has to be compensated by a “return current,” a flow back from the intracellular to the extracellular space to restore electroneutrality. This return current leaks out across the membrane as the synaptic current is conducted to the soma, establishing distributed “sources” at a distance to the sink. For a pyramidal neuron, most of the membrane area allowing the leakage is found in the distal branching of the apical dendrites and in the soma and basal dendrites, respectively. Consequently, a significant part of these sources typically would be located around the soma, at considerable distance to the sink. A source and a sink separated by a distance establish a current dipole, and so to a reasonable approximation, the synaptic input creates a dipole

potential. Indeed, more generally, one can make a multipole expansion of any charge configuration, where the contribution of higher terms falls off much faster with distance. Given effective electro-neutrality, there will be no monopole (sink without source or vice versa) contribution. But other than for very special charge arrangements, unlikely in realistic physiological scenarios, there will be dipole contributions arising similarly to the example just given. At some distance from the neuron, these dipoles will dominate over higher multipole contributions. Thus, while the impact of synaptic inputs is quite complicated (Linden et al. 2010), they essentially establish a current dipole in the neuron (Nunez and Srinivasan 2006).

In Fig. 5 we demonstrate two key facts: First, roughly spherical interneurons, and in general any neural source-sink configuration that is mostly “closed,” will not appreciably influence the EEG directly. It is true that a single input will always create a dipole, which, while weaker at a distance due to small size, could theoretically contribute; see Fig. 5c. However, the number of synapses on a neuron in the human brain is on average about 30,000 (DeFelipe et al. 2002), and with awake spontaneous firing rates of 0.5–5 spikes/s (Barth and Poulet 2012), neurons are bombarded by tens of thousands of synaptic inputs per second (Shu et al. 2003). Thus, *in vivo* Fig. 5d is more realistic. Second, aligned batches of pyramidal neurons, and in general any neural source-sink configuration that is mostly “open,” extend the dipole spatially so that one can talk of a “dipole layer” that will basically determine the EEG directly; see Fig. 5e. This is not fundamentally changed by the addition of “closed” configurations like interneurons; see Fig. 5e.

We have discussed how coherent activity strongly dominates the EEG signal. We now see that such activity at a synaptic level is precisely what is needed to create dipole layers like those shown in Fig. 5e and f, since it will make the sources and sinks appear in a coordinated fashion, whereas incoherent activity would cause the sources and sinks to appear at different times, preventing the dipole field from becoming spatially extended. The only remaining question is

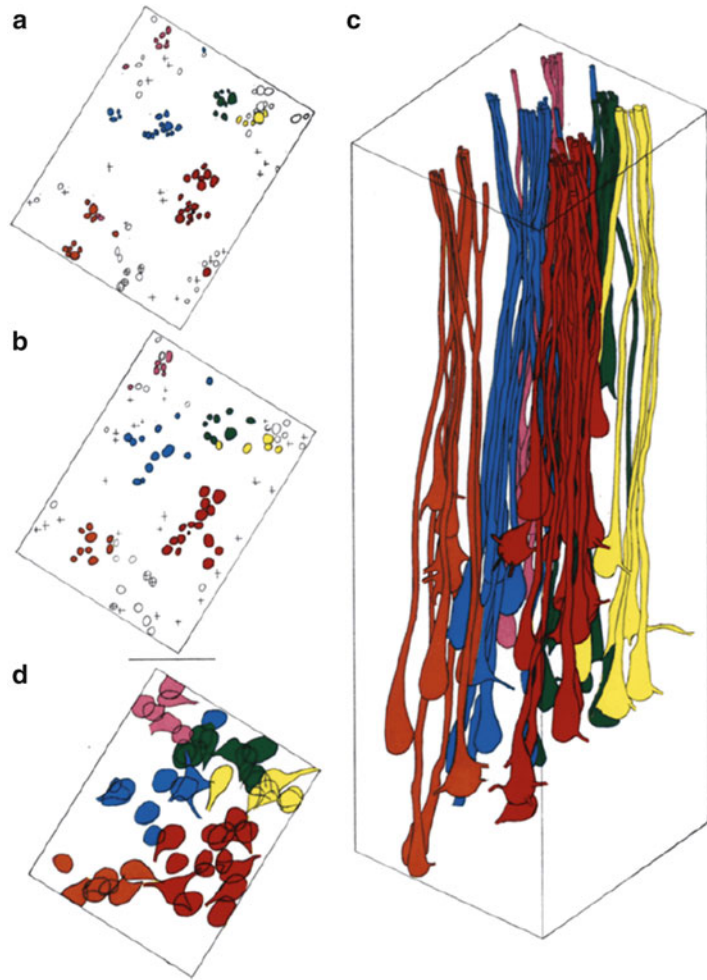


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Fig. 5 (a) Large dipole representing a layer V pyramidal cell with one excitatory synaptic input to the apical dendrites (sink: “-” label, blue color) and return current from the soma (source: “+” label, red). Equipotential lines are shown in green, representative field lines in black. An ECoG electrode can be imagined at the top of the figure and would record the variations of the potential indicated by the (cut) equipotential lines if moved left to right. (b) As

in (a), but with multiple excitatory inputs to the apical dendrites and sources more realistically resembling the pyramidal cell morphology including basal dendrites. Note that the basic dipole field remains. (c) Small dipole representing an interneuron with one excitatory synaptic input to the roughly spherical dendrites. Note the weakness and lack of variation of the potential at the top of the figure. (d) As in (c), but with multiple excitatory inputs to the roughly spherical dendrites. The size of the charge

Neuroimaging, Neural Population Models for,

Fig. 6 Reconstruction of dendritic bundles of pyramidal cells in layer V. (This is Fig. 2 of Massing and Fleischhauer (1973), reproduced with permission)



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whether one finds in the real brain an arrangement of pyramidal neurons like the one shown in Fig. 5e and f. Perhaps unsurprisingly – given the ease with which EEG can be recorded – there are several structures like this in the brain. In particular, the cortical layer V neurons have very long dendritic arborizations, which basically align perpendicular to the pia (see Fig. 6). Coherent synaptic activity in layer V neurons is hence a strong

candidate for the bulk of the EEG signal. As discussed above, such activity would lead to the formation of dipole layers with mesoscopic extent, oriented perpendicular to the pia. These are then precisely the dipoles whose volume conduction we discussed above.

In current practice, the complexities of the synaptic activation are generally ignored in source modelling of the EEG. Instead, the excitatory

Neuroimaging, Neural Population Models for, Fig. 5

(continued) configuration has been enlarged to avoid visual crowding. This “closed” configuration could also represent a clump of pyramidal neurons. The field is largely contained. (e) An “open” configuration that could represent a number of aligned pyramidal cells with inputs

as in (a). We see the beginning of a spatially extended dipole layer. (f) As in (e), but adding an interneuron with multiple inputs as in (d). We see that the smaller and closed charge configuration does not significantly disturb the dipole layer

mean soma membrane potential is used as a proxy (Jansen and Rit 1995; Liley et al. 2002; Robinson et al. 1997). This quantity is computed from some form of sum of excitatory postsynaptic potentials (EPSPs) and inhibitory ones (IPSPs), where the latter contributes negatively, since they hyperpolarize the membrane. The concrete model can range from a simple “instantaneous” subtraction of EPSPs and IPSPs (Jansen and Rit 1995) to voltage-dependent weights representing Nernst potentials and additional membrane dynamics with a proper time constant (Liley et al. 2002). One can argue that for “dipole-friendly” neural sources, say the layer V neurons, and for a surface measurement of the LFP, say with an ECoG electrode, the following holds (Speckmann and Elger 2005): The LFP will be roughly proportional to the membrane potential, however, with different signs according to the type of input – excitatory synaptic input to the apical dendrites and inhibitory input to the soma/basal dendrites contribute *negatively* – whereas excitatory synaptic input to the soma/basal dendrites and inhibitory input to the apical dendrites contribute *positively*. Thus, the simplifying assumption commonly made in NPMs amounts to claiming that one of these signs dominates so that the effect of excitation and inhibition does not become confused in the summation. Typically one would assume here that the negative sign dominates, i.e., most excitation arrives in the apical dendrites and most inhibition in the soma or basal dendrites (Miller et al. 2010). However, there is clearly a scope here for improving biological fidelity in the future.

Having dealt with the EEG, we can discuss MEG quickly. If we consider the electric field lines in Fig. 5, they show us essentially the induced current flow. However, note that we have plotted the extracellular field. The intracellular, primary current in the simplest case, Fig. 5a, flows against the extracellular electric field line, i.e., cations travel from the sink in the apical dendrites straight down to the soma, whereas the extracellular, secondary (or return) current then flows from the source to the sink as shown by the extracellular electric field lines. Of course, the actual path of these currents would be modified by the morphology of the neuron and the

composition of extracellular space, respectively. Current flow induces magnetic fields, which circle the currents. In our Fig. 5, the magnetic field lines are located in the plane perpendicular to the page. The weak magnetic fields of a mesoscopic (dipole) source can be measured with highly sensitive SQUID magnetometers. This is the basis of the MEG signal, and it makes clear that the EEG and the MEG are essentially two different ways of observing the same physical process.

However, there are in practice some differences (Baillet et al. 2001). In particular, looking at Fig. 5a again, we see that there are potential differences both along the top and bottom of the panel, as well as along the sides. This means that theoretically, at least the EEG measuring the potential against a reference can pick up contributions that are either tangential (parallel to the skull, idealized as a sphere) or radial (perpendicular to the skull, idealized as a sphere). In practice, however, EEG sensitivity reduces quickly with distance from the electrode, and we have argued that the actual neural sources are perpendicular to the pia. Consequently the EEG primarily captures radial sources from the gyri, where the pia runs close to and parallel to the skull. However, there will be some contributions from where the pia folds away from the skull down into a sulcus, creating dipoles tangential to the skull but not too distant from the electrode. In contrast the MEG essentially detects only tangential dipoles (and since again the signal reduces quickly with depth, mostly the same tangential dipoles high up in the sulci that “interfere” with the EEG measurement). The reason is that the coil surfaces of the SQUID magnetometers in an MEG are usually arranged flush with the surface of a partial sphere placed around the head for recording. They can then only record radial magnetic fields. If a current dipole is radial (e.g., if we imagine in Fig. 5a that the pia is on the top), then its magnetic field is tangential and will not be seen in the MEG. That the EEG signal derives from radial sources “contaminated” by tangential ones, whereas the MEG only from tangential ones, explains in part why the MEG can achieve higher spatial localization than the EEG. In addition, the smearing of the EEG signal by volume

conduction is largely absent for MEG. However, MEG technology is orders of magnitude more expensive; hence, EEG continues to be more commonly used. As far as modelling is concerned, both signals are ultimately proportional to the same current dipole strength. However, recent efforts to reconstruct the functional connectivity of cortical oscillations have focused on MEG (Brookes et al. 2012; Hipp et al. 2012).

Voltage-sensitive dye (VSD) imaging (Chemla and Chavane 2010; Grinvald and Hildesheim 2004) is yet another method to basically measure the same underlying signal, if applied to sizable parts of the cortex. The basic principle here is that certain dyes bind to the cell membrane and change their absorbance, fluorescence, or birefringence in proportion to changes of the membrane potential. The other factor that determines the amount of light one can record is then simply the area of the membrane successfully stained with the dye. Since these dyes can be applied to the cortical surface and since by far the largest fraction of (unmyelinated) membrane available belongs to the dendritic arborizations, once again the synaptic input drives the signal. However, it is less clear which neural groups will contribute most to the VSD signal, making comparisons to EEG/MEG problematic. It should be noted though that while VSDs typically stain only superficial layers I–III, layer V pyramidal cells which we have identified as likely dominating EEG/MEG also have extensive dendritic trees in these layers. The optical resolution obtained from VSD light emissions is maximally about 0.5 μm , though the pixel size for large-scale recordings we are concerned with here is more in the 50 μm range, and the temporal resolution is in milliseconds or less, making this as superior modality where it can be applied (Roland et al. 2006). However, this is an invasive method *in vivo*, since one has to penetrate the skull to apply the dye and then observe the light, if one is not applying the VSD *in vitro* to a cortical slice or to cultured neurons anyhow. Some VSDs are also phototoxic and have lasting pharmacological effects. This basically excludes recordings from humans on ethical grounds. Finally, for large-scale recordings, a “macroscope” (a microscope with large numerical aperture at low magnification)

is required with windows in the millimeter to centimeter range.

Modelling VSDi with NPMs is still in its infancy. One can view the extensions of the “laterally interconnected synergetically self-organizing map (LISSOM)” model in (Sit and Miikkulainen 2007) as the construction of crude NPM. A neural field model containing three layers and six populations (Haeusler and Maass 2007) has been used to simulate the line-motions illusion in mammalian visual cortex and the spread of activity in rat barrel cortex upon whisker stimulation (Grimbert and Chavane 2007; Grimberty 2008). Wilson and Cowan (1972, 1973) and Amari (1977) type of neural fields have been used to model the VSD response of the visual cortex as well (Markounikau et al. 2010; Meyer 2007). Finally, the Jansen and Rit (1995) neural mass has been used in a description of VSD data concerning the connection between spontaneous and evoked activity in the visual cortex (Nguyen Trong et al. 2012).

Metabolic-Hemodynamic Signals: fMRI BOLD

EEG and MEG have excellent temporal resolution but modest to poor spatial resolution. At best one can localize activity with centimeter accuracy with these modalities. Furthermore, these electrophysiological signals are largely surface measures and are prone to error and bias for reconstructing subcortical brain activity. It should be mentioned though that the MEG at least can probably discriminate activity from the hippocampus, amygdala, and thalamus (Attal and Schwartz 2013). However, fMRI based on blood-oxygen-level-dependent (BOLD) contrast (Buxton 2009; Huettel et al. 2008; Logothetis 2008; Ramsey et al. 2002) can resolve activity essentially within the entire brain volume with millimeter accuracy. In combination with structural MRI providing a direct match to the underlying anatomical geometry, this has led to fMRI BOLD becoming immensely popular in cognitive neuroscience. While much initial research was directed toward functional specialization (“localizing

brain function”), more recently integration and connectivity have become the focus (Friston 2002; Mather et al. 2013; Poldrack 2012). Several methodological developments are of particular interest to NPMs: pattern-information fMRI (Formisano and Kriegeskorte 2012), which approaches the idea of neural population activity from the image analysis side; connectivity analysis based on fMRI (Biswal et al. 1995; McIntosh et al. 1996; Smith 2012), which parallels the efforts to integrate realistic brain connectivity mentioned above; and causal modelling of fMRI (Breakspear et al. 2010; Friston et al. 2003; Stephan et al. 2008; Stephan and Roebroeck 2012), which points the way forward for determining NPM state and parameters from data.

The basis of the fMRI BOLD signal remains incompletely understood. The “physical” aspect of the signal expression, which concerns exploiting differences in the magnetic susceptibility of oxyhemoglobin and deoxyhemoglobin, will not concern us here. The corresponding technology and signal analysis have been worked out sufficiently to leave the underlying physiology as the main challenge (Norris 2006). The key problems are the so-called neurovascular coupling, i.e., how neural activity influences the brain vasculature, as well as the ensuing hemodynamics, which ultimately creates the differences in deoxyhemoglobin concentration in tissue that the MRI records. We start with the hemodynamics and then come back to the question of neurovascular coupling later.

While the actual hemodynamics in the brain is highly complex (Handwerker et al. 2012), practically all studies using NPMs have opted for some variant of the simple “Ballon” (Buxton 2012) or “Balloon-Windkessel” description (Friston et al. 2000, 2003). The reason is primarily simplicity: to the NPM written in terms of ordinary or partial differential equations (ODEs or PDEs), this hemodynamic model adds only four further ODEs plus one observation equation. We provide here a version of the Balloon-Windkessel model for convenience.

The starred variables indicate the fixed point solutions of the ODE system for arbitrary neural

activity u^* . If one identifies this with the average resting state of the brain, compared to which either evoked activity or spontaneous activity fluctuations establish a BOLD contrast, then one needs to demand $y^* = 0$. It follows that $v^* = 1$ and $q^* = 1$; thus, $f^* = 1$ and finally $u^* = 0$. In other words, with this interpretation the neural activity u indicates the *deviation* from the resting state, not the absolute activity. The coupling parameter ε translates this activity into a vasodilatory impulse. In practice this parameter has to be adjusted to deliver an appropriate hemodynamic response given some model of neural activity u . As a rough guide one can use the following upper limit: if u is a sine wave with amplitude A , then setting $\varepsilon = \omega_0^2 \zeta / A$ will limit the change to the normalized flow f to less than 71%. We note that our form of Eq. 1 makes more transparent than the equivalent original one in Friston et al. (2000) that the vasodilatory signal is here modelled as a damped harmonic oscillator forced by the neural activity. The oscillator is significantly underdamped ($\zeta < 1/\sqrt{2}$) and has a resonant frequency $\omega_0 \sqrt{1 - \zeta^2} / (2\pi) = 0.088 \text{ Hz}$. This makes obvious that this hemodynamic response and hence ultimately the BOLD contrast will low-pass filter the neural activity, highlighting in particular changes at “glacial” frequencies of about 0.1 Hz.

The remaining question of the neurovascular coupling can now be stated like this: which function of one or more variables of the NPM should be used as a model of neural activity u ? There is unfortunately currently no clear answer to this question. To a considerable degree this is so because the experimental determination of the underlying physiological processes is far from finished (Hyder and Rothman 2012; Iadecola 2004; Lauritzen et al. 2012). Riera and co-workers assume that the excitatory and inhibitory synaptic activities contribute (roughly) equally by determining the concentration of nitrous oxide (Riera et al. 2005, 2006, 2007). Sotero and Trujillo-Barreto (2007, 2008) relate excitatory and inhibitory synaptic activity to total oxygen consumption as well as directly driving cerebral blood flow with excitation. Bojak

et al. (2010, 2011) only consider excitatory synaptic activity as driving glutamate uptake of astrocytes. More variety can be found in the current literature, but given the rather severe impact of the subsequent hemodynamics, it is possible that a lot of the details of the neurovascular coupling are not reflected in the final BOLD contrast. Here more work is needed to establish the right level of modelling for concrete applications. However, it is clear that the modelling of fMRI BOLD is possible with NPMs, both in temporal and spatial aspects; cf. Fig. 7.

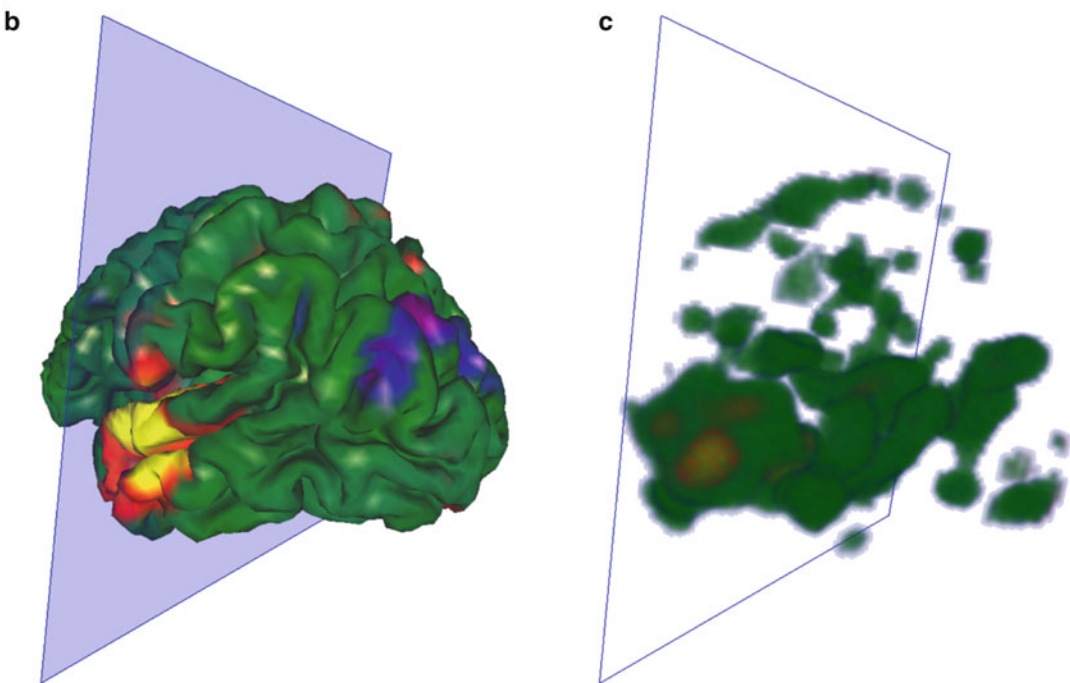
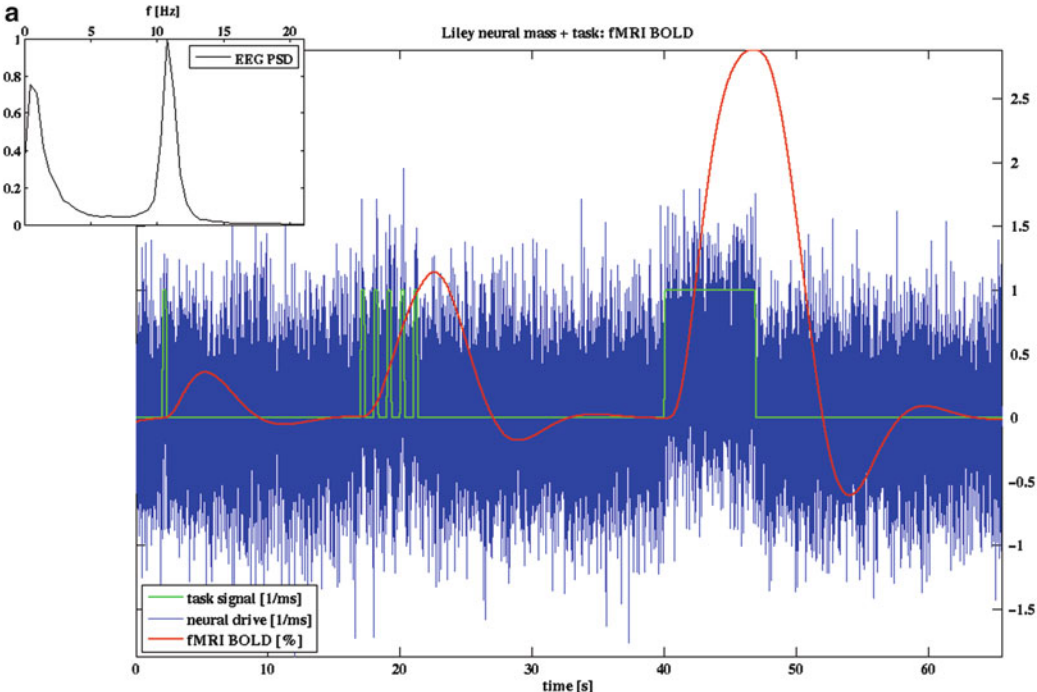
The Balloon-Windkessel model is classically a “single-compartment model,” which ignores spatial embedding of the vascular anatomy and fails to ensure adherence to the basic laws of conservation (mass, momentum, charge, etc.). Recent work, marrying high-resolution fMRI acquisition with the treatment of the ensuing nonlinear mathematics, has addressed these limitations (Aquino et al. 2012, 2014); cf. Fig. 8. After deriving a closed set of PDEs from physiological principles, this work predicts that at sufficiently high spatial resolution, the hemodynamic signal in response to a spatially discrete visual stimulus unfolds as a travelling wave across the cortical surface for up to 5 mm. High-resolution fMRI of the visual cortex confirmed this prediction, yielding physiologically plausible parameter estimates for the PDEs (Fig. 9). While research into the spatial extent of the BOLD signal is in its early days, it is arguably an important development. In principle it should allow the disambiguation of the neuronal and hemodynamic contributions to the spatial properties of the BOLD signal. This is of particular relevance when inverting continuum NPMs or models that are defined on a highly resolved spatial mesh.

Multimodal Neuroimaging

The field of multimodal neuroimaging (Biessmann et al. 2011; Blinowska et al. 2009; Freeman et al. 2009; Mulert et al. 2008; Stufflebeam and Rosen 2007) is thus far dominated by statistical approaches. While the

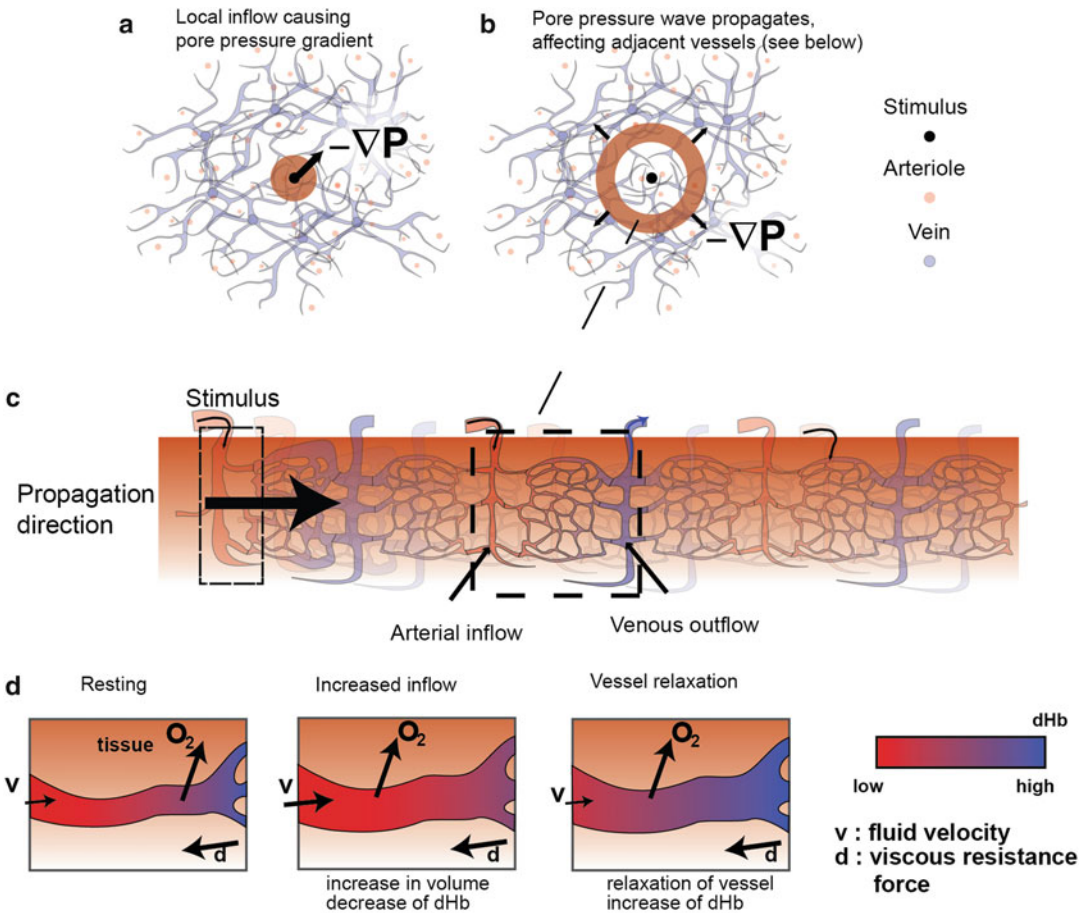
methods being employed are often extremely complex and sophisticated, they share a similar objective, namely, to co-register the data from different modalities to the same location in the brain at the same time and then combine the evidence of activity there (Martinez-Montes et al. 2004). In consequence, if both modalities show high activity at a time in a location, then the statistically combined result will show a high result there; if both are low then the combination will be low; and if only one of them is high but the other low, the result depends on the details of the method and its assumptions but will be somehow intermediate. While this makes intuitive sense, it relies on the fundamental assumption that different neural states generate signals for the different modalities such that the resulting signals are distinct in every modality and covary in some relatively simple way across modalities. However, we have seen that the signal generation for neuroimaging is very involved, and a priori it is not clear that this assumption will hold true. For example, the EEG may be driven by the balance between inhibitory and excitatory synaptic activity, whereas fMRI BOLD may be driven dominantly by excitatory synaptic activity alone. In this case a neural state with both high excitation and high inhibition may show little signal in the EEG, as these contributions cancel, whereas it would lead to a large fMRI BOLD response. Or a large inhibitory input in the absence of excitation may exert a strong influence on the EEG, but not on fMRI BOLD. Only large excitation without corresponding inhibition would likely register a large signal in both modalities and be guaranteed to appear in the combined result above some threshold.

Clearly what is needed here is a proper generative model, and we have asserted that NPMs can provide it. This is in particular true for simultaneous recordings of multimodal data, since the same predicted neural state can be used in different ways to provide the initial stage of the different signal expressions for the various modalities. Currently, research has focused on combining EEG/MEG and fMRI predictions with NPMs. The focus of Kötter and colleagues, as recently



Neuroimaging, Neural Population Models for, Fig. 7 (a) A Liley neural mass (Liley et al. 2002) predicts the EEG alpha rhythm (time series as *blue* line, corresponding normalized power spectral density as *inset*) but also the fMRI BOLD response (*red* line) given additional “task signal” excitatory input (*green* line).

(Bojak I 2012, unpublished). The compression of many oscillations on the long timescale makes the EEG time series appear noisy. (b) A prediction of fMRI BOLD on the cortical surface rendered (c) into voxels, where only voxels above an activity threshold are shown. (Bojak et al. 2010, 2011)

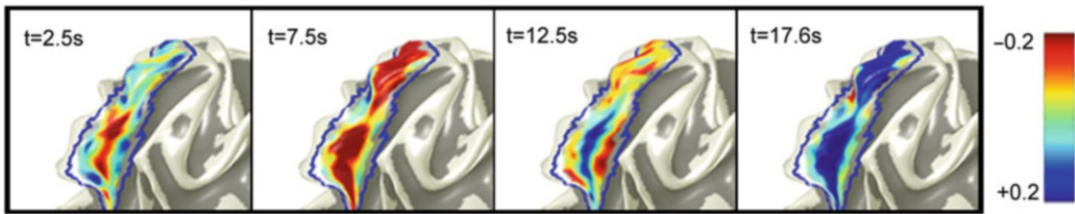


Neuroimaging, Neural Population Models for, Fig. 8 Physiologically derived hemodynamic response function. (a) Local spatiotemporal input causes a change in arterial inflow of blood, setting up a pressure gradient ∇P . (b) This mass inflow deforms the surrounding tissue, exerting pressure on nearby vessels. (c) The rise in pressure causes further volume changes in adjacent vessels, which propagate outwards. Damping of the response occurs through blood viscosity and losses occur via outflow. (d)

The increase of local inflow increases oxygenated hemoglobin (oHb), reducing the amount of local deoxygenated hemoglobin (dHb). As oxygen is simultaneously passively extracted from blood, oHb is converted to dHb, causing a delayed rise of dHb during vessel relaxation. This change in the ratio of oHb to dHb drives the BOLD signal. (This is Fig. 1 of Aquino et al. (2012), reproduced under the Creative Commons Attribution License)

reviewed in Deco et al. (2011), was on investigating resting-state oscillations and the so-called default mode network (Raichle et al. 2001). A series of papers have established the ability to fit auditory task data (Babajani et al. 2005; Babajani and Soltanian-Zadeh 2006; Babajani-Feremi et al. 2008; Babajani-Feremi and Soltanian-Zadeh 2010). Riera and co-workers fit auditory and visual task data (Riera et al. 2005,

2006, 2007). Alpha rhythm blocking and correlation with BOLD have been studied as well (Sotero et al. 2007; Sotero and Trujillo-Barreto 2008; Valdes-Sosa et al. 2009). An investigation on how much information EEG and fMRI BOLD can contribute to a combined signal has been made by Deneux and Faugeras (2010). Bojak et al. (2010, 2011) studied the dependence of the predictions on the assumptions about brain



Neuroimaging, Neural Population Models for, Fig. 9 Spatiotemporal snapshots showing the fMRI BOLD response to a discrete visual stimulus. Colors represent percentage signal change as indicated by the color

bar. (This is part of Fig. 3 of Aquino et al. (2012), reproduced under the Creative Commons Attribution License)

connectivity, as shown in Fig. 10. A first complete and freely available software package for carrying out such investigations has become available (Ritter et al. 2013; Sanz Leon et al. 2013).

Bayesian Model Selection and Inversion

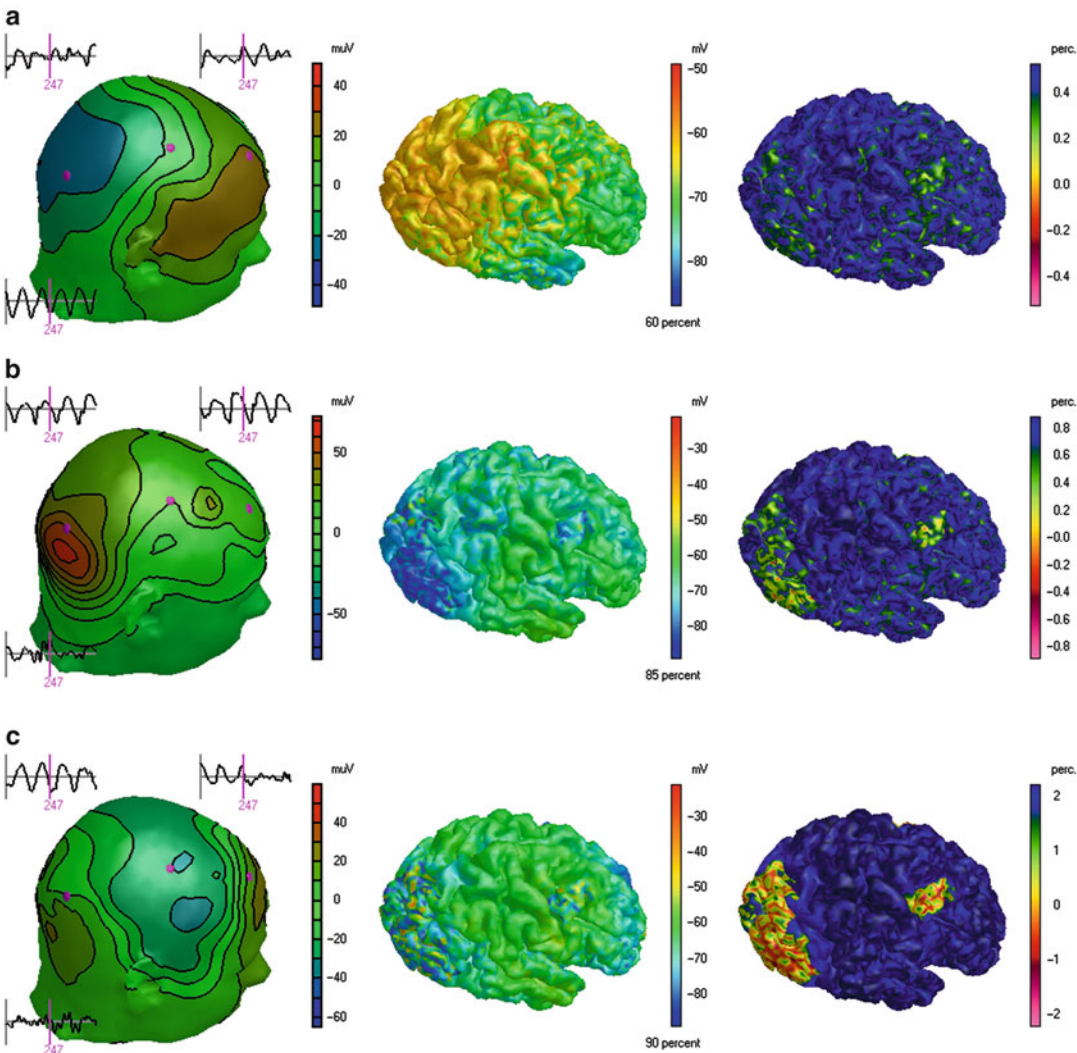
Thus far we have chiefly focused on the physical aspects of embedding NPMs into cortical geometry and the forward model that maps neuronal activity from their cortical sources into sensor space. These measurement functions are crucial as they allow one to use NPMs to predict a broad range of cognitive and pathological states, from resting-state conditions (Cabral et al. 2011; Deco and Jirsa 2012; Honey et al. 2007; Robinson et al. 2001) over anesthesia (Bojak and Liley 2005) to epilepsy (Breakspear et al. 2006), which can then be tested against empirical recordings. However, arguably an even more powerful role for detailed forward models is that they enable the estimation of the likelihood of a particular NPM given a particular data set. That is, when framed in an appropriate variational scheme – such as empirical Bayes – forward models allow one to estimate the relative posterior likelihood of one or more models. Using an appropriate term that penalizes models for their complexity, this approach then allows one to infer which model, among a family of competing models, is most likely (or has the highest exceedance likelihood). It is then possible to infer the parameter values of the winning model – or, alternatively, estimate

model parameters across families of models, where each model contributes to the average according to its own likelihood (Trujillo-Barreto et al. 2004).

Dynamic causal modelling (DCM) exemplifies this approach, initially adopting standard variational techniques (Friston et al. 2003) before more recently moving toward innovative approaches based on free energy (Friston et al. 2007). Early work combining DCM and NPMs used a version of the Jansen and Rit (1995) model to analyze EEG- and MEG-evoked responses (David et al. 2006; Kiebel et al. 2006). This was followed by a frequency-domain analysis of steady-state responses (Moran et al. 2009, 2011). Daunizeau et al. (2009) then extended these methods in order to take spatial activity spreading into account, including stochastic effects and biologically more realistic propagation later on (Daunizeau et al. 2012). Finally, with increasingly sophisticated forward models and variational schemes, multimodal fusion using symmetrical model inversion is also becoming increasingly feasible (Valdes-Sosa et al. 2011).

Summary

NPMs are a natural candidate for the prediction and analysis of neuroimaging data, in particular, of the noninvasive kind that can be recorded without ethical constraints from humans. By their mathematical construction, NPMs describe precisely those compact and collective actions of



Neuroimaging, Neural Population Models for, Fig. 10 A model of the cortex with over 17 thousand neural masses and over 30 million connections (Bojak et al. 2010, 2011). The *middle* column shows the LFP (mean excitatory soma membrane potential) prediction, the *left* column the volume-conducted prediction of scalp EEG potentials including the recordings from three

electrodes shown in *purple*, and the *right* column shows the simultaneous fMRI BOLD prediction. As the strength of connectivity between anterior visual cortex and frontal eye field is raised from (a) 60% over (b) 85% to (c) 90% of the strength of background connectivity, drastic changes in the brain dynamics occur which are particularly visible in the fMRI BOLD prediction

neurons that due to the practical measurement physics also dominate the signal recordings. Much progress has been made in the last three decades in clarifying and specifying the signal expression part of this prediction “pipeline.” In consequence, we can now match the underlying NPMs (and NPM-driven physiological models) to

the measured data with unprecedented accuracy. This should lead to a new phase of expansion and sophistication in the development of NPMs driven by experimental data. We believe that the current surge of interest in NPMs is just a beginning and that the marriage of neuroimaging and NPMs will have a long and fruitful scientific future.

$\frac{ds}{dt} = \varepsilon u(t) - 2\zeta\omega_0 s(t) - \omega_0^2[f(t) - 1]$ $s^* = 0$	Neural activity u , unit 1/s Vasodilatory signal s , unit 1/s Coupling ε , unit 1/s Natural frequency $\omega_0 = 0.639/\text{s}$ Damping $\zeta = 0.510$	(1)
$\frac{df}{dt} = s(t)$ $f^* = 1 + \frac{\varepsilon u^*}{\omega_0^2}$	Normalized flow f , unit free	(2)
$\tau \frac{dv}{dt} = f(t) - v^{1/\alpha}(t)$ $v^* = f^{*\alpha}$	Normalized volume v , unit free Grubb's exponent $\alpha = 0.32$	(3)
$\tau \frac{dq}{dt} = \frac{f(t)}{\rho} \left[1 - \left(1 - \rho^{1/f(t)} \right) \right] - v^{1/\alpha-1}(t)q(t)$ $q^* = \frac{v^*}{\rho} \left[1 - \left(1 - \rho^{1/f^*} \right) \right]$	Normalized deoxyhemoglobin q , unit free Resting oxygen extraction fraction $\rho = 0.34$ transit time $\tau = 0.98 \text{ s}$	(4)
$y = V_0 \left\{ 7\rho[1 - q(t)] + 2 \left[1 - \frac{q(t)}{v(t)} \right] + (2\rho - 0.2)[1 - V(t)] \right\}$ $y^* = V_0 \left\{ 7\rho[1 - q^*] + 2 \left[1 - \frac{q^*}{v^*} \right] + (2\rho - 0.2)[1 - V^*] \right\}$	fMRI BOLD contrast y , unit free Resting blood volume fraction $V_0 = 0.02$	(5)

Cross-References

- Amari Model
- Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism
- Brain Atlases
- Connectivity Analysis in Normal and Pathological Brains
- Determining Network Structure from Data: Nonlinear Modeling Methods
- Down Under Neural Population Models
- Dynamic Causal Modelling with Neural Population Models
- Electrocorticogram (ECoG)
- Epilepsy, Neural Population Models of
- Extracellular Potentials, Forward Modeling of
- Forward and Inverse Problems of MEG/EEG
- Gamma Rhythm, Neural Population Models of the
- Imaging Analysis, Bayesian
- Inverse Problems in Neural Population Models
- Jansen-Rit Model
- Local Field Potential, Relationship to BOLD Signal
- Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG)

- Local Field Potential: Relationship to Membrane Synaptic Potentials
- Local Field Potentials: LFP
- Mesoscopic Anatomy and Neural Population Models
- Multiscale Brain Connectivity
- Network Theory in Neuroscience
- Neural Field Model, Continuum
- Neural Population Model
- Propagator, Axonal
- Software for Neuroimaging Data Analysis
- Spontaneous Activity, Models of
- Synaptic Connectivity in Neural Population Models
- Voltage Sensitive Dye Imaging, Intrinsic Optical Signals
- Wilson-Cowan Model

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Neuroinflammation, Glia, and Cytokines: Networks of Networks

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Definition

Cytokines are immuno- and neuromodulatory proteins secreted by immune cells, endothelial cells, pericytes, neurons, and glia. Cytokines function through network interactions at the

intracellular, intercellular, and tissue levels of analysis. These proteins influence excitability in neurons and neuroinflammatory functions of glia. Glial cells including astrocytes and microglia are generally implicated in CNS homeostasis. These cells monitor the neurochemical milieu in the CNS through dynamic filopodia. Astrocytes and microglia regulate responses to injury, infection, neurodegeneration, and hyperexcitability through cytokine release. The relative proportions of cytokines in the CNS microenvironment are thought to coordinate a balance between homeostasis, neuroinflammation, and disease. Hence, many studies analyze and interpret data through a broad categorization of cytokines into pro- and anti-inflammatory groups. However, the complexity of intra- and intercellular cytokine signaling and regulatory interaction networks necessitates a new conceptual framework that explicitly considers the dynamics of multiscale interactions and regulatory influences between cytokines. A convergence of cell type-specific assays, unbiased/high-dimensional data analysis, and computational modeling is required to identify critical control points in these regulatory networks governing homeostasis and neuroinflammation.

Detailed Description

Cytokine Networks and Regulation

Cytokines are soluble peptides that are secreted by immune and many nonimmune cell types throughout the body. Their signature functions involve coordination of primary immune responses to injury and infection, resolution, repair, and remodeling. Cytokines influence chemoattraction and cell phenotype polarization through intracellular signaling and transcriptional regulation. In the CNS, cytokines have been shown to influence neuronal excitability, cellular energetics, and processes implicated in neurodegeneration, infection, and injury. Such processes include inflammatory signaling, phagocytosis, fibrosis, and the regulation of blood flow and blood brain barrier integrity. CNS cells both secrete and respond to extracellular cytokines through G-protein coupled receptor signaling.

A wealth of experimental data shows that cytokines influence the production and responses to other cytokines, in terms of both autocrine and paracrine signaling (Anderson et al. 2015; Benveniste 1992). Thus, there exists a cytokine regulatory interaction network within each cell type as well as across cells in a tissue (Fig. 1).

In the early 1990s, Benveniste and colleagues highlighted the concept of “cytokine networks” in the context of neuroscience (Benveniste 1992). Their work demonstrated that so-called pro-inflammatory cytokines such as tumor necrosis factor- α (TNF α) and interleukin 1- β (IL1 β) stimulated the upregulation of both “pro-” and “anti-inflammatory” cytokines including IL10 and transforming growth factor- β (TGF β). This work showed that cytokines respond to changes in the levels of other cytokines with distinct kinetic profiles, and the underlying interaction networks are densely coupled with both positive and negative feedbacks (Anderson et al. 2015). While the designation of cytokines as either pro- or anti-inflammatory has provided useful heuristics regarding the molecular basis of the immune response and immunosuppression, there are important shortcomings to the binary classification.

Cytokine perturbations have yielded pleiotropic effects and therapeutic outcomes that were unexpected according to existing pro/anti categorizations. For example, the canonical pro-inflammatory cytokine TNF α was shown to confer neuroprotection to brain injury and β -amyloid induced cell death, as well as reparative remyelination under conditions associated with multiple sclerosis (Sriram and O’Callaghan 2007). Administration of the anti-inflammatory cytokine IL-10 has shown inconsistent therapeutic effects for treating conditions associated with multiple sclerosis and deleterious effects for treating conditions associated with Alzheimer’s disease (Lobo-Silva et al. 2016). Importantly, human clinical trials have shown that interventions involving TNF α inhibition were associated with exacerbated symptoms for multiple sclerosis patients (Connor 2011). It has been proposed that the timing of a therapeutic intervention relative to disease progression is critical for treatment efficacy.

Collectively, our current knowledge is inconsistent with the prevailing paradigm in which cytokines are considered to be either “good” or “bad” for tissue function and organ/organism health. Available data are consistent with the notion that the function of an individual cytokine cannot be isolated from its role within a coupled regulatory network, the behaviors of which are constrained by network connectivity and interaction kinetics. Investigative approaches following the network view will require new multiplex time-series data and integrated modeling approaches (Anderson and Vadigepalli 2016). At the cellular level, it is necessary to improve our understanding of the kinetics and mechanisms of cytokine interactions, which involve multifaceted molecular functions including transcriptional regulation, biochemical signaling, and receptor regulation/trafficking (Cilfone et al. 2013; Rodriguez-Fernandez et al. 2013).

Glia and Cellular Microenvironment

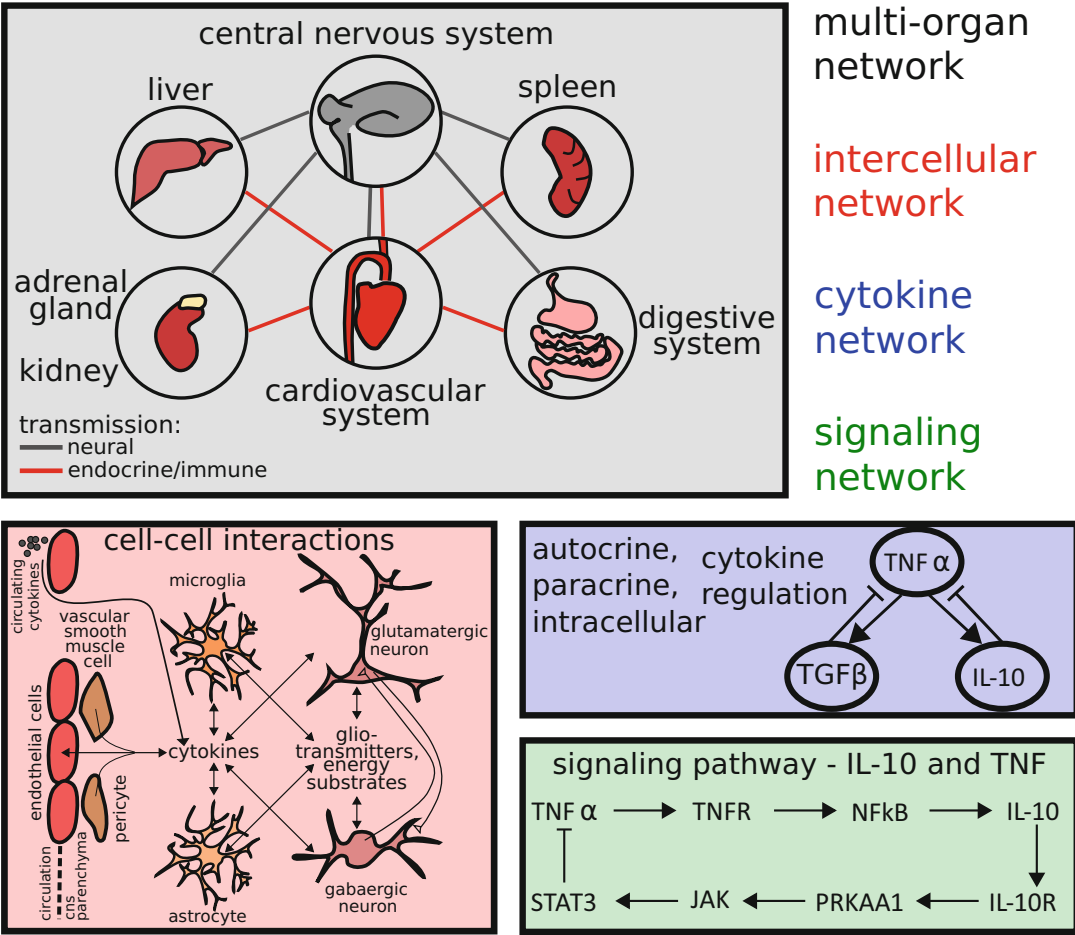
While most CNS cell types have been documented as capable of cytokine production, microglia and astrocytes are currently considered to be the primary contributors to cytokine regulation in the CNS. Microglia are self-renewing resident macrophages of the CNS that are derived from the hematopoietic system early in embryological development. Astrocytes have a distinct developmental origin in the neuroectoderm, as do neurons (Reemst et al. 2016). In a healthy state, microglia and astrocytes survey the neurochemical milieu in the CNS parenchyma, provide energy substrates to neurons, and influence synaptic transmission through “quad-partite” synapses (Schafer et al. 2013). Under pathological conditions, glial cells migrate to sites of injury or degeneration where they perform a number of context specific functions. In addition to cytokine secretion and regulation of neurochemistry, glial cells exert mechanical influences that are manifested in morphological changes (Anderson et al. 2017a). Studies at the single cell level have been informative in regard to how glial cells collaborate to regulate homeostasis in aging and pathogenic responses (Hammond et al. 2019; Masuda et al. 2019).

Glial cells, microglia in particular, are believed to exhibit pro- or anti-inflammatory phenotypes, where phenotype polarization is controlled by extracellular cytokines. However, it has been argued that immune cells exhibit a range of phenotypic states that fall outside of the pro/anti axis (Perry et al. 2007). Furthermore, small subsets of cells within a population could exert a disproportionate influence on the neurochemical microenvironment. For example, less than 5% of macrophages in a cell population can account for ~60% of the cytokine released from the cell population following an inflammatory stimulus (Xue et al. 2015). Single cell omics assays are beginning to unravel the true complexity in the distribution of functional phenotypes of glia and neurons. Such atlases of molecularly defined CNS cell phenotypes need to be analyzed in the context of interactions between microglia, astrocytes, neurons, and other cells, to further our understanding of neuroinflammation.

Neuroinflammation

A critical aspect of many neuroinflammatory conditions is the infiltration of peripheral immune cells and the diffusion of peripheral cytokines into the CNS. Under inflammatory conditions associated with neurodegeneration or traumatic injury, monocytes and lymphocytes enter the CNS and contribute to inflammatory regulation therein. Understanding the functional contributions of peripheral immune cells to pathological responses is complicated (Greenhalgh et al. 2018). It is also widely accepted that peripheral tissues release substances into circulation that can influence the CNS. The liver releases “hepatokines” (hepatic cytokines), muscles secrete myokines, and adipose tissues secrete adipokines into circulation. Therefore, circulating cytokines from multiple sources can access the CNS. The inevitable conclusion is that CNS inflammation is coupled to the organismal physiological state, the study of which necessitates a network of networks approach to probe the multiorgan interaction dynamics (Anderson et al. 2017b; Fig. 1).

The conventional characterization of neuroinflammation as a good versus bad phenomenon, based on the predominant expression of pro- versus anti-inflammatory cytokines and



Neuroinflammation, Glia, and Cytokines: Networks of Networks, Fig. 1 Networks of networks underlying CNS regulation. Physiological homeostasis depends on multi-organ communication (gray box). Multi-cellular

interactions involve cytokine signaling in the CNS (red box). Cytokine regulation involves cytokine networks (blue box). Intracellular signaling pathways mediate cytokine interactions (green box)

changes in cell morphology/function, is an oversimplification. Studies of cytokine expression have shown that protein levels often show less variation between healthy and inflammatory conditions as compared to transcript levels (Perry et al. 2007). Various combinations of cytokine balances are observed under distinct inflammatory conditions, clearly pointing to a multidimensional cytokine state space that needs to be considered, rather than a conventional linear axis spanning good and bad neuroinflammatory states. Moreover, inflammatory signaling is present during development when synaptic pruning occurs and inflammatory signaling is implicated in

learning/memory (Wu et al. 2015). In general, inflammation has evolved as a means to maintain homeostasis in the organism. The functional outcome of inflammation critically depends on the combination of inflammatory markers expressed and the duration of signaling activity. A central difficulty in understanding neuroinflammation is mapping molecular and cellular functions to physiological, metabolic, and functional states of the CNS tissue. This task is difficult given that molecular interaction networks are embedded in multicellular interaction networks, and the signal processing proceeds dynamically following an inflammatory trigger. It is

often not possible to distinguish causes from consequences of network output. While blocking specific network elements may provide limited insight into therapeutic approaches, the ablation approach provides limited insight into the functional role of the corresponding element in the context of the embedded network. Mathematical and computational approaches, including modeling, are needed to address these issues.

Computational Modeling of Cytokine Networks, Glia, and Neuroinflammation

Mathematical and computational approaches are integral to understanding complex systems. The high-dimensional state space underlying neuroinflammation generally precludes the application of formal mathematics, necessitating the use of computation. Computational approaches typically include either machine learning or modeling. Both machine learning and modeling approaches have a vast spectrum of conceptual and technical paradigms. While machine learning is well suited to define groups of related cytokines (unsupervised) or define groups of cytokines/cell states that are associated with particular phenotypic states (supervised), these approaches typically offer limited insight as to how biological properties relate to observed data in terms of “mechanisms.” Machine learning approaches are particularly well suited for inferring network structures and identifying potentially important network elements. Modeling approaches are generally much more concerned with providing an explanation for system behavior in terms of biological functions. The networks of networks underlying neuroinflammation can be conceived as a layered set of functions across scales: neuroinflammation state = f (distribution of cell states across cell types, cell-cell interactions, microenvironment), cell state = f (relative cytokine levels), cytokine levels = f (cell signaling, molecular interaction networks), where all variables are time-dependent (Fig. 1). For instance, cytokine networks consist of interactions between discrete cytokines at a course-grained level of analysis. Each interaction edge results from multiple signaling proteins, which are often arranged in complex motifs involving feedback regulation.

In turn, each signaling event (e.g., receptor-ligand binding, protein phosphorylation) is the result of structural protein modifications that can be considered as a network of conformational states. Machine learning applications are generally agnostic to the functional forms (e.g., linear versus sigmoidal), whereas these functional forms are integral to model development and interpretation. However, the idea has been advanced that better understanding the underlying functional forms of a particular problem can improve the performance of optimization algorithms (Wolpert and Macready 1997). It is sometimes the case that model complexity precludes the generation of understanding without the aid of machine learning approaches, in which case machine learning paradigms can be integrated with modeling to enhance progress (Anderson et al. 2016). Modeling approaches in the context of neuroinflammation and elsewhere have yielded important insights that are difficult if not impossible to derive from alternative approaches.

Both machine learning and dynamic models have been leveraged to study CNS disease, as reviewed previously (Anderson and Vadigepalli 2016). For example, a Boolean logic-based model addressed how/why microglia fail to phagocytose β -amyloid in aging and Alzheimer's disease (Anastasio 2015). A key to the utility of computational approaches to neuroinflammation is the formulation of important questions that can help explain unexpected findings or reveal system properties. Agent-based models are also well suited for studying neuroinflammation, as demonstrated through studies of peripheral immune function, because the computational framework supports multiscale representations of intracellular cytokine signaling and cell to cell interactions (Cilfone et al. 2013). Thus, agent-based models can simulate intracellular and multicellular networks in tandem. Studies of populations of networks representing a spectrum of individual differences are also becoming popular modeling approaches with potential implications for precision medicine.

Dynamic ordinary differential equation models are particularly useful for gaining an understanding of how systems work and what

sorts of tradeoffs govern their behaviors. For instance, our analyses of microglial cytokine networks revealed counterintuitive influences of IL10 on TNF α that were related to both network topology and the relative kinetics of multiple cytokines (Anderson et al. 2015). To understand system functions and determine an optimal therapeutic intervention strategy, it is useful to distinguish between the extent to which a given variable contributes system behavior and effect of removing the variable from the system (contribution versus sensitivity). Model analyses have revealed cases in which the removal of variables with large contributions to physiological processes shows relatively small consequences for system behavior (large contribution, small sensitivity). In contrast, removal of a variable with a relatively small functional contribution in the intact system can lead to comparatively drastic influences on function (small contribution, large sensitivity). Such a scenario can occur when redundant functional mechanisms are available to compensate for the absence of a variable that is typically associated with a prominent influence on system behavior, as revealed by model analysis (Pradhan et al. 2016).

Regardless of the problem's scale, the integration of multiple experimental and computational approaches helps to generate deeper insights. Studies that combine statistical approaches to experimental data analysis with dynamic modeling have been applied successfully to generate novel understanding of system behavior under the general paradigm of control theory (Cowan et al. 2014; Davis 2006). Doyle and colleagues approached the problem of understanding cardiovascular control by classifying relevant physiological variables as either homeostatically controlled variables, control actuators, disturbance variables, and network feedback variables. In the context of physiology, actuators are control elements that generate physical or chemical movement (e.g., the motor neuron controls muscle fiber contraction), while disturbance variables can represent changes in the demands imposed on the system (e.g., elevated workload imposed on the muscle). Key insights of general importance were that actuator variability is responsible for maintaining homeostasis in the face of fluctuating disturbances, and actuator saturation can balance

tradeoffs between system efficiency and the homeostasis of controlled variables (Li et al. 2014). In a conceptually similar approach, Ogunnaike used a process control-based approach to describe a system characterized by a digital-to-analog signal conversions between single cell behaviors and the cell population responses (Ogunnaike 2006). Such control theory-based paradigms provide important examples of integrated approaches that could enhance our understanding of neuroinflammation.

Approaches from fields throughout neurosciences and elsewhere provide critical tools for integrated studies of neuroinflammation in which modeling is used to gain insights and generate predictions. An important avenue for future research would be to integrate computational models of intra- and inter-cellular cytokine networks with multiscale models of cell signaling influences on ion channel function and excitability (Makadia et al. 2015). Moreover, considering neuroinflammation in the broader context of multiorgan networks will enhance our understanding of CNS diseases and their potential treatments (Anderson et al. 2017b). In conclusion, the mechanistic and functional relationships connecting cytokines, glia, and neuroinflammation represent networks within networks of signaling and functional mechanisms interacting across multiple spatial and temporal scales.

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Neuromechanics of Balance

► Neuromechanics of Postural Control

Neuromechanics of Joint Coordination

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Definition

“Neuromechanics of joint coordination in locomotion” addresses the control of synchronized

dynamics across multiple limb segments during legged locomotion. It requires integrating perspectives, principles, and methods across the disciplines of neuroscience and biomechanics. The neurophysiological basis for locomotion is tuned to the intrinsic biomechanical constraints and conditions presented by both the organism's biology and the implicit mechanical tasks required of legged locomotion. It is, therefore, necessary to study joint coordination within the context of identifiable performance goals, which are defined by the biomechanics of the task. Joint coordination can be then viewed as the changes that occur at one joint in response to deviations at another joint with the superseding goal to support a task-level locomotor performance goal.

Detailed Description

Redundancy Is Intrinsic to Legged Locomotion

Legged locomotion requires the coordinated output of numerous neuromechanical elements. Within a single limb these elements can include thousands of motor units across several muscles that cross multiple joints, creating motor redundancies at each level of organization. For example, in the human leg, there are an infinite number of ankle, knee, and hip joint angle combinations that can satisfy any one single end-point (toe) position. These angular positions are a result of muscle-tendon unit lengths influenced by the nervous system to act across the joints. How the nervous system selects from among the many possible joint angle combinations to maintain a consistent end-point position during a task is considered a fundamental problem in motor control (Bernstein 1967). This problem of motor redundancy has been traditionally studied in the control of upper extremity movements but can be similarly applied to the control of the legs during locomotion where the position of the toe relative to the body changes through a characteristic pattern over time.

It is not well understood how the joints of the leg are coordinated during locomotion. One possibility is that the nervous system controls each

joint independently during locomotion. For example, the nervous system could potentially assign values for each joint angle at each instant in time throughout the gait cycle independent of other joints. But, this would require many high-level computations to ensure that a performance goal, such as toe position, be met during stepping. Alternatively, to reduce bandwidth at the highest levels of the neural controller, the coordination that occurs across joints may be relegated to lower levels of the nervous system where the compensatory actions across joints are made through relatively automatic regulatory processes such as through spinally mediated pathways or even passive mechanics. This latter solution would allow higher levels of the controller to directly set and modify performance level goals, such as toe position, that may be governing the joint coordination regulated at lower levels. There is mounting evidence for this latter solution, which would suggest that the locomotor control system is hierarchically organized (Loeb et al. 1999). If an automatic regulatory process can coordinate the joints for the purpose of satisfying this performance goal, then joint-level redundancy could actually lead to more consistent locomotor performance as it allows for immediate access to alternative solutions in the face of natural variation and perturbation (Schöner and Kelso 1988; Latash et al. 2002).

Locomotor Performance Goals Provide Context for Joint Coordination

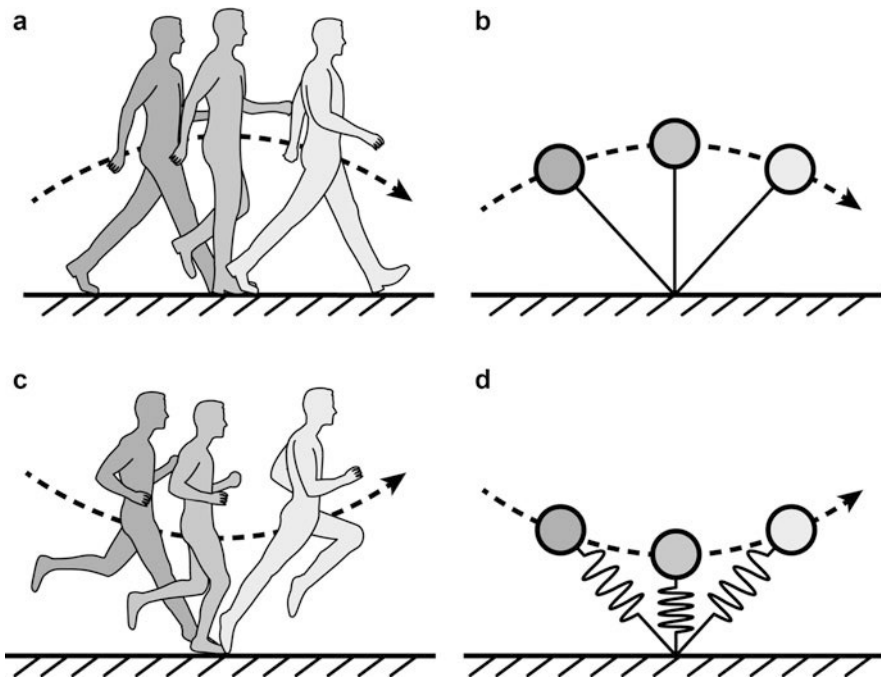
Viewing the seemingly complex actions of the joints within the context of limb performance goals provides a framework within which to synthesize control principles for joint coordination. The identification of these locomotor performance goals, however, remains an active area of research. The biomechanical constraints of locomotion are important to consider in this regard because they bound the space within which the nervous system is likely to act. They provide important clues as to how the control of these complex joint movements is organized. Notably, independent findings from biomechanics and neurophysiology have proposed similar ideas about how the locomotor system may organize the

neuromechanical control of the joints during legged locomotion. Both control schemes suggest a considerable hierarchical reduction in the number of parameters that are attended to at higher levels of the nervous system.

Using evolution as a natural experiment to uncover locomotor performance goals across species, a wide range of morphologies and taxonomic groups are observed to exhibit very similar center of mass dynamics (Cavagna et al. 1977; Dickinson et al. 2000; Full and Koditschek 1999). Two major biomechanical templates for describing the center of mass dynamics of legged locomotion are the inverted pendulum model of walking and the spring-mass model of running (Fig. 1). For example, birds, mammals, and arthropods all exhibit the same spring-mass dynamics of the center of mass during running, often referred to as a bouncing gait (Dickinson

et al. 2000). The fact that a 2-legged bird, a 4-legged horse, and a 6-legged cockroach all move their bodies in the same way suggests that the biomechanical performance goals for running are fundamental to legged locomotion and are low dimensional in nature. Furthermore, the highly variable morphological “details” of the limbs (i.e., the number of joints and muscles, type of skeleton) appear inconsequential to body dynamics. The nervous systems across all of these different groups of animals coordinate the elements of their respective neuromechanical systems to satisfy these simple biomechanical templates for body center of mass dynamics.

The center of mass dynamics is controlled in large part by the net actions of the legs. Therefore, it is important to understand limb function and its role in governing joint coordination to achieve



Neuromechanics of Joint Coordination, Fig. 1 Walking involves a cyclical rise and fall of the body’s center of mass with each step, where the body is at its highest point in the middle of the stance phase (a). The center of mass dynamics of walking in a number of legged animals has been successfully idealized with an inverted pendulum model characterizing the stance phase of walking as a point mass upon a massless, rigid strut (b).

Running, trotting, and other bouncing gaits involve a similar rise and fall of the body’s center of mass to walking; however, the body is now at its lowest point in the middle of stance phase (c). Bouncing gaits across a wide range of animals have been successfully idealized as a point mass sitting atop a massless linear spring or mass-spring model (d)

consistent center of mass dynamics. The inverted pendulum and spring-mass models each implicate overall hip-to-toe length, orientation, and end-point force as important parameters that are likely controlled during locomotion (Dickinson et al. 2000). For example, humans maintain a highly consistent relationship between limb force and limb length (typically referred to as a “leg stiffness”) in running and hopping gaits. This spring-mass model that describes running and hopping is robust against changes in ground viscoelasticity (Ferris et al. 1998; Moritz and Farley 2003) and application of mechanical loads to individual joints (Ferris et al. 2006; Chang et al. 2008). The biomechanics of locomotion, therefore, limits the set of likely locomotor performance goals, which can be tested as hypothetical neural control targets.

Neurophysiological studies also suggest that the sensorimotor control of locomotion is simplified through a hierarchical reduction in the number of control parameters represented at the highest levels of control. These parameters reflect the same limb performance goals independently suggested from biomechanics. For example, dorsal spinocerebellar tract neurons within the cat spinal cord are observed to integrate a large amount of sensory information from the periphery into relatively simple neural representations that ascend into the cerebellum (Bosco et al. 1996, 2000, 2003, 2006; Bosco and Poppele 2000, 2003; Poppele et al. 2002). These studies of sensory encoding suggest that general limb kinematics (hip-to-toe length and orientation) and kinetics (end-point force) are monitored by the central nervous system. Motor systems also indicate that relatively simple, low-dimensional control signals from synergistic muscle activations represent task-level commands. Thus, a handful of muscle synergies can account for the complex, high-dimensional motor output observed during locomotion (Chvatal and Ting 2012, 2013; Chvatal et al. 2011; Ivanenko et al. 2004). These studies indicate that sensorimotor control of the muscles is intrinsic to the patterns of joint coordination during locomotion, which naturally emerge as a result and can be used as a window into the control schema of the nervous system.

Uncontrolled Manifold Framework for Testing Task Space Utilization

Looking at joint coordination in the context of whole limb function provides a way to reduce dimensionality of the system in a comprehensible manner in which the nervous system may itself be operating. The uncontrolled manifold (UCM) concept introduces a computational approach to mathematically transform cycle-by-cycle variability of joint dynamics from an anatomically defined coordinate system into one derived by their effect on a hypothesized control parameter (Scholz and Schöner 1999; Latash et al. 2002). Over many repetitive gait cycles, one can use the UCM approach to quantify the variance structure of the joint dynamics within this goal-defined task space. For example, a nonrandom distribution of joint angle variance that distributes and aligns with a subspace of equivalent solutions for limb length indicates a strong likelihood that the nervous system is selectively minimizing only those joint angle deviations that lead to inconsistent limb lengths. In contrast, joint angle deviations within this subspace result in consistent limb kinematics and are left “uncontrolled” within this manifold. This type of control is characterized by a minimal intervention strategy where the deviations in joint dynamics that do not negatively affect performance are allowed to accumulate in this task equivalent space (Todorov and Jordan 2002).

For example, if we were to investigate the variance structure of a set of three joint angles relative to their influence over a performance goal such as leg length, we could estimate the 2-dimensional manifold as the null space ($\vec{\epsilon}$) of a Jacobian (J) that relates small changes in the joint angles to small changes in leg length relative to a reference posture ($\vec{\Theta}^0$, Eq. 1).

$$0 = J \left(\vec{\Theta}^0 \right) \cdot \vec{\epsilon} \quad (1)$$

We analyze the data at specific time slices within the gait cycle over many successive cycles. We define our reference leg posture ($\vec{\Theta}^0$) as the average set of joint angles measured at that

specific time in the gait cycle over all trials. Projecting the deviations of joint angles ($\vec{\Theta}$) from this reference posture onto the null space ($\vec{\varepsilon}_i$) determines the fraction of deviations that did not affect the performance goal, which we will call goal equivalent deviations ($\vec{X}_{GED}$, Eq. 2). Others have referred to these as task-irrelevant deviations since they do not alter the hypothesized performance goal (see Todorov and Jordan 2002). The remaining fraction is then deemed to be orthogonal to the null space, which we refer to as non-goal equivalent deviations ($\vec{X}_{NGED}$, Eq. 3) or task-relevant deviations.

$$\vec{X}_{GED} = \sum_{i=1}^n \vec{\varepsilon}_i^T \cdot \left(\vec{\Theta} - \vec{\Theta}^0 \right) \cdot \vec{\varepsilon}_i \quad (2)$$

$$\vec{X}_{NGED} = \left(\vec{\Theta} - \vec{\Theta}^0 \right) - \vec{X}_{GED} \quad (3)$$

The amount of variance normalized per degree of freedom (n) parallel to the UCM is then defined as goal equivalent variance (σ_{GEV}^2 ; Eq. 4).

$$\sigma_{GEV}^2 = \frac{\sum \vec{X}_{GED}^2}{nN_{cycles}} \quad (4)$$

And, the amount of the variance per degree of freedom (d) orthogonal to the UCM is defined as non-goal equivalent variance (σ_{NGEV}^2 ; Eq. 5).

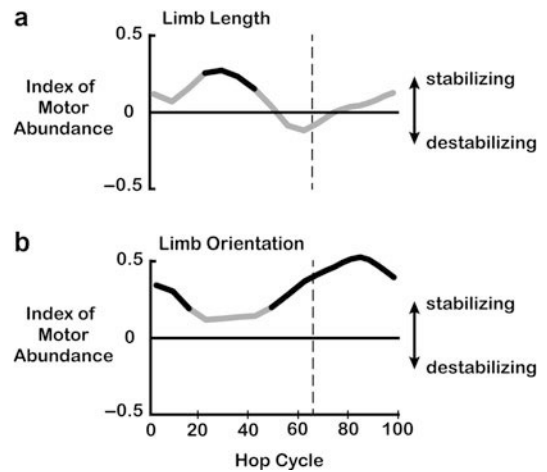
$$\sigma_{NGEV}^2 = \frac{\sum \vec{X}_{NGED}^2}{d \cdot N_{cycles}} \quad (5)$$

To quantify the variance structure over all locomotor cycles, we can compare the relative amounts of σ_{GEV}^2 and σ_{NGEV}^2 through a normalized difference calculation, which we term the index of motor abundance (IMA, Eq. 6). An IMA value greater than zero indicates that the joint angle deviations having a direct effect on deviations in leg length were preferentially minimized, indicating leg length to be a likely performance goal for locomotion. An IMA equal to zero indicates no preference for minimizing deviations of leg length since all joint angle deviations were randomly distributed in the task space.

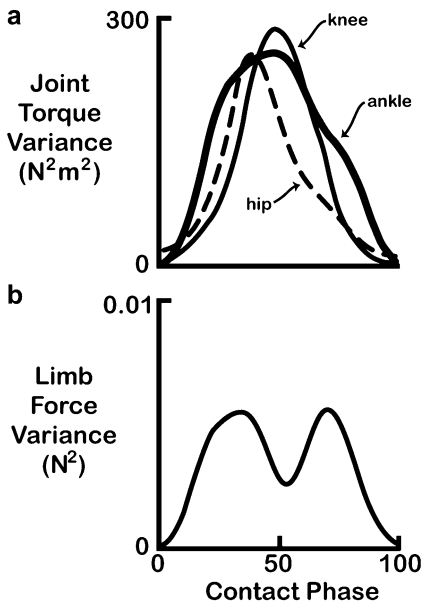
$$IMA = \frac{(\sigma_{GEV}^2 - \sigma_{NGEV}^2)}{(\sigma_{GEV}^2 + \sigma_{NGEV}^2)} \quad (6)$$

This general approach has been used to test the hypothesized control parameters: limb length, limb orientation, and limb force during human hopping. Human hopping is a commonly used experimental paradigm for locomotion that provides spring-mass dynamics of the center of mass, while giving a highly controlled experimental design to study the coordinated actions of the joints. Recent studies have shown that, indeed, subjects selectively minimize joint kinematic deviations in the task-relevant dimension to result in more consistent values of limb length and limb orientation (Auyang and Chang 2013; Auyang et al. 2009; Fig. 2).

Furthermore, humans also minimize joint torque deviations in the task-relevant dimension to stabilize peak limb force during hopping (Yen et al. 2009; Yen and Chang 2010). The practical result is that despite generating large and highly



Neuromechanics of Joint Coordination, Fig. 2 During hopping and running, the length and orientation of the hip-to-toe limb kinematic vector are stabilized by the coordinated actions of the joints. Limb length (a) and limb orientation (b) are made more consistent from cycle to cycle through joint actions as evidenced by the nonrandomized variance structure of the joint kinematics when viewed in the task space relative to each of these parameters (i.e., a positive IMA value). Limb length is stabilized during the stance phase (a), whereas limb orientation is typically stabilized during the aerial phase (b). (Adapted from Auyang and Chang 2013)



Neuromechanics of Joint Coordination, Fig. 3 The variance of joint torques is at its peak during the middle of stance phase of hopping and running (a). Yet, the force variance at this same instant is experiencing a local minimum (b). This indicates that the peak forces generated on the ground are highly consistent even when joint torques are at their greatest magnitudes and most variable

variable joint torques from one hop to the next, the variability of the peak limb force generated against the ground is minimized (Fig. 3).

A closer look at joint torque coordination effects on force stabilization is permitted with a data permutation technique that allows isolation of the variance structure due only to joint torque covariance (Yen and Chang 2010). This analysis reveals that the effectiveness of joint torque coordination to produce more consistent force is rate dependent, and a trade-off exists at higher hopping frequencies where individual control of the ankle joint torque is the dominant strategy for stabilizing force. Study of human walking within the framework of the UCM concept has revealed similar control strategies for stabilizing force in a hierarchical manner (Toney and Chang 2013).

Neural Mechanisms for Joint Coordination During Locomotion

It is not clear what substrates within the mammalian nervous system form the neural

representations of locomotor performance goals; however, evidence for such a control strategy is increasing. In two species, hip-to-toe limb kinematics are preferentially preserved through coordinated changes in the joint kinematics after neuromuscular injury. In awake behaving cats (Chang et al. 2009) and rats (Bauman and Chang 2013), paralysis in the ankle extensor muscles through peripheral nerve damage leads to large joint angle deficits at the ankle during locomotion. Significant, associated changes also occur in the hip, knee, and toe joint kinematics. The net result of all of these changes to the joint kinematics, however, resulted in no change in the hip-to-toe limb length and limb orientation trajectories (see Rat Video, <http://youtu.be/XsM3f0UYG5w>). This preservation of limb kinematics after neuromuscular injury occurred despite fundamentally different interjoint coordination patterns adopted across the joints (Bauman and Chang 2013). Importantly, the same muscle nerve injury paradigm does not elicit immediate preservation of limb kinematics in a walking decerebrate cat preparation where the cerebral cortices have been removed (Stahl and Nichols 2011). This indicates that the maintenance of limb kinematics after injury requires cortical input. Increases in cortical activity during cat locomotion are associated with walking in complex environments and specifically implicated for making modifications during locomotion (Beloozerova and Sirota 1993a, b, 1998; Drew et al. 2008). Subpopulations of motor cortical neurons are suggested to modify the magnitude and phase of muscle synergies that control limb trajectory (Drew et al. 2008). This finding supports earlier suggestions that reduced dimensionality and covariance of joint kinematics in human locomotion is not due to biomechanical coupling, but involves a control process including the neural representation of limb kinematics (Ivanenko et al. 2008). The persistence of limb kinematics through large-scale, coordinated adaptation of joint kinematics after injury appears to require involvement from higher brain centers.

Rapid spinal mechanisms are in place, however, that may explain the more subtle coordinative changes that occur on a regular basis during normal, steady-state locomotion. Heterogenic

proprioceptive feedback from the muscles of the leg is seen to help stabilize end-point position in the cat hindlimb (Bunderson et al. 2007). Spinal pathways in the cat that send force and length feedback between ankle extensor muscles and knee extensor muscles can account for these automatic adjustments across the joints. A strong excitatory coupling exists from the vastus muscles crossing the knee to the soleus muscle crossing the ankle (Wilmink and Nichols 2003). For example, an induced knee flexion would stretch the vastus muscles crossing the knee joint and cause excitation of the soleus muscle. The resulting ankle extension would tend to compensate for the induced knee flexion to preserve hip-to-toe leg length. Additionally, there is a strong bidirectional force-dependent inhibition between the triceps surae group and the quadriceps group (Wilmink and Nichols 2003). Thus, an induced increase in knee torque would generate a decrease in ankle torque and vice versa, resulting in a tendency to maintain end-point force. Although the effect of these spinal pathways has not been tested with regard to locomotor performance goals, they provide a testable hypothesis for regulatory pathways at lower levels of the nervous system with which automatic coordinated adjustments may take place across the joints on a stride-by-stride basis. These spinal pathways also provide the framework within which greater magnitude chronic adaptations can be made over longer periods of time with involvement of the higher brain centers, such as is required after a neuromuscular injury.

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Neuromechanics of Postural Control

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Synonyms

[Neuromechanics of balance](#); [Sensorimotor control of balance](#); [Sensorimotor control of posture](#)

Definition

Although *postural control* often refers to the restoration of a particular body configuration defined by joint angles, in the context of standing balance control, it more generally refers to the strategies used to maintain the body's orientation and equilibrium in an unstable gravitational field, which may require a change in body configuration. *Neuromechanics* refers to the complex interactions between the nervous system and the musculoskeletal system in producing movements. These interactions result from the fact that the nervous system generates signals that activate muscles, but the forces and movements generated depend upon the state (e.g., displacement and velocity of muscles, tendons, and joints) as well as mechanical loads and forces associated with the musculoskeletal system and the environment. In turn, these neural signals to muscles are modified by the central nervous system in

part based on sensory signals generated by forces and movements of the body.

Detailed Description

Although the act of standing up seems like a simple motor task, our ability to balance while doing so is the result of complex neuromechanical interactions. There are many levels of contributions from both the nervous system and musculoskeletal system in producing posture and movement, which may be both complementary and redundant. Moreover, the neuromechanical interactions can change with any number of factors, including movement context, body configuration, the availability of sensory information, impairments to sensorimotor processing, and the ability of muscles to produce force. Understanding the multiplicity of solutions for maintaining postural control during standing is important for understanding how we move and how this ability is impaired across a range of neurological and musculoskeletal deficits, including Parkinson's disease, stroke, sensory loss, muscle atrophy, and limb loss, as well as normal changes with aging. Computational analyses and modeling techniques play a key role in dissociating the contributions of musculoskeletal dynamics versus sensorimotor processing to standing balance control when combined with experimental results.

Neuromechanics of Quiet Standing

Even in the absence of external perturbations, the body is in constant motion, referred to as postural or body sway. It has been debated whether this postural sway is due to feedforward neural mechanisms that cause the body to oscillate in the absence of any sensory input or from feedback motor signals in response to fluctuations in sensory signals that may be due to both movement and sensory noise. Although intrinsic muscle and tendon stiffness have been proposed to stabilize quiet standing, torque-actuated inverted pendulum models demonstrate that the necessary ankle stiffness is much higher than that measured experimentally

(Morasso and Schieppati 1999; Peterka 2002). Fluctuations in center of pressure (CoP) displacement have been reproduced by postural control models incorporating both feedforward and feedback neural control mechanisms. For example, a single inverted pendulum model controlled using delayed position and velocity feedback with simulated sensory noise can reproduce a wide variety of common time and frequency domain CoP measures (Maurer and Peterka 2005; Peterka 2002). In contrast, sway-like motion has also been demonstrated using a predictive feedforward mechanism (Gawthrop et al. 2009; Loram et al. 2005). Resolving this debate is challenging given limitations in system identification techniques in conditions where sensory noise is greater than external perturbations such as in quiet standing (van der Kooij et al. 2005).

Neuromechanics of Multisensory Integration During Postural Control

The flexible integration of sensory signals from the proprioceptive, vestibular, and visual systems is necessary for accurate estimation of body orientation with respect to vertical during perturbations to standing balance control. The variations in reliance on visual, vestibular, and visual information for feedback control of postural orientation have been demonstrated using a simple inverted pendulum model of the body controlled with a delayed feedback signal in which the reliance of different sensory signals could be changed (Peterka 2002). The model was used to reproduce experiments that produce sensory conflict by perturbing only the visual system (rotating a visual surround) or only the proprioceptive and vestibular systems (rotating the support surface with eyes closed). The reliance on proprioceptive information causes subjects to align their body with the tilting of the support surface, which occurs only for small support-surface rotation amplitude and frequencies. However, at larger amplitudes, subjects must increase their reliance on vestibular information to align themselves with the vertical when they can no longer stabilize themselves when orienting to the tilting of the

surface (Peterka 2002). Further, the model can predict the inability of individuals with vestibular loss to maintain stability at larger amplitudes with eyes closed because the proprioceptive strategy fails.

Neuromechanical Interactions During Balance Control

Variations in sensorimotor feedback with changes in body mechanics are also necessary to maintain balance in response to perturbations. This can be demonstrated by examining frontal-plane balance control in response to lateral perturbations where the distance between the feet changes the mechanics of the body. The necessary covariations in neural and mechanical contributions to postural stability can be demonstrated using a simple computational or robotic model of the body as two rigid legs connected by a pelvis with variable distance between the feet. In response to lateral motion of the support surface, a delayed feedback signal based on hip angle position and velocity drives the torque about that joint. As stance width is altered, the same sensorimotor feedback gain values can no longer be used to stabilize the system. Further, similar effects on postural stability in response to a lateral perturbation can be generated by changing either neural feedback gains or stance width, demonstrating neuromechanical redundancy in postural control. Indeed, large differences in the sensorimotor response to sensory signals are necessary to produce the same center of mass (CoM) motion when standing at wide versus narrow stance widths. However, within a given stance width, there is some allowable variability in the magnitudes of feedback gains that can be used to maintain balance that is corroborated by variations in neural feedback gains observed across individuals (Bingham et al. 2011).

Neuromechanics of Multisegmental Movement Strategies for Balance

Multisegmental biomechanical models reveal that biomechanical as well as neural influences govern the choice of multi-joint movement strategy in

balance control. Different multi-joint coordination strategies can be used to achieve the same higher task-level outcome due to redundancy in joint space. Typically, small perturbations to standing balance elicit motions predominantly about the ankle (“ankle” strategy), whereas larger perturbations that tend to place the CoM near the edge of the base of support evoke flexion or extension at the hips (“hip” strategy). While biomechanical models demonstrate the insufficiency of the ankle strategy for keeping the feet on the ground for larger perturbations (Kuo and Zajac 1993), there likely exist other reasons such as head or trunk stability that lead to the preferred selection of the ankle strategy for small perturbations. Models incorporating sensory dynamics and state estimation further demonstrate that selection of movement strategies may also depend on the ability of the nervous system to obtain reliable sensory information (Kuo 2005; van der Kooij et al. 1999).

Neuromechanics of Muscle Activity During Balance Control

Using neuromechanical models to reproduce muscle activity in response to perturbations has provided evidence that sensory estimates of body position drive the spatiotemporal patterns of muscle activity during perturbation to balance. In contrast to joint-based information, CoM kinematics reflect the task-level goal of maintaining the CoM over the base of support in balance control (Safavynia and Ting 2013a). Using a simple inverted pendulum model consisting of a delayed feedback on CoM acceleration, velocity, and displacement, the magnitude and timing of muscle activity can be reproduced in response to postural perturbations (Lockhart and Ting 2007; Welch and Ting 2008). Note that this model assumes that the CoM is accurately estimated by multisensory integration mechanisms (Peterka 2002). The model demonstrates that a “predictive” burst of muscle activity due to acceleration of the CoM at the onset of the perturbation allows a muscle to reach maximal activation prior to the peak displacement of the CoM; previously this burst was attributed to the triggering of a fixed neuromotor programs in response to perturbations. The neural

signals reflecting errors in CoM kinematics with respect to the desired position may also recruit motor modules or muscle synergies (Ting and McKay 2007) for balance control (Safavynia and Ting 2013b). Motor modules coordinate muscles across multiple joints and can produce consistent biomechanical outputs necessary across various postural strategies control (Chvatal et al. 2011; Ting and Macpherson 2005; Torres-Oviedo and Ting 2007).

While more complex musculoskeletal models have been useful in studying movement, none have yet been developed for postural control that have been rigorously validated across experimental conditions compared to the models described above.

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NeuroML

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Definition

NeuroML (Cannon et al. 2014; Crook et al. 2007; Gleeson et al. 2010; Goddard et al. 2001) is an international, collaborative initiative to develop a declarative computational language for describing detailed models of neurons, neuronal networks, and neural systems.

Detailed Description

Computational modeling is an important tool in the study of the complexity of neural dynamics.

However, existing simulation environments, tools for neuroanatomical analysis, and data analysis tools use a variety of data formats, making it difficult to exchange models or reproduce computational studies. The NeuroML project was initiated to address these issues (Goddard et al. 2001). As outlined on the website at <https://www.neuroml.org/>, the main aims of the NeuroML initiative are:

1. To create the specifications that define an XML language for describing the biophysical properties, anatomy, and network architecture of neuronal systems at multiple spatial scales
2. To provide greater transparency and accessibility of models, facilitating the exchange of models among researchers
3. To aid the development and promotion of software tools and databases that support NeuroML to facilitate model sharing
4. To encourage researchers who create models within the scope of the initiative to exchange and publish their models in the NeuroML format

History

The term “NeuroML” was first introduced by Goddard et al. (2001) following meetings in Edinburgh at which initial templates for the language structures were discussed. The proposal was built on general-purpose structures already proposed by Gardner et al. (2001). Initially, NeuroML development was centered around a software library, the NeuroML Development Kit (NDK), designed by Fred Howell and Robert Cannon to simplify the process of interacting with XML serializations of models; however, no particular structures were defined for use in describing models. Instead, users were free to invent their own structures and serialize them via the NDK, with a goal that some consensus would emerge around the most common structures used for describing models. In practice, few users developed or used such structures, hindering wider adoption.

Following discussions with Howell and Cannon about the need for a common data format

for describing widely used model components, Sharon Crook worked independently on a language for describing neuronal morphologies in XML, MorphML (Qi and Crook 2004). Similarly, while working with Angus Silver to develop neuroConstruct (see ► “neuroConstruct”), Padraig Gleeson developed a simulator-independent representation for morphologies, ion channels, and networks. It was agreed that these efforts should be merged under the banner of NeuroML, and the version 1.x structure of NeuroML was created (Gleeson et al. 2010). This version of the language was designed with three levels (incorporating MorphML, ChannelML, and NetworkML), allowing application developers to choose which parts of the language to support. XML schema files for this version of the standard have been available since 2006. As NeuroML documents became more widely used by multiple simulation platforms and visualization resources, there was a need for explicit, machine-readable descriptions of the mathematical details underlying the higher-level neuroscience-based components in NeuroML. Thus, in the latest version of NeuroML (version 2.0), the mathematical details of the neuroscience components are defined in a domain-independent XML-based language as described below.

NeuroML Structure

The structure of NeuroML is designed in a modular way and centers around objects based on high-level neuroscience concepts such as cells, channels, and synapses, which provide the core model types. This conceptual framework parallels the approach used to derive and define neuroscience models in the literature. NeuroML allows for descriptions of detailed neuronal morphologies and their electrical properties such as the passive membrane properties and the location and densities of active membrane conductances. The language also provides for the associated descriptions of the ion channel and synapse models, as well as three-dimensional neuronal network models based on these components. NeuroML also includes descriptions of single-compartment (point) neuron models that are

widely used in the literature and of networks of these more abstract neuron models. Additionally, structures for metadata can be used to annotate any NeuroML model.

Gleeson et al. (2010) provide an overview of the structure of NeuroML for version 1.x, as well as examples of its use, and testing of the mapping of NeuroML to multiple simulation platforms. With version 2.0, NeuroML underwent a major update to allow for greater extensibility of the language and to provide machine-readable definitions for the core model types. In this version, the structure and dynamical behavior of the core model types (ion channels, cells, synapses, current sources, etc.) are based on underlying definitions provided in LEMS (the Low Entropy Model Specification language) (Cannon et al. 2014). Developed by Robert Cannon, LEMS is a domain-independent XML-based language for specifying hierarchical mathematical models of physical entities. Applications which support NeuroML can choose to support only the set of high-level model concepts in the language (as was the case when supporting NeuroML version 1.x), or they may make use of the underlying mathematical definitions provided by LEMS and in this way support any new model types added in the future.

There are several additional advantages provided by using LEMS to describe the model component structure and dynamics that underlie each element in NeuroML. One is that this machine-readable format can be used to enforce correct handling of the dimensions for the physical variables in the model. Another is that LEMS facilitates the construction of models across spatial scales that include components developed within the systems biology community that are described in SBML (Hucka et al. 2003). This allows these two communities to exchange models, technical experience, and ideas. In addition, NeuroML version 2.0 is accompanied by a suite of application programming interfaces in Java (jNeuroML) and Python (pyNeuroML) that simplify the process of interacting with models that are expressed in NeuroML and LEMS. jNeuroML allows a user to validate, simulate, translate, and analyze models in NeuroML 2.0. pyNeuroML provides the same functionality in Python with a number of other features to convert, visualize, and analyze models.

NeuroML Community

Information about the NeuroML specification, libraries, and documentation is available at the NeuroML website (<https://www.neuroml.org/getneuroml>). A large number of software applications and tools provide some support for NeuroML. A list of these tools and their level of support also is available on the NeuroML website (https://www.neuroml.org/tool_support). Information about the application programming interfaces jNeuroML and pyNeuroML can be found in either of these locations. Examples of NeuroML models can be found at NeuroML-DB, a database of models in NeuroML format (<https://neuroml-db.org>), as well as Open Source Brain (<http://www.opensourcebrain.org>; ► “Open Source Brain”). The use of NeuroML as a standardized format for describing models allows for automated characterization of model behaviors at NeuroML-DB and for web-based model simulation, visualization, and analysis at Open Source Brain.

An elected editorial board guides the development of NeuroML. This board (<https://www.neuroml.org/editors>) consists of five members who define and document the core specification of the language, oversee tool development, maintain the website, and provide oversight of basic support for the further development of the NeuroML language.

Cross-References

- [neuroConstruct](#)
- [Open Source Brain](#)

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electrical activity, canonically through metabotropic G-coupled protein receptors. In contrast to classical neurotransmission, which directly opens ion channels, neuromodulators can act either synaptically or extra-synaptically (e.g., hormonal pathways) to modify neuronal activity. Because neuromodulators can simultaneously target many neurons, our understanding of their function on networks has progressed furthest in small systems with known connectivity. In particular, much research has been conducted within invertebrate central pattern generator (CPG) networks. These networks exhibit spontaneous electrical discharges that drive rhythmic muscle contractions to produce simple behaviors such as chewing, breathing, and locomotion.

Neuromodulation

► Parkinson's Disease: Deep Brain Stimulation

Neuromodulation for Bladder and Bowel

► Methodologies for the Restoration of Bladder and Bowel Functions

Neuromodulation in Small Networks

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Definition

Neuromodulators are signaling molecules that induce long-lasting or network-wide changes in

Detailed Description

Neuromodulation, while often receiving less attention than direct synaptic communication between neurons, is a vital and ubiquitous feature of neuronal networks of all sizes. Modulation may be achieved by traditional small-molecule neurotransmitters, such as dopamine (DA) or GABA, or by small peptides and may act locally within a small network or globally across the entire nervous system. The diversity of function achieved by neuromodulation is a critical feature of neural systems that must be considered by computational neuroscientists as they strive to build accurate models of brain function.

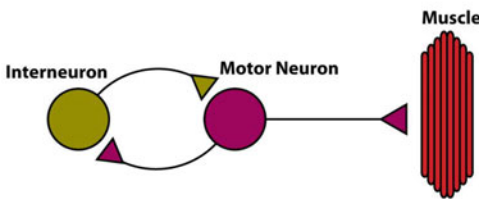
Modulation can be distinguished from synaptic transmission by its limited spatial and temporal specificity. In the mammalian brain, modulatory substances such as dopamine, norepinephrine, histamine, serotonin (5-HT), and acetylcholine are broadly released by projections capable of producing lasting effects through much of the central nervous system (CNS) simultaneously. In smaller networks modulators can serve a similar function; they may be released locally to affect a small group of cells in a central pattern generator or may be released in a paracrine fashion or as circulating hormones, influencing computation at many foci.

Work done with invertebrate systems, especially those of central pattern-generating networks, has shown that modulatory substances can affect neural computation at essentially every level of function (Fig. 1), adding richness and flexibility to circuitry that is not readily apparent from even the most accurate map of synaptic connectivity. Modulation may act directly on membrane conductances in the soma or spike generating regions of neurons, driving oscillations or affecting changes in gain (Marder 2012). After action potentials are generated, neuromodulation can shape features of spike propagation in axons (Ballo et al. 2012). When these signals reach their targets, neuromodulation may again be present to modify information transmission both at synapses between neurons (Zhao et al. 2011; Marder 2012; Nusbaum and Blitz 2012) and at the final nervous system output to muscles (Brezina et al. 1996, 2000, 2003).

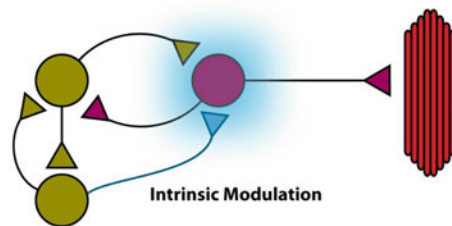
Furthermore, the application of a single modulator can affect multiple targets within a neuromuscular system. For example, the application of the neuropeptide myosuppressin elicits two dramatic effects on cardiac output in lobsters: a decrease in heart rate and an increase in cardiac muscle contraction force (Fig. 2a). The first effect appears to result from changes in the intrinsic dynamics of the cardiac CPG, which slows the rhythmic activity of motor neurons (Fig. 2b). The second effect stems from an increase in muscle sensitivity to neural input, perhaps by modulating the neuromuscular junction (Fig. 2c).

The diversity of modulatory targets, modulatory substances, and sites of modulatory action in the nervous system is striking and perhaps even staggering; evolution has evidently found heavily modulated neuronal environments advantageous, without regard for how difficult it might be to

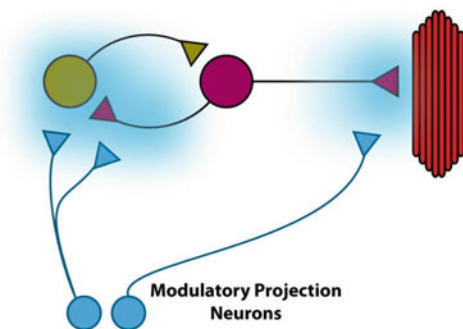
a. Unmodulated Network



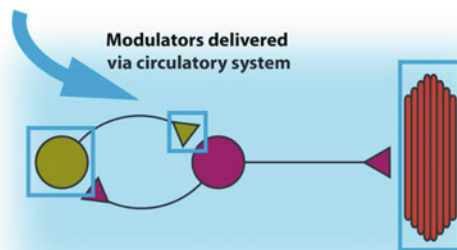
c. Intrinsic Modulation



b. Extrinsic Modulation (Paracrine)



d. Extrinsic Modulation (Hormonal)



Neuromodulation in Small Networks, Fig. 1 Neuromodulators can be delivered by multiple mechanisms and can target multiple components of a network. (a) A schematic diagram of a simple motor network without any modulatory influences. (b) A network that is subject to modulation by projection neurons that are extrinsic to the motor network (at bottom, in cyan). (c) A network

that is subject to modulation from internal sources (cyan *synapse*). (d) A network that is affected by hormonally delivered neuromodulators. The entire system is bathed in low levels of modulator (cyan *background*), and individual components of the network that express receptors are specifically targeted (shown schematically as cyan *boxes*)

understand such networks as an observer. The task for the computational neuroscientist is to first understand the power of neuromodulation to affect networks at all levels and to consider that even at the level of relatively simple, small networks, modulation grants a much wider range of function, and significantly more computational power than can be otherwise achieved. This entry summarizes what is currently known about neuromodulation in the context of small invertebrate pattern-generating networks, with a focus on results which are relevant to the computational neuroscientist, especially those that involve explicit *in silico* investigation.

Neuromodulators Affect Neural Systems at the Network Level

Neuromodulation May Be Required for Network Output

While neuromodulation is classically thought to provide functional tuning to the output of pre-configured neuronal networks, in some cases, modulation is required for small pattern-generating networks to produce any functional output at all. This requirement may arise from either intrinsic modulation, in which the modulatory sources are located within the network itself, or from extrinsic modulation, in which modulatory signals originate from distal regions of the animal and may be released either locally or hormonally (Fig. 1).

Extrinsic Modulatory Requirement

In the stomatogastric ganglion (STG) of crustaceans, neuromodulatory inputs from anterior sources, such as the paired commissural ganglia (CoG), are required for the production of two rhythmic motor patterns which operate at different frequencies: the pyloric and gastric mill rhythms (Marder and Bucher 2007). When these inputs are severed or pharmacologically blocked, either the network falls completely silent or the frequency of these rhythms decreases substantially. One important target of this modulation is an excitatory inward current present in many stomatogastric

neurons known as I_{MI} (Swensen and Marder 2000, 2001). The activation of this current is necessary to induce spontaneous bursting in pace-maker cells, which drive the rest of the CPG network. This is a classic example of network reliance on extrinsic modulation.

Intrinsic Modulatory Requirement

In the *Tritonia* swim network, the dorsal swim interneurons (DSI) are part of the canonical CPG and participate in rhythm generation through direct ionotropic neurotransmission; however, they also signal through metabotropic receptors to modulate the strength of a synapse in the circuit between two other neurons known as VSI and VFN. Swimming behavior in this animal is an episodic response to sensory inputs, which involves a switch from a non-bursting to a transient bursting mode. A computational study that searched the space of parameters in a network constrained by the topology of the *Tritonia* swim CPG found that it is difficult to construct a network with static parameters capable of matching this *in vivo* behavior; most bursting models either were oscillatory indefinitely or produced intrinsic bursting without a sensory trigger (Calin-Jageman et al. 2007). Because both the bursting and non-bursting modes of this network are relatively stable, the intrinsic modulation is required to alter network parameters during canonical output, thus allowing the CPG to perform its function.

Neuromodulators Can Fine-Tune Network Output

In addition to providing a drive that may be essential for network function, modulatory substances often tune features of output more subtly. These tuning functions, especially when conferred by a diverse range of modulatory substances, grant substantial flexibility to networks that is often important for behavior, allowing output features to be adjusted without changing the canonical pattern. Two experimental systems have provided detailed examples of these modulatory tuning

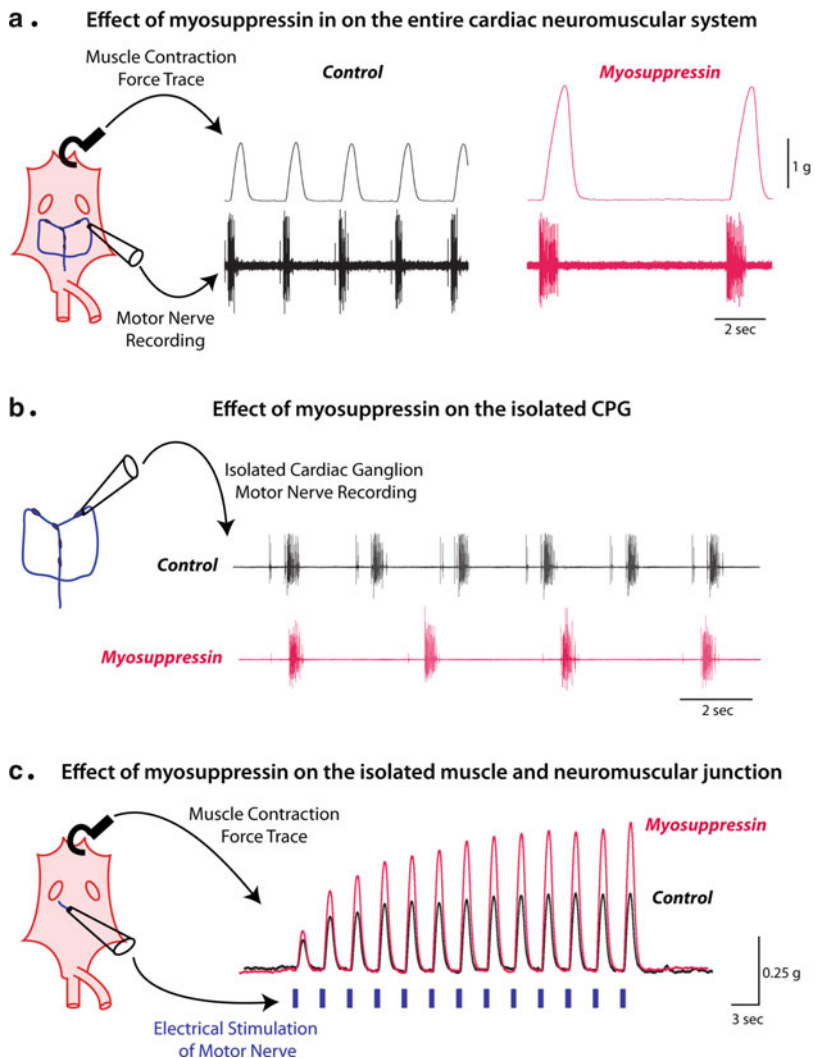
controls, but these are representative of what is seen in all nervous systems.

Crustaceans In the STG of crabs and lobsters, a wide variety of modulatory substances are capable of influencing properties of the pyloric rhythm while maintaining its triphasic output pattern (Marder and Bucher 2007). A detailed investigation of modulation of the various cells of the pyloric CPG found that while many different modulators converge on the same inward current (I_{MI}) in different neurons, the subset of circuit neurons upon which each substance acts is different (Swensen and Marder 2000). Thus, each

modulator is capable of influencing the network in a slightly different manner, producing distinct outputs that vary in features such as spikes per burst of motor neurons and phase relationships (Marder 2012). The ability of targeted modulation to evoke different versions of the pyloric rhythm was experimentally verified in a dynamic clamp study, in which the modulatory input current was computationally simulated in a neuron called PY while a modulator that does not affect this current was bath-applied to the STG. This manipulation was able to mimic the network effects of a different modulator which biologically turns on the equivalent current in PY (Swensen and Marder 2001).

Neuromodulation in Small Networks,

Fig. 2 Crustacean myosuppressin (a peptide hormone) modulates the cardiac system at multiple sites (All data are reproduced, with permission, from Stevens et al. (2009)). (a) The effect of myosuppressin in semi-intact heart preparations, in which motor neuron activity and muscle output are simultaneously recorded. Myosuppressin elicits a decrease in heart rate and an increase in cardiac muscle contraction force. (b) The effect of myosuppressin on the isolated cardiac ganglion, which contains the cardiac CPG. Myosuppressin elicits a decrease in motor neuron burst frequency, which appears to be responsible for the decrease in heart rate in panel A. (c) The effect of myosuppressin on a stimulated cardiac muscle preparation. Myosuppressin increases contraction force to the same electrical stimulation, which appears to be responsible for the increase in muscle contraction amplitude in panel A



Another well-studied crustacean motor circuit is the cardiac ganglion, which controls the frequency and strength of heart contractions. Neuromodulators are delivered to this system hormonally through the hemolymph or directly through extrinsic nerve fibers from the central nervous system. These modulators fine-tune both heart rate and cardiac muscle contraction force to meet behavioral demands (Fig. 2; Cooke 2002), for example, by eliciting an increase in heart rate when lobsters run on an underwater treadmill (Guirguis and Wilkens 1995).

Mollusks Well-studied modulated small networks also exist in mollusks, such as the snail *Lymnaea* and the sea slug *Aplysia*. An extensively studied CPG controls feeding behavior in *Aplysia* by operating a sequence of muscle contractions important for both ingestive and egestive feeding behavior (Cropper et al. 2004). A diverse set of neuropeptides have been characterized which shape a number of features of this network, including activation of fictive feeding patterns in quiescent preparations (Sweedler et al. 2002) and inhibition of motor neuron spiking (Furukawa et al. 2001). Neuropeptides also inhibit muscle contraction in the periphery at both the esophagus and stomach (Fujisawa et al. 1999; Furukawa et al. 2001).

This modulation can also alter the specific details of the neuromuscular transform at these output synapses. The neuromuscular junction of the *Aplysia* accessory radula closer (ARC) muscle is modulated by an extensive array of modulatory neuropeptides released from interneurons and sensory neurons, which provide the ability to tune various features of this function. These substances act presynaptically to regulate the release of ACh onto muscles to initiate contraction and also act through G protein-coupled receptors to alter many features of muscle contraction such as latency, amplitude, and relaxation rate (Brezina 2010). This scenario gives the animal extensive control despite the paucity of direct innervation; only two motor neurons innervate the ARC muscle. A semi-realistic model containing interactions

between neurons, modulators, and musculature at the periphery argues that modulation improves performance and appears to be required for the range of spiking behaviors, both regular and irregular, apparent in the biology (Brezina et al. 2005). This work again emphasizes the important function of modulation to give networks the ability to more flexibly control output than is possible with fixed network parameters.

Neuromodulators Can Switch Network Modes and Circuitry Through Multiple Mechanisms

Neuromodulation is also able to switch small neural networks between multiple modes, allowing for a much greater flexibility and diversity of responses than is obvious only from considering the connectome, or connectivity, of the system.

In *C. elegans*, the entire wiring diagram of the nervous system is known from electron micrograph reconstructions; a description of the connections among the 302 neurons was published decades ago (White et al. 1986). Yet it remains difficult to reliably identify important features of network function, due to the presence of extensive neuromodulation. More than 200 neuropeptide genes have been identified, the protein products of which actively reconfigure circuitry in response to sensory stimuli and environmental factors (Bargmann 2012). This modulation affects circuitry in a variety of ways. In one example, octanol avoidance in well-fed animals is mediated by a nociceptive sensory neuron called ASH. Following starvation, octanol avoidance behavior becomes distributed among three nociceptive neurons (Chao et al. 2004). The well-fed state can be mimicked by exogenous application of modulatory substances such as serotonin, dopamine, octopamine (OA), and some neuropeptides (Horvitz et al. 1982). In addition to influencing which neurons participate in particular behaviors, the same neuron may play a role in strikingly different behaviors depending on modulatory tone. The aforementioned ASH neuron, for example, is also capable of driving social aggregation

behavior, but does so only when the activity of a modulatory neuropeptide, *npr-1*, is low (Bargmann 2012). Thus, the well-known wiring diagram in this species serves more as a starting point for analysis of functional circuitry than an end, as which connections are active and important at any given time depends extensively on neuromodulation.

In the mollusk *Aplysia*, the feeding CPG network also features modulation that switches the modes of network output. Here, the same underlying circuitry supports both ingestive and egestive feeding behavior, and the expression of either depends heavily on neuromodulation. Neuropeptides have been implicated in biasing network output for either ingestion or egestion (Jing and Weiss 2001; Kupfermann and Weiss 2001; Morgan et al. 2002), and even thought to play a more direct role in network switching (Vilim et al. 2010). Vilim et al. (2010) showed that two structurally related peptides have distinct actions on neurons in the network, yet can work together to cause a switch between these two network modes and to depress contractions in feeding muscles.

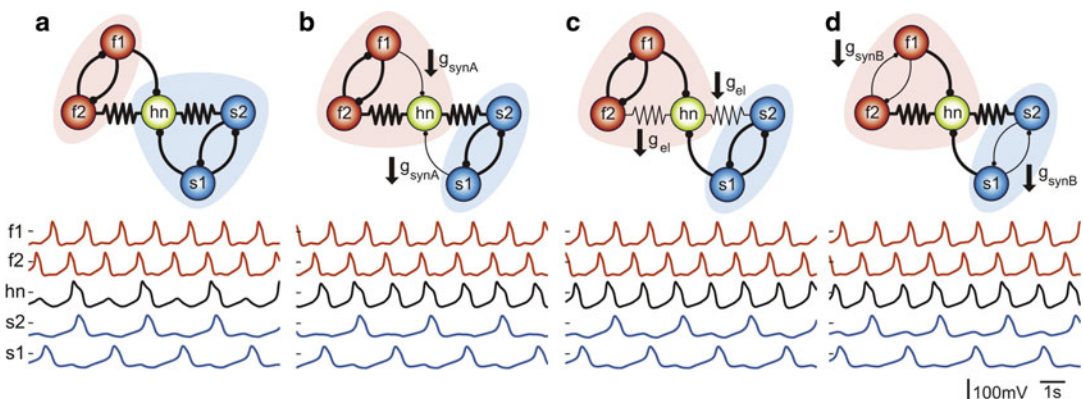
The idea that neuromodulation can switch small rhythmic networks between operational modes was investigated in a recent modeling study using a reduced model system motivated

by the linked oscillators present in the STG. Gutierrez et al. (2013) created a simplified network of model neurons in which two oscillatory pairs of neurons, one with a fast period and one with a slow period, were coupled through a “hub” neuron, which was capable of oscillating in time with either pair (Fig. 3a). The authors found that there were many potential targets within the network at which modulation influenced the behavior of the hub neuron. Significantly, the three entirely different circuit mechanisms could switch the hub neuron from oscillating with the fast pair to oscillating with the slow pair (Fig. 3b–d). Altering network parameters is a key feature of neuromodulation, as is a diversity of targets within neural systems, and thus this work implies that neuromodulation is likely to be a key player in networks that feature the coupling of multiple oscillatory units.

Variability and Robustness of Neuromodulatory Signaling

An essential requirement of neuronal systems is to produce robust behaviors despite the intrinsic variability and randomness of biological systems (Marder and Goaillard 2006). Many network

N



Neuromodulation in Small Networks, Fig. 3 Computational model of switching network behaviors with neuromodulation. (a) The “baseline” model network, consisting of five oscillating cells. The hub neuron (hn, in green) oscillates at the frequency of the slowly oscillating half center (s1 and s2, in blue), twice as slow

as the quickly oscillating half center (f1 and f2, in red). (b–d) Three example circuit manipulations, which may be induced via neuromodulatory mechanisms, which switch the behavior of the hub neuron to oscillating at the frequency of the fast half center (Figure reproduced from Gutierrez et al. (2013))

parameters vary over severalfold ranges: the maximal conductances of ionic currents, the strength of chemical synapses, and the strength of modulator-invoked currents (Marder and Taylor 2011; Roffman et al. 2012). This variability is not entirely random: it may result from homeostatic regulation mechanisms that tune intrinsic conductances and synaptic strengths such that functional output is maintained despite stochastic channel turnover and environmental perturbation (O'Leary and Wyllie 2011; Williams et al. 2013b). The inherent variability in the underlying structure of CPGs poses a problem for robust modulation, because altering network properties will yield variable effects depending on the initial parameters of the circuit (Grashow et al. 2009).

Most commonly, the effects of neuromodulators are qualitatively robust but quantitatively variable; neuromodulators generally affect measures of network activity in the same direction, but the magnitude of these effects is variable. In many cases the variability in a neuromodulatory effect is correlated with visible characteristics of baseline network activity. For example, in rhythmically bursting leech heart interneurons, the application of myomodulin usually increases burst frequency and intra-burst spike frequency; the magnitude of this change ranges from 0% to 50% across preparations and is correlated with the baseline frequency and intra-burst spike frequency of the rhythm (Tobin and Calabrese 2005). In another example from the crustacean STG, a number of neuromodulators produce consistent increases in the cycle frequency of the pyloric CPG upon their application, but these effects are only significant when the initial frequency of the pyloric rhythm is low (Nagy and Dickinson 1983; Nusbaum and Marder 1989; Skieba and Schneider 1994; Fu et al. 2007; Ma et al. 2009). These results have an intuitive explanation: the excitatory effects of a modulator can saturate when the system is already excited to begin with (similarly, the firing rate of a spiking neuron will saturate at some frequency due to the absolute refractory period). Additionally, the saturating nature of these modulators is sensible from a design perspective, because they can function to stabilize network output within physiologically useful bounds (Marder 2012).

A number of other experiments have reported more perplexing results, in which modulators do produce qualitatively distinct effects on network activity across preparations. Wiwatpanit et al. (2012) reported that the application of the neuromodulatory peptide C-type allatostatin (C-AST) to the heart of the lobster *Homarus americanus* produced a continuum of effects on the peak contraction force of the cardiac muscle. In some preparations, C-AST produced a significant decrease in peak force, in others it produced increases in peak force, in still others it showed biphasic responses in which peak contraction force first decreased, and then steadily increased over time; and sometimes no effect was observed at all (Wiwatpanit et al. 2012). A recent study showed that these qualitatively opposing results arise not only from variability in the effects of AST-C but from the nonlinear neuromuscular interface and variability in baseline CPG activity (Williams et al. 2013a).

Similar inconsistencies were observed in the STG of the spiny lobster *Panulirus interruptus*. Here, bath application of 5-HT produced a substantial increase, decrease, or no change at all in the cycle frequency of the pyloric rhythm, variability which was linked to the expression levels of different 5-HT receptors (Spitzer et al. 2008). These results are less intuitive from a design perspective, which provides an opportunity for theoretical work to bring clarity to these issues.

Interactions Between Neuromodulators

Due to experimental constraints, it is common for researchers to characterize neuromodulators one at a time, under controlled conditions. This does not, however, capture the complexity of biological systems, in which many different modulators are simultaneously present. The surprisingly large number of neuropeptide modulators has given rise to the field of neuropeptidomics, which seeks to characterize all bioactive peptides for a given species. Using mass spectrometry and transcriptome mining techniques, 31 families of crustacean neuropeptides have been identified, some of which contain over two dozen isoforms within

a single species (Christie et al. 2010). Genetic techniques have identified large numbers of neuropeptides in *C. elegans* (Husson et al. 2007; Li and Kim 2008) and *D. melanogaster* (Clynen et al. 2010). Additionally, modulatory neurons can co-release several modulators or transmitters onto one or more neural targets (Nusbaum et al. 2001). How can we extrapolate results from carefully controlled, in vitro experiments on neuromodulation to understand the messier organization of real biological systems?

Modulators Act Through Convergent and Divergent Chemical Signaling Pathways

Understanding the interactions of multiple signaling molecules is a difficult but frequently studied problem within the field of systems biology (Boonen et al. 2009). Within this conceptual framework, neuromodulators, including neurotransmitters, hormones, and growth factors, form complex signaling networks that both diverge and converge (Fig. 4). A signaling pathway is said to branch or diverge when an upstream element acts on multiple downstream targets, such as a modulator that binds to two different receptors. Different pathways are said to converge when two or more upstream elements act on the same downstream target, for example, two different modulators that activate the same signal transduction pathway. In general, upstream elements can either activate or repress downstream targets. Given the complexity of such signaling networks (Fig. 4a), and the nonlinearities inherent in biochemical processes and electrical signaling in neurons, it is unsurprising that the effects of multiple neuromodulators on network activity are not simply additive (Mesce 2002).

Neuromodulatory signaling pathways have been shown to converge on common targets in many vertebrate and invertebrate systems (Kaczmarek and Levitan 1987). In the crustacean STG, at least six different modulators activate the same voltage-dependent current (see Fig. 4b; Swensen and Marder 2001). Thus, when two of these modulators are applied in high

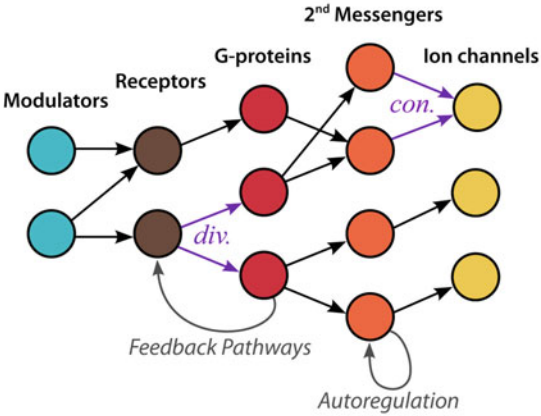
concentrations to isolated cells, they can occlude each other's effects. There are two points that may be drawn from these observations. First, the simultaneous application of several modulators can produce saturating effects due to convergence; it is possible, therefore, that convergence is a mechanism that safeguards the network from overmodulation (Marder 2012). Second, neuromodulatory signaling pathways exhibit degeneracy, defined as the ability for distinct elements to elicit the same functional output (Tononi et al. 1999). Degeneracy within a system is thought to contribute to its robustness, for example, by providing the ability to withstand partial deletions, and its evolvability, by allowing changes to be functionally incorporated (Whitacre 2010).

Individual modulators can also simultaneously tune multiple network parameters through divergent signaling pathways. For example, dopamine activates five different currents in the anterior burster neuron of the crustacean STG (Fig. 4c; Harris-Warrick et al. 1998; Harris-Warrick and Johnson 2010). Divergence may be advantageous in two respects. First, divergent structure increases the computational complexity and capabilities of the signaling network. Effectively, this structure stores information about how the neuronal circuit should be tuned in response to changing levels of a neuromodulator (Brezina and Weiss 1997; Brezina 2010). Divergence may also provide the network with a stability mechanism by scaling parameters with opposing effects. For example, dopaminergic modulation of the STG has been shown to activate both inward and outward currents across different cells in the circuit. Harris-Warrick and Johnson (2010) have suggested that this balance may allow dopamine to alter the bursting activity of STG neurons without depolarizing or hyperpolarizing the cells too much, which could either cause them to firing tonically or fall silent (Harris-Warrick 2010).

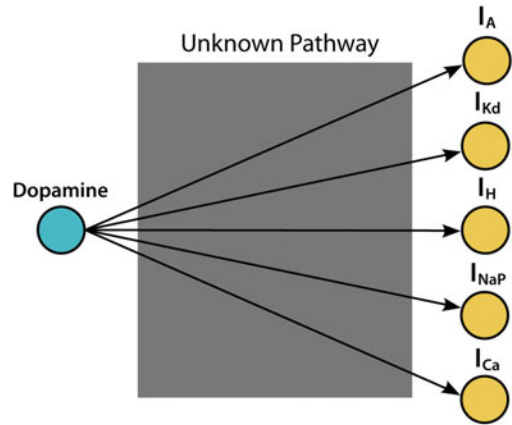
Nonlinear Interactions Between Modulators

In theory, the structure of neuromodulatory signaling pathways can accommodate many

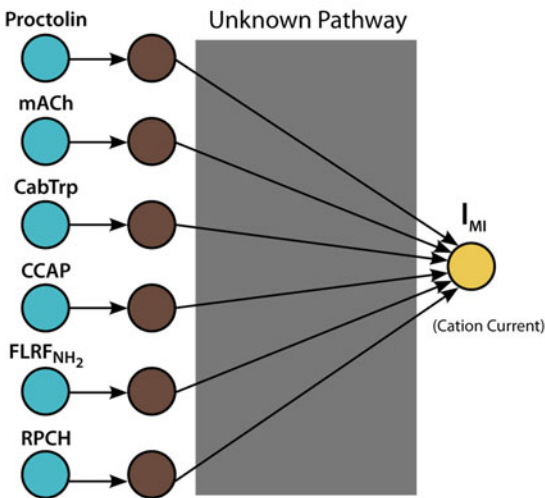
a. Idealized Modulatory Signaling Network



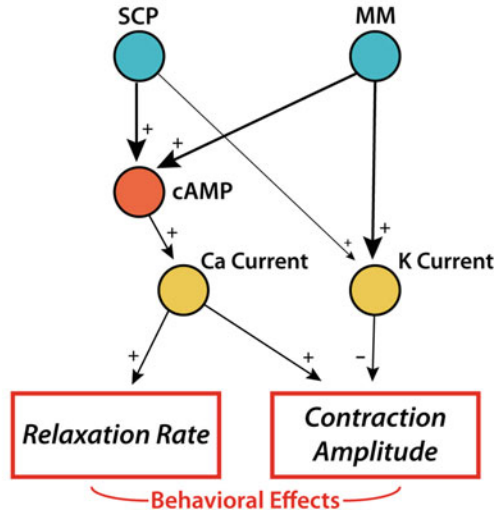
c. Effects of Dopamine on the AB neuron in the STG



b. Modulatory Control of I_{MI} in the LP neuron of the STG



d. Control of the ARC muscle in Aplysia by two modulators



Neuromodulation in Small Networks, Fig. 4 Modulatory signaling pathways contain convergent and divergent structure. (a) A schematic diagram showing two hypothetical modulators that exert physiological changes through G protein-coupled receptors. These biochemical pathways contain divergent (example labeled “div.” in purple) and convergent (example labeled “con.”) pathways. In principle, it is possible for modulatory pathways to include feedback and autoregulatory connections (in gray), but these possibilities are poorly understood within the current literature. (b) An example of

convergence in crustacean STG: six different modulators converge to activate the same voltage-dependent current in the lateral pyloric (LP) neuron (see Swensen and Marder 2000). (c) An example of divergence in the crustacean STG: the application of one modulator (dopamine) alters the activity of five different ionic currents (see Harris-Warrick et al. 1998). (d) The signaling pathways of two neuropeptides that affect the contraction dynamics of the ARC muscle in Aplysia contain convergent and divergent connections (see Brezina et al. 1996)

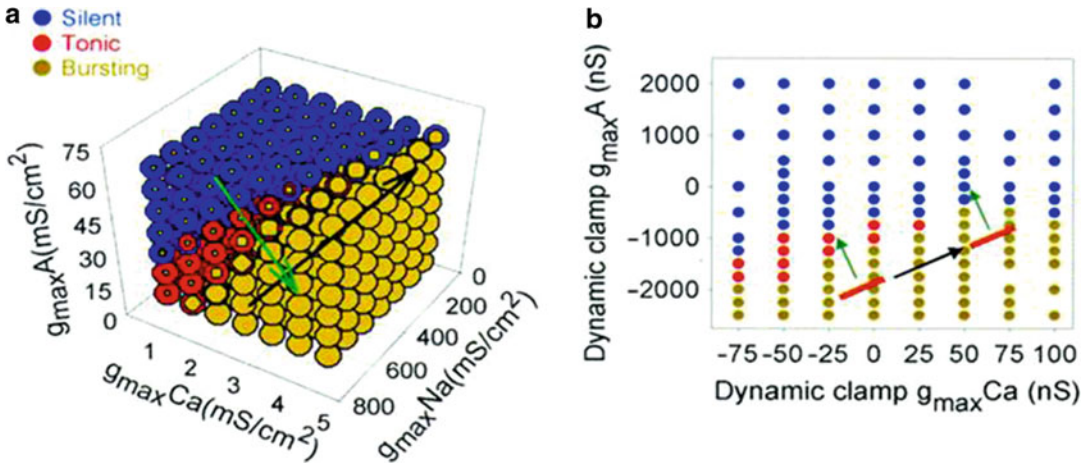
complex and nonlinear interactions between modulators (Brezina and Weiss 1997; Alon 2006). However, relatively few studies have directly examined combinatorial interactions between

different neuromodulators. Preliminary results, however, suggest that interactions between modulators can produce complex and behaviorally relevant effects:

- In the pre-Bötzinger complex of mice, the pharmacological blockade of the excitatory modulator substance-P produces little to no response, as long as two other excitatory modulators, serotonin and noradrenaline, are present. However, during the chronic blockade of serotonergic and noradrenergic receptors, the acute blockade of substance-P produces significant decreases in respiration frequency (Doi and Ramirez 2010).
- In the cardiac sac of the spiny lobster *Panulirus interruptus*, the application of the neuropeptide proctolin alone does not induce rhythmic bursting. However, the application of red pigment-concentrating hormone (RPCH) appears to potentiate the effects of proctolin, allowing it to elicit a strong motor pattern. This can occur even when RPCH is applied at low, subthreshold levels (Dickinson et al. 1997).
- In the medicinal leech (*Hirudo medicinalis*), fictive swimming motor patterns can be induced by the application of either serotonin or octopamine, and this effect is lost when the modulator is washed out of the preparation. However, the reverse effect is observed when both modulators are simultaneously applied. During the initial application of both modulators, little to no fictive swimming patterns is produced, but upon washout of the modulators, strong rhythmic pattern is observed (Mesce et al. 2001).
- In the moth *Manduca sexta*, heart rate is controlled by a variety of neuromodulators including the excitatory modulators octopamine and type-2 cardioacceleratory peptides (CA₂). The application of octopamine at subthreshold levels substantially potentiates the heart's response to CA₂, but the subthreshold application of CA₂ does not significantly affect the heart's response to octopamine (Prier et al. 1994).
- A study of neuromuscular transmission in the yellow crab *Eriphia spinifrons* and the crayfish *Procambarus clarkia* showed that the application of octopamine consistently lessened the excitatory effects of 5-HT, even though octopamine alone produced variable effects across preparations, either increasing or decreasing transmission (Djokaj et al. 2001).

What mechanisms can explain these interactions between modulators? It is possible that different modulatory pathways interact directly through excitatory and repressive connections between their signaling cascades, similar to other chemical signaling networks that have been extensively investigated in *E. coli* (Alon 2006). While this possibility is of outstanding interest, it has not been seriously tested to date, because neuromodulatory signaling pathways in small invertebrate networks are not well-characterized.

Even without direct chemical interactions, the complexities inherent within neuron membrane dynamics admit the possibility of nonlinear interactions between modulators. Goldman et al. (2001) examined this second possibility in a conductance-based model neuron and in biological STG neurons. By simulating the activity of the model neuron across many different maximal conductance combinations, they constructed a map of neural activity across a conductance space (Fig. 5a). A similar (but more restricted) map was experimentally determined by varying maximal conductance parameters of injected dynamic clamp currents (Fig. 5b). Within both of these maps, each point represents a different set of maximal conductances, the activity pattern of the neuron at that point is represented by its color, and the effects of a modulator can be visualized as a vector that moves the model from one point to another. This serves as a simple, but useful, approximation of biological modulation as modulators can have many other effects in addition to changing the maximal conductance of an intrinsic current. In Fig. 5, the black arrows show the effects of a modulator that largely preserves neural activity, in what Goldman et al. (2001) refer to as an insensitive direction of modulation. In contrast, the modulatory shift denoted by the green arrow qualitatively changes the behavior of the model cell, considered a sensitive direction of modulation. In Fig. 5b, note that the black modulator can shape the effect of the green modulator in a nonlinear fashion: the green modulator produces tonic spiking behavior when applied alone, but produces bursting behavior when co-applied with the black modulator. This result stems from the fact that the boundaries between qualitatively



Neuromodulation in Small Networks, Fig. 5 Neuromodulators can tune network parameters in sensitive (*green arrows*) and insensitive (*black arrows*) directions through global parameter space (Data is reproduced, with permission, from Goldman et al. (2001)). (a) A global activity map of a single-compartment

model neuron when the maximal conductances of three voltage-dependent currents are independently varied. Each dot illustrates the activity pattern of the neuron in that region of parameter space. (b) A similar activity map for a biological neuron when the strength of two dynamic clamp currents is altered

different activity patterns in conductance space are curved (i.e., nonlinear).

How Many Modulators Are Needed to Control Network Output?

Modulators can alter the activity of individual neurons and connected networks, but to what degree can they precisely control this output? Within the parameter space of a circuit, the effects of a single neuromodulator can be visualized as pushing the network along a one-dimensional path. In Fig. 5, we approximated these paths as vectors, but these paths would be more realistically captured as nonlinear curves (see Brezina and Weiss 1997). Additionally, these curves would have finite length since the effects of a modulator saturate at high concentrations. This one-dimensional case can be easily generalized. The coordinated actions of two neuromodulators can move the system along a finite, two-dimensional surface in parameter space. This is analogous to two linearly independent vectors that define a 2D plane; when the two modulators are combined at different concentrations, the network is moved in a unique direction

within a 2D region of space. In general, a system with N distinct modulators can independently control the parameters of the network within a finite N -dimensional region (Brezina and Weiss 1997). Equivalently stated, a neuromodulatory system requires at least N distinct modulators to independently control N different network parameters. However, modulators may hold less combinatorial power in practice, as they may be co-released under naturalistic conditions (Nusbaum et al. 2001).

One notable experimental study on the accessory radula closer (ARC) muscle of *Aplysia* supported this basic theoretical framework; the authors demonstrated that two features of muscle output, the amplitude and relaxation rate of muscle contractions, could be independently controlled by changing the relative concentrations of two neuropeptide signals (Brezina et al. 1996). Because small neuronal networks tend to be influenced by many different neuromodulators, it is possible that modulatory systems are designed to have broad control over network parameters (Brezina 2010). However, the extent of neuromodulatory control over circuit parameters remains an open experimental question in many systems.

Implications for Modeling

The extensive study of neuromodulation in small, pattern-generating invertebrate networks has led directly to modeling work described here and must also serve to inform modelers as they grapple with future issues, particularly in light of recent focus on obtaining the synaptic wiring diagram from more complex systems. While there is a wealth of invaluable information present in the connectome, when similar “wiring diagrams” of neuromodulation have been attempted, the results can be at least as complex, even in small systems (Brezina 2010). The extensive convergence and divergence of modulator actions, the huge number of modulatory substances, and the wide variety of cellular and network properties which are thereby affected amount to a staggering amount of complexity and flexibility which allows even very small networks to perform a variety of highly tuned and behaviorally relevant functions. Further, these actions and substances still elude complete description, as even in very well-studied systems, entire new families of modulatory neuropeptides are still being discovered.

A thorough consideration of the full richness of modulation will serve computational neuroscience well: their intrinsic and extrinsic origins; their diverse site of action, at every level of neuronal computation; their ability to gate network output entirely or simply fine-tune it; their extensive overlapping convergence and divergence; and their complicated interactions and modulatory connectome. All of these important features of neuromodulation are present even in small networks and are critical to reaching a proper theoretical understanding of circuit function both at this level and at the level of the entire nervous system.

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Neuromorphic Cognition

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Synonyms

Neuromorphic cognitive systems; Neuromorphic electronic systems; Neuromorphic real-time behaving systems

Definition

The hallmark of cognitive behavior is the ability of an agent to select an economically advantageous action based on immediate external stimuli as well as on their longer-term context. Neuromorphic cognition refers to the cognitive abilities of systems or agents implemented in neuromorphic electronic VLSI technology whose processing architecture is similar to the distributed, asynchronous one of biological brains. Neuromorphic agents are typically real-time behaving systems composed of multiple asynchronous event-based VLSI chips that integrate networks of silicon neurons and dynamic synapses together and that are interfaced to event-based neuromorphic sensors and robotic actuators. In order to express cognitive performance, these agents require a hardware infrastructure that supports local learning and decision making, for distributed communication and for the elaboration of state-dependent processing. We describe examples of such mechanisms and present a method for efficiently implementing neuromorphic cognition in these agents.

Detailed Description

Digital computers provide prodigious computational power and memory for the simulation of models of cognition. Nevertheless humans and many animals including insects still outperform the most powerful computers in real-world cognitive tasks. This disparity between the effectiveness of biological nervous systems and computers is primarily attributable to differences in their elementary processing devices and to the kinds of computational primitives they implement (Indiveri and Horiuchi 2011; Mead 1990). Rather than using Boolean logic, precise digital representations, and clocked operations, the nervous systems perform robust and reliable computation using hybrid analog/digital unreliable components; they employ distributed, event-driven, collective, and massively parallel mechanisms, and they implement adaptation, self-organizing, and learning strategies, on multiple spatial and

temporal scales. Understanding these principles, and how they can lead to behaviors that exhibit cognitive qualities, remains a major challenge for science.

The goal of *neuromorphic cognition* is to understand the neural mechanisms used by the brain to achieve cognition, as well as to implement them using electronic neural systems whose physics of computation and architectural constraints are based on those of the biological nervous systems. During the last decade the neuromorphic engineering community has made substantial progress in this endeavor by designing *neuromorphic sensors* and *neuromorphic hardware* and *spiking neural networks* and by developing the platform technology necessary for constructing distributed multi-chip systems of sensors and neuronal processors that operate asynchronously and communicate using action potential like signals (or spikes) (Chicca et al. 2007b; Merolla et al. 2007). In particular, it is now possible to build large multi-chip neuromorphic systems that combine multiple sensors with spiking neural network chips, robotic actuators, and end-effectors, as well as with conventional digital computing systems (e.g., for data logging, or further analysis). Usually, each chip specializes in a specific neural function (such as visual sensing, auditory sensing, filtering, spike-based learning).

The ability to construct distributed systems from collections of heterogeneous neuromorphic subsystems is largely due to the development of a very simple communication scheme, the “address-event representation” (AER), that is analogous to action potential communication between biological neurons. In AER, signal sources (such as silicon retina pixels or silicon neurons) each have a unique address. They signal their current activation by transmitting their address asynchronously on a digital bus. These AER events can then be routed to various target processors, in an analogous manner to axons routing somatic spikes to synapses.

Until recently, systems of this type have been mainly reactive, responding directly to stimuli with less regard for their embedding context in

either the observed world or within the economic goals of the agent. This limitation has been due to their inability to autonomously extract, and reason over, more sophisticated models of world and self, abilities that are characteristic of *cognitive* systems. The step from reaction to cognition in neuromorphic systems is not an easy one, because the principles of cognition remain to be unraveled. Discovering these principles, and learning how to implement them in neuromorphic technology, is now an active domain of research. For example, considerable effort is devoted to developing electronic circuits that are considered to provide “necessary conditions” for cognition, such as the abilities to:

1. Interact with the environment efficiently in real time, with appropriate temporal dynamics.
2. Store memories and to learn about the nature and statistics of their input signals.
3. Make weighted decisions.
4. Generate appropriate sequences of behavior.

These are only necessary conditions. To build neuromorphic cognitive systems, the challenge is not only to develop the appropriate hardware circuits and systems but more generally to understand what kinds of computational models asynchronous spiking neurons can support and how to configure the hardware neurons to perform desired tasks using a particular computational approach. Recent projects have obtained promising results in this direction (Eliasmith et al. 2012; Giulioni et al. 2011; Indiveri et al. 2009; Neftci et al. 2013). For example, an important recent result offers a foundation for the design and construction of compact and effective cognitive neuromorphic systems (Rutishauser and Douglas 2009). These authors describe how state-dependent computation can be designed using coupled recurrent networks. In the next sections we will first present examples of basic neuromorphic building blocks that can be used for implementing the necessary conditions. Thereafter we describe a method that uses these building blocks and the principles of (Rutishauser and Douglas 2009) to “synthesize” a simple cognitive agent.

Temporal Dynamics in Neuromorphic Systems

Neuromorphic architectures and processing strategy are substantially different from those of conventional von Neumann computers. The von Neumann architecture calls for a small number of complex processors, which are each able to access a very large common memory storing code, data, and partial results. Memory access and the processing of that data are highly orchestrated, occurring synchronously at very high clock rates. The processors are time multiplexed, computing on partial results that must be transferred from and to the external memory banks.

By contrast, neuromorphic spiking neural network architectures are composed of massively parallel arrays of simple processing elements in which memory and computation are co-localized. This design does not allow for the virtualization of time and the rapid transfer of partial results back and forth between the computing units and memory banks situated outside the architecture core. Instead, the synapse and neuron circuits of neuromorphic architectures must process input spikes on demand, as they arrive, and must produce their output responses in real time. Consequently, the processing elements must operate with time constants that are well matched to those of the natural world signals they are designed to process. This constraint is not easy to satisfy using conventional analog VLSI circuits, whose transistors operate in the *strong-inversion regime* (Sze 1981), because the demand for long time constants can lead to area-expensive solutions. The area cost can be avoided by neglecting the requirement for matching and modeling the neural dynamics instead at accelerated, unrealistic time scales (Brüderle et al. 2011; Schemmel et al. 2007; Wijekoon and Dudek 2008). An alternative solution to this problem is to use current-mode design techniques (Tomazou et al. 1990) and log-domain circuits operating in the *weak-inversion regime* (Liu et al. 2002). The time constants of these circuits are proportional to the circuit capacitance and inversely proportional to a reference current. If the reference current is a subthreshold one, then this current can be as small

as fractions of pico-amperes. Time constants of milliseconds would therefore require capacitors of only femtofarads, which can be implemented with very compact designs in standard VLSI technologies. Following this approach it is possible to build compact low-power neuromorphic circuits that can faithfully reproduce the dynamics of synaptic transmission observed in biological synapses (Destexhe et al. 1998) and that can implement sensory and signal processing systems for agents that need to interact with the environment in real time (Liu and Delbruck 2010).

An example of a compact subthreshold log-domain circuit that has often been used to reproduce biologically plausible temporal dynamics is the differential pair integrator (DPI) (Bartolozzi and Indiveri 2007). Using log-domain circuit analysis (Bartolozzi and Indiveri 2007; Drakakis et al. 1999; Frey 1993), and with reasonable assumptions of non-negligible input currents (Bartolozzi et al. 2006), it can be shown that the DPI circuit is equivalent to a first-order linear integrator which faithfully reproduces the dynamics of synaptic transmission observed in biological synapses (Destexhe et al. 1998).

Spike-Based Learning and Plasticity Mechanisms

One of the key properties of cognitive neural systems is their various forms of *plasticity*. In particular, “long-term” plasticity (Abbott and Nelson 2000) can produce sustained changes in the strength of individual synapses and so learn about the state of the environment.

Implementations of *long-term* plasticity mechanisms in neuromorphic VLSI chips provide a method of self-calibration, by which synaptic weights can be set automatically, without the overhead of dedicated wires and pins that would be required to load individual synapses from an external source.

Fortunately, plasticity mechanisms based on the timing of the spikes map very effectively onto silicon neuromorphic devices (Fusi et al. 2000; Häfliger et al. 1997; Indiveri et al. 2006; Mitra and Indiveri 2009; Bofill-i Petit and Murray

2004). A popular class of spike-driven learning rules is based on the spike-timing-dependent plasticity (STDP) (Abbott and Nelson 2000; Markram et al. 1997). In STDP the relative timing of pre- and postsynaptic spikes determines how the efficacy of a synapse is updated. There are several implementations of STDP learning chips (Arthur and Boahen 2006; Indiveri et al. 2006; Mitra and Indiveri 2009; Bofill-i Petit and Murray 2004), and a wide range of theoretical models have been proposed. Both the theoretical models and the VLSI implementations indicate that STDP can be effective in learning to classify spatiotemporal spike patterns (Arthur and Boahen 2006; Gütiç and Sompolinsky 2006), although, in its simplest form, the STDP algorithm is unsuitable for learning different patterns of mean firing rates (Abbott and Nelson 2000).

An interesting issue that arises for physical implementations of plasticity mechanisms, be they biological or electronic, is that the synaptic weights they update are both bounded (they can neither increase indefinitely nor assume negative values) and have limited resolution. This restriction on the precision and range of the weights imposes strong constraints on the network's capacity to store and retain synaptic memories. For example, in attractor networks with bounded synapses (Giulioni et al. 2011), if the long-term changes in synaptic weight cannot be arbitrarily small, the network's memory trace decays exponentially with the number of stored patterns.

In addition to the problem of overwriting the stored synaptic values with new ones, neuromorphic VLSI implementations must also address the problem of possible decay of the stored synaptic weight voltages with time (e.g., due to leakage). One effective strategy for protecting stored memories against decay is to permit only two stable synaptic efficacy states per synapse and allow only a very low average number of transitions from one stable state to the other (Fusi 2002). By modifying only a random subset of the synapses with a small probability, memory lifetimes increase by a factor inversely proportional to the probability of synaptic modification (Fusi 2002).

Given a stochastic mechanism for the weight update, and provided neurons are stimulated via a large number of redundant synaptic circuits, hardware implementations of spike-based learning networks can be shown to have computational properties analogous to the ones of ideal networks, with unbounded synapses (Fusi 2002). Where neuromorphic sensors interface with the environment, the input signals are inherently noisy. The noise of these input spike patterns is sufficient to drive the stochastic update mechanism required to increase memory lifetimes. In addition, by permitting only two stable synaptic states to store on long time scales the values of the weights, it is sufficient to use a bistable circuit that restores the synaptic state to either its high rail or its low one, depending if the weight is above or below a set threshold. In this way memory is preserved even in the absence of stimuli or when the presynaptic activity is very low.

Brader and colleagues (Brader et al. 2007) have proposed a spike-based learning rule using bistable synapses that is able to classify patterns of mean firing rates. This model is also able to account for classical STDP behavior, as well as the additional rich phenomenology observed in neurophysiological experiments on synaptic plasticity. This rule has been implemented using neuromorphic analog/digital circuits (Chicca et al. 2013) and has been applied to real-time spike-based learning and classification (Giulioni et al. 2009, 2011; Mitra et al. 2008).

Soft Winner-Take-All Circuits

Winner-take-all (WTA) networks are well suited for implementing decision making and context-dependent action selection operators and are easily implemented using neuromorphic circuits. These types of networks typically consist of a group of interacting neurons that compete with one another in response to an input stimulus. The neurons with the strongest responses suppress competing neurons to win the competition. Competition is achieved through a recurrent pattern of connectivity involving both excitatory and inhibitory connections. Cooperation between neurons

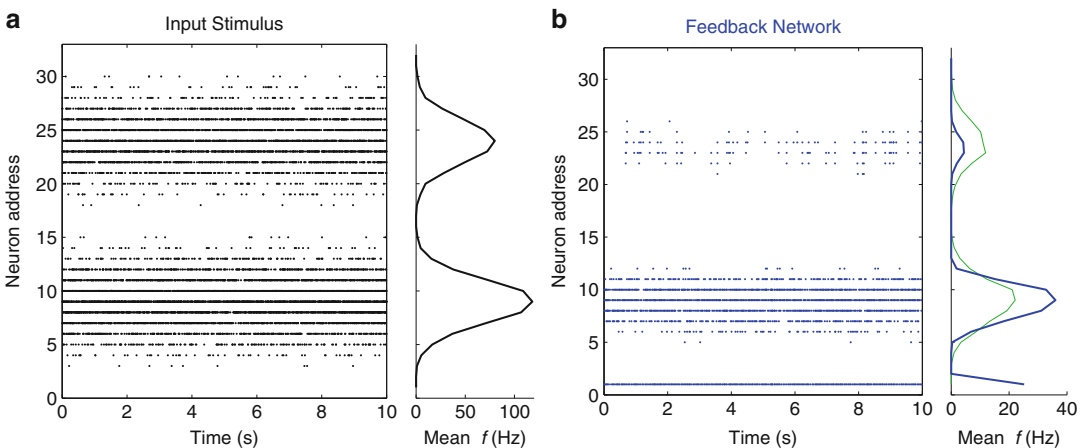
with similar response properties (e.g., close receptive field or stimulus preference) is mediated by excitatory connections. Competition and cooperation make the output of individual neuron depend on the activity of all neurons in the network and not just on its own input. According to the relative strengths of recurrent excitation versus inhibition, the network may select only one winner (hard winner-take-all) or a small population of likely winners (soft winner-take-all) (Amari and Arbib 1977; Dayan and Abbott 2001; Hansel and Sompolinsky 1998; Wilimzig et al. 2006). WTAs are useful computational primitives because they perform linear operation such as amplification and locus invariance, as well as nonlinear operations such as selective amplification (or selective suppression) and multi-stability (Chicca et al. 2007a; Douglas and Martin 2007; Hahnloser et al. 2000).

The computational abilities of sWTA networks have been used for solving feature extraction and pattern classification problems in simulation (Ben-Yishai et al. 1995; Bennett 1990; Pfeiffer et al. 2010) and in neuromorphic VLSI (Chicca et al. 2007b; Hahnloser et al. 2000). Interestingly, the pattern of connection of the WTAs is consistent with the pattern of connections observed in

the superficial layers of the neocortex (Binzegger et al. 2004; Douglas and Martin 2004), suggesting that the neurons of these layers may make use of this computational primitive (Douglas et al. 1995; Somers et al. 1995).

The examples of WTAs listed above make use of continuous valued outputs that can be interpreted as discharge rates. However, in neuromorphic implementations, where communication is usually by spikelike address events, it is more convenient (and more biologically correct) to implement these primitives using spiking neurons. Several examples of VLSI sWTA networks of spiking neurons can be found in the literature (Abrahamsen et al. 2004; Chicca et al. 2004; DeYong et al. 1992; Hylander et al. 1993; Indiveri et al. 2001; Oster and Liu 2004). Figure 1 shows experimental data measured from one of such neuromorphic WTA networks (Chicca 2006; Chicca et al. 2004). This example shows how the VLSI spiking neural network can perform nonlinear selection. An input stimulus (see Fig. 1a) consisting of Poisson trains of spikes, with a mean frequency profile showing two Gaussian-shaped bumps with different amplitude, is applied to the input synapses of each neuron in the soft WTA network. The chip output response

N



Neuromorphic Cognition, Fig. 1 Raster plot and mean frequency profile of input stimulus (a) and sWTA network response (b). The input stimulus (a) consists of Poisson trains of spike; the mean frequency profile over neuron address shows two Gaussian-shaped bumps of activity with different amplitude. (b) The sWTA network chip

response shows how the bump with higher amplitude is selected and amplified while the other one is suppressed. The response of the pure feed-forward network (no sWTA dynamics) to the input is shown for comparison (thin trace in the mean frequency profile)

is a series of spike trains produced by the output silicon neurons (see Fig. 1b). The mean frequencies measured from each spike raster in Fig. 1b show how the soft WTA network selects and amplifies the Gaussian bump with higher activity while suppressing the other one, with respect to the baseline condition.

Synthesizing Cognition in Neuromorphic Architectures

The previous sections described examples of circuits and circuit design techniques that can be used to implement the necessary components for endowing neuromorphic systems with cognitive abilities. Neftci and colleagues have recently described a method that combines many of these elements into a neuromorphic agent able to express simple real-time cognitive behaviors (Neftci et al. 2013).

Their method recognizes three conceptual layers of processing: firstly, a high-level *behavioral* model, in which the target cognitive task is cast as a state machine that captures the state-dependent organization of the required behavior (Fig. 2b); secondly, an intermediate abstract *computational* layer, comprising a field of neurons configured as many modular sWTA networks; and finally, an *implementation* layer composed of distributed neuromorphic hardware such as CMOS VLSI neurons and synapses and their event communication infrastructure.

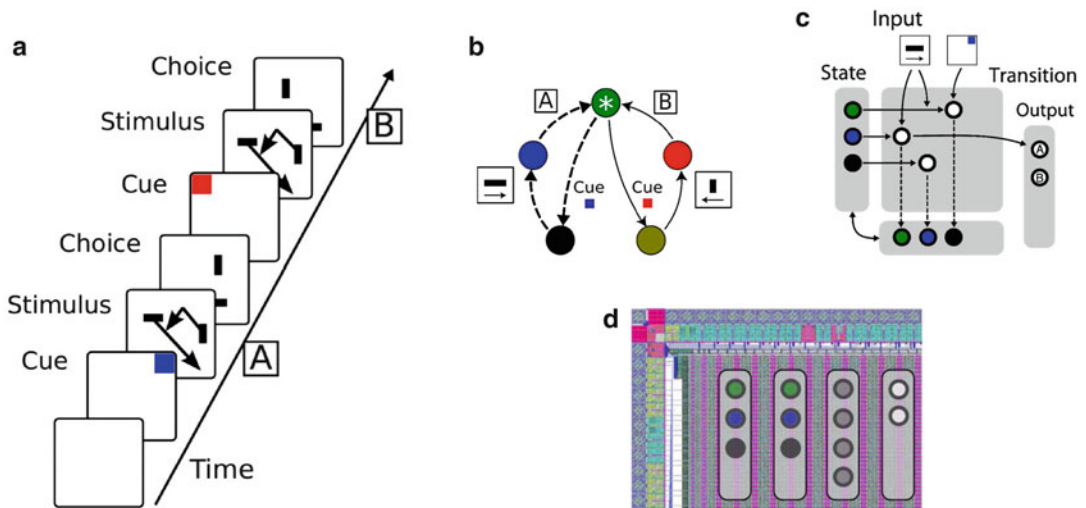
The method begins by creating the intermediate general-purpose computational layer. The model neurons of this theoretical and therefore precise layer are supported by the relatively imprecise electronic neurons of the implementation layer. These two layers are related by mapping the necessary model neuron parameters onto the circuit bias voltages of the electronic neurons via an automatic procedure in which the circuit biases are calibrated against the model parameters by a series of population activity measurements.

Finally, the high-level behavioral model is embedded in the computational layer by the introduction of sparse connections between sWTA modules so that the overall network gives rise to

attractors that encode the behavioral states of the cognitive model. Additional connections are introduced to provide the necessary transitions between the attractor states (Rutishauser and Douglas 2009). The transitions are conditional on external input. These coupled sWTA networks form a “soft-state machines” which, unlike conventional finite-state machines, combine analog and digital processing in the same circuit.

An example of a task similar to those used in laboratory settings to probe cognition in primates is shown in Fig. 2a. The cognitive neuromorphic agent is challenged with this same task. The agent is implemented using both electronic spiking neural networks and a neuromorphic *silicon retina* sensor that responds to visual patterns displayed on a screen (Fig. 2a) with trains of spikes. The visual scene is composed of independently moving horizontal and vertical bars. Depending on the current context, the neuromorphic agent is required to respond differently to these bars. The context in force is determined by a cue that is transiently shown at the beginning of the experiment and that must be remembered. In the first context the agent must produce response **A** when it observes a horizontal bar entering the right half of the screen; and in the second context it must produce response **B** when it observes a vertical bar entering the left half of the screen. Under all other conditions, the agent should remain silent. The relevance of this task is twofold: It requires processing of real-time dynamic visual stimuli in a state-dependent fashion, and it is comparable in complexity to the tasks used to probe cognition in behavioral studies of humans and animals. The neuromorphic agent was able to perform this task successfully and reliably and produce the correct output by activating the appropriate place-encoded neurons.

The important contribution of this work is that it provides a systematic way to install reliable processing on the underlying unreliable neuromorphic hardware, in a way that simplifies the programming of the desired high-level behavior. This approach is analogous to the software one used to program and compile computational processes in general-purpose digital computers, except that the underlying neuromorphic



Neuromorphic Cognition, Fig. 2 (a) The cognitive task: depending on a contextual cue, certain motions of a horizontal and a vertical bar must be detected. (b–d) Three-level concept for synthesizing the required behavior in an electronic neuromorphic VLSI system. (b) High-level state machine behavioral model that describes the task shown in (a). Filled circles denote states, arrows denote state transitions, and symbols denote input conditions for transition. The asterisk marks the idle state. (c) Computational layer composed of sparsely interconnected sWTA modules, which are configured to express the state machine specified in (b). Each shaded rectangle represents an sWTA module which normalizes the activities of its associated excitatory populations. Colored circles indicate attractor states

established by sparse interconnections (indicated by the *bidirectional arrow*) between the two orthogonal state-holding sWTA modules. Colors conform to states shown in (b). The populations and connections shown in (c) correspond to the “blue” context, indicated by *dashed arrows* in (b). Context cues and direction of motion data are input to the populations (gray circles) of the transition generating sWTA module (large square). The transition sWTA connects to a further output sWTA module. (d) Layout of the analog/digital spiking neural network chip whose voltage and current biases, and routing tables, are automatically configured to implement the computational layer. Rectangles illustrate sWTA neuronal modules

hardware is radically different from digital ones in both system concept and electronic implementation. Because our networks are implemented using spiking neurons and synapses with biologically plausible dynamics, they cast light on how both brains and future neuromorphic technologies could implement cognitive behaviors.

Discussion

So far neuromorphic engineering has succeeded in providing the physical infrastructure for constructing visual and auditory sensors, spiking neural networks, and event-driven effectors that are similar in organization if not in size to the nervous systems of biology. Until now the tasks that these neuromorphic systems have been able to perform are quite simple, so that even the most

sophisticated VLSI systems created were reactive in quality, mapping rather directly sensory percepts to simple actions. Of course, intelligent systems are not simply reactive. Instead, given some knowledge of its environment and its internal state, and some approximate behavioral objectives, an intelligent agent comes to reason that certain combinations of actions are more likely to achieve an objective than others. While we may recognize these properties in the behavior of animals, it has been extraordinarily difficult to evoke them in artificial systems, be they either symbolic or connectionist in design.

Neuromorphic cognition faces the challenge of implementing such properties in real-time behaving sensory-motor systems. This not only requires to identify the organization principles of the brain but also to develop the technology and method for instantiating cognition on physical implementations

of neurons and synapses. Although the neuromorphic neuron and synapse circuits are fabricated using standard CMOS VLSI foundries, they are unlike conventional industrial digital or analog circuits. They are a hybrid of analog and digital asynchronous circuits, and their analog transistors usually run in the subthreshold regime in order to emulate very compactly the crucial functional characteristics of neural systems (Indiveri et al. 2011; Liu et al. 2002). Consequently, neuromorphic circuits are subject to substantial fabrication variability (device mismatch) and operating noise. Unlike digital circuits, analog circuits require dedicated signal restoration mechanisms to avoid signal corruption through successive stages of processing (Sarpeshkar 1998). A similar signal restoration problem holds for biological neurons, as was quickly recognized by von Neumann when he considered alternative architectures for early computers (von Neumann 1958). The sWTA networks described in the previous sections and the neuromorphic circuits that emulate neural dynamics can be used to form signal restoration mechanisms that support reliable computation, even when implemented with imprecise hardware components. Furthermore, given the progress made in spike-based learning and plasticity methods for neuromorphic architectures (Mitra et al. 2009; Pfeiffer et al. 2010; Serrano-Gotarredona et al. 2013) and given the recent developments in methods for synthesizing cognition in neuromorphic systems (Eliasmith et al. 2012; Neftci et al. 2013), the challenge of building bioinspired intelligent agents that can interact with the environment in real time and express cognitive abilities is much more accessible.

Cross-References

- [Neuromorphic Engineering: Overview](#)
- [Neuromorphic Hardware, Large-Scale](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)
- [Spiking Network Models and Theory: Overview](#)

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Neuromorphic Cognitive Systems

► Neuromorphic Cognition

Neuromorphic Electronic Systems

► Neuromorphic Cognition

Neuromorphic Hardware, Large-Scale

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Synonyms

Large-scale; Neuromorphic system

Definition

A neuromorphic hardware system is an electronic system for information processing, based, to a certain degree, on the example of the biological nervous system. The operation of the whole system resembles the behavior of a network built from “neurons” and “synapses.” The degree of biological realism varies greatly between different research projects and targeted applications. Large-scale neuromorphic hardware projects target system sizes in the order of at least 10^6 synapses, but some aim for up to 10^{14} . Therefore, scalability is an important aspect of large-scale neuromorphic hardware, which also distinguishes it from medium- and small-scale neuromorphic hardware.

Detailed Description

Since its invention by Carver Mead (Mead 1989) in the 1980s, the term neuromorphic hardware has undergone a big shift in meaning. Was it originally coined for analog circuitry mimicking biological synapses and neurons by maintaining a direct equivalence between membrane currents and voltages in biology and electronics, it is now used for a broad class of microelectronic-based information processing systems built for the purpose of emulating neural systems.

Especially in the field of large-scale neuromorphic systems, a lot of technologies enabling the necessary amount of scalability are adopted from the field of high-performance computing, for example, network protocols and hardware (Moore et al. 2012). In some extreme cases large-scale neuromorphic systems resemble specialized highly parallel computer systems containing no structural elements identifiable as synapses or neurons (Furber and Temple 2007).

What distinguishes all large-scale neuromorphic hardware from high-performance computing systems is that they are purposely built and optimized for the emulation of neural networks. This usually gives them some advantages compared to numerical simulations on traditional computers, like lower energy consumption, faster emulation/simulation speed, and better temporal resolution due to continuous time operation.

Possible disadvantages are lower flexibility, lower precision, more difficult operation, and incompatibility with standard software simulators. Due to the greatly varying circuit techniques used in contemporary large-scale neuromorphic systems, each has its unique set of advantages and disadvantages and needs to be carefully examined for its adequacy for a certain experiment.

The large amount of research invested in the future of high-performance computing has made it obvious that exascale computing will be very expensive, mostly due to its tremendous demand for electrical energy (Kogge et al. 2008). Large-scale neuromorphic computing could be a possible alternative for greatly reducing the energy needed for emulating brain-sized models of biological nervous systems in the near future (Silver et al. 2007).

As stated above, large differences exist in the technical realization of large-scale neuromorphic system, despite being all implemented in contemporary very large-scale integration (VLSI) technology. The most basic distinction is the technical implementation of the neuron emulation. Large-scale neuromorphic systems can be divided in two categories: those using a physical neuron model and those using a numerical neuron model.

Physical Neuron Model

A physical neuron model in a large-scale neuromorphic hardware system is based on an electronic circuit built from metal-oxide-semiconductor field-effect transistors (MOSFET). Arranged around a capacitor that implements the neuron’s membrane capacitance, the circuit emulates the operation of the different ion channels located in the neuron’s cell membrane. By its operation the circuit continuously solves the differential equation for the membrane voltage.

The level of complexity can range from simple leaky integrate-and-fire models (Schemmel et al. 2006) to Hodgkin-Huxley or similar models which are able to replicate complex neuron behaviors like adaptation or bursting (Millner et al. 2010). Also synapses might be either simple current sources or complex conductance-based synapses with built-in short-term plasticity. Although the majority of large-scale neuromorphic systems

implements only point neuron models, some projects have published the first results using multi-compartment neuron models (Indiveri et al. 2011).

In nearly all large-scale neuromorphic hardware implementations based on analog circuits, the action potentials are transmitted as digital signals. Therefore, the neuron acts as analog-to-digital converter, while the synapse resembles a digital-to-analog converter.

To support learning, contemporary large-scale neuromorphic hardware projects usually include some kind of synaptic plasticity, for example, spike timing-dependent plasticity (Markram et al. 2012). Physical neuron models operate in continuous time. The time scale between the electronic circuit and the biological system it models can be different. Existing systems use time scales from 1 to 10^5 , termed “real time” and “(highly) accelerated” models, accordingly. Accelerated systems facilitate the research of long-time behavior of neural systems, like development and learning, as well as statistical and parameter analysis, where a similar network is emulated repeatedly.

Each neuron in the neuromorphic hardware system corresponds to one neuron of the emulated network. Therefore, to scale these systems up, a lot of silicon area is needed. Since the synapses greatly outnumber the neuron circuits, it is important to keep their size as small as possible. For example, a large-scale system with 10^{12} synapses each occupying $100 \mu\text{m}^2$ will need at least 100 m^2 silicon area or approximately 1500 silicon wafers with 30 cm diameter.

Most physical model-based large-scale neuromorphic systems store the synaptic strength in static memory (SRAM) in close vicinity or directly within the synapse circuits. Large research effort is currently invested to reduce the area associated with this storage by using resistive or floating gate memory circuits instead (Adhikari et al. 2012).

Numerical Neuron Model

In large-scale neuromorphic hardware based on numerical neuron models, a digital circuit calculates the membrane voltage, which is represented

by a binary number. It implements a numerical integration algorithm to solve the differential equations of the model. Since this numerical model has no relation to the biological real time, its operation can be synchronized to the whole network model in any suitable way. For example, one neuron circuit can be multiplexed to calculate the membrane voltages of a whole population of emulated neurons. By using industry standard dynamic memory (DRAM), a neuromorphic hardware based on numerical neuron models can emulate much larger synapse numbers than its counterpart based on physical neuron models, but at the cost of an equally higher energy consumption.

The architecture ranges from fixed-function integrator circuits implementing a certain neuron model like integrate-and-fire (Merolla et al. 2011) to systems based on full-blown microprocessor cores capable of running arbitrary complex models, limited only by memory capacity and processing speed.

System Level

On a higher level, any large-scale neuromorphic hardware implements some kind of high-bandwidth programmable interconnect system which allows the replication of the emulated network’s topology within the neuromorphic system. According to the continuous time operation of large parts of their system, the communication protocol used in such an interconnect system is usually a simple fire-and-forget type of protocol, carrying the destination neuron address as its sole payload. Handshake-based systems like the original address event representation (AER) scheme are not usually employed in large-scale system, due to the round-trip delay associated with the handshake signals.

To cope with the varying bandwidth demand of a neural network, where short high-activity bursting phases might be intermixed with long quiet periods, a high level of over-provisioning of communication bandwidth is employed. To alleviate the cost associated with such over-provisioning, the power consumption of the interconnect

hardware must be strongly correlated to the data rate (Schemmel et al. 2010).

Some implementations also digitize the time of the neural events, which allows them to better equalize the available bandwidth. In addition to the destination address, an event packet in this case also contains a time-stamp field, storing the time the event has to arrive at its destination. A network based on time-stamped event packets can be easily extended to implement the delays of the emulated network by adding the delay value to the time-stamp field.

Cross-References

- [NEST: the Neural Simulation Tool.](#)
- [Neuromorphic Cognition.](#)
- [Neuromorphic Engineering: Overview.](#)
- [Neuromorphic Technologies, Memristors.](#)
- [NEURON Simulation Environment.](#)
- [PyNN: a Python API for Neural Network Modelling.](#)
- [Spike-Timing Dependent Plasticity, Learning Rules.](#)
- [Spiking Network Models and Theory: Overview.](#)

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Neuromorphic Real-Time Behaving Systems

- [Neuromorphic Cognition](#)

Neuromorphic Sensors, Cochlea

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Synonyms

[Event-driven artificial cochleas](#); [Silicon cochleas](#); [Spiking cochleas](#)

Definition

The biological cochlea is a bony, fluid-filled structure in the inner ear. It performs the transduction between the pressure signal representing the

acoustic input and the neural signals that carry information to the brain. The cochlea is spiraled from the base to the apex, containing approximately 2.5 turns. The internal part of the cochlea is divided into three chambers (scalae): scala vestibuli, scala media, and scala tympani; Reissner's membrane separates the first chamber from the second chamber, and the basilar membrane (**BM**) separates the second and third chambers. A specialized structure, the organ of Corti, sits atop the basilar membrane. It contains both the inner and outer hair cells (**IHCs** and **OHCs**, respectively). The tips of these cells have hairlike structures, called stereocilia. Deflections in the stereocilia of the IHCs generate neural signals that travel to the brain. Neural signals from the brain can alter the length and width of the OHC cell bodies, affecting the mechanical properties of the BM, and thus its response to sound vibrations.

Airborne sound enters the ear via the ear canal and vibrates the eardrum, which in turn causes vibration of the three middle ear bones, one of which causes the cochlear fluid to vibrate. These small bones perform impedance transformation through a leveraging action, so that airborne sound can be transmitted into the fluid-filled cochlea.

At the base of the cochlea, the physical characteristics of the BM (it is narrower and stiffer) are such that it responds with greater movement to high frequency stimuli, whereas at the apex, the BM is wider and more flexible, so that it responds better to low frequency stimuli. Each position along the BM can thus be assigned a characteristic frequency that produces the greatest deflection at that place.

When the BM moves, the organ of Corti is displaced. The stereocilia of the IHCs are then displaced by the viscous drag of the cochlear fluid, making the displacement of the IHC's stereocilia proportional to the velocity of the basilar membrane motion. This movement of the stereocilia causes a change in membrane potential within the IHC, which in turn causes the release of neurotransmitter from the IHC. This release causes spiking activity in neurons, the spiral ganglion cells, whose axons make up the auditory nerve.

The stereocilia of the OHCs are attached to another structure, the tectorial membrane, and they are thus displaced due to the shear between the rigid upper surface of the organ of Corti and

the tectorial membrane. The OHCs change their length as a function of their membrane potential and provide active undamping of the mechanical structure. This allows the selectivity of the cochlear filters to adapt as a function of the intensity of the input sound.

Detailed Description

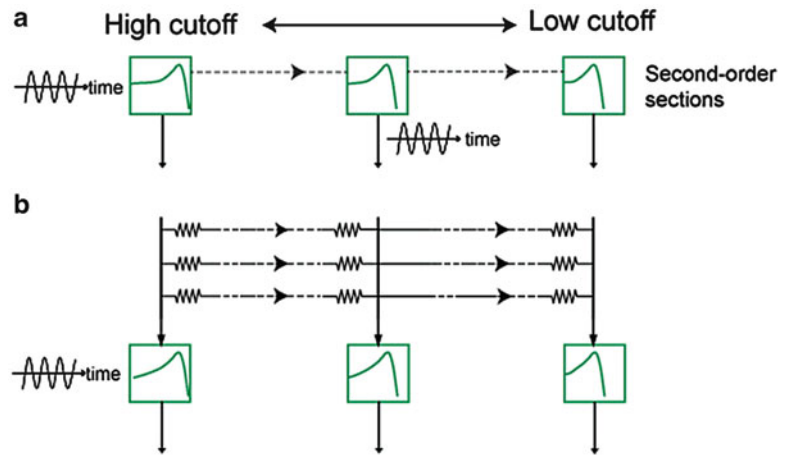
Biological cochleas use a space-to-rate encoding in which the input sound is encoded as trains of pulses created from the outputs of a set of broadly frequency-selective channels (Shamma 1985). The pulses are phase locked for low frequencies, and this phase locking disappears for frequencies above around 3 kHz (Palmer and Russell 1986). Encoding the information this way allows sparser sampling of frequency information according to the active frequency channels rather than the maximal sampling rate required to capture all information from a single audio source.

Silicon cochleas have been developed for over 20 years starting with the work of Lyon and Mead (1988). These designs model the biophysics of the BM as a large number of coupled filter stages. The architecture of the silicon cochlea varies from the cascaded architectures (Watts et al. 1992; Sarpeshkar et al. 1998; van Schaik et al. 1996) first introduced by Lyon and Mead (1988), modeling the phenomenological output of the cochlea, to a resistively coupled bank of band-pass filters (Watts et al. 1992; Wen and Boahen 2006; Fragniere 2005; Hamilton et al. 2008) modeling the role of the BM and the cochlear fluid more explicitly (Fig. 1). The cascaded architecture is preferred over the coupled band-pass architecture for better matching, ease of implementation, and a sharp high frequency roll-off of the filters.

The IHCs have been modeled as half-wave rectifiers (**HWRs**) along with possible models of automatic gain control of outer hair cells (Hamilton et al. 2008; Wen and Boahen 2009; Katsiamis et al. 2009). Recent cochleas also include circuits that model the role of spiral ganglion cells by asynchronous output quantization in the time domain with transmitted data encoded using the address-event representation (**AER**) (Wen and Boahen 2009; Lazzaro et al. 1993;

Neuromorphic Sensors, Cochlea,

Fig. 1 Architectures of cochleas. (a) Cascaded and (b) resistive-coupled stages



Kumar et al. 1998; Sarpeshkar et al. 2005; Georgiou and Toumazou 2005; Abdalla and Horiuchi 2005; Chan et al. 2007; Liu and Delbruck 2010; Liu et al. 2010a).

set by the amplitude and frequency of the input and the amount of charge needed to generate an event.

Filter Channel Circuits

Each stage of the filter bank usually consists of a second order section (SOS) filter in the case of the cascaded architecture. The characteristic frequencies of the filters along the cascade vary logarithmically with position similar to the approximate logarithmic dependence of the preferred frequency selectivity with position along the basilar membrane of the biological cochlea.

Each SOS consists of two forward filters, made from a transconductance amplifier and a capacitor, and one feedback transconductance amplifier. The difference of the outputs of the forward filters within a single SOS is the input to the subsequent IHC circuit. This difference readout adds a desirable zero to the transfer function without introducing undesirable gain proportional to frequency, as would occur with a temporal high-pass filter (van Schaik et al. 1996). It sharpens the filter response to approximate closer a band-pass response and reduces the phase accumulation across the cascade.

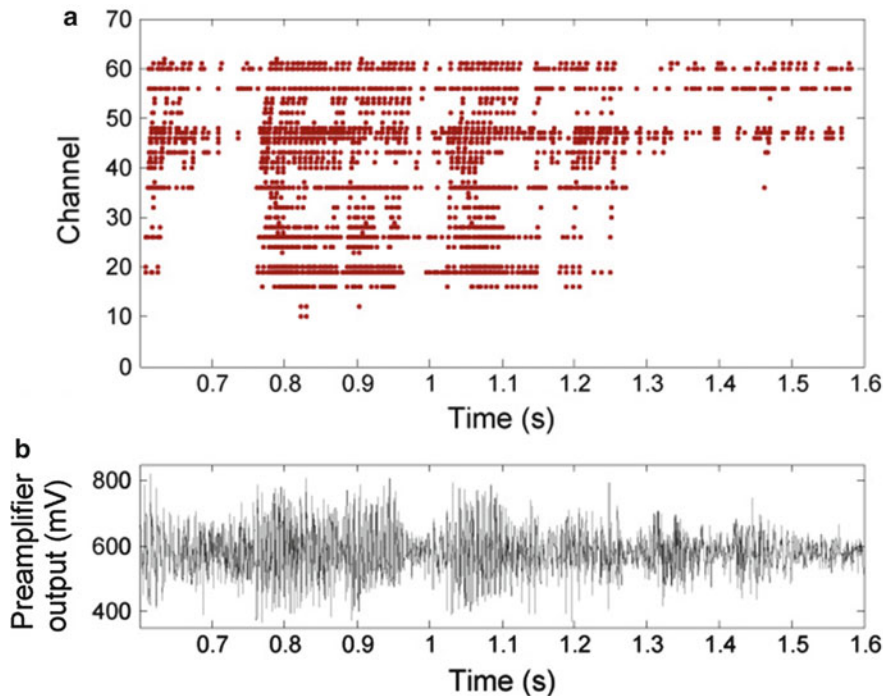
A half-wave rectification circuit implementing the IHC is a simplified model of the response of the IHCs of the biological cochlea. The circuit output drives spiral ganglion cell (SGC) circuits, each implemented as an integrate-and-fire neuron model. The number of events created in a cycle is

Event Data from Cochlea

Figure 2 shows the SGC outputs (AER events) and the analog input sound waveform from the latest binaural cochlear system with 64 channels, called the AEREAR2. The outputs are in response to a spoken sentence at a distance of 1 m from the system at normal speech volume (65 dB LAF SPL as measured with a Bruel & Kjaer 2250).

The AEREAR2 system implements a model of the BM, the IHC, and multiple SGCs with different thresholds driven by each IHC. It is the first fully integrated system that combines features of previous silicon cochlea designs that are robust to mismatch, along with novel features for easier programmability of the architecture and operating parameters. The chip includes integrated microphone preamplifiers (Baker and Sarpeshkar 2003), local gain adjustment, and on-chip digitally controlled biases (Delbruck and Lichtsteiner 2006). The individual basilar membrane and SGC circuit signals can also be digitized and read into the computer through the USB port. It has open-sourced host software APIs and algorithms which enable rapid development of application scenarios (Delbruck 2007). A bus-powered USB board enables easy interfacing of the AEREAR2 to standard PCs for control and processing.

The time-stamped AER events with a 1 ms resolution are sent to a PC where they are processed



Neuromorphic Sensors, Cochlea, Fig. 2 Response to spoken sentence “The shadow vanished.” (a) Events or SGC outputs from the 64 channels of one ear of the binaural AEREAR2. (b) Sampled audio from right

microphone preamplifier output. Low channels correspond to high frequencies and high channels to low frequencies. Best characteristic frequencies range from 100 Hz to 20 kHz

for applications. For natural sounds, off-chip microphone preamplifiers (MAX9814) with 20 dB range of automatic gain control or on-chip microphone preamplifiers with an 18 dB range of digitally controllable gain can be used. Input can also be applied from a PC sound card directly to the filter cascade (i.e., bypassing the preamplifiers).

In Fig. 2a, the dots represent events recorded from the AEREAR2 in response to a spoken sentence. Some channels are more excitable than others and have background activity leading to a sustained background event rate of about 4 keps. The average event rate is 80 keps and the peak event rate is around 325 keps. The sampled microphone output recorded using the onboard ADC is displayed in Fig. 2b.

Applications

Various cochlea implementations including the binaural AEREAR2 have been used for various

auditory tasks including spatial audition (Chan et al. 2007, 2010; Abdalla and Horiuchi 2008; Finger and Liu 2011). Processing is done on the asynchronous spike events rather than on spectrograms generated from sampled raw audio inputs. Post-processing can be cheaper because only a sparse stream of events needs to be processed. This event-based system is being tested for other auditory tasks such as speaker identification (Chakrabartty and Liu 2010; Liu et al. 2010b, 2012; Abdollahi and Liu 2011) and multi-sensor fusion.

Cross-References

- [Auditory Sensing Systems: Overview](#)
- [Neuromorphic Cognition](#)
- [Neuromorphic Engineering: Overview](#)
- [Peripheral Nerve Interface Applications, Cochlear Implants](#)

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Neuromorphic Sensors, Head Direction

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Definition

A neuromorphic VLSI head-direction system is a physical circuit (VLSI) model of the head-direction cell system found in the mammalian brain used to maintain and update a compass-like estimate of the animal's orientation in the environment. Currently, the physical circuit implementations are constructed in mixed-mode (analog and asynchronous digital) VLSI circuits that model spiking neural networks.

Detailed Description

A head-direction cell (described in mammals) is a type of neuron that has been found to become active when an animal is oriented in a particular direction with respect to the environment (Taube et al. 1990a; Sharp et al. 2001). With different neurons responding to different directions, the head-direction cell *system* is thought to reflect the animal's estimate of its orientation in the environment with respect to some reference orientation. While individual neurons maintain their orientation preference to each other in different environments, the system's overall reference orientation varies with the environment. The reference orientation appears to be linked to sensory cues (e.g., visual landmarks), and the activity is updated by vestibular and other self-motion signals. Head-direction cells have been found in many different areas of the hippocampal formation (hippocampus, entorhinal cortex, post-subiculum, etc.) linking their activity to spatial navigation (O'Keefe and Dostrovsky 1971; Hafting et al. 2005; Taube et al. 1990a; Moser et al. 2008) and memory tasks. More than a read-out of orientation, it is believed that the system of neurons operates collectively as an integrator of angular velocity (i.e., a "ring integrator"), converting vestibular signals (or other sensory- or memory-based information) into changes of orientation (Sharp et al. 2001; Taube 2001; Stackman and Taube 1997; Taube and Bassett 2003) and actively maintaining this estimate, even when sensory information is unavailable.

The ring-integrator model of the system consists of neurons or neuron groups connected in a ring. One and only one "location" on the ring should be active at a time, indicating the current estimate of orientation with respect to a reference angle. To operate as an integrator of angular velocity (which is available from the vestibular and visual systems), the neural activity in the ring should be self-sustaining and should move around the ring with a velocity proportional to the angular velocity of the animal. In modeling the head-direction system, the basic ring model is widely used; however, the mechanisms for movement of the activity on the ring vary significantly (e.g.,

Skaggs et al. 1995; Zhang 1996; Xie et al. 2002; Redish et al. 1996; Goodridge and Touretzky 2000). Only recently have spiking neurons and more detailed network connections been used to simulate these systems (Song and Wang 2005; Degris et al. 2004; Stratton et al. 2009).

VLSI Models

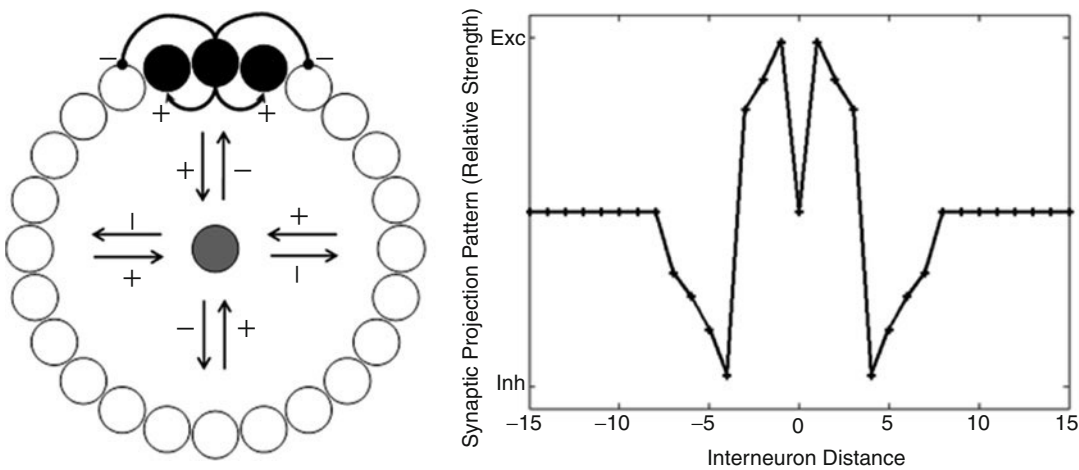
In the neuromorphic VLSI field, several different spiking neuron ring "oscillators" have been described that could function as a head-direction cell system; however, the ability or intention to variably control the speed and direction of the activity around the ring was always very limited (e.g., Wolpert 1996; Chicca et al. 2004; Sridharan et al. 2008). The work by Massoud and Horiuchi (2011a) addresses the speed control issue directly and is described below. A key limitation in the development of all of these neural models of the head-direction system has been the lack of information about the biological network interconnections that define the computation. To our knowledge, there has only been one explicit effort to model the head-direction system in VLSI-based spiking neurons (Massoud and Horiuchi 2011a).

In this work, a population of spiking VLSI neurons (representing the head-direction cells) is connected in a ring architecture (Fig. 1). Neighboring neurons up to seven neurons away are interconnected via recurrent synaptic connections with local excitation and surround inhibition. This center-surround recurrent projection is designed to produce self-sustaining spiking activity and promotes an active group size that is approximately the same size as the excitatory region of the connectivity kernel. There is a global inhibitory neuron (spiking) that receives excitation from all locations on the ring that projects inhibition back onto the ring uniformly to form a "winner-take-all" function, allowing only one location on the ring to be active at one time. Many variations of this center-surround feedback structure in neuromorphic VLSI with spiking neurons can be found throughout the literature (e.g., Indiveri et al. 2001; Chicca et al. 2004; Merolla and Boahen 2006). These neurons and connections satisfy

the need to produce a self-sustaining estimate of orientation and to allow the representation of only one orientation at a time.

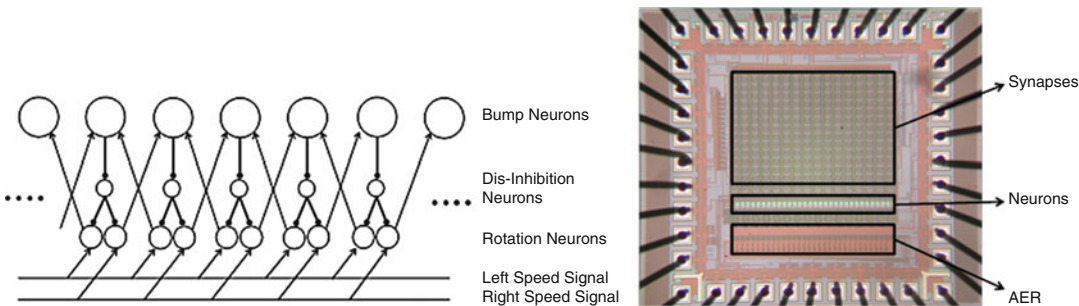
To move this “bump” (i.e., “group”) of activity around the ring in response to angular velocity, three additional movement-related neurons are associated with each location on the ring (Fig. 2). The additional neurons are labeled “disinhibition,” “left rotation,” and “right rotation.” To drive the rotation system, two input signals are used: “leftward speed” and “rightward speed.” These two speed-indicating inputs project

globally to their corresponding rotation neurons and fire spikes at a rate proportional to the leftward and rightward rotation speeds of the animal and do not fire spikes in the non-preferred direction. The left rotation neuron at each location projects excitation one step to the left, and the right rotation neuron projects excitation one step to the right. To prevent these rotation neurons from indiscriminately activating neurons throughout the ring, the disinhibition neurons (which are tonically active) suppress the rotation neurons at all locations *except* where the bump of activity



Neuromorphic Sensors, Head Direction, Fig. 1 A ring of neurons (*left*) each with local and global connections. A limited version of the local connections of one neuron is shown for clarity. The neuron in the center of the ring (*shaded gray*) is the global inhibitory neuron. This feedback inhibition allows only one group of neurons (“bump”)

to be active at a time (*shaded in black*). The global inhibitory neuron normalizes the total network activity through inhibitory feedback. Additional neurons and connectivity for moving the bump activity (discussed below) are not shown. (From Massoud and Horiuchi 2011a)



Neuromorphic Sensors, Head Direction, Fig. 2 *Left:* Connectivity diagram of the bump movement neurons. The arrow head indicates an excitatory connection, and the circle-shaped head indicates an inhibitory connection.

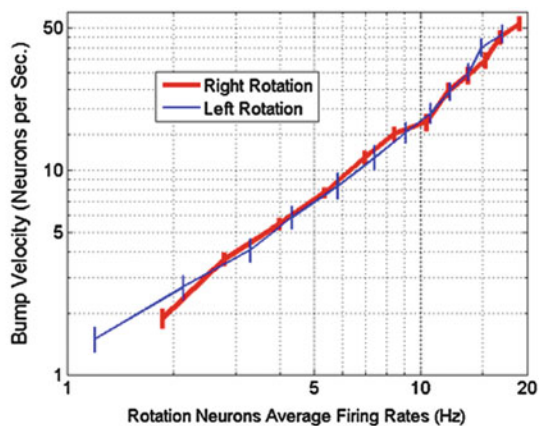
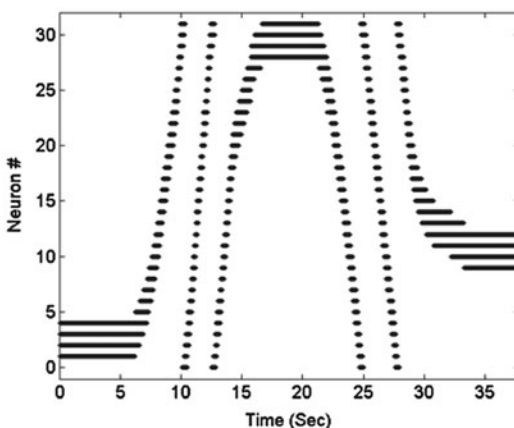
The network connections that maintain bump activity (see Fig. 1) are not repeated here for clarity. (From Massoud and Horiuchi 2011a). *Right:* Neuromorphic VLSI implementation of the system

is. The active head-direction cells of the bump inhibit the disinhibition neurons, allowing the rotation neurons to cause a shift in the bump location. By disinhibiting the rotation neurons, the angular velocity signal is able to drive the rotation neurons at a rate proportional to the input. In this system, when disinhibited, these neurons are configured to faithfully transmit one output spike for each input spike.

While this spike-based neural network has been demonstrated in a “mean-rate” mode (i.e., firing rate approximating a continuous variable) where the spiking rates are higher and the time constants are longer, the use of the more pulsatile mode of spiking neurons (i.e., lower firing rates and short time constants) creates some interesting phenomena that can be useful to the operation of the system (Fig. 3). In the recurrent connections that create the bump profile, local excitation can produce a synchronizing and rate-discretizing effect when the neuron with the largest input fires first, sending a pulse of excitation to its neighbors. If a neighboring neuron is then driven to spike, it will trigger another excitation pulse locally, entraining more local neurons. Both the surround inhibition and the global inhibitory neuron will limit the growth of this process. Within the “winning group” of neurons, although each neuron may receive different levels of input,

they will each fire a spike (with different latencies) whenever the leading neuron fires a spike first. The entire winning group will tend to fire at the rate of the fastest neuron and in temporally staggered order, but the group firing will appear roughly synchronous. The choice of synaptic weight and time constant will modulate the degree to which this synchronous firing occurs.

A second phenomenon associated with the spiking representation is the reduction in position drift of the activity bump due to fabrication mismatch in the transistors. When a winning group is firing stably, it actively suppresses its neighbors via lateral connections and the global inhibitory neuron. Because this spike-triggered inhibition occurs right after the winning group fires, increasing the gain of the inhibition increases suppression of the nonwinners, but very weakly reduces the firing rate of the winning neurons. Similar observations have been made in other VLSI systems (e.g., Sridharan et al. 2010; Giulioni et al. 2011). For this reason, it is possible to tune the parameters such that a significant additional input to the neighbors is required to shift the pattern left or right. When the system is operated with less pulsatile currents, the bump pattern becomes prone to drifting around the ring and into local minima (locally favored positions) created by transistor fabrication mismatch.



Neuromorphic Sensors, Head Direction, Fig. 3 *Left:* Demonstration of the movement of the activity bump around the ring in both directions with variable rotation speed. *Right:* Plot of the average bump velocity on the ring

(in neurons/sec) as a function of the rotation input signal (spikes/sec). The vertical bars represent one standard deviation from the average. (From Massoud and Horiuchi 2011a)

Discussion: Related Work in the HD System and Related Neural Systems

In addition to the head-direction cell system described above, Massoud and Horiuchi (2011b) have used the HD system (in a hybrid software/hardware system) to demonstrate how the short-term memory of objects sensed in different directions can be used to correct the integrator for velocity integration errors.

With more neuromorphic VLSI researchers entering the field and a strong interest in the computational neuroscience community to model the hippocampal formation and navigation-related areas, more VLSI models are certain to emerge, particularly as their potential for guiding micro-aerial vehicles increases.

Cross-References

- Neuromorphic Cognition
- Neuromorphic Engineering: Overview
- Neuromorphic Hardware, Large-Scale
- Vestibular Prosthesis, Interface

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Neuromorphic Sensors, Olfaction

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Definition

Neuromorphic olfaction is an emergent field of research which aims at unraveling computational principles of biological olfactory systems and translating them into algorithms and devices. The resulting technology has high potential for a wide range of practical applications (detection of chemical species, diagnosis, crime prevention and security, etc.) as well as a tool for basic research to verify hypotheses about the sense of smell in biological systems. Neuromorphic olfactory systems are composed of a sensing part which provides selective responses to particular chemical as input to a biologically inspired computational stage.

Detailed Description

Most animals rely on smell as sensory modality for survival and reproduction: it allows them to

detect predator, food, and mates. The biological olfactory system is an ideal model for the study of information processing in biological neural networks. Furthermore, knowledge about animal olfaction could be used to improve performances of artificial olfactory systems. The technology for artificial smell is still in the early stages of developments, but it has a wide range of possible applications ranging from quality control in food industry and detection of harmful substances (e.g., bacteria, drugs, explosives, etc.) for crime prevention and security to diagnosis in medicine.

Neuromorphic olfaction aims at understanding the computational properties of the sense of smell in biological systems and building artificial systems operating on similar principles and based on neuromorphic VLSI circuits. The challenges in neuromorphic are twofold: On the one hand, chemosensors need to be developed that match their biological counterparts in performance. On the other hand, algorithms and computing substrates are needed to analyze sensor data to quickly arrive at a detection and accurate identification of the odor stimulus. In the following, we give an overview on chemosensor technology, including biohybrid systems, and on neuromorphic implementations of algorithms for scent detection and identification.

Chemosensor Technology

Strictly speaking, there exist no neuromorphic chemosensors in the sense that the technology mimics the neuronal principle used by biological olfactory neurons. The majority of today's chemosensors operation is based on the measurement of the resistance of a sensing material that is exposed to vapor. The mechanism that causes the resistance change varies with sensor technology. Another recent approach are biohybrid sensors. In biohybrid sensors, the actual chemosensing step is performed by biological sensors, like isolated olfactory receptors, genetically engineered cells expressing the receptors, or preparations of olfactory tissue. The biological response is read out with an electronic circuit.

Most approaches have in common that the identity of the volatile (or solute chemical) is derived from the combinatorial activity of a sensor array, much like the olfactory system evaluates the combinatorial activity pattern of the diverse olfactory receptors in the nose. Each individual sensor has a specific response spectrum. These response spectra are typically rather broad, i.e., the sensor responds to a wide range of odorants. Hence, odor spectra usually overlap considerably between sensors. At the expense of a reduced coding space compared to nonoverlapping spectra, overlapping odor spectra enable partial redundancy in odor representation, which may be used to increase signal-to-noise ratio or the robustness against receptor dropouts.

Electronic Chemosensors

Three major classes of chemosensor can be distinguished according to their basic mode of operation: polymer and metal oxide (MOX) sensors, optical chemosensors, and piezoelectric sensors. A detailed description of electronic chemosensor technology is beyond the scope of this entry; we will only provide a concise overview on the available technologies. An in-depth review with references to original literature is provided by Arshak et al. (2004).

In polymer sensors and MOX sensors, the vapor is absorbed by the sensing material, interacts with it, and generates a change in the resistance of the material. This resistance change can be measured, and it acts as the output signal of the sensor. The sensor's selectivity to odorants is influenced by the composition of the sensing material, that is, the polymer components, or the metal alloy in MOX sensors. In addition, the sensors can be coated with thin films to change their selectivity. Varying the thickness and material of the film provides an additional possibility to influence sensor selectivity. MOX sensors require high temperatures to operate (150–500 °C), and ligand selectivity changes with temperature. Hence, the same sensors will provide different selectivity at different temperatures. This

circumstance can be exploited to create a sensor array with diverse characteristics from one single sensor material, by arranging a number of identical sensors next to each other and creating a temperature gradient. Polymer and MOX sensors are relatively cheap to build. The rich choice of commercially available materials enables the design of sensors with diverse characteristics. Both sensor types have fast response and recovery times. On the downside, polymer and MOX sensors are sensitive to changes in relative humidity. Hence, humidity must either be controlled or calibrated for when working with those sensors. MOX sensors have high power consumption due to the heating element that is required for their operation.

Optical chemosensors consist of fibers that are coated with fluorescent material. Upon interaction with volatiles, this material changes its fluorescent properties, e.g., spectrum, intensity, or wavelength of the fluorescence. This fluorescence is measured and converted into a voltage output signal. Optical chemosensors are immune to electromagnetic interference and fit a small and light package. As a disadvantage, this approach requires complex circuitry to measure the fluorescence change. In addition, fluorescent dyes are susceptible to bleaching due to light exposure and decay with time.

Piezoelectric sensors indirectly measure the mass of absorbed volatiles. Two kinds of piezoelectric sensors can be distinguished: surface-acoustic wave (SAW) sensors and lever-based sensors. In SAW sensors, a SAW with a frequency around 400 MHz is created on the sensing material. This frequency changes when molecules are absorbed. The exact amount of frequency change depends on the mass of the absorbed molecules. In lever-based sensors, a small lever that is coated with odor-absorbing material is attached to an electrode. The resonant vibration frequency of this lever changes with odor absorption and can be measured. Using different coatings, these sensors can be tuned to a wide variety of odors. They provide high sensitivity and respond quickly. On the downside, they require complex circuitry to measure frequency changes.

Biohybrid Systems

By definition, biohybrid approaches employ biological sensors for chemical sensing, like biological receptors, tissue, or even the entire animals. Animals have been used for centuries to enhance and complement human olfactory sensing, e.g., as in using dogs for scent tracking, and “whole-animal biosensors” are actually used in practice (see Persaud (2012) for a review). Cell-based biosensors exploit cellular responses to chemical and other external stimulation to detect a wide range of environmental cues (Persaud 2012).

Another approach is to couple biological olfactory receptors (ORs) and other chemosensitive proteins or other olfactory proteins with an electronic readout (reviewed in Persaud (2012) and in more detail Du et al. (2012)). This approach faces two major challenges: First, olfactory receptors or other olfactory peptides must be extracted or synthesized in sufficiently pure form. Second, these probes must be immobilized on a transducer in order to achieve reliable coupling with the electronic readout.

Four principal methods are available to produce receptors for OR-based biosensors: extraction from biological tissue or cells, cell-based expression of ORs using genetic methods, cell-free expression using the expression machinery *in vitro*, and chemical synthesis (for olfactory peptides). Extraction from living tissue is convenient because the natural protein structure and connections to transduction machinery in the cell are maintained. On the downside, extraction of specific ORs is inefficient. Hence, it is difficult to achieve specific ligand selectivity with this approach. Moreover, as the extracted ORs retain some cellular components, they must be provided with a culturing environment, much like natural cells, which presents a major challenge to the applicability of e-noses with extracted ORs. Obviously, this is difficult to achieve in commercial e-nose approaches.

Heterologous expression of ORs abolishes some of these disadvantages. Using well-established expression systems in human embryonic kidney (HEK) and yeast cells, the production of specific ORs is feasible (reviewed in Du et al.

(2012)). As in the extraction approach described above, the ORs retain their location in the membrane. In addition, through manipulation of the amino acid sequence of the OR protein, it is possible to furnish the OR proteins with cellular tags that facilitate their immobilization on the sensor substrate. On the other hand, expression systems are not very efficient due to the relatively low throughput of protein synthesis (Hamana et al. 2010).

Cell-free protein synthesis is a promising tool to enable cost-efficient OR production with high throughput. Protein synthesis is performed by adding DNA or mRNA and the other components required for protein synthesis (e.g., amino acids, nucleotides, ATP) to the cellular protein synthesis machinery *in vitro* (Katzen et al. 2005). Kaiser et al. (2008) report successful production of the human variant of the I7 receptor and its usage in a biosensor (Kaiser et al. 2008).

The highest abstraction from biological OR production is provided by direct chemical synthesis of OR-based biosensors, as reported by Sankaran et al. (2011a, b). First, odorant-binding domains are heuristically determined from the OR sequence, using computational modeling to predict the binding selectivity. Then, a polypeptide is designed from the amino acid residues involved in odorant binding in LUSH, an odorant-binding protein in *Drosophila*. This polypeptide is synthesized and used as a biosensor. This approach is particularly efficient due to the fact that only comparably short polypeptides are produced instead of the entire ORs and their transduction machinery. Moreover, there are many possibilities to design polypeptides in order to produce sensor peptide collections with diverse ligand selectivity.

In order to use OR vesicles or OR-derived peptides in biosensors, they must be immobilized on a transducing electrode. The most straightforward method for immobilization is to coat the electrode with a suspension of ORs. This method has been widely applied and the parameters for immobilization have been investigated (see Du et al. (2012) for references). A more complicated, but also more specific, approach is provided by immobilizing ORs using a self-assembled multi-layer strategy. In this approach, OR-specific

antibodies bound to the electrode using compound peptides, as reported by Hou et al. (2006). The specificity of the antibodies allows for directed immobilization of the desired OR to a specific location on the transducer. The olfactory peptides developed by Sankaran et al. (2011a, b) have been immobilized by direct covalent binding to the electrode, enabled through an AU-S chemical bond.

Taken together, biohybrid sensors address many of the shortcomings of purely electronic sensors, for example, ligand selectivity and response time. However, practical implementations of such devices are yet to be developed, as the technology to produce biological receptors and fixate them on electrode substrates evolves.

Neuromorphic Implementations

To our knowledge, the first truly neuromorphic olfaction device was proposed in 2007 by Koickal et al. (2007). The authors presented a fully integrated neuromorphic olfaction chip comprising a chemosensor array, a signal conditioning circuitry, and a spiking neural architecture with on-chip spike time-dependent plasticity (Markram et al. 1997). The very-large-scale integration (VLSI) device was fabricated using Austria Micro Systems (AMS) 0.6 μm CMOS process. Odor-sensitive material (carbon black composite) was deposited in post-processing. The device contains different sensor types to react to different chemicals. The signals produced by the chemosensor array were preprocessed for DC signal cancellation and constituted the input for the first layer of a spiking neural network. Hence, they can be considered the equivalent of olfactory receptor neurons (ORNs). A second layer modeled the projection neuron (PN). Each PN integrated inputs from several ORNs and produced the output of the olfaction device. Lateral inhibition in the PN layer enhanced selectivity of the neuronal response. The complete system was integrated in a single chip. On-chip test results demonstrated the functionality of all components as well as the signal path through the entire neuromorphic device. System circuit simulation

results were described to evaluate network performances. A further prototype chip was designed and testing and evaluation of this device was mentioned as future work. Unfortunately, there was no follow-up of this promising system by the authors, who continued this line of research using conventional digital hardware (Pearce et al. 2013). More in general, neuromorphic implementation of olfactory devices were not reported in the literature for some years and only recently the research community has shown renovated interest in this field (Beyeler et al. 2010; Ng et al. 2011; Hsieh and Tang 2012; Imam et al. 2012; Pfeil et al. 2013).

A hardware model of the antennal lobe (AL) of the fruit fly *Drosophila melanogaster* was described in Beyeler et al. (2010). Unlike in the above-described publication, the focus here was not on odor classification but rather on simulation of the biological system and the transformation of odor representation. The authors presented the results of a linear simulation, a spiking simulation with integrate-and-fire (IF) neurons, and a real-time hardware emulation using neuromorphic VLSI chips. They used an input data set of neurophysiological recordings from ORNs of *Drosophila* and studied the role of global feedforward inhibition. The results demonstrated that inhibition could be used by the AL to increase angles between odor pairs and therefore improve odor discriminability.

The gas recognition device proposed by Ng et al. (2011) offers an interesting solution to gas identity coding: 2D spatiotemporal patterns of spikes are generated in response to gas exposure. Gas identification is performed through match with a reference gas stored in a library of 2D spatiotemporal signatures. Spatiotemporal signatures are concentration invariant and unique for each gas. Gas concentration is encoded in the latency of the spikes. Classification performances are evaluated with three gases and 94.9% correct detection rate is achieved.

A complementary approach was proposed in 2012 by Hsieh and Tang (2012). They described a VLSI implementation of a spiking neural network inspired by the rodent olfactory bulb. A single chip can be trained to produce mean frequency

encoding of up to three gases or odor categories. Classifying more than three odors requires multi-chip systems (not presented in the paper). Classification performance was evaluated with three gases using odor data sampled by a commercial e-nose (Cyrano329). The system achieved 87.59% correct detection rate.

A hardware model of the glomerular layer of the mammalian olfactory bulb was recently described in Imam et al. (2012). As in Beyeler et al. (2010), the authors focus on detailed simulation of the biological system and study the transformation of odor representation in the olfactory bulb. The authors show that the implemented network improves the signal-to-noise ratio of odor representation and generates sharply tuned responses which are normalized with respect to the global activity. To perform odor classification, the output representation should be further processed by any pattern recognition system. Unfortunately, no quantitative data is shown to evaluate network performances in terms of odor separability (as compared to the input representation). Nevertheless, this model is not only an important step toward biomimetic neuromorphic olfaction systems but also a useful testbed to evaluate hypotheses on olfactory coding in spiking networks.

Another recent study implemented an olfaction-inspired network on a mixed-signal neuromorphic platform that reduces the receptive field overlap through lateral inhibition (Pfeil et al. (2013), section “Insect Antennal Lobe Model”). It is a neuromorphic implementation of an earlier approach to olfaction-inspired processing and classification of multivariate data (Schmuker and Schneider 2007). In contrast to the work by Imam et al., the focus of Schmuker and Schneider (2007) was on the classification of odors with a network that adapts the architecture of the insect olfactory system, but without claiming to reproduce the biological template in the closest detail. It consisted of a three-layer architecture, mimicking (1) ORN, (2) PN and lateral inhibition, and (3) a naive Bayes classifier that modeled higher brain areas which assign a certain odor quality to the input vector of ORN activities. The recent study

by Schmuker et al. (2014) implemented and applied a neural network on neuromorphic hardware for the classification of generic multivariate data sets. The network model is directly inspired by the olfactory system of insects and builds upon earlier work. It combines (1) a virtual receptor approach to convert any real data into ORN spike trains, (2) a decorrelation layer with glomerular structure and lateral inhibition, and (3) plastic synapses from the PNs onto distinct pools of association neurons (ANs) where each pool represents a single data class. Reward-based learning in the training phase optimizes the weights between PNs and ANs. In the test situation the network performed on par with the naive Bayes classifier on a number of different data sets including e.g. the well-known MNIST data set of handwritten digits.

Table 1 summarizes the published studies neuromorphic implementations of olfactory circuits.

Future Directions for Research

The development of effective neuromorphic olfactory systems is hindered by open challenges at the level of the sensors as well as the computational part. Depending on the technology used, gas sensors still deal with problems like sensor degradation, trial-to-trial variability, poor selectivity, or comparably low signal-to-noise ratios, requiring the signal to be averaged over long exposure times in order to arrive at reliable scent identification. Biohybrid approaches address many of these issues but require unconventional technology which makes it difficult to fabricate them in large quantities.

Sensor variability and poor chemosensor selectivity are also common in the biological system and might be tackled in the computational stage of neuromorphic olfactory systems. Evolution found good solutions for discriminating behavioral relevant odors despite the limitations of the sensory front end. Researchers working in the field of neuromorphic olfaction should tightly cooperate with biologist and modelers to advance the

Neuromorphic Sensors, Olfaction, Table 1 List of described neuromorphic systems with key features for comparison

	Hardware				Model	
	Chip size	Technology	Sensors	NN size	Glomeruli	Class. Perf.
Koickal et al. (2007)	50 mm ²	AMS 0.6 μm	3 × 3	9 ORNs, 3 PNs, 81 synapses	3	NA
Beyeler et al. (2010)	15 mm ²	AMS 0.35 μm	NA	23 ORNs, 23 PNs, 69 synapses	23	NA
Ng et al. (2011)	7.68 mm ²	In-house 5 μm	4 × 4	NA	NA	94.9%
Hsieh and Tang (2012)	1.78 mm ²	0.18 μm	NA	48 mitral cells, 6 cortical cells, 48 synapses	12	87.59%
Imam et al. (2012)	NR	0.45 μm	NA	256 neurons, 1024 × 256 synapses	48	NA
Pfeil et al. (2013)	25 mm ²	0.18 μm	NA	100 neurons, 480 synapses	10	NA
Schmuker et al. (2014)	25 mm ²	0.18 μm	NA	178 neurons	10	87–96%

Abbreviations: *NN* neural network, *ORN* olfactory receptor neuron, *PN* projection neuron, *NA* not applicable, *NR* not reported

understanding of the neurophysiological basis of animal olfaction and derive principle that can be applied to biologically inspired olfactory systems.

Cross-References

- Computational Olfaction
- Neuromorphic Engineering: Overview
- Olfaction: Overview

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Neuromorphic Sensors, Vision

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Definition

Neuromorphic sensors are artificial man-made sensors that try to imitate some of the working principles or structures of their biological counterparts. A neuromorphic vision sensor is,

therefore, an artificial man-made vision sensor that mimics some of the working principles or structures found in living animals' visual systems.

Detailed Description

Conventional video cameras are based capturing a sequence of still frames. Improving a camera means normally to increase the total number of pixels (resolution) and/or to increase the number of frames per second that can be captured, while reducing sensor area, power consumption, and possibly fabrication cost. These cameras just capture the light intensities of visual reality. If they are to be used in an artificial vision system (e.g., for robotics), then subsequent computing resources need to be allocated to analyze the sequence of captured frames and extract relevant information for decision making. The more resolution or the higher frame rate a camera has, the more computing power is required for performing artificial vision.

In the biological domain, biological retinæ do not capture sequences of still frames. Biological retinæ include sophisticated focal-plane processing circuitry that performs powerful signal preprocessing on the pixel-level light intensities, before sending visual information to the visual cortex in the brain.

A wide variety of neuromorphic vision sensors have been reported by researchers, including simple luminance to frequency transformation sensors (Culurciello et al. 2003), time-to-first spike coding sensors (Ruedi et al. 2003; Chen and Bermak 2007), foveated sensors (Azadmehr et al. 2005), temporal contrast vision sensors (Lichtsteiner et al. 2008; Posch et al. 2011; Serrano-Gotarredona and Linares-Barranco 2013), motion sensing and computation systems (Ozalevli and Higgins 2005), and spatial contrast sensors (Boahen and Andreou 1992; Ruedi et al. 2003; Costas-Santos et al. 2007; Leñero-Bardallo et al. 2010), to mention just a few. Here we will briefly describe only three such focal-plane preprocessing computations and explain very simplistically how the computations can be

performed using dedicated chip circuitry resulting in compact retina chips. These focal-plane computations are as follows: (1) spatiotemporal light average, (2) spatial contrast, and (3) temporal contrast.

Spatiotemporal Light Average

One of the first focal-plane neuromorphic computations reported was obtaining a spatiotemporal average of luminance, covering a certain spatial range and temporal range. This can be done by using a diffusive grid, as shown in Fig. 1. Each node i in the grid represents a pixel and contains a photo diode and a capacitor. The grid includes resistive (diffusive) interconnections among neighboring pixels, which can be made using resistors or transistors (Mead 1989; Liu et al. 2002). This way, if there is a gradient in pixel photo current I_{phi} levels for a given pixel neighborhood, it will translate into a gradient in pixel voltages V_i , thus producing “diffusive currents” flowing through the diffuser elements from pixel to pixel, trying to compensate the photo current (light) gradient. The result is that the voltage profile formed at the pixel nodes will be a smoothed version of the original light profile, and each pixel

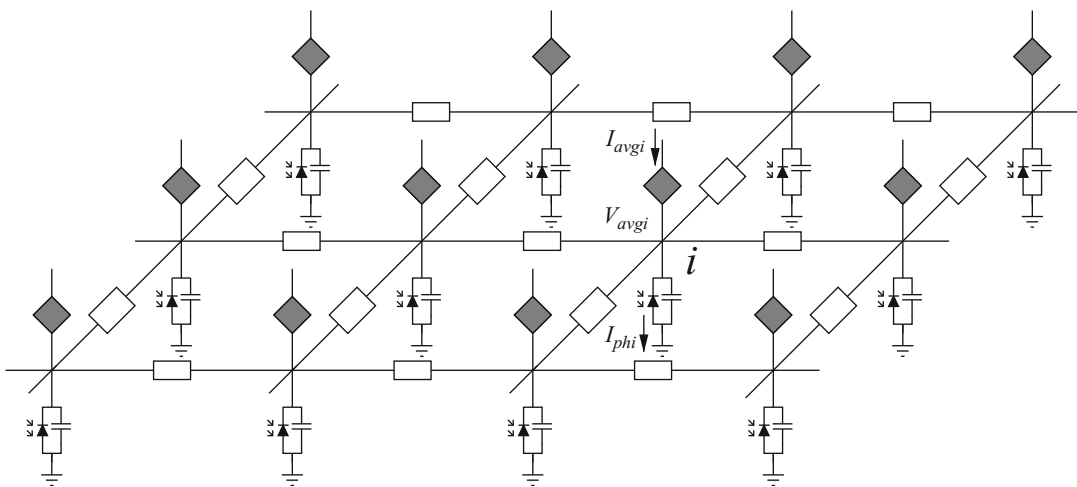
voltage represents an average over a given local spatial region. The effect of the capacitor at each pixel is to introduce an additional temporal average for the case photo currents that are changing in time. This spatiotemporal average pixel voltage representation can be translated, for each pixel, into a current I_{avgi} , using some circuit element (represented by a gray diamond in Fig. 1).

Spatial Contrast Computation

Using the spatiotemporal average current I_{avgi} together with a replica of the pixel photo current I_{phi} in a “current ratio computing circuit” and subtracting a reference (unity in this case), one obtains a representation of spatial contrast:

$$I_{conti} = \frac{I_{phi}}{I_{avgi}} - 1 = \frac{I_{phi} - I_{avgi}}{I_{avgi}}$$

Figure 2 illustrates a pixel signal profile through a one-dimensional section where the photo current profile shows a step, the average light profile is a smoothed version of this step, and the spatial contrast is a normalized light-level-independent profile highlighting the regions with changes of light.



Neuromorphic Sensors, Vision, Fig. 1 Schematic illustration of diffusive grid for spatiotemporal pixel-neighborhood average computation

Temporal Contrast Computation

Temporal contrast is the relative variation of light over time at a single pixel. Therefore, no inter-pixel interaction is required. Figure 3 illustrates a possible pixel diagram for computing temporal contrast at the focal plane. Pixel photo current I_{phi} is transformed into a log voltage $V_{logi} = V_o \log(I_{phi}/I_o)$, where V_o and I_o are constants. This voltage is fed into a voltage differencing amplifier that computes how much V_{logi} has changed since the previous reset,

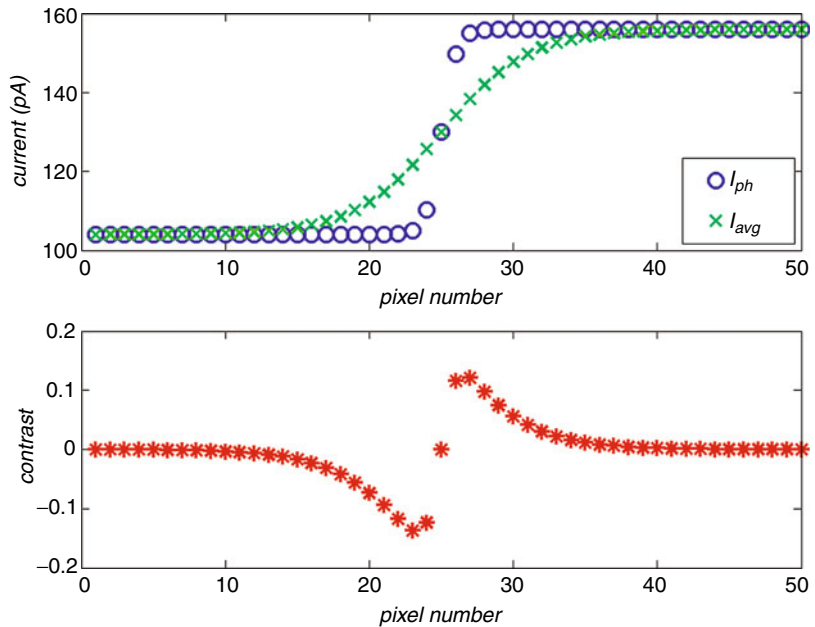
$$V_{di}(t) = \frac{C_1}{C_2} (V_{logi}(t) - V_{logi}(t_{reset}))$$

The reset signal itself is triggered whenever voltage V_{di} reaches either a positive V_H or negative V_L threshold. Therefore, two consecutive resets at t_1 and t_2 satisfy $V_{logi}(t_2) - V_{logi}(t_1) = (C_2/C_1)V_{H/L}$, or equivalently,

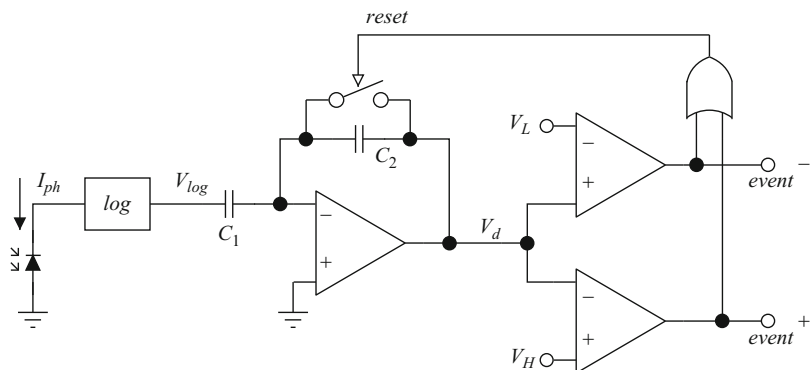
$$\begin{aligned} \frac{\Delta I_{phi}}{I_{phi}} &= \frac{I_{phi}(t_2)}{I_{phi}(t_1)} - 1 = \exp\left(\frac{C_2}{C_1} \frac{V_{H/L}}{V_o}\right) - 1 \\ &= \theta_{H/L} \end{aligned}$$

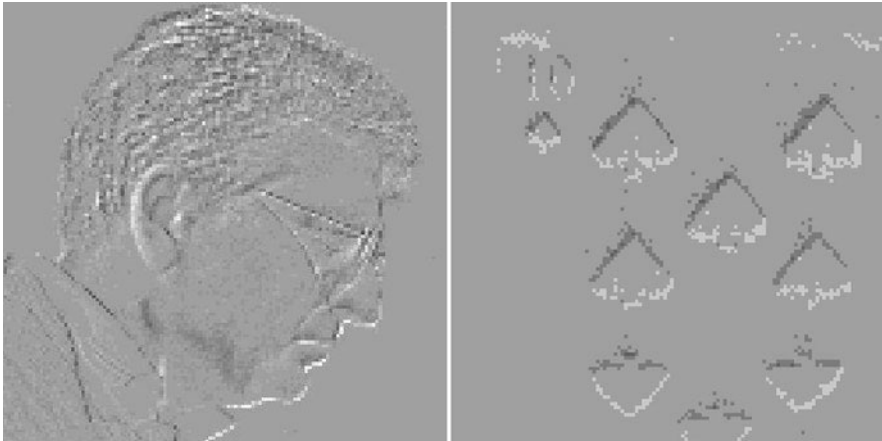
This means that the relative temporal change of light $\Delta I_{phi}/I_{phi}$ has reached an upper θ_H or lower θ_L contrast threshold. Whenever a pixel senses a

Neuromorphic Sensors, Vision, Fig. 2 Illustration of photo current average and spatial contrast computation over a one-dimensional section of a sensor. *Top*: sensed photo current from 50 pixels on a line, where around pixel 25 there is a step in light (circles) and computed average current using a diffusive network (crosses). *Bottom*: spatial contrast computation from the above photo currents and average currents



Neuromorphic Sensors, Vision, Fig. 3 Simplified circuit schematics of a typical temporal contrast computation pixel





Neuromorphic Sensors, Vision, Fig. 4 Illustration of temporal contrast (DVS) retina output. Retina contains an array of 128×128 pixels similar to those in Fig. 3. Whenever a pixel senses a change of relative light above a threshold, it sends out a positive (*white* in the figure) or negative (*black* in the figure) event. *Left*: The retina is observing a slowly moving head. The image is reconstructed from 40,000 events collected during 250 ms. The number of events collected per pixel is gray

coded. Background *gray* represents zero events, *brighter gray* represents a net positive number of events per pixel, and *darker gray* represents a net negative number of events per pixel. *Right*: recording from the same retina when observing a poker card deck browsed very quickly (in less than 1 s) in front of the retina. This recording contains 1000 events obtained during 634 μ s (microseconds)

temporal change of light reaching one of the thresholds, it sends out an “event,” which consists of the pixel coordinates and polarity of light change (x, y, p). This way, the sensor output is a “flow” of events representing the changing visual scene, without being constraint to any frame time.

Figure 4 shows illustrative examples of images reconstructed from recorded event flows from a 128×128 pixel temporal contrast retina (Serrano-Gotarredona and Linares-Barranco 2013), either for a slowly moving scene (Fig. 4 left) or from a very fast moving scene (Fig. 4 right).

Cross-References

- [Neuromorphic Cognition](#)
- [Neuromorphic Engineering: Overview](#)

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potential. However, considering a ratio of 1000 synapses to 1 neuron, as observed in biological networks, the bottleneck in designing large- to very large-scale networks is likely to be integrating synapses and related connectivity. Artificial synapses with synaptic plasticity require three computational elements: generation of synaptic current, storage of synaptic weight, and plasticity calculation. Memristors present the advantage of combining these three elements in a single component with a surface area of only a few hundred square microns.

Neuromorphic System

► Neuromorphic Hardware, Large-Scale

Neuromorphic Technologies, Memristors

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Synonyms

Memristive hardware artificial neural networks

Definition

Like biological networks, hardware neuromorphic networks are built up of neurons and synapses. The emergence of memristors, innovative electronic components with plasticity properties similar to those of synapses, offers a new technological solution for building neuromorphic VLSI.

Detailed Description

The design of analog silicon neurons has now been mastered (Indiveri et al. 2011), lowering computational cost down to a picojoule per action

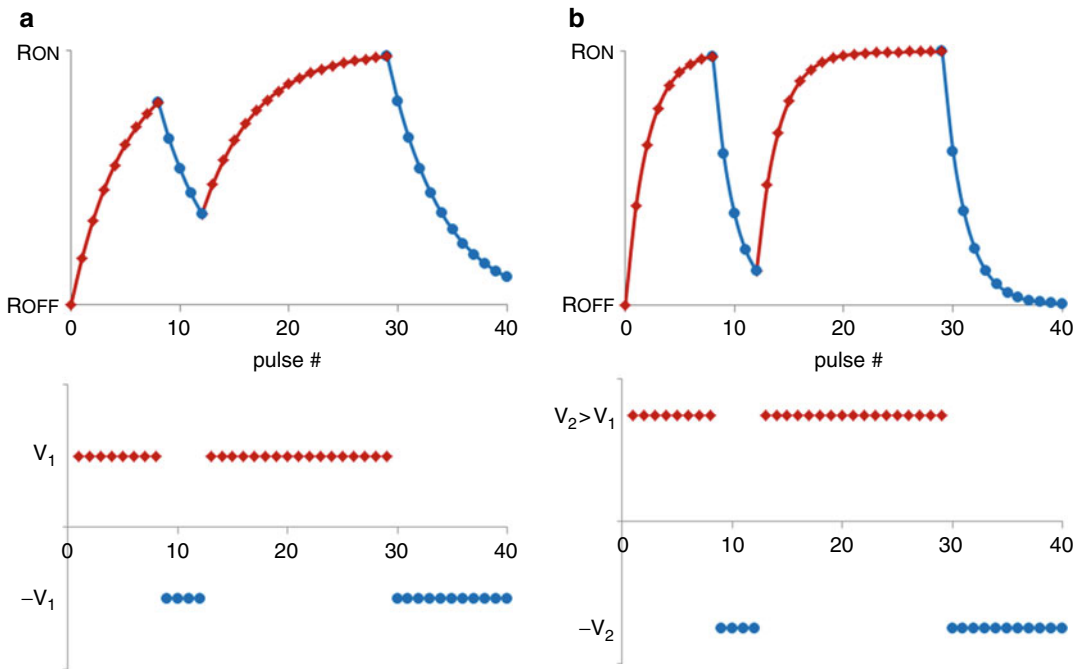
Memristive Principle

Memristors were originally envisioned by Leon Chua in 1971 (Chua 1971; Strukov et al. 2008). He considered the memristor as a fourth elementary, passive, two-terminal component, based on capacitor-inductor duality, unlike the resistor. Among the many descriptions of the memristor phenomenon in the literature, we focus here on the one best suited to neuromorphic design.

A memristor can be roughly described as a resistor which value depends on the current passing through: the stronger the current, the lower the resistance. In other words, similar to biological synapses, the more a memristor is used, the easier it is to use.

Taking a closer view, this phenomenon is only operative above a threshold voltage. Below that threshold voltage, a memristor is equivalent to a resistor and follows Ohm's law. Above it, variations of the memristor resistance depend on the applied voltage (value and application period). Due to the present fragility of these components, the voltage is only applied for short, repeated periods (less than a few hundred nanoseconds), rather than a single, long period. Figure 1 illustrates variations in the memristor resistance, depending on the applied voltage pattern. The increase and decrease of the memristor resistance is reversible depending on the polarity of the applied voltage.

One very important point regarding memristor function is the associated memory phenomenon. There are several processes underlying memristors properties: thermal effect,



Neuromorphic Technologies, Memristors, Fig. 1 Pulse response of a simulated memristor showing resistance potentiation and depression. *Top*: Resistance pulse response. *Bottom*: Voltage pulse patterns applied to

the memristor. (a) Pulse response with a low voltage V_1 (V_1 is above the threshold voltage). (b) Pulse response with a higher voltage V_2 ($V_2 > V_1$). In this latter case, the potentiation and depression phenomena are faster

redox-related chemical effect, and electronic effect. However, all these processes rely on a modification in the material, which implies that the memristor resistance is maintained, even when it is no longer connected to an energy source.

To summarize, that single nano-component provides a value (resistance) dependent on events (voltage and time), a memory point, and an adaptation mechanism.

Memristive Hardware Artificial Neural Networks

The intrinsic properties of the memristor make it an excellent candidate to replace existing solutions for hardware synapses in neuromorphic analog VLSI: (i) capacitors, which require periodic refreshment of the voltage across their terminals; (ii) floating-gate transistors, which require high voltages to program the value stored on the

floating gate; and (iii) digital memory points, which require digital-to-analog converters.

However, as previously described, the memristor's plasticity depends on the voltage applied to the terminals, whereas classical plasticity in neuromorphic systems, known as spike-timing-dependent plasticity (STDP), depends on the relative timing of events. It is then necessary to convert the time difference between two action potentials into a difference in voltage at the memristor terminals (Linares-Barranco et al. 2011). This point is now solved by IC designers, and focus is now on enhancing the characteristics of memristors. Depending on the memristor technology, there may be a dissymmetry between the increase and decrease in value of the resistance, and/or the number of write cycles may not be suitable for industrialization, and/or the technology may not be directly compatible with standard VLSI process.

Memristors offer undeniable advantages for future design of very large-scale neuromorphic devices. Their present limitations should be

overcome in the near future, thus providing neuroscience with a new performing tool for investigating neuronal mechanisms.

Cross-References

- [Neuromorphic Engineering: Overview](#)
- [Neuromorphic Hardware, Large-Scale](#)
- [Spike-Timing Dependent Plasticity, Learning Rules](#)
- [Spiking Network Models and Theory: Overview](#)

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NeuroMorpho.org

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Definition

NeuroMorpho.Org is a freely accessible online database of three-dimensional digital

reconstructions of neuron morphologies that are described in the scientific literature. The goal of the project is to enable reuse of these valuable data for research and to encourage data-sharing in the neuroscience community (Ascoli 2006). To this aim, the project identifies publications containing neuronal reconstructions and contacts the authors asking them to make their data available to others (Halavi et al. 2012).

Detailed Description

New data is uploaded to the database periodically during version releases. Version 5.7, released in May 2014, included 11,335 reconstructions contributed by 144 laboratories worldwide from 24 species and 29 brain regions. These data represent more than 30,000 h of manual reconstructions and 72 m of traced axonal and dendritic branching. Since the first public release in August 2006, the website has received over 135,000 unique visits from 146 countries. More than 3.2 million reconstruction files have been downloaded and used in over 200 published articles.

Various reconstruction software systems exist to generate the 3D morphologies from microscopy (Parekh and Ascoli 2013). Each of these offers multiple options to customize the process according to individual user preferences, and every researcher typically makes different selections based on their scientific interests. As a result, reconstructions come in a variety of formats, each containing an assortment of details, occasional inconsistencies, and unique features. Hence, all contributed data undergo a standardization procedure, in which each reconstruction is processed, measured, imaged, annotated with relevant meta-data, and uploaded to the database (Halavi et al. 2008).

Each reconstruction's information page includes its metadata, an image, a link to the original publication, a set of measurements computed with L-Measure, a 3D animation, and direct access to online interactive visualization. Additionally, each reconstruction is included as both the standardized version and the original version from contributing authors, along with a log of

changes made during the standardization procedures as well as a list of notes addressing any other specific and relevant details. The standardized version of the reconstruction is available in the SWC format, but reconstructions can also be downloaded in NEURON, Genesis, and NeuroML formats.

Users can query the database via a number of functionalities on the website (Ascoli et al. 2007). Using the Browse By functionality, users can browse the database by species, brain regions, cell types, or archive names. With the Search By Metadata functionality, users can narrow their search by selecting filters within a number of categories such as species, brain region, cell type, experimental protocol, and contributing author to name a few. Cross-category searches generate even more specific results. Reconstructions can also be searched by morphological measurements with the Search By Morphometry functionality. Users can specify neuron tree types (apical or basal dendrite, axon, whole neuron) and combine 21 morphometric parameters with Boolean logic or ranges. The Search By Keyword function is yet another way to search the database using specific input queries (e.g., “dendritic targeting, non-fast spiking”).

The website also provides access to a database of mined publications in the Literature Coverage section. Publications identified as containing neuron reconstructions are classified based on the availability of reconstructions, and these can be further explored by their year of publication and details such as species and brain region. The Help section of the website includes a Quickstart guide that explains how to find and download reconstructions, an FAQs section, and useful Tools & Links related to neuron reconstructions.

One of the most common experimental goals of digital reconstruction is to establish neuronal identity. Nonetheless, data downloaded from the repository have a number of other applications in computational neuroscience and in educational outreach (Parekh and Ascoli 2013). The reconstructions can be used to design and validate anatomically realistic virtual models of neuronal growth and to provide detailed compartmental representations of membrane biophysics to run

electrophysiological simulations. Furthermore, the 3D digital formats of reconstructions make them ideally suited to run complex morphometric analyses and to estimate potential network connectivity.

Technical advancements in tissue processing, image acquisition, and morphological reconstruction are leading to high-throughput data collection. With the expected forthcoming deluge of information, data curation and management will continue to become even more necessary to maximize the opportunity for scientific discovery. Databases like NeuroMorpho.Org are crucial as they not only contribute to data storage and distribution but also help formulate standards for file sharing, metadata annotation, and ontology development to facilitate smarter searches.

Cross-References

- [Databases and Data Repositories in Computational Neuroscience: Overview](#)
- [neuroConstruct](#)
- [NeuroElectro Project](#)
- [NeuroML](#)
- [NEURON Simulation Environment](#)
- [Neuronal Model Databases](#)
- [Neuroscience Information Framework \(NIF\)](#)

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Neuromuscular Control Systems, Models of

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Synonyms

[Models of neural control of movement](#); [Models of neuromotor control](#)

Definition

The neuromuscular control system is the network of neurons and muscles involved in the control of movement and posture. In many instances, the definition of the system also includes the sensors, sensory processing circuitry, and/or the passive mechanical structures that influence movement. Models of neuromuscular control systems, which are mathematical representations of one or more components, are used extensively in scientific investigations of neural control and in engineering development of biomimetic systems.

Detailed Description

An animal's ability to move is critical for exploration, interaction with the environment, and ultimately, survival. Neuromotor systems have been some of the most studied in neuroscience because movement is a readily observable behavior and the experimental environment can often be altered to manipulate the demands on the motor control system. The experimental paradigms and data derived from these studies have been used to form the theoretical foundations of our understanding of the neural control of movement and have had a broad impact on our understanding of neural systems that underlie the control of other physiological processes. Models of neuromuscular control systems provide a quantitative

representation that can be used in basic science investigations and for engineering applications.

Models of Neuromuscular Control Systems Have Been Used for a Variety of Applications in Science and Engineering

Models of neuromuscular control systems have primarily been used for developing and testing theories of motor control (Diedrichsen et al. 2010; Franklin and Wolpert 2011; Krakauer and Mazzoni 2011; Scott 2012; Scott and Norman 2003; Shadmehr and Mussa-Ivaldi 2012; Shenoy et al. 2013; Todorov and Jordan 2002; Wolpert and Kawato 1998). The complexity of the system components (sensory, neural, and motor) necessitates the use of computational approaches to quantitatively investigate and evaluate theories of motor control. Given the high degree of interaction between the sensory, neural, and motor components, it is often critical to include multidimensional dynamic models of the sensory as well as motor components in order to effectively use simulations of neural systems (Abbas and Full 2000; Cheng and Loeb 2008; Ekeberg 1993; Kambara et al. 2013; Pinter et al. 2012; Zelik et al. 2014).

Models of neuromuscular control systems have also been used in the design of biomimetic systems (Abbas 2011; Abbas and Abraham 2014; Ambroise et al. 2013; Bar-Cohen 2006; Schiff 2012; Verdaasdonk et al. 2009). There is a growing interest in the design of control systems that mimic neural systems in an effort to endow machines with sensorimotor control capabilities such as those exhibited by nearly all animals. Biomimetic systems have been used to control robots that walk (Verdaasdonk et al. 2009), robots that manipulate objects, and robots that autonomously interact with each other and the environment (Bar-Cohen 2006; Burdet et al. 2013). These efforts may not only produce robots with impressive capabilities, but they may also provide a real-world testbed for evaluating theories of motor control in a system that includes arrays of sensor and time-dependent actuators and that has to operate in a complex environment.

Finally, models of neuromuscular control systems have also been used extensively in the development of rehabilitation strategies and devices (Abbas and Riener 2001; Jung 2011; Peckham 2007; Scott and Norman 2003). For many years, one area of research and development has investigated the use of electrical stimulation to activate paralyzed muscles of people with spinal cord injury to restore functions such as standing or hand grasp, to enable exercise, or to facilitate neuromotor rehabilitation. In these systems, short electrical pulses delivered by electrodes generate action potentials in nerve fibers for the purpose of controlling movement or posture. A critical component of the technology, therefore, is the neural control system – i.e., that component of the technology that decides how to activate muscles in order to achieve the desired movement or posture. In some instances, the control systems have utilized very traditional engineering control approaches; other designs have utilized models of neural control structures. Computer-based studies that use movement simulation have been an important tool in the development of these neural control systems that use electrical stimulation. Although a large portion of this work has been directed at developing systems for people with spinal cord injury, models of neural control and movement simulation have also been used in the development of rehabilitation technology for individuals who have experienced a stroke or traumatic brain injury and for the development of advanced prosthetic limbs.

Sensory↔Neural↔Motor Interactions are Fundamental to Neuromuscular Control

In order to achieve effective interaction with the environment, neural control systems must gather data from the environment and have a means of acting on it. Control of movement involves a complex integration of sensory information to produce neural signals that activate muscles. Spatially distributed arrays of transducers gather information about the body and the external world, and the individual transducers have

response properties that are dynamic and non-linear (Kandel et al. 2013; Mileusnic et al. 2006). Furthermore, the sensitivity and dynamic range of the sensors can be actively modulated by the nervous system in a task-dependent manner. Action potentials in motor neurons generate muscle contractions that produce forces; the forces are transmitted to skeletal segments through tendons. In a given motor unit, the timing and frequency of action potentials in the motor neuron are determined by the properties of the motor neuron itself and the pattern of inputs it receives from the neural control system. The dynamic processes of muscle contraction and movements of skeletal segments (Abbas and Full 2000; Cheng and Loeb 2008; Chiel et al. 2009; Pinter et al. 2012; Ting et al. 2012; Zelik et al. 2014) all have time constants that are much greater than the neural dynamics and a large amount of the sensory information delivered to the neural control system is derived directly from muscles and tendons.

For the investigator studying the neural control system, the implications of this complex interaction are clear: the neural control system should not be studied in isolation. The sensors and actuators have dynamic properties that are actively modulated by the nervous system and that strongly influence the nervous system. These sensory-neural-motor interactions are not only important for the successful completion of any given task, but the interactions are also likely to be a major contributing factor to the versatility of neural control systems.

The Use of a Priori Knowledge Is Fundamental to Motor Control

Many observations in motor control experiments suggest that the nervous system uses a priori knowledge (or estimates) of the physical properties of the system to be controlled in order to deliver appropriate patterns of motor signals. This basic idea is embedded in several widely used theories of motor control, such as motor programs, internal models (Davidson and Wolpert 2005; Franklin and Wolpert 2011; Krakauer and Mazzoni 2011; Todorov and Jordan 2002;

Wolpert and Kawato 1998), central pattern generators (Abbas and Full 2000; Ekeberg 1993; Grillner et al. 2008; Verdaasdonk et al. 2009), and synergies (Bicchi et al. 2011; Duysens et al. 2013; Gentner et al. 2013).

In the control of single-segment movements, knowledge of the inertial load is used to modulate the amplitude and duration of muscle activation patterns; in multi-segment systems, knowledge of the intersegmental dynamics is used to produce coordinated movements. The use of such knowledge is apparent in ballistic tasks, such as throwing a dart, as well as repetitive tasks, such as walking.

In addition to using estimates of the physical properties, the nervous system can also utilize estimates of the noise in the environment to influence motor outputs. A simple, yet readily observable, example of how the nervous system uses estimates of the noise is to compare muscle activation patterns when standing on a bus as it moves from a smooth, paved road onto a bumpy, unpaved one. In both cases, the objective is to stand upright on a moving vehicle, but the expectation of noise on the bumpy portion of the road would alter motor outputs in a manner that stiffens the body in order to stabilize it.

An important implication of this use of *a priori* knowledge is that it enables anticipatory, rather than reactive, activation of muscles. Given the long time constants for activation of muscles and the high inertia of the body and external loads, this anticipatory activation is essential for many tasks. For example, in human walking, the anticipatory activation of the knee extensors prior to foot contact ensures sufficient knee extension torque to support the transfer of body weight to the lead limb.

Models of Neuromuscular Control

As with any modeling exercise, the form and characteristics of a model of neuromuscular control will be selected to meet the needs of the task at hand, and the only meaningful definition of a “good” model is one that helps to solve the problem being addressed. Over the past several

decades, a wide range of models of neuromuscular control have been developed and utilized; a few general forms of models are briefly described below.

Feedback Control Models

Some, but not all, sensory inputs to the neural control system provide feedback. The smell of freshly baked bread from the next room provides input that may strongly influence the activities of the motor control system, but does not provide information that is a result of ongoing motor activity. In contrast, while reaching to grasp a piece of that bread, the sensory inputs from visual, proprioceptive, and tactile sensors provide feedback – i.e., information that is a result of ongoing motor activity. Such feedback plays a critical role in most neuromotor activities and is therefore included in many models of neuromotor control.

Some of the earliest and most basic quantitative models of the neural control of movement used traditional feedback control system structures. The system to be controlled (i.e., the “plant”) was modeled using a linear transfer function and negative feedback produced activation that regulated position about a setpoint. Pioneering studies used models that included linear components to describe the control of eye movements (Cook and Stark 1967; Robinson 1973; Young and Stark 1963) and control of the cardiovascular system (Katona et al. 1970).

The primary advantages of using a linear systems approach are that the model parameters can be derived using input/output data and the relatively simple structure of the model enables extensive mathematical characterization and analysis. However, for most models of biological systems, this model structure is insufficient because it fails to capture important nonlinear properties, it fails to capture the time-varying characteristics, and it is over-reliant on feedback. Over the past several decades, there have been substantial advances in the development and use of models of neuromotor control systems that have specifically addressed these and other shortcomings of the linear systems approach (Franklin and Wolpert 2011; Marmarelis 1997; Ting et al. 2012; Todorov and Jordan 2002).

Although there are clearly shortcomings to the linear feedback model, the concept of negative feedback is used in many models of neural control that use nonlinear or adaptive approaches (Jung et al. 1996; Krakauer and Mazzoni 2011; Marmarelis 1997; Morasso et al. 1999; Todorov and Jordan 2002; Wolpert and Kawato 1998) to achieve a higher degree of biological fidelity.

Motor Programs

An early form of a model that has been used to explain or implement anticipatory activation is the notion of a “motor program.” In this formulation, the nervous system has a set of pre-stored patterns of activation (programs) that it can replay to perform a specific task. The program may activate a set of muscles to produce coordinated movements, and simple scaling rules may explain some of the versatility that would be required to make the same movement with different loads. Although this basic idea may be attractive, in its purest sense it does not adequately describe an animal’s ability to produce a rich set of behaviors in a complex environment. A more complex version of the motor program idea may be consistent with recent neurophysiological evidence (Esposito et al. 2014).

Internal Models for Predictive Control

The notion of an internal model has been extensively used to explain many observations in motor control. The internal, or forward, model predicts the relationship between actions and their consequences (Shadmehr and Mussa-Ivaldi 2012; Shadmehr et al. 2010; Wolpert and Kawato 1998) and therefore enables much more than simply stereotyped actions. The internal model may include representations of the muscle dynamics, limb dynamics, as well as the environmental load and sensory response properties. This approach has been utilized in a number of model systems (Davidson and Wolpert 2005; Franklin and Wolpert 2011; Krakauer and Mazzoni 2011; Todorov and Jordan 2002; Wolpert and Kawato 1998).

The support for an internal model has been greatly strengthened by studies that require motor learning (Shadmehr and Mussa-Ivaldi

1994; Shadmehr and Mussa-Ivaldi 2012). In a paradigm in which subjects were asked to move a manipulandum in a center-out-and-back pattern, the movements in an unloaded condition follow a straight path. After an unnatural external force field is imposed, movement patterns are initially nonlinear, but subjects eventually learn to adjust motor activation patterns in order to restore the linear out-and-back trajectories. Most importantly, the movement patterns are disrupted after the force fields removed in a manner that would be predicted by an internal model that incorporates a model of the unnatural force field in the environment (Shadmehr and Mussa-Ivaldi 1994).

Although there is strong evidence in support of internal models for predictive control, the specific neurophysiological structures that may instantiate such a model have not been identified. The cerebellum has been viewed as a likely source of the computation and adaptation involved in implementation of an internal model (Moberget et al. 2014), and there is indirect evidence from clinical observations of people with cerebellar disorders (Izawa et al. 2012). However, the nature of a putative internal model and the neurophysiological basis for it are active areas of research.

In some views, the internal model is used by the nervous system for optimal control – i.e., control that uses specific criteria to maximize performance and minimize cost (Diedrichsen et al. 2010; Franklin and Wolpert 2011; Todorov 2004; Wolpert et al. 1995). This notion of optimal control has been extensively employed, but the extent of its utility has been questioned (de Rugy et al. 2012; Loeb 2012). One important logistical problem in quantitatively evaluating the theory is that the cost function has to be known, or assumed. If one produces a cost function that is optimized by a particular movement, this does not prove that the nervous system optimized the movement (this is akin to the observation that “correlation does not prove causation”). Perhaps, more importantly, most observations of biological control systems that provide evidence for “optimal” control may also be viewed as supporting a theory of “just good enough” control (Loeb 2012). This is an active area of debate and is likely to be an active area of research in the future.

Central Pattern Generators

The concept of a central pattern generator (CPG) is often used to describe the neural control of cyclic movements such as walking, breathing, swimming, or chewing. The foundation of this model of neuromotor control is a group of neurons that produces a cyclic pattern of activity in motoneurons in order to produce cyclic movements. There is a wide range of evidence in many species indicating that both cellular and network structures may contribute to the generation of the observed oscillatory patterns and that these patterns are strongly influenced by sensory inputs (Grillner et al. 2008; Harris-Warrick et al. 1995; Ivanenko et al. 2009; Kandel et al. 2013; Tazerart et al. 2008; Van de Crommert et al. 1998). Note that in many systems there is little or no evidence to support the existence of a CPG that is capable of oscillating in the absence of sensory input, and, in many cases, well-timed sensory feedback is essential to produce functional oscillatory patterns. In addition, although the representations often depict a CPG as a group of neurons that is distinct from all other neural structures, it is clear that the neurons involved in producing oscillatory patterns are not distinct populations and can be involved in other aspects of motor control such as non-oscillatory movements, reflexes, and/or coordination.

Mathematical models of CPG systems can be implemented using a set of equations that describe a general oscillator (Ermentrout and Terman 2010; Izhikevich 2010; Schultheiss et al. 2012) or equations that are based on the fundamental biophysics of the neuron membrane (Ekeberg 1993; Grillner et al. 2008; Jung et al. 1996). The biophysical models typically have a capacitive membrane with passive conductance channels as well as active channels that may be voltage and time dependent (Grillner et al. 2008; Kandel et al. 2013). The network connections among neurons in the model also contribute to the oscillatory behavior. Reciprocal inhibition or self-inhibition can be used as a mechanism to contribute to the termination of a burst (Grillner et al. 2008). Mutual inhibition between two sides of an oscillator can be used to silence one side while the other is active (Grillner et al. 2008).

While the core structure of the model produces the basic oscillatory pattern, most CPGs also require mechanisms to modulate their patterns of activity in order to produce functional movements. Inputs to the CPG can be used to initiate/terminate oscillatory activity or to alter the frequency or duty cycle of the oscillatory pattern. Sensory signals can also alter the oscillatory pattern by mechanisms that affect movement amplitude, frequency, or duty cycle (Grillner et al. 2008). Phase resetting can occur when a sensory input alters the pattern in a manner that shifts the phase of oscillatory pattern; the phase dependence of the response to such inputs enables a variety of behaviors (Ermentrout and Terman 2010; Schultheiss et al. 2012).

Synergies

The musculoskeletal structure of many animals enables production of a number of movements to perform a rich set of tasks. Multiple muscles articulate many degrees of freedom of movement of the skeletal structure. One consequence of this versatile arrangement is that there are often multiple options to achieve a given task. There is kinematic redundancy in that many postures can achieve the same goal: for example, I can reach to grab the cup in front of me with my elbow tucked in close to the body or with it pointing out to the side. There is also kinetic redundancy in that many patterns of muscle activation can achieve the same set of joint moments to produce a movement. The redundancies provide clear advantages by affording options for task execution that may be essential in a given environment (e.g., keeping my elbow close to the body when I reach for that cup of coffee while seated on a plane), but it also poses a dilemma in that the neural control system must “choose” from a number of feasible options.

Synergies have been incorporated into many models of neuromotor control to reduce the number of degrees of freedom and therefore solve the “redundancy problem.” In this model, the nervous system is structured in a manner that it preferentially activates groups of muscles in a particular pattern in order to produce a complex movement. For example, a flexor synergy has been proposed as a means of using a single command for flexion

to drive the hip, knee, and ankle extensors and therefore generate a coordinated limb flexion movement (Duysens et al. 2013). In addition to being used for voluntary task execution, synergies may also be utilized to produce coordinated reflex actions and may facilitate learning. The organization of muscles into synergies may be incorporated into an internal model structure or into the central pattern generator structure (Duysens et al. 2013). In either of these arrangements, the synergy could facilitate movement execution, feedback, and motor learning, but the extent to which synergies explain the organization of motor systems may be limited (de Rugy et al. 2013).

Cross-References

- [Control of Breathing, Integration of Adaptive Reflexes](#)
- [Oculomotor Control, Models of](#)
- [Somatosensory System: Overview](#)
- [Spinal and Neuromechanical Integration: Overview](#)
- [Vertebrate Pattern Generation: Overview](#)

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NEURON

► NEURON Simulation Environment

Neuron Model(s)

► Mammalian Motor Nerve Fibers, Models of

NEURON Simulation Environment

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Synonyms

NEURON

Definition

NEURON is a simulation environment that is primarily used for creating and using computational models of individual neurons and networks of neurons.

Detailed Description

This entry surveys key aspects of the NEURON simulation environment (NEURON hereafter). For more detailed coverage of these and related topics, please see *The NEURON Book* (Carnevale and Hines 2006), documentation at NEURON's web site neuron.yale.edu, or our chapter on numerical integration (Carnevale and Hines 2014).

Domain of Utility

NEURON is a “domain-specific” simulator in the sense that, by design, it has features that make it particularly well-suited for constructing and simulating certain kinds of models. It emerged from a collaboration between John Moore and Michael Hines at Duke University. Their initial aim was to develop software for models used to complement experimental research on spike initiation and

conduction in squid axon (Hines 1992, 1994). NEURON's domain of utility subsequently broadened in response to requests and contributions from other neuroscientists who began to adopt their software and apply it to a much wider range of problems (see neuron.yale.edu/neuron/credits).

At the center of this domain are anatomically detailed models of biological neurons with detailed anatomical structure and complex membrane properties and networks of such neurons. It has also been used to implement and simulate models as diverse as networks of artificial spiking cells (Lytton and Omurtag 2007, ModelDB accession number 105507); hybrid nets that combine artificial spiking cells and mechanistic models of biological neurons (Yu et al. 2013, ModelDB accession number 144570); cardiac muscle cells (Courtemanche et al. 1998, ModelDB accession number 3800); and networks of arteriolar smooth muscle (Crane et al. 2001, ModelDB accession number 3785). For a more complete perspective on the range of models that have been implemented with NEURON, see the NEURON Bibliography neuron.yale.edu/neuron/static/bib/usednrm.html.

Software and Hardware Requirements

NEURON runs under all currently popular operating systems (UNIX/Linux/macOS and MS Windows) on hardware that ranges from Mac and PC laptops to high-performance computing environments such as workstation clusters and massively parallel supercomputers.

Development and Project Support

NEURON is under active development, with support from NIH. It uses an open-source development strategy, with all source code available from the nrm and iv repositories at github.com/neuronsimulator, so interested individuals may start their own private development forks. Contributions of code or programming effort to NEURON's official repository are encouraged, but all decisions about what is included in that repository and official releases of NEURON are up to the final judgment of Michael Hines.

User Base

As of this writing, there are more than 2000 NEURON users; over 1500 are registered with the NEURON Forum, and the others subscribe to the old NEURON mailing list. In recent years, each annual meeting of the Society for Neuroscience includes about 50–60 presentations that report new work that involves NEURON, and new publications that used NEURON are appearing at a rate of >120 per year; the total number of such publications is currently >2100 (see the NEURON Bibliography, discussed above in “[Domain of Utility](#)”). Authors of many of these articles have shared their source code via ModelDB, which currently contains more than 670 NEURON models (see senselab.med.yale.edu/modeldb).

User Support

Documentation

The NEURON Book provides detailed information about NEURON and its internals (especially the standard run system), as well as numerous usage examples. Links to the Programmer’s Reference, tutorials on common tasks, and key publications about NEURON are posted at the online documentation page neuron.yale.edu/neuron/docs.

Support on Specific Topics

The NEURON Forum neuron.yale.edu/phpBB is an online resource where users may ask questions and share their own expertise. Currently it has more than 16,000 posts in over 3800 question-and-answer threads. Additional support is available by telephone and email for those who have more specialized problems or prefer confidentiality.

Courses

Since 1998 the NEURON development team has presented a 1-day “executive summary” course at most annual meetings of the Society for Neuroscience and a multiday intensive hands-on course in spring or summer at academic institutions and research centers such as UC San Diego, HHMI/Janelia, Wright State University, Emory University, and University of Minnesota. We have also

presented a range of courses on NEURON at other venues, including KAIST www.kaist.edu in Daejeon, Korea (2010), and IST ist.ac.at in Klosterneuburg, Austria (2012).

Models in NEURON

A NEURON model may involve one or more cells and may include any combination of “biophysical model cells” and “artificial spiking cells.” These terms have particular meanings in the NEURON simulation environment. The term “biophysical model cell” implies a mechanistic representation of a cell or an isolated part of a cell that requires numerical integration of the cable equation or of at least one ordinary differential equation.

The term “artificial spiking cell” is reserved for a particular subset of what are broadly called “integrate and fire cells”: those whose behavior is defined by equations that have analytical solutions. Artificial spiking cells can be simulated extremely efficiently, because the future values of their states can be calculated directly from their current values. Such a cell imposes no computational burden until it receives an input; furthermore, when an input arrives, the cell’s states can be updated by mere algebraic calculation, which is orders of magnitude more efficient than numerical integration (see Chap. 10 in Carnevale and Hines 2006).

Interactions between cells in a network model may include any of the following:

- Synaptic transmission, which may involve use-dependent and/or associative plasticity. The pre- and postsynaptic cells may be any combination of biophysical model cell and artificial spiking cell. Two kinds of synaptic transmission can be represented:
 - Spike triggered: the effect on the postsynaptic cell depends only on the fact that there was a presynaptic spike. The pre- and postsynaptic cells may be any combination of biophysical model cell and/or artificial spiking cell. Note that artificial spiking cells may interact with other cells only by spike-triggered synaptic transmission.
 - Continuous transmitter release: the effect on the postsynaptic cell varies continuously as

a function of a time-varying quantity in the presynaptic cell.

- Gap junctions.
- Ephaptic interactions.
- Molecular diffusion across the extracellular space (Newton et al. 2018).

Programming with NEURON

NEURON can be used as a general-purpose programming environment for problems that have nothing to do with computational neuroscience, but its primary use is for building models and running simulations. Models may be created, managed, and used to generate publication quality results in any of the following ways:

- Writing statements in any combination of hoc and/or Python
- Using GUI-based tools such as the CellBuilder or Network Builder
- Combined use of GUI-based tools and user-written code

General-purpose C code can also be embedded in VERBATIM blocks in NMODL files (see “[Program Architecture](#)” below) and called by hoc or Python statements.

In addition to being controllable via hoc or Python, NEURON binds these two languages together, allowing functions written in Python to call hoc or vice-versa. NEURON’s hoc has been considerably extended beyond the simple language originally described by Kernighan and Pike (1984). The principal additions include object-oriented programming, a graphical user interface, and features specifically useful for implementing mechanistic models of biological neurons and networks of neurons, e.g., “sections,” which represent unbranched neurites (cables) and have anatomical and biophysical properties. Python provides access to the wide range of analysis and visualization libraries available for that language, online help, vector arithmetic, a more object-oriented interface, and richer return types for NEURON methods. NEURON’s neuroscience-specific graphics classes (PlotShape, RangeVarPlot) offer dedicated support for use with Python graphics.

NEURON’s reaction-diffusion module (neuron.rxd (McDougal et al. 2013; Newton et al. 2018)) provides a compact specification for defining intracellular and extracellular chemical dynamics without regard to numerical integration details. This allows users to focus on key aspects of the model itself, such as region (e.g., extracellular, ER, cytosol), species (e.g., IP3, calcium), and reactions or state transitions. In recent versions, reactions are just-in-time compiled, and 3D deterministic simulations employ a threaded version of the Douglas-Gunn alternating direction implicit method to achieve high runtime performance. Species declared using the neuron.rxd module may be used to modulate channel dynamics defined in, e.g., NMODL, and their concentrations automatically change in response to corresponding currents computed in NMODL. Local dynamics specified using neuron.rxd are exportable to SBML for use with other simulators.

GUI Tools

NEURON has a suite of graphical tools that can be used to build models and generate publication-quality results without having to write a single line of program code. These tools can also be employed in conjunction with user-written code to exploit the complementary strengths of programming and the GUI. They are especially helpful when interactive use is beneficial, e.g., in model development, debugging, and exploration of model properties and behavior. There are too many to list and describe here, but the following deserve special mention.

Import3D

Converts detailed morphometric data into models. Accepts Eutectic, SWC, NeuroLucida version 1 and 3 text files, and MorphML files and can export the results as reusable hoc code or to a CellBuilder. Reports errors found in morphology data and can be used to diagnose and fix errors.

Channel Builder

Creates new voltage- and/or ligand-gated ion channels specified either by Hodgkin-Huxley style ordinary differential equations or as Markov

schemes. Gating may be deterministic or stochastic (Hines and Carnevale 2005).

CellBuilder

Builds and manages properties of model cells. Simplifies specification of algorithmically controlled spatial variation of biophysical properties. Can automatically discretize models according to the d_lambda rule, which ensures that compartment length is no longer than a user-specified fraction of the AC length constant at 100 Hz (Hines and Carnevale 2001, 2005; Carnevale and Hines 2014). Can export source code in hoc for cell classes that are reusable, e.g., for network models (Hines and Carnevale 2008); can also import and export level 2 NeuroML for compatibility with other simulators.

Network Builder

Prototypes small networks. Can export source code in hoc that may be mined for reusable components such as cell classes.

Linear Circuit Builder

Adds linear circuit elements (resistors, capacitors, inductors, op amps) to a model, e.g., to represent microelectrode properties, dynamic clamp, gap junctions, ephaptic interactions, extracellular stimulation, or generation of extracellular fields. Can export reusable hoc code that may be combined with user-written code.

Impedance Tools

Analyze a model cell's electrical signaling properties, computing and displaying its "electrotonic transformation" (Carnevale et al. 1995, 1997; O'Boyle et al. 1996), input and transfer impedances, and voltage attenuation and transfer ratios.

Model View

Generates a concise, browsable textual and graphical summary of the properties of a model cell, as it exists in the computer after execution of model setup code. This is extremely useful when working with models that are specified in procedural programming languages. To the best of our knowledge, no other simulator that employs

procedural model specifications has a similar feature. The Model View tool can export level 1 and level 2 NeuroML for compatibility with other simulators.

Variable Time Step

Analyzes a model's system equations and automatically selects the most appropriate adaptive integrator. Facilitates manual specification of the state error tolerances that govern step size and integration order and can automatically select appropriate error tolerance for all state variables (Carnevale and Hines 2014).

Model Setup and Simulation Execution

Before a simulation can be run, NEURON executes the user's "model specification" which defines the properties that are to be represented in a model. This results in the creation of internal data structures that reflect the model's system equations and will be used during simulation execution. Model setup typically takes much less time than simulation execution does, because setup only needs to be done once, whereas executing a simulation requires numerical integration of the model's system equations, which is computationally very costly, especially if many time steps are involved.

NEURON has a powerful and flexible standard run system for controlling and coordinating the sequence of actions that occur during simulation execution. At a minimum, each "run" consists of two phases that are performed by compiled routines operating at machine code speed: initialization and solution of an initial value problem based on the model's system equations. The main loop that supervises this process is written in hoc, but most runtime is consumed by numerical integration, even though that is done by compiled code.

Much of the standard run system is implemented in hoc, and users can modify it as necessary in order to accomplish additional tasks such as:

- Preprocessing of input data, e.g., in order to modify the model specification or to serve as input signals that are applied to a model during solution generation.

- Custom initialization (often required for complex models, especially those that involve ion accumulation mechanisms).
- Postprocessing simulation results, e.g., to extract measures such as firing rates.

NEURON also has an event system that is an important complement to the standard run system. Indeed, events make it possible to use a few hoc or Python statements to implement complex “virtual experimental protocols” such as predetermined or conditional perturbations of one or more model parameters that might otherwise have required much tweaking of the standard run system.

Parallel Simulation Execution

NEURON supports three styles of parallel simulation: multithreaded, bulletin-board style, and distributed simulation. These can be used individually or in any combination.

Multithreaded parallel simulation is suitable for machines with multicore (i.e., shared memory multiprocessor) CPUs. It is very easy to use since little or no change to source code is required. It is most useful for small nets and complex models of individual cells. However, speedup is sublinear because of interprocess communication overhead.

In bulletin board style parallel simulation, a “master” processor posts tasks to a “bulletin board.” “Worker processors” take tasks from the bulletin board and return results to the master via the bulletin board. This is particularly suitable for “embarrassingly parallel problems,” i.e., running large numbers of simulations, as is often necessary to evaluate plasticity and learning rules, optimize models, or explore parameter space. Interprocessor communication is managed by MPI (www.mpich.org). Converting a serial program to a form that is suitable for bulletin board parallel execution requires relatively minor modification of model source code. Load balance is achieved automatically, and speedup is very nearly proportional to number of processors.

Distributed simulation involves breaking a model into multiple parts so that each processor deals with a subset of the model’s system equations; again, interprocessor communication is managed by MPI. Parallelizing a serial program

may require considerable modification to source code, paying special attention to achieving good load balance. In NEURON, even individual neurons can be split into pieces and distributed over multiple processors for the sake of load balance (Hines et al. 2008a, b). With good load balance, speedup is very nearly proportional to number of processors as long as each processor has enough work to keep busy (200 or more states that require numerical integration) (Migliore et al. 2006).

Program Architecture

NEURON’s computational engine is implemented in compiled code, mostly C and C++. The GUI tools are implemented mostly in hoc, an interpreted language with syntax similar to C (Kernighan and Pike 1984); some tools such as Import3D and Model View also rely on some Python code, and the Print and File Window Manager is implemented in compiled code.

A compiled language called NMODL is available for adding new equations (algebraic equations, ordinary differential equations (ODEs), and kinetic schemes), state machines, and arbitrary C code in order to implement such things as new biophysical mechanisms (e.g., voltage- or ligand-gated channels, transport mechanisms, synaptic mechanisms), artificial spiking cell classes, and mathematical functions. There are also classes that can be used to add new linear equations that implement electrical circuits made out of linear elements (via the Linear Circuit Builder GUI tool) and sets of ODEs and kinetic schemes that specify the properties of voltage- and ligand-gated ion channels (via the Channel Builder GUI tool). Reaction-diffusion can be implemented with NMODL, but a more flexible multiscale approach is to use the `neuron.rxd` module described above.

CoreNEURON

A major target of active development in NEURON is to reduce both memory usage and runtime for large models on modern nonuniform memory architectures, such as Intel Xeon Phi and NVIDIA GPU, in which multiple memories range widely with respect to size and bandwidth/latency. To this end we are working on CoreNEURON (Kumbhar

et al. 2019; CoreNEURON github repository (2019)), a library for NEURON that enables simulations of models up to 7 times larger than would ordinarily fit into memory, while achieving a speedup of up to 5–7 times compared to what is ordinarily possible on the same hardware. Most existing NEURON models require little or no change to be executable by CoreNEURON. By default, simulation results are numerically identical between NEURON and CoreNEURON; optionally selectable performance optimizations are available which cause differences due to accumulation of double precision round off errors.

CoreNEURON's advantages result from extracting and optimizing NEURON's computational engine, meaning just the part of NEURON that is directly responsible for numerical solution of the equations that describe the model itself. Since CoreNEURON omits everything that is not essential for simulation execution, the process of translating a model specification from source code (hoc, Python, NMODL) into a form suitable for simulation execution can leave out a great deal of detail that regular NEURON would have needed – and that is why it can handle much larger models. CoreNEURON's optimizations primarily involve revising memory layout to make more efficient use of modern CPU and GPU architectures, e.g., by vectorization of model data structures, and avoidance of data transfer overhead.

Numerical Methods

Models that involve biophysical model cells with significant spatial extent and anatomical branching are equivalent to families of partial differential equations with boundary conditions as needed at their ends to implement coupling at branch points. NEURON generates approximate solutions to initial value problems involving these equations by numerical integration of the ordinary differential equations that result from spatial discretization of the cable equations. Its spatial discretization strategy uses the central difference approximation to the second spatial derivative of membrane potential; consequently simulations have second-order accuracy in space.

NEURON offers several different numerical integration methods and is implemented in such

a way that one may switch from one integrator to another without having to revise a model's source code. The default integrator for fixed time step solutions is fully implicit Euler, which has first-order accuracy in time and excellent stability. Also available are Crank-Nicholson, which has second-order accuracy in time but can generate spurious oscillations if a model's equations are too stiff, and a collection of adaptive integrators that automatically adjust time step and integration order to satisfy user-specified local error criteria. Simulations of networks with multiple cells connected by spike-triggered synaptic transmission can optionally use “local variable time step” integration, in which each cell has its own independent time step and integration order that are automatically adjusted. Selection of the most appropriate adaptive integrator and determination of relative error scale factors for each state variable are simplified by the VariableTimeStep tool, a GUI-based tool that can automatically determine the necessary settings. Readers who seek more information about these methods are referred to Carnevale and Hines (2014) or Chaps. 4 and 7 in *The NEURON Book* (Carnevale and Hines 2006).

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Neuronal Activation

► Intraspinal Stimulation

Neuronal Avalanches

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Synonyms

Balanced propagation; Critical branching process; Neuronal cascades; Power-law distributed patterns; Scale-invariant patterns

Definition

Spatiotemporal patterns comprised of local neuronal activity events that follow scale-invariant statistics. Pattern statistics is quantified by a power law distribution in pattern size, s , and pattern duration, t . The balanced propagation of activity during avalanche unfolding takes on the form of a branching process. Specifically, the probability distribution $P(s)$ takes the functional form of a power law $P(s) \sim s^{-\alpha}$, with exponent $\alpha = 3/2$, and $P(t) \sim t^{-\beta}$ with $\beta = 2$. The branching parameter, σ , estimated by the ratio of future to current events during an avalanche is critical, i.e., $\sigma = 1$. On average, neuronal activity neither grows nor decreases during avalanching.

Detailed Description

History of Neuronal Avalanches

Experimentally, neuronal avalanches were first identified in 2003 in the spontaneous activity of cortex slice cultures and cortex slices from rat (Beggs and Plenz 2003). The scale-invariant

nature of avalanches signifies a specific order in the commonly observed strong fluctuations of spontaneous brain activity. Such scale-invariance is in line with early suggestions by Per Bak (Stassinopoulos and Bak 1995; Bak 1997) that the brain should self-organize into a critical regime where avalanches of activity allow neurons to flexibly establish input-output relationships. Early implementation of neural networks (Chen et al. 1995; Eurich et al. 2002; Zhao and Chen 2002) derived from the Olami-Feder-Christensen model for earthquakes (Olami et al. 1992) introduced the formation of scale-invariant activity cascades in threshold-coupled neuron-like elements. Experimental confirmation of avalanches in spontaneous neural activity quickly progressed from in vitro systems including dissociated cortex cultures and leech ganglia (Mazzoni et al. 2007; Pasquale et al. 2008) to in vivo meso-scale LFP recordings in rodents (Gireesh and Plenz 2008) and nonhuman primates (Petermann et al. 2009; Priesemann et al. 2009), rodent spiking activity (Ribeiro et al. 2010) and macroscale recordings in humans using fMRI (Fraiman et al. 2009), EEG and ECoG (Solovey et al. 2012; Priesemann et al. 2013), and MEG (Palva et al. 2013; Shriki et al. 2013). Latest technological advances allowed neuronal avalanches to be identified in local pyramidal group activity in cortical layer 2/3 using 2-photon imaging with genetically encoded intracellular calcium (Bellay et al. 2015) and voltage-sensitive indicators (Scott et al. 2014). Latest conceptual developments demonstrate neuronal avalanches in vivo to be exclusive to the awake state (Scott et al. 2014; Bellay et al. 2015; Fagerholm et al. 2016) and to provide a statistical framework for the variability encountered in sensory evoked responses when accounting for systematic changes in event rate during responses (Yu et al. 2017). Theory and simulations predict that networks with neuronal avalanches are positioned at a critical point where they optimize numerous aspects of information processing (e.g., Kinouchi and Copelli 2006). This was experimentally confirmed for dynamic range (Shew et al. 2009) and information capacity (Shew et al. 2011; Yang et al. 2012) in cortex slice cultures and recently in vivo (Gautam et al.

2015; Fagerholm et al. 2016) (for review see Chialvo 2010; Shew and Plenz 2013; Hidalgo et al. 2014). Moreover, recent ex vivo experiments in turtle suggest that adaptation to visual input may maintain neuronal avalanche dynamics in visual cortex (Shew et al. 2015; Clawson et al. 2017). Importantly, systematic deviations from avalanche dynamics have been identified in abnormal brain dynamics such as epilepsy, schizophrenia, and sleep deprivation (Worrell et al. 2002; Osorio et al. 2010; Meisel et al. 2012, 2013, 2015; Milton 2012; Arviv et al. 2016; Seshadri et al. 2018). These dependencies on brain state as well as neurotransmitters that regulate the excitation/inhibition balance, such as GABA_A and glutamate (Beggs and Plenz 2003; Stewart and Plenz 2006; Mazzoni et al. 2007; Shew et al. 2011; Gautam et al. 2015), the neurotransmitter acetylcholine (Pasquale et al. 2008), and the neuromodulator dopamine (Stewart and Plenz 2006; Gireesh and Plenz 2008; Beggs and Plenz 2003; Mazzoni et al. 2007; Pasquale et al. 2008; Shew et al. 2011) suggest that the brain actively maintains avalanche dynamics. A subset of neuronal avalanches termed coherence potentials identify avalanches of high temporal coherence across space in analogy to propagating structures in turbulent flow or “gliders” in the game of life (Thiagarajan et al. 2010; Plenz 2012). For reviews on criticality and neuronal avalanches see (Chialvo 2010; Plenz 2012; Hesse and Gross 2014; Plenz and Niebur 2014; Cocchi et al. 2017; Muñoz 2017).

Data Sets and Critical Exponents

A dataset consisting of simultaneous, continuous recordings of local activity from numerous sites forms the basis of avalanche analysis. Continuous recordings are typically comprised of single neuron spike densities (2-photon imaging), the local field potential at a single electrode, fMRI single voxels, single electrode EEG and ECoG, or single sensor MEG activity. By simultaneously observing these activities from many sites, statistical inferences can be made whether activity at one site might relate to subsequent activity on other sites. The essential transformations require

(1) thresholding of local, continuous activity to obtain the amplitude and time of significant local neuronal activity events and (2) the clustering of spatially distributed events based on their temporal proximity. Thus, at its core, avalanche analysis involves three parameters: (a) the threshold thr , a temporal resolution Δt , and spatial resolution Δd . This general approach is motivated by the insight that information on causal spatial interactions between elements in a network is often not experimentally accessible, yet, if these interactions exist, they should give rise to temporal dependencies in the form of activity cascades. Specifically, spatiotemporal activity cascades are defined as neuronal avalanches only if the probability distribution $P(s)$ of cascade size s takes the functional form of a power law $P(s) \sim s^{-\alpha}$, with exponent $\alpha = 3/2$ and the probability distribution of lifetimes is $P(t) \sim t^{-\beta}$ with $\beta = 2$. The branching parameter, σ , estimated by the ratio of future to current events during an avalanche is $\sigma = 1$, i.e., critical, that is, on average neuronal activity neither grows nor decreases during avalanching. These exponents are predicted by the theory of branching processes (Harris 1963; Larremore et al. 2012) or high-dimensional directed percolation (Muñoz et al. 1999; Buice and Cowan 2009) and are most commonly found in more biologically realistic models of avalanche dynamics (de Arcangelis et al. 2006; Levina et al. 2007; Meisel and Gross 2009; de Arcangelis and Herrmann 2010; Millman et al. 2010; Poil et al. 2012; Rybarsch and Bornholdt 2014a; Hernandez-Urbina and Herrmann 2017). The empirical determination of these critical exponents, though, is challenging and requires elaborate scaling analyses based on large data sets as shown in the original publication of neuronal avalanches (Beggs and Plenz 2003). Such scaling analysis is often limited by the size of the available data set supporting a more relaxed definition of neuronal avalanche identification with, e.g., power law slope $\alpha = 1-2$ as a first pass. This exponent range still implies that the mean size of cascades diverges in an infinite system. Conversely, cascades that fail to demonstrate power law statistics are not considered neuronal avalanches (Fig. 1).

Methods of Neuronal Avalanche Data Analysis

Step 1. Obtain simultaneously recorded time series of local activity. Determine a significance threshold thr for local activity and obtain time and amplitude of suprathreshold peak events. The threshold thr is often estimated in multiples of the standard deviation of the signal fluctuation individually calculated for each local time series. This approach normalizes against heterogeneities introduced by differences between, e.g., local sensors/electrodes.

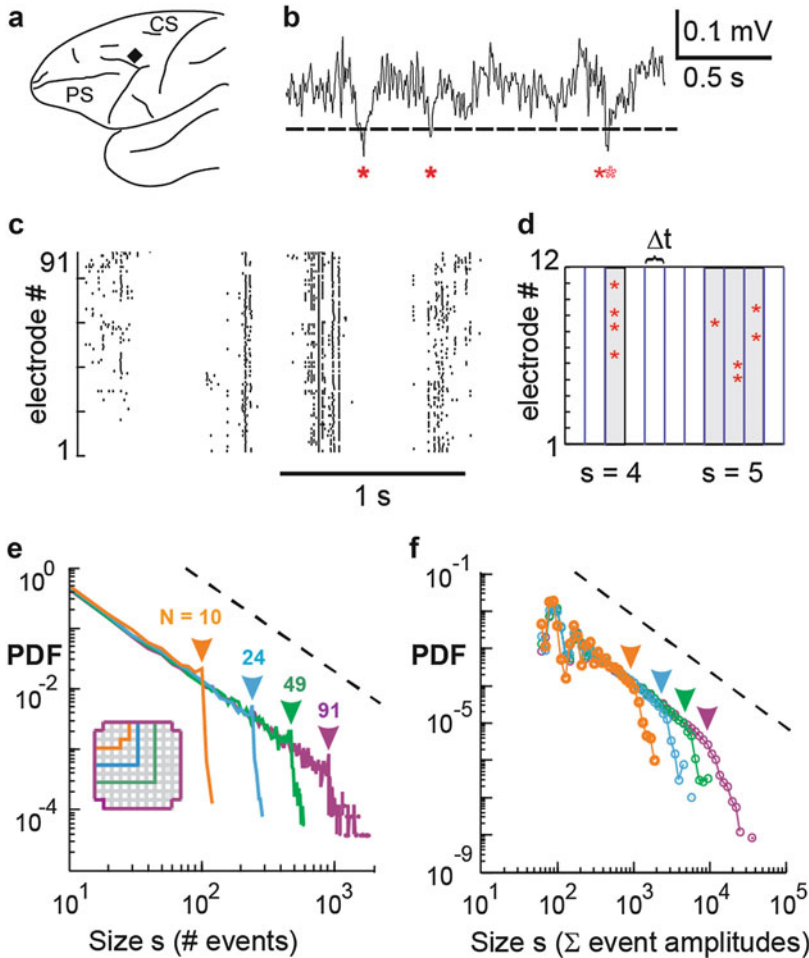
Step 2. Identify spatiotemporal activity clusters. Choose a temporal resolution Δt at which suprathreshold events from Step 1 will be binarized. Concatenate successive time bins of length Δt that contain at least one local suprathreshold event. The resolution Δt is often estimated by the average inter-event interval in the system, IEI , (not of the local time series). This IEI quantifies how much time passes between successive events in the system. It typically depends on the speed of activity propagation, v , and the spatial sampling distance Δd of the sampling grid (e.g., electrode array, subsampled neuronal population in 2-photon imaging, or spatial resolution in MEG or fMRI). In general, if v is constant, then $\Delta t = \Delta d/v$ at which $\alpha = 3/2$. Such rescaling was demonstrated experimentally for neuronal avalanches (Beggs and Plenz 2003; Pasquale et al. 2008).

The concatenation of successive time bins provides an unbiased cluster detection mechanism. Clusters that consist of a single time bin with just one local event reflect local, non-propagated activity. Clusters consisting of a single time bin with multiple local events capture synchronous – within resolution Δt – distant events. Clusters that consist of several consecutive time bins each with one local event represent ideal, unbranched cascading activity. Clusters with multiple consecutive time bins and numerous local events reflect intermediate realizations between instantaneous synchronization and idealized cascades. Importantly, the criterion that clusters end when the concatenation encounters a time bin with no local event establishes an unbiased

estimator for periods with and without activity. An alternative approach that does not rely on a temporal resolution is to add local events, e.g., spikes from all neurons, and threshold the resulting population vector (Poil et al. 2012; Del Papa et al. 2017) to obtain activity periods

with corresponding number of active local events foregoing any spatial resolution of clustered activity.

Step 3. *Compute statistics of clusters.* The two most commonly examined cluster parameters are cluster size s and cluster lifetime t . For a



Neuronal Avalanches, Fig. 1 Neuronal avalanche analysis. (a) Sketch of macaque brain with microelectrode array locations (square in premotor cortex). CS: central sulcus; PS: principal sulcus. (b) An example trace of an LFP signal, showing the detection of negative LFP deflections crossing threshold (marked by asterisks) at 2.5 SD (dashed line). (c) Raster plot of local events detected from all 91 electrodes in a period of 2 s. Local suprathreshold events are represented by individual dots in the plot. (d) Local events occurring during either the same or consecutive time bins are detected as a spatiotemporal cluster with size, s , defined as the number of events involved. (e) Avalanche size distributions are plotted in double-logarithmic coordinates for four observation windows,

i.e., groups of electrodes in the recording array. The size of the observation window, N , is defined as the number of electrodes within the window (see inset for spatial coverage of the windows). The positions of arrows indicate the values of the corresponding N . (f) Continuous avalanche size distributions are plotted for the same observation windows with the size of an avalanche defined as the summated absolute amplitudes of all local events involved. The positions of arrows indicate the values of N times mean absolute events amplitude across all electrodes. For visual comparison, a power law with exponent -1.5 is shown in e and f (dashed lines). (Modified from Yu et al. 2014. <https://doi.org/10.1371/journal.pone.0099761.g001>)

continuous time series such as the LFP or spike density, cluster size s can be expressed as the number of suprathreshold events, the sum of event peak amplitudes or summed area of suprathreshold event. Typically, differential sensitivities in local site measures are removed by adequate normalization (e.g., z-scoring to remove electrode differences in LFP recordings or heterogeneities in fluorescence marker expression in 2-photon imaging) and thus either size definition will give similar results for the corresponding distributions of s (see, e.g., Beggs and Plenz 2003; Plenz 2012; Bellay et al. 2015). The lifetime t is typically expressed in number of time bins of length Δt , also called number of generations. If expressed in absolute time, the number of generations is multiplied by Δt .

Step 4. *Generate probability distribution of cluster parameters such as size and lifetime.* Plot the histogram of s and of t and normalize to obtain corresponding probability density functions. Given the potential scale-invariant outcome, histograms should be obtained with logarithmic binning if possible and visualized in double-logarithmic plots. If the resulting size and lifetime distribution are power laws, these plots will appear as straight lines and the dataset has passed the first test for neuronal avalanches.

Step 5. *Quantitatively assess how close the distribution is to a power law.* There are two important aspects to take into account, when estimating size and lifetime distributions. First, as is to be expected for any scale-invariant dynamics, finite-size sampling of clusters will impose cut-offs on size as well as duration distributions (see, e.g., Priesemann et al. 2009; Klaus et al. 2011; Yu et al. 2014; Levina and Priesemann 2017). In the presence of a clear lower or upper cut-off, the use of cumulative distributions is discouraged. Cumulative distributions are heavily distorted by cut-offs particularly when only few orders of magnitudes are covered in parameter space (Yu et al. 2014). In general, it is advised to use a scaling approach to test for the robustness of the distribution and to identify distortions from subsampling (Priesemann et al. 2009; Ribeiro

et al. 2010, 2014; Levina and Priesemann 2017) as well as cut-offs introduced by finite-size effects. For example Beggs and Plenz (2003), Pasquale et al. (2008), Priesemann et al. (2009), and Yu et al. (2014) explored the systematic shift in cut-off with electrode array size and Bellay et al. (2015) normalized for the effect of neuronal population size in 2-photon imaging. After properly identifying cut-offs and subsampling effects, several approaches can be used to test for the presence of a power against alternative distributions (see, e.g., Clauset et al. 2009; Yu et al. 2014). The deviation from a true power law can be quantified (e.g., Shew et al. 2009; Tetzlaff et al. 2010), which is particularly desirable when comparing a system's change in cluster statistics due to pharmacological manipulation or during development. For a thorough analysis, distribution dependencies on threshold thr as well as Δt or Δd are encouraged. For example, the slope of the power law for sizes, α , changes systematically with Δt and can be collapsed accordingly (Beggs and Plenz 2003; Petermann et al. 2009). Similarly, it is advisable that distributions are shown to be robust to threshold thr used in the analysis within a reasonable range, i.e., above noise and within a range to obtain sufficient suprathreshold local events (Petermann et al. 2009). If used with respect to external events, proper use of Δt and thr allows for analyzing cluster distribution during behaviorally relevant periods (Yu et al. 2017). Given the dependence of slope distributions on the three parameter Δt , Δd , and thr , the exact identification of critical exponents can be challenging for limited data sets.

Step 6. *Quantitatively assess scaling between cluster size and lifetime.* Cluster lifetime and cluster size have been shown to be connected by the avalanche shape with a scaling relationship (Sethna et al. 2001; Papanikolaou et al. 2011). Specifically, the average size $\langle s \rangle$ versus lifetime t has been shown to follow a scaling relationship with exponent $\gamma = \beta - 1/\alpha - 1$. For a critical branching process that describes avalanche unfolding, $\gamma = 2 = 2 - 1/1.5 - 1$ and the avalanche waveform is a parabola. For comparison, an unbiased random walk with

$\alpha = 4/3$ - and $\beta = 3/2$ exhibits $\gamma = 1.5$ (di Santo et al. 2017). For experimental data, the calculation of γ and avalanche waveform has been used as further evidence that neuronal avalanches indicate critical dynamics in cortex (Friedman et al. 2012).

Open Questions and Future Research

Neuronal avalanches represent a statistical description of fluctuations in neuronal activity. The relationship between scale-invariant neuronal statistics and the underlying dynamics is currently an intense area of research. In human ECoG, avalanche statistics corresponds to critical eigenmodes of an autoregression matrix of order 1 that approximates the near temporal evolution of time series (Solovey et al. 2012). The relationship of the largest eigenvalue of connectivity matrices being critical and the emergence of avalanche statistics has been explored by Larremore et al. (2012). Commonly, scale-invariance is found in balanced processes such as the return times in an unbiased random walk. Accordingly, neural models with inherently balanced propagation can produce scale-invariant outcomes in many ways. Recently, the notion of “causal avalanches” was introduced, where the synaptic, i.e., causal, contribution to avalanching is tracked in neural models (Martinello et al. 2017). Causal avalanches provide an answer to avalanche statistics obtained in models that exhibit a first-order phase transition (Millman et al. 2010), but these models do not produce power law statistics when avalanches are based on temporal proximity as is found in experiments. Besides power law statistics and branching ratio, experimentally determined neuronal avalanches exhibit numerous additional features that are challenging to model. Neuronal avalanches co-emerge with brain oscillations (Gireesh and Plenz 2008), captured in some models (Poil et al. 2012; di Santo et al. 2018). The temporal organization of neuronal avalanches shows distinct conditional dependencies on avalanche size and inter-avalanche intervals (Lombardi et al. 2012, 2014, 2016; Plenz 2012), which are sensitive to the excitation/inhibition balance and for which current models do not account. Similarly, the spatial spread of avalanches in cortical slice cultures obeys a fractal dimension lower

than 2 (Plenz 2012), and its relation to the topology of the underlying neuronal network is unknown. In light of neuronal avalanches and their potential advantages for information processing (see “History of Neuronal Avalanches”), the relationship between neuronal avalanches, criticality, and synaptic plasticity is an extremely active area of research (e.g., Bornholdt and Rohl 2003; Levina et al. 2007; Meisel and Gross 2009; de Arcangelis and Herrmann 2010; Rybarsch and Bornholdt 2014b; Berger et al. 2017; Del Papa et al. 2017; Hernandez-Urbina and Herrmann 2017; Michiels van Kessenich et al. 2018).

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Neuronal Cascades

► Neuronal Avalanches

Neuronal Model Databases

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Synonyms

Brute-force model databases; Neuronal parameter-measure model databases; Neuronal simulation databases

Definition

A *neuronal model database*, in contrast to neuronal databases that collect experimental data, holds instances of computational models of one type. This model can be of a single neuron or a neuronal network, which is replicated by varying its input model parameters to yield many instances that are inserted into a searchable database. Each entry in the database corresponds to one model instance, which contains: (1) values of the varied parameters (e.g., maximal conductance, reversal potential, synaptic weights) required to uniquely identify and sufficient to re-simulate the model; and (2) several key output characteristics from the model simulation (e.g., firing rate for a single neuron or a bursting period in a network). The resulting database is often used to study the relevant properties (response to stimulus or firing activity characteristics) of the model across a domain of parameter ranges.

Detailed Description

The Need for Neuronal Model Databases

In neuronal parameter space exploration, the traditional method for finding neuronal models that fit specific criteria is called *hand-tuning*, which is labor intensive, subjective and aims to optimize model parameters to a single solution (DeSchutter and Bower 1994). Furthermore, it is known that a single model may not explain all possible solutions in the parameter space because of the

interdependencies between model parameters (Foster et al. 1993; DeSchutter and Bower 1994). A better approach is to conduct systematic searches in the parameter space; and early attempts (Bhalla and Bower 1993; Goldman et al. 2001) have been used to optimize models to a predefined outcome. To make extensive systematic searches a more general tool, Prinz et al. (2003) proposed constructing neuronal model databases with sufficient information such that they can be used to answer subsequent questions about the same model (Hudson and Prinz 2010; Soofi et al. 2012). Prinz et al. (2003) also showed that multiple models with disparate parameter values can be found which exhibit similar output activity (such as response properties or firing characteristics).

Finding a group of models, rather than a single solution, that fit response criteria has been known to be a more robust in optimization problems. In machine learning, a set of algorithms called *ensemble learning* does exactly this to improve on generalization capabilities of solutions found (Opitz and Maclin 1997). Therefore, when applied to finding neuronal models, the approach is sometimes called *ensemble modeling* (Prinz 2010).

Brute-force Neuronal Model Databases

The most common type of model database is constructed using the *brute-force* approach (Table 1). This approach covers the parameter space with models for each possible combination of discrete parameter values selected from within a range (Prinz et al. 2003, 2004; Calin-Jageman et al. 2007; Günay et al. 2008; Doloc-Mihu and Calabrese 2011; Marin et al. 2013). The result is a coarse grid structure in a multidimensional space.

The model database constructed by Prinz et al. (2003) contained about 1.7 million single-compartment, conductance-based models of a lobster stomatogastric neuron. A parameter space of eight dimensions was explored by varying each maximal conductance density to have six distinct values between 0 and a conductance-specific maximum at equal intervals. The database included electrophysiological measurements for each model, such as spontaneous activity type (e.g., silent, tonic, bursting), firing times, and

Neuronal Model Databases, Table 1 Comparison of neuronal databases (*DBs*). *STG* stomatogastric, *CPG* central pattern generator, *MS* microsoft (Redmond, WA), *GP* globus pallidus, *wrkstns* workstations

Study	Model	Num. models	Simulator	Hardware	DB format	DB size	Index?
Prinz et al. (2003)	Lobster STG neuron	1.7 m	Custom C++	Cluster	ASCII	2 DVDs	No
Prinz et al. (2004)	Lobster STG network	20 m	Custom C++	Cluster	ASCII	1 DVD	No
Calin-Jageman et al. (2007)	Tritonia swim network	2 m	NeuronPM	wrkstns	MS Access	?	?
Günay et al. (2008)	Rat GP neuron	100 k	Genesis	Cluster	MATLAB	100 MB	No
Günay and Prinz (2010)	STG neuronal network + sensors	20 m	Custom C++	Cluster	MATLAB/MySQL	450 GB	Yes
Doloc-Mihu and Calabrese (2011)	Leech heart network	10.5 m	Genesis	Cluster	Java/MySQL	3 GB	Yes

additional voltage extrema information. This database was used for a thorough analysis of conductance effects on firing activity types and yielded important information like percentages of neuron models in this parameter space that were silent or firing tonically.

Prinz et al. (2004) extended the same model to construct a database of a network of three representative pyloric neurons of the lobster stomatogastric ganglion. The network model was simulated about 20 million times, while varying seven synaptic weights to five different levels, as well as five or six different versions of the three neurons in the network. Analysis of the network model database showed that similar network activity can be obtained from disparate parameters of individual model neurons and synaptic connections. An extended version of the network model database was later constructed to include about 300 activity sensor measurements in each neuron (Günay and Prinz 2010). The network sensor database was analyzed with a machine learning method (Günay and Prinz 2009), which resulted in finding the optimal parameters of neuron-localized activity sensors that would be useful for maintaining stable network activity.

Adoption of Neuronal Model Databases by Others

To our knowledge, several other groups also adopted the brute-force model database approach.

Calin-Jageman et al. (2007) applied it to study the Tritonia escape swim by constructing a database of about two million motor central pattern generator neuron network models. The neuron models were constructed using a hybrid integrate-and-fire scheme, showing that the approach can easily be applied to simpler neuronal models. Günay et al. (2008) applied the brute-force approach to study a vertebrate system by modeling neurons of the globus pallidus in the rat. About 100,000 multi-compartmental conductance-based models were simulated with five different current injection stimuli, which resulted in a database of about 500,000 items. Doloc-Mihu and Calabrese (2011) simulated 10.5 million instances of a leech heart half-center oscillator (HCO) circuit conductance-based model to construct a database that they used to categorize and analyze different activity types. This study focused on HCO model bursting activity characteristics such as period and burst regularity to analyze the instances' robustness in the parameter space. This database is important because it was later used to create another database that combines simulations with analysis of model bifurcation structure (Marin et al. 2013). Most recently, Williams et al. (2013) used a hybrid experimental and computational approach to study animal-to-animal variability in the phasing of the crustacean cardiac motor pattern. They simulated about 15,000 Morris-Lecar models of cardiac ganglion cells. Adoption of the brute-force model database approach by all of these studies shows that it

continues to be a useful tool in computational modeling of neurons and networks.

Database Storage and Other Technical Details

The techniques used for the construction of neuron model databases varied among the studies reviewed above. In particular, different researchers have personal preferences for simulation language, environment, and target hardware (see Table 1). However, it is relevant to discuss some techniques, such as the ones used for storage and access of database content. Prinz et al. (2003) and several other following studies did not save complete simulation traces and instead saved a few critical measurements, which allowed simulation and storage of a large number of models. However, this meant that simulations had to be analyzed online and could only be repeated later individually. The resulting database by Prinz et al. (2003) was stored in ASCII encoded files split into smaller pieces. ASCII files are often preferred for saving simulation output because of the simplicity of viewing and analyzing the results with existing software. Furthermore, partial recovery of corrupted ASCII files is possible, although parsing and extracting information from them is inefficient and they occupy a large amount of space. Another disadvantage is that querying the database requires writing custom programs. In contrast, binary formats (e.g., binary files and SQL databases) come with efficient querying systems (e.g., SQL language) and offer more efficient storage and faster indexed access (e.g., through hash maps). However, they can only be viewed through special software and partial recovery may be more difficult in the case of corruption.

Günay et al. (2008) stored and analyzed the database in MATLAB (MathWorks Inc, Natick, MA), using a toolbox specifically developed for model database analysis, named as Pandora (Günay et al. 2009). The approach taken with Pandora was different because of (1) its offline analysis of previously simulated output files, which provided greater flexibility in designing analysis routines to handle unexpected simulation outcomes and (2) the detailed information

extracted about action potential characteristics. However, the MATLAB environment places a limit on memory items and requires purchasing a license.

Formal database management systems (DBMS) can overcome memory limitations and are available free of charge (e.g., MySQL, Oracle Corp). In Günay and Prinz (2010), the saved information was similar to that of Prinz et al. (2004), but it resulted in too many measurements (about seven billion sensors) to be saved in ASCII format as in the previous versions of the databases. Using the MySQL tool for the network sensor database provided easy access in the standard and powerful structured query language (SQL), including a web interface for browsing and high-performing indexing optimizations for data queries. Doloc-Mihu and Calabrese (2011) also used MySQL to maintain the database of results by first saving intermediate simulation results in ASCII format and then analyzed them offline with custom Java (Oracle Corp.) programs.

Most of these studies used high-performance computing clusters to run the simulations, with the notable exception of Calin-Jageman et al. (2007), who took advantage of free times of workstations in school laboratories by creating a special version of the neuron simulator called NeuronPM (Calin-Jageman and Katz 2006).

Limitations, Alternatives, and Future Directions

There are some major limitations to constructing model neuronal databases with a brute-force approach. First, a uniform coverage of the parameter space is expensive; i.e., the number of models grows exponentially with added grid points and parameters. Therefore, brute force searches are often employed as coarse grid exploratory searches to help with further fine tuning into more interesting regions of the parameter space. Second, uniformity of parameter space coverage may be both wasteful and nonbiological. Because activity types of neuronal models are distributed nonlinearly across the parameter space, Nowotny et al. (2007) suggested that the ratios of activity types in this space may not properly reflect the

ratios in living systems. The multidimensional grid constructed by brute force methods is an unnatural representation of the parameter space and may not directly correspond to a sampling of living neurons, which were found to have some parameter constraints (such as conductance coregulations). One solution to this would be to scan the parameter space using random sampling (Ball et al. 2010). Both of these limitations are specific to the brute-force method and not about neuronal model databases themselves.

For parameter search, there are two main alternatives to the brute-force method: parameter optimization and bifurcation analysis. Both of these methods are still compatible with the idea of maintaining a database of the models found. The first alternative is employing an optimization algorithm to find models that match a specific criterion. One such popular optimization approach uses *genetic algorithms*, which are employed by Neurofitter and by multi-objective evolutionary algorithms for finding a set of good neuronal models. Optimization methods explore more fine-grained values of parameters than the brute force method; however, they are not guaranteed to provide complete coverage of the space. Therefore, if a database is constructed, it would not contain a general solution and would only be useful for the criterion selected.

A second alternative approach that still gives a general overview of the parameter space is bifurcation or phase-plane analysis of dynamical systems (Strogatz 2006). These methods can track regions of parameter space that exhibit physiological activity types without wasting resources scanning uninteresting parts of the parameter space. Therefore, they are efficient and thorough. However, bifurcation analysis requires tracking few parameters at the same time, so it is more difficult for being systemically applied to a space with a large number of parameters. Further developments in these methods would be extremely valuable for parameter search and constructing neuronal model databases that can answer general questions. In one such recent study, strengths of bifurcation and brute-force database approaches were combined (Marin et al. 2013); such an approach could become the next frontier in this field.

Cross-References

- [Bifurcation Analysis](#)
- [Databases and Data Repositories in Computational Neuroscience: Overview](#)
- [Hybrid Parameter Optimization Methods](#)
- [Multi-objective Evolutionary Algorithms](#)
- [NDVis-Neuro](#)
- [Neuronal Model Hand-Tuning](#)
- [Neuronal Parameter Sensitivity](#)
- [Neuronal Parameter Space Exploration](#)

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Neuronal Model Hand-Tuning

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Synonyms

Manual parameter tuning

Definition

In all mathematical models of neuronal systems, there will be a number of parameters whose values have not been determined by experimental studies. Appropriate values for these parameters must then be determined for the model to replicate the desired experimental behavior or to exhibit the desired dynamics. Hand-tuning is the process of manually adjusting parameter values, simulating the model and determining if the adjustments result in the desired model behavior. This method contrasts with automated parameter optimization algorithms in which parameter values to be tested and determination of model fitness are computed by an optimization algorithm.

Detailed Description

In developing a neuronal model, some amount of parameter hand-tuning is unavoidable. Even if an automated parameter optimization algorithm is to be used, hand-tuning may initially be necessary to identify ranges of parameter values to search over or to identify preliminary estimates of model sensitivity to parameters for determining which parameters to vary in an automated optimization. However, in some cases, hand-tuning to identify optimal parameter values may be a preferred or unavoidable method.

An immediate advantage of hand-tuning is its ease: no additional coding or development of a fitness measure is necessary. The modeler sets

parameter values for the model, simulates the model, and observes the model behavior, requiring no further computational resources than those needed to implement a single model simulation run. However, hand-tuning has a number of significant disadvantages as has been discussed elsewhere (Prinz 2007). It is extremely time consuming. While some parallelization may be implemented by simulating and observing results from multiple parameter sets simultaneously, it generally is a serial process. It is difficult and potentially frustrating to understand the effects of changes in parameters on model results given the strong nonlinearities of neural models. Thus, determining appropriate parameter changes to obtain desired results can be difficult. Results of hand-tuning may be subjective in that the modeler chooses the specific parameter values to be tested and if a fitness function is not quantitatively defined, an optimal fit may be decided by only a visual test. Finally, the end result is only a single optimal parameter set which may have limited utility or relevance given the variability of behavior among neurons of the same type or the occurrence of similar model behavior with different but perhaps related parameter sets (Ball et al. 2010; Hudson and Prinz 2010).

One potential advantage of taking the effort to optimize parameters by hand-tuning is that the modeler will certainly develop a deep intuition and understanding of the model's sensitivity to parameters. By observing the effects of each change in parameters and minding how the changes relate to the desired model output, the modeler can directly gain knowledge about how model characteristics are affected by certain parameters and combinations of parameters. Thus, while developing this understanding represents a source of difficulty of parameter hand-tuning, overcoming this difficulty can lead to significant insights that can benefit the modeler and the modeling work.

Implementing parameter hand-tuning is best considered under certain conditions. The number of parameters to be varied should be small, and estimates of bounds on parameter values should be available, so that the dimension and extent of the parameter space to be searched are not too large.

The desired model output should be directly affected by the varied parameters, which is related to the identifiability of the parameters (Chis et al. 2011; Little et al. 2010). For example, if the desired model output is a particular profile of a frequency-current curve or of action potential afterhyperpolarization, hand-tuning is easier if the varied parameters directly affect firing frequency or the time course of membrane repolarization, respectively. Hand-tuning is much more difficult if the desired model output involves higher-order properties of neural behavior that depend on the action or interaction of multiple parameters (Li and Vu 2013). Additionally, hand-tuning may be a preferred option when the desired model output needs to only display certain qualitative features, rather than fit specific, quantitatively characterized behaviors or experimental data. In this case, defining a fitness function for an automated parameter optimization algorithm may be more challenging than parameter hand-tuning.

Despite its limitations and disadvantages, several studies have implemented parameter hand-tuning successfully in complex neural models, including multi-compartment models of single cells (Booth et al. 1997), and small networks of synaptically coupled neurons (Nadim et al. 1995) and electrically coupled neurons (Soto-Trevino et al. 2005).

Cross-References

- [Hybrid Parameter Optimization Methods](#)
- [Neurofitter](#)
- [Neuronal Parameter Space Exploration](#)

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Neuronal Model Output Fitness Function

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Synonyms

Objective; distance; error; cost; or match functions in neuronal model optimization

Definition

A fitness function is a procedure, typically analytical, which quantifies the degree to which a data set or solution meets a given goal. In neuronal modeling, fitness functions typically compare the result of a computer simulation against biological activity for the purpose of guiding parameter optimization.

Detailed Description

Background

Computational models are widely used in neuroscience. These models vary greatly in the level of

biological verisimilitude. At one extreme are detailed conductance-based compartment models that model neuron conductances with physiologically derived differential equations, appropriately distributed on accurately reproduced neuron anatomies (Skinner 2006). At the other extreme are highly abstract models with greatly simplified individual neurons and synapses, e.g., integrate and fire neurons with simple on/off synapses. All such models have free parameters which must be fit before the model faithfully reproduces the biological activity of the system of interest. In some cases, it is possible to experimentally measure neuronal parameter values, such as maximal conductance values and passive membrane properties. However, this typically requires many experiments, and these parameters often vary across similarly behaving neurons. The resulting models typically require hand-tuning of parameter values, a time-consuming and difficult process, before the desired activity is reproduced.

An alternative approach is to fit the model by adjusting its parameter values until a desired activity is obtained. When the model is very simple, or where the goal is to reproduce only the most general features of activity (e.g., the neuron fires action potentials upon depolarization), it may be possible to hand-tune, or to exhaustively survey all possible parameter values (the *search space* or *parameter space* of the model). For most models, however, this is impossible, due to the large number of free parameters, the resolution at which the parameter space must be explored, and the computational time required. Instead, parameter fitting is automated using algorithms which adjust the parameter values until the desired target output is achieved. Intrinsic to this process is the use of an *objective function* to quantitatively compare the activity of the model against the target biological activity. Many such functions have been used. They are properly called *fitness functions*, when they yield high values for similar activity, or *distance functions* or *error functions* when they yield low values for similar activity. It is common however in computational neuroscience to refer to any objective function used in optimization as a fitness function, and we will continue this usage below.

Note that there is no inherent requirement that fitness function output will vary in a way that can be used to direct parameter optimization. For instance, consider a distance function that gave a distance of zero (identical output, i.e., good fitness) only for a narrow range of parameter values for which the model's activity closely reproduces the target, and one (poor fitness) otherwise. Though valid, such a measure would have very limited utility. Even when a model has only a few parameters, model output may change abruptly with small changes in parameter values. Finding the right set of parameter values may therefore require an unfeasibly fine-grained search to escape the plateau of poor fitness. A good fitness function is responsive to changes in model activity throughout the parameter space, so that fitness changes can drive the optimization process towards the desired activity, ideally with a strong gradient and few plateaus or local minima. An additional concern is that nearly identical spontaneous activity can be produced with widely different sets of parameter values, both in conductance-based neuronal models (Prinz et al. 2004; Achard and De Schutter 2006) and in actual neurons (Schulz et al. 2006). Model parameter fitting may therefore require a means to perturb the activity of the model and the target neuron, to provide additional information which may help separate otherwise identically behaving neurons. We cover this aspect of model parameter fitting, and how it relates to the choice of fitness functions, in a final section below.

To illustrate the use of fitness functions, the Morris-Lecar conductance model of giant barnacle muscle fibers (Morris and Lecar 1981; Ellner and Guckenheimer 2006) is used herein. This model includes a calcium conductance, delayed rectifier, and leak conductance, governed by the following system of equations:

$$C \frac{dV}{dt} = -g_{Ca} M_{SS} (V - V_{Ca}) - g_K N (V - V_K) - g_L (V - V_L)$$

$$\frac{dN}{dt} = \frac{N - N_{SS}}{\tau_N}$$

where M_{SS} and N_{SS} , the steady-state activation values, are

$$M_{SS} = \frac{1}{2} \left(1 + \tanh \frac{V - V_1}{V_2} \right)$$

$$N_{SS} = \frac{1}{2} \left(1 + \tanh \frac{V - V_3}{V_4} \right)$$

and the time constant is

$$\tau_N = \tau_0 \operatorname{sech} \frac{V - V_3}{2V_4}$$

The maximal conductance values, reversal potentials, slope and half-maximal activation voltages, and base time constant are the free parameters of the model. Depending on their values, the Morris-Lecar model can produce a variety of intrinsic activity.

Fitness Functions and Model Parameter Optimization

In neuronal modeling, objective or fitness functions measure the similarity between the activity of a neuron and that of a neuronal model. These functions express this difference as a scalar value. In optimization, this value is minimized (error, distance, or cost functions) or maximized (fitness functions proper). As a trivial example, if the goal were to obtain a neuronal model having a particular resting membrane potential (V_{rest}), the absolute value difference between the V_{rest} of the model and the desired resting potential could be used as a distance measure. The optimization process would explore various parameter values, and this distance measure would drive the optimization process to choose parameter values whose models' resting potentials were increasingly closer to the target.

A fitness function evaluated over the set of all possible model parameter values produces a *fitness landscape*. This can be visualized intuitively as a physical landscape, where the height – the fitness of the model's output compared to the

target activity – varies as a function of surface location, i.e., the parameter values of that model. As traditionally defined, better fitness is indicated by greater absolute fitness function values. In practice, however, cost, distance, or error functions are often used, in which case better fitness is indicated by smaller error values (it is this choice that is used in Fig. 5 here). A fitness function is considered a *distance metric* if it satisfies four conditions:

- Nonnegativity: $d(a,b) \geq 0$, for all a,b
- Identity: $d(a,b) = 0$ if and only if $a = b$
- Symmetry: $d(a,b) = d(b,a)$, for all a,b
- Triangle inequality: $d(a,b) \leq d(a,x) + d(x,b)$, for all a, b , and x

Many fitness functions used in neuronal modeling fail one more of these criteria, notably the identity and the triangle inequality. For instance, the phase plane fitness distance (see below) fails the identity condition because different waveforms can give zero distance. When the goal is to produce a particular activity with high fidelity, this may be a concern. In many cases, however, the difference between the “different” waveforms is a simple phase shift, which may be irrelevant to the modeling goals. In such situations, the insensitivity of phase plane distance to phase differences is actually an advantage.

Having chosen a fitness function, the next step is optimization, using this fitness function to determine the parameter values which produce the target activity (Moles et al. 2003; Prinz 2007; Van Geit et al. 2008). This is done by evaluating the fitness associated with a particular set of parameter values and adjusting those parameter values to improve the fitness (or reduce the error) between the model’s activity and the target. When the fitness landscape gradient can be calculated, and no plateaus or local minima (high error “pockets” on the landscape where error further increases in all directions), simple gradient descent can be used to fit the parameters (Bhalla and Bower 1993). When local minima do exist, techniques such as simulated annealing (Van Geit et al. 2008) can be used to escape them. In cases

where the gradient of the fitness function is unknown, a simplex descent (Nelder and Mead 1965) will find minima if they exist, but can become trapped in plateau regions of the fitness landscape. In general, the fitness landscapes of most models and fitness functions are not suitably well behaved, and these methods do not give good results.

An alternative optimization strategy is to use heuristic approaches that incorporate elements of randomness. While not guaranteed to find the global minimum, these approaches often provide good performance in acceptable time for problems that are otherwise intractable. Evolutionary algorithms, for example, are based upon the principles of natural selection and treat the parameters of the model as a genetic code and its behavior as a phenotype (Keren et al. 2005). An initial population of individuals is created with random genotypes, and each individual’s phenotypic fitness is evaluated. Then, during each generation, individuals compete, the population is reduced by survival of the fittest, survivors may recombine by exchanging or otherwise transforming parameters, and mutated offspring are generated. With each successive generation, the fitness of the population improves. Swarm optimizers are based upon the behaviors of social organisms (Hanrahan 2011), such as bees, ants (Dorigo et al. 1999), or even cats (Saha et al. 2013), and move a population of candidate solutions within the parameter space using rules governing their individual and collective position and velocity. A further sophistication is the use of metaheuristic optimization methods (Osman and Laporte 1996), in which different heuristic approaches are sequentially used either randomly or in response to population characteristics reaching set trigger values.

Unfortunately, in general, there is no way to know a priori which optimization approach will work best, and for any approach, there may be fitness landscapes which can give poor results. Since fitness landscapes depend in part on fitness function, it also follows that which optimization approach will work best depends on the fitness function chosen. Identifying which fitness

functions and optimization procedures will give good results inevitably involves a degree of trial and error. Another difficulty is that a particular fitness function and optimization procedure may perform well for some parameters but not others. It is thus sometimes desirable to incorporate multiple fitness functions by weighted summation or by changing fitness functions with successive generations.

Fitness Functions

The selection or design of appropriate fitness functions depends on many factors, most notably how similarity is assessed and what features are important to replicate. If the goal is to reproduce a spike train, for example, a fitness function which is sensitive to activity below spiking threshold, but relatively insensitive to spike timing or count, is a poor choice. On the other hand, such a fitness function could be a good choice for adjusting the conductance parameters of a slow-wave oscillator. Too many fitness and distance functions have been used in neuronal modeling to exhaustively survey all of them. We instead cover below only the more common ones. These may provide adequate performance for a given modeling task or can be used as starting points for designing ad hoc functions. In general, neuronal modeling fitness functions can be grouped by whether they primarily assess continuous activity, discrete activity (spike trains), or both.

Continuous Activity Fitness Functions

Continuous activity fitness functions quantify the difference between two continuous waveform traces or time series, a and b . Without loss of generality, these will be assumed to be continuous functions, though in practice these are typically time series obtained by regular sampling of neuronal activity and matched resampling of model output. Also, the two waveform traces are assumed to be of equal duration, t_{tot} , as it is common to simulate model response to match the duration of the target.

Waveform Distance

The simplest fitness function is waveform distance, D_w , which directly compares two waveforms of equal length t_{tot} :

$$D_w = \frac{1}{t_{\text{tot}}} \left(\int_{t=0}^{t_{\text{tot}}} |a(t) - b(t)|^p dt \right)^{1/p}$$

With $p = 1$ (Manhattan distance), this function measures the mean absolute difference between the waveforms (Fig. 1a); more commonly the Euclidean distance, $p = 2$, is used. Assuming t_{tot} is held constant throughout the optimization, D_w with $p = 2$ is the familiar root mean squared error measure (Bhalla and Bower 1993):

$$D_{\text{RMS}} = \sqrt{\frac{1}{t_{\text{tot}}} \int |a(t) - b(t)|^2 dt}$$

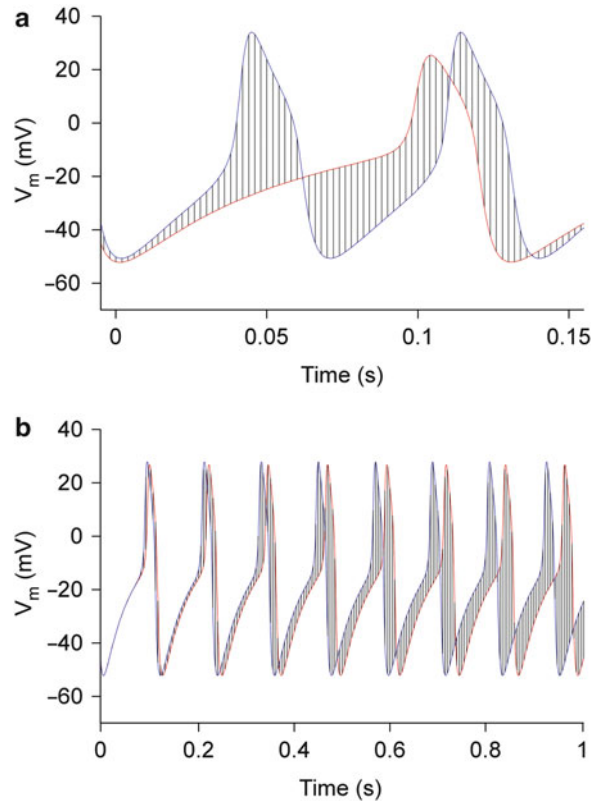
Waveform distance satisfies the criteria required to be a distance metric, provided the $1/p$ exponent is maintained in the D_w equation. It is, however, highly sensitive to phase differences between the waveforms, yielding increasingly large error measures as otherwise identical waveforms become increasingly out of phase. This difficulty can be overcome by entraining the neuron and model with an appropriate stimulation (e.g., a current pulse), or by calculating waveform distance as a function of time offset, analogous to cross-correlation (see below),

$$D_w(\tau) = \frac{1}{t_{\text{tot}}} \left(\int |a(t + \tau) - b(t)|^p dt \right)^{1/p}$$

and then taking the minimum such $D_w(\tau)$ as the scalar distance value. Where resting potential or amplitude is irrelevant to the modeling goals, the waveforms can be normalized by mean and/or variance prior to computation of waveform distance. With long periodic samples (Fig. 1b), waveform distance becomes highly sensitive to slight cycle frequency differences, producing pathological fitness landscapes with large plateaus

Neuronal Model Output Fitness Function,

Fig. 1 Waveform distance (D_W) calculation between two Morris-Lecar model membrane voltage traces. Waveform distance is a commonly used simple fitness function when fitting non-spiking neuronal models. In its simplest form, it measures the mean difference between two waveform traces (a). It is highly sensitive to phase differences (see text) or with long samples of periodic waveforms, even slight frequency differences (b), which can overwhelm the contribution of differences of other characteristics such as amplitude or waveform shape



of high error which increase in the immediate neighborhood of the target. Due to the relatively short duration of the spikes compared to typical waveform samples, waveform distance is relatively insensitive to differences in spike count or timing.

Phase Plane Distance

Another method to avoid the phase sensitivity of waveform distance is to use *phase plane distance*, D_{ph} , which, loosely, calculates the overlap of the two waveforms in a two-dimensional half-phase plane, e.g., $(dV/dt, V)$ for voltage traces (LeMasson and Maex 2001). This measure bins each waveform into a two-dimensional density matrix M of suitable size and resolution and then measures the differences between bin counts (Fig. 2):

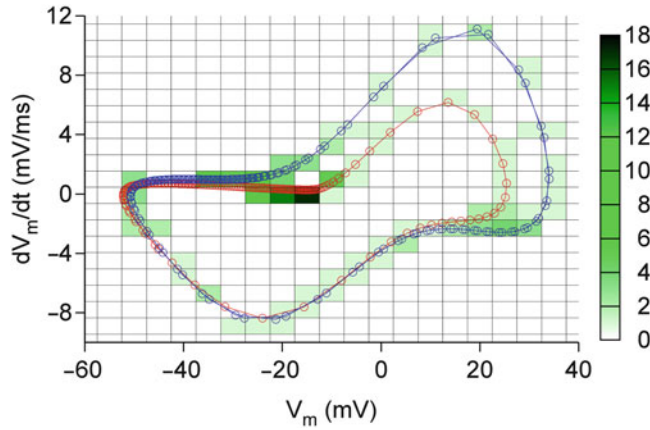
$$D_{ph} = \left(\sum_i \sum_j \left| \frac{M_a(i,j)}{N_a} - \frac{M_b(i,j)}{N_b} \right|^p \right)^{1/p}$$

where N_a and N_b are the number of samples. Because difference is only measured within bins, a miss (two samples falling in adjacent bins) is as good as a mile (the same two samples in widely separated bins). Matrix extents and resolution can thus strongly affect the performance of the metric. Too coarse a grid will be insensitive to small differences, notably in spiking activity. Too fine a grid will detect such features, but dissimilar waveforms will give errors which fail to decrease appreciably until the waveforms become very similar, resulting in plateaus on the fitness landscape.

Linear Synchrony Measures

Linear synchrony measures (Kreuz 2013) can be used as fitness functions. The cross-correlation between two waveform traces is one such commonly used measure:

$$C(\tau) = \int_{t=k}^{t_{tot}-k} \hat{a}(i+\tau) \hat{b}(i) dt$$



Neuronal Model Output Fitness Function, Fig. 2 Phase plane distance (D_{ph}) calculation between two Morris-Lecar model voltage traces. Phase plane distance bins regularly sampled response waveforms (see Fig. 1) into a density matrix in the half-phase plane (e.g.,

dV/dt vs. V for a membrane potential recording). The mean pairwise difference between bin counts yields the distance between the two traces. Phase plane distance is insensitive to waveform phase differences

where $\hat{a}$ and $\hat{b}$ are the waveforms normalized to zero mean and unity variance, and $-k < \tau < k$ is constrained so as to provide overlap between the two waveform traces over the range in which cross-correlation is evaluated. $C(\tau)$ ranges from 1 for complete correlation, through 0 for independent waveforms, to -1 for complete anti-correlation. Thus, the maximum $|C(\tau)|$ over all τ can be used to measure the phase-independent similarity between the two waveforms. Note this value should be maximized, not minimized, by the optimizer.

Discrete Activity Fitness Functions

In many neuronal models, it is assumed that information is coded primarily in the timing and rate of action potentials and that the slow-wave activity of the neuron and amplitude and shape of the action potentials are irrelevant. In such models, fitness functions which consider only spike timing are used. Many such measures exist (Victor 2005; Kreuz et al. 2007; Victor and Purpura 2010; Kreuz 2011; Houghton and Victor 2012). These take, as input, a discrete time series comprising the times of the action potentials in the spike train and calculate distance from differences in features such as the spike count, timing, or interspike interval (Fig. 3).

Spike Count, Spike Time, and Interspike Interval Distances

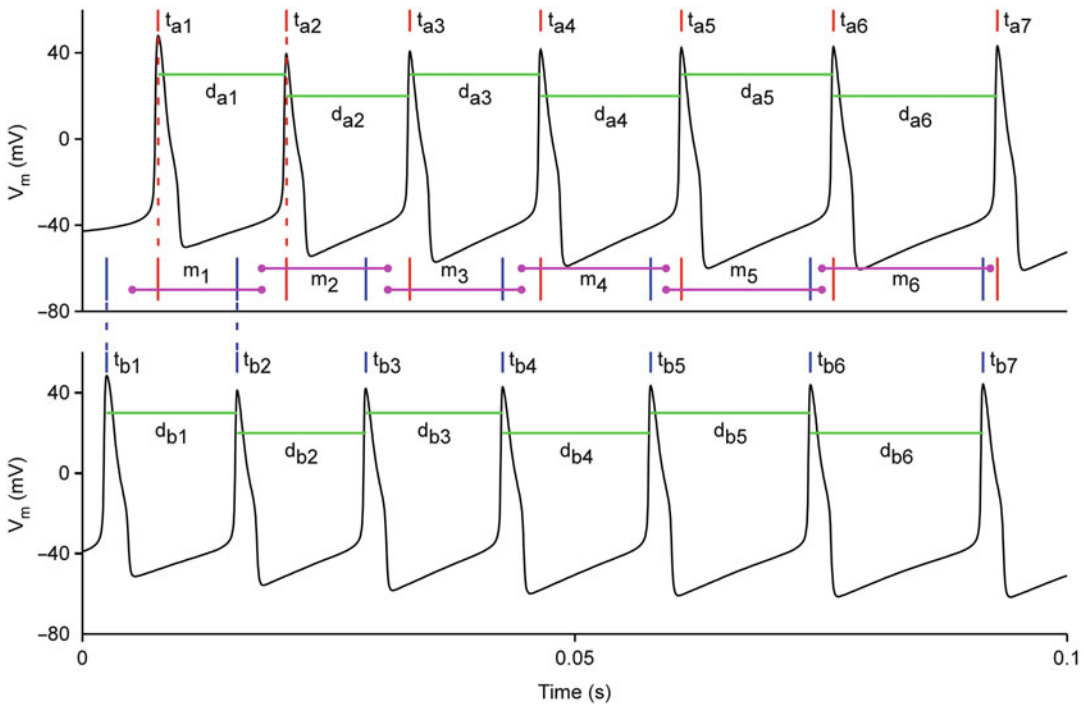
Spike count (D_{SC}), spike time distance (D_{ST}), and interspike interval distance (D_{IS}) are relatively simple measures:

$$D_{SC} = |N_a - N_b|$$

$$D_{ST} = \frac{1}{N} \left(\sum_{i=1}^N |t_a(i) - t_b(i)|^p \right)^{1/p}$$

$$D_{IS} = \frac{1}{N-1} \left(\sum_{i=1}^{N-1} |d_a(i) - d_b(i)|^p \right)^{1/p}$$

where N_a and N_b are the number of spikes in a and b , $N = \max(N_a, N_b)$, $t(i)$ is the time of the i th spike, and $d(i) = t(i+1) - t(i)$ is the interspike interval time. D_{ST} measures the degree of coincidence between the two spike trains and is thus sensitive to phase differences, whereas D_{IS} is insensitive to phase. D_{ST} and D_{IS} are both sensitive to missing spikes in either or both spike trains, which can be a concern when attempting to model real neuron recordings.



Neuronal Model Output Fitness Function, Fig. 3 Spike train measures used in some spike timing-based fitness functions. Many fitness functions used to

quantify difference between spike trains rely upon basic features such as the timing of the spikes (t), the interspike interval (d), or the mean of paired interspike intervals (m)

Spike Time Alignment and Interval Alignment Distances

The spike time alignment distance (Victor and Purpura 1996), similar to string edit distance, measures the minimum total cost required to transform one spike sequence into another by inserting, removing, or moving spikes (Fig. 4). Insertion or removal of a spike are both assigned cost of 1, and changing the time of a spike by Δt is assigned a cost of $q\Delta t$, where q is a tuning parameter of the function. For $q = 0$, spike time alignment distance measures differences in spike count. For small values of q , the function is more sensitive to differences in spike rate than spike timing. For larger values of q , spike time alignment distance becomes comparable to D_{ST} but with less sensitivity to missing spikes. For very large values of q , however, the algorithm removes and reinserts spikes rather than moving them, which can be overcome by using unequal insertion and deletion costs. The interval alignment distance is analogous, measuring the cost to change interspike intervals, $q\Delta d$.

Kernel Methods

An alternative approach with discrete data is to convolve the spike trains with a suitable kernel to transform them into continuous functions and then use measures suitable for continuous time series (Fig. 5). The van Rossum distance (van Rossum 2001; Fig. 5, left column) convolves each spike train with a half-exponential kernel:

$$k_{vR}(t) = \begin{cases} e^{-t/\tau} & t \geq 0 \\ 0 & t < 0 \end{cases}$$

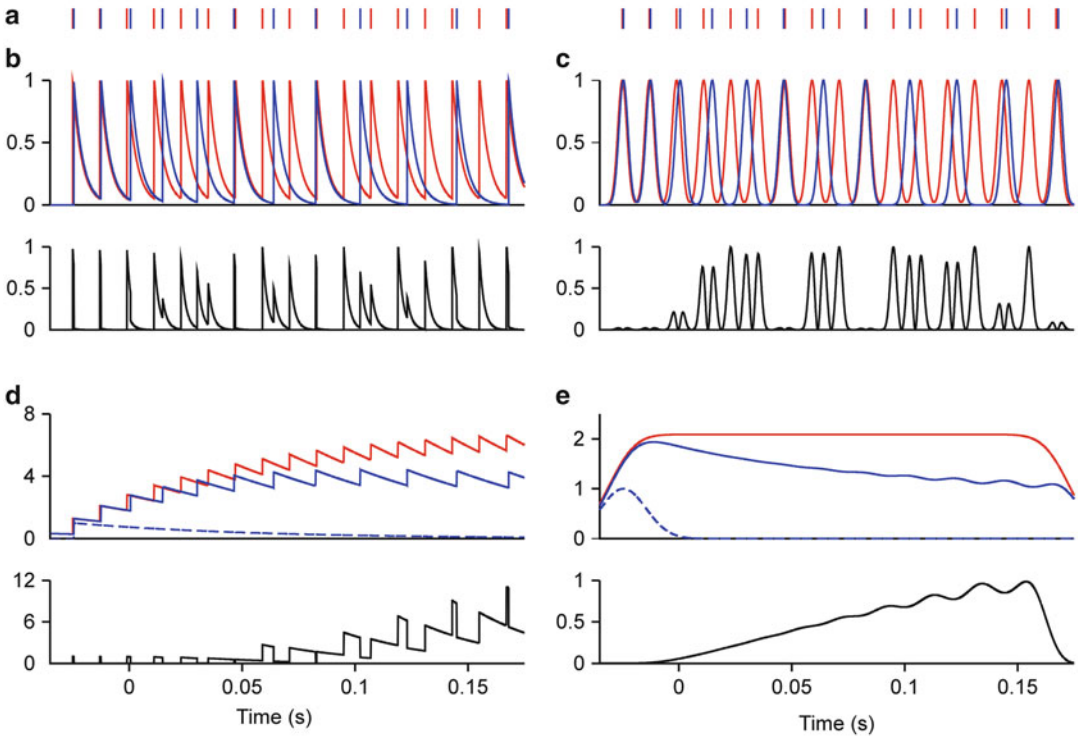
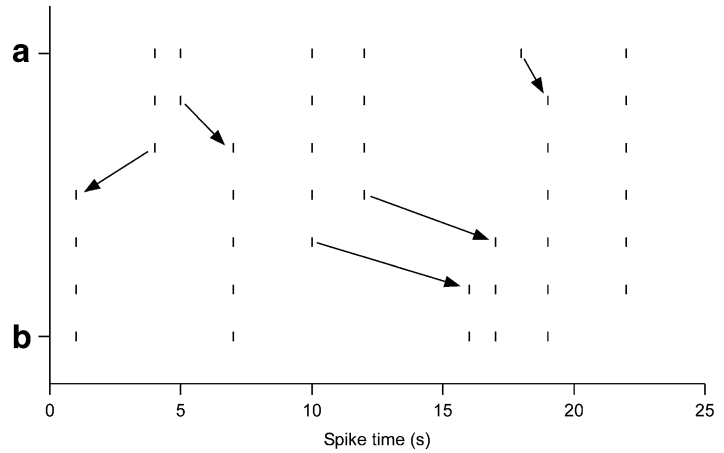
to produce continuous waveform traces and then calculates mean square difference of the convolved waveforms:

$$D_{vR} = \frac{1}{\tau} \int_{-\infty}^{\infty} [(a * k_{vR})(t) - (b * k_{vR})(t)]^2 dt$$

When τ is small, the van Rossum distance is sensitive to spike coincidence, as the convolved

Neuronal Model Output Fitness Function,

Fig. 4 Spike time alignment distance. The spike time alignment distance measures the total “cost” to transform one spike train (*a*) into another (*b*). Insertion or removal of a spike has a fixed cost of 1; moving a spike by Δt has a cost of $q\Delta t$. For small values of q , the algorithm compares spike count; for larger q values, it is a coincidence detector



Neuronal Model Output Fitness Function,
Fig. 5 Kernel-based spike timing measures. Kernel approaches convolve discrete spike trains (*a*; *red*, constant frequency spike train; *blue*, spike train of decreasing frequency) with a kernel such as a half-exponential (*b*, *d*) or Gaussian (*c*, *e*) to create continuous waveform traces. Then, the difference between the continuous waveform traces is quantified using a measure such as waveform distance (*black traces*, showing time-wise square difference between *red* and *blue traces*). The temporal width of

the kernel is a tuning parameter; when this is small (*b*, *c*), these methods primarily measure spike timing coincidence (note how coincident spikes yield low area under the corresponding black traces and thus low waveform distance). With larger kernels (*d*, *e*; convolved waveform of first spike shown in *dashed blue*), these methods are more sensitive to differences in spike rate (note divergence of *red* and *blue traces* and thus *black trace* of increasing amplitude, as the frequency of the two spike trains diverges)

waveforms overlap extensively only when the spike timing is very similar (Fig. 5b). With larger τ (Fig. 5d), the function becomes a rate measure. A Gaussian kernel has also been used (Schreiber et al. 2003; Fig. 5c, e), typically with cross-correlation instead of waveform distance. As with van Rossum distance, the function's sensitivity to rate or timing depends upon kernel size.

Parameter-Free Methods

The Victor-Purpura and kernel methods rely upon a parameter to adjust the time sensitivity of the fitness function. Parameter-free alternatives are sometimes desirable, e.g., when spike frequency varies over a wide range. The parameter-free spike distance, D_{SPIKE} , is calculated as follows. First, for each spike train, three continuous functions are created. One, $t_p(t)$, is the time of the nearest previous spike, or the beginning of the recording if before the first spike. The second, $t_f(t)$, is the time to the nearest next spike, or the end of the recording if after the last spike. The final, $w(t)$, is the width of the interspike interval between these two:

$$t_p(t) = \max(t_a(i) | t_a(i) \leq t \forall i)$$

$$t_f(t) = \min(t_a(i) | t_a(i) \leq t \forall i)$$

$$W_a(t) = t_{f_a}(t) - t_{p_a}(t)$$

and similarly for the second spike train (b). The mean interspike interval is also calculated:

$$\overline{W}(t) = \frac{w_a(t) + w_b(t)}{2}$$

Next, differences across the two spike trains are calculated, by measuring the difference from t_p or t_f in one spike train to the nearest spike in the other spike train.

$$\Delta t_{p_a}(t) = \min(t_{p_a}(t) - t_b(i) \forall i)$$

$$\Delta t_{f_a}(t) = \min(t_{f_a}(t) - t_b(i) \forall i)$$

and, again, similarly for spike train b . For each spike train, a locally weighted average function is calculated:

$$S_a(t) = \frac{\Delta t_{p_a}(t)(t - t_{p_a}(t)) + \Delta t_{f_a}(t)(t_{f_a}(t) - t)}{W_a(t)}$$

and, again, similarly for $S_b(t)$. Finally, the time-varying dissimilarity profile is calculated:

$$S(t) = \frac{S_a(t)w_b(t) + S_b(t)w_a(t)}{2 - w(t)^2}$$

Integrating this over the total recording time gives the scalar D_{SPIKE} distance:

$$D_{\text{SPIKE}} = \frac{1}{t_{\text{tot}}} \int_{t=0}^{t_{\text{tot}}} S(t) dt$$

A similar parameter-free method, D_{ISI} , exists based upon interspike intervals instead of spike timing.

Hybrid and Alternative Methods

Fiducial-Point Distance

The fiducial-point distance, D_{fp} , utilizes both continuous waveform data and spike timing data. The times of matched action potentials in the two waveforms are used as “fiducial points,” i.e., fixed reference points (Ambros-Ingerson et al. 2008), to align the continuous data prior to comparing them. The times of the N_a action potentials in waveform a , $t_a(i)$, and the N_b action potentials in waveform b , $t_b(i)$, are first identified. Only the minimum of the two, $N = \min(N_a, N_b)$ are used. The interspike intervals, $d_a(i)$ and $d_b(i)$, and their mean, $m(i) = (d_a(i) + d_b(i))/2$, are calculated (see Fig. 3) for all $i \leq N$. The $N + 1$ fiducial points, $q_a(i)$ and $q_b(i)$, are calculated as follows:

$$q_a(i) = \begin{cases} 0 & i = 0 \\ t_a(i) & 0 < i < N \\ \max(t_a(N), t_b(N)) & i = N \\ t_{\text{end}} & i = N + 1 \end{cases}$$

Then, stretch factors are calculated for each waveform and for each interspike interval: $s_a(i) = d_a(i)/m(i)$ and $s_b(i) = d_b(i)/m(i)$. Finally, waveform distance is calculated using these stretch

factors to shrink or expand each section between spikes so that the spike times coincide:

$$D_{fp} = \frac{1}{t_{\text{tot}}} \left[\sum_{i=0}^N \int_{t=0}^{m_i} |a(s_a(i)t + q_a(i)) - b(s_b(i)t + q_b(i))|^p dt \right]^{1/p}$$

Mutual Information

Mutual information is the reduction in uncertainty about one variable from having knowledge of another. It is often used in neuroscience to estimate the degree to which the response of a neuron is due to its driving input, but can also be used as a nonlinear measure to compare neuron and model activity. Formally, mutual information is defined as

$$I(X; Y) = \sum_{x \in X} \sum_{y \in Y} P_{XY}(x, y) \log \frac{P_{XY}(x, y)}{P_X(x)P_Y(y)}$$

where P_{XY} is the joint probability distribution and P_X and P_Y are the marginal probability distributions. Typically, this is estimated by measuring some characteristic or feature of the data, such as spike count or timing, and then binning the data to estimate the probability distribution of this feature. Other information-based measures, such as transfer entropy, can also be applied (Gray 1990).

Feature-Based Approaches

Real neurons often produce different responses to repeated identical perturbation (Nowak et al. 1997). This can be problematic if the fitness function is overly sensitive to the noise component. An alternative approach is to isolate multiple features of interest in the voltage or current response of the neuron, such as spike rate or action potential shape (height and duration). A multiple objective optimization method is then used which compares the model's activity against the reference simultaneously in each of these features (Deb 2001). This method can produce good fits to noisy data, finding parameter values which reproduce the desired features of interest (Druckmann et al. 2007).

Driving Input

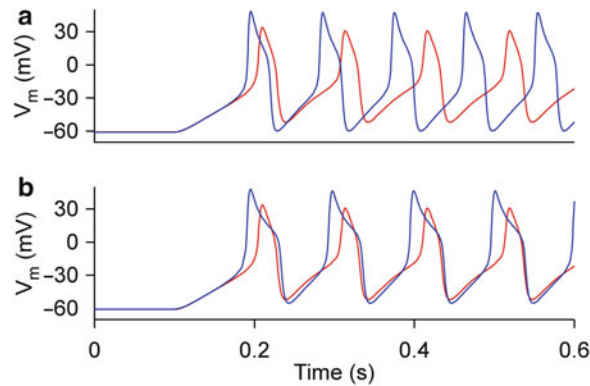
It is often desirable in neuronal modeling to reproduce a neuron's activity with the intention of obtaining insights into the neuron from the fitted parameters of the model. However, many neuronal models can produce essentially identical activity across a wide range of parameter values (Prinz et al. 2004; Achard and De Schutter 2006). As a trivial example, for many different combinations of parameter values, the Morris-Lecar model will produce identical, quiescent output, a constant resting membrane potential. However, once stimulus current is applied, the model produces periodic oscillations whose frequency and amplitude depend upon parameter values (Fig. 6a).

Even when the spontaneous activity of the model does vary with differing parameter values, a particular fitness function may not be sensitive to these differences. Again considering the Morris-Lecar model, two different parameter combinations can produce rhythmic output of the same cycle frequency but different amplitude and shape (Fig. 6b). If amplitude and shape are important features to consider in fitting the model, waveform distance with long sample duration would be a poor choice, as its very high sensitivity to frequency differences could overwhelm its response to other differences, and thus it may drive the optimizer to fit only target frequency. With appropriate perturbation, these two model neurons may begin to produce activities with different frequencies, which this fitness function could then detect.

When fitting to real neurons, where some of the membrane potential response is due to the intrinsic noise of the neuron, repeating the stimulation can be useful. Ideally, the fitness functions used to fit a model to these neurons would be relatively insensitive to variations in neuronal activity across these repeats, but sensitive to differences across neurons.

Current Clamp

Current pulses, steps, or ramps are commonly used as driving input to neuronal models or real neurons. Differences in response amplitude, slow-wave frequency, spike rate and timing, delay until first spike onset, or other features may all vary depending upon



Neuronal Model Output Fitness Function, Fig. 6 Neuronal models can produce similar activity with different parameter values. (a) Two Morris-Lecar models with different parameters but identical resting potentials respond differently to the injection of constant current (90 nA, beginning at 0.1 s). (b) Models with

different parameters can also produce output which is distinctive, but not every fitness function is sensitive to these differences. Waveform distance with long samples would measure these two waveforms as relatively similar due to their equal frequency

current amplitude or ramp slope. These can then provide useful information which can facilitate parameter fitting. A more general approach is to drive the neuron or model with noise due to the ability of noise stimulation to elicit consistent responses with high information content (Tateno and Pakdaman 2004). Such noise may include Gaussian white noise, or pink noise. Ornstein-Uhlenbeck process noise, which more closely approximates synaptic input, has also been used, notably in stochastic models (Tuckwell et al. 2002; Koutsou et al. 2013). Noise stimulation is commonly used when studying spike trains. An advantage of current clamp perturbation is that there is a closed feedback loop in which the states of the ionic conductances, which depend upon the membrane potential, in turn drive changes in that membrane potential. Thus, the responses of the neuron and model include all of the interactions and temporal dynamics of the neuron's own membrane and conductances. For instance, single, relatively simple perturbations (a current pulse) can trigger relatively long-lasting, large, self-generated responses (an action potential, a burst of action potentials). As such, provided the perturbations are of sufficient amplitude and duration to trigger conductance activation, the ability of current clamp perturbation to explore large regions of the neuron or model activity

space depends much less on the fine details of the perturbation than in voltage clamp.

Voltage Clamp

In voltage clamp, assuming no space clamp limitations, the membrane potential throughout the neuron is constrained to the command potential. It is thus impossible to drive a neuron or model through a wide range of phase space without a driving input whose characteristics match the dynamic response of the conductances. In such conditions, noise stimulations can thus be a poor choice, as the neuron spends most of its time in intermediate membrane potentials where conductances are not appreciably activated, and excursions to depolarized or hyperpolarized potentials, when they do occur, are rarely long enough to activate any but the fastest conductances. Sine or square wave chirps, or other stimulations which appreciably activate the voltage-dependent conductances and thus explore a wide range of conductance states, may be a better choice if voltage clamp is to be used. Again, absent space clamp concerns, voltage clamp can be advantageous for modeling as the absence of intrinsic activity produced by the closed feedback loop simplifies the fitness landscape, and may allow isolation of conductances with different temporal dynamics.

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Neuronal Model Reduction

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Definition

The act of reducing the complexity of a mathematical neuron model while preserving its essential features.

Detailed Description

The biophysical description of ion channels distributed on a three-dimensional neuron membrane is a typical example of a complex mathematical neuron model. In such models, the voltage dependence of ion channels follows the formalism of Hodgkin and Huxley. Therefore, each patch of membrane is characterized by the membrane potential, x_1 , and the state of activation/inactivation for every ion channel type, $x_2, \dots, x_n$. These state variables evolve according to a differential equation arising from biophysics and biochemistry. The equations are typically of first order in time, but nonlinear. Given the nonlinear functions $f_1, f_2, \dots, f_n$, the evolution of n state variables follows:

$$\begin{aligned}\frac{dx_1}{dt} &= f_1(x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_k) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_k) \\ &\dots \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_k)\end{aligned}\quad (1)$$

where $y_1, y_2, \dots, y_k$ represent k external variables, typically variables from the surrounding membrane patches. More complete models take into account intracellular and extracellular concentration of ions, neurotransmitters, neuromodulators, etc. The mathematical neuron model is obtained by combining systems of equations such as in Eq. 1 for membrane patches throughout the

neuron morphology. Overall, the equations can describe synaptic activation, ion fluxes, membrane potential dynamics, and action potential generation.

Taking a phenomenological perspective, a neuron integrates all excitatory and inhibitory input until it reaches a threshold. Once the threshold is reached, it emits an action potential and integration is reset. This integrate-and-fire model does not model the ionic concentrations or many other biophysical properties. It overlooks some dynamical features of neurons such as adaptation or dendritic spikes but can reproduce the activity of real neurons in some degrees.

In many applications, it is essential to achieve a correct mapping between synaptic input and action potential output. Simpler description can often approximate this mapping correctly. Neuronal model reduction is the process of deriving the simpler description from the complex one. For a single patch of excitable membrane such as described by Eq. 1, there are two typical approaches: dimensionality reduction of the dynamical system and the functional approach. These approaches can be used to reduce the morphologically complete description as well.

Dimensionality Reduction in Dynamical Systems

Analysis of the dynamical system may reveal state variables that covary. When this is the case, it is possible to reduce the dimensionality of the system by setting one state variable as proportional to the other. Investigating further may uncover a separation of time scale between one subsystem and another. This allows to reduce the dimensionality further. Also, the form of the nonlinearities ($f_1, f_2, \dots, f_n$) can be approximated by simpler descriptions without qualitative change in the resulting dynamics.

A classical example of neuronal model reduction of this type was reported by Fitzhugh (1961) and Nagumo et al. (1962). They performed a reduction of the Hodgkin-Huxley equation from four dimensions to two. The Fitzhugh-Nagumo equations can be written in the same formalism as Eq. 1:

$$\begin{aligned}\frac{dx_1}{dt} &= f_1(x_1, \dots, x_2, y_1) \\ \frac{dx_2}{dt} &= f_2(x_1, \dots, x_2)\end{aligned}\quad (2)$$

where x_1 is the membrane potential, x_2 is an abstract recovery variable, y_1 is the injected current, f_1 is polynomial linear in x_2 but of third order in x_1 , and f_2 is bilinear. This simple equation can describe the generation of action potential and many dynamical features of the Hodgkin-Huxley equations.

The presence of different ion channels can lead to a variety of functions f_1 and f_2 (Izhikevich 2007). The model of Morris and Lecar (1981) is another classical example. Using sigmoidal functions, they derived a reduced model of barnacle giant fibers activity.

Another approach to reduce the dimensionality of excitable systems is to introduce a threshold. The basic assumption here is that action potentials are stereotypical events. Once the threshold is reached, the state variables undergo a simple update rule. Introducing a threshold leads to a reduction of complexity because the nonlinear dynamics responsible for the action potential are replaced by a simple update rule. The Izhikevich model (Izhikevich 2003) and the adaptive exponential integrate-and-fire model (Brette and Gerstner 2005) offer a general framework for such reductions.

More general approaches for model reduction can be used. The first step in these methods involves rewriting Eq. 1 in matrix form. Then matrix decompositions such as the singular value decomposition are used. These methods are variants of proper orthogonal decomposition (Chaturantabut and Sorensen 2010), and they have been applied to the Hodgkin-Huxley equations (Kellems et al. 2010). A twofold reduction in dimensionality was achieved while preserving accurate spiking and subthreshold behavior of detailed single-neuron models (Kellems et al. 2010).

Functional Approach

Instead of reducing the system of differential equations, it can be more efficient to approximate

the solution. For a single external variable, y_1 , the general approach is summarized by the Volterra expansion:

$$\begin{aligned}x_1(t) &= \int F_1(t-s)y_1(s)ds \\ &+ \int \int F_2(t-s, t-s')y_1(s)y_1(s')dsds' \\ &+ \dots\end{aligned}\quad (3)$$

where F_1 and F_2 are functions that have to be determined empirically Bialek et al. (1991). Marmarelis and Naka (1973) used the Volterra expansion to model the membrane potential (x_1) given a time-dependent stimulus (y_1). In this approach, the state variable x_1 is seen as a functional of the external variable y_1 .

The Volterra expansion is an infinite series. Truncating the series leads to a reduction of model complexity. For neuron models, however, keeping only the two first terms is often insufficient. Indeed the nonlinearity of action potential generation requires higher-order terms.

Three other functional approaches can be seen as variants of the Volterra expansion: the cascade linear nonlinear model (LNL; Marmarelis and Marmarelis 1978; Korenberg and Hunter 1986), the nonlinear autoregressive Volterra model (NARV; Eikenberry and Marmarelis 2013), and the spike-response model (SRM; Kistler et al. 1997). In the cascade approach, the Volterra expansion is fed into a static nonlinearity. This nonlinearity can account for some of the nonlinear effects, thus reducing the relative importance of higher-order terms of the expansion. The NARV and SRM add a static nonlinearity as well but also a filter for the past spiking history. In the SRM, the subthreshold membrane potential is modeled as a sum of first-order effects from the external current y_1 and current pulses at the times of past action potential, y_2 :

$$\begin{aligned}x_1(t) &= \int K_1(t-s)y_1(s)ds \\ &+ \int K_2(t-s)y_2(s)ds\end{aligned}\quad (4)$$

where K_1 and K_2 are filter functions that must be determined empirically (see also reduction heuristics in Gerstner and Kistler (2002)). The likelihood of firing an action potential is a nonlinear function of x_1 . The NARV approach is distinct from the SRM in two points: the second external variable is a nonlinear function of the past $x_1(t)$, and second-order terms are included. All these variants were shown to improve the accuracy of the reduction.

Functional expansions rely on a proper method for estimating the filter functions. Calculating the Wiener filter is the classical method for finding a filter function such as F_1 , but multilinear regression can also be used. The Wiener filter and the multilinear regression are both based on a measurement of a correlation matrix between input (y_i) and output (x_1). Cascade models can be characterized using a correlation matrix (Hunter and Korenberg 1986; Chichilnisky 2001). Other variants such as the SRM are characterized using a gradient ascent of the likelihood to observe a given spike train (Paninski 2004) or using multilinear regression and likelihood ascent in two successive steps (Mensi et al. 2012).

Morphological Reductions

Dendritic and axonal processes have complex three-dimensional shapes. A detailed treatment of membrane potential and ion concentration on such a morphology is achieved by discretizing space.

When the membrane is passive and the system of equations is linear, drastic reductions are possible. For instance, Rall was the first to show the existence of an equivalent cable for dendritic trees. It is also Rall who described a Green's function approach consistent with the functional approach described above. His work is reviewed by Rall (1995).

A linear filter can still be applied for weakly active dendrites (Koch 1984) or nonuniform membrane conductances (London et al. 1999). For dendrites with strongly active ion channels or with elaborate distribution of synaptic conductances, these reductions do not apply.

Formal dimension-reduction methods apply well to dendritic trees. The use of singular

value decomposition was successfully applied to large dendritic trees (Kellems et al. 2009). The reduced models, however, remain fairly complex.

For a more drastic reduction, one approach has been to treat dendrites in terms of conceptually distinct compartments (Mel 2007). Each compartment can be modeled by more phenomenological models. One classical example is the Pinsky-Rinzel model which reduced pyramidal neuron models to a dendritic and a somatic compartment linked by a resistance (Pinsky and Rinzel 1994). Each compartment followed the dynamics of a restricted set of ion channels.

Reduction of Neural Networks

Neurons interconnect to form neural networks. Neuron model reduction can be applied to neural networks as well. Networks can be reduced to the dynamics of its subpopulations. The mean-field approach is often used for reducing a population of integrate-and-fire neurons (Renart et al. 2004). The mean-field approach can also be used to reduce a population of SRM neurons (Naud and Gerstner 2012). In both cases, the reduction of the network model is based on a simpler description of the single neurons. Neuron model reduction is more than an economy of equations and parameters; it creates a link between the different levels of description.

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Further Reading

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Neuronal Parameter Co-regulation

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Synonyms

[Conductance co-regulation](#); [Conductance scaling](#)

Definition

Neuronal parameter co-regulation is the exploration or alteration of distinct subsets of parameters (e.g., synaptic or membrane conductances) and how these parameters act in concert leading to changes in, or conservation of, neuronal output.

Detailed Description

The underlying ionic conductances found within a model neuron represent the parameters which determine the characteristics and output of a given model cell. These parameters are usually derived from biological data, such as voltage-clamp measurements of ionic conductance characteristics in defined cell types. The range over which these parameters can vary in a given system is referred to as the “parameter space” with a dimensionality dictated by the number of parameters allowed to vary in the system.

One area of interest in neuroscience, and a focus of modeling studies, is the interaction of distinct underlying physiological characteristics in the ultimate output generation of a neuron. In other words, the understanding of how relative contributions of conductances work in concert ultimately determines the voltage trajectory of a given neuron under different conditions. One computational method to probe for these relationships is the process of neuronal parameter co-regulation. In short, parameter co-regulation seeks to understand how conductances may work together as “modules” to constrain output, rather than each parameter being entirely independent (Franklin et al. 2010). Biological data have been accumulating for some time suggesting this to be a normal part of neuronal function, and are briefly discussed below. In addition, two computational methods to investigate this co-regulation are outlined below, utilizing both hand-tuning (Traub et al. 1991; De Schutter and Bower 1994) and model neuron database approaches (Prinz et al. 2003).

Biological: Correlation and Co-regulation of Ion Channels and Conductances

To some extent, the general concept of neuronal parameter co-regulation in neurons is rooted in part in studies that demonstrated the capacity of cells to homeostatically maintain appropriate output during perturbation of one or more different membrane conductances (Turrigiano et al. 1994; Desai et al. 1999; Golowasch et al. 1999; Galante et al. 2001; MacLean et al. 2003). These studies demonstrated that by experimentally manipulating specific membrane conductances and/or neuronal activity (pharmacologically, via gene expression, electrophysiologically), compensatory changes can occur among other conductances that stabilize and restore output of the cell.

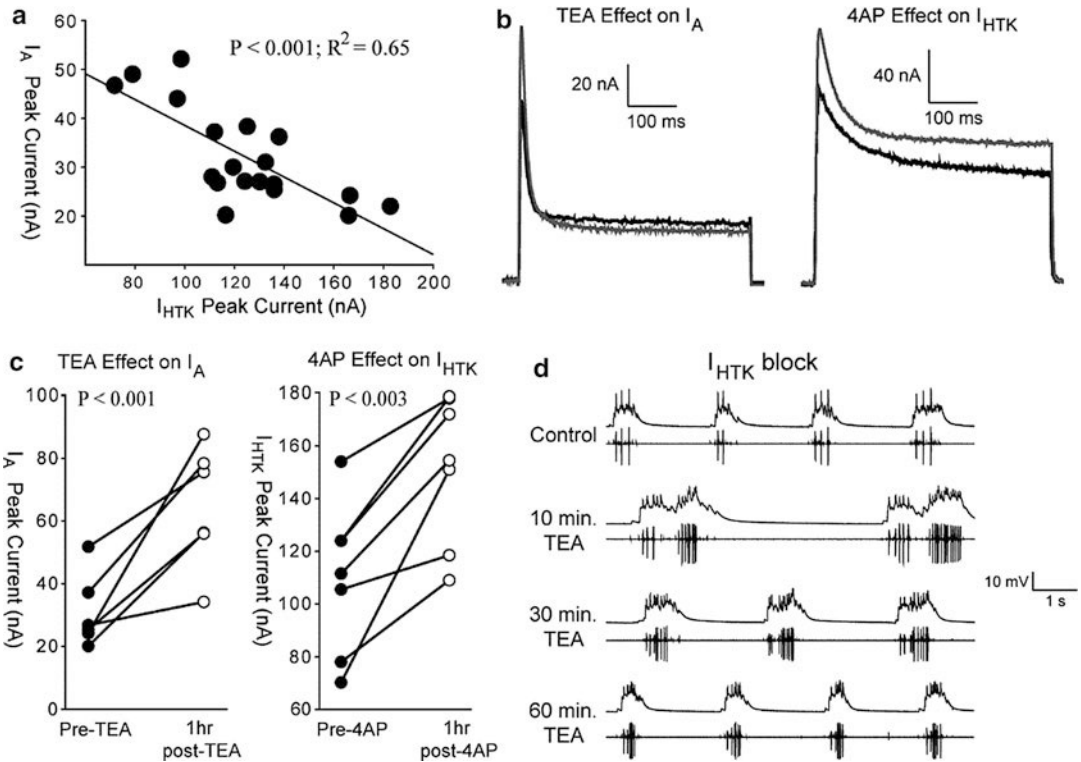
These experiments not only laid the groundwork for an understanding of conductance co-regulation but also raised an important question: Is neuronal parameter co-regulation a fundamental aspect of cellular function or solely a

response to perturbation? This question makes the following prediction: if parameter co-regulation is a regular part of neuronal function, then populations of neurons should reveal existing relationships among conductances that are co-regulated. These relationships should include correlated patterns of ionic conductances, as well as perhaps other aspects of channel function (such as ion channel mRNAs), among the population of cells. Indeed, these relationships have been reported in multiple studies, including at the level of $G_{\max}/I_{\max}$ (Khorkova and Golowasch 2007; Ransdell et al. 2012; Temporal et al. 2012) as well as ion channel mRNA levels (Schulz et al. 2007; Tobin et al. 2009; Temporal et al. 2012). As an example, work by Ransdell et al. (2012) presented in Fig. 1 encapsulates these concepts from detecting correlated neuronal parameters (in this case I_A and I_{HTK}), demonstrating compensation to manipulating these conductances, and identifying compensatory upregulation of conductances that potentially underlies the compensation.

While many of these compensation and parameter co-regulation studies have focused on $G_{\max}$ or similar measures, this has more recently been extended to other conductance parameters. For example, in dopaminergic neurons of the substantia nigra, conductance values of I_A and I_H , which have been shown to be co-regulated in other systems (MacLean et al. 2003), were found to covary and interact at the level of their *voltage dependence* of their biophysical properties to influence rebound properties of these neurons (Amendola et al. 2012). Thus novel forms of neuronal parameter co-regulation continue to emerge through increasingly sophisticated experimental approaches.

Computational Approaches to Neuronal Parameter Co-regulation

Neuronal parameter co-regulation has been extensively studied using computational approaches, and modeling approaches have played a fundamental and formative role in our understanding of this phenomenon (LeMasson et al. 1993; Liu et al.



Neuronal Parameter Co-regulation, Fig. 1 Compensation and neuronal parameter co-regulation in a crustacean cardiac motor neuron. In cardiac “large cell” motor neurons of the crab, **(a)** I_A and I_{HTK} (high-threshold K^+) magnitudes are strongly negatively correlated across a population of cells among multiple individuals. **(b)** Representative recordings show an increase in I_A after block of I_{HTK} with tetraethylammonium (TEA) exposure (*left*) and an increase in I_{HTK} with block of I_A after 4-aminopyridine (4AP) exposure (*right*). Black

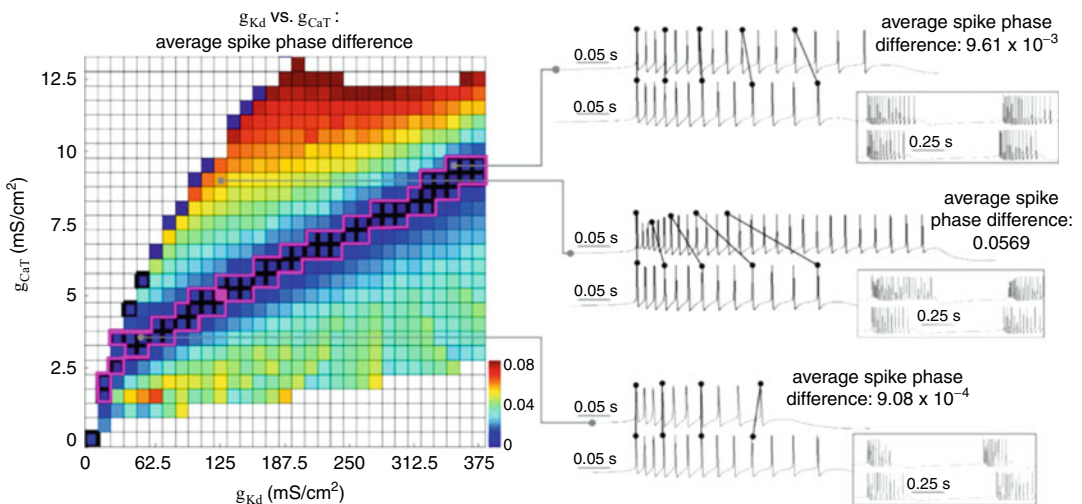
trace is the control, gray trace is the same cell after 60 min exposure to blocker. **(c)** Quantified effects of TEA (*left*) and 4AP (*right*) on the peak I_A and I_{HTK} , respectively. The same cell before (*black*) and after (*white*) is connected with a solid line. **(d)** Recordings of the effects of TEA exposure on network output over time show the ability of these cells to compensate (presumably through the increase in I_A shown in panel **c**) for block of the current to restore neuronal output. (Figure adapted from Ransdell et al. 2012)

1998; Prinz et al. 2003; Taylor et al. 2009). With the complexity of interactions among conductances within a neuron, and the experimental limitations in how many of these parameters effectively can be measured and manipulated, computational approaches have been at the forefront of these investigations. With more novel aspects of biophysical properties now being considered (Amendola et al. 2012), the complexity inherent in these systems continues to grow exponentially. Here we discuss a basic overview of two distinct ways in which computational approaches have been brought to bear on the concepts of parameter co-regulation.

Computational: Neuronal Parameter Co-regulation via Hand Tuning

A single model neuron can be chosen from within a given parameter space, with the final value for each of the parameters determined by the process of neuronal model hand tuning to match a specific neuronal output. The process of neuronal parameter co-regulation can then be applied to this model neuron to determine the impact on neuronal output when multiple parameters are altered in concert with one another. An example of such an approach is found in Soofi et al. (2012) as follows:

In this study, the authors are using a conductance-based model neuron to determine whether covarying pairs of parameters (membrane conductances) result in neuronal output that matches experimentally observed properties of spike phase maintenance in their biological neurons. Because their model neurons contain 8 distinct membrane conductances, there are 28 pairwise relationships between conductances that can be covaried. For illustrative purposes, we will look at one particular conductance pair, G_{CaT} vs. G_{Kd} . The investigators begin with a canonical value set for a model neuron with biologically relevant output. To study the effects of pairwise parameter variation on their output measure (spike phase), the G_{CaT} and G_{Kd} values were varied independently by multiplying the canonical value by a set of factors ranging from 0 to 3 in increments of 0.1. The investigators then quantified the impacts of this parameter co-regulation and determined that positive co-regulation of these two parameters leads to maintenance of neuronal output (as measured by spike phase), as seen in Fig. 2.



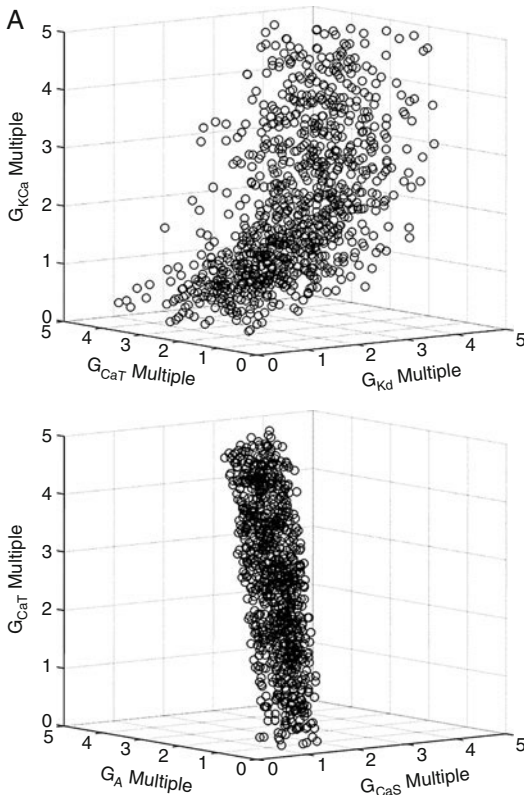
Neuronal Parameter Co-regulation, Fig. 2 Original voltage traces show that positively varying G_{CaT} and G_{Kd} supports spike phase maintenance. Three pairs of voltage traces are shown whose phase differences are highlighted on the bar plot. Traces are normalized by their respective periods; the first spike of each burst is aligned. The *lower* trace in each pair represents one burst from the canonical model neuron, marked on the plot with a *magenta square*. The *upper* trace represents one burst from a model for

Computational: Neuronal Parameter Co-regulation via Database Construction and Analysis

A population of model neurons that exists within a particular n -dimensional parameter space can also effectively be utilized to examine neuronal parameter co-regulation. For example, a neuronal parameter space exploration can be undertaken to first generate a population of model neurons. This population of model neurons can then either be selected for particular output features (Taylor et al. 2009; Ball et al. 2010) or subdivided into different output types (Prinz et al. 2003; Hudson and Prinz 2010) to determine whether relationships exist among subsets of parameters in the selected cells. An example of such an approach is found in Ball et al. (2010) as follows:

In this study, the authors are using a conductance-based model neuron database to determine whether covarying sets of parameters (membrane conductances) result in neuronal output that matches experimentally observed

which G_{Kd} and G_{CaT} varied from their canonical values. *Black lines* drawn between action potential peaks in the *upper* and *lower* traces show the divergence in phase between every third action potential of each burst. Traces in the *insets* have not been normalized by period to demonstrate the differences in the periods between the original and canonical bursts. (Data reproduced with permission from Soofi et al. 2012)



Neuronal Parameter Co-regulation, Fig. 3 Maximal conductance relationships in a population of randomly generated neuron models constrained by χ^2 values representing the model output. A, Distribution of model cells in two representative three-dimensional plots: G_{KCa} , G_{CaT} , and G_{Kd} (top) and G_{CaT} , G_{CaS} , and G_A (bottom). The axes represent conductance values as multiples of those in the nominal model. (Data reproduced with permission from Ball et al. (2010))

properties of driver potential generation in their biological neurons. Their model neurons contain 7 distinct membrane conductances, which vary over a continuous 0.1x–5x range from the canonical model parameter values. To determine whether any parameter co-regulation was responsible for the observed output, the investigators randomly simulated thousands of different 7-dimensional conductances sets and then selected only those neurons that had biologically relevant output. This method of “rejection sampling” (Robert and Casella 2004) results in a population of model neurons with appropriate output, but no predetermined conductance values. After selecting based on distinct output features,

the investigators determined that multiple parameter co-regulation patterns emerged among the ionic conductances in their data, including two 3-way relationships as seen in Fig. 3.

Cross-References

- [Neuronal Model Databases](#)
- [Neuronal Model Hand-Tuning](#)
- [Neuronal Parameter Space Exploration](#)

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Neuronal Parameter Non-uniqueness

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Synonyms

Degeneracy; Distributed robustness; Neutral space

Definition

Parameter non-uniqueness refers to the ability of biological systems to generate a similar (or even identical) functional output using vastly different solutions in the properties of their underlying components. As such, parameter non-uniqueness is tightly linked to the notion of degeneracy but also to the notion of neutral space, which refers to regions of a parameter space where variations in the parameters' values have no effect (therefore, the term neutral) on the system's output (function/phenotype) (Wagner 2005).

Methodologically, however, parameter non-uniqueness means that the dynamics of a biological system such as the neuron might not be captured by modeling a unique set of parameters but rather by modeling a population of models covering the biological neutral space of solutions (non-unique sets of parameters) (Marder and Taylor 2011).

Detailed Description

Background: Non-uniqueness of Parameters in Non-neuronal Systems

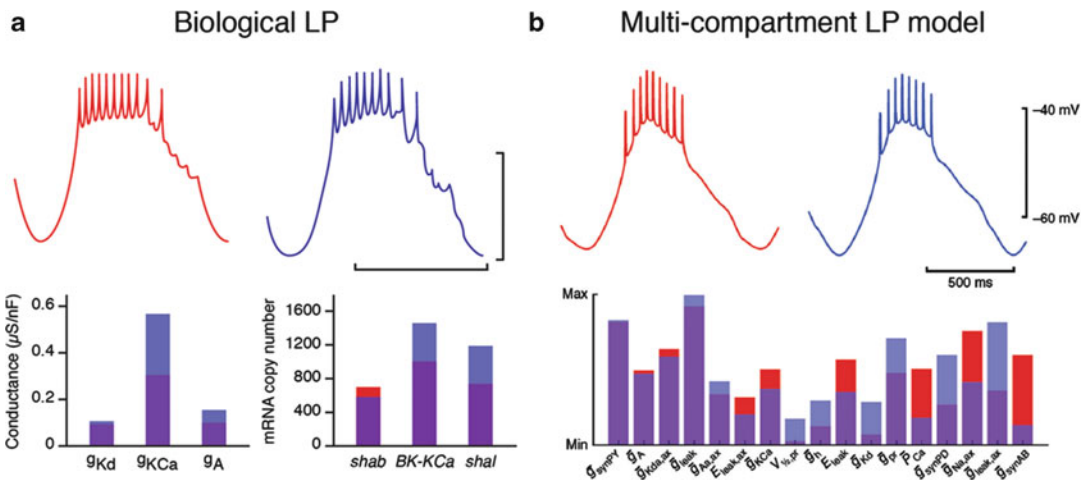
The fact that biological systems are able to generate identical phenotypes using variable solutions has been experimentally observed in various biological systems at multiple integration levels. The most famous example is probably the degeneracy of the genetic code, whereby the same amino acid is encoded by up to six different nucleotide triplets (Goldberg and Wittes 1966). But the first observation of parameter non-uniqueness has probably to be attributed to the English embryologist Conrad Hal Waddington who suggested that the development of biological organisms is surprisingly stable in the face of the numerous, and often deleterious, genetic variations observed across individuals (Waddington 1957). Recent studies on the development of the nematode *Caenorhabditis elegans* have directly demonstrated that various genetic and cellular solutions are available to generate a stable vulval organ (Félix and Wagner 2006), such that genetic mutations or loss of one cell type does not prevent

correct organ development. These examples illustrate how parameter non-uniqueness relates to the notion of distributed robustness, where the robustness of a biological system is distributed among many distinct components, such that failure (or strong variation) in one of the components does not compromise function or phenotype (Wagner 2005).

Multiple Biophysical Solutions for a Same Pattern of Neuronal Activity

Similar examples have been observed at the neuronal level, in particular concerning the multiple biophysical solutions (combinations of ion channels) used by neurons to generate a same pattern of firing (Marder and Goaillard 2006). While pharmacology experiments using toxins targeting ion channels have long demonstrated that partial blockade of most voltage-dependent ion channels

strongly alters neuronal output, a number of experimental studies have demonstrated that the level of expression of a specific ion channel can vary in a twofold to fivefold range across neurons of the same type, even when these neurons display virtually identical patterns of activity (Marder and Goaillard 2006; Fig. 1a). Therefore, the combinations of levels of expression of the voltage-dependent ion channels used by one given neuronal type to generate its archetypal pattern of activity are non-unique. The non-uniqueness of neuronal parameters is probably best demonstrated by the extreme case of transgenic animals where genes coding for specific ion channels have been deleted: several studies have indeed demonstrated that neurons of a given type may continue to produce their typical pattern of activity even in the absence of one of their essential ion channels (such as a fast sodium channel, or a transient potassium channel). One may believe that this compensation is due to the presence of



Neuronal Parameter Non-uniqueness, Fig. 1 Non-uniqueness of biophysical parameters in biological and theoretical crustacean neurons. (a) top, voltage traces from two lateral pyloric (LP) neurons recorded from two different animals and displaying highly similar firing patterns. Bottom, bar plots showing the conductance levels (left) and the expression levels (right) of three potassium channels (*shab*, *g_{Kd}*; *BK-KCa*, *g_{KCa}*; *shal*, *g_A*) involved in the electrophysiological activity of the LP neuron. Although the two LP neurons display virtually identical patterns of activity, their underlying conductance levels or the expression levels of the corresponding ion channels are quite different. (b) top, voltage traces of two multi-compartment Hodgkin-Huxley LP models generated by

randomized screening of the parameter space and displaying highly similar firing patterns. Bottom, bar plot showing the conductance levels and gating properties of the conductances most significantly involved in defining the firing pattern of the LP neuron. As with the biological LP neurons, the two models display highly variable underlying biophysical parameters (bottom) that contrast with their similarity in activity patterns (top). Color coding: red on top corresponds to a higher value for the red LP neuron, blue on top corresponds to a higher value for the blue LP neuron. Scale bars in (a) and (b) correspond to the same time and voltage ranges (a: Modified from Marder and Goaillard 2006. b: Modified from Marder and Taylor 2011)

fully functionally redundant ion channels, whose function is revealed by the absence of the deleted ion channel; but the loss of a transient potassium channel in pyramidal neurons is in fact compensated by a compensatory increase in expression of a delayed rectifier potassium channel already expressed by the neuron in normal conditions. There again, the presence of non-unique combinations of parameters (including solutions where one parameter takes the 0 value) provides the neurons with robustness to perturbations, in particular genetic losses of function. Moreover, recent studies have demonstrated that the non-uniqueness of ion channel parameters not only applies to levels of expression but also to the gating properties of ion channels (voltage-dependence, kinetics): similar patterns of activity are generated by neurons presenting highly variable voltage dependences (up to 20 mV variation across neurons of a same type) for a same ion channel.

In the face of these experimental observations, several theoretical studies have been performed using dense screening of parameter spaces (database approaches) instead of hand-tuning of parameters. Maximal conductance values for each ion current were varied over a large range to simulate the observed variations in expression levels, and variability in the gating properties was also included (for review, see Marder and Taylor 2011). Consistent with the experimental results discussed before, these studies have demonstrated that myriad solutions are available to generate a given type of activity, even when complex models of neurons or of small neuronal networks (multi-compartment Hodgkin-Huxley modeling with up to 16 different biophysical parameters) are considered (Fig. 1b). These studies suggested that non-unique solutions are available because of the dense functional overlap between ion channels and the pleiotropy of ion channels: each firing feature (action potential threshold, resting membrane potential, firing frequency, etc.) is defined by the activity of several functionally overlapping ion channels while each ion channel usually participates in defining several distinct firing features (pleiotropy). The necessity to have functionally overlapping pleiotropic components to generate non-unique

solutions is not specific to the non-uniqueness of neuronal parameters, but rather seems to be a general feature of robust biological systems. Conrad Hal Waddington was the first one to identify these two properties as underlying the robustness of development of biological organisms to genetic variations (Waddington 1957).

Random or Nonrandom Solutions?

The essential question that arises from these experimental and theoretical observations is whether the non-unique solutions are mainly random, meaning that parameters can be varied independently (and the neutral space has pretty much a Mexican hat shape corresponding to random Gaussian variation of each parameter), or whether the neutral space of non-unique solutions has a specific shape suggesting that equivalent solutions correspond to correlated variations in parameters. Here appear the first discrepancies between experimental studies and theoretical studies: while theoretical studies suggest that no correlation in underlying parameters is needed to model a same firing pattern, experimental studies have demonstrated the widespread occurrence of correlations in the levels of expression of ion channels (discussed in the ► [“Neuronal Parameter Co-regulation”](#) entry) (Marder and Goaillard 2006). While it is tempting to speculate that correlations in functionally overlapping ion channels may “help” find equivalent solutions for a same pattern of activity, the discrepancies between theory and biology mainly suggest that correlated variations in neuronal parameters are not needed per se to perform a same computational operation, but that they may rather represent responses to non-computational biological constraints (such as limiting the energy expenditure of the neuron) that are not taken into account in theoretical models of neuronal activity.

Cross-References

- [Failure of Averaging](#)
- [Neuronal Parameter Co-regulation](#)

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Neuronal Parameter Sensitivity

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Definition

Sensitivity of a quantity to a parameter at a fixed point of the parameter space measures the relative change of the quantity in relation to a relative change of the parameter. There are two interrelated formal definitions of sensitivity.

Consider a real-valued function $C = C(p)$ of a real variable p . Let $C(p)$ be defined for the two values of p , $p = p_0$ and $p = p_0 + \Delta p$, where Δp is some number. Then sensitivity S of $C = C(p)$ to the change of p from p_0 to $p_0 + \Delta p$ is defined as

$$S = \frac{C(p_0 + \Delta p) - C(p_0)}{C(p_0)} \div \frac{\Delta p}{p_0}. \quad (1)$$

For example, $S = 2$ means that the relative increase of $C(p)$ from $C(p_0)$ to $C(p_0 + \Delta p)$ is two times the relative increase of p from p_0 to $p_0 + \Delta p$. Notice that in Eq. 1, the value of S depends on p_0 and Δp and there are no other

requirements to $C(p)$ except for it being defined for $p = p_0$ and $p = p_0 + \Delta p$.

If the function $C = C(p)$ is differentiable at p_0 , then S is defined as

$$S = C'(p_0) \frac{p_0}{C(p_0)}, \quad (2)$$

where $C'(p_0)$ is the derivative of C at $p = p_0$. In this case, S does not depend on Δp .

Formula (2) requires an explicit formula for $C'(p_0)$. In neuronal modeling, such formulas are rarely known. Using Eq. 1 instead of Eq. 2 is equivalent to using the approximation

$$C'(p_0) \approx \frac{C(p_0 + \Delta p) - C(p_0)}{\Delta p} \quad (3)$$

instead of the exact value of $C'(p_0)$ in Eq. 2.

Detailed Description

Informally, the sensitivity of an entity to a parameter quantifies how much the entity changes given a small change of the parameter. In neuronal modeling, such entities can be the period of tonic spiking, the maximal value of the membrane potential during a spike, the total value of calcium entering the neuron during a spike, etc. Accordingly, a parameter could be any factor that specifies the neuronal (synaptic or network) model, such as, for example, the maximal conductance of an ionic current, the size of a dendrite, the duration of an applied current, and so on.

In what follows, we clarify some important subtleties of calculating and using sensitivities, and then as an example, consider an application of sensitivity analysis to an important physiological problem.

Theory

An obvious requirement for using Eqs. 1 and 2 is $C(p_0) \neq 0$ since relative changes to zero values are not defined. Hereafter, we assume that this requirement holds.

Another basic requirement for Eq. 1 is that $C(p_0 + \Delta p)$ exists. This may not be the case if at some value of p between p_0 and $p_0 + \Delta p$ the dynamical system under consideration experiences a bifurcation. For example, if C is the period of neuronal bursting, then at $p_0 + \Delta p$, the system may have no periodic solution at all (Izhikevich 2010). In some cases, sensitivities can be evaluated near the points of bifurcation using special methods of bifurcation theory. We do not consider such methods here. In this entry, we assume that the parameters of the model are not close to bifurcation values. In what follows, we also assume that there is no explicit formula for $C'(p_0)$. If such formula is known, then calculation of S according to Eq. 2 is trivial.

A sensitivity calculated using Eq. 1 for just one new value of the parameter is of limited value. For example, one may explore how an entity changes when one of its parameters changes by 1% and determine a parameter to which the entity is most (or least) sensitive. However, such a result will be specific for 1% changes of the parameters. For 0.5% parameter changes, the entity may be most (or least) sensitive to other parameters.

Because of these considerations, sensitivities are most worthwhile when they essentially do not depend on the magnitudes of relative parameter changes when the latter are sufficiently small. Exact independence is possible only in the case when $C = C(p)$ depends on p linearly. Then the approximation (Eq. 3) gives the exact value of $C'(p_0)$ for any Δp . In all other cases, the calculated value of sensitivity S is an approximation to the limit value of S for $\Delta p \rightarrow 0$ provided the limit value exists.

When C has the first and the second derivatives at $p = p_0$, the existence of the limit follows from the following expression for the error of the approximation (Eq. 3):

$$C'(p_0) - \frac{C(p_0 + \Delta p) - C(p_0)}{\Delta p} = \frac{\Delta p}{2} C''(\xi). \quad (4)$$

Here, ξ is some value of p from the interval $(p_0, p_0 + \Delta p)$. The theory does not specify the value of ξ ; it claims only that such a value exists

(Thomas et al. 2009). The expression in the right-hand side of Eq. 4 has the limit of zero when $\Delta p \rightarrow 0$. Because of that, the limit

$$\lim_{\Delta p \rightarrow 0} \frac{C(p_0 + \Delta p) - C(p_0)}{\Delta p}$$

exists and is equal to $C'(p_0)$.

A limit may also exist when $C(p)$ is defined only at discrete values of p . In this case, it is a limit of a sequence.

In some cases, continuity and differentiability of C are known or can be proved. A notable example is the period of a periodic solution to a neuronal model of the form

$$\frac{dx}{dt} = F(x; p). \quad (5)$$

Here, x is the vector of dependent variables (membrane potentials in compartments, activation variables, etc.). Vector function $F = F(x; p)$ depends on x and parameter(s) p . Suppose F is differentiable with respect to the components of x and p and suppose when $p = p_0$, the system (5) has a periodic solution with the period $T = T(p_0)$. Then for p near p_0 , the system also has a periodic solution with a period $T(p)$, and $T(p)$ is differentiable at p_0 (see, e.g., Hartman 1964). This result provides a basis for exploring sensitivity of $T(p)$ to various parameters (see, e.g., Olypher and Calabrese 2007).

In general, differentiability of F with respect to the components of x and p implies differentiability of the solution $x = x(t, p)$ with respect to p . In some cases, this fundamental property can be used to prove differentiability of $C(p)$.

Generalizations

Most often, $C = C(p)$ depends on a number of parameters so that p is a vector: $p = (p^1, p^2, \dots, p^n)$. If there exists a partial derivative $\frac{\partial C(p_0)}{\partial p^i}$ of C with respect to p^i at $p_0 = (p_0^1, p_0^2, \dots, p_0^n)$, then the sensitivity of C to p^i at $p = p_0$ is defined (cf. Eq. 2) as

$$S = \frac{\partial C(p_0)}{\partial p^i} \frac{p_0^i}{C(p_0)}. \quad (6)$$

Formula (6) can be generalized to define sensitivities with respect to simultaneous changes in several parameters.

For example, let S_i be the sensitivity of C to p^i and S_j be the sensitivity of C to p^j , $i < j$, at $p = p_0$ defined according to Eq. 6. Then, a weighted sum of S_i and S_j approximates the relative change of C when p changes from p_0 to $\hat{p} = (p_0^1, \dots, p_0^i + \Delta p^i, p_0^{i+1}, \dots, p_0^{j-1}, p_0^j + \Delta p^j, \dots, p_0^n)$:

$$\frac{C(\hat{p}) - C(p_0)}{C(p_0)} \approx S_i \cdot \frac{\Delta p^i}{p_0^i} + S_j \cdot \frac{\Delta p^j}{p_0^j}$$

Since

$$C(\hat{p}) - C(p_0) \approx \frac{\partial C(p_0)}{\partial p^i} \Delta p^i + \frac{\partial C(p_0)}{\partial p^j} \Delta p^j. \quad (7)$$

Notice that if Δp^i and Δp^j are chosen such that

$$\frac{\partial C(p_0)}{\partial p^i} \Delta p^i + \frac{\partial C(p_0)}{\partial p^j} \Delta p^j = 0 \quad (8)$$

then according to Eq. 7, $C(p)$ does not change in a linear approximation.

Calculating Sensitivities

Most commonly, validity of sensitivity values is established empirically. In the simplest case, one calculates S for a sequence of decreasing values of Δp and notices convergence of the calculated values of S to some value. Then the final result is chosen depending on the accepted level of accuracy. For example, it can have two decimal places.

If convergence is not apparent, then one possibility is that C depends highly nonlinearly on p near $p = p_0$. Such a situation is not rare since dynamical systems often model neuronal behavior best of all when the system parameters are close to their bifurcational values (Izhikevich 2010). If this is the case, then the sensitivity analysis is not applicable.

Sometimes S does converge to some value with the decrease of Δp , but the convergence is slow. That can be caused by the limited accuracy of the calculated values of $C(p_0 + \Delta p)$. For example, the system may need a considerable simulation time to get to an attractor state, it may be an accumulation of round-off errors, etc. Then it may be possible to improve the convergence of $S = S(\Delta p)$ using various techniques that can be found in textbooks on numerical methods in sections on numerical differentiation (see, e.g., Atkinson 1989).

For example, one can use more accurate approximation formulas for the first derivative such as

$$C'(p_0) \approx \frac{C(p_0 + \Delta p) - C(p_0 - \Delta p)}{2\Delta p}.$$

A related technique is using Richardson extrapolation where the approximations to $C'(p_0)$ obtained for different values of Δp are combined in a special way to increase the accuracy of the result (Atkinson 1989).

Application

The popularity of the sensitivity analysis in neuroscience rests on three factors. First, the concept of sensitivity is appealing to experimentalists who study how neuronal responses change provided certain changes of experimental parameters. Second, the formula (1) for calculating sensitivity is very simple. Finally, the values of sensitivity obtained often make sense and help to understand neuronal functioning.

Sensitivities make changes of various entities comparable. For example, if one entity changes by 10% and another by 5% when a parameter changes by 1%, then we conclude that the first entity is two times more sensitive to the changes of the parameter than the other one even if the units of those entities are different, e.g., millivolts and milliseconds. In models, such comparability is often achieved by making all dependent and independent variables and all parameters in the model dimensionless and normalized. For example, a normalization of the membrane potential $V(t)$ can be

achieved by substituting $V(t)$ with another variable, $V(t)/V_{max}$, where V_{max} is a maximal value of $V(t)$ during a spike. Partial derivatives calculated for dimensionless and normalized variables are conceptually similar to sensitivities.

Sensitivity analysis has proven to be a valuable tool in various studies of neuronal modeling. One particular application relates to the exploration of activity-dependent homeostatic regulation in neurons. Experiments show that neurons can maintain their functionality by readjusting biophysical properties, such as densities of ionic channels, in response to external changes (see, e.g., Khorkova and Golowasch 2007). An important general question is how changes in some model parameters can be compensated for by changes in other parameters, so that the system's output is preserved.

In neuronal models, possible compensatory changes of parameters can be revealed by computing sensitivities or more precisely the corresponding partial derivatives. In the example below, this was done for a model of a central pattern generator that paces the heartbeat in the leech (Lamb and Calabrese 2012). The model consists of two neurons that inhibit each other; g_{SynS} is the maximal conductance of the synaptic current. Each neuron is an intrinsic rhythmic burster for the parameter values considered. One of the ionic currents that makes rhythmic bursting possible is a hyperpolarization-activated inward current with the maximal conductance g_h . The model shows a good match with experimental output when $g_{SynS}^* = 150nS$ and $g_h^* = 4nS$. For this set of parameters, p^* , the model demonstrates stable alternating bursting of the neurons with the period $T(p^*) = 7.91$ s. Suppose g_{SynS} increases or decreases. What change of g_h can compensate for the change g_{SynS} to preserve the period $T = 7.91$ s?

Let in Eq. 8 $C = T$, $p^i = g_{SynS}$, and $p^j = g_h$. Then according to Eq. 8, the equation for the compensatory change of g_h in linear approximation has the form

$$g_h = \chi \cdot (g_{SynS} - g_{SynS}^*) + g_h^* \quad (9)$$

where $\chi = -[\partial T(p^*)/\partial g_h]^{-1} \cdot [\partial T(p^*)/\partial g_{SynS}]$. Calculations have shown that $\chi = 0.012$.

Equation 9 describes a line in the plane of g_{SynS} and g_h that has a slope of 0.012 and passes through the point (150, 4). Linearity of the approximation means that when g_{SynS} and g_h change along the line (Eq. 9), the deviation of the period from the value of 7.91 s is close to a linear combination of the quadratic terms $(g_{SynS} - 150)^2$, $(g_h - 4)^2$, and $(g_{SynS} - 150) \cdot (g_h - 4)$. The closer the point (g_{SynS}, g_h) is to the point (150, 4), the closer is the corresponding period to 7, 91.

Exact compensation is achieved when g_{SynS} and g_h change along a curve to which the line (Eq. 9) is the tangent line at point (150, 4). The existence of such a curve follows from the implicit function theorem (Conway 1990; Thomas et al. 2009). One of the key premises of the theorem is that $\partial T(p^*)/\partial g_h \neq 0$. In the case considered, the estimated value of $\partial T(p^*)/\partial g_h$ was -0.63 s/nS.

The above analysis can be generalized to the case of more than two parameters. Suppose there are m independent characteristics of a neuronal model, defined at a point p^* of an n -dimensional parameter space. The implicit function theorem states that under certain conditions, there is a manifold passing through p^* such that m characteristics do not change their values when the parameters vary along the manifold. In the above example with g_{SynS} and g_h , the curve was a manifold of dimension one. In the general case, the dimension of the manifold is equal to $n - m$. The theory shows that even if one parameter in the model changes, then to compensate for its change and preserve the values of all m characteristics, one has to change at least m other parameters.

Partial derivatives of the characteristics with respect to the parameters at p^* are the coefficients of the hyperplane tangent to the manifold at the point; in the example above, the tangent hyperplane was a tangent line. Changes of the parameters along the hyperplane do not change the values of the characteristics in linear approximation.

If the dimension of the parameter space is equal to n and only one characteristic C is considered, then the manifold passing through p^* has dimension $n-1$. The gradient of C at p^* , $\nabla C(p^*) = (\partial C(p^*)/\partial p^1, \partial C(p^*)/\partial p^2, \dots, \partial C(p^*)/\partial p^n)$, is orthogonal to the manifold at p^* and shows the direction and magnitude of the greatest rate of increase of C at p^* .

Sensitivity of neuronal models to parameters can be studied by other methods. In particular, one may create a database of characteristics of neuronal models obtained for various values of the model parameters and then use data mining methods to identify how parameter changes affect the characteristics (Hudson and Prinz 2010). The accuracy of such analysis depends considerably on the grid of the parameter points for which the model is simulated. An advantage of this approach is that it provides information for large domains of the parameter space.

In summary, the sensitivity analysis is a relatively simple computational tool that helps understand smooth changes in neuronal and network properties resulting from small changes of the model parameters near a point of the parameter space. This tool is effective when the neural characteristics of interest exist for all the parameter values considered and do not change abruptly. In all the circumstances, numerical accuracy is a critical condition for an application of the sensitivity analysis.

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Neuronal Parameter Space Exploration

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Synonyms

Neuronal parameter space search; Sweeping the parameter space of neuron models

Definition

A parameter is a measurable characteristic that is used to define a system. The range of possible values that a parameter can assume is referred to as *parameter space*. The number of dimensions of the parameter space is equal to the number of parameters that is allowed to vary. *Exploration* of the parameter space is the act of choosing various sets of parameter values within the space and determining the resultant output of the system. *Neuronal parameter space exploration* is the investigation of the parameter space for a model of a single neuron or neuronal network.

Detailed Description

Neuron Model Hand-Tuning and Optimization Techniques

A common interest among neuroscientists is to determine the underlying parameters of a particular biological neuron from experimental data, such as a recorded voltage trace. A neuroscientist might approach this problem by using a *neuron model*, for which the output and underlying parameter values are known (Dayan and Abbott 2001). One way of using a neuron model to estimate the parameters of a biological neuron is to (1) vary the parameters of the neuron model, (2) determine the model output, and (3) make further modifications to the parameter

values based upon the difference between the model output and the output of the biological neuron. The above steps are repeated until the model output matches the biological output within an acceptable margin of error. The terminal set of parameter values for the neuron model is then a candidate for the unknown parameters of the biological neuron (Marder and Selverston 1992). This method of parameter space exploration, if performed in such a way that the user monitors the output of the search process and continually makes adjustments to the parameters, is known as hand-tuning (Mainen and Sejnowski 1998; Prinz et al. 2003; Haufler et al. 2007; see entry on ► [“Neuronal Model Hand-Tuning”](#)). Such a process can also be automated, either by applying heuristic methods for neuronal model generation or by the use of brute-force construction and exploration, as described below.

Due to the complexity of modern neuron models, the act of hand-tuning model parameters can be slow and difficult. Automated optimization techniques are commonly used instead (Van Geit et al. 2008). There are two major components of these optimization techniques that are generally independent of one another. The first component is the error function which indicates how closely the model output, given the chosen parameters, matches the target output. The fitness function (see entry on ► [“Neuronal Model Output Fitness Function”](#)) serves a similar purpose to the error function. In general, when matching model output to some target output, one desires to minimize the error function or maximize the fitness function.

Error functions may be constructed in many ways. For example, one might use a feature-based approach by comparing single features of interest in the biological data (e.g., spike height or firing rate) to those same features in the model data. Another method is to perform a point-to-point comparison between the model and biological data by calculating the root-mean-square of the difference between their voltage traces (Van Geit et al. 2008). One can also calculate several feature-based error functions and determine a set of trade-off solutions that takes all of them into account (Druckmann et al. 2007; Handl et al.

2007; Smolinski and Prinz 2009; see entry on ► [“Multi-objective Evolutionary Algorithms”](#)). Several other types of error functions exist; the best choice is largely dependent upon the features of the data that are germane to the research question at hand.

The second component of automated optimization techniques is the search algorithm, which is the method used to minimize the error function. There are many types of search algorithms. Examples include evolutionary algorithms (see entries ► [“Evolutionary Algorithms”](#) and ► [“Multi-objective Evolutionary Algorithms”](#)), genetic algorithms, and gradient descent algorithms. In theory, for an optimization problem, it is often desired that a search algorithm will terminate at the global minimum (i.e., where the value of the error function is smallest). In the case of neuron models, finding a single global minimum is often not possible. It is more feasible to instead seek a set of solutions that resembles the target activity to a degree that is deemed acceptable by the user (Van Geit et al. 2008).

Neuron Model Database Construction and Analysis

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Another interest of neuroscientists is to gain a holistic understanding of how *all* model parameters affect model output. One might be interested, for example, in knowing how neuronal output is affected when two or more parameters are varied at once (see entry on ► [“Neuronal Parameter Co-regulation”](#)). In this case, one first simulates the neuron model output for every possible combination of parameter values within chosen ranges and then analyzes the information afterward. This alternative method of parameter space exploration is referred to as the construction and analysis of neuronal model databases (Prinz et al. 2003, 2004; Marder and Goaillard 2006; see entry on ► [“Neuronal Model Databases”](#)).

A neuroscientist may be interested in gaining an overall understanding of how the underlying parameters of neuron models influence neuronal output, rather than finding a parameter set that produces model output matching a specific set of

experimental data. In this case, constructing a neuron model database (or analyzing a previously constructed one) may be a more appropriate method of neuronal parameter space exploration than an automated optimization technique. To construct a neuron model database, one can choose an appropriate range for each parameter in the neuron model and then cover the entire parameter space with a randomly or evenly distributed set of simulation points (see entry on ► [“Neuronal Model Databases”](#)). One can then define a solution space of interest by (1) choosing a range of values for any given feature(s) of neuronal output (e.g., a burst duration of 0.5–0.6 s) and then (2) stipulating that any neuron models exhibiting output feature values that fall within the designated range are part of the solution space. The database, which contains both the output measure values and parameter values for each model, provides information on where the solution space is located in parameter space. This approach, known as ensemble modeling, takes into account the variability of both input parameters and output features in neuron models (Prinz 2010). By examining the location and shape of the solution space, the researcher can determine the sensitivity of the neuronal output to each parameter (see entry on ► [“Neuronal Parameter Sensitivity”](#)), as well as the effect of varying two or more parameters at once on the neuronal output (see entry on ► [“Neuronal Parameter Co-regulation”](#)). One can also gain insight into whether very different parameter sets can result in similar output and, conversely, whether very similar parameter sets can produce dissimilar outputs (see entry on ► [“Neuronal Parameter Non-uniqueness”](#)).

Choosing a Method of Neuronal Parameter Space Exploration

In the case of hand-tuning neuron models, one uses the output from the previous parameter set to inform which parameter set to examine next. An analogy can be drawn to making an expedition to an unexplored jungle and using clues from the environment to locate a specific object, such

as a downed aircraft. In the case of database construction, the model output does not inform the direction of exploration (i.e., which parameter values are chosen for modification); rather, the entire space is first explored and then analyzed *post hoc*. Within our jungle analogy, this type of analysis is akin to an expedition that maps the entire jungle. Greater resources are required to complete the latter task, but a more complete view of the system’s output emerges from the analysis.

Neuronal parameter space exploration can take on many forms. Which method is “best” is strongly dependent upon the researcher’s scientific question.

Cross-References

- [Evolutionary Algorithms](#)
- [Multi-objective Evolutionary Algorithms](#)
- [Neuronal Model Databases](#)
- [Neuronal Model Hand-Tuning](#)
- [Neuronal Model Optimization: Overview](#)
- [Neuronal Model Output Fitness Function](#)
- [Neuronal Parameter Co-regulation](#)
- [Neuronal Parameter Non-uniqueness](#)
- [Neuronal Parameter Sensitivity](#)

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Neuronal Parameter Space Search

► Neuronal Parameter Space Exploration

Neuronal Parameter Space Visualization

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Definition

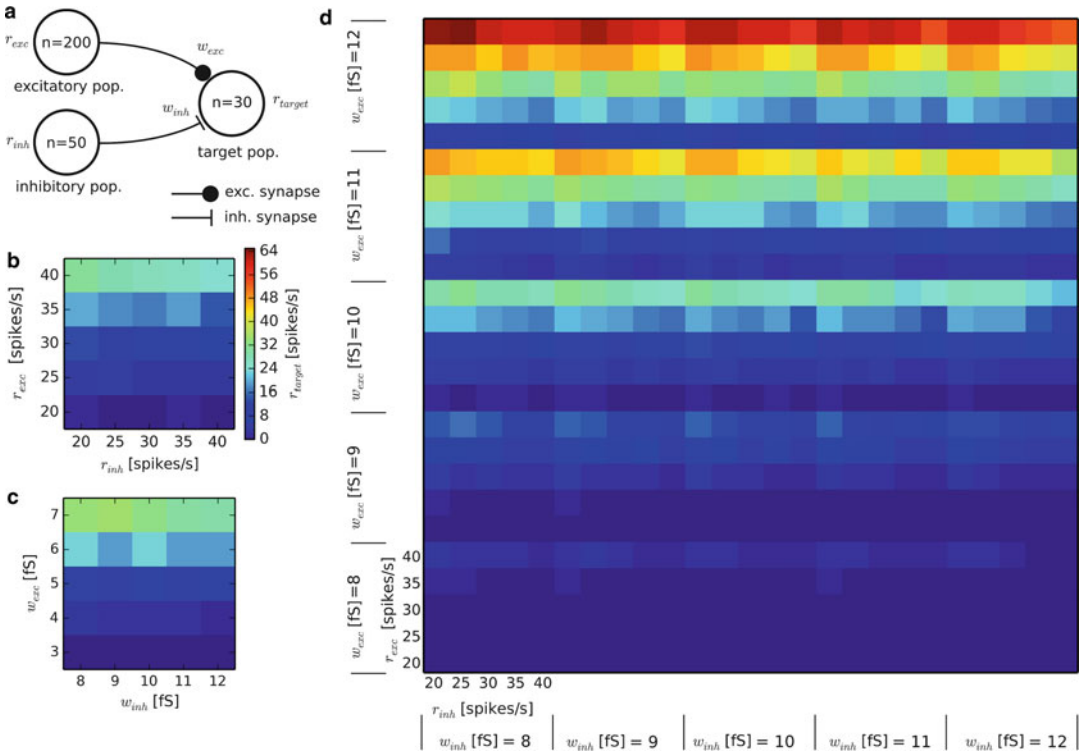
The visual display of the behavior of a neuron, a neuron model, or a network of neurons or neuron models, for a number of parameters which govern model behavior or describe a series of observations.

Detailed Description

Computational neuron and network models have a number of free parameters that influence the models' behavior. For example, a leaky integrate-and-fire model may allow for adjusting two parameters, the leak conductance and the resting potential. More parameters are needed to characterize more elaborate point neuron models like the Izhikevich model (4 parameters; Izhikevich 2007) or the exponential adaptive integrate-and-fire model (6 parameters, Gerstner and Brette 2005). Biophysical models that contain cable equations for passive membranes and Hodgkin–Huxley-type dynamics for active channels easily reach parameter counts of a dozen or more. Even higher parameter counts are achieved when coupling several neurons in a network, since synaptic coupling strengths have to be taken into account (Prinz et al. 2003).

A straightforward approach is to visualize parameters in a pair-wise fashion on the two-dimensional plane. In this approach, the output of the model is encoded into a single variable, the *fitness function*. As an example, Fig. 1a shows a simple network that consists of three neuronal populations and two Poisson spike sources which drive a population of integrate-and-fire neurons. It is uncomplicated to visualize the effect that the firing rates of the excitatory and the inhibitory populations have on the firing rate of the target population (Fig. 1b): The firing rate of the inhibitory population r_{inh} is plotted on the x-axis and the firing rate of the excitatory population r_{exc} is plotted on the y-axis. The firing rate of the target population is encoded in the color of the “pixel” at the associated coordinates. Therefore, this approach is also termed “pixelization.” The same strategy can be applied to visualize the effect of changing the synaptic weights of both populations on the target population, w_{inh} and w_{exc} (Fig. 1c). These plots represent a two-dimensional slice through the parameter space of the network model. The resulting visualization is easy to interpret.

For complex models, more than two parameters need to be accommodated in the visualization. This can be achieved by dimensional



Neuronal Parameter Space Visualization, Fig. 1 (a) A sample network to explore multidimensional parameter visualization. The excitatory and inhibitory populations are modeled as Poisson populations consisting of 200 and 50 independent Poisson processes, respectively. They project on the neurons in the target population with connection probability $p_{conn} = 0.1$. The target population consists of 30 integrate-and-fire neurons. Network code is available online (Schmuker 2013). (b) Average spike count of neurons in the target population for $w_{exc} = w_{inh} = 10$ fS and

varying input firing rates. (c) Average target neuron spike count for $r_{exc} = r_{inh} = 30$ spikes/s and varying input weights. (d) Visualization of the effect of all four parameters r_{exc} , r_{inh} , w_{exc} , and w_{inh} on target spike count by dimensional stacking. For example, in the lower left 5×5 tile, the weights are constant at $w_{\{inh,exc\}} = 8$ fS, while r_{inh} and r_{exc} vary. In the next 5×5 tile to the right, identical parameters are used except that w_{inh} has increased by one step. In the upward direction, w_{exc} is increased

stacking (LeBlanc et al. 1990; Taylor et al. 2006), which allows visualizing a much larger number of parameters on the two-dimensional plane. First, the network performance is evaluated for each parameter combination on a discrete grid. Each evaluation yields a one-dimensional “fitness” value which can be encoded into a color code. Dimensional stacking projects the multidimensional parameter grid onto the two-dimensional plane in a hierarchical fashion without any loss of information (Fig. 1d). Considering the network in Fig. 1a, it is possible to visualize the effect of all four parameters r_{inh} , r_{exc} , w_{inh} , and w_{exc} in a single plot using this approach.

Dimensional stacking is well suited to visualize the parameter space of complex models with many

parameters (see Taylor et al. 2006 for examples). However, it requires that parameter combinations are sampled on a regular, discrete grid. The resolution of the grid is limited by practical constraints of computing power: For example, if p parameters are each to be sampled at s sample points, the number of simulations needed is s^p . Hence, achieving a good resolution in parameter space becomes very difficult with increasing parameter numbers. Also, the arrangement of parameters in the visualization hierarchy has great influence on the interpretability of the display (i.e., which parameter varies most quickly on each axis, which one second most quickly, etc.). Certain heuristics can be used to come up with a useful arrangement (see Taylor et al. 2006 for an overview).

In cases where regular sampling is not possible or not practical, other approaches can be used to visualize neuronal parameter space. For example, observed model states can be plotted on a two-dimensional plane. Consider the shape of an action potential, which can be characterized by its height in mV and width at half-maximum. For an ensemble of action potentials produced by a family of neuron models, the distribution of spikes can be plotted as points in this two-dimensional parameter space (see Fig. 2f in Prinz et al. 2003). Dimensionality reduction techniques can be applied if more parameters need to be visualized, like principal component analysis (PCA) or multidimensional scaling (MDS). For more complicated parameter landscapes, nonlinear approaches to low-dimensional embedding have been put forward, like ISOMAP (Tenenbaum et al. 2000) and locally linear embedding (LLE, Roweis and Saul 2000). These methods are able to accurately represent manifolds embedded in high-dimensional space. Such manifolds may occur, for example, if some of the parameters are interdependent or if the model design forbids certain parameter combinations.

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Neuronal Parameter-Measure Model Databases

► [Neuronal Model Databases](#)

Neuronal Population Biopotentials

► [Local Field Potential and Deep Brain Stimulation \(DBS\)](#)

Neuronal Population Vector

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Synonyms

[Population vector](#)

Definition

The *neuronal population vector* is the outcome of a computation by which weighted neural activities of individual elements in a population yield an estimate of the population's functional operation.

Detailed Description

The neuronal population vector is the outcome of a computation. It requires a behavioral measure in multidimensional space, a neuronal population, and an orderly variation of neural activity of the constituent elements in the population with the behavioral measure. The computation is a *weighted vectorial sum* of neural activities that

yields an estimate of the behavioral measure. In the original application (Georgopoulos et al. 1983), the behavioral measure was the direction of arm movement in 2-D space, the neuronal population consisted of cells recorded extracellularly in the monkey motor cortex during movements of different directions, and the orderly variation of neural activity was the *directional tuning* of rate of firing of action potentials, manifested as highest activity with movements in a particular direction (the cell's *preferred direction*) and progressively less activity with movements farther and farther away from the preferred direction. The plot of cell activity against movement direction yields a directional *tuning curve*. An example of directional tuning and preferred direction is shown in Fig. 1.

More generally, neural activity can come from single cells, multiunit activity, signals derived from integrated synaptic events (e.g., electroencephalogram, magnetoencephalogram), or other signals indirectly related to neural events (e.g., functional magnetic resonance imaging).

In the following example, we have (a) the direction of movement, $\vec{M}$; (b) the neuronal population consisting of N cells; (c) the preferred direction of the i th cell, $\vec{C}_i$, a vector of unit length; (d) the cell activity (or its change from a given level) for movement $\vec{M}$, $d_{i\vec{M}}$; and (e) a weight $w_{i\vec{M}}$ defined as a scalar multiplier $F(d_{i\vec{M}})$. Then, the population vector $\vec{P}(\vec{M})$ is the direction of movement estimated from the neural activity during the movement $\vec{M}$:

$$\vec{P}(\vec{M}) = \sum_i^N w_{i\vec{M}} \vec{C}_i \quad (1)$$

where

$$w_{i\vec{M}} = F(d_{i\vec{M}}) \quad (2)$$

The steps in this computation are illustrated in Fig. 2.

Figure 3 shows neuronal population vectors for 8 arm movement directions calculated from contributions of 241 directionally tuned cells.

There are three basic attributes of the population vector: (a) its variable error or *precision*

(i.e., how much its direction varies across repeated calculations), (b) its constant error or *accuracy* (i.e., how much its direction differs from the direction of the movement to be predicted, namely, the angle between $\vec{P}(\vec{M})$ and $\vec{M}$), and (c) its *length* (related to the instantaneous velocity of the movement). Hence, when the population vector is integrated over time, it yields estimates of movement trajectories (i.e., position).

The two components in the calculation of the population vector include the *tuning function* and the *preferred direction*.

Tuning Function

Motor directional tuning is widespread in the brain (Mahan and Georgopoulos 2013). The tuning function $d_{i\vec{M}}$ is unimodal of potentially various forms. It is typically determined empirically by fitting experimental data. A common directional tuning function is the cosine function:

$$d_{i\vec{M}} = a + b \cos \theta_{\vec{C}_i \vec{M}} \quad (3)$$

where $\cos \theta_{\vec{C}_i \vec{M}}$ is the angle between the cell's preferred direction and the direction of the movement and a and b are regression coefficients. A similar tuning function is the power function

$$d'_{i\vec{M}} = ce^{k \cos \theta_{\vec{C}_i \vec{M}}} \quad (4)$$

This function allows for variation in the tuning width and thus is more versatile. Other tuning functions (e.g., Gaussian) are possible.

Given a neuronal population composed of directionally tuned cells, the question is what kind of scalar multiplier $F(d_{i\vec{M}})$ to use as a weight for the preferred direction. Three functions are commonly used:

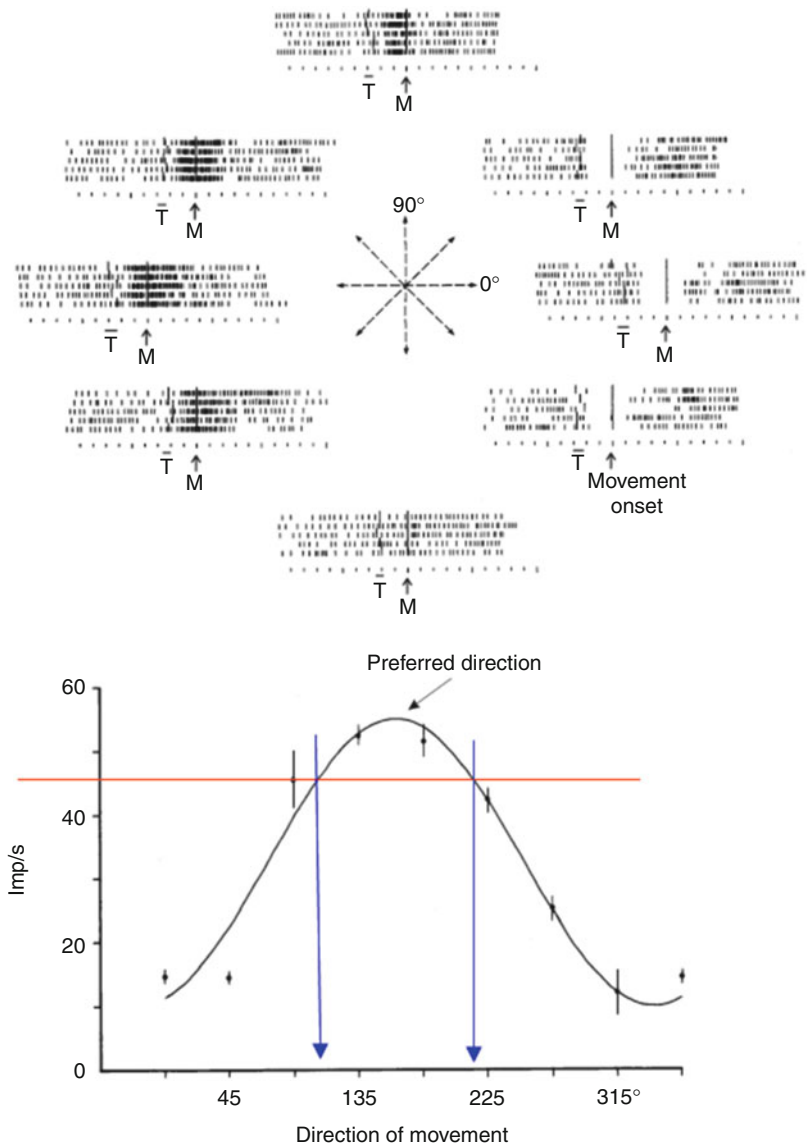
$$F(d_{i\vec{M}}) = d_{i\vec{M}} \quad (5)$$

$$F(d_{i\vec{M}}) = d_{i\vec{M}} - d_{i\vec{M}} \quad (6)$$

Neuronal Population Vector, Fig. 1

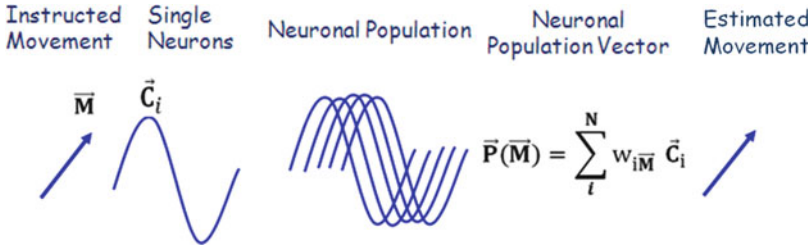
Directional tuning and preferred direction. The *top panel* illustrates the orderly variation of the neural discharge of a single cell in the motor cortex of a monkey during arm movements in eight directions (five trials per direction). The average discharge rate (*filled circles, ±SEM*) is plotted in the *bottom panel* with a fitted cosine curve, with the preferred direction at the peak of the fitted curve. The ambiguity of the curve with respect to other movement directions is indicated by the *red horizontal line* at a given discharge rate: the line crosses the curve at two symmetric points corresponding to two different movement directions (*blue arrows*). This ambiguity points to the need for a unique, unambiguous coding of movement direction by a neuronal population.

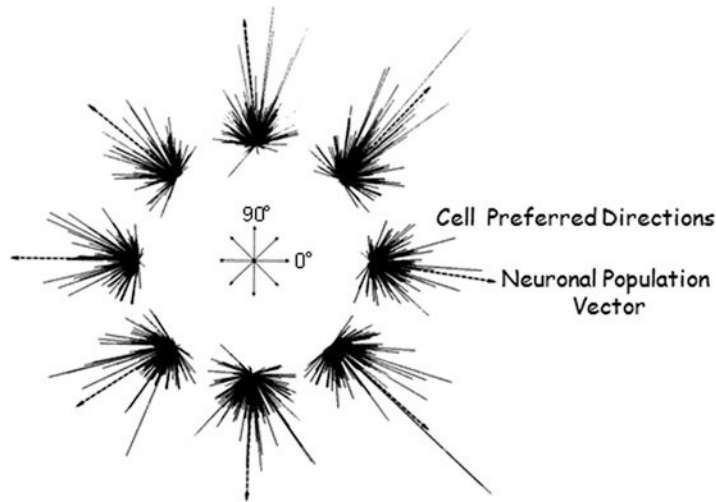
T target onset, *Imp/s* impulses per second. Tics on the abscissa indicate 100 ms intervals. (Adapted from Georgopoulos et al. 1982; reproduced with permission by the publisher)



Neuronal Population Vector, Fig. 2

Schematic illustration of the population vector coding procedure





Neuronal Population Vector, Fig. 3 Accurate coding of eight movement directions by the population vector computed from the discharge rates of 241 neurons recorded in the motor cortex. Each one of the eight clusters consists of (a) the weighted preferred directions of the 241 cells

(solid lines) and (b) the calculated neuronal population vector (dotted arrow). The arrows in the center diagram indicate the direction of the instructed movement. (Adapted from Georgopoulos et al. 1983 with permission by the publisher)

$$F(d_{i\vec{M}}) = \frac{d_{i\vec{M}} - d_{i\vec{M}}}{d_{i\vec{M}}} \quad (7)$$

where $\bar{d}_{i\vec{M}}$ is the mean discharge rate, over all movement directions. Formally, the same functions can be used by substituting the observed $d_{i\vec{M}}$ by its estimated value $t_{i\vec{M}}$ from the corresponding tuning equation.

Preferred Direction

The preferred direction is the direction at the peak of the tuning curve. When calculating the population vector, the empirically calculated preferred direction is most frequently used. Alternatively, the distribution of the preferred directions can be optimized (to approach a uniform distribution) by taking into account the trial-to-trial variability in discharge rate (Salinas and Abbott 1994). This yields an *optimal linear estimator* for the population vector.

Applications

The neuronal population vector has been used extensively in various applications, including the

coding of the direction of arm movement in the monkey (Georgopoulos et al. 1986, 1988), the coding of direction of movement in the cockroach (Levi and Camhi 2000) and the leech (Lewis and Kristan 1998), the coding of prey motion direction in the dragonfly (Gonzalez-Bellido et al. 2013), the coding of faces in the inferotemporal cortex (Young and Yamane 1992), and the coding of mental tracing (Crowe et al. 2005; Gourtzelidis et al. 2005). As a measure to read out time-varying directional information, the population vector has been successfully used to visualize neural processing in mental rotation (Georgopoulos et al. 1989, 1993) and memory scanning (Pellizzer et al. 1995). One powerful application has been in neuroprosthetics, where neural activity recorded from the motor cortex of a tetraplegic woman was used to calculate instantaneous population vectors by which the subject controlled a prosthetic arm for feeding and playing (Collinger et al. 2013; Courtine et al. 2013).

Cross-References

- [Efficient Population Coding](#)
- [Neural Coding](#)

- **Neural Population Model**
- **Population Encoding/Decoding**

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Neuronal Simulation Databases

► Neuronal Model Databases

Neuron-Glial Interaction Modeling

► Neuron-Glial Interactions

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Synonyms

[Axon-glial signaling](#); [Computational glioscience](#); [Microglia modeling](#); [Neuron-glial interaction modeling](#); [Synapse-astrocyte bidirectional signaling](#)

Definition

Dependence of neuronal function on glial cells and vice versa, which consists of the interplay of potentially multiple signals that can be both of neuronal and of glial origin. This interplay may be facilitated by the specific arrangement of neurons versus glia in different brain areas and occurs on time scales extending from milliseconds to months, as well as on spatial scales ranging from subcellular and synaptic levels to those of networks and whole-brain structures.

Detailed description

Most animals share the ability to move in response to external stimuli, which results from having developed complex neural structures that allow for sophisticated processing of sensory information. From a phylogenetic perspective, as the nervous system changed from a simple net-like structure, such as in jellyfish (*Cnidara*), to condensed ganglia and centralized brains – starting with flat interstitial worms (*Acoelomorpha*) up to mammals (*Chordata*) – a new cell type could be recognized in morphological studies: glial cells (Hartline 2011; Laming et al. 2000). The importance of this new cell type for a functional brain is arguably reflected by the increase in the relative number of glial cells during evolution: there are roughly equal numbers of glial cells and neurons in mammals (Herculano-Houzel 2014) whereas, by contrast, glia constitutes only 10% of invertebrate neural cells in *Drosophila* or *C. elegans* (Hartline 2011; Bullock and Horridge 1965).

It is currently unknown whether glial cells from different clades share similar functions: the molecular, morphological, and physiological identity of glial cells across and within clades indeed remains a topic of active investigation (Hartline 2011). In the mammalian brain, the most numerous glial cells appear to fall into two categories: (i) macroglia, which is prominently constituted of oligodendrocytes and astrocytes and (ii) microglia (Lawson et al. 1990; Pelvig et al. 2008). Significantly, despite their different developmental origin – macroglia originating

from the embryonic ectoderm while microglia deriving from the mesoderm – both cell types share a common feature: that is the physical proximity to neurons by an elaborated branched anatomy that interweaves with neural processes (Kettenmann and Ransom 2013). This feature can be regarded as the teleological evidence of the purpose of glia for being an integral part of both the structure and function of neural networks of the mammalian brain.

Oligodendrocytes, for example, are responsible for myelination of axons, which is essential for their trophic support to attain long lengths while allowing for evolved organisms, like mammals and vertebrates in general, to achieve great sizes (Nave 2010). At the same time, myelination provides axons with high membrane electrical resistance and low capacitance, which prevents current loss and enables rapid and efficient conduction of action potentials – a prerogative of complex nervous systems to operate quickly and efficiently (Zalc and Colman 2000). As nervous systems increase in complexity, and this complexity correlates with the increasing sophistication of neurological function, a trend in increased complexity is also observed for astrocytes (Verkhratsky and Nedergaard 2016). Humans and primates indeed possess astrocytes that are larger and more branched than rodent astrocytes, with human's astrocytes generally being the largest (Oberheim et al. 2009). In agreement with this trend, if we graft human astrocytes in mice, we get animals that show enhanced learning and memory capabilities (Han et al. 2013). Finally, microglia, too, can be framed within the evolutionary perspective, in connection with the appearance of compact neural masses and the increased demand thereby of specialized phagocytic and immune functions, including mechanisms of neural protection (Pósfai et al. 2019). Remarkably, microglia invades the neural tube during embryogenesis before epithelial cells, neurons, and macroglia, being in the ideal position to regulate angiogenesis as well as neuro- and gliogenesis. It is now emerging that such regulation could extend beyond embryonic life as microglia can promote the formation and dismantling of functional neuron-glial networks by axon reorganization during

development and by regulation of genesis and pruning of synapses in the mature brain (Pósfai et al. 2019).

Although lagging behind classical computational neuroscience, theoretical and computational approaches are beginning to emerge to characterize different aspects of neuron-glial interactions (De Pittà and Berry 2019a). This chapter aims to provide essential knowledge on neuron-glial interactions in the mammalian brain, leveraging on computational studies that focus on structure (anatomy) and function (physiology) of such interactions in the healthy brain. Although our understanding of the need of neuron-glial interactions in the brain is still at its infancy, being mostly based on predictions that await for experimental validation, simple general modeling arguments borrowed from control theory are introduced to support the importance of including such interactions in traditional neuron-based modeling paradigms.

Anatomy of Neuron-Glial Interactions

Myelination of Axons by Oligodendrocytes

Myelination by oligodendrocytes and axon growth seem to be entirely interdependent since there are direct relationships among the age at which axons are myelinated, their final diameter in the adult, and the development of the associated oligodendrocytes (Butt 2013). Accordingly, oligodendrocytes and their axons should be considered together as functional units rather than separate functional entities. Myelinated axons can thus be thought to be functionally specialized since internodes provided by myelinic ensheathing and nodes of Ranvier develop in a concerted fashion to fulfill specific computational tasks (Tomassy et al. 2016; Hughes et al. 2018).

Electrical cable theory (FitzHugh 1962; Goldman and Albus 1968; Moore et al. 1978; Waxman 1980; Richardson et al. 2000) predicts that regulation of myelin thickness, internode length, and node geometry by oligodendrocytes (Ullén 2009; Fields 2008; Arancibia-Carcamo et al. 2017) could account for fine-tuning of action potential (AP) shape and conduction velocity

(Kimura and Itami 2009; Tomassy et al. 2014; Ford et al. 2015; Hughes et al. 2018) with important functional consequences. For instance, variations of internodal length associated with axon diameter dictate the extent of co-activation of nodal Na^+ with low-threshold K^+ channels.

In turn, a triaxial cable model of myelinated axons in sound processing circuits reveals how the synchronous activation of these channels may account for large, fast-rising and brief APs, differentiating axons that can propagate APs at high rates, and that belong to neurons that encode for high-frequency sounds, from axons that cannot, and instead depart from neurons that respond to low-frequency sounds (Halter and Clark Jr 1991; Ford et al. 2015). In those circuits, adjustments of internodal length may also occur in close register with nodal diameter, crucially setting the timing of AP arrival at synaptic terminals, which, in turn, underpins precise binaural processing of temporal information for sound localization (Carr and Konishi 1990; Carr et al. 2001; Carr and Soares 2002; McAlpine and Grothe 2003; Seidl et al. 2010; Ford et al. 2015). Together with delays induced by the AP-generation dynamics (Fourcaud-Trocmé et al. 2003) and those rising from synaptic processing (Markram et al. 1997), axonal conduction delays due to myelination by oligodendrocytes are an important property of neural interactions, which may induce a wealth of dynamical states with different spatiotemporal properties and domains of multistability that could serve different computational purposes (Roxin et al. 2005; Roxin and Montbrió 2011).

Müller Glia in the Retina

Formation of axon-myelin units by oligodendrocytes to fulfill specific functional tasks is only one of the possibly many cases of how neuronal structures and glial cells' morphology develop in a tight association. Another example is the retina of the vertebrate eye. Notably, this structure is inverted with respect to its optical function so that light must pass through several tissue layers before reaching the light-detecting photoreceptor cells. In doing so, projected images on the retina would rapidly deteriorate due to light scattering by optical and geometrical inhomogeneities of

those different layers if it were not for specific properties and arrangement of structures and cell assemblies of the retina that ensure correct vision (Tuchin 2000; Masland 2001). In this scenario, the most common type of retinal glial cells, known as Müller cells, shows a characteristic cylindrical, funnel-like shape that spans the entire thickness of the retina and functions as the waveguide of visible light from the retinal surface to the photoreceptor cell layer (Franze et al. 2007). Numerical solution of the Helmholtz equation in a model of retinal tissue suggests that this property of Müller cells to guide light crucially enhances vision acuity since, like fiber optics that penetrate through the retinal layers, these cells can propagate light straight down to the photoreceptor cell they associate with (Labin and Ribak 2010). In particular, every mammalian Müller cell is coupled, on average, to one cone photoreceptor cell, that is responsible for sharp seeing under daylight conditions (i.e., photopic vision), plus several rod photoreceptor cells, serving low-light-level, night (scotopic) vision (Reichenbach and Robinson 1995). Remarkably, the spectrum of light transmitted through Müller cells, derived from theoretical calculations based on data of the human parafoveal retina, matches almost perfectly the absorption spectra of the medium- and long-wavelength human cone photoreceptors, predicting a gain in photon absorption by a factor of ~ 7.5 by these photoreceptors, and by a factor of by human short-wavelength cones (Labin et al. 2014). At the same time, the spectrum of light leaking outside Müller cells matches the absorption spectrum of human rod photoreceptors. In this fashion, Müller cells provide a mechanism to improve cone-mediated photopic vision, with minimal interference with rod-mediated scotopic vision since not only they guide light of relevant wavelengths for cone visual pigments directly towards cones but also they allow for light of wavelengths more suitable for rod vision to leak to surrounding rods (Labin et al. 2014).

Astrocytes and Regulation of Volume Transmission

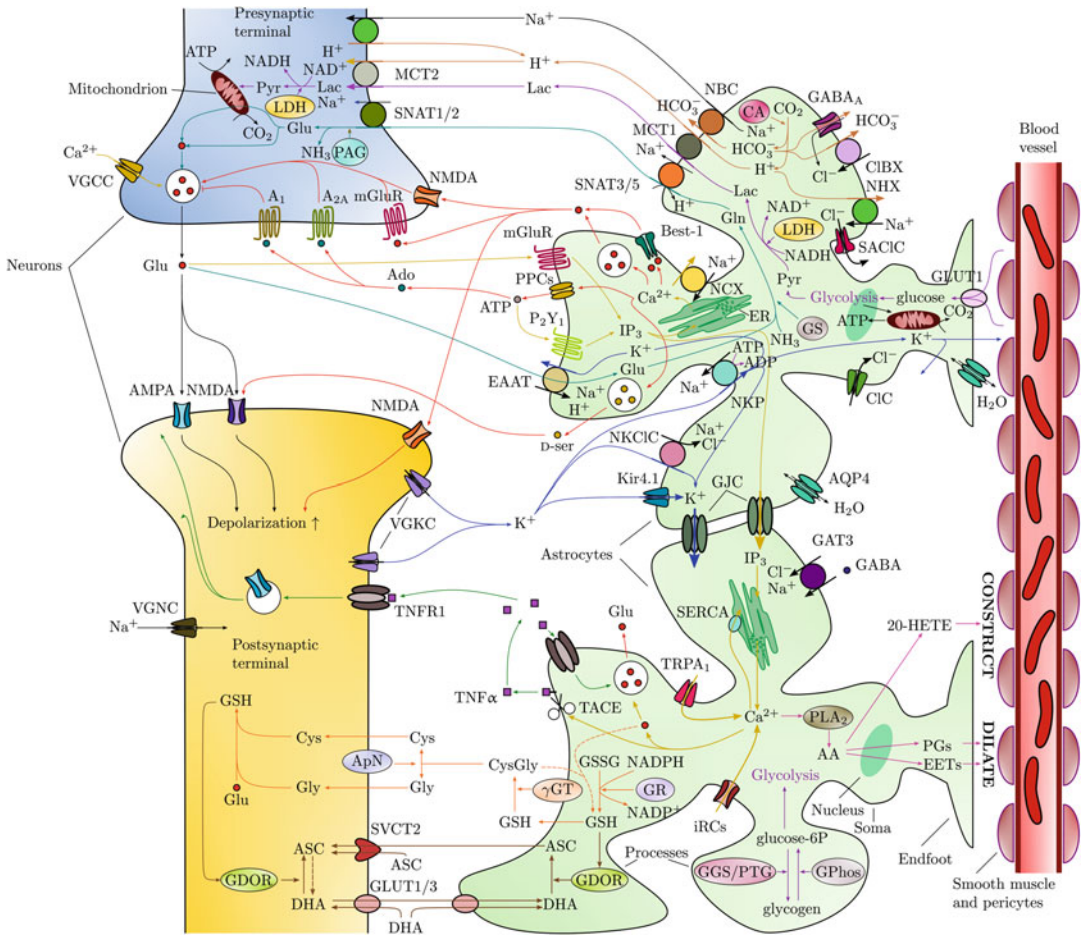
Broadly speaking, the factors underpinning morphogenesis of neuronal structures in tight

association with glial cells remain poorly understood, although they are thought to encompass a combination of transcriptional programs and a battery of molecular signals that seem to be regulated both developmentally and regionally, in a cell-specific manner (Jadhav et al. 2009; Eroglu and Barres 2010; Götz 2013; Stassart et al. 2013). A paramount example of this complex combination of factors is provided by astrocytes, which are glial cells predominantly found in the cortex and hippocampus and are recognized as critical regulators of the neuronal connectome in those brain regions (Fields et al. 2015). In the postnatal, developing brain, astrocytes are indeed found in spatially distinct domains and express domain-specific genes that are needed to support the formation of specific neural circuits and neuronal subtypes (Molofsky et al. 2014). On the other hand, they also secrete a variety of molecules that regulate with spatiotemporal specificity all stages of the genesis of functional neural circuits, such as the establishment of immature (silent) synapses between axon and dendrites, the conversion of these silent synapses into active ones by insertion (and maintenance) of functional receptors, and the elimination of excess synapses and synaptic pruning to refine connections in neural circuits (Allen 2013; Clarke and Barres 2013). Remarkably, this close relationship between astrocytes and synapses continues in the adult brain, with the processes of astrocytes that infiltrate into the neuropil and wrap themselves around synapses in a seemingly nonrandom fashion (Reichenbach et al. 2010), engaging in a multitude of signals (Fig. 1), with figures approaching 20–180 thousand synapses contacted by a single astrocyte in the rodent brain (Bushong et al. 2002), but ~270 thousand to 2 million synapses per astrocyte in the human brain (Oberheim et al. 2009). What are the possible functional purposes of this ensheathing?

One obvious possibility is that processes of astrocytes are strategically positioned at synaptic loci to act as physical barriers that constrain and regulate extracellular diffusion of neurotransmitters (Ventura and Harris 1999). With this regard, a realistic reconstruction of the extracellular space (ECS) in between astrocytic processes and glutamatergic synapses of the hippocampus – one of the brain structures where the

morphological association of astrocytes with synapses has been best-characterized (Seifert and Steinhäuser 2017) – revealed a strong anisotropy for glutamate diffusivity, directly imputable to the peculiar arrangement of astrocytes with the surrounding neuropil (Kinney et al. 2013). This anisotropy ensues from the nonuniform width of ECS, which forms thin sheets in the periastrcytic space and grows wider into tunnels in correspondence with synapses and axons. Monte Carlo diffusion simulations show that the diffusion rate of glutamate through the neuropil critically depends on the proportion of sheets versus tunnels, since the smaller median extracellular width of astrocyte-delimited sheets poses a diffusion barrier to glutamate molecules, corralling them into tunnels which favor their diffusion instead (Kinney et al. 2013). This scenario, along with the expression of glutamate transporters by perisynaptic astrocytic processes (Danbolt et al. 2002), would ultimately provide a mechanism to canalize glutamate to specific targets while keeping low the risk of excitotoxicity brought forth by the fact that glutamate is not normally destroyed in the ECS (Rothstein et al. 1996).

The degree of astrocytic ensheathing at glutamatergic synapses indeed directly dictates the rate of glutamate uptake by glial transporters – the primary mechanism of glutamate uptake in the adult brain (Danbolt 2001) – regulating the time course of this neurotransmitter in the synaptic cleft and its potential to spill out to neighboring synapses (Clements 1996). Remarkably, the degree of astrocyte ensheathment seems inversely correlated with the size of dendritic spines (Medvedev et al. 2014), suggesting that, in agreement with independent theoretical arguments (Barbour 2001), smaller synapses are best sealed by astrocytic processes to minimize glutamate spillover. On the contrary, glutamate spillover could occur at larger synapses, for which the degree of astrocytic ensheathing is only up to approximately one-third of their perimeter (Ventura and Harris 1999). To the extent that thin-spine versus large-spine synapses can respectively be assimilated to silent versus functional synapses (Matsuzaki et al. 2001), the latter possibility hints a crucial role of astrocytic ensheathing



Neuron-Glial Interactions, Fig. 1 Common interactions between astrocytes and glutamatergic synapses. *Yellow pathway*: astrocytic calcium signaling; *red pathway*: gliotransmission (both glutamatergic and purinergic); *green pathway*: cytokine (TNF α) signaling; *turquoise pathway*: glutamate-glutamine cycle; *blue pathway*: K⁺ buffering; *purple pathway*: astrocyte-to-neuron lactate shuttle; *brown pathway*: pH buffering; *orange pathway*: glutathione metabolism; *brown pathway*: ascorbic acid exchange; and *magenta pathway*: vascular coupling. Modified from De Pittà and Berry (2019b). (--->) (indirectly) promoting pathway, $\vdash$ inhibiting pathway. 20-HETE 2-hydroxy-eicosatetraenoic acid, AA arachidonic acid, Ado adenosine, AMPA α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, ADP (ATP) adenosine diphosphate (triphosphate), AQP4 aquaporin channel type 4, ApN ectoaminopeptidase N, ASC ascorbic acid (reduced vitamin C), Best-1 bestrophin-1 ion channel, CA carbonic anhydrase, CIBX Cl⁻/HCO₃⁻ exchanger, CIC chloride channel, Cys cysteine, CysGly cysteinylglycine, DHA dehydroascorbic acid (oxidized vitamin C), EAAT excitatory amino acid transporter, EETs epoxyeicosatrienoic acids, ER endoplasmic reticulum, GABA γ -Aminobutyric

acid, GAT GABA transporter, GDOR glutathione-dependent dehydroascorbate reductase, GGS/PTG glycogen synthase/UTP-glycogen-phosphate uridylyl-transferase, GJC gap junction channel, Glu glutamate, glucose-6P glucose 6-phosphate, GLUT glucose transporter, Gly glycine, GPhos glycogen phosphorylase, GR glutathione reductase, GS glutamine synthetase, GSH glutathione (reduced form), GSSG glutathione (oxidized form), γ GT γ -glutamyl transpeptidase, IP₃ inositol 1,4,5-trisphosphate, iRCs ionotropic receptor channels, Kir inwardly rectifying K⁺ channel, Lac lactate, LDH lactate dehydrogenase, MCT monocarboxylate transporter, mGluR metabotropic glutamate receptor, NAD⁺ (NADH) oxidized (reduced) nicotinamide adenine dinucleotide, NADP⁺ (NADPH) oxidized (reduced) nicotinamide adenine dinucleotide phosphate, NBC Na⁺-coupled bicarbonate transporter, NCX Na⁺/Ca²⁺ exchanger, NH₃ ammonia, NHX Na⁺/H⁺ exchanger, NKCC Na⁺-K⁺-Cl⁻ co-transporter, NKP Na⁺/K⁺-ATPase pump, NMDA N-Methyl-D-aspartate, P₂Y₁ metabotropic purinergic receptor, PAG glutaminase, PGs prostaglandins, PLA₂ phospholipase A₂, PPCs purine-permeable ion channels, Pyr pyruvate, SACIC swell-activated chloride channel,

in the regulation of glutamate clearance at functional excitatory synapses, with the potential to regulate independent synaptic activation versus synaptic cross-talk (Huang and Bergles 2004).

Physiology of Neuron-Glial Interactions

General Modeling Framework

If the reciprocal disposition of neurons with respect to glial cells in the brain fulfills essential anatomical constraints for their interaction, the existence of two-way dynamic signaling, from neurons to glia and vice versa, accounts for the physiology of this interaction. With this regard, a common framework to model networks of interacting neurons (Ermentrout and Terman 2010) may be borrowed to illustrate essential functional consequences of neuron-glial interactions. Denoting by $\mathbf{x}$ and γ the activities of neuronal and glial interacting ensembles, respectively, defined as column vectors in $\mathbb{R}^N$ and $\mathbb{R}^G$, then the glial activity can generally be described by

$$\tau_\gamma \dot{\gamma} = -\gamma + \mathcal{F}_\gamma(\mathbf{b}_\gamma + \mathbf{I}_\gamma(\mathbf{x}, \gamma)) \quad (1)$$

where $\mathcal{F}_\gamma : \mathbb{R}^g \rightarrow \mathbb{R}^G$ ($g \geq G$) represents the glial input-output transfer function. The argument of this function – that is the input to glia – consists of (i) an external bias $\mathbf{b}_\gamma \in \mathbb{R}^g$ coming, for example, from brain areas away from the neuron-glial ensemble under consideration and of (ii) a recurrent input $\mathbf{I}_\gamma(\mathbf{x}, \gamma) : \mathbb{R}^{N+G} \rightarrow \mathbb{R}^g$ due to neuronal and glial activities within the ensemble itself. The physiological correlate of γ , along with the choice of $\mathcal{F}_\gamma$ and $\mathbf{I}_\gamma$, depend on what “glial activity” refers to, and it will be clarified below. Similarly, without specifying for now what “neuronal activity” is, an equation analogous to 1 may be written for $\mathbf{x}$, i.e.,

$$\tau_x \dot{\mathbf{x}} = -\mathbf{x} + \mathcal{F}_x(\mathbf{b}_x + \mathbf{I}_x(\mathbf{x}, \gamma)) \quad (2)$$

where $\mathcal{F}_x : \mathbb{R}^n \rightarrow \mathbb{R}^N$, $\mathbf{b}_x \in \mathbb{R}^n$ and $\mathbf{I}_x(\mathbf{x}, \gamma) : \mathbb{R}^{N+G} \rightarrow \mathbb{R}^n$ ($n \geq N$). In the previous equations, what the “activities” $\mathbf{x}$ and γ refer to are suitable measurables of neuronal and glial physiology, respectively. Membrane voltage, firing rate, and synaptically released neurotransmitters are typical examples of such measurables for neurons. For glia instead, cytosolic calcium is probably the most hitherto studied readout of these cells in response to neuronal stimulation, yet possibly not the only one, since other intracellular ions like Na^+ , K^+ , H^+ , Cl^- , or HCO_3^- , along with a whole cassette of molecules involved in the genesis of calcium signaling, could also be indicators of glial stimulation (De Pittà and Berry 2019b). At the same time, the notion of neuronal and glial ensembles is somehow broad. We may encompass by this notion brain structures, including whole networks of neurons and glia, or components of these networks, for example, myelinated axons with their oligodendrocytes, or groups of synapses with their perisynaptic glial processes (of astrocytic or microglial origin). In this context, the emerging notion that calcium homeostasis, as well as the homeostasis of other ions and macromolecules, could be compartmented within the glial cell’s morphology (Breslin et al. 2018, see also ▶ “Intracellular Calcium Signals in Astrocytes, Computational Modeling of”), allows using equations akin to 1 and 2 to model dynamics of neuron-glial interactions at multiple spatial scales, where scale-specific aspects of such interactions may be lumped into the choice of the transfer functions $\mathcal{F}_i$ (with $i = \mathbf{x}, \gamma$), their input arguments $\mathbf{b}_i$, $\mathbf{I}_i$, and ultimately, the components of the activity vectors $\mathbf{x}$ and γ .

The functions $\mathcal{F}_i$ and $\mathbf{I}_i$ are generally nonlinear with respect to their input variables. This hinders

Neuron-Glial Interactions, Fig. 1 (continued) SERCA (sarco)endoplasmic reticulum Ca^{2+} -ATPase, *SNAT* Na^+ -coupled neutral amino acid transporter, *SVCT2* Na^+ -dependent vitamin C transporter 2, *TACE* TNF α -converting enzyme, *TNF α* (*TNFR*) tumor necrosis

factor alpha (receptor), *TRPA* transient receptor potential channel, *VGCC* voltage-gated Ca^{2+} channel, *VGKC* voltagegated K^+ channel, *VGNC* voltage-gated Na^+ channel

any attempt to look beyond the general form of Eqs. 1 and 2 to fathom neuron-glial interactions with the aim to derive different mechanisms of action and function that could be shared (or not) by different pathways of interaction. The situation greatly simplifies if we limit our analysis to the first order expansion of $\mathbf{I}_i$ around the resting point $(\mathbf{x}_0, \gamma_0)$. In this case, Eqs. 1 and 2 become

$$\tau_\gamma \dot{\gamma} \approx -\gamma + \mathcal{F}_\gamma(\mathbf{b}_{0_\gamma} + \mathbf{W}_\mathbf{x}(\mathbf{x} - \mathbf{x}_0) + \mathbf{J}_\gamma(\gamma - \gamma_0)) \quad (3)$$

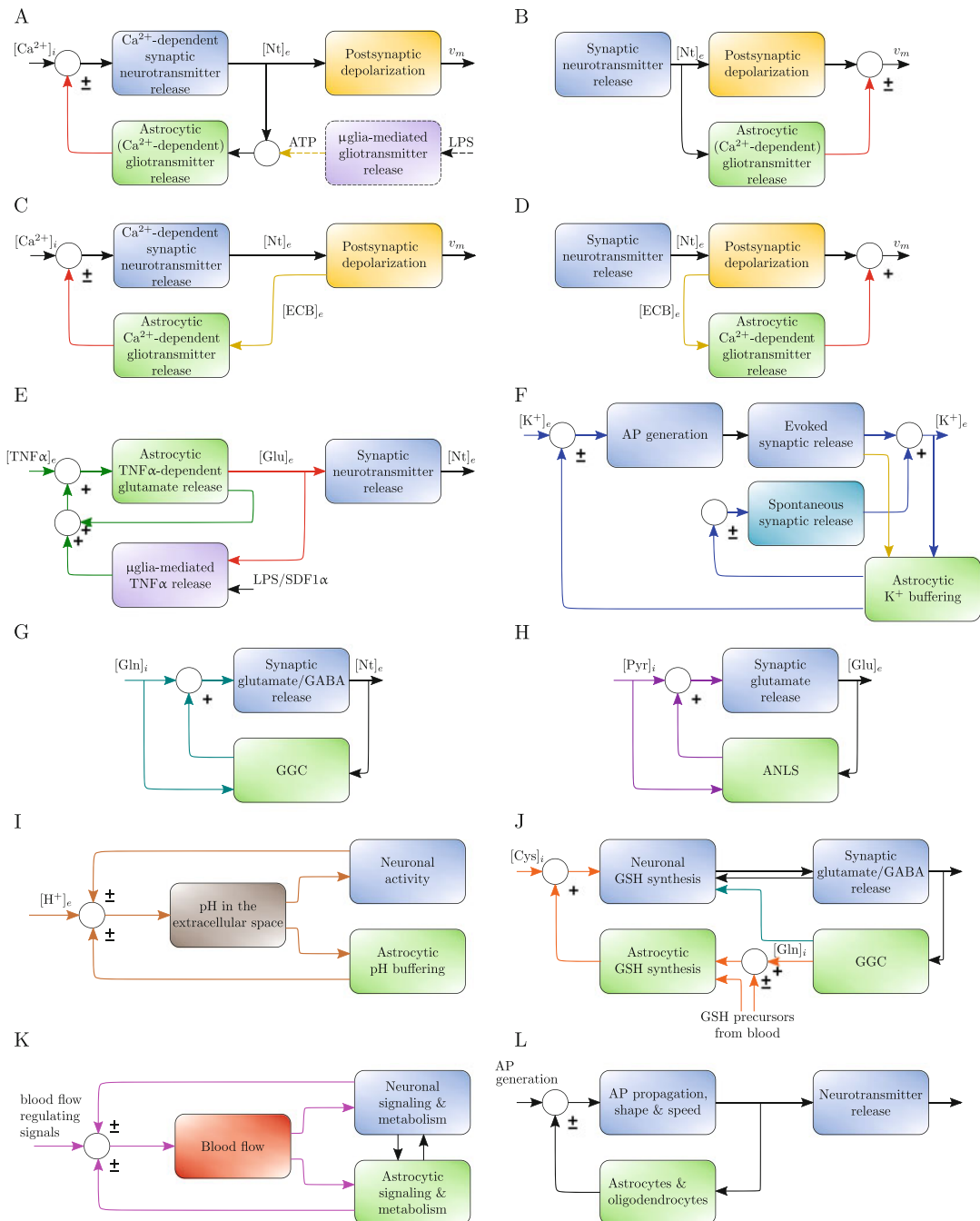
$$\tau_\gamma \dot{\mathbf{x}} \approx -\mathbf{x} + \mathcal{F}_\mathbf{x}(\mathbf{b}_{0_\mathbf{x}} + \mathbf{J}_\mathbf{x}(\mathbf{x} - \mathbf{x}_0) + \mathbf{W}_\gamma(\gamma - \gamma_0)) \quad (4)$$

where, for $i = \mathbf{x}, \gamma$, $\mathbf{b}_{0_i} = \mathbf{b}_i + \mathbf{I}_i(\mathbf{x}_0, \gamma_0)$, $\mathbf{J}_i = (D_i \mathbf{I}_i(i, j))_{(\mathbf{x}_0, \gamma_0)}$ and $\mathbf{W}_i = (D_j \mathbf{I}_i(i, j))_{(\mathbf{x}_0, \gamma_0)}$, with $D_\mathbf{x} \mathbf{I}_i = \left(\frac{\partial \mathbf{I}_i}{\partial x_0}, \dots, \frac{\partial \mathbf{I}_i}{\partial x_{N-1}} \right)$ and $D_\gamma \mathbf{I}_i = \left(\frac{\partial \mathbf{I}_i}{\partial \gamma_0}, \dots, \frac{\partial \mathbf{I}_i}{\partial \gamma_{G-1}} \right)$. In this way, it is possible to distinguish between different contributions to the evolution of neuronal (glial) activity by $\mathcal{F}_\mathbf{x}$ ($\mathcal{F}_\gamma$), in particular separating those that are due to neuronal (glial) elements weighted by the matrix $\mathbf{J}_\mathbf{x}$ ($\mathbf{J}_\gamma$) from those that result instead from glial (neuronal) elements and that are weighted by the matrix $\mathbf{W}_\mathbf{x}$ ($\mathbf{W}_\gamma$). Because matrices $\mathbf{J}_\mathbf{x}$, $\mathbf{J}_\gamma$ lump couplings of neuronal (respectively glial) activities with themselves, whereas matrices $\mathbf{W}_\mathbf{x}$, $\mathbf{W}_\gamma$ couple neuronal activities with glial activities and vice versa, we hereafter refer to them as *homotypic* and *heterotypic* weight (or connection) matrices, respectively.

The input terms associated with heterotypic connections represent the actual interaction pathways, for signaling from neurons to glia ($\mathbf{W}_\mathbf{x}\mathbf{x}$), and vice versa, from glia to neurons ($\mathbf{W}_\gamma\gamma$). In several practical scenarios (Fig. 2), this signaling is mediated by specific molecules or ions, that may themselves be regarded as measures of neuronal (glial) activity, or can alternatively be expressed in terms of $\mathbf{x}$ (respectively γ). Consider, for example, synaptically evoked gliotransmission (Araque et al. 2014, see also *yellow* and *red* pathways in Fig. 1). This form of neuron-glial interaction consists of the

activity-dependent release of neuroactive molecules from astrocytes, including neurotransmitters like glutamate, ATP, GABA, or D-serine that, for their glial origin, are termed “gliotransmitters.” The release can be triggered by synaptically-released neurotransmitters and be mediated by different intracellular pathways that often associate with transient calcium signaling in the astrocyte (Savtchouk and Volterra 2018). In turn, gliotransmitters can modulate synaptic transmission both presynaptically – binding to receptors that regulate the probability of release of neurotransmitter-containing synaptic vesicles – and postsynaptically, gating receptors/ion channels that control neuronal depolarization (and excitability). In this description, synaptically-released neurotransmitters mediate neuron-to-astrocyte signaling, whereas gliotransmitters are responsible for the astrocyte-to-neuron signaling. To couple these two signaling pathways by the above framework, however, biophysical correlates for their functional interdependence must also be explored. For the dependence of gliotransmitter release on synaptic release, at least at first approximation, gliotransmitter release is expected to rise with synaptic neurotransmitter release (Araque et al. 2014). For the dependence of this latter on gliotransmitter release instead, the reasoning is as follows: (i) activation of presynaptic receptors by gliotransmitters increases with gliotransmitter release; in turn (ii) modulation of intrasynaptic Ca^{2+} , which is linked with p – the synaptic release probability (► “Biophysical Models of Calcium-Dependent Exocytosis”) – correlates with the degree of receptor activation by gliotransmitters; and (iii) synaptic release is proportional to p . In this fashion, the simplest scenario sees γ in the above equations reducing to a scalar variable that is associated with the fraction of gliotransmitter-activated receptors, whereas p replaces $\mathbf{x}$. Then, assuming that at rest $\gamma_0 = 0$, $p_0 = p^* > 0$, the simplest model for the presynaptic pathway of synaptically-evoked gliotransmission (Fig. 2a) derived by Eqs. 3 and 4 reads

$$\tau_\gamma \dot{\gamma} = -\gamma + \mathcal{F}_\gamma(b_{\gamma_0} + W_\gamma p + J_\gamma \gamma) \quad (5)$$



Neuron-Glial Interactions, Fig. 2 Feedback and feedforward pathways in neuron-glial interactions. (a) Pre-synaptic pathway of gliotransmission stimulated by presynaptically released neurotransmitters; (b) postsynaptic pathway of gliotransmission stimulated by presynaptically released neurotransmitters; (c) presynaptic pathway of gliotransmission triggered by postsynaptic endocannabinoid release; (d) postsynaptic pathway of

gliotransmission mediated by postsynaptic endocannabinoid release; (e) modulation of glutamatergic gliotransmission by $TNF\alpha$. (f) K^+ buffering and regulation of neuronal activity; (g) glutamate-glutamine cycle (GCC); (h) astrocyte-to-neuron lactate shuttle (ANLS); (i) extracellular pH homeostasis; (j) glutathione synthesis; (k) neurovascular coupling; and (l) gliotransmission mediated by postsynaptic endocannabinoid release. $[Ca^{2+}]_i$ intracellular

$$\tau_p \dot{p} = p^* - p + \mathcal{F}_p((1 - J_p)p^* + J_p p + W_p \gamma) \quad (6)$$

where b_{γ_0} may or not be present, depending on the presence or not of other mechanisms triggering gliotransmitter release that are independent of stimulation of the very synapse modulated by gliotransmission, e.g., microglia-mediated Ca^{2+} signaling in the astrocyte (Pascual et al. 2011). The homotypic weight J_γ accounts for the theoretically-predicted phenomenon of gliotransmitter-triggered gliotransmission (Larter and Craig 2005), whereas the homotypic weight J_p can generally be accounted by mechanisms of short-term plasticity (► “Short-Term Plasticity, Biophysical Models”). With regard to the heterotypic weights instead, it generally is $W_\gamma > 0$ regardless of the nature of synaptic neurotransmitters, that is both excitatory and inhibitory neurotransmitters are excitatory for glial activation (Durkee et al. 2019). The sign of W_p instead is dependent on the nature of gliotransmission, which can either decrease or increase synaptic release (De Pittà et al. 2015). Remarkably, while the sign of W_p is set by functional and anatomical features of synapse-astrocyte ensembles (De Pittà 2019), the further possibility that the polarity of gliotransmission could also depend on specific patterns of activity (Covelo and Araque 2018) can be accounted by the choice of $\mathcal{F}_p$.

If we aim for a more general understanding of gliotransmission on synaptic transmission, it is then useful to think of the efficacy (or strength) of synaptic transmission in terms of the product $w = p \cdot q$, where q is the probability of activation of postsynaptic receptors by the presynaptically-released neurotransmitter. In this context then, choosing $\mathbf{x} = (p, q)^T$ with $q_0 = q^* > 0$ results in the system of three equations in the general form of

$$\begin{aligned} \tau_\gamma \dot{\gamma} &= -\gamma \\ &+ \mathcal{F}_\gamma(b_{\gamma_0} + W_\gamma^{(p)} p + W_\gamma^{(q)} q + J_\gamma \gamma) \end{aligned} \quad (7)$$

$$\begin{aligned} \tau_p \dot{p} &= p^* - p + \mathcal{F}_p((1 - J_p)p^* - W_p^{(q)} q^* \\ &+ J_p p + W_p^{(q)} q + W_p^{(\gamma)} \gamma) \end{aligned} \quad (8)$$

$$\begin{aligned} \tau_q \dot{q} &= q^* - q + \mathcal{F}_q(-W_q^{(p)} p^* + (1 - J_q)q^* \\ &+ W_q^{(p)} p + J_q q + W_q^{(\gamma)} \gamma) \end{aligned} \quad (9)$$

The coupling factors J_q , $W_\gamma^{(q)}$, $W_p^{(q)}$, and $W_p^{(\gamma)}$ ensue from the consideration of endocannabinoid signaling, which may retrogradely suppress synaptic activity while, at the same time, triggering Ca^{2+} -dependent gliotransmitter release from the astrocyte (Navarrete et al. 2014). In particular, because this signaling pathway depends on postsynaptic depolarization (v_m), and this latter is dependent on incoming synaptic activity by w , it is safe to assume that endocannabinoid signaling can be expressed in terms of p and q by a proper choice of the transfer functions $\mathcal{F}_\gamma$, $\mathcal{F}_p$, and $\mathcal{F}_q$ and their input arguments I_γ , I_p , and I_q in the original Eqs. 1 and 2 (Figs. 2c, d). On the other hand, when no retrograde signaling (including endocannabinoid) is taken into account, then $J_q = 0$ and also $W_\gamma^{(q)} = W_p^{(q)} = W_p^{(\gamma)} = 0$, allowing for a significant simplification of the above equations. Even more so if the analysis is restricted to the sole postsynaptic pathway of gliotransmission without considering any mechanism of short-term plasticity, for which, synaptic dynamics reduces to $\tau_p \dot{p} = p^* - p$ and $\tau_q \dot{q} = q^* - q + \mathcal{F}_q(-W_q^{(p)} p^* + q^* + W_q^{(p)} p + W_q^{(\gamma)} \gamma)$ with γ being described by an equation like 5. In this scenario, gliotransmission release (γ) becomes uncoupled from q (but not the opposite), and the dynamics of both γ and q is driven by p (Fig. 2b). The resulting $q(t)$ can essentially be expressed in

Neuron-Glial Interactions, Fig. 2 (continued)
(cytosolic) calcium concentration, $[\text{Cys}]_i$ ([Gln]_i) intracellular cysteine (glutamine) concentration, $[\text{ECB}]_e$ ($[\text{TNF}\alpha]_e$) extracellular endocannabinoid (TNF α) concentration, $[\text{K}^+]_e$ ($[\text{H}^+]_e$) extracellular K^+ (H^+) concentration,

$[\text{Nt}]_e$ ($[\text{Glu}]_e$) extracellular neurotransmitter (glutamate) concentration, v_m membrane potential, AP action potential, LPS lipopolysaccharide, $SDF1\alpha$ stromal cell-derived factor 1 alpha

terms of $p(t)$ but, differently from a stand-alone synapse, the effect of p on q (and thus on v_m) also incorporates, possibly in a nonlinear fashion, the effect of gliotransmission. Remarkably, this scenario could underpin several examples of neuron-glia interactions such as: (i) regulation of long-term synaptic plasticity by D-serine released from astrocytes in the hippocampus, hypothalamus, and the cortex (Bains and Oliet 2007); (ii) AMPA receptor internalization in the cerebellum by D-serine originating from Bergmann glial cells (Kakegawa et al. 2011); (iii) AMPA receptor insertion by adrenergic stimulation of ATP release from hypothalamic astrocytes (Gordon et al. 2005); (iv) modulation of AMPA and GABA receptor trafficking by astrocytic TNF α (Stellwagen et al. 2005); and (v) slow inward and outward currents (SICs and SOC s) respectively mediated by glutamate and GABA from astrocytes (Fellin et al. 2004; Le Meur et al. 2012).

The distinction between homotypic versus heterotypic couplings brought forth by Eqs. 3 and 4 allows the analysis of otherwise complex neuron-glia interactions in terms of combinations (to the first-order approximation) of feedback and feedforward mechanisms, which can conveniently be illustrated by functional diagrams such as those in Fig. 2. Furthermore, consideration of these diagrams can help classify different pathways of interaction between neurons and glia based on their coupling mechanisms. In this fashion, activity-dependent presynaptic pathways of gliotransmission can all be assimilated to a feedback mechanism on synaptic release, which can be either positive or negative, depending, as previously stated, on the nature of astrocyte-synapse coupling and synaptic dynamics (Fig. 2a). Conversely, the postsynaptic pathway of gliotransmission is tantamount to a feedforward mechanism on postsynaptic membrane depolarization, which can also be positive or negative, depending on the gliotransmitter type and whether gliotransmission promotes receptor internalization or insertion (Fig. 2b). Consideration of endocannabinoid signaling does not change the essence of these mechanisms, except for the fact that a further intermediate processing stage must be taken into account for the regulation of

endocannabinoid release from postsynaptic terminals (Fig. 2c). Nonetheless, differently from other pathways of synaptic transmission, in this latter case, postsynaptic pathways of gliotransmission may also feedback on endocannabinoid release since this process depends on postsynaptic depolarization (Fig. 2d). On the other hand, glutamatergic gliotransmission could also contemplate the existence of positive feedback on the astrocyte by its release of the cytokine TNF α (Fig. 2e). Constitutive extracellular levels of this cytokine ([TNF α] $_e$) may indeed promote glutamate release from astrocytes but can also regulate the production of TNF α by these cells (Santello et al. 2011). Furthermore, microglia could also regulate glutamatergic gliotransmission, releasing ATP as part of their immune response, and thereby promoting Ca $^{2+}$ -dependent glutamate release from astrocytes (Pascual et al. 2011). Alternatively, extracellular glutamate ([Glu] $_e$) may trigger the release of TNF α from microglia, which could stimulate the further release of glutamate from astrocytes in, yet another, positive feedback fashion (Bezzi et al. 2001).

Potassium ion homeostasis is also involved in multiple feedback pathways mediated by glia (Fig. 2f). Neuronal activity results in local accumulations of extracellular K $^{+}$ ([K $^{+}$] $_e$) that may promptly be abated by spatial buffering by glia (Kofuji and Newman 2004). Significantly, synaptically evoked Ca $^{2+}$ signaling in astrocytes (*yellow pathway*) can also regulate [K $^{+}$] $_e$ to modulate both spontaneous synaptic release at excitatory synapses and neuronal firing (Wang et al. 2006). In the cerebellum, Ca $^{2+}$ -dependent K $^{+}$ uptake by Bergman glia can dramatically alter the firing dynamics of Purkinje cells (Wang et al. 2012b). At cortical axons instead (Fig. 2l), depolarization of myelinating oligodendrocytes following AP conduction is speculated (Debanne et al. 2011) to alter extracellular levels of K $^{+}$ and Na $^{+}$ locally, at nodes of Ranvier, thereby transiently promoting action potential generation which could speed up AP conduction by 10% (Yamazaki et al. 2007). On the other hand, astrocytes, too, could influence AP generation at nodes of Ranvier, specifically by increasing AP duration by Ca $^{2+}$ -dependent glutamate release, although the activity requirements

for this pathway are not known (Sasaki et al. 2011).

Very often, a signaling pathway or a biophysical process may be shared by different mechanisms of neuron-glial interactions. Extracellular glutamate and its uptake by astrocytes, for example, are key components of the so-called glutamate–glutamine cycle (GCC), as well as of the astrocyte-to-neuron lactate shuttle (ANLS) (see ► “Brain Energy Metabolism”). In the GCC (Fig. 2g), glutamate taken up by astrocytic transporters is converted into glutamine, which is transported back to neurons, where it is presumably reconverted to glutamate, thereby guaranteeing the supply of this neurotransmitter to sustain synaptic transmission (Xiang et al. 2003). In the ANLS instead (Fig. 2h), astrocytic lactate – ensuing from ATP demand to counteract intracellular Na^+ accumulation by glutamate uptake – is shuttled to neurons where it is converted to pyruvate, which is necessary for ATP synthesis by mitochondria, and thus it mediates a positive feedback loop that can sustain the energetic cost of prolonged neuronal firing activity (Allaman et al. 2011). Remarkably, both ANLS and GCC could also be integral components of other pathways of neuron-glial interactions. Lactate, for example, may also cover synaptic energy demand indirectly by triggering prostaglandin release from astrocytes, which, in turn, increases blood flow and thereby, glucose supply to neurons (Attwell et al. 2010). Alternatively, it could also operate as gliotransmitter (Tang et al. 2014). Glutamine produced by GCC, on the other hand, could also be a precursor of glutathione (GSH) in the synthesis of this latter by astrocytes (Fig. 2j), which is a key process in neuroprotection by glia. Neurons are also capable of synthesizing GSH from glutamate, but this is constrained by their intracellular availability of cysteine and glycine. Astrocytes can, however, backup on the availability of these two amino acids in neurons by releasing GSH, which is extracellularly cleaved to produce cysteinylglycine that neurons, in turn, cleave to supply cysteine and glycine to their intracellular resources (Dringen 2000). Finally, glutathione metabolism could also be linked with vitamin C (ascorbic acid) exchange between neurons and

glia as illustrated by the *brown pathway* in Fig. 1 (Castro et al. 2009; May 2012).

In several cases, neuron-glial interactions add to existing neuronal feedback mechanisms. Two examples, respectively, are the control of extracellular pH and the regulation of blood flow by astrocytes. Neuronal electrical activity results in extracellular alkalinization and intracellular acidification around neuronal cell walls, which can considerably alter neuronal excitability and synaptic currents (Deitmer and Rose 1996). This is put in place by a multitude of diverse mechanisms that rely on physiochemical buffers, metabolic reactions, and membrane transport systems within neurons and in the interstitial fluid that make extracellular and intracellular neuronal pH completely interdependent. On the other hand, intracellular pH of astrocytes is also dependent on extracellular pH, and astrocytes, akin to neurons, express a variety of transport and buffering mechanisms that make them capable of influencing H^+ homeostasis locally and brain-wide actively. By similar arguments, both neurons and glial cells require a constant supply of metabolites and chemical species by the bloodstream. Yet, they can regulate blood flow by the independent release of vasoactive signals (Attwell et al. 2010), as well as do so in interaction with each other by the other neuron-astrocyte interaction pathways hitherto presented.

The existence of feedback and feedforward pathways of interactions between neuronal and glial elements challenges traditional connectomics. We come to realize in fact that neurons are not merely connected by synapses but also by extracellular glial-mediated pathways. Moreover, for some of these pathways, like at synapses where signal transmission is traditionally assumed to occur in one direction only – from the presynaptic terminal to the postsynaptic one – this directionality is replaced by a neuron-glial signaling network that is inherently recurrent. Recurrent connections are essential in network theory since they can control the stability of network activity and its robustness to noise. Accordingly, the model of an autaptic neuronal oscillator may conveniently be adopted to get a flavor of the potential relevance of glia-mediated synaptic recurrence on neuronal firing

(Volman et al. 2007). The autaptic oscillator consists of an excitatory neuron that exhibits periodic firing employing self-synapses (i.e., autapses) whose strength critically controls the neuron's firing rate and its stability (Seung et al. 2000). In this fashion, when all autapses also stimulate the same astrocytic domain and are equally affected by release-decreasing gliotransmission ensuing from it, activity-dependent fluctuations of neuronal firing rate emerge in phase opposition with astrocytic Ca^{2+} spikes (Volman et al. 2007). The mechanism would not be surprising per se if it were not for the fact that it can also be observed in the presence of irregular bursting by the autaptic neuron. The theory of autaptic oscillators (without astrocyte) predicts in fact that the positive feedback exerted by excitatory autapses on the neuron only allows this latter to maintain its firing rate at the onset of stimulation, or to increase it, ultimately reaching unrealistic (epileptiform) firing rates (Seung et al. 2000). This scenario is avoided in the presence of release-decreasing gliotransmission, however, because any self-amplifying increase of neuronal activity that could be triggered, for example, by a burst of APs, promotes gliotransmitter release from the astrocyte, which promptly counteracts the neuron's runaway by excitation by depressing autaptic transmission. In this fashion, the negative feedback exerted by gliotransmission on synapses competes with the positive autaptic feedback to prevent the neuron from persistently generating APs at high rates. Rather, the opposite happens, as prolonged periods of depressed synaptic excitation, consistent with the long-lasting effect of release-decreasing gliotransmission observed *in vitro* (Araque et al. 1998), substantially modify the firing statistics of the autaptic neuron, accounting for large interspike intervals. The ensuing neural bursting may accordingly be thought of as the alternation of APs with irregular periods of no activity and explains why the Gaussian distribution of interspike intervals otherwise observed for an autaptic neuron without astrocyte is instead heavy-tailed in the presence of gliotransmission (Volman et al. 2007).

Modulation of Neural Excitability

Two pathways for regulation of neuronal excitability by glia have hitherto been explored by

computational studies: one by glia-mediated control of K^+ homeostasis and the other by modulation of excitatory synapses by astrocytes. In the first case, the fact that cortical astrocytes, Müller glia in the retina, or Bergmann glia in the cerebellum, buffer extracellular K^+ redistributing it to sites of lower concentration, locally changes the resting membrane potential of neurons by the ► “Goldman-Hodgkin-Katz Equations” as well as the Nernst potential of individual ions (► “Nernst Equation”), thereby modulating the neuron's threshold for AP generation. This modulation can be crucial to set the tone of neuronal firing in healthy physiological conditions since blocking glial buffering could turn random firing maintained by random external stimulation into periodic bursting, and eventually lead to permanent spike inactivation (Bazhenov et al. 2004). Mechanistically, glial K^+ buffering can be by different combinations of passive and active transport systems, which, however, share an interplay between glial ATP-driven Na^+/K^+ pumps (NKPs) and Kir channels. Depending on neuronal activity, this interplay can mediate nontrivial positive feedback on neuronal firing, for example, promoting AP generation in conditions of low neuronal firing (Somjen et al. 2008) or turning regular spiking dynamics into bursting (Somjen et al. 2008; Øyehaug et al. 2012; Cui et al. 2018).

Control of neuronal firing by modulation of excitatory synaptic transmission by astrocytes could instead occur, in principle, both by pre- and postsynaptic pathways of gliotransmission, and intrasynaptically, by glutamate uptake by astrocytic transporters. In the first scenario, the rationale for modulation essentially follows that of Eqs. 7, 8 and 9, where Ca^{2+} -dependent gliotransmission could be triggered either by synaptically activated astrocytic metabotropic receptors (De Pittà and Brunel 2016) or by Na^+ influx into the astrocyte by glutamate transporters which in turn regulates Ca^{2+} influx into the astrocyte by $\text{Na}^+/\text{Ca}^{2+}$ -exchangers (Flanagan et al. 2018), though this latter possibility requires experimental validation. In the second scenario, detailed kinetic models of astrocytic transporters and AMPA and NMDA synaptic receptors suggest instead that control of glutamate clearance by astrocytic

transporters could modulate postsynaptic receptors' activation and desensitization thereby modulating the kinetics of postsynaptic current. This results in subtle changes in spike arrival timings and spike failures that modulate the firing pattern of the postsynaptic neuron (Allam et al. 2012).

Neuron-Glial Interactions in Neural Networks

The importance of uptake of neurotransmitters such as glutamate and GABA by astrocytes in setting the tone of neural network activity has only been partially explored in the framework of ► **"Neural Mass Action"** modeling, yet producing two interesting predictions (Garnier et al. 2016). First is the observation that a deficiency of GABA uptake by astrocytes increases the threshold for neuronal activation in a linear fashion. Second is the prediction that, in the presence of deficient astrocytic glutamate uptake, neural activity may either be reduced or enhanced or may display a transient of high activity before stabilizing around a new regime whose firing frequency is close to the one measured in the absence of astrocyte deficiency. Significantly, the somehow counterintuitive possibility that neural activity could decrease despite extracellular glutamate accumulation due to deficits in astrocytic uptake, may be observed only in the presence of sufficient interneuron hyperexcitability.

More generally, in the framework of neuronal network theory, modulation of neuronal excitability and synaptic transmission by glia is expected to modulate the balance of excitation (E) versus inhibition (I) with the potential to regulate network activity dramatically. This possibility follows by the analysis of the few available neuron-glia network models, which come in different flavors in terms of the combination of different E-I network configurations and different choices of neuronal (and synaptic) models and astrocytic signaling pathways (Savin et al. 2009; Ullah et al. 2009; Volman et al. 2013; Savtchenko and Rusakov 2014). Nonetheless, all these models eventually envisage an effect of glial signaling in terms of a modulation of synaptic drive, either at excitatory (Savin et al. 2009; Savtchenko and Rusakov 2014) or excitatory and inhibitory synapses (Ullah et al. 2009; Volman et al. 2013;

Garnier et al. 2016), which accounts for the emergence of variegated network activity. With this regard, a model by Ullah et al. (2009) considers the effect of astrocytic regulation of extracellular K^+ and Na^+ on firing dynamics of both excitatory and inhibitory neurons with voltage-dependent synaptic inputs. Accordingly, neuronal membrane potential dynamics depends on K^+ and Na^+ homeostasis regulated by astrocytes and so does the network's E-I balance. In this framework, brief (30 ms-long) step increases of E-to-E synaptic strength, which could loosely ensue from glial glutamate exocytosis, promote transient increases of neuronal firing, whose duration, however, depends on extracellular K^+ concentration (Ullah et al. 2009). In particular, for plausible non-pathological values of this concentration, the network could display transient episodes of persistent enhanced firing, which are reminiscent of persistent activity during UP states (Sanchez-Vives and McCormick 2000; Amzica et al. 2002; McCormick et al. 2003), as well as during delay periods of working memory tasks (Funahashi et al. 1989; Goldman-Rakic 1995).

Similar observations may also be made by other models which consider different scenarios of gliotransmission, such as short-term modulations of E-to-I synaptic connections by glutamatergic or purinergic gliotransmission (Savtchenko and Rusakov 2014), or homeostatic upregulation of excitation by glial $TNF\alpha$, although this latter scenario could also account for the emergence of paroxysmal activity in various pathological conditions (Volman et al. 2013). Significantly, these models identify in the spatial extent of gliotransmission a further key factor for the regulation of glia-mediated episodes of increased network activity, ranging from their frequency and duration (Volman et al. 2013) to the degree of network synchronization and the average firing rate of single neurons during their occurrence (Savtchenko and Rusakov 2014). With this regard, the transient depression of synapses within an astrocytic anatomical domain, which could mimic release-decreasing gliotransmission or temporary disruption of release-increasing gliotransmission, correlates with a decrease of neuronal firing and synchronization,

which is more significant for larger astrocytic domains (Savtchenko and Rusakov 2014).

Regulation of Synaptic Transmission and Plasticity

Modulation of synaptic release probability by gliotransmitters may occur on multiple time scales (De Pittà et al. 2015). On the one hand, it may last for tens of seconds up to a few minutes, thus affecting synaptic transmission and network computations only temporarily. In this context, theoretical investigations hint that synapses that display short-term depression can turn facilitating, and vice versa, by gliotransmission (De Pittà et al. 2011). At the same time, the filtering characteristic of the synapse for incoming APs also changes based on the history of astrocytic activation (De Pittà 2019). On the other hand, it is also possible for gliotransmission and its effects on synaptic transmission to last for tens of minutes: that is on time scales that could promote long-term plastic changes of the synapse. In this latter scenario, the change of synaptic weight w_{ij} of a synapse from neuron j to neuron i respectively firing at x_j , x_i , and in the presence of gliotransmitter release at rate γ , may be expressed by $\dot{w}_{ij} = F(w_{ij}; x_i, x_j, \gamma)$, where F is a generic function which we can expand about $x_i = x_j = \gamma = 0$, so that

$$\begin{aligned} \dot{w}_{ij} \approx & c_2^{\text{corr}} x_i x_j + c_2^{\text{pre}} x_i^2 + c_2^{\text{post}} x_j^2 \\ & + c_2^{\text{g-pre}} x_i \gamma + c_2^{\text{g-post}} x_j \gamma + c_2^{\text{glia}} \gamma^2 \\ & + c_1^{\text{pre}} x_i + c_1^{\text{post}} x_j + c_1^{\text{glia}} \gamma \\ & + c_0(w_{ij}) + O(x_i, x_j, \gamma) \end{aligned} \quad (10)$$

In the absence of gliotransmission ($c_2^{\text{g-pre}} = c_2^{\text{g-post}} = c_2^{\text{glia}} = c_1^{\text{glia}} = 0$), the above equation results in prototypical **“Hebbian Learning”** by $c_2^{\text{corr}} > 0$ (or anti-Hebbian learning for $c_2^{\text{corr}} < 0$) (Gerstner and Kistler 2002). This, however, may not be the case in the presence of gliotransmission, insofar as the requirements for associativity encompassed by Hebbian plasticity may not be sufficient to generate a change of synaptic weight. Correlation between pre- and postsynaptic activities reflected by c_2^{corr} in fact now sums with correlations between these activities and the effect of gliotransmission on pre-

($c_2^{\text{g-pre}}$) and postsynaptic receptors ($c_2^{\text{g-post}}$) (De Pittà and Brunel 2016), including additional effects on synaptic weight borne by gliotransmission alone which, for example, could mirror SICs which could be independent of postsynaptic activity (Wade et al. 2011).

Broadly speaking, how modulations of synaptic plasticity by glia could ultimately affect learning remains to be investigated, although few theoretical studies offer some enticing insights into the topic. Porto-Pazos and collaborators investigated performance of an astrocyte-inspired learning rule to train deep networks in data classification (Porto-Pazos et al. 2011; Alvarellos-González et al. 2012; Mesejo et al. 2015). They consider a feedforward network architecture where each neuron in the intermediate (hidden) layers associate with an astrocyte that modulates all the neuron’s outgoing connections. Each astrocyte is described by a quadruple (μ, κ, a, b) and requires μ stimulations by an associated synapse within κ consecutive time steps to get activated. Upon an astrocyte’s activation, the weights of all synapses associated with that astrocyte are increased by a factor a which could mimic either persistent increases of synaptic release by gliotransmission (Perea and Araque 2007; Navarrete et al. 2012) or LTP following enhanced postsynaptic NMDA receptor activation by astrocytically released D-serine (Henneberger et al. 2010). Conversely, if a neuron associated with an astrocyte remains inactive μ times within κ time steps, then the weights of its outgoing synapses are decreased by a factor b – a behavior that loosely reflects the termination of the aforementioned gliotransmitter-mediated effects, and accounts, in the long run, for pruning of inactive synapses (Hua and Smith 2004).

Several variants of the learning rule were tested, mostly dealing with different handling of astrocyte activations by consecutive neuronal firing exceeding μ ; yet, regardless of the details of the learning (training) procedure, the trained neuron-glia networks were able to outperform identical networks without astrocytes in all discrimination tasks taken into account (Porto-Pazos et al. 2011; Alvarellos-González et al. 2012). The training was, however, successful if potentiation

by astrocytes was less than depression by astrocyte inactivity, that is $a < b$ (Alvarellos-González et al. 2012; Mesejo et al. 2015). Because the change in synaptic weight mediated by an astrocyte at a synapse i at time t depends on the synapse's weight value at the previous update instant $t-1$, i.e., $\Delta w_i(t) = a \cdot w_i(t-1)$ for potentiation and $\Delta w_i(t) = b \cdot w_i(t-1)$ for depression, the $a < b$ condition assures that potentiation and depression do not cancel out at individual synapses, and that depression globally dominates, possibly preventing the network's runaway by excitation. On the other hand, the fact that $\Delta w_i(t)$ depends on $w_i(t-1)$, which in turn depends on $w_i(t-2)$ by $\Delta w_i(t-1)$ and so on, suggests that the relative contribution of potentiation over depression at any time at a given synapse depends on the history of synaptic updates which, in turn, reflects the history of the associated astrocyte's activation.

There is circumstantial evidence that astrocytes could modify the threshold for LTD versus LTP induction, such as in the supraoptic nucleus – where astrocytic coverage of synapse is reduced during lactation (Panatier et al. 2006). In these conditions, stimuli that are expected to induce LTP, elicit LTD instead, possibly for a reduced NMDA receptor activation by lower extracellular concentrations of astrocytic D-serine due to the increased extracellular space. Based on this experimental finding, and the observation that astrocytic D-serine could gate LTD or LTP induction (Zhang et al. 2008; Henneberger et al. 2010), Philips et al. (2017) devised a modified version of the BCM rule (Bienenstock et al. 1982; Gerstner and Kistler 2002) where the threshold rate of postsynaptic firing for induction of LTD versus LTP varies proportionally with astrocyte activation, and investigated how this rule affects development of orientation preference maps (OPMs) in a self-organizing network model of the primary visual cortex (V1) (Stevens et al. 2013). In their formulation, activation of an astrocyte is computed by the weighted sum of activities of all synapses within the astrocyte's anatomical domain of radius R , while the modified BCM rule only applies to excitatory connections, whereas inhibitory connections and excitatory afferents are trained by a classical Hebbian paradigm. This allows choosing the spatial range of

inhibitory connections to match short-distance lateral inhibitory connections found in V1 (Kisvárdy et al. 1997), while leaving the spatial range of lateral excitatory connections dependent on astrocytic radii.

This choice not only allows reproducing map orientation experimentally observed in V1 but also reveals that, upon reduction of astrocytic radius, periodicity of OPMs increases while width of individual hypercolumns decreases (Philips et al. 2017). Inasmuch as astrocyte size varies across species (Oberheim et al. 2009; López-Hidalgo et al. 2016), these results predict a causal link between astrocytic radius and different hypercolumn widths observed in different species (Kaschube et al. 2010). On the other hand, the model fails to explain why V1 in rodents displays a typical salt-and-pepper configuration (Ohki et al. 2005), inasmuch as it predicts the emergence of such configuration in the limit of $R \rightarrow 0$, that is in the absence of astrocytes, which is in apparent contradiction with experimental evidence (Schummers et al. 2008; Chen et al. 2012; Perea et al. 2014).

The type of sliding threshold introduced by Philips and co-workers is conceptually different from the one in the original BCM rule (Bienenstock et al. 1982). In this latter, the sliding threshold is a local quantity that depends on the history of the activation of individual postsynaptic neurons. Conversely, by exploiting the concept of “synaptic islands” – namely sets of synapses stimulating and being regulated by the same astrocyte (Halassa et al. 2007) – Philips and colleagues de facto consider a “global” threshold that modulates weight of many synapses in parallel, based on the integral of their activation by their associated astrocyte. In this way, it is as if each astrocyte in Philips et al.'s model supervised the signal inducing plastic changes (i.e., the “teaching signal”) throughout the whole synaptic territory defined by its anatomical radius.

The emerging view of Ca^{2+} compartmentation in astrocytes (Bazargani and Attwell 2016) suggests that, if Ca^{2+} is the mediator of gliotransmission (Sahlender et al. 2014), then its “globality” could be non-trivially defined, as it would likely depend, from time to time, on dynamics of Ca^{2+} microdomains, rather than be

solely defined by the astrocyte radius (Volterra et al. 2014). On the other hand, insofar as the criteria for globality are met, we shall note that the underpinning Ca^{2+} signal could be generated either by postsynaptically released endocannabinoids (Navarrete et al. 2014) or by different presynaptic pathways that are related to presynaptic neuronal firing. These presynaptic pathways could include the spillover of synaptically released neurotransmitters from the synaptic cleft (Araque et al. 2014), as well as other Ca^{2+} pathways linked with extracellular ion homeostasis (Fig. 1). Remarkably, if we consider this second option – namely that the global Ca^{2+} -dependent, gliotransmitter-mediated teaching signal carries information about the activity of presynaptic neurons – it is possible to envisage a biologically plausible learning rule to learn precise spike patterns and reproduce them precisely and robustly over trials. This argument was elegantly demonstrated by Brea et al. (2013) in recurrent networks where neurons were arbitrarily separated between visible versus hidden ones. In those networks, teaching to and accurate recall from visible neurons of an arbitrary spiking sequence is possible devising a learning rule that minimizes the Kullback-Leibler divergence of the spiking distribution produced by the network from the target distribution (i.e., the sequence to be learned). Such learning rule also discriminates between visible and hidden neurons and specifically modulates those synapses onto hidden neurons based on a threshold for LTD vs. LTP that is updated at each time step to account for the global activity of visible neurons. As the same authors argue that astrocytes could mediate this threshold, they also note that for this possibility to be realistic, astrocytes “need to know” which neurons are visible and which are hidden – a scenario that could be brought forth by a combination of the reciprocal arrangement between astrocytes and neuronal and vascular structures, and the chemical signals between them yet to be identified.

Glial Cytokine Signaling

There is emerging evidence that, apart from macroglia, microglia, too, could be involved in the genesis and function of neural circuits in the healthy brain (Kettenmann et al. 2013). This

possibility is further supported by the growing recognition that molecules like proinflammatory cytokines such as $\text{TNF}\alpha$, which are generally associated with the microglial immunocompetent response, but could also be released from astrocytes (Bezzi et al. 2001), may be found in healthy, non-inflamed brain tissue, possibly with a signaling role other than proinflammatory (Wu et al. 2015). Significantly, microglial could control extracellular $\text{TNF}\alpha$ in a bimodal fashion, first increasing it up to a peak concentration, and then recovering its constitutive extracellular concentration (Chao et al. 1995). Because at constitutive concentrations of <300 pM, $\text{TNF}\alpha$ seems necessary for glutamatergic gliotransmission, but above those concentrations, it could promote neurotoxicity (Santello and Volterra 2012), modeling of “Cytokine Networks, Microglia and Inflammation” may be used to identify critical macro- and microglial pathways underpinning this dual signaling role by $\text{TNF}\alpha$. In this context, variance-based global sensitivity analysis of a microglial cytokine signaling network identifies two further cytokines – IL-10 and $\text{TGF}\beta$ – as possible key regulators of microglial $\text{TNF}\alpha$. Both those molecules are promoted by $\text{TNF}\alpha$ while exerting negative feedback on it. However, because the kinetics of IL-10-mediated feedback is faster than that by $\text{TGF}\beta$, they can end up exerting opposing effects on extracellular $\text{TNF}\alpha$, depending on temporal differences in their expression: reduction of $\text{TNF}\alpha$ peak concentration by IL-10 may indeed be counteracted by the ensuing reduction of $\text{TGF}\beta$ production with the potential to turn the traditionally anti-inflammatory action of these cytokines, proinflammatory instead (Anderson et al. 2015).

The study of $\text{TNF}\alpha$ signaling, possibly of (micro)glial origin, is also linked with homeostatic mechanisms of synaptic plasticity (Steinmetz and Turrigiano 2010). A case study is the mechanism of ocular dominance plasticity (ODP) whereby monocular deprivation (MD), during a critical period of development, causes a rearrangement of neuronal firing properties in the binocular visual cortex. In this fashion, cells that are initially biased to respond to inputs from the closed eye end up responding more strongly to inputs from the open eye (Wiesel 1982). As

revealed by experiments in the visual cortex of juvenile mice, MD-triggered ODP results from two separable plastic processes: (i) a rapid, Hebbian-like LTD, that is responsible for weakening the closed eye's response within the first 3 days of MD and (ii) a slow homeostatic response where TNF α – possibly of glial origin – scales up excitatory synapses and strengthens the open eye's response approximately by the third day of MD (Kaneko et al. 2008). Because of the large separation between time scales of Hebbian versus homeostatic plasticity, conventional models of synaptic plasticity where Hebbian and homeostatic plasticity are assumed to compete to set synaptic strength cannot account for MD-induced ODP. In those models, in fact, a small perturbation of synaptic strength away from equilibrium is promptly amplified by the fast positive feedback of Hebbian plasticity, and this amplification can hardly be prevented by the slow homeostatic feedback, making the network prone to instability (Toyoizumi et al. 2014; Zenke et al. 2017). To avoid this scenario, an adequate description of MD-induced ODP should leverage instead on the consideration that observed Hebbian LTD and glial homeostatic scaling are independent of each other during MD (Kaneko et al. 2008) so that they both must separately reach their own stable state for the network to be stable. This could, in principle, be accounted for by the fact that plastic changes induced both by Hebbian learning and by homeostatic scaling can saturate to minimal and maximal values, making these two plasticity mechanisms inherently stable (Beattie et al. 2002; O'Connor et al. 2005). However, in practice, at least two further conditions must be met to be able to reproduce ODP robustly (Toyoizumi et al. 2014). First, homeostatic plasticity must also scale minimum and maximum values of synaptic strength attained by mere Hebbian learning. Second, homeostatic scaling must depend on instantaneous neuronal activity, like postsynaptic depolarization, since this latter correlates with extracellular glutamate levels, which, in turn, regulate the glial release of TNF α (Bezzi et al. 2001; Stellwagen and Malenka 2006). Based on these arguments then, it is possible to devise a working model of

MD-induced plasticity where synaptic strength w can be recast as the product of two factors: a synapse-nonspecific factor H , applicable to the whole postsynaptic cell and controlled by slow glial TNF α -mediated homeostatic scaling, and a synapse-specific factor ρ regulated by fast Hebbian plasticity, i.e., $w = H \cdot \rho$ (Toyoizumi et al. 2014). This description of synaptic strength then accounts for the intriguing possibility that slow glial TNF α signaling in the visual cortex could intrinsically balance with fast Hebbian plasticity by instantaneously rescaling the range of synaptic strength values attained by Hebbian learning. The multiplicative scaling envisaged by the expression for w is critical for glial homeostasis to maintain the relative strength between different synapses. Moreover, because it also affects minimal and maximal synaptic weights, it can thereby bring the network's activity level toward equilibrium without disturbing the intrinsic stability of the Hebbian dynamics and without being overwritten by this latter. In parallel, the presumed instantaneous dependence of H on (post)synaptic activity guarantees network stability making glial homeostasis able to readily follow perturbations of the network's activity caused by fast Hebbian learning (Toyoizumi et al. 2014).

Temporal and Spatial Scales of Neuron-Glial Interactions

Morphology and Structural Plasticity

The large heterogeneity of glial cells, even within individual types such as oligodendrocytes, microglia, and astrocytes, makes the notion of average cell anatomy of little significance. The number of axons myelinated by single oligodendrocytes, for example, considerably changes with axon caliber, and so does the degree of myelination in terms of internodal lengths, ultimately dictating different conduction speeds. Oligodendrocytes are generally classified into four types, depending on the caliber of the axons they myelinate, with the possibility for intermediate types to exist too. Accordingly, types I/II are found in association with small (<4 μm) axons, whereas types III/IV myelinate

larger axons. The morphological values provided in Table 1 are from Butt (2013).

More complicated is the description of microglia since, in the healthy brain, these cells display a ramified morphology whose processes continuously extend and retract at rates of 0.4–3.8 $\mu\text{m}/\text{min}$ (Nimmerjahn et al. 2005). The classical study by Lawson et al. (1990) arguably still provides the most comprehensive characterization of microglia anatomy and distribution in the brain up-to-date. Accordingly, microglia were shown to be present in large numbers in all major divisions of the brain but not to be uniformly distributed. There is, in fact, a more than five-fold variation in the density of microglial processes between different regions, with higher density in the hippocampus, average one in the cortex and hypothalamus, and lower one in the cerebellum. Overall, microglia surface density ranges between ~ 50 and 140 cells/ mm^2 , with individual cells displaying a large variability in surface area, from <200 μm^2 in the cortex to >500 μm^2 in the hippocampal formation, which likely associates with variegated morphological complexity, as reflected by a perimeter-to-convex perimeter ratio of 5 for cortical microglia but >8 for microglia in the hippocampus. Volumetric data on microglia is not yet available.

Protoplasmic astrocytes represent the main astrocyte type in the gray matter and appear to be among the most structurally intricate cells of the brain (Reichenbach and Wolburg 2013). They display a highly branched morphology with some degree of polarization that is probably region-specific (Chao et al. 2002). At least one of the cell branches (or “processes”) is bearing one or several perivascular endfeet such that the surfaces of the blood vessels in the CNS are virtually completely ensheathed by astrocytic endfoot plates (Mathiisen et al. 2010). Astrocyte volume in rodents has been reported to range from $14,700$ – $22,906$ μm^3 in the cortex to $65,900$ – $85,300$ μm^3 in the hippocampus (Bushong et al. 2002; Ogata and Kosaka 2002; Chvátal et al. 2007; Halassa et al. 2007). These figures, however, are not indicative of the morphological complexity of these cells, as mirrored instead by a large surface-area-to-volume ratio in the range of 18.9 – 33.0 μm^{-1} (Hama et al. 2004).

Single anatomical domains of cortical astrocytes were reported to include from 4 to 8 neuronal somata (Halassa et al. 2007). A direct measure of the number of synapses within an astrocytic domain instead is not available but can be estimated from synaptic densities. With this regard considering an average of 0.89 synapses/ μm^3 in the cortex (Kasthuri et al. 2015) and 2.13 synapses/ μm^3 in the hippocampus (Kirov et al. 1999), we get figures for the number of synapses within the above astrocytic volumes that equal to $\sim 13,000$ – $20,400$ synapses/astrocyte in the cortex and $\sim 140,000$ – $182,000$ synapses/astrocyte in the hippocampus.

It is not clear to what extent the number of synapses ensheathed by astrocytes could change during activity by structural plasticity of perisynaptic astrocytic processes (Haber et al. 2006), and cell swelling (Florence et al. 2012), but, likely, the functional interactions between astrocytic and synaptic elements do so. Typical rate values for changes of cell morphology and ECS shrinkage ensuing from astrocytic swelling can then be estimated by experimental observations that directly link these changes with (putative) functionally relevant levels of neuronal activity. With this regard, perisynaptic astrocytic processes undergo multiple retractions and protrusions of >5 μm length in correlation with neuronal activation (Haber et al. 2006), and LTP induction correlates with an average remodelling rate of <40 nm/s in hippocampal astrocytic processes (Perez-Alvarez et al. 2014). Putative physiological HCO_3^- increases in the ECS trigger astrocytic swelling, which can be quantified in terms of percentage variation of the cell’s surface area to baseline HCO_3^- concentrations. This swelling can be well described by a monoexponential curve of the type $\Delta_{\text{max}}(1 - \exp(-rt))$ with $r = 0.08$ s, $\Delta_{\text{max}} \approx 20\%$, resulting in an initial linear rate of surface area increase of ~ 1.5 $\Delta\%/s$ ($\Delta\%/s$: percentage variation in the unit time) (Florence et al. 2012). Alternatively, ECS shrinkage, possibly related to astrocyte swelling, appears to increase linearly with duration of stimulation by rates in between ~ 0.3 and 0.7 $\Delta\%/s$, and to recover original volumes upon cessation of stimulation with decay times >10 s (Larsen et al. 2014).

Neuron-Glial Interactions, Table 1 Some relevant spatial and temporal scales of glial signaling in the murine brain

Description	Range	Units
<i>Morphological features</i>		
Oligodendrocytes (type I/II)		
Associated fiber diameter	<4	μm
Number of myelinated axons per cell	10–50	–
Internodal length	~10–350	μm
Associated axonal conduction speed	<20	μm/s
Oligodendrocytes (type III/IV)		
Associated fiber diameter	>4	μm
Number of myelinated axons per cell	1–10	–
Internodal length	~400–1000	μm
Associated axonal conduction speed	80–120	μm/s
Microglia		
Surface density	50–140	cells/mm ²
Surface area	>200–500	μm ²
Perimeter-to-convex perimeter ratio	>5–8	–
Astrocytes (protoplasmic type)		
Cell volume	14,700–85,300	μm ³
Surface area-to-volume ratio	18.9–33	μm ^{–1}
Neurons per cell	4–8	–
Synapses per cell	13,000–182,000	–
<i>Structural plasticity</i>		
Process motility		
Astrocytes	<40	nm/s
Microglia	0.4–3.6	μm/min
Astrocytic swelling		
HCO ₃ [–] -mediated percentage cell surface area increase	<1.5	Δ%/s
Activity-dependent associated ECS shrinkage	<0.3–0.7	Δ%/s
ECS volume recovery time	>10	s
<i>Non-astrocytic Ca²⁺ signaling</i>		
Oligodendrocytes (soma)		
Rise time	5.2–7.7	s
Decay time	5.5–7.8	s
FWHM	11.6–16.8	s
Microglia (soma)		
Rise time	0.5–1.1	s
Decay time	4.9–5.1	s
FWHM	2.6–5.2	s
<i>Astrocytic Ca²⁺ signaling</i>		
Soma		
Frequency	5.8–9.2	mHz
Rise time	2–20	s
Decay time	3–25	s
FWHM	5–160	s
Processes		
Frequency	6–8	mHz
Rise time	<0.2–5	s
Decay time	6–10	s
FWHM	0.35–3	s

(continued)

Neuron-Glial Interactions, Table 1 (continued)

Description	Range	Units
Endfeet		
Frequency	29–40	mHz
Rise time	3–18	s
Decay time	2–30	s
FWHM	0.75–12	s
Onset delay (from stimulation)	<0.3–3	s
Microdomain volume		
Soma	~890–10,000	μm^3
Processes	~37–85	μm^3
Propagation		
Intracellular speed	~8–24	$\mu\text{m/s}$
Intercellular speed	~8–80	$\mu\text{m/s}$
<i>GGC and ANLS</i>		
Glutamate uptake		
Rise time	0.9–6	ms
Decay time	4.6–5.4	ms
GABA uptake rate		
Rise time	410–544	ms
Decay time	0.9–4.3	s
Glutamine synthesis	0.13–0.21	$\mu\text{mol/min}$
Lactate metabolism (rise/decay time)	4.1–5.2	s
<i>Glilotransmission</i>		
Presynaptic pathway (glutamate, release-increasing)		
Rise time	>0.05–28.3	s
Decay time	5.9–95.7	s
Presynaptic pathway (purines, release-decreasing)		
Rise time	1.6–8.2	s
Decay time	8.2–12	s
Postsynaptic pathway		
LTP rate (D-serine)	0.3–4.0	$\Delta\%/min$
TNF α -mediated AMPA receptor variation	± 5 –12	$\Delta\%/min$
TNF α -mediated GABA $_A$ receptor variation	–0.3–0.7	$\Delta\%/min$
<i>Ion homeostasis</i>		
K $^+$ buffering		
Rise time	0.8–5.1	s
Decay time	3.9–18.6	s
Propagation	>30	$\mu\text{m/s}$
Na $^+$ spatial buffering	>2–80	$\mu\text{m/s}$
<i>Vascular coupling</i>		
Vasodilation		
Max % variation upon astrocytic Ca $^{2+}$ stimulation	5–8	$\Delta\%$
Percentage vessel diameter change rate	>0.05–0.37	$\Delta\%/min$
Vasoconstriction		
Max % variation upon astrocytic Ca $^{2+}$ stimulation	9–27.5	$\Delta\%$
Percentage vessel diameter change rate	1.6–1.7	$\Delta\%/s$
Onset delay from astrocyte activation	<1–3	s

Calcium Signaling

Study of Ca^{2+} signaling in microglia and oligodendrocytes is still in its infancy and the only estimates of rise (τ_r), decay times (τ_d), and full width at half maximum (FWHM) of this signaling pathway may be derived from purinergically evoked Ca^{2+} elevations in microglia in vivo (Brawek et al. 2017; Brawek and Garaschuk 2017) and oligodendrocyte in situ (James and Butt 2001). Time constant are estimated by fitting experimental Ca^{2+} traces ($c(t)$) by a difference of two exponential, i.e., $c(t) = C (\exp(-t/\tau_d) - \exp(-t/\tau_r))$ where C is a normalization factor equal to $C = (T^{\tau_d} - T^{\tau_r})^{-1}$ with $T = \tau_r/\tau_d$ and $\tau_x = \tau_r\tau_d/(\tau_d - \tau_r)$. Accordingly, for oligodendrocytes (based on $n = 20$ Ca^{2+} traces): $\tau_r = 6.5 \pm 1.2$ s, $\tau_d = 6.7 \pm 1.1$ s, and FWHM = 14.2 ± 2.6 s; and for microglia ($n = 6$): $\tau_r = 0.8 \pm 0.3$ s, $\tau_d = 5.0 \pm 0.1$ s, and FWHM = 3.9 ± 1.3 s.

The vast majority of observations on glial Ca^{2+} signaling has been made so far on astrocytes, although several aspects of this signaling remain to be investigated and cannot be challenged by present techniques (Rusakov 2015). For example, it is not yet possible to resolve Ca^{2+} signals in fine perisynaptic astrocytic processes (e.g., lamellae or filopodia), although we are now in the conditions of resolving Ca^{2+} dynamics in the three-dimensional space (Bindocci et al. 2017). Generally speaking, when considering astrocytic Ca^{2+} signals in vivo, different factors beyond development and technical approaches must be taken into account, such as whether these signals were recorded in awake or asleep/anesthetized animals, what brain area they occurred in, if they are spontaneous or evoked by stimulation, and in this latter case, what stimulus protocol was adopted (Rusakov 2015). In what follows, we only consider estimates for protoplasmic astrocytes, which constitute the main astrocyte type of the rodent's gray matter. The reader should keep in mind that Ca^{2+} dynamics in other astrocyte types as well as in Müller cells and Bergmann glia could be different (Matyash and Kettenmann 2010).

In astrocytes, spontaneous somatic/whole cell Ca^{2+} signals are rare ($\nu \approx 5.8\text{--}9.2$ mHz) and characterized by a rise time in the range of $\tau_r \approx 2\text{--}20$ s,

a decay time $\tau_d \approx 3\text{--}25$ s, and a full width at half maximum FWHM $\approx 5\text{--}160$ s (Hirase et al. 2004; Nimmerjahn et al. 2004; Wang et al. 2006; Bindocci et al. 2017). Recent estimates of these quantities in microdomains of astrocytic processes and endfeet provide: $\nu \approx 6\text{--}8$ mHz, $\tau_r < 0.7\text{--}5$ s, $\tau_d < 6\text{--}10$ s, FWHM $\approx 0.35\text{--}3$ s in processes, and $\nu \approx 29\text{--}40$ mHz, $\tau_r < 3\text{--}18$ s, $\tau_d < 2\text{--}30$ s, FWHM $\approx 0.75\text{--}12$ s at endfeet (Bindocci et al. 2017). The onset delay of these events can be remarkably short and follow neuronal stimulation within $<0.3\text{--}3$ s (Winship et al. 2007; Bindocci et al. 2017; Stobart et al. 2018). Significantly, there appears to exist a clear distinction in distribution of values of ν , τ_r , and τ_d with respect to Ca^{2+} events whose FWHM is below versus above ~ 1.5 s (Bindocci et al. 2017). Furthermore, size of Ca^{2+} microdomains in processes appears slightly larger during stimulation with respect to resting state, i.e., $60.7 \pm 24.3 \mu\text{m}^3$ versus $40.50 \pm 3.11 \mu\text{m}^3$, whereas a large dynamical richness of Ca^{2+} events is reported at the somatic level, with average signaling volumes of the order of $4470 \pm 1051 \mu\text{m}^3$, with largest events being in the order of $6375 \pm 1106 \mu\text{m}^3$ (estimated range of $\sim 890\text{--}10,000 \mu\text{m}^3$) (Bindocci et al. 2017). Intracellular Ca^{2+} propagation may be estimated in the range of $\sim 16 \pm 8 \mu\text{m/s}$ (Di Castro et al. 2011, Supplementary Fig. 5), whereas speed of intercellular Ca^{2+} waves, measured mostly in brain slices so far, is in the range of $\sim 8\text{--}20 \mu\text{m/s}$ (Scemes and Giaume 2006; Oberheim et al. 2009), although a recent study in vivo reported on large Ca^{2+} waves that could recruit >80 astrocytes, and propagate as fast as $61 \pm 22 \mu\text{m/s}$ (Kuga et al. 2011).

Glutamate-Glutamine Cycle and Astrocyte-to-Neuron Lactate Shuttle

Both GGC and ANLS rely on glutamate (and GABA) uptake by astrocytic transporters. The transporter currents for these two neurotransmitters recorded in hippocampal astrocytes display a marked time scale separation. In the adult mice, the 20–80% time rise of astrocytic glutamate uptake was estimated in the range of 0.92–1.65 ms (Diamond 2005) although some

investigators suggest that a longer 10–90% rise time, up to 5.98 ± 0.38 ms, could also be reached (Kinney and Spain 2002). Decay times are instead reported in the range of 4.64–5.43 ms. GABA uptake is substantially slower with 10–90% rise and decay time constants comprised between >410.5–543.83 ms and >0.93–4.34 s, respectively (Kinney and Spain 2002). A further limiting factor of GGC and ANLS is substrate availability, for which little is known in vivo so far. Nuclear magnetic resonance data in anesthetized rats suggest a rate of glutamine synthesis by astrocytes between ~ 0.13 and $0.21 \mu\text{mol}/\text{min} \cdot \text{g}$, which is nearly half of the estimated consumption rate of glutamate by Krebs cycle, thus hinting glutamine synthesis as a major metabolic pathway in the rat cortex (Sibson et al. 1997; Rothman et al. 2003). For lactate production by individual astrocytes, astrocytic intracellular NADPH signaling in response to synaptically activated metabotropic glutamate receptors (mGluRs) can be adopted as the readout of different scenarios of neuronal activity and brain states in conditions of simulated hyperemia (high pO_2) or vasoconstriction (low pO_2) (Gordon et al. 2008). This is because the enzyme that is responsible of lactate synthesis – i.e., lactate hydrogenase – is NADPH-dependent (Fig. 1, *purple pathway*) so that increases and decreases of NADPH following mGluR-mediated astrocytic activation can directly be linked to intracellular lactate metabolism by astrocytes, resulting in estimates for rise and decay time constants for this latter in between 4.1 and 5.2 s, with lower values associated with high pO_2 and vasoconstriction (Gordon et al. 2008).

Gliotransmission

Estimates of time scales of modulation by gliotransmitters should be based on experimental data (mostly in situ) that provide information on the time evolution of the effect of gliotransmission on synaptic transmission. Table 1 includes such estimates for short- and long-term effects of release-increasing glutamatergic gliotransmission, and short-term, release-decreasing purinergic gliotransmission (Perea and Araque 2007; Covelo and Araque 2018). A biexponential function (section “Calcium Signaling”) can be used to fit

time series data of synaptic release probability ($p(t)$) following astrocytic Ca^{2+} activation (set at $t = 0$), thereby obtaining: for glutamatergic gliotransmission $\tau_r > 0.05$ – 0.2 s, $\tau_d = 5.9$ – 6.7 s ($n = 2$, short-term); $\tau_r = 6.2$ – 28.3 s, $\tau_d = 18.7$ – 95.7 s ($n = 3$, long-term); for purinergic gliotransmission ($n = 2$): $\tau_r = 1.6$ – 8.2 s, $\tau_d = 8.2$ – 12.0 s. It is also possible to estimate the rate of D-serine-dependent synaptic potentiation in terms of percentage variation of synaptic strength in the unit time, under the assumption of a linear increase of synaptic strength in the presence of activity-dependent D-serine release from astrocytes. The range of values for this postsynaptic pathway of gliotransmission provided in Table 1 was estimated from Yang et al. (2003) and Takata et al. (2011).

Concerning regulation of AMPA and GABA_A receptors by glial TNF α (Stellwagen and Malenka 2006), the average rate of change for expression of postsynaptic AMPA and GABA_A receptors by glial TNF α (Stellwagen and Malenka 2006) may be derived from the ratio between the total percentage change or receptor expression with respect to control ($\Delta\%$) over the duration of TNF α stimulus (T_α). In this fashion, for hippocampal receptors: $157\% \pm 15\%$ increase of AMPA receptors, and $12\% \pm 4\%$ decrease of GABA_A receptors were reported for TNF α applications of $T_\alpha = 15$ – 25 min (Stellwagen et al. 2005), whereas a decrease of 25–30% of GABA_A receptors was measured for $T_\alpha = 45$ min (Pribiag and Stellwagen 2013). These data translate into rate values of ~ 5 – $12 \Delta\%/\text{min}$ and ~ -0.3 – $0.7 \Delta\%/\text{min}$, respectively, for AMPA and GABA_A changes. One should, however, keep in mind that the effect of TNF α is region and/or cell-specific, insofar as the AMPA-to-NMDA ratio was shown to increase from 1.75 to 3 in hippocampal pyramidal cells in the presence of TNF α ($T_\alpha = 1$ – 2 h), but to decrease from 3.7 to 2.5 at medium spiny neurons in the striatum (Lewitus et al. 2014).

Ion Homeostasis

Extracellular ion homeostasis depends on the brain region and evolves with ongoing neuronal activity. At the rat’s optic nerve, glia K^+ buffering

displays a typical bi-exponential behavior, with a rise time that may slightly increase from ~ 0.83 s to ~ 1.6 s as a 10 Hz stimulus is delivered either for 1 s or 10 s (Ransom et al. 2000). Buffering time by re-equilibration of extracellular K^+ concentration, mostly by inward-rectifying K^+ channels in combination with NKPs, is typically large, being comprised between 3.9 ± 1 s and 18 ± 0.6 s (Ransom et al. 2000; D'Ambrosio et al. 2002; Chever et al. 2010). Significantly, this buffering time may considerably shorten in the presence of glial Ca^{2+} signaling, and thereby modulations of glial NKPs, with both rise and decay time of extracellular K^+ converging to ~ 0.9 – 5.0 s (Wang et al. 2012a, b). There is little information on the spatial extent of glia-mediated K^+ buffering in vivo, although intracellular recordings in glia pairs in the suprasylvian gyrus suggest that it is probably fast, with propagation speeds >30 $\mu\text{m}/\text{second}$ (Amzica et al. 2002). Intriguingly, intracellular Na^+ propagation in hippocampal astrocytes (although demonstrated so far in situ) could be at least twofold faster but decay to 2 – 10 $\mu\text{m}/\text{s}$ for intracellular glial sites >60 μm far from the stimulus locus (Langer et al. 2012).

Regulation of the Blood Flow

Ca^{2+} -dependent regulation of blood flow by astrocytes is dependent on brain state, possibly with vasoconstriction observed in the presence of hyperemia, and vasodilation in association with hypoemia (Gordon et al. 2008). The onset of astrocyte-mediated dilations or constrictions in different brain areas, generally occurs within <1 – 3 s from the start of astrocytic Ca^{2+} signaling (Zonta et al. 2003; Mulligan and MacVicar 2004; Otsu et al. 2015). On the other hand, astrocytes seem to promote vasoconstriction to a larger magnitude then vasodilation, since reported percentage decreases of blood vessel diameters mediated by astrocytes could be $>20\%$, whereas observed increases are generally $<10\%$ (Zonta et al. 2003; Mulligan and MacVicar 2004; Gordon et al. 2008). This is mirrored by linear rates of percentage vessel diameter variation that range between 1.6 and 1.7 $\Delta\%/s$ for vasoconstriction (Mulligan and MacVicar 2004) but only between >0.05 and 0.3 $\Delta\%/s$ for vasodilation (Zonta et al. 2003).

Significantly, these figures depend on the number of astrocytic endfeet simultaneously activated on the same blood vessel, since, for example, a single endfoot could trigger a $9.1 \pm 0.7\%$ vasoconstriction, but multiple endfeet could account for a threefold larger reduction of vessel diameter (Mulligan and MacVicar 2004).

Conclusion

Modeling of neuron-glia interactions is an emerging field of computational neuroscience. The ubiquity of these interactions and the possibility that they may occur within the time and spatial scales that are usually ascribed to neuronal and synaptic function calls for a revision of current neuron-based modeling paradigms to include potentially relevant effects mediated by glial cells. The modeling arguments discussed in this chapter go in such direction, further hinting a fundamental design of neuronal circuits where their structure and function are possibly intertwined with that of glia, thereby challenging the traditional Neuron Paradigm of the brain, in favor of an extended, more realistic neuron-glia one.

Cross-References

- [Biophysical Models of Calcium-Dependent Exocytosis](#)
- [Brain Energy Metabolism](#)
- [Goldman-Hodgkin-Katz Equations](#)
- [Hebbian Learning](#)
- [Intracellular Calcium Signals in Astrocytes, Computational Modeling of](#)
- [Nernst Equation](#)
- [Neural Mass Action](#)
- [Short-Term Plasticity, Biophysical Models](#)

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Neuropathologies and Networks

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Synonyms

[Network disorders](#)

Definition

Brain disorders often coincide with changes in the white and gray matter organization. When we view the gray matter brain regions as nodes of a network, the white matter fiber tracts become the edges. Changes in the nodes or edges of a network can be a sign of brain network disorders. Edge changes might affect spatial features such as the distance between connected nodes or the three-dimensional trajectory of fibers and topological features such as the fiber strength given by the extent of myelination or the thickness of fiber tracts. Such local changes can affect the global modular hierarchical, small-world, or rich-club organization.

Detailed Description

Types of Brain Networks

For brain networks, nodes could be neurons or cortical areas and edges could be axons or fiber tracts. Thus, edges could refer to the *structural connectivity* of a neural network. Alternatively, edges could signify correlations between the activity patterns of nodes forming *functional connectivity*. Finally, a directed edge between two nodes could exist if activity in one node modulates activity in the other node forming *effective connectivity* (Sporns et al. 2004; Kaiser 2011).

Edges could be binary, in that only existing and nonexistent edges are distinguished. In this case, changes could only consist of the formation or removal of edges. Such changes would affect the number of edges of a node or, in other words, the degree of a node. Alternatively, edges could be weighted. For functional networks, weights could signify the correlation between the time series of activity in two nodes in the range of -1 to 1 . For structural networks, weights could indicate the strength of a connection given by the fiber diameter and volume or by the number of streamlines or the fractional anisotropy (FA) in diffusion imaging.

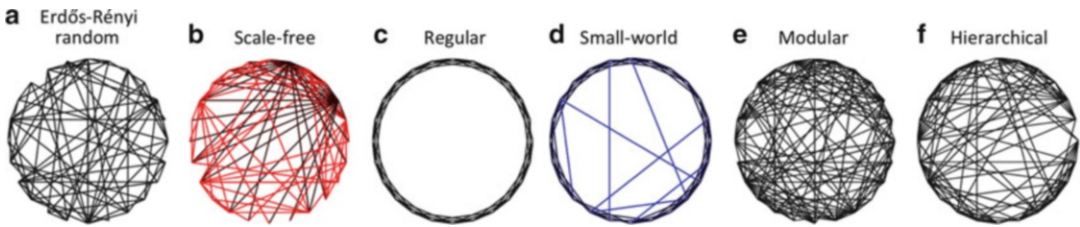
It is important to keep in mind that edge weights could either use metric or ordinal scales leading to different analysis approaches. For example, while the number of streamlines is a metric scale, the connection strength in the CoCoMac database of macaque tract tracing data is on the ordinal scale (1:weak, 2:medium, 3:strong). Unlike a metric scale, a connection in the macaque brain labeled with a strength of 2 is not twice as large as a strength of 1.

Network Topologies

Brain networks can show features of several classes of archetype networks (Fig. 1). For example, an individual brain network might have properties of small-world, modular, and hierarchical networks. In addition, network topology might differ at different levels of organization with random or regular axonal connectivity for small neuronal populations and modular connectivity for cortico-cortical fiber tracts (Kaiser and Varier 2011).

Random Networks

Whereas many networks are generated by a random process, the term random network normally refers to the type of Erdős-Rényi random networks (Erdős and Rényi 1960). Random networks are generated by establishing each potential connection between nodes with a probability p . This probability, for a sufficiently large network, is



Neuropathologies and Networks, Fig. 1 *Types of networks.* (a) Erdős-Rényi random network. (b) Scale-free network with dark edges (*top*) indicating highly connected nodes or hubs. (c) Regular or lattice network with high connectivity between neighbors. (d) Small-world network

with blue edges (*top*) representing shortcuts of the network. (e) Modular network with two modules. (f) Hierarchical network with two modules consisting of two sub-modules each. Thus, there are two hierarchical levels of organization. (Adapted from Kaiser 2011)

then equivalent to the edge density of the network, i.e., the connection density. The process of establishing connections resembles flipping a coin where an edge is established with probability p and not established with probability $q = 1 - p$. Therefore, the distribution of node degrees follows a binomial probability distribution.

Scale-Free Networks

Scale-free networks are characterized by their specific distribution of node degrees. The degree distribution follows a power law where the probability that a node with degree k exists or the frequency of occurrences for real-world networks is given by $P(K) \sim k^{-\gamma}$. For functional connectivity between voxels in human MRI, γ was found to be 2.0 (Eguiluz et al. 2005) whereas γ was 1.3 for functional connectivity of neurons in the hippocampus determined through calcium imaging (Bonifazi et al. 2009).

Small-World Networks

Many networks exhibit properties of small-world networks (Watts and Strogatz 1998). The term small world refers to experiments in social networks by Stanley Milgram where a person could reach any other person through a relatively short chain of acquaintances, the “six degrees of separation” (Milgram 1967). Small-world networks are in the middle between regular networks where neighbors are well connected and no long-range connections exist and random networks where long-range connections exist, but there are no more connections between neighbors of a node than between any two nodes in the network (Watts and Strogatz 1998).

Modular and Hierarchical Networks

Clusters or modules are parts of a network with many connections (high edge density) within such a part and few connections (low edge density) to the remaining nodes of the network. There are many different algorithms to detect clusters of a network (Hilgetag et al. 2000b; Girvan and Newman 2002; Palla et al. 2005). Hierarchical networks follow a modular organization at different levels: modules at a gross resolution might consist of several sub-modules at a more fine-grained resolution. For example, network analysis approaches can identify a network module that represents the macaque visual system, but further analysis of this module can identify the dorsal and ventral stream as sub-modules (Hilgetag et al. 2000a).

Spatial Network Features

Brain networks also have spatial properties in that each node and edge has a three-dimensional location and extension may it be volume for nodes or diameter and trajectory for edges. The actual wiring between nodes can also inform us about functional constraints. For example, long-distance connections are costly in that their establishment and their maintenance uses energy (Laughlin et al. 1998). On the other hand, long-distance connections can form shortcuts that lead to faster information integration and, consequently, accelerated reaction time (Kaiser and Hilgetag 2006).

Between groups, it can be tested whether the distribution of connection lengths is changing (Kaiser et al. 2009). Looking at the length

distribution is especially useful to identify changes in the frequency of long-distance connections (Kaiser 2011). Here, distance could be either the Euclidean distance between the centers of brain regions/neuron locations or the actual length of the trajectory that a fiber tract or axon is following through three-dimensional space. As connections tend to grow in a straight line and fiber tracts are mostly not strongly curved (Hilgetag and Barbas 2006), the Euclidean distance can often be a useful approximation of connection length (Kaiser 2011).

Network Changes for Neuropathologies

Changes for network disorders can involve any single or combination of topological or spatial features discussed above. However, here we will focus on three changes that are well studied: changes in hub organization, changes in modular architecture, and changes in long-distance connectivity. In this fast-moving field, we can only show a small selection of studies and brain diseases.

Starting with neurodevelopmental disorders, schizophrenia is characterized by changes in the connection length distribution (Alexander-Bloch et al. 2013), in small-world and modular organization (Micheloyannis et al. 2006; Bassett et al. 2008; Liu et al. 2008), and in other functional connectivity measures (Woodward et al. 2011).

For epilepsy, the modular organization of functional connectivity (Chavez et al. 2010; Vaessen et al. 2013), the link between structural and functional connectivity (Zhang et al. 2011), and various other neuroimaging biomarkers (Mishra et al. 2011) are affected.

For ageing-related diseases, hub functional connectivity changes were shown for late-life depression (Bohr et al. 2013), and various network changes were shown for dementia and Alzheimer's disease (de Haan et al. 2009; Xie and He 2011; Raj et al. 2012).

These changes in structural and functional connectivity are presumed to have direct implications on the dynamics and function of neural systems. Changes in the modular architecture with stronger

links between modules can facilitate the spreading of activity and presumably increase the likelihood of epileptic seizures (Kaiser et al. 2007; Kaiser and Hilgetag 2010). Highly connected nodes or hubs can be crucial for the integration of information either within modules (provincial hubs) or between modules (connector hubs) (Sporns et al. 2007; Zamora-Lopez et al. 2010).

Summary

Conceptually, any deviation of the network organization in healthy subjects can be argued to be linked to brain pathologies. For example, both cognitive deficits in patients and the intelligence quotient in healthy subjects can be linked to brain network properties (Stam et al. 2007; van den Heuvel et al. 2009). Stam and colleagues proposed that changes in small-world organization, moving the network either closer to a random network or closer to a regular network, are a signpost of diseases (Reijneveld et al. 2007). Kaiser, Hilgetag, Bullmore, and others argued that changes in the (hierarchical) modular organization are linked to diseases (Kaiser et al. 2007; Meunier et al. 2010). Sporns and colleagues argue that links to the hub organization, the rich-club network, are linked to cognitive deficits in patients (van den Heuvel et al. 2012; Collin et al. 2013). Finally, changes in the frequency of long-distance connections might be linked to the integration of information in neural systems (Kaiser and Hilgetag 2006).

Cross-References

- [Connectivity Analysis in Normal and Pathological Brains](#)
- [Human Connectome Project](#)
- [Multiscale Brain Connectivity](#)
- [Wiring Principles, Optimization](#)

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Neuropercolation and Neural Population Models

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Definition

Neuropercolation is a family of probabilistic models based on the mathematical theory of probabilistic cellular automata on lattices and random graphs. Neuropercolation is motivated by the structural and dynamical properties of large-scale neural populations. Neuropercolation extends the concept of phase transitions to interactive neural populations exhibiting frequent sudden transitions in their spatiotemporal dynamics. Neuropercolation develops equations for the probability distributions of macroscopic state variables by generalizing percolation theory as an alternative to models based on differential equations.

Detailed Description

Mathematical Description of Neuropercolation

Neuropercolation uses the tools of random graphs and percolation theory developed over the past 50 years to establish a rigorous model of brain

networks with complex dynamics (Erdos and Renyi 1960; Bollobás 1985; Bollobas and Riordan 2006). Neuropercolation is a natural domain for modeling collective properties of brain networks, especially near critical states, when the behavior of the system changes abruptly with the variation of some parameters. Consider a graph on a d dimensional lattice; in cortical models usually two-dimensional lattices are studied ($d = 2$). In the original bootstrap percolation model, the sites are active or inactive (1 or 0), and their activation evolves in time step-by-step. At first, each site is activated with probability (p), and then they are updated according to a given rule. In the original bootstrap percolation model, the update rule is deterministic: an active site always remains active, and an inactive site becomes active if at least k of its neighbors is active at the given time (Aizeman and Lebowitz 1988).

If the iterations ultimately lead to a configuration when all sites become active, it is said that there is “*percolation*” in the lattice. A main question of bootstrap percolation concerns the presence of percolation as the function of lattice dimension d , initial probability p , and neighborhood parameter k . A fundamental result of percolation theory states (Bollobas and Riordan 2006) that on infinite lattices, there exists a critical probability $p_c = f(d, p, k)$ with the property, that for

$$p > p_c \text{ there is percolation}$$

$$p \leq p_c \text{ there is no percolation}$$

The above critical property is valid for arbitrary initial configurations, with the exception of some special configurations of zero measure in the configuration space. Next, the case of majority percolation is considered, when k is the majority of the nodes in the neighborhood. For example, in the 2-dimensional square lattice with direct neighbors, the majority is $k = 3$, as the neighborhood consists of five nodes (the four neighbors and the node itself). In neuropercolation, the bootstrap property is relaxed, i.e., a site is allowed to turn from active to inactive. Related mathematical concepts are described by cellular automata, such as Conway’s Game of Life, Chua’s cellular neural

networks, Ising spin lattices, and Hopfield nets (Berlekamp et al. 1982; Hopfield 1982; Chua 1998; Newman et al. 2002).

Neuropercolation incorporates the following major generalizations of percolation based on the features of the neuropil, the filamentous neural tissue in the cortex:

1. *Noisy interaction*: The dynamics of the interacting neural populations is inherently nondeterministic due to dendritic noise and other random effects in the nervous tissue and external noise acting on the population. Neuropercolation includes a small random component ($\varepsilon > 0$) in the majority voting rules. In the simplest random update case, a node follows the majority with probability $(1 - \varepsilon)$, and it follows the minority with probability (ε) .
2. *Long axonal effects*: In neural populations, most of the connections are short, but there are relatively few long-range connections mediated by long axons. The effect of long-range axons is similar to small-world phenomena (Watts and Strogatz 1998).
3. *Inhibition*: The cortex contains excitatory and inhibitory connections. Inhibition contributes to the emergence of sustained narrow-band oscillations in the neural tissue. Inhibition is modeled by the interaction of excitatory and inhibitory populations in neuropercolation models.

Neuropercolation for Local, Mean Field, and Mixed Neighborhoods

Neuropercolation can have local, mean field, and mixed neighborhoods (Kozma et al. 2005). Local neighborhoods include the direct neighbors of the node in each dimension; e.g., in the 2-dimensional square lattice, the five neighbors are left/right, up/down, and the central node. In the mean field model, randomly selected grid nodes are used to define the neighborhood of a node, instead of considering specified local neighborhoods. Mixed models start with local neighborhood in a lattice and have a few local connections replaced

(rewired) by randomly selected connections from the whole lattice.

Mathematically rigorous description is possible in specific mean field models, where various conditions have been derived for stable fixed-point solutions and phase transitions between stable fixed points. It can be shown that there is a critical noise level (ε_0) with the following property (Balister et al. 2006), for

$$\varepsilon_0 \leq \varepsilon \text{ has one stable fixed point,}$$

$$\varepsilon_0 > \varepsilon \text{ has two stable and one unstable fixed points}$$

In the 2-dimensional squared lattice, $\varepsilon_0 = 7/30$. Let ρ denote the activation density of the nodes across the lattice. Near the critical point, the activation density (ρ) versus noise (ε) relationship approximates the following power law behavior with very good accuracy:

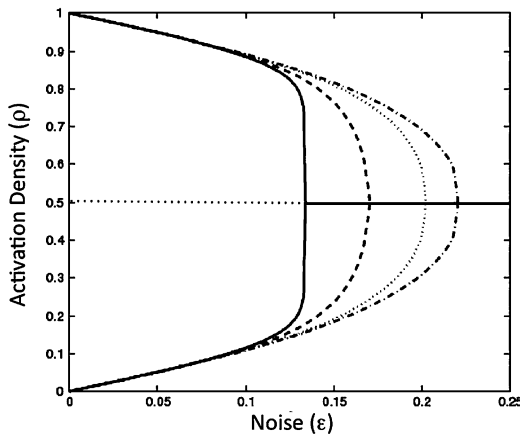
$$|\rho - 0.5| \propto (\varepsilon - \varepsilon_0)^\beta,$$

where $\beta = 0.5$ is the critical exponent. Similar scaling relationships are valid for the susceptibility (χ) and correlation length (ξ), as in Ising models (Binder 1981; Makowiec 1999):

$$|\rho - 0.5| \propto |\varepsilon - \varepsilon_0|^{-\gamma}, |\rho - 0.5| \propto |\varepsilon - \varepsilon_0|^{-\nu}.$$

Here γ and ν are the critical exponents of susceptibility and correlation length, respectively. Local and mixed models pose very difficult mathematical problems. In local models over finite lattices and for small noise ($\varepsilon \approx 0$), it has been proven that the system exhibits transitions between two metastable states in the following sense (Balister et al. 2010). It spends a long time at a high-density configuration and then rapidly transits to a low-density state, where it again resides for a long time. The transitions occur through some peculiar configurations, which can be considered as precursors of the phase transitions. For related concepts of “Dragon King” events, see Sornette and Quillon (2012).

Analytical solutions are not available for models with mixed neighborhoods describing



Neuropercolation and Neural Population Models, Fig. 1 Activation density in neuropercolation models with various levels of rewiring. The rewiring ratio is given as follows: *solid* no rewiring (local), *dash* 6.25%, *dotted* 25%, and *dash-dot* 100% rewiring (mean field). The horizontal dotted line at density = 0.5 level shows the unstable fixed point. (After Kozma et al. 2005)

long axon effects, and such systems are studied using Monte Carlo simulations (Puljic and Kozma, 2005). Figure 1 illustrates the simulation results for various neuropercolation models with local, mixed, and mean-field neighborhoods.

Higher-Order Neuropercolation Models

Multilayer neuropercolation models have been built for implementing hierarchical models of cortical populations (Freeman 1975; Freeman 2001; Kozma and Freeman 2009; Kozma and Puljic 2013). The results indicate that multilayer neuropercolation produces intermittent phase transitions resembling the ones observed in brains. Long axons communicating across mesoscopic cortical distances control the rapid switching from one pattern to another. The functional advantage of a network structure with overlapping hubs, similar to the observed “Rich Club,” has been analyzed based on the pioneer neurons concept (Bollobas et al. 2009; Zamora-López et al. 2011; Bullmore and Sporns 2012).

Cross-References

- [Bifurcations, Neural Population Models and](#)
- [Chaos, Neural Population Models and](#)
- [Network Theory in Neuroscience](#)
- [Neural Mass Action](#)
- [Neural Population Model](#)
- [Phase Transitions, Neural Population Models and](#)

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Neuropharmacological Modeling Alterations in Ionic Homeostasis

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Definition

Modelling ion fluctuations will permit better understanding of the role of perturbed ion homeostasis in the pathophysiology of nervous system diseases and will assist in guiding therapeutic interventions.

Detailed Description

The impact of ion channel gating has been modelled in great detail through colossal efforts invested by the neurocomputation community (Hines et al. 2004). However, understanding ion dynamics in itself bears equal importance as a crucial determinant of transmembrane currents.

Modulation and disruption of ion homeostasis plays a critical role in development, signaling, and in the pathophysiology of several diseases of the nervous system (De Koninck 2006). Since ion homeostasis is determined by the interaction between synaptic inputs, ion channels, and the activity of pumps and transporters, understanding the latter is of the utmost importance. These studies however raise many experimental difficulties because specific ion fluctuations are more difficult to measure than currents. Such difficulties in measurement have also slowed the development of models of ion homeostasis. Recently, improvements in measurement techniques such as the use of ion-sensitive dyes, time-resolved fluorescent measurements, and holographic microscopy to assess osmolarity have improved spatial and temporal resolution (Kaneko et al. 2013; Marquet et al. 2005). These have been paralleled by the development of new modelling techniques such as the use of finite element methods in neuroscience (Lopreore et al. 2008) spurring renewed interest in investigating ion dynamics as well as their functional impact.

Single-Compartment Model

Changes in mechanisms of ion regulation can translate into changes in ion concentrations as measured under resting conditions. For instance, a decrease in activity of the K^+Cl^- cotransporter KCC2 can be modelled by an accumulation of intracellular Cl^- ($[Cl^-]_i$), while the expression of carbonic anhydrase (CA) can be described by an increase in intracellular HCO_3^- (Rivera et al. 2005). However, this basic description fails to capture many consequences of perturbed ion homeostasis. Indeed, during development or in pathological pain, the effects of KCC2 hypofunction on Cl^- dynamics affects the rate and extent of the shift of Cl^- reversal potential (E_{Cl}) in response to overt Cl^- load, before any impact on baseline E_{Cl} can be measured (Cordero-Erasqui et al. 2005).

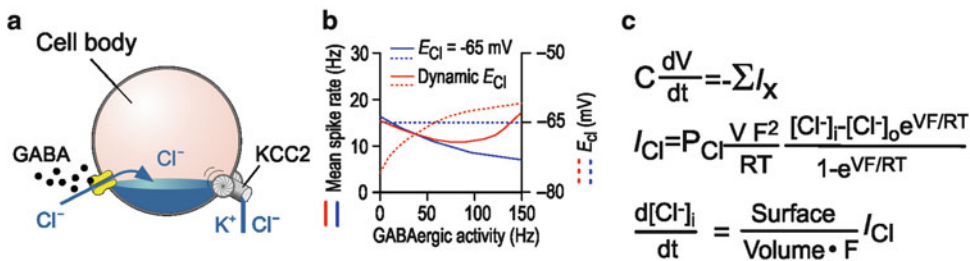
The simplest approach to describe ion dynamics is to reduce the neuron to a single spherical compartment and to extend the system of

differential equations describing electrical activity by including the ion concentrations as additional dynamic state variables. These supplementary variables are then needed to describe each ionic species considered. Single-compartment models can lead to nontrivial predictions such as the failure of drugs enhancing GABA_A-mediated activity to treat neuropathic pain in some conditions (Fig. 1; Asiedu et al. 2009; Doyon et al. 2011). Their simplicity also makes them amenable to use in network modelling, which has led to predicting that KCC2 activity may limit [K⁺]_o accumulation during epileptic seizures, contrary to what might be expected given that KCC2 normally extrudes K⁺ from the cell (Krishnan and Bazhenov 2011). Describing many ionic species rapidly leads to high-dimensional models which renders a full mathematical analysis of their solutions

intractable. Dimensionality reduction offers a promising approach to simplify multidimensional models while preserving the topologies of the solutions (Kepler et al. 1992).

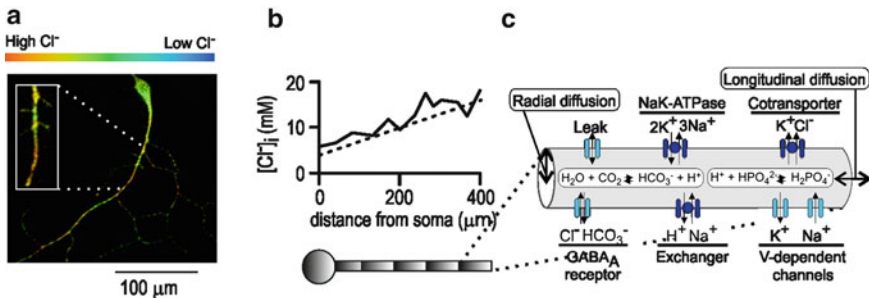
The Multi-compartmental Approach

Single-compartment models fail to capture the impact of geometry beyond the radius of the soma and are limited to treat ionic concentrations as uniformly distributed. However, electrophysiology and Cl⁻-sensitive dye measurements have demonstrated the presence of functionally important intracellular concentration gradients (Doyon et al. 2011; Fig. 2). Such gradients can be permanent, result from differential expression of transporter, or can occur transiently after a focal



Neuropharmacological Modeling Alterations in Ionic Homeostasis, Fig. 1 Single-compartment modelling. (a) Schematic diagram showing how dynamic interactions between synaptic Cl⁻ influx and KCC2 Cl⁻ extrusion regulate [Cl⁻]_i. (b) Simulation of a neuron submitted to joint excitatory and inhibitory input. In a model using a

fixed E_{Cl} value, increasing inhibitory activity brings down ISR while the same leads to paradoxical excitation in a model accounting for dynamical Cl⁻ fluctuations. (c) Equations describing Cl⁻ fluctuations in a single-compartment model



Neuropharmacological Modeling Alterations in Ionic Homeostasis, Fig. 2 Multi-compartmental modelling. (a) Fluorescence lifetime imaging microscopy of Cl⁻-sensitive dye MQAE. Primary culture of hippocampal

cell at 13 days *in vitro*. (b) Values of [Cl⁻]_i as a function of distance from the center of the soma extracted from measurement in A. (c) A schematic diagram explaining the components of multi-compartmental modelling

synaptic activation. In either case, these gradients will have a significant impact on excitability and signaling (Baldi et al. 2010). An approach to simultaneously describe ion fluctuations in the soma, dendrites, and axon is to construct multi-compartmental models in which the neuron is divided in sections of simple geometry. The NEURON software has developed modules allowing the addition of ion dynamics to cable theory-based models offering a tool flexible enough to model chemical reactions playing a role in ion homeostasis such as Ca^{2+} buffering or CA-mediated HCO_3^- production. Multi-compartmental models have been used to study Ca^{2+} signaling and to investigate local Cl^- -mediated ionic plasticity (Raimondo et al. 2012).

Finite Element Modelling

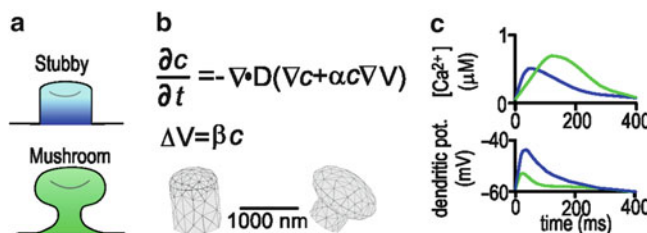
Though very useful, multi-compartmental models fail to capture the impact of ionic fluctuations at submicroscopic scale and cannot accurately describe the complex geometries of neural substructures. The development of modelling tools free from these limitations is motivated by the following observations: (1) Spine geometry is believed to play a pivotal role in the integration of electrical signals (Yuste 2013; Fig. 3). (2) The high current density and small volume of nodes of Ranvier produce large ionic fluctuations – the resulting high density electric field may play a role in synchronizing electrical activity of axons (Yu et al. 2012). (3) Extracellular ionic fluctuations during a synaptic event play an important role in

signaling and may modulate the activity of presynaptic channels. The method of finite elements, which has been applied with great success to industrial problems, has also proven useful to study ion homeostasis in submicroscopic structures yielding a significant gain in precision when compared to cable theory models (Lopreore et al. 2008).

Treating ion concentrations as continuous quantities is valid only when the number of ions in each spatial element is large. When nanometric elements are considered or when micromolar Ca^{2+} concentrations are taken into account, simulations may lead to aberrant predictions such as fractions of ions being present in a nanodomain. Since modelling the displacement of individual ion is computationally impractical, hybrid methods and the use of partial derivative stochastic equations offer promising solutions (Modchang et al. 2010). One caveat of using fine spatial elements is that modelling a whole neuron can become computationally impractical, requiring the use of multi-scale modelling methods. Alternatively, the method of finite elements with adaptive meshes may be used to decrease computation time while preserving the quality of the solutions (Bois et al. 2012). Both approaches give rise to many technical challenges calling for collaboration between neuroscientists and applied mathematicians.

The Modelling of Pumps and Transporters

Ion fluctuations result from the activity of pumps and transporters, but the modelling of these



Neuropharmacological Modeling Alterations in Ionic Homeostasis, Fig. 3 Finite element method. (a) Diagram of stubby and mushroom-shaped dendritic spines. (b) Equations and meshes used in the finite element method. Here D stands for the diffusion coefficient, c for

concentration, $\alpha = 2 F/RT$, and $\beta = 2 F/\epsilon$, with ϵ being the electric permittivity of the medium. (c) Simulation results describing $[\text{Ca}^{2+}]$ accumulation (*top*) in the spine head during an AMPA event as well as dendritic EPSP (*bottom*) for the mushroom and stubby geometries

pumps and transporters also poses great challenges. For one, as opposed to ion flux through channels which may be characterized by a passive flux through an open pore, ion transport through pumps and exchangers is the end result of many steps consisting of ion binding, unbinding, and protein conformational changes. Models have been built to replicate each of these steps, yielding important mechanistic descriptions (Christiansen et al. 1983). An alternative approach is to model ion transport according to thermodynamic principles. To do so, one can compute the free energy associated with ion transport and assume that the level of transport is an increasing and saturating function of this free energy. Such simplification does not significantly compromise the accuracy of the model (Brumback and Staley 2008). Furthermore, in the case of KCC2, the rates of internalization, oligomerization, phosphorylation, and membrane localization can themselves depend on activity, making the level of active cotransporters likely to change with time (Puskarjov et al. 2012). To make accurate predictions on long time scales (minutes or hours), transition rates between cotransporter states should be understood and modelled.

In conclusion, modelling alterations in ion homeostasis is essential to understand pathologies and assess the potential efficacy of treatment strategies. For example, paradoxical pain resulting from chronic morphine treatment may be explained by ionic mechanisms (Ferrini et al. 2013). Understanding these mechanisms motivated the development of drugs acting directly to re-establish ionic homeostasis such as KCC2-positive modulators as potential therapeutics (Gagnon et al. 2013).

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Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation

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Synonyms

[Channelopathy](#); [Drug effect](#); [Mechanisms of excitability](#); [Modifiers](#); [Pharmacogenomics](#)

Definition

Ion channels are both the primary cause of excitability disorders (e.g., epilepsy; myotonia; cardiac arrhythmia) and the principle target of many pharmaceutical compounds. Because ion channels

both respond to and regulate the cellular response to stimuli, they are the dominant molecules governing excitability of neurons and networks. Computational models of drug effects and genetic mutations reveal the mechanisms underlying channel function, allowing prediction to be validated in silico and generating new hypotheses that can be tested via biological experimentation.

Detailed Description

Ion channels containing an intrinsic ion permeable path can be broadly divided into two main functional categories, based on the mechanism by which they undergo the changes in protein conformation that opens or closes the ion permeation pathway (Sharman et al. 2013), allowing ions to flow down their electro-chemical gradient. Voltage-gated ion channels, like cationic potassium, sodium and calcium channels or anionic chloride channels, respond to changes in transmembrane voltage. In contrast, ligand-gated channels, frequently referred to as receptor channels, can be regulated by the extracellular binding of circulating or locally released molecules such as glycine, GABA, or NMDA, or by the binding of an intracellular molecule such as ATP (e.g., P2X), calcium (e.g., K_{Ca} or RyR), or sodium (e.g., K_{Na}).

Pharmacologically, ion channel function can be modulated by the interaction of pharmacophores with the site of activation: the ligand binding pocket or the transmembrane voltage sensing domain. They can also be modulated by direct steric occlusion of the ion permeation pathway. Importantly, the most deleterious of pathogenic mutations are generally located in these same critical regions of the channel protein. The degree of mutation and proximity to these critical sites are generally predictive of the severity of the clinical phenotype (Zuberi et al. 2011; Giudicessi et al. 2012).

Computational homology protein modeling, in combination with biological experimental data, offers insights into the mechanism of drug activity, and serve to identify amino acid residues integral to protein function, drug binding and pathological impact of disease-causing mutations

(Mullins et al. 2010). Many ion channel subfamilies share extensive identity and similarity in functional domains (Doupnik et al. 1995) but have distinct responses to pharmaceuticals (Furutani et al. 2009). *In silico* homology models can reveal those regions and specific residues responsible for pharmaceutical binding (Bertaccini et al. 2013; Verheij et al. 2012) and reactivity within the pore that respond biologically when mutated *in vitro* (Furutani et al. 2009). By understanding the mechanism of drug action and the protein structure responsible for enabling function, it is now possible to optimally design molecules with increased target affinity (Verheij et al. 2012), and these designer compounds can be used to correct pathophysiological states (Zhang et al. 2012). For example, a hERG channel (Kv12.1) activator was designed to potentiate the potassium channel delayed rectifier (I_{Kr}) current in *silico* and *in vitro* (Zhang et al. 2012). When applied to an iPSC-derived cardiomyocyte model of Long QT Syndrome, this molecule was able to correct the prolonged action potential duration resulting from a dysfunctional mutant Kv7.1 channel. This study highlights how molecules can be designed to elicit specific physiological reactions to treat excitable diseases.

Computational models populated with known ion channel biophysical properties measured experimentally can produce normally functioning neurons in *silico*. These models then provide a platform for establishing the mechanism of drug effect, and permit exploration of the contribution of ion channel activity to overall neuronal function. We can thereby begin to understand the basis of pharmacological activity, while elucidating essential ion channel components responsible for neuronal physiology observed *in vitro* in both normal and pathophysiological states. These models are also frequently used to isolate the contribution of an ion channel (sub)population to neuronal or network function (e.g., action potential generation, spike frequency), and to validate experimental results or generate testable hypotheses (Traub et al. 2003; John and Manchanda 2011; Martell et al. 2012; Shevtsova et al. 2011).

Many pharmaceuticals that have been shown to have an effect *in vivo*, have mechanisms of action and ion channel targets that remain

obscure. Development of models can help clarify these mechanisms, particularly in cases where a “dirty drug” has effects on multiple target channels. The development of these models requires an understanding of modulation and inhibition by pharmacological agents obtained from *in vitro* experimentation. Classical examples of such modulation are the complete block of voltage-gated sodium channel by TTX, or the enhanced activation of calcium-activated potassium channels (BK_{Ca}) by increased intracellular Ca^{2+} ion levels. By testing hypothetical targets in computation neuronal models, it is not only possible to identify likely candidate molecules but also to elucidate mechanisms of action (e.g., modulation of gating currents) which can then be confirmed by biological experimentation (Yau et al. 2010; Oh et al. 2012). Alternatively, the biological impact of pathogenic mutations and neuronal dysfunction can be modified in *silico*. These computational models of dysfunctional neurons can then be used to assess the efficacy of compounds (e.g., polyunsaturated fats, cAMP activators) or biological modifiers (e.g., ion channel accessory subunits) to correct nerve cell pathology (Tigerholm et al. 2012; Tigerholm and Fransén 2011).

Ultimately, the utilization of computational models as an extension of biological experimentation, and as a platform for validating or resolving competing hypotheses of ion channel function and modulation, enhances our comprehension of the mechanism of activity of both intrinsic and extrinsic ion channel targeting molecules. By generating models of both the normal and pathophysiological states, it is possible to optimally design molecules to combat or cure disease through reduction or enhancement of specific neuronal function in targeted neuron populations.

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Neurophonic

- [Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of](#)

Neuroprostheses

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Neuroscience Information Framework (NIF)

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Detailed Description

The Neuroscience Information Framework (NIF; <http://neuinfo.org>; Gardner et al. 2008) is currently managed, maintained, and hosted by researchers in the Center for Research in Biological Systems (CRBS) at the University of California, San Diego. The NIF system has grown since 2008 from a modest catalog of 300 resources

developed during the first phase of NIF to the largest source of neuroscience resources on the web. As defined here, resources include data, databases, software/web-based tools, materials, literature, networks, or information that would accelerate the pace of neuroscience research and discovery.

The current NIF system was developed to provide practical approaches for finding, searching, and integrating biomedical resources of relevance to neuroscience, including:

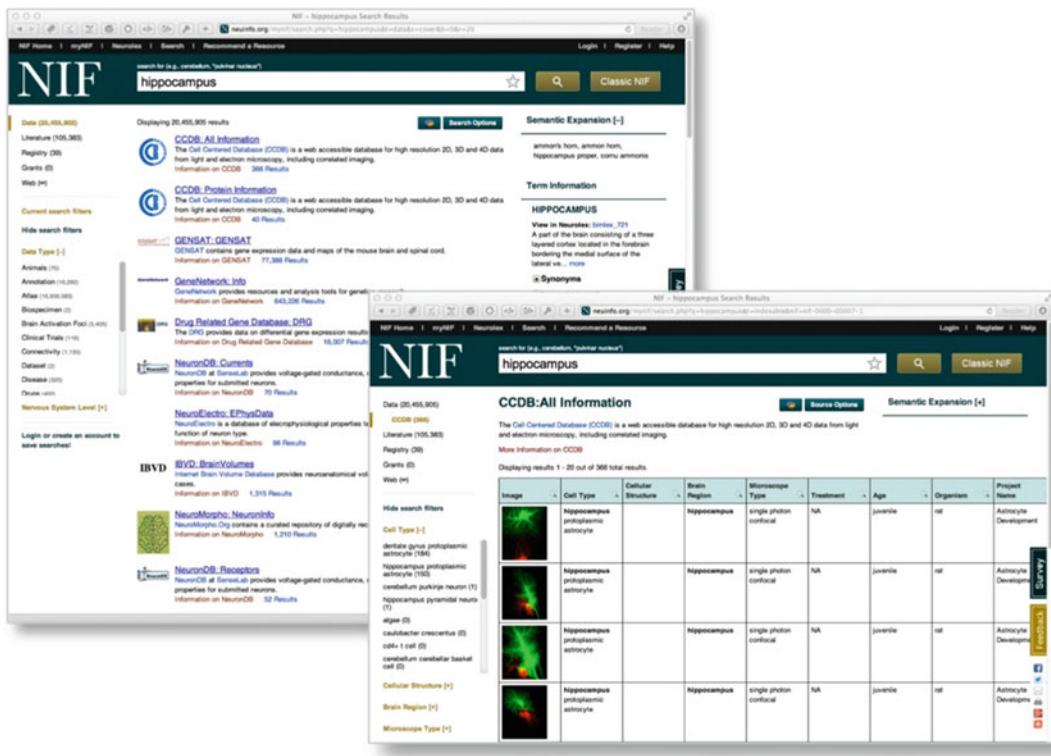
- A biomedical resource catalog for both data and tools (Cachat et al. 2012).
- A public-federated biomedical data repository (Fig. 1)
- An ontology for neuroscience (Imam et al. 2012).
- A unique and flexible technology platform for finding and sharing resources, undergirded by

an advanced semantically enhanced search system

- Text mining tools for resource identification and tracking in the biomedical literature (Bandrowski et al. 2012).
- Tools and services for easy sharing of data and linking of data to articles, websites, etc. (Marenco et al. 2008).

History of NIF

The NIF project started in 2006 under the leadership of Dr. Dan Gardner at Weill Medical College of Cornell University as an initiative of the NIH Blueprint consortium. NIF was tasked with surveying the neuroscience resource landscape and to develop a resource description framework and search



Neuroscience Information Framework (NIF), Fig. 1 NIF discovery portal showing search results from the data federation (left) and from a specific resource (right)

strategy for locating, accessing, and utilizing these resources. Most of these resources were created through significant investment of government dollars but remained largely unknown or underutilized by the research community they were created to serve. The first phase of the NIF, completed in 2008, resulted in the first version of the NIF Registry, a catalog of neuroscience-relevant resources annotated with a controlled vocabulary covering multiple dimensions (e.g., organism, nervous system level, and resource type).

UCSD assumed leadership of the project in 2008, leading a consortium of five universities in the creation of the current NIF system. Based on the initial survey, it was apparent that most resources, particularly databases, were not adequately searched through a simple metadata scheme but required deeper access. In addition, most of these data sources were part of what is known as the “hidden web,” that is, content that is not readily accessible to search engines like Google. It was also apparent that the simple controlled vocabulary developed for resource curation during the first phase was not adequate to support the diversity of resources or neuroscience concepts in a way that promoted search.

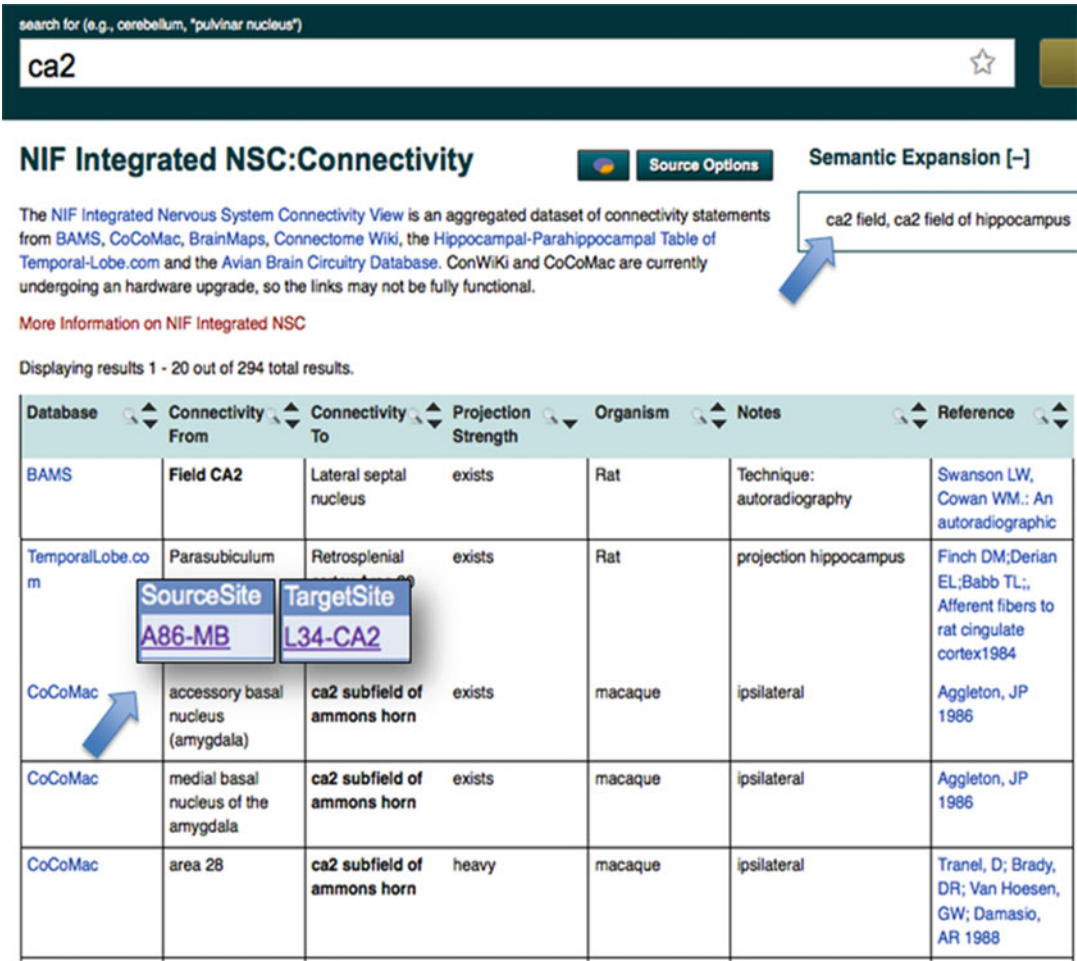
Based on this requirement, the NIF system expanded from a simple catalog, with high-level metadata on resource type and coverage, to a comprehensive system that allowed deeper registration of individual data resources through innovative data federation technologies as well as identification of resources from the primary biomedical literature. During this phase, the NIF registry grew from a registry of 300 resources and 5 federated databases to over 6000 resources and 200 federated databases and data resources, amassing the largest searchable collection of biomedical data on the Internet (Cachat et al. 2012). NIF also developed the NIFSTD ontologies, a set of community ontologies implemented in OWL covering the major domains of neuroscience which were assembled from existing ontologies in use in the broader life science community but enhanced with neuroscience-specific content. The NIFSTD ontologies are used to provide a semantic framework for searching and annotating diverse content.

Mission

The NIF has as its mission to provide added value to existing biomedical resources by increasing their accessibility, visibility, utility, and interoperability, regardless of their current design or capabilities and without the need for extensive redesign of their components. As NIF has documented in its Resource Registry, there are thousands of resources made available through the Internet that are relevant to neuroscience research. However, despite the availability and increasing power of Internet search engines, these types of resources continue to be difficult to find and access. NIF provides a uniform access point for searching across and within these digital resources, with a special emphasis on databases. To accomplish this, NIF deploys an infrastructure that allows resources to be searched and discovered at multiple levels of integration, from superficial discovery based on a limited description of the resource to deep content query through the NIF federation services. The NIF has adopted a federated model whereby resources are developed and maintained independently but through the use of central indices, distributed query capabilities, and an extensive ontology for neuroscience, they can be cross-queried and integrated into a unified system. NIF provides a portal to resource discovery whereby these different web-accessible resources, along with the published literature, may be searched and also provides a set of tools and services that promote interoperability among resources, including the NIF vocabularies and a brokering service linking resources together.

Overview of NIF Infrastructure and Current System

NIF's infrastructure comprises four primary modules: resource management and data ingestion, index management, semantic information management, and data access and analysis. NIF employs a combination of user contribution and automated discovery, including text mining of the literature, to continually discover web-accessible resources that are relevant for neuroscience. Descriptions of these resources are maintained in



Neuroscience Information Framework (NIF), Fig. 2 NIF integrated view for nervous system connectivity: showing search results for the Ca2 field of the hippocampus. Note that the semantic expansion includes terms that users did not specifically ask for, but are synonyms of the user's term (*top arrow*). The result set comes from BAMS (Brain Architecture Management System),

TemporalLobe.com, and the CoCoMac database. All fields have been aligned and projection strength has been mapped to one of seven values. In the case that the original terminologies were not easily interpretable as brain regions, they were translated (*bottom blue arrow* from CoCoMac shows the source data labels for the accessory basal nucleus and the CA2 subfield of Ammon's horn)

the NIF Registry. For those resources that share their data, automated agents, via the DISCO dashboard (Marenco et al. 2008), automatically retrieve the latest data from these selected resources to ensure that information contained within NIF is current. The environment also allows new data resources to be added to the system with an interface for registering core information about the data resource and annotating the data/resource with ontology terms to declare the semantic relationships contained therein.

Semantic Infrastructure

NIF has created a semantic infrastructure for biomedical information, meaning that any data resource should be accessible by its content and the concepts it represents. This means any biomedical researcher should be able to discover a resource regardless of how the original resource and its data were modeled and structured or how a specific term was spelled or described. This mandate was challenging because it was not only

important to have a standardized vocabulary with synonyms, but the entire system from data ingestion to search services needed to be aware of the semantics of the data (Fig. 2).

NIF Integrated Views

Within the resources in the NIF Data Federation, there are collections of data that cover the same theme. In these cases, NIF provides an integrated view across similar resources to make it easier to align and compare different resources of the same type (Fig. 2). Some examples include NIF Connectivity, a view across six different connectivity databases (see figure above); NIF Animal, primarily transgenic animals available for sale (or by material transfer agreement); and NIF Software, contents of several software repositories designed for neuroscience and for the software branch of the NIF Registry.

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Neutral Space

► [Neuronal Parameter Non-uniqueness](#)

NineML

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Synonyms

[9ML](#)

Definition

NineML is a markup language for describing neuronal network models. It is intended to provide a mechanism for scientists to publish and share unambiguous, mathematically explicit model definitions, with the aims of promoting reproducibility and reusability of components. NineML has a two-layered architecture, with an “abstraction” layer that is used to define mathematically the behavior of components, such as neurons, synapses, and connectivity rules and a “user” layer that is used to specify network structure in terms of populations of neurons and the projections between them, on the basis of the components described in the abstraction layer.

Detailed Description

NineML is defined in terms of an object model. The current specification is available at <http://software.incf.org/software/nineml/wiki/nineml-specification>. The canonical serialization of this object model is as an XML document, but

NineML documents can also be created using a domain-specific language (NineML “native” syntax) and using a Python API.

Figure 1 shows a simple abstraction layer example that defines an integrate-and-fire neuron. The NineML abstraction layer dynamics module defines two principal objects, Regimes and Transitions. Each Regime defines a number of ordinary differential equations. The model can be in only one Regime at a time and remains in that Regime until either some condition is met (e.g., one of the state variables passes some threshold) or an external event arrives (e.g., an action potential from another neuron). At this point, a Transition occurs to the same or some other Regime, during which state variables may be changed discontinuously and events emitted. Components can expose state variables or derived variables through Ports, which allow components to be connected together (e.g., synapse models and neuronal membrane models) and to send or receive events. The integrate-and-fire neuron has two Regimes, one describing the usual behavior of the neuron, in which the membrane is depolarized by injected or synaptic currents, the other describing the refractory behavior after a spike, in which the membrane potential is clamped to a fixed

value. Detection of the threshold crossing, reset of the membrane potential, and emission of a spike event is described by one Transition, the end of the refractory period by another.

The NineML project was initiated by the International Neuroinformatics Coordinating Facility (INCF) Program on Multiscale Modeling, originally developed by an INCF taskforce, and is now developed as a community-based project at <https://github.com/INCF/nineml>.

NineML has considerable overlap with ► NeuroML version 2 (<http://www.neuroml.org/>) and the LEMS language (<http://www.psics.org/lems/>), with LEMS corresponding roughly to the NineML abstraction layer and NeuroML to the user layer.

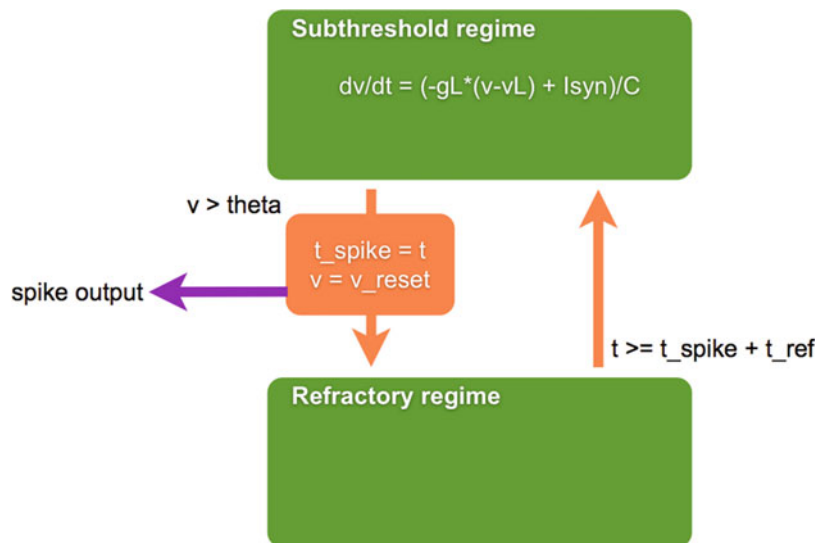
SpineML (<http://bimpa.group.shef.ac.uk/SpineML/>) is a derivative of the NineML language that adds a third layer, for description of simulation experiments. SpineML uses XSLT to provide code-generation for several simulation platforms.

Cross-References

► [NeuroML](#)

N

NineML, Fig. 1 An integrate-and-fire neuron represented using the NineML abstraction layer. Green boxes represent Regimes, orange arrows Transitions



Nitric Oxide Neuromodulation

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Synonyms

Nitric oxide volume signaling

Definition

Neuromodulators are a class of neurotransmitter that diffuse into the region surrounding an emitting neuron and affect potentially large numbers of other neurons by modulating their responses, irrespective of whether or not they are electrically connected to the modulating neuron. Nitric oxide (NO) is a particularly interesting example of a neuromodulator because of its very small size and gaseous state. The type of modulatory signaling NO is involved in is sometimes known as volume signaling and is in sharp contrast to the connectionist point-to-point electrical transmission picture that dominated thinking about the nervous system for many decades, whereby neural signaling could only occur between synaptically connected neurons.

Detailed Description

Background

The discovery that the toxic gas nitric oxide (NO) is synthesized in biological systems and functions as a physiological signaling molecule earned Robert Furchgott, Louis Ignarro, and Ferid Murad the Nobel Prize in 1998. By showing that physiological functions could be regulated by information carried from cell to cell by a gas, their research suggested an entirely new way of

thinking about how cells communicate with one another.

Increasing blood flow was the first physiological function attributed to NO. It was known that the cells of the endothelial lining of blood vessels released a factor which caused the relaxation of circular muscle leading to vessel dilation and increased blood flow. The endothelial factor was unstable and thus elusive. But the combined work of the three Nobel laureates showed conclusively, if unexpectedly, that this factor was NO.

If this were the whole story, there would be of little or no relevance for our understanding of brain function. When, however, Solomon Snyder and colleagues isolated an enzyme from the mammalian brain that synthesized NO and showed that it was present in subpopulations of neurons (Bredt and Snyder 1990), interest in NO's signaling functions switched from endothelial cells to neurons.

Three forms of the NO-synthesizing enzyme, known as NOS, have been identified; it is the neuronal form (nNOS) which attracted most interest among neuroscientists (Bredt and Snyder 1990; Bredt et al. 1990; Mungrue and Bredt 2004). Since NO is both a signaling molecule and a toxic-free radical gas, its generation by nNOS must be strictly controlled. The primary regulator of nNOS activity is the concentration of calcium inside the nNOS-expressing neurons (Bredt and Snyder 1990). Intracellular calcium concentration in resting neurons is very low – below that required for the synthesis of NO. However, as a consequence of electrical activity, calcium enters the neuron via voltage-gated calcium channels, and the concentration rises transiently from micromolar to millimolar levels. At these elevated levels, the synthesis of NO is triggered. Calcium therefore neatly links the synthesis of NO in the brain to the electrical activity of neurons. Because NO is so small (the tenth smallest molecule of the universe) and non-polar, it can diffuse more or less freely away from its source, unimpeded by the lipid bilayer of the cell membrane. Thus, for NO, release is an inevitable consequence of NO synthesis.

Calcium influx in electrically excited neurons both triggers NO release and the release of conventional neurotransmitters from synaptic

vesicles. The two modes of release, diffusive and vesicular, are not mutually exclusive alternatives at the neuronal level. Neurons capable of NO synthesis also store conventional neurotransmitters in synaptic vesicles. NO is therefore best regarded as a co-transmitter, acting in conjunction with classical inhibitory and excitatory transmitters.

Clearly NO signaling violates some of the classical tenets of synaptic transmission, and there has been an understandable reluctance to regard NO as a genuine neurotransmitter. Perhaps the term neuromodulator is more appropriate. Neuromodulators are a class of neurotransmitter that, rather than causing excitation or inhibition directly, modulate the responses of neurons to direct excitatory and inhibitory transmitters. A modulator may, for example, enhance or facilitate the inhibitory effect of an inhibitory neurotransmitter. In this way modulators are synaptic gain-control agents. Whereas direct inhibition and excitation is mediated by transmitter-gated ion channels, modulators bind to receptors that regulate the synthesis of the so-called second messengers, and it is these that can change the sensitivity of a neuron to other neurotransmitters.

Because they act indirectly via a neuron's metabolic machinery, the temporal dynamics of neuromodulator effects are delayed and more long-lasting than the quick and transient effects of the classical transmitters. The spatial dynamics of neuromodulation are also noteworthy with respect to signaling by NO. As noted above, the physical properties of NO allow it to diffuse into the volume surrounding an emitting neuron. Therefore, depending on the size of the affected volume, a NO-emitting neuron may modulate large numbers of other neurons within the affected volume. Importantly then, an nNOS-expressing neuron may communicate with other neurons irrespective of whether or not they are connected by synapses. In this way NO is a particularly interesting example of a neuromodulator because it can act as a non-synaptic volume signal. This clearly is in sharp contrast to the connectionist point-to-point synaptic transmission picture that dominated thinking about the nervous system for many decades.

In the traditional connectionist model of neuron-to-neuron communication, neurons generate brief electrical signals (action potentials), which propagate along wire-like axons terminating at highly localized junctions (synapses) on other neurons, where the release of a neurotransmitter is triggered. The neurotransmitter is confined to the region of the synapse, and here the receiving neuron is equipped with receptors that directly translate the chemical signal into a brief electrical signal, either excitatory or inhibitory (Purves 1997; Brazier 1961). Hence, in standard artificial neural network (ANN) models based on this incomplete picture, chemical signaling can be safely factored out, leaving only the idea of electrical signals flowing between nodes in a network.

However, the discovery of non-synaptic chemical signaling by NO has potentially greatly extended the spatial scale over which neurons can communicate. The most important feature of this derives from the ability of NO to diffuse away from its site of release and to occupy a volume of the nervous system perhaps containing many other neurons and synapses (Edelman and Gally 1992). Crucial to understanding the functional significance to volume signaling by NO (and perhaps other gases) is a measure of the spatial and temporal dynamics of NO diffusion. We need to know how large is the affected volume and how long does it take for NO to occupy it. As these questions have proven to be difficult to answer empirically (Philippides et al. 2003), an important alternative approach has been to develop realistic computational models of diffusion to illuminate the parameters of NO-mediated volume signaling.

The following section looks at how NO diffusion in the nervous can be modeled computationally and how this can be used to illuminate neuromodulatory mechanisms. We will also explore how volume signaling can now be added to the growing list of phenomena in the nervous system that might be a source of inspiration for new and perhaps improved styles of ANNs. This is probably especially true for ANNs intended for use as artificial nervous systems in robots or simulated autonomous agents, an area where biomimetic techniques are often particularly fruitful. Classes of ANN directly inspired by NO

signaling, which can be used in robotic applications or to shed light on biological questions, will be discussed later in this article.

Modeling NO Diffusion in the Nervous System

The features that make NO different to a standard neurotransmitter – its free diffusion through neural structure with no discrete target receptor and thus inactivation – make the basis of a model relatively straightforward. Movement is governed by Fick's second law of diffusion; essentially molecules move from high concentration to low concentration. NO does not have a specific inactivating mechanism and is lost through reaction with oxygen species and metals as well as with heme-containing proteins (Lancaster 1996; Vaughn et al. 1998a). This means that the movement of other molecules and receptors and their interactions need not be modeled and instead a more general loss function can be used, typically as concentration-dependent decay throughout the volume being modeled. These features were the basis of the first wave of models of diffusion (Gally et al. 1990; Edelman and Gally 1992; Montague et al. 1991; Lancaster 1994, 1996, 1997; Wood and Garthwaite 1994) which prompted key insights into the action of this kind of messenger, for instance, noting it as a “four-dimensional volume signal” (Edelman and Gally 1992), and highlighting the potential range of action of a diffusible signal (e.g., Wood and Garthwaite 1994).

To make these general points, it was not important to model in detail the structure of either the volume within which the neuron was diffusing (meaning that space and time were typically handled coarsely) or the source neuron itself which was typically taken to be a point in space. This meant they were unable to capture two very important features of NO signaling.

The first regards the production of NO and follows from the fact that nitric oxide synthase (NOS, responsible for the production of NO) is soluble and thus highly likely to be distributed throughout a neuron's cytoplasm. This means

that the volume containing NOS is the source and the whole surface of the neuron is a potential release site for NO, in marked contrast to conventional transmitter release. These properties suggest that the 3D structure of the NO source will have a profound influence on the dynamics of NO spread. Hence, an accurate structure-based model of neuronal NO diffusion is an indispensable tool in gaining deeper insight into the signaling capacity of the molecule. The second is that depletion of NO might also be spatially heterogeneous. While a general decay rate can be assumed for most tissue, reflecting background oxidization and binding events, certain structures (importantly including blood vessels containing very high concentrations of NO-binding hemes) can have a much higher decay rate and effectively act as NO sinks. The kinetics of these reactions are not understood perfectly (Wood and Garthwaite 1994), but empirical data indicates either first- or second-order decay (Laurent et al. 1996; Lancaster 1996; Vaughn et al. 1998b; Liu et al. 1998; Thomas et al. 2001).

These considerations gave rise to a second set of more detailed NO diffusion models (Philippides et al. 1998, 2000, 2005a; Vaughn et al. 1998a, b; Ott et al. 2007) based on the modified diffusion equation shown in Eq. 1. The terms on the left-hand side describe the general diffusion process and those on the right-hand side model NO production and depletion mechanisms:

$$\begin{aligned}\frac{\partial C(\mathbf{x}, t)}{\partial t} &= D \nabla^2 C(\mathbf{x}, t) \\ &= P(\mathbf{x}, t) - \lambda C(\mathbf{x}, t) \\ &\quad - S(\mathbf{x})(C(\mathbf{x}, t))^n\end{aligned}\quad (1)$$

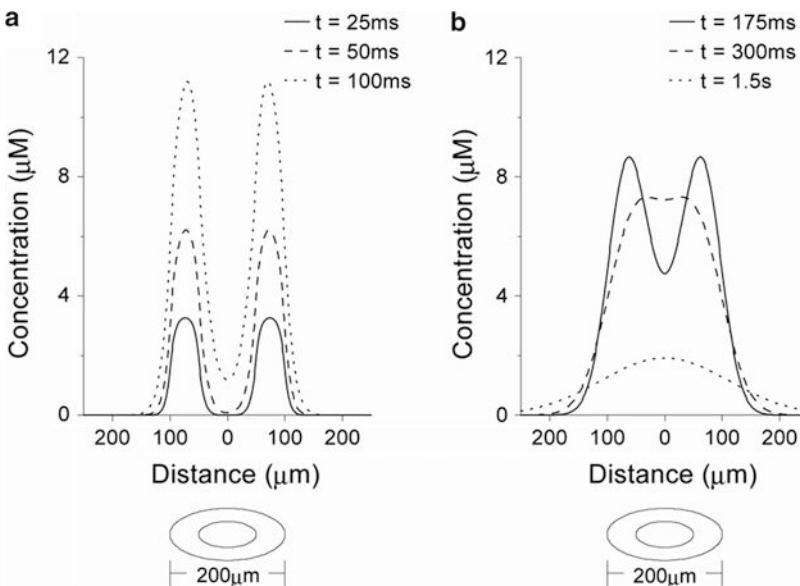
where $\mathbf{x}$ is a point in space; $C(\mathbf{x}, t)$ is the concentration at point $\mathbf{x}$ and time t ; D is the diffusion coefficient, typically $3300 \mu\text{m}^2 \text{s}^{-1}$; and $P(\mathbf{x}, t)$ is the concentration of NO produced per second at point $\mathbf{x}$ and time t . $\lambda C(\mathbf{x}, t)$ models background inactivation of NO at all locations in the modeled volume as first-order decay with an inactivation rate (half-life) of λ . In contrast, $S(\mathbf{x})(C(\mathbf{x}, t))^n$ models spatially localized NO sinks such as blood vessels where the decay rate is greatly elevated within a discrete region. Decay can be

modeled as first order ($n = 1$) or second order ($n = 2$), though the latter is mainly used for very strong blood flow such as when modeling diffusion of NO from endothelial cells surrounding large blood vessels (Vaughn et al. 1998a, b).

Armed with these equations, the time course of NO diffusion from neurons of different shapes and sizes was modeled in the presence of different levels and types of decay. Figures 1 and 2 show the results generated by the first accurate model of NO diffusion from a continuous biologically realistic structure (Philippides et al. 1998, 2000, 2003). The source was a large neuron-like structure modeled as a hollow sphere as NO is synthesized throughout the cytoplasm but not in the nucleus. In this case, there are no sinks and thus $S(\mathbf{x}) = 0$ in Eq. 1 and decay rate λ is set so that the NO half-life is 5 s. $P(\mathbf{x}, t)$ is a constant value for all points inside the hollow spherical source during synthesis (the amount of NO produced per second by a single NO-producing unit multiplied by the density of these units) and 0 elsewhere, and thus

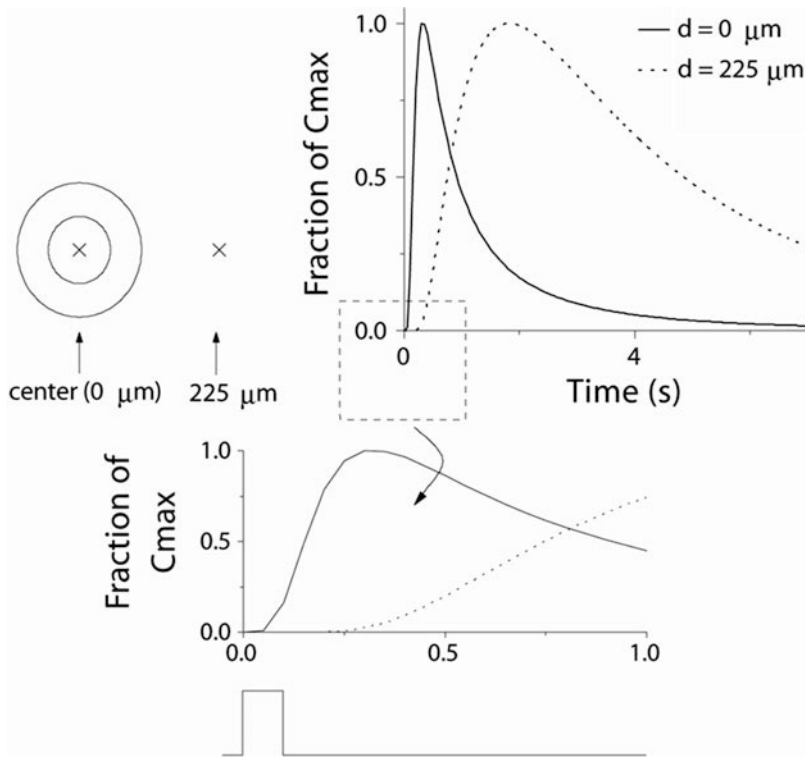
the solution is radially symmetric. (For full details of modeling methods and biological justification for parameter values, see Philippides et al. 2000, 2003, 2005a).

Examination of the time course of the evolution of NO concentration during and after 100 ms of NO synthesis shows two very interesting observations. Firstly, the NO concentration remains elevated within and throughout the cell for significant lengths of time after the end of synthesis: a “reservoir” effect (Fig. 1). Second, when viewed over time, there is a delay before the concentration peaks at points where NO is not synthesized, both within the neuron itself and outside it (Fig. 2). Further, the delay increases, while peak concentration decreases, with distance from the NO source neuron. To determine the volume affected by NO, we would need to know the physiologically effective NO concentration, which is likely to vary depending on a number of factors. However, taking a threshold of 0.1 μM (close to the equilibrium dissociation constant for the NO



Nitric Oxide Neuromodulation, Fig. 1 Concentration of NO plotted against distance from the center of a hollow spherical source neuron of inner radius 50 μm and outer radius 100 μm for a 100 ms burst of synthesis starting at time $t = 0$. The graphics underneath each plot depict the source structure. (a) Concentration of NO at times $t = 25$, 50, and 100 ms, two time points during and one at the end

of synthesis. (b) Concentration of NO after synthesis at times $t = 175$, 300, and 1.5 s. The reservoir effect following the end of synthesis is clearly seen as the centrally accumulated NO is trapped by the higher surrounding concentrations. (Figure used with permission from Philippides et al. 2000)



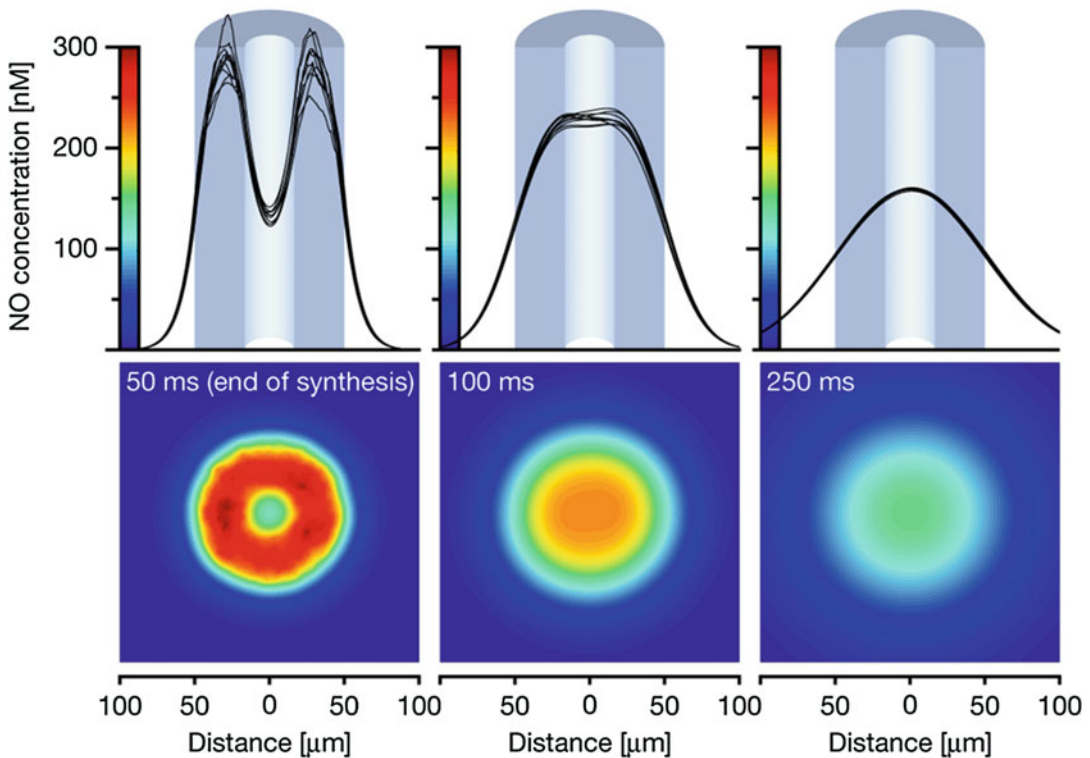
Nitric Oxide Neuromodulation, Fig. 2 Concentration of NO plotted against time after synthesis for a hollow spherical source of inner radius 50 μm and outer radius 100 μm for a 100 ms burst of synthesis. Here the *solid line* depicts the concentration at the center of the cell (0 μm), while the *dotted line* shows the concentration at 225 μm from the *center*. Because the absolute values attained at the two positions differ from one another markedly, the concentration is given as a fraction of the peak concentration attained. These peak values are 7.25 μM (*center*) and

0.25 at 225 μm . The cell and the points at which the concentration is measured are depicted to the *left* of the main figure. Note the high central concentration, which persists for a long time (above 1 μM for about 2 s). Also, there is a significant delay to a rise in concentration at distant points which is more clearly illustrated in the expanded inset figure. The square-wave beneath the inset figure represents NO synthesis. (Figure used with permission from Philippides et al. 2000)

receptor soluble guanylyl cyclase, Stone and Marletta 1996), with 100 ms of NO synthesis within the walls of hollow spherical neurons with radii over 10 μm , a volume approximately three times the source radius would be affected. Although, importantly, the concentration time course would depend on distance from the source. While spatially localized NO sinks such as small blood vessels do affect diffusion, they do not alter these overall properties (Philippides et al. 2000).

In many instances, however, NO is not produced in one source but in multiple distinct sources. For instance, the mushroom bodies (MB) of the locust (*Schistocerca gregaria*) are composed of parallel axons of intrinsic neurons

(Kenyon cells, KCs) arranged in a tubular structure in which peripheral NOS-positive KC axons form NO-producing zones, the tube “walls,” surrounding central cores of NO-receptive KC axons, which do not produce NO. This segregated architecture requires NO to spread at physiological concentrations up to 60 μm from the outer regions of the tube where it is synthesized to the target axons in the inner NO-receptive cores (Fig. 3). Despite NO being produced by small numbers of distinct sets of KCs in response to odors and that single KCs in the tube walls cannot produce enough NO to generate effective signals in the central targets, they act cooperatively and a reservoir of NO builds up in the NOS-negative cores.



Nitric Oxide Neuromodulation, Fig. 3 Sparse activity in the nitric oxide (NO) synthase (NOS)-positive *outer* region of the mushroom body (MB) yields a strong volume signal in the NOS-negative core. The MB is made up of a parallel array of 30,525 Kenyon cell axons represented as 0.5 μm diameter fibers within a tubular region of 99 μm diameter. Axons within the inner 33 μm diameter tubular core of the MB are NOS negative and designated as targets. The remaining 27,212 NOS-positive axons form an annular “wall” (shown as a *dark gray* cutout in the *upper* part) around the core and are potential NO sources. In

10 independent runs of the diffusion model, a random 5% of these peripheral NOS-expressing Kenyon cell axons in the tube wall synthesize NO simultaneously for 50 ms. NO half-life is 5 s though results are qualitatively similar for other values. The resultant NO concentrations are shown along a line through the center of the stalk as 10 superimposed plots (*upper* part) and, for a single run, in a cross-section through the MB (*lower* part) at the end of synthesis, 50 and 200 ms later. (Figure used with permission from Ott et al. 2007)

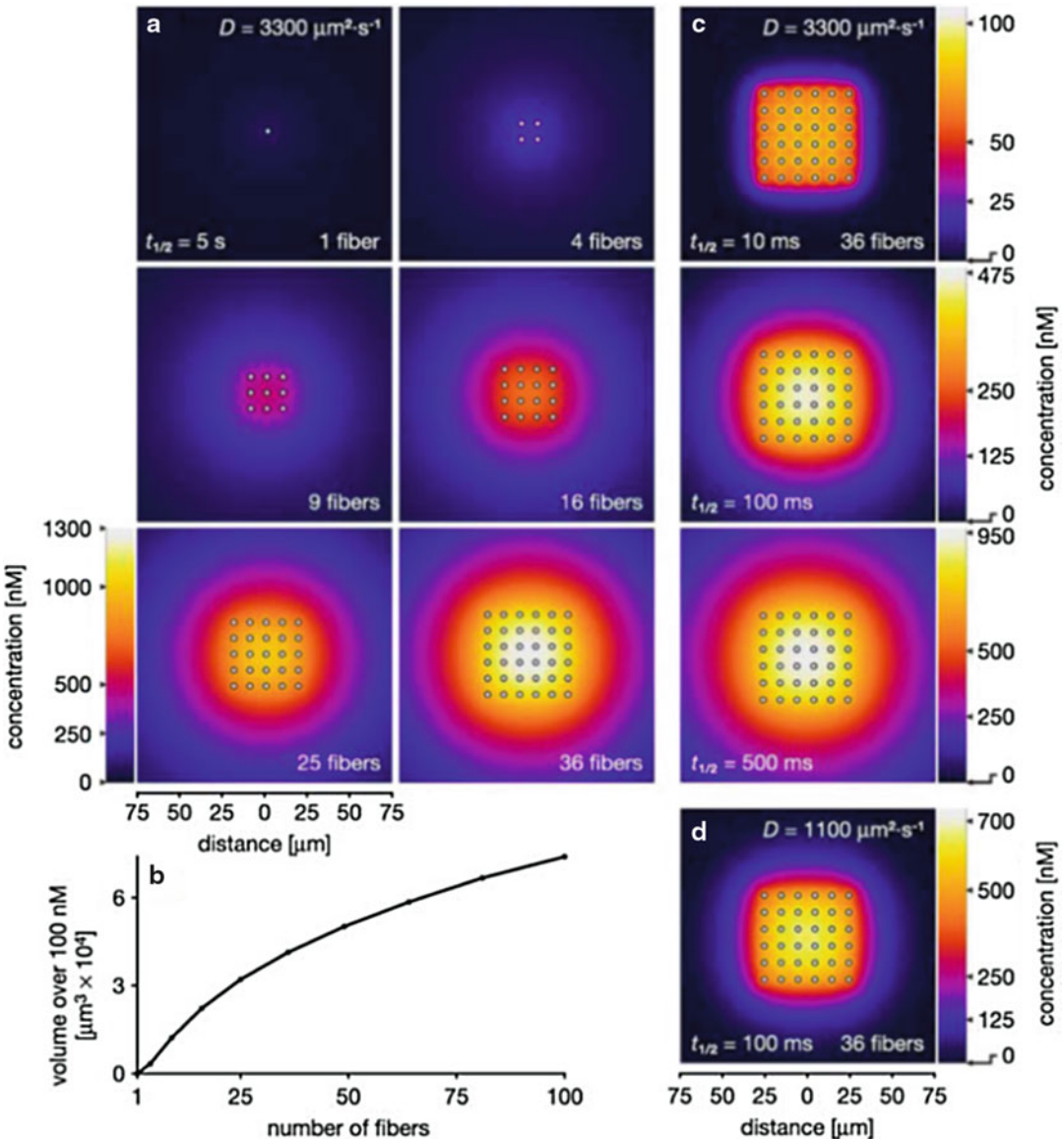
N

During synthesis, NO is highest in the tube walls containing the NOS-positive axons, and the resulting concentration gradient drives NO into the center where it accumulates. About 50 ms after the end of synthesis, the peak concentration is in NOS-negative cores where NO remains locally elevated for several 100 ms. Further, NO signals in the core of the MB are highly invariant for a given percentage of randomly selected active sources. Importantly, the general features of the diffusion dynamics illustrated here are unaffected by the strength or duration of the synthesis pulse, showing that an effective volume signal can be produced by segregated small sources.

Such cooperative volume signaling can again be seen in a model of NO production in the optic lobe of the locust (Fig. 4). Here NO is again produced in multiple distinct fine fibers of approximately 2 μm diameter. As with the locust mushroom body, despite a single fiber producing an ineffective concentration, NO from multiple fibers summate to produce effective concentrations over large regions (Fig. 4a, b). This is also the case if sources are arranged irregularly instead of in parallel arrays and if their firing is asynchronous. Finally, the volume signal persists despite large changes to the parameters governing diffusion, namely, the half-life of NO, $t_{1/2}$, and the diffusion

coefficient, D . When half-life is reduced to 100 ms (Griffiths and Garthwaite 2001), 1/50 of the value used in Fig. 4a, the concentrations in the target volume fall to only approximately one-third

(250–475 vs. 700–1300 nM). Further reduction of $t_{1/2}$ to 10 ms yields a more spiky concentration distribution with 100 nM peaks at the fibers. However, at least 50% or more of this peak



Nitric Oxide Neuromodulation, Fig. 4 Cooperative volume signals produced by ordered arrays of parallel NO-synthesizing fibers at the end of a 1 s burst of NO synthesis. Fiber diameters (2 μm) and spacing (10 μm) approximate that in the locust optic lobe (Elphick et al. 1996). (a) NO concentration in slices across increasing numbers of active fibers (white dots). A single fiber is a relatively ineffectual NO source (1 fiber in a), but increasing numbers (4–36 fibers) result in cumulative buildup of NO. (b) As the number of fibers increases, so does the

volume of tissue over a particular concentration, here 100 nM. NO half-life $t_{1/2}$ is 5 s in a and b. (c) The cooperative volume signal is robust to variation in NO half-life $t_{1/2}$ within the limits reported in the literature, from top to bottom $t_{1/2} = 10, 100$, and 500 ms. (d) Strong cooperation is still observed when $t_{1/2}$ is relatively short (100 ms) and D is reduced to $1100 \mu\text{m}^2\cdot\text{s}^{-1}$, one-third of its standard value. (Figure used with permission from Philippides et al. 2005a)

concentration is still reached everywhere throughout the target volume. Similarly, while reducing the speed of diffusion dramatically by decreasing D to a third of its standard value and using a relatively short half-life, $t_{1/2} = 100$ ms, means that the spread of the volume signal outside of the source array is limited (compare Fig. 4d with bottom middle of Fig. 4a), a strong cooperative volume signal is still observed within the array.

The examples in Figs. 3 and 4 show that small discrete NO sources can act to produce a cooperative volume signal, despite asynchronous activity and irregular arrangement and spacing. In these contexts, the diffusion process can be seen as a spatiotemporal integrator of neural activity in discrete sources. Interestingly, while the two features seen in large continuous sources still exist – concentrations within the source neurons persist after the end of synthesis and central concentrations can peak after synthesis has ended – there is one key difference. With these dispersed sources, the dynamics of diffusion mean that the concentration quickly becomes quite uniform within and close to the volume containing the NO sources. This means that if the goal of the signaling system is to produce an even concentration within a volume, this is best achieved with a network or plexus of fine NO-producing fibers, perhaps giving rise to a different type of volume signal (explored in abstract form in the plexus GasNet model described below and in Philippides et al. 2005b). In turn this work led to further theoretical and empirical investigations that have provided experimental evidence for the kind of cooperative signaling predicted by the models described above (Steinert et al. 2008).

GasNets: NO-Inspired ANNs

Detailed models of long-range neurotransmitter diffusion in the nervous system are necessarily computationally expensive so the use of such models in the study of whole behavior-generating circuits has so far been beyond the state of the art. Hence, to further investigate the functional roles of volume signals and related mechanisms in the generation of behavior, a number of authors have

advocated the study of more abstract artificial robot nervous systems incorporating simplified models of volume signaling and related processes (Grand 1997; Husbands et al. 1998; Kondo et al. 1999; Eggenberger et al. 2000; Kondo 2007; Buckley 2008). These systems are computationally tractable and can generate sensorimotor behaviors in real time in simulations or in the real world.

This section describes a style of artificial neural network directly inspired by NO neuromodulation, making use of an analogue of volume signaling. The class of artificial neural networks developed to explore artificial volume signaling are known as GasNets (Husbands et al. 1998). These are essentially standard neural networks augmented by a chemical signaling system comprising a diffusing *virtual* gas which can modulate the response of other neurons. As outlined below, a number of GasNet variants, inspired by different aspects of real nervous systems, have been explored in an evolutionary robotics (Floreano et al. 2008) context as artificial nervous systems for mobile autonomous robots.

Evolutionary robotics involves populations of artificial genomes (lists of characters and numbers, the members of which act as “genes”) which encode the structure and other properties of artificial neural networks that are used to control autonomous mobile robots required to carry out a particular task or to exhibit some set of behaviors. Other properties of the robot, such as sensor layout or body morphology, may also be under “genetic” control. The genomes are mutated and interbred creating new generations of robots according to a Darwinian scheme (i.e., an evolutionary search algorithm) in which the fittest individuals are most likely to produce offspring. Fitness is measured in terms of how well a robot behaves according to some evaluation criteria; this is usually automatically measured. Evolutionary robotics can operate with fewer assumptions about neural architectures and behavior-generating mechanisms than other methods; this means that whole general classes of designs and processes can be explored (Floreano et al. 2008; Vargas et al. 2014). This makes it a particularly attractive technique for synthesizing models in

neurobiology, allowing explorations of possible processes and mechanisms as in the work described here (Flozano et al. 2008).

GasNets have been shown to be significantly more evolvable, in terms of speed to a good solution, than other forms of neural networks for a variety of robot tasks and behaviors (Husbands et al. 1998; McHale and Husbands 2004; Smith et al. 2003; Philippides et al. 2005b). They are being investigated as potentially useful engineering tools and as a way of gaining helpful insights into biological systems (Philippides et al. 2000, 2003, 2005b; Husbands et al. 2010).

By analogy with biological neuronal networks, GasNets incorporate two distinct signaling mechanisms, one “electrical” and one “chemical.” The underlying “electrical” network is a discrete time step, recurrent neural network with a variable number of nodes. These nodes are connected by either excitatory or inhibitory links with the output, O_i^t , of node i at time step t determined by the following equation:

$$O_i^t = \tanh \left[k_i^t \left(\sum_{j \in \Gamma_i} w_{ji} O_j^{t-1} + I_i^t \right) + b_i \right]$$

where Γ_i is the set of nodes with connections to node i and $w_{ji} = \pm 1$ is a connection weight. I_i^t is the external (sensory) input to node i at time t and b_i is a genetically set bias. Each node has a genetically set default transfer function gain parameter, k_i^0 , which can be altered at each time step according to the concentration of diffusing “gas” at node i to give k_i^t (as described later).

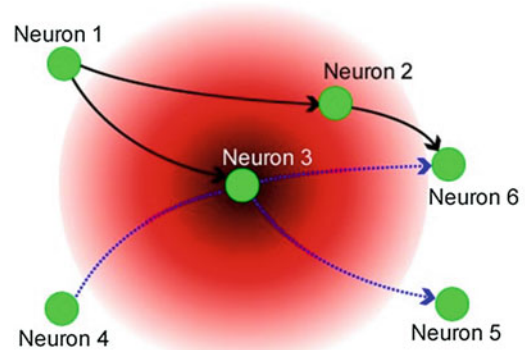
In addition to this underlying network in which positive and negative “signals” flow between units, an abstract process loosely analogous to the diffusion of gaseous modulators is at play. Some units can emit virtual “gases” which diffuse and are capable of modulating the behavior of other units by changing their transfer functions. The networks occupy a 2D space; the diffusion processes mean that the relative positioning of nodes is crucial to the functioning of the network. Spatially, the gas concentration varies as an inverse exponential of the distance from the emitting node with spread governed by a parameter, r , genetically set for each node, which governs the

radius of influence of the virtual gas from the node as described by the equations below and illustrated in Fig. 5. The maximum concentration at the emitting node is 1 and the concentration builds up and decays linearly as dictated by the time course function, $T(t)$, defined below:

$$C(d, t) = \begin{cases} e^{-2d/r \times T(t)} & d < r \\ 0 & \text{else} \end{cases}$$

$$T(t) = \begin{cases} 0 & t = 0 \\ \min \left(1, \left(T(t-1) + \frac{1}{s} \right) \right) & \text{emitting} \\ \max \left(0, \left(T(t-1) - \frac{1}{s} \right) \right) & \text{not emitting} \end{cases}$$

where $C(d, t)$ is the concentration at a distance d from the emitting node at time t and s (controlling the slope of the function T) is genetically determined for each node. The range of s is such that the gas diffusion timescale can vary from 0.5 to 0.09 of the timescale of “electrical” transmission (i.e., a little slower to much slower). The total concentration at a node is then determined by summing the contributions from all other emitting nodes (nodes are not affected by their own emitted gases to avoid runaway positive feedback). The diffusion process is modeled in this simple way to provide extreme computational



A GasNet. Neuron 3 is emitting gas, and modulating neuron 2 despite there being no synaptic connection.

Nitric Oxide Neuromodulation, Fig. 5 A basic GasNet showing excitatory (solid) and inhibitory (dashed) “electrical” connections and a diffusing virtual gas creating a “chemical” gradient

efficiency, allowing arbitrarily large networks to be run very quickly.

For mathematical convenience, in the original basic GasNet, there are two “gases”: one whose modulatory effect is to increase the transfer function gain parameter (k_i^t) and one whose effect is to decrease it. It is genetically determined whether or not any given node will emit one of these two gases (gas 1 and gas 2) and under what circumstances emission will occur (either when the “electrical” activation of the node exceeds a threshold or the concentration of a genetically determined gas in the vicinity of the node exceeds a threshold; note that these emission processes provide a coupling between the electrical and chemical mechanisms). The concentration-dependent modulation is described by the following equation, with transfer function parameters updated on every time step as the network runs:

$$k_i^t = k_i^0 + \alpha C_1^t - \beta C_2^t$$

where k_i^0 is the genetically set default value for k_i ; C_1^t and C_2^t are the concentrations of gas 1 and gas 2, respectively, at node i on time step t ; and α and β are constants such that $k_i^t \in [-4, 4]$. Thus, the gas does not alter the electrical activity in the network directly but rather acts by continuously changing the mapping between input and output for individual nodes, either directly or by stimulating the production of further virtual gas. The general form of diffusion is based on the properties of a (real) single source neuron as modeled in detail in Philippides et al. (2000, 2003). The modulation chosen is motivated by what is known of NO modulatory effects at synapses (Baranano et al. 2001). For further details, see Husbands et al. (1998), Philippides et al. (2005b), and Husbands et al. (2010).

When they were first introduced, GasNets were demonstrated to be significantly more evolvable than a variety of standard ANNs on some noisy visually guided evolutionary robotics tasks (Husbands et al. 1998). Typically the increase in evolvability, in terms of number of fitness evaluations to a reliable good solution, was an order of magnitude or more. The solutions found were often very lean with few nodes and connections,

typically far fewer than were needed for other forms of ANN (Husbands et al. 1998, 2010). But the action of the modulatory gases imbued such networks with intricate dynamics: they could not be described as simple. Oscillatory subnetworks based on interacting “electrical” and “gas” feedback mechanisms acting on different timescales were found to be very easy to evolve and cropped up in many forms, from CPG circuits for locomotion (McHale and Husbands 2004) to noise filters and timing mechanisms for visual processing (Husbands et al. 1998; Smith et al. 2002). GasNets appeared to be particularly suited to noisy sensorimotor behaviors which could not be solved by simple reactive feedforward systems and to rhythmic behaviors.

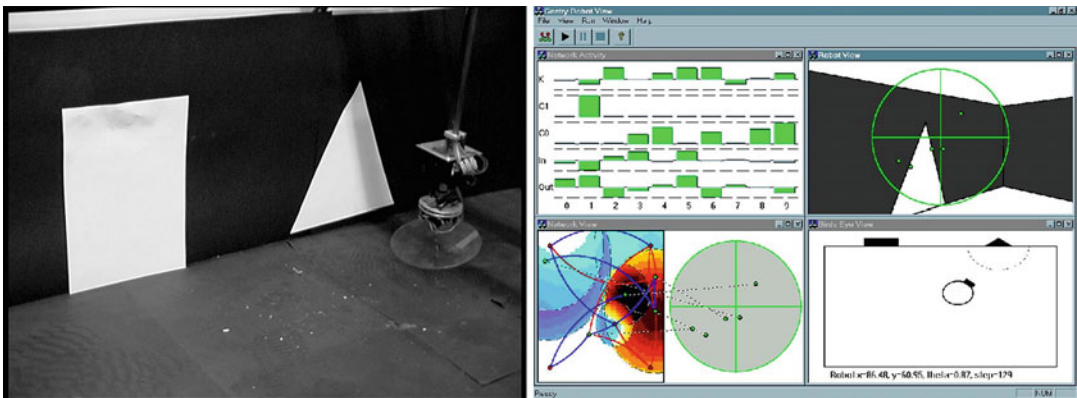
Two extensions of the basic GasNet, the receptor and the plexus models, incorporated further influence from neuroscience (Philippides et al. 2005b). In the receptor model, modulation of a node is now a function of gas concentration and the quantity and type of receptors (if any) at the node. This allows a range of site-specific modulations within the same network. In the plexus model, inspired by a type of NO signaling seen in the mammalian cerebral cortex (Philippides et al. 2005a), as described earlier in this article, the emitted gas “cloud,” which now has a flat concentration, is no longer centered on the node controlling it but at a distance from it. Both these extended forms proved to be significantly more evolvable again than the basic GasNet. Other varieties include nonspatial GasNets where the diffusion process is replaced by explicit gas connections with complex dynamics (Vargas et al. 2007) and versions with other forms of modulation and diffusion (Husbands et al. 2010). In order to gain insight into the enhanced evolvability of GasNets, detailed comparative studies of these variants with each other, and with other forms of ANN, were performed using the robot task illustrated in Fig. 6 (Philippides et al. 2005b; Husbands et al. 2010).

Starting from an arbitrary position and orientation in a black-walled arena, a robot equipped with a forward-facing camera must navigate under extremely variable lighting conditions to one shape (a white triangle) while ignoring the

second shape (a white rectangle). The robot must successfully complete the task over a series of trials in which the relative position and size of the shapes varies. Both the robot control network and the robot sensor input morphology, i.e., the number and positions of the camera pixels used as input and how they were connected into the network, were under evolutionary control as illustrated in Fig. 6. Likewise, the network architecture (including number of nodes) and all properties of the nodes and connections and gas diffusion parameters were all set by the evolutionary search algorithm. Because of the noise and variation, and limited sensory capabilities (only very few pixels are used), this task is challenging, requiring robust, general solutions. The gantry robot shown in the figure was used. The evolutionary search algorithm employed a special validated simulation of the robot and its environment to calculate fitness (by measuring behavioral performance) (Husbands et al. 1998, 2010). Neural controllers evolved in this manner generate the same behavior when downloaded onto the real robot.

The comparative studies revealed that the rich dynamics and additional timescales introduced by

the gas played an important part in enhanced evolvability, but were not the whole story (Philippides et al. 2005b; Husbands et al. 2010). The particular form of modulation was also important; multiplicative or exponential modulation (in the form of changes to the transfer function) was found to be effective, but additive modulations were not. The former kind of modulations may well confer evolutionary advantages by allowing nodes to be sensitive to different ranges of input (internal and sensory) in different contexts. The spatial embedding of the networks also appears to play a role in producing the most effective coupling between the two distinct signaling processes (“electrical” and “chemical”). By exploiting a loose, flexible coupling between the two processes, it is possible to significantly reduce destructive interference between them, allowing one to be “tuned” against the other while searching for good solutions. It has been suggested that similar forces may be at play in spiking networks, where subthreshold and spiking dynamics interact with each other, which have been evolved to drive vision-based robot behaviors (Floreano et al. 2006, 2008). In the most successful varieties of GasNet, dynamics,



Nitric Oxide Neuromodulation, Fig. 6 *Left* The gantry robot. A CCD camera head moves at the end of a gantry arm allowing full 3D movement. In the study referred to in the text, 2D movement was used, equivalent to a wheeled robot with a fixed forward pointing camera. A validated simulation was used: controllers developed in the simulation work at least as well on the real robot. *Right*: The simulated arena and robot. The *bottom right* view shows the robot position in the arena with the triangle and rectangle. Fitness is evaluated on how close the robot approaches

the triangle. The *top right* view shows what the robot “sees,” along with the pixel positions selected by evolution for visual input. Only the values of these pixels from the camera image are fed into the neural network as visual input signals. All other pixel values are discarded. In this way the visual sensor morphology is effectively evolved. The *bottom left* view shows how the genetically determined pixels are connected into the control network whose gas levels are illustrated. The *top left* view shows current activity of nodes in the GasNet

modulation, and spatial embedding act in concert to produce highly evolvable degenerate (Tononi et al. 1999) networks.

Conclusions

Nitric oxide neuromodulation is an important example of a nonclassical neural signaling mechanism which reveals subtle new dimensions to the functioning of the nervous system. Simple connectionist point-to-point notions of information transfer are no longer valid: new understandings and new metaphors are needed.

Detailed models of neural processes incorporating diffusing chemicals are computationally very expensive and to date have been restricted to small numbers of neurons rather than whole behavior-generating neuronal circuits. Computational studies of NO neuromodulation in functioning circuits have therefore been of a more abstract nature and have resulted in new styles of ANN that have direct engineering applications. However, recent advances in parallel computing, including the advent of general purpose GPU computing, mean that we are about to enter an era where larger-scale detailed models will be feasible. This will allow important advances in understanding the functional roles of NO neuromodulation through the careful integration of computational and experimental studies of (biological) neural circuits operating under the influence of NO modulation.

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Nitric Oxide Volume Signaling

► Nitric Oxide Neuromodulation

N-Methyl-D-Aspartate (NMDA) Receptors, Conductance Models

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Definition

A glutamate receptor that is permeable to calcium ions and the current can be regulated by the postsynaptic membrane potential in addition to the binding of glutamate. NMDA receptors can act as coincidence detectors where presynaptic glutamate release combines with postsynaptic depolarization to pass calcium ions that initiate signaling pathways leading synaptic plasticity and other postsynaptic processes.

Detailed Description

NMDA receptors are named for the selective agonist (*N*-methyl-d-aspartate) that does not bind well

to other glutamate receptors. The receptor is non-selective to cations and can allow Na^+ , K^+ , and Ca^{2+} to cross the membrane. The permeability to Ca^{2+} renders this synaptic receptor important for initiating signaling cascades.

The channel can be blocked by extracellular magnesium ions that are released when the postsynaptic neuron depolarizes, greatly reducing the resistance of the pore to current flow. Because the receptor is voltage regulated, the NMDA current causes a depolarizing current and calcium ion injection when postsynaptic depolarization is coincident with presynaptic spikes.

Kinetics of NMDA Receptors

Mathematical representations of NMDA currents include the time-dependent synaptic conductance, $g_{\text{NMDA}}(t)$, and the voltage dependence of the current, $B(V)$.

$$I_{\text{NMDA}}(t) = g_{\text{NMDA}}(t)B(V)(V(t) - E_{\text{NMDA}}) \quad (1)$$

The time-dependent synaptic conductance represents the opening and closing kinetics of the receptor channels and may be based on a double exponential function (or a similarly shaped function).

$$g_s(t) = \bar{g}_s \left(e^{-t/\tau_1} - e^{-t/\tau_2} \right) \quad (2)$$

where τ_1 is the onset time constant ($\tau_1 < 2$ ms) and τ_2 is the decay time constant ($\tau_2 > 50$ ms) (Jahr and Stevens 1990). NMDA currents have a longer decay than AMPA currents (Jonas and Spruston 1994) and typically have a substantially smaller peak current.

The peak current is dependent on the postsynaptic membrane potential.

$$B(V) = \frac{1}{1 + ae^{-bV}c[Mg^{2+}]_o} \quad (3)$$

where $[Mg^{2+}]_o$ is the external magnesium concentration and the constants a , b , and c are derived empirically (Destexhe et al. 1998; Jahr and Stevens 1990) and typically $a = 0.33/\text{nM}$, $b = 0.06/\text{mV}$, and $[Mg^{2+}]_o \approx 1$ nM.

Computational Relevance

The importance of NMDA receptors for neural computation is twofold: (1) strengthen glutamatergic currents when a neuron is in an excited state and (2) initiate signaling cascades near the site of the synapse that lead to long-term changes.

Due to the long decay constant of NMDA receptors, the NMDA current can contribute significant depolarizing current to the postsynaptic neuron even though the peak current is much less than AMPA receptors. This is particularly true when the postsynaptic cell is in an excited state. NMDA receptors strengthen glutamatergic input in an excited state because the voltage dependency increases the current. This mechanism allows neurons to be controlled by a modulatory input so that their sensitivity to excitatory inputs is adjusted. The resulting responses can, for example, alter the sensitivity of sensory pathways in a nonlinear manner by descending inputs (Ossipov and Porreca 2006).

The ability of NMDA receptors to inject calcium ions into neurons when the timing of synaptic inputs is coincident with postsynaptic activity provides a mechanism for Hebbian synaptic learning (Collingridge and Bliss 1987). Many biological processes are sensitive to calcium signaling, and NMDA receptors provide an important calcium source for synaptic dynamics. If the signaling cascade leads to long-term potentiation of the synapse, then the participation of the presynaptic neuron in the excitation of the postsynaptic neuron leads to a strengthening of that particular synapse (Hebb 1949).

The amount and type of synaptic plasticity induced by NMDA receptors depend on the cell type and calcium influx. Examples of long-term potentiation (Collingridge and Bliss 1987) and long-term depression (Dudek and Bear 1993) have been found that depend on activation of NMDA receptors, but typically, potentiation requires a higher level of calcium influx than depression (Lisman 1989). Thus, the short-term dynamics of NMDA receptors are responsible for the long-term dynamics of the synaptic currents that affect the population dynamics of the neural circuitry.

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Noise Attenuation

- [Peripheral Nerve Signal Processing, Denoising](#)

Noise Cancellation

- [Peripheral Nerve Signal Processing, Denoising](#)

Noise Enhancement of Weak Subthreshold Signals

- [Stochastic Resonance: Balance Control and Cochlear Implants](#)

Noisy Neural Network

- [Boltzmann Machine](#)

Nomenclature of Ion Channels (IUPHAR Scheme)

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Synonyms

[Clone nomenclature](#)

Definition

The International Union of Basic and Clinical Pharmacology (IUPHAR) nomenclature of ion channels is an agreed standard for naming the voltage-gated and ligand-gated ion channels encoded in the genomes of human, mouse, and rat. The nomenclature is based on functional characteristics and structural protein motifs.

Detailed Description

Overview of Channel Naming

In rat, mouse, and human, there are over 140 channel subunits in the superfamily of voltage-gated-like ion channels and over 70 types of ligand-gated ion channel subunits. Typically, a subunit has many names, reflecting the history of its discovery and subsequent investigation. The IUPHAR Committee on Receptor Nomenclature and Drug Classification has worked to produce a unified nomenclature of the channel subtypes, which is designed to indicate the function of the ion channel. This scheme is also called clone nomenclature, as the properties of subunits are measured by heterologous expression of cloned receptors. Subunits can also be

referred to by gene nomenclature, i.e., the name of the gene that encodes the channel protein.

In the IUPHAR nomenclature, each name comprises a family identifier, followed by a type and, in some cases, a subtype. Overviews of the nomenclature for voltage-gated and ligand-gated subunits are given by Catterall and Gutman (2005) and Collingridge et al. (2009), respectively. Full details of the nomenclature are available from the official database of the IUPHAR Committee on Receptor Nomenclature and Drug Classification. For each subtype, this database has details such as other names for the channel, links to other databases of genes, drugs and proteins, associated proteins (including pore-forming subunits and auxiliary subunits), ion selectivity, voltage dependence, activators, tissue distribution, and physiological function. Many of the subtypes are expressed outside the brain.

There is also a more informal classification of the dynamics of currents arising from channels, for example, “delayed rectifier potassium current” or “T-type calcium current.” In the IUPHAR scheme these terms are used in the description of a channel type. The dynamics of ion channels depend not only on the primary subunits (which the IUPHAR scheme refers to) but also on the expression of auxiliary subunits, which cluster around the primary subunits that form the channel pore. This classification by ionic currents is used widely by electrophysiologists and modellers. Table 1 shows the relationship between the

current types, the clone nomenclature prefix, the human gene prefix, and the ionic current names (Sterratt et al. 2011).

The IUPHAR Scheme for Voltage-Gated Ion Channel Subunits

Ion Channels with a Principal Permeant Ion

The name of a channel that has a principal permeant ion contains the name of the ion, a letter to indicate whether the channel is principally gated by voltage or calcium, and then two numbers to indicate the type and subtype of the channel. For example, the T-type voltage-gated calcium channel is named Ca_v3.1, and the calcium-gated small/intermediate conductance potassium channel is named K_{Ca}3.1. There are some quirks in the system: for example, K_{Ca}4.2 is actually activated by sodium rather than calcium.

There are two families of potassium channel that are not strongly gated by voltage or calcium which have their own suffices: (i) Pairs of K_{2P} subunits with 2 P-loops form an entire channel, which has four P-loops. These channels give rise to leak currents in neurons. (ii) K_{ir} inwardly rectifying potassium channels open very quickly on hyperpolarization, depending on the extracellular potassium concentration.

There are also two families of calcium channel of less relevance to neuroscience. (i) CatSper channels were the first cation channel discovered

Nomenclature of Ion Channels (IUPHAR Scheme), Table 1 The relationship of ionic current types to the clone and gene nomenclatures

Current type	Official IUPHAR receptor prefix	Human gene prefix	Current names
Sodium	Na _v	SCN	I _{Na} , I _{NaP}
High-voltage-activated calcium	Ca _v 1, Ca _v 2	CACNA1	I _{CaL} , I _{CaN} , I _{CaR}
Low-voltage-activated calcium	Ca _v 3	CACNA1	I _{CaT}
Delayed rectifier and A-type potassium	K _v 2.2, K _v 3.2, K _v 1.4, K _v 3.4, K _v 4.1, K _v 4.2, ...	KCNA, KCNB, KCNC, KCND	I _{DR} , I _A
Calcium-dependent potassium	K _{Ca} 1, K _{Ca} 2	KCNMA, KCNN	I _C , I _{AHP}
Inward rectifier potassium	K _{ir}	KCNJ	I _{Kir}
Hyperpolarization-activated cyclic nucleotide gated	HCN1–4	HCN1–4	I _h

in sperm and are specific to sperm cells. (ii) TPC (two-pore channels) are cation ion channels related to the CatSper channels; TPC1 is found in kidney, liver and lung.

Nonspecific Ion Channels

There are three classes of channel in the IUPHAR scheme that are significantly permeable to more than one ion:

- CNG (cyclic nucleotide-gated family), activated by cyclic nucleotides such as cAMP and cGMP
- HCN (hyperpolarization-activated, cyclic nucleotide-gated family), activated in response to hyperpolarization
- TRP (transient-receptor potential family), gated by heat and second messengers

Chloride Channels

Chloride channels are not covered by the IUPHAR scheme.

IUPHAR Scheme for Ligand-Gated Ion Channel Subunits

The IUPHAR also has a scheme of naming 71 types of ligand-gated ion channel subunits, including the following: 5-HT₃ receptors, GABA_A receptors, glycine receptors, ionotropic glutamate receptor subunits, nicotinic acetylcholine receptors, P2X receptors, and ZAC. This scheme does not tend to be referred to in computational neuroscience studies.

Cross-References

- [Calcium-Dependent Potassium Channels](#)
- [Delayed Rectifier and A-Type Potassium Channels](#)
- [High-Voltage-Activated Calcium Channels](#)
- [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)
- [Inward Rectifier Potassium Channels](#)
- [Low-Voltage-Activated Calcium Channels](#)
- [Sodium Channels](#)

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Nonclassical Receptive Fields

- [Center-Surround Processing, Computational Role of](#)

Non-constitutive Exocytosis

- [Biophysical Models of Calcium-Dependent Exocytosis](#)

Non-inactivating Potassium Current/Conductances

- [Delayed Rectifier and A-Type Potassium Channels](#)

Noninvasive Brain-Computer Interfaces

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Synonyms

[Noninvasive brain-machine interface](#)

Definition

A noninvasive *brain-computer interface* (BCI) is a device that allows users to send messages or

commands to devices, friends, family, or others through direct, noninvasive measures of brain activity.

Detailed Description

BCIs are communication and control systems that do not depend on the brain's normal output pathways such as peripheral nerves and muscles (Wolpaw et al. 2002). Hence, BCIs provide alternate methods to interact with the outside world not only for healthy people (Allison et al. 2007; Guger et al. 2009; Blankertz et al. 2010) but also for patients who cannot use their muscles but are cognitively intact (Nam et al. 2012; Sellers et al. 2010).

Noninvasive BCIs record information from sensors placed on or very close to the head. No surgery is required to implant recording devices, and noninvasive BCIs do not use any painful or hazardous methods. The most common BCI recording mechanism is the electroencephalogram (EEG), which uses electrodes placed on the surface of the head. These electrodes detect electrical changes in brain activity with millisecond resolution, thus providing insight into the timing and location of different mental activities. Electrodes are usually placed in an electrode cap, which allows fairly precise positioning of electrodes over distinct brain regions. Electrode caps and other electrode systems can fit in a purse or small bag. They are lightweight, relatively inexpensive, and easy to use. Most conventional electrodes require a small amount of electrode gel under each electrode to get a good connection between the scalp and each electrode.

Other noninvasive approaches have also been used in BCI research. A few BCIs have used magnetoencephalography (MEG), which records the brain's magnetic activity. These systems measure brain activity as quickly as EEG systems, although they measure a different type of activity. Functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) both measure changes in the brain's blood flow, rather than directly measuring electrical activity. The blood oxygenation

level-dependent (BOLD) signal reflects increased blood flow and oxygen consumption in brain areas that are active, such as motor areas involved in imagined movement. Blood flow changes take a few seconds to develop enough for reliable discrimination of brain states, which limits the speed of BCIs that rely on these methods. Also, fMRI systems (like MEGs) are neither affordable nor portable. Unless there are significant advances in these or other noninvasive neuroimaging approaches, EEG-based BCIs remain the most common means of noninvasive brain monitoring for BCIs.

Tasks in Noninvasive BCIs

In any BCI, a critical defining feature is the set of mental activities (and corresponding brain signals) that the BCI can detect. Many mental activities that might seem obvious control tasks for a noninvasive BCI – such as imagining an image, thinking of a specific word, or wishing to perform a goal – and do not elicit patterns of mental activity that can be reliably discriminated by noninvasive brain imaging methods. Thus, BCI developers have had to rely on mental activities that produce robust changes in the EEG or whatever method is used. Aside from producing distinct brain activity patterns, any mental activities in BCIs should be relatively easy for the subject to perform, quickly and repeatedly, and should ideally be relatively intuitive for the desired BCI application. For example, imagining left hand movement to move an avatar left or control a grasping device on the left hand seems like an intuitive, natural mapping between mental activity and output.

Most noninvasive BCIs rely on imagined movement or attention, and attention-based BCIs are typically divided into P300 BCIs and SSEP BCIs, described further below. The following subsections describe these three BCI approaches. Each section includes a figure drawn from a recent publication that depicts the electrode distribution and protocol from that study. The methods in these examples are not universal, but are typical of many BCIs that use that approach.

Motor Imagery BCIs

Many noninvasive (and invasive) BCIs record changes in neural activity associated with imagined movement. For example, a user might imagine moving the left hand, right hand, or foot. These activities each produce distinct patterns of event-related (de)synchronization, or ERD/S, over different sensorimotor regions. ERD/S typically entails changes in the frequency spectra around 8–14 Hz and sometimes beta harmonics of these frequencies. By analyzing these power spectra over different sites, a BCI can determine which movement the user imagined and thereby convey information from the user (Guger et al. 2003; McFarland et al. 2010; Vidaurre and Blankertz 2010). Motor imagery BCIs often rely heavily on central electrodes and surrounding sites, shown in Fig. 1b.

Motor imagery BCIs typically begin with a training period, which trains the user on the task and provides information about each user’s ideal frequencies and spatial regions that improves classifier performance. Motor imagery BCIs may entail longer training, lasting from several minutes to many sessions over months or years, to continue to improve performance (McFarland et al. 2010; Vidaurre and Blankertz 2010). Figure 1a shows the structure of a typical training session. Subjects are initially asked to look at a fixation cross on a monitor and may receive some cue (such as a tone). Next, an arrow points to a specific direction, indicating that the subject should perform corresponding motor imagery. For example, a left arrow might instruct the

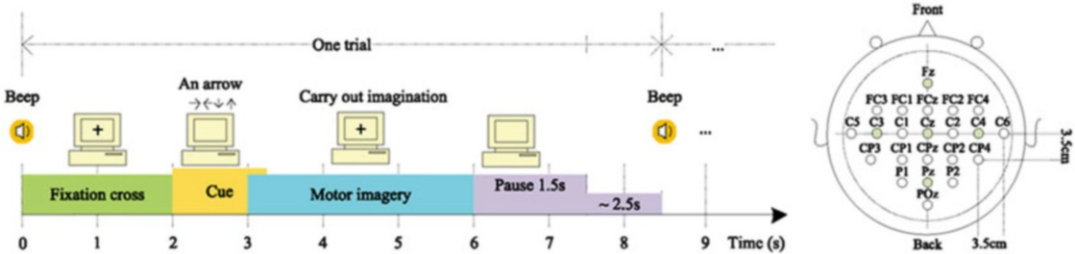
subject to imagine moving the left hand. After the subject performs this imagery for several seconds, the trial ends, and there is a pause before the next trial.

Motor imagery BCIs often entail at least 5–10 min of training data to customize parameters for each subject. Online trials may use a similar trial structure, but present feedback throughout the motor imagery and/or at its end. A classical form of feedback has been a bar extending to the left or right; the direction indicates one of two movement directions, and the bar indicates the strength of the classification (Guger et al. 2003). Motor imagery BCIs have also provided feedback through many other applications and devices, such as spellers (Müller et al. 2008), orthoses (Do et al. 2013), and virtual environments (Leeb et al. 2007).

P300 BCIs

BCIs may rely on two types of attention-dependent EEG signals: P300s and steady-state evoked potentials (SSEPs). Each of these approaches relies on voluntary modulation of attention. When a user chooses to pay attention to a certain stimulus, thereby ignoring other stimuli, distinct patterns of EEG activity may be used to identify the target. Most attentional BCIs require a working visual system to produce distinct visual evoked potentials (VEPs), but have been validated with other stimuli as well.

When a person silently counts a certain stimulus (such as a flash or tone), the brain may produce



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Fig. 1 Structure of a motor imagery study (Wang et al. 2012). The *left panel* shows one example of the structure of

each motor imagery trial. The *right panel* shows the electrode locations from that study

a series of transient event-related potentials (ERPs), including P300s, which are more robust than the ERPs elicited by ignored stimuli. ERPs are derived by isolating the time period after each flash (such as 800 ms) and measuring the voltage at each electrode site. These ERPs reflect attentional processing and updating of memory and context and can be elicited by visual, tactile, and auditory stimuli (Polich 2007). The P300 is most pronounced over parieto-occipital electrodes (Krusienski et al. 2008), and so P300 BCIs rely most heavily on posterior electrodes (see Fig. 2, right panel). Most P300 BCIs use a spelling application, in which different icons are presented on a computer monitor. These icons typically include letters, numbers, other characters, or commands (see Fig. 2, left and middle panels). The user is asked to focus on a specific character, called the target, and silently count each time the target flashes.

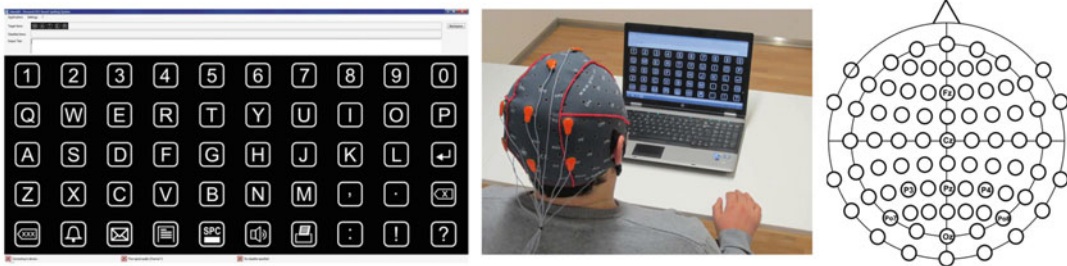
The flashing strategy has changed in recent years. Until recently, most P300 BCIs flashed characters by changing to color-reversed versions of the same character or flashing a solid color (Guger et al. 2009). However, recent work showed that the face-speller, in which characters change to a famous face, can elicit more robust ERP differences than a conventional P300 BCI and thereby improve performance (Kaufmann et al. 2011; Jin et al. 2012). Also, canonical P300 BCIs used the “row-column” flash approach, in which one row or column was highlighted in sequence (Farwell and Donchin 1988; Allison and Pineda 2003). One study found that a single character speller, which

flashed only one letter at a time, was inferior to the canonical row-column approach (Guger et al. 2009). More recent work found that “splotch” patterns that group characters in patterns that avoid rows and columns produce better results (Boccanfuso et al. 2005; Townsend et al. 2010; Jin et al. 2011).

Like motor imagery BCIs, P300 BCIs require a training period that usually lasts about five minutes. After that, the classifier is automatically updated with the best combination of electrode sites and weights for the different times after each flash. The P300 BCI is then ready for online use. About three target flashes are needed to produce sufficiently robust ERP differences for accurate classification. In a spelling application, the classified letter is normatively presented at the top of the monitor.

SSEP BCIs

Steady-state evoked potentials may also change based on voluntary attention, such as when subjects are asked to focus on a stimulus on one hand or one oscillating LED. Most BCI research involving steady-state potentials has used visual-based stimuli called steady-state visual evoked potentials (SSVEPs). The user may view a monitor with oscillating icons or a device with oscillating LEDs and focus on one of these visual targets. Occipital areas of the brain, over the primary visual cortex and nearby regions, will show an increase in the frequency of the oscillating stimulus and often harmonics as well (Allison et al.



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Fig. 2 Structure of a P300 BCI system. The *left panel* is a spelling matrix, and the *middle panel* shows a subject

using that matrix. The *right panel* shows electrode positions typical in P300 BCIs (Image from Guger et al. (2012b))

2010; Luo and Sullivan 2010; Panicker et al. 2011). Figure 2 presents one SSVEP study in which a user observed a box with four LEDs that each oscillated at a different frequency (10, 11, 12, or 13 Hz). By focusing on one of these frequencies, the user could convey one of four directional signals. About half of all subjects attained 100% accuracy, with about 35% more in the 90–100% accuracy range (Guger et al. 2012a). This approach has been used to control a mobile robot (Kapeller et al. 2013; Fig. 3).

While SSVEP BCIs have been widely validated, they would not work for users who cannot see. Steady-state auditory evoked potential (SSAEP) BCIs have been explored, but were less promising than ERP-based BCIs (Hill and Scholkopf 2012). Vibrotactile stimulation can elicit steady-state somatosensory evoked potential (SSSEP) activity at the eliciting stimulus frequency. Focusing attention on one of the frequencies (such as a vibrotactile stimulator on the left or right hand) increases power at the associated frequency, primarily over fronto-central electrode locations contralateral to the attended frequency. Thus, SSSEP BCIs rely on sensorimotor areas somewhat similar to motor imagery BCIs. SSSEP-based BCI systems allow users to communicate by focusing on a specific tactile stimulus

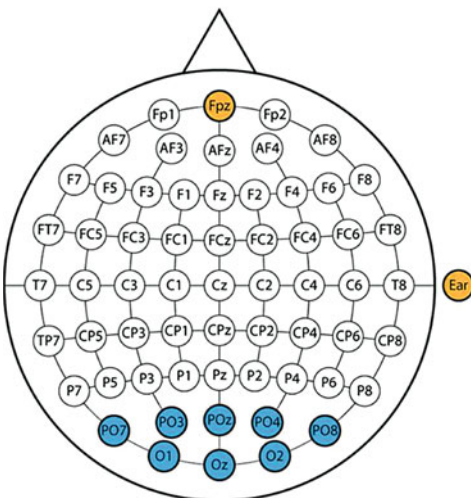
to convey information, such as designating the left hand for “yes” (Severens et al. 2013). The somatosensory system of behaviorally nonresponsive patients remains functional, even though their visual system is impaired.

Hybrid BCIs

Hybrid BCIs (abbreviated hBCIs) combine a BCI with another way that someone can convey information. An hBCI could combine a variety of input signals (shown in Fig. 4), such as:

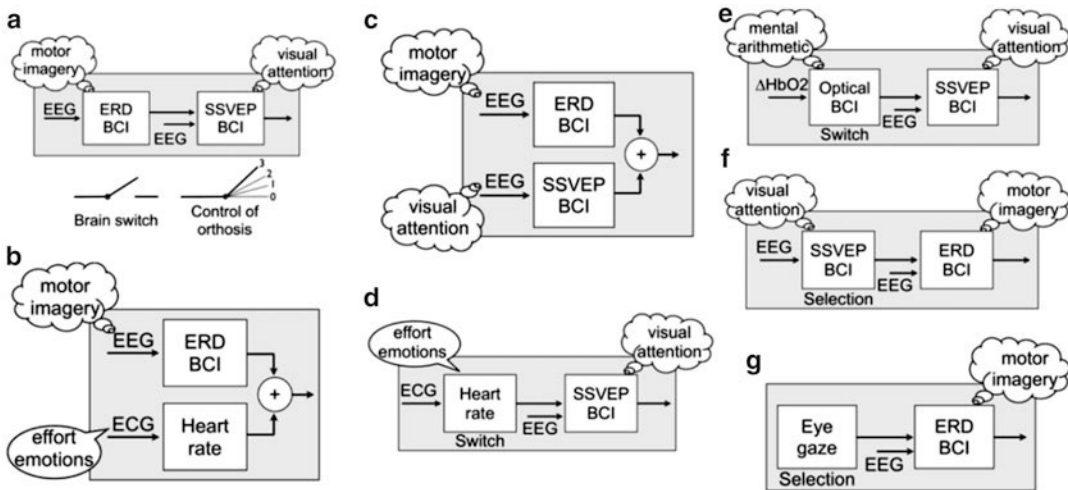
1. Two same types of brain signals (e.g., EEGs)
2. Two different types of brain signals (e.g., EEG and near-infrared spectroscopy, NIRS)
3. One brain signal (e.g., EEG) and another physiological signal (heart rate or HR changes)
4. One brain signal (e.g., EEG) and another conventional input (e.g., eye tracker)

The first two systems may be classified as a “pure” hybrid, the third system as a “physiological” hybrid, and the fourth system as a “mixed” hBCI. Although hBCI research received little attention until recently, it has already gained significant attention (Pfurtscheller et al. 2010;



Noninvasive Brain-Computer Interfaces,
Fig. 3 Structure of an SSVEP BCI system. The *left panel* shows an electrode montage with a heavy emphasis

on occipital sites, which is common on SSVEP BCIs. The *right panel* shows the user observing the device with four LEDs (Image from Guger et al. (2012a))



Noninvasive Brain-Computer Interfaces, Fig. 4 Different types of hBCIs (From Pfurtscheller et al. 2010). Each panel presents a different way that a BCI may be combined with another input device

Allison et al. 2010, 2012; Müller-Putz et al. 2011; Choi and Jo 2013; Yin et al. 2013).

HBCIs may operate in a simultaneous and/or sequential manner. In a sequential BCI, the user controls one of the different input mechanisms at a time, rather than simultaneously. The sequential hBCI approach may use the output of one system as the input of the other system. For example, the first system could function as a “Selector” or “Brain Switch.” In some cases, the first BCI in a hybrid system simply turns the second BCI on or off. This approach has been validated with BCIs that combine ERD and SSVEP or SSVEP and P300 (Pfurtscheller et al. 2010; Panicker et al. 2011). A different approach to sequential hBCIs complements a BCI with another input system for other input for different goals. For example, one hBCI combines P300 and motor imagery BCIs to control a BCI mouse, select icons, or spell (Yu et al. 2013).

In a simultaneous hBCI, two input signals are processed at the same time. P300 and SSVEP measures have been combined to provide two signals to improve detection accuracy (Li et al. 2013; Allison et al. 2014). In these approaches, the user focuses on a target that both flashes and oscillates, thus eliciting both transient and steady-state attention-related changes. A different approach explored the combination of P300 and

SSSEP activity to improve accuracy (Severens et al. 2013). Some work has demonstrated simultaneous hBCIs that require users to perform different tasks simultaneously, essentially using two different BCIs at once, such as ERD-SSVEP (Allison et al. 2010) or P300-SSVEP (Panicker et al. 2011; Li et al. 2013). Hence, users might move a cursor in one direction with one BCI while simultaneously moving the cursor in another direction with another BCI. In Yao et al. (2013), users performed selective motor imagery while also focusing on a vibrotactile ring on one wrist. This hBCI approach improved accuracy. Choi and Jo (2013) combined multiple BCIs in a sequential and simultaneous fashion.

Therefore, different hBCIs have reduced disadvantages of the conventional “single” BCI system in different ways. They may provide a brain switch or enable a standby mode. HBCIs can increase accuracy and information transfer rate (ITR) by providing more selections, allowing control of more axes, or combining two signals to improve accuracy. A BCI might provide communication when the other system is not available, such as when the user is fatigued (Millan et al. 2010; Pfurtscheller et al. 2010; Allison et al. 2010, 2012; Müller-Putz et al. 2011).

This is not an exhaustive list of signals that could be used in noninvasive BCI systems. The

first BCI publication that showed a BCI helping a severely disabled patient relied on an EEG-based approach called slow cortical potentials (SCPs). A patient with late stage ALS learned to voluntarily produce slow changes in his SCP activity to move a cursor up or down, thereby controlling a spelling application (Birbaumer et al. 1999). However, this approach required months of training, did not allow rapid communication, and had a high illiteracy rate. Hence, SCP BCIs have received little attention of late. Other groups have developed BCIs based on spectral changes associated with the imagination of common mental tasks, such as writing, singing, performing math, or rotating an object (Millan and Mourino 2003; Sepulveda et al. 2007; Friedrich et al. 2012). These BCIs may be promising for some users, but also have not been as prominent as the three major noninvasive BCI approaches.

Feature Extraction and Translation

The success of a given BCI approach largely depends on effectively extracting relevant features from the brain signal measurements and translating these features into device commands. While many feature extraction and translation strategies have been explored for various types of BCIs, some commonly used approaches are summarized below.

Motor Imagery: Because motor imagery produces localized activity over the motor cortex, it is common to use a bipolar electrode reference or a Laplacian spatial filter centered over the region of interest, such as the right-hand region of the cortex. Likewise, since motor imagery produces changes in oscillatory activity in known frequency bands, measurements of the spectral amplitude or power in selected frequency bands are commonly used as features. One straightforward approach is to compute the bandpower of the EEG by bandpass filtering the EEG in the band of interest (e.g., μ or β) then squaring and smoothing the result. This gives a measurement of the temporal power fluctuations in the band of interest. Other spectrum estimation techniques such as Fast Fourier Transform (FFT)-based

methods and autoregressive (AR) models are commonly used to estimate the amplitude or power of the EEG within a band. Common spatial patterns (CSP) is another effective feature extraction approach that computes a set of optimal spatial filters for discriminating signal variance within a band.

With the spectral features extracted, for instance, modulation of the 12 Hz amplitude at Laplacian filtered C3, these features can be translated into continuous device control commands. While discrete classifiers can be used for translation, linear or nonlinear regression models such as ordinary least squares or support vector machine (SVM) regression can be advantageous in terms of user training and graded continuous control.

P300: Unlike motor imagery, the P300 and related ERPs are generally more broadly distributed spatially and the most useful features are time-domain amplitudes. For certain paradigms, such as the P300 speller, a generalized set of electrode locations is usually been defined for effectively capturing the response. The EEG is typically smoothed using a lowpass filter with a cutoff between 10 and 30 Hz and decimated by the corresponding factor to reduce the dimensionality. The ERPs are typically extracted within a 500–1000 ms poststimulus window. The resulting spatiotemporal amplitude features are then classified using a linear or nonlinear classifier such as stepwise linear discriminant analysis (SWLDA) or SVMs.

SSEPs: Because SSEPs are generally characterized by localized oscillatory activity, processing of these responses is very similar to motor imagery. For SSVEP, only electrodes overlying the occipital cortex are processed. Individual electrodes referenced to a frontal electrode can be effective, or spatial filtering methods such as CSP can be applied. Because SSVEP responses can occur at a sub-Hertz resolution over a comparatively wide band compared to motor imagery, FFT and AR methods are preferred over bandpower methods. The spectral features are then translated using any preferred classifier, which is typically multiclass. One of the most effective approaches for SSVEP is canonical correlation analysis (CCA), which computes

temporal correlations with reference sinusoids and an optimized spatial filter.

Major Challenges and Solutions

BCI Illiteracy

One of the persistent challenges in BCI research is finding a BCI that works for any user. BCI illiteracy occurs when a user is unable to attain effective control with a BCI (Allison et al. 2010; Kübler and Müller 2007; Pfurtscheller et al. 2010). This phenomenon may be more prominent in imagined movement BCIs, in which approximately 20% of users do not exhibit BCI performance adequate for effective control (Guger et al. 2003; Allison et al. 2013; Vidaurre and Blankertz 2010). Other work that explored universality with P300 and steady-state visual evoked potential (SSVEP) BCIs found that these approaches may work for a larger percentage of users, but not necessarily all of them (Allison et al. 2010; Guger et al. 2009, 2012a). Different methods to reduce illiteracy have been explored, such as improved training, proper instructions to users, and improved signal processing (Neuper et al. 2005; Leeb et al. 2007). However, even with these new techniques, some of the users still cannot use a resulting BCI system (Vidaurre and Blankertz 2010; Grosse-Wentrup and Schölkopf 2013).

BCIs that rely on endogenous signals (e.g., motor imagery-based BCIs) may not require visual stimulation to elicit evoked potentials but still require visual stimuli to provide instructions and feedback (Blankertz et al. 2010; McFarland et al. 2010). To provide BCIs for users with visual deficits, some researchers have turned to auditory or tactile stimuli to elicit necessary brain activity and provide feedback (Muller-Putz et al. 2012; Ortner et al. 2013).

Practical Field BCIs

Early BCIs recorded activity from users in shielded labs, with instructions to limit unnecessary movement, using fairly bulky equipment, with considerable expert help (Farwell and

Donchin 1988); (Wolpaw et al. 1991). Since then, there have been many efforts to validate BCIs outside of the lab, ideally with patient groups (Kübler et al. 2009; Sellers et al. 2010; Muller-Putz et al. 2012; Pineda et al. 2012; Ortner et al. 2013). A major challenge noted in extending BCIs to real-world use is robustness (Millan et al. 2010; Wilson et al. 2012; Allison et al. 2013; Schalk et al. 2012). BCIs should ideally work well at any time, in any location, with minimal equipment and assistance.

Improved signal processing and better electrode design have made EEG-based BCIs more robust to noise. Newer BCI amplifiers are much lighter and smaller than earlier designs. Wireless electrodes eliminate cables, which can generate noise, snag on equipment, and become tangled (Wilson et al. 2012). Newer BCIs rely on intelligent, self-adaptive software that can automatically customize many signal processing parameters to each user without help. Hence, the user gains improved accuracy (after a brief training session) without expert help. Some BCIs can detect when users are inattentive or producing no signal intended for BCI control, allowing for asynchronous operation and a standby mode (Muller-Putz et al. 2006; Sepulveda et al. 2007; Panicker et al. 2011). Intelligent software can also reduce errors through automatic error correction, effective feedback, and adapting to the environment (Millan et al. 2010; Allison et al. 2012; Wilson et al. 2012).

Until recently, each electrode required a small amount of electrode gel to attain good contact with the skin. The process of preparing each electrode for recording was somewhat messy and tedious and meant that EEG recording sessions (including for BCIs) typically required at least 20 min of preparation time. However, recent work from different groups has validated dry electrodes, which are more comfortable and require much less time to prepare. These electrodes can offer signal quality and BCI performance comparable to conventional gel electrodes (Lin et al. 2010; Zander et al. 2011; Chi et al. 2012; Guger et al. 2012b). These electrodes are often placed in a headband, headphones, or other head-mounted device. Wearable dry electrodes have also gained

attention among manufacturers developing BCI games for popular audiences, although these less expensive electrodes yield lower signal quality (Lin et al. 2010; Chi et al. 2012; Duvinage et al. 2013).

New Patient Groups

Some recent studies have shown that BCI technology may be useful for rehabilitation of different conditions – not just for communication and control. For example, BCI-assisted stroke therapy could better discern brain activity that predicts stroke therapy and recovery and inspire improved therapy using BCIs along with other techniques, such as robot-assisted therapy (Silvoni et al. 2011; Cincotti et al. 2012; Sarac et al. 2013; Teo and Chew 2014). Using a motor imagery BCI may also increase brain plasticity in motor areas and thus improve recovery from motor deficits resulting from stroke. Other work showed that BCI technology could help patients with other conditions, such as ADHD and autism (Pineda et al. 2012; Lim et al. 2012). These advances could make BCIs to a much wider group of patients.

Recent work has uncovered another patient group that may need BCIs. Depending on disease etiologies and varying degrees of brain damage, patients can have a range of conditions that are labeled as disorders of consciousness (DOC), including the vegetative state (VS) and the minimally conscious state (MCS), often including locked-in syndrome. DOC patients are diagnosed as “behaviorally nonresponsive” when they do not show any behavioral response to commands or repeated clinical examinations. Some patients diagnosed as behaviorally nonresponsive such as VS or MCS may in fact be conscious and able to communicate through a BCI. For example, some VS patients could modulate BOLD activity in the fMRI in response to instructions, such as thinking about playing tennis or moving in their homes (Owen et al. 2006). Three of 16 patients followed commands and performed specific motor imagery tasks (Cruse et al. 2011).

Very recent results showed that P300 and other BCIs may be able to both detect awareness and provide communication for some such patients. Some users did indeed exhibit differential ERP responses to autobiographical questions and could use the BCI to provide yes/no and even three-choice replies that could be used for communication. These people might otherwise remain unable to communicate and may remain misdiagnosed as permanently vegetative, affecting end-of-life decisions (Muller-Putz et al. 2012; Lule et al. 2013; Ortner et al. 2013, Risetti et al. 2013). There seems to be a particularly pressing need to help these patients, who seem to have an even greater need than others.

Conclusion

Noninvasive BCIs are communication systems that rely on direct, noninvasive measures of brain activity. Most noninvasive BCIs use one of the three types of EEG activity: ERD/s, P300 and related ERPs, and SSEPs. The first activity is usually elicited through imagined movement tasks, and the latter two categories usually involve visual attention. BCIs have been validated with a wide variety of patients and other end users and are becoming increasingly practical to a broader variety of people. Improved electrodes and amplifiers, wireless BCIs, better signal processing, hBCIs, reduced dependence on experts, wider field validation, and reduced cost, weight, and bulk (among other factors) are also making BCIs more useful and practical. New or existing companies may develop BCI products that appeal to a wider group of healthy users and further encourage smaller, cheaper, more convenient BCIs.

On the other hand, very few people use BCIs today. BCI illiteracy is a concern, particularly with patients in field settings. Most healthy users who use BCIs do so for fun or novelty, not for any practical benefit. Very few patients use BCIs, and most patients who do are supported by a local research group. Efforts to improve BCIs in various ways may help, and the next several years may see BCIs translate to new patient groups.

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Noninvasive Brain-Machine Interface

► Noninvasive Brain-Computer Interfaces

Nuclear Medicine, Molecular Imaging

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Numerical Integration Methods

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Definition

For the purpose of this chapter, numerical integration is defined as methods for the computation of approximate numerical solutions of initial value problems that involve the cable equation. This may seem a rather narrow focus, but the fact is that most computational models of biological neurons and networks include mathematical representations of the origin, propagation, and interaction of electrical signals. It has been noted that the deterministic diffusion of chemical signals is described by equations that are formally equivalent to those that govern the spread of electrical signals and are amenable to similar computational approaches (Carnevale and Hines 2006; Zador and Koch 1994). Readers who wish more detail on these and related topics are referred to Chap. 4 in Carnevale and Hines (2006), as well as Iserles (2008), Polyanin et al. (2008), and Wolfram Research (2013). Phenomena that involve small numbers of molecules or ions require methods that are beyond the scope of this chapter.

Detailed Description

The aim of this chapter is to provide an intuitive introduction to numerical integration in the context of simulating model neurons. It begins with a brief discussion of the nature of the equations that are to be solved, then examines some approaches that have been employed to solve them, and ends with some comments to help users apply numerical integration to their own models.

The Nature of the Problem

The spread of electrical signals along an unbranched neurite is governed by the one-dimensional cable equation, a partial differential equation (PDE) that is a statement of conservation of charge in an anatomically extended structure. The cable equation is often written as

$$\frac{\partial V}{\partial T} + F(V) = \frac{\partial^2 V}{\partial X^2} \quad (1)$$

where T and X are time and anatomical distance scaled by factors related to the physical size of a neurite and the electrical properties of its membrane and cytoplasm, and V and F are continuous functions of T and X (Rall 1977; Jack et al. 1983). Branched cellular architectures can be accommodated by combining multiple instances of the cable equation (one for each unbranched neurite) with appropriate boundary conditions. An analytical solution to the cable equation would express membrane potential as $v(t, x)$, a continuous function of time and position. In special cases it is possible to solve the cable equation analytically, and those solutions have produced many general insights into neuronal function (Rall 1977; Jack et al. 1983; Segev et al. 1995).

However, models that include the anatomical and biophysical complexities of real cells typically produce equations that do not have analytical solutions. The classical example is the Hodgkin-Huxley model of spike propagation along squid axon (Hodgkin and Huxley 1952):

$$C_m \frac{\partial v}{\partial t} + \bar{g}_{na} m^3 h (v - e_{na}) + \bar{g}_k n^4 (v - e_k) + g_l (v - e_l) = \frac{1}{4D} \frac{\partial}{\partial x} \left(\frac{D^2}{R_a} \frac{\partial v}{\partial x} \right) \quad (2)$$

In this equation, the gating variables h , m , and n are governed by first-order ordinary differential equations (ODEs) whose rate constants depend on local membrane potential v , and the parameters C_m , $\bar{g}_{na}$, $\bar{g}_k$, and g_l (specific membrane capacitance and channel conductance densities) may vary with position; furthermore, equations with such complexities must be solved numerically.

Discretization of the Cable Equation

A broad class of strategies for numerical solution of initial value PDEs is based on the notion of discretization. Discretization involves approximating a PDE, whose dependent variables are temporally and spatially continuous, with a set of difference equations that relate the dependent variables to each other at a finite set of points in time and space. This is done by approximating the temporal and spatial derivatives with algebraic difference formulas, and it produces a family of difference equations. The difference equations are then solved algebraically in order to compute the future values of state variables from their present (and possibly past) values. Instead of producing a solution that is a continuous function of time and position, the result is an approximate solution $v_{ij} = v(t_i, x_j)$ over a finite set of points in time and space. The error introduced by discretization depends on the algebraic formulas used to approximate the derivatives and the size of the temporal and spatial intervals between adjacent solution points.

Here we introduce basic concepts involved in discretization and then explore the stability and precision of various integration methods in the context of some simple models. This discussion is guided by the fact that models of neurons that involve biological anatomical and biophysical details pose a special challenge because the equations that describe them are very stiff, that is, they are characterized by a wide range of time constants. For example, even though neurons typically have membrane time constants on the order of tens of milliseconds, longitudinal redistribution of charge along the length of a neurite has sub-millisecond kinetics, and short neurites or dendritic spines can introduce sub-microsecond time constants. Single-compartment model neurons are not immune from stiffness, because some voltage- and ligand-gated ion channels (especially spike sodium channels and AMPAergic synaptic channels) have sub-millisecond time constants. Some voltage- and ligand-gated potassium channels are much slower, on the order of hundreds of milliseconds, while ion accumulation and active transport can produce concentration changes and shifts

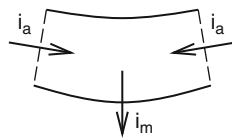
of membrane potential that evolve over seconds or minutes.

Because of the stiffness of neural models, explicit integration methods (methods that predict future values from present and past values) can require impractically small Δt to avoid instability; this is illustrated below. Also, stability issues aside, the utility of high-order methods in fixed time step integration can be limited by the necessity of using short time steps to follow the time course of rapidly changing state variables. Consequently, only a few of the many methods that have been developed for numerical solution of PDEs are suitable for simulating models of biological neurons and networks.

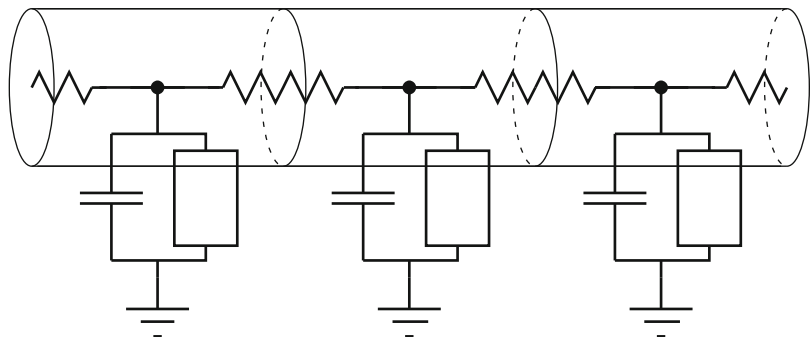
Spatial Discretization

Spatial discretization is the first step in transforming the cable equation to algebraic difference equations. It approximates a spatially continuous physical system by a set of coupled compartments, each of which is small enough that membrane current density can be treated as nearly uniform over its surface. Figure 1 portrays such a region; as indicated by the arrows, axial currents i_a are reckoned as positive if they enter the region, and membrane current i_m is positive when it exits.

Numerical Integration Methods, Fig. 1 A compartment with approximately uniform membrane current density



Numerical Integration Methods, Fig. 2 Equivalent circuit of a discretized cable



If membrane current density varies widely over a model cell, many compartments will be needed to satisfactorily represent this variation. The ODE that describes membrane potential in the j th region is

$$C_{mj} \frac{dv_j}{dt} + i_{ion_j} = \sum_j \frac{V_k - V_j}{r_{jk}} \quad (3)$$

where the left-hand side is the sum of the capacitive and ionic membrane currents in the j th region and the right-hand side is the sum of the axial currents that enter this region from its immediate neighbors.

If the compartments are of equal size and the points at which membrane potential and currents are computed are located at the compartment centers, the right-hand side of Eq. 3 is the central difference approximation to the PDE's second spatial derivative

$$\frac{\partial^2 v}{\partial x^2} \approx \frac{v_{j+1} - 2v_j + v_{j-1}}{\Delta x^2} \quad (4)$$

where Δr is the resistance of the cytoplasm between adjacent compartment centers. Figure 2 shows the equivalent electrical circuit for three adjacent compartments along a neurite that has been discretized according to the central difference approximation.

Each compartment's membrane properties is depicted as the parallel combination of a capacitor and a box that represents the contribution of ion channels to transmembrane current. These are attached to a node in the middle of the compartment, at which membrane potential is to be calculated; each node is separated from adjacent nodes by cytoplasmic resistance.

The accuracy of the central difference approximation is $O(\Delta x^2)$, i.e., the local error introduced by replacing the second partial derivative in space with the central difference approximation is proportional to the square of the distance Δx between adjacent nodes (Iserles 2008). As a consequence, the central difference approximation leads to numerical solutions that can be treated as piecewise linear approximations to the real solution. In other words, if v_j and v_{j+1} are second-order accurate at adjacent nodes x_j and x_{j+1} , linear interpolation can be used to find an order accurate value v^* at any point x^* that lies between them.

The outcome of spatial discretization can be rearranged and written in vector form as

$$\frac{dy}{dt} = F(y, t) \quad (5)$$

where the elements of y include not only the membrane potentials in each compartment but also the state variables associated with other dynamic processes such as ion channel gating and concentrations of ions and second messengers. The right-hand side includes t to acknowledge the possible presence of time-varying parameters (e.g., synaptic conductances) or signal sources such as current or voltage clamps.

Temporal Discretization

Temporal discretization completes the transformation of a PDE to a set of algebraic equations by substituting an algebraic approximation for the temporal derivatives. There is a wide variety of temporal discretization schemes that are characterized by different degrees of stability and orders of accuracy. Those that are most relevant to computational neuroscience are discussed in section “Specific Integration Methods” below.

Specific Integration Methods

An ideal numerical integration method would generate highly accurate solutions quickly and robustly regardless of the details of the model. Unfortunately it is not possible to meet all these

goals simultaneously. In general, there is a tradeoff between speed, stability, and accuracy.

Explicit Euler

The explicit Euler method is conceptually the simplest and easiest to implement. This is a first-order accurate approach (local error is proportional to Δt) that predicts the solution at the next time t_{i+1} , from the values of the state variables and their derivatives at the current time t_i . It approximates the ODE of Eq. 5 with

$$y_{i+1} = y_i + F(y_i, t_i)\Delta t \quad (6)$$

so advancing a solution from one time to the next requires only calculation of the derivatives followed by some multiplications and additions.

However, the total computational cost of a simulation depends not only on how much effort is needed to advance from one step to the next but also on the number of advances that must be performed. Explicit Euler’s weakness is that Δt must be smaller than the smallest time constant in the system in order to ensure stable solutions that are free of spurious oscillations. For example, consider the ordinary differential equation (ODE)

$$\frac{dy}{dt} = -\frac{y}{\tau} \quad (7)$$

According to the explicit Euler method, given y_i at time t_i , the “recurrence equation” that generates y_{i+1} at time t_{i+1} is

$$y_{i+1} = y_i(1 - \Delta t/\tau) \quad (8)$$

The graphs in Fig. 3 compare the analytical solution for Eq. 7 with $\tau = 1$ and initial condition $y = 1$ (left panel, dashed line) to numerical solutions calculated by the explicit Euler method using different values of Δt . In both graphs the horizontal axis is time in seconds. If $\Delta t < \tau/2$ (left panel, solid line, $\Delta t = 0.5$), the numerical solution evolves smoothly with time and converges toward the analytical solution. Even though there is some error in the numerical solution, the solution is stable because the error decreases at each new time step and approaches 0 in the limit as $t \rightarrow \infty$.

If Δt lies in the interval $(\tau/2, t)$ (right panel, dashed line, $\Delta t = 1.9$), the numerical solution shows spurious oscillations. That said, it is still stable because error decreases with time and the solution converges toward the analytical solution. However, if $\Delta t > 2\tau$, the solution becomes unstable: each advance of the solution now amplifies whatever error was already present, so the oscillations grow without limit (right panel, solid line, $\Delta t = 2.1$).

The instability of the explicit Euler method is a particular problem for multicompartmental models because spatial discretization introduces very fast time constants, especially when very small compartments are present. Consider a model cell that has a 10 μm diameter spherical soma to which a cylindrical spine with diameter = length = 1 μm is attached. Let all membrane be passive with resting membrane potential 0 mV, specific membrane conductance and capacitance 0.001 S/cm² and 1 $\mu\text{F}/\text{cm}^2$, respectively, and cytoplasmic resistivity 160 Ωcm . The electrical equivalent circuit for this model is shown in Fig. 4, where the soma's parameters are $r_0 = 3.183\text{e}2$ meg Ω and $c_0 = 3.142\text{e}-3$ nF, the spine's parameters are $r_1 = 3.183\text{e}4$ meg Ω and $c_1 = 3.142\text{e}-5$ nF, and the coupling resistance between them is $r_a = 1.0186$ meg Ω . This circuit has two time constants: the slower one is 1 ms, and the faster is $\sim 3.2\text{e}-5$ ms.

If membrane potential is 1 mV in the soma and spine when $t = 0$, v_0 and v_1 should follow a monoexponential decay described by e^{-t} , i.e., membrane potential in the soma and the spine

should both decay toward 0 with a time constant of 1 (Fig. 5).

One might think that this model could be simulated using the explicit Euler method with $\Delta t = 0.1$ ms. However, the simulation blows up after 0.4 ms, as shown below. This happens because finite precision arithmetic introduces roundoff errors, which are magnified at each step until they completely dominate the simulation (Fig. 6).

Implicit Euler

Like explicit Euler, the implicit Euler method also has first-order accuracy. It differs from explicit Euler in that its recurrence equation is based on the derivative at the new time t_{i+1} , i.e.,

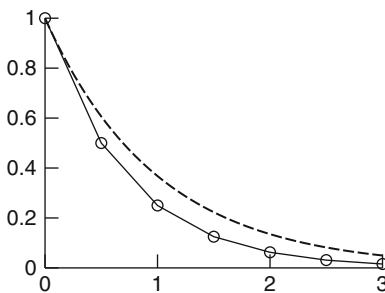
$$y_{i+1} = y_i + F(y_{i+1}, t_{i+1})\Delta t \quad (9)$$

Gathering all terms at time t_{i+1} to the left-hand side produces a set of algebraic equations

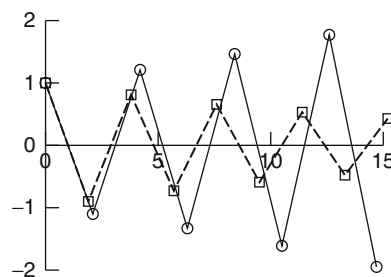
$$y_{i+1} - F(y_{i+1}, t_{i+1})\Delta t = y_i \quad (10)$$

which must be solved in order to compute the solution at the new time. Now we see why this is called the implicit Euler method: the new value of y is not computed directly from the previous value, but instead is implicit in a set of equations.

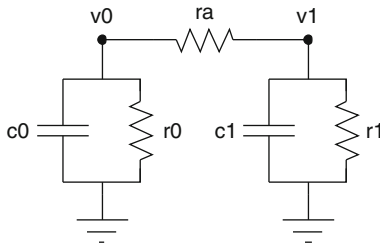
It is clear that implicit Euler requires more computations to advance from one step to the next than explicit Euler does. That said, solving Eq. 10 is easier than it might seem, because the rows on its left-hand side that correspond to the nodes of the



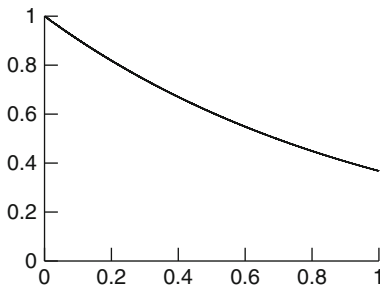
Numerical Integration Methods, Fig. 3 Left: given a small enough time step, the explicit Euler solution (solid line) is a stable approximation to the analytical solution of



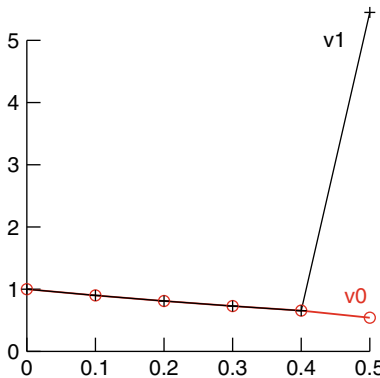
Eq. 7 (dashed line). Right: oscillations and frank instability may result if the time step is too large. See text for details



Numerical Integration Methods, Fig. 4 Closely coupled compartments, such as those in this simple model, are a special problem for the explicit Euler method. See text for details



Numerical Integration Methods, Fig. 5 Analytical solution for the time course of membrane potential in the model of Fig. 4 if both compartments start at the same initial condition



Numerical Integration Methods, Fig. 6 The explicit Euler method is unstable even though the integration time step is small compared to the time constant that governs the decay of membrane potential in Fig. 5. See text for details

discretized cable equations are equivalent to a tri-diagonal matrix and can be solved very efficiently (Hines 1984), a consequence of the fact that neurons are singly connected branched structures.

Implicit Euler's extra computational effort is compensated by its greatly improved stability. Applying it to Eq. 7, temporal discretization yields

$$y_{i+1} + \frac{y_{i+1}}{\tau} \Delta t = y_i \quad (11)$$

so the recurrence equation is

$$y_{i+1} = \frac{y_i}{1 + \frac{\Delta t}{\tau}} \quad (12)$$

which is stable for any combination of positive τ and Δt , i.e., any plausible circumstance. Figure 7 illustrates numerical solutions generated from Eq. 12 for $\tau = 1$ and initial condition $y = 1$.

The analytical solution is plotted as a dashed line; the numerical solution in the left panel used a time step Δt of 0.5, and those in the right panel used Δt of 1, 2, and 5, respectively (thin, medium, and thick lines). Note that all numerical solutions converge on the analytical solution and that there are no spurious oscillations. Implicit Euler also handles stiff models very nicely; the two-compartment model described earlier poses no problem for it.

One useful feature of implicit Euler is that even when Δt is large compared to any time constant in a linear system, it still tends to produce solutions that are qualitatively correct; for a nonlinear system Δt must be small enough to capture important features of the solution trajectory (e.g., an action potential). For a stable linear system, a single-step approaches the steady-state solution as $\Delta t \rightarrow \infty$ (Chap. 4; Carnevale and Hines 2006).

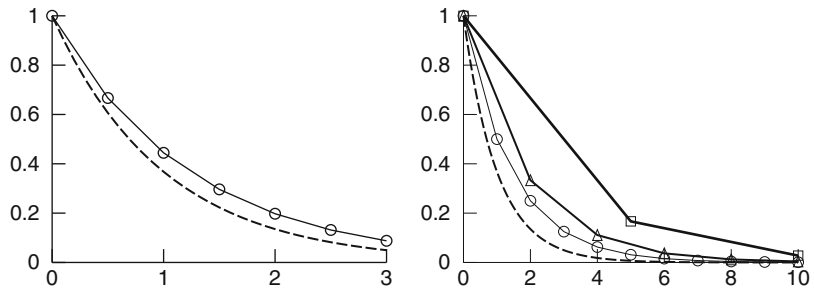
Crank-Nicholson

The Crank-Nicholson (C-N) method applies the central difference approximation to both time and space, so it is second-order accurate in both (Crank and Nicholson 1947). C-N is conceptually equivalent to using implicit Euler to advance by $\Delta t/2$, then using explicit Euler to advance by another $\Delta t/2$, and involves little more effort than a single implicit Euler advance:

$$y_{i+1} = 2y * -y_i \quad (13)$$

Numerical Integration Methods,

Fig. 7 Numerical solutions to Eq. 7 that are generated with the implicit Euler method are stable even if the time step is large compared to the time constant



where y^* is the intermediate result produced by the implicit Euler half-step advance

$$y^* - F(y^*, t_i + \Delta t/2) \Delta t/2 = y_i \quad (14)$$

To understand why, consider this example that involves a single ODE. The implicit Euler half step is equivalent to starting at point $(t, y(t))$

$$(t, y(t)) \bullet$$

and moving to an intermediate point $(t + \Delta t/2, y^*)$ where the slope $F(t + \Delta t/2, y^*)$ points back to $(t, y(t))$.

$$\begin{array}{l} \bullet \\ \text{dy/dt} = F(t + \Delta t/2, y^*) \\ \bullet \\ (t + \Delta t/2, y^*) \end{array}$$

The explicit Euler half step then uses this same slope $F(t + \Delta t/2, y^*)$ to move from the intermediate point $(t + \Delta t/2, y^*)$ to the new solution point $(t + \Delta t, y(t + \Delta t))$.

$$\begin{array}{l} \bullet \\ \text{dy/dt} = F(t + \Delta t/2, y^*) \\ \bullet \\ \text{dy/dt} = F(t + \Delta t/2, y^*) \\ \bullet \\ (t + \Delta t, y(t + \Delta t)) \end{array}$$

Since the slope is the same for both half steps,

$$\begin{aligned} y(t + \Delta t) &= y(t) + 2(y^* - y(t)) \\ &= 2y^* - y(t) \end{aligned} \quad (15)$$

This result readily generalizes to a system described by a family of ODEs.

The advantages of C-N over first-order methods for dealing with time are that it offers greater accuracy for nearly the same computational effort when more accuracy is necessary and it allows use of larger Δt without sacrificing

accuracy when speed is important. Also, second-order accuracy in time means that linear interpolation produces second-order accurate values between adjacent solution times.

However, C-N is prone to spurious oscillations if the system equations are too stiff. This occurs if

$$\frac{\Delta t}{\tau_m} > \frac{2}{1 + 4\left(\frac{\lambda}{\Delta x}\right)^2} \approx \frac{1}{2} \left(\frac{\Delta x}{\lambda}\right)^2 \quad (16)$$

where τ_m is the membrane time constant, λ is the DC length constant, and Δx is compartment length – in other words, when the model's spatial discretization is too fine for the integration time step (Carnevale and Hines 2006). It can also happen if the model includes a voltage clamp, because voltage clamps introduce very fast time constants. Note that even if oscillations do occur, they die out with time, so C-N is stable.

Higher-Order Methods and Adaptive Integration

Methods that have a higher order of accuracy are tempting because of the possibility that the extra computational cost of using a high-order method will be repaid by the ability to take fewer, longer steps between simulation points without compromising simulation results. However, this advantage comes at the cost of greater computational burden per time step. Also, high-order methods tend to be unstable when applied to stiff equations unless Δt is kept small (Iserles 2008).

An alternative strategy for efficiently generating accurate simulations is to use an adaptive integration scheme, in which the computer

automatically adjusts integration step size and/or order of integration so that local error lies below a user-specified criterion. Adaptive integration can often reduce total run time, but the computational overhead per advance is larger than with fixed Δt methods and some simulations will actually slow down.

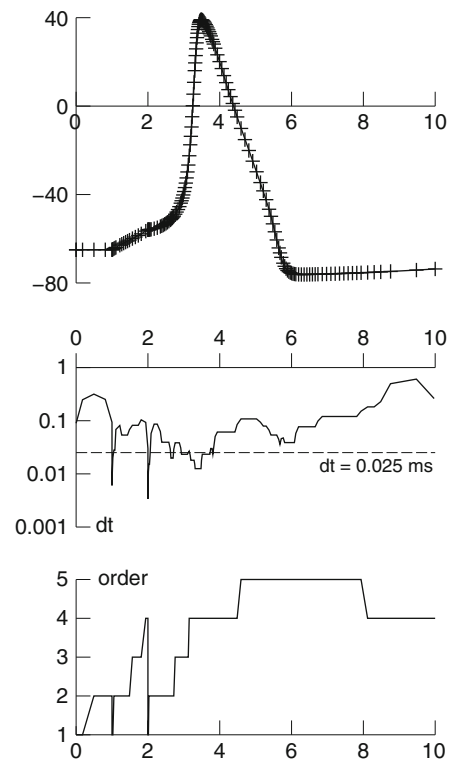
The principal advantage of adaptive integration is improved quality of the numerical results, since local error is controlled and solution points are calculated at shorter time intervals when state variables are changing rapidly and at longer intervals when not much is going on.

This is illustrated in the following figure, which shows an action potential generated by NEURON (Carnevale and Hines 2006) from a single-compartment model with $100 \mu\text{m}^2$ surface area and Hodgkin-Huxley membrane properties subjected to a $0.01 \text{ nA} \times 1 \text{ ms}$ stimulus current that started at $t = 1 \text{ ms}$. The simulation used the CVODES adaptive integrator of the SUNDIALS suite (Hindmarsh et al. 2005) with absolute error tolerance 0.001. The + marks on the voltage trace indicate the times at which solutions were generated; the other two graphs show how Δt and integration order were varied during the simulation in order to satisfy the error criterion. For most of the simulation, integration order was >2 and Δt was substantially longer than 0.025 ms, NEURON's default for fixed time step integration (dashed line in middle graph). Note that Δt became very small and order dropped back to 1 at the start and end of the stimulus current; this happened because an abrupt parameter change constitutes a new initial value problem and forces restart of the integrator (Fig. 8).

Practical Considerations

How to Select Δt and Δx

The general idea is to make Δt and Δx small enough that the simulation captures important features of model behavior in space and time with reasonable accuracy, but not so small as to needlessly prolong simulation time, increase storage requirements, or make results susceptible to cumulative roundoff error. Even if run time is not important, the tactic



Numerical Integration Methods, Fig. 8 Hodgkin-Huxley spike calculated by adaptive integration. *Top trace:* each solution point is marked by a +. *Middle and bottom traces:* integration time step and order vary to satisfy the error criterion

of cutting Δt and Δx in order to reduce the error from one time step to the next (“local error”) is eventually limited by the accumulation of local error, which increases global error.

That said, certain models and integration methods may limit one's options. As we have seen, the explicit Euler method becomes unstable if Δt is larger than the fastest time constant in the model, and avoidance of oscillations with the Crank-Nicholson method requires use of time steps small enough that temporal error does not outweigh spatial error (Eq. 16). Even with methods for which stability or oscillations are not an issue, it is important to remember that accuracy at short spatial scales may require the use of short time steps and vice versa (e.g., simulations of the time course of Ca^{++} concentration in the near vicinity of open channels). Often an empirical approach is necessary, such as making

Δt smaller until simulation results are qualitatively unchanged, then doing the same for Δx , and repeating until there is no further qualitative change in results.

Hines and Carnevale (2001) described various rules of thumb for spatial discretization of the cable equation and introduced a new approach called the “d_lambda rule” which bases spatial discretization on the AC length constant λ_f at a frequency f so high that membrane current is almost exclusively capacitive and ion channel density doesn’t matter. The rationale is that good temporal accuracy implies the accurate simulation of signal propagation at “high” frequencies. According to the d_lambda rule, a neurite is represented by N pieces of equal length where N is just large enough to satisfy

$$\frac{\text{Neurite length}}{N} < d_lambda \lambda_f \quad (17)$$

where the AC length constant for a cylinder with diameter d μm , cytoplasmic resistivity R_a Ω cm, and specific membrane capacitance C_m $\mu\text{F}/\text{cm}^2$ is

$$\lambda_f \approx \frac{1}{2} \sqrt{\frac{d}{\pi f R_a C_m}} \quad (18)$$

Membrane capacitive current far outweighs ionic currents at frequencies at least 5 times faster than the frequency that corresponds to the membrane time constant, i.e., $f > 5/(2 \pi \tau_m)$. For most cells, it turns out that 100 Hz is more than fast enough, and d_lambda = 0.1 at 100 Hz is sufficient to produce good results.

The advantages of the d_lambda rule include the facts that it is effective, avoids excessive discretization, and is easily automated. The NEURON Simulation Environment offers the d_lambda rule as a feature of its CellBuilder tool, but in principle it could be easily implemented for any multicompartmental simulator.

Physiological Precision

Any discussion of the accuracy of numerical integration in the context of empirically based

modeling in computational neuroscience would be incomplete without asking the question: how precise must a simulation be in order to be useful? The answer is it depends.

One concern often raised about empirically based models is the limited precision of experimental data. In order to be useful for simulation, such data are often fit to functions that may have a sound theoretical basis yet are only capable of approximating the actual relationships between dependent and independent variables. For parameters that result in a trajectory passing near a separatrix, simulation results may be highly sensitive to variation in any model parameter or simulation parameter (e.g., Δt , Δx , order of integration) (Chap. 4; Carnevale and Hines 2006); the same is true for the behavior of a system that lies near a bifurcation.

It is widely acknowledged that results that depend on very finely tuned parameters are biologically implausible because they seem unlikely to be robust.

But what degree of accuracy is justified by natural biological variability, let alone the quality of the data from which parameters are estimated? Golowasch et al. (2002) pointed out the wide range of parameter values observed in normally functioning neurons and provided evidence for covariance between parameters. To minimize the effects of biological variability and to avoid the confounding effects of parameter covariance, it would be best for all parameters to have been acquired in a single set of experiments on a single cell or network. However, this is not possible; modelers must rely on parameters gathered from experiments performed in different labs on different cell types from different species.

Seldom mentioned is another, deeper issue: the results of any model simulation are at least four times removed from the original physical system. The first separation occurs with the formulation of a conceptual model, which of necessity is a simplified representation of physical reality. Indeed, simplification affects all research, even that which does not involve computational modeling, because it is an unavoidable consequence of the way we develop an understanding of complex systems. Two more separations are imposed when the time and space derivatives are replaced

by discretization formulas; this produces a new system that is only an approximation to the original physical system. The fourth separation happens when the discretized equations are solved numerically. Each of these separations is a potential source of error that could reduce the value of a simulation as a means for gaining insight into the original physical system. Discretization schemes and numerical integration methods are useful to the extent that the errors they introduce are manageable and allow at least a qualitative understanding of the original conceptual model.

To summarize, numerical integration applied to computational neuroscience models computes an approximate solution to one or more equations that are themselves approximations, and everything rests on partial knowledge inferred from imprecise measurements. In light of this, judgment is required when applying numerical methods so that results have what might be called “physiologically appropriate precision.”

Acknowledgments This work was supported by NIH award R01NS011613.

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Oculomotor Control, Models of

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Definition

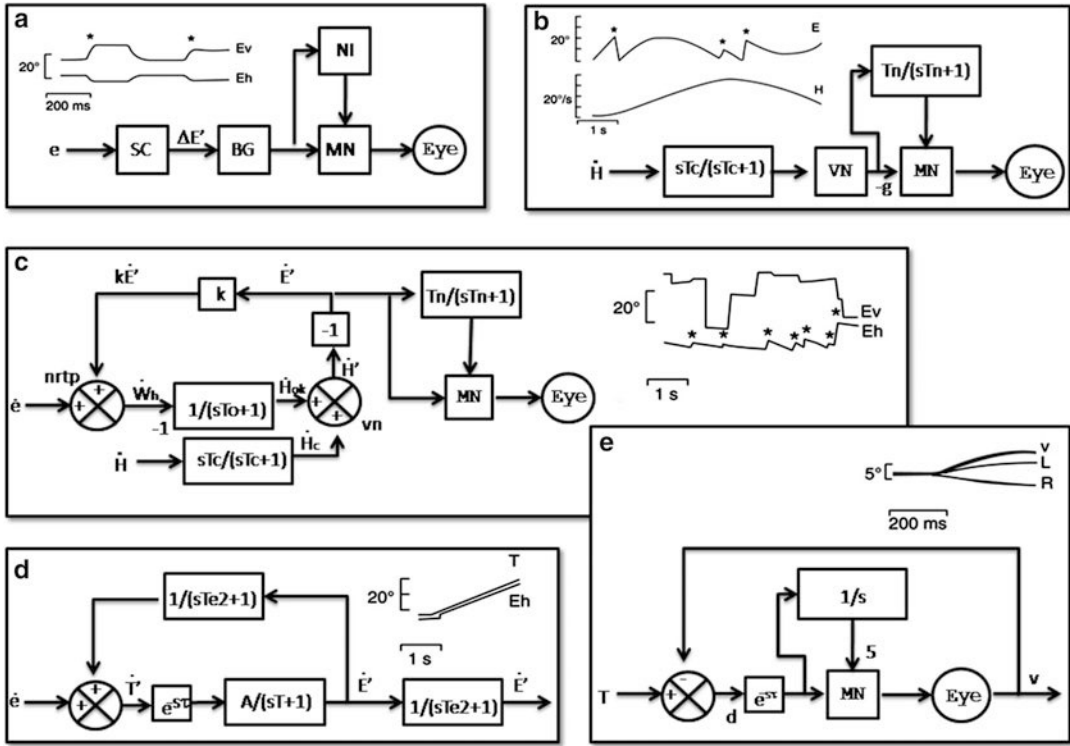
A system of differential equations simulating the part of the brain that is responsible for the control of ocular movements. Each equation describes the evolution of the output of one unit (which can be a single neuron, a group of similar neurons, or the aggregate operation of a nucleus or brain area) given the inputs it receives and its intrinsic properties.

Detailed Description

The oculomotor system is one of the best understood parts of the mammalian brain. It is made up of more than 50 different classes of cells occupying several areas and nuclei distributed through much of the brain of higher mammals. Computer models allow us to organize the mass of available information about this system, to determine whether existing knowledge is sufficient to account for its overall properties as well as of the

cells that comprise it, and to derive precise quantitative predictions in order to guide future research. Models are validated against experimental evidence, in that (1) model output should fit oculomotor psychophysics, (2) the activation functions of model units should fit known neurophysiology, (3) connections between model units should fit known neuroanatomy, and (4) “lesion”/“activation” of model units should fit neurology and the results of lesion, ablation, reversible inactivation, and central microstimulation studies. Ideally, model assumptions and predictions are consistent with all four classes of experimental data, *simultaneously*. However, reliance on unknown connections, discharge patterns, and the generation of unheard of motor responses is sometimes valuable as it can lead to the design of experiments to see if they reflect reality, and the “discovery” of previously unseen or disregarded entities (cells, anatomical connections, or patterns of eye movements).

There are five different kinds of eye movements each controlled, largely independently, by one of the five different oculomotor subsystems. Modeling efforts generally target one of these subsystems and, accordingly, I will describe them separately. Figure 1 provides examples of these movements, recorded from primates ((a) rapid eye movements, saccades; (b) vestibuloocular responses, VOR; (c) optokinetic responses, OKR; (d) smooth pursuit; (e) vergence/divergence) together with block diagrammatic illustrations of the subsystems responsible for



Oculomotor Control, Models of, Fig. 1 The different types of eye movements executed by monkeys and the subsystems that serve their execution (Modified from a previous publication of the author, 2009). (a) Saccades. (b) VOR. (c) OKR. (d) Smooth pursuit. (e) Vergence. Note

the difference in the time scales employed. *Upward trace deflection* indicates rightward movement. *Asterisks* in (a–c) mark saccades. The abbreviations are explained in the text

their execution. All five oculomotor subsystems feed into the final common path, the motoneurons (MNs), which innervate one of the six extraocular muscles in each eye.

To generate an eye movement, the signals carried by OMNs must fit the mechanics of the eye, the surrounding orbital tissue and contracting/relaxing muscles (collectively referred to as the oculomotor plant). Knowledge of the dynamics of the plant allows one to calculate the signals needed to drive it. Accordingly, considerable modeling and experimental effort has been invested in elucidating these. If the transfer function of the oculomotor plant (the Laplace transform of its impulse response) were a single pole low-pass filter (this is what is assumed with the use of the expression $1/[sT_e + 1]$, T_e being its time constant), it would need pulse-step increments in force to produce a saccade (Robinson 1981a). The assumption that the transfer function of the

oculomotor plant has additional poles and zeroes (the roots of its denominator and numerator polynomials, respectively) leads one to expect more complex control signals (Goldstein 1987; Sklavos et al. 2005).

Models of the Saccadic System

Saccades are the rapid eye movements with which humans and other primates explore the visible world. Figure 1a includes a minimalist illustration of the neural subsystem entrusted with their control. Its central unit is the BG (burst generator). This is a fairly complex circuit (Moschovakis et al. 1996) made of several classes of neurons and is often modeled in its own right (e.g., Scudder 1988; Moschovakis 1994). The BG compares desired gaze displacement (desired gaze direction according to others) with actual gaze

displacement (direction). It uses a frequency code to specify the size of saccades (in that the frequency of discharge of its cells increases with the size of the movement) in a Cartesian frame of reference (in that a leftward horizontal BG is responsible for leftward horizontal saccades, an upward BG is responsible for upward saccades while additional burst generators deal with rightward and downward movements). Because the signals compared are entirely confined to the central nervous system, the control loop concerned is known as a “local loop.”

The BG sends signals to motoneurons both directly and indirectly through a neural integrator (NI). This is also a fairly complex piece of neuronal machinery (Moschovakis 1997) that is also modeled separately (Sklavos and Moschovakis 2002). Its transfer function, $T_i/(sT_i + 1)$, has a time constant (T_i) very long relative to that of the eye (more than two orders of magnitude longer). Together the BG and the NI match the command signals to the mechanical properties of the eye (collectively acting as the inverse model of later literature in a process known as impedance matching). In addition signals exiting the BG and the NI must respect eye conjugacy (the fact that during saccades, smooth pursuit, etc., the eyes move in the same direction and by roughly the same distance) and ensure the implementation of Hering’s law of equal innervation. Finally, neural machinery must be deployed to ensure the implementation of Descartes’ rule (i.e., that antagonist muscles will be inactivated when synergists are activated) and to couple orthogonal burst generators (as in the case of oblique saccades).

The box labeled SC stands for the superior colliculus, also a piece of circuitry that has been extensively modeled (e.g., Waitzman et al. 1991; Arai et al. 1994; Bozis and Moschovakis 1998). It serves as the model’s sensorimotor interface and ensures the accuracy of the movement relative to the location of the target that elicits it. The SC is a layered midbrain structure that uses polar coordinates to represent retinal error ((e) the distance between the fovea and the retinal representation of visual targets) in terms of the rostrocaudal and mediolateral location of active neurons in a sheet of similar cells comprising its superficial layers: targets near the fovea are represented rostrally and

peripheral targets caudally while medial (lateral) sites represent upper (lower) targets. A similar place code is employed in its deeper layers to represent movement metrics which contrasts the frequency code that motor-related brain structures usually employ for this purpose.

Models of the VOR

Figure 1b contains a simplified illustration of the three-neuron arc that serves the vestibuloocular response (Robinson 1981b). Disregarding the adaptation of the peripheral end organ, its lumped transfer function relates eye velocity in the head $\dot{E}$ to head velocity in space $\dot{H}$ and in Laplace transform notation is $\frac{\dot{E}(s)}{\dot{H}(s)} = -g \frac{sT_{vor}}{sT_{vor} + 1}$. Its gain, g (the negative sign indicates that the eye moves in a direction opposite to that of the head), is close to 1 and is under cerebellar adaptive control to compensate for modifications of the biology that accrue with the passage of time (e.g., the power of the glasses that the subject wears). The lumped transfer function of the VOR is the product of the transfer functions of all units between the end organ that senses head movement and the eye. The left-hand unit stands for the former (T_c being the time constant of the cupula). The difference between T_c (about 5 s) and T_{vor} (about 15 s; Robinson (1981b)) must be due to some other signal reaching the secondary vestibular neurons (VN; the $\dot{H}_{oA}$ signal considered below). The VN signal is sent to extraocular motoneurons, either directly or through a neural integrator (marked $T_n/(sT_n + 1)$) similar to that of the saccadic system. The simple circuitry of Fig. 1b provides an adequate account of the generation of the slow phases of vestibular nystagmus. The additional machinery needed to generate the quick phases (marked with asterisks) may involve additional classes of saccade-related neurons (Kitama et al. 1995) and has been the object of modeling efforts dedicated to it (Chun and Robinson 1978).

Models of the OKR

Because the transfer function of the canals (the leftmost unit of Fig. 1b) is $\frac{\dot{H}_c}{\dot{H}} = \frac{sT_c}{sT_c + 1}$, the VOR

compensates head velocity by only 37% 4 s ($= T_c$) after the onset of head movement and by less than 5% after 12 s. The optokinetic subsystem was developed to address this lack of sustained (i.e., low frequency) responses of the vestibular system to head movements. Figure 1c adds a block diagrammatic illustration of this second, optokinetic, subsystem onto the vestibular one and emphasizes the fact that the two subsystems cooperate closely. The summing junction on the right stands for the vestibular nuclei (VN) which receive both a transient estimate of head velocity from the vestibular end organ ($\dot{H}_c$) and the optokinetic signal ($\dot{H}_{ok}$) from the positive feedback loop on the left. The latter combines an efference copy of the eye velocity command sent to the plant ($\dot{E}'$) with retinal slip velocity ($\bar{e}$) to estimate the velocity of the movement of the visual world relative to the head ($\dot{W}_h = -\dot{H}_v$), the visual system's estimate of head velocity (on the leftmost summing junction, tentatively identified as the NRTP, the nucleus reticularis tegmenti pontis). The high-frequency components of this signal are removed by the low-pass unit $1/(sT_o + 1)$ to avoid duplication of the high-frequency range of the vestibular signal. The gain of its forward path, $\dot{H}_{ok}/\dot{e}$, is $-G_{ok}/(sT_{okan} + 1)$, where $G_{ok} (= 1/1 - k)$ is about 3–5 if eye velocity is 70–80% of drum velocity, and Tokan is the time constant of the optokinetic after-nystagmus (measured by rotating a drum at a constant velocity around the subject to drive the system to a steady state and then turning the lights off to open the outer, non-illustrated feedback loop that minimizes retinal slip velocity). The additional machinery needed to generate the quick phases of the optokinetic nystagmus (marked with asterisks in Fig. 1c) has also been the object of modeling efforts (e.g., Anastasio 1997).

Models of the Smooth Pursuit System

This phylogenetically most recent oculomotor subsystem is poorly developed in cats but evolved in foveate animals such as primates (Eckmiller

1987). Unlike afoveate stabilization of retinal images accomplished by the VOR and OKR, pursuit can stabilize images on a miniscule part of the retina while ignoring retinal slip everywhere else (Robinson 1981a). As with the OKR, relatively recent models of pursuit (e.g., Lisberger et al. 1987) also use a positive feedback loop such as that shown in Fig. 1d (modified from Robinson et al. 1986). Additional important features include the emphasis on the reconstruction of target velocity ($\dot{T}'$) from desired eye velocity ($\dot{E}'$) and retinal slip velocity ($\dot{e}$) and use of a delay (τ) on the forward limb of the feedback loop and of a model of the short plant lag ($1/sT_{e2} + 1$) on its return limb. The fact that smooth pursuit normally starts with a saccade provides one more example of the close cooperation between distinct oculomotor subsystems.

Models of Disjunctive Eye Movements (Vergence/Divergence)

To look between distant and close targets, the eyes must be moved disjunctively, i.e., in different directions, the right eye to the left and the left eye to the right in the example shown in Fig. 1e. The resulting change of the angle between the two lines of sight (vergence angle, v) is slow, largely dominated by the dynamics of the plant. The time course of v is almost exponential (with a time constant roughly equal to 0.2 s) in response to a sudden change of retinal disparity (a steplike jump of the target from far to near). Figure 1e illustrates an early model of the vergence system that emphasizes their time course (Robinson 1981a). It includes a delay (τ) of about 160 ms (the unit marked $e^{-s\tau}$), the experimentally determined latency of the system's response, and the notion that central pathways convey to extraocular movers a signal proportional to retinal disparity and five times its time integral. More recent models of the vergence system emphasize its interaction with the much faster saccadic system in a manner that allows for surprisingly quick changes of vergence angle.

Cross-References

- [Basal Ganglia: Control of Saccades](#)
- [Connectionist Models of CPG Networks](#)
- [Neuromechanics of Joint Coordination](#)
- [Spinal and Neuromechanical Integration: Overview](#)
- [Vestibular System: Overview](#)

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Further Reading

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Odor Learning

- [Large-Scale Models of the Olfactory Bulb](#)

Odor Processing

- [Large-Scale Models of the Olfactory Bulb](#)

Olfactory Computation and Adult Neurogenesis

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Definition

The initial processing of olfactory information (“olfactory computation”) by the brain is performed in the olfactory bulb. Strikingly, even in adult animals the largest population of neurons

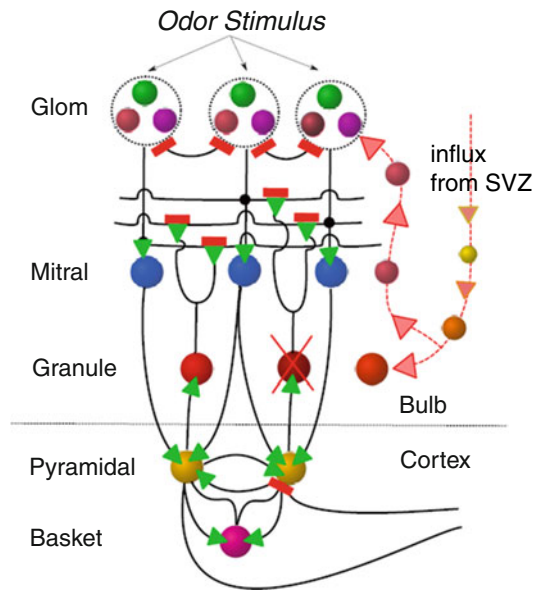
in this network is undergoing persistent turnover through neurogenesis and apoptosis, i.e., through the addition of new neurons and the subsequent death of a large fraction of them. This endows the network with computational power that yet has to be fully explored.

Detailed Description

Anatomy of the Olfactory Bulb

Olfactory processing begins with millions of olfactory receptor neurons (ORN) in the nasal epithelium. Each ORN expresses exactly one receptor gene, which determines the ORN's sensitivity spectrum across all odors. The number of different active receptor genes ranges from 50 in drosophila and 350 in humans to over 1000 in mice and rats (Murthy 2011). All ORNs expressing a given receptor gene project to a small number of glomeruli in the outermost layer of the olfactory bulb. Taken together, the inputs to all the glomeruli form an activation pattern or "olfactory image" that constitutes the first representation of an odor in the olfactory bulb. An initial reshaping of these patterns is performed in the glomeruli through intra- and inter-glomerular inhibition involving various types of periglomerular cells, external tufted cells, and short-axon cells (Fig. 1). Each glomerulus drives multiple mitral and tufted cells, which represent the principal cells of the olfactory bulb and project to various cortical regions.

A second reshaping of the odor representation arises from the mutual inhibition of mitral/tufted cells via granule cells, which constitute the largest population of neurons in the olfactory bulb. This inhibition is mediated by reciprocal dendrodendritic connections between mitral/tufted cells and granule cells on the secondary dendrites of the mitral/tufted cells. Since these dendrites can span across large fractions of the olfactory bulb, this inhibition can be long range. The reciprocal connections are comprised of glutamatergic, excitatory synapses from the mitral/tufted cells to the granule cells that are colocalized with GABAergic, inhibitory synapses from the granule cells back onto the



Olfactory Computation and Adult Neurogenesis, Fig. 1 Major cell types of the olfactory bulb and some of their connections with the cortex. The glomeruli (*glom*) are comprised of an ensemble of external tufted (*green*), periglomerular (*red*), and short-axon cells (*purple*). New adult-born periglomerular and granule cells arrive from the subventricular zone (*SVZ*). Excitatory (inhibitory) synapses are marked by *triangles* (*bars*)

respective mitral/tufted cells. The granule cells also receive centrifugal excitatory input from cortical structures like piriform cortex.

Physiology of Adult Neurogenesis

The olfactory bulb and the dentate gyrus are the only major brain areas in mammals to which new neurons are added in a steady stream even in adult animals. This has been best studied in rodents where on the order of 30,000, new interneurons arrive in the olfactory bulb every day (Kelsch et al. 2010). The vast majority of them develops into granule cells and a small fraction into periglomerular cells. Both cell types integrate functionally into the already established circuitry of the olfactory bulb. While a large fraction of the new neurons survives only for a brief period of 2–3 weeks, some new neurons survive for many months.

Adult-born periglomerular cells and granule cells differ in various aspects of their development (Lepousez et al. 2013). Periglomerular cells develop the ability to spike before their excitatory synaptic contacts appear and there is no strict order in which glutamatergic and GABAergic synapses are established (Kelsch et al. 2010). In contrast, in granule cells GABAergic inputs arise before glutamatergic ones, and the sodium currents that underlie action potentials develop only after synapses receiving excitatory inputs are formed. Moreover, the proximal synapses representing excitatory inputs from mitral cell axon collaterals and from cortical structures develop before the distal reciprocal synapses with mitral cells (Kelsch et al. 2010).

Even after their integration into the bulbar circuit, the adult-born cells undergo further development. Young adult-born periglomerular cells are more excitable than mature ones; this may also hold for granule cells (Lepousez et al. 2013). Proximal synapses of granule cells can undergo significant long-term potentiation, but only while the cells are young (Kelsch et al. 2010). Structurally, however, even in mature adult-born granule and periglomerular cells, the synapses exhibit substantial turnover, which is reduced in response to enriched odor exposure (Livneh and Mizrahi 2012).

The most striking feature of periglomerular cells and granule cells is the precise regulation of their survival and death. Their survival probability strongly depends on environmental factors. Odor enrichment during a critical period enhances their survival, while odor deprivation reduces it. In granule cells the critical period lasts from about 14 to 28 days after they are born (Lazarini and Lledo 2011); it begins therefore before the granule cells' distal synapses with the mitral cells are developed. The survival of periglomerular cells is sensitive to enrichment at least for 6 weeks. The detailed mechanisms controlling the survival are not yet understood. It is clear, however, that the apoptosis is the result of a precisely regulated program that removes the cells predominantly during postprandial slow-wave sleep (Lepousez and Lledo 2011). On the cell level, survival is enhanced if the excitability of granule cells is

increased by genetic means and vice versa (Kelsch et al. 2010).

Impact of Adult Neurogenesis on Behavior

Adult neurogenesis has substantial impact on the ability of animals to discriminate similar odors and to retain odor memories. Spontaneous odor discrimination is often assessed using a habituation task that makes use of the fact that animals lose interest in an odor that is presented repeatedly. If after habituation to an odor an animal explores a new odor significantly longer, it is clear that it is able to discriminate between the two odors. It has been found that mice can learn to discriminate spontaneously between very similar test odors if they are presented repeatedly over the course of 5–10 days with odors that are related to the test odors. This perceptual learning is compromised if adult neurogenesis is suppressed (Lazarini and Lledo, 2011).

Adult neurogenesis plays also a role in memory. In the habituation task, mice with intact neurogenesis remember an odor after a single exposure for at least 120 min. With adult neurogenesis suppressed, however, they treat a repeated odor as a novel odor after as little as 60 min. Similarly, in a long-term memory task in which mice have to retrieve a reward from one of the two odorized holes, intact animals remember the correct odor association for 5 days, while animals without neurogenesis do not. Interestingly, even though animals with and without functional neurogenesis do not remember an odor any more after 30 days, the intact animals relearn the previously memorized odor faster than those with suppressed neurogenesis (Sultan et al. 2010). It is important to note that this enhancement of long-term memory through neurogenesis is only found when the animals are trained on an operant task, i.e., if the animals actively have to associate an odor with a decision. Tasks in which the relevant odor is only passively associated with a reward do not enhance neurogenesis and their memory is not compromised when neurogenesis is suppressed (Lazarini and Lledo 2011).

Computational Modeling

So far, adult neurogenesis in the olfactory bulb has been studied from a modeling perspective only to a limited extent. Motivated by the general notion of the importance of contrast enhancement in early sensory processing and by the observation that in zebra fish the olfactory bulb reshapes odor representations such that the correlation between the activity patterns representing similar odors is reduced (Friedrich and Laurent 2001), the focus has been on the decorrelating function of the olfactory bulb.

Due to the high dimension of odor space, the two-dimensional activity patterns evoked by odor stimuli in the input layer of the olfactory bulb are fractured. Thus, in contrast to the stimuli of the visual, auditory, and somatosensory system, these patterns are not characterized by a smooth map. Instead, the chemical response spectra of neighboring glomeruli are not much more similar than those of glomeruli that are far apart (Murthy 2011). A neuronal network that has to process such complex activation patterns is quite likely to reflect that complexity. Surprisingly, sparse random networks of thresholding neurons quite effectively decorrelate such patterns (Wiechert et al. 2010).

At the same time, it has been pointed out that many odors do not have an inherent meaning to animals and that the interpretation of these odors is learned by experience (Wilson and Stevenson 2006). This suggests that the olfactory networks adapt to their odor environment. From this perspective it is natural to assume that one role of the turnover of interneurons in the olfactory bulb is to restructure the network and to enable it to adapt to the demands of the animal's environment. Such processes could generate networks that reflect the complexity of the representations of the relevant odorants.

In an early adaptive computational model, the effective mutual inhibition between pairs of mitral cells was taken to depend on the product of their activities, averaged across an odor ensemble (Cecchi et al. 2001). This simple evolution of the effective inhibition was sufficient to allow the network to learn to decorrelate the stimuli. In

later work the granule cells were modeled explicitly with a steady stream of new cells connecting to randomly chosen mitral cells through reciprocal synapses (Chow et al. 2012). It was found that if the cells' survival required that their activity across an odor ensemble surpass a threshold, such networks learn to decorrelate even very similar stimuli. This process could underlie the neurogenesis-dependent perceptual learning observed experimentally. As had been found experimentally, new granule cells were found to be more likely to respond to novel odors in this model. The decorrelation achieved by this network can be understood to arise in part from a normalization in which the activities of different mitral cells – averaged across the odor ensemble – are evened out.

Possible consequences of the experimentally observed enhanced excitability and plasticity of young adult-born interneurons have not yet been explored theoretically.

Conclusion

Adult neurogenesis represents a fascinating aspect of olfactory computation. It plays an important role in the processes underlying odor discrimination and memory. Modeling has so far only elucidated its possible role in odor decorrelation, which may contribute to odor discrimination. Since the granule cells involved in the neurogenetic turnover receive substantial direct glutamatergic input from cortical areas, it seems likely that adult neurogenesis plays a much more refined role in odor processing than is apparent in experiments so far. What this role might be is yet unknown.

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Olfactory Computation in Antennal Lobe and Mushroom Bodies

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Definition

The olfactory system maps complex and high dimensional stimuli (odors) into unique and reproducible dynamic ensembles of neuronal activity. In the insect, olfactory receptor neurons (ORNs) synapse onto a smaller group of excitatory projection neurons (PNs) and inhibitory local neurons (LNs) in the antennal lobe (AL) (Fig. 1). The odor information is then transferred to the mushroom body (MB), a structure

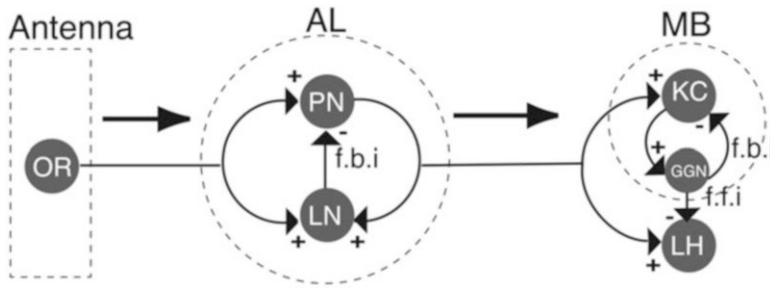
analogous to the olfactory cortex and where olfactory memories are formed. Inhibitory circuits of the AL and the MB shape the odor representation as it progresses through the olfactory system. The insect system is advantageous for studying and modeling olfactory coding because it is relatively simple and amenable to genetic manipulation.

Detailed Description

Olfactory neurons respond to static stimuli with oscillatory and temporally structured responses. The presence of odor-elicited oscillations in the olfactory systems of many animals including insects suggests oscillatory neural synchrony may play a fundamental role in odor encoding. Indeed, when the 20 Hz oscillations were specifically blocking by locally injecting picrotoxin into the antennal lobe (AL), locust olfactory neurons in a brain area called the beta lobe underwent a breakdown in the specificity of odor responses (MacLeod et al. 1998), and honeybees, in a behavioral test, lost the ability to discriminate odors (Stopfer et al. 1997). These results demonstrate oscillatory synchronization of AL neurons is needed for fine odor discrimination.

Computational models helped reveal mechanisms of synchronized network oscillations. Spikes in excitatory cells trigger spikes in widely-branching postsynaptic inhibitory neurons, whose spikes, in turn, produce inhibitory potentials in excitatory cells. This inhibition systematically delays and synchronizes the generation of the next excitatory response, thereby creating widespread network oscillatory synchrony (Borgers and Kopell 2003). A model of spike synchronization in the honeybee AL, also dependent on local inhibition, has been proposed to explain the experimentally-observed impairment of sensory discrimination when inhibition is blocked (Linster and Cleland 2001).

Interestingly, AL oscillations are generally not evoked by the first presentation of an odorant. Oscillations, rather, emerge gradually over the course of multiple encounters with a given odorant, provided the encounters occur close together in time. Electrophysiological (Stopfer and



Olfactory Computation in Antennal Lobe and Mushroom Bodies, Fig. 1 Information flow in the insect olfactory system. Olfactory receptor (OR) neurons in the antenna provide simply-structured input to the antennal lobe (AL). There, projection neurons (PNs) and local neurons (LNs) interact in part through feedback inhibition (*f.b.i*) to transiently synchronize spiking, and to generate

complex temporal firing patterns in PNs. PNs then provide distributed and temporally structured output to the Mushroom body (MB) and lateral horn (LH). In the MB, intrinsic neurons called Kenyon cells (KCs) interact through feedback inhibition with the unique Giant Gabaergic Neuron (GGN), resulting in very sparse and specific firing in KCs. GGN also provides feedforward inhibition (*f.f.i*) to the LH

Laurent 1999) and computational (Bazhenov et al. 2005) evidence suggests the increase in oscillatory synchronization results from activity-dependent plasticity within the AL. Models indicate that this plasticity, when engaged by repeating odor stimuli (as often occurs in nature) achieves robust stability against noise.

In the locust, GABA_A-dependent synchronization of a given pair of PNs is generally transient. Usually, after a few hundred milliseconds of firing spikes that are phase-locked to the oscillations, the synchrony between action potentials in a given PN and the field potential oscillations is lost; then, other subsets of PNs become synchronized. Computer models of the locust AL have suggested that the transient nature of PN synchronization could be explained by variations in inhibitory drive from inhibitory LNs over the duration of the odor-elicited response (Bazhenov et al. 2001a). Transient increases in feedback inhibition lead to increases in the timing precision of PN spikes.

Recent theoretical work led to a new strategy based on graph coloring theory to describe transient AL network dynamics (Assisi et al. 2011). In inhibitory neuronal networks, LNs that are not interconnected are given a particular “color”; these LNs can be active at the same time and can collectively inhibit LNs associated with a different color. In a model of the AL, these dynamics lead to alternating patterns of firing among groups

of LNs. This model of inhibitory network dynamics mediated by lateral inhibition between LNs can account for transient synchronization patterns of olfactory neurons in the AL. The role LN-LN inhibition may play in promoting competition among olfactory glomeruli has been also explored (Linster et al. 1994; Kerszberg and Masson 1995) and a model of olfactory memory based on altering lateral inhibition in the honeybee’s AL has been proposed (Linster and Masson 1996).

While the synchronization of PNs in the insects’ antennal lobe is eliminated by picrotoxin application, experiments performed *in vivo* have established that the slower firing pattern structures (alternating depolarizing and hyperpolarizing modes) are not affected by this treatment (MacLeod et al. 1998; Stopfer et al. 1997). In locusts, the origins of slow temporal patterning have been explored with electrophysiological studies and computational models. The patterns begin in olfactory receptor neurons, which respond to odors with a variety of simple firing patterns. The heterogeneity of these responses is an essential ingredient for the generation of more elaborate patterns downstream in the AL (Raman et al. 2010). In the AL, the slow inhibitory receptors between LNs and PNs, which operate with a time constant of a few hundred milliseconds, are essential for translating the simple but varying input received from the receptor neurons into the stimulus-specific slow temporal patterning of PN

responses (Bazhenov et al. 2001b). The sequences in which these modes appeared differ among PNs, and vary reliably with the stimulus. Relatively slow calcium and calcium-dependent potassium channels of PNs may further contribute to slow temporal patterning in the AL (Sivan and Kopell 2006).

What is the functional significance of the temporal structure in olfactory neuron responses? As shown in zebrafish (Friedrich and Laurent 2001) the slow temporal patterning in mitral cells appears to play a major role in the decorrelation of odor representations. The responses of a population of mitral cells to chemically similar odorants were highly correlated at the onset of the odor stimulation, but became progressively less correlated over the duration of the odor response. Recent computer modeling of the AL suggested that odor-specific evolution of PN activity can lead to an optimal encoding of the odor representation that decreases the overlap between odor-elicited PN spiking patterns (Assisi et al. 2012). This increases the ability of downstream neurons to discriminate between odors. A balance between inhibitory and excitatory connections mediated by local AL interneurons enhances the decorrelation of similar odors while keeping the representation robust in the presence of noise.

In insects, output from relatively small populations of olfactory neurons in the AL fans out broadly to large interneuronal ensembles in the mushroom body (Fig. 1). Fully half of all PNs synapse directly upon each KC, a connectivity scheme that maximizes the coding space available for odors (Jortner et al. 2007). Electrophysiological recordings indicate that Kenyon cells (KCs) of the mushroom body respond sparsely and specifically to odors: a given odor induces a brief response in only a small subpopulation of KCs (Perez-Orive et al. 2002). Mechanisms contributing to the specificity of this response include intrinsic nonlinear conductances in the KCs that respond best to coincident input from PNs, and inhibitory input from GGN (Papadopolou et al. 2011) that regulates the amount of firing in KCs (Fig. 1). Physiological and modeling results show the precise timing established by AL circuitry is

maintained not only within KCs, but also by their neural followers in the beta lobe (Cassenaer and Laurent 2007). Interestingly, odor specific timing precision is maintained in the beta lobe neurons, in part, by spike-timing dependent plasticity (STDP).

Computational models of the insect olfactory system have explored the proposal that AL circuitry reformats information about odors, distributing it into the identities of PNs responding to the odor, and into the relative timing of spikes in those PNs. Temporal features appear to become critical when discrimination tasks are more challenging, such as discriminating among PN ensembles that substantially overlap. Thus, the AL actively sharpens information about the olfactory stimulus by employing time and transient synchrony as coding dimensions. Understanding and testing hypotheses about these complex biological processes has been greatly facilitated by the use of computational models.

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Olfactory Computation in Glomerular Microcircuits

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Definition

The first, superficial computational layer of the vertebrate olfactory bulb consists of discrete spheroid clusters of neuropil known as glomeruli.

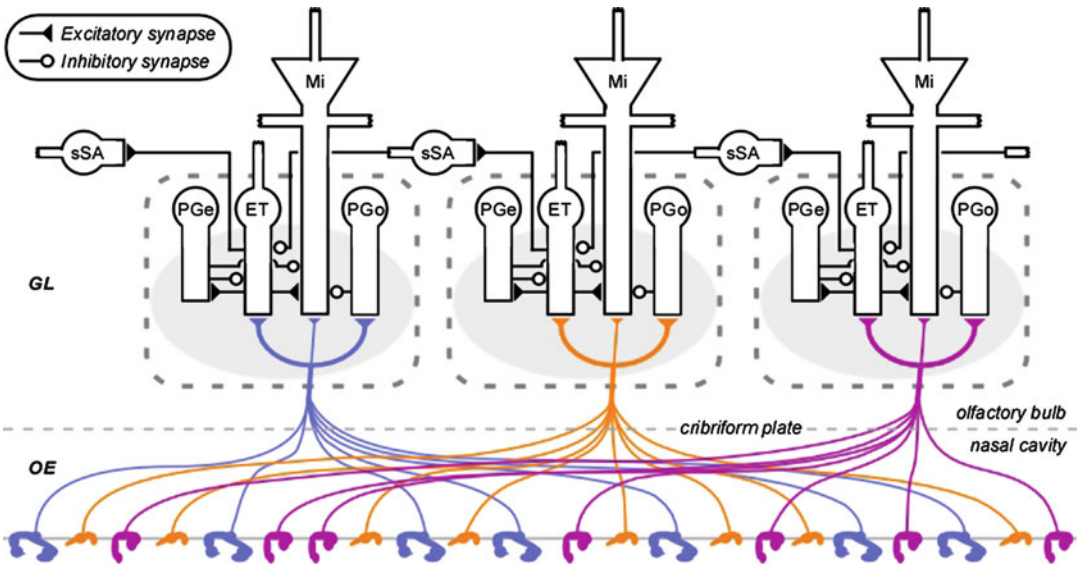
Within these glomerular microcircuits, primary olfactory sensory neuron axonal arbors interact with the dendrites of olfactory bulb principal neurons and multiple classes of local interneurons. The computations within and among these glomerular microcircuits determine how the primary sensory information arriving in the olfactory bulb is transformed prior to subsequent computations in the deep olfactory bulb and other regions of the brain. Among the important computations in the glomerular layer are a high-dimensional form of contrast enhancement and a competitive global normalization of activity levels across a population of second-order sensory neurons.

Detailed Description

The Olfactory Bulb

The olfactory bulb (OB) is the target of primary olfactory sensory neuron (OSN) axons that project across the blood-brain barrier at the cribriform plate (Fig. 1). Each OSN expresses, canonically, one type of odorant receptor protein from a family of hundreds (depending on species), and the specific receptor protein expressed determines the chemoreceptive field of that OSN. Critically, the axons of “sister” OSNs that express the same receptor converge together and arborize in the same location, forming a spheroid tangle of neuropil that is visible at the light microscopic level and known as a *glomerulus*. Inhaled odorants will bind to multiple odorant receptors with different affinities and hence will activate multiple glomeruli to differing degrees in patterns characteristic of that odor. These odor-specific patterns of glomerular activation are the basis for odor recognition.

Odor information is exported from the OB and propagated into the rest of the brain via mitral cells (Mi) and middle/deep tufted cells, the principal neurons of the OB. Importantly, while mitral cells can be activated directly by OSN input to glomeruli, the majority of their afferent excitation appears to be indirect, mediated via external tufted (ET) cell interneurons (Fig. 1). Mitral cell output also is strongly regulated by interactions with local interneurons within the glomerular-layer



Olfactory Computation in Glomerular Microcircuits, Fig. 1 Schematic diagram of glomerular microcircuitry in the olfactory bulb. Three different classes of olfactory sensory neuron in the olfactory epithelium (OE) of the nasal cavity project to three corresponding glomeruli (gray ovals) in the olfactory bulb glomerular layer (GL). Within each glomerulus, the sensory neurons activate principal neurons including mitral cells (Mi) and middle/deep tufted cells (not shown) as well as local interneurons including the excitatory external tufted (ET) cells and the inhibitory periglomerular (PG) and superficial short-axon

(sSA) cells. Some PG cells receive direct afferent input from olfactory sensory neurons (PGo), whereas the majority receive their afferent input indirectly via external tufted cells (PGe). PG and sSA neurons – particularly the latter – interconnect glomeruli nonspecifically, ultimately delivering broadly sourced feedback inhibition onto mitral cells (Banerjee et al. 2015) via intermediary ET cells (Whitesell et al. 2013). Deep bulbar circuitry (the interconnectivity of mitral cell lateral dendrites with granule cells) is not depicted

microcircuit (as well as a deeper layer of OB circuitry not discussed here) that transform these raw afferent representations; these local interactions also appear to act on mitral cells predominantly via ET cells (Whitesell et al. 2013). Specifically, as in other sensory systems, these early transformations of olfactory inputs include (1) the dynamic sharpening of primary sensory representations (Cleland 2010), (2) mitigation of the confounding effects of stimulus intensity (i.e., odorant concentration; Cleland et al. 2011), and (3) the constraining of absolute input intensity to levels that can be managed by follower circuitry. Unlike other sensory systems, however, the similarity space in which olfactory representations are embedded is computationally high-dimensional. Hence, similarity-dependent computations such as contrast enhancement (aka sharpening of the representation, a form of signal decorrelation) require algorithmic solutions capable of

computing in high-dimensional spaces. These solutions are implemented in the microcircuitry of the OB glomerular layer.

High Dimensionality

The high dimensionality of the system arises from the diversity of primary odorant receptors and the lack of a common physical basis function by which to organize their receptive fields. The chromatic receptive fields of the three types of cones in the human retina share the common basis of wavelength, and the diverse receptive fields of auditory hair cells all can be mapped along a one-dimensional basis of auditory frequency, but the receptive fields of olfactory receptors are essentially arbitrary with respect to one another. Given that, for any pair of odorant receptors, a ligand exists that will activate one and not the other, each odorant receptor type must be treated as independent. The similarity space that can contain all

possible odorant inputs therefore has the same dimensionality as the number of different odorant receptor types expressed – over 1000 in mice, roughly 350–400 in humans.

Critically, of course, not all possible odorant inputs or combinations thereof are equally likely. In any given, finite universe of odorants, the dimensionality of odor space can be reduced, often substantially. (Indeed, the putative dimensionality of olfactory similarity space has been measured in some studies, though the results obtained in these studies have more to do with the particular, limited set of odorants selected than with the nature of the olfactory system *per se*). A corollary of this principle is that any quantitative description of olfactory similarity space depends on the statistical structure of the olfactory environment – that is, how likely is it that any given odorant from this environment will differentially activate any given pair of odorant receptors? If the olfactory system is to be able to interpret any possible combination of receptor inputs received, then the high dimensionality of the input space is unavoidable.

Glomerular Microcircuitry

In general, each half of each OB in mice contains one glomerulus for each olfactory receptor type, to which the converging axons of that family of OSNs project (Mombaerts 2006). Because the high dimensionality of the olfactory similarity space cannot be continuously projected onto the two-dimensional surface of the OB, physical proximity cannot serve as a proxy for receptive field similarity as it can, for example, in the retina or the cochlear nucleus. The classical algorithm, nearest-neighbor lateral inhibition, therefore can be ruled out as an effective solution for olfactory contrast enhancement.

Instead, each intraglomerular microcircuit effectively generates its own inhibitory surround in olfactory similarity space by generating feed-forward inhibition of its own mitral cells that successfully inhibits excitatory throughput when the glomerulus is weakly or moderately activated, but that is overcome by direct OSN-to-mitral excitation when the glomerulus is strongly activated. That is, stimulation in the center of the chemoreceptive

field is propagated, whereas stimulation at the edge of the chemoreceptive field is inhibited below baseline. By eschewing competitive connections among different glomeruli, this non-topographical contrast enhancement algorithm is independent of olfactory dimensionality and will function irrespective of how many different olfactory receptors exist and irrespective of the comparative similarities of their receptive fields in any given environmental context (Cleland and Sethupathy 2006; Fukunaga et al. 2014). Moreover, the degree of sharpening produced by this microcircuit can be dynamically regulated by top-down inputs, such as cholinergic neuromodulation (Chaudhury et al. 2009; D'Souza and Vijayaraghavan 2012).

Non-topographical contrast enhancement uses relative levels of afferent excitation at each glomerulus as a proxy for ligand-receptor potency at the corresponding olfactory receptor and hence depends upon the global normalization of input activation levels across glomeruli to mitigate the confounding effects of concentration. Global feedback normalization preserves relational patterns of activity among glomeruli while also serving to constrain absolute afferent input levels within the relatively narrow dynamic ranges of follower neurons. In the OB, several mechanisms appear to contribute to the latter goal of matching absolute input activity levels to the needs of follower circuitry while preserving sensory information (Cleland et al. 2011); one of these in particular also underlies the competitive global normalization necessary to generate relational representations (Cleland et al. 2007; corrected implementation in Banerjee et al. 2015). Specifically, glomeruli across the OB are interconnected by a heterogeneous, laterally projecting network of GABAergic/dopaminergic periglomerular (PG) and superficial short-axon (SSA) cells.

Note that the nomenclature of these glomerular-layer inhibitory interneurons is evolving. The majority of these neurons express GAD67 and DAT and release both GABA and dopamine. This population is morphologically diverse and sometimes is treated as a single heterogeneous class (e.g., the DAT+ neurons of Banerjee et al.

2015), comprising most of the classically defined PG neurons and all of the classically defined sSA neurons. More recent work has established a clearer class difference within this heterogeneous population that corresponds reasonably to distinct PG and sSA cell types; specifically, GAD67+/DAT+ neurons with large somata and axons correspond to the sSA class, while those with smaller somata and no axon initial segment correspond reasonably to the PG class (Galliano et al. 2018). The PG class can be subdivided further into PGe and PGo subtypes by virtue of whether or not they receive direct input from the olfactory nerve (Fig. 1). Finally, a separate, smaller class of GAD65+, non-dopaminergic interneurons also is often grouped into the PG cell category and may contribute to both PGe and PGo morphological subtypes (discussed in Sethupathy et al. 2013).

Activation of these neurons inhibits mitral cells broadly across the OB, thereby feeding back a globally averaged level of inhibition across the mitral cell population that can mediate gain control (Banerjee et al. 2015). This operation constrains the dynamic ranges of absolute MC activation levels, thereby fulfilling a necessary prerequisite for non-topographical contrast enhancement (Cleland et al. 2007).

Summary

Glomerular microcircuitry in the OB is able to regulate the sharpening of sensory representations and normalize absolute input intensities so as to deliver more consistent and reliable sensory information to the neural circuitry of the deep OB, as well as to extrabulbar follower regions such as the anterior olfactory nucleus, piriform cortex, and olfactory tubercle. Additionally, lateral projections by ET cells selectively connect “sister” glomeruli (associated with the same odorant receptor type) across the OB and modulate the response properties of associated mitral cells (Zhou and Belluscio 2008). External tufted cells also are intrinsically resonant at roughly respiratory frequencies, bursting rhythmically when activated (Hayar et al. 2004), and may serve to temporally coordinate strongly activated and weakly

activated regions of the OB. Mitral cells also are intrinsically resonant, but at a faster beta-band frequency (Desmaisons et al. 1999); their resonance may govern the transformation of OB output into an energetically efficient metric based on spike timing that is relevant to computations within deep OB circuitry (Li and Cleland 2017) and potentially plastic. The essential function of glomerular layer microcircuitry appears to be to manage the physical complexities of odorant inputs, such as high dimensionality and uncontrollable stimulus intensities, thereby transforming afferent odor representations into a more manageable, diagnostic, and energetically efficient form.

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Further Reading

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Olfactory Computation in Mitral-Granule Cell Circuits

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Synonyms

[Vertebrate olfactory bulb computation](#)

Definition

Olfactory computation in mitral-granule cell circuits refers those operations between mitral and granule cells that can directly modulate the mitral cell firing behavior. In vertebrates, they are carried out by the reciprocal synapses established

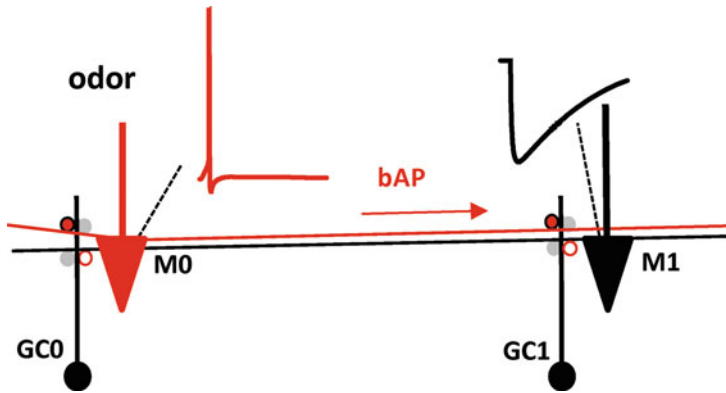
between mitral cells' lateral dendrites and spines on granule cell dendrites (Shepherd 2004).

Detailed Description

Mitral-granule cell circuits are formed by the continuous and dynamic reconfiguration of their synaptic connections during the entire life of the organism. Although, to date, there is no direct experimental evidence for plasticity of these synaptic connections, their sparse and distributed nature is well established (Willhite et al. 2006) and widely acknowledged as being the main mechanism responsible for the lateral inhibition effects observed in the olfactory bulb (Yokoi et al. 1995). This entry focuses on the circuitual aspects of the mitral-granule reciprocal synapses, rather than on how they can be established or destroyed through LTP/LTD or cells' turnover processes. All mitral-granule circuits are activated by a canonical sequence of steps, in which (a) an odor input facilitates one or more mitral cell somatic action potentials (APs); (b) these APs backpropagate along the lateral dendrites, releasing glutamate thereby activating granule cells along their way; and (c) granule cells locally inhibit the lateral dendrites of the mitral cells to which they are connected. The relative location of the activated granule cell with respect to the soma of a mitral cell can generate different circuits with different computational properties, such as (1) *distance-independent lateral inhibition*, (2) *synchrony*, and (3) *gating effects*.

Distance-Independent Lateral Inhibition

While granule cells connect to dendrodendritic synapses along the full span of the lateral dendrites, the inhibition from any granule cell onto the mitral cell is local. As such, those granule cells near to the mitral cell soma can more easily regulate its firing than those far away. The implication for one mitral cell to strongly laterally inhibit another is that the granule cell shared between the two mitral cells must be near to the soma of the target neuron. While inhibition is local, because of the broad field of granule cells,



Olfactory Computation in Mitral-Granule Cell Circuits, Fig. 1 Distance-independent lateral inhibition. Inhibition can be independent of the relative distance between mitral cells (*M0* and *M1*) if it is imposed locally by granule cells (*GC0* and *GC1*) activated by a

backpropagating action potential (*bAP*). In this simulation an action potential was generated on *M0* (red trace). Its backpropagation activated *GC1* (closed red circle on *GC1*), generating an inhibitory response (open red circle on *GC1*) close to the soma of *M0* (black trace)

there is a population of granule cells that will be near to the body of any given mitral cell, and the circuit can ironically obtain distance-independent lateral inhibition. This is schematically shown in Fig. 1, where the synapses relevant to the circuit are highlighted in red (excitatory and inhibitory synapses are represented by closed and open circles, respectively). A somatic action potential elicited in *M0* backpropagates (*bAP*) along the *M0* lateral dendrites (in red). It activates both *GCs* (closed red circles), but the consequent inhibition (open red circles) on *M1* (black trace) is mainly determined by *GC1*, which is close to the soma and independent from the location of *M0*, provided that the AP can backpropagate along the lateral dendrite.

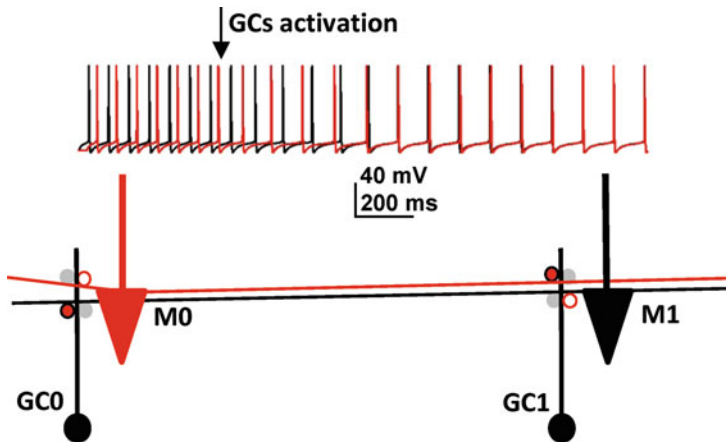
Synchrony

When two similar neurons receive a correlated signal, they can synchronize. If two mitral cells are near each other and share granule cells near their somas, they will mutually inhibit each other and synchronize. Similarly, if the two mitral cells in Fig. 1. were activated by an odor, they provide a correlated signal onto their shared granule cells. As such, the granule cells become synchronized and provide a correlated signal onto the mitral cells, which might be widely separated. Such synchrony is reliant on backpropagating

action potential travelling the full span of the lateral dendrites. However, this may not always be the case. A typical circuit exhibiting this effect is shown in Fig. 2. The two mitral cells receive the same input, but starting at different times. At $t = 500$ ms the granule cells are activated and the mitral cells synchronize.

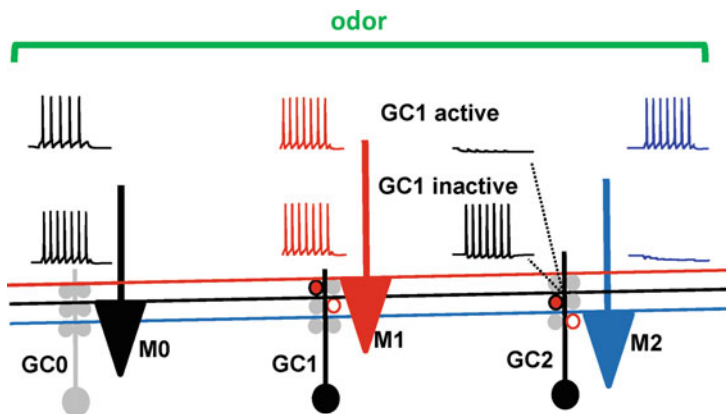
Gating Effects

Gating effects occur when the backpropagation of action potentials is blocked by the local (dendritic) inhibition activated by other mitral cells. A typical example is illustrated in Fig. 3, with three mitral cells (*M0–M2*) and three granule cells (*GC0–GC2*). All mitral cells receive the same odor input with different latency, and only the mitral-granule synapses relevant to this circuit are highlighted in red (excitation and inhibition are represented by closed and open circles, respectively). The plots show membrane potential of *M0–M2* soma and lateral dendrite of *M0* at 800um from the soma during simulations with *GC1* active or inactive. Note that the firing of *M2* (blue traces) depends on *GC1* local activation through *M1* (black trace close to *GC1* soma). In this case (top traces), the backpropagation of the APs along the *M0* lateral dendrite (black traces) is blocked by *GC1*



Olfactory Computation in Mitral-Granule Cell Circuits, Fig. 2 Mitral cells synchronization. Two mitral cells (*M0* and *M1*) were activated by the same input, but starting with a 20 ms relative latency. At $t = 500$ ms the granule cells (*GC0* and *GC1*) were activated and the mitral

cells synchronized (*black* and *red* traces). The reciprocal synapses involved in this circuit are shown in *red*, with excitation and inhibition represented by *closed* and *open circles*, respectively



Olfactory Computation in Mitral-Granule Cell Circuits, Fig. 3 Gating effects. Three mitral cells (*M0–M2*) receive the same odor input with different latency. The plots show somatic potential of *M0–M2* (traces above the soma) and the membrane potential of the *M0* lateral

dendrite (in *black*) at 800 mm from the soma (traces indicated with *dotted lines*), during simulations with *GC1* active or inactive. The reciprocal synapses involved in this circuit are shown in *red*, with excitation and inhibition represented by *closed* and *open circles*, respectively

activity, *GC2* will not be activated, and *M2* can fire APs. With *GC1* inactive, APs from *M0* can freely backpropagate until they activate *GC2*, inhibiting *M2*.

Interactive simulations of the circuits illustrated in Figs. 1, 2, and 3 can be downloaded from the ModelDB section of the Senselab database suite (<http://senselab.med.yale.edu/>, accession number 149415).

Cross-References

► [Olfaction: Overview](#)

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Olfactory Cortex

► [Olfactory Cortical Associative Memory Models](#)

Olfactory Cortical Associative Memory Models

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Synonyms

[Autoassociative networks](#); [Heteroassociative networks](#); [Olfactory cortex](#); [Piriform cortex](#)

Definition

The olfactory provides an ideal system to explore the proprieties of associative networks, like storage and retrieval of memory patterns, for a number of reasons: its principal cells share many of the fundamental proprieties with associative networks; the system is only one synapse away from its main sensory input, facilitating experimental manipulation in animals; and the olfactory cortex shares many similarities with other well-known associative systems of learning and memory, like the hippocampus.

Detailed Description

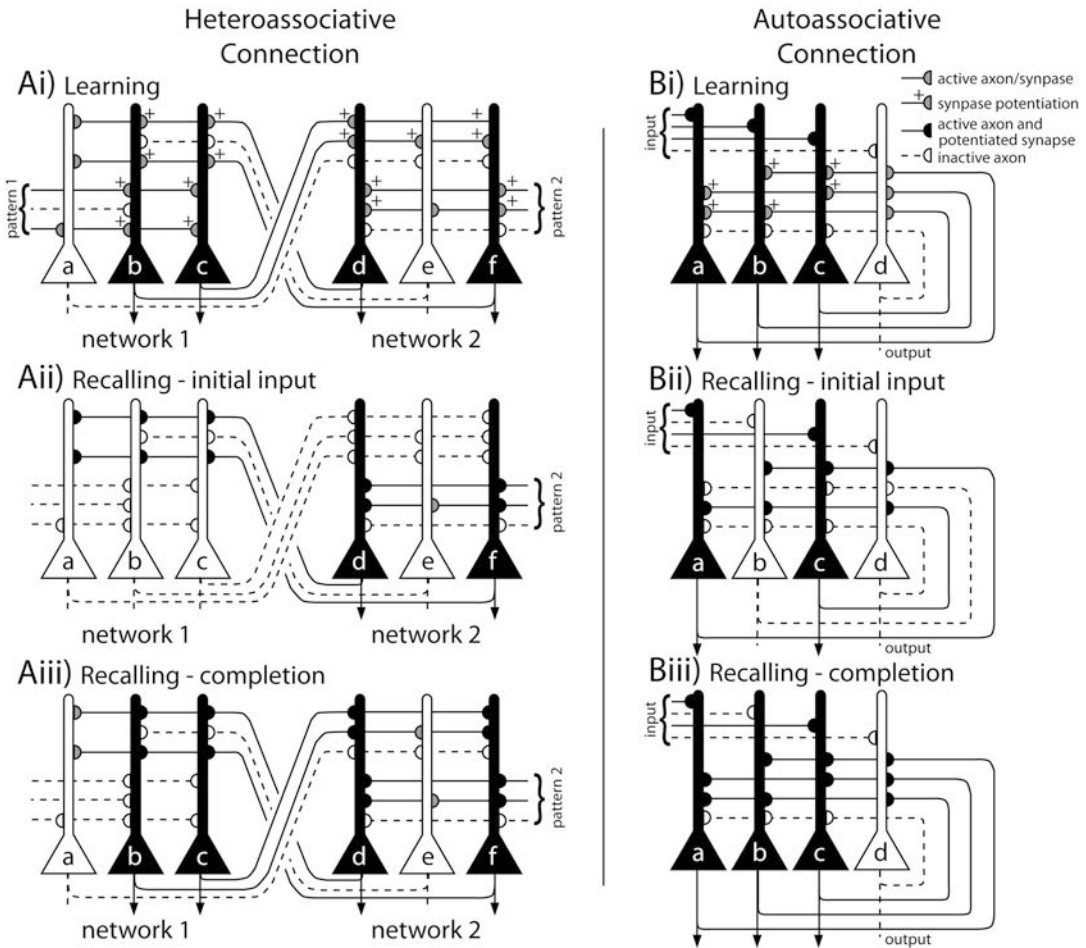
Associative Networks

Associative networks are among the most fundamental group of neural networks in the brain, enabling the storage, retrieval, and association of complex patterns of neuronal activation. These features, for instance, provide the brain the ability to correlate independent events, reconstruct previously learned patterns from fragmented or distorted inputs, and elicit outputs from previously stored patterns using novel inputs.

One important characteristic of these associative networks is the capacity of some of its neurons to change the strength of the connection between elements (neurons) based exclusively in local conditions like the level of synchronization of inputs converging to these neurons. Another characteristic is the fact that memories are “spread” over the neural network so that individual connections between neurons participate in the storage of different memories (Haberly and Bower 1989; Rolls and Treves 1994, 1998).

In general, associative networks can be roughly divided in two distinct groups: hetero-associative networks, where the associations occur between different, but interconnected, networks and autoassociative networks, where the associative connections are recurrent, exciting neurons within the network (Rolls and Treves 1998). However, it’s important to keep in mind that these definitions many times blend together, where autoassociative networks will also interact with other neural networks creating hetero-associative connections. Figure 1 was adapted from Haberly (2001) and shows examples of the dynamics in heteroassociative networks (Fig. 1A) and autoassociative networks (Fig. 1B).

Figure 1A shows a structure composed by a pair of reciprocally connected networks being used for pattern correlation. During the learning step (Fig. 1Ai), network 1 is activated by the input pattern 1 at the same time that neurons in network 2 are excited by input 2. The temporal co-activation of these two neuronal groups increases the weights of the synapses between



Olfactory Cortical Associative Memory Models, Fig. 1 Examples of associative networks. (A) Heteroassociative network composed by two interconnected networks. (Ai) Networks 1 and 2 represent two different regions in the brain. When patterns 1 and 2 are activated at the same time, the synapses between the active neurons (black) undergo Hebbian potentiation and have their synaptic weights increased (represented by the + sign), while other synapses remain unchanged. (Aii) During the recalling step, only pattern 2 was presented, activating neurons d and f in network 2. (Aiii) However, the activation of d and f is enough to evoke the learned firing patterns

in network 1 as well. (B) In autoassociative networks, each neuron makes recurrent connections that contact other neurons in the network. (Bi) The network receives an input pattern where neurons a, b, and c are activated. The co-activation potentiates the synapses between these cells. (Bii) After learning, the network receives a corrupted or altered version of the original input. The activation of neurons a and c helps the autoassociative connections to fire neuron b recovering the original pattern activation, a process known as *pattern completion* (These figures were adapted from Figs. 4 and 5 in Haberly (2001))

firing neurons (represented in Fig. 1Ai by the synapses with + signs), a process known as Hebbian potentiation. On the other hand, this potentiation doesn't occur between neurons that were not co-active (e.g., neurons a and d, in Fig. 1Ai). Over time and a series of repetitions, these synapses become strong enough to recall

the firing pattern even if only one of the inputs is active, as shown in Fig. 1Aii, Aiii. Architectures of this kind allow neuronal activations in one area of the brain to become functionally joined to an unrelated pattern in a different area so that the occurrence of one pattern reconstructs the other.

Figure 1B illustrates the dynamics of an auto-associative network, where neurons make excitatory connection within the network. Figure 1Bi shows the neuronal response to a novel input pattern. The synapses of active neurons undergo Hebbian potentiation while the connections between active and inactive neurons remain unaltered. When a partial (or corrupted) pattern is provided to the network, it directly excites a subset of the cells that represent a memory, as shown in Figure 1Bii; then, through the recurrent excitatory connections reinforced during the learning step, these cells excite all the cells that represent the memory, notably those that did not receive direct input from the partial pattern (Fig. 1Biii), in a process known as *pattern completion*. This repair process is possible because the memory is so redundantly encoded that the still active cells can reactivate the neurons that stop firing (Marr 1971; Hopfield 1982). It also provides some level of robustness to errors and other external perturbations to a given memory.

Olfactory Cortex as a Model for Associative Memory

In Haberly and Bower (1989), the authors present a series of arguments about why the olfactory cortex (OC) provides an ideal system for the study of associative memory functions:

- Pyramidal cells (Pyr), the principal cells in the OC circuitry, share many of the fundamental proprieties with associative networks. These cells receive inputs and send outputs to the olfactory bulb and many high-order areas of the cortex, indicating that the system might integrate and associate olfactory information with other sensorial components (Shipley and Geinisman 1984; Schoenbaum and Eichenbaum 1995; Johnson et al. 2000; Sosulski et al. 2011). Besides that, the primary axons of Pyr cells in some subregions of the olfactory cortex give rise to a profusion of collateral branches that connect to other local Pyr cells (Haberly and Shepherd 1973; Price 1973), similar to the autoassociative network in Fig. 1B.
- The OC is only one synapse away from the olfactory sensory neurons, responsible for the transduction of the odor molecules to action potentials. This proximity to its main sensory inputs is extremely convenient for experimental analysis. Besides that, Pyr cells display a remarkable laminar segregation of inputs from different neuronal groups, for example, afferent inputs are restricted to distal apical dendrites while association connections with other Pyr cells are centered in more proximal portions of the apical dendrites (Haberly 2001).
- The OC receives cholinergic inputs from the horizontal limb of the diagonal band of Broca (HDB) (Brashear et al. 1986; Zaborszky et al. 1986). Acetylcholine (ACh) is shown to affect the activation of Pyr cells and other neurons in the OC (Tseng and Haberly 1989; Barkai and Hasselmo 1994), as well as excitation and synaptic plasticity in associative connections between Pyr cells (Williams and Constanti 1988; Hasselmo and Bower 1992; Hasselmo and Barkai 1995; Patil et al. 1998). Behaviorally, cholinergic modulation has been linked to changes in the odor memory formation in the OC (Wilson 2001; Barkai 2005; Linster et al. 2009).
- There are many parallels between the OC and the entorhinal-hippocampal system, a region that is believed to play an important role in learning and memory. For instance, both systems are organized as a distributed network, with different areas performing distinct sets of operations in parallel; both systems present a broad overlapping spatial organization rather than the columnar pattern organization presented in deeper layers of the neocortex; the systems also present a forward flow of information from their input structures (olfactory bulb for the OC and entorhinal cortex for the hippocampus) and back projections connecting the different structures in the information streams. A detailed description of the parallels between the OC and the hippocampal system and the OC and other cortical regions can be found in Haberly (2001).

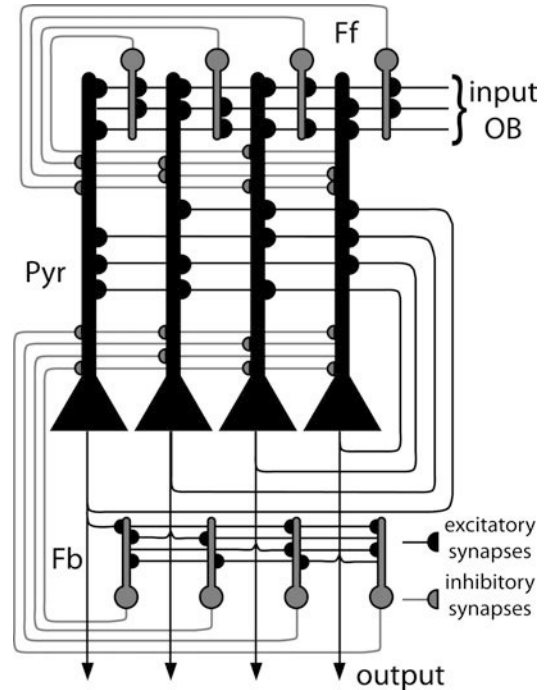
Example of a Model of Olfactory Cortical Associative Memory

The example presented here was published in de Almeida et al. (2013). This model investigates the influence of cholinergic modulation in the olfactory bulb (OB) and impact of this modulation in the formation of odor memories in the piriform cortex (PC). The PC is the largest area of the OC and shares many similarities with the other areas of the OC (Haberly and Bower 1989). The model presented here is restricted to the PC network; the OB model is out of the scope of this article. However, a detailed description of both models can be found in de Almeida et al. (2013), and source code of these models (implemented in MATLAB programming language) can be downloaded from the modelDB website (Hines et al. 2004).

Network Architecture

The model is composed by one group of principal cells (Pyr cells) and two groups of inhibitory interneurons, defined as feed-forward cells (Ff) and feedback cells, as shown in Fig. 2.

The PC network receives projection from mitral cells in the OB. These projections are assumed to randomly connect to Pyr neurons (Linster et al. 2009; Stokes and Isaacson 2010). The two groups of inhibitory interneurons modulate the activity of Pyr cells. In vivo recordings of excitatory and inhibitory postsynaptic currents show that Ff interneurons are activated by many different odorants, in contrast to Pyr neurons whose activation is much more odorant specific (Poo and Isaacson 2009; Isaacson 2010; Stokes and Isaacson 2010). In the model, Pyr cells receive input from 20% of the mitral cell inputs (Linster et al. 2009) and are inhibited by 30% of the Ff network, as measured by Stokes and Isaacson (2010). Ff cells, however, receive excitatory inputs from a larger number of mitral cells (40%) than the Pyr cells. The second group of interneurons, the Fb cells, is recruited by the activation of Pyr cells and sends its inhibitory projections back to the same group of Pyr neurons. Each Fb cell is excited by 18% of the Pyr network,



Olfactory Cortical Associative Memory Models, Fig. 2 Simplified structure of the piriform cortex (PC).

The system receives excitatory input from mitral cell axons in the OB. These axons connect to pyramidal (Pyr) and feed-forward (Ff) cells. Pyramidal cells work as an auto-associative network, projecting their axons to other Pyr neurons and to feedback (Fb) cells. This last group of interneurons then makes inhibitory synapses to the Pyr cells (Stokes and Isaacson 2010)

and each Pyr cell is inhibited by 35% of the Fb network (Stokes and Isaacson 2010).

Model Equations

All cells in the network are represented as single-compartment leaking integrate and fire neurons (Abbott 1999; Dayan and Abbott 2001), where the evolution of the membrane voltage is described by a first-order differential equation:

$$\tau \frac{dv(t)}{dt} + v = V^{ext}(t) \quad (1)$$

where τ is the membrane time constant and $V^{ext}(t)$ is the total external input over time. The input coming from a given presynaptic neuron at time t is a function of the synaptic strength W_{ij} , the conductance change $g_i(t)$ in cell i , and the

Olfactory Cortical Associative Memory Models, Table 1 Model parameters

General parameters (shared by all neurons)	$v^{\text{hyper}} = -10 \text{ mV}; \theta^{\text{min}} = -2 \text{ mV}$
Pyramidal cell (Pyr)	$t^{\text{refrac}} = 2 \text{ ms}; \tau = 10 \text{ ms}; \beta = 10; \theta^{\text{max}} = 17 \text{ mV}$
Feed-forward cell (Ff)	$t^{\text{refrac}} = 2 \text{ ms}; \tau = 5 \text{ ms}; \beta = 5; \theta^{\text{max}} = 17 \text{ mV}$
Feedback cell (fb)	$t^{\text{refrac}} = 2 \text{ ms}; \tau = 5 \text{ ms}; \beta = 5; \theta^{\text{max}} = 17 \text{ mV}$
Mitral input to pyramidal cell	$g^{\text{max}} = 0.84; E_N = +70 \text{ mV}; \tau_1 = 1 \text{ ms}; \tau_2 = 2 \text{ ms}$
Mitral input to feed-forward cell	$g^{\text{max}} = 2.4; E_N = +70 \text{ mV}; \tau_1 = 1 \text{ ms}; \tau_2 = 2 \text{ ms}$
Feed-forward inhibition	$g^{\text{max}} = 0.056; E_N = -10 \text{ mV}; \tau_1 = 4 \text{ ms}; \tau_2 = 8 \text{ ms}$
Feedback inhibition	$g^{\text{max}} = 0.8; E_N = -10 \text{ mV}; \tau_1 = 4 \text{ ms}; \tau_2 = 8 \text{ ms}$
Pyramidal to feedback cell	$g^{\text{max}} = 0.8; E_N = +70 \text{ mV}; \tau_1 = 1 \text{ ms}; \tau_2 = 2 \text{ ms}$
Pyramidal cell association fibers	$g^{\text{max}} = 5.0; E_N = +70 \text{ mV}; \tau_1 = 1 \text{ ms}; \tau_2 = 2 \text{ ms}$

difference between the Nernst potential $E_{N,ij}$ of the specific channel type and the current membrane potential $v_j(t)$ of the postsynaptic neuron j , as described in Eq. 2:

$$V_j^{\text{ext}}(t) = W_{ij} g_{ij}(t) [E_{N,ij} - v_j(t)] \quad (2)$$

The communication between neurons in the network occurs through discrete action potentials that are a function of the membrane potential:

$$F_i(V) = \begin{cases} 0 & \text{if } V \leq \theta^{\text{min}} \\ \left(\frac{V - \theta^{\text{min}}}{\theta^{\text{max}} - \theta^{\text{min}}} \right) & \text{if } \theta^{\text{max}} < V < \theta^{\text{min}} \\ 1 & \text{if } V \geq \theta^{\text{max}} \end{cases} \quad (3)$$

where $F_i(V)$ represents the continuous output (for OSNs and PGs) or the instantaneous spiking probability (for the remaining neuronal groups). θ^{min} and θ^{max} represent the minimum threshold and the saturation threshold of the output/probability function, respectively. β defines the nonlinearity of $F_i(V)$. Finally, $g_i(t) = g(t - t_i^{\text{fire}})$ represents the time course of the conductance given by Eq. 4:

$$g(t) = g^{\text{max}} \left(e^{\frac{-t}{\tau_1}} - e^{\frac{-t}{\tau_2}} \right) \quad (4)$$

where τ_1 and τ_2 are, respectively, the rising and falling times of the conductance and g^{max} is a constant with no unit representing the maximum conductance of a given channel. After firing, the voltage of each spiking neuron is reset to a hyperpolarization potential v^{hyper} and remains inactive

for a refractory period t^{refrac} ; for details on the parameters, see Table 1.

The synaptic modifications of the pyramidal associative fibers were implemented using a Hebbian learning similar to that proposed by Jensen et al. (1996), where the synaptic efficiency is enhanced if both pre- and postsynaptic neurons fire together and reduced if not. Each Pyr-Pyr connection has a synaptic weight initially set to a random minimal value between zero and 0.02, which is approximately 10% of the average maximum W observed in after one training session in the network. The synaptic enforcement has been shown to depend on NMDA receptors that allow the influx of Ca^{2+} , as long as sufficient postsynaptic depolarization is provided. The rise of Ca^{2+} triggers a cascade of events that ultimately results on a long-term potentiation in AMPA- and NMDA-mediated synaptic responses (Bliss and Collingridge 1993). The model assumes that the postsynaptic depolarization is attributed to back propagation from the action potential of the postsynaptic cell described by Eq. 5:

$$i^{\text{post}}(t) = \frac{t}{\tau^{\text{post}}} \exp \left(1 - \frac{t}{\tau^{\text{post}}} \right) \quad (5)$$

where the time course of this depolarization at the postsynaptic neuron (τ^{post}) is 2 ms.

The kinetics of NMDA channels depends on the binding of glutamate on the receptors. In the model, its time course is described by Eq. 6:

$$b^{\text{glu}}(t) = \exp \left(-\frac{1}{\tau^{\text{NMDA}f}} \right) \left(1 - \exp \left(-\frac{1}{\tau^{\text{NMDA}r}} \right) \right) \quad (6)$$

where $\tau^{NMDA^f} = 7$ ms and $\tau^{NMDA^r} = 1$ ms characterize the kinetics of NMDA receptors. Finally, the synaptic enhancement between neurons i and j is described by Eq. 7:

$$\frac{dW_{ij}^{syn}}{dt} = (1 - W_{ij}^{syn}) \frac{t_j^{post}(t - t_j^{fire}) b_j^{glu}(t - t_j^{fire} - t^{delay})}{\tau^{pp}} + (0 - W_{ij}^{syn}) \left(\frac{t_j^{post}(t - t_j^{fire})}{\tau^{pp}} + \frac{b_j^{glu}(t - t_j^{fire} - t^{delay})}{\tau^{np}} \right) \quad (7)$$

where t^{delay} is the time it takes an action potential to travel from the soma to the synapses of a recurrent collateral. If t_j^{post} and b_j^{glu} peak together, the synaptic weight between neuron i and j is driven to one with the characteristic time τ^{pp} (50 ms); if the events are asynchronous, the synaptic efficacy is decreased with time τ^{np} ($\tau^{pp} = \tau^{np} = 250$ ms).

Different Models of Associative Network in the OC

Several models have been proposed to explore the associative memory functions necessary for odor learning in the OC (Haberly and Bower 1989; Ambros-Ingerson et al. 1990; Hasselmo et al. 1990). More specifically, many research groups proposed computational models exploring how the cholinergic modulation regulates the acquisition of odor memories in the OC. ACh suppresses neuronal adaptation and excitatory synaptic transmission between Pyr cells while promoting long-term potentiation (LTP) between these synapses (Williams and Constanti 1988; Hasselmo and Bower 1992, 1993; Barkai and Hasselmo 1997). These results provided a theoretical framework for linking the neuropharmacological effects of acetylcholine to a role in memory function, where two distinct scenarios are observed: a *learning mode* where ACh modulation in the OC is ON and a *recalling mode*, where ACh modulation is OFF. The possible effects of this modulation in associative networks were investigated in Hasselmo et al. (1992), Hasselmo and Barkai (1995), Liljenstrom and Hasselmo (1995), Barkai and Hasselmo (1997), Linster and Hasselmo (2001), Linster et al. (2003, 2009).

Besides ACh, the impact of other neuromodulators in associative networks of the OC was, so far, little explored. One exception is noradrenaline, whose role in the OC was explored in a computational model in Hasselmo et al. (1997). According to the authors, noradrenergic modulation appears to enhance the encoding of sensory inputs and suppress excitatory transmission of associative connections between Pyr cells, effects somewhat similar to ACh modulation.

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Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response

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Synonyms

[Dose-response functions](#); [Concentration-response functions](#); [Activation of the olfactory sensory neurons as a function of odor concentration](#)

Definition

Mathematical modeling of the response of olfactory sensory neurons (OSNs) to odor stimuli refers to models able to predict the OSNs response to a mixture of N odorants ($N \geq 2$) starting from the responses to individual components.

Detailed Description

Most real-world odors are complex mixtures consisting of dozens, often hundreds of components, and olfactory systems have evolved to recognize and discriminate them. The sensory process starts with the interaction of odorant molecules with the olfactory receptors (ORs) located on the cilia of olfactory sensory neurons (OSNs). The ORs occupy a small area in the upper part of the nasal epithelium and detect the inhaled odorant molecules. Although the detection of an odor molecule in the environment is primarily a chemical and biochemical process, the signal which is sent to the brain announcing this detection is transduced into electrical activity. Indeed, the odorant molecules binding to receptors activate specific *G-proteins* that initiate a cascade of intracellular signaling events leading to the generation of an action potential that is propagated along the olfactory sensory axon to the olfactory bulb of the brain (Buck and Axel 1991; Firestein and Shepherd 1991). The axons of the olfactory bulb neurons, in turn, project to subcortical and cortical regions where higher-level processing of olfactory information allows the discrimination of odors by the brain (see Fig. 1).

In this entry we focus on initial event of olfactory perception, that is, the interactions of odorant molecules to ORs and then the activation of the OSNs as a function of the odor concentration (i.e., a dose-response function). It has been widely demonstrated that, in most cases, the response of OSNs to (single) odor stimuli can be conveniently reproduced by a *sigmoidal shape* with concentration, usually implemented as a *Hill function*. Moreover, the dose-response curve for a *binary odor mixture* at a fixed concentration ratio is still of sigmoidal shape in most

cases, and it is usually compared with the curves for the individual components. However, the response to a mixture of odorants is not a simple function of the response to the individual components, and its properties are empirically classified as follows (Fig. 2):

Suppression, when the response to the mixture is between the response to the single components.

Synergy, when the response to the mixture is higher than both components.

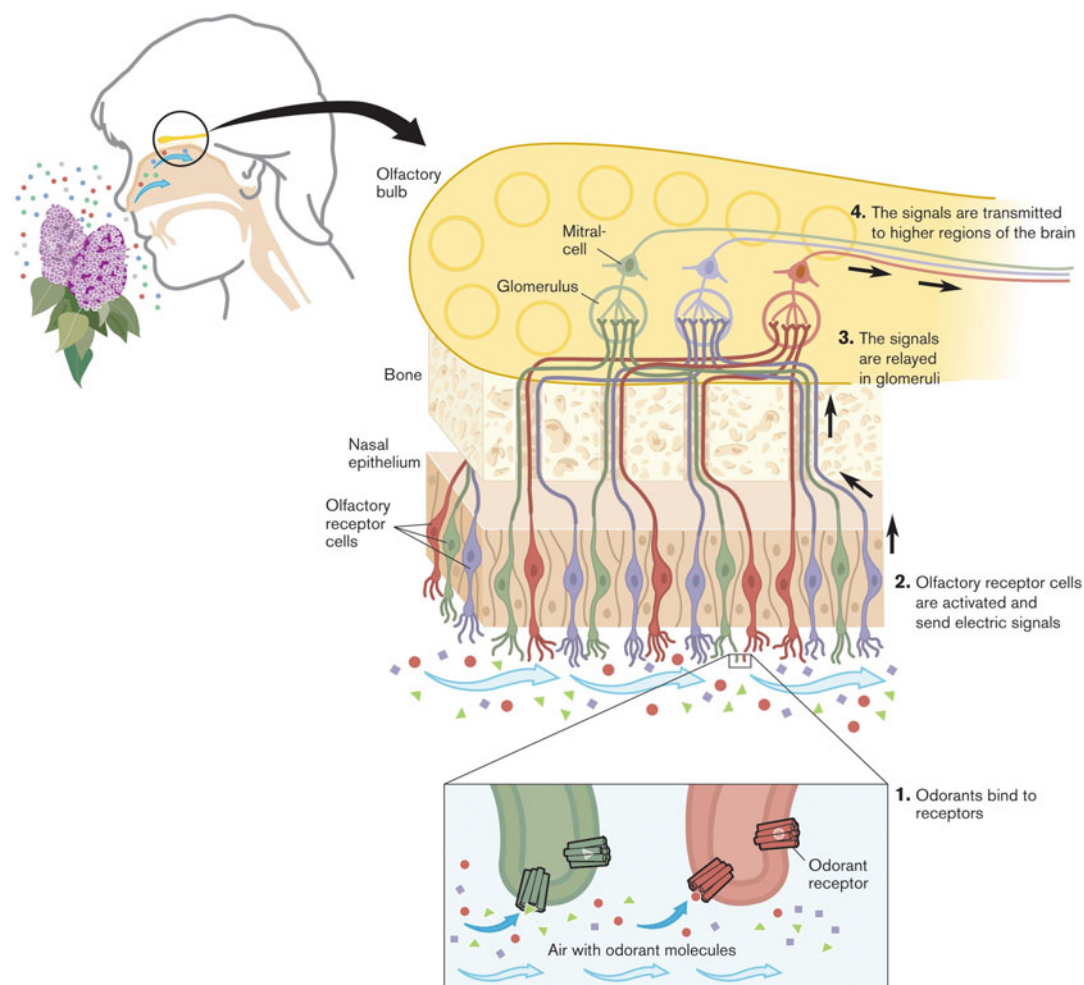
Inhibition, when the response to the mixture is lower than both components.

Hypoadditivity, when the response to the mixture is similar to the most effective component.

Overshadowing, when the response to the mixture is similar to one of the components.

In literature were proposed different models to determine the responses of olfactory sensory neurons to odor (binary) mixtures from the responses to the individual components (Rospars et al. 2008; Cruz and Lowe 2013; Marasco et al. 2016). In particular, the models proposed in Rospars et al. (2008) and Cruz and Lowe (2013) are able to reproduce all cases of suppression, but it can be mathematically demonstrated that they cannot reproduce mixtures exhibiting synergy, and inhibition, at least in the region of the maximum response (Marasco et al. 2016). Moreover, in Rospars et al. (2008) and Cruz and Lowe (2013), it has been assumed that the Hill coefficient, describing cooperative effects in the transduction cascade, is a property of the neurons instead of the odors. However, there are experimental findings showing that the response of the same OSN to different odorants may exhibit different Hill coefficients (Pongrácz et al. 1993; Wachowiak and Cohen 2001).

Recently in Marasco et al. (2016) has been proposed a mathematical model able to predict all types of mixture interactions among N odorants (with $N \geq 2$). In this model all the typical, experimentally measurable, characteristics of the dose-response curves (i.e., steepness, midpoint, and asymptotic value) can be



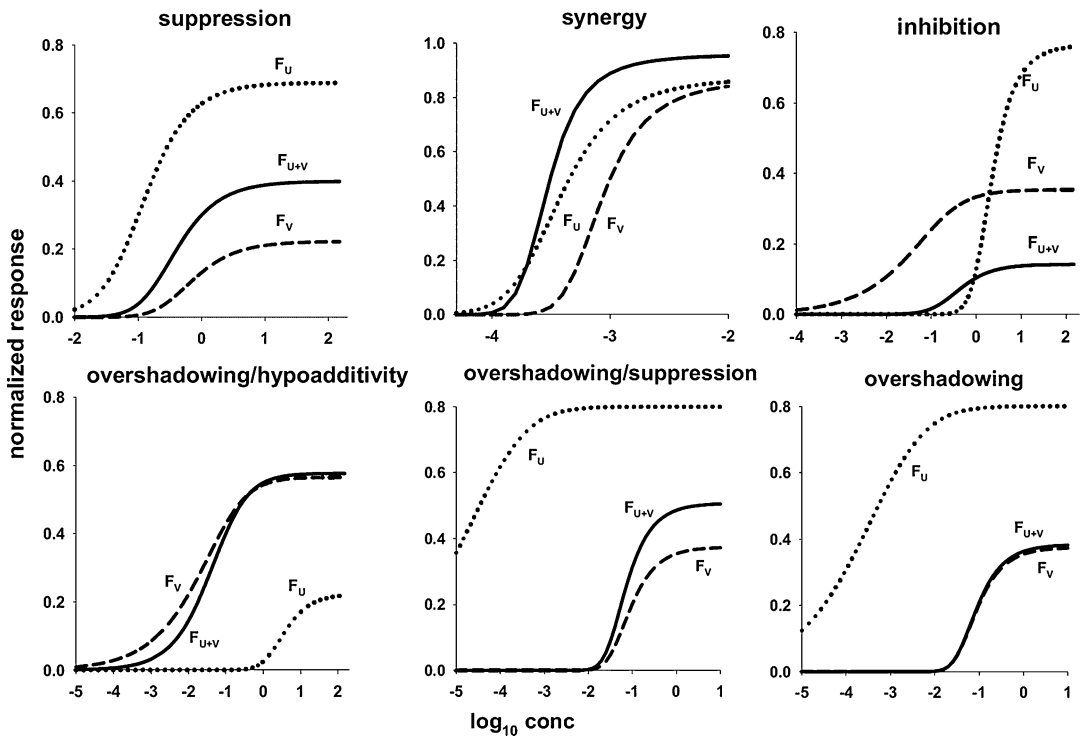
Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response, Fig. 1 The human olfactory system (Press Release 2004), © The Nobel Assembly at Karolinska Institutet]

mathematically expressed by a nonlinear combination of the parameters for the individual components. Furthermore, it is shown that it is possible to find suitable mathematical conditions for all parameters and concentrations, in such a way to make it possible to design mixtures with specific properties. The results suggest a way to predict the overall behavior of a receptor type in response to a mixture composed of any number of components, provided that the individual response curves and their relative concentration ratios are known. A rigorous analysis of the mathematical structure of the three-dimensional *odor response space* (ORS) suggests that any dose-

response curve of an odor receptor can be obtained as a combination of three (out of four) *primary odor responses* with specific properties, opening the way to an objective procedure to obtain specific olfactory receptor responses by manipulating mixtures in a mathematically predictable manner.

Mathematical Models for the Response of OSNs to Single Odors and Mixtures

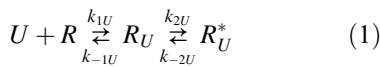
In this section, we present the models proposed in literature (Rospars et al. 2008; Cruz and Lowe 2013; Marasco et al. 2016) to describe the responses of OSNs to single odors and mixtures.



Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response, Fig. 2 Typical set of odor response to single odors (F_U and F_V) and their binary mixture (F_{U+V}) (Marasco et al. 2016)

Kinetic Schemes and Assumptions Underlying Rospars et al. (2008) and Cruz and Lowe (2013) Models

Rospars et al. model (Rospars et al. 2008) is based on the following kinetic reactions describing the odorant molecules that bind to the ORs and activate them



where k_{1U} , k_{-1U} are the binding (association) and release (dissociation) rate constants, R_U is the bound receptor-ligand complex, and R_U^* is the activated complex.

In this scheme the receptors can be in three states: free R , bound R_U , and activated R_U^* , and the total constant concentration of receptors is $R_T = R + R_U + R_U^*$. At equilibrium the system

of differential equations relative to reactions (1) leads to the concentration of the activated complex as a function of odorant concentration (Rospars et al. (2008), Supplemental notes)

$$R_U^* = \frac{R_{MU}^*}{1 + \frac{K_U}{U}} \quad (2)$$

where $K_{1U} = \frac{k_{-1U}}{k_{1U}}$ and $K_{2U} = \frac{k_{-2U}}{k_{2U}}$ are the equilibrium dissociation and deactivation constants, and

$$R_{MU}^* = \frac{R_T}{K_{2U} + 1}, K_U = \frac{K_{1U}K_{2U}}{K_{2U} + 1} \quad (3)$$

Moreover, the effect of the transduction cascade interposed between the ORs activations and the measured OSNs responses is modeled as a transformation that maps the *hyperbolic function* (2) with the Hill coefficient $n = 1$ into a *Hill*

function with $n \neq 1$ followed by a linear transformation (see Eq. 5₁).

The binary mixture model proposed in Rospars et al. (2008) is obtained as an extension of the single odorant model in which the molecules of two different odorants U and V compete for the same receptors R . We recall that the *competitive interaction* arises when two or more ligands can bind to the same receptor binding site, although only one can be bound at a time. This mechanism could involve either two *agonist* odorants, i.e., molecules that are able to activate the receptor, or one agonist and one *antagonist* (the latter being a molecule that binds to the receptor but is unable to activate it). Nevertheless, experimental data suggests that both competitive and non-competitive interactions occur at the OR level (Rospars et al. 2008; Cruz and Lowe 2013). Then, assuming that the receptors can be bound and activated by both U and V according to reactions (1) for U and equivalent reactions for V , instead of (2) we obtain

$$R_{U+V}^* = \frac{R_{MU}^* \frac{U}{K_U} + R_{MV}^* \frac{V}{K_V}}{1 + \frac{U}{K_U} + \frac{V}{K_V}}, \quad (4)$$

where R_{MU}^* , R_{MV}^* , K_U , and K_V are given by Eq. 3.

Then, by analogy with the case of single odorants, to model the OSN responses to binary mixture, the authors introduced a Hill coefficient n (see Eq. 5₂). We remark that in this approach the Hill coefficient n is the same for both compounds appearing in the mixture, i.e., *the Hill coefficient n characterizes the OSN and it is independent of the odorants*.

In Cruz and Lowe (2013), following the kinetic schemes of Rospars et al. (2008), the authors empirically model the activation of the olfactory sensory neurons via the transduction cascade (see Eq. 9₂). In particular, the case of a single odorant U is obtained setting $V = 0$ in the dose-response function for competitive binary mixture (see Eq. 9₁). Also in this case, the Hill coefficient appearing in the binary mixtures model characterizes the OSN and it is independent of the odorants.

Rospars et al. Models

In Rospars et al. (2008), the authors proposed the following models for the response of OSNs to single odors and binary mixtures

$$F_U = \frac{F_{MU}}{1 + \left(\frac{K_U}{U}\right)^n},$$

$$F_{U+V}(U, V) = \frac{F_{MU} \left(\frac{U}{K_U}\right)^n + F_{MV} \left(\frac{V}{K_V}\right)^n}{1 + \left(\frac{U}{K_U}\right)^n + \left(\frac{V}{K_V}\right)^n} \quad (5)$$

where U and V are two odors (and also their concentrations), n is a Hill coefficient, K_U , K_V , F_{MU} , and F_{MV} are constants depending on the receptor kinetic properties.

In particular, for the dose-response function to single odor F_U , the Hill coefficient n modulates the steepness of the curve, K_U the midpoint, and F_{MU} the asymptotic value.

As it is usual to keep unchanged the quality of the odor in a binary mixture under a change of its concentration, it suffices that the ratio of concentrations of the two odor components remains constant (Rospars 2013). In other classical protocols, as in Cruz and Lowe (2013), the concentration of a single component is varied while that of the other remains constant. In the first case, it has been widely demonstrated that the response can be conveniently reproduced by a logistic curve as a function of concentration $U + V$. Then, in Rospars et al. (2008) is proved that if $U = rV$, where r is a positive constant, Eq. 5₂ becomes

$$F_{U+V}(M) = \frac{F_{Mp}}{1 + \left(\frac{K_p}{M}\right)^n}, \quad (6)$$

where $M = U + V$, and

$$F_{Mp} = \frac{F_{MU} r^n K_V^n + F_{MV} K_U^n}{(K_U^n + r^n K_V^n)},$$

$$K_p = (1 + r) K_U K_V \sqrt[n]{\frac{1}{r^n K_V^n + K_U^n}}. \quad (7)$$

Therefore, F_{Mp} is the asymptotic value of function $F_{U+V}(M)$, and the concentration of M at half maximum response $F_{Mp}/2$ is K_p .

To test the model, the authors fitted the experimental data on the response to single odors determining the parameters n , common to both odors, the midpoints K_U and K_V , and the asymptotic values F_{MU} and F_{MV} . Then, using Eqs. 6 and 7 each dose-response curve for binary mixtures was determined. Finally, the predicted responses were compared to their observed counterparts (see Rospars (2013), Figs. 6–7). In 47% of comparisons, the Hill curve fitted to the experimental data was statistically undistinguishable from those predicted by the model. In these cases, it can be assumed that the odorant-OR interactions were competition, or at least that the effects of a different nature were too weak to reach statistical significance (see Rospars (2013), Fig. 6). In the other half, the shifts of curves along the concentration axis (*affinity modification*) and the changes of maximal responses (*efficiency modification*) with respect to model predictions indicate that noncompetitive interactions, like antagonism and allosterism, occur (see Rospars (2013), Fig. 7).

This approach is able to explain all cases of suppression, but it cannot reproduce mixtures exhibiting synergy, and inhibition, at least in the region of the maximum response (Rospars 2013, Fig. 7). In fact, from Eq. 7 for all r we obtain

$$\min(F_{MU}, F_{MV}) \leq F_{Mp} \leq \max(F_{MU}, F_{MV}), \quad (8)$$

i.e., the asymptotic value of function F_{U+V} is always located between the single-odorant curves.

Finally, it has also been noted (Cruz and Lowe 2013) that it cannot take into account the self-mixture case, i.e., it should be $F_{U+U}(U, U) = F_{U+U}(2U, 0)$.

Cruz and Lowe Models

In Cruz and Lowe (2013), instead of Eqs. 5 and 6, it was proposed to use for single odors and binary mixture the following (empirical) models

$$F_U = \frac{F_{\max}}{1 + \frac{1}{\eta_U} \left(1 + \frac{K_U}{U}\right)^n}, \quad (9)$$

$$F_{U+V}(U, V) = \frac{F_{\max}}{1 + \left[\frac{1 + \frac{U}{K_U} + \frac{V}{K_V}}{\eta_U \frac{U}{K_U} + \eta_V \frac{V}{K_V}} \right]^n},$$

where n is a Hill coefficient, $F_{\max}$ is the maximal response, and η_U and η_V are the efficiencies of activation of transduction by each odorant.

Differently from Rospars et al. (2008), the introduction of the new parameter η offers the possibility to use the same $F_{\max}$ for all odors while allowing different asymptotes. For example, if we consider the model for single odors Eq. 9₁, the asymptotic value of function F_U writes

$$\text{asy}_U = \frac{F_{\max}}{1 + \frac{1}{\eta_U}}. \quad (10)$$

As with the model of Rospars et al., if the concentrations U and V of the odorants are such that $U = rV$, Eq. 9₂ becomes a Hill function

$$F_{U+V}(M) = \frac{F_{\max}}{1 + \frac{1}{\bar{\eta}} \left(1 + \frac{\bar{K}}{M}\right)^n} \quad (11)$$

where the parameters $\bar{\eta} = \bar{\eta}(r, \eta_U, \eta_V, K_U, K_V)$ and $\bar{K} = \bar{K}(r, K_U, K_V)$ assume the form

$$\bar{\eta} = \frac{\eta_U r K_V + \eta_V K_U}{K_U + r K_V}, \quad \bar{K} = \frac{(r+1)K_U K_V}{K_U + r K_V}. \quad (12)$$

In this case, the asymptotic value of function $F_{U+V}(M)$ is

$$\text{asy}_M = \frac{F_{\max}}{1 + \frac{1}{\bar{\eta}}}, \quad (13)$$

and the concentration of M at half maximum response $\frac{F_{\max}}{2(1 + \frac{1}{\bar{\eta}})}$ is

$$\text{EC}_{50} = \frac{\bar{K}}{\sqrt[2]{2 + \bar{\eta}} - 1}.$$

From Eq. 12 we obtain

$$\min(\eta_U, \eta_V) \leq \bar{\eta} \leq m \max(\eta_U, \eta_V)$$

and owing to Eq. 13 for all r we have

$$\min \left(\frac{F_{\max}}{1 + \frac{1}{\eta_U^n}}, \frac{F_{\max}}{1 + \frac{1}{\eta_V^n}} \right) \times \leq \frac{F_{\max}}{1 + \frac{1}{\bar{\eta}^n}} \leq \max \left(\frac{F_{\max}}{1 + \frac{1}{\eta_U^n}}, \frac{F_{\max}}{1 + \frac{1}{\eta_V^n}} \right). \quad (14)$$

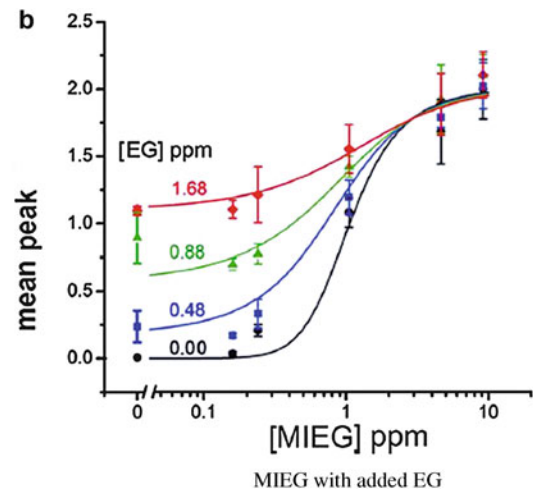
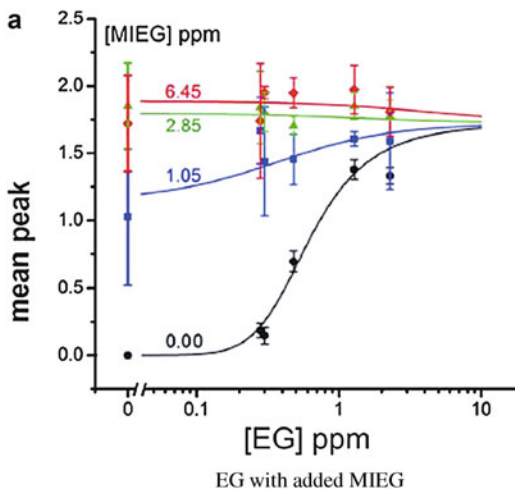
Although this model is consistent with the self-mixture case, due to Eq. 14 the model cannot reproduce mixtures exhibiting synergy or inhibition in their maximal response.

Contrary to Rospars et al. (2008), in Cruz and Lowe (2013) the binary mixtures are tested at a fixed concentration of one of the components, and the model (9)₂ represents the glomerular dose responses. As we see in Fig. 3, the model is consistent with the mixture responses of *moderate sensitivity glomeruli* (Cruz and Lowe 2013). We remark that in Cruz and Lowe (2013) is assumed

that in a binary mixture the odorants compete for the same receptor binding site in the population of OSNs projecting to a given glomerulus. Although each odorant have its own independent binding affinity K and efficiency of transduction activation η , a common Hill coefficient n still describes cooperativity of the shared transduction cascade as well as the upper limit $F_{\max}$ of the response with transduction fully activated. Nevertheless, the glomerular dose-responses curves for binary mixtures of the odorants EG (eugenol) and MIEG (methyl isoeugenol) in Fig. 3, although refer to the same glomerulus, exhibit different values for all parameters. This indicates that the experiments were (probably) carried out on different OSNs even though the dose-response functions refer to the same glomerulus.

Marasco et al. Models

The major problem with Rospars et al. (2008) and Cruz and Lowe (2013) approaches is that these models are able to reproduce all cases of suppression, but they cannot reproduce (binary) mixtures exhibiting synergy, and inhibition, at least in the region of the maximum response (see Eqs. 8 and 14). To determine a model able to describe each type of interaction among two or more odorants



Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response, Fig. 3 Glomerular dose responses. (a) $F_{\max} = 2.01$, $K_{EG} = 0.49$, $K_{MIEG} = 1.04$,

$n = 4.17$, $\eta_{EG} = 1.63$, $\eta_{MIEG} = 2.18$; (b) $F_{\max} = 2.12$, $K_{EG} = 0.71$, $K_{MIEG} = 1.13$, $n = 4.47$, $\eta_{EG} = 1.45$, $\eta_{MIEG} = 2.01$

(see Fig. 2 for a binary mixture), it is necessary to expand the space of allowed Hill functions. Then, assuming that the Hill coefficient in the mixture model (9)₂ depends on the odorants U and V , Marasco et al. (2016) proposed to describe the dose-response functions for a given type of OSNs in the presence of single odor and mixtures as follows:

$$F_U(U) = \frac{F_{\max}}{1 + \frac{1}{\eta_U} \left(1 + \frac{K_U}{U}\right)^{n_U}}, \quad (15)$$

$$F_{U+V}(U, V) = \frac{F_{\max}}{1 + \left[\frac{1 + \frac{U}{K_U} + \frac{V}{K_V}}{\eta_U K_U + \eta_V K_V} \right]^{n_{U+V}}},$$

where

$$n_{U+V} = \frac{n_U \eta_U K_V U + n_V \eta_V K_U V}{\eta_U K_V U + \eta_V K_U V}. \quad (16)$$

Moreover, Eq. 15₂ can be easily generalized to a model for a mixture of $N \geq 2$ odorants as follows:

$$F_{MIX}(U_1, \dots, U_N) = \frac{F_{\max}}{1 + \left[\frac{1 + \sum_{i=1}^N \frac{U_i}{K_{U_i}}}{\sum_{i=1}^N \eta_{U_i} \frac{U_i}{K_{U_i}}} \right]^{n_{MIX}}} \quad (17)$$

where

$$n_{MIX} = \frac{\sum_{i=1}^N n_{U_i} \eta_{U_i} \frac{U_i}{K_{U_i}}}{\sum_{i=1}^N \eta_{U_i} \frac{U_i}{K_{U_i}}}. \quad (18)$$

If $U = rV$ where r is a positive constant, Eq. 15₂ becomes

$$F_{U+V}(M) = \frac{F_{\max}}{\left\{1 + \frac{1}{\bar{\eta}} \left(1 + \frac{\bar{K}}{M}\right)^{\bar{n}}\right\}}, \quad (19)$$

where the parameters $\bar{\eta} = \bar{\eta}(r, \eta_U, \eta_V, K_U, K_V)$, $\bar{K} = \bar{K}(r, K_U, K_V)$ and $\bar{n} = \bar{n}(r, n_U, n_V, \eta_U, \eta_V, K_U, K_V)$ assume the form

$$\begin{aligned} \bar{\eta} &= \frac{\eta_U r K_V + \eta_V K_U}{K_U + r K_V}, \\ \bar{K} &= \frac{(1+r) K_U K_V}{K_U + r K_V}, \\ \bar{n} &= \frac{r n_U \eta_U K_V + n_V \eta_V K_U}{r \eta_U K_V + \eta_V K_U}. \end{aligned} \quad (20)$$

Similarly, setting for all $i \in \{1, \dots, N-1\}$, $U_i = r_i U_N$ where r_i are positive constants, and $M = \sum_{i=1}^N U_i$ we obtain

$$F_{MIX}(M) = \frac{F_{\max}}{1 + \frac{1}{\eta_{MIX}} \left(1 + \frac{K_{MIX}}{M}\right)^{n_{MIX}}} \quad (21)$$

where

$$\begin{aligned} \eta_{MIX} &= \frac{\sum_{i=1}^{N-1} \frac{r_i}{K_{U_i}} \eta_{U_i} + \frac{1}{K_{U_N}} \eta_{U_N}}{\sum_{i=1}^{N-1} \frac{r_i}{K_{U_i}} + \frac{1}{K_{U_N}}}, \\ K_{MIX} &= \frac{\left(1 + \sum_{i=1}^{N-1} r_i\right)}{\sum_{i=1}^{N-1} \frac{r_i}{K_{U_i}} + \frac{1}{K_{U_N}}}, \\ n_{MIX} &= \frac{\sum_{i=1}^{N-1} n_{U_i} \eta_{U_i} \frac{r_i}{K_{U_i}} + n_{U_N} \eta_{U_N} \frac{1}{K_{U_N}}}{\sum_{i=1}^{N-1} n_{U_i} \frac{r_i}{K_{U_i}} + n_{U_N} \frac{1}{K_{U_N}}}. \end{aligned} \quad (22)$$

The asymptotic values of the functions (19) and (21) are

$$\text{asy}_M = \frac{F_{\max}}{1 + \frac{1}{\bar{\eta}}}, \quad \text{asy}_{M_{MIX}} = \frac{F_{\max}}{1 + \frac{1}{\eta_{MIX} n_{MIX}}}, \quad (23)$$

and the concentrations of M at half maximum response are

$$\begin{aligned} \text{EC}_{50} &= \frac{\bar{K}}{\sqrt[n]{2 + \frac{1}{\bar{\eta}} - 1}}, \\ \text{EC}_{50_{MIX}} &= \frac{K_{MIX}}{n_{MIX} \sqrt[n]{2 + \frac{1}{\eta_{MIX} n_{MIX}} - 1}}. \end{aligned} \quad (24)$$

It should be noted that if $n_U = n_V$, then Marasco et al. binary mixture models (15)₂ and (19) reduce

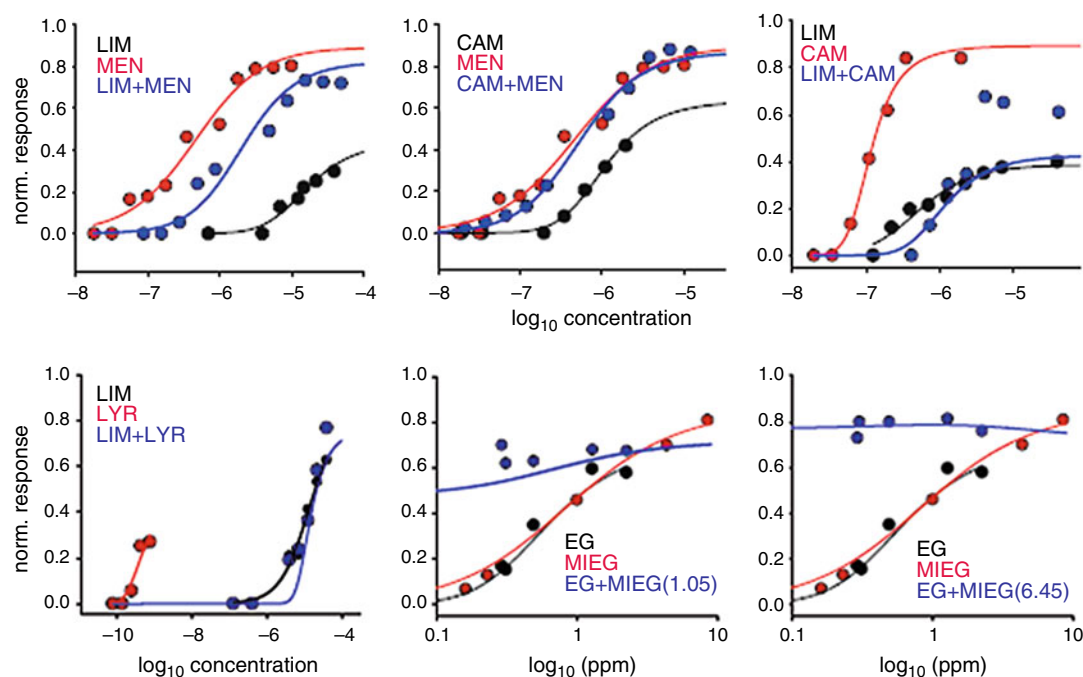
to those proposed in Cruz and Lowe (2013), i.e., models (9)₂ and (11), respectively.

The model (15)₂ can take into account all types of interaction between odors in a binary mixture as reported in Fig. 2. Moreover, since all the experimentally measurable characteristics of the curve for the mixture (i.e., steepness, asymptotic value, and midpoint) can be expressed by a non-linear combination of the parameters for the individual components, it is thus possible to find mathematical conditions for all parameters and concentrations to design mixtures with specific properties (Marasco et al. (2016), Appendix A.3 and Figs. 2–3). In particular, it is mathematically demonstrated that synergy cannot be obtained for concentration values below the midpoint of the component with the lower Hill coefficient (Marasco et al. (2016), Appendix A.3).

The binary mixture model (15)₂ is validated through three set of experimental data obtained using different protocols (Rospars et al. 2008;

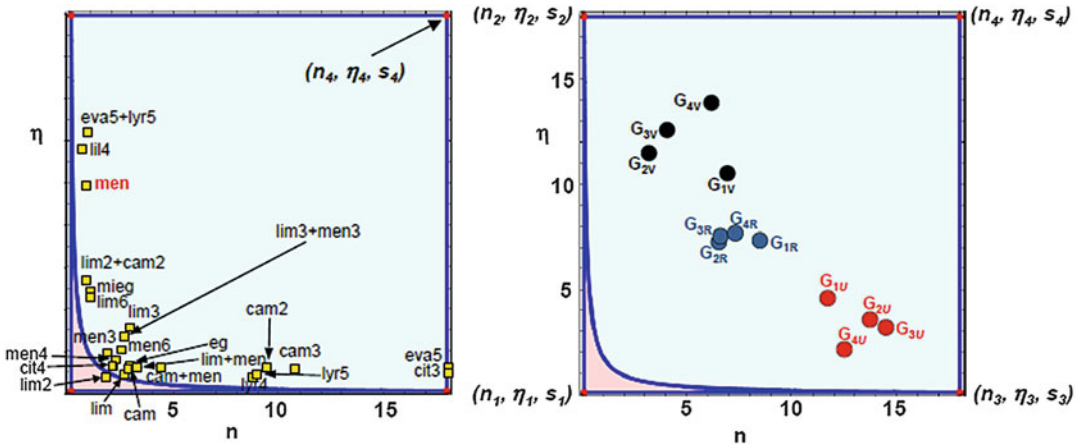
Cruz and Lowe 2013; Duchamp-Viret et al. 2003). In almost all cases, it is obtained a very good qualitative and quantitative agreement with experimental data (see Fig. 4, and (Marasco et al. (2016), Appendix A.4 and Tables S2–S3)).

In particular, the first four panels of Fig. 4 demonstrate that the model is able to correctly reproduce suppression (Fig. 4, top left), hypo-additivity (Fig. 4, top center), and inhibition (Fig. 4, top right and bottom left). The bottom central and right panels of Fig. 4 refer to binary mixtures as a function of the concentration of one odor (EG) with a second odor added at a fixed concentration (MIEG). Also in this case the model was in very good agreement with experiments over the entire concentration range that was tested. To confirm these results both the average square error (MSE) and the absolute percentage error (MAPE) have been used to quantitatively compare the experimental data with the predicted data (Marasco et al. (2016), Appendix A.4 and



Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response, Fig. 4 Model validation against experimental findings. In each panel are reported the experimental responses recorded in an OSN to two single odors (black and red symbols) and to their

mixture at the same dilution (blue symbols) as a function of the odor concentration. Black and red lines represent best fits of experimental points, according to Eq. 15₁. The blue line in each panel represents the model prediction for the mixture using Eqs. 19 and 15₂



Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response, Fig. 5 The odor response space can be generated by a three vector basis. (left panel) The sets $B_1 = \{(n_{\min}, \eta_{\max}, s_2), (n_{\max}, \eta_{\min}, s_3), (n_{\max}, \eta_{\max}, s_4)\}$, and $B_2 = \{(n_{\min}, \eta_{\min}, s_1), (n_{\min}, \eta_{\max}, s_2)\}$,

$(n_{\max}, \eta_{\min}, s_3)\}$ cover every odorant $F_{(n,\eta,s)}$ in the cyan and pink area, respectively. (right panel) Any target odor O_R can be obtained as a mixture of odors in a mathematically predictable manner

Tables S2–S3). There are three cases in which the model failed to reproduce experimental findings (Marasco et al. 2016, Fig. 5). The possible reasons for this discrepancy could be due to both a model limitation and to the way in which the experimental results for the mixture are determined and represented in Rospars et al. (2008) and Duchamp-Viret et al. (2003).

The Mathematical Structure of the Odor Response Space (ORS)

In this section, the mathematical structure of the odor response space (ORS) introduced in Marasco et al. (2016) and its consequences are analyzed.

In color vision, it has been found a set of “primary colors” that can be combined in varying amounts to produce a range of colors belonging to the color perception space. On the contrary, the possibility to express the response of olfactory sensory neurons (OSNs) to odor stimuli in terms of a few elementary and objective responses, i.e., the “primary odor responses”, remains still open.

In Marasco et al. (2016), using experimental constraints and provided that any OSN response curve can be represented as a Hill function of the odor concentration, it is demonstrated that the odor response space is three-

dimensional, and the dose-response function of any odor receptor can be obtained from three (out of four) primary components with specific properties.

Let us consider the function

$$F_{(n,\eta,s)}(X) = \frac{F_{\max}}{1 + \left(\frac{1+sX}{\eta s X}\right)^n}, \quad (25)$$

where the variable X ranges in the real positive numbers, and the parameters n, η, s are positive as well. Note that when $s = 1/K$ and X is an odorant concentration ($U, V, M, \dots$), we get Eqs. 15₁, 19, or 21. In this way OSN responses are univocally identified by the triples (n, η, s) and the **odor response space** writes

$$ORS = \left\{ \frac{F_{\max}}{1 + \left(\frac{1+sX}{\eta s X}\right)^n} \right\}_{n,\eta,s \in \mathbb{R}^+}. \quad (26)$$

Let us introduce two **composition laws**

$$(n, \eta, s) \times \bullet (n', \eta', s') = \left(\frac{n\eta s + n'\eta' s'}{\eta s + \eta' s'}, \frac{\eta s + \eta' s'}{s + s'}, s + s' \right),$$

$$\alpha \ast (n, \eta, s) = (n, \eta, \alpha s), \alpha \in \mathbb{R}_+, \quad (27)$$

where $(n, \eta, s) \bullet (n', \eta', s')$ identifies a mixture of two odorants (n, η, s) and (n', η', s') , i.e.,

$$(n, \eta, s) \bullet (n', \eta', s') \leftrightarrow F_{(n, \eta, s) \bullet (n', \eta', s')} = \frac{F_{\max}}{1 + \left(\frac{1 + (s + s')X}{(\eta s + \eta' s')X} \right)^{\frac{\eta \eta s + \eta' \eta' s'}{\eta s + \eta' s'}}$$

$\alpha \times (n, \eta, s)$, $\alpha \in \mathbb{R}_+$ identifies the odorant (n, η, s) at concentration αX , i.e.,

$$\alpha \times (n, \eta, s) \leftrightarrow F_{\alpha \times (n, \eta, s)} = \frac{F_{\max}}{1 + \left(\frac{1 + s(\alpha X)}{\eta s(\alpha X)} \right)^n}.$$

Owing to Eq. 27, to mix odorants (n, η, s) , (n', η', s') at a fixed ratio r ($U = rV$) is equivalent to consider the following combination

$$\left[\frac{r}{r+1} \times (n, \eta, s) \right] \bullet \left[\frac{1}{r+1} \times (n', \eta', s') \right].$$

The operation $\bullet$ is commutative and associative, i.e., a mixture of several odorants does not depend on the way one mixes them but only on the reciprocal ratios. On the other hand, we cannot have “opposite odorants”, because of the positivity constraints of the parameters (n, η, s) . This prevents the operations (27) from defining a vector space structure; in fact the odor space can be mapped only on the positive octant $\mathbb{R}_+^3$

$$(ORS, \bullet, \times) \mapsto (\mathbb{R}_+^3, +, \cdot)$$

by means of the application

$$(n, \eta, s) \mapsto (n\eta s, \eta s, s), \quad (28)$$

from which we obtain that

$$\begin{aligned} (n, \eta, s) \bullet (n', \eta', s') &\mapsto (n\eta s, \eta s, s) + (n' \eta' s', \eta' s', s'), \\ \alpha \times (n, \eta, s) &\mapsto \alpha(n\eta s, \eta s, s). \end{aligned} \quad (29)$$

As in $\mathbb{R}^3$ three independent vectors (i.e., a basis) suffice to generate the whole space, also in ORS , under the appropriate constraints, any odor response

can be represented by a combination of three primary responses. In detail, choosing a basis in $\mathbb{R}_+^3$

$$\begin{aligned} \mathbf{e}_1 &= (n_1 \eta_1 s_1, \eta_1 s_1, s_1), \\ \mathbf{e}_2 &= (n_2 \eta_2 s_2, \eta_2 s_2, s_2), \\ \mathbf{e}_3 &= (n_3 \eta_3 s_3, \eta_3 s_3, s_3), \end{aligned} \quad (30)$$

every vector $(n\eta s, \eta s, s) \in \mathbb{R}_+^3$ is uniquely obtained as a linear combination of Eq. 30, i.e.,

$$\begin{aligned} \forall (n\eta s, \eta s, s) \exists! (\alpha_1, \alpha_2, \alpha_3) : \\ (n\eta s, \eta s, s) = \sum_{i=1}^3 \alpha_i (n_i \eta_i s_i, \eta_i s_i, s_i), \end{aligned} \quad (31)$$

where the scalars $\alpha_1, \alpha_2, \alpha_3$ must be positive and fulfilling some mathematical constraints (Marasco et al. (2016), Appendix A.5).

From Eq. 29 we have

$$\begin{aligned} [\alpha_1 \times (n_1, \eta_1, s_1)] \bullet [\alpha_2 \times (n_2, \eta_2, s_2)] \\ \bullet [\alpha_3 \times (n_3, \eta_3, s_3)] \mapsto \sum_{i=1}^3 \alpha_i (n_i \eta_i s_i, \eta_i s_i, s_i), \end{aligned} \quad (32)$$

hence an odorant $(n, \eta, s) \in ORS$ is a combination of three **primary responses**

$$\begin{aligned} F_{(n_1, \eta_1, s_1)} &= \frac{F_{\max}}{1 + \left(\frac{1 + s_1 X}{\eta_1 s_1 X} \right)^{n_1}}, \\ F_{(n_2, \eta_2, s_2)} &= \frac{F_{\max}}{1 + \left(\frac{1 + s_2 X}{\eta_2 s_2 X} \right)^{n_2}}, \\ F_{(n_3, \eta_3, s_3)} &= \frac{F_{\max}}{1 + \left(\frac{1 + s_3 X}{\eta_3 s_3 X} \right)^{n_3}}, \end{aligned}$$

by means of positive scalars $\alpha_1, \alpha_2, \alpha_3$, fulfilling some mathematical constraints (Marasco et al. (2016), Appendix A.5). Due to these restrictions, no triple can cover the whole space, i.e., a basis formed by a triple cannot generate all possible responses. However, if we suppose that odorant parameters (n, η, s) are (experimentally) constrained as follows

$$n \in [n_{\min}, n_{\max}], \eta \in [\eta_{\min}, \eta_{\max}], s > 0, \quad (33)$$

then, the convex hull given by the four vertices

$$\begin{aligned}
 (n_{\min}, \eta_{\min}, s_1), s_1 > 0, (n_{\min}, \eta_{\max}, s_2), s_2 > 0, \\
 (n_{\max}, \eta_{\min}, s_3), s_3 > 0, (n_{\max}, \eta_{\max}, s_4), s_4 > 0,
 \end{aligned}
 \quad (34)$$

covers every odorant $F_{(n,\eta,s)}$ verifying Eq. 33 (see Fig. 5 (left panel), and (Marasco et al. (2016), Appendix A.5).

To illustrate practical consequences of this approach, the authors consider the problem of synthesizing a target odor, O_R , smelling let's say as a rose. This would be represented by the set of OSN responses that can be considered essential to smell a rose ($G_{1R}, \dots, G_{4R}$, blue symbols in Fig. 5 (right panel)). Then, the analysis predicts that it could be conveniently obtained with a mixture of odors activating the same OSNs (red and black symbols in Fig. 5 (right panel)) combined with coefficients that can be mathematically determined (Marasco et al. (2016), Appendix A.6).

Cross-References

- [Biophysical Models of Olfactory Mitral and Granule Cells](#)
- [Computational Modeling of Olfactory Behavior](#)
- [Computational Olfaction](#)
- [Olfaction: Overview](#)
- [Olfactory Computation in Glomerular Microcircuits](#)
- [Olfactory Computation in Mitral-Granule Cell Circuits](#)

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Olivocerebellar Pathway

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Definition

The olivocerebellar pathway originates in the inferior olive in the brain stem, projects to the cerebellar cortex, and terminates as climbing fibers on the dendrites of the cerebellar cortical Purkinje cells.

Detailed Description

Cerebellar Function and Information Processing

The cerebellum is involved in a wide range of processes, including cognitive functions (Thach 1996; Schmähmann 1997, 2010), but is best known for its pivotal role in the control of movement. This role is usually described as regulatory,

as the cerebellum is in principle not essential for initiation or execution of movements. Rather, cerebellar deficits result in a lack of coordination (Babinski 1899, 1906; Holmes 1917, 1939; Chambers and Sprague 1955; Dow and Moruzzi 1958; Ito 1984).

The regions of the cerebellum that are related to motor control receive a wide variety of sensory inputs and generate motor-related outputs according to internal rules of computation. These rules are determined by the connectivity of cerebellar cortical neurons and their intrinsic properties. Hence, the computational constraints on the information processing underlying cerebellar function are to a high degree determined by the information content of inputs to the cerebellum together with the structural organization of its internal circuitry.

The Olivocerebellar Pathway

The olivocerebellar pathway constitutes one of the principal inputs to the cerebellum and is considered a key determinant of cerebellar functional organization and of its mode of operation (Oscarsson 1980). The inferior olive is the only source of cerebellar climbing fibers, and the integrity of the inferior olive and the olivocerebellar pathway is crucial for cerebellar function (Oscarsson 1980; Voogd and Bigaré 1980).

Motor learning and motor adaptation are considered salient features of the cerebellar mode of operation (Ito et al. 1974; Robinson 1976; Thach 1998), and the long-term synaptic plasticity underlying these phenomena is fundamental to the information processing of cerebellar neuronal networks (Ekerot and Kano 1985; Ito 1989, 2001; Hansel et al. 2001). Climbing fiber input is thought to be instrumental in the induction of cerebellar synaptic plasticity in the context of motor learning and motor adaptation (Gilbert and Thach 1977). Impulses in the climbing fibers generate the largest depolarizing event observed in any neuron, a highly characteristic burst of potentials usually referred to as a “complex spike” (Gilbert and Thach 1977; Simpson et al. 1996).

Cerebellar Organization: Olivocerebellar Zones and Microzones

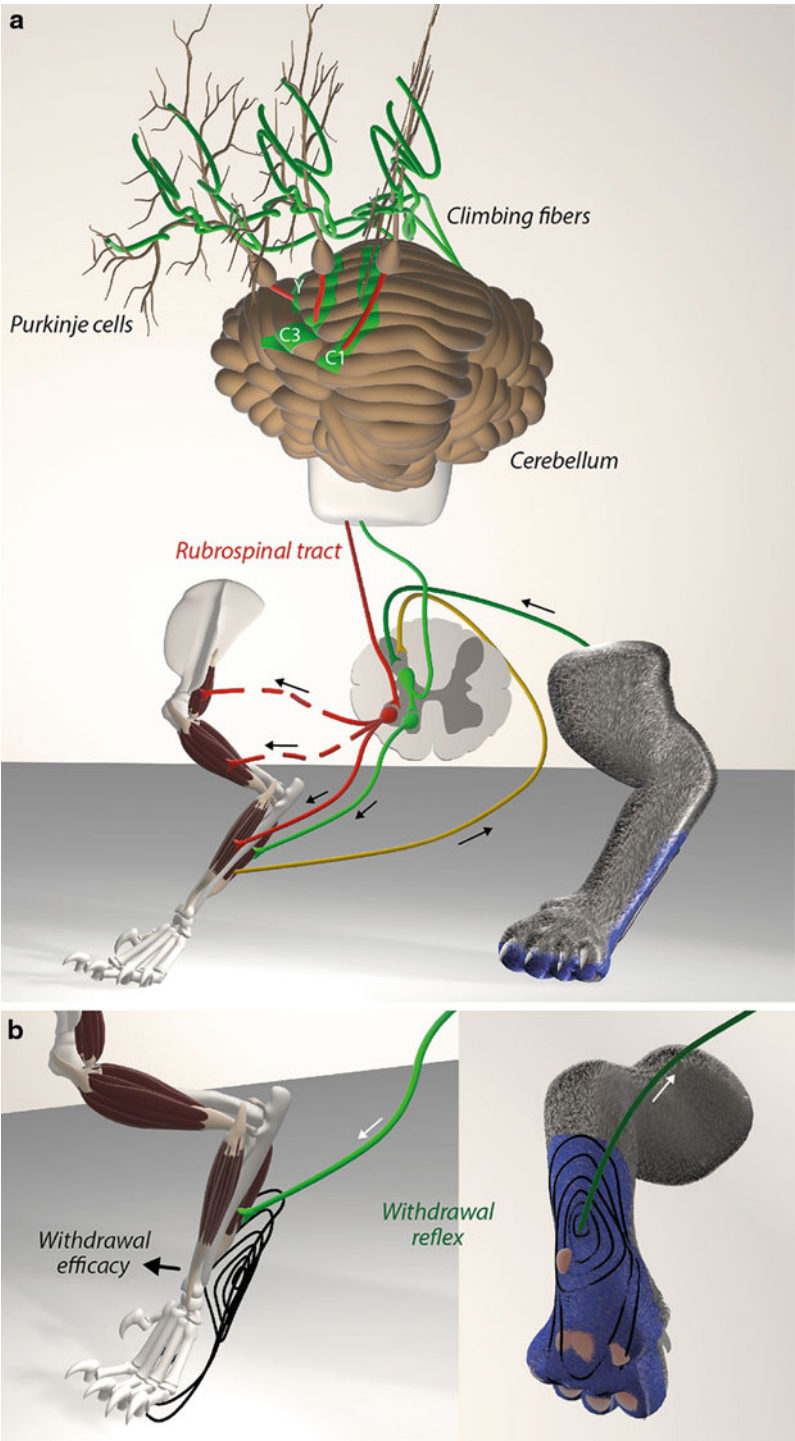
Different subdivisions of the inferior olive project to different regions of the cerebellar cortex and serve different functions (Oscarsson 1980; Voogd and Bigaré 1980). Modern accounts of cerebellar functional organization emphasize its high degree of compartmentalization, with a division of the cerebellar cortex into a number of sagittal zones as organizing principle (Oscarsson 1979). Individual zones are typically 1–2 mm wide and characterized by their specific olivocerebellar and corticonuclear connectivity (Fig. 1a, top panel) (Oscarsson 1979, 1980; Voogd and Bigaré 1980).

Within each zone, smaller units – “microzones” – can be identified by electrophysiological means and are defined by the specific characteristics of their climbing fiber input (Andersson and Oscarsson 1978; Oscarsson 1979; Ekerot et al. 1991). A microzone is a narrow longitudinal strip of cerebellar cortex within which all Purkinje cells receive climbing fiber input from highly similar receptive fields. Microzones with similar characteristics but located in different sagittal zones are the defining components of multi-zonal (olivo–corticonuclear) “microcomplexes” (Fig. 1a) (Garwicz 2002; Apps and Garwicz 2005). These may be thought of as fundamental processing units and the cerebellar counterparts of cerebral cortical columns.

Spino–Olivocerebellar Relationships

The most extensively studied subdivisions of the inferior olive and the corresponding cerebellar cortical zones are related to various aspects of motor control, such as the vestibuloocular reflex or voluntary limb movements (Ito 2013). As regards limb movement control, the intricate interconnectivity between spinal cord withdrawal reflex circuitry and the olivocerebellar pathway to which it connects has been particularly well characterized with respect to information content (Fig. 1a and b) (Garwicz 2002; Apps and Garwicz 2005).

In brief, olivocerebellar climbing fibers projecting to the cerebellar zones controlling



Olivocerebellar Pathway, Fig. 1 Spino–olivocerebellar connectivity. Functional interrelationships between spinal withdrawal reflex circuits and cerebellar multi-zonal microcomplexes controlling the rubrospinal and

corticospinal tracts (the latter not shown). (a) *Upper panel* shows dorsal view of cat cerebellum, with the forelimb-related areas of sagittal zones C1, C3, and Y schematically indicated by green on the cerebellar

rubrospinal and corticospinal tracts monitor the activity of individual withdrawal reflex modules acting upon single limb muscles (Garwicz et al. 2002). Although it was postulated already in the early 1970s that the olivocerebellar climbing fibers may convey information about the activity in “lower motor centers” (Oscarsson 1973), it was not until 30 years later that more direct evidence was obtained to support this notion (Garwicz et al. 2002).

Encoding of Sensorimotor Information in the Olivocerebellar Pathway

The detailed spatial encoding of sensory information mediated by the olivocerebellar pathway shows that an individual olivocerebellar climbing fiber afferent conveys information representing the skin area that is moved when a specific single limb muscle contracts (Fig. 1b, right panel). The distribution of response amplitudes or sensitivity to stimulation within this skin area reflects in great detail the withdrawal efficacy of the muscle (Fig. 1b, left panel) (Schouenborg and Kalliomäki 1990; Schouenborg and Weng 1994). Notably, the biomechanics are adapted to a standing limb position, with the distal limb segment in touch with and supported by the underlying surface.

In addition, the same climbing fiber receives input from group II muscle afferents, originating mainly in the same muscle (Fig. 1a, bottom panel) (Jörmell et al. 1996; Garwicz et al. 2002). Therefore, an individual climbing fiber monitors both

the input and the output elements of an individual spinal withdrawal reflex module. This convergence emphasizes the integrated sensorimotor nature of the information conveyed by the olivocerebellar climbing fibers and indicates that climbing fiber signals that arise from the spinal cord might be pre-processed by spinal withdrawal reflex circuits (Garwicz 2002; Apps and Garwicz 2005).

Input–Output Relationships of Olivo–Corticonuclear Processing Units

A multi-zonal (olivo–corticonuclear) microcomplex (MZMC) typically controls a muscle synergy acting across several limb segments (Ekerot et al. 1995). The distal-most muscle in the muscle synergy seems to have a roughly antagonistic action to the muscle associated with the input side of the circuit (Fig. 1a, bottom left). For instance, an MZMC receiving its climbing fiber input from the withdrawal reflex that activates a palmar flexor of the wrist has a receptive field that has as its center an area of skin on the ventral forepaw just proximal to the central footpad. When the limb is in a standing position, the action of this muscle is to withdraw this particular area of skin away from the stimulus. By contrast, the muscle synergy that constitutes the output from this specific MZMC seems to include the approximate antagonist of this muscle, which is a dorsal flexor of the wrist (Ekerot et al. 1995; Garwicz 2002; Apps and Garwicz 2005).



Olivocerebellar Pathway, Fig. 1 (continued) surface. Purkinje cells represent microzones with similar climbing fiber input, mediated via the olivocerebellar pathway. *Lower panel* shows the organization of spinal circuitry related to the withdrawal reflex module acting on the palmaris longus muscle. Reflex output from spinal cord to palmaris longus indicated by *light green*; reflex input from the skin (*dark green*) and from the muscle itself (*yellow*). The spinal interneuron (*light green*) is shown to project both to reflex output motor neuron and to the inferior olive, the origin of the olivocerebellar pathway.

The cerebellar output from the same multi-zonal (olivo–corticonuclear) microcomplex, mediated via the rubrospinal tract, is shown schematically in red. Note that the main output from the microcomplex is to the antagonist of the muscle that constitutes the output of the associated spinal withdrawal reflex module. **(b)** The distribution of sensitivity within the receptive field on the skin (*right panel*) corresponds in detail to the withdrawal efficacy of the muscle (*left panel*) when the limb is in the standing position, i.e., acting against a surface

Cross-References

- [Cerebellum: Overview](#)
- [Deep Cerebellar Nuclei](#)
- [Long Term Depression in the Granule Cell-Purkinje Cell Synapse](#)
- [Modeling Cerebellar Learning: Input Minimization](#)

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Olivocochlear Bundle

► [Physiology and Function of Cochlear Efferents](#)

Olivocochlear Efferents

► [Physiology and Function of Cochlear Efferents](#)

Olshausen-Field Model

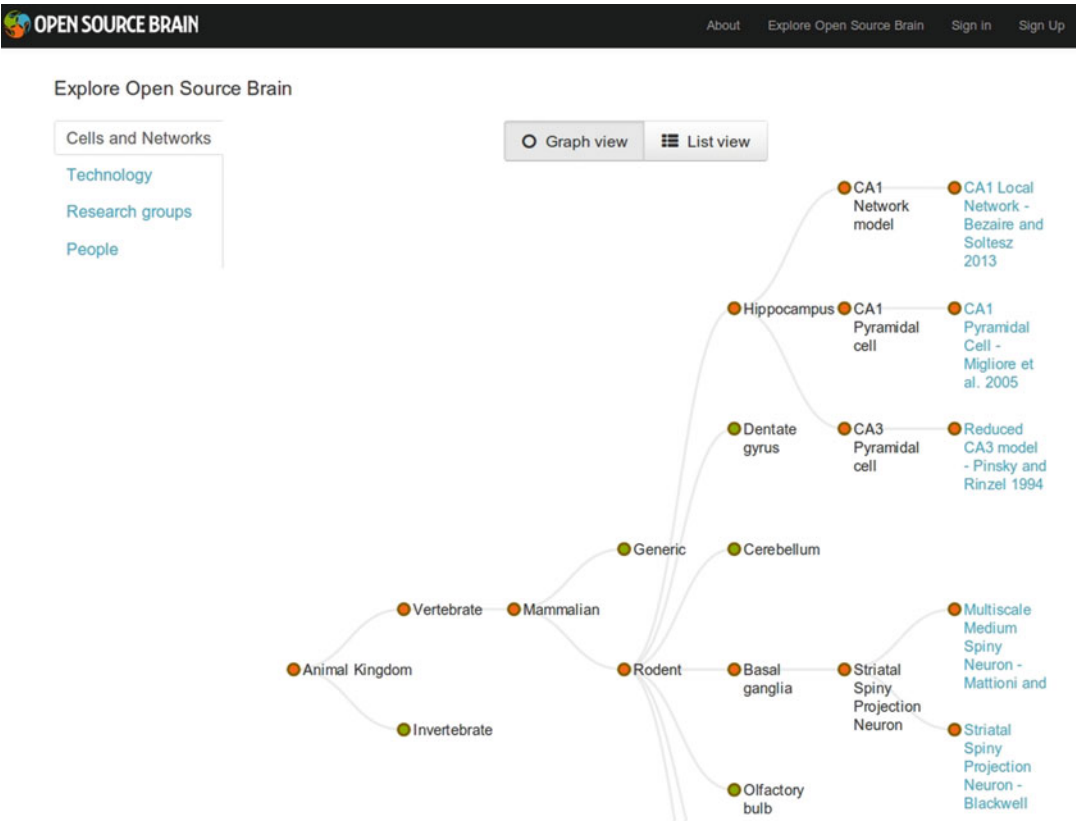
► [Independent Component Analysis of Images](#)

Open Source Brain

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Definition

Open Source Brain (<http://www.opensourcebrain.org>) is an online repository of computational models of ion channels, synapses, neurons, simple network models, and more detailed three-dimensional models of neuronal microcircuits from multiple brain regions and species. It is intended to facilitate sharing and collaborative



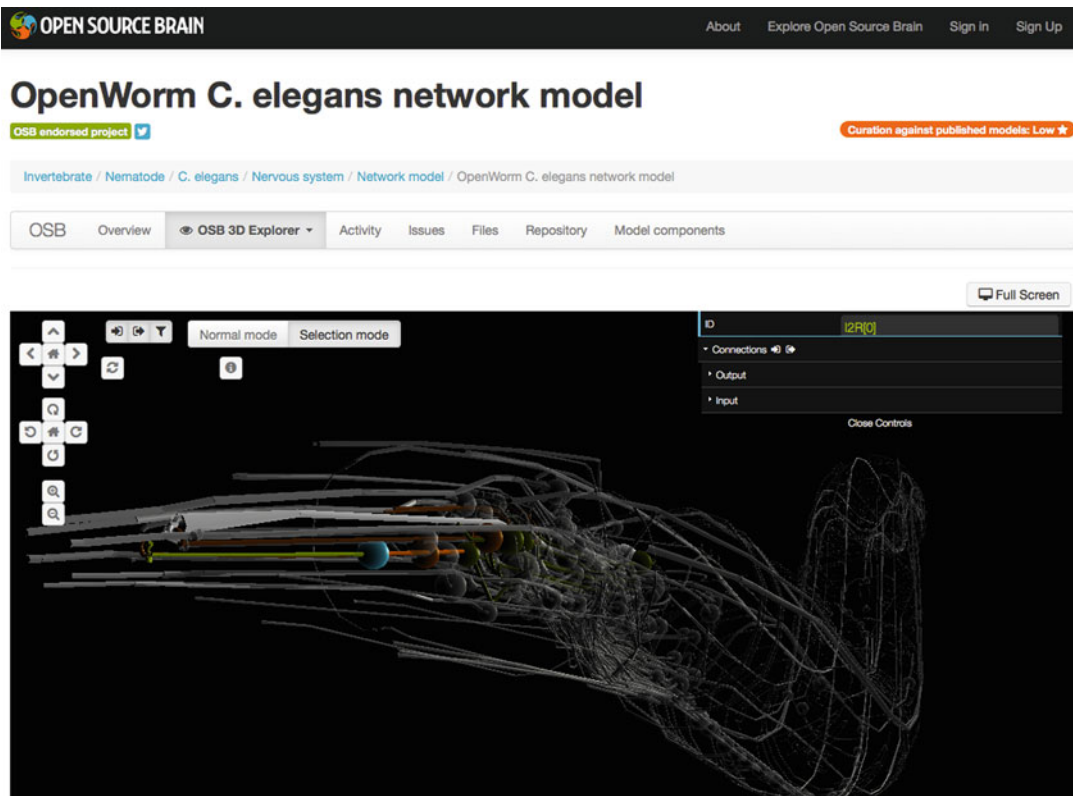
Open Source Brain, Fig. 1 The interface for browsing the cell and network models on OSB

development of neuronal models by researchers around the world.

Detailed Description

The ever-increasing complexity of models and applications used in computational neuroscience makes it clear that no one researcher or lab can implement and maintain detailed models which are applicable to a broad range of research questions and can be used across the diverse applications available for simulation and analysis. A more collaborative approach to neuronal model development, inspired by the success of the open source software movement, is required (Davison 2012). The Open Source Brain repository (OSB, <http://www.opensourcebrain.org>) is being developed to enable researchers to collaboratively develop

computational models of cells and networks which are well tested and documented and can be run across multiple simulators. This is enabled through the use of advanced distributed version control technologies (<http://www.github.com>) and by converting the models to open, standardized formats like NeuroML (Gleeson et al. 2010), allowing the models to be used by the increasing range of simulators and other applications in the NeuroML “ecosystem” (http://www.neuroml.org/tool_support.php). Models can also be specified in the cross-simulator Python-based PyNN language (Davison et al. 2008). Greater interoperability underdevelopment between NeuroML and PyNN means that a wide range of neuronal model types, from large-scale point neuron models to morphologically and biophysically detailed three-dimensional network models, is supported by OSB.



Open Source Brain, Fig. 2 Using the OSB 3D Explorer to visualize the *C. elegans* connectome as developed by the OpenWorm project

The current version of OSB contains models from diverse brain regions including the neocortex, cerebellum, and hippocampus; invertebrate models; as well as more abstract cell and network models (Fig. 1). OSB complements existing model archives (e.g., ModelDB) which have traditionally concentrated on providing snapshots of already published models. The cell, ion channel, synapse, and network models in OSB develop over time to ensure they reflect known physiology and best practices in modeling. Users can comment on/extend/debug any other model as well as contribute their own. Many of the projects on OSB include support for neuroConstruct (Gleeson et al. 2007), a graphical tool which facilitates running a local copy of the model in a number of supported neuronal simulation environments, including NEURON, GENESIS, and MOOSE.

A major recent addition to the functionality of OSB is the 3D Explorer, allowing cells and networks in NeuroML version 2.0 format to be viewed inside the browser (using WebGL and so requiring no additional software to be installed) and their structure and physiological properties examined (Fig. 2). This means modelers need only commit models in NeuroML 2 format to a project repository (e.g., on GitHub) to have access to this advanced feature.

As well as providing cell and network models from specific brain regions, OSB contains a number of “Technology Showcase” projects, with the aim of illustrating how OSB can interact with other specialist neuroinformatic resources and tools. These include NeuroMorpho, which provides neuronal reconstructions in multiple formats including NeuroML; NeuroElectro, which provides structured data on electrophysiological properties of identified neurons which can be used to test the behavior of OSB models; and Virtual Fly Brain, which provides detailed information on *Drosophila* neurons and brain regions. Close links with other initiatives including NIF/NeuroLex (<https://www.neuinfo.org>) and the OpenWorm project (<http://openworm.org>) are also being developed.

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Optic Flow Fields

► Optic Flow Processing

Optic Flow Processing

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Synonyms

Directional motion; Matched filters; Motion parallax; Optic flow fields; Optical flow; Relative motion; Velocity vector fields

Definition

Optic flow describes the geometrical projection of relative motion between the visual environment and a moving optical system. It is commonly formalized by a distribution of local velocity vectors, observed at many different positions within the optical system’s visual field. Together, the local velocity vectors constitute a pattern of coherent image motion called an optic flow field. The

direction and magnitude of the velocity vectors depend on the instantaneous self-motion of the optical system which may be decomposed into its translation and rotation components. The magnitude of translation-induced contribution to a given velocity vector depends on the distance between the optical system and objects within the visual field, while the rotation-induced contribution is distance invariant. Given its properties, optic flow contains a significant amount of information about the self-motion and relative distance information that can be exploited for guidance and control tasks.

Detailed Description

The intimate relationship between self-motion and specific patterns of image motion was noticed early on by J. J. Gibson in the mid-twentieth century. In his book *The Perception of the Visual World* (1950) and later in *The Ecological Approach to Visual Perception* (1979), Gibson mainly focused on qualitative properties of optic flow. But it was undoubtedly his work that provided the conceptual foundation for later quantitative approaches on how optic flow may be exploited to estimate self-motion, which were mainly driven by computer vision and visual neuroscience. The first mathematical descriptions of optic flow fields became available in the mid-1970s (e.g., Nakayama and Loomis 1974; Koenderink and van Doorn 1975) and 1980s (e.g., Horn and Schunck 1981). From then on, researchers in computer vision, natural sciences, and engineering started to take advantage of the formal relationship between the self-motion components of optical systems – either eyes or cameras – and the resulting optic flow fields (e.g., Barron et al. 1994).

Movements in Space

Any movement in space may be described as a combination of translation and rotation, conveniently parameterized as the projections of their components onto the cardinal axes of a Cartesian

coordinate system that has its origin in the center of the optical system. The components are often referred to as thrust, slideslip, and lift in terms of translations along the x-, y-, and z-axis, respectively, while rotations around these axes are called roll, pitch, and yaw (Fig. 1). Together, the projections onto the cardinal axes define the translation vector, $\mathbf{T} = [T_x, T_y, T_z]^T$, and the rotation vector, $\mathbf{R} = [R_x, R_y, R_z]^T$, which results in 6 degrees of freedom, where the superscript T denotes the transpose of a vector.

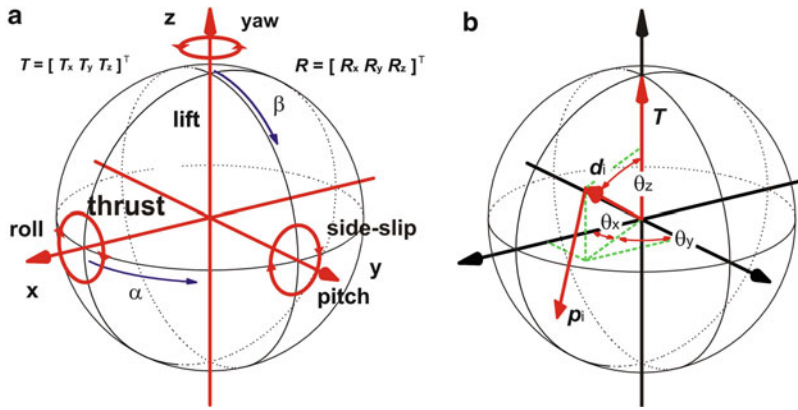
Local Image Shifts Quantified as Parallax Vectors

From the center of the coordinate system, the lines of sight to any given points in a spherical visual field may be described by direction vectors $\mathbf{d}_i$, where the index i ($= 1, 2, \dots, N$) refers to the number of different points observed. During self-motion, the observed points in the visual field change their location over time relative to the optical system depending on where they are observed and what the self-motion components $\mathbf{T}$ and $\mathbf{R}$ of the optical system are. The resulting image shifts of the observed points are equivalent to the temporal derivative of the direction vectors, $\mathbf{d}_i$, and are described as local parallax vectors, $\mathbf{p}_i$, according to a basic vector equation. Using the notation proposed by Koenderink and van Doorn (1987), each local parallax vector, $\mathbf{p}_i$, is defined as.

$$\mathbf{p}_i = \frac{\partial \mathbf{d}_i}{\partial t} = -(\mathbf{T} - (\mathbf{T} \cdot \mathbf{d}_i)\mathbf{d}_i)/D_i - (\mathbf{R} \times \mathbf{d}_i), \quad (1)$$

where $\mathbf{T}$ denotes the translation vector, D_i gives the distances of the observed points along directions $\mathbf{d}_i$, and $\mathbf{R}$ is the rotation vector. The expression $(\mathbf{T} \cdot \mathbf{d}_i)$ on the right-hand side of Eq. 1 gives the dot (scalar) product between the translation vector and the direction vectors $\mathbf{d}_i$, and the operator $\times$ symbolizes the cross product, here calculated between the rotation vector and the observation directions $(\mathbf{R} \times \mathbf{d}_i)$.

To gain some intuition on how self-motion components and parallax vectors are related to one



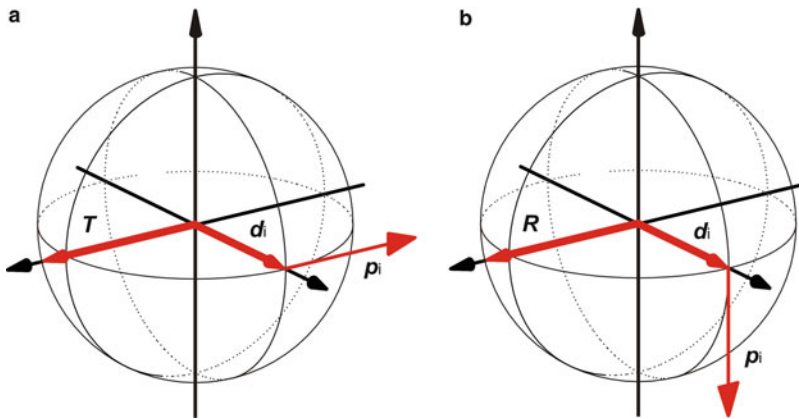
Optic Flow Processing, Fig. 1 Self-motion components in a Cartesian coordinate system. (a): Self-motion components T and R may be described in terms of 6 degrees of freedom. Translation components along the x-, y-, and z-axis are called thrust, sideslip, and lift, respectively. Rotation components along the same axes are called roll, pitch, and yaw. (b) The variables θ_x , θ_y , and θ_z describe the angles between the direction, d_i , upon which the parallax vector, p_i , is observed, and the cardinal axes of the coordinate system. We will need those angles later during the discussion of local scaling factors applied to the observation directions, d_i . In this case, the parallax vector has been observed during a translation, T , along the positive z-axis. Note that the angles θ_i , ($i = x, y, z$), are different from the

angle Θ between the observation directions, d_i , and the self-motion vectors T or R . In the example given here, where the self-motion vector, T , corresponds to the positive z-axis, the angle $\Theta = \theta_z$. As the visual field is spherical, we may represent local image shifts, p_i , as tangent vectors on the surface of a unit sphere. The directions of R , T , and d_i may be described in terms of two angles, the horizontal azimuth, α , and the vertical elevation, β . The azimuth ranges from $-180^\circ \leq \alpha \leq 180^\circ$, with $\alpha = 0^\circ$ corresponding to the positive x-axis in Cartesian coordinates and the elevation ranging from $0^\circ \leq \beta \leq 180^\circ$, where $\beta = 0^\circ$ corresponds to a direction along the positive z-axis; and $\beta = 90^\circ$ describes the equator of the visual field

another, we should first consider the translation- and rotation-dependent contributions on the right-hand side of Eq. 1 separately. Let us assume the optical system undergoes a pure unit translation along the positive x-axis, i.e., $T = [1 \ 0 \ 0]^T$. The resulting image shift is observed in direction $d_i = [0 \ 1 \ 0]^T$, which corresponds to the positive y-axis and thus a lateral viewing direction at the equator of the visual field (Fig. 2a). In this case, T and d_i are orthogonal to one another and the dot product ($T \cdot d_i$) becomes zero. The result is a parallax vector, p_i , that is equal to $-T$ which may be plotted as a tangent vector in a spherical representation of the visual field with its basis originating at d_i (Fig. 2a). The translation-dependent term in Eq. 1 states that p_i is scaled by the distance, D_i , between the center of the optical system and the point in the visual field along direction d_i . We can easily relate this distance dependence to our everyday experience. When sitting on a train or in a car moving along a straight line, close visual objects rush past very quickly, while trees or hills in the distance seem to hardly move at all.

In contrast to the translation-induced contribution to the parallax vector, the rotation-induced contribution does not depend on distance, as is clear from the second term on the right-hand side of Eq. 1. During a pure counterclockwise rotation of the optical system around the positive x-axis, $R = [1 \ 0 \ 0]^T$, we chose the same observation direction as before, $d_i = [0 \ 1 \ 0]^T$, and calculate the cross product, $-(R \times d_i)$, to obtain the rotation-induced local parallax vector, p_i (Fig. 2b). Like in a case of translation-induced relative motion, the resulting p_i plotted as a tangent vector on the sphere points in the direction opposite to the change of d_i over time (Fig. 2b).

In the next step, we may apply Eq. 1 to compute optic flow fields composed of parallax vectors measured at N different directions, d_i , in the visual field. Again we consider the global properties of translation- and rotation-induced optic flow fields separately. This time we compute a pure lift translation, $T = [0 \ 0 \ 1]^T$, and again a pure roll rotation, $R = [1 \ 0 \ 0]^T$. For this purpose, we set in Eq. 1 the



Optic Flow Processing, Fig. 2 Local motion parallax vectors due to translation and rotation. (a) Translation-induced local parallax vector, p_i , observed at direction, d_i , given a thrust translation, T , along the positive x-axis. The distance to objects in the visual environment, D_i , was set to

unity. (b) Rotation-induced local parallax vector, p_i , observed at direction, d_i , given a counterclockwise roll rotation, R , around the positive x-axis. For further explanation, see text

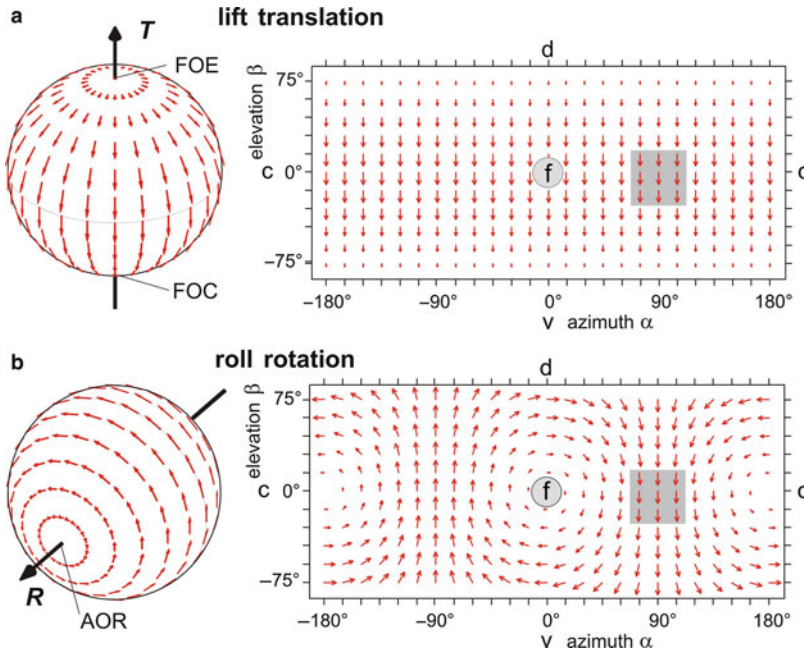
rotation and translation vectors to zero, respectively. To keep matters simple, we assume a uniform distance distribution, i.e., $D_i = 1$, for all directions, d_i , when calculating the translation-induced component of the individual parallax vectors.

Figure 3a, b shows the global structure of such translational and rotational optic flow fields – for clarity all individual parallax vectors were multiplied by a scaling factor of 0.1. The flow fields were calculated for a lift translation (a) and roll rotation (b), respectively. In both cases, the directional distribution of the local parallax vectors is determined by the self-motion vectors R and T . The orientation of R and T defines the location of the two singularities within the optic flow fields where the magnitude of the local image shifts, or parallax vectors p_i , becomes zero. The singularities are separated by an angle of 180° . Right in between the two singularities, i.e., 90° off the orientation of R and T , the projection of the relative motion becomes maximum, which is easily verified by revisiting the rotation- and translation-dependent terms in Eq. 1. At any other location, the magnitude of the parallax vectors follows the function $|p_i| = \sin(\Theta)$, where Θ is the angle between the self-motion component and the observation direction d_i . In translation-induced optic flow fields, the two singularities are often referred to as focus of expansion (FOE), located in the direction of translation T ,

and the focus of contraction (FOC) in the opposite direction $-T$. Singularities within a rotation-induced flow field coincide with the orientation of the axis of rotation (AOR), defined by R and $-R$.

A fundamental difference in the global structure of translation- and rotation-induced optic flow concerns the respective directional distribution of the parallax vectors. While all image shifts p_i within a translation flow field are aligned along great circles connecting the FOE with the FOC, image shifts in a rotation flow field are oriented along parallel circles centered on the AOR (Fig. 3a, b). Another general feature of translational and rotational parallax vectors is that at any given direction d_i , they are orthogonally oriented to one another when the self-motion axes of translation and rotation are co-aligned. This means that they can be most easily distinguished, which is a helpful feature when extracting translation- and rotation-induced self-motion components.

For various reasons, it has proven useful to transform the spherical representation of optic flow into a 2-dimensional cylindrical projection. Such dimensionality reduction naturally comes with an increasing transformation error toward the pole regions of the sphere where the area is overrepresented by a factor of $1/\sin(\beta)$, with β being the elevation (cf. legend Fig. 2). A cylindrical projection, however, allows us to



Optic Flow Processing, Fig. 3 Global structure of optic flow fields. (a) Optic flow field generated during lift along the positive z-axis. The distance to objects in the visual environment, D_o , was set to unity. FOE and FOC give the focus of expansion and contraction, respectively, which are defined by the translation vector, T , and indicate the two singularities in the flow field. (b) Optic flow field generated during roll rotation, R , around the positive x-axis. AOR stands for axis of rotation which defines the two singularities in the flow field. To visualize the entire global flow field, it may be transformed into the two-dimensional plane using a cylindrical projection. For better

intuition when presenting the flow field, the elevation, β , has been redefined to range from $+90^\circ \geq 0 > -90^\circ$. This results in the direction $\alpha = \beta = 0^\circ$ coinciding with the positive x-axis, i.e., the location in the equator of the visual field in front of the observer (f). Letters d , v , and c stand for dorsal, ventral, and caudal, respectively. Note that in the equatorial region in the right lateral hemisphere (gray area), the parallax vectors point downward in both flow fields; they are ambiguous with respect to the self-motion component that caused them. For further explanation, see text (Modified from Krapp and Hengstenberg 1996)

directly visualize the entire spherical optic flow field in a single figure as a function of azimuth, α , and elevation, β (Fig. 3a, b, right panels).

Estimating Self-Motion Parameters from Noisy Optic Flow Fields

So far we considered the properties of optic flow assuming that all parameters were perfectly well known which enabled us to compute translation- and rotation-induced flow fields. Optical systems – or biological visual systems – generally have to solve the inverse problem. To be useful for guidance and control of technical systems or, equivalently, the control of posture and gaze in animals, the task is a continuous estimation of R and T

which may be used to generate feedback signals driving the appropriate motor plants. I should emphasize that both technical and biological systems have also access to inertial measurements of state changes using accelerometers and gyroscopes or equivalent mechanoreceptive systems. But inertial sensor systems – although being able to initiate immediate stabilizing action – do not necessarily provide information as to whether or not compensatory motor activity has yielded the desired effect. Another problem concerns the dynamic range of the sensors. Some inertial measurement sensors and many mechanoreceptor systems are not particularly sensitive in the low end of their dynamic range resulting in a low gain for sensing slow drifts or angular rotations. Vision, on the other hand, covers the low-end dynamic range

but is notoriously slow due to long delay times and heavy computational overheads when processing local image shifts. Biological visual systems also have limited bandwidth for the processing of image shifts due to high linear and angular velocities. We will return to the topic of dynamic range fractioning further below.

Why exploit optic flow to estimate self-motion? For instance, one of the components in human gaze control is driven by the vestibuloocular reflex (VOR) where the oculomotor pathway receives inputs from the fast vestibular system that measures angular accelerations of the head (e.g., Angelaki and Cullen 2008). Ideally, small head rotations should be quantitatively compensated for by motor action of the eye muscles counterrotating the eye balls in their orbits. But the only way of knowing whether the counterrotation fully compensated for the head or body movement is to measure the remaining relative motion between the eyes and the visual surroundings. Adjusting the motor commands sent to the eye muscles requires an estimate of the rotational optic flow component analyzed by the motion vision system. Another vision-dependent mechanism enabling the control of posture and gaze is the oculomotor reflex. To support an equilibrium posture and a stable gaze also requires an estimate of self-motion parameters $\mathbf{R}$ and $\mathbf{T}$. In general, whenever animals – including humans – are endowed with vision, they will have developed the analysis of optic flow as a mechanism that complements mechanoreception for the control of their motor actions.

In the following, we will discuss the theoretical limits of estimating $\mathbf{R}$ and $\mathbf{T}$ based on noisy optic flow fields. Noise, in this context, may be introduced by internal or external factors, for instance, as a result of imperfections in measurements of local parallax vectors or uncertainties in the distance distribution within the cluttered visual surroundings (see below). As a starting point, it will be useful to revisit the work by Koenderink and van Doorn (1987) who proposed an iterative least square solution for the recovery of $\mathbf{R}$ and $\mathbf{T}$, also known as the KvD algorithm. As Eq. 1 states, we are dealing with an expression that contains one known quantity on the left-hand side – at least under the assumption

that the optical system is able to measure the parallax vectors, $\mathbf{p}_i$. On the right-hand side, the only parameter known is the distribution of directions, $\mathbf{d}_i$, at which the parallax vectors are observed. The unknown parameters on the right-hand side of Eq. 1 are the distances to objects in the visual field, D_i , as well as $\mathbf{T}$ and $\mathbf{R}$. This clearly is an ill-posed problem due to the fact that the contribution to $\mathbf{p}_i$ induced by $\mathbf{T}$ is under-defined. The same $\mathbf{p}_i$ may result from a slow translation at close distance to visual objects or from a fast translation in an environment where the objects are at large distances. Although the contribution to $\mathbf{p}_i$ based on $\mathbf{R}$ is sufficiently well defined, $\mathbf{R}$ and $\mathbf{T}$ cannot be estimated based on a single parallax vector induced during a combination of translation and rotation.

Koenderink and van Doorn (1987) tackled this problem by introducing a local scaling factor μ_i , or “reduced nearness,” defined as $\mu_i = T/D_i$, where T denotes the speed of the translation vector $\mathbf{T}$ along the direction of the unit vector $\mathbf{t}$ according to the relationship $\mathbf{T} = \mathbf{t}T$. By introducing reduced nearness, the KvD turns an ill-posed problem into a tractable one. It allows for the retrieval of the direction of translation vector, $\mathbf{t}$, rotation vector, $\mathbf{R}$, and the local reduced nearness, μ_i , given the parallax vectors, $\mathbf{p}_i$, are measured at $N \geq 5$ different directions, $\mathbf{d}_i$. The introduction of reduced nearness modifies Eq. 1 to.

$$\mathbf{p}_i = -\mu_i(\mathbf{t} - (\mathbf{t} \cdot \mathbf{d}_i)\mathbf{d}_i) - (\mathbf{R} \times \mathbf{d}_i) \quad (2)$$

The KvD is based on minimizing the squared error, E , between a set of measured parallax vectors, $\mathbf{p}_i$, and a set of parallax vectors, $\mathbf{p}'_i$, calculated from fitted parameters $\mathbf{t}'$, $\mathbf{R}'$, and μ'_i , under the constraint that $|\mathbf{t}'| = 1$. The error E is formalized by.

$$E = 1/N \sum (\|\mathbf{p}_i - \mathbf{p}'_i\|)^2 + \lambda((\mathbf{t}' \cdot \mathbf{t}') - 1), \quad (3)$$

where λ is the Lagrange multiplier ensuring the constraint $|\mathbf{t}'| = 1$ is met. After working out the partial derivatives $\partial/\partial \mathbf{R}'$, $\partial/\partial \mathbf{t}'$, and $\partial/\partial \mu'_i$ for the right-hand side of Eq. 3, three equations are obtained which can be used in an iterative procedure to estimate $\mathbf{t}'$, $\mathbf{R}'$, and μ'_i :

$$\mathbf{t}' = -v \left\{ [\mathbf{I} - \langle \mu'_i \mathbf{d}_i \otimes \mu'_i \mathbf{d}_i \rangle]^{-1} [\langle \mu'_i \mathbf{p}_i \rangle + (\mathbf{R}' \times \langle \mu'_i \mathbf{d}_i \rangle)] \right\}, \quad (4a)$$

$$\mathbf{R}' = [\mathbf{I} - \langle \mathbf{d}_i \otimes \mathbf{d}_i \rangle]^{-1} [\langle \mathbf{p}_i \times \mathbf{d}_i \rangle + (\mathbf{t}' \times \langle \mu'_i \mathbf{d}_i \rangle)], \quad (4b)$$

$$\mu'_i = -\mathbf{t}' \cdot (\mathbf{p}_i - (\mathbf{d}_i \times \mathbf{R}')) / (1 - (\mathbf{t}' \cdot \mathbf{d}_i)^2), \quad (4c)$$

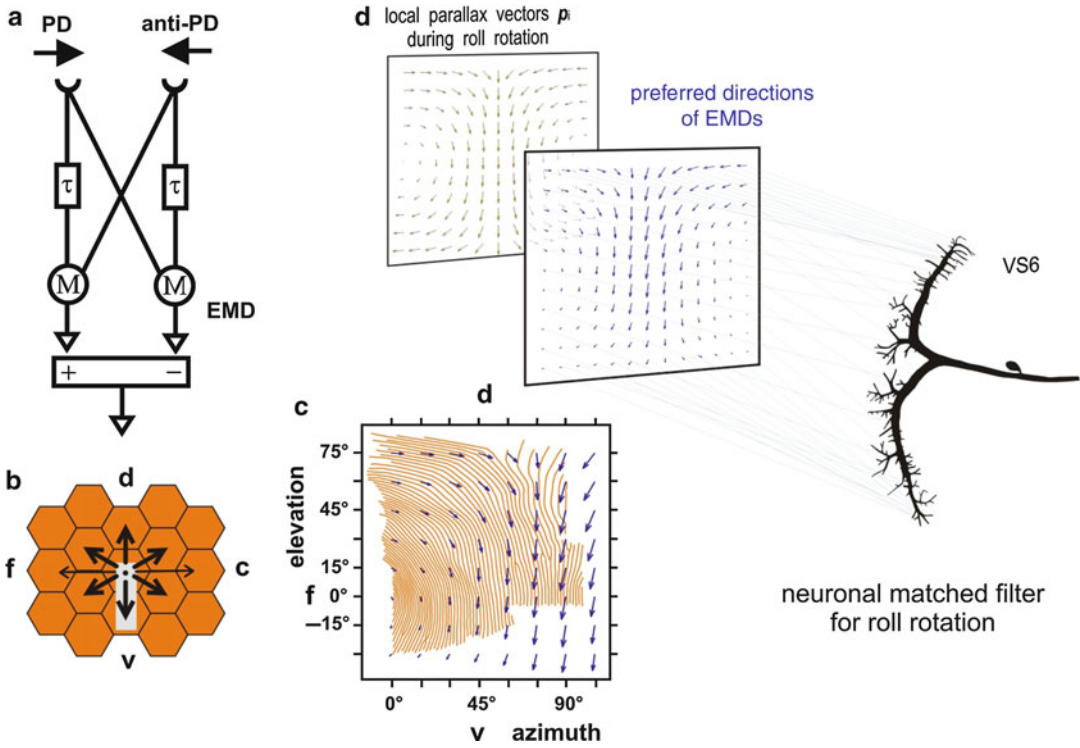
where $\mathbf{I}$ is the identity matrix, v is a factor forcing $|\mathbf{t}'| = 1$, $\otimes$ symbolizes the dyadic (tensor) product, and arguments in pointed brackets, $\langle \dots \rangle$, are averages over all N observation directions. It is worth discussing the terms on the right-hand side of the iteration equations for the estimate of $\mathbf{t}'$ and $\mathbf{R}'$ more closely.

Apparent translation and rotation: It may come as a surprise to find the cross product between the estimated rotation and the average across all observation directions multiplied by the reduced nearness, $(\mathbf{R}' \times \langle \mu'_i \mathbf{d}_i \rangle)$, in the iteration equation for the estimate $\mathbf{t}'$. Similarly, in the equation for the rotation estimate, $\mathbf{R}'$, the term $(\mathbf{t}' \times \langle \mu'_i \mathbf{d}_i \rangle)$ is included. These terms in Eq. 4a and 4b describe the so-called “apparent translation” and “apparent rotation” terms, due to the rotational and translational components of self-motion, respectively (Koenderink and van Doorn 1987). They are the inevitable consequence of the fact that a parallax vector observed in direction $\mathbf{d}_i$ could have been the result of a translation *or* a rotation. This is easily illustrated by comparing the same region of two optic flow fields where one was caused by lift translation and the other one by clockwise roll rotation (Fig. 4). The parallax vectors in this region of the equatorial visual field are quite similar and, for the position $\alpha = 90^\circ$, point in exactly in the same direction. The apparent terms, however, do also suggest a practical solution to this problem. The estimates $\mathbf{t}'$ and $\mathbf{R}'$ are both applied to the average $\langle \mu'_i \mathbf{d}_i \rangle$. If the

observation directions are appropriately chosen so that their average is equal to zero, then the cross product with the estimated translation and rotation, and thus the “apparent” terms, also equals zero. The best way to achieve this is a pair-wise observation of parallax vectors in opposite directions. The reason being that parallax vectors in a translation flow field observed at opposite locations in the visual field assume the same direction, but those observed at equivalent locations in a rotation flow field point in opposite directions (cf. Figure 3), which allows us to distinguish between the two cases. The best strategy would certainly be to observe parallax vectors at many paired locations over as large a solid angle as possible – ideally 4π – which would enable the analysis of optic flow generated in both visual hemispheres. We will later show examples of optic flow processing in insects which reflect an approximation of exactly that strategy.

The matrices of observation directions: The results of the averaged dyadic products including nearness estimates $\langle \mu'_i \mathbf{d}_i \otimes \mu'_i \mathbf{d}_i \rangle$ in Eq. 4a and $\langle \mathbf{d}_i \otimes \mathbf{d}_i \rangle$ in Eq. 4b are 3×3 matrices, subtracted from the unit matrix $\mathbf{I}$. These matrices are independent of either $\mathbf{t}'$ or $\mathbf{R}'$ and simply indicate the overall distribution of the chosen directions, $\mathbf{d}_i$, at which parallax vectors $\mathbf{p}_i$ are observed. The same reasoning put forward in the last paragraph as a way to reduce the apparent terms may be applied here, which introduces a very useful simplification of iteration Eqs. 4a and 4b. Assuming a sufficiently high number of pair-wise observation directions reasonably covering the visual field will significantly reduce the off-diagonal elements of the matrices, or even make them disappear (Dahmen et al. 2001). We can then rewrite Eqs. 4a and 4b which may be used as the initial estimates, $\mathbf{t}_0'$ and $\mathbf{R}_0'$:

$$\mathbf{t}_0' \cong - \frac{\langle \mu'_i \mathbf{p}_{x,i} \rangle / \langle \mu_i'^2 \sin^2(\theta_{x,i}) \rangle}{\langle \mu'_i \mathbf{p}_{y,i} \rangle / \langle \mu_i'^2 \sin^2(\theta_{y,i}) \rangle} \quad (5a)$$



Optic Flow Processing, Fig. 4 Processing and integration of directional motion information. (a) The sign and amplitude of the output signal produced by an elementary movement detector (EMD) depends on the direction of motion. Motion in the detector's preferred direction (PD) and anti-preferred direction (anti-PD) results in positive and negative outputs, respectively. M stands for multiplication and τ is the time constant of a filter modeling the delay stage. For further information, see text modified from Borst and Egelhaaf (1989). (b) In the fly hexagonal eye lattice directional motion is analyzed by sets of EMDs (thick black arrows) along the ommatidial rows. Along the vertical rows mostly next neighbor interactions are implemented. The analysis of the two oblique rows is combined to result in horizontal motion sensitivity (thin arrows). Individual detectors will not be able to distinguish

between motion due to translation or rotation. (c) Red lines indicate the orientation of "vertical" rows in the one quadrant of the right eye plotted over azimuth and elevation. The local preferred directions (LPDs, blue vectors) of vertical cells (VS cells) follow roughly the orientation changes of the vertical rows which are most conspicuous in the dorsofrontal part of the eye. Data from Petrowitz et al. (2000). (d) A lobula plate tangential cell (LPTC) integrates the outputs of retinotopically arranged arrays of EMDs. The VS6 cell receives input only from those EMDs, the preferred direction of which is aligned with the direction of local parallax vectors in an optic flow field induced during roll rotation. The VS6 cell receptive field may be considered a matched filter for roll-induced optic flow. For further explanation, see text. (Redrawn from Egelhaaf et al. 2002)

and

$$R_0' \cong \frac{\langle p_{y,i} d_{z,i} - p_{z,i} d_{y,i} \rangle / \langle \sin^2(\theta_{x,i}) \rangle}{\langle p_{z,i} d_{x,i} - p_{x,i} d_{z,i} \rangle / \langle \sin^2(\theta_{y,i}) \rangle} \frac{\langle p_{x,i} d_{y,i} - p_{y,i} d_{x,i} \rangle / \langle \sin^2(\theta_{z,i}) \rangle}{\langle p_{y,i} d_{z,i} - p_{z,i} d_{y,i} \rangle / \langle \sin^2(\theta_{x,i}) \rangle} \quad (5b)$$

where $\theta_{x,i}$, $\theta_{y,i}$, and $\theta_{z,i}$ give the angles between d_i and the cardinal axes of the coordinate system

(cf. Fig. 1b). These initial estimates are obtained in a single calculation step. Given an appropriate distribution of observation directions which minimizes the apparent term in Eq. 4a, the translation estimate, t_0' , is simply obtained from the average across the nearness-scaled parallax vector components, normalized by averages of the products of the squared nearness and observation direction components. Similarly, under the same assumptions regarding the distribution of observation

directions, the rotation estimate, $\mathbf{R}_0'$, in Eq. 4b is based on the averages of the cross products between the parallax vector components and the components of the observation directions, normalized by the averages of the squared components of the observation direction. These initial estimates provide already a fairly decent approximation of the actual self-motion parameters. But in case local parallax vector observations are noisy, the distribution of observation directions has been less favorably chosen, and the distance or nearness distribution is inhomogeneous, the full iteration process using Eqs. 4a, 4b, and 4c clearly improves the results. Choosing a reasonable number of observation directions, say 50, distributed evenly over the 4π visual field enables stable estimates of the three parameters $\mathbf{t}'$, $\mathbf{R}'$, and μ_i' within about 10–20 iterations. Obviously, the exact number of iterations required also depends on the overall noisiness of the observed parallax vectors, $\mathbf{p}_i$.

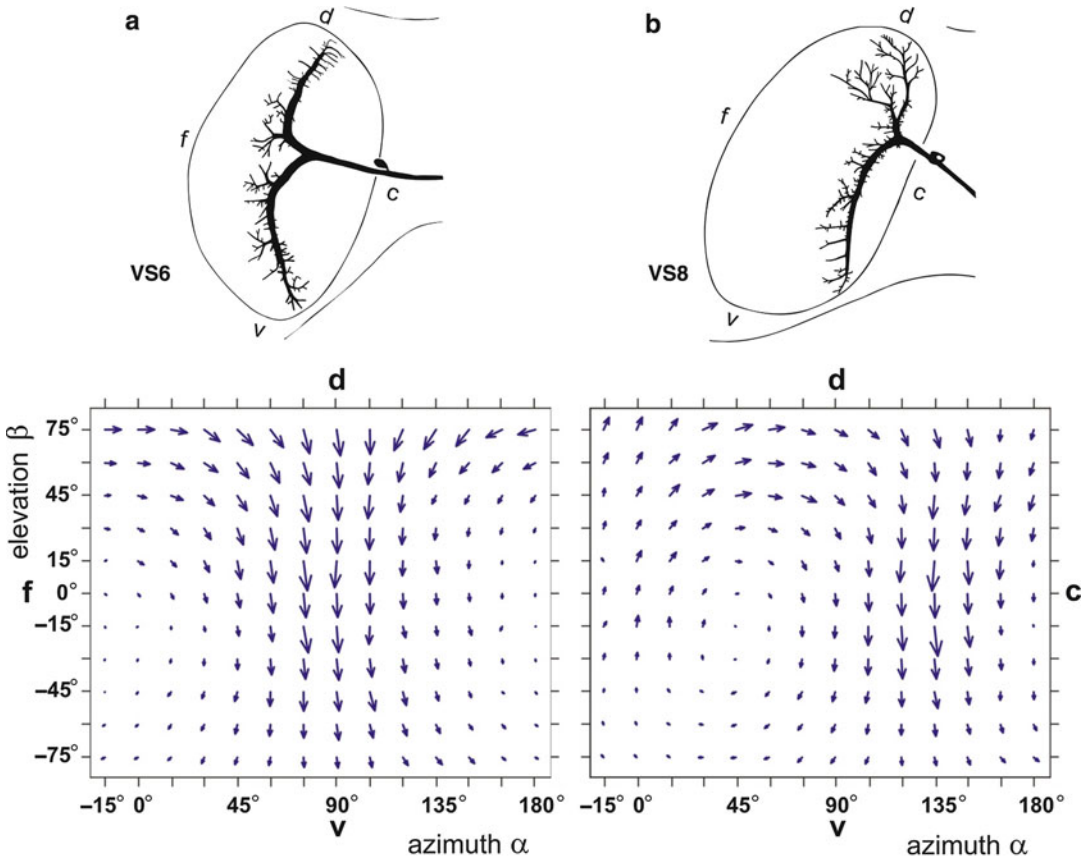
So far we considered the general case, independent of the nature of the optical system moving relative to a static environment. On the one hand side, it is the beauty of the KvD algorithm that it does not bother about questions concerned with the implementation of mechanisms which enable the measurement of local parallax vectors. The KvD algorithm and later applications of it simply point out the principle limits of retrieving self-motion parameters from optic flow fields. In the next section we will discuss the mechanisms required for detecting the direction of motion in biological visual systems and how specific adaptations in the visuomotor pathway of a simple model system, the common blowfly, shed some light on the strategies underlying neuronal processing of optic flow.

Matched Filter for Optic Flow Processing

When estimating self-motion components from optic flow fields, the visual system does not have the luxury of spending time on an iterative procedure. It also has to solve the problem of the ambiguity of local parallax vectors which may potentially increase the apparent motion terms in

Eqs. 4a and 4b, and it has to establish a neural mechanism that measures the $\mathbf{p}_i$ in the first place. Flying insects, with their compound eyes endowing them with nearly 4π vision, are in a prime position to process optic flow. Depending on the species, they analyze visual motion at around hundreds (fruit flies), thousands (blowflies), or even tens of thousands (dragonflies) of locations spread across the visual field (e.g., Land and Nilsson 2012). This enables them to establish a favorable distribution of observation directions, $\mathbf{d}_i$, which helps to keep the apparent motion terms small. In addition – except for situations where they are subjected to unpredictable disturbances of their flight attitude and trajectory – they may structure their self-motion by alternating phases of translation and rotation, which further reduces the apparent motion terms during the different phases. Such alternating flight patterns have been studied in blowflies and were proposed to play an important role in estimating relative distance from analyzing translational optic flow (cf. ► “Visual Processing in Free Flight,” this volume).

But how is the local parallax vector analyzed? Ideally, what the visual system needs to measure is the direction and magnitude of the $\mathbf{p}_i$. We should start with a brief introduction of elementary movement detectors (EMDs) which were proposed by Hassenstein and Reichardt (1953) based on a behavioral input–output analysis in beetles several decades ago. The phenomenological model derived from the experimental results reflects the necessary and sufficient conditions required to generate a time-averaged output, the sign of which indicates the direction of motion with respect to the measuring axis of the EMD (rev., Reichardt 1961, 1987). An EMD has to (i) sample light intensity changes at two neighboring locations of the eye, (ii) process the resulting signals in an asymmetric way, and (iii) combine the two signals in a nonlinear way, e.g., approximated by a multiplication operation (e.g., Reichardt 1987; Borst and Egelhaaf 1989, 1993). The fully opponent EMD consists of two mirror-symmetrical half-detectors, the outputs of which are subtracted from one another at a common integration stage. As a result, at the integration



Optic Flow Processing, Fig. 5 Receptive field organization of VS cells in the fly motion vision system. The upper panels show a morphological reconstruction based on injections of fluorescent dye during intracellular recordings from the cells. (a, bottom): Local preferred directions (LPDs) and motion sensitivities (LMSs) were determined from visual motion stimulation within small fractions of the receptive field at different positions in terms of azimuth, α , and elevation, β . LPDs and LMS define the orientation and length of each individual vector. The LPD distribution of the VS6 cells is highly similar to the

distribution of the local parallax vectors, p_i , in an optic flow field induced by a counterclockwise roll rotation. There is a conspicuous dorsoventral asymmetry in the LMS distribution which differs from the symmetrical distribution of magnitudes in a roll-induced flow field. (b, bottom): LPD and LMS distribution within the receptive field of the VS8 cell. While the LPDs reflect the preference of this cell for a body rotation in between roll and pitch (cf. singularity at $\alpha = 45^\circ$ and $\beta = 0^\circ$), the LMS distribution shows a similar asymmetry as found in the receptive field of the VS6 cell. (Redrawn from Krapp et al. 1998)

stage, motion in the preferred (PD) and anti-preferred direction (AD) of the detector produces on average a positive and a negative signal. Figure 5b shows a simplified version of an EMD. The model basically performs a spatio-temporal correlation of light intensity changes at adjacent positions in the eye. A mathematical description of the computational properties of EMDs in the invertebrate (e.g., Reichardt 1987) and the vertebrate visual system (e.g., Adelson

and Bergen 1985) suggests that the basic functional structure of correlation-based EMDs is quite ubiquitous (Borst and Euler 2011).

In terms of the potential implementation of the EMDs in the visual system of flies, two stages were identified a long time ago. As confirmed by quantitative behavioral experiments in fruit flies (Buchner 1976) and later electrophysiological studies in blowflies (Riehle and Franceschini 1984), the inputs to the EMDs in the compound

eyes of insects are provided by individual facets, or ommatidia, arranged in the hexagonal eye lattice. Ample electrophysiological evidence obtained in blowflies suggested that the subtraction stage may correspond to the dendrites of wide-field motion-sensitive interneurons in the posterior part of the third visual neuropile, the lobula plate (e.g., Hausen 1984). How and where the core operation of the EMD, i.e., the nonlinear combination of the two input signals, may be implemented remained unclear but is currently under heavy investigation in the fruit fly using neurogenetical approaches (cf. ► “Visual Motion Detection in *Drosophila*,” this volume).

Regarding optic flow processing in insects, the key message is that in any observation direction a set of EMDs with different preferred directions analyze local image motion and thus the system has access to a quantity that is related to the parallax vectors $\mathbf{p}_i$. I will later discuss the issue that the output of an EMD is not linear in the velocity domain, but depends on several parameters describing the spatiotemporal properties of the motion stimulus. The next question is: How may the self-motion parameters $\mathbf{t}$ and $\mathbf{R}$ be recovered in a non-iterative fashion?

We should revisit Eqs. 5a and 5b which provide the initial estimates of the self-motion parameters. An intuitive interpretation would be based on the following example proposed by Dahmen et al. (2001) in a slightly different notation: To retrieve the rotation component $\mathbf{R}_a$ around axis $\mathbf{a}$, we design a directional template, $\mathbf{U}_a^R$, which consists of a set of unit vectors $\mathbf{u}_{a,i}^R$ that are all aligned with flow vectors induced by the rotation around $\mathbf{a}$ observed at directions $\mathbf{d}_i$:

$$\mathbf{U}_a^R = -[\mathbf{a} \times \mathbf{d}_i]/\sin\theta_i, \quad (6)$$

where θ_i gives the angle between $\mathbf{a}$ and $\mathbf{d}_i$. To evaluate the contributions of the local parallax vectors of the current optic flow field to $\mathbf{R}_a$, all $\mathbf{p}_i$ are projected onto the local template vectors $\mathbf{u}_{a,i}^R$:

$$m_i^R = \mathbf{p}_i \cdot \mathbf{u}_{a,i}^R = [\mathbf{p}_i \times \mathbf{d}_i] \cdot \mathbf{a}/\sin\theta_i. \quad (7)$$

Averaging over all contributions m_i^R multiplied by $1/\sin\theta_i$, we make sure we obtain properly scaled contributions of the flow vectors $\mathbf{p}_i$ to the rotational component $\mathbf{R}_a$. The best *one-step* estimate of the alignment between the current rotation and a rotation around the specific axis, $\mathbf{a}$, is obtained by applying weighting factors $w_i^R = \sin^2\theta_i$ to the average of the local projections, which is consistent with the result of Eq. 5b.

Similarly, we may construct a directional template $\mathbf{U}_a^t$ to estimate the component $\mathbf{t}_a$ along unit translation $\mathbf{a}$ where the unit vectors $\mathbf{u}_{a,i}^t$ at observation directions $\mathbf{d}_i$ are parallel to the parallax vectors induced by $\mathbf{a}$:

$$\mathbf{U}_a^t = -[\mathbf{d}_i \times \mathbf{a}] \times \mathbf{d}_i/\sin\theta_i. \quad (8)$$

The projection of the current $\mathbf{p}_i$ onto the local template directions $\mathbf{u}_{a,i}^t$ results in local contributions:

$$m_i^t = \mathbf{p}_i \cdot \mathbf{u}_{a,i}^t = \mathbf{p}_i \cdot \mathbf{a}/\sin\theta_i \quad (9)$$

We again scale, this time by $1/\mu_i \sin\theta_i$, taking into account the relative nearness or inverse distance, and average across all contributions after applying local weightings $w_i^t = \mu_i^{-2} \sin^2\theta_i$ to arrive at Eq. 5aa.

These considerations on best *one-shot* estimates – based on specific directional templates – allow us to make some predictions about the properties of any neural mechanisms underlying the processing of optic flow to recover self-motion information. For one, neurons involved in this functional context should respond to visual motion in a directional-selective way. Secondly, they should have extended receptive fields, ideally comprising both visual hemispheres, to reduce the ambiguity inherent to local parallax vectors (apparent terms). And finally, to be able to act as templates matching the directional distribution of local parallax vectors in a specific optic flow field, their directional preference should depend on the directions in which they analyze local visual motion.

Response Properties of Lobula Plate Tangential Cells

I mentioned earlier that the common integration stage of the two EMD half-detectors was localized on the dendritic input arborization of large motion-sensitive interneurons in the fly lobula plate. These lobula plate tangential cells (LPTCs) have long been studied in dipteran flies with respect to their morphology and physiological response properties, mostly in blowflies (Hausen 1984, 1993; ► “Visual Processing in Free Flight,” this volume) and more recently in fruit flies (► “Visual Motion Detection in *Drosophila*,” this volume). In each half of their visual system, blowflies employ about 60 individually identified LPTCs (e.g., Hausen 1993) which receive input from retinotopically arranged local motion-sensitive neurons, the function of which was suggested to be equivalent to the elements of the EMD providing half-detector outputs (e.g., Borst and Egelhaaf 1989). According to their morphology, physiology, or function, LPTCs may be divided into three classes: cells tuned to the movement of small moving objects that are involved in figure-ground discrimination (FD cells, e.g., Egelhaaf 1985), intrinsic cells contributing to the neural mechanisms underlying figure-ground discrimination (CH cells, e.g., Hausen 1984), and heterolateral cells propagating motion information to the contralateral lobula plate by means of action potentials (H cells and V cells, e.g., Hausen 1993) and two distinct subpopulations constituting the horizontal system, HS (Hausen 1982), and the vertical system, VS (Hengstenberg 1982). The three HS and ten VS cells in the blowfly encode motion information in a mixed signal mode, a combination of graded membrane potentials and action potentials (Hengstenberg 1977). They are chemically and electrically connected to multimodal descending neurons (Strausfeld and Seyan 1985; Gronenberg and Strausfeld 1990; Gronenberg et al. 1995; Haag et al. 2007) and motor neurons (Strausfeld et al. 1987) which, in turn, provide various motor systems with sensory feedback in the context of stabilization reflexes as well as object detection and collision avoidance (e.g., Taylor and Krapp

2007; Krapp and Wicklein 2008; ► “Visual Processing in Free Flight,” this volume).

There are an excessive number of publications available on the response properties of LPTCs which were used as model systems to study a large variety of fundamental questions in neuroscience ranging from the nature of the neural code and circadian rhythms in information processing to dendritic integration and sensorimotor control. In this context, I will focus on the HS and VS cells and their role in optic flow processing. These cells have extended receptive fields and respond to visual motion in a fully opponent way: They produce graded depolarizing membrane potential shifts and action potentials when the cells are stimulated in their preferred direction and are hyperpolarized upon visual motion in their anti-preferred direction (e.g., Hausen 1984). Because of their physiological properties, these cells were identified as ideal candidates for processing optic flow and estimating the fly’s self-motion parameters.

A detailed electrophysiological analysis of the distribution of local preferred directions at many locations within the receptive fields of tangential cells has, in most cases, shown a high degree of similarity with the distribution of local velocity vectors in specific optic flow fields (Krapp and Hengstenberg 1996). This suggested that the ten VS cells, for instance, are involved in estimating body rotations of the fly around horizontal axes, while the receptive fields of two out of the three HS cells were found to be matched to optic flow fields induced during rotations about slightly different vertical rotation axes (Krapp 2000; Taylor and Krapp 2007). More recent research provides evidence that HS cells are also involved in global distance estimation based on the processing of optic flow during phases of translational self-motion (e.g., Lindemann et al. 2005; ► “Visual Processing in Free Flight,” this volume).

Figure 5 shows the receptive field organization of two VS cells, VS6 and VS8. Here, each individual vector plotted over azimuth and elevation indicates the local preferred direction (LPD) and local motion sensitivity (LMS) to a locally confined directional motion stimulus (Krapp and Hengstenberg 1997). By applying the KvD

algorithm, the specific rotation axes these cells are tuned to could be calculated. The VS6 cell would respond best during a roll rotation of the animal (cf. Figs. 3a and 5a), while the VS8 cell prefers rotation around an axis between the roll and the pitch axis of the animal (Krapp et al. 1998). The results suggested that the receptive fields of the majority of LPTCs studied so far can be interpreted as matched filters for optic flow where each individual LPD may represent a weighted local unit vector, $\mathbf{u}_{a,i}^R$, of a directional template, $\mathbf{U}_a^R$, as described in the previous section. By selectively integrating the outputs of EMDs, the preferred direction of which is aligned with the directions of local parallax vectors in a specific optic flow field, the output of the LPTC signals the very self-motion component that has caused it (Fig. 4d).

Several studies on the receptive field organization of LPTCs suggested that the LPDs are virtually set in stone (Krapp 2014). They are innate and do not require any early visual experience for the development of their specific distribution (Karmeier et al. 2001) and are related to the orientation of the ommatidial rows within the hexagonal eye lattice (Fig. 4) along which directional motion is analyzed (Buchner 1984). The stimulus-invariant conservation of the LPDs is in fact a necessary condition that enables LPTCs to estimate self-motion parameters from the optic flow fields the fly experiences (Krapp et al. 2012).

A very different situation is found for the LMS distribution within the receptive fields. The first marked difference between the magnitude distribution of parallax vectors in rotational optic flow fields and the LMS distribution found in VS cells is that the former is symmetric with respect to the flow field singularity, while the latter is not (cf. Figs. 3a and 6a). The LMS distribution basically indicates the sensitivity of the cell to directional motion determined as the difference between motion in the preferred and anti-preferred direction – essentially quantifying the height of a directional tuning curve. Many studies have shown in the past that the sensitivity to directional motion in LPTCs depends on a number of stimulus parameters (e.g., Hausen 1984) and the adaptational state of the cell (e.g., Harris

et al. 2000) as well as the animal's locomotor state (e.g., Longden and Krapp 2009; Maimon et al. 2010).

How can we interpret the LMS distribution in LPTCs? Taking an engineering perspective and considering the LPTCs as *optimized matched filters* for optic flow to estimate the translation and rotation components of self-motion may provide an answer to this question.

Optimized Matched Filters for Optic Flow

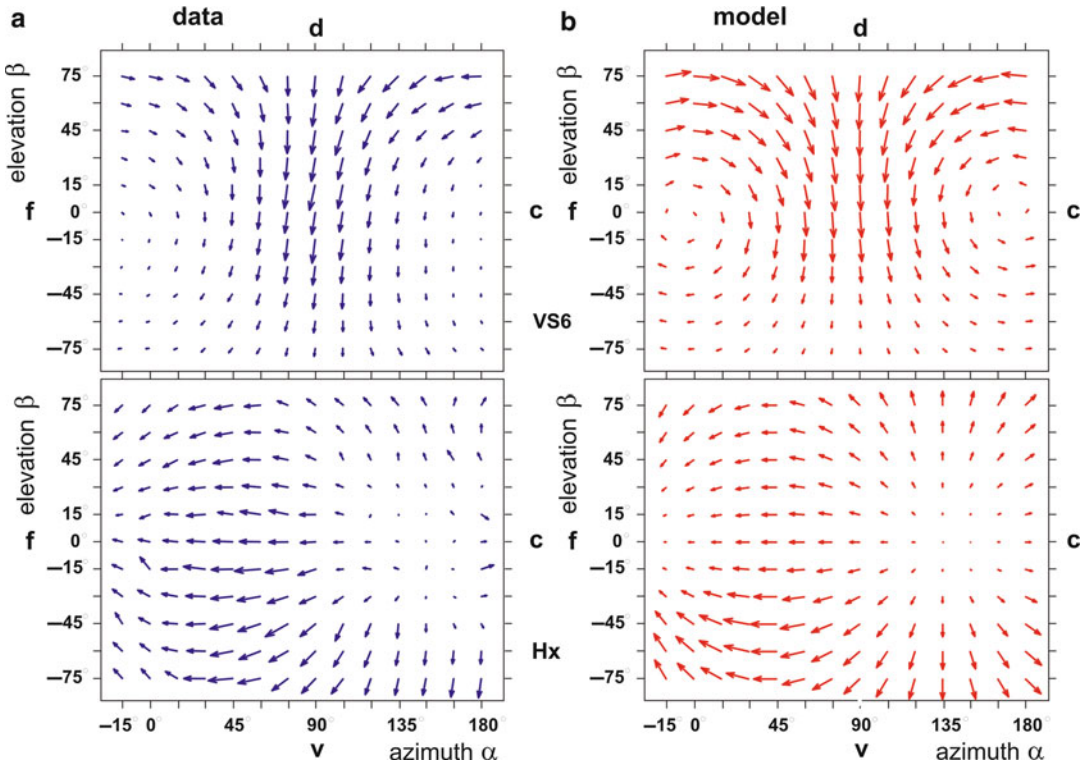
To appreciate the LMS distribution in LPTCs, we combine aspects of the KvD algorithm with the concept of the one-step estimate outlined in the section before the last. Taking into account Eqs. 6, 7, 8, and 9, we may rewrite Eqs. 4a and 4b to quantify the output of matched filters tuned to a unit self-motion $\mathbf{a}$:

$$t_{a,0} = n \langle \mu_i^2 \sin \theta_i \mathbf{p}_i \cdot \mathbf{u}_{a,i}^t \rangle, \quad (10)$$

$$R_{a,0} = n \langle \mu_i^2 \sin \theta_i \mathbf{p}_i \cdot \mathbf{u}_{a,i}^R \rangle, \quad (11)$$

where n is a suitable normalization factor. As described in the section on *one-step* estimation, $\mathbf{u}_{a,i}^t$ and $\mathbf{u}_{a,i}^R$ are unit vectors aligned in parallel with optic flow vectors induced by translation or rotation along or around $\mathbf{a}$, respectively (Dahmen et al. 2001). This simple model predicts a dependence of the LMSs on $\sin \theta_i$, where θ_i is again the angle between the self-motion axis, $\mathbf{a}$, and the observation directions, $\mathbf{d}_i$, here represented by the unit vectors $\mathbf{u}_{a,i}$. As mentioned in the last section, such $\sin \theta_i$ -dependence was not found in the receptive field organization of the VS cells where the LMS distributions show a pronounced dorsoventral asymmetry.

A generalized model of an optimized matched filter proposed by Franz and Krapp (2000) implements the basic structure given by Eqs. 10 and 11 but introduces two modifications: (i) It applies weightings to the local contributions replacing the factors $\sin \theta_i$, and (ii) it assumes a velocity function, f , modeled after the temporal frequency



Optic Flow Processing, Fig. 6 Optimized matched filters for optic flow processing. Panels (a) and (b) show experimental data and model predictions regarding the weighting of local motion information. In LPTCs matched to rotational optic flow fields (VS6), the sensitivity to ventral motion is reduced. In cells matched to translational optic flow (Hx), the sensitivity distribution is inverted with

higher sensitivity in the ventral visual field. The model predicts a weighting of local parallax vector measurements which is in agreement with the experimental data. Optimal weights may reflect assumptions the visual system makes regarding the mean relative distance distribution within the visual environment. For further explanation, see text. (Data redrawn from Franz and Krapp 2000)

dependence of the EMD outputs (cf. previous section) to result in a filter response:

$$r = n \langle w_i f(\mathbf{p}_i \cdot \mathbf{u}_{a,i}) \rangle. \quad (12)$$

In a model described by Eqs. 10 and 11, the dot product between the parallax vectors, $\mathbf{p}_i$, and the template vectors, $\mathbf{u}_{a,i}$, implies a linear relationship between response and velocity of the form $f(x) = x$. This approximation is only valid within a range where the response of LPTCs is a monotonic function of velocity. Beyond that velocity range, the responses remain at a peak level before dropping off as the stimulus velocity is further increased. One way of modeling the nonlinear velocity characteristic of the EMDs is to introduce

a threshold value, P , below which the output is set to zero and above which the output is normalized to unity. Such a *plateau model* provides equalized responses in those cases where $|\mathbf{p}_i \cdot \mathbf{u}_{a,i}| > P$ and is formalized by.

$$r = n \langle w_i (\mathbf{p}_i \cdot \mathbf{u}_{a,i}) / |\mathbf{p}_i \cdot \mathbf{u}_{a,i}| \rangle. \quad (13)$$

We can now derive an analytical solution for the optimal weight applied in Eq. 13 which can be interpreted as the LMS distribution within the receptive fields of the VS cells. To define an optimality criterion, the following properties of optic flow fields in connection with the environment the filters will be used in may be considered: Translation-induced optic flow contributions

depend on the distance to visual objects in the surroundings. In case we are interested in estimating the rotation parameter, those contributions should be minimized so that the output of the optimized matched filter robustly indicates rotation. Assuming that the rotation of interest always occurs in combination with a broad variety of possible translations in a simplified “world model” approximating the average distance distribution of the environment, we could try to find the sets of weights, w_i , that minimizes the variance of the filter’s output. To describe the translations, a symmetrical 2-dimensional von Mises distribution with a center of mass in the thrust direction may be used. The world model assumes the average distances in the dorsal visual field to be twice as large as the distances in the ventral visual field, with an isotropic distribution of local variances, which essentially looks like a sphere, the bottom half of which is flattened. Finally, an additive uniform noise variance, σ_i , is included locally that takes into account stochastic variations in the output signals of the EMDs (for details, see Franz and Krapp 2000).

Under these assumptions, the optimal weight set for a matched filter indicating rotation is given by.

$$w_i = n \left\langle (\mathbf{p}_i \cdot \mathbf{u}_{a,i})^2 \right\rangle / (\Delta t_i^2 + \Delta \sigma_i^2), \quad (14)$$

where n ensures that the sum of all w_i in the *plateau* model causes a filter output of 1, Δt_i^2 is the local variance induced by the distance variability, and $\Delta \sigma_i^2$ gives the local noise variance. In observation directions where the average distance is small, the relative local distance variability is larger, and due to a larger contribution to the local parallax vector caused by translation, $\mathbf{t}$, along $\mathbf{u}_{a,i}$, the term Δt_i^2 becomes particularly large. As a result, local weights assigned to those directions, which are in the ventral visual field, are small. This corresponds to the LMS distribution found in the VS cells (Fig. 6a). A χ^2 test to assess the goodness of fit between the model-derived weights and the measured LMSs based on χ^2 -values did not indicate a significant difference between the two distributions.

Depending on the velocity function, f , implemented in the model, different optimal weights were predicted with respect to their dependence on the angle Θ between the filter’s preferred axis, $\mathbf{a}$, and the observation directions. Although both models produced a dorsoventral asymmetry for the weights, in case of the linear model, the weights showed a $\sin \Theta$ -dependence, which is in agreement with Eq. 13 but significantly different from the experimental data. The plateau model, assuming unit contributions from EMDs when the threshold value P was exceeded, resulted in a $\sin^2 \Theta$ -dependence which, as mentioned above, was consistent with the LMS distributions found in the receptive fields of the VS cells (Franz and Krapp 2000).

The same approach applied to predict the optimal weights of a matched filter that indicates a specific horizontal translation produced a distribution similar to that of LMSs found within the receptive field of an LPTC that resembles a translational optic flow field. In this case, the dorsoventral asymmetry was inverted. Locations in the ventral part of the receptive field were assigned higher weights than those in the dorsal part – a result that, again, was in agreement with the experimental findings (Fig. 6).

Taking into account the modeling results, the dorsoventral asymmetry of the LMS distribution in LPTCs can be easily interpreted from the functional point of view. An optimal matched filter that indicates the presence of a specific rotation component should do so no matter what translation the animal is engaging on at the same time. As the fly is likely to maneuver closer to the ground than to the sky, it will introduce substantial translation-induced contributions to the local parallax vectors especially in the ventral visual field. Reducing the weights in the ventral visual field will reduce those contributions. The higher weight given to measurements of parallax vectors in dorsal visual field where the distances are larger makes perfect sense as translation-induced optic flow is scaled down by its distance dependence. Applying a similar rationale, the inverted sensitivity or weight distribution in matched filters estimating translation components may also be readily explained. In this case, more reliable signals are expected in the

ventral visual field, while the dorsal visual field would feature stronger contributions to the filter output by unwanted rotation-induced parallax vectors. An interesting observation regarding the LMS distribution of all ten VS cells is that their dorsoventral asymmetry shows the same dependence on elevation. It is tempting to assume that this asymmetry in the LMS distribution reflects an internal model of the average distances in the world the fly has developed over the time course of evolution.

Conclusions

The beauty of the concept of optic flow is that it allows us to clearly point out what can and what cannot be retrieved from visual relative motion in terms of self-motion parameters. Inspired by Gibson (1950) and thoroughly developed formally by theoretician and computer vision scientists (e.g., Koenderink and van Doorn 1987; Barron et al. 1994), it has certainly benefited research in visual neuroscience over the last few decades, in particular the work on arthropods. Although vertebrates such as primates and birds have long been studied regarding the neural mechanisms underlying optic flow processing (e.g., Lappe 2000), in these animals, a straightforward application of the mathematical framework to the local receptive field properties of individual cells has hardly been achieved. One of the reasons is that cells in visual areas concerned with higher-order motion vision in monkeys, such as MST and MSTd, have highly nonlinear integration properties. Local motion stimuli, which were successfully used in flies, are mostly ineffective to induce measurable responses in otherwise directional-selective cells. Only if comparatively large areas are presented with motion patterns ($\varnothing > 30^\circ$) the cells respond to rotational or translational flow field approximations but may as well not show a high degree of specificity (e.g., Tanaka et al. 1989, 1993; Duffy and Wurtz 1991a, b). A characterization regarding flow field specificity in the pigeon basal optic root has been quite successful (e.g., Wylie and Frost 1999) – in particular the evidence of a common reference frame for optic flow processing neurons and the measuring axes of the semicircular canals

in the vestibular system (Wylie et al. 1998). But again, detailed mappings of local directional preferences, as achieved in the fly, have not yet been obtained.

Despite their small size which has been a major limitation for electrophysiological studies, one of the great advantages of flies is that they are complex enough to address fundamental questions in neuroscience and yet simple enough to obtain conclusive answers. Their limited behavioral repertoire, which in many cases allows for a quantitative input–output characterization, provides a well-defined context for what the nervous system is required to achieve. In particular with respect to visuomotor control, flies are among the most successful model systems used. Their motion vision pathway supporting flight and gaze control has been – and still is – exceptionally well studied using a combination of neuroanatomical, electrophysiological, and computational approaches which may be directly linked to specific behavioral tasks. By applying neurogenetics in fruit flies, major progress has been made over recent years to identify the neural correlates of the EMD (► “Visual Motion Detection in *Drosophila*,” this volume), the holy grail not only for invertebrate researchers but also regarding the question of how neurons multiply.

Despite the considerable level of detail at which motion vision in flies has been studied and our recent advances in understanding the neural mechanisms underlying optic flow processing, there are still a number of unsolved issues to consider. In the context of the VS cells, one of the questions is: How is the complex receptive field organization in these neurons achieved? Comparatively, recent research suggested that the VS cells are coupled among each other, either directly by means of electrical synapses or through another interneuron (Haag and Borst 2004). As a consequence, their receptive fields based on retinotopic inputs are smaller along the azimuth if determined in the dendrite than they are when measured in the axon (Elyada et al. 2009). The coupling between the VS cells nicely explains the enormous receptive field extent, which is far bigger than it would be predicted solely based on synaptic input to their dendritic arborization. A question that still needs answering is: How do

the dendritic branches and the axons of the local input elements find each other in the correct directional-selective input layers (Buchner and Buchner 1984) of the lobula plate to establish a specific optic flow template?

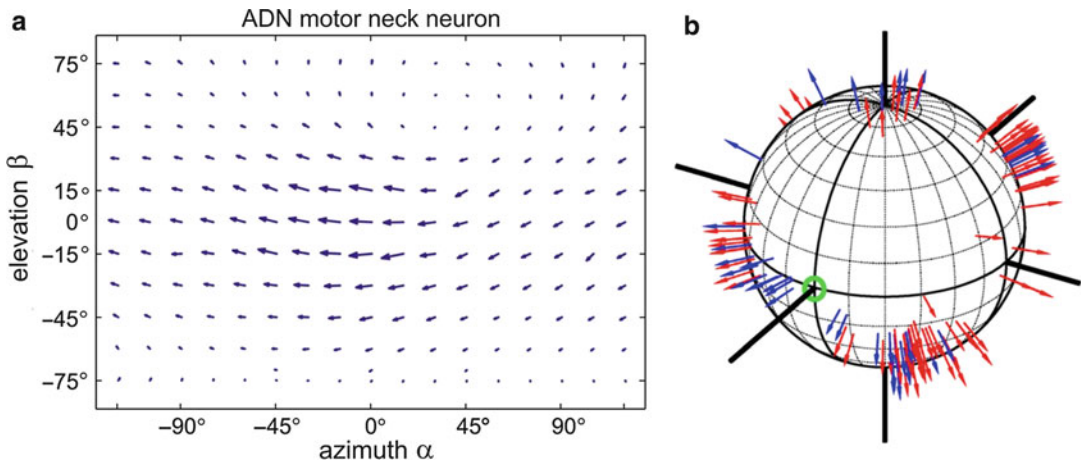
Another proximate question concerns the non-linear properties of the EMDs in the velocity domain (Reichardt 1987), the fact that motion and contrast adaptation changes the cells' input–output characteristic (Maddess and Laughlin 1985; Harris et al. 2000) and that local inputs are not linearly integrated on their dendrites (Borst et al. 1995). How useful are the LPTC for behavioral control, if they do not provide a feedback signal that represents absolute velocity?

Before attempting an answer, there is an ultimate question that should be addressed, which was long puzzling people working in the area. Why are there so many LPTCs? The number of VS and HS cells per brain hemisphere is already 13. The two cellular systems alone comprise 26 cells – and there are many more that could function as matched filters for optic flow. From the technical point of view, six cells would be enough to retrieve all possible self-motion components. A potential answer may be related to another heavily researched area in neuroscience concerned with sensorimotor transformations (e.g., Krapp 2010). Sensory signals are normally obtained in local coordinate systems, which – in this case – would be defined by the orientation of the ommatidial rows in the eye lattice (cf. Fig. 4b, c). But what needs to be controlled are motor systems, the pulling planes of which may be described in entirely different coordinates. The mechanisms underlying the transformation from sensory signals into appropriate motor commands could be quite complicated, and a small number of degrees of freedom regarding the motor system may already allow for a vast number of possible solutions, if the problem is not constrained.

The LPTCs seem to perform exactly this task. They integrate local motion information on their dendrites, but their output reflects exactly what is needed to control the behavior: information about specific self-motion components or – more technically – about state changes. Each of them has a preferred self-motion axis, and together the LPTCs set up a high-dimensional coordinate

system, where the number of dimensions is equal to the number of different matched filter axes they cover. The distribution of those axes seems not to be random. After studying the arrangement, it was recently hypothesized that the preferred rotation axes of the VS cells are ideally suited to sense one of the natural modes of motion that flying systems encounter, a “Dutch roll” (Taylor and Krapp 2007). The basic idea is that the sensory coordinate system set up by the LPTCs corresponds to the motor coordinate systems it controls – a design that would considerably simplify a sensorimotor transformation required for flight stabilization (Krapp et al. 2012). For this to work efficiently, one crucial condition has to be fulfilled: The visual system needs to stay aligned with the inertial vector, which means the head has to be stabilized in the horizontal plane.

Evidence in support of this “mode-sensing hypothesis” comes from studies of motor neurons supplying the fly neck muscles which control the animal's gaze (Huston and Krapp 2008). Neck motor neurons receive input from LPTCs such as the HS and VS cells, either directly or via descending neurons (Gronenberg and Strausfeld 1990; Gronenberg et al. 1995). Neck motor neurons have large visual receptive fields and respond to visual motion in almost the same way as LPTCs, but some of them require mechanosensory input simultaneously to generate action potentials, which is a necessary condition for muscle contraction (Huston and Krapp 2009). Figure 7a shows parts of a neck motor neuron receptive field that responds to horizontal motion induced during yaw rotation. Its visual receptive field looks almost identical to the receptive field of a so-called HSE cell. The only difference is that it receives stronger input from the contralateral eye. This large binocular receptive field helps to reduce apparent terms due to translation (cf. Eq. 4b) which makes perfect sense for a neuron that controls head rotations. Using the KvD algorithm on the receptive field organization of each of the neck motor neurons studied, their preferred rotation axes were computed. The resulting distribution of axes is compared in Fig. 7b with the distribution of the preferred rotation axes of all 26 HS and VS cells and shows a high degree of overlap (Huston and Krapp 2008). Almost all neck



Optic Flow Processing, Fig. 7 Visual receptive field of a fly neck motor neuron and the preferred rotation axis distributions of neck motor neurons and LPTCs. (a) The neck motor neuron receptive field is matched to an optic flow field generated by a rotation around a slightly tilted vertical body axis. (b) Preferred axes of neck motor

neurons (red arrows) and LPTCs (blue arrows) show a high degree of overlap, suggesting that the sensory coordinate system (LPTC) and the coordinate system controlling the fly's gaze are co-aligned. For further explanation, see text. (Redrawn from Huston and Krapp 2008)

muscles in flies are innervated only by a single motor neuron. It is likely, therefore, that the pulling planes of the muscles are predicted by the preferred rotation axes of the neck motor neurons, which still needs to be tested experimentally. The results so far are compatible with the idea that the high number of LPTCs may be interpreted along the lines of the mode-sensing hypothesis (Krapp et al. 2012): There should be roughly as many matched filters for specific optic flow fields as there are axes in the motor systems that need to be controlled.

To get back to an earlier question regarding the suitability of LPTC signals for motor control, there is another essential aspect that should be considered. Motion vision alone would not be sufficient to support the high maneuverability and gust tolerance of flies. The limited bandwidth and long processing delays of the visual system are complemented by fast and low latency mechanosensory systems, such as the halteres in dipteran flies signaling angular rotation rates (Hengstenberg 1993) or the antennae measuring air flow changes (Taylor and Krapp 2007). One of the current and future challenges will be to understand how optic flow-based and mechanosensory signals are integrated to control flight and gaze as efficiently as dipteran flies

do. A proof of concept study where matched filters for optic flow were implemented in a linear control engineering framework did indeed enable autonomous flight of a quadcopter (Hyslop et al. 2010). But only if we understand multisensory gaze and flight stabilization well enough to extract the underlying biological control design, we may eventually reach a performance level in artificial micro air vehicles their natural counterparts achieve.

Cross-References

- [Visual Motion Detection in *Drosophila*](#)
- [Visual Processing in Free Flight](#)

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Optical Flow

► Optic Flow Processing

Optical Imaging Spectroscopy

► Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

Optimal Energy Allocation in Reliable Neural Sensory Processing

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Definition

Emerging results in the information theory of *reliable computation* may yield theoretical predictions on optimal energy allocation to noisy neurons in sensory processing and experimental tests of optimality hypotheses. Predictions come from optimizing structure and energy allocation for given reliable computations with noisy neurons.

Detailed Description

Theoretical neuroscience often relies on optimality principles derived from information theory as an approach to develop hypotheses for experimentally measurable physical properties of the brain, cf. (Varshney et al. 2016) and references therein. Such information-theoretic principles, however, nearly always focus on the brain as an information transmission and storage system, rather than as a *computation* system. On the other hand, a traditional approach in

computational neuroscience is to investigate the properties of specific biologically plausible circuits and architectures. Information-theoretic principles for computation can, however, be used to make predictions on optimal energy allocation for noisy neurons to achieve reliable computation. The basic idea is to understand the fundamental trade-offs among energy, network structure, and computational reliability (Chatterjee and Varshney 2017).

To outline the information theory yielding biological predictions, consider a simple binary L -layer feedforward neural network with n inputs and a single output constructed from neurons with energy-dependent failure rates. Let $\mathcal{N}_\ell$ be the set of neurons in layer ℓ , and let $N_\ell = |\mathcal{N}_\ell|$; the input layer is $\mathcal{N}_1$, and the output layer is $\mathcal{N}_L$ (with only one active neuron). For a neuron $g \in \mathcal{N}_\ell$, let the set of paths to the output neuron be $\mathcal{P}_g$. An L -layer neural network is therefore an L -partite graph, which we denote as $\mathcal{G}_L$.

Inputs to the neural network are ± 1 . The neural network has a fixed connection pattern between neurons in the various layers, e.g., full connectivity or d -regular connectivity between layers, and there are real-valued weights on the edges. For each neuron there is an associated activation function, which has a real-valued input and an output, that is, ± 1 . The input to the activation function is a sum of the outputs of the neurons of the previous layer, weighted by the edge weights.

A neuron g can fail independently of any other neuron with probability ε_g . When a neuron fails, it flips the output from $+1$ to -1 and vice versa. Neuron g consumes energy e_g for its operation, and ε_g depends on e_g . Thus ε_g can be tuned by an appropriate choice of e_g . For a neuron with probability of failure ε_g and energy consumption e_g , let the *energy-failure function* be $\varepsilon_g = \chi(e_g)$, assumed convex and nonincreasing.

The goal in structuring the neural network and allocating energy e_g to each of its neurons is to use the *minimal energy* in computing a given function such that the output is correct for all inputs with probability at least $1 - \delta$, despite the fact individual neurons may have failure rates $\varepsilon_g > \delta$.

A key analysis technique is called *information propagation*. Pippenger (1988) developed the technique of analyzing information flow for δ -reliable computation in noisy logic circuits, which makes use of strong data processing inequalities (Polyanskiy and Wu 2016). Building on this, for δ -reliable computation by a neural network with the same failure probability of each neuron in a layer, the following must be satisfied:

$$\ln \frac{1}{1-h(\delta)} \geq 4 \sum_l \varepsilon^{(\ell)} - \min_{g \in \mathcal{N}_1} \ln |\mathcal{P}_g|, \quad (1)$$

where $\varepsilon^{(\ell)}$ is probability of failure of neurons in layer ℓ . Moreover, the minimum energy consumption for δ -reliable computation is no more than the solution of:

$$\begin{aligned} \min_{\varepsilon^{(\ell)}, 1 \leq \ell \leq L} \sum_{\ell} N_{\ell} \psi(\varepsilon^{(\ell)}) \text{ s.t. } \sum_{\ell} \varepsilon^{(\ell)} \leq \gamma(\delta), \\ \text{and } 0 \leq \varepsilon^{(\ell)} \leq 1 \text{ for all } \ell, \end{aligned} \quad (2)$$

where $\gamma(\delta) = \frac{1}{4} \left(\ln \frac{1}{1-h(\delta)} + \ln \pi^G(L) \right)$ and $\psi = \chi^{-1}$. Using the KKT conditions (Boyd and Vandenberghe 2004) and some structural properties, at the minimum,

$$\begin{aligned} N_1 \psi'(\varepsilon^{(1)}) &= N_2 \psi'(\varepsilon^{(2)}) = \dots \\ &= N_L \psi'(\varepsilon^{(L)}). \end{aligned} \quad (3)$$

For a polynomial energy-failure function $\chi(e_g) = a/(1 + e_g)^{\beta}$, $\beta > 1$, under G and δ for which (3) holds:

$$\varepsilon^{(\ell+1)} = \varepsilon^{(\ell)} (N_{\ell}/N_{\ell+1})^{\beta/(1-\beta)}.$$

This implies a power-law relation between energy consumption per neuron across different layers.

Note the following relations between the model and sensory cortex. First, neurons have energy-failure functions, χ , described by quantal synaptic failure rate ε_g that is nonuniform across different neurons due to heterogeneous energy

allocations for energy efficiency. Second, the volumes and neuron densities of different brain regions in sensory processing can be combined to characterize neuron number N_{ℓ} . Third, neurogeometry yields estimates of neuronal network structural properties, such as neuron degree d and network structure g_L .

Interestingly, neuroenergetic studies show the metabolic glucose rate in different brain regions (essentially e_g) is a power-law function of their degree of connectivity, as above, since the average degree of a neuron is the ratio of the number of neurons in its layer to that in the next layer. A natural approach to test further optimality hypotheses is to see whether the different aspects of neural connectivity, reliability, and energy are all matched to one another as predicted by theory, as in measure-matching (Varshney et al. 2006).

To this end, note that nonuniform allocation rule (3) implies that $N_{\ell} \psi'(\chi(e^{(\ell)})) = c_{G, \delta}$ for each layer ℓ for some constant $c_{G, \delta}$ that depends only on the network and δ . That is, the per-neuron energy ratio between two layers is the ratio of the respective $\psi((\psi')^{-1}(c_{G, \delta}/N_{\ell}))$. For exponential and polynomial χ , $\psi \circ (\psi')^{-1}$ are proportional to $1/N_{\ell}$ and $1/N_{\ell}^{\beta/(\beta-1)}$, respectively. That is, for a polynomial χ , energy allocation should have per-neuron energy be inversely proportional to the number of neurons in the layer to the power $\beta/(\beta-1)$ (exponential is just $\beta = \infty$, so $\beta/(\beta-1) = 1$). As $\beta/(\beta-1)$ is a one-to-one function of β , it is sufficient to measure the power of N_{ℓ} which relates to per-neuron energy.

An immediate interpretation is that with decreasing number of neurons per layer in higher levels of sensory processing, per-neuron energy allocation should increase geometrically toward the output. Failures in initial layers may be masked in subsequent layers, maintaining reliable computation.

Cross-References

- [Information Measures of Redundancy and Synergy in Neural Activity](#)

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Optimal Experimental Design

- [Adaptive Stimulus Optimization](#)

Optimal Stimulus Design

- [Adaptive Stimulus Optimization](#)

Optogenetics

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Definition

Optogenetic tools are a broad class of genetically engineered proteins activated or inactivated by light of an appropriate wavelength. These include activators, such as the Channelrhodopsins, and suppressors, such as the Halorhodopsins and Archaeorhodopsins, along with other variants.

Detailed Description

Microbial Opsins

Many of the optogenetic tools currently in use in mammalian systems are derived from microbial opsins. These generally incorporate light-sensing and ion flux components in the same protein, as in Bacteriorhodopsin (Oesterhelt and Stoeckenius 1971), Channelrhodopsin-1 (ChR1) and Channelrhodopsin-2 (ChR2) (Nagel et al. 2002, 2003), and Halorhodopsin (eNpHR) (Gradinaru et al. 2008; Han and Boyden 2007; Zhang et al. 2007). In response to light stimulation, the Channelrhodopsins undergo conformational changes and allow nonspecific cation flow, resulting in depolarization and increased action potential output (Bamann et al. 2010; Hegemann et al. 2005; Kato et al. 2012; Nagel et al. 2003). In contrast, Halorhodopsin functions as a light-sensitive chloride channel, whose activation leads to hyperpolarization and decreased spike activity (Han and Boyden 2007; Kouyama et al. 2010; Zhang et al. 2007). Archaeorhodopsin functions as a light-sensitive proton pump whose activation likewise leads to hyperpolarization (Chow et al. 2010).

Subsequent engineering of identified microbial opsins has yielded a series of enhancements of opsin expression, light sensitivity, and photocurrent amplitude and kinetics. Modifications to Channelrhodopsin-2 gave rise to improvements in protein trafficking (Boyden et al. 2005; Gradinaru et al. 2007; Nagel et al. 2005), along with faster kinetics (e.g., ChETA) (Gunaydin et al. 2010). Similar enhancement of trafficking reduced opsin toxicity and enhanced insertion into the membrane (e.g., eNpHR3.0; Gradinaru et al. 2008), whereas other modifications increased light sensitivity (e.g., ArchT; Han et al. 2011). An additional series of mutations gave rise to the step function opsins (SFO), which can remain active for long periods (Bamann et al. 2010; Berndt et al. 2009; Yizhar et al. 2011).

Genomic screens have identified new classes of opsins, including one from *Volvox carteri* (VChR1) that was combined in chimeric form with the original ChR1 to produce the C1V1 construct, a Channelrhodopsin with high-amplitude

photocurrents that responds to red-shifted wavelengths (Zhang et al. 2008). Large-scale screens have identified several additional opsins with unique wavelength sensitivities, large amplitude photocurrents, or faster kinetics (Chow et al. 2010; Klapoetke et al. 2014). Most recently, development has focused on wavelength-shifted optogenetic tools that allow discrete optical manipulations of multiple targets in the same preparation or activation of cells deep in the brain via illumination through the skull (e.g., ReaChR, Chromson; Klapoetke et al. 2014; Lin et al. 2013).

Optogenetics in Mammalian Neurons

The first use of a microbial opsin as a tool in mammalian neurons was the introduction of ChR2 into hippocampal neurons *in vitro* (Boyden et al. 2005). This initial finding highlighted the millisecond-level precision of ChR2-mediated control of spike timing. Later innovations incorporated opsin sequences in Cre recombinase-dependent constructs, such as the DIO and FLEX versions (Atasoy et al. 2008; Sohal et al. 2009), and offered a high degree of cell type specificity (Cardin et al. 2009, 2010; Sohal et al. 2009). More recent work has made extensive use of the temporal fidelity and cellular targeting of optogenetics both *in vitro* and *in vivo*. Optogenetic tools have also been used to manipulate neuromodulatory levels (Goard and Dan 2009; Pinto et al. 2013).

Optogenetics provides significant advantages over other direct manipulation techniques, such as electrical stimulation, in dissecting circuit-level interactions. For example, highly specific optical targeting has allowed identification of the impact of sparsely represented local interneurons *in vitro* and *in vivo* (Adesnik et al. 2012; Pi et al. 2013), along with the relative impact of thalamocortical and cortico-cortical projections (Adesnik and Scanziani 2010; Cruikshank et al. 2007). Expression of ChR2 and either eNpHR3.0 or Arch in the same cell type further confers bidirectional control over the activity of targeted populations (Atallah et al. 2012).

A less well-appreciated advantage of optogenetic tools in the intact brain is the ability to extracellularly identify genetically distinct populations of neurons via optical tagging with ChR2, ChETA, or another depolarizing opsin variant (Cardin et al. 2009; Kravitz et al. 2013; Lima et al. 2009; Pi et al. 2013). The responses of ChR2-expressing cells to light pulses occur at short latencies with high temporal fidelity, allowing detection of sparsely represented cells, such as inhibitory interneurons or specific projection cells, whose action potential waveforms are not distinct from those of the surrounding population.

Optical Manipulation in Freely Moving Animals

Optogenetic tools have been successfully used in freely moving or head-fixed behaving animals where stimulation is delivered through an optical fiber to which the animal is tethered, either alone or in combination with electrophysiological recordings (Adamantidis et al. 2007; Adesnik et al. 2012; Aravanis et al. 2007; Gradinaru et al. 2007; Kravitz et al. 2010). Current efforts in technical development include work on wireless optogenetic manipulations in combination with electrophysiological recordings (Wentz et al. 2011).

Optogenetics in Combination with Optical Imaging

Optogenetic tools have been extensively used in combination with a number of imaging techniques *in vitro*. One fruitful approach has been Channelrhodopsin-assisted circuit mapping (CRACM), which allows optical mapping of synaptic inputs to individual neurons (Petreanu et al. 2007). Opsins have also been used in combination with 2-photon imaging *in vitro*, either alone or in conjunction with glutamate uncaging (Chiu et al. 2013; Packer et al. 2012). Although there have been examples of optogenetic tool use in conjunction with 2-photon imaging *in vivo* (Prakash et al.

2012; Wilson et al. 2012), this combined approach has remaining technical limitations.

Opto-fMRI

Optogenetic manipulations are highly compatible with functional MRI scanning. Several initial studies demonstrated that ChR2-mediated activation of excitatory neurons is associated with an increase in local BOLD signals in mice and that such manipulations can be used to confirm long-range connectivity between brain areas (Desai et al. 2011; Kahn et al. 2011, 2013; Lee et al. 2010). Interestingly, activation of inhibitory interneurons may also elicit a local increase in the BOLD signal (Urban et al. 2012), suggesting that cell type-specific optogenetic control may be useful in understanding the origins of the hemodynamic response.

Potential Limitations

Optogenetics has provided a transformative set of tools for neuroscience. Nevertheless, use of these constructs has some well-characterized caveats. The kinetics of individual proteins vary and can significantly impact the onset and offset rates of effective manipulation. In addition, some evidence suggests that ChR2-evoked action potentials may be associated with altered action potential waveforms or neurotransmitter release (Schoenenberger et al. 2011; Zhang and Oertner 2007). Several optogenetic constructs, particularly the Halorhodopsins, have been identified as toxic to neurons over moderate expression times (Gradinaru et al. 2008). Similarly, although Cre-dependent ChR2 mouse lines exist (Madisen et al. 2012), it remains unclear whether constitutive expression of membrane-inserted opsins impairs neuronal health. Finally, the use of optical stimulation at high intensities has been shown to cause optoelectronic artifacts in combination with metal electrodes, leading to large signals that may occlude neural activity (Cardin et al. 2010; Han et al. 2009). However,

each of these caveats may be overcome with appropriate experimental design.

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Oscillatory Network Activity Analysis

- [Spectral Interdependency Methods](#)

Oxygen Deprivation

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p42/p44 MAPK

► Extracellular Signal-Regulated Kinases, Models of

whose connectivity is only partially worked out. This lack of data has hindered network-level modeling, but this also presents an opportunity for modeling to help guide future experiments.

Pain Processing Pathway Models

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Definition

The main pathways involved in pain processing have been known for some time, but the precise microcircuitry remains surprisingly unclear. This has allowed very different theories of pain processing to persist. Specificity theory holds that pain is qualitatively distinct from other somatosensory percepts and that the underlying circuitry is arranged as labeled lines. Gate control theory holds that all inputs converge and that it is the level of activation in unspecialized neurons that code for pain. The truth lies somewhere in between. The dorsal horn of the spinal cord, which corresponds to the first synaptic relay point, comprises a diverse set of interneurons

Detailed Description

Types of Pain

Pain is usually caused by noxious stimulation – stimulation that has the potential to cause tissue damage. Such pain is referred to as nociceptive. Pain can also arise from damage to or dysfunction of the nervous system. This latter sort of pain, which is referred to as neuropathic, can result from insults to the peripheral or central nervous systems arising from trauma, diseases like diabetes and herpes zoster, or toxicity by chemotherapeutics and antiretrovirals (Baron et al. 2010; Costigan et al. 2009).

Neuropathic pain reflects abnormalities in the processing of somatosensory input. For instance, innocuous mechanical or thermal (warm or cool) stimulation can be improperly perceived as painful, and noxious stimulation can be perceived as more painful than normal. These phenomena are referred to as allodynia and hyperalgesia, respectively. Spontaneous pain (i.e., in the absence of any stimulation) can also occur. The problem is that these symptoms are often poorly controlled by currently available analgesics. For instance, opioids, despite being very effective against nociceptive pain, have a more variable effect on

neuropathic pain and can sometimes paradoxically worsen it.

Pain Theories and Predicted Microcircuitry

Heated debates have been waged over how pain signals are encoded. Those debates have centered primarily around the concept of specificity (Craig 2003; Perl 2007): Are certain neurons specific (i.e., dedicated) for encoding pain or is pain encoded by the activation level in nonspecific neurons? Intensity and gate control theories favor the latter. Specificity theory favors the former. Over the past several decades, experiments have identified neurons in the peripheral and central nervous systems that respond selectively to noxious stimulation, lending support to specificity theory. But numerous other observations are inconsistent with specificity theory, especially regarding the degree to which specificity is strictly maintained in downstream neurons.

The specificity (or tuning) of primary sensory neurons depends on what receptors they express and with what specialized sensory structures (e.g., Pacinian corpuscles, Merkel's disks, etc.) they associate (Gold and Gebhart 2010; Tsunozaki and Bautista 2009). The tuning of downstream central neurons, on the other hand, depends on which primary sensory neurons provide input; in other words, a central neuron will respond selectively to noxious stimulation if that neuron receives input exclusively from specialized nociceptors. An exclusive connectivity pattern such as this is the basis for labeled lines. However, cross-modal interactions – inhibition of pain by touch, inhibition of itch by pain, etc. – argue against labeled lines and suggest, instead, that input from differently tuned primary sensory neurons converge on central neurons (although this does not necessarily imply convergence to the point that central neurons are completely untuned). Notably, such interactions can be revealed by carefully constructed stimuli or by manipulation of the nervous system and also become apparent under certain pathological conditions (see below).

Cross-modal interactions are important if one considers that stimuli typically activate more than one type of primary sensory neuron. This is especially true for complex stimuli with multiple features, but even a simple stimulus involving deflection of a single hair, for example, will co-activate multiple types of sensory neurons given that multiple types of sensory neurons innervate each hair follicle (Abraira and Ginty 2013). It is important to note that tuning means that a neuron responds preferentially to a certain feature of a stimulus; it does not mean the converse, namely, that a stimulus activates only one type of sensory neuron. Therefore, stimuli *co-activate* differently tuned sensory neurons. If those differently tuned neurons give rise to labeled lines (which by definition should not talk to one another), then whether or not non-nociceptors co-activated along with nociceptors is irrelevant for the signal conveyed through the “pain” line. The fact that this is not what happens (i.e., that cross-modal interactions occur) thus suggests that more complicated microcircuitry exists and can read out the co-activation pattern. This is the basis for what has been referred to as population coding (Ma 2012) or, more specifically, as combinatorial coding (Prescott and Ratté 2012; Prescott et al. 2014).

Cross-Modal Interactions

Before reviewing what is currently known about the pain microcircuits and the pathways they form, we will consider a few examples of how stimulation does not always give rise to the expected percept. Like with illusions in other sensory modalities, somatosensory stimuli can be constructed or sensory processing otherwise manipulated in such a way as to trick the nervous system. Knowing how the system can be tricked can give significant insight into how the system is constructed.

Numerous observations suggest that the neural code for burning pain depends on the relative activation of different types of primary afferents that are differentially tuned to temperature. Burning pain can be evoked by noxious hot or cold

temperatures, but it can also be evoked by innocuous warm or cool temperatures under conditions that cause unmasking. First, one must appreciate that certain neurons are maximally responsive to cool, whereas others are maximally responsive to cold but also respond to cool. Despite modestly activating cold-tuned neurons, cool stimulation does not evoke pain *unless* the co-activation of cool-tuned neurons is blocked. Because the fibers of cool-tuned neurons are myelinated, whereas those of cold-tuned neurons are not, propagation in the former can be selectively blocked by ischemia (e.g., via a blood pressure cuff); with myelinated fibers blocked, cool stimulation is perceived as burning. This suggests that input from *cool* fibers masks the input from *cold* fibers until *cold* fibers are very strongly activated (by cold temperatures). Thus, it is not the absolute activation of *cold* fibers that codes for pain; instead, it is the activation of *cold* fibers relative to *cool* fibers that is important (Yarnitsky and Ochoa 1990). Calculating the ratio or difference of those two inputs necessitates that those two inputs eventually converge on a common postsynaptic target. Furthermore, recognizing this coding scheme has clinical relevance insofar as burning pain could potentially be treated by enhancing the activity of certain “masking” neurons rather than focusing exclusively on reducing the activity of “pain” neurons, or perhaps one could manipulate how the difference calculation is performed centrally.

Thunberg’s thermal grill illusion is also illustrative. In this illusion, spatially patterned innocuous warm and cool stimuli evoke burning pain. This involves the same unmasking phenomenon described above, but with an extra twist wherein cool input is masked by adjacent warm input rather than the cool input being blocked by manipulation of the nerve (Craig and Bushnell 1994).

One should recognize that what is referred to as masking in the pain literature bears a striking resemblance to what is called opponency in the retina. According to trichromacy, different colors are encoded by the relative activation of photoreceptor cells tuned to long, medium, or short wavelengths of light (roughly red, green, and blue), with downstream “opponent” cells that receive convergent input calculating the difference in

activation (Solomon and Lennie 2007). Drawing such analogies will likely help in the investigation of pain microcircuits by identifying which motifs one might expect to find there.

Primary Somatosensory Afferents

Somatosensory information is relayed to the spinal cord via primary sensory neurons. Primary sensory neurons all have their cell body located within a dorsal root ganglion (or the trigeminal ganglion in the case of cranial nerves) and are thus commonly referred to as DRG neurons. These sensory afferents can be classified according to their peripheral targets (skin, muscle, viscera, etc.), response properties (mechanosensitive, thermosensitive, etc.), neurochemical phenotype, and conduction velocity. On a gross level, afferents are very commonly designated as A- β , A- δ , or C fibers based on their axon diameter and myelination: A- β fibers are large and thickly myelinated (and therefore rapidly conducting), whereas C fibers are thin and unmyelinated (and therefore slowly conducting), and A- δ fibers are intermediate. It is commonly assumed that all A- β fiber functions are low-threshold afferents, whereas all A- δ and C fibers are nociceptors, but this is false; for instance, many C fibers respond to innocuous thermal or mechanical stimuli. Moreover, many C fibers are polymodal insofar as they respond to mechanical, thermal, and chemical stimulation or to two of those three stimulus modalities. C fibers are also classified according to whether or not they express certain peptides like substance P. In general, increasing knowledge of which ion channels and receptors are expressed in different cell types has led to increasingly sophisticated classification.

Pain Pathways

Sensory information entering the spinal dorsal horn is relayed by second-order neurons to a variety of supraspinal sites including the thalamus, caudal ventrolateral medulla, nucleus of the solitary tract, parabrachial nucleus, and

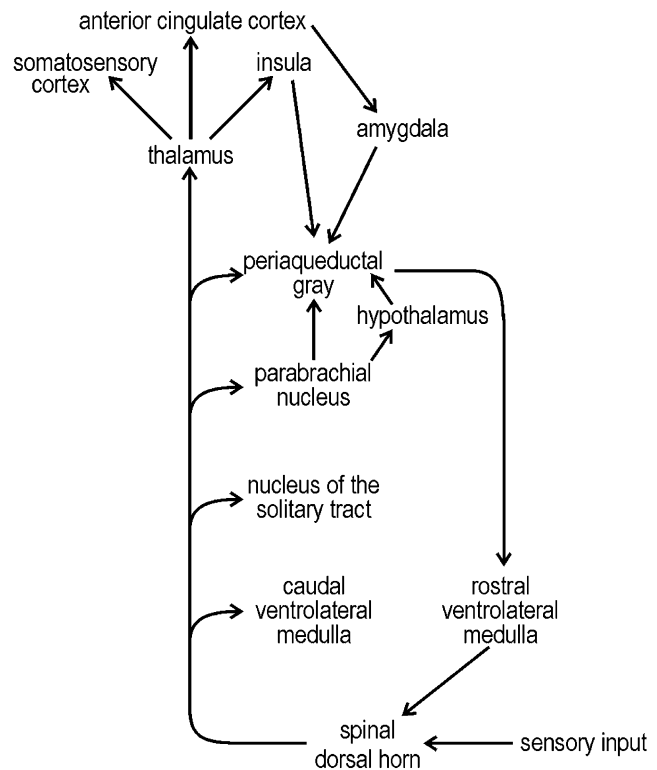
periaqueductal gray matter (Craig 2003; Dostrovsky et al. 2006). Pain-related sensory information is routed to multiple different areas of neocortex via different thalamic nuclei. In turn, descending tracts modulate processing within the spinal dorsal horn. Descending modulatory inputs include serotonergic fibers from the nucleus raphe magnus, noradrenergic fibers from the locus coeruleus, and GABAergic fibers from the rostral ventromedial medulla (Millan 2002). Figure 1 summarizes the most important pathways, but it is not exhaustive and nor does it include details like the specific thalamic nuclei through which connections to different parts of the neocortex are formed.

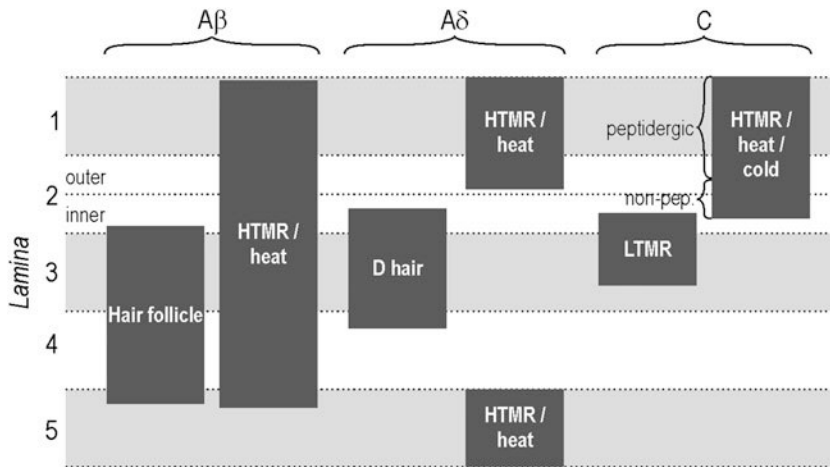
Significant processing occurs within the spinal cord before sensory information is relayed to higher areas. This spinal processing has been the focus of much research but the microcircuitry still remains largely unclear and modeling is scarce. The next section summarizes what is currently known.

Organization of the Spinal Cord Dorsal Horn

The central projections of different types of primary sensory neurons terminate in different layers, or lamina, within the spinal dorsal horn (Fig. 2) (Todd and Koerber 2006). Large myelinated A- β fibers also send collaterals into the dorsal columns, and those fibers ascend ipsilaterally to form synapses in the gracile or cuneate nuclei in the brainstem; it is only after this point that second-order neurons cross the midline (i.e., decussate) and ascend contralaterally to the thalamus. Fibers entering the spinal gray matter also form synapses ipsilaterally, and the vast majority of spinal neuron projection neurons decussate at or around the same spinal level before ascending contralaterally to supraspinal sites. The fact that some fibers ascend ipsilaterally whereas other ascend contralaterally is the basis for Brown-Séquard syndrome, which involves, among other changes, ipsilateral loss

Pain Processing Pathway Models, Fig. 1 Schematic of pain processing pathways





Pain Processing Pathway Models, Fig. 2 Afferent termination patterns in the spinal dorsal horn. The spinal dorsal horn is divided into layers or laminae (indicated along *left*). Different types of afferent fibers terminate

preferentially in different laminae. *HTMR* high-threshold mechanoreceptor, *LTMR* low-threshold mechanoreceptor. (Modified from Todd and Koerber 2006)

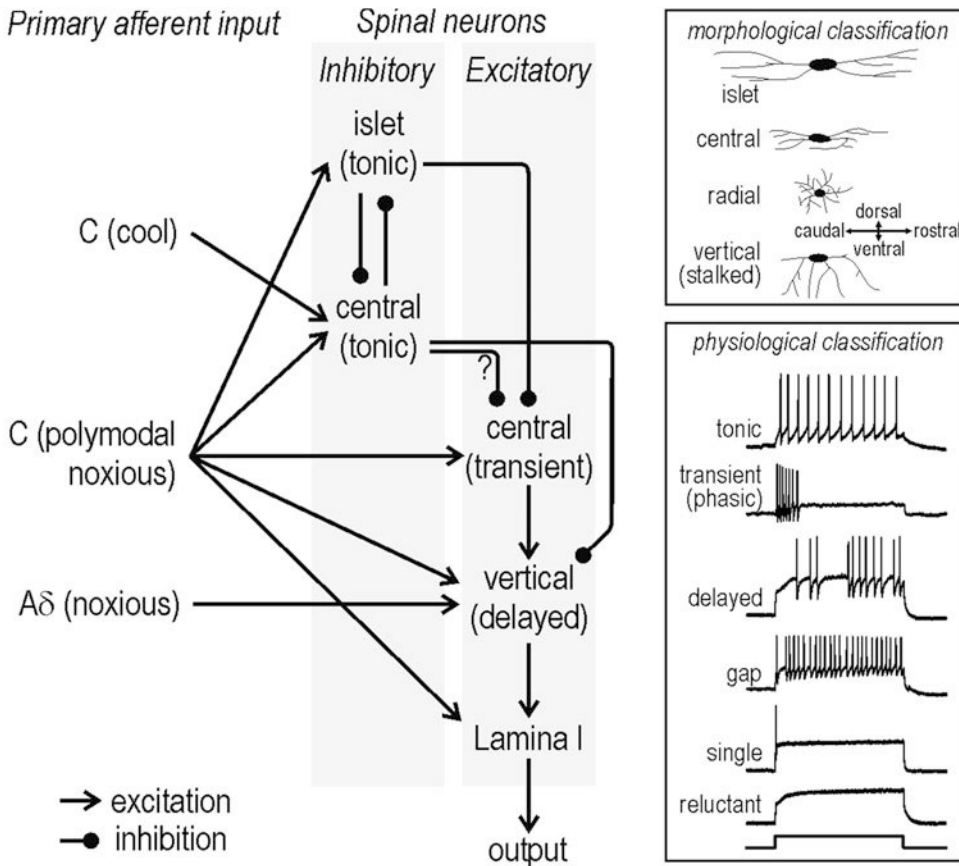
of fine touch sensation and contralateral loss of pain and temperature sensation after hemisection of the spinal cord. These sorts of clinical observations provided early evidence supporting labeled lines.

Pain-related sensory information is relayed from the spinal dorsal horn to motor neurons in the ventral horn, thus forming the circuits responsible for withdrawal reflexes. As an aside, most behavioral analysis conducted in preclinical animal studies focuses on withdrawal reflexes although such reflexes are not necessarily a good proxy for the perception of pain (Mogil and Crager 2004). Sensory information is also relayed from the spinal dorsal horn to supraspinal sites (see Fig. 1) via projection neurons whose cell bodies are located in laminae 1 and 5. Laminae 3, 4, and 6 are also the source of ascending fibers, but those fibers are not thought to carry sensory information directly associated with pain.

Interestingly, projection neurons comprise as few as 5% of all neurons in lamina I of rat lumbar segments, and although the same might not be true of all species or all spinal levels, it is safe to say that local interneurons predominate in terms of sheer numbers. This interneuron population is extremely heterogeneous and includes both

inhibitory and excitatory neurons (Todd 2010). Unfortunately, existing classification schemes are not comprehensive or consistently applied, which makes deciphering synaptic connectivity patterns especially difficult. Figure 3 summarizes what is currently known about microcircuits in the superficial dorsal horn (laminae 1 and 2) based on painstaking paired recording experiments. The microcircuitry in deeper lamina is even less well understood.

Despite this circuitry not being so well understood, it is nonetheless quite clear that the processing of sensory information at the spinal level is functionally important. For instance, intrathecal application of drugs to block fast inhibitory synaptic transmission can acutely produce spontaneous pain and mechanical allodynia, presumably mimicking the conditions that develop (more gradually) after nerve injury and result in neuropathic pain. Blockade of inhibition can also dramatically expand receptive fields, thus demonstrating that receptive fields are shaped by inhibition rather than being hardwired. Moreover, blockade of inhibition reveals low-threshold sensory input to neurons that are supposedly nociceptive specific. In short, numerous forms of plasticity and modulation occur at the spinal level (Sandkuhler 2009).



Pain Processing Pathway Models, Fig. 3 Microcircuitry in the superficial dorsal horn. Different morphological and physiological cells types are

shown on the *right*. The afferent input to and connectivity between these cell types is summarized on the circuit diagram. (Modified from Prescott and Ratté 2012)

Pain Pathway Models

Computational modeling has been conducted to help understand the basis for different intrinsic spiking patterns and the effects of synaptic changes such as disinhibition, but very little modeling has been conducted at the network level. There was some early work modeling the gate control theory in the spinal cord (Britton and Skevington 1989) but none since, to the best of my knowledge. Thalamocortical dysrhythmia, which is implicated in neuropathic pain, has been the focus on some recent modeling (Henning Proske et al. 2011). Overall, it is safe to say that the pain system has seen very little network-level modeling. This at least partly reflects the lack of

experimental data that are critical for building certain types of models: What are the cell types? How are they connected? How do those connections change under certain conditions? But by the same token, modeling might go a long way towards helping direct future experiments. For example, modeling could be used to help predict which microcircuit motifs exist within the spinal dorsal horn in order to carry out certain computations that are known, or suspected, to occur (Prescott and Ratté 2012). Modeling could also be used to help predict what computational processes go awry under conditions leading to neuropathic pain. The opportunities are plentiful and understanding of pain processing would greatly benefit from the insights modeling provides.

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Paired-Pulse Facilitation

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Parametric Spectral Analysis

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Definition

Neurobiological data are often collected in the form of time series. Spectral analysis is the systematic study of time series in the frequency domain. In parametric spectral analysis, time series are treated as realizations of a stochastic process, and a model, typically an autoregressive model, is fit to the data, from which spectral quantities of interest such as power, coherence, and Granger causality spectra are then derived.

Detailed Description

We start by reviewing the basic concepts in the theory of stochastic processes which is the mathematical foundation of time series analysis. From this review one can clearly see that parametric

modeling of time series is not an ad hoc approach but arises naturally from the theory of stochastic processes.

Stochastic Processes

If only one variable is being recorded over time, the time series is said to be univariate. An example of a univariate EEG time series demonstrating the alpha rhythm is shown in Fig. 1. If multiple variables are being recorded at every time instant, the time series is said to be multivariate.

Since successive values in a time series are in general dependent, e.g., not white noise, one can attempt to predict the current value from past observations. If an exact prediction can be made, the time series is said to be deterministic. If the current value is only partly determined by the past values, the time series is said to be stochastic (Chatfield 2004). Almost all experimentally recorded time series data in neuroscience are stochastic in nature. Such time series can be described mathematically as realizations of discrete stochastic processes.

Consider first the univariate case. A univariate discrete stochastic process, denoted by $X(t)$, is a collection of random variables indexed by time t where t takes integer values. Mathematically, $X(t)$ is fully characterized by its joint probability distributions. In practice, the key properties of $X(t)$ can be characterized by mean, variance, and auto-covariance function, defined as $\mu(t) = E(X(t))$, $\sigma^2(t) = E((X(t) - \mu(t))^2)$, and $R_{xx}(t_1, t_2) = E((X(t_1) - \mu(t_1))(X(t_2) - \mu(t_2)))$, respectively. Here E stands for mathematical expectation, which, when analyzing actual data, can be replaced by sample averaging across multiple trials/realizations.

In case there is only one trial/realization available, one can appeal to the ergodic property of the process and replace the averaging across trials by averaging over time in this single trial/realization (Papoulis 1991). For this to be applicable, however, the process needs to be stationary and ergodic.

A class of stochastic processes that have found wide applications in real-world problems is the wide-sense stationary stochastic processes or simply (for the purposes of this entry) stationary processes (Chatfield 2004). For a stationary process, the mean and variance are both constant, i.e., $\mu(t) = \mu$, $\sigma^2(t) = \sigma^2$, and the auto-covariance function has the form $R_{xx}(t_1, t_2) = R_{xx}(\tau)$, where $\tau = t_2 - t_1$ is referred to as the time lag or simply lag. From these definitions, it is clear that $\sigma^2 = R_{xx}(0)$.

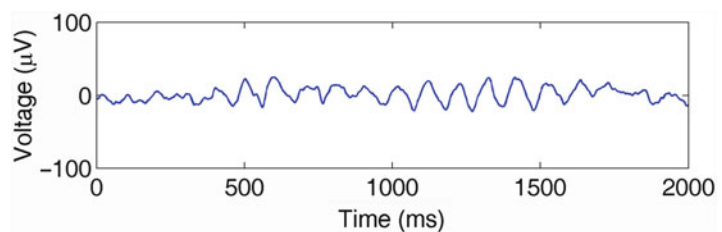
Because the auto-covariance function depends on the magnitude of the time series, making the comparison between different experimental conditions difficult, we typically normalize the auto-covariance function by $R_{xx}(0)$ to yield the autocorrelation function, $\rho_{xx}(\tau) = R_{xx}(\tau)/R_{xx}(0)$. The autocorrelation function measures the degree of linear dependence between $X(t)$ and $X(t + \tau)$ and has values between -1 and 1 . For stochastic processes encountered in applications, $\rho_{xx}(\tau) \rightarrow 0$ as $\tau \rightarrow \infty$, meaning that when the two random variables $X(t)$ and $X(t + \tau)$ are sufficiently separated in time, they are no longer correlated.

For a jointly stationary bivariate stochastic process $(X(t), Y(t))$, the cross-covariance function is defined as

$$R_{xy}(\tau) = E((X(t_1) - \mu_x)(Y(t_2) - \mu_y)) \quad (1)$$

where $\tau = t_2 - t_1$. Normalizing the cross-covariance function gives us the cross-correlation

Parametric Spectral Analysis, Fig. 1 EEG time series data from the occipital cortex of a human subject demonstrating the alpha rhythm



function which again takes values between -1 and 1 , that is,

$$\rho_{xy}(\tau) = R_{xy}(\tau) / \sqrt{R_{xx}(0)R_{yy}(0)} \quad (2)$$

$R_{xy}(\tau)$ characterizes the relation between the two time series and is an essential function for performing spectral analysis of bivariate stochastic processes. For a multivariate stochastic process $(X_1(t), X_2(t), \dots, X_n(t))$, the spectral analysis makes use of pairwise cross-covariance functions $R_{x_i x_j}(\tau)$ between $X_i(t)$ and $X_j(t)$, defined as $R_{x_i x_j}(\tau) = E\left((X_i(t_1) - \mu_{x_i})(X_j(t_2) - \mu_{x_j})\right)$. The corresponding cross-correlation function can also be similarly defined.

Spectral Analysis of Stochastic Processes

Spectral analysis is the systematic study of time series in the frequency domain. The three main quantities of interest are the power spectrum, coherence spectrum, and Granger causality spectrum. The power spectrum tells us how energy is distributed in different frequency bands, the coherence spectrum characterizes the degree of linear dependence between two time series at a given frequency, and the Granger causality spectrum quantifies the causal effects between two time series on a frequency-by-frequency basis (Ding et al. 2006).

For a univariate stationary stochastic process, the power spectrum is defined as the Fourier transform of the auto-covariance function defined in the previous section:

$$\begin{aligned} S_{xx}(f) &= \sum_{\tau=-\infty}^{\infty} R_{xx}(\tau) e^{-i2\pi f\tau} \\ &= R_{xx}(0) + 2 \sum_{\tau=1}^{\infty} R_{xx}(\tau) \cos(2\pi f\tau) \end{aligned} \quad (3)$$

where we have made use of the symmetry $R_{xx}(-\tau) = R_{xx}(\tau)$. Hence, $S_{xx}(f)$ is real and non-negative. Sometimes one is interested in the normalized power spectrum that is the Fourier transform of the autocorrelation function of the

process. An equivalent expression for the power spectrum is given by (Priestly 1981)

$$S_{xx}(f) = \lim_{N \rightarrow \infty} E(X(f)X^*(f))/N \quad (4)$$

where E denotes the mathematical expectation, $X(f)$ is the Fourier transform of $X(t)$, N denotes the length of data, and $*$ denotes the complex conjugate.

For a multivariate stochastic process $(X_1(t), X_2(t), \dots, X_m(t))$, an appropriate generalization of the power spectrum is the $m \times m$ spectral density matrix $S(f)$ defined as

$$S(f) = \begin{pmatrix} S_{x_1 x_1}(f) & \cdots & S_{x_1 x_{td}}(f) \\ \vdots & \ddots & \vdots \\ S_{x_{td} x_1}(f) & \cdots & S_{x_{td} x_{td}}(f) \end{pmatrix} \quad (5)$$

where $S_{x_i x_j}(f)$ is the cross-spectrum between $X_i(t)$ and $X_j(t)$ defined as the Fourier transform of the cross-covariance function $R_{x_i x_j}(\tau)$:

$$S_{x_i x_j}(f) = \sum_{\tau=-\infty}^{\infty} R_{x_i x_j}(\tau) e^{-i2\pi f\tau} \quad (6)$$

For $i \neq j$, $S_{x_i x_j}(f)$ is in general complex, yielding both amplitude and phase information. For $i = j$, $S_{x_i x_j}(f)$ reduces to the real (auto) power spectrum $S_{x_i x_i}(f)$ of the process $X_i(t)$. It can be shown that $S_{x_j x_i}(f)$ is the complex conjugate of $S_{x_i x_j}(f)$, and hence, $S(f)$ is a Hermitian matrix. As before, an equivalent expression for the cross-spectrum is given by (Priestly 1981)

$$S_{x_i x_j}(f) = \lim_{N \rightarrow \infty} E(X_i(f)X_j^*(f))/N \quad (7)$$

If we denote $(X_1(t), X_2(t), \dots, X_m(t))$ by the vector process $\mathbf{X}(t)$, the $m \times m$ spectral density matrix $S(f)$ is given by

$$S(f) = \lim_{N \rightarrow \infty} E(\mathbf{X}(f)\mathbf{X}^\dagger(f))/N \quad (8)$$

where $\mathbf{X}(f)$ denotes the Fourier transform of $\mathbf{X}(t)$ and $\mathbf{X}^\dagger(f)$ denotes the Hermitian conjugate of $\mathbf{X}(f)$.

A second quantity of interest in spectral analysis of stochastic processes is the spectral

coherence function between $X_i(t)$ and $X_j(t)$ (Chatfield 2004):

$$C_{x_i x_j}(f) = |S_{x_i x_j}(f)| / \sqrt{S_{x_i x_i}(f) S_{x_j x_j}(f)} \quad (9)$$

which sometimes is also called the ordinary coherence function or simply coherence function. This is the spectral analogue of the time-domain cross-correlation function.

A third quantity of interest in spectral analysis is Granger causality. The basic idea behind Granger causality can be explained in the time domain as follows. Consider two simultaneously recorded stationary time series. According to Wiener (1956), if the prediction of one time series is improved by incorporating the knowledge of a second one, then the second series is said to have a causal influence on the first. Granger (1969) later formalized the prediction idea in the context of linear regression models (see next section). Specifically, if the variance of the autoregressive prediction error of the first time series at the present time is reduced by inclusion of past measurements from the second time series, then the second time series is said to have a causal influence on the first one. Reversing the role of the two time series gives the causal influence in the opposite direction. The interaction discovered this way could be either reciprocal or unidirectional.

The derivation of the frequency-domain Granger causality, called Granger causality spectrum, is quite involved (see next section). The basic idea, however, is straightforward to appreciate. Again consider two stationary time series. Geweke (1982) showed that the spectral power at a given frequency f can be written as the sum of

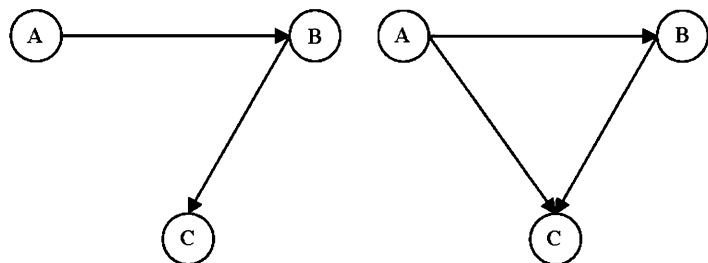
two terms: $\text{power}(f) = \text{intrinsic power}(f) + \text{causal power}(f)$. The intrinsic power can be thought of as the power generated locally near the recording site, whereas the causal power term is the power brought about by the input from the other time series. The Granger causality at frequency f is then defined to be $I(f) = \ln(\text{power}(f)/\text{intrinsic power}(f))$. From this definition, it is clear that when the causal power is zero, namely, there is no causal input from the other time series, $I(f) = 0$. When the causal power is greater than zero, we have $I(f) > 0$, which indicates nonzero causal influence from the other time series at frequency f . This can be quantified more precisely and the relevant formulas are given in the next section.

For three or more time series, patterns of connectivity can become more intricate. To illustrate, consider three time series A, B and C. A pairwise analysis will not be able to distinguish the two patterns shown in Fig. 2. In this case the concept of conditional Granger causality becomes necessary (Geweke 1984; Chen et al. 2006; Ding et al. 2006).

Parametric Spectral Analysis Using Autoregressive Models

The mathematical foundation of parametric modeling of stationary time series is the Wold decomposition theorem (Papoulis 1985). For simplicity, consider the univariate case. According to the theorem, any zero-mean stationary process $X(t)$, if $\rho_{xx}(\tau) \rightarrow 0$ as $\tau \rightarrow \infty$, can be represented by the following infinite moving average (MA) model:

Parametric Spectral Analysis, Fig. 2 To distinguish the two different connectivity patterns, a conditional Granger causality analysis is required



$$X(t) = \sum_{j=0}^{\infty} b_j \varepsilon(t-j) \quad (10)$$

where $\varepsilon(t)$ is white noise and $\sum_{j=0}^{\infty} |b_j|^2 < \infty$. If the MA model is invertible, that is, if the zeros of the polynomial $p(z) = \sum_{j=0}^{\infty} b_j z^j$ all lie outside the unit circle, the model can be inverted to obtain an autoregressive (AR) model (Chatfield 2004):

$$X(t) = \sum_{j=0}^{\infty} a_j X(t-j) + \varepsilon(t) \quad (11)$$

Further, if the coefficients $a_j \rightarrow 0$ as $j \rightarrow \infty$, then the model can be truncated at finite order p to give the autoregressive model of order p (AR (p) model):

$$X(t) = a_1 X(t-1) + a_2 X(t-2) + \dots + a_p X(t-p) + \varepsilon(t) \quad (12)$$

Here $\varepsilon(t)$ is a white noise process with $\text{var}(\varepsilon(t)) = \sigma^2$.

The Wold decomposition theorem implies that the properties of stationary time series can be fully captured by autoregressive models. Parametric spectral analysis starts with fitting an AR(p) model to the experimental data. For a univariate process the simplest method to estimate $a_1, a_2, \dots, a_p, \sigma^2$ is given as follows (Chatfield 2004): Both sides of the AR equation are multiplied by $X(t-k)$ ($k = 0, 1, 2, \dots, p$), and the expectation is taken. This results in the following Yule-Walker equations (using the definition of auto-covariance function and its symmetry properties):

$$\begin{aligned} R_{xx}(k) &= a_1 R_{xx}(k-1) + a_2 R_{xx}(k-2) + \dots + \\ &\quad a_p R_{xx}(k-p); k = 1, 2, \dots, p; \\ R_{xx}(0) &= a_1 R_{xx}(1) + a_2 R_{xx}(2) + \dots + \\ &\quad a_p R_{xx}(p) + \sigma^2; k = 0 \end{aligned} \quad (13)$$

Here the auto-covariances are estimated from the data $\{x_n\}_{n=1}^N$ (which is now considered to be

a realization of the AR model) using the following expression:

$$R_{xx}(k) = \frac{1}{N} \sum_{n=k}^N x_n x_{n-k} \quad (14)$$

Substituting these estimates into the Yule-Walker equations, we get $p+1$ linear equations with $p+1$ unknowns. These can be solved for $a_1, a_2, \dots, a_p, \sigma^2$. The model order p can be estimated using the Akaike Information Criterion (Akaike 1971) or other criteria. For multiple realizations the quantity in Eq. 14 is estimated for each realization and averaged across realizations.

Once we have the AR representation of the time series data, the power spectrum $S_{xx}(f)$ can be obtained using Eq. 4. From Eq. 12, the Fourier transform $X(f)$ of $X(t)$ is given by

$$X(f) = (1 - a_1 e^{-i2\pi f} - a_2 e^{-i4\pi f} - \dots - a_p e^{-i2\pi p f})^{-1} \varepsilon(f) \quad (15)$$

where $\varepsilon(f)$ is the Fourier transform of the error term $\varepsilon(t)$. Defining a transfer function $H(f)$ as $(1 - a_1 e^{-i2\pi f} - a_2 e^{-i4\pi f} - \dots - a_p e^{-i2\pi p f})^{-1}$, the above equation can be rewritten as

$$X(f) = H(f) \varepsilon(f) \quad (16)$$

Substituting this in Eq. 4 and using the fact that

$$\begin{aligned} E(H(f) \varepsilon(f) \varepsilon^*(f) H^*(f)) / N \\ = H(f) E(\varepsilon(f) \varepsilon^*(f)) H^*(f) / N \end{aligned} \quad (17)$$

we finally get

$$S_{xx}(f) = H(f) \sigma^2 H^*(f) = |H(f)|^2 \sigma^2 \quad (18)$$

Here $\sigma^2 = E(\varepsilon(f) \varepsilon^*(f)) / N$ is the variance of the error term $\varepsilon(t)$.

As a concrete example, suppose that the given time series data can be modeled as an AR (1) process:

$$X(t) = a_1 X(t-1) + \varepsilon(t) \quad (19)$$

The transfer function $H(f)$ is given by

$$H(f) = (1 - a_1 e^{-i2\pi f})^{-1} \quad (20)$$

Hence,

$$\begin{aligned} S_{xx}(f) &= H(f) \sigma^2 H^*(f) \\ &= \sigma^2 / (1 - a_1 e^{-i2\pi f})(1 - a_1 e^{i2\pi f}) \\ &= \sigma^2 / (1 + a_1^2 - a_1 \cos(2\pi f)) \end{aligned} \quad (21)$$

The above expression can be evaluated at any arbitrary frequency, giving rise to a high-resolution power spectrum of the data. Further, one can analyze the power spectrum as a function of the system parameters (a_1 and σ^2 in this case) that can provide further insight into the system underlying the recorded data.

Next, consider a multivariate time series. It can be represented using a vector AR (VAR) process of order p :

$$\begin{aligned} \mathbf{X}(t) &= \mathbf{A}(1)\mathbf{X}(t-1) + \mathbf{A}(2)\mathbf{X}(t-2) \\ &\quad + \dots + \mathbf{A}(p)\mathbf{X}(t-p) + \mathbf{E}(t) \end{aligned} \quad (22)$$

Here $\mathbf{X}(t) = (X_1(t), X_2(t), \dots, X_m(t))^T$ is a multivariate process; $\mathbf{A}(i)$'s are $m \times m$ coefficient matrices, where m is the number of time series simultaneously measured; and $\mathbf{E}(t) = (\varepsilon_1(t), \varepsilon_2(t), \dots, \varepsilon_m(t))^T$ is the vector white noise process where $\varepsilon_i(t)$'s are serially uncorrelated over time but have a contemporaneous $m \times m$ covariance matrix given by $\mathbf{\Gamma}$. The diagonal elements of $\mathbf{\Gamma}$ represent the variances of the individual white noise processes, and the off-diagonal terms represent the cross-variances between these white noise processes.

Using a procedure similar to that followed for the univariate process, the coefficient matrices $\mathbf{A}(i)$'s and the error covariance matrix $\mathbf{\Gamma}$ can be estimated from the multivariate experimental time series data using the multivariate analogue of the Yule-Walker equations. To obtain the spectral density matrix, we first obtain the Fourier transform $\mathbf{X}(f)$:

$$\begin{aligned} \mathbf{X}(f) &= (1 - \mathbf{A}(1)e^{-i2\pi f} - \mathbf{A}(2)e^{-i4\pi f} - \dots - \\ &\quad \mathbf{A}(p)e^{-i2\pi pf})^{-1} \mathbf{E}(f) \end{aligned} \quad (23)$$

Substituting in Eq. 8, we obtain

$$S(f) = \mathbf{H}(f) \mathbf{\Gamma} \mathbf{H}^*(f) \quad (24)$$

where all quantities are now $m \times m$ matrices and the transfer function matrix $\mathbf{H}(f)$ is given by

$$\begin{aligned} \mathbf{H}(f) &= (1 - \mathbf{A}(1)e^{i2\pi f} - \mathbf{A}(2)e^{i4\pi f} - \dots - \\ &\quad \mathbf{A}(p)e^{i2\pi pf})^{-1} \end{aligned} \quad (25)$$

From the spectral density matrix in Eq. 24, the power spectra of all individual processes and the coherence spectra between processes can be readily derived according to the definitions given earlier.

In computing the Granger causality, consider fitting a bivariate AR model to X_i and X_j . The formula for the frequency-domain Granger causality from X_j to X_i at frequency f is (Ding et al. 2006).

$$\begin{aligned} I_{x_j \rightarrow x_i}(f) &= \ln \frac{S_{x_i x_j}(f)}{S_{x_i x_j}(f) - (\Gamma_{x_i x_j} - \Gamma_{x_i x_j}^3 / \Gamma_{x_i x_j}) |H_{x_i x_j}(f)|^2} \end{aligned} \quad (26)$$

The Granger causality spectrum from X_i to X_j is obtained by interchanging the indices i and j in the above expression. It is important to note that according to the approach outlined above, for Eq. 26 to apply, we fit a separate bivariate AR model to X_i and X_j for different combinations of i and j . This limitation has been overcome in a recent paper where it is shown that for the entire multivariate data set, only a single vector AR model fit is necessary. From the model, the Granger causality within any subset of the recorded data can be calculated (Wen et al. 2013).

To illustrate the multivariate framework, consider the following 3-variable ($m = 3$) AR (1) process:

$$\begin{aligned} X_1(t) &= \varepsilon_1(t) \\ X_2(t) &= X_1(t-1) + \varepsilon_2(t) \\ X_3(t) &= \lambda X_3(t-1) + X_1(t-1) + \varepsilon_3(t) \end{aligned} \quad (27)$$

where $|\lambda| < 1$ is a parameter and the noise terms $\varepsilon_i(t)$'s are assumed to be uncorrelated with one another and have variances σ_i^2 . The above equations can be written in matrix form as

$$X(t) = \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & \lambda \end{pmatrix} X(t-1) + E(t) \quad (28)$$

Here the noise vector $E(t)$ has a diagonal covariance matrix $\Gamma = \text{diag}(\sigma_1^2, \sigma_2^2, \sigma_3^2)$ since the individual noise terms are uncorrelated with one another.

Taking Fourier transforms on both sides and simplifying, we get

$$\begin{pmatrix} 1 & 0 & 0 \\ e^{-i2\pi f} & 1 & 0 \\ e^{-i2\pi f} & 0 & 1 - \lambda e^{-i2\pi f} \end{pmatrix} X(f) = E(f) \quad (29)$$

Thus, $X(f) = H(f)E(f)$ where the transfer function matrix $H(f)$ is given by

$$\begin{aligned} H(f) &= \begin{pmatrix} 1 & 0 & 0 \\ e^{-i2\pi f} & 1 & 0 \\ e^{-i2\pi f} & 0 & 1 - \lambda e^{-i2\pi f} \end{pmatrix}^{-1} \\ &= \begin{pmatrix} 1 & 0 & 0 \\ -e^{-i2\pi f} & 1 & 0 \\ -e^{-i2\pi f} & 0 & \frac{1}{1 - \lambda e^{-i2\pi f}} \end{pmatrix} \end{aligned} \quad (30)$$

Substituting the expressions for $H(f)$ and Γ in Eq. 8, we get the spectral density matrix to be

$$S(f) = \begin{pmatrix} \sigma_1^2 & -e^{i2\pi f} \sigma_1^2 & \frac{(\lambda - e^{i2\pi f}) \sigma_1^2}{(1 + \lambda^2 - 2\lambda \cos(2\pi f))} \\ -e^{i2\pi f} \sigma_1^2 & \sigma_1^2 + \sigma_2^2 & \frac{(1 - \lambda e^{-i2\pi f}) \sigma_1^2}{(1 + \lambda^2 - 2\lambda \cos(2\pi f))} \\ \frac{(\lambda - e^{i2\pi f}) \sigma_1^2}{(1 + \lambda^2 - 2\lambda \cos(2\pi f))} & \frac{(1 - \lambda e^{i2\pi f}) \sigma_1^2}{(1 + \lambda^2 - 2\lambda \cos(2\pi f))} & \frac{\sigma_1^2 + \sigma_3^2}{(1 + \lambda^2 - 2\lambda \cos(2\pi f))} \end{pmatrix} \quad (31)$$

The diagonal terms represent the auto power spectrum of the three processes comprising the above VAR model, and the off-diagonal terms represent the cross-spectrum between these processes. As before, we can examine the behavior of these spectra as a function of the system parameters.

From the spectral density matrix in Eq. 31, we can compute the pairwise coherences using Eq. 9:

$$\begin{aligned} C_{x_1 x_2}(f) &= \frac{|S_{x_1 x_2}(f)|}{\sqrt{S_{x_1 x_1}(f) S_{x_2 x_2}(f)}} = \frac{\sigma_1}{\sqrt{\sigma_1^2 + \sigma_2^2}} \\ C_{x_1 x_3}(f) &= \frac{|S_{x_1 x_3}(f)|}{\sqrt{S_{x_1 x_1}(f) S_{x_3 x_3}(f)}} = \frac{\sigma_1}{\sqrt{\sigma_1^2 + \sigma_2^2}} \\ C_{x_2 x_3}(f) &= \frac{|S_{x_2 x_3}(f)|}{\sqrt{S_{x_2 x_2}(f) S_{x_3 x_3}(f)}} \\ &= \frac{\sigma_1^2}{\sqrt{(\sigma_1^2 + \sigma_2^2)(\sigma_1^2 + \sigma_2^2)}} \end{aligned} \quad (32)$$

In this simple case, all the pairwise coherences happen to be constant independent of frequency.

We can also obtain the pairwise Granger causalities using Eq. 26:

$$\begin{aligned} I_{1 \rightarrow 2}(f) &= \ln \left(\frac{\sigma_1^2 + \sigma_2^2}{\sigma_2^2} \right) \\ I_{1 \rightarrow 3}(f) &= \ln \left(\frac{\sigma_1^2 + \sigma_2^2}{\sigma_2^2} \right) \end{aligned} \quad (33)$$

The other pairwise Granger causalities are all zero.

Parametric Versus Nonparametric Spectral Analysis

We conclude by contrasting parametric spectral analysis with nonparametric spectral analysis. In nonparametric spectral analysis, the desired spectral quantities are obtained directly from the data using Fourier or wavelet transforms, in conjunction with various windowing techniques ranging from the simple (e.g., the periodogram method) to the more advanced (e.g., the multitaper method) (Percival and Walden 1993). The main advantage of the nonparametric spectral methods is that they are intuitive and have no need to go through an intermediate layer of data modeling. The disadvantages include limited frequency resolution and vulnerability to estimation bias when the data length is short. It used to be the case that directional measures such as the Granger causality could not be obtained from Fourier- or wavelet-based analysis. This limitation has recently been overcome via the introduction of spectral factorization methods (Dhamala et al. 2008a, b).

The advantages of the parametric method include the ability to resolve spectral quantities to arbitrarily high resolution in the frequency domain, smoother spectral estimates, being less vulnerable to the shortness of data windows, and the ability to generate the Granger causality spectra. The disadvantages include occasional difficulties in obtaining an optimal model that fits the data.

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Paraspinal Electrical Stimulation

► [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)

Paraspinal Magnetic and Transcutaneous Electrical Stimulation

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Synonyms

High-voltage paraspinal electrical stimulation; High-voltage percutaneous electrical stimulation; Magnetic paravertebral stimulation; Magnetic spinal stimulation; Paravertebral neuromagnetic stimulation; Spinal electromagnetic stimulation; Spinal neuromagnetic stimulation; Spinal root stimulation; Transcutaneous posterior root stimulation; Transcutaneous spinal cord stimulation; Transcutaneous spinal stimulation; Transspinal stimulation

Definition

Paraspinal magnetic and electrical stimulation target deep neural structures within the vertebral canal and in between neighboring vertebrae from a distance of several centimeters, with either magnetic coils or skin electrodes. The principal mechanism of stimulation at the neuronal level is the same for magnetic and electrical stimulation and is given by the induced electric field component or, in an equivalent way, the electric potential, generated along the anatomical path of the nerve fibers. Yet the generation of electric fields by electromagnetic induction or electrical stimulation bases on different physical principles, and the currents generated differ substantially, both as a function of time (pulse shape) and space (distribution in the body tissues). Induced ionic tissue currents secondary to externally applied, time-varying magnetic fields enter the spine

predominantly from its sides, while the currents generated by transcutaneous electrical stimulation penetrate it mainly from its back (or front). The motor fibers within the spinal nerves and anterior rootlets are the common targets of paraspinal magnetic stimulation. Different techniques of transcutaneous electrical stimulation either excite the motor fibers in the spinal nerves/anterior rootlets or selectively activate the sensory fibers within the posterior roots/rootlets. Furthermore, longitudinal tracts within the white matter of the spinal cord can be directly activated by high-voltage electrical stimulation. Neural networks of the spinal cord gray matter are exclusively activated transsynaptically, e.g., through the inputs provided by electrically stimulated sensory fibers. The applications of paraspinal magnetic and transcutaneous electrical stimulation depend on the stimulated neuroanatomy. They include the neurodiagnostic assessment of the functional integrity of lower motoneurons, neurophysiological studies of spinal cord neural networks, the generation of patterned muscle contractions for useful bodily functions, and neuromodulation applications.

Detailed Description

Magnetic and transcutaneous electrical stimulation applied over the spine and spinal cord produce electric fields by different physical principles. Paraspinal magnetic stimulation generates continuous, ionic current flows that close on themselves following the principles of electromagnetic induction. The current flow is largely constrained to planes parallel to the surface of the volume conductor in contact with the magnetic coil, i.e., to the back. Hence, the induced currents are mainly circular and oriented parallel to the frontal (coronal) plane. In transcutaneous electrical stimulation, the potential difference between the skin electrodes during a stimulation pulse causes current to flow from the anode to the cathode via the intermediate anatomical structures. Close to the paraspinal electrodes and also within the spine, current flows have directions perpendicular to the frontal plane. The current

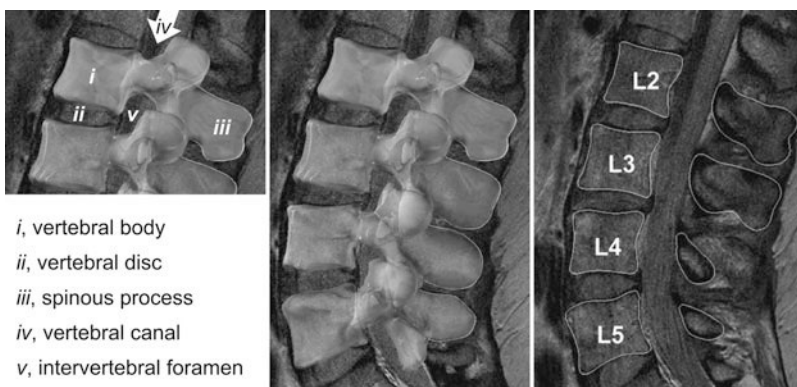
flows generated by paraspinal magnetic and electrical stimulation are thus very unlike.

Within the human body, the current flow is shaped by the electrical tissue properties and the numerous conductivity boundaries. The bony structures of the spine, owing to their high electrical resistance, have a considerable influence on the produced currents. Yet, unlike the brain, the spinal roots and spinal cord are not completely enclosed by bony material. The electrical resistance across the spine is reduced by soft tissues, including ligaments and disks, between neighboring vertebrae (Fig. 1). Structures within the “openings” of the spine have better electrical conductivities than the bones as well. The longitudinal, centrally located vertebral canal contains the spinal cord and spinal roots. It is formed by the vertebrae and, in the intervertebral spaces, by the ligaments. The intervertebral foramina (or neuroforamina) are the bilateral openings between every pair of vertebrae that allow for the exits of the spinal roots/nerves from the vertebral canal. The sacral canal is the continuation of the vertebral canal within the sacral bone of the pelvis. Its openings for the sacral roots of the cauda equina, the anterior sacral foramina, have a posteroanterior orientation.

A further important influence on the immediate stimulation effects is given by the fiber paths of the neural target structures, i.e., the alterations of their spatial orientation with respect to the electric field. Cervical and upper thoracic roots course laterally or slightly downward from the spinal cord to the respective intervertebral foramina. There, they have short, upwardly directed segments. Lumbar and sacral roots have a sharp, caudally directed bend as they exit the spinal cord, followed by a longitudinal component through the cauda equina. The roots then exit the canal at angles between 20° and 40° to the longitudinal axis, with a rather mediolateral orientation at the intervertebral foramina and a posteroanterior orientation at the anterior sacral neuroforamina.

General Principles of Nerve Stimulation

The substructure of a neuron most excitable by external stimulation is the myelinated axon. In magnetic stimulation, the activation of the axon is not directly caused by the magnetic field but by the electromagnetically induced electric field. The principal mechanism of neural stimulation is thus the same for paraspinal magnetic and electrical



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 1 Geometry of the human spine. Three-dimensional representation of the human lumbar spine (second to fifth lumbar vertebrae) constructed using magnetic resonance (MR) images and an MR image in sagittal plane. While the bony structures appear quite

massive in the three-dimensional representation, the section shows the extent of soft tissues with better electrical conductivities. The anterior to posterior direction is from left to right. (Reproduced from Xia et al. (2009) with permission from Springer Science and Business Media)

stimulation. The electric field $\mathbf{E}$ is a vector field given in V/m. Equally, the electric potential Φ , a scalar field measured in V, describes the stimulation effects upon the neural structures. Their relation is given by $\mathbf{E} = -\nabla\Phi$. The stimulation-generated electric field/potential distribution causes ionic currents to flow within the electrically conducting anatomical structures. A fraction of the current passes the nerve fiber membranes, thereby producing local depolarizations and hyperpolarizations. Depolarization of the membrane to a threshold level generates an action potential that normally propagates in both directions along the nerve fiber. Low excitation thresholds result from sudden changes of the electric field component or of the potential distribution along the axon's anatomical path. More precisely, the strongest depolarization is produced at the peak of the second-order spatial difference of the electric potential along the nerve fiber (Rattay 1999 and see entry ► [“Finite Element Modeling for Extracellular Stimulation”](#)). Equivalently, the depolarization is proportional to the negative-going, first-order spatial difference of the electric field tangential to the fiber path. Effective stimulation of a large-diameter myelinated axon requires changes of the electric potential across distances covering neighboring nodes of Ranvier, i.e., distances of few millimeters. Along such distances, large values of the second-order spatial difference of the electric potential can be present even in a non-focal electric field, if an axon (i) alters its spatial orientation within the field or (ii) passes electrical inhomogeneities of the tissues surrounding it. Considerable inhomogeneities arise across the intervertebral foramina, as well as at the interface between the spinal rootlets and the spinal cord (sudden change in conductance between the cerebrospinal fluid and the spinal cord). At the same sites, these inhomogeneities are added to by the alterations of the spatial orientation of the sensory and motor fibers, particularly those of the lumbar and sacral roots. Due to these low-threshold sites, deep neural structures can be stimulated, and the depolarization sites are predictable in spite of the distant stimulation and widespread fields.

Biophysics of Paraspinal Magnetic and Transcutaneous Electrical Stimulation

Paraspinal Magnetic Stimulation

Magnetic stimulation follows the fundamental principles of electromagnetic induction. A brief electric current pulse flowing in a coil of wires creates a time-varying magnetic field. The magnetic field passes unimpeded through biological tissues with low electrical conductivity and gives rise to an electric field. Within the electrically conductive tissues of the human body, the electric field causes ionic current flows. These induced secondary currents are circular, flowing in the opposite direction to the primary coil current, and are affected by the inhomogeneous and anisotropic electrical tissue properties. A principal difference between magnetic and transcutaneous electrical stimulation in the activation of deep neural structures is that these secondary currents do not flow from the body surface to the target but are induced without localized electrical “sources” or “sinks” within the body volume. The relatively low current densities at the skin below the coil result in a reduced excitation of nerve endings that may otherwise cause discomfort.

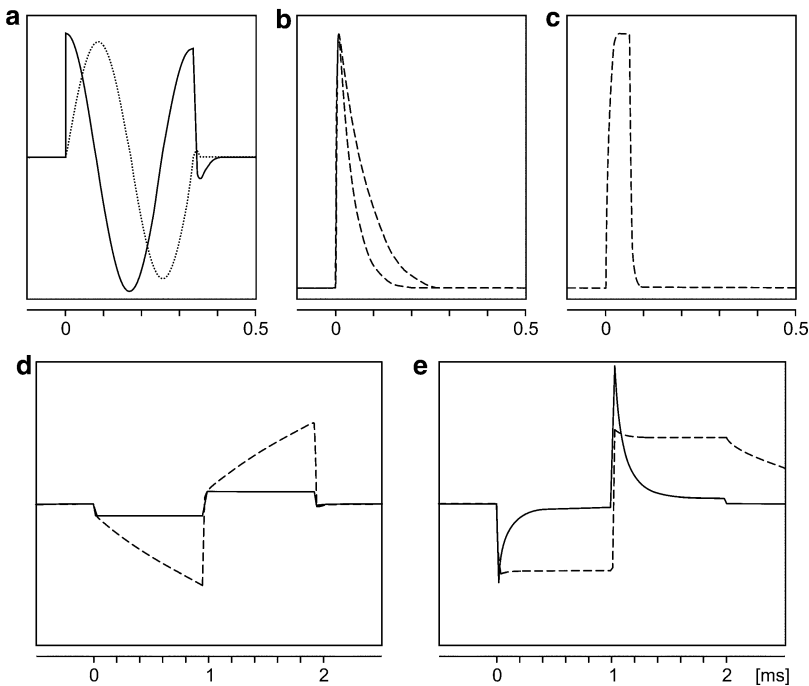
The magnetic field (i.e., the magnetic flux density $\mathbf{B}$) is a vector field given in tesla ($1 \text{ T} = 1 \text{ Vs/m}^2$). The magnetic field lines are closed loops, cross the coil plane at perpendicular angles, and curve outward from the coil. At the center of a round coil, maximum magnetic fields of 1–2.5 T are generated. The effective depth of magnetic stimulation is limited by the rapid (exponential) decay of the induced electric field along a line perpendicular to the coil's plane. As a function of time, the magnetic field exhibits the same waveform as the coil current. The current waveform and the current direction within the coil are thus critical electrical characteristics determining the stimulation effects. Monophasic (or near-monophasic) and biphasic (or damped oscillatory) waveforms are produced by conventional magnetic stimulators, usually with rise times of 50–200 μs and durations of 100–1000 μs . The monophasic coil current waveform has a rapid rise time and a slower decay to zero. The current producing the magnetic field flows in one

direction of the coil only. Thus, by flipping the coil, the direction of the secondary currents induced in the human tissues is reversed, which generally has an influence on the thresholds of the neural target structures. The waveform of a biphasic coil current pulse is a decaying full cycle of a sine wave (Fig. 2a, dotted line). With the secondary currents induced in either direction, the determination of the site of stimulation may become more difficult.

Like the induced electric field $\mathbf{E}$, the secondary tissue current $\mathbf{J}$ (current density in A/m^2) is a vector field, and $\mathbf{J} = \sigma \mathbf{E}$ (σ is the electrical conductivity given in Siemens per meter, S/m). During a stimulation pulse, $\mathbf{E}$ and $\mathbf{J}$ have the same time courses that follow the first time derivative of the primary coil current (Fig. 2a, solid line). The

stronger the applied magnetic field and the faster the field changes (first time derivative of the magnetic flux density, $d\mathbf{B}/dt$), the greater the current induced within the body tissues.

Basic principles of the spatial electric field and current distribution induced by magnetic stimulation are derived from controlled experimental conditions and simplified models (Cohen and Cuffin 1991; Maccabee et al. 1991, 1996; Miranda 2005). The electromagnetically induced tissue current is continuous and closes on itself within the volume conductor. Enclosed are regions where the current flows are zero ("null points"). The spatial distributions of the electromagnetically induced electric fields are different for different coil geometries. Standard coils are circular (round) coils and figure-8 (double



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 2 Pulse shapes of paraspinal magnetic and electrical stimulation. (a) Biphasic pulse of a magnetic stimulator; the *dotted line* is the basic waveform of the coil current and the magnetic flux density and the *solid line* is that of the induced electric field and secondary tissue current. (b and c) show the voltage across a resistor produced by the Digitimer D180 (decay constant set at 50 and 100 μs) and the Digitimer D185, respectively, both applied in high-voltage electrical stimulation. (d and e) are the

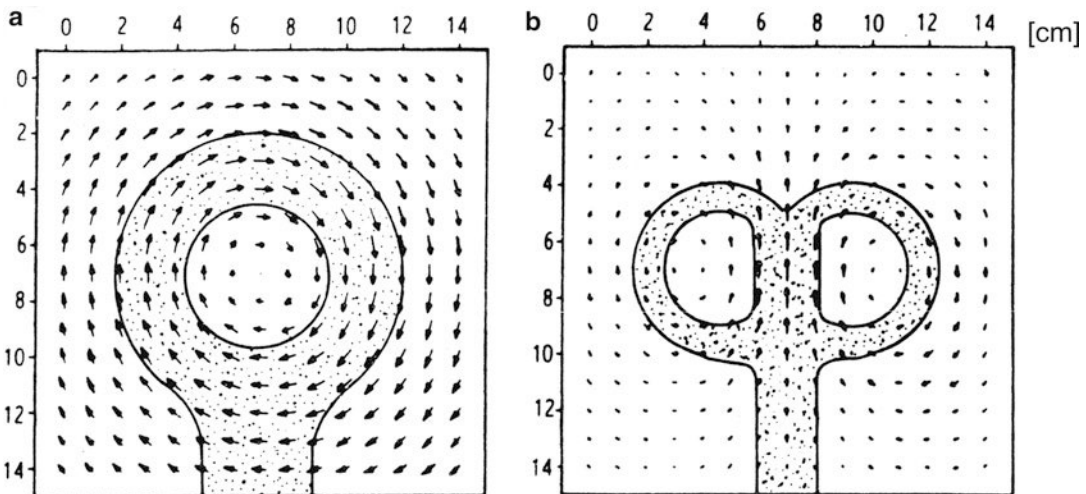
biphasic pulses of a current-controlled and a voltage-controlled stimulator, respectively, as used for transcutaneous spinal cord stimulation. *Solid lines* are currents through and *dashed lines* are voltages across an individual, measured at the electrodes during stimulation. The scaling of the ordinates is arbitrary; the figures compare the stimulation voltages/generated currents as a function of time for the various stimulation techniques. Different timescales in (a–c) versus (d–e)

circular, butterfly) coils. A figure-8 coil consists of two circular (or D-shaped) coils with opposite current direction placed side by side. In a homogeneous volume conductor, a circular coil held flat to its (planar or spherical) surface induces an annular current flow opposite in direction to the primary coil current and in planes parallel to the air-conductor interface (Fig. 3a). The current density is maximal beneath the windings of the coil and rapidly falls off toward the coil center, while the decay when moving outward from the coil is more gradual. The result is a broad, very non-focal distribution of the induced currents. Some directional sensitivity of the induced current distribution can be achieved by a figure-8 coil (Fig. 3b). The current loops superimpose maximally under the region of the long axis of the junction of the two coil wings. Positioning the junction above a target area produces a maximum current flow through it with currents of lower density returning in circles on both sides.

The suppression of electric field components perpendicular to the volume conductor's surface in contact with the magnetic coil is due to boundary effects. An electric field component perpendicular to a planar infinite boundary is not

induced, regardless of the coil type or orientation (the normal component of the current flow at the tissue-air boundary must be zero). Similarly, when paraspinal magnetic stimulation is applied, the vectors of the electric field and current density are initially parallel to the boundary of the back as well, and thus the currents induced within the volume conductor are predominantly parallel to the frontal plane. For further information on the biophysics of magnetic stimulation, see Miranda (2005), Epstein (2008), Riehl (2008), and Sommer (2008).

The influence of the spine on the electric field distribution induced by magnetic stimulation was described using human cervical-thoracic and lumbosacral spine segments immersed in a saline-filled container (Maccabee et al. 1991, 1996). The electric fields induced by a circular coil and a large figure-8 coil were measured within the intervertebral foramina, the vertebral canal, and the sacral canal. The direction of the electric field across the intervertebral foramina and within the vertebral canal is similar to that expected in a homogeneous volume conductor. Thus, induced currents enter and exit the spine from its sides. Due to "current-tunneling" effects, the maximum



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 3 Electric fields induced by (a) a circular and (b) a figure-8 magnetic coil oriented flat against the bottom surface of a cylindrical tank filled with isotonic saline. The electric field distributions are represented by current arrow diagrams in a plane parallel to the bottom

surface; magnitudes and directions are derived from measurements using a coaxial cable probe. The arrows are equally spaced, and the relative current densities are indicated by the size of each arrow. (Reproduced from Maccabee et al. (1991) with permission from Elsevier Scientific Publishers)

electric field intensities produced in and near an intervertebral foramen are more than two times larger than within the vertebral canal. More importantly, the first-order spatial difference of the electric field across the intervertebral foramen is more than 10 times larger than along the vertebral canal. Accordingly, paraspinal magnetic stimulation preferentially excites fibers within the spinal roots/nerves at the intervertebral foramina (Ugawa et al. 1989). Large-intensity electric field components are induced in several neighboring intervertebral foramina simultaneously. Depending on the coil geometry and orientation with respect to the spine, current flow through the left and right foramina of the same intervertebral level can have the same or opposite directions. Moreover, the direction of current flow through the intervertebral foramina along a given side of the spine can change, with null points in between (e.g., circular coil positioned with its center directly over the spine). While the mediolateral orientation of the intervertebral foramina is ideally channeling the induced electric field, locally concentrating the induced current, such “hot spots” for stimulation are not produced at the anterior sacral foramina with their anteroposterior orientation. Stimulation of neural structures within the vertebral canal requires anatomical conditions that considerably influence the first-order spatial difference of the electric field tangential to the fiber paths. Such inhomogeneity arises at the interface between nerve rootlets and the spinal cord, where the electrical conductivity of the volume conductor as well as the spatial orientation of the fibers with respect to the generated electric field changes abruptly.

Paraspinal Transcutaneous Electrical Stimulation

In paraspinal transcutaneous electrical stimulation, a minimum of two electrodes are placed over the body surface with a configuration to produce tissue currents that partially pass the neural target structures. During a stimulation pulse, a potential difference between the electrodes is built up that causes ionic tissue currents to flow from the anode to the cathode. The current flows according to the electrical conductivities of the tissues and spreads due to the repulsive forces

exerted between like charges. The basic principles of the spatial electric field and current distribution generated by paraspinal transcutaneous electrical stimulation are derived from computer models (Ladenbauer et al. 2010; Szava et al. 2011). All currents generated within the volume conductor need to pass the electrode-skin interfaces and flow through several centimeters of low-conductivity tissues to reach the neural targets. High current densities develop directly below the skin electrodes, and less than 10% of the produced current flows through the volume containing the spinal roots and spinal cord. Close to the stimulating electrodes, the current flow is directed perpendicularly to the electrode-skin interface. Most of the current flows around the spine, while some current enters/exits the spine mainly via the soft tissues with better conductivities in a direction perpendicular to the frontal plane. With symmetrically midline-positioned electrodes, current penetration from the sides into the spine is minimal. The current direction within the spine and vertebral canal also depends on the placement of the skin electrodes. With cathode and anode placed longitudinally over the back, most of the current flows tangentially to the spinal cord in the vertebral canal, mainly concentrated in the better-conducting cerebrospinal fluid. Moreover, close to the vertebral levels of the paraspinal cathode and anode positions, currents enter/exit the spine in opposite directions. With one electrode over the back and one anteriorly placed (e.g., over the abdomen), the current enters and exits the spine and the vertebral canal in one direction, mainly perpendicularly to the frontal plane.

The stimulation of deep neural structures is made possible by the inhomogeneities of the electrical tissue properties around and within the spine and the bends of the fiber paths of the target neurons. These anatomical influences considerably reduce the thresholds of some neural structures at localized sites and thus create hot spots for external electrical stimulation. Details and biophysical principles are presented in Minassian et al. (2011) and in the entry ► [“Finite Element Models of Transcutaneous Spinal Cord Stimulation.”](#) Depolarization sites partially depend on the method of electrical stimulation applied, as well as the vertebral level of stimulation. Hot spots for

stimulation predicted by computer modeling are at the interface of the posterior rootlets and the spinal cord (selective stimulation of sensory fibers) and at the distal segments of the posterior and anterior roots close to the intervertebral foramina (Ladenbauer et al. 2010; Danner et al. 2011). In high-voltage stimulation, the most proximal segments of the anterior rootlets at their exits from the spinal cord can be locally targeted as well (de Noordhout et al. 1988).

Two stimulation methods, referred to as “high-voltage (paraspinal) electrical stimulation” and “transcutaneous spinal cord stimulation,” are described. They target different neural structures and differ in the time parameters of stimulation (pulse shape and duration) as well as the spatial arrangement of the stimulating electrodes (size and placement).

High-voltage electrical stimulation was primarily designed for supramaximal stimulation of the motor roots as close to their exits from the spinal cord as possible. It uses stimulators as employed in transcranial electrical stimulation of the motor cortex, where high-intensity pulses are applied to penetrate the cranium. Two stimulators are commonly used, the Digitimer D180 and D185 (Digitimer Ltd., Hertfordshire, England, UK). The D180 produces a spike-like pulse with a very fast rise time of 5 μ s and a decay constant of either 50 μ s or 100 μ s and has a maximal output of 750 V (Fig. 2b). The D185 produces a rectangular-like pulse of 50- μ s width and has a maximal output of 1000 V (Fig. 2c). Stimuli are delivered through electrodes with active areas of the cathode smaller than 1 cm². With a midline-positioned cathode over the target vertebral level, the anode can be positioned 2–3 vertebral segments rostrally (“conventional longitudinal median montage,” Rossini et al. 1994; Troni et al. 1996). More distant anodes, e.g., over the abdomen (“dorsoventral montage,” Troni et al. 1996) in the stimulation of lumbosacral roots, produce responses at lower intensities.

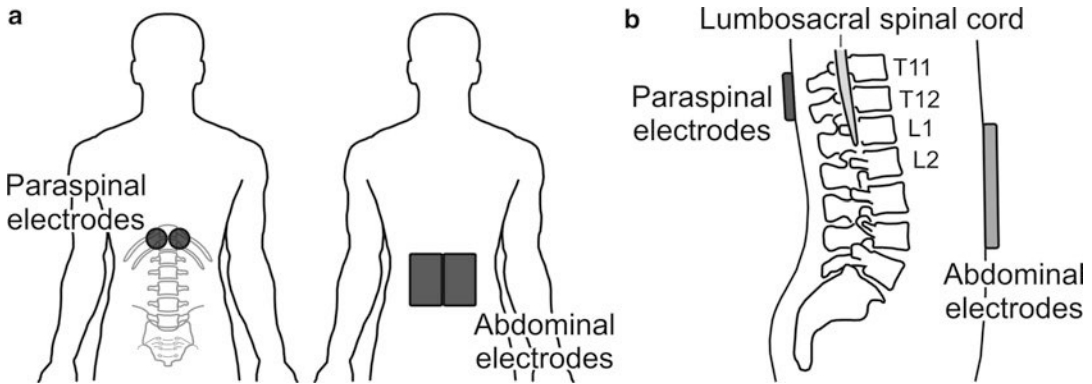
Transcutaneous spinal cord stimulation was designed to noninvasively stimulate similar sensory structures as with epidural implants over the lumbar spinal cord (Minassian et al. 2007; Ladenbauer et al. 2010). It uses equipment similar to that in functional electrical stimulation (FES) of

paralyzed muscles or in therapeutic transcutaneous electrical nerve stimulation (TENS). By using skin electrodes with large surface areas and applying longer pulse widths (Fig. 2d, e), the thresholds of the targeted neural structures are considerably reduced. This allows using conventional stimulators for continuous stimulation at a fixed frequency for a longer period of time. Stimulators that produce maximum stimulus intensities of 60–100 V (voltage-controlled stimulators) or 120–200 mA (current-controlled stimulators) are appropriate. The large electrodes and moderate stimulation intensities further reduce discomfort (Roy et al. 2012). When stimulation is applied in a continuous mode for neuromodulation applications, the output must be charge balanced to reduce the likelihood of skin damage or irritation. The electrode setups utilize paraspinally placed stimulating electrodes and anteriorly placed reference electrodes. The method described in Minassian et al. (2007) uses a pair of round electrodes (diameter 5 cm) over the paraspinal skin with a pair of rectangular reference electrodes (8 $\times$ 13 cm each) covering the lower abdomen (Fig. 4). The exact electrode dimensions are not essential, yet relatively large reference electrodes ensure a stronger stimulating effect over the spine. Symmetrical, biphasic rectangular pulses (1 ms width per phase) delivered by a constant-voltage stimulator require low stimulus intensities. The paraspinal electrodes act as cathode when the polarity of the biphasic stimulus pulse is changed at the edge between its first and second phase (Fig. 2e), and neural elements are stimulated at this abrupt change of polarity. Alternative stimulation setups use reference electrodes placed over the iliac crests (Dy et al. 2010; Roy et al. 2012). For further details, see Minassian et al. (2011).

Stimulated Neural Structures, Site of Excitation, and Evoked Muscle Responses

Paraspinal Magnetic Stimulation

Magnetic stimulation over the cervical and lumbar spinal cord normally excites motor fibers within the anterior roots/spinal nerves at the intervertebral foramina (Ugawa et al. 1989). The



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 4 Transcutaneous spinal cord stimulation. (a) Drawings of the stimulation and reference

electrodes over the back and abdomen, respectively, and (b) of their positions with respect to the spine and spinal cord

evoked responses, recorded with surface electrodes as compound muscle action potentials (CMAPs) from the respective muscles, are hence M-waves. The onset latencies of these M-waves are shorter than the total peripheral motor conduction time by the segment from the anterior horn cells to the intervertebral foramen. These onset latencies remain constant when moving the coil over the spine for some centimeters in rostral or caudal direction to the lowest-threshold site. Only with maximum stimulation, the sites of excitation along the motor fibers may migrate distally beyond the intervertebral foramina. Paraspinal magnetic stimulation does not allow for reliable supramaximal stimulation. Maximum attainable response amplitudes range from 10% to 90% of the maximal peripheral nerve M-wave. Large-amplitude responses cannot be obtained simultaneously in multiple muscles of a limb from a single stimulation site. Custom-made, large circular coils can be used to overcome some of these limitations (Matsumoto et al. 2009a). M-waves in response to magnetic stimulation over the cervical-thoracic spine are described in various C5-T1 innervated muscles of the shoulder (deltoid), arm (biceps, brachioradialis, extensor digitorum), and hand (thenar and hypothenar muscle groups). These responses have the lowest thresholds and are largest when the secondary tissue current is directed over the intervertebral foramina of the target motor roots and flows from

the midline toward the side. Such stimulation favors unilateral excitation (Mills et al. 1993). For details on coil placements, see Ugawa et al. (1989), Mills et al. (1993), Rossini et al. (1994), and Sandbrink (2008). Stimulation over the mid-thoracic spine (T7-T9) evokes M-waves in the abdominal and intercostal muscles (Chokroverty et al. 1995). Magnetic stimulation over the lumbosacral spine elicits M-waves in the muscles of the upper and lower leg and the foot (e.g., quadriceps femoris, tibialis anterior, gastrocnemius, extensor digitorum brevis, flexor hallucis brevis, and abductor hallucis). For stimulating lumbar roots exiting the spine through the intervertebral foramina, the induced current can be concentrated through these hot spots of stimulation when oriented from side to side, and motor fibers are activated at the most distal portion of the cauda equina. The situation is different for muscles with motor roots exiting from the anterior sacral foramina. With the coil held over the sacral bone, the sacral roots are stimulated in the most distal portion of the cauda equina, as suggested by the very short onset latencies of the M-waves, but the exact site of stimulation is not completely clear (Maccabee et al. 2011). For details, see Ugawa et al. (1989) and Maccabee et al. (1996).

A second localized activation site of the motor fibers is within the vertebral canal at the interface between the spinal cord and the anterior rootlets. Activation at these proximal sites is reported for

magnetic stimulation over the lumbosacral spinal cord and requires large coils and the induced tissue currents to be directed rostrally (Maccabee et al. 1996, 2011; Matsumoto et al. 2009b). Thresholds at these proximal hot spots are higher than those at the intervertebral foramina. M-waves elicited proximally are similar in appearance to those elicited in the distal cauda equina, but the onset latencies are longer by 1.9 ms for the vastus medialis, 2.3 ms for the tibialis anterior, and 3.5 ms for the abductor hallucis (Maccabee et al. 1996). The straight, relatively long intrathecal segments of the lumbosacral motor fibers between their two low-threshold sites are normally not activated by magnetic stimulation.

Apart from the M-wave, a second type of muscle response can be evoked by magnetic stimulation, i.e., a CMAP constituted of two partially superimposed response components, an M-wave and a later response with electrophysiological characteristics similar to the H-reflex (Maccabee et al. 1996). Such composite responses are only evoked in few lower limb muscles and with stimulation over the distal cauda equina. The H-reflex is a monosynaptic reflex usually initiated by the electrical stimulation of Ia afferent fibers from muscle spindles at the posterior knee and recorded from the soleus muscle. A “pure” H-reflex without contamination by a preceding M-wave is normally not obtained by magnetic stimulation.

There is no evidence for the direct electrical stimulation of neural structures within the spinal cord white or gray matter by magnetic coils. Paresthesias (tingling sensations) or motor responses in the lower limbs are not evoked with magnetic stimulation over the cervical-thoracic spine (Ugawa et al. 1989). Thus, stimulation of myelinated, large-diameter, and relatively superficially located fibers within long tracts of the spinal cord white matter does not occur. It is estimated that a sevenfold increase of the maximum output of conventional magnetic stimulators would be required for their excitation (Maccabee et al. 1991). Consequently, the direct electrical stimulation of the spinal cord gray matter interneurons or neural networks, which would require even higher thresholds, is considered impossible.

High-Voltage Electrical Stimulation

The principal neural targets of high-voltage paraspinal electrical stimulation are the motor roots, and the evoked responses are M-waves (Rossini et al. 1994). Midline-positioned electrodes activate muscles bilaterally and symmetrically (i.e., at similar thresholds). High-voltage electrical stimulation over the cervical spine excites motor fibers innervating the upper limb muscles. The site of excitation is within the anterior roots/spinal nerves close to the respective intervertebral foramina, estimated 2–4 cm distal to the anterior horn cells (Mills and Murray 1986). The latencies of the M-waves evoked in the upper limb are about 1.2–1.6 ms shorter than the total peripheral motor conduction time (Mills and Murray 1986; Rossini et al. 1994). At moderate stimulus intensities, the response latencies remain unchanged when moving the electrode in vertical or horizontal direction for several centimeters. With the cathode over the T1 vertebra and the anode over the C5 vertebra, all motor roots to the upper limb muscles are recruited (Rossini et al. 1994). A more selective stimulation is achieved by placing the cathode over the vertebra of the corresponding exit level of the target motor root, with a distant anode over the contralateral shoulder (Ugawa et al. 1989). High-voltage electrical stimulation over the cervical enlargement allows for supramaximal stimulation of the cervical motor roots, with maximum upper limb muscle responses at 250–300 V.

For stimulation over the lumbosacral spine, two low-threshold sites for the activation of the motor fibers can be distinguished. Cathodes over T11-L1 vertebral levels, corresponding to the level of the lumbosacral spinal cord, excite the motor fibers within the anterior rootlets at their exits from the spinal cord (de Noordhout et al. 1988; Troni et al. 2011). Cathodes over L3-S1 vertebral levels activate the anterior roots/spinal nerves close to the respective intervertebral foramina (de Noordhout et al. 1988). At very strong stimulus intensities, the motor roots may be activated at some site in between these low-threshold sites (de Noordhout et al. 1988). M-waves in the lower limbs have similar CMAP shapes when elicited from both low-threshold

sites, but with the more distal stimulation, the onset latencies decrease by 1.4 ± 0.6 ms for the quadriceps, 2.4 ± 1.2 ms for the tibialis anterior, and 3.0 ± 1.0 ms for the extensor digitorum brevis (de Noordhout et al. 1988). With the cathode placed midline over the spine and the anode over the contralateral iliac crest, threshold intensities for CMAPs elicited in the lower limb muscles range from 225 to 450 V, and maximum responses are obtained at 450–600 V (de Noordhout et al. 1988; Ugawa et al. 1989). A single stimulus pulse applied from a fixed stimulation site can generate simultaneous supramaximal stimulation of the L3-S1 motor roots when using a dorsoventral montage (Troni et al. 2011).

Both a direct M-wave and a later response similar to the H-reflex can be evoked in the soleus by high-voltage electrical stimulation over the T11-S1 vertebral levels (de Noordhout et al. 1988; Troni et al. 1996), hinting on the activation of large-diameter proprioceptive fibers in addition to motoneuron axons. The difference between the M-wave and reflex-response latencies is 1.2 ± 0.2 ms for stimulation over the lumbosacral spinal cord and 5.4 ± 0.9 ms for stimulation of the distal cauda equina (Troni et al. 1996). With the elicitation of maximal M-waves, the reflex component is canceled.

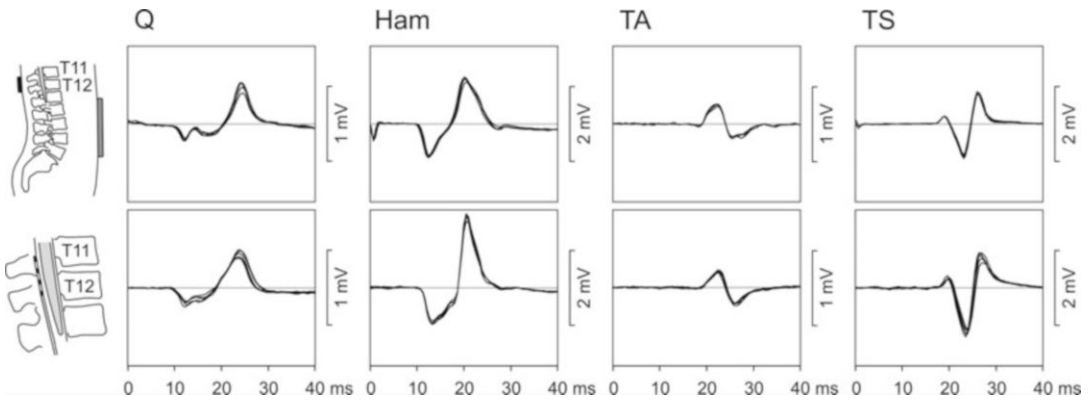
Maximal high-voltage electrical stimulation over the cervical-thoracic spine evokes low-amplitude responses in some lower limb muscles innervated by distant lumbar and upper sacral spinal cord segments (Mills and Murray 1986; Taylor and Gandevia 2004). In the relaxed muscle, they normally attain amplitudes $<10\%$ of the maximum M-wave evoked by electrical peripheral nerve stimulation. The thresholds of these responses are 300–750 V and are always higher than those of the M-waves evoked by the stimulation of the nearby spinal nerves. The distant responses result from the electrical stimulation of descending corticospinal tracts of the spinal cord white matter and the transsynaptic activation of lumbosacral motoneurons innervating the lower limb muscles. They are thus motor-evoked potentials and due to the stimulation of similar populations of corticospinal axons as activated by transcranial stimulation of the motor cortex

(Martin et al. 2008). The exact site of stimulation along the corticospinal axons below the stimulating paraspinal electrodes is not defined.

Transcutaneous Spinal Cord Stimulation

The targeted neural structures of transcutaneous spinal cord stimulation are sensory fibers projecting into the spinal cord. For stimulation over the T11-T12 spinous processes, overlying the lumbar spinal cord, the low-threshold sites are at the entries of the posterior rootlets into the spinal cord (Minassian et al. 2011). The evoked responses result from the electrical stimulation of Ia muscle spindle afferents and the subsequent monosynaptic activation of motor fibers innervating the lower limb muscles. According to their initiation and recording sites, they were termed posterior root-muscle (PRM) reflexes (Minassian et al. 2007). Alternative terminologies were suggested (Dy et al. 2010; Roy et al. 2012). A single pulse can consistently activate L2-S2 posterior root fibers bilaterally and thus evoke PRM reflexes in essentially all lower limb muscles simultaneously. Transcutaneous spinal cord stimulation thus activates similar populations of sensory fibers as stimulation through epidural implants over the lumbar spinal cord (Fig. 5).

PRM reflexes have some electrophysiological similarities with the H-reflex (Minassian et al. 2011). They are enhanced by background voluntary activation of the target muscle and suppressed by contraction of the antagonist muscles or vibration applied on the tendons of the lower limbs. They are further characterized by excitability changes lasting up to 10 s following a prior stimulus. The simultaneous stimulation of multiple posterior roots results in transsynaptic effects other than (homonymous) monosynaptic excitation that may influence the PRM reflex of the target muscle, particularly when repetitively elicited in close succession (Minassian et al. 2011; Roy et al. 2012). Onset latencies of PRM reflexes to single pulses applied at incremental intensities to the lumbar spinal cord stay invariant and amount to 10.3 ± 1.1 ms for the quadriceps, 11.2 ± 0.4 ms for the hamstrings, 19.1 ± 0.9 ms for the tibialis anterior, and 19.7 ± 1.1 ms for the triceps surae (Minassian



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 5 Posterior root-muscle (PRM) reflexes evoked by transcutaneous and epidural spinal cord stimulation in the quadriceps (Q), hamstrings (Ham), tibialis anterior (TA), and triceps surae (TS) in a single incomplete spinal cord-injured individual. The

similarities of PRM reflexes elicited by either technique imply that transcutaneous stimulation depolarizes (a subset of) the same neural structures as activated by implanted epidural electrodes. (For details, see Ladenbauer et al. 2010; Minassian et al. 2011)

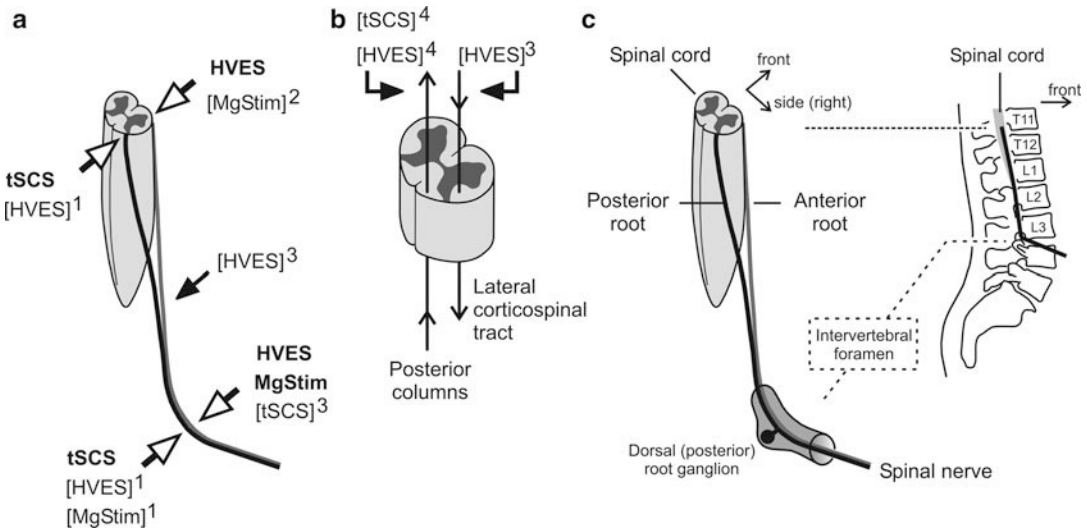
et al. 2007). Thresholds for eliciting PRM reflexes depend on the pulses applied (mono- or biphasic and their polarities), the individual physique, and the body position (e.g., supine or standing) and range from 20 to 40 V or 40 to 120 mA. The preferential activation of sensory roots minimizes an occlusion of the PRM reflex caused by antidromic volleys in the motor roots. Maximum PRM reflexes may attain amplitudes of up to 76% of the corresponding maximum M-wave (Kitano and Kocejka 2009) and depend on the excitability of the monosynaptic reflex in the target muscle (Roy et al. 2012).

Stimulation over the cauda equina (e.g., at L4-L5 vertebral levels) at incremental intensities results in a characteristic sequence of PRM reflex and M-wave elicitation, similar to the recruitment of sensory and motor fibers by stimulation of a mixed peripheral nerve (Minassian et al. 2007, 2011). Activation sites are at the intervertebral foramina, where posterior and anterior roots approach each other to form the spinal nerve. M-waves only are elicited in muscles innervated by the upper lumbar roots, e.g., quadriceps, that exit the spine rostral to such stimulation site. At threshold intensity, PRM reflex latencies are 13.3 ± 1.0 ms for the hamstrings, 21.1 ± 1.0 ms for the tibialis anterior, and 21.3 ± 1.1 ms for the triceps surae (Minassian et al. 2007). For

stimulation sites between the T11-T12 vertebrae and the distal cauda equina, M-wave and reflex contributions to the evoked composite CMAPs vary, depending on the position of the cathode along the lumbar spine (Roy et al. 2012).

Continuous transcutaneous stimulation (e.g., 30 Hz) over the T11-T12 vertebral levels produces paresthesias in the lower limb dermatomes (Hofstoetter et al. 2013b) that are normally associated with the stimulation of ascending sensory fiber branches within the posterior columns of the spinal cord white matter. The direct stimulation of the posterior columns is further suggested by the distribution of the paresthesias when graded stimulation is applied; with electrode placements evoking muscle responses in L2-L4 myotomes at threshold intensity, paresthesias are often produced in the L5-S2 dermatomes first. Yet computer simulations suggest that posterior column fibers have considerably higher thresholds than posterior root fibers; see Danner et al. (2011) and the entry ► “Finite Element Models of Transcutaneous Spinal Cord Stimulation.” Alternatively, the paresthesias can be explained by the stimulation of fibers from cutaneous receptors within the posterior roots as well.

Figure 6 summarizes the stimulated neural structures and their excitation sites for paraspinal magnetic and electrical stimulation.



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 6 Summary of neural structures directly stimulated by paraspinal magnetic (*MgStim*), high-voltage paraspinal electrical (*HVES*), and transcutaneous spinal cord stimulation (*tSCS*), respectively. Stimulation of (a) spinal root fibers and (b) long-tract fibers of the spinal cord white matter. Methods given in brackets indicate that stimulation is effective under specific conditions:

(1) reported in few muscles only, (2) only effective with specific magnetic coils and tissue current directions, (3) only with maximal stimulation intensities, and (4) not unequivocally demonstrated. *Open arrowheads* mark low-threshold sites of stimulation. (c) Drawing of the relevant anatomical structures; separation of the roots into several rootlets before entering the spinal cord is not illustrated

Applications

Lower Motoneuron Stimulation

Functional Assessment of the Cauda Equina and the Motor Root Conduction Time

One of the main clinical applications of paraspinal magnetic or high-voltage electrical stimulation is the neurodiagnostic assessment of the functional integrity of deeply located peripheral motor fibers. Within the cauda equina, the most proximal segments of the motor fibers can be affected by focal lesions caused by mechanical impacts to the spinal roots or root compressions. They are also involved in demyelinating peripheral neuropathies, with a degeneration of the myelin sheaths that slows down or completely blocks the conduction of action potentials. A method to assess the cauda equina is by the evaluation of the motor root conduction time (MRCT). The MRCT is calculated as the difference between the total peripheral motor conduction time (PMCT) and the latency of

the CMAP evoked by conventional paraspinal magnetic stimulation. The total PMCT is estimated by the F-wave method; for details, see Rossini et al. (1994) and Sandbrink (2008). The MRCT is the conduction time between the anterior horn cells and the actual site of activation of the motor fibers by paraspinal stimulation at the intervertebral foramen. Given a focal spinal root lesion, this neural excitation site would be distal to the affected segment of the motor fiber, and the latency of the CMAP would be normal, while the total PMCT would be delayed. The applicability of this method relies on the presence of F-waves and is therefore limited to a few distal muscles.

Alternatively, the lumbosacral MRCT can be estimated by paraspinal stimulation of the motor fibers at their two low-threshold sites, i.e., within the proximal and distal cauda equina, respectively. Large circular (Matsumoto et al. 2009b) and figure-8 (Maccabee et al. 1996) magnetic coils (both not commonly used in clinical practice), as well as high-voltage electrical stimulation

(de Noordhout et al. 1988), can activate the most proximal segments of the motor fibers at their origin from the spinal cord and their more distal portions at the cauda equina. The difference between the proximal and distal response latencies is the MRCT (or cauda equina conduction time, CECT; Maccabee et al. 2011). The CECT can be calculated for several roots simultaneously when recording CMAPs from multiple lower limb muscles. The total PMCT can be broken up into separate segments, including the cauda equina, upper leg, and lower leg conduction times (Maccabee et al. 2011). Axonal and (subtypes of) demyelinating neuropathies can be differentiated depending on the contributions of proximal or distal axon segments to the slowing of conduction. Axonal neuropathy involves degeneration of the entire axon rather than of the myelin sheath around the axon only, with the degeneration usually advancing from the axon's most distal portions toward the cell body.

The detection of cauda equina lesions and conduction blocks based on the measurement of the CMAP amplitude or area requires a technique providing for supramaximal stimulation, a criterion not fulfilled by conventional magnetic stimulation. High-voltage paraspinal electrical stimulation ensures supramaximal activation and can activate motor fibers within the anterior rootlets at their origin from the spinal cord, allowing for the exploration of the complete proximal nerve tract. The discomfort induced by high-voltage electrical stimulation is described as acceptable to excessive.

The cervical spinal nerves in the vertebral canal are short, and their conduction times have limited relevance for clinical diagnostics. The cervical MRCT can be calculated based on F-wave latencies and the response to paraspinal stimulation over the respective intervertebral foramina. Magnetic stimulation over the cervical and thoracic spine may be useful in the study of other deeply located nerves, such as the phrenic nerve and thoracic spinal nerves for the evaluation of nerve conduction velocity of the respiratory muscles. For details, see Rossini et al. (1994), Di Lazzaro and Oliviero (2005), and Sandbrink (2008).

Central Motor Conduction Time

Paraspinal stimulation combined with transcranial stimulation is used to calculate the conduction time in the fastest propagating central motor axons (i.e., axons of the upper motoneurons of the corticospinal tracts). Motor-evoked potentials (MEPs) elicited by transcranial stimulation of the motor cortex and electromyographically recorded from the target muscles provide for a noninvasive assessment of neurological disorders with upper motoneuron involvement. In clinical routine, the most important MEP parameter is the central motor conduction time (CMCT). The CMCT is the central component of the total MEP latency, i.e., the time from the stimulation of the cortex to the transsynaptic activation of the spinal motoneurons. The CMCT is obtained by subtracting the PMCT from the total MEP latency. The PMCT is estimated either by F-wave measurements or by paraspinal stimulation of the motor roots. For routine applications of motor root stimulation, many laboratories use conventional paraspinal magnetic stimulation. Since this method activates the motor roots in the region of the intervertebral foramen, the $CMCT_{mgn}$ calculated includes the conduction time along the anterior root and is estimated as too long (by 0.5–1.4 ms for cervical root stimulation and 3.0–4.1 ms for lumbosacral root stimulation; Sandbrink 2008). MEPs and the measurement of the CMCT can document corticospinal-tract involvement in patients with clinically evident upper motoneuron lesions. Further, the method may detect subclinical lesions, i.e., changes of the conduction properties of the corticospinal tract prior to clear clinical signs. Prolongation of the CMCT occurs with demyelination of the corticospinal fibers that contribute to the MEP, as in multiple sclerosis or segmental demyelination due to mechanical compression of the spinal cord (spondylosis or disk herniation). When recording from multiple muscles associated with different spinal cord segmental levels, the method may help identify the (rostrocaudal) location of a spinal cord lesion as well as assess mixed conus-cauda injuries. For further information, see Di Lazzaro and Oliviero (2005) and Sandbrink (2008).

Intraoperative Neuromonitoring

Nerve root damage is a potential neurological complication in lumbosacral spine surgery. High-voltage electrical stimulation of the proximal cauda equina can be applied to survey nerve root function during such surgery and to prevent potential damage to the nervous system. The principle is to provide for early detection of a nerve injury in an acute yet reversible state, hence allowing for immediate corrective procedures during surgery. During brief suspensions of the surgical procedure, single pulses are applied to produce supramaximal stimulation of the lumbosacral motor roots above the level of the surgical procedure. CMAPs are recorded from several muscles bilaterally innervated by L2-S2 spinal roots. Potential mechanical stress on the roots is immediately detected as a transient reduction of the CMAP amplitude in the respective muscles, caused by a conduction failure in the manipulated root. The technique is described in anesthetized patients undergoing lumbosacral surgery in degenerative spinal diseases (Troni et al. 2013).

Functional Magnetic Stimulation (FMS)

FMS produces patterned muscle contractions for useful bodily functions in people with upper motoneuron dysfunction. To this end, FMS applies timed, short sequences of repetitive magnetic stimulation (e.g., bursts of 25-Hz stimulation for 2 s) to the respective lower motoneurons. When the spinal cord is damaged, muscles below the level of the injury become (partially) paralyzed. Such paralysis does not only impede the ability to move but normally also affect the respiratory muscles, the gastrointestinal tract, and the bladder. Major muscles of inspiration include the diaphragm (primarily innervated by the phrenic nerve formed from the cervical nerves C3-C5), the parasternal muscles, and the external intercostal muscles (T1-T6 spinal nerves). Major muscles of expiration include the abdominal muscles (T7-L1 spinal nerves) and the internal intercostal muscles. Thus, with levels of injury from T12 to more rostral vertebrae, there is a progressive loss of respiratory motor function, with impairment of expiration and cough, further impairment of inspiratory and expiratory

function, and weakened respiration to the point at which ventilation cannot be self-sustained. FMS can be applied over the appropriate vertebral levels and to the respective motor roots to generate inspired and expired pressures. FMS of the cervical and upper thoracic nerves produces inspired volume and pressure and may be useful for enhancing inspiratory function and muscle conditioning. Similarly, FMS of the lower thoracic nerves produces expired volume and pressure and can be effective for simulating or restoring cough. An important advantage of FMS is that expiratory muscle activation can be achieved noninvasively. For limitations of the technique, see DiMarco (2005). Additional clinical applications of FMS include the stimulation of the sacral nerves for enhancing micturition and defecation function in selected spinal cord-injured persons with neurogenic bladder and bowel. For details on FMS as a therapeutic tool, see Lin and Hsiao (2005).

Corticospinal-Tract Stimulation

Evaluation of Corticospinal-Tract Function

The clinical value of high-voltage paraspinal electrical stimulation of corticospinal axons as a neurodiagnostic method is unclear. In principle, transcranial magnetic stimulation over the motor cortex together with high-voltage paraspinal stimulation at different vertebral levels may help localize alterations of the conduction properties along the fastest descending corticospinal axons and define the level of a spinal cord lesion. However, the technique does not allow for supramaximal activation, and the exact site of stimulation of the corticospinal tract below the paraspinal electrodes is not clear. Furthermore, with low-thoracic and more caudal stimulation sites, antidromic volleys within the posterior columns may add to the evoked response (Zidar 2001).

Human Motor Control Studies

High-voltage paraspinal stimulation of corticospinal axons may provide a measure of motoneuronal excitability for studying motor control of the lower limbs. The evoked responses are modulated in amplitude by volitional motor tasks

(Martin et al. 2008). These modifications provide information on the synaptic inputs onto the target motoneuron pools at the level of the spinal cord. The role of the corticospinal pathway in human motor control is normally investigated by transcranial magnetic stimulation over the motor cortex to evoke MEPs. Modulations of transcranially evoked MEPs during motor tasks can result from excitability changes within the motor cortex as well as at spinal cord segmental levels. In combination with transcranial magnetic stimulation, paraspinal stimulation may help identify changes of excitability at the motor cortex by providing a control for changes occurring at the lumbosacral segmental level (Martin et al. 2008).

Posterior Root Stimulation

Human Motor Control Studies

The H-reflex is a major noninvasive tool in human motor control studies. Due to the monosynaptic connections of Ia muscle spindle afferents to motoneurons, the H-reflex can be used to investigate excitability changes of the motoneuron pool supplied by the stimulated nerve. Transcutaneous posterior root stimulation extends H-reflex studies of a single muscle to the simultaneous assessment of monosynaptic reflexes at multiple lumbosacral segmental levels. This is relevant because motor control is organized multisegmentally, involving many muscles with state- and dynamic phase-dependent changes of their functional roles. Furthermore, posterior root stimulation can elicit monosynaptic reflexes in muscles that cannot be investigated by conventional peripheral nerve stimulation. PRM reflex modifications by motor tasks and passive movements were described in supine and standing positions and during treadmill stepping in subjects with intact nervous system as well as spinal cord injury (Minassian et al. 2007; Hofstoetter et al. 2008; Dy et al. 2010). For further details, see Minassian et al. (2011) and Roy et al. (2012).

Neuromodulation Applications

Neuromodulation therapies aim at improving functions in people with neurological disorders by continuous electrical or neuropharmacological

stimulation of specific neural networks of the central nervous system. Electrical stimulation methods in movement disorders, such as deep brain stimulation or epidural spinal cord stimulation, utilize electrodes implanted close to the input structures to the target neural networks. For the enhancement of motor control of the lower limbs by epidural spinal cord stimulation, local locomotor networks within the lumbar spinal cord are the natural targets. These networks are involved in the control of muscle tone, can execute stereotyped lower limb movements, and may remain functional below a severe damage to the spinal cord. Epidural lumbar spinal cord stimulation can control spinal spasticity (Dimitrijevic et al. 1986; Pinter et al. 2000), generate sustained extension (Jilge et al. 2004) and automatic flexion-extension movements of paralyzed lower limbs (Dimitrijevic et al. 1998; Minassian et al. 2004), facilitate task-specific training in clinically motor complete Harkema et al. 2011 and incomplete (Herman et al. 2002) spinal cord-injured individuals, and enhance endurance in people with residual walking capabilities (Huang et al. 2006). In many applications, the effects temporarily persist after the stimulation has been interrupted. For a review, see Minassian et al. (2012). Epidural lumbar spinal cord stimulation does not activate the locomotor networks directly but transsynaptically through large-diameter sensory fibers, predominantly within the posterior roots.

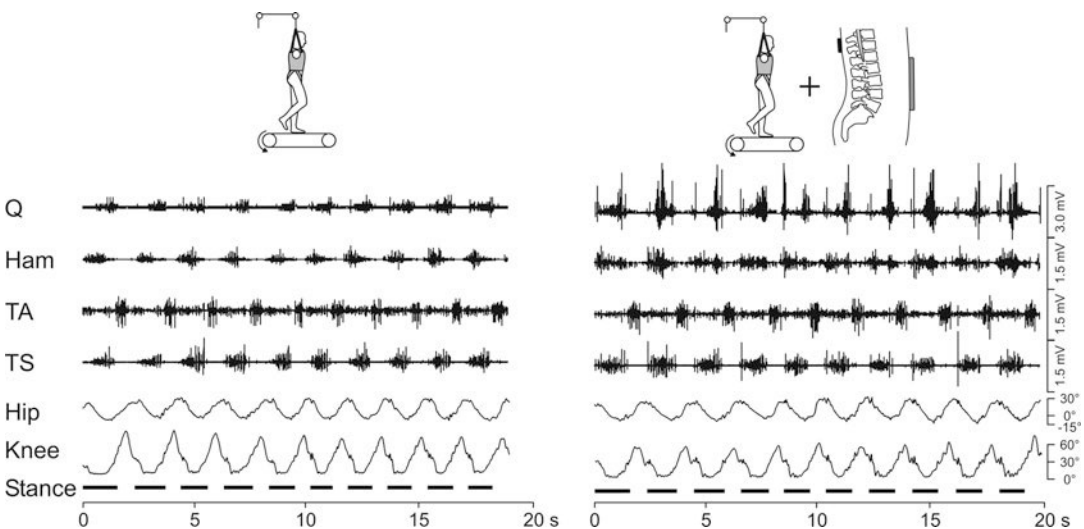
The consistent stimulation of these input structures also by transcutaneous spinal cord stimulation allows for its application as a neuromodulation method. When continuously applied, e.g., at a frequency of 30 Hz or 50 Hz, a “tonic drive” can be provided to the spinal cord below a lesion. Therapeutic applications of such tonic transcutaneous stimulation to alleviate spinal spasticity and enhance neural control of locomotion after spinal cord injury are being investigated (Minassian et al. 2011, 2012; Hofstoetter et al. 2013a, b). For the temporary modification of lower limb spasticity, 50-Hz stimulation is applied for 30 min in a supine position. The intensity is below the threshold for PRM reflexes but produces paresthesias in the lower limbs in individuals with remaining sensory

functions. Various manifestations of lower limb spasticity, such as clonus, spasms, and increased muscle tone, are modified after stimulation without loss of residual voluntary control (Hofstoetter et al. 2013b). During assisted, body-weight-supported treadmill stepping, continuous stimulation (e.g., 30 Hz) above the threshold for PRM reflexes has several effects in motor complete spinal cord-injured individuals, including suppression of clonus-like activities, augmentation of EMG activities of the paralyzed lower limb muscles generated by passive treadmill stepping, and generation of stereotyped, rhythmic EMG patterns not linked to the externally imposed gait cycle (Minassian et al. 2012). In motor incomplete spinal cord-injured persons performing active treadmill stepping, tonic transcutaneous stimulation at a sub-motor threshold level, producing paresthesias in the lower limb dermatomes, can immediately modify the voluntarily generated lower limb activities in a gait-phase appropriate way (Fig. 7). Augmented yet consciously controlled muscle activity may also lead to changes of the step kinematics, mainly to increase

maximum hip flexion angles and changes in stride length (Hofstoetter et al. 2013a). Further, 15-Hz stimulation can generate bilateral lower limb extension appropriate to produce a standing-up movement in spinal cord-injured people. As an assessment method, tonic transcutaneous posterior root stimulation may provide information on the altered physiology of spinal cord neural networks and can be complementary to the assessment via fast- and slow-conducting descending pathways.

Further Applications

Applications of paraspinal stimulation were described with evident neuromodulative effects but with the directly activated neural structures and the resulting physiological effects remaining speculative. Repetitive magnetic stimulation over the thoracic and lumbar spine reduces motoneuron excitability and spastic muscle tone in patients with spinal lesions (Nielsen and Sinkjaer 1997; Krause et al. 2004). Anodal direct current



Paraspinal Magnetic and Transcutaneous Electrical Stimulation, Fig. 7 Volitional treadmill stepping at 2 km/h of an incomplete spinal cord-injured person without and during the application of 30-Hz transcutaneous lumbar spinal cord stimulation. Electromyographic activities of the right quadriceps (*Q*), hamstrings (*Ham*), tibialis anterior (*TA*), and triceps surae (*TS*) along with goniometer

recordings of hip and knee angles and stance-phase markers. No manual assistance and body weight support provided. Stimulation was applied over the T11-T12 spinous processes at 27 V, an intensity generating paresthesias in the lower limb dermatomes without eliciting PRM reflexes

stimulation over the thoracic spine at 2–2.5 mA for 15–20 min modulates the excitability of central pain pathways in individuals with intact nervous system (Cogiamanian et al. 2011) and modifies spinal reflex activities in motor complete spinal cord-injured people (Hubli et al. 2013).

Cross-References

- [Finite Element Modeling for Extracellular Stimulation](#)
- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)
- [General Overview of Spinal Anatomy and Physiology Organization](#)

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Paravertebral Electrical Stimulation

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)

Paravertebral Neuromagnetic Stimulation

- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Parkinson's Disease: Deep Brain Stimulation

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Synonyms

[Chronic electrical stimulation](#); [Deep brain stimulation](#); [High-frequency stimulation](#); [Idiopathic Parkinson's disease](#); [Neuromodulation](#); [Paralysis agitans](#); [Shaking palsy](#)

Definition

Chronic electrical stimulation also called deep brain stimulation (DBS) of specific nuclei in the basal ganglia is currently used to treat patients with movement disorders related to Parkinson's disease (PD). This entry reviews the clinical uses of, and mechanisms of, DBS to treat symptoms developed by patients with PD. The hope is that computational studies will lead to the development of better stimulation protocols which have better efficacy and involve DBS closed-loop stimulators external batteries.

Detailed Description

Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative disease. The median age-standardized annual incidence rates within high-income countries of PD is 14 per 100,000 people in the total population and 160 per 100,000 people aged 65 years or older (Hirtz et al. 2007). Males than females after the age of 60 years have a higher incidence (Taylor et al. 2007). The prevalence rates have shown steady age-related increase, shifting from 41 per 100,000 in the 40–49 age group to 1903 per 100,000 in people

older than age 80 (Pringsheim et al. 2014). PD incidence and prevalence are expected to grow over the next decades because of increasing efforts at extending the life span. Among the chronic disorders, PD is also considered one of the most difficult and challenging syndromes, and it substantially increases caregiver burden (Hassan et al. 2012).

This condition produces a wide variety of axial and distal manifestations that develop progressively. By the time the manifestations are noticed, around 70–80% of the pigmented dopaminergic neurons of the substantia nigra pars compacta located in the midbrain have already degenerated. As will be discussed below, the exact origin of the disease is still unknown. There is no known cure for PD.

Motor manifestations begin very gradually and include voice changes, tremor of extremities (unilaterally and then bilaterally which usually decreases during voluntary movement), tremor of the face, abnormal posture/gait (stooped posture, shuffling gait, falls, and freezing of gait), stiffness/rigidity/difficulty moving (with less amplitude of movement), bradykinesia, muscular weakness, and poor balance and coordination in most patients. Other motor features may include micrographia, a masklike face expression, and reduced eye blinks. Initially these manifestations usually affect one side of the body more than the other. Not all motor manifestations are present in a specific patient. Non-motor manifestations affect domains such as psychiatric/cognitive (anxiety, depression, fatigue, hallucination, impaired memory/concentration, sleep disturbance, etc.) but also autonomic (drenching sweats, dyspnea, orthostatic hypotension, sexual dysfunction, seborrhea, constipation, bladder symptoms) and sensory/pain (sensory disturbance, olfactory deficit) in most patients.

Parkinson's disease dementia (PDD) is one of the non-motor complications of Parkinson's disease that can occur in approximately 10% of PD patients (Emre et al. 2007). The symptoms are widely variable, but generally it is characterized by impairment of visuospatial and executive functions. PDD is often complicated by many neuropsychiatric symptoms such as mood disturbances,

apathy, and psychosis (Garcia-Ptacek and Kramberger 2016).

Dementia occurs with PD progression and there are currently limited treatment options (Deeb et al. 2018).

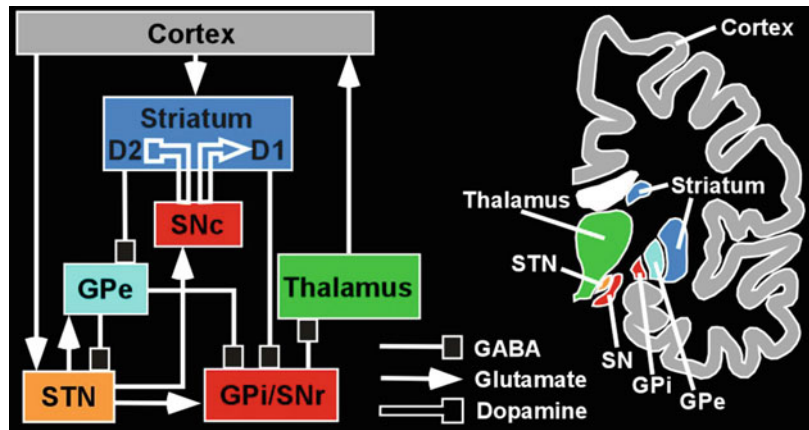
The prevalence of dementia in PD ranges from 20% to 40%. The PD phenotype presents pronounced variations across patients (Litvak et al. 2011).

The large spectrum of motor and non-motor manifestations listed above reflects multiple abnormal rhythms occurring in a large brain network of inhibitory and excitatory connections affected by the disease and involving the basal ganglia, thalamus, and cortex. Indeed, excessive synchronous activity throughout a corticobasal ganglia-thalamocortical network regulating the flow of information between the cortex and the spinal cord appears to be the hallmark of PD (McIntyre et al. 2004; Fig. 1). Furthermore, PD is not limited to the degeneration of the nigrostriatal dopamine system but is a widespread process involving multiple brain systems and neurotransmitters such as noradrenaline, serotonin, and acetylcholine.

Detailed Description of Parkinson's Syndrome

James Parkinson, a family physician in London, first described a “shaking palsy” or “paralysis agitans” in 1817 (Parkinson, see republication in 2002). During the nineteenth century, the disease was renamed Parkinson's disease by Charcot. In 1912, the presence of intracellular inclusion of Lewy bodies in brain cells of patients during postmortem examination was associated with PD. In 1917, the key role of a nucleus of the basal ganglia, i.e., the substantia nigra (pars compacta) in PD, was first described. Around 1959, the link between the presence of PD and the depletion of dopamine produced by neurons of the substantia nigra was established. Dopamine was shown to attenuate temporarily the symptoms in the 1960s. In the 1970s, the limitations of dopaminergic therapy used continuously over 5 years or more as a treatment of PD were discovered when side effects of the medication, e.g., severe motor fluctuations and on/off and wearing-off effects, became progressively as

Parkinson's Disease: Deep Brain Stimulation, Fig. 1 Highly simplified schematic view of the network circuitry affected by Parkinson's disease (McIntyre 2004) and illustrating the direct, indirect, and hyperdirect pathways



severe as or more severe than the symptoms caused by PD itself.

The physiological basis for PD remains unclear, and the process of neuronal death is still being actively explored. Several mechanisms have been proposed including mitochondrial dysfunction, protein mishandling, inflammation, oxidative stress, genetic and environmental factors, and aging (Pissadaki and Bolam 2013). But why would neuronal death affect specifically the substantia nigra pars compacta in PD? The explanation provided by Pissadaki and Bolam via computational modeling is that dopaminergic neurons are unmyelinated and each axon gives rise to more than one million synapses. This produces a high energy demand to propagate action potentials and renders these neurons highly vulnerable to any stressor perturbing energy production. It may eventually lead to cell death.

This cell death process probably involves multiple interacting causes such as genes, chemical agents, infective agents, and trauma. The syndrome is also associated with rare mutations in two genes encoding for alpha-synuclein and parkin which are somehow related to damaged proteins accumulating in neurons over time and leading to progressive cell death (Samii et al. 2004). The interaction between genes (up to 18 discovered so far) may confer increased susceptibility to PD which then appears usually before 50 years of age. These genes probably contribute to susceptibility to PD. Lewy body inclusion, as the hallmark of idiopathic PD

causing the death of nerve cells as previously believed, is questioned because these vesicles storing abnormal protein clumps of alpha-synuclein are found in PD (but not in all patients) as well as in other degenerative disorders such as Alzheimer's disease or even in persons with no neurological disease or no deficit in dopamine-producing nerve cells (Calne 2002).

Alpha-synuclein is coded by the gene SNCA. It accumulates initially in the olfactory system and lower brainstem and then travels in an anatomic pattern to involve other regions of the brain (Fahn 2018).

According to Calne (2002), the interplay of multiple genes with a specific but unknown environmental event causes the neurons to degenerate and die years later. This may explain why different forms of the disease exist. PD may take forms that vary from one patient to the other, and PD must also be distinguished from other similar conditions such as progressive supranuclear palsy and multiple system atrophy. This is why the diagnosis of PD often takes more than 1 year to be established in a relatively reliable way. Environmental factors hypothesized to play a role in inducing PD include exposure to pesticide, herbicide, and prolonged exposure to naturally occurring toxins. Some form(s) of influenza may also be associated with PD as the substantia nigra was shown to be vulnerable to viruses (Ogata et al. 1997). Recent evidence according to Calne (2002) also suggests that a brief event (e.g., injury from a toxin or a virus wounding nerve cells) may kill

some cells immediately and damage many others in ways that decrease their life expectancy. Recent and growing evidence on the bidirectional interactions between the gut microbiota and the central nervous system suggests that several health conditions including Parkinson's disease may be affected by intestinal microbiota (the "enteric" brain).

Pathophysiology of PD

As indicated before, the primary deficit in PD is the loss of neurons in the substantia nigra pars compacta. These neurons provide dopaminergic innervations to the striatum (caudate and putamen). Dopamine, a catecholamine synthesized by neuron terminals from metabolized tyrosine by tyrosine hydroxylase (to L -DOPA) and by dopa decarboxylase from L -DOPA to dopamine, can temporarily restore function. The action of dopamine is mediated by a family of dopamine receptor proteins (D1–D5) which can be divided into two groups having different structural and pharmacological properties (D1 and D5 on one side and D2, D3, and D4 on the other); however, D1 (excitatory) and D2 (inhibitory) appear to be the most important receptor sites with regard to PD. The exact effects of DBS on neurotransmitters are still being explored today (but see Shon et al. 2010).

Considerable effort has been devoted to exploring the link between dopamine loss and the spectrum of clinical features observed in PD (Albin et al. 1989; Alexander et al. 1990). As indicated already, the basal ganglia are part of the complex network including not only the cortex and the thalamus but also other structures such as the brainstem and cerebellum. This large network regulates the flow of information going to and from the cortex. The striatum is the principal input structure of the basal ganglia, and it receives excitatory glutamatergic input from a large region of the cortex (Fig. 1). The outflow of the striatum is divided into the direct pathway expressing primarily D1 excitatory receptors and the indirect pathway expressing primarily inhibitory D2 receptors. Dopamine appears to increase the activity of the direct pathway and reduce the activity of the indirect

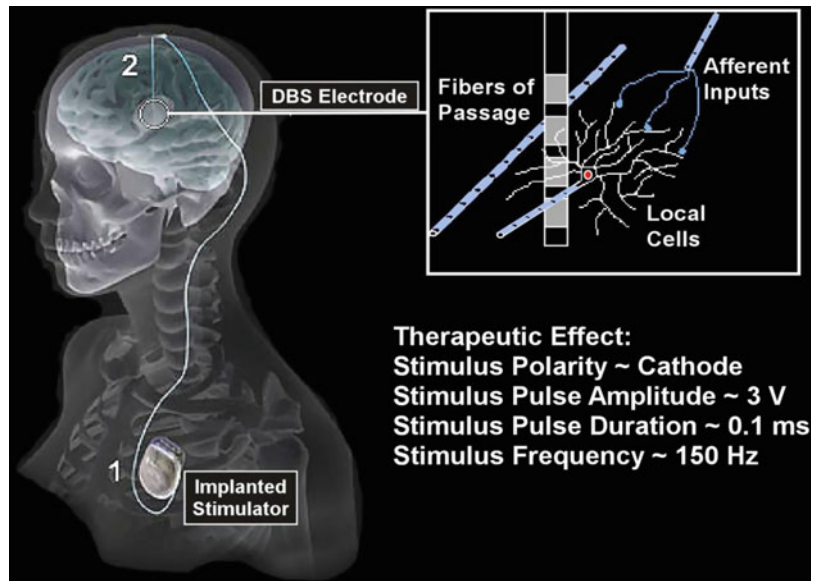
pathway, while PD produces the opposite effect. This imbalance is believed to explain the symptoms of the disease (Fig. 1). But what is the nature of pathological activity in the basal ganglia-cortex network? There is a first frequency band around 20 Hz closely related to bradykinesia and rigidity (but not directly related to muscle activity for bradykinesia) and a second frequency band around 10 Hz related to tremor and correlated with muscle activity. Litvak et al. (2011) examined the interconnectivity between brain areas and distinguished a network around 10 Hz in the temporoparietal-brainstem areas and another predominantly frontal network around 20 Hz.

Today, no treatment can stop the progression of the disease. But symptoms can be attenuated by pharmacologic intervention (L -DOPA, dopa agonists, etc.), ablative surgery, surgery for neuromodulation (DBS), and gene therapy. Pharmacologically during the early phase of the disease, the patient is treated with dopamine and dopamine agonists (acting on dopamine receptors) (Jankovic and Aguilar 2008). The treatment is given in the form of L -DOPA, which passes through the blood-brain barrier and is converted into dopamine. During the later phase of the disease inhibitors such as MAO-B (monoamine oxidase B), an enzyme metabolizing dopamine which delays or reduces the breakdown of dopamine, and COMP (catechol O-methyl transferase), which increase the half-life of L -DOPA, may be added. Anticholinergics are also used to improve symptoms such as tremor. Levodopa-induced motor complications appear after a few years of treatment and produce fluctuations in motor response and involuntary movements (dyskinesias). These complications may include strong wearing-off effects or freezing during long "off" periods between doses.

Deep Brain Stimulation

Deep brain stimulation (DBS) for PD involves continuous therapeutic electric stimulation of subcortical structures at frequencies >100 Hz using chronically implanted electrodes. It is a highly effective and reversible surgical procedure,

**Parkinson's Disease:
Deep Brain Stimulation,**
Fig. 2 DBS from McIntyre
(2004)



meaning that it has marked benefits and morbidity limited to around 0.2% (Fig. 2). Its origin goes back to work done on epileptic patients (Krause 1912), and its success is largely based on past long-term experience with surgical ablation of deep brain structures such as the ventrointermediate nucleus of the thalamus (Vim) which was replaced by Vim stimulation by Benabid et al. (1987).

A surgically implanted battery-operated pulse generator (IPG) delivers high-frequency electrical stimulation to targeted deep areas of the brain via one (unilateral) or two (bilateral) implanted platinum iridium electrodes (or leads) connected to the generator via an extension. The IPG or neurostimulator is subcutaneously implanted in the pectoral or abdominal region (Fig. 2). The insulated polyurethane extension is passed subcutaneously from the chest, the side of the neck, to the top of the cranium and connected to an electrode which is lowered slowly to a predetermined target. The system is subsequently programmed using radio signals.

The most common targets in PD today are the subthalamic nucleus (STN) and the globus pallidus internal segment (GPi), mainly proposed for the treatment of motor symptoms (Anand Rughani et al. 2018).

Increasing evidence from randomized clinical trials indicates that motor benefit is similar between both targets, including improvement in quality of life.

DBS of the STN reduces dopaminergic medication and offers possible mild benefit in non-motor domains and potential economic advantage (Ramirez-Zamora and Ostrem 2018).

Motor scores assessed in the “off” medication/“on” stimulation condition improve much more with STN stimulation (Rughani et al. 2018).

GPi DBS shows more likely a suppression of dyskinesia and an improvement in depression (Rughani et al. 2018). Overall, STN DBS has a higher risk for behavioral changes compared with GPi DBS. For these reason, target selection should be customized to each patient’s clinical manifestation and neuropsychiatric profile, allowing personalization of this therapy and improved individual outcomes (Ramirez-Zamora and Ostrem 2018).

Stimulation parameters (stimulus polarity, pulse amplitude, pulse duration, and stimulus frequency) are empirically adjusted by the clinician to minimize side effects while optimizing symptom reduction. DBS induces an electrical field in the tissue surrounding the contact. This electric field is strongest at the cathode and decays with distance.

DBS in PD reduces on average by 50% the motor scores of the UPDRS (Unified Parkinson's Disease Rating Scale) and the daily dose of L -DOPA, while patients' quality of life significantly increases. The effect of DBS is observed within seconds. The efficacy of DBS is now widely recognized, and over 80,000 patients worldwide benefit from this surgical intervention. This treatment option has been tried in a variety of disabling pathological conditions refractory to medications and other than PD including dystonia, essential tremor, chronic pain, obsessive compulsive disorders, Tourette's syndrome, and depression. These applications require different stimulation sites along the corticobasal ganglia-thalamocortical network (Fig. 1). Although DBS is the procedure of choice today, it is invasive and expensive and involves surgical risks (hemorrhage 1–2%, infection 3–5%) as well as hardware complications such as leads breaking, electrode malfunction, and battery failure. Furthermore, side effects (such as postural instability, depression, speech difficulties, gain of weight, decline in cognitive-motor functioning) are not uncommon.

There are still limitations in terms of effectiveness, side effects, and battery consumption. For these reasons only pathological neural activity can be suppressed while stimulating: adaptive DBS (aDBS), where stimulation is applied according to the level of pathological activity, might be advantageous (Beudel and Brown 2016).

Detailed Description of Deep Brain Stimulation

Electrical motor cortex stimulation goes back to the work of Aldini (1803) who applied noninvasive therapeutic cortical stimulation in a psychiatric patient for the first time. Extirpation of premotor and cortical motor zones was used to control movement disorders by Horsley (1890), Bucy and Buchanan (1932), Bucy and Case (1939), and Klemme (1940, 1942) often with limited success. Alberts (1972) showed that stimulation of the motor cortex at 60 Hz near the Rolandic fissure between motor and sensory sites evoked or augmented a 5 Hz tremor in PD patients, while Woolsey et al. (1979) observed that stimulating currents subthreshold for the elicitation of

movement resulted in disappearance of tremor and rigidity for short periods after stimulation of the primary motor cortex in a patient with severe PD.

Surgical interventions have been described since the 1940s and have consisted in lesioning various structures. The most common lesioned structures were the thalamus and the pallidum. The destruction of these targeted areas was successful in controlling the symptoms of PD, but the procedure was irreversible. After the discovery of the side effects of L -DOPA, surgical treatments were reintroduced in the 1980s. At that point, one nucleus of the thalamus (i.e., the Vim) was not irreversibly destroyed, as previously done, but chronically electrically stimulated. Other structures (GPi, STN, zona incerta) were shown to produce positive effects on the symptoms although these effects were slightly different.

DBS Indications and Benefits

DBS is used for patients with onset of PD of at least 4 years duration associated with 4 months of motor complications. It can improve tremor, rigidity, slowness of movements, and drug-induced dyskinesias (Pollo et al. 2014).

Patient inclusion criteria also contemplate dopamine-responsiveness and absence of significant cognitive dysfunctions and emotional stability with no severe psychiatric symptoms. Both sporadic and genetic PD patients are eligible for DBS (Moro and Lang 2006).

The benefits of DBS include attenuation of drug-induced dyskinesias and improvement in quality of life (Ruth-Mary de Souza et al. 2013).

Benefits of neuromodulation can be maintained for more than 10 years, but the effect of DBS might be maintained in all motor domains except axial symptoms (Hariz 2017).

The motor function attenuation consists in significant improvement in tremor and bradykinesia, but not in axial motor function. Improvement of non-motor features are pain, akathisia, cognitive function, emotion, activities of daily living (ADL) scores, autonomic function, and aspects of life such as employment, family roles, and social interaction.

DBS may have benefit in early PD when fewer neurons have been lost, reducing brain damage. STN DBS raises striatal dopamine levels and also increases levels after L-DOPA administration in patients experiencing the wearing-off phenomenon. It is also true that patients who had STN DBS in situ for 8–10 years had maintenance of motor benefits and functional improvement despite reduction in L-DOPA dose but had significant decline in postural stability, axial symptoms, and a nonsignificant decline in cognition (de Souza et al. 2013). STN DBS is effective in ameliorating PD symptoms; furthermore it is the only surgical procedure for PD that allows a radical decrease in medication (Hariz 2017).

DBS may modulate also non-dopaminergic networks, which may in the long term impact non-motor clinical features of PD (de Souza et al. 2013).

DBS also allows modification of the stimulation delivered to the precise brain targets: it allows to obtain maximal benefit with minimal side effects.

The individual clinical benefit of directional DBS is best observed for suboptimal electrode positions resulting in a narrow therapeutic window (Steigerwald et al. 2016).

DBS Disadvantages

The main disadvantages of DBS are the cost (approximately \$10,000 per unit), the increased risk of infection, the cost of maintenance, and battery exhaustion (Konstantin et al. 2017).

Stimulation may be limited by the apparition of acute disabling side effects such as tonic muscular contractions, dysarthria, conjugate eye deviation, paresthesia, or gait imbalance: the electrode size has an important influence on the occurrence of side effects (Pollo et al. 2014).

DBS Targets

The main targets for DBS are STN, GPi, Vim, pedunclopontine nucleus, caudal zona incerta, substantia nigra pars reticulata, and motor cortex.

The target is different in order to the symptom control.

GPi DBS causes less cognitive decline than STN DBS and can be taken into account in PD

patients with preoperative cognitive impairment: however STN and GPi are the main targets of DBS to alleviate motor symptoms.

Vim helps primarily with tremors.

Alternative DBS targets are pedunclopontine nucleus, caudal zona incerta, substantia nigra pars reticulata, and motor cortex. They are important for control of speech, swallowing, and non-motor symptoms such as memory impairment, attention decline, and sleep disturbances. (Mehanna et al. 2018).

Another target is the nucleus basalis of Meynert (NBM): it is the most important source of cholinergic innervations to the neocortex. The DBS of the NBM is a therapy for PDD.

The purpose is to provide insights into the cholinergic network underpinning cognitive dysfunction (Deeb et al. 2018).

DBS Innovations

The most recent advantages in the DBS field include interleaving of DBS pulses, fractionated current, directional steering of current, use of biphasic DBS pulses, and closed-loop stimulation. The next frontiers should be the remote internet-based programming.

DBS should improve mortality and it could have neuroprotective effects (Mehanna et al. 2018).

DBS Outcomes

Age at surgery and duration of the disease do not seem to influence the outcome. Postural instability and worse pre-DBS motor score are the strongest predictors of poorer functional and QOL outcomes. Furthermore there is a possibility of significant weight increase after DBS in advanced PD: it is a problem especially in case of obesity, diabetes, and other metabolic disorders (Mehanna et al. 2018).

DBS Mechanisms

The mechanisms of action underlying the beneficial effects of DBS are still actively debated, and progress has been relatively slow at first despite a large catalogue of hypotheses proposed about DBS underlying physiological mechanisms (for some examples, see Montgomery and Gale 2008; Johnson et al. 2008; Vitek 2008; Modolo

and Beuter 2009a, b; McIntyre and Hahn 2010; Miocinovic et al. 2013; Rubin et al. 2012). DBS was initially thought to suppress pathological rhythms (Vitek 2002; McIntyre et al. 2004; Hammond et al. 2008).

The electrical stimulation induced an inhibition of basal ganglia output structures, decreasing basic firing of neurons and suppressing spontaneous neuronal activity. The possibility of depolarization blockade may occur through K⁺-mediated effects, Na⁺ channel inactivation, presynaptic depression of excitatory efferents, and hyperpolarization of neuronal bodies and dendrites. DBS causes glutamate reduction and increases of inhibitory neurotransmitters such as GABA.

Neurovascular and neurogenic changes may be induced by electrical stimulation of the brain: in fact DBS induces an increase in blood flow and neurochemical changes that may be induced by stimulation of astrocytes and propagation of calcium waves resulting in release of glutamate (Martinez-Ramirez et al. 2015).

The comparable outcome after a lesion and during stimulation of a cerebral structure has led to the conclusion that DBS inhibited neuronal activity and decreased output from the stimulated structure, and this hypothesis was supported by a number of studies performed in humans and animals (see, e.g., Dostrovsky and Lozano 2002; Perlmutter et al. 2002). Other potential mechanisms invoked include a depolarization blocking of neuronal transmission through inactivation of voltage-dependent ion channels (Benazzouz et al. 1996; Beurrier et al. 2001; Bikson et al. 2001) and synaptic inhibition by stimulation of inhibitory afferents to the target nucleus (Dostrovsky et al. 2000; Breit et al. 2004) and synaptic depression by stimulation-induced neurotransmitters depletion (Urbano et al. 2002; Xia et al. 2004). DBS mechanisms were also described as creating a jamming of information by imposing an afferent stimulation-driven high-frequency pattern (Garcia et al. 2003; Hashimoto et al. 2003; Breit et al. 2004) or as “an informational lesion” (Grill et al. 2004) preventing pathological activity from spreading through the basal ganglia.

As pointed out by Montgomery (2012), the effects of DBS are not only local but also

system-wide. Indeed, for Lozano et al. (2002), stimulation of deep brain structures could potentially “backfire” to the thalamus and cortex. Studies proposed that DBS inhibited somatic activity at the site of stimulation (close to the electrode, mimicking the outcome of a lesion) and excited axons (output of the stimulated area). In other words, in a cell exposed to extracellular stimulation, the stimulus-induced action potential initiates in the axon rather than in the cell body and axonal spike output becomes time locked to the stimulus frequency as shown in a modeling study by McIntyre et al. (2004). In addition, fiber tracts of passage are activated. For example, the STN is surrounded by several major fiber tracks (lenticular fasciculus, field of Forel, zona incerta, cerebellothalamic fibers, etc.) as well as fibers coursing through the target nucleus (Johnson et al. 2008; Hammond et al. 2008). This paradox between inhibition of the stimulated structure and simultaneous activation of downstream structures was later shown to be related to the distance from the electrode. This explanation, however, does not entirely explain why therapeutic latencies differ between symptoms (Johnson et al. 2008). Another conclusion was that pathological synchronism in the STN is present in PD and this, rather than firing rate, is the pathological feature in PD. DBS changes the firing pattern of STN neurons (Carlson et al. 2010; Wilson et al. 2011).

Several studies focused more specifically on network activity (McIntyre and Hahn 2010; Asanuma et al. 2006) including short- and long-term effects, as well as local and distant effects of DBS (for examples, see Titcombe et al. 2001; Montgomery Jr and Gale 2008; Brown and Eusebio 2008; Santaniello et al. 2012). In the corticobasal ganglia-thalamocortical network, the best site of electrode implantation could be located theoretically at any point of the network (Fig. 1). This is confirmed by the fact that improvements have been reported when various structures along this network are stimulated. Combining modeling with experimental and clinical components brought new insights. Thus, neurostimulation therapy modulates activity in the corticobasal ganglia network. This modulation has been described as stimulation-induced

desynchronization of network oscillations (McIntyre and Thakor 2002). Thus, not only does DBS appear to override the irregular, pathological activity of the stimulated target with a regular pattern, but the effect produced spreads through then tire network (Xu et al. 2008; Johnson et al. 2008; McConnell et al. 2012; Miocinovic et al. 2013).

In brief, DBS effects are likely to result from a combination of local changes and modulation of distant structures within the corticobasal ganglia-thalamic loops. The involved mechanisms include the activation of afferent and efferent axons, with both antidromic and orthodromic spike propagation (Hanajima et al. 2004; Deniau et al. 2010; Santaniello et al. 2012). Studies are converging on the fact that excessive synchrony propagating and amplifying around this network can be explained by a resonance phenomenon (i.e., a sensitivity of neurons to afferences having frequencies close to their intrinsic frequency) and high-frequency DBS appears to attenuate subthalamic as well as cortical rhythms in PD.

As indicated above, pathological discharge patterns generated in the basal ganglia in PD propagate around the network, and DBS probably modulates brain rhythms, especially abnormal synchronous oscillatory activity in the beta band (Brown 2003, 2006; Wingeier et al. 2006) but also theta and alpha rhythms (Whitmer et al. 2012) in the STN and cortex (primary motor cortex, premotor cortex, somatosensory cortex, and orbitofrontal cortex) (Walker et al. 2009). This rhythmic activity manifests itself as oscillatory local field potentials (LFPs, i.e., extracellular voltage fluctuations in membrane potential of a local neuronal population), which are recorded with macroelectrodes at various sites within the network. Thus, part of the explanation of DBS effects is local suppression of pathological oscillations (i.e., excessive synchronous) in specific frequency bands throughout the corticobasal ganglia-thalamocortical network (Eusebio et al. 2012; Whitmer et al. 2012).

Two remarks to keep in mind. The first one raised by Johnson et al. (2008) is that methodological approaches vary greatly among studies and complicate the exploration of mechanisms,

and the second is that few attempts to model DBS effects were reported during the initial years (but see Tass 1999, 2000; Titcombe et al. 2001, Rubin and Terman 2004). DBS appears to cause a cascade of effects probably involving a combination of mechanisms; some of these mechanisms are still unknown (e.g., is there a gliomodulation in addition to a neuromodulation?). These mechanisms are currently being explored using imaging, electrophysiology, and model-based network level analysis incorporating network dynamics in response to stimulation (McIntyre and Hahn 2010; Liu et al. 2011).

DBS Surgical Procedure

For targeting and planning the implantation trajectories, preoperative T1 and T2 weighted high-resolution magnetic resonance images (3 T) are used, and they are co-registered with a stereotactic CT scan (Pollo et al. 2014).

The anterior commissure/posterior commissure (AC-PC) line is a helpful to determine the orientation of each lead within stereotactic space and assigned each directional setting to an orientation (Steigerwald et al. 2016).

The electrode is inserted under fluoroscopic control, and impedance through each contact is also measured as a confirmation that the stimulation takes place as intended (Pollo et al. 2014).

DBS Electrodes

The Vercise DBS device (Boston Scientific Corporation, Natick, Massachusetts, USA) is capable of delivering multiple source constant current allowing the allocation of completely different stimulation parameters independently to each of eight contacts of the electrodes. It allows the clinician to shape the current along the vertical axis of the electrode (Barbe et al. 2014). It is associated with a pulse generator capable of multiple independent current source control (MICC). MICC allows to distribute the stimulation current over any combination of electrodes of one lead in arbitrary proportions (Steigerwald et al. 2016).

The Infinity DBS device (St. Jude Medical – Abbott) consists of a directional, segmented lead that offers new ways to control stimulation and an IPG that is the first and only one compatible

with other manufacturers' existing extensions without use of adapters. With this technology, we can customize the therapy by targeting specific anatomical structures, steer current away from vulnerable structures, and support lead capture through secure lead fixation using the Guardian™ Burr Hole Cover auto-locking technology.

A further prospect is to shape or steer the current delivered according to all three axes.

Both electrode designs consistently showed a significant widening of the therapeutic window with stimulation in the best direction compared to the conventional spherical stimulation (Pollo et al. 2014); Dembek et al. 2017).

There was no difference in motor efficacy or stimulation amplitudes between directional and circular DBS in the short-term crossover. A relevant expansion of the therapeutic window is demonstrated with directional stimulation (Dembek et al. 2017).

Chronic implantation is now needed to establish the usefulness of directional steering in the long term (Mahlknecht et al. 2015). The observed side effects related to direction of stimulation were consistent with the anatomical location of the surrounding structures (Pollo et al. 2014).

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Particle-Based Stochastic Simulators

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Definition

A stochastic simulator that tracks the location and interactions of individual molecules of interest. Molecules are represented with minimal internal detail.

Detailed Description

Computational simulations are widely used in neuroscience, as in other branches of biology, to explore the implications of quantitative models. They are used to investigate the sequestration of calcium calmodulin kinase II (CamKII) in dendritic spines, the transmission of action potentials through networks of neurons, and the release of heterogeneous synaptic vesicles, among many other topics. Some simulations are used with abstract “toy models” to identify fundamental

biological principles, such as which signaling network topologies can transmit information particularly accurately. Others are tightly integrated with experimental work to build better understandings of particular systems.

Neuroscience simulation methods can be broadly categorized by the level of detail that they represent. At the coarse end of the scale, one can numerically integrate the differential rate equations that represent the kinetics of biochemical reaction and transport processes (Aldridge et al. 2006). Such integration methods typically assume few spatial compartments and ignore stochasticity. At the other extreme lie molecular dynamics approaches, in which one simulates the intricate motions of individual atoms within potential energy landscapes (Rapaport 2004). In moving along the continuum from coarser to finer levels of detail, these simulation methods typically address smaller total volumes of space, simulate shorter amounts of time, require more simulation parameters, and become more computationally intensive. They also consider space more realistically, such as by moving from a compartment description to a lattice, and then on to continuous space. In addition, the simulators change from using deterministic computations, which are appropriate when enough molecules are considered that their fluctuations become irrelevant, to stochastic computations, which account for natural fluctuations and are essential when there are few molecules.

Particle-based simulations lie toward the detailed end of this scale. They track the locations and interactions of all individual molecules of interest, while ignoring water and other molecules that are not of interest. They typically address sizes that range from single nanometers to tens of microns, and time scales from tens of nanoseconds to minutes. This level of detail makes them good for simulating problems involving molecular diffusion, chemical reactions, macromolecular complex formation, and/or molecule-membrane interactions. Their level of detail would also make them appropriate for investigating dynamics involving the conformations of cytoskeletal and nucleic acid filaments (Andrews 2014), although those topics have received less attention so far and

are minimally supported in current software. Particle-based methods lie between the coarser spatial Gillespie methods (e.g., Drawert et al. 2012) and the finer Brownian and molecular dynamics methods (Ermak and McCammon 1978; Rapaport 2004).

Naively, it might seem best to work at the highest possible level of detail because it is the most accurate. In fact though, the opposite is generally the case. It is typically best to work at the lowest level of detail that adequately addresses the research question at hand because doing so enables simpler models and faster simulations; the importance of faster simulations should not be underestimated because simulation speed largely dictates the pace of the research and determines the extent of parameter scanning and parameter fitting that are practical. Furthermore, there is little benefit in simulating a model with more detail than is in the model itself. For example, simulating encounters between structurally complicated proteins with subnanometer precision is not meaningful when those same proteins are being approximated as perfect isotropic spheres.

Many particle-based simulators have been developed over the past three decades (see reviews Blackwell 2013; Sokolowski and ten Wolde 2017; Schöneberg et al. 2014). Of these, we are aware of six that are being actively maintained, meaning in this case that they have had new releases in the past 3 years. These simulators are described below and in Table 1, listed roughly in order of increasing detail. The simulators that are not listed here (see Schöneberg et al. 2014) are generally less mature, with fewer features, less documentation, and/or more difficult installation.

MCell and Smoldyn

MCell (Stiles and Bartol 2001, <http://mcell.org>) and Smoldyn (Andrews et al. 2010, <http://www.smoldyn.org>) work at similar levels of detail. Both are able to represent molecules as point-like particles that diffuse freely and only interact when pairs of reactants collide with each other and then undergo a chemical reaction. These molecules can

also adsorb to surfaces, desorb from surfaces, and diffuse along surfaces. Both programs are mature, with easy installation, good documentation, and many features. MCell was initially developed for modeling reactions and diffusion in the neuromuscular junction (Stiles et al. 1996) and continues to be used for a wide variety of neuroscience simulations. MCell supports molecules with multiple states, such as arise with phosphorylation (Stefan et al. 2014). It has a graphical user interface that works with the open-source Blender software and provides excellent graphical output.

Smoldyn does not support graphical input but reads text input files instead. Smoldyn's graphical output, which displays as the simulation runs, is good but inferior to MCell's. On the other hand, Smoldyn runs about three times as fast as MCell, is more accurate (Andrews et al. 2010; Andrews 2017), and offers more features. All of Smoldyn's algorithms approach exactness, meaning perfect agreement with the underlying conceptual model, as time steps are reduced towards zero and it also simulates reaction rates, on-surface diffusion, and molecule-surface interactions quite accurately even with very long time steps. Smoldyn allows molecules to have excluded volumes, enabling simulations of macromolecular crowding. Smoldyn offers rule-based modeling, with either BioNetGen or a new wildcards method, for modeling the dynamics of multimeric complexes. It also offers multiscale simulation using spatial Gillespie approaches and has been combined with partial differential equation (PDE) methods in the popular Virtual Cell software (Schaff et al. 2016). Smoldyn is used particularly in the biophysics and systems biology communities.

E-Cell and eGFRD

The enhanced Green's Function Reaction Dynamics (eGFRD) algorithm (Takahashi et al. 2010) is an exact approach for simulating chemical reactions between molecules that can be represented as perfect spheres. Simulated molecules diffuse in agreement with ideal Brownian motion and

Particle-Based Stochastic Simulators, Table 1 Comparison of different simulators. See <http://www.smoldyn.org/simulators.html> for detailed notes about all table entries and any updates. System boundaries codes: R = reflecting, A = absorbing, P = periodic,

T = transmitting, and I = interacting. *Algorithm is exact but software produces incorrect results. †These benchmark run times are not comparable with others due to differing levels of detail

	MCell	Smoldyn	eGFRD	SpringSaLaD	ReaDDy
Time steps	$\sim 1 \mu\text{s}$	Ns to ms	Event-based	$\sim 10 \text{ ns}$	$\sim 0.1 \text{ ns to } \mu\text{s}$
Molecules	Points	Points, spheres	Spheres	Multi-spheres	Multi-spheres
Dimensions	2,3	1,2,3	3	3	3
System boundaries	R, A, P, T	R, A, P, T	P	R	P, I
Surfaces	Triangle mesh	Many primitives	–	1 flat surface	Plane, sphere
Surface molecules	1/tile, 2 states	Unlimit., 4 states	–	Unlimit., 3 states	–
Excluded volume	–	Excellent	Exact	Good	Excellent
Multimers	States only	Rule-based model	–	Explicit	Explicit
Allostery	–	Yes	–	Yes	–
Reaction accuracy	Very good	Excellent	Exact*	Excellent	Excellent
Dissociation products	Stochastic	Fixed separat.	Adjacent	Adjacent	Adjacent
Molec.-surf. interact.	Good	Excellent	–	To sites only	Potentials
Long-range interact.	–	–	–	–	Yes
Hybrid simulation	–	Sp. Gillespie, PDE	–	–	–
Benchmark run time	67 s	22 s	13 days†	9.1 months†	13 min.
Distribution	Executable	Executable	Self-compile	Java file	Self-compile
User interface	GUI, text	Text	Text	GUI	Python script
Graphical output	Excellent	Good	Partial support	Partial support	Good
Library interface	Python	C/C++	–	–	Python

nonreactive pairs of molecules reflect off of each other upon collision to account for excluded volume effects. Bimolecular reactions exactly obey the Collins and Kimball chemical reaction model, in which molecules are treated as hard spheres that have an “intrinsic reaction rate” when in contact (Rice 1985); this model is widely assumed in the particle-based simulation field. The eGFRD algorithm achieves this high level of detail by using an event-driven method in which it steps the simulation time from the moment of one interaction event to the moment of the next event. The two original algorithm developers, Takahashi and ten Wolde, have now implemented it in separate software:

E-Cell (Tomita et al. 1999, <http://www.e-cell.org>), a platform that offers simulators that work at several levels of detail, and eGFRD (<http://gfrd.org>), which only runs the eGFRD algorithm.

The eGFRD algorithm is very efficient for dilute systems because it does not simulate multiple diffusive steps between molecule encounters. However, it is slow for dense systems because these have a large number of molecule encounters and the algorithm performs complicated calculations at each one. For example, I found that it was several orders of magnitude slower than Smoldyn when simulating a Michaelis-Menten reaction that started with 10,000 molecules (Table 1). This

result agreed with speed differences found when testing reaction accuracy (Table 1) and in a prior macromolecular crowding study (Andrews et al. 2015).

SpringSaLaD and ReaDDy

SpringSaLaD (Michalski and Loew 2016, <http://health.uconn.edu/cell-analysis-modeling/ccam-software/>) and ReaDDy (Schöneberg and Noé 2013, <http://www.readdy-project.org>) were designed to bridge the gap between simulation approaches that treat molecules as perfect spheres and molecular dynamics methods. These simulators represent individual molecules as collections of spheres that are bound together with either springs, in the case of SpringSaLaD, or with interaction potentials, in the case of ReaDDy. Both simulators move the separate spheres by numerically integrating the equations of overdamped Langevin dynamics, a physical theory that combines the fluctuating forces that drive Brownian motion and the viscous drag forces that slow it down. This integration requires very short time steps, typically on the order of 1–10 ns (although not its main purpose, ReaDDy can also ignore inter-particle potentials, resulting in much faster simulations). SpringSaLaD represents cell membranes and other surfaces minimally, using a single planar membrane within the simulation volume, while ReaDDy represents surfaces using a combination of planes or spheres, each of which can interact with molecules through an interaction potential.

SpringSaLaD and ReaDDy are particularly useful for simulating the dynamics of protein complexes, such as the multiple subunits of CamKII, along with their interactions with surrounding molecules. This greater level of detail makes these simulators more computationally intensive. They are generally best for systems with a thousand molecules or fewer and can simulate up to a few milliseconds of total time.

Conclusion

Particle-based stochastic simulators are powerful tools for exploring the roles of spatial organization and stochasticity in cell-scale systems. They are used widely in neuroscience research at present

and will undoubtedly be used more in the future as the software improves, computers run faster, and biology research becomes more quantitative. Current simulators are able to accurately represent the diffusion, chemical reactions, complexation, and membrane interactions of individual molecules of interest. These simulators work at different levels of detail, ranging from MCell, which treats molecules as point-like particles, to ReaDDy, which addresses interaction forces between portions of molecules.

All of the tools described here are open source and have nonrestrictive licenses that allow for both commercial and noncommercial use. They are also works in progress that are frequently expanded and improved in response to users' needs. Although perhaps less evident, each simulator is also the product of many person-years of development and testing. If you need a capability that is not supported by one of these tools, I encourage contacting the teams that work on these programs for advice on working around limitations before spending time writing new code.

Cross-References

- [MCell](#)
- [MOOSE, the Multiscale Object-Oriented Simulation Environment](#)
- [Stochastic Simulators](#)

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Patch Clamp Technique

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Definition

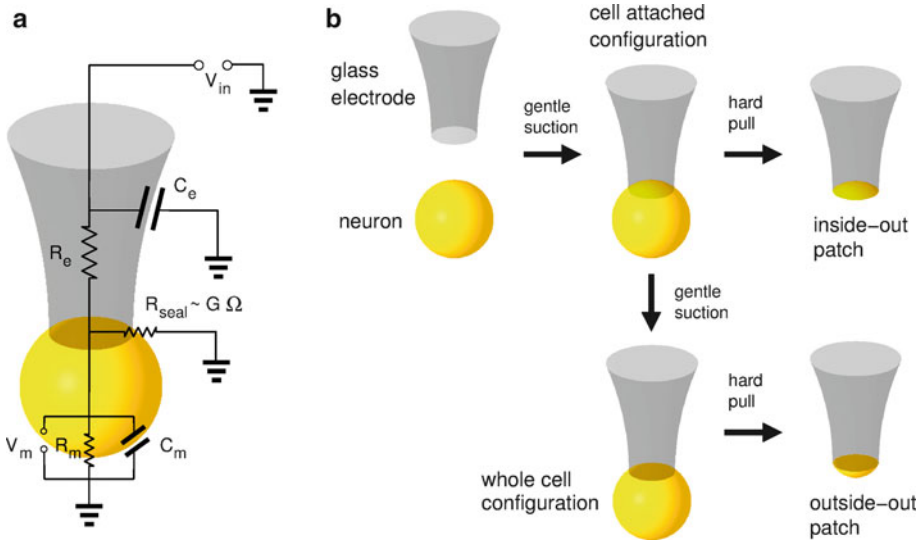
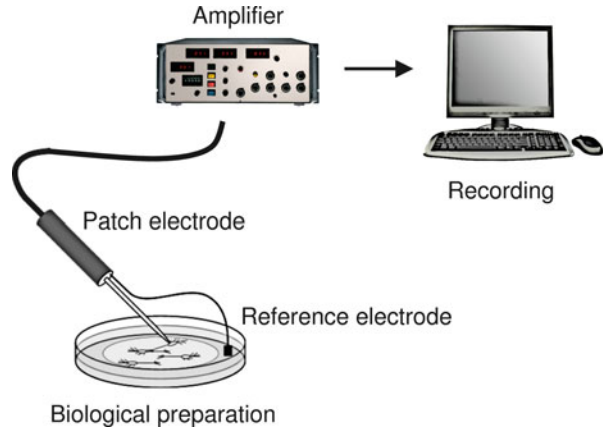
The patch clamp technique is an electrophysiological technique used to measure the currents passing through ionic channels and the membrane potential of electrically active cells. This technique was first introduced by Neher and Sakmann (1976), and it is now widely used in neuroscience to characterize the electrical properties of neuronal membranes.

Detailed Description

Patch clamp recordings are obtained by electrically isolating a patch of membrane using an electrolyte-filled glass capillary in close proximity to the cell membrane. A silver or silver chloride electrode inserted at the other end of the capillary will provide electrical continuity with a reference electrode placed in the extracellular bath solution (Fig. 1). The lipid bilayer which constitutes the cell membrane will seal onto the glass capillary forming what is generally described as a gigaseal, to indicate that the resistance between the tip of the pipette and the reference electrode is on the order of gigaohms (Fig. 2a). To obtain the gigaseal, mild positive pressure is applied at the back of the pipette so that liquid escapes from the approaching tip and pushes the membrane inward before the electrode touches the cell. This will create a dimple on the surface of the cell. When the tip of the pipette is close enough to the dimple, the positive pressure is released and a very gentle suction is applied allowing the membrane to seal

Patch Clamp Technique,

Fig. 1 Patch clamp recording setup. The patch clamp electrode is placed on a cell membrane, and the recorded signal is preamplified in the headstage. Further amplification occurs at the amplifier. The signal is then digitized and recorded on a measurement computer



Patch Clamp Technique, Fig. 2 Illustration of patch clamp configurations. (a) Equivalent electrical circuit of a whole-cell patch clamp recording configuration. (b)

Schematic illustration of how the four main patch clamp recording configurations are achieved

onto the glass. At this point, a small negative current is often applied to improve the quality of the seal and maintain the patch of membrane slightly hyperpolarized.

Setup

Once the gigaseal is obtained, the electrical properties of the membrane can be measured. The minimal setup required for patch clamp recordings is relatively simple (see Fig. 1). The glass capillary is mounted on a headstage which

contains a current-to-voltage circuit for voltage clamp recordings or a voltage follower circuit for current clamp. The headstage is in turn mounted on the micromanipulator to allow precise positioning of the pipette (not shown). The signals are then sent to the amplifier which will compensate for recording artifacts, filter the signal, and amplify it. The signal from the amplifier is then digitized by an analog-digital converter and visualized and stored on a computer. Before the widespread use of personal computers, the recordings were visualized and stored using oscilloscopes and chart recorders.

Single-Channel Patch Clamp

Single-channel recordings can provide information on the ionic gating properties of ionic channels (opening/closing time, inactivation, conductance, etc.) as well as their pharmacology (affinity to neurotransmitters, agonist, antagonists, etc.).

The first application of the patch clamp technique was to record current passing through a single ionic channel, more precisely an ionotropic acetylcholine receptor (Neher and Sakmann 1976); however, the properties of voltage-gated ionic channels can also be studied by applying voltage steps through the amplifier (see ► [“Voltage Clamp Technique”](#)). The solution in the patch pipette is very similar to the extracellular solution in which the cells are kept, but other substances of interest (e.g., neurotransmitter, agonists, or antagonists) can be added to this pipette solution to study the pharmacology of ionic channels.

Whole-Cell Patch Clamp

Patch clamp can be used to obtain an electrical recording of the activity of the entire cell by using the so-called whole-cell recording method. Whole-cell recordings are obtained by breaking the patch of membrane on which the gigaseal has been obtained. This is accomplished by applying negative pressure through the patch pipette, which for this type of recordings will contain a solution very similar to the intracellular medium (Ogden and Stanfield 1994). Once the cell is “opened,” the membrane potential of the entire cell can be controlled and the current measured (voltage clamp) or the membrane potential of the cell can be measured (current clamp).

Compared to traditional sharp electrode techniques, whole-cell patch clamp configurations have a relatively low access resistance (resistance between the electrode and the cell membrane, see Fig. 2a) allowing to resolve smaller currents and reducing the error due to drop in voltage across resistive elements. For these reason, whole-cell patch clamp has become the preferred tool for the study of the electrical

properties of mammalian neurons and neuronal networks (Stuart et al. 1993).

A disadvantage of whole-cell patch clamp over sharp electrode techniques is the risk of washing out the intracellular medium with the patch pipette solution. The dialysis of the intracellular solution is a major limitation for the study of plasticity mechanisms mediated by second messengers. To circumvent this problem, Horn and Marty (1988) introduced a technique called perforated patch, in which antibiotics (such as nystatin) are added to the patch pipette solution to create “holes” on the patched membrane. The artificially created non-ion-specific channels in the membrane are too small to allow macromolecules to diffuse back into the pipette and at the same time ensure a relatively low-resistance electrical connection between the patch clamp system and the interior of the cell.

Excised Membrane Patch Clamp

The need to study quickly changing concentrations of ions or neurotransmitters has led to the use of cell-free patching of membranes. Rapidly pulling the recording pipette away from the cell after the gigaseal is established will often leave a portion of membrane attached to the glass. Doing so in whole-cell or cell-attached configurations will lead to outside-out or inside-out excised membrane patch configurations (see Fig. 2). The main advantage of cell-free recordings is that they allow to study drug binding to both the extracellular and the intracellular domain of the cell by simply modifying the bath solution. However, even when using various tricks to improve the seal, the signal-to-noise ratio of these recording is often quite low, and in some cases, the channel kinetics in excised patch and in cell-attached patch have been reported to be different (Covarrubias and Steinbach 1990).

Modern Developments

Its low access resistance has made whole-cell patch clamp the ideal tool for the injection of

fast currents required for dynamic clamp and action potential clamp. Moreover, the rapid exchange of solution between the patch pipette and the cell allows rapid filling of the neuron with dye and fluorescent indicators. In the last two decades, the improved stability of micro-manipulators allowed researchers to patch cellular compartments (i.e., dendrites, axons, and presynaptic terminals) previously inaccessible to direct electrical recordings and manipulations (Williams and Stuart 2003; Debanne et al. 2011).

Cross-References

- [Dynamic Clamp Technique](#)
- [Voltage Clamp Technique](#)

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Pathological Changes in Peripheral Nerve Excitability

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Definition

Reversing pathological changes in nerve excitability is an important clinical goal. Achieving that goal requires identification of the underlying molecular changes and a clear understanding of how excitability is altered on the basis of those changes. Computational modeling plays an important role in addressing those issues. One approach involves incorporating known or suspected ion channel changes into normal axon models to test whether such changes can explain pathological changes in excitability. An alternative approach involves reproducing the pathological changes in excitability and then working backward to identify which ion channel changes may be involved.

Detailed Description

Nerve Injury: From Clinical Symptoms to Molecular Pathology

Peripheral nerves comprise axons of sensory, motor, and autonomic neurons. The signs and symptoms of nerve injury reflect which of those axons are damaged. The most obvious consequence of nerve injury is a loss of normal function which, for example, could manifest as numbness in the case of mechanosensory axons or paralysis in the case of motor axons. A less obvious

consequence of nerve injury is gain of function resulting from axonal hyperexcitability, manifesting as pain and spasticity for mechanosensory and motor axons, respectively. Nerve injury is thus associated with both negative and positive symptoms, where the proportion of each depends on the nature and extent of axonal damage and the recovery therefrom. This poses a clinical dilemma insofar as treatments intended to diminish negative symptoms often exacerbate positive symptoms and vice versa (Bowe et al. 1987).

Axonal damage can arise from trauma, through diseases such as diabetes and demyelination disorders, and via toxicity by chemotherapeutics and antiretrovirals (Baron et al. 2010). It remains unclear whether hyperexcitability is a direct consequence of axon damage or a compensatory response to it. In many cases, injury dysregulates the expression, trafficking, and/or insertion of ion channels. However, the homeostatic response to injury may, by overcompensating, lead to yet other problems. This is easiest to appreciate in the context of demyelination disorders where demyelination exposes axon membrane that is not normally involved in saltatory spike propagation – when the spike jumps from one Node of Ranvier to the next – but now must contribute to continuous spike propagation. Increasing the excitability of this newly exposed membrane by increasing the density of sodium channels and/or decreasing the density of leak channels can rescue the propagation failure, but excessive changes can result in hyperexcitability and ectopic spiking, including pathological patterns such as afterdischarge and spontaneous bursting (Calvin et al. 1982; Coggan et al. 2010). Notably, most of the axon is normally involved only in propagating spikes, not initiating them; accordingly, spike initiation at an atypical location, as often occurs at the site of damage, is termed “ectopic.”

Dozens of different ion channel subunits are up- or downregulated after nerve injury (LaCroix-Fralish et al. 2011). Some of those changes contribute to increasing excitability, whereas others counterbalance the former (i.e., decrease excitability). That said, many ion channel changes may have no effect on excitability but are

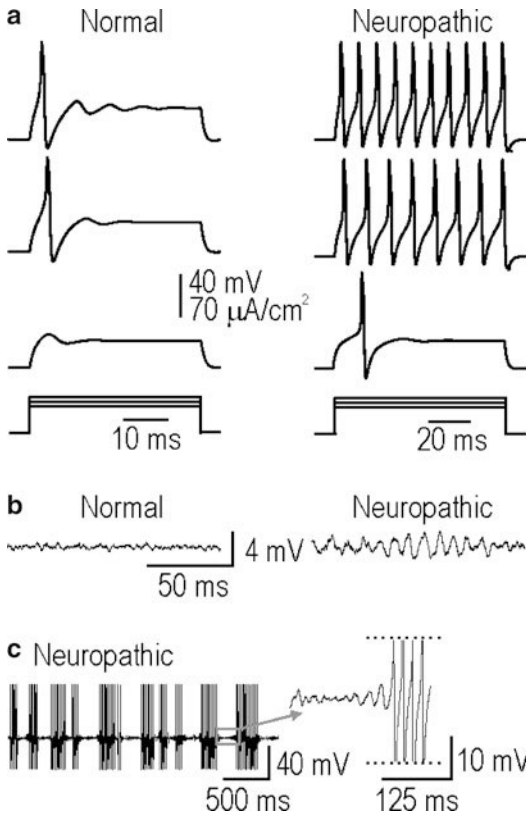
nonetheless correlated with excitability changes because they co-occur with changes in other “relevant” ion channels. Computational modeling plays an important role in deciphering causal relationships.

Modeling Changes in Axonal Excitability

It goes without saying that models of normal axons can be adapted to investigate injured axons. The more interesting discussion is how to use such models to investigate the sequence of events following injury. One approach is to test which molecular changes, acting alone or together, cause a pathological change in cellular excitability. This is referred to here as a *bottom-up approach*. Alternatively, one can use a *top-down approach*: using modeling to identify abstract mechanistic explanations for the altered excitability and then working backward from there to identify which observed molecular changes are causal. These two approaches will be illustrated by modeling efforts aimed at deciphering changes in somatosensory afferent excitability triggered by nerve injury and thought to contribute to chronic neuropathic pain.

Amongst somatosensory afferents, large diameter myelinated fibers have been shown to become hyperexcitable after nerve injury. These same fibers have been shown to mediate certain aspects of neuropathic pain, namely, hypersensitivity to normally innocuous mechanical stimulation. Hyperexcitability in those fibers has therefore been a significant focus of research. Injury to these axons produces a characteristic triad of qualitative changes in excitability: (1) altered spiking pattern, (2) membrane potential oscillations (MPOs), and (3) spontaneous bursting (Fig. 1).

On the one hand, computer models of this process are tightly constrained phenomenologically: they must reproduce the entire triad of pathological excitability changes. On the other hand, models are only loosely constrained mechanistically: our understanding is very incomplete with respect to which channels are expressed, let alone what the density is before vs. after injury. This allows for different models that provide different



Pathological Changes in Peripheral Nerve Excitability, Fig. 1 Reproduction of injury-induced excitability changes in a simple computer model. (a) Response evoked by sustained current injection switches from a single, onset-only spike under control conditions to repetitive spiking under neuropathic conditions. Membrane potential oscillations (b) and bursting (c) are also seen under neuropathic conditions (Modified from Rho and Prescott (2012). See Liu et al. (2002) for experimental data)

possible mechanistic explanations, thereby providing alternative testable hypotheses. For example, it had been assumed that the MPOs were responsible for the repetitive spiking and bursting; however, recent modeling has suggested an alternative explanation, as will be described below. In any case, the ultimate goal is to explain which of the various up- or downregulated ion channel subunits are responsible for this pathological pattern of axon excitability.

A bottom-up approach to this problem involves starting with a normal axon model and then adding or modifying ion conductances in an effort to reproduce the triad of pathological

excitability changes. Following this sort of approach, Kovalsky et al. (2009) reproduced pathological excitability by incorporating a set of sodium conductances that inactivated with rapid, intermediate, or slow kinetics. Including a range of inactivation kinetics improved upon an earlier model (Amir et al. 2002) by allowing the model to expand the voltage range across which MPOs were observed. Although successful in that respect, the MPOs in this model were characterized by an extremely narrow frequency band that was unlike experimentally observed MPOs, which show a broad peak in the power spectrum. These results suggested that upregulation of multiple different sodium channels (i.e., with a range of inactivation kinetics) is sufficient to produce MPOs and the associated changes in spiking. However, the potential role of other ion channels remained open, as did the mechanistic explanation for MPOs.

A top-down approach revealed a different, and arguably more complete, picture. Attempting to reproduce the same triad of excitability changes, Rho and Prescott (2012) started with a simple model that comprised a fast activation variable and a slow recovery variable. By systematically varying each parameter to test how excitability was altered, they found that many different parameter changes were capable of producing equivalent changes in excitability. Furthermore, because the model was two-dimensional (i.e., comprised only two state variables), it was amenable to nonlinear dynamical analysis. Phase plane and bifurcation analysis showed that qualitative changes in excitability arose from a qualitative change in the interaction between fast and slow ion channels. Under normal conditions, spikes were initiated through a quasi-separatrix crossing (Prescott et al. 2008). By contrast, under pathological conditions, spikes were initiated through a subcritical Hopf bifurcation. This single change in spike initiation mechanism could account for all three components of the neuropathic triad. Repetitive spiking occurred when stimulation exceeded the intensity needed to cause the Hopf bifurcation. Bursting occurred when a slow process like adaptation caused the system to drift back and forth across the

bifurcation point and its associated region of bistability. MPOs occurred because of noise-induced oscillations that developed when stimulation intensity was just below the intensity needed to cause a Hopf bifurcation.

Mechanistically, the Hopf bifurcation destabilized the fixed point. Because that fixed point was a focus, trajectories tended to spiral around the fixed point when that point was only weakly stable. Therefore, when the system was intermittently displaced from its weakly stable fixed point by noise, it would return to its fixed point via damped oscillations. According to this explanation, MPOs do not cause repetitive spiking; instead, MPOs and repetitive spiking are simply two different manifestations of the same dynamical process, namely, a subcritical Hopf bifurcation. MPOs in this model required noise. This illustrates an important point: although noise is ubiquitous in biological systems, its absence from many computer models can lead to certain mechanisms being overlooked. Importantly, noise-induced MPOs are characterized by a broad peak in the power spectrum, comparable to what is seen experimentally.

The observation that varying different parameters could give rise to the same excitability changes is also very important. The fast- and slow-activating conductances included in this simple model each represent multiple conductances with similar kinetics (Kepler et al. 1992); in other words, the simple model is a reduced version of a more biologically detailed model. A functionally equivalent yet higher-dimensional, detailed model would have a much greater number of parameters whose variation could cause neuropathic excitability. There is, in other words, a many-to-one mapping between molecular changes and a switch in spike initiation mechanism capable of causing neuropathic excitability. This many-to-one relationship constitutes *degeneracy* (Edelman and Gally 2001; Marder and Taylor 2011). If multiple different molecular changes are sufficient to cause neuropathic excitability, and multiple sufficient changes codevelop after nerve injury, then no single change will be necessary for the development of neuropathic excitability (Ratté et al. 2014). This is problematic

from a therapeutic perspective insofar as the ideal scenario for drug development is to have a single target that is necessary and sufficient for the pathological change. In this scenario, the pathology can be prevented or reversed when that target is hit by the appropriate drug. By contrast, if the molecular basis for neuropathic excitability is highly degenerate, then multiple different ion channels must be simultaneously targeted for the therapeutic intervention to be effective. Alternatively, one should step back to ask if there is a high-order, nondegenerate modulatory process that is coordinately regulating multiple ion channels and which would therefore constitute a better drug target.

Pros and Cons of Each Approach

Strictly speaking, the bottom-up approach requires knowledge (or reasonable suspicion) of which ion channels are changed and by how much. This information, however, remains largely unknown and is difficult to obtain through current experimental technologies. Alternatively, the bottom-up approach can be used in an exploratory fashion to identify which ion channels, if altered, could account for the change in excitability. This is essentially what Kovalsky et al. did in their study. On the other hand, a modeling study by Boucher et al. (2012) provides a good example in which a specific injury-induced change that has been quantified experimentally, namely, a leftward shift in the voltage-dependency of sodium channel activation and inactivation, was tested in a model in order to determine the effects of such a change on cellular excitability. A bottom-up approach is also very useful for testing how two or more molecular changes might interact if they occurred together.

The top-down approach is especially useful when the pattern of hyperexcitability is well described but the potential molecular causes are not, as is the case for the triad of neuropathic changes described in Fig. 1. Ideally a top-down model can reduce the phenomenology to a dynamical process within a low-dimensional space, as in the model of Rho and Prescott (2012). This provides the ability to explore the

dynamics using classical dynamical system tools to provide direct insight into the causes of pathology and relationships between different pathological manifestations.

Constructing a model that exhibits the desired pattern of hyperexcitability is an important goal for both modeling approaches. This is especially true for the top-down approach insofar as obtaining that model is a necessary first step before any other testing can be conducted. If the phenomenology of interest can be captured in a relatively simple model, then the top-down approach is feasible. It is notable that even quite simple models can manifest complex phenomena on the basis of nonlinearities. This is exemplified by the triad of neuropathic excitability changes discussed above. Nonetheless, other phenomena may require more complicated, higher-dimensional models. Finding the right parameter set for such a model can be extremely difficult. Furthermore, it is likely that there will be more than one appropriate set of parameters (degeneracy). This can be addressed through brute force modeling, in which a broad range of different parameter combinations is exhaustively tested. Alternatively, one can use genetic (or evolutionary) algorithms to help find appropriate parameter combinations more efficiently. But indeed, knowing that there is not a unique solution – that the molecular basis for cellular hyperexcitability is highly degenerate – is itself very important.

Conclusions

Nerve injury can cause a variety of changes in axonal excitability. Those changes can have debilitating consequences in terms of altered sensory, motor, and autonomic function, and so deciphering the basis for those changes is an important goal. Computer modeling can contribute significantly to delineating how such changes arise and how to strategically reverse them. Results from modeling studies indicate that changes in ion channel function or expression can qualitatively alter how action potentials are generated, which in turn affects various aspects of

excitability. The observation that equivalent excitability changes can arise on the basis of very different molecular changes is also very important.

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Pattern Formation in Neural Population Models

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Synonyms

[Turing-Hopf bifurcation](#)

Definition

Experimental studies have shown that neural population activity may exhibit certain well-structured spatiotemporal patterns, which reflect the properties of the neurons in the underlying network. The aim of neural population models is the reconstruction of such experimentally observed patterns or their prediction.

Detailed Description

Spatial patterns in neural populations and their temporal evolution have been observed experimentally in different neural structures. They emerge due to a strong interplay between the spatial physiological structure of the population, the intrinsic time scales, and the nonlinear interaction of elements. For instance, in a neural field model, these elements typically are the spatial axonal connectivity topology, the mean synaptic time scales, the nonlinear transfer function, and the additional nonlinear interactions such as synaptic depression.

One of the most important questions in the study of pattern formation is what the observed

pattern tells us about the underlying system or, put differently, why a certain pattern occurs. In this context, it is important to distinguish stimulus-induced patterns and spontaneous patterns.

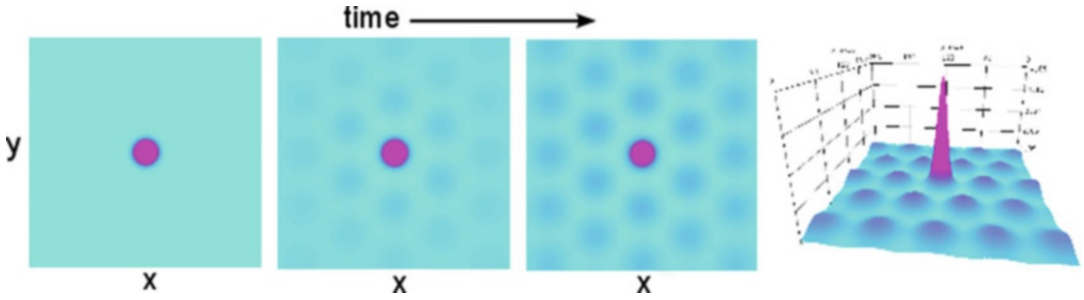
Stimulus-Induced Patterns

Neural populations are subjected to external inputs originating, e.g., from other neural areas or from electric stimulation by electrodes in physiological experiments. In the absence of external stimulation, the neural population may not exhibit any specific spatial pattern. For instance, the neural activity may be identical at each spatial location. Now inducing a localized stimulation for a longer time may reveal spatial structures or even induce complex spatio-temporal patterns. Figure 1 shows the effect of a localized stimulation on a neural field with hexagonal spatial interactions and finite axonal transmission delay. One observes that the center stimulus activates the neural population by a slow spread of activity. Since the spatial kernel exhibits excitation on a hexagonal lattice, this lattice emerges during the stimulation.

Considering a simpler rotational-invariant interaction kernel, finite axonal transmission speed, and a rotational-invariant stimulation, one does expect a spatial structure with the same rotational-invariant symmetry. Figure 2 shows the neural field activity retaining the spatial stimulus symmetry. However, the external stimulation induces oscillations of the activity bump although the stimulation is constant in time. The reason for this oscillation is the instability of the temporally constant activity bump induced by the finite axonal transmission speed which represents delayed interactions between neurons. It is important to mention that a similar stimulus in another neural field with different nonlinear actions may also lead to a break of rotational-invariant symmetry (Bressloff 2012).

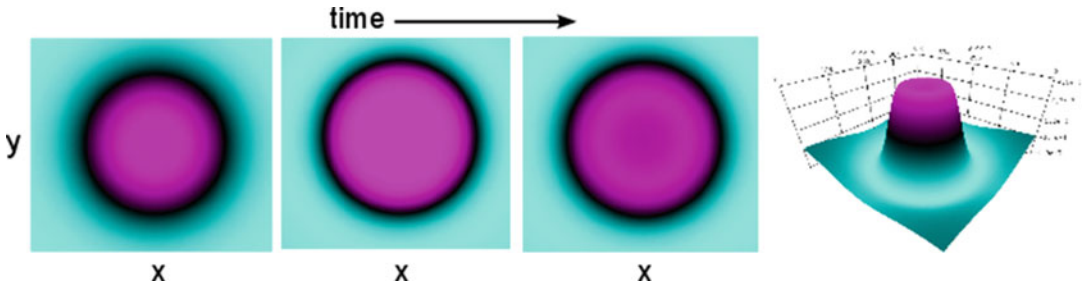
Spontaneous Patterns

If external stimuli are small, they do not evoke patterns as described in the previous section. However, spatial structures may occur



Pattern Formation in Neural Population Models, Fig. 1 Activity propagation in a homogeneous neural field involving a finite axonal transmission speed. The activity is induced by a constant external stimulus in the

center. *Left*: three snapshots of the activity spreading from the center with a finite propagation speed. *Right*: three-dimensional visualization at a late instant of time. Detailed description is given in Hutt and Rougier (2010)

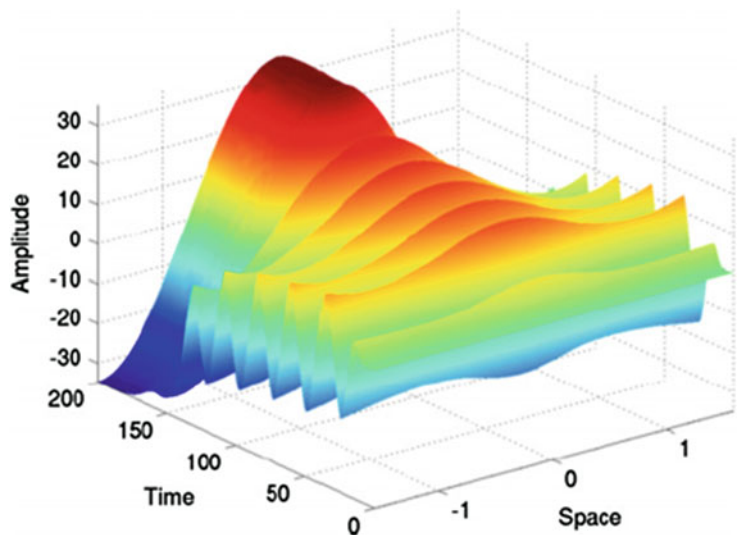


Pattern Formation in Neural Population Models, Fig. 2 Two-dimensional oscillating standing bumps (called breathers). *Left*: three snapshots illustrate the

oscillation. *Right*: three-dimensional visualization of the breather at one instant of time. Detailed description is given in Hutt and Rougier (2010)

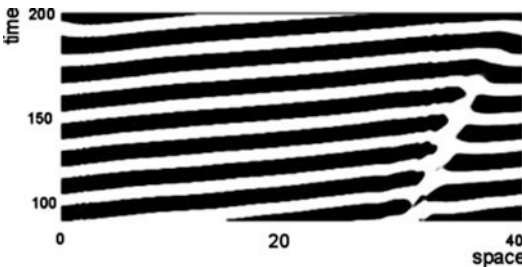
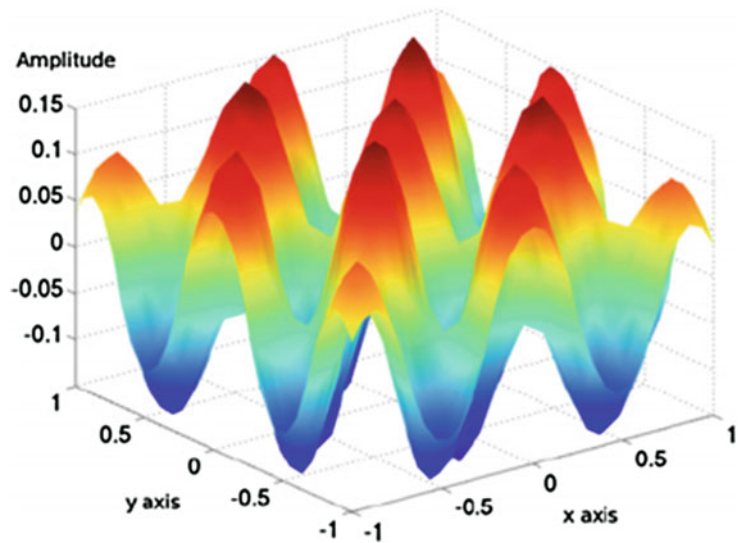
Pattern Formation in Neural Population Models,

Fig. 3 Illustration how an unstable constant state loses stability in an oscillatory manner and approaches a non-oscillatory new stable state (global bump) (Taken from Fig. 1 in Faye and Faugeras (2010), with permission)



Pattern Formation in Neural Population Models, Fig. 4

Regular spatial pattern (Turing pattern) emerged from an unstable spatially constant state (Taken from Fig. 13 in Faye and Faugeras (2010), with permission)



Pattern Formation in Neural Population Models, Fig. 5 Turing-Hopf (codimension-1) bifurcation in a one-dimensional neural field with a gamma-distributed local excitation-lateral inhibition kernel; see Hutt (2008) for more details on the mechanism

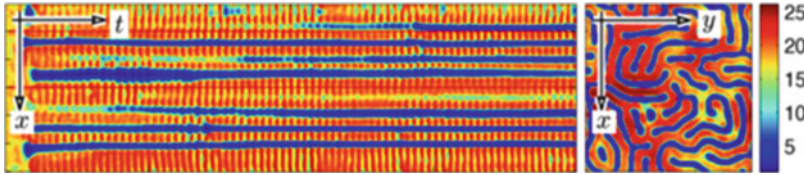
nevertheless. This is possible if a resting state constant in time becomes unstable. In the presence of small random fluctuations, e.g., in physiological parameters or the external input, the system leaves the vicinity of the resting state and approaches a new stable state. The existence of such a new stable state is strongly determined by both by the nonlinear dynamics close to the stationary state and the spatial interactions in the population (Bressloff 2012). Close to the bifurcation point, the linear dynamics of the resting state determines the approximate dynamics of the new stable resting state. For instance, if the resting state loses stability and the system leaves the vicinity of the state while oscillating, then the new stable state oscillates as well with a similar

frequency. Moreover, if the system prefers a certain spatial structure while losing stability, this spatial structure shows up in the new resting state.

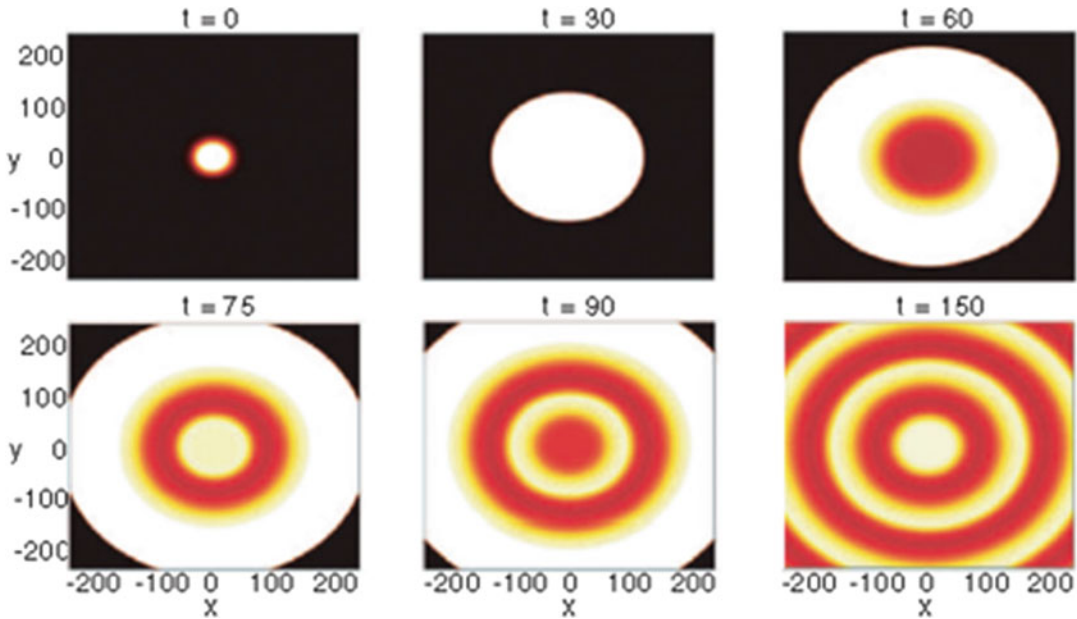
Initial Constant State

First, let us consider a spatially constant stationary state which is unstable (Fig. 3). Small perturbations push the system from this unstable state, and it then evolves according to the intrinsic properties of the unstable state. In the case of the field in Fig. 3, the neural field involves transmission delay between neurons, and the stationary state is oscillatory unstable. Hence it oscillates while approaching the new stable state, which is a constant spatial bump. Since the bump is stable, the system remains in this state. It is important to note that the initial unstable state was constant and the final stable state has a different spatial shape.

The new stable state may even exhibit a more complex pattern. One of the simplest but non-trivial cases is a Turing pattern that is constant in time but exhibits a regular spatial pattern with a single spatial frequency. The spatial pattern shown in Fig. 4 emerges from a constant state, and the selection of the spatial frequency results from the nonlinear spatial interaction in the system; see, e.g., Bressloff (2012) and Hutt et al. (2003) for further explanations.



Pattern Formation in Neural Population Models, Fig. 6 Turing-Hopf (codimension-2) bifurcation in a two-dimensional neural field (Taken from Fig. 5 in Steyn-Ross et al. (2013), with permission)



Pattern Formation in Neural Population Models, Fig. 7 An initial circular stimulation triggers the circularly spreading activity front followed by the onset of an oscillation with radius-dependent phase lag. This phase lag

leads to the impression of a pulsatile activity with rings spreading from the center. The neural field under study considers synaptic depression (Taken from Fig. 14 in Bressloff (2012), with permission)

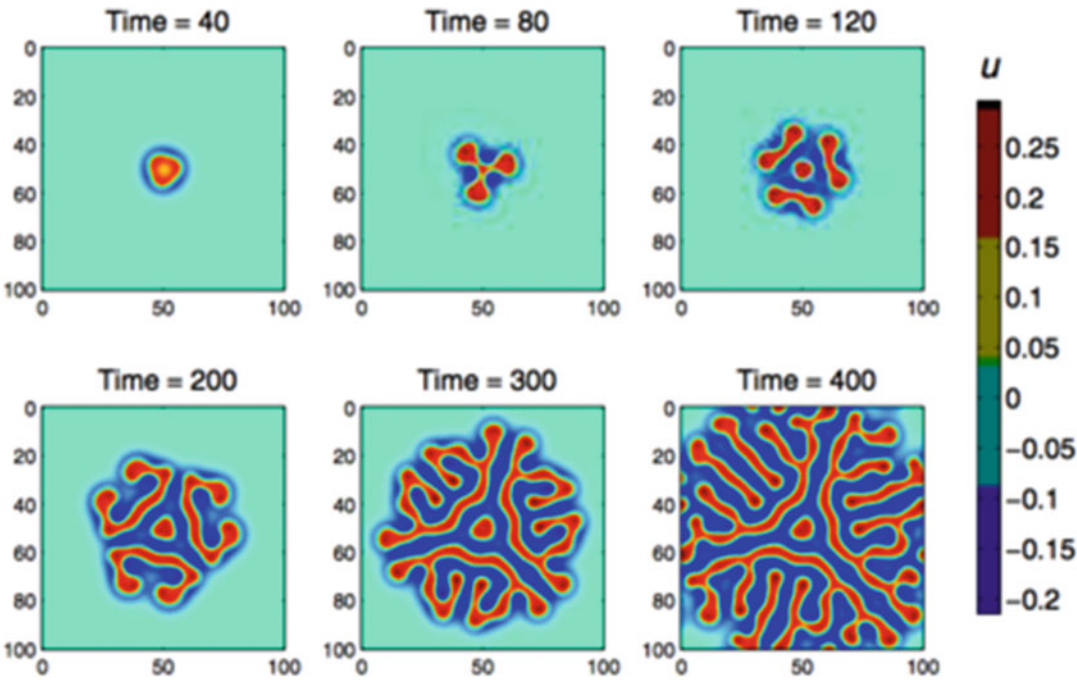
Turing instabilities are known to result from locally excitatory-laterally inhibitory interactions. This interaction enforces the local activity of neurons and reduces their activity in the neighborhood and hence prefers localized structures. Historically, this interpretation has been formulated first for partial differential equation models, where it holds true in most cases. However, it can be shown that this interaction type might lead to instabilities which exhibit a periodicity in space and time, so-called Turing-Hopf bifurcations. If the change of a single physiological parameter destabilizes a spatially constant state and a spatially and temporally oscillatory pattern emerges, then this instability is called wave instability or

sometimes codimension-1 Turing-Hopf instability, cf. Fig. 5.

If the change of one physiological parameter leads to a Turing bifurcation and the synchronous change of another parameters renders the system oscillatory unstable (Hopf instability), then two instabilities occur synchronously and the Hopf and Turing patterns overlap. This bifurcation is called Turing-Hopf codimension-2 bifurcation; cf. Fig. 6.

Initial Pattern

For initial constant states, the new stable pattern reflects the intrinsic spatial interactions. If the



Pattern Formation in Neural Population Models, Fig. 8 The localized initial triangular-shaped activity breaks the rotational symmetry and induces the growth of

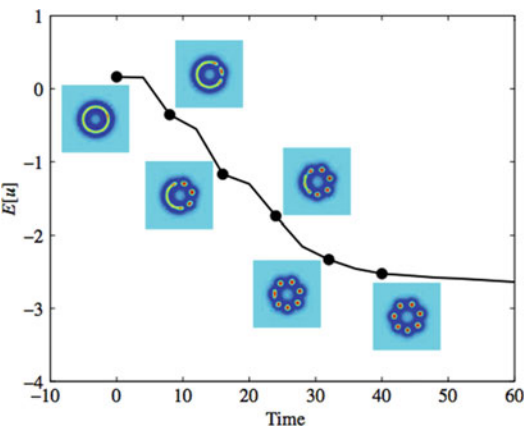
a complex pattern (Taken from Fig. 5 in Owen et al. (2007), with permission)

initial state has a certain spatial structure, the new stable state may take over this pattern or slightly modify it. Figure 7 shows the temporal evolution of a rotationally invariant structure, whose symmetry follows from the initial structure. However the involved nonlinearities lead to a complex spatiotemporal evolution while retaining the initial rotational symmetry.

This concept of retaining the initial symmetry is also present in Fig. 8 in the first part of the transition phase (until time = 80), where the evolving structure still has the triangular symmetry of the initial state. However, the further the system moves away from the initial state, the less pronounced is the initial structure, and the new complex structure does not resemble anymore the initial state.

Lyapunov Functional

In order to learn more about the transients from an unstable to a stable state, e.g., about the time when



Pattern Formation in Neural Population Models, Fig. 9 The Lyapunov functional $E[u]$ subjected to time during the transient phase from an unstable initial state (circle) to a circle of isolated bumps (Taken from Fig. 12 in Owen et al. (2007), with permission)

the system reaches the stable state, it is useful to compute the Lyapunov functional for neural fields $\mathcal{L}$ (French 2004). The functional $\mathcal{L}$ is computed at each instant taking into account the systems

properties and spatial activity. It decreases in time and reaches its local minimum when the state reaches a new stable state. For illustration, one can think of a high-dimensional landscape whose altitude is given by $\mathcal{L}$. Figure 9 shows the Lyapunov functional during the temporal evolution of a neural field, and the final state is reached when the Lyapunov functional does not change anymore.

Cross-References

- [Bifurcation Analysis](#)
- [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- [Bifurcations, Neural Population Models and](#)
- [Chaos, Neural Population Models and](#)
- [Neural Population Model](#)

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Perception, Bayesian Models of

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Definition

Bayesian models of perception use optimal statistical methods to perform inference based on perceptual data. These models are used in computational neuroscience and cognitive psychology to explain how the nervous system processes perceptual information.

Detailed Description

Bayesian inference provides the optimal statistical inference about unknown properties given a

Further Reading

Amari S (1977) Dynamics of pattern formation in lateral-inhibition type neural fields. *Biol Cybern* 27:77–87

stochastic process. Bayesian models of perception work under the hypothesis that the nervous system uses perceptual information as if it was able to optimally process the information according to a Bayesian inference model. The majority of models propose how the nervous system processes discrete cues (flash of light, auditory beep), but models have also been proposed for, e.g., learning in perception.

All Bayesian models start by specifying the generative process along with the associated probability distributions (e.g., prior and likelihood distributions). Using Bayes' rule (examples below), the generative process is reversed to an inference process to find the posterior probability distributions over the variables of interest. If a single variable estimate is needed (e.g., an experimental subject has to perform a button press), a subjective utility function can be combined with the posterior distribution to find the optimal response, e.g., the mean or the maximum of the posterior.

It is thus implicitly assumed in Bayesian models of perception that the nervous system is able to represent all the variables and the processes in such a Bayesian inference, including the likelihood, prior, decision process, etc.

Effect of Prior Knowledge

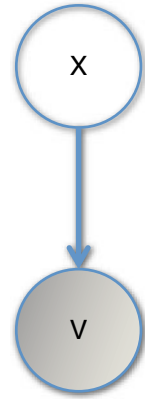
The simplest case of perceptual Bayesian inference involves a single cue having been generated from a single source (Fig. 1), e.g., the visual stimuli from a moving object providing some noisy information about the true velocity (Weiss et al. 2002). The task of inferring the true velocity of the object, X , requires the use of Bayes' theorem

$$P(X|V) \propto P(V|X)P(X) \quad (1)$$

which states that the posterior probability of the true property conditional on the observed variable $P(X|V)$ is proportional to the product of the likelihood function $P(V|X)$ and the prior $P(X)$.

Thus, the current sensory information and its associated uncertainty (given by the likelihood)

Perception, Bayesian Models of, Fig. 1 Simple Bayesian model for inference based on one cue. The *gray circle* indicates an observed variable, while *white* is unobserved



combine with previous information (given by the prior) to produce the new estimate of the unknown variable.

Usually, the prior and likelihood will be specified in a way such that the posterior has the same analytical form as the prior (i.e., conjugate), e.g., by using Gaussian probability distributions.

Once the posterior probability distribution for X is specified, $P(X|V)$, a subject is assumed to make a choice, $\hat{X}$, based on, e.g., the mean or maximum of the distribution (dependent on the subjective utility function specified).

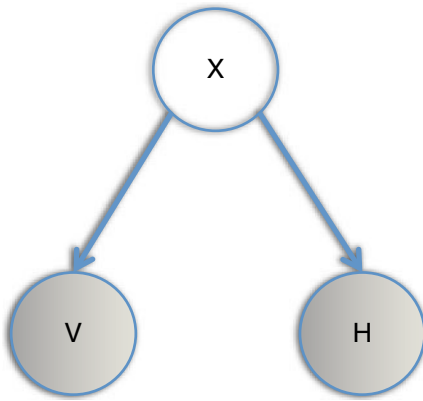
Cue Integration

When multiple cues provide independent information about the same source (see Fig. 2), it is optimal to combine the information from the two sources (Knill and Pouget 2004), e.g., haptic and visual information about the width, X , of an object

$$P(X|V, H) \propto P(V|X)P(H|X)P(X) \quad (2)$$

under the assumption that the uncertainty in the two percepts of the two stimuli are independent given the source.

Thus, the two current sensory cues and their associated uncertainty (given by the likelihoods) combine with previous information (given by the prior) to produce the new estimate of the unknown variable. When the likelihoods and priors are represented by Gaussian probability distributions,



Perception, Bayesian Models of, Fig. 2 Bayesian model for inference based on two cues

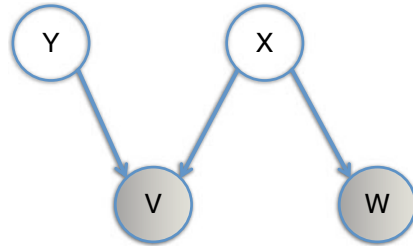
$N(\mu, \sigma^2)$, the posterior also becomes a Gaussian probability distribution, $N(\mu_X, \sigma_X^2)$, with the mean and variance specified through weighting the individual stimuli by their uncertainty:

$$\begin{aligned} \mu_X &= \frac{\mu_V/\sigma_V^2 + \mu_H/\sigma_H^2}{1/\sigma_Z^2}, \quad \sigma_X^2 \\ &= \frac{1}{1/\sigma_V^2 + 1/\sigma_H^2} \end{aligned} \quad (3)$$

Accordingly, subjects can decrease their perceptual uncertainty (σ_X^2 is smaller than either σ_V^2 or σ_H^2) and should rely more on the stimulus with smaller uncertainty. This linear weighted contribution has been tested for many combinations of either multi- or uni-sensory cues with generally good correspondence for small discrepancies between the cues (Trommershauser et al. 2011).

Explaining Away

Another potential way of cue interaction comes from a model that allows the inferred variability about one cue to be able to “explain away” the variance of another cue (Kersten et al. 2004) due to the generative structure (see Fig. 3). An example is the estimation of the shape of an object (e.g., concave or convex) given the visual image and a cue toward the location of the source of lighting:



Perception, Bayesian Models of, Fig. 3 Bayesian model for inferring a variable using explaining away

$$P(Y|V, W) \propto P(Y) \sum_X P(W|X) P(V|X, Y) P(X) \quad (4)$$

The knowledge about a cue for lighting direction W restricts the range of values for the true direction of lighting X in turn allowing a better estimate of the shape Y .

This model has been used to explain a number of phenomena in human vision (Knill and Richards 1996) where different cues influence the percept of a visual scene.

Causal Inference

When multiple sources and multiple cues are available in the world, a problem of cue assignment becomes apparent (Shams and Beierholm 2010). One Bayesian solution to this is to infer the potential causal structure that gave rise to the stimuli observed (see Fig. 4). For example, if two observed stimuli (V and A) may have arisen from either the same sources or separate sources, Bayesian inference can be used to infer the most likely causal structure:

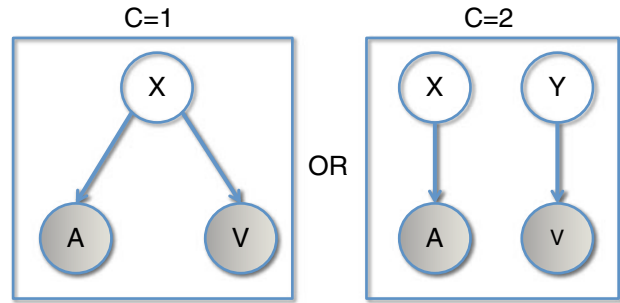
$$P(C|V, A) = \frac{P(V, A|C)P(C)}{\sum P(V, A|C)P(C)} \quad (5)$$

Once a probability for each causal structure has been inferred, the distribution of any unknown variable, e.g., X , can be found:

$$P(X|V, A) = \int P(X|V, A, C) P(C|V, A) dC \quad (6)$$

Perception, Bayesian Models of,

Fig. 4 Bayesian model for causal inference based on two cues and two possible causes



$$= P_{C=1}(X|V, A)P(C = 1|V, A) + P_{C=2}(X|A, V)P(C = 2|V, A). \quad (7)$$

where $P_{C=1}(X|V, A)$ is the posterior probability of X given A, V according to the single cause model ($C = 1$), similarly for $P_{C=2}(X|V, A)$.

Getting an estimate of $\tilde{X}$ such as the mean of the posterior is thus equivalent to performing model averaging:

$$\tilde{X} = P(C = 1|V, A)\tilde{X}_{C=1} + P(C = 2|V, A)\tilde{X}_{C=2} \quad (8)$$

where $\tilde{X}_C$ indicates the optimal estimate according to the causal structure C (e.g., see the solutions for one or two sources above). Several models have been proposed that although structurally different also try to explain subject behavior dealing with multiple cues and sources (see, e.g., Ernst (2006)).

Other Bayesian Models of Perception

Apart from models of cue combinations, other studies have also suggested Bayesian models for, e.g., visual learning (Orbán et al. 2008; Feldman 2001).

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Cognition, Bayesian Models of](#)

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Perceptron Learning

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Synonyms

[Learning in feed-forward neural networks](#)

Definition

The perceptron is a neural network based in the nonlinear McCulloch-Pitts neuron model. It is composed of a single layer of N neurons (presynaptic) that are connected by means of uni-directional or feed-forward connections, or synapses, to a unique (postsynaptic) neuron (see Fig. 1). This “single-layer” perceptron is the simplest feed-forward neural network. On the other hand, the perceptron learning algorithm is the procedure by which this network adjusts its connection intensities, or synaptic weights, and the postsynaptic neuron threshold (also known as bias) to correctly classify a given number of inputs into desired output values. The perceptron learning algorithm was proposed by F. Rosenblatt (1958). It is the first example of the so-called supervised learning, that is, learning with a teacher, since the connection intensities and the threshold are adjusted according to the error obtained in the classification of the inputs. The perceptron learning algorithm can be used to implement simple Boolean functions such as AND and OR but fails to correctly implement the XOR (exclusive-or) Boolean function (see below). In this last case, it is necessary to include additional layers of neurons, denoted as hidden layers (Peretto 1992). The network architecture, functioning, and use of

Rosenblatt perceptron is similar to other artificial neural network developed at the same time and known as “Adaline” proposed by B. Widrow and T. Hoff (1960).

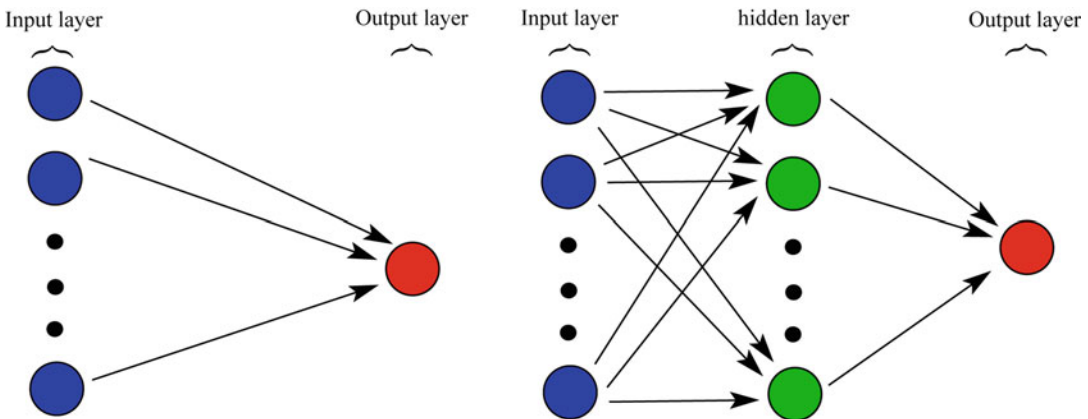
Detailed Description

The perceptron is a binary classifier which maps an input X (a vector with N real components) to an output value $Y(X)$ (a single binary value) in the form (see Fig. 2):

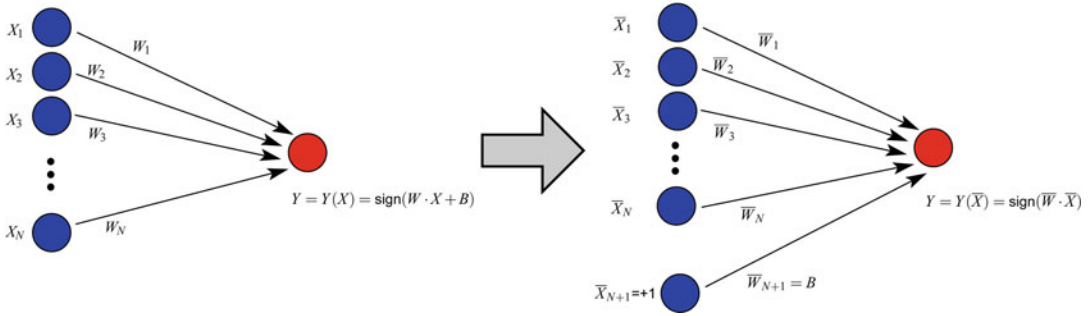
$$Y(X) = \text{sign}(W \cdot X + B) = \begin{cases} 1 & \text{if } W \cdot X + B > 0 \\ -1 & \text{Otherwise} \end{cases}, \quad (1)$$

where W is a vector of N real-valued synaptic weights, $W \cdot X$ is the dot product (which therefore computes a weighted linear combination of the inputs), and B is a “bias” term, that is, a constant term that does not depend on any input value and usually is related with a postsynaptic neuron threshold ($B = -\theta$).

In the case of a binary classification problem, the output value $Y(X)$, namely 1 or -1 , is used to classify X into one of two classes, C_1 or C_{-1} , respectively. These two classes then correspond



Perceptron Learning, Fig. 1 Scheme showing the architecture of a single-layer (left) and multiple-layer (right) perceptron with a hidden layer



Perceptron Learning, Fig. 2 Perceptron neural network with input and weights vectors X and W (left) and its transformation into a perceptron with extended input $\bar{X}$ and weights $\bar{W}$ vectors (right)

to two different decision regions in which the N -dimensional space of input vectors is separated by a hyperplane, denoted as decision boundary, and defined by the identity:

$$W \cdot X + B = 0.$$

The effect of the bias B is to alter the position of the decision boundary by means a shift around the position in the input space defined by the vector $X = 0$ without altering the orientation of this hyperplane.

For proper operation of the perceptron, the two classes of inputs vectors, C_1 and C_{-1} , must be linearly separable. That is, the input vectors X to be classified must be sufficiently separated from each other in the N -dimensional space to ensure that the decision surface consists of a hyperplane. On the contrary, if C_1 and C_{-1} are not linearly separable, the perceptron learning will never reach a point where all input vectors are classified properly. A well-known example of nonlinearly separable classes of input vectors where the perceptron algorithm fails to correctly classify the inputs is the Boolean exclusive-or (XOR) problem where the decision boundary is not a hyperplane.

Algorithm Description

The algorithm is able to determine the discriminant plane equation from a given number of correctly classified examples. For a better

understanding of the algorithm, it is more convenient to extend the dimensionality of the input and weights vectors as follows (see Fig. 2):

$$\begin{aligned} X &= (X_1, \dots, X_N) \rightarrow \bar{X} = (X_1, \dots, X_N, 1) \\ W &= (W_1, \dots, W_N) \rightarrow \bar{W} = (W_1, \dots, W_N, B). \end{aligned}$$

In this way, the bias is interpreted as a synaptic weight driven by a constant input equal to 1. Using this new notation, the condition in Eq. (1) for mapping the extended inputs $\bar{X}$ in the two classes C_1 y C_{-1} now becomes:

$$\begin{aligned} Y(\bar{X}) &= \text{sign}(\bar{W} \cdot \bar{X}) \\ &= \begin{cases} 1 & \text{if } \bar{W} \cdot \bar{X} > 0 \\ -1 & \text{Otherwise} \end{cases}, \end{aligned} \quad (2)$$

and the decision boundary is now given by the identity:

$$\bar{W} \cdot \bar{X} = 0.$$

Now select a set of extended inputs vectors $\bar{X}$ that will be considered as the training set, and assume that are correctly classified in class C_1 or in class C_{-1} . This means that there exists an extended weight vector $\bar{W}$ such that:

$$\begin{aligned} \bar{W} \cdot \bar{X} &> 0 & \text{if } \bar{X} \text{ belongs to class } C_1 \\ \bar{W} \cdot \bar{X} &\leq 0 & \text{if } \bar{X} \text{ belongs to class } C_{-1}. \end{aligned}$$

The perceptron learning algorithm then is performed as follows:

1. Initialization: An extended weight vector $\overline{W}_0$ is generated randomly at $t = 0$.
2. Test: At any iteration t , choose at random a training vector $\overline{X}$ from the training set and compute $\overline{W}_t \cdot \overline{X}$. If $\overline{X}$ is correctly classified with the current vector of weights $\overline{W}_t$, then choose:

$$\overline{W}_{t+1} = \overline{W}_t$$

and go to step 2. Otherwise:

- (a) if $\overline{W}_t \cdot \overline{X} > 0$ and $\overline{X}$ belongs to C_{-1}

$$\overline{W}_{t+1} = \overline{W}_t - \eta \overline{X}$$

and go to step 2,

- (b) if $\overline{W}_t \cdot \overline{X} \leq 0$ and $\overline{X}$ belongs to C_1

$$\overline{W}_{t+1} = \overline{W}_t + \eta \overline{X}$$

and go to step 2.

The parameter $\eta > 0$ describes the rate of learning of each iteration. This algorithm corrects the extended weight vector (weights and bias) whenever one of training vectors belonging to C_1 or C_{-1} has not been classified correctly. The perceptron convergence theorem guarantees that if the training set is linearly separable into C_1 or C_{-1} , then the weights vector $\overline{W}$ is updated only a finite number of times. The algorithm can be stopped when all vectors are correctly classified.

Since the output $Y(\overline{X})$ is binary, the algorithm can be written in a simpler way as follows:

1. Initialization: An extended weight vector $\overline{W}_0$ is generated randomly at $t = 0$.
2. Test: At any iteration t , choose at random a training vector $\overline{X}$ from the training set, and compute $\overline{W}_t \cdot \overline{X}$ and the binary output $Y(\overline{X})$ according to Eq. (2). Then update the weights according to the rule:

$$\overline{W}_{t+1} = \overline{W}_t + \frac{\eta}{2} [Y^c(\overline{X}) - Y(\overline{X})] \overline{X} \quad (3)$$

and go to step 2

where $Y^c(\overline{X})$ represents the correct output to the training input vector $\overline{X}$.

The weights updating rule (3) is similar to the so-called “Delta rule” or “backpropagation” algorithm first introduced in the “Adaline” learning algorithm (Widrow and Hoff 1960). In this sense, the perceptron can be considered as a particular case of the Adaline neural network for the case of binary outputs $Y(\overline{X})$ instead of a differentiable and, in general, nonlinear, real-value function $Y(\overline{X})$ of the inputs considered in the Adaline neural network. Since in this last case $Y^c(\overline{X})$ never exactly match the correct outputs, $Y^c(\overline{X})$ is necessary to introduce an error function $E = \frac{1}{2} [Y^c(\overline{X}) - Y(\overline{X})]^2$ and a convergence criterion over this error function for the correct classification of the inputs. In the case of the perceptron, however, one directly has $E = 0$ when the inputs $\overline{X}$ are correctly classified since $Y(\overline{X})$ and $Y^c(\overline{X})$ are binary, so no convergence criterion over E is needed.

The “Delta rule” in Adaline is obtained when weights are modified during learning trying to minimize the error E in the output of the network through a gradient descent procedure, that is,

$$\overline{W}_{t+1} = \overline{W}_t - \eta \nabla_{\overline{W}} E$$

which takes the form given by Eq. (3) for the perceptron.

Storage Capacity of Perceptrons

The maximum number P of random input vectors X^μ , $\mu = 1, \dots, P$ that can be trained and correctly classified in a perceptron with an input layer of N neurons was analytically computed by E. Gardner (1988) using a statistical mechanics framework and assuming that the weights were constrained such that $\sum_j \overline{W}_j^2 = N$. Within this framework, it is assumed that a training vector is correctly classified when the product:

$$Y(\overline{X}^\mu) \frac{1}{\sqrt{\sum_j \overline{W}_j^2}} (\overline{W} \cdot \overline{X}^\mu) > K,$$

being $K > 0$ a measure of the basin of attraction of each input vector X^μ . The resulting maximal storage capacity $\alpha_c = P/N$ was:

$$\alpha_c = \left[\int_{-K}^{\infty} \frac{e^{-\frac{z^2}{2}}}{\sqrt{2\pi}} (z + K)^2 dz \right]^{-1}$$

which gives $\alpha_c = 2$ for $K = 0$, a result previously obtained by T.M. Cover (1965).

Cross-References

► [Hopfield Network](#)

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Perceptual Alternations

► [Multistability in Perception Dynamics](#)

Perceptual Bistability/Tristability

► [Multistability in Perception Dynamics](#)

Perceptual Correlates

► [Prosthetic Vision, Perceptual Effects](#)

Perceptual Decision-Making

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Definition

Perceptual decision making is the process by which sensory information is used to guide behavior toward the external world. This involves gathering information through the senses, evaluating and integrating it according to the current goals and internal state of the subject, and using it to produce motor responses. In contrast to choice behavior and decision making in general, which are closely related concepts traditionally studied by psychologists, behavioral ecologists, and economists, perceptual decision making emphasizes the role of sensory information in directing behavior (e.g., during a choice). Thus, within neuroscience, the goal is to reveal the computational mechanisms whereby neural circuits encode, store, and analyze perceptual signals; combine them with other behaviorally relevant information; and use them to resolve conflicts between competing motor plans.

P

Detailed Description

Studies in perceptual decision making aim to explain the behavior of a subject in terms of the activity of relevant cells and molecules in its nervous system. This requires not only methods from psychology (to characterize behavior) and neurophysiology (to measure and record neuronal activity) but also mathematical and analytical methods to bridge the results at the two levels. So, behavior, neurophysiology, and computational modeling are three important themes that are interleaved in the rest of this entry.

Historically, the foundations of the field were clearly laid out by the 1960s, with some notable studies strongly integrating the three elements just

mentioned (Werner and Mountcastle 1963, 1965; Werner 1980). However, these early studies had two main limitations: first, they compared sensory experiences in one system, humans, with neural events evoked by similar stimuli but in different sensory systems, i.e., those of various anesthetized animals; and second, although many sophisticated analytical tools such as information theory and signal detection theory were already in use, their applicability was limited because cheap, powerful computers were not yet available. Contemporary studies, in contrast, typically combine psychophysical results with neurophysiological data obtained simultaneously from the same subject (Parker and Newsome 1998) and are often complemented by a wealth of computational analyses and model simulations.

Perceptual decision making has been investigated in numerous animal models, and each species has its own advantages and limitations. Determining how a specific neuron or population of neurons associated with a given sensory modality contributes to behavior is generally easier both in relatively simple organisms, such as worms (chemosensation), flies (visual motion), or leeches (touch), and in highly specialized ones, such as electric fish (electrosensation), bats, owls, or songbirds (audition). However, much work has traditionally been carried out in monkeys, which exploit multiple sensory modalities and have wide behavioral repertoires, and more recently in rodents. After discussing one example of a simple system and providing some historical and conceptual background, we focus mainly on two computational principles, originally derived from studies in monkeys, that broadly describe how perceptual decisions are generated.

Perceptual Decision Making in a Simple Organism

The nematode *Caenorhabditis elegans* has a nervous system of exactly 302 neurons whose anatomical connectivity, or wiring diagram, is virtually complete. This tiny worm produces movement by undulating its body. Within the confines of a Petri dish, much of its behavior

depends on the balance between two tendencies: whether to continue the bout of relatively straight movement in the current direction (known as a “run”) or to briefly stop and reorient to a new, random direction (i.e., making a “turn”). Individual neurons in this system can be characterized in great detail in terms of their genetic, functional, and molecular properties; thus, dynamic interactions between sensory receptor neurons, interneurons, and motor neurons can be tightly correlated not only with specific behaviors but also with specific neurotransmitters and signaling molecules (Faumont et al. 2012). For instance, avoiding a toxic substance involves relatively few steps: (1) on and off sensory neurons respond to increases or decreases in stimulus strength (substance concentration), respectively. (2) These sensory cells excite or inhibit two pools of opposing chemosensory interneurons, one that acts to maintain the current direction and another that promotes turns. (3) The two interneuron pools then activate two pools of premotor or command interneurons, one that enables forward movement and another that opposes it. (4) Motor neurons, which are distributed along the length of the worm and produce undulatory locomotion, receive input from the command interneurons via chemical synapses and gap junctions. (5) Finally, depending on the relative activations of the two pools of command interneurons, the undulatory movement may either continue, to prolong the current run, or stop, to generate a turn. In essence, the worm behaves as if at each point in time it flipped a coin to decide whether to turn or not, with the environment (sensed via sensory receptor neurons) and its internal state (set by specific neural responses and signaling molecules) determining the bias of the coin. This stochasticity, however, does not hinder identification of the relevant physiological and molecular events. Thus, by observing the worm’s movements, it is possible to precisely identify the cells and molecules that control sensory-driven behaviors (Faumont et al. 2012), say, determining whether a source of food is benign or pathogenic (Zhang et al. 2005) or whether to cross a dangerous region to reach a potential food source (Shinkai et al. 2011). An

essentially complete understanding of how this creature makes sensory-driven decisions seems achievable for any particular behavior.

C. elegans may seem “simple” because, considering all the possible combinations of its sensory inputs, internal states, and motor responses, the resulting space appears large yet manageable. In contrast, species with larger nervous systems are more complex in all respects: they collect much more sensory information per unit time; have a much larger variety of internal states, which will depend strongly on the history of each individual; and may produce many more motor actions. Accordingly, the number and variety of behavioral decisions that, say, a mouse can make – and can *learn* to make – must be astronomical and, for all practical purposes, infinite. To turn such complexity into an evolutionary advantage, an enormous degree of flexibility must be necessary. Indeed, whereas differences between certain, closely related species may often seem striking (e.g., compare a beaver to a naked mole rat), perhaps it is more remarkable that an individual from the same species can tune her perceptual and motor systems to become a pianist, a tennis player, a chess player, or a portrait artist (or, conceivably, all four). In what follows, we will not explicitly address the mechanisms that allow neural circuits to be functionally reconfigured – relatively little is known about this (Salinas and Bentley 2009; Marder 2011; Palmer and Kristan 2011) – but it is important to keep in mind that such flexibility must be a crucial property of all the neural circuits that will be discussed.

Importance of Task Design and Behavioral Context

In terms of behavior, perceptual decision making has been investigated mostly via two-alternative forced-choice tasks in which the subject has to use available sensory information (e.g., visual cues) to make a response. In general, the subject’s performance in such tasks depends on four factors that are at least partially independent and dissociable: (1) the sensory stimuli, (2) the subject’s perceptual capacity, (3) the subject’s motor capacity, and

(4) the subject’s internal state, which is partly set by the behavioral context. The importance of the last point cannot be overstated, as it includes potent modulators such as motivation or attention, which can drastically alter both motor planning and perceptual processing; in fact, context (e.g., thirst) determines whether a subject will cooperate in performing a given task in the first place.

Traditionally, there are four elementary questions that can be asked about the magnitude of a sensation, each one leading to one of four classic psychophysical tasks: “Is there anything there?” defines the detection problem; “What is it?” determines the recognition or identification problem; “How much of it is there?” corresponds to the scaling problem; and finally, “Is this different from that?” defines the discrimination problem – which, historically, is associated with the foundation of quantitative psychophysics (Werner 1980). Through these tasks, early research attempted to find systematic relationships between a stimulus parameter, such as the brightness of a light or the loudness of a sound, and the magnitude of the perceived sensation reported by human subjects. Weber’s law and the logarithmic and power-law relationships proposed by Fechner and Stevens, respectively, are well-known examples of this (Gescheider 1997), but a crucial realization was that such relationships cannot be fully distinguished unless something is known about the neural code interposed between the physical stimulus and the perceived sensation (Johnson et al. 1996). That is, behavioral studies are not enough; to understand perception, one must look at the underlying neuronal activity (Parker and Newsome 1998).

Early attempts to link perception and neurophysiology followed the classic psychophysical methodology. For instance, Werner and Mountcastle (1965) investigated the responses of primary mechanosensory afferents elicited by brief (~400 ms) tactile stimuli generated via a small probe (1 mm diameter tip) indenting the skin. They varied the amplitude of the indentation (0–600 μm), S , and found that, in cats and monkeys, under a variety of experimental conditions, the mechanosensory responses were well described by the relation $R = k S^n$, where R is

the number of action potentials evoked during stimulation, k is a constant, and n is a positive exponent typically smaller than 1. Besides establishing such relationship between physical stimulus and neuronal response, they also noted that magnitude estimates of touch sensations reported by humans under similar experimental conditions were also well fitted by a power law with slightly different k and n parameters. An interesting consequence of these relationships is that “the neural transforms intervening between input and the final verbal description of an introspective magnitude estimation must be linear for the intensive continuum” (Werner and Mountcastle 1965). In other words, when touching the hood of a car to feel whether it is running or not, the subjective intensity of the vibrations reported by a person must be directly proportional to the firing rate of the somatosensory neurons that are activated by the engine’s vibrations. Such proportionality between perceived magnitude and neuronal activity seems to remain true for other stimulus features too, such as the roughness of a surface (Johnson et al. 1996).

In contrast to these early studies, recent experiments are often more ambitious, aiming to investigate how other factors in addition to the physical properties of one stimulus impact perceptual performance. This may be achieved by manipulating reward amounts, stimulus probabilities, or temporal constraints; by introducing probabilistic reward schedules and other uncertainties; or by requiring the subjects to consider multiple stimulus features or cues simultaneously in order to maximize the likelihood of a correct response. Here, the subject has to consider all the task constraints, compute the net values of all the available options, and simply ask “Which option is more desirable?” The investigator then tries to determine how all the identified factors that may impact desirability are internally weighted and how they affect overall performance, the neural responses, and the perceptual judgment itself (Kennerley and Walton 2011; Padoa-Schioppa 2011; Cisek 2012).

Perceptual decisions generally involve the analysis of sensory information and the planning and execution of a motor action, both of which are

affected by task contingencies, even in the simplest cases. For example, when monkeys are trained to look at a single, highly salient target, their eye movements are more accurate and are triggered more rapidly, i.e., with shorter reaction times, or **RTs**, when a large reward is at stake than when a low reward is at stake (Takikawa et al. 2002). So, when motivated, the monkeys make haste without compromising accuracy. It is remarkable that motivation has an impact even on eye movements to single targets, because these are highly stereotyped and relatively effortless. Under somewhat more complicated conditions, when monkeys have to rapidly choose between a target and a distracter and the urgency of the discrimination varies across trials, the impact of the potential reward is more subtle: when a large reward is at stake, the eye-movement responses (i.e., saccadic RTs) become slightly *slower* than when a small reward is at stake, thus providing slightly more stimulus viewing time to the subjects, but the perceptual analysis itself proceeds more rapidly and more accurately for a given amount of viewing time (Shankar et al. 2011). This makes sense because both effects together, slower motor execution and faster/more efficient perceptual discrimination, increase the rate of successful outcomes per unit time in this case. These two examples show that motivation may impact performance in complex ways, not only by speeding up or slowing down the subject’s motor plans, as appropriate, but also by modulating the efficacy of the perceptual evaluation itself. More generally, contextual and internal factors may strongly influence how perceptual information is processed and whether it is taken into account at all (Kawagoe et al. 1998; Palmer and Kristan 2011).

Elementary Computational Principles in Perceptual Decision Making

Research on perceptual decision making in non-human primates has revealed two general computational principles that seem to apply across species, modalities and task conditions: one, that perceptual decisions depend on a comparison

between pools of neurons that are selectively tuned for the sensory features that distinguish each option, and two, that the influence of sensory information on the circuits that directly generate motor choices is not instantaneous, but rather accumulates gradually over time (Gold and Shadlen 2007; Heekeren et al. 2008). So, consider, for instance, a driver that reaches an intersection and must decide whether to step on the brake or the accelerator based on standard traffic light rules, i.e., green light $\rightarrow$ go, red light $\rightarrow$ stop. First, when the intersection is reached, competing motor plans for pressing the brake and the accelerator are initiated; once the stoplight is in view, groups of color-sensitive visual neurons are activated; the responses of red- and green-selective neurons then bias the competition in favor of the motor plans for pressing the brake or the accelerator, respectively; over time, one of these plans – namely, the one congruent with the actual color of the stoplight – increases much more than the other, until at a certain point (when activity exceeds a threshold level) it triggers the corresponding motor action. Several key issues are easy to appreciate from this example: how does the decision-making process change when the sensory information is degraded (e.g., the driver forgot her glasses), when the urgency of the decision increases (e.g., the car approaches the intersection very fast), when one of the actions is strongly preferred (e.g., the driver is in a hurry), or when the motor reactions are slow (e.g., the brake pads in the car are worn out)? All of these situations have experimental counterparts. We now discuss experimental results that support this general framework and illuminate specific aspects of the process whereby sensory information guides a motor choice.

Discriminating Randomly Moving Dots

Much of what is known about the two principles just mentioned derives from single-neuron recordings in awake monkeys trained to perform perceptual decision-making tasks. In such tasks, the animal is presented with a sensory stimulus (images displayed on a monitor, in the case of

vision), it must then analyze it according to the rules of the task and must report its judgment by making a particular motor action (Parker and Newsome 1998; Romo and Salinas 2001). One of the most studied tasks with this structure is the random-dot motion (**RDM**) discrimination task. The stimulus in this case is a cloud of flickering dots in which a fraction of the dots move in a given, fixed direction and the rest move in random directions. The subject watches the cloud for some time and must indicate the overall motion direction, typically either to the left or to the right, by making an eye movement to either a left or a right choice target. This particular type of stimulus is useful because the difficulty of the perceptual judgment can be tightly controlled by varying the coherence, i.e., the fraction of dots that move together. Also, there is a specific area in the brain that specializes in the analysis of visual motion, area MT, so a subject's behavior in this task depends crucially on how MT neurons respond; lesioning this area, for instance, greatly compromises a subject's capacity to perform motion discrimination tasks (Lauwers et al. 2000). In fact, in a series of elegant studies, Newsome and colleagues showed that there is an intimate, quantitative relationship between the behavior of a monkey in each trial of the RDM discrimination task and the neuronal activity evoked in area MT.

In their initial studies, Newsome and collaborators recorded from MT neurons, which respond selectively to motion in specific directions, in monkeys performing the RDM discrimination task (Newsome et al. 1989; Britten et al. 1996). They analyzed the responses of groups of neurons that preferred movement in one direction (say to the right) or the opposite (left), and made two important observations. First, as the dots moved to the right or to the left, one group of neurons was more active than the other, and the difference in activity varied as a function of coherence in a way that was similar to the monkey's own choice reports. More specifically, they compared the monkey's psychometric curve, which plots the probability of indicating motion to the right as a function of coherence, to an equivalent curve based on neuronal responses called the

“neurometric curve,” which is constructed by comparing the numbers of spikes evoked by a left- and a right-preferring neuron in single trials. Interestingly, the neurometric curves from pairs of neurons were very similar to the monkey’s psychometric curve, indicating that the animal’s sensitivity to motion could be fully explained by the sensitivity of the neurons.

The second observation they made referred to a small but statistically reliable correlation between the firing of the neurons and the monkey’s choices in individual trials, particularly when the motion was completely ambiguous (zero coherence). That is, when the RDM stimulus was uninformative, if a right-preferring neuron was slightly more active than average, the monkey was slightly more likely to indicate that the movement was to the right, and vice versa, when the neuron fired less vigorously than average, the monkey was less likely to make a decision in favor of the cell’s preferred direction. Although modest, the effect was reliable across neurons and stronger for units with higher sensitivities (Britten et al. 1996).

This result demonstrated a clear relationship between the behavior of single neurons and the behavior of a subject in single trials of a perceptual task. What is noteworthy here is not simply that a single neuron influences the monkey’s actions, which would be fairly trivial in the case of a motor neuron, for instance, the issue is that a single neuron contributes to what the monkey sees and thinks. The spikes fired by a neuron in a time window of a few hundred milliseconds have a measurable and predictable impact on the sensations that the monkey reports. Although this type of result is now relatively common, it is in fact quite remarkable, given the very large numbers of neurons in the brain that participate in any particular decision or judgment. Furthermore, it did not have to be this way. It is now known that the effects of single neurons on perceptual experiences are observable only because of the highly interconnected nature of the neural networks in the brain (Haefner et al. 2013); if the brain’s organization were different, such correlations between neuronal activity and perception would be undetectable.

Further Evidence of Competition Between Selective Pools of Neurons

Both lesion and single-unit studies provide correlative evidence that neurons may be involved in generating a particular behavior or that they convey sensory information that is crucial for such behavior, but they do not prove a direct, causal relationship. Electrical microstimulation can do so (Cohen and Newsome 2004). In microstimulation experiments, electrical current is delivered through an electrode, and its temporal pattern is such that the neurons within a certain radius of the electrode tip are activated. In this way, by stimulating during performance of a given task, it is possible to investigate what sensation those neurons transmit or, more generally, what effect their firing has on choice behavior.

This technique was exploited very effectively by Newsome and colleagues to provide further evidence that the activity of MT neurons directly contributes to the sensations of visual motion reported by monkeys. First, microstimulation of MT during performance of the RDM discrimination task resulted in an increased propensity of the monkeys to make a choice in line with the neurons’ preferred movement direction (Salzman et al. 1992). When neurons selective for leftward motion were stimulated, the monkey was more likely to choose the leftward target. Second, the bias produced by microstimulation was specifically in the preferred direction of the activated neurons regardless of the direction of the dots. This was established in a variant of the RDM task in which the dots were allowed to move in any direction and the monkeys were trained to indicate the perceived direction by making eye movements from the center of a circle to its edge, thus covering any angle within 360° (Nichols and Newsome 2002). Third, microstimulation was effective only when it overlapped in time with the RDM display, indicating that the firing of MT neurons is taken into consideration only during a certain critical time period within the sequence of events that comprise a choice trial (Seidemann et al. 1998). And finally, during stimulation trials, choices made toward the neurons’ preferred direction were sped up, whereas choices

made in the opposite direction were slowed down; but notably, the observed differences in RT were exactly as if the coherence of the dots had increased in the preferred direction of the neurons – unlike the somewhat less specific effects observed during stimulation in an oculomotor planning area (Hanks et al. 2006). So, when stimulating in MT, the measured choice and RT biases were coupled precisely as if the coherence of the RDM stimulus had been slightly different.

All of the results discussed so far based on the RDM discrimination task are in agreement with the first principle mentioned above, namely, that a perceptual discrimination results from a competition between neurons that are selective for sensory features that distinguish the available options. Numerous studies based on widely different experimental conditions indicate that this is, indeed, a general property of decision-making circuits. For instance, Afraz et al. (2006) trained monkeys to categorize images as either faces or non-faces. The animals reported their judgments by making an eye movement in one direction when a face was shown and in the opposite direction when a non-face (i.e., a random object) was shown. The difficulty of the task was varied by adding different amounts of noise to the images, such that classifying highly corrupted pictures was hard but doing so for relatively clear pictures was easy. Then, in some trials of the task, microstimulation current was injected into inferior temporal cortex, an area that is crucial for visual object recognition and is considered the end stage of the ventral visual processing pathway (Gross 1994). Again, as in the case of microstimulation of MT, the stimulation current generated a bias in the monkey's choices that was fully consistent with the sensory preference of the activated neurons: when the stimulating electrode was placed near a population of neurons that fired most strongly to faces, the monkeys were more likely to report that a face was shown. Significantly stronger effects were obtained when stimulation was applied in a particular time window (50–100 ms after image onset) rather than earlier or later, when the selectivity of the stimulated neurons was high rather than low, and when a large rather than a small number of face-

selective neurons were found around the electrode (Afraz et al. 2006). Thus, the specificity of the observed behavioral biases was highly consistent with the presumed properties of the artificially evoked activity. This experiment can be considered a generalization of the microstimulation experiments in MT (Salzman et al. 1992; Nichols and Newsome 2002) to a higher-order visual area and a much more complex class of visual stimuli, but mechanistically the conclusions are virtually identical.

Using a similar categorization task, Heekeren et al. (2004) used **fMRI** (functional magnetic resonance imaging) to investigate whether similar competitive mechanisms exist in humans. In each trial of their study, a noisy or degraded picture was shown and the subject had to categorize it as either a face or a house, and the difficulty of the categorization varied according to the amount of noise used. Faces and houses were chosen because these stimuli activate specific patches in ventral temporal cortex (analogous to inferior temporal cortex in monkeys) that are identifiable via fMRI, and their activations could be simultaneously resolved and monitored during the imaging sessions. The authors showed that the fMRI signal increased in the face-selective patches when the subjects reported seeing a face and decreased when they reported seeing a house, and conversely for the house-selective regions. Also, the strength of the responses decreased as the ambiguity of the displayed images increased. Thus, the results were consistent with the idea that the subjective experience of perceiving a face or a house depends on the relative levels of activation of face- and house-selective neurons within ventral temporal cortex, in agreement with the findings of Afraz et al. (2006).

A most striking demonstration of perceptual competition may be achieved under special sensory conditions based on ambiguous images. In that case, the conflict between two possible percepts is endless and unresolvable, and the moment-by-moment report of the subject's experience covaries across time almost perfectly with the activity of high-level visual neurons (Sheinberg and Logothetis 1997; Blake and Logothetis 2002). In binocular rivalry

experiments, different images are shown simultaneously to the two eyes – these can be simple, such as a vertical versus a horizontal grating, or complex, such as a house versus a butterfly – but only one of them is seen by the subject at any given time. The perceived image fluctuates spontaneously on a time scale of seconds, so if the image on the left eye is seen clearly, after a second or so, it is the image on the right eye that is seen exclusively. The transitions are stochastic, with the distribution of dominance times close to a gamma distribution. Presenting different images to the two eyes is convenient and efficient but not essential; similar effects can be obtained with normal (binocular) images that are ambiguous or illusory, such as the Necker cube.

What is remarkable in this paradigm is the close correspondence between the responses of neurons in high-level visual areas, such as inferior temporal cortex, and the subject's reports: if the images to the two eyes are, say, a face and a flower and the activity of a face-selective neuron is recorded, then whenever the neuron fires intensely the subject reports seeing a face, and vice versa, when the subject indicates seeing a flower, the neuron is relatively quiet, all this without the sensory stimuli ever changing (Sheinberg and Logothetis 1997; Blake and Logothetis 2002). Furthermore, during transitions, a change in neural activity (from low to high firing rate or vice versa) typically precedes a change in the subject's report (from the cell's non-preferred to the preferred image or vice versa). This indicates that populations of neurons that are selective for the left and right images alternate in their dominance to determine what the subject actually sees. The population responses reflect not only the stimuli but also an internal consensus that corresponds to the subjective perceptual interpretation of those stimuli. Importantly, this phenomenon is either absent or much weaker in earlier visual areas, such as primary visual cortex, where neurons predominantly encode the sensory stimuli regardless of the subject's awareness of them. Although the binocular rivalry paradigm requires very particular stimuli and presents a peculiar type of choice, because there is no correct or incorrect response, it reveals most eloquently the competitive nature of

the neural interactions that determine perceptual decisions. It is also interesting because the competition in this case seems to be purely perceptual, in that it is difficult to conceive in terms of a motor conflict between two possible actions, as has been done in many choice tasks and associated models (see below).

Deciding Is to Compare One Alternative Versus Another

The main question posed by Heekeren et al. (2004) in their categorization study mentioned above was this: if the subject's choice in each trial depends on the relative strength of the neural responses favoring faces versus houses, then where is such a comparison performed? Is it isolated to one area in the brain or distributed across a network? To answer this, the authors searched for brain locations for which the local fMRI signal was correlated with the absolute *difference* between the signals of the previously identified face- and house-selective regions. The rationale for this is simple: if two pools of sensory neurons provide perceptual evidence in favor of the two available options, then their responses must be compared somehow in order to generate an informed decision. Heekeren et al. (2004) found only one area that correlated closely with the difference in the face- and house-selective signals, the dorsolateral prefrontal cortex, and importantly, the activity in this area was predictive of the subject's choices across trials.

This study provides a particularly simple illustration (at least in appearance) of the comparison problem, but this is a key issue, because comparing separate sources of sensory evidence associated with alternative choices is the computation that lies at the heart of every discrimination. Many experimental and modeling studies in perceptual decision making have investigated this process, and two things have become clear: one, that the comparison arises gradually, both in time and across neural circuits, and two, that at least in species other than human, the comparison is intimately linked to the motor planning processes associated with the available (motor)

choices – and perhaps for some decisions they are indistinguishable (Cisek and Kalaska 2010). These findings essentially constitute the second computational principle stated earlier.

In the case of the RDM discrimination task, area MT provides the sensory evidence on which the perceptual judgment is based, but does not represent the decision itself. However, because this task typically requires subjects to indicate the net direction of motion with a saccade to one of two stationary targets, the corresponding motor plan to move the eyes should be indicative of the decision-making process (the alternative is that the saccadic plan simply represents the outcome of the decision process as computed in a different area, neither MT nor saccade related). Hence, investigators have recorded in areas of the brain responsible for planning eye movements, including the frontal eye field (FEF), lateral intraparietal area (LIP), and superior colliculus (SC), where microstimulation elicits saccades with precisely defined movement vectors. The idea is to understand how perceptual information (conveyed by the responses in MT) influences the oculomotor activity associated with a saccade (which conveys the monkey's decision). Note that the same rationale applies to any decision-making task in which the subject's judgment is reported via an eye movement or any other movement. In this approach, decision making is thus treated essentially as a problem of movement selection (Gold and Shadlen 2007; Cisek and Kalaska 2010).

Indeed, during the RDM task, the sensory information associated with the motion of the dots clearly modulates the oculomotor activity preceding a choice. To appreciate the specific effects that have been observed, first consider how oculomotor neurons fire before a saccade in a simple situation, when there is only one target in the visual field. When location x becomes the target of a saccade, the activity of neurons with movement fields at x starts increasing above the baseline level at a relatively constant rate (the buildup rate), and once the overall activity of that population exceeds a particular threshold level, then the saccade to location x becomes certain, with the onset of the eye movement

occurring about 10–20 ms after threshold crossing (Hanes and Schall 1996; Lo and Wang 2006; Heitz and Schall 2012). This buildup in activity from baseline to threshold is precisely what is referred to as a “motor plan.” Importantly, during saccades to single, unambiguous visual targets, which in monkeys typically take 100–300 ms, the buildup rate of the motor plan is inversely related to the measured saccadic RT: when the neural activity rises quickly (high buildup rate), the corresponding RT is short, and vice versa, when the neural activity rises more gradually (low buildup rate), the corresponding RT is long (Hanes and Schall 1996; Heitz and Schall 2012). From a modeling point of view, assuming that the rise in activity is linear (i.e., that the buildup rate is constant) is often a convenient simplification (Carpenter and Williams 1995; Brown and Heathcote 2007; Stanford et al. 2010).

Now, during the RDM task, two motor plans representing alternative choices compete with each other, and their buildup rates depend on the moving dots. When the coherence is high and the decision is easy, the buildup rate of one motor plan (the one congruent with the true motion direction) is much higher than the buildup rate of the alternative plan (which is congruent with the opposite direction as that of the dots); thus, the threshold for triggering a saccade is reached soon, the RT is typically short, and the choice is typically correct. In contrast, when the coherence is low and the decision is difficult, the two motor plans ramp up at similar, intermediate rates, and it takes longer for the motor conflict to be resolved; thus, threshold is reached late, the RT is typically long, and the probability that the choice is correct is close to chance. This interaction between motion information and oculomotor report via the buildup rates of the saccadic plans is very similar in LIP, FEF, and SC; is observed whether or not the monkeys have to wait for a go cue before responding; and varies only very subtly when four instead of two possible directions of motion are used (Shadlen and Newsome 2001; Horwitz and Newsome 2001a, b; Roitman and Shadlen 2002; Churchland et al. 2008). Thus, the oculomotor activity associated with the perceptual decision is neither purely sensory nor purely motor.

This scenario, in which the decision about the moving dots is instantiated as a competition between motor alternatives that is influenced by sensory information, has been successfully modeled by Wang and colleagues using relatively realistic networks of spiking neurons, which reproduce many features of the behavioral and single-unit experimental data in the RDM task (Wang 2002; Furman and Wang 2008). Simpler models, in which a decision variable rises to a threshold via a biased random walk, are surprisingly effective in replicating in quantitative detail much of the psychophysical data in this and other two-alternative forced-choice tasks (Smith and Ratcliff 2004; Palmer et al. 2005; Kraglich and Rangel 2011). Such reduced models, however, tend to be more difficult to interpret directly in terms of neuronal activity (Brunton et al. 2013; Zariwala et al. 2013; see below).

Gradual Influence of Perception on Motor Planning: Open Gate Versus Closed Gate

Gold and Shadlen (2000, 2003) used an elegantly designed microstimulation experiment to measure how perceptual information modulates the evolving decision-making process in FEF at each point in time. While monkeys performed the RDM discrimination task, some trials were interrupted by applying electrical microstimulation at a (suprathreshold) level sufficient to trigger a short-latency saccade. By analyzing the elicited saccade vectors in relation to the directions of the two possible choice targets, the authors determined which option was being favored at the moment the saccade was triggered; in this way, they could read out the state of the oculomotor competition before it was naturally resolved. By turning on the stimulator at different times relative to the onset of the motion stimulus, they could establish which motor plan was winning at any given time, and by how much. The patterns of evoked eye movements that they obtained indicated that the perceptual decision evolves gradually and that it depends on both viewing duration and motion strength: larger deviations in favor of

the correct motor choice were obtained as the coherence increased and as the monkey had more time to view the RDM stimulus. There was no temporal discontinuity or sharp transition in the data, as would have been expected if the saccadic plan reflected the presence or absence of a fully formed perceptual decision generated elsewhere. Therefore, in this case, the development of the perceptual judgment was indistinguishable from the development of the motor plan for indicating that judgment.

This result is conceptually quite important because it suggests that making a perceptual decision could be the same thing as making a motor choice; they could be one and the same neural process, as instantiated by various computational models in which decisions arise within motor planning circuits (Wang 2002; Cisek 2006; Beck et al. 2008; Furman and Wang 2008; Cisek et al. 2009; Stanford et al. 2010). This idea is attractive because it matches experimental data from many tasks, but it cannot be the whole story because, clearly, there are many perceptual decisions that do not lead to any immediate, predictable actions. Indeed, Gold and Shadlen (2003) performed a variant of their microstimulation experiment in which the direction of motion of the dots, left or right, was reported by making a saccade to a red or a green target, respectively. These targets, however, appeared after the RDM stimulus and at locations that varied randomly across trials, so the correct eye movement could not be predicted based on the motion of the dots alone. In that case, according to the observed saccade deviations, the motion stimulus had essentially no effect on the activity of FEF during the stimulus presentation period. Therefore, the ongoing influence of perceptual information on motor planning was seen only when there was a predictable association between the perceptual options (dots moving left or right) and the motor options (saccade to the left or to the right).

One way to think about these results is this: when there is a predictable mapping between perceptual and motor alternatives, perceptual information flows in an “open-gate” mode in which it continuously influences the competition between (pre-identified) motor plans; in contrast, when the

mapping is unknown, the gate is closed, and the perceptual decision is constructed and stored elsewhere (Cisek 2012). Presumably, the closed-gate mode is necessary for making decisions that will turn into actions over a long term or that are associated with as yet unspecified actions, whereas the open-gate mode may be necessary for making rapid decisions for which any delay in execution would be detrimental; think of stopping a penalty kick, hitting a fastball, or returning a 130 mph serve. In this latter mode, the system might bypass all processes that are not essential, thus explaining the apparent simplicity of the decision-making circuitry (e.g., Wang 2002; Furman and Wang 2008).

In this respect, it is interesting to compare the results of Gold and Shadlen (2000, 2003) to two sets of studies in which similar open-gate mechanisms seem to operate at widely different time scales. In the work of Stanford and colleagues (2010; Shankar et al. 2011), monkeys perform a choice task that simulates an urgent decision. The rules are simple: two yellow spots are shown and the subject must look at one of them when instructed. Crucially though, the cue that specifies which choice is correct (one spot turns red and the other green) is revealed *after* the go instruction, so the two motor plans always start *before* any perceptual analysis. The cue is delayed unpredictably and may not be shown at all in any given trial. In this way, depending on how much time the subject has to view the cue, choices go from fully random (i.e., guesses) to fully informed – but they are always relatively fast (RT is ~250 ms). Using this technique, Stanford and colleagues (2010; Shankar et al. 2011) found that, behaviorally, subjects required a total of about 130 ms of cue viewing time to reliably discriminate the red and green stimuli, but there was a much shorter, critical time window during which performance went from chance (< ~100 ms of viewing time) to 75% correct (at ~130 ms of viewing time). Now, neurophysiologically, the responses of oculomotor neurons recorded from FEF during performance of the task also changed as functions of cue viewing time: the buildup rates of the target- and distracter-related motor plans increased and decreased, respectively, once the cue information

became available, and the time course of the modulation matched that of the behavior. Thus, the results are consistent with the open-gate mode in the experiments of Gold and Shadlen (2000, 2003), except that the perceptual decision – or equivalently, the motor choice – evolved over a much shorter time scale (~30 ms).

Cisek and colleagues also concluded that a fundamental characteristic of decision-making processes is to resolve conflict between actions that may be planned simultaneously (Cisek and Kalaska 2005, 2010; Cisek 2006), but this was based on studies involving arm movements and a much slower time scale for responding (~500 ms). In one of their tasks, a sensory cue was shown first, followed by two choice targets of different colors, and the monkey simply had to reach for the target matching the color of the cue. In this case, the activity recorded from premotor cortex was associated almost exclusively with the correct target and showed little evidence of a conflict. In contrast, in a second task, the association rules and required movements were the same but the order of events was reversed: the two choice targets appeared first and the sensory cue that differentiated target from distracter was shown later. Notably, in this case, both motor plans were strongly activated initially, and the arrival of perceptual information resolved the conflict in favor of the correct one (Cisek and Kalaska 2005). In their view, decision making does not follow an intrinsic sequential arrangement of perception → cognition → motor selection; rather, perceptual information and other task contingencies, such as reward value or motivation, bias a motor selection process that is activated whenever multiple actions are possible (Cisek and Kalaska 2010). Motor preparation is informed by relevant cognitive or perceptual events whenever they occur but does not wait for them to unfold. The internal conflict gets resolved with them (leading to informed choices) or without them (leading to guesses). Klaes et al. (2011) reached similar conclusions too. Evidence of a continuous influence of perceptual input on motor representations (i.e., an open gate) is seen even when decisions require very high-level cognitive processes, such as language (Spivey et al. 2005).

Neurons that are considered decision related typically have both sensory properties (associated with specific sensory features) and motor properties (associated with a specific choice), and their rising activity typically represents a motor plan with a buildup rate that depends on the available perceptual information. However, if this is a truly general mechanism, then the gradual rise to a threshold could be a prominent signature of decision-making processes in general, regardless of the specifics of the sensory input and the subsequent motor activity. O'Connell et al. (2013) searched for such a signature in the EEG of human subjects. This was challenging because although the EEG has excellent temporal resolution (~1 ms), its spatial resolution is extremely poor. However, they used an elegant task design that allowed them to overcome the usual technical limitations and identify a neurophysiological signal with all the properties expected from an evolving decision variable. Participants viewed a striped annulus that was constantly flickering and whose contrast varied slowly (over ~2 s) during certain, unpredictable epochs, and their task was to press a button when they were sure that the stimulus was fading. The flicker was useful for identifying signals specifically related to the stimulus, and the slow time scales guaranteed that contrast decreases were detected accurately but with highly variable latencies. So, three signals were identified in the EEG, a standard one associated with motor activity, a sensory-related one that tracked the flicker, and a third one termed the central parietal positivity, or **CPP**. The CPP corresponded to an evolving perceptual decision in several ways (O'Connell et al. 2013): (1) it rose gradually, and before each button press, it reached a constant level that was independent of RT; (2) its rate of rise strongly correlated with RT; (3) when task difficulty was varied by making the contrast changes more or less slow, the CPP amplitude predicted the subject's choices, i.e., hits, misses, or false alarms; (4) it was identical for increases versus decreases in contrast and for two versions of the task based on visual and auditory stimuli, so it was modality independent; (5) it was absent when attention was directed away from the annulus and the subjects

had to detect an unambiguous, essentially instantaneous change in the fixation point; and (6) it was present – although significantly attenuated – in the absence of overt action. These results agree with the idea that ramping signals with mixed sensory and motor features are the hallmark of perceptual decision making, even when the associated action is nonspatial and relatively subtle (a button press).

In contrast to the studies just discussed, much less is known about perceptual decision making in tasks that impose a closed gate. In such cases, for instance, when the sensory-motor mapping is unpredictable, there may be some residual activity in motor planning areas, but characterizing it has been challenging (Horwitz et al. 2004; Bennur and Gold 2011). Also, what happens when the current sensory signal informs an action that may occur at an unknown time in the future, with other actions performed in the intervening time? Do such decisions also involve a progressive accumulation process with an activity threshold that serves as a trigger? Remarkably, recent work (Hayden et al. 2011; Krajbich and Rangel 2011) suggests that this may indeed be the case.

Hayden et al. (2011) developed an oculomotor choice task that mimics foraging behavior. In each trial, the monkey could choose between staying in the current “foraging patch” (i.e., making a saccade to a small square) and switching to a new patch (i.e., making a saccade to a bar). The first reward obtained in a new patch was always large, and subsequent rewards decreased steadily with each consecutive stay, but crucially, switching to the new, high-reward patch carried an up-front cost in the form of a long time delay (the “traveling time”), which was explicitly indicated by a visual cue (the length of the bar). Thus, for each choice, the monkey had to weigh the high cost of a large reward against the low cost of a diminishing reward. Because the traveling time varied for each new patch, monkeys exhibited a wide range of switching times, but their overall behavior was close to optimal in that the total reward harvested per session was close to the theoretical maximum. Notably, some neurons in the dorsal anterior cingulate cortex (**dACC**), an area that is generally linked to behavioral adjustment and the valuation of actions (Kennerley and Walton 2011),

indicated the likelihood of making a switch. These dACC neurons responded only around the time of the saccadic choice in each trial and were otherwise quiet. The perisaccadic response was weakest following a switch, but with each subsequent stay, it increased in intensity, and when it reached a particular level, the monkey again switched to a new patch. This increasing dACC activity is clearly analogous to the rise to threshold typical of motor plans, but it differed in various ways: it was intermittent rather than sustained, lacked any spatial selectivity, and developed over many intervening choices spanning tens of seconds. Nevertheless, it was associated with a particular action and was sensitive to reward size, and both its buildup rate and threshold level depended on the switching cost, as given by the visual cue. So, although a causal link still remains to be demonstrated, in this task the decision to switch patches again correlates with neural activity that rises to a threshold and is modulated by perceptual information, even though the temporal constraints and internal computations imposed by the task are much different from those reviewed earlier.

Further exploration of decisions made in the closed-gate mode, which are intrinsically more abstract, is an important goal for future studies (Padoa-Schioppa 2011; Cisek 2012).

Perceptual Decision Making Based on Tactile Stimuli

Beyond vision, similar perceptual discrimination mechanisms have been identified by Romo and colleagues in the somatosensory system of monkeys (Romo and Salinas 2001, 2003). Although the computational principles discussed above remain valid in this case, there are also some notable differences with respect to the studies based on RDM and other visual stimuli.

In the vibrotactile discrimination task used by Romo and colleagues, two mechanical vibrations of frequencies f_1 and f_2 in the flutter range (5–40 Hz) are delivered sequentially by a small, oscillating probe similar to the tip of a ballpoint pen, and the monkey has to press one of two push buttons to indicate whether $f_1 > f_2$ (medial button)

or $f_2 > f_1$ (lateral button). Note that the relevant comparison in this case is between the activities of the same group of neurons but sampled at different times; the circuit must compare the responses to the second stimulus to a stored memory trace of the responses to the first stimulus. In this paradigm, task difficulty is controlled by varying the difference between the two frequencies, but to a certain extent, it also depends on the delay between the two stimuli (Hernández et al. 1997). Neurophysiological recordings have shown that, again, two groups of sensory neurons are crucial for task performance: for one group, the firing rate increases monotonically as a function of stimulus frequency, so those neurons fire most intensely to frequencies near 40 Hz, whereas for the other group, the firing rate decreases monotonically with stimulus frequency, so their most vigorous responses are to frequencies near 5 Hz. Although such neural code for vibration frequency is simple, the neural operations required for discriminating f_1 versus f_2 are somewhat more complicated than in the RDM case, because both neuron types are activated twice (for the first and second stimuli) and the responses to the first stimulus must be stored in short-term memory.

Now, there are four interesting results about the neural underpinnings of this perceptual decision-making task. First, the preference for high frequencies develops earlier than that for low frequencies; that is, in primary somatosensory cortex (S1), there is a relatively large fraction of neurons with firing rates that increase as functions of stimulus frequency, whereas neurons with the opposite selectivity are virtually nonexistent (Salinas et al. 2000). In contrast, in secondary somatosensory cortex (S2) and areas downstream, the two types of selectivity are approximately equally common, roughly 60% monotonically increasing versus 40% decreasing (Salinas et al. 2000; Romo and Salinas 2003). This suggests that the circuit actively develops a sensory representation that naturally lends itself to a competition between two neural populations with opposite feature preferences.

Second, the activity of neurons in both S1 and S2 is significantly correlated with the monkey's choices in single trials (Salinas et al. 2000); that is,

when a neuron fires more intensely than average on a particular trial, the monkey is more likely to make one choice than the other on that trial (which choice depends on the tuning of the neuron, i.e., whether it is monotonically increasing or decreasing with stimulus frequency). Consistent with a causal role in generating the subject's perception of vibration on the skin, the direct activation of S1 neurons via microstimulation triggers perceptual sensations that, as far as can be measured psychophysically, are indistinguishable from those evoked by natural, mechanical stimuli (Romo et al. 1998). In particular, when the electrical current is of high frequency and the stimulated neurons presumably fire more intensely, the monkeys report high-frequency sensations, and vice versa when the stimulated neurons presumably fire weakly, the monkey reports are consistent with low-frequency sensations. This makes sense given the neural code for stimulus frequency found in S1, where the higher the stimulus frequency, the higher the evoked firing rates of those S1 neurons that respond to flutter stimuli. Furthermore, the microstimulation results remain true even when no mechanical stimuli are applied at all and the monkey's judgments are based on two artificially evoked sensations (Romo et al. 2000), which demonstrates that all the perceptual information needed to perform the task is derived from the firing of a localized population of neurons with a particular type of stimulus selectivity.

Third, neurons from multiple cortical regions (S2 and downstream) continue to fire throughout the delay period between the presentation of the first and second flutter stimuli, but these sustained responses are most robust in the prefrontal cortex (Romo et al. 1999; Romo and Salinas 2003), the area that is most strongly linked with short-term memory performance (Miller and Cohen 2001). The responses of PFC neurons are thus the neural correlates of the remembered first stimulus during the task.

And fourth, many neurons downstream from S1 that are activated during the comparison period of the task reflect the monkey's decision (Romo et al. 2002; Romo and Salinas 2003; Hernández et al. 2010). That is, shortly after the second

stimulus starts, some neurons fire very strongly whenever $f_1 > f_2$ but almost not at all whenever $f_1 < f_2$, and a complementary population responds in the opposite way, firing most strongly whenever $f_1 < f_2$. What is quite remarkable is that these same neurons typically respond to the first and/or second stimuli in a standard sensory fashion, that is, with firing rates that increase or decrease monotonically with f_1 or f_2 . Thus, in S1, the evoked responses are, in essence, fully determined by the current sensory input and are rather insensitive to task contingencies. In contrast, in S2 and downstream premotor areas, neurons also respond to the stimuli, but in general, their selectivities change dynamically: the responses first reflect f_1 or f_2 but later change to reflect either the difference between f_1 and f_2 or the sign of the difference, which is ultimately the variable that matters for the monkey's behavior. These interactions can still be understood as competitions between pools of neurons with different selectivities, except that for most neurons the pool membership changes dynamically as the relevant sensory information becomes available. Again, this is in line with the idea of an open gate through which sensory information flows and guides motor preparation, except that here the responses in premotor areas first reflect the sensory stimuli and then develop into a well-defined motor plan that correlates with the subject's motor choice.

Several models have been proposed to explain the neuronal dynamics observed in this task, and although those models capture many important features of the data, such as the sustained working-memory responses that encode f_1 and the comparison signals that encode the sign of $f_2 - f_1$, one aspect of the recorded data for which a plausible account is still lacking is the wide repertoire of response selectivities found experimentally (Jun et al. 2010; Barak et al. 2013). Neuronal preferences to various combinations of f_1 and f_2 vary tremendously, both across neurons and over time within the same neurons, but why? Answering this question may be key for obtaining a deeper understanding of the circuit mechanisms at play during perceptual decision making (Barak et al. 2013).

Integration of Sensory Evidence and the Speed of Perceptual Decisions

Studies based on the RDM discrimination task and others suggest that perceptual information can accumulate slowly over time to increase performance. Conceptually, the idea is that although instantaneous sensory responses are inevitably noisy, the random fluctuations in this activity can be averaged out by combining samples over time. This results in a more informative, integrated sensory response that gradually ramps up toward a discriminability criterion (Gold and Shadlen 2007; Beck et al. 2008). Simple integrator (or drift-diffusion) models that instantiate this process (Smith and Ratcliff 2004; Palmer et al. 2005) thus account for three general observations: (1) that RTs increase with increasing difficulty, (2) that performance increases with stimulus duration, and (3) that subjects can internally trade speed for accuracy (Zariwala et al. 2013). A key question is whether this is an essential mechanism – or perhaps *the* essential mechanism – for generating perceptually guided decisions. The issue is about how the second computational principle discussed above should be interpreted: does the rising activity associated with decision making represent primarily integrated sensory information, regardless of any movement preparation?

In our view, this sensory or computational interpretation is one extreme within a range of possibilities. Undeniably, sensory stimuli may influence motor plans even when the corresponding actions are highly stereotyped and predictable and the sensory information is irrelevant (Dorris et al. 2007). However, motor plans with a wide range of buildup rates arise even when the sensory signals triggering them are highly unambiguous (e.g., a single, high-contrast stimulus) or when no stimulus is present (e.g., spontaneous eye movements in the dark). This happens in the very same areas, and indeed the very same neurons, that are supposed to integrate sensory evidence. Furthermore, experimental evidence for a threshold mechanism is substantial only for responses linked to specific, imminent motor actions, saccades in particular (Hanes and Schall 1996; Roitman and Shadlen 2002; Stanford et al.

2010; Hayden et al. 2011; Heitz and Schall 2012), and perceptual difficulty and RT may be decoupled (Stanford et al. 2010; Salinas and Stanford 2013; Zariwala et al. 2013). So, a conservative answer to the question posed above is “not necessarily.” Here, we have adopted the view that, under many circumstances, namely, “open-gate” tasks, decision-related responses are motor plans with buildup rates that are modulated by perceptual information. That way, the yes/no question above turns into one of degree: how strongly does the buildup rate of the rising, choice-related activity depend on perceptual information?

This point merits some additional discussion for two reasons: first, because it involves key problems in computational neuroscience, such as the role of neuronal variability in determining behavior and the efficiency of neuronal population codes (Wang 2002; Beck et al. 2008), and second, because while integrator models have been highly successful at replicating psychophysical data in a vast variety of tasks (Smith and Ratcliff 2004; Palmer et al. 2005; Kragbich and Rangel 2011) and are thus the default tool for modeling decision-making performance, there are alternatives (Carpenter and Williams 1995; Brown and Heathcote 2007; Shankar et al. 2011). Two studies place important constraints on the possible underlying mechanisms for integrating sensory evidence.

Brunton et al. (2013) designed an auditory discrimination task in which two series of clicks stream concurrently from two loudspeakers, one on the left and one on the right, and the subject must indicate which side produced more clicks after a given amount of time (100–1200 ms in rats). The difficulty of the task depends on the difference in the number of clicks from the two sides, but the timing of individual clicks is random (it follows Poisson statistics), and the total click rate is always the same and relatively high (40 clicks/s), so the subjects cannot simply count. Now, any computational scheme for solving this task must integrate the clicks from the two sides and compare the results, but because each click is a discrete event, within any conceivable model, it is possible to determine how each

individual click contributes to the decision in each trial. This is a unique and tremendously powerful aspect of the task, for suppose that a model A with n parameters is constructed. The parameters can be fit using, say, half of the data, and then the model can be tested on the other half, but here is the key: once model A is specified, it will make a prediction about the expected outcome, left or right choice, *in each test trial*, because each trial consists of a unique sequence of clicks. Thus, model and behavior can be compared without averaging across trials. For this reason, many models with many parameters can be tested and differentiated unambiguously; the numbers of degrees of freedom they require (n) are always tiny compared to the dimensionality of the data that constrain them. Brunton et al. (2013) contemplated large families of integrator models that differed in their dynamics, time constants, sources of noise, etc., and compared their performance to that of individual rat and human subjects. They found that, for most subjects, there was no noise in the accumulator, and performance was limited by sensory or encoding noise. That is, a click could be missed or could be assigned to the wrong speaker, but once it was accounted for, its effect never faded. So, clicks that occurred near the beginning or the end of the trial had equal influence; the accumulator memory itself was perfect. In a standard integrator or drift-diffusion model, by contrast, the accumulator noise would have been high. This result is quite counterintuitive. It suggests that although the integration process itself can indeed be extremely efficient over a time scale of seconds, its mechanism is very different from the biased random walk assumed by standard models, at least under the conditions of this task.

Finally, when exposure to a sensory stimulus is prolonged, how much can performance increase? The answer to this question may depend heavily on task and stimulation conditions and on how these relate to an animal's natural behavior, but is there a general pattern (Uchida et al. 2006)? In the RDM discrimination task, behavioral studies in humans suggest that when coherence is relatively low, performance increases with the duration of the motion stimulus up to ~ 2 – 3 s of viewing time

(Burr and Santoro 2001; Palmer et al. 2005). But there may be something special about manipulating coherence to produce a weak motion signal: such long integration time constant is seen when coherence is low (and contrast is high) but not when the contrast of the dots is low (and coherence is high), in which case integration times are an order of magnitude lower (Burr and Santoro 2001). Also, a detailed analysis of neural activity in the standard RDM task suggests that the effective integration time in monkeys is more likely to be ~ 400 ms (Kiani et al. 2008). These results are consistent with the analysis of Uchida et al. (2006), who argue that for the most common perceptual judgments, such as those typically associated with saccades or sniffs, performance stops increasing beyond a fairly short period of sensory evaluation of ~ 200 – 300 ms. So, most perceptual decisions are fast. Long integration times may occur for relatively abstract or highly cognitive tasks – and relatively specialized circuit mechanisms are likely required to integrate robustly over a period of seconds or more, given the much shorter time constants of neurons and synapses. However, the more common scenario is likely to be one in which sensory information is sampled and processed quickly during short, discrete events, and there is little or no benefit in extending the deliberation period in such cases (Uchida et al. 2006).

This conjecture was directly examined by Zariwala et al. (2013), who investigated how the accuracy of perceptual choices changes with deliberation time in rats performing an odor categorization task. In each trial, a mixture of two odors was delivered, and the rat had to indicate which odor was present in a higher proportion. Under standard experimental conditions, the rats responded at any time after stimulus onset, and their performance varied between near chance (50% correct, for mixtures near 1:1) and near perfect (100% correct, for mixtures near 1:0 or 0:1) without a significant variation in odor sampling time, which was about 250 ms (here, the RT was equal to the sum of the odor sampling time plus the rat's movement time). So, in contrast to what is generally seen in, say, the RDM discrimination task (Roitman and Shadlen 2002; Palmer

et al. 2005), in this case, large variations in performance were not accompanied by changes in stimulus evaluation time. The authors attempted to reveal or create such a dependence through a large battery of task variants in which reward, punishment, trial length, response time, and stimulus and response predictability were manipulated, creating ample opportunity and motivation for the animals to integrate sensory information over long times. In every case, large changes in accuracy or response speed were achieved, yet no evidence of a trade-off was ever seen. When the rats extended their odor sampling time, performance did not increase, and vice versa, when performance did increase, there was no change in their timing relative to that in the standard task. Apparently, sampling the stimulus beyond 200–300 ms had no benefit (Zariwala et al. 2013).

Why was integration so limited in this case? An important possibility put forth by the authors is that, as in the clicks task (Brunton et al. 2013), the noise that limits performance in their categorization task may not be of the type postulated by integration (drift-diffusion) models, which represents random fluctuations in activity *within* each trial. Any variability *across* trials would diminish the benefits of integration. But note that any slow signal that sometimes favors one outcome and sometimes the other independently of the sensory evidence would have precisely such an effect. For instance, a preference for making one motor response over the other assigned randomly across trials would work (Brown and Heathcote 2007; Shankar et al. 2011; Salinas and Stanford 2013) and would be consistent with the broad framework outlined above – in which perceptual decisions arise when sensory information and internal motor plans interact to generate informed choices (Cisek and Kalaska 2010).

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Perceptual Errors

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Perceptual-Motor Dissociation

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Definition

Perception

Intuitively, perception is the process of becoming aware of physical objects or phenomena through the senses. However, to define it as an observable phenomenon without resorting to a highly subjective concept such as awareness, one must include additional measurable criteria. A less involved and more up-to-date view is that perception is the mental function by means of which the physical world (including within body processes) is represented and the process by means of which this function interacts with the physical world, together with the consequence of this interaction. This definition dissolves from the start the perception-action dissociation dilemma: according to it, the two concepts are indissociable.

Motor Event

Any movement caused by the muscles.

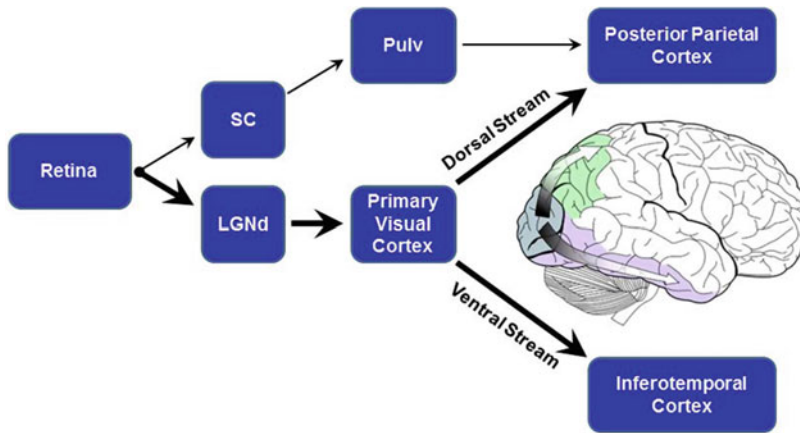
Detailed Description

In some sense, the necessity of a tight perception-action coupling has been posited at least since Helmholtz (1867/1962). He proposed that the perceptual stability of our visual world in the presence of continuous eye movements could be due to a *closed-loop* circuitry, whereby the visual-motion signal triggered by the displacement of the retina during an eye movement is cancelled out (up to some error) by the motor signal that induced that specific eye movement. Alternatively, such cancellation can be obtained by subtracting the *predicted* eye-movement *outcome* for a given motor command from the *actual* outcome.

In fact, this so-called *pseudo-closed-loop* scheme is the founding principle of modern *forward models* used in computational motor control (Jeannerod 1983, 1997; Wolpert et al. 1995; Warren 2006; Wolpert 2007). A wealth of empirical and modeling studies do indeed support a fine online interplay between perceptual and motor processes during motor planning and execution (e.g., Paillard 1960; Ingle 1982; Requin et al. 1988; Hommel et al. 2001). However, as this literature does not focus on the cognitive aspects of perception and is not controversial, it will only be alluded to in the remainder.

Opposite Views

Helmholtz's intuition notwithstanding, most of the twentieth-century *perceptual* research (with perhaps Gibson's (1950, 1979/1986) notable exception and that of a few followers) was entirely disconnected from the motor research. By the end of the last century, however, two major streams of thought pervaded both fields of research. In 1982, Ungerleider and Mishkin revealed two major sets of nerve projections in the monkey brain, both originating in the primary visual cortex, one projecting ventrally into the temporal lobe and the other projecting dorsally into the posterior parietal cortex (Fig. 1). They proposed that these two pathways have complementary functions: the ventral (or "what") pathway subserves object identification, whereas the dorsal (or "where") pathway allows spatial localization of these objects. This anatomical dichotomy was extended by Goodale and Milner (1992), who proposed an equivalent functional dichotomy between what they called "vision for perception" and "vision for action." A few years later, O'Regan and Noë (2001) revived Helmholtz's intuition and Gibson's ecological approach, as well as the more philosophical perspective of Maturana and Varela (1987), and documented the opposite view, according to which perception and action are inseparable. In fact, they pushed this view to its extreme, which is that perception cannot exist without action, and vice versa. In defense of this stand, Daniel Wolpert has argued that brains' *only*



Perceptual-Motor Dissociation, Fig. 1 Simplified representation of the two functional pathways for the treatment of visual information according to Ungerleider and Mishkin (1982; following Goodale and Humphrey 1998). Retinal stimulation is transmitted to subcortical structures (SC, Pulv, LGNd) and then cortical structures (PPC, V1). After having reached the visual cortex, information flows

along one of two streams: the dorsal pathway, which leads to posterior parietal cortex and is thought to subserve the visual control of action, and the ventral pathway, which is thought to subserve perception and whose integrity is considered necessary for conscious perception (LGNd lateral geniculate nucleus pars dorsalis, Pulv pulvinar, SC superior colliculus)

function is to sustain adaptable and complex movements, pointing out that originally active, brain-equipped creatures (such as sea squirts) that end up settling down for good on rocks digest their brains once they cease moving (see <http://freethoughtblogs.com/tokenskeptic/2011/12/13/why-we-dont-eat-our-own-brains-professor-daniel-wolpert-on-ted/>). Accordingly, Wolpert's postulate is that all mental processes – sensations, thoughts, and emotions – lead to interactions with the environment that eventually translate into muscle activity.

Arguments in Favor and Against the Dichotomy

Goodale and Milner's dissociative view (Goodale and Milner 1992; Milner and Goodale 1995, 2008; Goodale 2011) was originally based on a type of scientific observation referred to as a "double dissociation." Lesions of posterior parietal areas (dorsal stream) lead to a condition known as *optic ataxia*, which involves disturbances in visually guided action. Patients set before a mailbox slot are able to report its orientation but are incapable of correctly inserting a card into

it. Lesions of ventral visual areas, in contrast, lead to *visual agnosia*: these patients are unable to verbally indicate the orientation of the slot but can correctly insert a card into it. This double dissociation has been challenged based on observations suggesting that (1) optic ataxia is not a general disturbance of visually guided action, (2) visual agnosia is not a disturbance specific to perception, and (3) studies involving such patients were not well controlled (see Pisella et al. 2000, 2006; Rossetti et al. 2003, 2005; Cardoso-Leite and Gorea 2010).

Many other claims favoring a major distinction between perception and action have gone through similar cycles of debate. The dual-pathway theory gained support from various anatomical/imaging, neurophysiological, and neuropsychological studies, including studies based on visual illusions and on priming with allegedly "invisible" stimuli (presumably entailing differential perceptual and motor effects brought about by subsequently presented visible stimuli), and from studies contrasting perceptual and motor response latencies and accuracies. However, the conclusions drawn from such studies have each been rebutted on different grounds. Anatomical/imaging and neurophysiological evidence favoring the

dual-pathway theory was offset by evidence that both ventral and dorsal streams process information about the nature of objects and their locations in space (e.g., Konen and Kastner 2008) and that dorsal stream neurons show evident responsiveness to stimulus features supposed to be encoded in the ventral stream, such as shape and color; likewise, some prototypical dorsal-stream features such as motion were shown to be equally well processed in the ventral stream (see Cardoso-Leite and Gorea 2010). The differential perceptual-motor effects caused by visual illusions have been criticized due to the unmatched experimental conditions used to assess them (Franz 2001; Franz and Gegenfurtner 2008). The differential effects of “invisible” primes have been questioned because “invisibility” was poorly defined and/or assessed or because the prime affects the perception of the target stimulus meant to trigger the motor response (Reingold and Merikle 1990; Holender and Duscherer 2004; Cardoso-Leite and Gorea 2010). Finally, results contrasting perceptual and motor response latencies and accuracies were undermined by the observation that such performance differences can be accounted for by a unique processing pathway, if perceptual and motor processes are assumed to require different levels of evidence to trigger a decision (Gibbon and Rutschmann 1969; see Cardoso-Leite and Gorea 2010).

A False Dilemma?

The ultimate consequence of the dual-pathway theory is that *perception* can direct action *unconsciously*, that is, that one can act appropriately on objects that are not seen. This proposition is theoretically debatable, but its test is empirically intractable. On the theoretical side, it makes use of undefined or ill-defined concepts, namely, “perception,” “not seen,” and “consciousness.” While it is unanimously accepted that the retina will transform light into an electrical signal, the stage at which its propagation becomes “perception” has been under sustained debate since the nineteenth century (see Boring 1942). According to

signal detection theory (Green and Swets 1966), a stimulus is reported as “unseen” either because it is too weak to elicit a neural response or because the subject adopts a high decision criterion, that is, because he or she requires more (neural) evidence of its existence than actually provided by the neural system. The absence of “consciousness” can be related not only to either of these two causes but also to a variety of ambiguous interpretations of this concept.

On pure common sense grounds, it would be ludicrous to contest the patently obvious dissociation between perception and action. However, the claim that when tested under *strictly matched conditions*, subjects’ action system may use incoming information that is omitted by the sensory systems may forever remain undecided for at least three reasons. First, because it is impossible to objectify a percept without requiring subjects to perform a perceptual judgment that ultimately involves some sort of action. As a consequence, one cannot prevent an action from interfering with its perceptual cause, and vice versa. For example, asking subjects to react as rapidly as possible in response to a sensory stimulus will lead to perceptual judgment errors (as evidenced by the motor response) that do not occur with a non-speeded motor response. Second, because in the absence of a clear-cut definition of consciousness, the distinction between conscious and unconscious perceptual states will remain elusive, making it hard to determine what sensory information is “omitted” (or not) by the sensory systems. Finally, even if such frontiers between action and perception and between conscious and unconscious states are arbitrarily set, *strictly matched conditions* for testing perceptual and motor performances cannot be created. For example, the putative “dissociation” between accurately grasping an object and this object’s perceptually distorted size by a visual illusion may be accounted for by positing that grasping control is based on the absolute spatial location of the grasping points, whereas perceptual size judgments are based on an estimation of the distance between these grasping points. Also, the finger grip aperture varies during the course of action as it is regulated by an online correction through visual

feedback, whereas a perceptual judgment is made once and for all.

Cross-References

- ▶ [Brain Architecture Management System \(BAMS\)](#)
- ▶ [Brain Atlases](#)
- ▶ [BrainMap](#)
- ▶ [Computational Neuroanatomy: Overview](#)
- ▶ [Connectionist Models of CPG Networks](#)
- ▶ [Decision-Making, Motor Planning](#)
- ▶ [Embodied Cognition, Dynamic Field Theory of](#)
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- ▶ [Somatosensory Cortex: Neural Coding of Shape](#)
- ▶ [Target Selection vs. Response Selection](#)
- ▶ [Visual Illusions, Models of](#)

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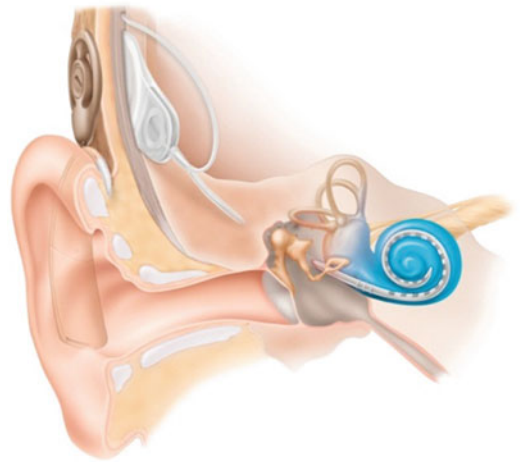
Peripheral Nerve Interface Applications, Cochlear Implants

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Definition

A cochlear implant is an implanted electronic device to activate the auditory nerve and restore hearing sensations to people who have lost their hearing. Modern cochlear implants consist of an implanted part and a part that is worn externally. The external part contains a microphone to pick up sound, a microprocessor to convert acoustic sound into electric signals, and a transmitter coil

to send the information across the skin to the implanted part. The implanted part contains a receiving antenna, a microprocessor to decode the transmitted signal, a current-controlled stimulator, and an array of electrodes inserted into the inner ear. Electric pulses delivered to the inner ear activate any remaining auditory neurons and initiate neural pulses to the brain, resulting in the sensation of sound and the ability to understand speech.



Detailed Description

History

The normal inner ear separates sounds into its constituent frequencies and distributes the different frequencies along the coils of the cochlear (inner ear). High-pitch sounds produce vibrations predominantly at the entry to the cochlea (base), and low-pitch sounds produce vibrations predominantly at the tip of the cochlea (apex). Those vibrations are carried by a membrane (basilar membrane), and small ciliated cells called hair cells sit on top of the vibrating basilar membrane. The tiny cilia at the top of these cells are displaced at the place of maximum vibration and activate auditory neurons that synapse on these cells. This starts the cascade of neural firing patterns that signal sound to the brain. However, in most types of deafness, these hair cells are missing

from disease, drugs, noise exposure, or genetics. When the hair cells are missing, the mechanical vibrations still occur and the neurons are still present, but there is no connection between them, resulting in deafness. The cochlear implant is designed to inject electric current pulses into the cochlea to activate the nerve directly, bypassing the missing hair cells.

Electric activation of hearing may have originated with Alessandro Volta, who placed a charged glass rod in his ear and reported a sound like thick boiling soup. Electric stimulation as a modern prosthesis started in the early 1950s with André Djourno and Charles Eyries, a surgeon and an engineer, in Paris. They placed copper wires into the auditory nerve in two deaf patients and activated it by an inductive coil. The patients heard sounds and found it to be helpful with lip reading for several months before the device failed (Eisen 2003).

In the 1960s several groups developed implants for the cochlea to provide hearing sensations to deaf patients. One of the most successful of these was William House in Los Angeles (House and Urban 1973), who developed the first commercially successful cochlear implant. Most early implants were single-channel devices that consisted of a single pair of wires (source and sink) that passed electric current across the auditory nerve. These devices were enthusiastically accepted by deaf patients, who received the sensation of sound and could distinguish environmental sounds based on their different sound patterns. The single-channel implant provided little speech recognition by itself but greatly aided lip reading and so enhanced face-to-face communication and relieved the isolation felt by many deaf people.

Modern Development

Because early cochlear implants used only a single channel of stimulation, it could not activate the different pitch regions distributed along the cochlear. Multichannel electrodes were designed to activate multiple pitch regions. Typically a linear array of electrodes was placed along a carrier tube, and this assembly was inserted into the scala tympani, one of the three chambers of the

cochlea. Following such an insertion electric pulses stimulating electrodes at the basal end of the cochlea elicited high-pitch sensations, and progressively lower-pitch sensations were evoked each successive electrode going toward the cochlear apex. Modern cochlear implants have between 12 and 22 electrodes spaced along the pitch dimension of the cochlea. Low-frequency information is presented to the electrode at the tip of the electrode in the cochlear apex, and higher frequencies are presented to each successive electrode toward the base, so that the most basal electrode carries the highest-pitch information.

Evolution of Speech Processing

Early cochlear implants tried many different strategies for processing speech information. The problem was how to break up speech information and present it to the implanted electrodes to maximize speech understanding. With the original single-channel CIs, recipients heard sounds but mostly could not understand speech. They could hear environmental sounds and could tell the difference between some sounds by their overall rhythm – like the regular pulsing of a telephone ring versus the steady sound of running water. After time some were able to identify some sounds that had distinctive patterns and could recognize a few familiar words. Multichannel CIs allowed the recognition of words and some sentences. In the 1980s CI designers thought that they needed to extract the most important information from speech and just present that to the implanted electrodes. It was thought that the full speech information would overwhelm and confuse implant listeners. However, in the early 1990s, it was realized that the best CI performance was achieved when the designers “got out of the way.” A new generation of implant speech processors simply filtered sound into 22 bands of different frequencies and presented a form of the raw information to the 22 electrodes. There was a dramatic improvement in implant performance when speech-processing strategies allowed the listener’s own brain to extract the important information for itself rather than having an algorithm doing it. Small improvements in this strategy resulted in continued improvements in the

function of cochlear implants until the early 2000s, when most post-lingually deafened adult patients were able to understand speech well enough to have a conversation over the telephone. On standard evaluations the average CI adult was able to recognize 80–90% of the words in simple sentences presented in quiet. While speech recognition is excellent with modern cochlear implants, patients still have problems when listening in noise and listening to music. Many patients are now receiving bilateral CIs to allow localization of sound in space and better hearing in noisy conditions.

Children with Cochlear Implants

William House implanted the first deaf child with a single-channel cochlear implant in 1980. Most researchers at the time thought that this was highly premature, but acceptance by patients and families was good. Now more than half of worldwide cochlear implants are done in young children. While the auditory information from a cochlear implant is crude compared to a normal ear, it has proven to be sufficient for deaf children to develop speech and language in an almost normal fashion. Many children with modern cochlear implants can attend normal schools with only minimal help. One interesting aspect of this success is for neuroscience – it shows that pattern recognition of the brain for speech is robust enough to develop even with a highly reduced signal coming from the cochlear implant. In this case the brain is receiving patterns of information that are greatly reduced from a normal ear but can learn to understand and reproduce speech at a high level. Cochlear implants are now routinely done in congenitally deaf children less than one year of age.

Future Directions

One factor that limits the performance of cochlear implants is the distance between electrodes and neurons. The electric signal spreads out in the conductive body fluid and allows interference between adjacent electrodes. New electrode designs, including some that will be injected into the hearing nerve directly, are

being developed to improve the selectivity and independence of each electrode. It is the hope that more electrodes with high selectivity will allow the transmission of harmonic pitch and improved access to music.

New implant technology may allow the entire cochlear implant to be implanted under the skin, eliminating the external microphone and signal processor. This will improve the cosmetic appearance and allow the implant to be used even under water. An internal battery would be charged overnight.

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Peripheral Nerve Interface Applications, EMG/ENG

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Synonyms

[Peripheral neural interfaces](#); [Recording the peripheral nervous system](#)

Definitions

The electromyogram (EMG) is a record of electrical activity of muscles. Electrical activity in muscle arises from action potentials in muscle fibers. To record muscle electrical activity, small electrodes are placed on the skin over a muscle (surface EMG) or in the muscle (intramuscular EMG). The patterns of electrical activity can be displayed on a screen, played over a loudspeaker, stored to disk, and/or used as a control signal for a prosthesis or other device. EMG activity has been used as an approximate measure of the level of activation of the muscle or of muscle force.

The electroneurogram (ENG) is a recording of electrical activity from one or more neurons and typically refers to recordings made from bundles of axons in peripheral nerves. As with EMG, the recorded activity can be displayed on a screen, played over a loudspeaker, stored to disk, and/or used as a control signal for a prosthesis or other device. An ENG is obtained by placing an electrode in or near neurons to reveal activity of a single neuron or multiple neurons, depending upon the size and location of the recording electrode with respect to the neurons.

Detailed Description

Background

EMG is a measure of electrical activity in any of the three types of muscle tissue – smooth, cardiac, or skeletal (striated). Smooth muscle activation is controlled by the autonomic nervous system, hormones (e.g., Angiotensin II, Endothelin, and Epinephrine), metabolic factors (e.g., adenosine, CO₂, O₂), physical factors (e.g., via stretch receptors), and/or activity in neighboring cells. Smooth muscles can also be spontaneously active. Contractions in cardiac muscle fibers are initiated by electrical activity in neighboring cells or by endogenous currents that endow the cells with pacemaker properties. Striated muscles are activated by action potential generated by motor neurons of the spinal cord. The action potentials arrive at the neuromuscular junction and cause synaptic release of acetylcholine (ACh). ACh

causes local depolarization of the motor end plate generating action potentials in muscle fibers. The muscle action potential propagates along the muscle fiber and causes the release of Ca⁺² from stores within the muscle, which then leads to a contraction via a mechanism known as excitation-contraction coupling (Sandow 1952). In striated muscle, the release of Ca⁺² triggers a cascade of reactions that produces relative movement of the actin and myosin filaments, which generates a contraction of the muscle fiber (Merletti and Parker 2004). A typical muscle fiber membrane potential is about −90 mV and is more negative than that of a typical motor neuron. The muscle action potential lasts for about 2–5 ms with an absolute refractory period of 1–3 ms. The conduction velocity along a striated muscle fiber is about 4–6 m/s. An EMG recording consists of weighted summation of the depolarization waves that propagate through a muscle whether it is smooth, cardiac, or striated. Measured EMG potentials can range from less than 50 μV to 30 mV, depending on the muscle type, electrode type, and electrode location (Merletti and Parker 2004).

In 1849, the first recording of striated muscle electrical activity was done by Reymond (Du Bois-Reymond 1848). In 1890, Marey (1890) also recorded electrical activity from striated muscle and coined the term electromyography. However, it was not until the late 1930s and early 1940s that EMG found its first clinical uses (Denny-Brown and Pennybacker 1938; Golseth 1950; Weddell et al. 1943). As a clinical diagnostic tool, EMG is used in the diagnosis of neurological disorders (e.g., stroke (Bradley et al. 1998; Johnson et al. 1975), amyotrophic lateral sclerosis (ALS) (de Carvalho et al. 2008; Mitsumoto 1997), neuromuscular deficiencies (e.g., muscular dystrophy (Bushby et al. 2010)), movement disorders, and biomechanical problems (Kimura 2013; Preston and Shapiro 2013). Other applications of EMG are in biofeedback training as a method for rehabilitative physical therapy (Brucker and Bulaeva 1996), human-machine interfaces (Alsayegh 2000), ergonomic assessment (Kumar and Mital 1996), and in gaming technologies (Krepki et al. 2007). Furthermore, EMG has been used in control of

prostheses and orthoses for over five decades (Herberts et al. 1973; Kuiken et al. 2009; Scott 1967; Tenore et al. 2007) and in orthotics (DiCicco et al. 2004; Scott 1967). In research, EMG is used to assess motor control and learning, in the study of neuromuscular physiology, and in gait and postural analysis (Winter 2009).

ENG provides a direct measure of bioelectrical activity in neurons arising from the movement of ions across the cell membrane. The movement of ions is driven primarily by concentration gradients and is regulated by the opening and closing of channels. The action potential consists of an influx of Na^+ , Ca^{2+} , and/or Cl and an efflux of K^+ (Kandel et al. 2000). With electrodes placed near or in neural tissue, one can measure the tissue electrical activity. Electroneurograms can be obtained by recording neural activity with electrodes inserted in the soma of neurons (intracellular) or with electrodes positioned in the medium surrounding neurons (extracellular). In the peripheral nervous system, ENG can be obtained by recording extracellular action potentials from neurons in the peripheral ganglia or from axons of peripheral nerve bundles. Depending on the design and placement of the electrodes used to record neural activity, an ENG can contain activity of a single neuron or the superposition of signals from many active axons in a nerve.

The first ENG from a single nerve fiber was recorded by Edgar Adrian in 1928 using a Lippmann electrometer (Adrian 1928). In 1953, the first Iridium recording microelectrode was developed (Dowben and Rose 1953). The first simultaneous recording from multiple units with a multielectrode array from a patient during brain surgery was published by Marg and Adams in 1967 (Marg and Adams 1967). In the peripheral nervous system, ENG is used for many purposes: as a diagnostic tool for the assessment of motor disorders (Hoffmann and Krechel 2011) (e.g., ALS (Lei et al. 2002), multiple sclerosis (MS) (Nesrulaeva et al. 2011)), in biofeedback (e.g., for closed loop systems in stimulation of end organs and muscles and in control of orthotics and prostheses (Dhillon et al. 2004; Micera et al. 2010; Navarro et al. 2005)).

Acquisition and Presentation

There are two primary types of EMG recordings: surface EMGs (sEMG) and intramuscular EMGs (iEMG). sEMG recording electrodes are placed on the skin over a muscle of interest. Electrodes for sEMG are typically made of Ag-AgCl and attached to the skin with an adhesive collar. These EMG electrodes detect EMG signal through the skin using a conductive gel between the electrode and the skin. Dry sEMG electrodes are made of stainless steel and other alloys. The electrodes detection surface depends on the type of material used, but for Ag-AgCl it is at a range between 0.5 and 1.5 cm. sEMG electrodes are either placed in the unipolar, bipolar, or even quadpolar configuration. In a unipolar configuration, the EMG is recorded from a single electrode placed on the muscle with the reference ground electrode placed in an electrically neutral location, e.g., near a bony prominence. Bipolar EMG recording requires two electrodes placed next to each other along the longitudinal axis of the muscle in the direction of the depolarization current propagation. The inter-electrode separation for bipolar recording is between 0.25 and 1.5 cm. sEMG electrodes are not specific; they record signal from a large set of active motor units that produce the overall contraction of a muscle. Unipolar sEMG electrodes detect neural activity from a larger area of muscle tissue than bipolar sEMG electrodes. However, bipolar electrodes are the most common recording configuration used since they provide a high signal-to-noise ratio. Additional information on surface EMG recording can be found in the following references: Criswell (2010) and Kasman and Wolf (2002). iEMG recording electrodes are placed in the muscles. Intramuscular electrodes are selective in that they record action potentials from a small number of motor units depending on the electrode geometry and placement. iEMG can also be used to provide recordings from deep muscles not accessible to surface electrodes. Intramuscular electrodes come in many different designs: simple single filament needle, concentric single filament, bifilar, quadfilar, and macro-electrode (Trontelj et al. 2004). Implantable EMG sensor systems

have also been developed that have the ability to wirelessly transmit signals to an external receiver (Weir et al. 2009).

Recorded EMG signals are the sum of many trains of action potentials from many motor units plus sources of noise present in the environment including the recording apparatus. The contribution of each motor unit to the recorded EMG will depend upon the fiber size (larger fibers generate larger signals) and the distance from the recording electrode (the signal produced by the fiber will attenuate as it passes through the resistive medium). EMG signal frequencies range from 1 Hz to few kHz with amplitudes from few μV to mV (Reaz et al. 2006). A good EMG recording requires good electrode design, electrode placement near muscle depolarization sources, sound recording amplifier design, grounding techniques, and noise reduction methods (Fridlund and Cacioppo 1986).

The EMG recording system amplifies and conditions the EMG signals. Typical recording systems are equipped with low noise, high common mode rejection ratio (CMRR >90 dB), and high input impedance ($\text{M}\Omega$ – $\text{G}\Omega$) differential amplifiers with high bandwidth (0.1–5 kHz) that amplify the EMG signal acquired by electrodes. The amplified signals are then passed through a sequence of high-pass (0.1–100 Hz), low-pass (500–1000 Hz), and notch (60 Hz) filters to remove contaminants of the EMG signal, such as movement artifacts and power line noise. The amplified, conditioned EMG signals can then be digitized by analog-to-digital converters (8–16 bit) and then processed, stored, and/or displayed (De Luca 1979; Fridlund and Cacioppo 1986).

EMG signals can be displayed on an oscilloscope or on a computer screen as multiple traces where the ordinate (y-axis) represents the amplitude of the signal and the abscissa (x-axis) time. They can also be presented as audio signals. Another method to visualize EMG signals as a dynamic heat map where the color intensity represents the amplitude of the signal, the abscissa time, and the ordinate the channels.

ENG signals are at least an order of magnitude lower in amplitude and higher in frequency than EMG signals. To record ENG, many neural

machine interfaces (NMI) have been developed. Some NMIs are selective recording devices, recording only from few neurons/axons while others are designed to record from many sources. However, with higher selectivity comes increased level of invasiveness (Navarro et al. 2005). To achieve selectivity, electrodes must be placed closer to axons or neuron cell bodies and thus are more invasive than electrodes that are placed distant from neural sources. The cuff electrode is a peripheral neural interface. It is a tubular sheath with two or more recording contacts on its inner surface connected to lead wires (Testerman 1982). Cuffs are placed around nerves and record a sum of neural activity from many axons. The flat interface nerve electrode (FINE) is a variant of the multi-contact cuff that is designed to achieve better recording selectivity by flattening the nerve to distribute fascicles across the array of contacts (Tyler and Durand 2002). Penetrating microelectrodes (PME) are inserted in a fascicle of a peripheral nerve. PMEs are used in microneurography to measure multiunit peripheral nerve activity to investigate peripheral nervous system physiology and pathophysiology (Nystrom and Hagbarth 1981; Vallbo et al. 1979). Longitudinal intrafascicular electrodes (LIFEs) are made of a thin (25–100 μm) Pt-Ir insulated wire with 1–2 mm exposed active site (Malagodi et al. 1989). LIFEs offer high selectivity because they interface with a subset of axons within a fascicle of a peripheral nerve. The thin-film LIFE (tfLIFE) is a flexible micromachined polymer structure with multiple active contacts that are smaller in surface area than those of the LIFE (Yoshida et al. 2000). The multielectrode array (MEA) is an array of needle electrodes; these can be made of stainless steel, tungsten, or conductive silicon. Several variants of microwire MEAs use an array of single-contact electrodes made of stainless steel or tungsten and are usually arranged in a two-dimensional grid to access spatially distributed sets of fibers. Conductive silicon has been used to put multiple contacts on a single probe in the Michigan probe (Suner et al. 2005) and to create a high-density array with 100 contacts in the Utah array (Campbell et al. 1993). If designed with appropriate dimensions, these MEAs can achieve

simultaneous recordings from multiple fascicles. Regenerative electrodes are a large array of pores or conduits in which axons could regenerate (Akin et al. 1994; Devor and Govrinlippmann 1979; Kovacs et al. 1992). A recording electrode is placed in each pore in order to record from the small group of axons that may grow through the pore as it regenerates toward the target organ.

As with EMG, the recorded ENG signal consists of the superposition of signals emanating from many individual neurons and several noise sources. The contribution of a given neuron is influenced by the neuron fiber type and location: size and proximity to the electrode both increase the amplitude of the recorded signal. With any ENG electrode, the specific features of the ENG recorded signals are also influenced by the size and shape of the active contact (i.e., recording surface), and placement of the electrode determines recording volume shape and size (i.e., pickup distance around the electrode). Finally, the recording configuration (unipolar, shared reference, bipolar recording, tetrad recording, etc.) also influences the information content of ENG. The amplitude of the recorded neural activity usually lies between 1 and 100 μV , and the frequency content ranges from few Hz to 10 kHz, depending on whether the signals recorded are single spikes, a superposition of many spikes (e.g., compound action potentials), or local field potentials (LFP).

ENG must be amplified and conditioned prior to processing and/or analysis. A neural recording system typically includes an initial amplifier stage and a signal conditioning stage to attenuate energy in specific frequency bands. The structure of the ENG recording system is similar to that of an EMG recording system. The initial neural signal amplifier usually requires a low referred noise ($<2\mu\text{Vpp}$), high common mode rejection ratio (CMRR >90 dB), high input impedance ($\text{M}\Omega$ for low impedance electrodes and $\text{G}\Omega$ for high impedance electrode), and high-gain (1000–500,000) differential recording capability with high bandwidth (0.01–10 kHz). Amplifiers are followed by a set of filters (signal conditioning stage) in sequence, consisting of high pass (0.01–1000 Hz), low pass (500–10,000 Hz), and notch (50 or 60 Hz) to

remove contaminants of the ENG signal, such as, EMG noise, neural tissue background noise, movement artifacts, and power line noise. The amplified, conditioned ENG signals are usually digitized by analog-to-digital converters (16–18bits) and either stored or transferred to a computing machine for further analysis and/or display.

The rich information content in multichannel, high-bandwidth ENG recordings can be extracted using various analysis methods or by displaying the information in a useful manner. Individual traces representing the time series of multiple channels can be vertically stacked to simultaneously provide visual information regarding single-channel dynamics and patterns across channels. However, this kind of representation is limited in its ability to convey information content that spans multiple time scales and has complex spatial patterns. An alternative is to use dynamic heat maps where channels are represented as ribbons unfolding in time with the color intensity at the current time representing the signals strength. A precursor to dynamic heat maps are raster plots for spike event data visualization (Drongelen 2007). Yet another method of representation is raster plot put in a form of a tunnel view (Walter et al. 2004) in which the trains of spikes are clustered dynamically in a way to represent the correlation between data events.

Analysis Methods

Raw EMG and ENG signals contain valuable information, but extracting that information from the set of recordings usually requires online or off-line signal processing and/or machine learning methods (Reaz et al. 2006). Signal processing methods include frequency domain, time domain, or mixed mode methods. For example, frequency domain methods include Laplace, Fourier, and Z transforms, power spectral density, and signal phase calculations, while time domain methods include time series analysis (moving averages and higher moments, cross-auto/correlations, convolutions, etc.). Mixed mode methods are methods such as band-pass filters, spike rate calculations, wavelet analysis, short Fourier

transforms, etc. Machine learning procedures are algorithms used to uncover statistical regularities in data. They involve learning information from previous data and generalization to new data (i.e., prediction). Some of the most common methods of machine learning used in EMG/ENG processing are principal component analysis (PCA), independent component analysis (ICA), support vector machines (SVM), and artificial neural networks (ANN) (Drongelen 2007; Hinton 2011; Lewicki 1998).

EMG/ENG processing often utilizes a sequence of steps designed to remove noise and to find temporal and spatial (multiple channels) regularities in signals. Linear/nonlinear filtering techniques are used to remove noise from the signals. For example, one useful measure of activity on a recorded channel is spike frequency: either instantaneous spike frequency or spike frequency calculated over a time window. For this calculation, simple thresholding or a Schmitt trigger can be used to detect spike events in noisy signals. These techniques require the selection of a threshold value, which is often selected as a multiple of the recorded quiescent activity (e.g., three times the standard deviation of the signal recorded with the subject at rest). Wavelet denoising (Moshou and Hostens 2000) and Wiener filters (Aschero and Gizdulich 2010) can also be used to remove noise from ENG/EMG. A matched filter approach can sometimes be used if muscle action potentials or neural spike information are available a priori (Drongelen 2007; Lewicki 1998) to filter iEMG/ENG spikes from noise.

Since EMG is a sum of the activity of many motor units and likewise ENG is a sum of many neuronal action potentials from a number of neurons, further processing might be needed to decompose the EMG/ENG to its contributing sources. For some applications, separating the biological sources is necessary. Decomposing EMG/ENG to its constituent components relies on the assumption that each source action potential (spike) has a distinct shape and temporal characteristic. To achieve this decomposition, many algorithms have been developed. These algorithms are of two basic types: spike

identification or classification and decomposition, known also as sorting. After band-pass filtering in the frequency range of interest of EMG/ENG data to accentuate spikes, detected spikes are superimposed on top of each other, a method known as alignment, to detect and extract identifiable features of the spike. These features are later used to reprocess EMG/ENG data. After spike identification, EMG/ENG signals are decomposed to their primary constituents using a variety of methods some of which are template matching and convolution filtering (Lewicki 1998). Another related method used for decomposition of EMG/ENG signals is known as wavelet decomposition, which relies on the use of templates of generic spikes (wavelets), such as Symlet and Daubechies wavelets, to sort neural or muscle sources (Reaz et al. 2006). Often EMG/ENG signals have a low-frequency (<50 Hz) modulation of interest. There are many signal processing methods that have been used to extract the modulating signal from EMG/ENG recording. They are all essentially low-pass filtering techniques. Some examples are root mean square (RMS) of the signal or signal absolute value (AV) over a moving window, Gaussian filtering (Lehky 2010), Kaiser filtering (Massot et al. 2012), etc.

The processing methods presented above only allow analysis of the temporal or frequency characteristics of individual EMG/ENG signals. Pattern classification or machine learning methods can be used to analyze the spatial patterns across a group of signals. Either supervised or unsupervised classification (regression models) (Hinton 2011) can be used. Unsupervised models such as independent component analysis or principal component analysis can recover essential components of EMG/ENGs by removing correlated channels and keeping only independent sources. In supervised methods, such as support vector machines and artificial neural networks, the input EMG/ENGs are correlated to some behavioral signals such as the movement of an arm, visual signal, or movement of a cursor on screen, which are deemed related to the EMG/ENG signals. These methods are used in an attempt to remove all components that are not related to intended behavior from the ENG/EMG data

(Abdelghani et al. 2013a, b; Bitzer and van der Smagt 2006; Micera et al. 2010; Sinkjaer et al. 2003).

This list of analysis methods presented is only a few of many processing techniques that have been used to analyze EMG/ENG data. A detailed review of EMG analysis is given by Reaz et al. (2006) and of ENG analysis is given by Van Drongelen (2007).

Computational Models

Computational modeling and simulations of EMG/ENG signals is particularly interesting for developing new EMG/ENG analytical tools. Simulation enables testing of scenarios that are not feasible in limited and controlled experimental settings. Furthermore, it enables the formulation of prediction that can be tested with a targeted experimental protocol. Lee et al. (2008) have produced a volume conductor model to simulate surface EMG due to current sources located at different depths of muscle tissue. With their method, they studied EMG electrode configuration and spacing. Stalberg et al. (Stalberg and Karlsson 2001) simulated an EMG from a muscle with its motor unit as it was picked up by concentric needle electrodes under pathological situations such as myopathy. Li et al. (2013) used simulated EMG data to compare the performance of several multichannel EMG decomposition algorithms. ENG simulation is also a rich area of study with many mathematical and simulation software packages published (Bower and Beeman 1998; Brette et al. 2007; Gewaltig and Diesmann 2007; Hines and Carnevale 1997). An example is the simulation of neural signals recorded by multiple longitudinal fascicular electrodes implanted in peripheral nerves for the purpose of testing neural decoders to control advanced prostheses (Abdelghani et al. 2013a, b).

Cross-References

- Correlation Analysis of Parallel Spike Trains
- Estimation of Neuronal Firing Rate

- Neural Coding
- Peripheral Nerve Interface, Epineural Electrode
- Peripheral Nerve Interface, Intraneural Electrode
- Peripheral Nerve Models
- Peripheral Nerve Signal Processing, Denoising
- Spike Train Analysis: Overview

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Peripheral Nerve Interface Applications, Neuropathic Pain

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Synonyms

Nerve pain; Neuralgia; Neurodynia

Definition

Neuropathic pain (NP) is a direct consequence of lesions or disease affecting the central or peripheral somatosensory system. Peripheral nerve interfaces are systems for delivery of therapeutic modalities directly to the peripheral nervous system, such as the management of NP.

Detailed Description

Pain is a subjective feeling of physical suffering and discomfort from the sensory modality of nociception (pain perception) by activation of terminal receptors. A direct activation of pain pathways can also result in the perception of pain without extrinsic activation of end receptors. Such “neuropathic pain” may be caused by disease or injury. The International Association for the Study of Pain (IASP) defined NP as “pain caused by a lesion or disease of the somatosensory system” (IASP 2011; Jensen et al. 2011).

Patients with NP may have reduced sensation to touch and temperature in affected areas (negative signs and symptoms). They may have spontaneous non-painful sensations (paresthesias), with episodes of shooting or burning pain. They may also have pain evoked by usually non-painful mechanical or thermal stimuli (hyperalgesia).

Electrical peripheral nerve stimulation (PNS) can be of therapeutic use in the management of NP (Slavin 2008; Stanton-Hicks 2009). Soon after the “gate control” theory of pain was proposed by Melzack and Wall in 1965, Wall and Sweet demonstrated the effects of peripheral nerve stimulation on pain perception (Wall and Sweet 1967). There followed a number of publications on PNS for NP (Nashold et al. 1979; Waisbrod et al. 1985). In the ensuing decades, peripheral nerve stimulation for NP has gained wider clinical application (Gildenberg 2006; Slavin 2011a).

Pathomechanics of Neuropathic Pain

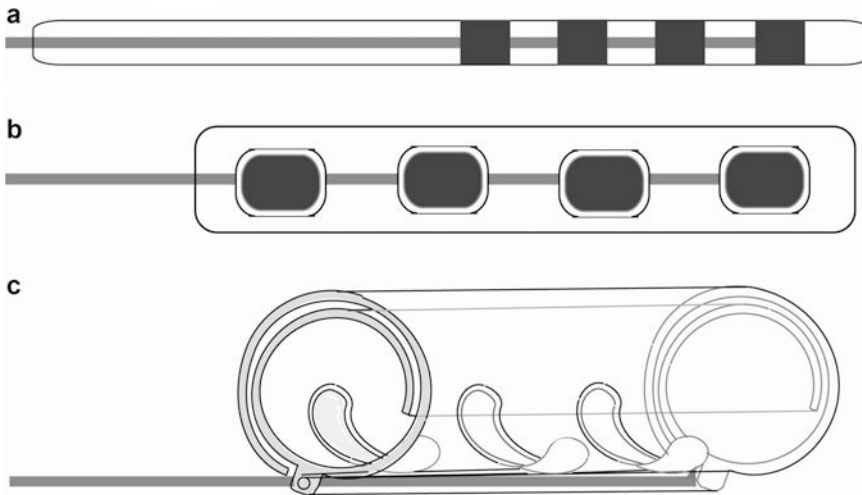
NP can arise in a variety of clinical conditions such as diabetes, trauma, or autoimmune disease (Campbell and Meyer 2006). Pathology has been attributed to the abnormal sensitization of nociceptors with ensuing changes in spinal dorsal horn neurons and altered C-fiber activity. Central neurons in the thalamus and primary sensory cortex may also be sensitized. Following localized nerve injuries, inflammation may also play a role in NP (Nickel et al. 2012). Changes in the expression of sodium channel isoforms have been implicated in NP (Lai et al. 2003; Rogers et al. 2006).

Peripheral Nerve Stimulation for Neuropathic Pain

PNS has been applied to a number of peripheral nerves to treat a variety of conditions such as migraine, occipital neuralgia, and postherpetic pain. Peripheral sensory nerves supply demarcated areas of skin surface, which may show altered sensibility in NP. Such nerves are targets of PNS for therapy as in the periorbital and inguinal areas. Regional anesthetic nerve block has not been definitely shown to have any predictive value in the efficacy of PNS for NP (Slavin 2008).

Nerve Interfaces for Neuropathic Pain

The electrode interface is the transition plane from current flow by electrons in the technological



Peripheral Nerve Interface Applications, Neuropathic Pain, Fig. 1 (a) Percutaneous lead electrode with four contacts, with connecting lead wire on the

left, (b) paddle-type electrode with four contacts, and (c) cuff electrode with three contacts

hardware to ionic currents in physiological media. Electrodes may be noninvasive to provide stimulation through the skin surface or implanted on or near the nerve. The metal electrode contact at the interface is connected to an electrical pulse generator, external for surface and percutaneous systems or implantable (IPG).

(Navarro et al. 2005). They may also provide selective activation of target nerves without spill-over currents, with established safety records for some designs (Naples et al. 1988). Cuff electrodes have been used for phantom limb pain in amputation stumps for kHz frequency nerve block (Soin 2012). They are not widely used for PNS in NP.

Implanted Systems

Percutaneous leads are the most commonly used and can be inserted through the skin to be seated near a target nerve (Fig. 1). The cylindrical electrodes have linear arrays of 4–8 ring-shaped metal contacts that transfer electrical charge to the target nerve.

Flat paddle-shaped electrodes, with metal contact interfaces on one surface, backed by insulating material have been used since the late 1980s (Slavin 2011b). These electrodes are manufactured by a number of companies with 4, 8, or 16 electrode contacts.

Nerve cuff electrodes with cylindrical geometry can wrap around the trunk of peripheral nerves and may conform to their shape. The electrical interface is positioned close to neural tissue, which can lower the threshold currents and decrease the power demands of stimulators

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Peripheral Nerve Interface Applications, Obesity

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Definition

The peripheral nervous system interfaces with multiple organs and mediates a myriad of biochemical processes that affect the balance of

energy storage and consumption. This interface has long been studied as a target to alter the balance of weight homeostasis.

Detailed Description

Health issues arising from the increasing prevalence of obesity and metabolic syndrome are becoming a global predicament. For the first time, more people will expire secondary to issues from weight excess than famine.

Weight homeostasis is based on the simple balance between energy intake and energy expenditure. Obesity, or excess accumulation of fat, occurs if there is an imbalance. The interaction between the gastrointestinal tract, the brain, and the autonomic nervous system controls and modulates energy homeostasis. As a result, electronic manipulation of each of these components can potentially alter signals and change dietary intake and metabolic rate. In fact, electrical stimulation or blockade using pacemaker technology has been placed on the stomach, the vagus nerve, the sympathetic nerves, and directly into the hypothalamus in experimental trials to treat obesity.

The sympathetic and parasympathetic nervous systems, which arise from the spinal cord, supply the vital organs and affect their function. Activation of these nerves is often part of a reflex mechanism which involves the efferent signal with an afferent limb which relays signals back to the CNS and often to the hypothalamus. The hypothalamus also has connections to higher brain centers and therefore is paramount in the regulation of metabolism (Van Baak 2001).

Overall, increased activity of the SNS results in decreased energy uptake with increased energy expenditure. Conversely, PSNS activity results in increased energy uptake and decreased energy consumption. Obesity is a product of energy intake exceeding energy expenditure and can be caused by an imbalance at any level of this complex system (Van Baak 2001).

The word vagus actually means wanderer in Latin. It is the interstate highway that connects the brainstem to our vital systems controlling our heart rate, breathing, and gastrointestinal tract. For

surgeons, the vagus nerve is best known for its function in acid production, motility, and pancreatic secretion. This effect constitutes part of the efferent limb of the vagus nerve. Theoretically, it has been suggested that if efferent vagal activity is blocked, then gastric emptying would be delayed. This would result in increased satiety and reduced hunger. Additionally, blocking pancreatic activity would cause reduced or inefficient digestion of ingested food. Two randomized controlled trials (EnteroMedics) have been completed utilizing a pacemaker with thresholds that block vagal efferent signals (Waataja et al. 2011). Both studies failed to show a significant difference in weight loss in the experimental group. They did, however, show a tendency that patients treated were more likely to lose weight and further refinement with better patient selection may allow for clinical application.

The afferent sensory limb interestingly constitutes 80% of the function of the nerve, and distension of the stomach results in a powerful neuronal signal relaying satiety to the brain both directly and via the hormones. Cholecystokinin (CCK) and ghrelin, two powerful hormones involved in hunger, activate vagal afferent pathways (Van Baak 2001). Thus it would be reasonable to stimulate vagal afferents attempting to mimic satiety or fullness. Trials with both direct vagus nerve stimulation and indirect vagus nerve stimulation with leads on the stomach have been attempted. Roslin et al. showed impressive weight loss in a canine model treated with bilateral vagus nerve stimulation. A brief six-patient clinical trial was not able to replicate these results (Roslin and Kurian 2001). Direct gastric stimulation (Transneuronix) underwent two multicenter randomized trials in the United States after numerous nonrandomized trials suggesting efficacy. Neither controlled trial showed statistical significance (Cigaina 2004). Another method of indirect stimulation has been utilized by Metacure. A sensing pathway attempts to detect the intake of food, timing the pacing cycle.

Low SNS tone is associated with a low metabolic rate and hyperphagia. Low urinary adrenaline excretion (a marker of low SNS tone) has been shown to be associated with weight gain. The SNS stimulates thermogenesis and that dietary manipulation influences noradrenaline turnover (Van Baak). Conversely, sympathetic activation has

been associated with enhanced meal-induced satiety showing that the SNS has a dual effect, working on both sides of the energy balance equation. Stimulation of the sympathetic system to increase metabolic rate has been attempted. Leptos did animal efficacy trials with placement of abdominal leads (Dobak 2004). Several clinical cases were done in Europe without exciting or beneficial results. Therefore, the United States trial was cancelled.

Clearly, the wiring pathway is intact. There is little question that peripheral nerves are both an input channel and output conductor that regulate energy intake and utilization. However, how to manipulate these connections and the language to send the proper signal remain to be determined.

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Peripheral Nerve Interface Applications, Respiratory Pacing

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Synonyms

Diaphragm pacing; Phrenic nerve pacing; Respiratory electrical stimulation

Definition

Respiratory pacing is a technique that uses patterned repetitive electrical stimulation to activate ventilatory muscles in order to increase airflow in the lungs. Respiratory pacing is usually used in cases of cervical spinal cord injury (SCI) where the connection between the respiratory drive centers and the respiratory nerves has been lost, though other disorders may also be candidates. Pacing may be delivered by peripheral nerve stimulation (typically the phrenic nerve that innervates the diaphragm), intramuscular stimulation (typically the thoracic diaphragm), or spinal cord stimulation. Respiratory pacing is used as an alternative to mechanical ventilation which may cause trauma to the lungs and other respiratory and psychological complications.

Detailed Description

Background

Respiratory pacing provides a solution for individuals with chronic ventilatory insufficiency or those individuals with high-level spinal cord injuries where the brain can no longer drive the lungs enough to maintain gas exchange necessary for survival. Respiratory pacing is a technique to supply adequate ventilation to the lungs such that appropriate gas exchange (respiration) can occur. Respiratory pacing uses functional electrical stimulation (FES) to activate the muscles of ventilation. The diaphragm has been the primary target for respiratory pacing as it provides the majority of inspiratory activity. Early efforts in the 1940s and 1950s (Sarnoff et al. 1948, 1950) and later in the 1960s (Glenn et al. 1964) and 1970s (Glenn et al. 1976; Glenn 1978) focused on providing stimulation to the phrenic nerve in order to drive the diaphragm. In the 1980s, motor point stimulation of the diaphragm muscle was demonstrated (Nochomovitz et al. 1983, 1984, 1988; Peterson et al. 1986). Refinements in devices and laparoscopic surgery for motor point stimulation in the diaphragm followed (DiMarco et al. 2002; Onders et al. 2004a, b, 2005). Because of the importance of maintaining adequate ventilation, respiratory pacing has had continual scientific attention with

numerous publications, including a wealth of review articles on the topic (DiMarco 2005, 2009, 2018; Jarosz et al. 2012; Onders 2012; Le Pimpec-Barthes et al. 2016; Hachmann et al. 2017).

As the primary muscle of breathing, the thoracic diaphragm (innervated by the phrenic nerve, arising from cervical nerves 3–5) provides 65% of vital capacity (Jarosz et al. 2012). The external intercostal muscles assist in inspiration by increasing the size of the chest. Additional muscles in the neck and trunk provide small contributions to inspiration. Active expiration is typically not required during quiet breathing where expiration is primarily passive. During conditions such as exercise, expiration is assisted primarily by the internal intercostal muscles and the abdominal muscles, decreasing the size of the chest and abdominal cavities, respectively.

Ventilation is controlled by the autonomic nervous system, with limited voluntary control. Respiratory rhythm and pattern generation arises from neurons and neural circuits in the brainstem. At the heart of the respiratory control system is a central pattern generator (CPG). This CPG can functionally reconfigure during other behaviors such as coughing, swallowing, vocalization, and vomiting (Lindsey et al. 2012). Ventilatory rate is primarily controlled by blood levels of CO₂, with additional control based on blood levels of O₂ (Dean and Nattie 2010; Guyenet 2014; Guyenet and Bayliss 2015). Mechanoreceptors prevent over inflation of the lungs (Herring Brewer reflex (Schelegle 2003; Harris and St John 2003; Ahmed 2007; Leiter and Manning 2010)). The most common cause of loss of ventilation is cervical SCI. With SCI at the fifth cervical vertebrae or higher, the connection between the respiratory centers in the brainstem and the phrenic nerve is damaged. This loss of respiratory control necessitates the use of artificial ventilation including respiratory pacing. Other disorders which are candidates for respiratory pacing include congenital central hypoventilation syndrome (Diep et al. 2015; Kasi et al. 2016) and central sleep apnea (Ponikowski et al. 2012; Abraham et al. 2015). Amyotrophic lateral sclerosis (ALS) has also been evaluated as a target for respiratory pacing (Amirjani et al. 2012; Scherer and Bedlack

2012). However, a recent study showed evidence of increased number of adverse events in ALS patients with respiratory pacing compared to those with mechanical ventilation support (McDermott et al. 2015).

Stimulation Approaches

A number of different methods using FES for respiratory pacing have shown success. In all FES systems, some surviving neuromuscular tissue must remain. In the case of spinal cord injury, the spinal cord, motoneurons, and muscles distal to the injury typically remain intact. Stimulation of any of this intact tissue can activate otherwise paralyzed muscles to contract and cause functional movement. In order to get a useful contraction capable of evoking a breath, sufficient stimulation frequencies with sufficient charge delivery are needed. Slow motor units require 25–30 Hz while fast motor units require 80–100 Hz stimulation frequencies to allow fused contractions of the muscles (Wuerker et al. 1965; Venkatasubramanian et al. 2006). While open-loop (feed-forward) control systems for electrical stimulation are common (Jarosz et al. 2012), closed-loop (feedback) and adaptive controllers have the possibility of correcting for fatigue and electrode instability (Abbas and Triolo 1997). This is important as electrically stimulated muscles have time-varying, nonlinear properties, which complicate control (Crago et al. 1980a, b; Durfee and Palmer 1994). There are three major approaches for respiratory pacing: phrenic nerve stimulation, intramuscular stimulation, and spinal cord stimulation.

Phrenic nerve pacing was established as a clinical modality in the 1980s (Glenn et al. 1984). In this technique, electrodes are attached to the phrenic nerve in the neck or the thoracic cavity to increase diaphragm function. Most often extraneural electrodes like nerve cuffs are utilized although in the future it may be possible to use intraneural electrodes such as the longitudinal intrafascicular electrode (LIFE) (Venkatasubramanian et al. 2006). In current open-loop phrenic pacing systems, the electrodes are connected to an electrical impulse generator and stimulator implanted under the skin. This stimulator receives wireless commands from

an external transmitter. Phrenic pacing has successfully provided respiration for spinal cord injured individuals on a chronic basis without the need for mechanical ventilation. The electrodes are placed on the nerve after a cervical or thoracic surgical procedure. Historically, surgeries required very invasive bilateral thoracotomies (Onders 2012), but newer surgeries are typically performed thoracoscopically, decreasing surgical risk (Fodstad 1987; Vanderlinden et al. 1988; Shaul et al. 2002; Morgan et al. 2003). Commercially available devices for respiratory phrenic pacing include the Astrostim system from Atrotech in Finland, the Vienna phrenic pacemaker from Medimplant in Austria, and the Avery Mark IV Breathing Pacemaker System from Avery Biomedical Devices in the USA (only the Avery system is available in the USA) (Onders 2012).

Intramuscular respiratory pacing involves placing electrodes in the muscles of ventilation near the motor point, beneath the surface, of each muscle (Jarosz et al. 2012). Electrodes with leads that cross the skin are typically placed in the diaphragm, but can also be placed in secondary muscles such as the intercostals to further increase ventilation (DiMarco et al. 2005). These devices do not require the complicated surgeries needed for most phrenic stimulators. While surgery is still invasive, it can be done laparoscopically as outpatient surgery through the abdomen (Onders et al. 2004b). Commercially available devices include the NeuRx RA/4 System from Synapse Biomedical in the USA.

High frequency spinal cord stimulation is an emerging technique for respiratory pacing (DiMarco and Kowalski 2013; Kowalski et al. 2013; DiMarco et al. 2019). Electrodes are placed on the epidural surface of the upper thoracic spinal cord (T1-3). This technique results in asynchronous firing of phrenic motoneurons, which may lead to a more physiological activation than the synchronous firing seen in phrenic nerve and intramuscular stimulation. No commercially available devices are currently in production.

Recently, a new approach has been developed where a venous catheter equipped with

stimulating electrodes is inserted into the subclavian vein and used to stimulate the phrenic nerve through a transvenous approach (Abraham et al. 2015; Costanzo et al. 2016; Reynolds et al. 2017). This minimally invasive transvenous phrenic stimulation approach has been able to provide both unilateral and bilateral phrenic nerve stimulation in patients with central sleep apnea (Ponikowski et al. 2012; Abraham et al. 2015) and temporarily in patients undergoing cardiac surgery in an investigational study (Reynolds et al. 2017). Currently, only the *remedē* system from Respicardia has been approved for treatment of central sleep apnea in the USA.

Limitations and Alternatives

While breathing is an immediate need provided by mechanical or stimulated ventilation, coughing is an important behavior that is not always supported by pacing systems. Individuals with impaired ventilation have an increased risk of respiratory infections, particularly in the absence of cough (Zimmer et al. 2007). Cough is necessary for clearance of mucous and can also be necessary to prevent choking if food becomes lodged in the respiratory system. Simulated coughs can be performed using abdominal thrusts by an assistant and stimulation of the abdominal muscles or corresponding spinal motor pools (Jaeger et al. 1993; Lee et al. 2008; DiMarco et al. 2009; McCaughey et al. 2016).

While modern electrode design minimizes some risks, all methods of respiratory pacing have the risk of electrode failure. Electrode failure can arise in a number of ways: the electrode may move from its target location (exacerbated by significant tissue movement at the site), it may corrode over time (causing electrode damage as well as tissue toxicity), and it may suffer from mechanical failure of the circuit path (Venkatasubramanian et al. 2006). Pacing effectiveness may change over time. Fatigue is particularly important following respiratory muscle atrophy commonly seen following use of a mechanical ventilator. While in an uninjured system, motor units are physiologically recruited slow to fast, electrical stimulation typically

results in reverse recruitment, fast (fatigable) to slow. This leads to significant difficulties with graded recruitment and muscle fatigue. The amplitude of the stimulation also needs to be tuned as the muscles strengthen following prolonged use of respiratory pacing devices. Early implantation of pacing systems following injury will decrease the adaptation time as well as decrease the chance of respiratory illnesses (Onders 2012). As mechanical ventilation (always a bridge to pacing systems) typically involves hyperventilation of users, PCO₂ levels are reduced. As pacing systems are designed to provide normal ventilation, acidosis may arise as PCO₂ levels return to normal (Onders 2012). When pacing is extended to sleep, airway obstructions may occur and upper airways may collapse. Tracheostomy valve caps may be implemented to prevent collapse if it occurs (Onders 2012). Diseases such as chronic obstructive pulmonary disease which increases mucous production and reduces airflow in the respiratory system may also limit the effectiveness of respiratory pacing systems and relegate individuals to mechanical ventilation systems.

The primary alternative to respiratory pacing is mechanical ventilation. With mechanical ventilation devices, air is forced into the lungs with positive pressure. While very effective at providing airflow to the lungs, these devices have significant physiological and psychological complications. Speech, noise, social stigma, risk of infection, caregiver requirements are all additional negative factors of mechanical ventilator usage (DiMarco 1999). Finally, posterior lobe atelectasis, barotrauma, pneumonia, and other respiratory complications are the leading cause of death for SCI individuals on ventilators (Krause et al. 2004; Shavelle et al. 2006). In the case of individuals with SCI, depending on the degree of injury, exercise and pulmonary rehabilitation without the use of a ventilator or pacing system may be possible. However, as most individuals with respiratory insufficiency have limited motor control, they may be unable to perform the exercises typically prescribed for cases such as COPD without the use of ventilatory assist (Aboussouan 2009).

Cross-References

- [Computational Models of Mammalian Respiratory CPG](#)
- [Coupled Oscillations in Neural Control of Breathing](#)
- [Neuromuscular Control Systems, Models of](#)
- [Pre-Botzinger Complex Rhythm Generation](#)
- [Vertebrate Pattern Generation: Overview](#)

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Further Reading

http://en.wikipedia.org/wiki/Phrenic_nerve_pacing

Peripheral Nerve Interface Applications, Sensory Restoration

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Synonyms

[Sensory stimulation](#)

Definition

Sensory restoration is a process for providing information to the nervous system about either the external environment or internal body state, typically by replacing or augmenting sensory pathways that are dysfunctional as a result of disease or injury. Examples of pathways in the peripheral nervous system that might be targeted for sensory restoration include proprioception (i.e., limb position sense), cutaneous sensation (i.e., sense of touch), and internal organ state (e.g., bladder fullness). Sensory restoration is

typically achieved by recording from an electrical transducer and translating that recording into a set of electrical impulses which are delivered to peripheral nerves via a stimulating electrode. Sensory information is encoded by varying the amplitude, frequency, and anatomical location of the stimulating impulses.

Detailed Description

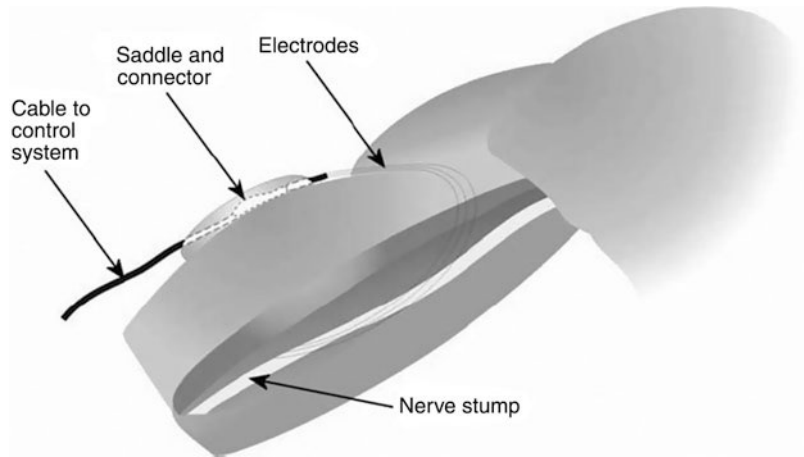
Sensory restoration is a process for replacing or augmenting damaged or dysfunctional afferent pathways in the nervous system to provide information about the external environment or internal body state. This process can be achieved by recording signals such as pressure, temperature, force, or position and encoding those signals into electrical impulses that are delivered to peripheral nerves by stimulating electrodes.

For example, sensory restoration might be used to provide an amputee with a sense of touch from a prosthetic hand. A device to achieve this might include a pressure transducer in the tip of a prosthetic finger to sense contact with objects. Information from that transducer would be encoded as stimulus pulses and passed through a stimulating electrode to activate the nerves in the user's arm. By varying the amplitude, frequency, or anatomical location of the stimulus pulses, the device could provide the user with a graded sense of touch that is perceived as emanating from the appropriate location on the hand.

Procedures for implementing sensory restoration are in the early stages of development, and, to date, devices to stimulate sensory pathways have been fairly crude and have only been tested in small populations. Experiments in animals have demonstrated that it is possible to inject sensory information into the nervous system, although it has been difficult to determine what those animals perceive during sensory stimulation. In one study, stimulating electrodes implanted in the median, ulnar, and radial nerves of a monkey evoked measurable responses in somatosensory cortex with appropriate latencies (Ledbetter et al. 2013). In another study, electrodes implanted in the dorsal root ganglia of cats were used to stimulate sensory

Peripheral Nerve Interface Applications, Sensory Restoration,

Fig. 1 A schematic of the implant used by Dhillon et al. (2004), to restore sensation in amputees. Fine wires were threaded through peripheral nerve stumps in the residual limb and electrical stimulation was used to evoke sensory percepts. (Reprinted with permission from Dhillon et al. 2004. © 2004 Elsevier)



afferents (Weber et al. 2011). Impulses were patterned after the firing patterns of sensory afferents recorded during leg movement, and the cortical response to stimulation was similar to the cortical response to leg movement.

Further studies have focused on sensory restoration in human subjects and have mainly focused on restoring cutaneous sensation and proprioception for amputees. Multiple studies have involved stimulation of the median nerve in healthy subjects and amputees, with subjects reporting experiences of throbbing, vibration, and fist clenching (Anani et al. 1977; Clippinger et al. 1974). In another set of studies, electrodes were implanted in the median nerves of amputees, with subjects reporting sensations of touch, joint movement, and limb position during stimulation. Some of those subjects (Fig. 1) demonstrated improved control of a prosthetic limb during sensory feedback (Dhillon et al. 2004; Dhillon and Horch 2005).

Effort has also been focused on stimulation of the sciatic nerve for sensory restoration in lower extremity amputees. In one study, stimulation was modulated based on prosthetic foot ground contact and knee angle (Clippinger et al. 1982). During stimulation, subjects demonstrated improved balance control and improved ability to function in the dark.

These results demonstrate the promise of sensory restoration, though significant future work will be required to establish stable electrical

interfaces with the peripheral nerve, develop a better understanding of the encoding of sensory information, and optimize the delivery of that sensory information into the nervous system.

Cross-References

- [Peripheral Nerve Interface, Epineural Electrode](#)
- [Peripheral Nerve Interface, Intraneural Electrode](#)
- [Peripheral Nerve Interface, Regenerative](#)
- [Proprioception](#)
- [Somatosensory System: Overview](#)

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Peripheral Nerve Interface Applications, Sleep Apnea

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Definition

Obstructive sleep apnea (OSA) is characterized by frequent collapse of the upper airways (UAWs) during sleep, and patients with OSA experience many apneas (breathing pauses) during the night.

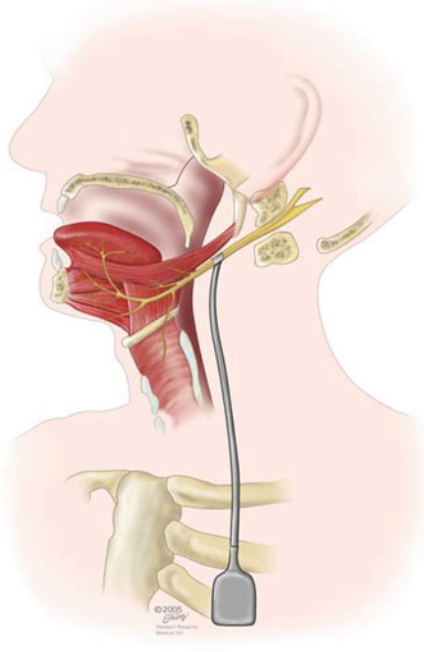
Detailed Description

The severity of this condition is graded by the apnea-hypopnea index (AHI) that indicates the number of apneic episodes per hour (normal AHI < 5 and severe AHI > 30). Sleep is therefore interrupted often, and this condition leads to a lowering of oxygen saturation in the blood. These patients often experience many symptoms such as chronic fatigue, impaired memory, congestive heart failure, decreased libido, and hypertension. This is a serious problem that affects 1–4% of the population (Gislason et al. 1988).

Both men and women are affected but in different numbers (Olsen et al. 1995). Several muscles contribute to maintain the patency of the airways with the genioglossus being the strongest contributor by generating tongue extrusion. Other muscles such as the styloglossus and the hypoglossus contribute to the activity of the tongue and generate retraction. During sleep however, muscle tone decreases, and as the genioglossus relaxes, the tongue collapses into the oropharynx and obstructs airflow (Schwartz et al. 1998).

Solution

The application of continuous positive airway pressure (CPAP) using a mask is the most common and a highly effective method to prevent airway collapse (Littner et al. 2002). However, only about half of patients with OSA can sleep comfortably with a mask. Surgical procedures such as uvulopalatopharyngoplasty (UPPP) can also help, but for many patients the symptoms can resume following surgery. Electrostimulation of the hypoglossal nerve is a more recent approach. Since the largest branch of the hypoglossal nerve carries efferent axons to the genioglossus muscle, stimulation of the whole nerve has been shown to generate tongue retraction and prevents obstruction of the airways. This can be achieved by placing a nerve cuff electrode around the hypoglossal nerve and applying electrical pulses to the nerve (Fig. 1). Animal studies have shown that stimulation of the hypoglossal nerve during sleep prevents obstruction (Sahin et al. 1999). Several clinical studies have also clearly shown that electrical stimulation delivered during the night to the hypoglossal nerve after the onset of sleep significantly reduced the mean apnea-hypopnea index during NREM and REM sleep stages and reduced the severity of oxyhemoglobin desaturation (Schwartz et al. 2001). The long-term stimulation was well tolerated with complete or nearly complete suppression of the apneas. Moreover, since the hypoglossal nerve carries almost exclusively motor fibers and only



Peripheral Nerve Interface Applications, Sleep Apnea, Fig. 1 Electrical stimulation for OSA: A cuff electrode is placed around the hypoglossal nerve to activate the genioglossus muscle and protrude the tongue. The stimulation can be either synchronized with respiration or open loop

few sensory fibers, the stimulation can be applied with sufficient strength and minimal discomfort, paresthesia, or pain or more importantly without waking the patient.

Implementation

There is no commercially available neural stimulation device at this time for this indication, but it is an active area of research and technological development. There are three companies currently involved in developing a neuro-prosthetic device for patients with OSA. All three approaches use a nerve cuff electrode placed on the hypoglossal nerve but differ in how and when the stimulation is applied. One design synchronizes the stimulation to inspiration since the airways may require

opening during this phase of breathing. Inspiration is detected with a pressure sensor (<http://www.inspiresleep.com/>). Another design also synchronizes the stimulation with the inspiration but uses plethysmography to detect inspiration (http://www.apnexmedical.com/downloads/Apnex_Medical_Fact_Sheet.pdf; http://www.apnexmedical.com/downloads/apnex_medical_hgns_therapy_faqs.pdf). Finally, a third design does not implement synchronized stimulation but applies pulse stimulation continuously to maintain the tone in the muscles to prevent collapse (<http://imtheramedical.com/>). All three start-ups are involved in clinical trials and should have a product in the market within a few years. Given the large number of patients with untreated severe OSA, the advent of this technology on the market should have a significant clinical impact.

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Peripheral Nerve Interface Applications, Vagal Nerve Stimulation

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Synonyms

Vagus nerve stimulation

Definition

Vagal nerve stimulation (VNS) is a device-based neuromodulation therapy for drug-resistant forms of epilepsy, depression, and other conditions, that stimulates nerve fibers in the cervical vagus nerve or auricular branch of the vagus nerve (ABVN) using intermittent pulses of current delivered through implanted or external, noninvasive electrodes. VNS works by modulating activity in the central nervous system (CNS) and other peripheral tissues supplied by the vagal nerves in the thorax and abdomen, evidenced by regional and diffuse changes in brain blood flow, metabolism, and electrical activity in the CNS, as well as changes in organ system function via direct stimulation of vagal efferents or by eliciting reflexes via stimulation of vagal afferents.

Detailed Description

Vagal Nerve Anatomy

The vagal nerves are the largest and most evolved nerves in the human body. Using acetylcholine (ACh) as a sole neurotransmitter, the vagal nerves mediate many sensory and parasympathetic functions within the autonomic nervous system. The left vagus comprises ~100,000 axons; 65–80% are visceral afferent sensory fibers with sensory receptors located in the aorta, heart, lungs,

esophagus, larynx, pharynx, gastrointestinal tract, and various visceral organs (Foley and DuBois 1937; Rutecki 1990). The vagi also supply sensory fibers to the outer ear canal via the ABVN. Vagal efferents project from the dorsal motor nucleus (DMN) of the vagus to their effectors. The afferent fibers project primarily to the nucleus tractus solitarius (NTS), where diffuse projections convey the visceral (and some somatic) sensory information throughout the central nervous system (CNS), including areas in the limbic system and cortex that regulate emotion. Many of the afferent fibers participate in autonomic reflexes involved in maintaining homeostasis; these have myelinated projections from the somata in the nodose ganglion to the NTS, DMN, area postrema, nucleus cuneatus, and medial reticular formation (Paintal 1973). The NTS directly communicates with the reticular formation, area postrema (AP), and DMN; it also indirectly communicates with the thalamus, hypothalamus, amygdala, cingulate gyrus, and orbitofrontal cortex via the locus coeruleus (LC) and parabrachial nucleus (PB) (George and Aston-Jones 2010; George et al. 2007).

Implantable and External VNS Systems and Emerging Applications

FDA-approved or CE-marked VNS can be administered through implanted or external, noninvasive electrodes connected to an implanted or external pulse generator. When implanted, a pacemaker-like device delivers intermittent pulses of electrical energy to the left or right cervical vagus nerve through helical or cuff electrodes in open-loop fashion. Noninvasive VNS devices come in two forms: (1) transcutaneous auricular VNS (taVNS or tVNS) devices stimulate the auricular branch of the left or right vagus nerve at the tragus and/or cymba/cavum conchae and (2) noninvasive cervical VNS (nVNS) devices stimulate the left or right cervical vagus nerve through the skin surface (Yuan and Silberstein 2016a, b, c). Implantable devices provide more selective neural interfaces at the expense of invasive surgery and postoperative complications, while noninvasive devices provide a lower-risk, nonsurgical option at the expense of treatment

specificity and challenges around patient compliance.

In the United States, implantable VNS devices (e.g., VNS Therapy System from LivaNova, Inc.) are approved for drug-resistant epilepsy and depression, but are only considered a medically necessary treatment for drug-resistant epilepsy (UnitedHealthcare 2018); noninvasive cervical VNS devices are approved for chronic or episodic migraine and cluster headache (e.g., gammaCore nVNS from electroCore, Inc.). A percutaneous tVNS system was recently approved in the United States for the treatment of opiate withdrawal syndrome (Bridge Stimulator from Innovative Health Solutions, Inc.). In the European Union (EU), implantable VNS devices are approved for epilepsy (LivaNova), depression, autonomic imbalance, and heart failure (e.g., CardioFit VNS System from BioControl Medical, Ltd); noninvasive cervical VNS devices (nVNS) are approved for chronic or episodic migraine and cluster headache, while transcutaneous ABVN stimulation devices are approved for epilepsy (NEMOS tVNS from Cerbomed GmbH), depression, and pain (VITOS tVNS from Cerbomed GmbH) (Ben-Menachem et al. 2015).

There are numerous emerging applications of VNS. These include, but are not limited to: autoimmune inflammatory disorders (e.g., rheumatoid arthritis and Crohn's disease), Alzheimer's disease, anxiety disorders, autism spectrum disorder, bipolar disorder, bulimia, cerebral palsy, chronic pain/back or neck pain, fibromyalgia, gastroparesis and other small bowel motility disorders, narcolepsy, obesity, obsessive compulsive disorder, sleep disorders, tinnitus, and Tourette's syndrome (Ben-Menachem et al. 2015; UnitedHealthcare 2018; Yuan and Silberstein 2016a, b, c). In most instances, VNS is delivered in an open-loop fashion, but responsive (e.g., AspireSR from LivaNova, Inc. (UnitedHealthcare 2018), which automatically triggers stimulation based on characteristic changes in heart rate that precede seizure onset in certain patients) and closed-loop systems are emerging based on research funded by the DARPA ElectRx program, NIH SPARC program and the GSK Bioelectronics Innovation Challenge.

Implant and Dosing Procedure

Under general anesthesia, the VNS device housing is surgically implanted and secured in the left chest wall. A stimulation lead is routed under the skin from the device housing to the left cervical vagus nerve. The helical electrode at the distal end of the stimulation lead is wrapped around the cervical vagus nerve and secured to surrounding tissue. After a 2+ week patient recovery period, the device is turned on and programmed with a wand-like device that is placed over the skin where the device housing is located. Stimulation is intermittent and commonly programmed for 30 s of monophasic, constant-current stimulation every 5 min. Individual parameters are adjusted on a patient-to-patient basis to fine-tune the therapeutic efficacy and minimize the occurrence and severity of side effects (Marangell et al. 2007).

Common side effects, such as dyspnea, cough, and hoarseness, depend on the intensity of the stimulus parameter settings, and furthermore on the nerve fibers activated by a stimulus. To minimize patient discomfort, the intensity is slowly increased over 2-week intervals until a balance between the maximum stimulus intensity and the patients' willingness to accept any side effects is located (George and Aston-Jones 2010). This process is often complicated and time consuming for the patient and physician. Table 1 summarizes the recommended protocol for stimulus parameter adjustments after implantation. Table 2 summarizes available device settings and common variations for epilepsy and depression (Labiner and Ahern 2007).

Therapeutic Mechanisms of VNS

Implantable VNS therapy has been available since 1994 in Europe and 1997 in the United States as a therapy for treatment-resistant partial-onset seizures, where it has helped tens of thousands of patients with drug-resistant temporal lobe epilepsy (TLE) experience significant seizure rate reductions. The use of VNS as an alternative therapy for drug-resistant major depressive disorder (MDD) came after epileptic patients reported mood improvements in the NeuroCybernetic Prosthesis System trials in the 1990s (Ben-Menachem et al. 1994) (and the successful

Peripheral Nerve Interface Applications, Vagal Nerve Stimulation, Table 1 VNS adjustment protocols (Labiner and Ahern 2007)

Efficacy enhancement protocol	Side effect reduction protocol
A. every 2 weeks, increase the pulse amplitude in 0.25–0.5 mA increments until the maximum tolerated level is reached (starting 2 ⁺ weeks after device implantation)	A. Reduce pulse amplitude
	B. Reduce pulse duration
B. Gradually increase the duty cycle if the maximum tolerated pulse amplitude fails to produce a therapeutic response after 1–3 months	C. Reduce pulse repetition frequency
	D. Reduce device on time

Peripheral Nerve Interface Applications, Vagal Nerve Stimulation, Table 2 VNS device settings (Labiner and Ahern 2007)

Parameter	Range	Discrete steps/values	Start value	End value
Pulse amplitude	0–3.5 mA	0.25 mA	0.25 mA	1–2 mA
Pulse duration	0.13–1.0 ms	0.13, 0.25, 0.5, 0.75, 1.0 ms	0.25, 0.5 ms	0.25, 0.5 ms
Pulse repetition frequency	1–30 Hz	1, 2, 5, 10, 15, 20, 25, 30 Hz	20, 30 Hz	20–30 Hz
Duty cycle	10–100%	On versus off time	10%	10%
Device “on”	7–60 s	7, 14, 21, 30, 60 s	30 s	30 s
Device “off”	0.2–180 min	5–60 min ($D_t = 5$ min) 60–180 min ($D_t = 30$ min)	5 min	5 min

off-label use of antiepileptic drugs for mood disorders (Ballenger and Post 1980; George et al. 2000; Post et al. 1986)). Several treatment-resistant epileptic patients implanted with the VNS device reported mood enhancements that could not be explained by the VNS-mediated reduction in seizure frequency. Positron-emission tomography (PET) studies subsequently proved that VNS reduces cingulate activity, the same effect seen from many successful antidepressant therapies (George et al. 2000), and alters limbic blood flow and metabolism (Henry et al. 1998). Di Lazzaro et al. applied transcranial magnetic stimulation (TMS) over the motor cortex and proved that long-term VNS significantly decreases motor cortex excitability in epileptic patients that have received VNS therapy for 10 or more weeks (Di Lazzaro et al. 2004). In 2007, this experiment was repeated in VNS patients with MDD, where the same reductions in motor cortex excitability were seen (Bajbouj et al. 2007). Other investigations show VNS-induced changes in neurotransmitter levels (Ben-Menachem et al. 1995; Kralh et al. 1998). Due to these promising data, the first VNS device for the treatment of unipolar refractory MDD was implanted by Rush and colleagues

in 1998 (George et al. 2000; Rush et al. 2000). Response rates (i.e., a patient is a responder if a standardized depression rating scale score is reduced by 50% or more in response to the therapy) of 27–40% were observed after at least 8 weeks of VNS therapy; robust and durable antidepressant responses are seen after 12 or more months of VNS therapy (George et al. 2002, 2005). The FDA approved VNS for refractory MDD in July 2005.

Many of the VNS studies published to date conclude that VNS imparts its antiepileptic and antidepressive effects through the activation of vagal afferent fibers. This is a logical conclusion, because (1) the device is intended to treat neuronal network-level disorders in the CNS; (2) vagal afferent fibers primarily project to the NTS and onward to the LC, where a chemical lesion was shown to significantly attenuate VNS-mediated anticonvulsive activity (Kralh et al. 1998); and (3) evoked potentials from VNS have been repeatedly observed in neural recording/imaging studies. However, the conclusion that VNS works by activating unmyelinated C fibers of the vagus nerve (Woodbury and Woodbury 1990) is debated, because (1) destruction of C fibers does

not destroy the antiepileptic effect of VNS and (2) stimuli found to be effective in epilepsy are likely of insufficient strength to activate the unmyelinated, afferent C fibers (Evans et al. 2004; George et al. 2002). Various biophysical (Mourdoukoutas et al. 2018; Pelot and Grill 2018), phenomenological and machine learning approaches to VNS optimization (Ward et al. 2015) are in development, which could help to unravel the mechanisms-of-action of VNS therapy and lead to improved titration of VNS parameters for the various indications that are already in clinical use or approaching regulatory approval.

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Peripheral Nerve Interface, Epineural Electrode

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Synonyms

[Nerve cuff electrode](#)

Definition

Epineural electrodes are neural interface devices that are placed on or around peripheral nerves. They include one or more electrical contacts that can be used to stimulate or record action potentials from those nerves. These devices are not designed to penetrate through the perineurium and therefore tend to provide macroscale, rather than microscale, interfaces with the nerve. Because the perineurium remains intact and the electrode contacts are relatively large, the interface tends to be stable over time and less sensitive to micromotion and encapsulation than a microelectrode interface. The size and epineural nature of these electrodes often result in a lower degree of selectivity, both for stimulation and recording, than can be achieved via a penetrating microelectrode interface.

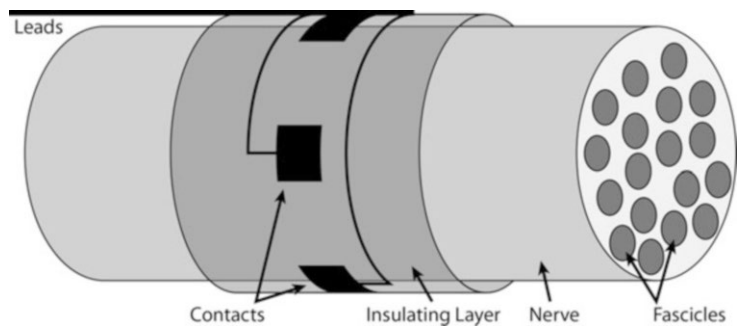
Detailed Description

Epineural electrodes are devices designed to be placed on or wrapped around peripheral nerves to provide an interface for electrical stimulation and recording. There are a wide variety of device designs and configurations, but the structure (Fig. 1) typically includes a layer of insulating material, such as silicone, placed on or wrapped around the nerve along with one or more electrical contacts embedded in the insulating material. The insulating layer provides both mechanical stability and electrical insulation for improved recording as well as control of the flow of current during stimulation. For stimulation applications, this insulation and the intimate contact between nerve and electrode typically result in the activation of the nerve by significantly smaller currents than are required for muscle-based stimulating electrodes (Fisher et al. 2008). Depending on the application, the electrical contacts can range from a single, small square of conducting material to multiple large bands that wrap around the nerve. Electrical contacts are typically made of conducting metals such as platinum or stainless steel, although some newer designs use conducting polymers such as polypyrrole (Green et al. 2008). The contacts are connected to a set of leads which route signals away from the implantation site.

Stimulating Electrodes

A variety of epineural electrode designs have been implemented for stimulation applications with

Peripheral Nerve Interface, Epineural Electrode, Fig. 1 An epineural electrode. The device includes an insulating layer placed on or wrapped around the nerve and embedded with contacts connected to leads that route away from the implant site



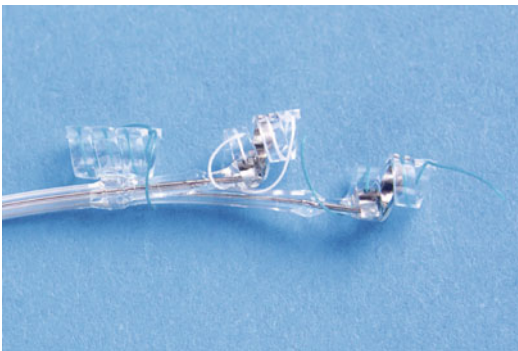
varying degrees of clinical translation and varying degrees of success. Initial designs relied on plastic or rubber tubing wrapped around the nerve for the insulating layer (Dubkin 1970). These designs had significant potential for inducing nerve damage due to the high mechanical stiffness of the material and the occlusion of blood flow to the nerve. As such, a number of electrode designs were developed to mitigate these risks, while also working to improve the selectivity of epineural stimulation.

The Huntington Medical Research Institute helical electrode (Fig. 2) has seen the most clinical success, by far, of any epineural electrode to date (Amar et al. 2008). The simple device, which is designed to coil around the nerve, includes either one or two electrical contacts and is not intended to selectively activate individual fascicles within the nerve. Instead, the device has been used to stimulate the vagal nerve for applications that do not require selectivity such as the control of epilepsy and depression. The device has been implanted in over 70,000 patients to date (Cyberonics 2013).

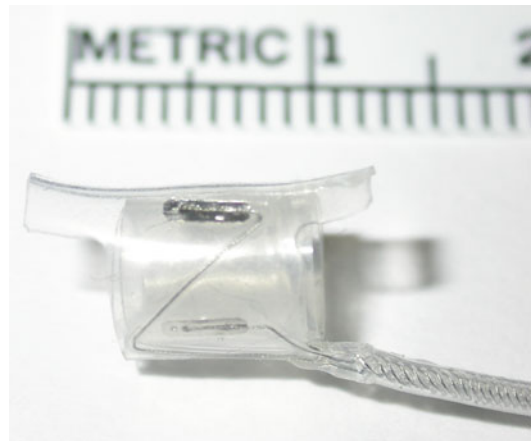
The self-sizing spiral nerve cuff electrode (Fig. 3) was designed to wrap snugly around the nerve while still providing the ability to expand to accommodate swelling of the nerve tissue (Naples

et al. 1988). This design relies on differential stretching of two layers of silicone rubber to achieve a spiral shape that can expand and contract as the pressure within the cuff changes.

These devices have been implanted in human subjects at a variety of anatomical locations as part of neuroprostheses. In one study, a four-contact spiral nerve cuff was implanted around the right optic nerve of one subject with retinitis pigmentosa (Veraart et al. 1998). The subject reported experience of phosphenes in distinct locations around the field of vision during stimulation through each of the electrode contacts. In another study, nine spiral nerve cuff electrodes were implanted in the upper extremities of two individuals with paralysis from spinal cord injury (Polasek et al. 2009). Four-contact nerve cuffs were implanted around the radial nerves of two subjects and the musculocutaneous nerve of one subject. Six additional one-contact nerve cuff electrodes were implanted around the axillary, suprascapular, long thoracic, and thoracodorsal nerves of the same two subjects. Monopolar stimulation through each electrode could produce selective activation of at least one muscle. These



Peripheral Nerve Interface, Epineural Electrode, Fig. 2 The Huntington Medical Research Institute helical electrode, which has two contacts for nonselective bipolar stimulation and a third coiled section for added stability. (Adapted with permission from Amar et al. (2008). © 2008 IEEE)



Peripheral Nerve Interface, Epineural Electrode, Fig. 3 The self-sizing spiral nerve cuff electrode. As pictured, the device has four contacts designed to be equally spaced around the circumference of the nerve. Each contact can be connected to a separate channel of stimulation

electrodes were implanted for up to 3 years with little change in the response to stimulation. In a third study, eight spiral nerve cuff electrodes were implanted on bilateral femoral nerves of four individuals with paralysis from spinal cord injury (Fisher et al. 2008, 2009, 2013). These electrodes generated sufficient knee extension moment to facilitate standing in all subjects, and the response to stimulation was stable for up to 1 year after implantation.

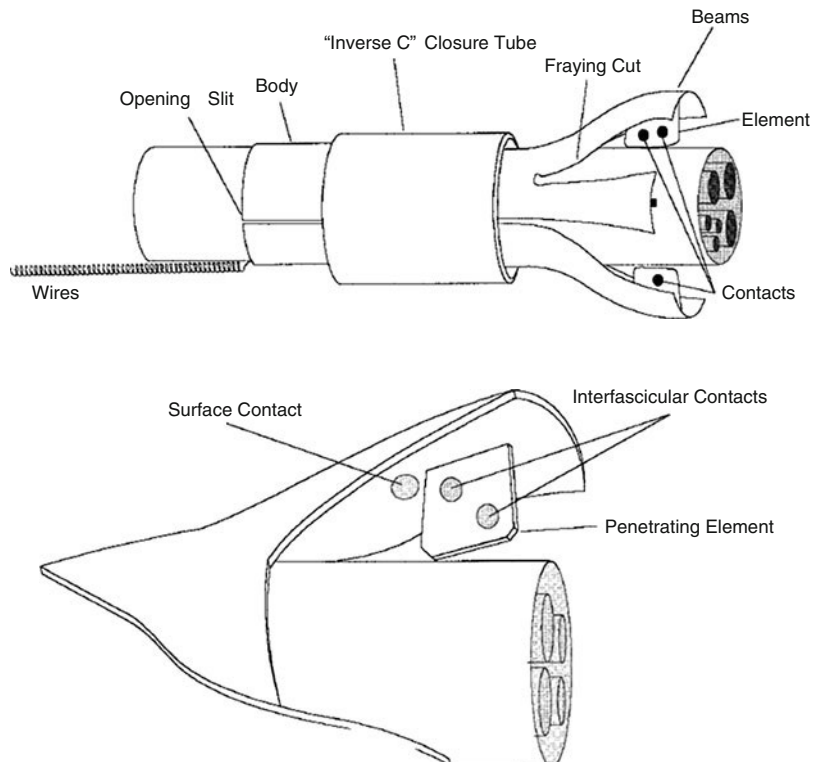
While the self-sizing spiral nerve cuff has been shown to provide a highly stable stimulation interface with peripheral nerves, it has had limited success at selectively activating multiple independent muscle populations. In both animal experiments and human studies, the device has been demonstrated to selectively activate one or more muscles independently, but a single self-sizing spiral nerve cuff has not been demonstrated to selectively activate more than four muscles (Polasek et al. 2009; Fisher et al. 2009, 2013; Polasek et al. 2007). This limited selectivity results from both the number of contacts within

the electrode and the electrode's circular cross section, which causes fascicles near the center of the nerve to be equally distant from all contacts, preventing selective activation (Veltink et al. 1989; Altman and Plonsey 1988). This geometric limitation has led to the development of other designs that may be better suited for achieving selective activation of multiple fascicles.

The slowly penetrating interfascicular nerve electrode (SPINE) improves on the nerve cuff electrode design by including a larger number of contacts on fins (Fig. 4) that are designed to slowly penetrate into the epineurium but not through the perineurium, leaving fascicles intact (Tyler and Durand 1997). The device consists of silicon rubber tubing sliced longitudinally into four beams, with an element including three contacts extending radially into the lumen from each section of the tube. A second piece of tubing is wrapped around the body of the cuff to maintain closure of the electrode and generate the force required to allow the fins to penetrate into the epineurium. The SPINE was implanted acutely

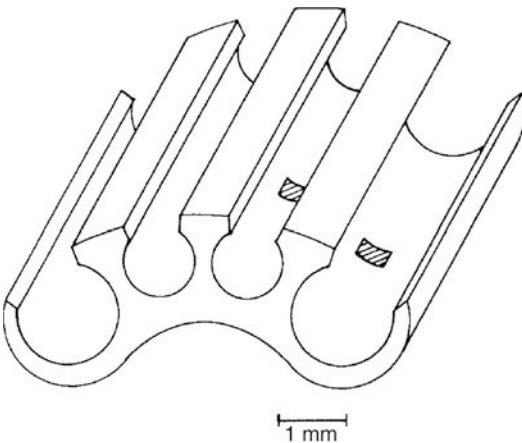
Peripheral Nerve Interface, Epineural Electrode, Fig. 4

The slowly penetrating interfascicular nerve electrode. Elements with electrical contacts are designed to penetrate into the epineurium between fascicles to achieve a more selective interface with the nerve. (Adapted with permission from Tyler and Durand (1997). © 1997 IEEE)



around the sciatic nerves of six cats and achieved a moderate improvement in selectivity over the traditional nerve cuff design. The SPINE has not, however, undergone any chronic safety testing and, as such, has not been implanted in any human subjects to date.

The multigroove electrode (Fig. 5) is another device designed to penetrate the epineurium but leave fascicles intact (Koole et al. 1997). The device requires the surgeon to tease apart fascicles and place them into separate grooves during implantation. In one study, multigroove electrodes with two grooves were implanted on the sciatic nerves of eight rats and achieved selective activation of two branches of that nerve (Koole et al. 1997). As with the SPINE, to date, the device has not been translated for chronic human use.

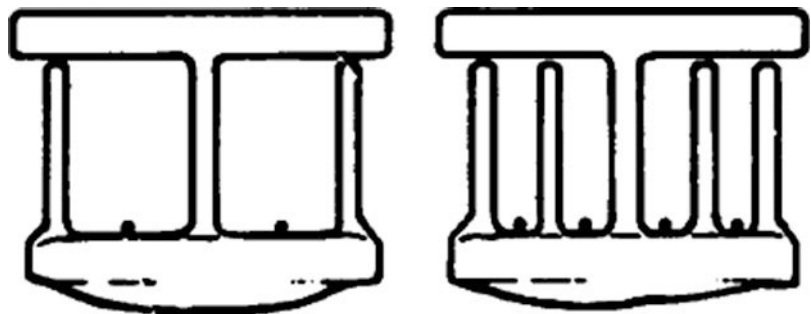


Peripheral Nerve Interface, Epineural Electrode, Fig. 5 A multigroove electrode. Each groove is designed to house one or more fascicles. (Adapted with permission from Koole et al. (1997). © 1997 IEEE)

Book electrodes (Fig. 6) are another class of epineural electrodes that avoid the geometric limitations of nerve cuff electrodes through the use of a more rectangular cross section. This cross-sectional shape decreases the distance between fascicles and contacts within the electrode and can improve the ability to selectively activate each fascicle. A variety of designs have been implemented including devices with a single lumen as well as others with multiple separate lumina. Separated lumina can be created with multiple flaps that divide the rectangular cross section (Brindley 1977). Book electrodes have seen wide clinical adoption as part of a neuroprosthesis to stimulate the sacral spinal roots for bladder control (Martens and Heesakkers 2011). The devices have been implanted in over 1500 patients and multiple studies have demonstrated their ability to selectively activate individual spinal roots and achieve stable interfaces lasting 16 years or more (Martens and Heesakkers 2011; Brindley 1994).

Another book-type electrode, the flat interface nerve electrode (FINE; Fig. 7), has a similar rectangular cross section but has multiple contacts along the lumen (Tyler and Durand 2002). The device differs from other book electrodes in that it is designed for use on the peripheral nerves, rather than the spinal roots, and is designed specifically to reshape round nerves to a flatter cross section. The device has multiple small electrical contacts designed to achieve a relatively high degree of selectivity and has been demonstrated to achieve sub-fascicle level selectivity on the sciatic nerve of cats (Leventhal and Durand 2003). To date, the device has been implanted acutely on the femoral nerves of six human subjects and has demonstrated the ability to selectively activate at least

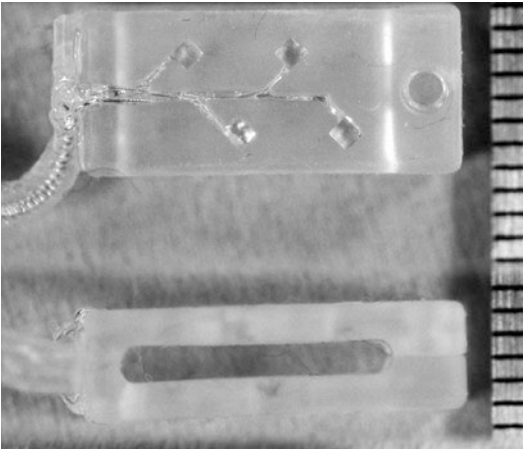
Peripheral Nerve Interface, Epineural Electrode, Fig. 6 Typical book electrodes with multiple lumina. Each lumen contains a single stimulation contact. (Reproduced from Brindley (1977) with permission from BMJ Publishing Group Ltd)



four, but possibly as many as six, muscles (Schiefer et al. 2010).

Recording Electrodes

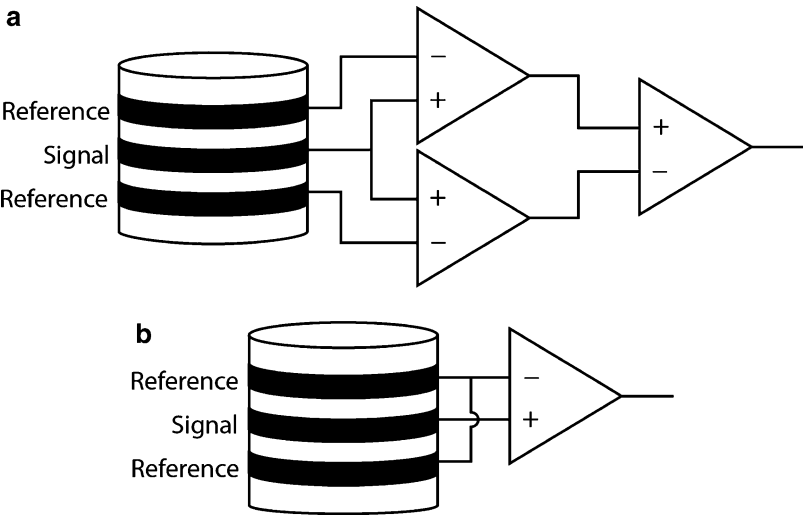
The electroneurogram (ENG) signal recorded from epineural electrodes consists of electrical



Peripheral Nerve Interface, Epineural Electrode, Fig. 7 The flat interface nerve electrode. The device is designed to reshape round nerves to a rectangular cross section to decrease the distance between fascicles and contacts in order to improve selectivity. As pictured, the device has eight contacts which can each be connected to a separate channel of stimulation. (Adapted with permission from Schiefer et al. (2010). © IOP Publishing. All rights reserved)

signals recorded from many axons simultaneously and is often contaminated by other bioelectric signals such as the electromyogram signal from nearby muscles. To reduce noise and improve signal-to-noise ratio (SNR), epineural recordings are usually performed in a tripole or virtual tripole configuration (Fig. 8). The tripole configuration relies on the double-differentiated potential recorded from a contact of interest and two nearby reference contacts aligned longitudinally with the nerve. The virtual tripole uses a similar configuration of contacts but shorts together the two reference electrodes and uses the difference between the signal of interest and the shorted references. These configurations have dual benefits of reducing common-mode noise and improving SNR by exploiting the triphasic nature of action potentials. By measuring the difference between potentials recorded longitudinally along the nerve, the tripole and virtual tripole configurations increase signal amplitude by measuring the peak-to-peak rather than absolute voltage from the triphasic action potential. By varying the spacing between contacts, these configurations can also provide some selectivity in recording action potentials from axons of specific diameters based on their associated velocities and wavelengths. The tripole configuration generally has better SNR but requires additional amplifiers near the electrode to perform the differencing operations, so the virtual tripole configuration is more commonly used in practice.

Peripheral Nerve Interface, Epineural Electrode, Fig. 8 Typical recording configurations for epineural electrodes. (a) Tripole configuration. The signal is double-differentiated with respect to two surrounding reference signals. (b) Virtual tripole configuration. The signal is differentiated with respect to the shorted surrounding reference signals



While the configuration of contacts is different for recording and stimulating electrodes, similar form factors have been used for both applications, with slight differences in design. Nerve cuff electrodes are commonly used for recording applications, though the insulating layer for recording versions is often longer than for stimulating versions. This is necessary to accommodate the additional contacts in the tripole and virtual tripole configurations.

A number of studies have used nerve cuff recordings from the common peroneal and sural nerves to detect foot contact for closed-loop neuroprostheses to correct foot drop (Hansen et al. 2003; Hoffer et al. 1996). Another study placed a nerve cuff electrode around the radial nerve to detect slip at the fingertips as part of a neuroprosthesis to restore hand grasp after spinal cord injury (Hoffer et al. 1996). Many animal studies have relied on cuff electrodes and FINEs for recording ENG signals from nerves throughout the body (Hoffer et al. 1987, 1996; Yoo and Durand 2005; Wodlinger and Durand 2011). Some of those studies have also focused on the development of techniques such as beam-forming and blind source separation to selectively record from individual fascicles within mixed nerves (Wodlinger and Durand 2009, 2011; Calveti et al. 2011).

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Peripheral Nerve Interface, Intraneural Electrode

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Definition

Peripheral nerve intraneural electrodes are characterized as having the active recording or stimulation contact located within the epineurium sheath of a peripheral nerve. The most common intraneural electrodes have active contacts within the smaller nerve-fiber bundles of the fascicle.

Detailed Description

Peripheral nerve intraneural electrodes were originally developed to improve the selectivity and signal-to-noise ratio of neural recordings using microneurography techniques. This allowed researchers to acquire single-unit afferent action

potentials by using needle electrodes placed within the endoneurium of individual nerve fibers. The most common intraneural electrodes have active contacts that are placed inside the perineurium of the smaller fascicle nerve bundles; thus, these electrodes are referred to as intrafascicular electrodes. The electrode technology has since been improved and expanded to multi-site recording and stimulating electrodes. Stimulation via intraneural electrodes requires less current to generate muscular force producing action potentials than stimulation through extraneural electrodes. Intrafascicular electrodes also provide a way to selectively activate small groups of motor units within a single muscle, which can provide fine-tuned gradation of force production from a single muscle. Intraneural electrode technology development can be grouped into three distinct groups based on the design of the electrodes: longitudinal intrafascicular electrodes (LIFEs), microelectrode arrays (MEAs), and sieve electrodes (Navarro et al. 2005).

Longitudinal intrafascicular electrodes, or LIFEs, are a Teflon-insulated Platinum-Iridium wire, 20–30 cm in length and 25 μm in diameter with 1 mm of exposed wire. The LIFE is surgically threaded beneath the perineurium of a fascicle with the length of the insulated electrode running longitudinal to the nerve fibers. Early versions of the LIFE were shown to be effective for stimulation selectivity and multi-unit recording. Recent research has used chronically implanted LIFEs to evoke object discrimination through afferent sensory stimulation in upper-limb amputees using strain-gauged myoelectric prostheses. Modifications have been made to the standard LIFE to add multiple electrode contact sites and improve on implantation techniques and mechanical stiffness. Polymer-based LIFEs (polyLIFEs) have been created that use a more flexible metallized Kevlar fiber. These polyLIFEs have been used in human upper-limb amputee research to record peripheral motor neuron activity for control of grip force and hand position of a mechanical prosthesis, as well as to return tactile and proprioceptive sensory information via stimulation. A version of the LIFE using a shape

memory alloy wire allows the electrode contact site to be micromanipulated after implantation. Thin-film LIFEs (tLIFEs) were created to improve on the mechanical mismatch between metal wires and neural tissue. Multi-contact tLIFEs have been implanted chronically in human upper-limb amputees and have been used to decode motor intent for various hand positions as well as return tactile information from a phantom hand. The transverse intrafascicular multielectrode (TIME) uses an electrode similar to multi-contact tLIFEs but threads the electrode transversely across the nerve. Threading the electrode across one or more fascicles allows for greater selectivity because more individual nerve fibers are likely to be in proximity to the multiple electrode contacts. Modifications to LIFEs and the TIME, including multiple filaments and corrugated structures, allow for increased electrode count and separation between contact sites to improve recording and stimulation selectivity as well as provide better chronic implantation stability (Ortiz-Catalan et al. 2012; Yoshida et al. 2010).

Microelectrode arrays (MEAs) were originally developed for cortical recording experiments and are designed to penetrate neural tissue. MEAs commonly consist of either a thin penetrating substrate with multiple electrode contact sites or a grid of penetrating microelectrodes. Only a few MEAs have been translated to peripheral nerve applications. The most commonly used peripheral nerve MEA is the Utah Slanted Electrode Array (USEA) which is a 10×10 grid of penetrating microelectrodes that vary in length from 0.5 to 1.5 mm and have 400 μm spacing. The USEA is pneumatically inserted into the peripheral nerve, and the grid spacing and varied depths of electrodes on the USEA allow for good cross-sectional electrode tip coverage across the diameter of a peripheral nerve. This provides a high level of selectivity for single and multi-unit recordings from various afferent and efferent nerve fibers throughout the nerve, as well as very selective and graded muscle force production from multiple muscles using stimulation currents below 100 μA . There have been some human

studies using MEAs in peripheral nerves, but the majority of the research has been done with animal studies. Some of the various applications include using the USEA as a neural recording platform to decode limb positions and using the USEA as a neural stimulation platform to control bladder function. A large body of animal research using acute and chronically implanted USEAs has focused on interleaved multielectrode stimulation to evoke fatigue-resistant coordinated movements using multiple muscles across multiple skeletal joints (Navarro et al. 2005; Ortiz-Catalan et al. 2012).

Sieve electrodes are an intraneural peripheral nerve interface that is mainly used for the regeneration of severed nerves. The sieve is made up of a polymer disk with metallized holes for use as electrodes and is placed in the middle of a chamber in close proximity to the two ends of a severed nerve. When the nerve fibers from the severed ends regrow and connect through the metallized holes, they interface with the electrode contacts. Stimulation via these electrodes may also improve axonal regrowth. Sieve electrodes were originally designed with holes that had similar diameter to single nerve axons (2–10 μm) to provide a high level of selectivity, but it was found that nerve regeneration failed with such small holes. Nerve fiber regrowth requires long-term chronic studies, and sieve electrodes have only been tested in animal research (Navarro et al. 2005; Ortiz-Catalan et al. 2012).

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Peripheral Nerve Interface, Regenerative

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Definition

Regenerative peripheral interfaces (RPIs) are implantable devices that rely on the spontaneous regenerative capability of the injured peripheral nervous system to establish a bidirectional flow of information between the transected nerves in amputees and smart robotic prosthetics. RPIs are designed to provide intuitive movement and natural feel to advanced prosthetics for amputees and are characterized by the placement of multi-electrode arrays (MEAs) in the regenerative path of their transected peripheral nerves. The MEAs detect motor commands from the brain as extracellular action potentials (AP) in the microvolt range traveling down their amputated nerves and use them to control the robotic prosthetic limb. In addition, RPIs can translate information from sensors populating the robotic limb to the user, by electrically stimulating axons in the nerve that elongate from neurons in the dorsal root ganglia.

Detailed Description

Regenerative Peripheral Interfaces (RPIs)

RPIs constitute a selective yet invasive type of peripheral nerve interface device first proposed in the early 1970s, as transected nerves were shown to grow through porous materials or into grooves (Brindley 1972; Mannard et al. 1974), leading to the idea microelectrode arrays with holes can be fabricated for recording from axon

fibers the regenerating through (Llinas et al. 1973). The first regenerative electrode was fabricated by drilling holes through silver wires to record multiunit potentials from regenerated *Xenopus* motor fibers (Mannard et al. 1974). Subsequently, chronic recordings of action potentials were obtained in the regenerated rabbit sciatic nerve using a 10-channel silicon-based sieve electrode (Edell et al. 1982). Advanced micro-fabrication techniques allowed the development of sieve multielectrodes capable of both recording and stimulating from regenerated fibers.

Types of RPIs

Several RPI devices have been developed, including those that rely on the regeneration of transected axon through perforated devices, microchannel electrode arrays, and electrodes placed in the lumen of nerve guides. The main types include the following:

Sieve Electrode Array

In this type of RPI, the regenerating axons are interfaced as they grow through a perforated substrate resembling a sieve, with ring electrodes on some of the holes. The first report of neural recording using this type of electrode was published by Edell (1986), who used a sieve electrode etched in silicon and wired to a percutaneous connector, to record spontaneous and evoked neural activity from the regenerating rabbit peroneal nerve. This work was extended by Bradley et al. (1997), who recorded neural activity using a sieve electrode implanted into the rat glossopharyngeal nerve for up to 13 weeks, in response to taste and thermal stimuli in the tongue. Regeneration was also demonstrated in sieve electrodes implanted in rat lumbar spinal roots and in the eighth cranial nerve of the toadfish.

However, the silicone sieve design proved to partially block nerve regeneration allowing only a small fraction of primarily sensory neurons to grow through the perforations. In addition, these electrodes also cause compressive axon damage due to the inability of the ring electrodes to accommodate the increment in fiber diameter

that axons undergo as they mature and remyelinate (Navarro et al. 1998). The development of softer polyimide sieve electrodes alleviated some of these limitations and improved reliability (Stieglitz 1997; Lago 2007). However, recordings have been obtained only in a subset of the animals tested, and a low proportion of the electrodes on the sieve provide recordable signals (Lago et al. 2005).

A modification of the sieve electrode in which regenerating axons terminate in a compartment that contains cells that serve as surrogate targets for the regrowing axons, known as biohybrid arrays, has been proposed, but has not been implemented or tested (Stieglitz et al. 2002).

Microchannel Electrode Array (MCE)

In this device, regenerating axons grow through a nerve conduit with microchannel electrodes after directly suturing the severed nerve. This design was first proposed by Susuki and colleagues (1997) who fabricated them in polyimide with multiple channels for recording and stimulating sites which allow the regeneration of axons. More recently, MCE are fabricated using soft polymers such as polyimide or polydimethylsiloxane (PDMS; Lacour 2008). The size of the microchannels has been demonstrated to be critical as 70% regeneration ensues through 100- μ m-wide channels but fails if channels are 35 μ m (Lacour 2009). The length is also critical as regeneration can be achieved through 4–5-mm-long microchannel arrays, but with a much reduced quality in implants longer than 1 cm. In addition, the regenerated “mini nerves” are ensheathed with fibrous tissue that sometimes can cover up to half of the available channel area. Such mini nerves were recently proven by Fitzgerald et al. (2012) to be functional by inserting a fine tungsten microelectrodes into the silicone array.

Recently, Minev et al. (2012) demonstrated the recording of tactile-evoked nerve activity in anesthetized rats using gold electrodes patterned into PDMS microchannels, in which small fibers teased from the dorsal roots were threaded inside the microchannels in acute experiments.

While MCE are a promising new type of RPI, recording and stimulating of regenerating fibers in fully awake animals remain to be demonstrated.

Regenerative Multielectrode Interface (REMI)

This interface relies on a microelectrode array placed in the lumen of nonbiodegradable polyurethane tube that serves as a nerve guide. The transected peripheral nerve is sutured to both ends of the REMI conduit allowing axons to regenerate through the platinum MEA in the lumen with minimal or no restriction. This type of regenerative interface is completely encapsulated by the regenerated tissue during nerve repair, forming a monolithic structure that anchors the RPI to the nerve, making it less susceptible to micromotion injury. The REMI was demonstrated to record action potentials as early as 8 days post implantation, with high signal-to-noise ratio, and for as long as 3 months in some animals, with minimal inflammation at the nerve tissue-metal electrode interface (Garde et al. 2009). This electrode allows normal nerve regeneration across the nerve conduit, and the recording of spontaneous and evoked action potentials in fully awake animals, as indicated by a battery of behavioral tests including plantar mechanoreception and thermal nociception assays.

Seifert and collaborators (2012) used a high-throughput gene array to confirm that the REMI does not interfere with normal regeneration as indicated by the normal expression of genes involved in nerve inflammation, cell death, neural injury and repair, and the histological changes that occur in parallel to early neural activity.

Regenerative interfaces are unique in that biological cues can be used to guide the regenerative path of growing axons into compartmentalized electrodes, a strategy suggested to achieve modality-selective regenerative neural interfaces. This possibility has been supported by reports indicating that NGF and NT-3 can selectively attract TrkA nociceptive axons and TrkC proprioceptive axons *in vitro* and partially *in vivo*; respectively (Lotfi et al. 2011). However, the

feasibility of modality-specific neural interfacing in segregated REMIs remains to be demonstrated.

Limitations

Invasiveness

The implantation of RPIs requires invasive surgery; however, this might be justified in most amputee cases in which the transected nerve in the limb stump remains functional but disconnected from its normal targets.

Nerve Regeneration Interference

Electrodes placed in the regenerative path of axons can actually present a physical barrier to their growth. Indeed, target innervation success is reduced compared to that of nerves regenerating through a nerve guide without regenerative electrodes. This limitation has been characterized as drastic in the sieve interfaces, where only 10% of regenerating myelinated axons succeeded in crossing the electrode, most of which are sensory and not motor axons.

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Peripheral Nerve Models

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Synonyms

[Axon model](#)

Definition

Peripheral nerve models are computational models of one or more axons. Many models have been created. Variation in models typically pertains to the specific ionic currents and their conductances through the axon membrane. Another common variation pertains to the method used to model myelination. Typically, peripheral nerve models are nonlinear in nature and require solving systems of differential equations, although there are fast approximation techniques that can provide insight into the trends in axonal response to varied stimulation. In the neurosciences, peripheral nerve models are more typically used to study single neurons, whereas, in biomedical and neural engineering, peripheral nerve

models are more typically used in large population models to study the global response to electrical nerve stimulation or for nerve recording, primarily for use in functional electrical stimulation (FES) neuroprosthetic or neuromodulation systems.

Detailed Description

Anatomy

Briefly, peripheral axons fall within two categories – myelinated and unmyelinated – depending on the presence of periodically spaced sheaths of myelin enrobing the axon. A small portion of the axon membrane remains exposed between adjacent myelin sheaths known as the node of Ranvier. Both types of axons frequently appear in fascicles – bundles of axons within a nerve that are isolated from each other by a perineurial sheath. The axons within a fascicle are collectively referred to as endoneurium. The remainder of the nerve is referred to as the epineurium. Peripheral nerves can contain anywhere from a single fascicle to dozens of fascicles and the same nerve across species can contain a vastly different number of fascicles.

Note, within this entry, the term “nerve” will be used to refer to a population of axons and is not to be confused with the axon, or neuron, itself. Additionally, the models discussed in this entry are electrochemical in nature. Mechanical models of nerves will not be addressed.

Applications

The basis of all peripheral nerve models is the axon. Individual models of axons may be used to accurately represent experimental data. These models tend to be more detailed, incorporating numerous types of ion channels. They may also incorporate sophisticated representations of myelination and the space between the myelin and the axonal membrane: the periaxonal space. Used alone, this type of model can be used to provide insight into how an axon will respond to direct extracellular or

intracellular stimulation. This type of axon model may also be used *en masse* to study or predict the response of nerves to electrical stimulation, a common technique in the field of neural engineering. Additionally this technique can be used to model nerve recording. To this end, population models may incorporate a volume conductor model in which the spread of voltage (potential) in space is determined.

Alternatively, axon models may be simpler and designed not with the intent? of perfectly reproducing the shape of the action potential or studying the effects of electrical stimulation on a nerve. Instead, these models are mostly interested in the binary nature of neurons (the so-called “all-or-none” response) and are typically used to assess the flow of information in neural networks. As neural networks are more accurate models for the central nervous system, they are beyond the scope of this entry.

The Cable Equation

Before discussing specific models, it is important to discuss the cable theory, as it is the basis for all peripheral axon models. The cable theory was developed to describe signal propagation and decay in underwater cables, specifically those used for transatlantic telegraphs. Scientists in the late nineteenth century recognized similarities between peripheral axons and cables and began to apply them to axon models. The cable, or axon, can be represented by a circuit (Fig. 1).

Where C_m and R_m describe the membrane capacitance and resistance, respectively, and R_i describes the internal resistance to current flow. Although this model is strictly electrical in nature, it is analogous to ionic flow in the nerve. The analysis of this model produces the equation

$$\lambda^2 \frac{\partial^2 V_{\tau d}}{\partial x^2} - \tau \frac{\partial V_{\tau d}}{\partial t} - V_m = 0$$

$$\tau = C_m R_m$$

and

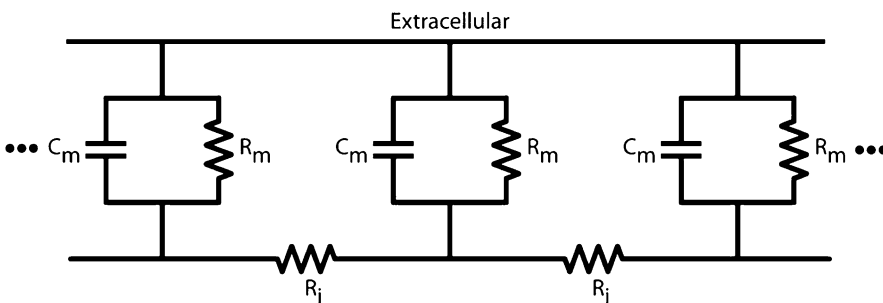
$$\lambda^2 = \frac{R_{\tau d}}{R_i}$$

This equation describes the deviation in membrane voltage from a resting potential, $V_m = V_i - V_e$, as a function of distance along the axon, x , and time, t . This model was subsequently adapted to account for insulative myelin and the resting membrane voltage, V_r , typically assumed to be -65 mV (Fig. 2).

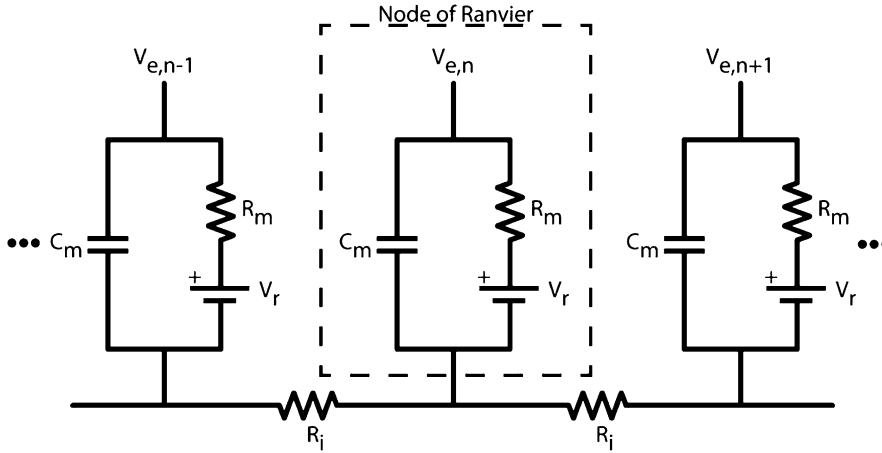
This model was further refined to account for specific ionic currents that cross the membrane. These adaptations will be discussed in the following sections.

The Hodgkin-Huxley Model

In 1952, Sir Alan Hodgkin and Sir Andrew Huxley published a seminal series of papers that



Peripheral Nerve Models, Fig. 1 An electrical circuit representation of a passive, unmyelinated axon. Compartments of membrane resistance, R_m , and capacitance, C_m , are separated internally by resistance within the axon, R_i



Peripheral Nerve Models, Fig. 2 Adaptation of the circuit shown in Fig. 1 to account for myelination. Here, the extracellular voltage, V_e , can differ at each node, n .

A battery is included to maintain resting membrane voltage or reversal potential, V_r , typically -65 mV

detailed the dynamics of ion channels in a node of Ranvier in the squid (*Loligo pealei*) giant axon. Their model captured the dynamics of a propagating action potential as a function of voltage-gated sodium and potassium ion channels as well as a leakage current that accounted for the transmission of all other ions. The researchers recognized that whether the ion-selective channels in the axonal membrane allowed the flow of an ion depended on both membrane voltage and time. That is, the membrane resistances in the cable model were ion specific and variable. The equivalent electrical circuit for the membrane was adapted to Fig. 3.

Using circuit analysis,

$$I = I_C + I_{Na} + I_K + I_L$$

can be expanded to

$$I = c_m \frac{dV_m}{dt} + g_k(V_m - E_K) + g_{Na}(V_m - E_{Na}) + g_L(V_m - E_L)$$

where $g_x = 1/R_x$, the conductance of ion x . Hodgkin and Huxley explicitly defined the ionic conductances as functions of time and voltage, thus allowing them to further expand the equation to

$$I = c_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_L (V_m - V_L)$$

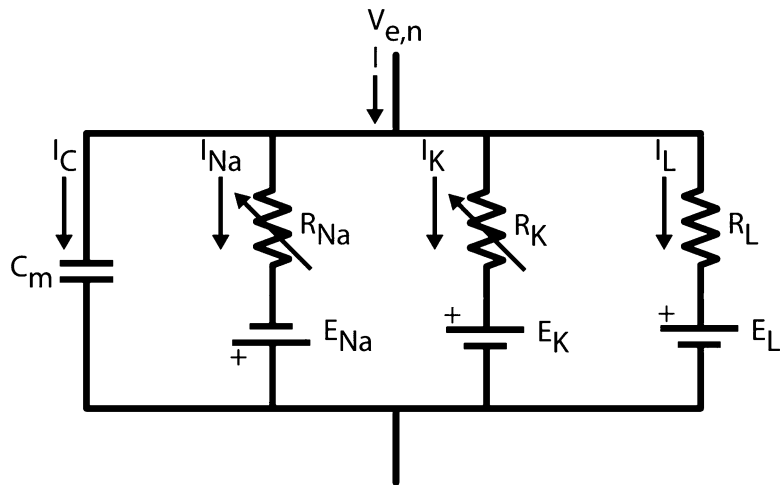
where $\bar{g}_{Na}$, $\bar{g}_K$, $\bar{g}_L$ and refer to the maximum sodium, potassium, and leakage conductance, respectively. E_{Na} and E_K are the equilibrium potentials for sodium and potassium. Additionally, Hodgkin and Huxley determined the probability that a voltage-gated sodium channel, m^3h , or potassium channel, n^4 , was open. These probabilities are themselves dependent on voltage and time:

$$\begin{aligned} \frac{dn}{dt} &= \alpha_n(1-n) - \beta_n n, \quad \alpha_n = \frac{V_m + 10}{100 \left(e^{\frac{V_m + 10}{10}} - 1 \right)}, \quad \beta_n = 0.125 e^{\frac{V_m}{20}} \\ \frac{dm}{dt} &= \alpha_m(1-m) - \beta_m m, \quad \alpha_m = \frac{V_m + 25}{10 \left(e^{\frac{V_m + 25}{10}} - 1 \right)}, \quad \beta_m = 4 e^{\frac{V_m}{18}} \\ \frac{dh}{dt} &= \alpha_h(1-h) - \beta_h h, \quad \alpha_h = 0.07 e^{\frac{V_m}{20}}, \quad \beta_h = \frac{1}{10 \left(e^{\frac{V_m + 30}{10}} + 1 \right)}, \end{aligned}$$

Following the seminal work of Hodgkin and Huxley, many researchers adapted the H-H model, incorporating additional ion channels and adjusting maximum conductances and reversal potentials in an effort to accurately describe the particular axon under investigation.

Peripheral Nerve Models, Fig. 3

Adaptation of the simplified nodes shown in Fig. 2 to account for different ionic currents and reversal potentials. Transmembrane sodium current, I_{Na} , is assumed to be governed by a single type of sodium channel, as is potassium current, I_K



Accounting for Myelin

While the work of Hodgkin and Huxley, Frankenhaeuser and Huxley, and many others was instrumental to the fields of computational neuroscience and neural engineering, many treated the myelin between the adjacent nodes of Ranvier as a perfect insulator, resisting all ionic current flow through the axonal membrane. Depending on the application, this simplification may be acceptable, but research has shown that this is not true. Other models have attempted to account for myelin.

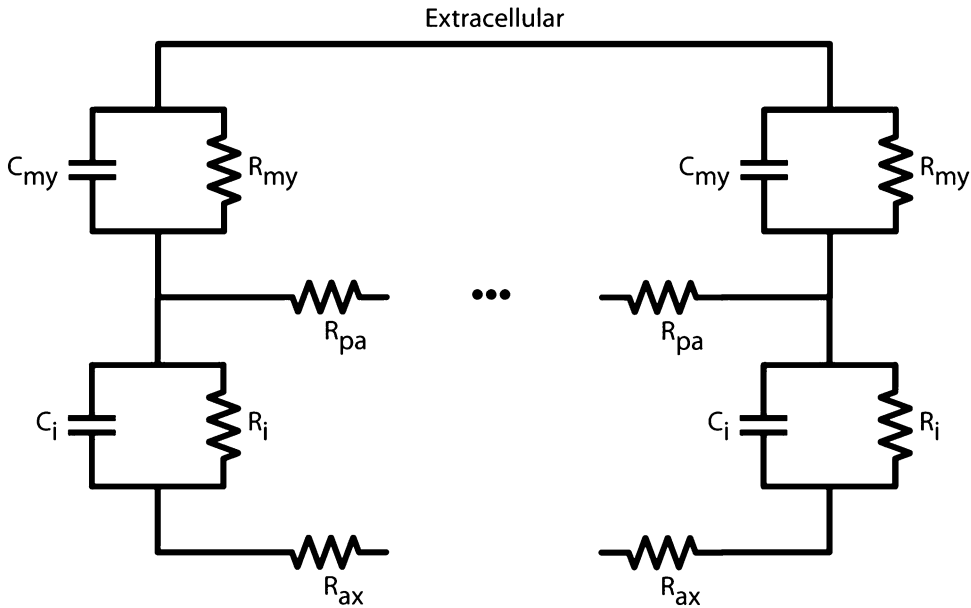
In 1962, Richard FitzHugh represented myelin as a series of passive high-impedance compartments consisting of a capacitor and resistor in parallel similar to that shown in Fig. 1. Model results better represented observations from mammalian axons. However, models were unable to reproduce common features of mammalian action potential spike trains such as depolarizing afterpotentials. Such detail was not captured until the introduction of the double-cable axon model, which accounted for the periaxonal space between the myelin and the axon (Fig. 4).

In 1985, Blight characterized myelin as a 10-compartment circuit model, accounting for the internodal (i) and myelin sheath (my) capacitance and resistance. In 1990, Awiszus expanded this representation to include potassium and sodium currents in parallel through the intranodal axonal membrane. A year later Halter and Clark

refined the model to account for differences in myelin thickness along the internode: the myelin adjacent to the node (MYSA), the fluting of the myelin (FLUT), and the stereotypical myelin with uniform thickness (STIN). This model has been subsequently refined to include different types of ion channels, such as slow potassium, fast potassium, fast sodium, and persistent sodium channels, and electrogenic ion pumps (Stephanova and Bostock 1995). In 2002, McIntyre, Richardson, and Grill published a double-cable axon model, commonly referred to as the MRG model, which is considered to be a very accurate representation of a mammalian peripheral axon to electrical stimulation.

Extensions of the Single Axon-Model: Volume Conductors and Populations of Axons

When the response of an axon to extracellular electrical stimulation is of interest, the distribution of potential (voltage) within a volume conductor must be determined. The simplest representation of volume conductor is that of a homogenous, isotropic medium in which the source of stimulation is at a sufficiently far distance from the axon so as to represent the source as a point source. In such cases, the voltage at each node of Ranvier and along each internode can be calculated by the equation



Peripheral Nerve Models, Fig. 4 To account for the space between the axon membrane and the myelination, the periaxonal space, the double-cable axon model was developed, which utilizes two modified cable models in

parallel. This model has subsequently been modified to account for different ionic currents, similar to those seen in Fig. 3

$$V = \frac{I}{4\pi\sigma R}$$

where σ is the conductivity of the medium and R is the distance from the point source to the location of interest along the axon. There are alternative equations to describe the voltage associated with a disc electrode as well as when the medium does not satisfy the assumptions of homogeneity and isotropy, such as when an electrode is on the surface of the skin. Typically, as models become more complicated and incorporate more tissues with dissimilar conductances, researchers turn to finite element models, commonly referred to as finite element method (FEM) or analysis (FEA).

The techniques described above can be extended to simulate populations of axons, such as would be encountered when electrically stimulating or recording from a peripheral nerve. In these cases, each axon is typically treated independently with the underlying assumption that no axon directly impacts the reaction of any other axon to electrical stimulation. With the continued improvement in computing power and access to

computer clusters, a few researchers have developed full-nerve, three-dimensional, multi-fasciculated population models. While most of these studies have simplified fascicular geometry, assuming fascicles to be of equal size and uniform distribution, a few studies have based the nerve model on histological cross sections taken from the nerve being modeled, the largest study of which was published recently by Schiefer et al. (2012).

Time Considerations

As the complexity of the models increases, the time required to simulate the axon(s) does as well. With the computing power of today's computers, this time cost can be tolerated for a small number of axons. However, simulating large populations of axons or conducting sensitivity analyses with a fine resolution of the swept variable can lead to extended simulation times, even if parallel computing techniques are employed. The appropriate model depends on the nature of the study.

Typically, the simplest model that can sufficiently answer the question is optimal.

Simplifications and Approximations

Due to the computational overhead required to simulate large populations of axons, researchers have attempted to develop other techniques that approximate axon activation without the need to simulate the non-linear dynamics of the axon. Many of these techniques only captured axonal behavior under a narrow set of conditions. In 1992, Warman published a predictive method that accounted for the redistribution of internal currents and captured more axonal behavior, but still broke down under certain conditions. Recently, Peterson published a method that overcame some of those limitations while remaining fast.

Software Packages

Multiple software packages exist to simulate ion channels, single axons, networks of axons, populations of axons, and volume conductors. NEURON is a freeware designed specifically to model axon dynamics and is easily adaptable to facilitate addition or manipulation of ion channels. The Scientific Computing and Imaging (SCI) Institute at the University of Utah has also released software to simulate neuron responses to electrical stimulation. Of course, these models can also be developed in programming languages such as C/C++ or MATLAB. Neurocal is a MATLAB-based modeling package freely available on the MathWorks File Exchange. While there are numerous finite element packages, many cannot handle the complexity of most neural models. Exceptions include SCIRun, COMSOL, and ANSYS (formerly Ansoft) Maxwell.

Cross-References

- [Action Potential Initiation](#)
- [Axon, Modeling](#)

- [Cable Equation](#)
- [Cable Theory: Overview](#)
- [Computational Models of Neuromodulation](#)
- [Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons](#)
- [Fitzhugh–Nagumo Model](#)
- [Hodgkin–Huxley Model](#)
- [Morris–Lecar Model](#)

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Further Reading

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Peripheral Nerve Signal Processing, Denoising

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Synonyms

Filtering; Noise attenuation; Noise cancellation

Definition

A signal-processing method used to decrease or eliminate noise from a peripheral nerve recording through the attenuation or estimation and subtraction of the components of the raw electro-neurogram of non-nerve action potential origin or not of interest.

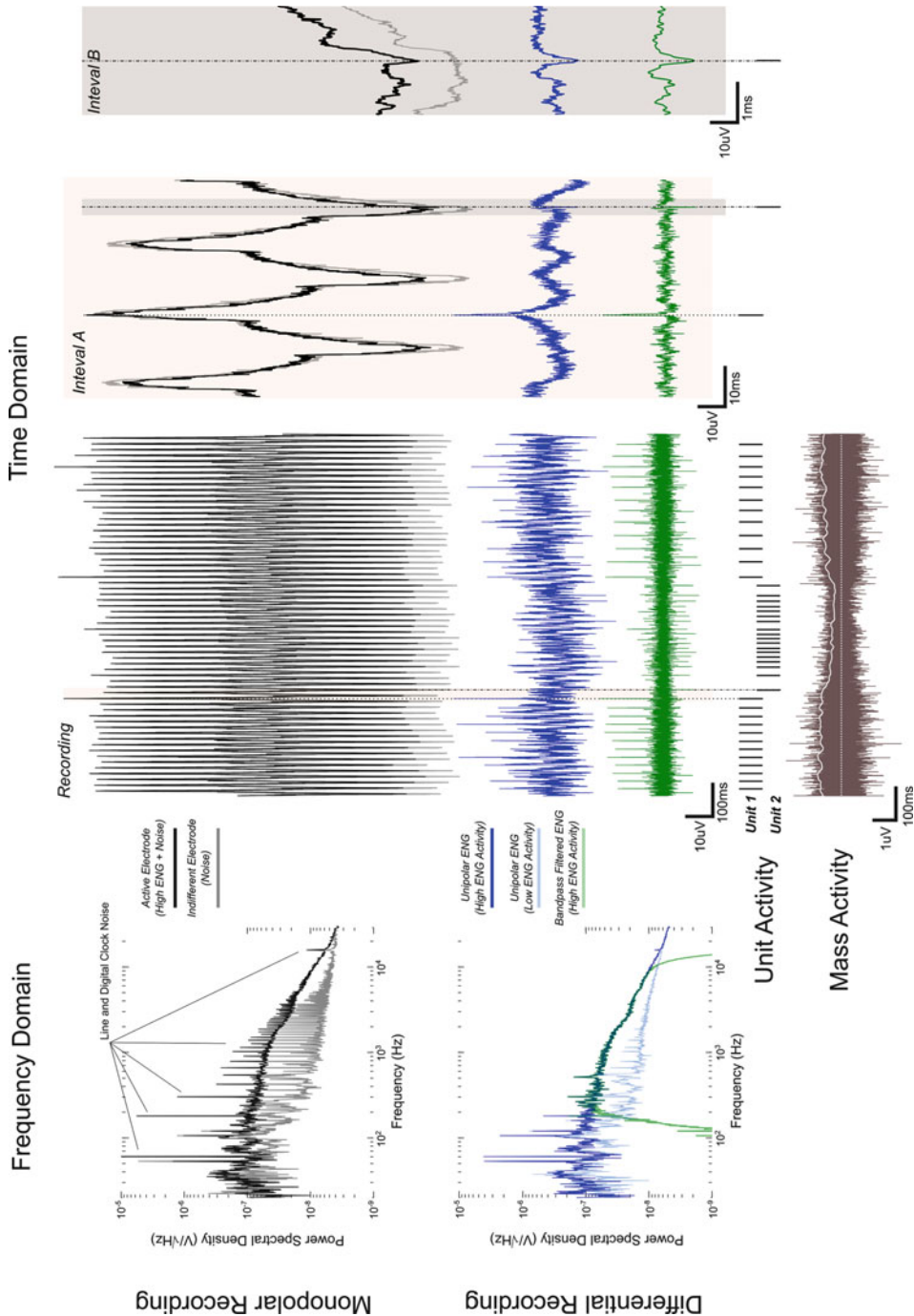
Detailed Description

The raw electrical activity obtained through electrodes placed in or around the peripheral nerve consists of the extracellularly measured propagating action potentials of the active fibers within the nerve bundle along with the superimposed electrical pickup from other nearby bioelectrically active tissues and non-bioelectric sources. Since the signal of interest, the nerve activity, can be orders of magnitude smaller than the noise in the raw electro-neurograms, signal processing to denoise the recording is necessary. Noise attenuation or denoising is an optimization that maximizes the signal and minimizes the noise to improve the signal-to-noise ratio of a recording to facilitate the extraction of signal or information in subsequent signal-processing steps. Thus, by definition, it is important to know something about and understand the nature of the detectable nerve signal and noise sources seen by the receiver.

Peripheral nerve bundles contain a multiplicity of nerve fibers that project to/from the central nervous system to peripheral end organs. Each peripheral end organ is typically wired to a single nerve fiber (axon). The nerve fiber and the end organ(s) it innervates are the smallest unit of control available to the body and is called the sensory (afferent) or motor (efferent) unit. The nervous system conveys information from one part of the body to another using a bioelectric impulse, the action potential, that travels up (afferent) or down (efferent) the nerve fiber. This communication is digital in that the unitary action potential by itself only conveys that an event has happened. It can be considered a single digital bit of information. Magnitude is conveyed in two ways: by modulating the frequency of action potentials transmitted through a single nerve fiber (rate code) and by modulating the number of fibers projecting to/from the end organ (population code).

Neural interfaces detect the information contained within the nerve bundle by measuring the extracellular action potential as they transit the region of sensitivity of the neural interface through a low-noise, high-input impedance electrometer (headstage amplifier). In general, the activity that is captured is the superimposed activity of many nerve fibers. The mass activity modulates as a function of both the rate and population codes and thus the energy of the nerve activity. Neural interfaces designed to resolve the activity of single nerve fibers (single-fiber action potentials or SFAP), additionally, can resolve the rate code of a small subset of that total population.

The extracellular action potentials detected are at most on the order of ~ 100 μV in amplitude and occupy a bandwidth between ~ 100 Hz up to several 10 's of kHz. The distance of the active nerve fiber to the electrode contact, electrode contact size, and impedance of the space surrounding the nerve and electrode have a large effect on the magnitude and bandwidth of the action potential detected. Neural interfaces with small contacts ~ 10 μm immediately in contact with the nerve fiber (< 50 μm distance and intrafascicular) can record extracellular action potentials on the high end of the amplitude and bandwidth range, while those with larger contacts and greater nerve fiber



Peripheral Nerve Signal Processing, Denoising, Fig. 1 (continued)

to electrode distances ($>100\ \mu\text{m}$ distance and extrafascicular) will have amplitudes in $\sim 1\ \text{uV}$ range and $<10\ \text{kHz}$ bandwidth (Yoshida and Stein 1999; Stein et al. 1975).

Noise sources of bioelectric in origin include the bioelectric activity of the heart and nearby muscles. They may also include the extracellular action potentials of nerve fibers that do not project to the activity of interest. Non-bioelectric noise sources include chemoelectric (electrode potential changes in temperature, environmental chemical species concentrations), mechanical disturbances to the electrode Stern layer (motion artifact), electromagnetic pickup of radio-frequency sources, and electrical power lines (Webster and Clark 2010) (Fig. 1).

Noise attenuation processing techniques exploit the differences that exist between the extraneural action potential and the various noise sources. Current methods (1) estimate the noise and subtract the noise estimate (differential recording) and (2) take advantage of differences in the frequency content of nerve activity and noise (spectral filtering) (Ge and Farina 2013).

Differential Recording

Potentials are by definition measurements relative to a point defined as ground. For biopotential measurements, a single ground point is defined on the body by the ground electrode. This point serves as the reference potential for all potentials as well as the common current return node for the headstage amplifier. The record of the raw electrical potential measurements relative to the ground electrode is defined as the monopolar recording.

In general, the ground electrode is a large, low-impedance electrode that is not matched in size or impedance to the active electrode. As such, the noise pickup is dominated by the active electrode (Purves 1981).

The simplest method to reduce noise in a recording is to place a second, size-matched electrode in the vicinity of the first active electrode such that it picks up common environmental noise but is insensitive to the nerve activity. This electrode is called an indifferent electrode and provides an estimate of the environmental noise seen by the active electrode. This estimate can then be subtracted either in hardware through a differential amplifier or later in software by a simple subtraction to eliminate some or all of the environmental noise in the measurement. Recordings that result from the subtraction of the noise with respect to an indifferent electrode are defined as the unipolar recording. A more advanced technique is to apply an adaptive filter that predicts the nonneural noise components in the monopolar recording, which can be subtracted to optimally remove the environmental noise.

Alternatively, a second active electrode displacing longitudinally or laterally the nerve but in the vicinity of the first active electrode could be used instead of the indifferent electrode. This case is defined the bipolar recording configuration. The configuration eliminates the need for an indifferent electrode and is effective for environmental noise attenuation but results in a complicated recording case where the activity measured is the sum of the activity of the uncommon nerve activity and the difference of the common nerve activity.



Peripheral Nerve Signal Processing, Denoising, Fig. 1 Analysis of recordings taken from the peripheral nerve in the frequency domain (spectrograms) and the time domain at various stages of denoising. The time domain records are shown at three zoom levels. The lowest zoom level resolves the rate or mass activity, while the highest zoom level resolves the single-unit action potential. The upper row shows the raw monopolar recording, while the second row shows the same recording after (1) subtraction of the indifferent recording and (2) band-pass filtering. The frequency

domain figures show the spectrograms for high levels of nerve activity and no nerve activity (or noise). Note the inclusion of in- and out-of-band noise in the monopolar recording case, which are largely eliminated through the subtraction from the estimate of the noise. Finally, band-pass filtering was applied to reveal the single-unit activities. Once the single-unit activity is resolved, the rate code can be captured. Alternatively, the focus can be an estimate of the population code, through analysis of the mass activity

Differential recording does not eliminate noise that presents themselves independently on each active or indifferent electrode channel, such as non-common mode bioelectric activity, stochastic thermal noise, or shot noise.

Spectral Filtering

Spectral filtering advantage of differences in the frequency composition of the extracellular action potential and noise sources. It defines the bandwidth of nerve activity as the signal and spectral frequencies that lie outside the bandwidth of interest as noise. The bandwidth of nerve activity ranges between ~100 Hz and 6 kHz (Stein et al. 1975) or 30 kHz (Qiao et al. 2012) depending upon the type of neural interface used. Typically, two classes of filters, band pass and notch, are used to filter raw electroneurograms. Band-pass filters are used to attenuate out-of-band noise such as the electrode interface potential, ECG, distant EMG, and out-of-band thermal noise. Notch filters can be applied to reduce the line noise and its harmonics which can extend into the bandwidth of nerve activity. It should be noted that noise sources that share the neural bandwidth, in-band noise, are not attenuated by these spectral methods.

Spectral filters can be implemented as classical linear filters in hardware or software or by applying classical linear filters (FIR, IIR, FIR-IIR). Although these filters can effectively reduce the out-of-band noise, they can also distort the waveform and introduce artifacts and instability depending upon the definition of the filter order (cutoff sharpness), filter type (Chebyshev, Paynter, Butterworth, Bessel), and passband selection. Generally speaking, these artifacts occur with higher-order and narrowly defined filters with filter types designed to have a steeper roll-off. If waveform fidelity is important, then lower-order filters or filters with flatter roll-off in the frequency domain (Bessel) or digital multiresolution, wavelet, or decomposition techniques (Strang and Nguyen 1997; Mallat 1999; Citi and Micera 2013; Citi et al. 2008) are better choices.

The selection of the filtering method heavily depends upon the type of neural signal to be extracted and the needs of the subsequent signal-processing steps to obtain this information. For example, if the desired signal is the population code, which can be obtained through analysis of the energy of the mass activity recorded by the neural interface, it may be sufficient to use a tightly defined band-pass filter centered on the maximum energy peak of the neural spectrum at approximately 1 kHz. However, if the desired signal is the rate code from an identified single unit, then the shape and timing of the single-unit waveform are essential and filtering techniques that retain the shape information of the unit, such as wavelet denoising, are appropriate.

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Peripheral Nerve Signal Processing, Multipole Cuff Methods

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Synonyms

Multi-array nerve electrode; Multi-contact nerve electrode; Multielectrode array

Definition

A method of obtaining motor or sensory information from the peripheral nervous system for the purpose of implementing closed-loop control of neuroprosthetic systems (e.g., functional electrical stimulation devices or electrical neuromodulation therapies).

Detailed Description

The peripheral nerve can consist of one or more bundles of nerve fibers (defined as a fascicle) that are tightly enclosed within a thin layer of connective tissue called the perineurium. The fascicle, in turn, is surrounded by the endoneurium, which is constructed from connective, collagen, and vascular tissue. As the nerve traverses distally from the spinal cord, the typically single (mono-fascicular) configuration of the peripheral nerve begins to diverge into multiple branches at various distal locations.

Due to this highly organized structure, the peripheral nervous system offers an attractive target for many neuroprosthetic devices that can include functional electrical stimulation (FES) systems for restoring lost neurological function or electrical neuromodulation therapies for treating chronic medical disorders. In contrast to

clinical applications that interface the central nervous system (e.g., deep brain stimulation), the peripheral nerve not only provides a minimally invasive target that can selectively activate specific neural pathways, but it also makes recording neural activity a potentially elegant solution for obtaining physiological information that can be used to control neuroprosthetic devices in a closed-loop fashion.

The Electroneurogram (ENG)

Ongoing electrical activity obtained from a peripheral nerve is commonly referred to as the electroneurogram (ENG). The reliable measurement of such activity is affected by the particular device used to interface with the nervous system and also by the manner in which the recorded signal is processed. The literature in this area of research indicates myriad factors that influence the quality of the recorded ENG: location of the recording electrode, configuration of electrode contacts, total number of recording sites, and sources of noise. Therefore, the objective of obtaining high-fidelity neural signals (i.e., large signal-to-noise ratio (SNR)) is critically dependent on both the optimal design of peripheral nerve interfaces and correspondingly effective signal-processing techniques.

Nerve Cuff Electrodes

Over the past several decades, various different types of electrodes have been developed for peripheral nerve recording. Among those, the nerve cuff electrode has been one of the most widely studied peripheral nerve interfaces. This design entails an insulating layer (i.e., nerve cuff) – consisting of silicone or polyimide – that completely encircles the nerve. Individual electrode contacts – typically constructed from platinum or iridium oxide – are embedded within the inner surface of the nerve cuff such that electrical coupling occurs at the external surface of the nerve. As demonstrated by long-term implant studies, this design provides a stable mechanical

substrate with minimal acute and/or long-term tissue damage (Larsen et al. 1998; Grill and Mortimer 2000; Romero et al. 2001).

Evolution of Multipole (Multi-contact) Electrodes

Recent advances in electrode fabrication technology and data-processing techniques have supported the development of multipole electrodes that can record differential neural activity generated by multiple ENG sources. The source (s) of ENG activity can range from an individual nerve fiber to an entire population of axons within a single nerve fascicle. The spiral nerve cuff electrode is an extensively studied type of nerve electrode, where the insulating layer is constructed such that, by default, the electrode cuff curls into a cylindrical shape (Romero et al. 2001; Rozman et al. 2000; Naples et al. 1988). This design allows for (1) a “self-sizing” cuff that adjusts to the diameter of the nerve, (2) an even distribution of electrode contacts around the circumference of the nerve, and (3) optimal spatial resolution for selectively recording multiple ENG sources.

The Flat Interface Nerve Electrode (FINE) is an alternative electrode design aimed at improving upon the performance of the spiral electrode (i.e., round cross section). It was envisioned that fascicles located near the center of a circular nerve trunk could be better accessed electrically by slowly reshaping the nerve into a flatter, rectangular cross section (Yoo and Durand 2005; Tyler and Durand 2002). Interestingly, recent work has shown that some peripheral nerves naturally exhibit flat or oval cross sections (i.e., reshaping mechanism may not be necessary), such as near the major branching point(s) of the hypoglossal, sciatic, and pudendal nerves.

Nerve Recording Technique: Artifact Suppression

Due to the close proximity of electrically active muscle tissue, the ENG obtained from peripheral

nerve electrodes are prone to contamination by muscle-derived signal artifacts. Although conventional band-pass filtering techniques can provide modest improvements in the signal-to-noise ratio (SNR), a quasi- or pseudo-tripolar electrode recording technique has been used as a highly effective solution (Stein et al. 1975). This technique was originally described as involving three circumferential electrode contacts equally spaced along the length of a nerve cuff electrode. The two contacts located at the either end of the nerve cuff electrode are electrically shorted, and thus, the ENG is obtained by recording the difference in electrical potential between the two shorted electrode contacts and the remaining middle contact. By modifying the contacts at both ends of the nerve electrode, the pseudo-tripolar configuration can further attenuate any externally generated artifact that would otherwise produce a linearly varying signal along the length of the cuff (Rahal et al. 2000a, b; Andreasen and Struijk 2003). This technique can be applied to any multipole nerve cuff electrode.

Intrafascicular Electrodes

An intrafascicular electrode denotes a type of neural interface, where the electrode contact (s) is located within a nerve fascicle and therefore gains direct physical contact with nerve fibers. Despite the invasive nature of this electrode design (i.e., compromised perineurium), it can achieve remarkably superior ENG recordings compared to that of conventional nerve cuff electrodes. Examples range from single-channel wire-based electrodes, such as the longitudinally implanted intrafascicular electrode (LIFE) (Lawrence et al. 2003; Lefurge et al. 1991), to multielectrode arrays (MEA) such as the Utah Slanted Electrode Array (USEA), which consists of 100 needle-shaped electrodes (Branner et al. 2004). It is important to note, however, that effective long-term use of intrafascicular electrodes has yet to be demonstrated.

Information Content of Neural Activity

Inasmuch as the physical design of an electrode determines the quality and quantity of the recorded ENG activity, the method by which the electrical signals are subsequently processed is equally important for extracting physiologically relevant information.

Changes in ENG Activity

The most basic approach to processing ENG activity is to apply a band-pass filter (e.g., 1–2 kHz) that can isolate the frequency components most relevant to neural activity. The filtered signal can then be rectified, integrated, binned (e.g., several millisecond windows), and compared to a predetermined threshold value. Processed ENG data can be further applied to sophisticated computational approaches, such as artificial neural networks (Micera et al. 2001) or models that analyze the variance of the rectified-integrated signal to determine any statistically significant changes in ENG activity (Kurstjens et al. 2005). Further refinement of the recorded ENG can be achieved by characterizing the signal and noise components. This can involve subspace decomposition methods that use statistical information (e.g., higher-order statistics) about particular segments of the signal (Upshaw and Sinkjaer 1998). This approach is suitable for whole nerve recording, where a simple “on-off” signal is sufficient as a feedback signal.

Analysis of Mixed Signals

However, in many cases, the nerve can consist of multiple fascicles that convey a multitude of functionally disparate information. One may be interested in selectively recording from only one particular fascicle or from multiple sources of neural activity. To this end, mixed signal algorithms such as blind source separation (BSS) are an effective tool for processing ENG recordings. This approach is particularly attractive as the algorithm depends on statistical independence, and

not on any modeled estimate of each recorded signal. Traditional approaches – such as inverse problem algorithms – can provide very precise estimates of multiple sources, but require significantly more computational time, whereas beamforming (spatial filter) algorithms strike a good balance between computational speed and precision of source localization. Although numerous studies have validated these signal-processing algorithms using ENG activity obtained from multipole nerve cuff electrodes (Teshfayesus and Durand 2007; Zariffa et al. 2011; Wodlinger and Durand 2011), further work is needed to determine feasibility for long-term clinical use.

Future Direction

In summary, the use of peripheral nerve activity obtained from multipole electrodes holds much promise as an effective means of clinically implementing closed-loop control strategies in neuroprosthetic and neuromodulation systems. Despite the important advances that were highlighted in this very brief overview, an optimum solution for reliably obtaining information from the peripheral nervous system remains to be determined.

Cross-References

- [Neuromodulation: Overview](#)
- [Somatosensory System: Overview](#)

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Peripheral Nerve Signal Processing, Source Localization

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Detailed Description

Background

Peripheral nerve trunks are composed of many individual nerve fibers (axons) which are segregated into several fascicles. The axons grouped in each fascicle tend to share a common peripheral endpoint, making them anatomically, if not functionally, distinct from those in other fascicles. This suggests that it may be feasible to identify the fascicles from which activity recorded by nerve cuff electrodes originates. For example, given several fascicles terminating separately in extensor and flexor muscle groups, this localization and subsequent separation of signals travelling to these groups could allow the control of prosthetics in people with amputated limbs.

Techniques

Techniques for source localization and separation in peripheral nerves are similar to those in other areas of biomedical signal localization and separation, such as EEG/MEG and ultrasound. These techniques are often referred to as beamforming (or spatial filtering) from ultrasound theory where transmit and/or receive beams of the device are steered and focused to provide added sensitivity in a given spatial location. Techniques may be nonadaptive, in that they only use an a priori model (often finite element based) of the geometry and physics of the situation, or adaptive, in the sense that they also use information from the recorded signals. Three applications of these techniques to the peripheral nerve case are discussed below.

Pathway-Level Beamforming

Zariffa et al. (2009; Zariffa and Popovic 2009) used a very general experimental lead field approach to generate classifiers for various combinations of activity. For example, by stimulating the various branches of the sciatic nerve intraoperatively, they were able to build a classifier that could classify compound action potentials based on their branch of origin. Equation 1, below, is used to estimate the source signals:

$$s = (H^T H)^{-1} L^T [L(H^T H)^{-1} L^T + \lambda I]^{-1} o \quad (1)$$

where s is the vector of source signal estimates, L is the lead field matrix, H is a reweighting matrix based on the weighted minimum-norm technique, λ is a regularization parameter for Tikhonov regularization (Tikhonov and Arsenin 1977), and o is the vector of observed voltages on each contact of the electrode. Focusing on “pathway” rather than “fascicle” restricts the problem to the components we are able to stimulate, potentially providing more functionally useful distinctions, but is shown to have difficulty when multiple branches are active simultaneously.

Fascicle-Level Beamforming

Fascicles are each surrounded by a thin membrane known as the perineurium. Unlike the epineurium which forms the loose outer connective tissue of the nerve, the perineurium constitutes the equivalent of the blood-brain barrier in the peripheral nerve and is composed of tight junctions making it higher impedance. This high-impedance membrane makes signals originating from the same fascicle difficult to distinguish but helps to separate signals originating in distinct fascicles.

Wodlinger and Durand (2009, 2011) propose and validate a technique to achieve separation of both large compound action potential-type signals and artificially generated noise-like fascicular level signals in an *in vivo* rabbit model. Figure 1 provides an example of using this algorithm to

both separate mixed fascicular signals and identify the fascicles of origin. A finite element model was used to generate the lead field matrix L , which was then used to calculate the “transformation matrix” (M) of filters for each pixel (i) as in (2) and (3):

$$LM_{:,i} = \delta_i \quad (2)$$

$$M_{:,i} = \frac{LM_{:,i}}{\|LM_{:,i}\|} \quad (3)$$

Images of activity within the nerve could then be produced by multiplying the vector of observed signal on each contact, O , by the transformation matrix, M . Sources were then localized from the resulting images, either manually or through automated image analysis. The iterative technique comprised of (4) and (5) below was then applied to optimize filters for the sources (fascicles) present in the nerve:

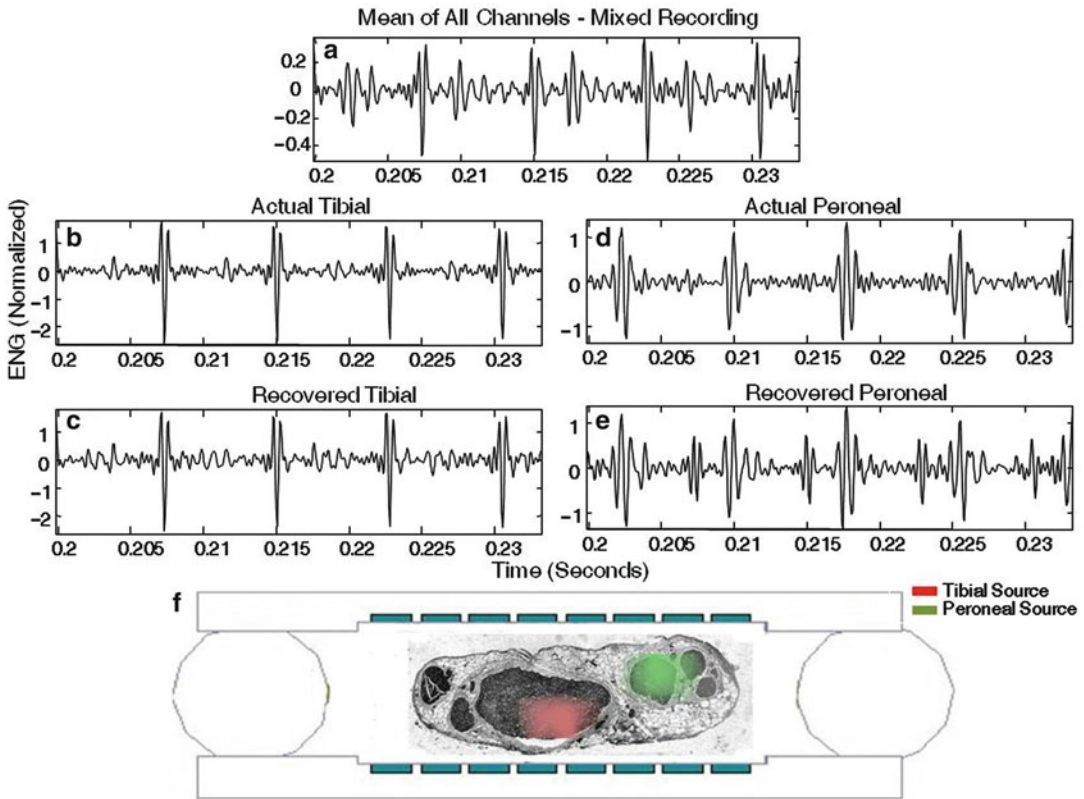
$$f_i^n \rightarrow f_i^{n+1} = S_i^T M \quad (4)$$

$$\begin{aligned} S_i^n &\rightarrow S_i^{n+1} \\ &= S_i - \sum_{(j|j \neq i)} (M f_i^T)^T S_j (S_j - S_i) \end{aligned} \quad (5)$$

where S is the source location image, created initially using $S_i = OM_i$, and f is the filter for each source. Iterations were stopped when there was no improvement in the signal-to-interference ratio or a predefined threshold was reached. Overall, the technique separated tibial and peroneal signals from recordings on the main sciatic trunk with an RMS error of $14 \pm 10\%$ of signal mean.

Adaptive Beamforming

Adaptive beamforming techniques use information about which sources are currently active to adjust their filters or lead field model to improve accuracy. In this way, the iterative portion of the technique described above may be considered adaptive if the calculation was repeated at each timestep depending on which sources had been



Peripheral Nerve Signal Processing, Source Localization, Fig. 1 Separation of peroneal and tibial components from cuff recording on rabbit sciatic nerve using beamforming filters. (a) The mean of all 16 channels (for clarity) for a signal created by adding a normalized recording during tibial stimulation with a normalized recording during peroneal stimulation. The beamformers were applied to this signal to generate an estimate for each branch, shown in (c, e) (recovered signal). The equivalent single-branch signals (calculated by applying the filters to

the single-branch recordings directly) are shown for comparison in (b, d). Aside from some cross talk in (e), the separation is nearly complete. (f) Histology from this experiment overlaid with the location estimates of the tibial and peroneal sources and placed approximately within a schematic of the cuff electrode. Histology confirms that the fascicles overlaid by the beamforming location estimate correspond to the correct branches of the nerve. (Figure and caption are from Wodlinger and Durand 2011)

active (and the ratio of their activities) in the previous timestep. Many other adaptive techniques exist, including the hierarchical method described in Calvetti et al. (2011) and an adaptation of the CHAMPAGNE technique (Tang et al. 2012).

Current State of the Art

Techniques which penetrate the nerve to record from particular pathways directly have already

enjoyed some success in animal and first-in-man studies (Micera et al. 2008, 2010; Dhillon et al. 2004; Dhillon and Horch 2005). The signal processing techniques presented here allow more useful signals to be harvested from less-invasive recording methods which may be more robust in the long term since the perineurium is not compromised by the electrode. Computational and acute animal studies have been completed by a number of groups (Zariffa et al. 2009; Zariffa and Popovic 2009; Wodlinger and Durand 2009, 2011; Calvetti et al. 2011; Tang et al. 2012),

demonstrating that these techniques effectively separate functionally or anatomically independent signals. Chronic animal and human studies to validate the general hypothesis of robustness are a subject of future work.

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Peripheral Nerve Stimulation Technique, Nerve Block

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Synonyms

Direct current nerve block (DC block); Electrical nerve block; High-frequency nerve block; Kilohertz-frequency alternating current (KHFAC) nerve block

Definition

“Nerve block” is an electrical method of inducing block of the conduction of action potentials in peripheral nerves. This type of block can be obtained by three distinct methods: collision block, direct current (DC) block, and kilohertz-frequency alternating current (KHFAC) nerve block. Collision block stimulates the nerve at a rapid rate and uses antidromic annihilation of action potentials of interest. The clinical use of this technique is limited. DC blocks action potentials by two different mechanisms – depolarization block and hyperpolarization block – but typically damages the nerve within a few seconds. KHFAC block produces a rapid and reversible nerve block and is potentially safe for long-duration applications.

Detailed Description

Background

There is an unmet clinical need for a method for rapidly and reversibly blocking peripheral nerves. This will have potential applications in the treatment of motor, sensory, and autonomic conditions where the pathology is based on the overactivity of neural signals. Present clinical methods of

nerve block have many disadvantages including prolonged activation and reversibility times. KHFAC block offers many advantages and has been the subject of increased research interest over the last decade.

Characteristics of KHFAC Nerve Block

KHFAC nerve block was initially investigated in amphibians (Tanner 1962) and later in mammals, using frequencies of 100 Hz–10 kHz, demonstrating nerve block for frequencies greater than 4 kHz (Bowman and McNeal 1986). Recently it has been conclusively demonstrated that KHFAC can be used to quickly, repeatedly, and reversibly block conduction in the peripheral nerves (Kilgore and Bhadra 2004; Tai et al. 2004; Bhadra and Kilgore 2005; Kilgore and Bhadra 2013 [review article]). KHFAC nerve block has been tested in multiple mammalian *in vivo* models, including rat, cat, dog, and monkey.

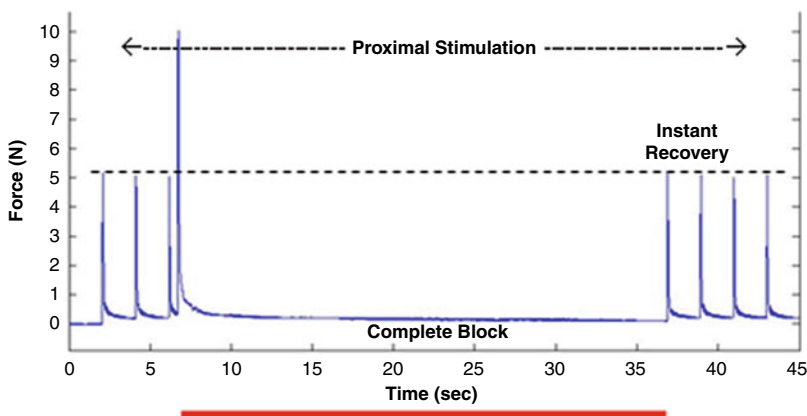
An example of the typical experimental results using KHFAC nerve block is shown in Fig. 1. KHFAC neural conduction block can occur as quickly as 50 ms. KHFAC block can be reversed simply by turning the high frequency off, and in most cases, the nerve returns to normal conduction in less than a second (Bhadra and Kilgore 2005). It is possible to obtain a graded/partial

HFAC neural conduction block by using amplitudes which are less than the block threshold (minimum current required to completely block a nerve) (Bhadra and Kilgore 2005). The most ideal block characteristics are found at frequencies in the range of 10–40 kHz delivered through electrodes that surround the nerve (nerve cuff electrodes).

KHFAC nerve block characteristically has an initial short period of rapid firing, manifested as a large muscle twitch (the onset response) before the block is established (Bhadra and Kilgore 2005). This onset response is affected by a large number of variables and has been intensely investigated. Multiple methods have been established to reduce or eliminate the onset response.

Mechanisms of KHFAC Nerve Block

There are two modern hypotheses about the mechanism of KHFAC block. One, based on computer simulations, suggests that elevated potassium levels cause block. The other hypothesis, based on computer simulations along with some experimental data, suggests that the mechanism of the KHFAC-induced conduction block is a depolarization-induced sodium channel inactivation (Ackermann et al. 2011).



Peripheral Nerve Stimulation Technique, Nerve Block, Fig. 1 KHFAC block of the rat sciatic nerve at 30 kHz. A test stimulus at 0.5 Hz is delivered proximally to generate supramaximal gastrocnemius muscle twitches, (2–43 s). KHFAC block is delivered from 7 s (red bar), blocking conduction. Initially the KHFAC produces a large

activity, the “onset response.” After the onset, the nerve is fully blocked. After 30 s of KHFAC delivery, the block is turned off (at 37 s) and twitches due to the test stimulation return instantly. The muscle twitches before and immediately after block are identical (dashed line), showing the instantaneous reversibility of this method

Clinical Investigations

Three commercial entities are pursuing systems based on KHFAC block for obesity control (EnteroMedics), spinal cord stimulation for chronic pain (Nevro), and reduction of pain from amputation neuromas (Neuros Medical).

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Peripheral Nerves, Anatomy and Physiology of

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Definition

Peripheral nerves are formed by axonal extensions of neurons in the dorsal root ganglia and spinal cord (spinal nerves), brain stem (cranial nerves), or sympathetic and parasympathetic

ganglia (autonomic nerves) that connect the central nervous system (brain and spinal cord) with the rest of the body to maintain homeostasis, mediate sensation, movement, and coordination. The 43 pairs of sensory and motor nerves in the human body are composed of bundles of axons embedded in a collagenous matrix (endoneurium), ensheathed by connective tissue (perineurium), and wrapped by an external connective layer (epineurium). The cellular components of peripheral nerves include Schwann cells, fibroblasts, endothelial-like cells, and macrophages (Stewart 2003).

Detailed Description

Types of Peripheral Nerves

Peripheral nerves are also classified in reference to the main function that they serve, as either motor sensory or autonomic nerves.

Motor Nerves

This nerves are composed by fibers elongating from motor neurons in the ventral spinal cord and brain stem, and innervate skeletal muscle, visceral smooth muscle, cardiac muscle, or glands. Motor neurons are further subdivided into alpha (α) and gamma (γ) neuron types. The alpha motor axon and its associated muscle fiber constitute a motor unit. Action potentials traveling on motor neurons convey intent and magnitude for muscle activation.

Sensory Nerves

Axons extending from the dorsal root ganglion (DRG) innervate sensory receptors in the skin, muscle, and joints. Sensory fibers transduce mechanical, chemical, or thermal stimuli from specialized receptors in the skin and muscle into electrical signals and convey them to the spinal cord and brain for perception and appropriate response. Sensory neurons are classified by modalities: (i) proprioceptors for body position; (ii) mechanoreceptors for touch, pressure, and vibration; (iii) thermoreceptors for innocuous cold or warm temperatures; (iv) nociceptors for pain-inducing high-threshold stimuli; and

(v) puriceptors that respond to itch-inducing compounds.

Such receptors are innervated by sensory neurons in the DRG, which is formed by a heterogeneous cellular population including large myelinated proprioceptive neurons that express TrkC receptors that bind to neurotrophin 3 (NT-3) and medium-size mechanoreceptive neurons that bind to brain-derived growth factor (BDNF) and/or glial-derived growth factor (GDNF) via its respective TrkB and Ret receptors. Sensory neurons responsive to pain, temperature, and itch are either peptidergic neurons expressing TrkA receptor that binds to nerve growth factor (NGF) and neuropeptides such as calcitonin gene-related peptide and substance P, or non-peptidergic neurons expressing Ret receptors and expressing the isolectin B4.

Autonomic Nerves

These nerves are formed by axons from the sympathetic and the parasympathetic paravertebral ganglia. Autonomic nerves convey information from the medulla, pons, and hypothalamus to organs and glands, and participate in the involuntary control of heart rate, digestion, respiration, salivation, perspiration, pupillary dilation, urination, and sexual arousal. Postganglionic axons release acetylcholine (parasympathetic) or norepinephrine (sympathetic) neurotransmitters to control their target organs.

Physiology

Neurons transmit information via waves of membrane depolarization known as action potentials (APs). Sodium channels open after strong stimuli which cause membrane depolarization and the generation of APs. Potassium channels are involved in repolarization of the axon membrane. In myelinated axons, both Na and K channels are concentrated at the nodes of Ranvier and mediate saltatory nerve conduction. Myelinated axons conduct APs at a rate of up to 120 m/s, whereas unmyelinated fibers conduct at a rate of 2–4 m/s (Krarup et al. 1988). Non-painful touch of the skin is sensed by low-threshold

mechanoreceptors (LTMRs), which are classified as A β -, A δ -, and C-LTMRs according to their action potential conduction velocities. In the glabrous skin, A δ afferents are rapid-adapting (RA) neurons that innervate the Pacinian and Meissner's corpuscles, which are vibration receptors that encode texture. The highest spatial acuity of mammalian touch receptors provides object features such as edges and curvature and involve A β afferents innervating Merkel receptor cells.

PNS Injury and Regeneration

Each year, approximately 360,000 people in the United States suffer a peripheral nerve injury (PNI), which is a leading cause of lifelong disability (Kelsey et al. 1997; Taylor et al. 2008). Peripheral nerve injuries result in paralysis, sensory loss, and lack of autonomic control distal to the injury site.

Cellular Response to Injury

Axonal injury results in disruption of target-derived trophic factors normally conveyed to the soma by axonal transport. If the axon is transected, sodium and calcium diffuse into the injured axoplasm triggering action potentials. Both of these events result in the dispersal of Nissl substance that labels rough endoplasmic reticulum (chromatolysis) and upregulation of transcription factors including Atf3, c-Jun, Stat3, and Sox11, which activate a number of different signaling pathways including the MAPK/JNK/ERK, the AKT/p38, and the JAK/STAT/mTOR (Kiryu-Seo and Kiyama 2011). These changes result in increased TrkA and TrkB expression. Conversely, neurofilaments, neurotransmitters, and postsynaptic receptors are downregulated (Patodia and Raivich 2012).

Wallerian Degeneration

Severe injury to the nerve results in Wallerian degeneration, a process of degeneration of nerve fibers distal to the injury site through the infiltration of macrophages, which clear myelin debris and reutilize its lipid content for regeneration and remyelination. The upregulation of c-Jun in

Schwann cells has been shown to be a key regulator of Wallerian degeneration by inducing the expression of trophic factors and adhesion molecules, the formation of endoneurial tubes or bands of Büngner, and promoting myelin clearance (Fawcett and Keynes 1990).

Spontaneous Axonal Regrowth

Transected nerves in which the gap between the proximal and distal stumps is less than 1 cm apart regenerate from the proximal into the distal stump spontaneously. The transected axon swells, increases production of mitochondria and microtubules, and extends 6–10 collateral branches down the endoneurial tubes of the distal segment. The rate of elongation is 3–4 mm/day after crushing and 2.5 mm/day after sectioning the nerve (Fugleholm et al. 1994). Regenerating axons are 1–2 μm in diameter and enlarge in the 2–6 months after reinnervating their targets (Navarro et al. 1994). The environment through which axons regenerate consists of Schwann cells, and their basal lamina contains primarily laminin, fibronectin, and collagen. It has been demonstrated that without the Schwann cells, either axonal regeneration fails or axonal growth is compromised.

Guidance Molecules

Nerve injury leads to the upregulation of neurotrophic factors and their receptors in the degenerating nerve segment and in the denervated end targets, including neurotrophins such as nerve growth factor (NGF), BDNF, NT-3, and NT-4 (Carroll et al. 1998; Chen et al. 2002). Nerve regeneration is known to respond to concentration gradients of guidance molecules which orient axonal outgrowth toward the denervated target (Zheng and Kuffler 2000). The regenerative path of adult motor neurons in the spinal cord and sensory neurons in the DRG can be controlled by specific growth factors. Specifically, the induced expression of NGF has been shown to guide the regenerative path of DRG axons both into the spinal cord and in the periphery (Romero et al. 2001; Hu et al. 2010). In addition, delivery of growth factors such as BDNF and GDNF has been shown to enhance nerve regeneration and

functional recovery in a rat model of delayed nerve repair (Gordon 2009).

Accuracy of Regeneration

Injured nerves are capable of reinnervating their original targets; however, this process is not without errors. Axonal regeneration is more accurate following crush compared to transection injuries as regenerating axons usually grow along their parent tubes and are guided directly back to their targets (Brown and Butler 1976). If the nerve is transected, regenerating sprouts can enter inappropriate tubes in the distal stump ending in aberrant targets. The expression of the peptide L2/HNK1, NCAM and polysialic acid in the regenerative motor axons, and the release of trophic factors by the distal stump are thought to influence selective reinnervation, and pruning of axons that reinnervate erroneous targets contributes towards the specificity of nerve regeneration (Madison et al. 1996; Eberhardt et al. 2006).

Remyelination

Schwann cells dedifferentiate from myelinating to regenerative types after injury and participate in nerve regrowth and remyelination. Remyelination requires the axonal release of neuregulin-1 type III to instruct the Schwann cells; however, this process does not completely restore myelin thickness to pre-injury levels, and axons remain long-term hypomyelinated (Schroder 1972). The distance between internodes is also smaller than normal, usually around 400 μm , which may explain the lower conduction velocities of regenerated nerve fibers (Burgess and Horch 1973; Hildebrand et al. 1985).

Nerve Repair

Primary tensionless end-to-end attachment of a completely severed peripheral nerve is the preferred method of nerve repair as it mediates partial nerve regeneration and functional recovery. If the gap is too long for a tensionless reattachment, the recommended “gold standard” is the use of autologous nerve grafts to bridge the gap defect. However, donor site morbidity, scarce number of usable donor nerves, and suboptimal functional recovery drastically limit this alternative (Zochodne 2012).

Allogenic or xenogenic nerve grafts have been proposed but require immunosuppression to prevent graft rejection. Decellularized nerve allo-/xenografts have also been investigated, but the functional recovery achieved is limited. Clinical alternatives in the form of simple hollow tubes made of biosynthetic materials (i.e., polylactic-coprolactone, polyglycolic acid, type I collagen) are currently FDA-approved and commonly used for reconstruction of short peripheral nerve injuries. Synthetic materials continue to be developed in order to improve the functional efficacy of biosynthetic nerve guides in nerve repair (Pfister et al. 2011). Simple tube nerve repairs are, however, inferior to nerve autografts and decellularized allografts, presumably due to the lack of endoneurial microstructure of conduits which in turn results in the clustering of regenerating fibers. Luminal fillers such as polyamide filaments, collagen filaments, polyester filaments, PGA filaments and gelatin fibers, and multi-luminal microchannels have shown promising results (Tansey et al. 2011).

Limitations in PNS Regeneration

The causes of unsuccessful repair include failure of axons to regenerate after chronic axotomy and innervation of incorrect targets. The first leads to weakness and poor sensory recovery since axons connect to inappropriate regions of the skin, leading to qualitatively abnormal and poorly localized sensation, and the second to poor muscular control as muscles receive inputs from axons originally connected to different muscles. Furthermore, spontaneous nerve regeneration proceeds through short but not long nerve gap defects (Hoke and Brushart 2010).

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Peripheral Neural Interfaces

► [Peripheral Nerve Interface Applications, EMG/ENG](#)

Peripheral Vestibular Signal Processing

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Definition

Vestibular End Organ

The vestibular end organ is located in the inner ear next to the cochlear of the auditory system. The end organ comprises two components. The three semicircular canals, which are roughly orthogonal, sense rotational head movement while the two otolith organs (utricle and saccule), which are also orthogonal, sense linear head acceleration.

Processing

Signals from the vestibular end organ carry head velocity and acceleration information that is

modified at the level of the brainstem to control the eye movements that stabilize vision when the head moves (vestibuloocular reflex) and to control the muscles that control posture and balance (vestibulospinal reflexes).

Detailed Description

Sensory System

The vestibuloocular reflex (VOR) is mediated by the six semicircular canals and four otolith organs (horizontal, anterior and posterior canals, and the utricle and saccule from both inner ears). The canals are arranged in such a way that each canal on the left side has an almost parallel counterpart on the right side. Each of these three canal pairs work in a *push-pull* fashion. When one canal is stimulated, its corresponding partner on the other side is inhibited, and vice versa. This push-pull system makes it possible to sense all directions of rotation. For example, while the *right horizontal canal* gets stimulated and sends the dominant signals to the central vestibular system during head rotations to the right, the *left horizontal canal* gets stimulated during head rotations to the left. Vertical canals (the anterior and posterior canals) are coupled in a crossed fashion, for example, head rotations that are excitatory for an ipsilateral anterior canal are inhibitory for the contralateral posterior canal, and vice versa. At one end of each semicircular canal, the canal expands forming a bulbous structure, the ampulla. Within the ampulla there is a saddle-shaped structure, the crista ampullaris, which consists of a ridge of sensory hair cells (Landolt et al. 1975). The cupula extends across the ampulla, forming a tight hydraulic seal around the internal wall of the ampulla (Dohlman 1971; Lim 1973). During head motion the inertia of the endolymph fluid within the canal causes the cupula to bend, thereby stimulating the sensory hair cells.

The otolith organs comprise the saccule and utricle. They are sensitive to gravity and linear acceleration. The maculae of these organs are an array of hair cells that have their cilia embedded in a gelatinous matrix, dense with calcium carbonate crystals, that floats in viscous endolymph fluid.

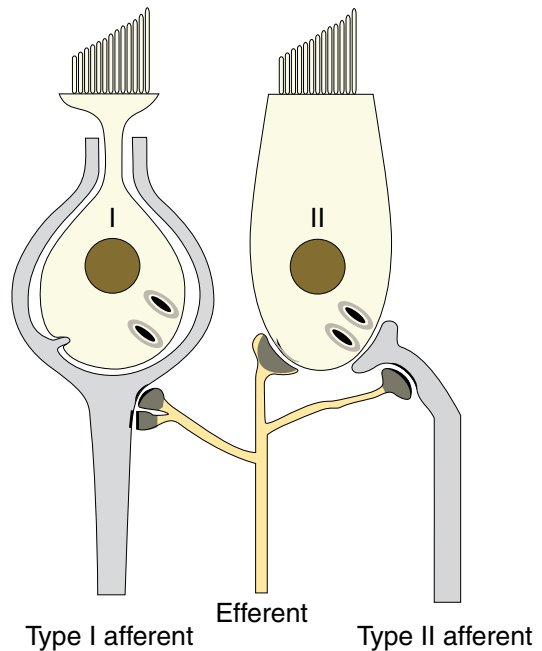
Deflection of the dense matrix during head acceleration stimulates the hair cells and afferent nerves. Due to their orientations in the head, the utricle is most sensitive to horizontal head movement, whereas the saccule is sensitive to vertical head movement.

There are two types of sensory hair cells, type I and type II (Wersall 1956). In the canals, type I hair cells are concentrated on the central zone of the crista ampullaris, whereas type II hair cells lie mainly on the peripheral zone (Spoendlin 1966; Lindeman 1969; Tsuji et al. 2000). In the otolith organs, type I hair cells are located near the midline (striola) of the macula, whereas type II hair cells are further from the striola. Type I and type II hair cells are morphologically distinct. The Type I has a calyx (cuplike) structure that surrounds the hair cell, whereas the type II has a bouton (knob-like) structure that forms a synapse with a vestibular afferent.

Sensory Signals

Vestibular *afferents* can receive synaptic input from one or both hair cell types. Some 20% of afferents have type I input only, 10% type II input only and 70% dimorphic (both type I and II) input. The variation in the inter-spike interval of an afferent's background discharge rate defines its regularity. A low variation (normalized coefficient of variation [CV^*] < 0.1) indicates regular, and a high variation (CV^* > 0.1) indicates irregular (Goldberg et al. 1984). Vestibular afferents that get most of their synaptic input from the central zone of the crista ampullaris, where type I hair cells are concentrated, are predominantly irregular in their resting discharge rate. Afferents that arise from the peripheral zone, where type II hair cells are concentrated, are predominantly regular in discharge rate (Baird et al. 1988). Taken together these findings suggest that type I hair cells mediate irregular discharging afferents, whereas type II hair cells mediate regular afferents.

Vestibular *efferents* project to the peripheral vestibular organs, where they innervate the vestibular neuroepithelium extensively (Lindeman 1969). The innervation pattern in the periphery is diffuse with individual efferent fibers terminating onto multiple hair cells and afferent fibers that



Peripheral Vestibular Signal Processing, Fig. 1 Vestibular efferents terminate on type I afferents (with excitatory effects) and type II hair cells (inhibitory) and their afferents (excitatory)

innervate the vestibular end organs (see Fig. 1). Specifically, efferent terminals make direct contact with vestibular type II hair cells, and evidence in non-mammals suggests they have inhibitory effects. In contrast, efferent terminals do not contact type I hair cells directly, due to the surrounding calyx terminal. Rather, efferent terminals contact the outer surface of the calyx and the parent axon and have strong excitatory effects in mammals (Goldberg and Fernández 1980).

Signal Processing

Models of the VOR in the alert monkey have suggested a highly modifiable (phasic) component of the reflex (Lisberger and Pavelko 1986; Lasker et al. 1999; Minor et al. 1999). This phasic component is probably mediated by irregularly discharging vestibular afferents that predominantly encode head acceleration, rather than regularly discharging afferents that have relatively linear encoding of head velocity between 2 and 20 Hz (Hullar and Minor 1999). This phasic component has high sensitivity, and so is large during

excitation, but can rapidly go into cutoff (negative saturation) during inhibition. In contrast, the less modifiable (tonic) pathway that is probably mediated by regular afferents has little susceptibility to inhibitory cutoff. The phasic component appears to be responsible for most of the increase in VOR response that occurs for contexts such as lens magnification (Clendaniel et al. 2001) and during near viewing (Lasker et al. 2002; Migliaccio et al. 2004, 2008).

The flocculus of the vestibulocerebellum plays an important role in partially restoring the amplitude and symmetry of the VOR after a large injury to one of the two balance organs (e.g., Babalian and Vidal 2000). The Purkinje cells in the flocculus participate in adjusting the VOR during viewing contexts that require fast changes in response, e.g., during near viewing (Lisberger and Fuchs 1978; Snyder and King 1996). The floccular target neurons (FTN) receive input from both the flocculus and primary vestibular afferents and are thought to be important for VOR adaptation (Lisberger 1994; Blazquez et al. 2006). The modulation changes of FTN neurons correspond with changes in the VOR response induced by training with visual-vestibular conflict (Lisberger 1994; Lisberger et al. 1994a, b; Galiana and Green 1998). Thus they appear to make a major contribution to VOR adaptation and calibration.

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Peripheral Vision, Models of

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Synonyms

[Compulsory averaging](#); [Crowding models](#); [Faulty integration](#); [Forced texture processing](#); [Pooling models](#)

Definition

Peripheral vision differs significantly from foveal vision. Models of peripheral vision attempt to

capture these differences mechanistically and/or predict task performance arising from these differences. Visual acuity, contrast sensitivity, color vision, and motion perception all vary with eccentricity, i.e., with distance from the center of gaze. However, a more consequential difference concerns peripheral vision's degradation in the presence of clutter, a set of phenomena known as crowding. A dominant, biologically inspired, model of crowding hypothesizes that peripheral vision encodes its inputs in terms of a rich set of local summary statistics. This pooling model of crowding has similar architecture to standard feed-forward hierarchical models of vision, and to convolutional networks, with the most notable difference being that pooling occurs over sparse, sizeable regions that grow linearly with eccentricity. Coarse encoding as a function of eccentricity leads to substantial confusions and ambiguities, which in turn provides a strong constraint on performance of many visual tasks.

Detailed Description

The visual field, the entire spatial scope of vision, subtends approximately 180° horizontally and 120° vertically (Traquair 1927). Less than 1% of the visual field lands within the fovea, i.e., the central rod-free area of the retina, subtending approximately 1.7° of visual angle in diameter. Peripheral vision refers to visual processing of the rest of the visual field and has considerable loss of information relative to the fovea. This begins at the retina, which employs variable spatial resolution to get past the bottleneck of the optic nerve. However, it does not end there, but rather continues into visual cortex, where foveal representation receives approximately half of the available cortical resources (Tootell et al. 1982). The reduced density of photoreceptors coupled with reduced cortical resources leads to reduced ability to resolve high spatial frequencies with increasing distance from the point of gaze. Acuity (the ability to resolve fine details) diminishes approximately linearly with eccentricity, over a fairly wide range of eccentricities. Data-driven models of peripheral acuity have simply approximated, e.g., the spacing necessary to

resolve a grating, or the letter size necessary for recognition, as a linear function of eccentricity (Levi et al. 1985; Anstis 1974). Additional models have approximated the area of the brain dedicated to processing 1° of visual angle as a function of eccentricity, known as the cortical magnification factor (Horton and Hoyt 1991; Strasburger et al. 2011). Image processing-based models have captured both the information loss due to reduced acuity and changes in the contrast sensitivity function by filtering the input stimulus as a function of eccentricity to remove subthreshold spatial frequency content (Anstis 1998; Geisler and Perry 1998).

Reduced peripheral acuity has only a tiny effect, compared with peripheral vision's sensitivity to clutter, known as visual crowding. At its core, crowding is the inability to identify an object in the periphery when there are others in proximity; the objects can be detected but are difficult to identify (Levi et al. 2002). Korte (1923) described that in viewing peripheral text, firm localization of both the letters and their constituent elements was extremely difficult and error-prone (as discussed more recently in (Strasburger et al. 2011)). More generally, peripheral vision is locally ambiguous in terms of the phase and location of features. Observers have difficulty distinguishing 180 degree phase differences in compound sine wave gratings in the periphery (Bennett and Banks 1991; Rentschler and Treutwein 1985) and show marked position uncertainty in a bisection task (Levi and Klein 1986). Furthermore, such ambiguities appear to exist in processing of real-world objects and scenes, although we rarely have the opportunity to be aware of them; peripheral vision tolerates considerable image variation without giving us much sense that something is wrong (Freeman and Simoncelli 2011; Koenderink et al. 2012). Unlike acuity losses, which impact only tasks relying on quite high spatial frequencies, crowding occurs with a broad range of stimuli (Pelli and Tillman 2008). It is ever-present in real-world vision, where the visual system is faced with cluttered scenes full of objects and textures. Crowding constrains what we can perceive at a glance, which in turn constrains visual performance.

Modeling Crowding

Based on the phenomenology, a number of researchers have suggested that crowding might occur due to peripheral texture processing mechanisms. These ideas originated with Lettvin's suggestion of crowding as giving the observer only a statistical representation of the visual input (Lettvin 1976) and continued through more recent theories of crowding as "forced texture processing" (Pelli et al. 2004) and compulsory averaging (Parkes et al. 2001). Relatedly, other work has suggested that crowding arises from integration over large receptive fields (or "pooling regions") that grow with eccentricity (c.f., Flom et al. 1963; Levi et al. 1985; He et al. 1996; Bouma 1970). Such pooling over large regions is also reminiscent of texture processing mechanisms, presumed to compute summary statistics over sizeable regions of the visual field (Rosenholtz 2016). The most successful, biologically plausible, texture models have described texture using a rich set of image statistics (Heeger and Bergen 1995; Portilla and Simoncelli 2000; Gatys et al. 2015), suggesting that peripheral vision might also encode its inputs using a high-dimensional set of summary statistics (Rosenholtz 2016).

Balas et al. (2009) operationalized peripheral texture processing by suggesting that peripheral vision might compute texture statistics within sparse local pooling regions that overlap and tile the visual field. They suggested as a candidate set of image statistics those used in a state-of-the-art model of texture appearance (Portilla and Simoncelli 2000). Specifically, after a prefiltering stage that mimics acuity losses, the model computes, within each pooling region, the marginal distribution of luminance; luminance auto correlation; correlations of the magnitude of responses of oriented V1-like wavelets across differences in orientation, neighboring positions, and scale; and phase correlation across scale. Computing a given second-order correlation merely requires taking responses of a pair of V1-like filters, point-wise multiplying them, and taking the average over the local region. Freeman and Simoncelli (2011) provided the first full instantiation of this model in a form that could take as input a substantial portion

of the visual field. Balas, Rosenholtz, and others have studied this model extensively, calling it the Texture Tiling Model, or TTM (Keshvari and Rosenholtz 2016; Rosenholtz et al. 2012b).

The TTM mechanism has clear connections to standard models of hierarchical encoding for object recognition and to convolutional neural networks (Riesenhuber and Poggio 1999; Krizhevsky et al. 2017; Yamins et al. 2014). The proposed mechanism differs from standard models in two main ways: First, the nonlinearities used to compute second-order correlations do not match those in the standard object recognition models nor in convolutional neural networks. Second, standard object recognition models do pool the outputs of feature detectors, but the pooling regions tend to be small relative to the support of those feature detectors, and not to grow with eccentricity (Chen et al. 2017).

The rich, high-dimensional set of statistics encoded by TTM provides an efficient, compressed encoding. It preserves a great deal of useful information about the visual input and yet loses considerable information, precluding perfect reconstruction of the original stimulus. The ambiguities and confusions arising from this encoding appear to constrain performance at a wide range of visual tasks, from crowded peripheral object recognition (Balas et al. 2009; Rosenholtz et al. 2012b; Rosenholtz et al. 2012a; Keshvari and Rosenholtz 2016), through visual search (Rosenholtz et al. 2012b; Zhang et al. 2015; Chang and Rosenholtz 2016), to scene perception (Rosenholtz et al. 2012a; Ehinger and Rosenholtz 2016).

Though other models of peripheral crowding have been proposed and demonstrated to predict a subset of phenomena (Wolfe 1975; Krumhansl and Thomas 1977; Wilkinson et al. 1997; Parkes et al. 2001; Baldassi et al. 2006; May and Hess 2007; Greenwood et al. 2010; van den Berg et al. 2010; Nandy and Tjan 2012; Chaney et al. 2014), they have not been as extensively tested. Many of the alternative models are not image computable and as a result cannot easily be generalized to arbitrary visual inputs, making testing them prohibitive.

Limitations of Current Models and Future Paths

Pooling mechanisms of crowding are largely hypothesized to be feed-forward, whereas connections in visual cortex and throughout the visual system are not unidirectional. What, if any, role feedback mechanisms might play in crowding remains unclear (Clarke et al. 2014). Future models of peripheral vision will need to capture temporal aspects of the stimuli, such as motion or flicker, as well as the encoding of different information from the two eyes, such as binocular disparity. A number of questions also remain as to the pooled summary statistics: whether any statistics or feature detectors are missing from the model and whether more biologically plausible features might lead to better predictive power. In addition, given recent success of deep learning techniques to optimize the features measured by a computational neural network, questions also remain as to whether improved models might learn their features instead of using hand-coded image statistics.

Cross-References

- [Efficient Population Coding](#)
- [Hierarchical Models of the Visual System](#)
- [Large-Scale Neural Networks: Vision](#)
- [Neural Coding](#)
- [Receptive Field Modeling](#)
- [Sensory Coding, Efficiency](#)

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Pharmacogenomics

► [Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation](#)

Phase Correlation

► [Phase-Locking Methods](#)

Phase Models, Noisy

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Definition

Neural oscillators can be reduced to simple one-dimensional models where the only variable is the time-like phase of the oscillator. If the inputs to the oscillator are small enough, this phase description remains valid even if the inputs are “noisy.” Using the noisy phase description of an oscillator allows us to do many otherwise difficult calculations. We review these calculations in this entry.

Detailed Description

Noise is ubiquitous in the nervous system and has been the subject of many experimental and theoretical studies (Laing and Lord 2009). Most of the techniques for analyzing the effects of noise depend on the use of very simple models such as the leaky integrate-and-fire model or other scalar models. Many neurons generate periodic firing (oscillations) when subjected to a tonic drive but because they are subjected to many uncontrolled environmental inputs, the oscillations are subjected to noise. In absence of any inputs a deterministic limit-cycle oscillator can be characterized by its *phase* which for simplicity we will take to

be the time since the last peak in the voltage. This is called the zero phase and if the limit cycle has a period T , then we identify the phase as $\theta = (2\pi/T)t$ where t is the time since the last spike. (The normalization of the phase is not necessary but is an intuitively appealing convention as the phase lies on the circle of radius 1.)

Before describing the phase of an oscillator in the presence of noise, we introduce an important concept, the *phase response curve* (PRC). The PRC describes the effect of a small perturbation of the oscillator (in the context of neurons, this is a brief current input, e.g., as in a synapse). That is, suppose that the perturbation occurred at a phase, θ (i.e., at t milliseconds after the last spike, where $\theta = 2\pi t/T$). This will cause the next spike to occur at some time $\hat{T}(\theta)$, whereas in absence of the perturbation, the neuron would have fired at T , the interspike interval. The change in phase as a consequence of this perturbation is (Kuramoto 1984)

$$\Delta(\theta) := \frac{2\pi}{T} (T - \hat{T}(\theta)).$$

The function $\Delta(\theta)$ is the PRC for the neuron and will be positive (negative) if the perturbation caused the neuron to spike earlier (resp. later) than it would have in absence of any inputs. As we will see shortly, the PRC is very useful in computing spike statistics, the effects of inputs, and the effects of coupling. Computing the PRC of real neurons can be as simple as perturbing the neuron with a square current pulse and measuring the change in the timing of the next spike. However, as no neuron is perfectly periodic (as there are many sources of uncontrolled noise), the computation of the PRC is rarely so easy and as such, there are many methods for trying to estimate it for real neurons (see Torben-Nielsen et al. (2010) for a review). See the entry ► [“Weak Coupling Theory,”](#) by Lewis for more details about the phase response curve.

When assessing synchrony between neurons, there are many metrics. In this entry, we will look at pairs of neural oscillators and compute the distribution of their phase difference. Typically, experimental neuroscientists do not have access to

the phase of a neuron (although there are methods to extract a “phase” from a voltage trace using the Hilbert transform (Stiefel et al. 2010)), but rather look at the cross-correlation, $CC(t_2 - t_1)$, of the spike trains. When the neurons are identical weakly perturbed oscillators, Pfeuty et al. (2003) showed that

$$CC(t_2 - t_1) := \frac{\langle S_1(t_1) S_2(t_2) \rangle}{\langle S_1(t) \rangle \langle S_2(t) \rangle} = P(2\pi(t_2 - t_1)/T)$$

$S_{j(t)}$ is the spike train and $P(\phi)$ is the density of the phase differences between the two neural oscillators. Thus, to assess cross-correlation, it is sufficient to study the phase-difference density. (This density is a normalized histogram of the phase differences between the two oscillators.)

Phase Reduction

A general asymptotically stable limit cycle with weak perturbations has the form:

$$\frac{dX}{dt} = F(X(t)) + \varepsilon G(t, X(t))$$

where $X' = F(X)$ has an exponentially stable limit cycle, $U(t)$, ε is a small parameter, and G is some perturbation. If we write $X(t) = U(\theta(t)) + \varepsilon Y(t)$, then

$$\frac{d\theta}{dt} = 1 + \varepsilon Z(\theta) \cdot G(t, U(\theta)) + O(\varepsilon^2) \quad (1)$$

In these coordinates, θ , the phase lies between 0 and T , the period. A suitable rescaling of θ will yield equations that are 2π periodic. The key object here is $Z(\theta)$ called the *adjoint function*, the unique T -periodic solution to

$$\frac{dZ}{dt} = -D_X F(U(t))^T Z, Z(t) \cdot \frac{dU(t)}{dt} = 1$$

The adjoint function is sometimes called the *infinitesimal PRC* or *iPRC*. For the rest of this entry, when I talk about the PRC, I mean the iPRC and not the shift due to a generalized stimulus. If X represents, say, the *Hodgkin-Huxley* equation, that is, $X = (V, n, m, h)$, then we can write $Z = (V^*, n^*, m^*, h^*)$ in components. The

component labeled V^* is linearly proportional to the infinitesimal phase resetting curve for the HH equation when perturbed by brief application of a current pulse. Thus, if the only inputs into your neural oscillator are currents applied to the voltage variable, the $G(t, U(\theta)) = [I(t, \theta)/C_m, 0, \dots, 0]$ (where C_m is the membrane capacitance) and Eq. 1 becomes

$$\frac{d\theta}{dt} = 1 + \varepsilon \Delta(\theta) I(t, \theta) / C_m \quad (2)$$

We have dropped the higher-order terms in ε and replaced the voltage component of the adjoint with the iPRC which can be estimated for neurons. The beauty of Eq. 2 is that, with certain technical assumptions (Teramae et al. 2009), it holds even if the current includes a broadband noisy signal. (In the case where the noise is delta correlated, there is an additional term of the form $-\varepsilon^2 \Delta(\theta) \Delta'(\theta)$ which does not contribute much when ε is small (Teramae and Tanaka 2004; Teramae et al. 2009).) Equation 2 will be the focus of the rest of this entry. We will use it to compute various effects of noise on the oscillator and also to relate it to some common statistical measures of neurons.

Statistical Properties

Henceforth, we will rescale time in such a way that the unperturbed period of the oscillator is 2π and the frequency is 1. Let us replace the current in Eq. 2 by a noisy current, $\eta(t)$, that has zero mean and correlation, $C(\tau) := \langle \eta(t) \eta(t - \tau) \rangle$. For example, if η is a white noise process (or say an Ornstein-Uhlenbeck (OU) process), then $C(\tau) = \delta(\tau)$ (or for the OU process, $C(\tau) = \gamma \exp(-\gamma|\tau|)$). (In some cases, the OU process is scaled so that $C(\tau) = \exp(-\gamma|\tau|)$.) (Note that an OU process is the solution to the stochastic equation, $dx/dt = -x/\tau + \xi(t)/\sqrt{\tau}$ where $\xi(t)$ is a white noise process.)

The first question that arises is whether the noise affects the frequency of the neuron. Goldobin et al. (2010) provide a simple formula for the correction of the natural frequency (Ω):

$$\Omega = 1$$

$$+ \varepsilon^2 \int_0^{2\pi} \Delta'(\phi) \int_0^\infty C(s) \Delta(\phi - s) ds \, d\phi \quad (3)$$

The second part of the expression also involves additional terms (not shown) whose size is proportional to $1/K$ where K is proportional to the rate of attraction to the limit cycle. For strongly attracting limit cycles, K will be big. If the noise is white, then the correlation, $C(t)$, is a Dirac delta function and the second term vanishes. Thus, with white noise, the mean frequency is barely affected.

The noise causes jitter in the spike times which are equivalent to a slow diffusion of the phase. That is, the mean value of the phase is very weakly perturbed by the noise (cf. the above formula), but there will be a systematic drift equivalent to a random walk in phase. The phase reduction lets us compute the diffusion coefficient (D):

$$D = \varepsilon^2 \int_0^{2\pi} \int_0^\infty \Delta(\phi) \Delta(\phi + s) C(s) ds \, d\phi. \quad (4)$$

For white noise, ($C(\tau) = \delta(t)$), we see that the diffusion is proportional to the integral of the square of the iPRC. That is, the larger the iPRC (e.g., the more sensitive the neuron is to perturbations), the larger will be the diffusion and hence a noisier neuron. The interspike interval histogram can be approximated as a Gaussian centered at T with a width proportional to $\sqrt{(2D)}$. We should also remark that near bifurcations of the limit cycle, the iPRC will be very large and thus, as expected, very sensitive to noise.

Noise makes the estimate of the iPRC subject to measurement errors as well. As the effects of noise on the period of the oscillator are very small (cf. Eq. 3), the mean of a noisy iPRC is the same as the deterministic iPRC. However, the variance depends strongly on the noise and, furthermore, it is phase dependent. Ermentrout et al. (2011) compute this phase dependence for the case of weak white noise. With noise of amplitude ε and a perturbation of magnitude β occurring at phase ϕ in the cycle, the variance (Var) is

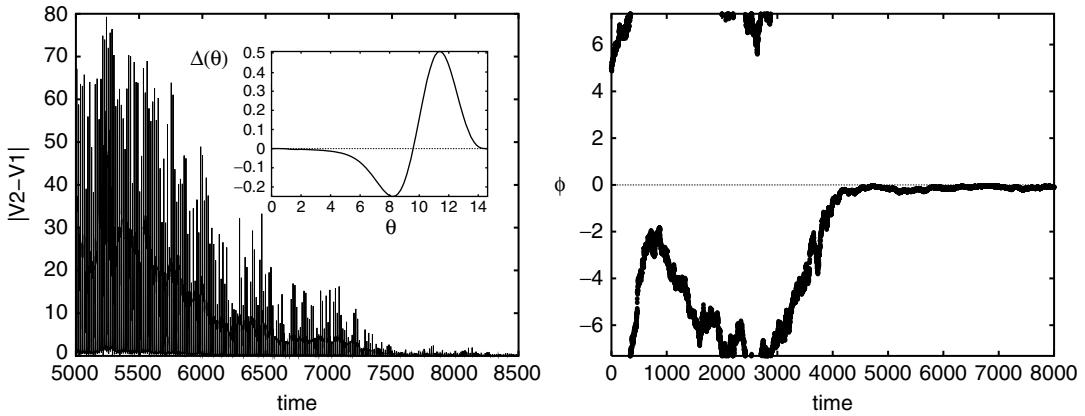
$$\text{Var}(\phi) = \varepsilon^2 \left(\int_0^{2\pi} \Delta^2(s) ds + 2\beta \Delta'(\phi) \int_0^\phi \Delta^2(s) ds + \int_\phi^{\phi+\beta\Delta(\phi)} \Delta^2(s) ds \right)$$

Suppose that we create a frozen noisy signal (one which we can exactly repeat) and we apply it to the same neuron over multiple trials. If there are no other sources of noise to the neuron, then over time, even though the neuron starts out at different states, the trials will eventually line up. If there is a small amount of independent noise, then the trials will nearly line up (Mainen and Sejnowski 1995) but will have some jitter. The rate at which the trials line up is exponential with exponent, λ_0 . Figure 1 shows this phenomena for a pair of HH neurons driven with a current of $10 \mu\text{A}/\text{cm}^2$ and noise of amplitude $\varepsilon^2 = .0625 \text{ mV}^2/\text{ms}$. The left panel shows the voltage difference as a function of time and the right shows the evolution of the phase difference for the phase-reduced pair. The inset shows the iPRC of the HH equations. Goldobin et al. (2010) compute λ_0 , called the *leading Lyapunov exponent* for the phase-reduced system:

$$\lambda_0 = -\varepsilon^2 \int_0^{2\pi} \Delta'(\phi) \int_0^\infty \Delta'(\phi - s) C(s) ds \, d\phi. \quad (5)$$

Note that with white noise, $\lambda_0 = -\varepsilon^2 \int_0^{2\pi} [\Delta'(\phi)]^2 d\phi$. Abouzeid and Ermentrout (2009) showed that for smooth iPRCs with a fixed diffusion, D , the iPRC that makes this exponent most negative with white noise is $\Delta(\phi) = -\sin \phi$. That is, the sinusoidal iPRC will rapidly cause two phase models to synchronize when subjected to identical noise. (See below for the more general setting.)

The phase reduction also allows us to compute several quantities related to neural coding that are generally difficult or impossible to calculate explicitly. The *spike-triggered average* (STA) is the average value of a stimulus to a neuron conditioned on the spike time. That is,



Phase Models, Noisy, Fig. 1 (Left) Stochastic synchronization of two HH neurons subjected to identical noise (inset shows iPRC). (Right) Synchronization of the phase model

$$\text{STA}(t) = \langle I(t_{sp} - t) \rangle_{\text{spike times}}$$

The STA tells you what aspects of the stimulus that neuron is interested in. Another quantity that gives insight into the “features” of the stimulus that cause spiking is the *spike-triggered covariance* (STC):

$$\text{STC}(t_1, t_2) = \langle I(t_{sp} - t_1) \rangle_{\text{spike times}} - \text{STA}(t_1)\text{STA}(t_2)$$

With weak white noise, both of these quantities can be computed for the noisy phase model (Ermentrout et al. 2007b; Arthur et al. 2012; Ota et al. 2012).

$$\begin{aligned} \text{STA}(t) &= -\varepsilon^2 \Delta'(T - t) \\ \text{STC}(t_1, t_2) &= \varepsilon^2 \delta(t_2 - t_1) + \varepsilon^4 \Delta''(T - t_2) \Delta(T - t_1) H_0(t_2 - t_1) \\ &\quad + \varepsilon^4 \Delta''(T - t_1) \Delta(T - t_2) H_0(t_1 - t_2) \end{aligned}$$

where $H_0(t)$ is the step function with $H_0(0) = 1/2$. The first term in the covariance arises from the autocorrelation of the stimulus. The formula for the STA can be used to estimate the iPRC as it is reasonably easy to experimentally estimate the STA. To estimate the iPRC from the STA, one needs only to integrate the STA and change the sign. Since integration is a “smoothing” operation, the STA method is an excellent way to estimate the iPRC (Burton et al. 2012). A review of

methods for estimating the iPRC is given in Torben-Nielsen et al. (2010).

Noise and Coupling

It is well known that coupling of oscillators via synapses or through gap junctions can lead to *phase-locking*; that is, the two oscillators will spike with a characteristic timing difference. Two commonly observed patterns are synchrony and *anti-phase* where they fire at exactly one half a cycle apart. In the case of synchrony, the distribution of phase differences is a delta function centered at 0. However, if the oscillators are subject to *independent* noise, we can expect that the phase difference will not be identically zero, but rather, there will be some drift. Let us consider coupling that is weak enough so that the phase reduction is valid and noise that is also weak. For simplicity of exposition, suppose the synapses are not time dependent, but, instead, just functions of the phase (voltage). Then, the two coupled phase models are

$$\begin{aligned} \theta'_1 &= 1 + \varepsilon S(\theta_2) \Delta(\theta_1) + \sqrt{\varepsilon} \xi_1(t) \Delta(\theta_1) \\ \theta'_2 &= 1 + \varepsilon S(\theta_1) \Delta(\theta_2) + \sqrt{\varepsilon} \xi_2(t) \Delta(\theta_2). \end{aligned} \quad (6)$$

The oscillators are identical and the noise is white. Here $S(\theta)$ is the pulse coupling. The phase density is found to be

$$P(\phi) = N \exp \left(- \left(\frac{1}{\sqrt{2D}} \right) \int_0^\phi g(s) ds \right)$$

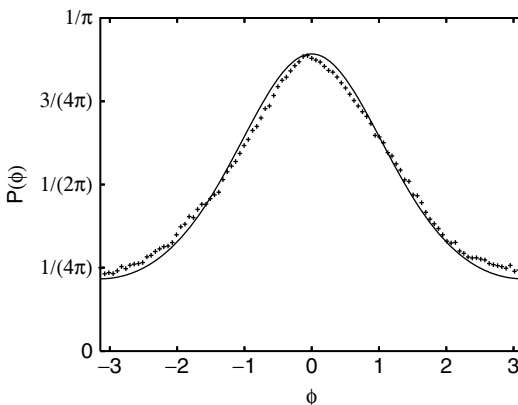
where D is the diffusion coefficient calculated above, N is a normalization so that the integral of P is 1, and

$$g(\phi) = \int_0^{2\pi} [S(t + \phi) \Delta(t) - S, (t), \Delta, (t - \phi)] dt.$$

The function $g(\phi)$ is the coupling function between the two oscillators (see entry ► “[Weak Coupling Theory](#)”). Values of ϕ where g vanishes represent phase-locked states and if $g'(\phi) < 0$, then it is a stable phase-locked state. The phase-difference density, $P(\phi)$, will have local maxima at stable locked states and local minima at unstable locked states. Thus, the phase differences will most (least) likely be found in the vicinity of phases that represent stable (unstable) locked states of the noise-free model. Figure 2 shows an example with a delta function synapse and a sinusoidal iPRC. The simulations and formula for the density agree very well.

Stochastic Synchronization

When two dynamical systems receive identical noise, then if the noise is not too strong, they will often synchronize (Pikovsky et al. 2003;



Phase Models, Noisy, Fig. 2 Effect of noise on coupling $\Delta(\theta) = -\sin \theta$, $S(\theta) = \delta(\theta)$, $\epsilon = 0.1$ theory and simulation are shown

Teramae and Tanaka 2004; Ermentrout et al. 2007a; Nakao et al. 2007; Arai and Nakao 2008). Figure 1 illustrates this phenomenon with the Hodgkin-Huxley model. The two oscillators (both the full spiking model and the phase-reduced system) converge to the same trajectory even though they started far out of phase. This phenomena is called *stochastic synchronization* and the rate of convergence to synchrony is determined by the Lyapunov exponent that was computed above for the phase model. In real biological systems, there is always extraneous noise so that there will never be perfect synchrony. Furthermore, no two neurons are the same so there will also be heterogeneities. Thus, we would like to characterize the degree of synchrony, that is, the phase density, for two oscillators receiving partially correlated noise. If the noise is small, then $P(\phi)$ can be calculated in a wide range of situations such as with colored noise, differently shaped iPRCs, and different natural frequencies (Burton et al. 2012). For simplicity of exposition, we consider only the case where the noise is white and partially correlated (Marella and Ermentrout 2008). The equations are similar to Eq. 6, but, rather than coupling, there is correlated noise:

$$\begin{aligned} \theta'_1 &= 1 + \epsilon \xi_1(t) \Delta(\theta_1) \\ \theta'_2 &= 1 + \epsilon \xi_2(t) \Delta(\theta_2). \end{aligned} \quad (7)$$

To introduce correlation, $\xi_i(t) = \sqrt{c} \zeta(t) + \sqrt{1-c} \zeta_i(t)$ where c is the correlation and $\zeta_{1,2}$ are independent. Thus, when $c = 0$, the two phase oscillators are driven with independent noise and when $c = 1$, they receive identical noise. Marella and Ermentrout (2008) computed the phase density for identical oscillators receiving white noise:

$$\begin{aligned} P(\phi) &= \frac{N}{1 - c \frac{h(\phi)}{h(0)}}, \text{ where} \\ h(\phi) &= \int_0^{2\pi} \Delta(s) \Delta(s + \phi) ds \end{aligned} \quad (8)$$

N is a normalization so that $P(\phi)$ integrates to 1. The function $h(\phi)$ is an even function of ϕ as can be seen from its definition and $h(0) \geq h(\phi)$.

Note also that $h(0)$ is proportional to the diffusion constant in Eq. 4 (for $\tau \rightarrow 0$, the white noise case). Thus, we can see that the bigger the difference between $h(0)$ and $h(\phi)$, the sharper will be the phase density. To lowest order in the magnitude of the noise, $P(\phi)$ is independent of the noise magnitude; intuitively, while strong common noise will push the oscillators together, the strong independent noise will push them apart.

Figure 3 shows the results of simulations and theory applied to the oscillator with $\Delta(\theta) = \sin(a) - \sin(a + \theta)$ where a is a parameter. Clearly, when $a = 0$, the peak is sharpest and synchronization is much better than when $a = \pi/2$. In general, the larger the DC component in the iPRC, the broader the peak. This is connected to the Lyapunov exponent, Eq. 5 since a purely DC iPRC (constant iPRC) has zero derivative and will

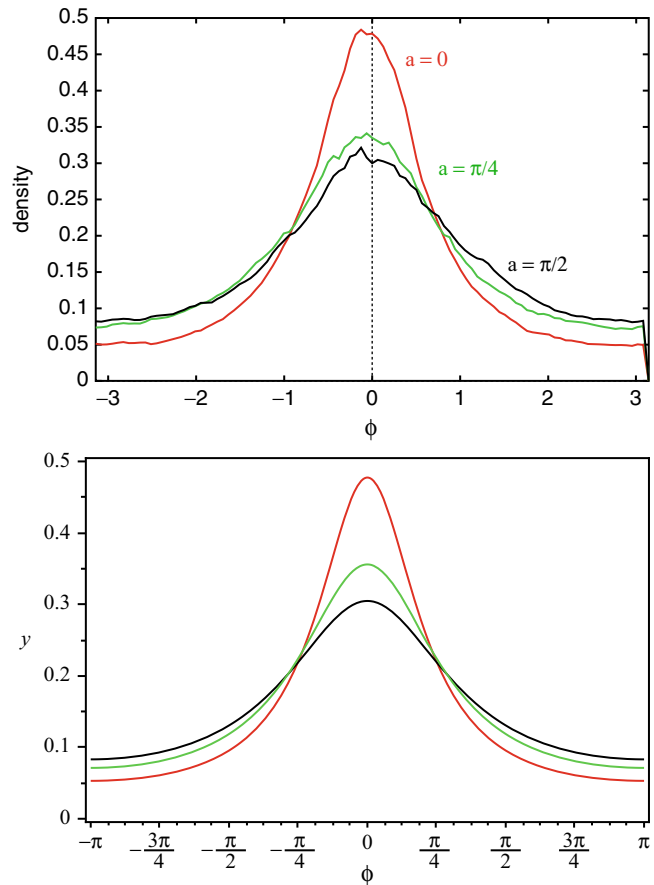
not cause any synchronization. Only the modulatory part of the iPRC contributes to the synchronization, but the DC part contributes only to the diffusion, so the optimum way to synchronize through common inputs is to reduce the DC component relative to the modulatory components (Abouzeid and Ermentrout 2009). The formula for $P(\phi)$ is not particularly transparent; however, $P(0)$ is the peak of the cross-correlation function, so the larger this is, the tighter the synchrony. For small values of c , the following formula holds:

$$P(0) = \frac{c}{2\pi} \left(1 - \frac{\langle \Delta \rangle^2}{D} \right)$$

where $\langle \Delta \rangle$ is the average of the iPRC and D is the diffusion coefficient defined above. Thus, if the iPRC is such that the regions where the phase

Phase Models, Noisy,

Fig. 3 The phase density for two oscillators receiving noise with correlation 0.8. *Top*, simulations with three different iPRCs; *Bottom*, theory from Eq. 8



is advanced exactly balance where it is delayed (e.g., $\Delta(\theta) = -\sin \theta$), then $P(0)$ will be maximal.

In sum, the reduction of noisy isolated and/or coupled oscillators to phase models allows one to compute many aspects of their dynamics. As expected, independent noise fights against synchrony for coupled oscillators; in contrast, correlated noise can induce synchrony even when the oscillators are not connected.

Cross-References

► [Weak Coupling Theory](#)

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Phase Response Curve, Measurement and Shape of General

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Definition

The phase response curve (PRC) is a measure of how an arbitrary stimulus affects the timing of action potentials in a periodically firing neuron depending upon the phase of the oscillation when the stimulus is applied. The shape of this function can determine a lot about how a network of neurons will synchronize when coupled (see entries on ► [“Weak Coupling Theory”](#) and ► [“Pulse-Coupled Oscillators”](#)). The shape of a neuron’s PRC is determined by its intrinsic dynamics, as well as by the shape of the stimulus that is applied. Any change in the shape of the PRC may affect how networks synchronize or how quickly they synchronize. What influences the shape of the PRC to an arbitrary stimulus?

This section will review how intrinsic factors, such as firing rate, potassium channel and sodium channel kinetics, and causality, as well as extrinsic factors, such as synaptic kinetics, reversal potentials, and delays, affect the shape of the PRC.

Detailed Description

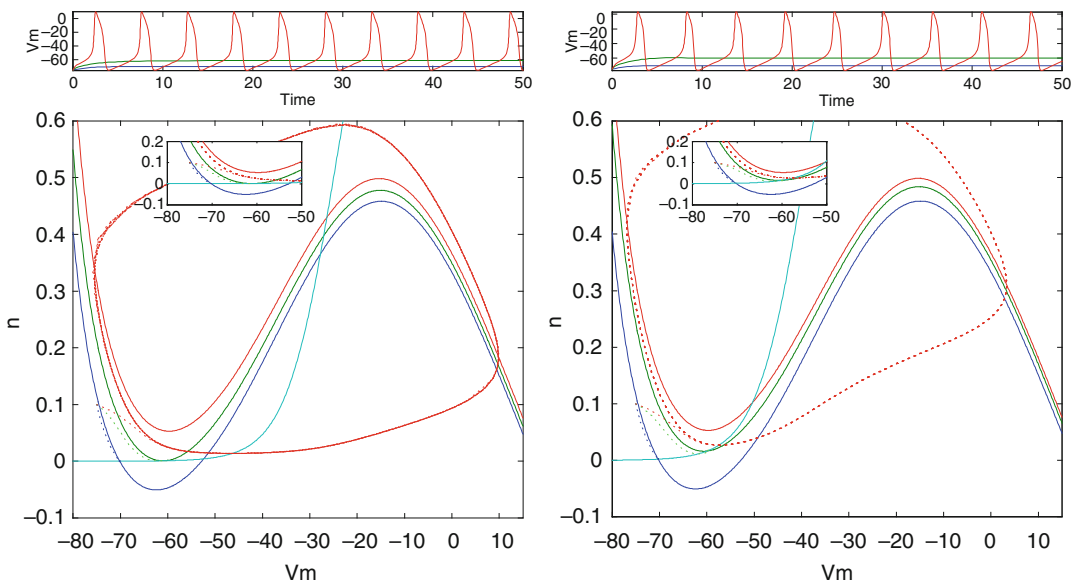
Theoretical Analysis of the PRC Shape

Many neurons, when driven with sufficient current, will fire periodically. The PRC, by definition, is a measure of how a stimulus perturbs the neuron from this period as a function of the phase at which the stimulus is applied. To represent the neuron's activity, we usually measure a state of the neuron, such as the voltage, and plot it against time. An example of a voltage trace taken from a

computational model of a neuron is shown at the top of Fig. 1. However, there are often other states (such as the sodium channel activation and the potassium channel activation), which are important in determining the cell's behavior. These states may or may not be observable. To understand what influences the shape of the PRC, we will start with a brief description of a simple computational model and how to analyze its behavior as a dynamical system. We can then go on to look at how various parameters in the model affect the PRC's shape.

Phase Plane Analysis of $I_{NaP,K}$ Model

To illustrate how the PRC depends on different factors, we will use a phase plane analysis of a simple computational model, the persistent sodium plus potassium, the $I_{NaP,K}$ (Izhikevich



Phase Response Curve, Measurement and Shape of General, Fig. 1 Periodic firing and the limit cycle in phase space. Bifurcation from rest to firing in $I_{NaP,K}$ model neuron as current injected into neuron is changed. Left column shows saddle node bifurcation for model, using n -half activation = -25 mV, while in the right panels, the model goes through a Hopf bifurcation using n -half activation = -39.5 mV. Top row, voltage trace under three conditions: subthreshold (blue), at threshold (green), and superthreshold (red). Middle, n -nullcline plotted in cyan and V -nullcline plotted for three different amounts of injected current (solid blue = $-10 \frac{\mu A}{cm^2}$, green = 4.5 , red = 20) as well as the corresponding state space behavior starting at initial condition $V(0) = -75$, $n(0) = 0.1$ for the different currents in the same color (dotted lines). The major difference in the two bifurcation types is clear from the insets: the green trace shows the voltage nullcline at the bifurcation point. For the saddle node on the left, it is tangent to the cyan n -nullcline, whereas on the right the intersection at the bifurcation point occurs as the slope of the V -nullcline changes direction

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2007). This model incorporates a fast voltage-gated sodium channel, a persistent sodium channel, and a potassium channel. While this model is not an accurate model of a mammalian neuron, it is convenient to illustrate the dynamics of a neuron. It is closely related to the Morris-Lecar neuron (Rinzel and Ermentrout 1989).

In the $I_{NaP,K}$ model, two states determine the cell's behavior: the voltage and the potassium channel activation. This means that the state of the neuron can be determined unambiguously at any time by knowing the voltage and the potassium conductance states. The equations determining the behavior of the $I_{NaP,K}$ model are as follows:

$$\frac{dv}{dt} = \frac{1}{C}(I - g_l(V - E_l) - g_{Na}m_\infty(V)(V - E_{Na}) - g_K n(V - E_K))$$

$$\frac{dn}{dt} = (n_\infty - n)/\tau_n$$

$$m_\infty(V) = \frac{1}{1 + e^{\frac{V_m - V}{k_m}}}$$

$$n_\infty(V) = \frac{1}{1 + e^{\frac{V_n - V}{k_n}}}$$

where V is the membrane voltage in millivolts; n is the cellular inactivation, a combination of the sodium inactivation and the potassium current; $C = 1 \frac{\mu F}{cm^2}$, is the membrane capacitance; $g_l = 8 \frac{mS}{cm^2}$ is the maximum leak conductance; $E_l = -80$ mV is the reversal potential of the leak current; $g_{Na} = 20 \frac{mS}{cm^2}$ is the maximum sodium conductance; $E_{Na} = 60$ mV is the sodium reversal potential; $g_K = 10 \frac{mS}{cm^2}$ is the maximum potassium conductance; $E_K = -90$ mV is the potassium reversal potential; $V_m = -20$ mV is potential at which half of the sodium channels are open; $k_m = 15$ mV is the slope at half activation; $V_n = -25$ mV is the half activation potassium channel; and $k_n = 5$ is the slope at half activation.

In analyzing dynamical systems, it is helpful to plot the nullclines in state space. The nullclines are the functions in state space along which the derivative of one of the states is zero. The voltage nullcline (plotted in blue in middle panel of Fig. 2)

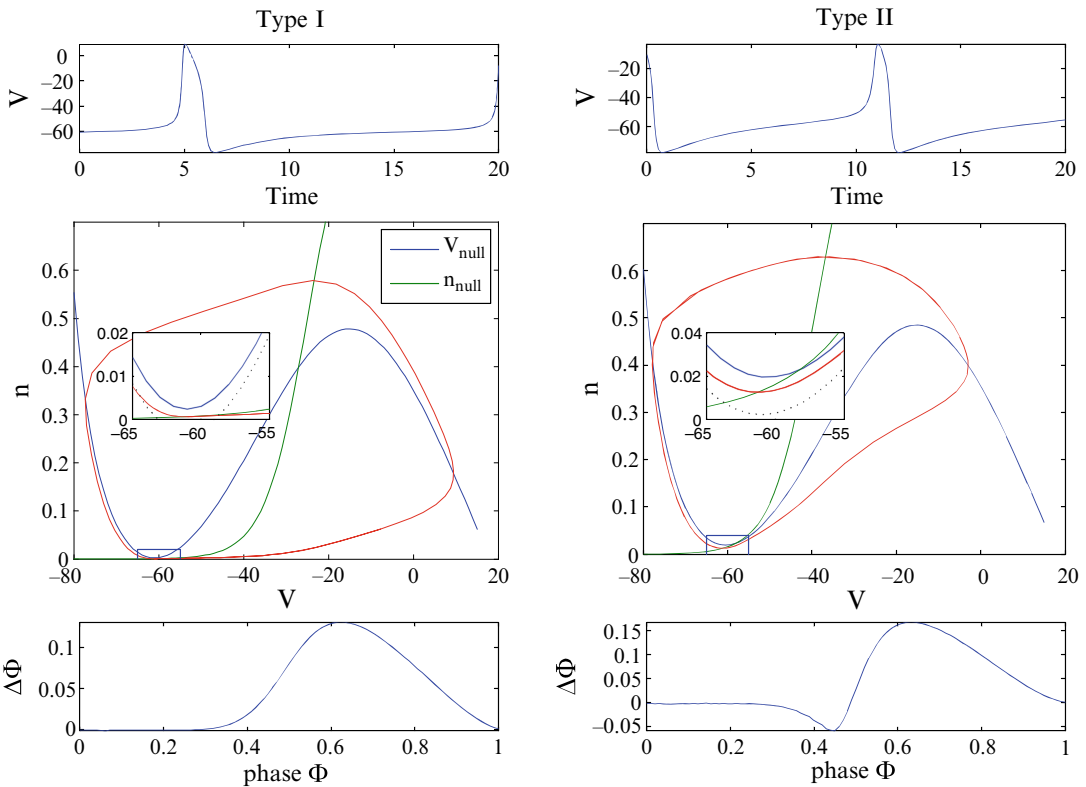
is determined by setting $\frac{dV}{dt} = 0$ and then solving for n in terms of V :

$$n_{V_0} = (I - g_l(V - E_l) - g_{Na}m_\infty(V)(V - E_{Na})) / (g_K(V - E_K))$$

Likewise, the inactivation state n -nullcline (plotted in green in middle panel of Fig. 2) is determined by setting the $\frac{dn}{dt} = 0$ and again solving for n in terms of V :

$$n_{n_0} = n_\infty$$

Crossing points of the nullclines, where the derivatives in both the V and n directions are zero, are called fixed points. Some fixed points are *stably attracting*, meaning if the neuron's state is perturbed from the fixed point, it will return to the fixed point, while others are *unstable* fixed points, where the neuron's state will accelerate away from the fixed point after perturbation. At low currents there exists a stable fixed point and neuron will sit at rest. As current is injected into the neuron, the V -nullcline shifts upward. At some current value, the intersection goes away or becomes unstable, and the neuron begins to fire periodically. This is an example of a *bifurcation*, which is a qualitative change in the dynamics of a dynamical system that is produced by varying parameters. More detail is given in the entry on ► “Excitability: Types I, II, and III.” In the $I_{NaP,K}$ model, the stable fixed point can become unstable through a bifurcation in one of the two ways: in the first, the V -nullcline initially intersects the other nullcline in three points, but as depolarizing current is added to the model, the nullcline shifts up until two of the intersections are lost simultaneously. At the point of the bifurcation, the voltage nullcline (green trace in the left middle panel of Fig. 1) becomes tangent to the n -nullcline; the two crossing points merge into a single point that is stable in some directions and unstable in others; this is called a *saddle node*. The bifurcation is called a *saddle node bifurcation* as shown in the left column of Fig. 1; trajectories that pass near this saddle node can be arbitrarily slow. In the other bifurcation, the angle of the lone intersection



Phase Response Curve, Measurement and Shape of General, Fig. 2 Types I and II PRCs. The left column represents the dynamics of the $I_{NaP,K}$ model when the half activation of the n -channel is at -25 mV and input current is 5, while in the right column the half activation is at -39.5 mV and input current is 10. Top: voltage traces

from the $I_{NaP,K}$ model. Middle: nullclines determine phase advance. The type of PRC depends on the bifurcation of the neuron from rest to spiking. **Bottom:** Type I PRCs only have phase advances given a small excitatory input, whereas Type II PRCs can have both advances and delays

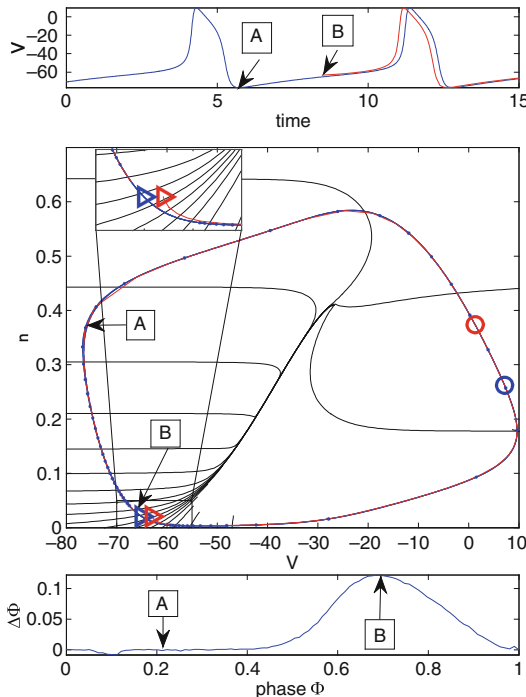
P

between the two nullclines changes until the stable fixed point becomes unstable, resulting in repetitive spiking with onset at a nonzero threshold frequency. This is called a *Hopf bifurcation* and is shown in the right column of Fig. 1. The difference between the model in the left and right condition is the half activation voltage of the n -state (cyan curve). In the left column, the half activation is at -25 mV, and in the right column, it is at -39.5 mV.

When a neuron is firing periodically and the voltage is plotted against the potassium activation, the trace forms an orbit. If the orbit is a stable behavior, meaning that if the neuron's state is perturbed off the orbit by a small amount, it will return to the orbit, it is called a limit cycle. The orbit for a periodically firing $I_{NaP,K}$ neuron is

shown in the middle panel of Fig. 3. The phase of the oscillation can be thought of as the angle of a hand on a clock, where the hand starts at some point in the center of the orbit (such as the unstable fixed point in the center of the orbit) and the tip of the hand points to the current state of the cell. If the voltage and the inactivation are thought of as a Cartesian coordinate representation of the neuron's state, the phase angle is a polar representation.

When a neuron is stimulated by an external input, such as a synaptic input or an injected current from an electrode, it pushes the neuron's state off its orbit. Because the orbit is stable, the neuron's state will return back to the orbit. However, when it returns to the orbit, the phase may be advanced or delayed. The degree to which the



Phase Response Curve, Measurement and Shape of General, Fig. 3 Top, voltage plotted against time of a periodically firing $I_{NaP,K}$ model neuron. At time 8.5, a stimulus is applied which instantaneously increases the voltage by 4 mV. The *red trace* indicates the voltage trace after the stimulus is applied. Middle, voltage (V) plotted against cellular inactivation (n). The periodically firing neuron follows an orbit in this state space representation. The *blue dots* represent the states sampled at each 0.1 ms. The higher density along the orbit indicates slower moving state. The *black lines* are isochrons, sampled at every 0.5 ms. They represent points in state space along which initial conditions will result in all points on the line converging to the same phase on the limit cycle. The *blue triangle* represents the phase of the neuron before the stimulus and the *red triangle* represents the phase immediately after. The voltage and inactivation follow the *red curve* after the stimulus and converge back onto the stable limit cycle. 3 ms after the stimulus is applied, the unperturbed and perturbed states are plotted as *blue and red circles*. The stimulus has moved the neuron across isochrons advancing the phase of the neuron. Bottom, by repeatedly stimulating the neuron at different phases, the time difference between the unperturbed condition and the stimulated condition is the phase response curve

phase is shifted depends on the phase of the neuron's cycle at the time of stimulus, the shape of the stimulus pulse, and the dynamics of the neuron that determine how the state returns to the orbit.

The phase response curve can be directly determined by plotting the relationship between the cycle period and the phase of the cycle at which the stimulus was applied. The cycle period is determined by choosing a point along the orbit and measuring the time it takes to complete a cycle and return to the same point. This time will vary to different degrees when the stimulus is applied at different phases of the cycle. The PRC for the $I_{NaP,K}$ model is shown at the bottom of Fig. 3.

Type I and Type II PRCs

If the phase response curve is strictly positive, i.e., a weak excitatory input only can advance the spike time, it is called a Type I or Class I PRC (Rinzel and Ermentrout 1989). The $I_{NaP,K}$ model can produce both Type I (left column) and Type II (right column) PRCs, as shown in Fig. 2. These types are closely tied to two classes of cell excitability that Hodgkin described as Type I and Type II neurons (Hodgkin 1948). Hodgkin characterized Type I cells as those that have sharp thresholds and can fire at very slow firing rates. As the $I_{NaP,K}$ model goes through a saddle node bifurcation, it has a sharp threshold and can fire at arbitrary low firing rates, and for excitatory inputs, the phase response curve only contains advances of the next spike. Alternatively, if a stimulation can both advance and delay the next spike with an excitatory input, the PRC is called Class II or Type II. An example of the $I_{NaP,K}$ neuron model with parameters to generate Type II behavior occurs when a neuron is very close to a Hopf bifurcation.

Measuring the Phase Response Curve

The phase response curve to an arbitrary stimulus wave form can be measured by the direct method: a stimulus is applied to the neuron, and the change in spike time from the unperturbed interspike interval is measured. In Figs. 3 and 4, a stimulus is simulated by instantaneously adding 2 mV to the neuron's voltage. This simulates a very strong but very short pulse. In Figs. 5, 6, 7, 8, 9, and 10, a more realistic stimulus is applied to simulate synaptic input to the cell:

$$g_{\text{syn}}(t) = \frac{1}{\tau_s - \tau_f} \left(e^{-\frac{t}{\tau_s}} - e^{-\frac{t}{\tau_f}} \right)$$

where τ_s is the slow decay time constant of the synapse, τ_f is the fast rise time constant, and $\frac{1}{\tau_s - \tau_f}$ is a normalization factor so that the total area under the curve is 1 independent of the shape of

the synaptic conductance. In these simulations, because the $I_{\text{NaP,K}}$ neuron has such a short period (about 7 ms), we used a fast synapse with short time constants $\tau_s = 0.5$ ms and $\tau_f = 0.25$ ms.

When adding the synapse to the model, the voltage equation becomes

$$\frac{dv}{dt} = \frac{1}{C} \left(I - g_I(V - E_I) - g_{\text{Na}} h_{\infty}(V) (V - E_{\text{Na}}) - g_K n(V - E_K) - g_{\text{syn}}(t) (V - E_{\text{syn}}) \right)$$

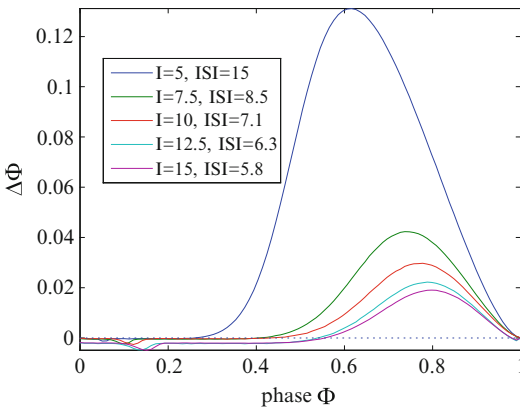
The synaptic waveform can be written as a differential equation:

$$g_{\text{syn}}(t) = \frac{g_{\text{syn}}^{\text{max}}}{\tau_s - \tau_f} (s - f)$$

where

$$\frac{ds}{dt} = -s/\tau_s$$

$$\frac{df}{dt} = -f/\tau_f$$



Phase Response Curve, Measurement and Shape of General, Fig. 4 Effect of firing rate on the shape of PRC measured with voltage perturbation. As more current I is applied to the neuron, the firing rate increases and the interspike interval (ISI) decreases. At higher firing rates, neurons become dominated by their own internal dynamics and become less sensitive to external perturbations

The variable s represents the slow component of the synapse and f is the fast component. To simulate a synaptic input, 1 is added to both the s and f variables at the time of the input, and the states s and f are integrated along with the V and n states. The coefficient $g_{\text{syn}}^{\text{max}}$ scales the synaptic amplitude. What are s and f ?

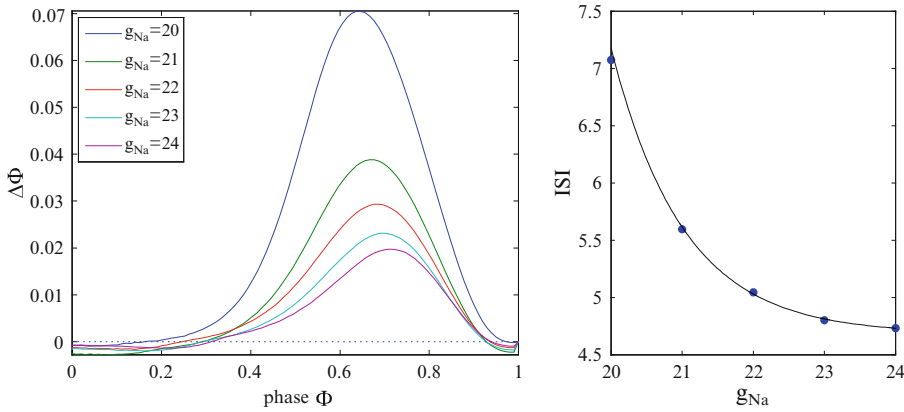
To measure the PRC in a model, a simulation is run from the start of an action potential, for example, the upward crossing at -20 mV, to the onset of the stimulus time, the stimulus is applied, and then the numerical simulations are continued until the voltage crosses the threshold again. The PRC is determined by plotting the difference between the measured interspike intervals (ISI) given the stimulus at phase ϕ , $\text{ISI}(\phi)$, from the unperturbed ISI:

$$\Delta(\phi) = (\text{ISI}_{\text{un}} - \text{ISI}(\phi)) / \text{ISI}_{\text{un}}$$

The direct method can be used to detect the effect of changes in the shape of the stimulus as well as the effect on changes in the dynamics of the neuron. For sufficiently weak coupling, the results of the direct method agree with that predicted by convolving the PRC in response to an infinitesimally brief and weak input (see entry on ▶ “Weak Coupling Theory”) with the shape of the arbitrary perturbation.

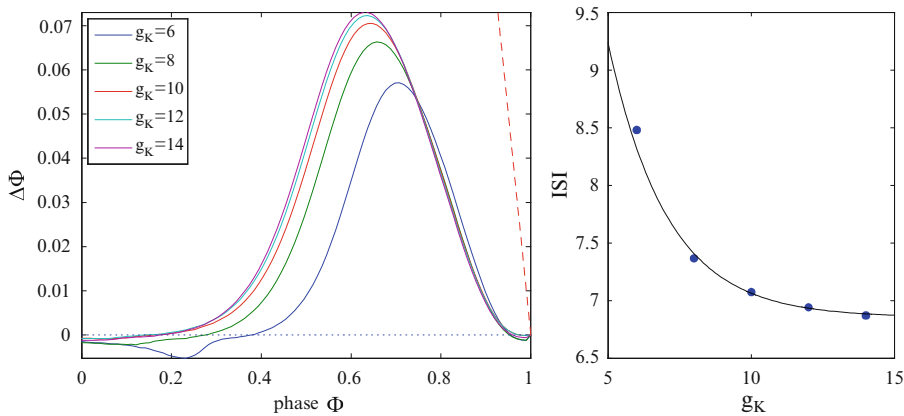
Isochrons

When a neuron is perturbed off the orbit, it may return to the orbit either ahead or behind the phase of its unperturbed orbit. There are lines in state



Phase Response Curve, Measurement and Shape of General, Fig. 5 Effect of changing fast voltage-gated sodium channel conductance on the shape of the PRC. PRC measured with synaptic input waveform ($I = 10 \frac{\mu\text{A}}{\text{cm}^2}$ for all simulations, $g_{Na} = 20 \frac{\text{mS}}{\text{cm}^2}$ in all other simulations shown). Increasing the fast voltage-gated sodium

conductance makes the model less sensitive to inputs that occur after the neuron recovers from the action potential. This may be partially be attributed to the increased firing rate. The right panel shows that as g_{Na} increases, the interspike interval decreases



Phase Response Curve, Measurement and Shape of General, Fig. 6 Effect of voltage-gated potassium channel conductance on the shape of the PRC. Default potassium conductance is $10 \frac{\text{mS}}{\text{cm}^2}$. As potassium conductance g_K

is increased, the $I_{NaP,K}$ model becomes more sensitive to synaptic inputs. The red dotted line is the causality line, as discussed below

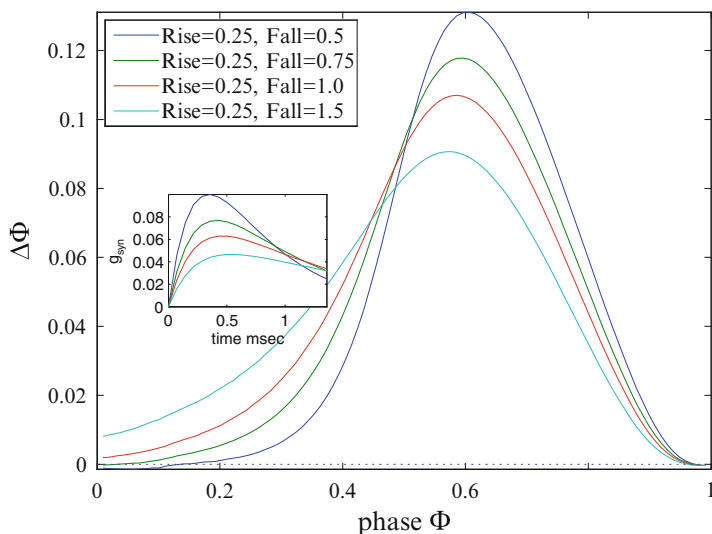
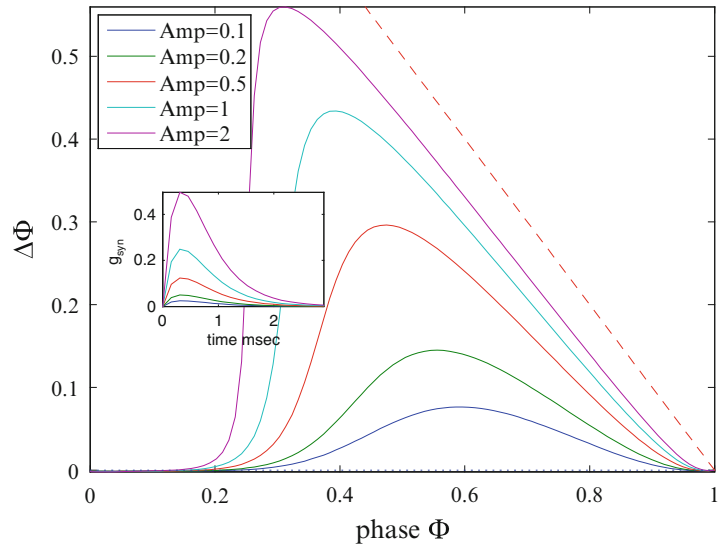
space where if the state of the neuron is placed at any point along the line, the neuron will converge to the same phase of the orbit. These lines are called *isochrons* (Greek *iso*, same; *chronos*, time). The isochrons for the $I_{NaP,K}$ model are shown in Fig. 3. To find these isochrons in a computational model, we use a trick: an attracting point in state space when integrating the model forward in time becomes a repelling point when integrating the model backward in time.

Therefore, we choose initial conditions very close to the orbit and then integrate them backward in time. As the points diverge, new points can be inserted or, if the points get too far away from the limit cycle, eliminated. The resulting isochrons plotted at 1 ms intervals starting at the threshold at -20 mV are plotted in the middle panel of Fig. 3.

When a stimulus moves the state of the neuron across these isochrons, it causes a phase advance.

Phase Response Curve, Measurement and Shape of General,

Fig. 7 Response to synaptic amplitude limited by causality. Stimuli cannot advance the action potential to a time prior to the onset of the stimulus. The line of causality is plotted as a red dashed line $C(\phi) = 1 - \phi$. It is impossible to advance a spike above this line. As an excitatory stimulus amplitude is increased, the shape of the PRC is affected by the line of causality, forcing the peak to the left



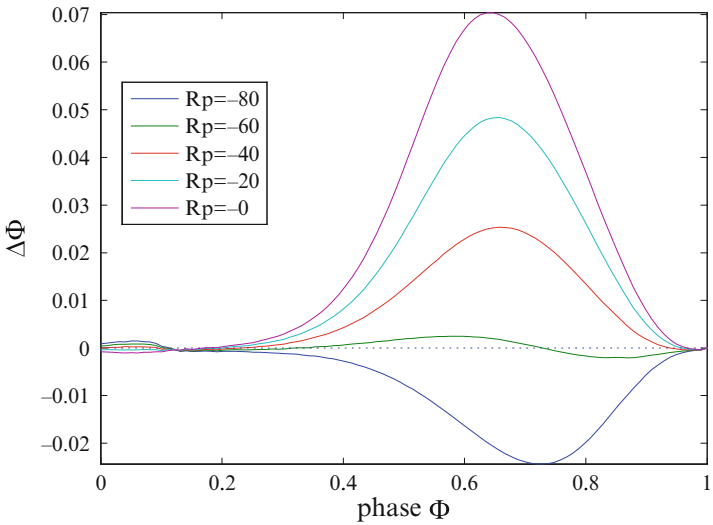
Phase Response Curve, Measurement and Shape of General, Fig. 8 Effect of the synaptic time constant on the PRC. As the falling time constant of the synapse is increased (synaptic waveforms are plotted in inset), when preserving total charge, the amplitude becomes smaller and

the peak shifts slightly to the right. Faster synapses tend to elicit larger PRCs than slower ones. Slowing of the synapse smooths over the cell dynamics, making the PRC flatter. Slowing of the synapse also acts like a time delay, moving the PRC forward in phase

The phase advance may not be realized until the neuron has relaxed back to its orbit. An example of a 2 mV stimulus moving the state across the isochrons is shown in Fig. 3. When the state is plotted 3 ms later, and compared to the unperturbed state at the same time, it can be seen that the stimulus resulted in a phase advance. The

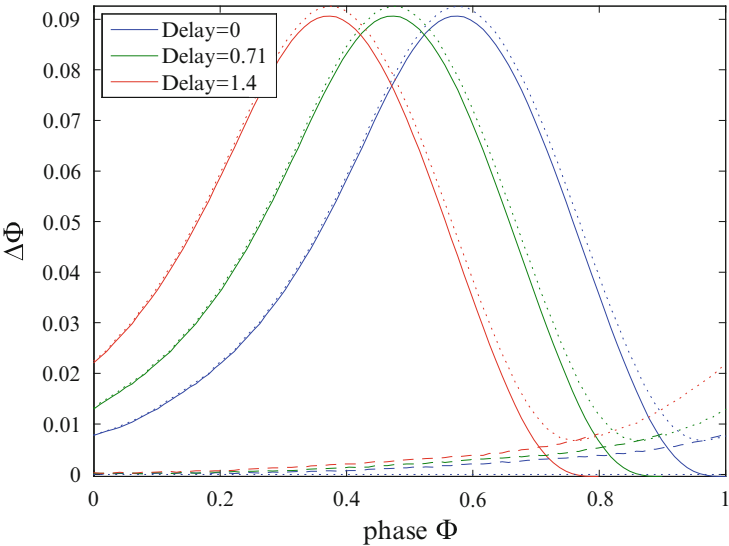
shape of the phase response curve is therefore directly related to how the stimulus causes the neuron to cut across these isochrons.

If the isochrons are dense near the phase at which the stimulus is applied, the phase advance will be larger than it would be if the stimulus was applied at a phase where the isochrons are widely



Phase Response Curve, Measurement and Shape of General, Fig. 9 Effect of synaptic reversal potential on PRC. Excitatory and inhibitory synaptic inputs differ by their kinetics and by the synaptic reversal potential. In this plot, the kinetics are held constant as the reversal potential is changed. Because of the nonlinearities of the neuron, and the different effects of causality on spike advance versus spike delays, excitatory and inhibitory inputs are not symmetric around the resting potential, i.e., if the neuron at rest

is at -60 mV and if the neuron's response is linear, then a synaptic input with a reversal potential of -80 mV should have the same shape but with a sign reversal as a synaptic input with a reversal potential at -40 mV. It can be seen that the blue and red lines are not the same, indicating that there are nonlinearities in the response. Generally, PRCs for inhibitory synaptic inputs usually peak at the very end of the phase, while excitatory inputs tend to peak earlier



Phase Response Curve, Measurement and Shape of General, Fig. 10 Effect of synaptic delay on phase response curve, second-order PRC, and total PRC response. As synaptic inputs are delayed, the PRC shifts to the left (*solid line*). Secondary PRCs measure the effect of spike advance on the interspike interval following the

stimulus period (*dashed line*). As synaptic inputs are delayed, more of the current is applied on the subsequent interval, resulting in significant phase advances on the second period. The second-order PRC and the primary PRCs can be added together to estimate the total effect of the synapse on the spike times (*dotted lines*)

spaced. However, the degree of phase advance also depends on the direction of the stimulus with respect to the isochrons. If the stimulus moves the states orthogonal to the isochrons, the phase advance will be maximal for a given stimulus amplitude. If the stimulus moves the state along isochrons, the phase advance will be minimal. In the middle panel of Fig. 3, the stimulus increases the voltage (i.e., moves it to the right). When the stimulus is applied at the phase indicated by **A**, it moves the state along the isochrons, resulting in a small change of phase. A stimulus applied at the phase indicated by **B** moves the state across isochrons, resulting in a large change.

The shape of the PRC is also dependent on how long the neuron dwells in states sensitive to inputs and in states that are not sensitive to inputs. In the neuron model, the phase does not progress linearly with time. Dots are plotted along the orbit at 0.1 ms intervals. It can be seen from the density of dots that the neuron spends more times at phases during the recovery period, where there is a high density of dots, than at the action potential, where the density is low. Because the neuron spends a good portion of the time in the recovery phase where the cell is insensitive to voltage perturbations, the PRC is flat for a good portion of the phase. As the neuron approaches threshold again, it becomes sensitive again to inputs.

The remaining sections will detail how changes in the dynamics of the cell and the synapse affect the measured PRC. The first part will focus on changes intrinsic to the neuron, such as changes in the kinetics of voltage-gated ion channels which may be caused by drugs or ion channel mutations. The second part will focus on changes extrinsic to the neuron, such as changes to the shape of the synapse.

Intrinsic Effects on PRC Shape

Firing Rate of the Neuron

As the current applied to a neuron increases, the firing rate generally increases. This in turn affects the neuron's sensitivity to synaptic inputs. As its sensitivity changes to inputs, the ability of the network to synchronize may

change. Changes in PRC shape as a function of firing rate can be used to explain how networks of neurons synchronize at certain firing rates and desynchronize at others.

Tonic excitatory synaptic drive depolarizes a neuron and increases its firing rate. As the firing rate increases, the period shortens, but the action potential and the recovery time do not. Therefore, the proportion of the PRC dedicated to the action potential and recovery time increases. In this model there is a small phase delay when a stimulus is applied during the action potential (at the beginning of the phase), as can be seen as a small dip in the PRC in Fig. 4. As the ISI shortens as the applied current is increased, the action potential width does not change; therefore this phase at which the action potential ends moves to the right, as can be seen with the rightward movement of the dip. This illustrates that the proportion of the PRC affected by the action potential increases as the ISI decreases.

It can also be seen in Fig. 4 that at the slow firing rate, when the input current $I = 5 \frac{\mu A}{cm^2}$, the phase response curve is quite large, but at the high firing rate, when the input current $I = 15 \frac{\mu A}{cm^2}$, the peak of the PRC decreases. This is because when a neuron is driven to fire very rapidly, its dynamics are dominated by its internal dynamics, which are determined by gating of the ion channels; therefore, if the cell receives a synaptic input when it is firing rapidly, its phase will not change dramatically. At smaller currents the firing rate of the neuron slows, and the neuron becomes more sensitive to external inputs.

Ion Channel Kinetics

There are many parameters associated with the voltage-gated sodium and potassium currents: maximum conductance, half activation voltage, slope at half activation, and the time constants. The kinetics of these channels can be affected by different drugs and by genetic mutations. PRCs are a powerful tool to relate these changes at the molecular level to changes in network behavior.

In Fig. 5 PRCs from the $I_{NaP,K}$ model are shown as the maximum sodium conductance is changed. Increasing the sodium conductance decreases the peak of the PRC. This may be due

to the fact that sodium conductance and firing rate are negatively correlated, as shown in the right panel of Fig. 5. Because increases in sodium conductance result in higher firing rates and shorter ISIs, the neuron becomes less sensitive to synaptic inputs. The peak of the PRC also shifts to the right with increased sodium conductance. That may be attributed to effects from the line of causality, addressed later.

In Fig. 4 the PRC was measured using an instantaneous change in voltage, while in Fig. 5 it is measured with a realistic synaptic input. The PRC shape looks different due to the synaptic dynamics. The blue curve in Fig. 5 corresponding to $g_{\text{Na}} = 20 \frac{\text{mS}}{\text{cm}^2}$ with synaptic input can be compared directly to the red curve in Fig. 4 corresponding to $I = 10 \frac{\mu\text{A}}{\text{cm}^2}$ with a voltage change. Because the synaptic input is applied over a finite time, it smooths and advances the PRC to the left.

The voltage-gated potassium current is important in the recovery of the neuron from an action potential and restoring the cell to rest. It can be seen in Fig. 6 that as the voltage-gated potassium current is increased from 6 to $14 \frac{\text{mS}}{\text{cm}^2}$ (default is $10 \frac{\text{mS}}{\text{cm}^2}$), the cell becomes more sensitive to synaptic inputs and for a longer portion of the phase. Like the sodium conductance, increasing potassium conductance decreases the ISI. In contrast to the sodium conductance, increasing the potassium conductance makes the cell more sensitive to synaptic inputs. The increased potassium current helps the cell recover from the action potential faster letting the cell spend more of its phase near threshold where it is sensitive to inputs.

Causality

When a stimulus is applied, the maximum amount that it can advance the spike is to immediately elicit an action potential. The stimulus cannot make the neuron fire an action potential prior to the time the stimulus is applied. This is called *causality*. The causality line can be plotted on the PRC graph, $C(\phi) = 1 - \phi$, shown as dashed red lines in Figs. 6 and 7. It is zero when $\phi = 1$ and increases at a 45° angle backward from the end of the phase (note that the figure does not have the same scale for the x and y direction). Instantaneous activation

of an action potential would result in points along this line. Because a stimulus cannot advance an action potential to a time prior to the onset of the stimulus, it is not possible for points to exist above this causality line.

For very small stimulus amplitudes, as the amplitude is increased, the PRC will increase proportionally. However, as the stimulus amplitude becomes larger, the stimulus transitions from modulating the spike times to eliciting spikes. This can be seen when the PRC begins to hug the line of causality. As seen in Fig. 7, as the stimulus amplitude increases, the peak of the PRC is forced to the left by the causality limit. The PRC cannot actually be on the line of causality because the synaptic waveform is finite, and there will always be a time lag between the onset of the stimulus and the threshold crossing of the action potential. This lag will result in a PRC that is slightly below the line of causality, even for the largest stimulus. Plotting the PRC with the line of causality is a good tool to assess whether the stimulus is inducing linear or nonlinear responses. If a large number of points are sitting along the line of causality, it implies that the stimulus is evoking an action potential rather than phase advancing and the response is therefore nonlinear.

For inhibitory inputs, increasing the amplitude can delay the spike almost indefinitely. Therefore, for large stimulus amplitudes, changing the sign of the stimulus, even without changing any other parameters, may result in asymmetries in the PRCs due to the different effects of causality on delaying versus advancing stimuli. This is one of the reasons why an excitatory and an inhibitory synaptic input may elicit PRCs which are not symmetrical.

Extrinsic Effects on PRC Shape

Synaptic Time Constants

The shape of a synaptic conductance waveform is dependent on the neurotransmitter release, the clearing of the neurotransmitter from the synapse, and the receptor density and kinetics. The synaptic release and receptor kinetics can change on the short time scales caused by short-term potentiation and facilitation, as well as by neuromodulators and

drugs. Changes in receptor density can be affected by long-term potentiation or homeostatic plasticity. All of these changes can alter the way networks of neurons synchronize on fast time scales, such as with the waxing and waning of population oscillations, or over slow time scales, such as with the development of pathological behaviors. The PRC is also affected by the synaptic reversal potential, which can change with the accumulation of ions in the extracellular and intracellular space.

As the rates of neurotransmitter uptake and enzymatic breakdown are changed, the time constants of the synaptic waveform are affected. Here we use an alpha function to simulate the synaptic conductance waveform:

$$g_{\text{syn}}(t) = \frac{1}{\tau_s - \tau_f} \left(e^{-\frac{t}{\tau_s}} - e^{-\frac{t}{\tau_f}} \right)$$

In Fig. 8 we vary the time constant of the synaptic decay. As the decay time is increased, the synapse smooths over a larger portion of the cell's phase. To normalize the stimulus waveforms, the total charge passed is held constant as the time constants are changed. Therefore, the peak synaptic amplitude is greater for synapses with faster kinetics. Because neurons are more sensitive to fast inputs, faster synapses tend to elicit taller PRCs than slower ones, given the same total charge. The slowing of the synapse also acts like a time delay by shifting the peak of the PRC to the left. The effect of time delay will be addressed in a later section.

Synaptic Reversal Potential

The synaptic current is a function of the synaptic conductance waveform and the synaptic reversal potential. $I_{\text{syn}} = g(\text{syn})(E_{\text{syn}} - V_m)$. In Fig. 9 the synaptic conductance waveform is held constant, but the synaptic reversal potential is varied from an inhibitory synaptic reversal potential of -80 mV to an excitatory synaptic reversal potential of 0 mV. If the neuron's response was strictly linear, applying a synaptic input with a reversal potential 20 mV above rest and one 20 mV below rest would result in the same PRCs but with a sign reversal. However, it can be seen that these PRCs are not, indicating that the response is nonlinear. One obvious difference between PRCs measured

with inhibitory and excitatory synaptic inputs is that spike delays are less affected by causality limits than advances. This results in inhibitory PRCs being more skewed to the right than excitatory PRCs, which skew more to the left as stimulus amplitude increases. But the neuron's dynamics are also nonlinear; this can be seen in Fig. 3 by the fact that the isochrons do not have left-right symmetry around the orbit. Therefore, any finite stimulation that perturbs the neuron significantly off the orbit does not elicit a symmetric effect when pushing the state of the neuron to the right compared to that of a stimulus pushing it to the left of the orbit.

Synaptic Delay

There can be a significant lag, on the order of milliseconds, between the presynaptic action potential and the EPSP observed postsynaptically. As cells get further apart, the propagation time from the soma of the presynaptic cell to the synaptic release site can become significant. For synaptic inputs that occur at distal points on the dendrite, propagation time from the synapse to the soma of the postsynaptic cell can also become significant. Furthermore, the EPSPs from synaptic inputs on distal dendrites can become more smeared out over time as the electrical impulse travels down the dendrite, which effectively acts as a further delay. These synaptic delays can affect the shape of the PRC and have a significant role in determining how a network will synchronize (Crook et al. 1998; Woodman and Canavier 2011; Canavier et al. 2013). Drugs that affect potassium channels can dramatically change the way synaptic inputs propagate along the dendrite, significantly changing the effective synaptic delay times.

PRCs measured with different synaptic delays are plotted in Fig. 10. It can be seen that as the delay gets longer, the PRC shifts forward in phase. For example, if a stimulus is applied at 0.7 of the phase with a delay of 0.1 , it will look the same as a stimulus applied at 9.8 of the phase with a delay. The PRC is shifted forward proportional to the delay. The most significant effect is that the stimulus may not arrive until after the neuron has spiked. In this case, the effect of the stimulus may be observed on the subsequent period. This can be observed in the *higher order PRCs*, described next.

Higher Order PRCs

If a stimulus is finite in duration and the neuron's response takes some time to return back to its orbit, the effect of the stimulus may not be completely resolved by the time the first action potential occurs. Therefore, the effect may be observed on the timing of the second spike after the onset of the stimulus. The measurement of the effect of the stimulus on the interspike interval during which the stimulus was initiated is called the *primary PRC*; the measurement of the effect on the subsequent ISI is called the *secondary PRC*. In general, the effect of the stimulus on any interval following the interval during which the stimulus is initiated is called a *higher order PRC*. Analyzing the primary PRC's effect on network synchrony may lead to erroneous results if higher order effects on subsequent intervals are ignored. The higher order PRCs can be added to the primary PRC to assess the total effect of stimulus on the neurons.

Second-order PRCs are plotted in Fig. 10 as dashed lines. It can be seen that as the synaptic delay is increased, the secondary PRC becomes significantly larger. This is because synaptic inputs initiated at the end of the period may be applied to the next period resulting in significant phase advance of the second action potential. In the case of the $I_{NaP,K}$ neuron, the secondary PRC is flat for the majority of the period except at the very end of the period, where the synaptic input from the previous cycle leaks into the second period. The flatness of the secondary PRC in the early phases indicates that the neuron has recovered from the synaptic input applied early in the first period by the time the second period starts. If the cell's dynamics are slow to recover, the secondary PRC can be significant. In theory, because a PRC is a measurement of the effect of a stimulus on the orbit of a neuron in state space, the PRC itself should be periodic with the phase. However, often it can be seen that for the primary PRC, the phase advance that occurs as a result of stimulation at the beginning of the phase does not match the phase advance due to stimulation at the end of the phase. This indicates that there is a significant effect in the higher order PRC.

The total PRC is the cumulative effects of the first- and second-order PRCs. It can be measured

by calculating the phase advance of the second (or later) spike after the stimulus is applied. The total PRC is plotted as a dotted line in Fig. 10. While the primary and secondary PRC are not periodic (the beginning and the end of the phase do not match), the total PRC is periodic.

Conclusions

Changes in the shape of a PRC may help to determine how network dynamics are altered as a function of cellular level changes. Because neuronal dynamics are highly nonlinear, there are no hard and fast rules that relate changes in ion channel conductance to changes in phase response curves. Therefore, the best approach to understanding these relationships remains performing numerical simulations confirmed with physiological experiments directly measuring the effect of changes in ion channel kinetics on PRC shape.

In general, excitatory inputs will advance spikes, while inhibitory inputs delay spikes. Because of causality, excitatory inputs generally are more skewed to the left. Time delays skew the PRC to the left. Therefore, excitatory inputs with significant delays can result in desynchronization of networks. If the beginning and the end of the phase of the primary PRCs do not match, this is an indication that the stimulus has not been fully applied or the neuron has not returned to the limit cycle by the time the neuron spikes. If this is the case, including higher order PRCs may be necessary to fully characterize the neuron.

Cross-References

- [Excitability: Types I, II, and III](#)
- [Pulse-Coupled Oscillators](#)
- [Weak Coupling Theory](#)

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Phase Response Curve, Measurement of the Infinitesimal

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Definition

The infinitesimal phase response curve (iPRC) is a measure of an oscillator, which specifies how the phase of that oscillator shifts, as a function of the phase of a perturbation as the width and height of the pulse go to zero, approximating a continuous time delta function (see ► [“Weak Coupling Theory”](#)). In neurons, the iPRC measures the spike time shift in response to the injection of a small

current (or less often a conductance) pulse at a given time. The iPRC should scale linearly with pulse area.

Detailed Description

The iPRC of neurons is of interest for several reasons. First, by using the iPRC, a prediction can be made about the synchronizing properties of synaptically coupled neurons. Given small conduction delays and weak coupling between neurons, nonnegative PRCs (type I PRCs or monophasic PRCs; see ► [“Phase Response Curve, Measurement and Shape of General”](#)) typically lead to synchronization between neurons only if they are coupled via inhibitory connections. In contrast, iPRCs with a negative part (type II PRCs or biphasic PRCs) may lead to synchronization in networks with excitatory coupling (Rinzel and Ermentrout 1998; Hansel et al. 1995).

Secondly, the iPRC type is often indicative of the bifurcation type leading to the transition from non-spiking to spiking state. Moreover, the iPRC type correlates with the excitability type of a neuron (Rinzel and Ermentrout 1998). iPRCs are variable between and within neuronal cell types (pyramidal neurons, Reyes and Fetz 1993; Tsubo et al. 2007; inhibitory interneurons, Tateno and Robinson 2007), across firing frequencies (Gutkin et al. 2005) and neuromodulatory conditions (Stiefel and Gutkin 2012). Determining the iPRC of a neuron hence provides us with significant information regarding its class and functionality.

The high-dimensional dynamics of a neural oscillator can be projected down to a one-dimensional system. In such projection, the state of a neuron as an oscillator is determined by the phase only. The phase monotonically increases at a rate corresponding to the oscillator’s frequency and is reset to 0 every full 2π . When a hypothetical infinitesimally small perturbation (current pulse) is injected into a neuron, then the spike time shifts as a function of the perturbation phase are described by the infinitesimal PRC (iPRC). When a realistic (but still weak and not directly causing a spike) input is injected into a neuron, the PRC is the convolution of the iPRC

with the input waveform (see ► [“Weak Coupling Theory”](#)).

The most straightforward way to determine the iPRC is by injecting brief pulses at random interspike phases into a neuron and plotting the phases against the resulting phase shift. The pulses must be large enough to overcome the effects of background noise, but not so large that they summate nonlinearly. The phase shift is divided by the area under the pulse to get the iPRC in units of phase reset per unit of current (or conductance; see Achuthan et al. 2011). As the observed phase shift data is usually rather noisy, a post-processing step is used to fit a smooth curve to the data (Reyes and Fetz 1993). The intrinsic jitter of the spike times as well as noisiness of observed phase shifts results in the major drawback of this approach: that is, a large number of sweeps with injected perturbations and their resulting phase shifts need to be collected.

An alternative approach is to inject a continuous fluctuating current into the neuron (Izhikevich 2010; Netoff et al. 2005). These current fluctuations will then cause the neuron to emit a spike train. In parallel, a spike train can also be predicted from the fluctuations and a candidate iPRC. The prediction is derived by treating the fluctuations as a series of individual perturbing pulses, and the expected phase shift is their cumulative effect. The iPRC is then determined by optimizing a curve that minimizes the error between the spike times predicted by the candidate iPRC and the observed spike times. The total error is the sum over the square of the differences between these expected phase shifts and the measured phase shifts. The continuous fluctuation can be a convolution of synaptic potential-like waveforms, white or colored noise.

However, the parameters of such an iPRC fitting algorithms do not necessarily converge within a reasonable number of optimization rounds. This is due to the loss of temporal information about the injected fluctuation, which is lost as the error signal is averaged over all phases and all spikes. Optimization methods based on minimizing an error matrix solve this problem (Torben-Nielsen et al. 2010).

A third alternative to the direct and parameter-optimization-based methods is to average the inputs between spikes. Such an average over the inputs over all interspike intervals, integrated and reversed in time, is equivalent to the iPRC (Ermentrout et al. 2007). Scaling the interspike intervals in an additional preprocessing step makes this method more robust against spike timing fluctuations (Ota and Aoyagi 2012).

In conclusion, a number of data analysis methods exist to determine the PRC of a neuron. As in all of time-series analysis, we first need to judge the quality (such as stationarity, noise levels) and quantity of our data. Based on this judgment, we then decide if and how we can determine PRCs. The averaging and parameter-optimization-based methods can potentially outperform the direct method in the face of noise and low spike numbers. These data analysis methods can also be applied to experimental data which was not originally recorded with PRC determination in mind.

Cross-References

- [Phase Response Curve, Measurement and Shape of General](#)
- [Weak Coupling Theory](#)

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Phase Response Curve, Topology of

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Definition

Phase response curves (PRCs) describe how an oscillator responds to input perturbations given at various times during the oscillator cycle. Phase resetting, and by extension PRCs, can be classified as weak or strong based on a geometric analysis of perturbations to the limit cycle (Glass and Winfree 1984). This geometric classification of

PRCs is distinct from that based on the bifurcation structure of the state space (Rinzel and Ermentrout 1989).

Detailed Description

Introduction

Many types of biological systems exhibit oscillations. In neuroscience, oscillations are evident at a variety of spatial and temporal scales, from the repetitive firing of action potentials (single neuron, milliseconds to seconds) to the circadian rhythms evident in the suprachiasmatic nucleus (thousands of neurons, one day).

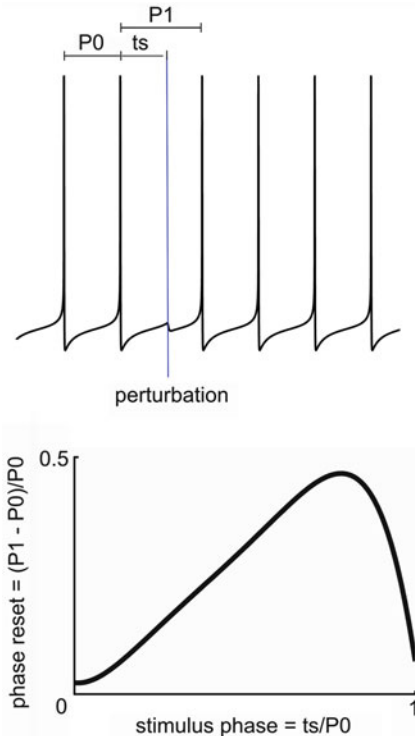
Computational modeling has evolved since the pioneering work of Hodgkin and Huxley, but for many neural systems, sufficient data may not exist to construct a detailed, conductance-based biophysical model. Nor may it be necessary. A key question for many neural systems is how neurons coordinate the timing of their oscillations (e.g., action potentials) to produce a stable pattern. This question is fundamental for a range of systems, ranging from central pattern-generating circuits to the transient synchrony of neural ensembles in higher-level function (Fell and Axmacher 2011).

Limit Cycle Oscillations and Geometric Phase Resetting

How to answer this question? We first assume that the oscillation is a limit cycle – a trajectory through state space that is repeated reliably every cycle. The phase of a limit cycle, defined over an interval of 0–1 or 0– 2π , describes the current state of the oscillator. A common example of this process is the second hand of a clock. The period of the oscillation (1 min) describes how long it takes for one complete traversal of the limit cycle; the phase is mapped to the location the second hand is currently pointing to.

Assuming a limit cycle oscillation, we make a second assumption – perturbations to the oscillation move the state of an oscillator forward (advance) or backward (delay) along the limit cycle. The phase response curve (PRC) is a function that characterizes how the limit cycle is

advanced or delayed as a function of the phase where the input to the oscillator arrived; there are many variants of this assumption that differ in the details, but they all ultimately assume a characterization of the advance or delay of the oscillation. This formulation has the advantage that it can be experimentally measured (or computationally simulated), assuming the component oscillator can be isolated. An example of the phase response curve and how it is measured is shown in Fig. 1. The time between the oscillator spike and the input perturbation is the stimulus interval t_s ; normalized by the unperturbed period, this becomes the stimulus phase. Phase resetting is defined as the difference between the perturbed oscillator cycle and an unperturbed oscillator cycle,



Phase Response Curve, Topology of,
Fig. 1 Measurement of the phase resetting curve. *Top*, a perturbation arrives at some interval t_s within the interspike interval. This normalized by the unperturbed period P_0 is the stimulus phase. The phase resetting is calculated by normalizing the change in period length of the perturbed interval (in this case $P_1 - P_0$, but it can also be calculated $P_0 - P_1$) by the unperturbed period P_0 . The phase resetting curve or phase response curve is plotted below. (Example is from the model of Wang and Buzsaki 1996)

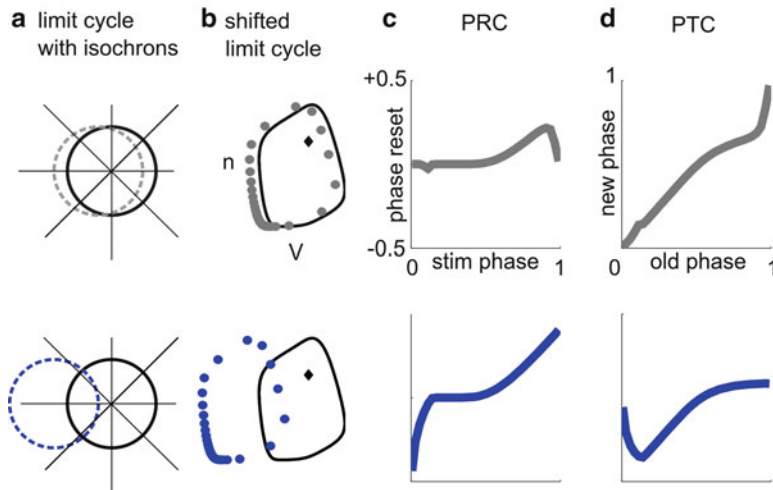
normalized by the unperturbed period. The amount of phase resetting is dependent on when the oscillator cycle the perturbation is received.

In addition to the phase response curve, information about the phase resetting of an oscillator can be presented on the phase transition curve (PTC), which plots the old phase against the new phase (Glass and Winfree 1984, 1988; Winfree 2000). The old phase is equivalent to the stimulus phase of the PRC, and the new phase is the phase after all perturbation effects are accounted for. The phase transition curve is algebraically related to the PRC, where the new phase is defined as the old phase (stimulus phase) plus the phase resetting.

The winding number of a PTC refers to the number of cycles traversed by the new phase as the old phase traverses one complete cycle from 0 to 1 (Glass and Winfree 1984, 1988). PTCs that increase in new phase from 0 to 1 as old phase is increased from 0 to 1 have a winding number of 1 and are called type I curves; PTCs where new phase does not cover a unit circle (traverse all phases on the circle) when old phase is varied from 0 to 1 have a winding number of 0 and are labeled type 0.

The PTC for a type 1 curve traverses all new phases, but the PTC for a type 0 curve does not. To understand why, we follow the reasoning used in Glass and Winfree (1984) and Glass and Mackey (1988): first assume that a limit cycle encircles an unstable fixed point. Intersecting the limit cycle are lines emanating from the unstable fixed point; these isochron lines demarcate points that have the same phase. For clarity, only eight of the possible oscillator isochrons are shown in Fig. 2, column A. Perturbations push the system off the limit cycle (Fig. 2, column B). A weak perturbation to the oscillator pushes the system off the limit cycle slightly. If weak perturbations are applied at various old phases between 0 and 1, we can redraw the limit cycle as the dotted curve in Fig. 2, column A or as the points in column C.

The strength of the applied perturbations affects how far the limit cycles are shifted; weak perturbations shift the limit cycle, but the unstable fixed point in the center remains enclosed by the limit cycle. In the weak perturbation case, the limit cycle can still progress through all the isochrons it did before the perturbations (Fig. 2, column A);



Phase Response Curve, Topology of, Fig. 2 Examples of weak (*top*) and strong (*bottom*) geometric phase resetting. In the limit cycle schematic (column **A**), the lines represent isochrons, the black trace is the unperturbed limit cycle, and the *dotted curves* represent the shifted limit cycle; the fixed point in the center of the limit cycle is still enclosed by the shifted limit cycle in the weak case but not in the strong case. Column **B** shows the unperturbed (black) and shifted (gray or blue) limit cycle in phase space, represented here as the potassium activation variable n versus membrane voltage V . Shifted limit cycles are calculated by finding n and V of the perturbed limit cycle shortly after perturbation onset. Notice that the weakly shifted limit cycle encloses the fixed point (represented

by a *black diamond*), while the strongly perturbed limit cycle does not. Column **C** illustrates the phase resetting curve in each case, where stimulus phase and phase resetting are defined as in Fig. 1. Column **D** shows the phase transition curve for each case; old phase is equivalent to PRC stimulus phase and new phase is old phase minus the phase resetting (because we have defined our phase reset as $(P1 - P0)/P0$). The model used to generate columns **B** through **D** is the $I_{NaP} + I_K$ model from Izhikevich (2007); parameters are identical to those used in Fig. 4.30 (p. 114). Perturbations to measure the PRC were instantaneous voltage shifts of -10 mV (*top*) and -60 mV (*bottom*)

since the limit cycle can traverse all these phases, the PTC is a continuous function that maps old phases (stimulus phases) to new phases of similar value (Fig. 2, column E). Strong perturbations shift the oscillator limit cycle so far that the unstable fixed point is no longer inside the limit cycle; this makes it impossible for the oscillator to traverse all the phases that were accessible before the strong perturbation. The oscillator new phases are restricted to a subset of the previous old phases. Therefore, the PTC new phases only span a subset of the 0–1 range. To our knowledge, Demir et al. 1997 is the only published example with figures that illustrate the shifted limit cycle (set of new phases) of a perturbed model neuron.

Biological oscillators can show both type 0 and type 1 phase resetting. The transitions between type 1 and type 0 phase resetting, however, are difficult to observe experimentally (Krogh-Madsen et al. 2012). Spiking neurons tend to exhibit type 1 phase resetting (Netoff et al. 2005; Preyer and

Butera 2005; Schultheiss et al. 2010; Wang et al. 2013), but type 0 resetting is possible (Perkel et al. 1964; also see the list in Winfree 2000, p. 116, for type 0 resetting in physiological systems). Bursting neurons can show type 1 phase resetting with very weak inputs, but tend to show type 0 phase resetting (Prinz et al. 2003; Sieling et al. 2009).

Phase Resetting Theory in Computational Neuroscience

The application of PRCs in computational neuroscience is most often to infer synchrony among a population of neurons. With such approaches, either weak coupling or pulsatile coupling is typically assumed. A fundamental assumption underlying weak coupling is that perturbations to the limit cycle are sufficiently small (Ermentrout and Kopell 1984) and that increased perturbation size increases the PRC linearly (Schwemmer and Lewis 2012). The pulsatile coupling framework makes no restrictions on the size of the

perturbation as long as the oscillator returns to its limit cycle by the time the next input is received (Oprisan et al. 2004; Canavier and Achuthan 2010). The weak coupling assumptions, and the definition of weak, are fundamentally distinct from the geometrical terms defined by Winfree. We refer to the notions of weak and strong here as *mathematically weak* (or strong) and those by Winfree as *geometrically weak* (or strong).

In networks with weak coupling, the assumption that oscillator perturbations be suitably small means the phase resetting is mathematically weak. Systems with mathematically weak phase resetting show geometrically weak type 1 phase resetting. In contrast, systems with geometrically strong type 0 phase resetting will not show mathematically weak phase resetting. Geometrically weak type 1 phase resetting can be either mathematically strong or weak.

The geometric classification of type 1 or type 0 phase resetting is also distinct from the type I or type II phase resetting classifications common in the computational neuroscience literature (Rinzel and Ermentrout 1989). There is little to no correlation between the two classification schemes. This classification is based on the relationships between applied current and steady-state spike frequency (Hodgkin 1948), which are also related to the bifurcation associated with the modeled fixed point (Rinzel and Ermentrout 1989).

Discussion

Geometric phase resetting provides an effective classification scheme for neural systems. The geometric method is similar to the pulsatile coupling regime (Krogh-Madsen et al. 2012); such resetting is easily realizable experimentally but pulsatile coupling assumptions require that the same types of inputs present in the coupled system must be used to measure the PRC if the PRC is to have any predictive power. Geometric phase resetting classification is applicable over a wider range of inputs than is phase resetting based on weakly coupled oscillators; in turn, coupled system phase predictions using weak coupling theory can be independent of input type, provided those

inputs are small (Krogh-Madsen et al. 2012). Geometric and mathematical resetting are therefore complementary approaches to understand patterned activity in neural systems.

Cross-References

- [Bifurcations Dynamics of Single Neurons and Small Networks](#)
- [Pulse-Coupled Oscillators](#)
- [Weak Coupling Theory](#)

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Phase Synchrony

► Phase-Locking Methods

Phase Transitions, Neural Population Models and

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Definition

A neural population model pictures the cortex as a continuum of excitable tissue comprised of

densely interconnected excitatory and inhibitory neurons, with cortical activity encoded as population-average firing rates. For certain ranges of cortical parameters, such models can exhibit multistability, with access to multiple equilibrium (homogeneous and stationary) and non-equilibrium (patterned or dynamic) spatiotemporal states. These distinct states may be identified with particular phases of normal and pathological brain activity such as wakefulness, anesthetic coma, and seizure. Transitions between states can be induced by variations in a control parameter such as neurotransmitter concentration and subcortical stimulation and can be likened to the thermodynamic phase transitions (e.g., melting, freezing) of physical science.

Detailed Description

Equilibrium Phase Transitions

The underlying mechanisms of commonly observed thermodynamic phase transitions – such as water freezing and ice melting – can be explained using the theory of equilibrium statistical mechanics developed in the late nineteenth and early twentieth centuries. State variables, such as pressure, temperature, and specific volume (inverse density), are linked by an equation of state that maps out a distribution or manifold of equilibrium coordinates as illustrated in Fig. 1. Each point on the manifold corresponds to local minimum of free energy and so acts as an “attractor” for the system. The different regions correspond to the different phases (gas, liquid, solid). Phase transitions occur when temperature and pressure are changed sufficiently to force the system to move from one equilibrium phase to another.

Such equilibrium phase transitions are known to exhibit universal properties – such as power law divergences in length and timescales – at the critical point. These divergences arise from markedly increased sensitivity to perturbations that manifests as large, slow spatial and temporal fluctuations in an order parameter (such as density), a phenomenon referred to as critical slowing down.

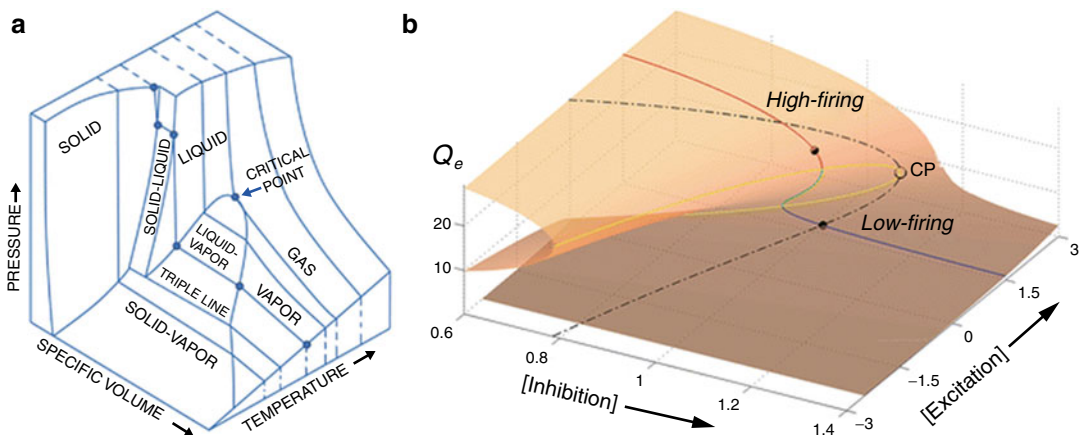
In the brain, the transition from normal wake to deep sleep – either natural or anesthetic drug induced – can be regarded as a phase transition between distinct brain states. In both cases, there is a surge in low-frequency cortical activity as the point of transition is closely approached, suggesting onset of critical behavior. For the anesthetic transition, this unexpected and paradoxical transient boost in EEG power at (or near) the moment of loss of consciousness is known as the drug biphasic effect (Kuizenga et al. 2001).

The anesthetodynamic phase transition was first modeled by Steyn-Ross et al. (1999) using a continuum of excitable tissue containing populations of densely interlinked excitatory and inhibitory neurons (see Encyclopedia entry ► “Anesthesia, Neural Population Models of” for further details). Anesthetic effect is modeled as a strengthened hyperpolarizing drive from inhibitory synapses, with the hyperpolarizing influence increasing with drug concentration. This model predicts that the manifold of equilibrium states can contain a reentrant fold (see Fig. 1b) in which the upper (high-firing) and lower (low-firing) stable nodes are separated by

an unstable mid-branch saddle. A drug-induced trajectory along the upper branch will eventually collapse to the lower branch, and this downward jump is supposed to represent the transition into anesthetic unconsciousness. Close to transition, surges in low-frequency EEG power are interpreted as a form of critical slowing arising from close approach to the saddle-node annihilation point.

Nonequilibrium Phase Transitions

The transition between two stable phases of brain activity (e.g., from wake to drug-induced sleep during anesthetic loss of consciousness) is characterized as an *equilibrium phase transition* if the cortical state changes from one spatially uniform stationary state on the equilibrium manifold to another. Alternatively, the cortex may undergo a *nonequilibrium phase transition* in which the system breaks the symmetry of the homogeneous stationary state by spontaneously evolving to a qualitatively different kind of state that is oscillatory in time or patterned in space. The formalism describing these kinds of symmetry-breaking transitions was developed by the Brussels group



Phase Transitions, Neural Population Models and, Fig. 1 Comparison between the manifold of equilibrium states of matter for a pure substance (*left*) and the equilibrium states of activity for a homogeneous cortical model (*right*). If gas and liquid states of the substance are equivalent to high- and low-firing states of the cortex, then thermodynamic pressure, temperature, and specific volume are roughly analogous to inhibitory drive, excitatory drive, and cortical firing rate (Q_e), respectively. At the

critical point in (a), gas and liquid become indistinguishable. CP marks the corresponding coordinate in (b) at which high- and low-firing states of the cortex merge continuously. At lower values of cortical excitation, the folded region allows the cortex to access multiple steady states (a modified from http://en.wikipedia.org/wiki/File:PVT_3D_diagram.png under Creative Commons license; b modified from Steyn-Ross et al. (2013) with permission of the authors)

led by Nicolis and Prigogine (1977) with their work on reaction–diffusion chemical systems such as the Brusselator, demonstrating emergence of temporal oscillations (Hopf bifurcation) and spontaneous pattern formation (Turing bifurcation).

Many cortical researchers have investigated nonequilibrium phase transitions and self-organization in neural population models. In addition to equilibrium transitions to fixed-point attractors, Wilson and Cowan (1972, 1973) also described far-from-equilibrium behaviors such as the emergence of limit cycles, traveling waves, and Turing structures. Ermentrout and Cowan (1979a, b) extended the continuum approach to include the rise and fall times of dendrite dynamics and the effect of spatially distributed (exponential and Gaussian) synaptic connections; they established connectivity conditions under which a homogeneous equilibrium state would destabilize in favor of spatially inhomogeneous oscillations (i.e., oscillating Turing patterns). In an extensive review, Ermentrout (1998) examined a wide range of nonequilibrium spatiotemporal behaviors that could be generated by a continuum model of the cortex, including global oscillations, wave fronts joining an excited state to a resting state, traveling and stationary pulses, traveling waves, and stationary Turing patterns. The Turing solution required a Mexican-hat connectivity with local excitation – to stabilize a narrow pulse of neural activity – and lateral (nonlocal) inhibition to prevent the excitatory activity from spreading.

Temporal Rhythms via Hopf Bifurcation

The emergence of specific cortical rhythms – such as the delta (≤ 4 Hz), alpha (8–12 Hz), and gamma (25–100 Hz) oscillations of human EEG – is commonly modeled as a Hopf instability that destabilizes the equilibrium state when a control parameter is varied. In their continuum model of electrical activity in the cerebral cortex, Rennie et al. (2000) showed that a weakly damped gamma resonance can become less damped (i.e., moves closer to resonance) as subcortical excitation is increased and that the gamma

damping is particularly sensitive to dendritic decay rates at inhibitory synapses.

Bojak and Liley (2005) argue that the alpha rhythm is a ubiquitous feature of human resting EEG, so they looked for evidence of a damped alpha resonance in order to tune the parameter settings for their continuum model; effectively, such tuning places the cortex close to a Hopf bifurcation in the alpha-frequency range.

Breakspear et al. (2005) investigated the emergence of absence seizure EEG patterns in a continuum thalamocortical model (due to Robinson et al. 2002) by varying the strength of the excitatory connection between cortex and thalamus. For a sufficiently strong coupling, the model exhibited a supercritical Hopf bifurcation to large-amplitude periodic dynamics of frequency ~ 3 Hz. Similar low-frequency seizure-like oscillations via Hopf bifurcation have been demonstrated by several other workers with purely cortical models that lack thalamic circuitry (Kramer et al. 2005; Liley and Bojak 2005; Wilson et al. 2006).

Spatial Patterns via Gap-Junction-Mediated Turing Bifurcation

In reaction–diffusion chemical systems, it is well known that the homogeneous equilibrium state can destabilize in favor of a spatially periodic patterned structures if the inhibiting agent diffuses more rapidly than the activator (Turing 1952). For the cortex, this corresponds to having long-range inhibition together with local excitation. Traditionally, this is arranged with a suitably shaped connectivity kernel describing the extent and strength of axonal connections between excitatory and inhibitory neural populations (Wilson and Cowan 1972), the implicit assumption being that neurons communicate exclusively via spikes acting at chemical synapses. However, it is evident that adjoining neurons can also communicate directly via diffusive electrical synapses (gap junctions), and these are ubiquitous throughout the central nervous system (Bennett and Zukin 2004). Since layer 1 of the cortex is predominantly (over 90%) comprised of inhibitory

neurons (Wozny and Williams 2011), conditions for Turing self-organization via strong long-range diffusive inhibition may be satisfied.

Steyn-Ross et al. (2007) introduced gap-junction diffusion into a continuum model of the cortex and established conditions for the emergence of stationary Turing patterns. In recent work, Steyn-Ross et al. (2013) investigated the interaction between a ~ 3 -Hz Hopf instability – brought on by anesthetic prolongation of the inhibitory chemical synaptic response – and the Turing spatial instability and found that the anesthetic coma state was characterized by a slow-wave oscillation that was chaotic in space and time. They postulated that a similar Turing–Hopf mechanism might underpin the slow oscillation of natural sleep.

Cross-References

- Anesthesia, Neural Population Models of
- Bifurcation Analysis
- Bifurcations Dynamics of Single Neurons and Small Networks
- Bifurcations, Neural Population Models and
- Chaos, Neural Population Models and
- Epilepsy, Neural Population Models of
- Gamma Rhythm, Neural Population Models of the
- Pattern Formation in Neural Population Models
- Sleep, Neural Population Models of

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Phase-Amplitude Coupling

► [Theta-Gamma](#) [Cross-Frequency](#) [Analyses](#)
([Hippocampus](#))

Phase-Frequency Coupling

► [Theta-Gamma](#) [Cross-Frequency](#) [Analyses](#)
([Hippocampus](#))

Phase-Locking

► [Somatosensory Neurons: Spike-Timing](#)

Phase-Locking Methods

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Synonyms

[Phase correlation](#); [Phase synchrony](#); [Timulus locking](#)

Definition

Phase locking is a fundamental property of dynamical systems and implies an interaction between processes or system components and their state dynamics. Phase locking is statistically indicated by a nonrandom phase or phase difference distribution. Phase is a quantitative description of the state of a given process/component of the system and its temporal evolution. As such, phase is directly meaningful and comparable between different levels of study, and there it

differs, e.g., from signal amplitude of which the physiological meaning is dependent on experimental conditions. In computational neuroscience, phase is typically extracted from time series of neuronal activity. Phase locking can be estimated between two or more such time series and is then termed phase synchrony or phase correlation or between one time series and events such as sensory stimuli and is then termed stimulus locking. Finally, phase-locking methods can also be adapted to assess phase-amplitude and amplitude-amplitude coupling.

Detailed Description

Estimation of Phase

To explicitly represent frequency-band-limited phase and amplitude dynamics, most real-valued continuous signals can be transformed by filtering to a complex form. A popular choice is to convolve the signal with a complex wavelet, such as the Gabor or Morlet wavelet (Sinkkonen et al. 1995; Tallon-Baudry et al. 1996). In applications where the filter yields real-valued output, the complex form can be obtained by finding the imaginary part with the Hilbert transform. For segments of stationary signals, the phase estimation can be achieved with spectral measures as well, such as with the Fourier transform. These three approaches are formally equivalent (Bruns 2004) although spectral methods yield constant-sized frequency bins, while wavelets can be scaled with frequency to give a constant time-frequency resolution.

Let us denote the filtering operation with a center frequency f generically with the operator T_f so that the filtered signal $x(t, f)$ is obtained from the original signal $x_o(t)$ by

$$\begin{aligned} x(t, f) &= T_f[x_o(t)] \\ &= a_x(t, f) e[i\theta_x(t, f)], \end{aligned} \quad (1)$$

where i is the imaginary unit and $a_x(t, f)$ denotes the amplitude and $\theta_x(t, f)$ the phase of $x(t, f)$ (Fig. 1a). An array of such time series will be denoted by $X(t, f) = [x_f(t, f)] = A_x(t, f) e[i\Theta_x(t, f)]$, where

$j = 1 \dots n_s$ and n_s is the number of sensors or sources. Comparable phase time series can also be produced from point process time series (Rosenblum et al. 2004).

Definition of Phase Difference

With the phase estimates, one can either proceed directly to phase-locking estimation when the aim is to study phase locking of neuronal activity to specific event or further evaluate *phase differences* to examine interactions between time series.

The generic $n:m$ -phase difference ω_{nm} of signals x and y (Tass et al. 1998) is given by

$$\omega_{n,m} = n\theta_x - m\theta_y, \quad (2)$$

where the small integers n and m determine the frequency ratio $nf_x = mf_y$ of filters $\mathbf{T}_{f_x}$ and $\mathbf{T}_{f_y}$. For assessing the classical within-frequency phase synchrony, $n = m = 1$. Hence, for frequencies of a single sample of each signal against each other's signal is given by f_x and f_y , the $n_s \times n_s$ -sized pairwise phase difference matrix $\Phi_{n:m}$ the complex outer product, $\otimes$, so that

$$\Phi_{n,m}(t, , f_x, f_y) = (X/|X|)^n \otimes (Y/|Y|)^{*m}, \quad (3)$$

where the asterisk $*$ denotes the complex conjugate.

The phase difference can also be used to represent more complex state relationships such as amplitude-phase interactions, “nested oscillations” that are characterized by the phase locking of the amplitude envelope of a faster oscillation with the phase of a slower oscillation. The phase difference matrix, Φ_{AP} for nested oscillations is given by filtering the amplitude envelopes A_x of the faster oscillation at f_x with the filter $\mathbf{T}_{f_y}$ that was used to obtain the slower oscillation at $f_y < f_x$ (Vanhatalo et al. 2004).

$$\Phi_{AP} = [\mathbf{T}_{f_y}(A_x)/|\mathbf{T}_{f_y}(A_x)|] \otimes (Y/|Y|)^*. \quad (4)$$

It is important to note that this quantification of the nonuniformity of Φ_{AP} with a phase-locking value (see below) assumes a unimodal distribution of the fast oscillation amplitudes along the

slow oscillation phase. An interaction in which the amplitude of the fast oscillation peaks twice, or more formally m times during the slow cycle, can be explicitly assessed as a $1:m$ -amplitude-phase interaction. Here the amplitude envelopes A_x are filtered with a filter $\mathbf{T}_{mf_y}$ at frequency mf_y , and then the corresponding metric, Φ_{AmP} is given simply by

$$\Phi_{AmP} = [\mathbf{T}_{2f_y}(A_x)/|\mathbf{T}_{2f_y}(A_x)|] \otimes (Y/|Y|)^{*m}. \quad (5)$$

Φ_{AmP} is quantifiable with the phase-locking value. Alternatively, $1:m$ -amplitude-phase coupling can be implicitly assessed with Φ_{AP} and a histogram-based statistic (see below).

Characterization of amplitude dynamics with phase differences and circular statistics can be further extended also to amplitude-amplitude interactions by filtering the amplitude envelopes A_x and A_y to a slower frequency band $f_z < f_x, f_y$ with $\mathbf{T}_{f_z}$. Now the phase difference matrix, Φ_{AA} , is

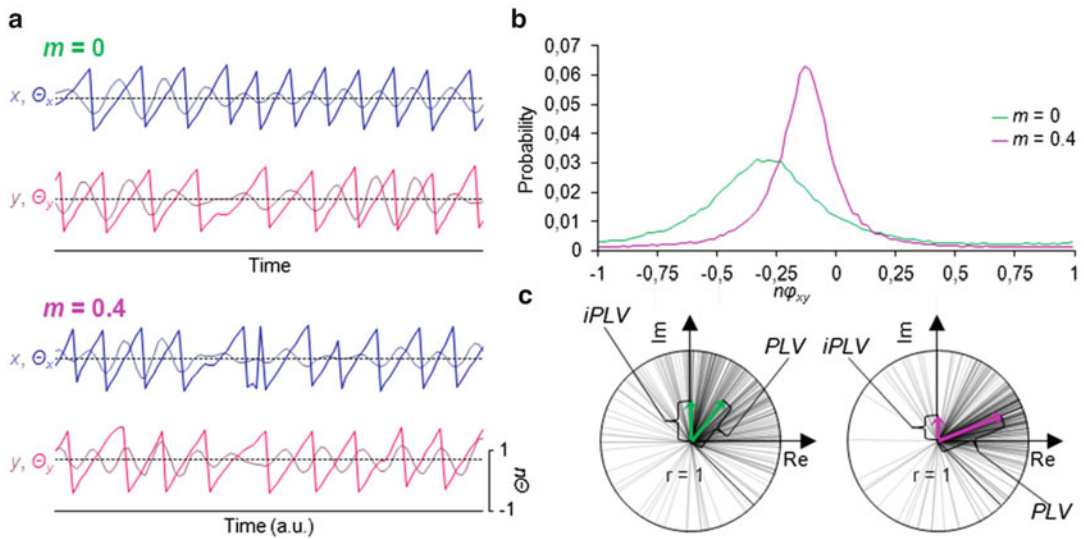
$$\Phi_{AA} = [\mathbf{T}_{f_z}(A_x)/|\mathbf{T}_{f_z}(A_x)|] \otimes [\mathbf{T}_{f_z}(A_y)/|\mathbf{T}_{f_z}(A_y)|]^*. \quad (6)$$

The advantage of characterizing amplitude interactions with phase estimators is that their phase dynamics are independent of variability in the absolute amplitudes, and hence large amplitude events do not exert a strong bias like they do in cross-correlation analyses, for example.

Quantification of Phase Locking: The Phase-Locking Value and Alternative Measures

With the phase or phase difference data, the presence of statistically significant phase locking can be assessed with a number of circular statistics. The most common of them is the phase-locking value/factor (PLV, PLF) that is given by means of the complex phases (Jervis et al. 1983; Sinkkonen et al. 1995).

$$\text{PLV} = n_t^{-1} \left| \sum \Phi \right|. \quad (7)$$



Phase-Locking Methods, Fig. 1 PLV and imaginary PLV (iPLV) measure the strength of phase correlation but are biased by linear signal mixing. (a) Real parts ($x(t)$ and $y(t)$) and phases ($\Theta_x(t)$ and $\Theta_y(t)$) of two-phase coupled signals in the absence ($m = 0$) and presence ($m = 0.4$) of linear mixing where $x_{\text{mixed}} = x + my$ and $y_{\text{mixed}} = y + mx$. Linear mixing biases the phase difference between the

signals toward zero. (b) Phase difference distribution between signals $x(t)$ and $y(t)$ in the absence ($m = 0$) and presence ($m = 0.4$) of linear mixing. The phase difference of the simulated coupling between the signals was -0.3π . (c) PLV and iPLV defined graphically as the absolute value and imaginary part, respectively, of the mean of complex phase values on the unit circle

where n_t is the number of Φ samples pooled across trials and/or time (Fig. 1b, c). PLV is 1 for perfect coupling (delta-function phase distribution) and approaches 0 for a uniform phase distribution when $n_t \rightarrow \infty$. If the Φ samples are independent and the marginal phase distributions are uniform, the no-interaction null hypothesis is characterized by uniformly distributed Φ and can be tested with the Rayleigh test. When Φ are pooled across time, i.e., when the independence condition is not met because of redundancy and/or when the underlying process is not sinusoidal (see Nikulin et al. 2007), surrogate data are needed for statistical testing.

Five characteristics of PLV warrant attention. First, PLV is biased, i.e., positively dependent on the number of samples (Vinck et al. 2010; Aydore et al. 2013). Hence, if two conditions are to be compared, the number of samples must be equalized. Alternatively, a similar but unbiased metric, pairwise-phase consistency (Vinck et al. 2010; see also squared PLV in Aydore et al. 2013) can be used, but its computational cost scales with $n_s^2 n_t^2$, whereas the cost of PLV is proportional only to $n_s^2 n_t$.

Second, PLV is appropriate only for unimodal phase distributions. The nonuniformity of arbitrary distributions can be estimated with Shannon entropy and conditional probability-based indices for phase (difference) histograms (Tass et al. 1998).

Third, 1:1-phase (and also amplitude) correlations estimated with PLV are influenced by linear mixing such as volume conduction in electrophysiological recordings, which leads to inflated numbers of false-positive observations (see Fig. 1b, c). This problem can be partially solved by noting that linear mixing always has a zero-phase-lag influence, which is fully captured by the real part of PLV or that of coherence, and that true neuronal interactions may often involve a conduction-delay-related phase lag. Measures such as imaginary coherence (Nolte et al. 2004), the imaginary part of PLV, and weighted phase-lag index (Vinck et al. 2011) ignore the real part of the complex phase differences. These measures are hence insensitive to linear mixing while revealing the phase-lagged interactions. The disadvantages of these approaches include insensitivity to true near-zero-phase-lag interactions and the

dependence of the measure value on the phase difference per se in addition to the strength of the interaction.

Fourth, PLV is a measure of correlation and does not disclose causal relationships or the lack thereof between the signals. Directional phase interactions can be estimated with histogram-based phase transfer entropy without sample-size or linear mixing bias (Lobier et al. 2014).

Fifth, PLV among all other interaction metrics is crucially dependent on the signal-to-noise ratio of the phase estimate. Hence, albeit phase is mathematically independent of amplitude, the accuracy of phase estimates in noisy signals with variable amplitudes will be dynamically dependent on the amplitude. When making inferences about differences in phase locking, one needs to consider the putative contribution of concurrent differences in signal-to-noise ratio (Palva et al. 2010).

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Phase-Phase Coupling

► [Theta-Gamma Cross-Frequency Analyses \(Hippocampus\)](#)

Phototransduction Biophysics

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Synonyms

[Biophysical mechanisms that photoreceptors use to sample light information](#); [Phototransduction cascade](#); [Phototransduction mechanisms](#)

Definition

Phototransduction biophysics comprises intracellular molecular reactions and ion fluxes through ion channels on the photoreceptor membrane that converts light into an electrical signal. Phototransduction biophysics serves the purpose of counting photons and integrating these counts to an estimate – a macroscopic voltage response – of light changes from a small area of visual space. To do this task well in vastly varying light conditions, photoreceptors rely upon stochastic adaptive sampling of light information.

Detailed Description

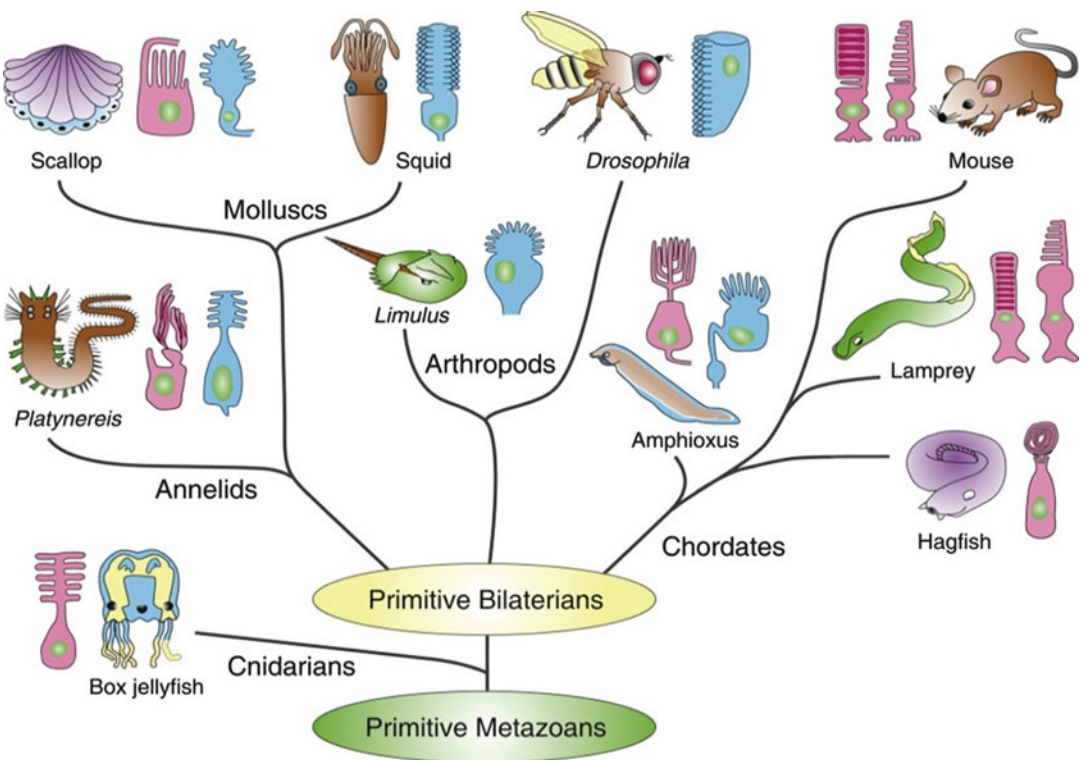
Basic Structure of Photoreceptor Cells

Photoreceptor cells of most animals are highly polarized, consisting of light-sensitive and light-insensitive parts (Fig. 1). The light-sensitive part

is derived either from cilia or microvilli (Fain et al. 2010), forming a specialized light guide, such as the vertebrate rod/cone outer segment or fly photoreceptor rhabdomere, which facilitates directional photon capture along its longitudinal axis. Membrane elaborations – discs in rods or microvilli in fly photoreceptors – are enriched with the visual pigment protein rhodopsin. This absorbs light and activates a G-protein-based transduction cascade, bringing about the opening or closing of ion channels. Conversely, a photoreceptor's light-insensitive parts, which in vertebrate rods/cones form the inner segment, contain the cell body, axon, and synaptic machinery to transmit the resulting electrical signals to the retina network.

Microvilli Are Sampling Units

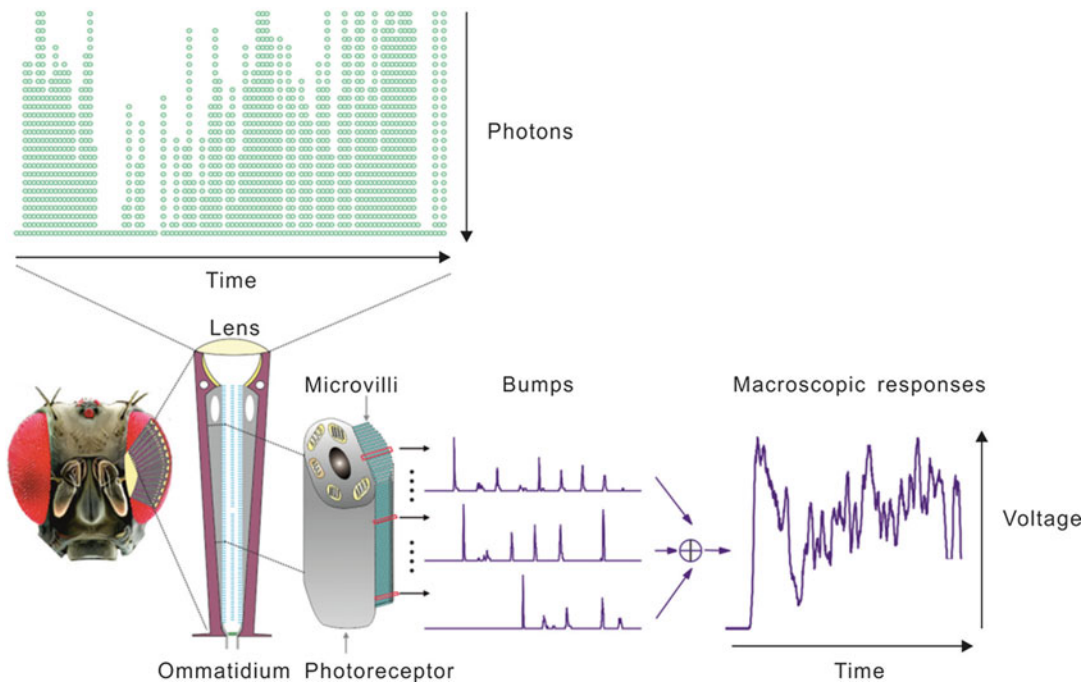
In a photoreceptor of the fruit fly (*Drosophila melanogaster*), each of its ~30,000 microvilli



Current Biology

Phototransduction Biophysics, Fig. 1 Phototransduction biophysics. Ciliary and microvillar photoreceptors. Photoreceptor types in principal eyes illustrated as

ciliary (red) or microvillar (blue). Mammals and other vertebrates have ciliary photoreceptors (rods and cones). (From Fain et al. (2010))



Phototransduction Biophysics, Fig. 2 Phototransduction biophysics, *Stochastic adaptive sampling in a Drosophila photoreceptor*. Photons are sampled by a population of 30,000 microvilli, stacked layer by layer on one side of the photoreceptor soma, forming the light-guiding

rhabdomere. In the microvilli, the rate, size, and speed of their photon-evoked elementary responses (bumps or samples) vary stochastically yet adapt continuously, integrating to a consistent (anti-aliased) macroscopic response

can be considered to be a photon counting or sampling unit (Fig. 2). Within a microvillus, following absorption of one photon by a single rhodopsin molecule, the phototransduction cascade culminates in the opening of ~ 15 TRP/TRPL channels (transient receptor potential and TRP-like channels; Hardie and Postma 2008). The resulting influx of calcium, magnesium, and sodium ions generates a quantum bump (sample). Although the exact mechanism of how TRP/TRPL channels are gated is still unclear, most aspects of microvillar phototransduction are known in sufficient detail (Hardie and Postma 2008; Hardie 2012; Hardie and Franze 2012) to allow the construction of molecularly explicit, stochastically operating computational models that accurately simulate the encoding of visual information (Song et al. 2012). The close correspondence between intracellular recordings and model simulations further suggests that vision benefits from stochasticity in phototransduction

biophysics, with variable samples of microvilli summing up largely invariable responses to natural light patterns at different conditions (Faivre and Juusola 2008; Song et al. 2012).

Basic Rules of How a Photoreceptor Samples Light Information

A *Drosophila* photoreceptor is an imperfect photon counter that, nonetheless, produces highly reproducible macroscopic responses. Its responses to light stimuli can be largely predicted by these basic counting rules:

- A single microvillus (sampling unit) can produce only one bump (sample) at a time (Howard et al. 1987; Hochstrate and Hamdorf 1990; Pumir et al. 2008; Song et al. 2012).
- After producing a bump, a microvillus remains refractory (unavailable to sample) for up to

hundreds of milliseconds; during this period, it fails to respond to other photons (Hochstrate and Hamdorf 1990; Scott et al. 1997; Mishra et al. 2007; Liu et al. 2008).

- Bumps from up to 30,000 microvilli integrate to yield the macroscopic response.
- Microvilli availability sets a photoreceptor's maximum sample rate (bump production rate), adapting its macroscopic response to a light stimulus (Howard et al. 1987).
- Global calcium accumulation and membrane voltage affect samples of all microvilli. These global feedbacks strengthen with brightening light to reduce the size and duration of bumps, adapting the macroscopic response (Wong and Knight 1980; Wong et al. 1982; Juusola and Hardie 2001b).

Phototransduction Reactions: From Photon Absorption to a Bump

Phototransduction in *Drosophila* is a canonical G-protein-coupled phospholipase C-based cascade (Hardie and Postma 2008; Yau and Hardie 2009; Hardie 2012). Essential elements of the cascade including the channels are localized within a microvillus (Fig. 3), which together with its ~30,000 neighbors form the light-guiding rhabdomere.

As in all photoreceptors, the cascade is initiated by absorption of a photon by a chromophore (3-OH 11-*cis* retinaldehyde) covalently attached to rhodopsin (R). Photoisomerization of the 11-*cis* retinal to the all-trans configuration by a single photon converts R to the active metarhodopsin state (M), which catalytically activates a heterotrimeric Gq-protein releasing the active Gq α subunit. About 5–10 Gq α subunits are released by each activated M within the same microvillus during the brief but variable latency period, and diffuse in the plane of the membrane before binding to and activating a phospholipase C (PLC) molecule. Each of the 5–10 PLC molecules (Fig. 3) thus activated and then hydrolyzes the minor membrane phospholipid, PIP₂, at a rate of ~1000 molecules per second, causing a physical contraction of the

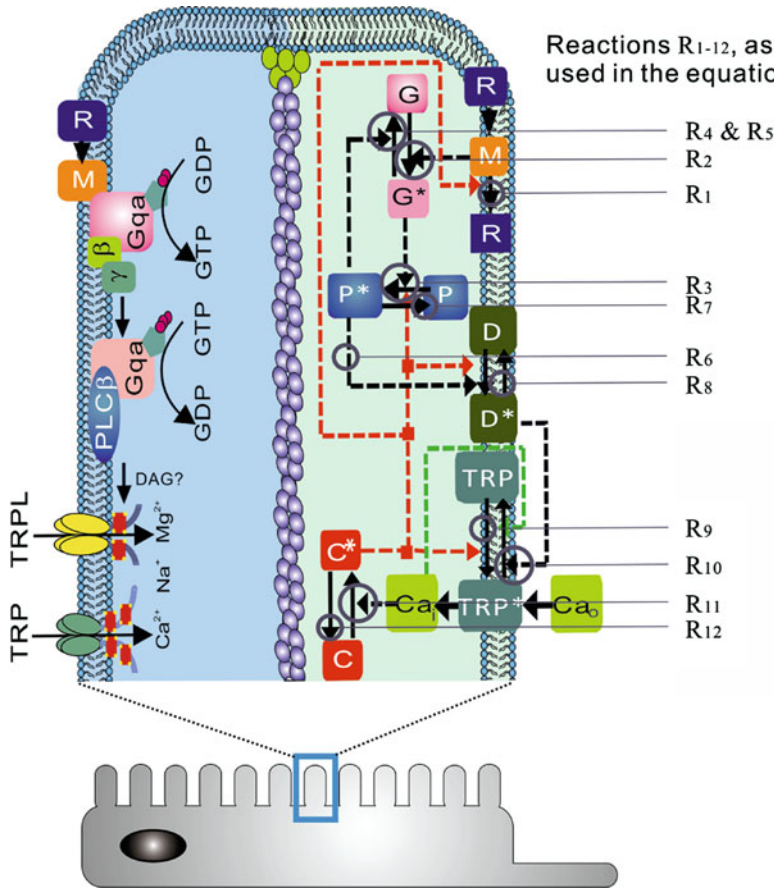
microvillar membrane as well as yielding inositol triphosphate (InsP₃), diacyl glycerol (DAG), and a proton.

Although still debated, the most recent evidence suggests that it is the combination of membrane contraction and proton release that then results in the gating of the Ca²⁺ permeable TRP (and TRPL) light-sensitive channels (Huang et al. 2010; Hardie and Franze 2012). Powerful positive feedback mediated by Ca²⁺ influx via the first activated TRP channel rapidly facilitates activation of the remaining channels in the microvillus. This floods the microvillus with up to ~1 mM Ca²⁺, rapidly terminating the response by Ca²⁺-dependent negative feedback at multiple targets including the channels themselves. The final electrical response to a single effectively absorbed photon is a ~10 pA quantum bump (Fig. 4a), representing the opening of most of the ~20 TRP channels in a single microvillus.

The macroscopic light-induced current (LIC) represents the summation of the quantum bumps of variable sizes (Fig. 4b) and timings (Fig. 4c), independently generated over the 30,000 microvilli.

Why Some Absorbed Photons Fail to Be Counted?

In a microvillus, the likelihood, size, and timing of a new bump depend upon the success, stochasticity, and finite speed of phototransduction reactions, all partly affected by the history of past bumps in the same microvillus and global Ca²⁺ levels integrated from bumps across the whole cell (Fig. 4a). In darkness, virtually every absorbed photon causes a bump (nearly 100% quantum efficiency), but with brightening illumination, the quantum efficiency of a microvillus decreases. Rarely, the cascade molecules may fail to activate their upstream targets and the signal dies. More often, the reactions stop prematurely because the photons arrived before the refractory period (50–200 ms) of the last bump had faded. Here, intra-microvillar calcium provides sequential positive and negative feedbacks to multiple targets, amplifying the signal



Phototransduction Biophysics, Fig. 3 Phototransduction Biophysics, Each microvillus contains a full transduction cascade, which generates variable bumps or failures to absorbed photons. Left side: molecular participants in microvillar phototransduction reactions. *M** meta-rhodopsin, *C** Ca^{2+} -dependent feedback, which acts as negative feedback to multiple targets, *D** DAG, *P** G-protein-PLC complex. Right side: the corresponding

reactions, R₁–R₁₂ (indicated by black arrows), as used in the stochastic model (see Eqs. below) and in Fig. 4a. Red dotted arrows indicate negative feedbacks; green dotted line, positive feedbacks. In this schematic, DAG? stands for the yet unresolved gating mechanism that includes production of DAG, InsP₃, proton, and physical microvilli contraction (Adapted from Song et al. (2012))

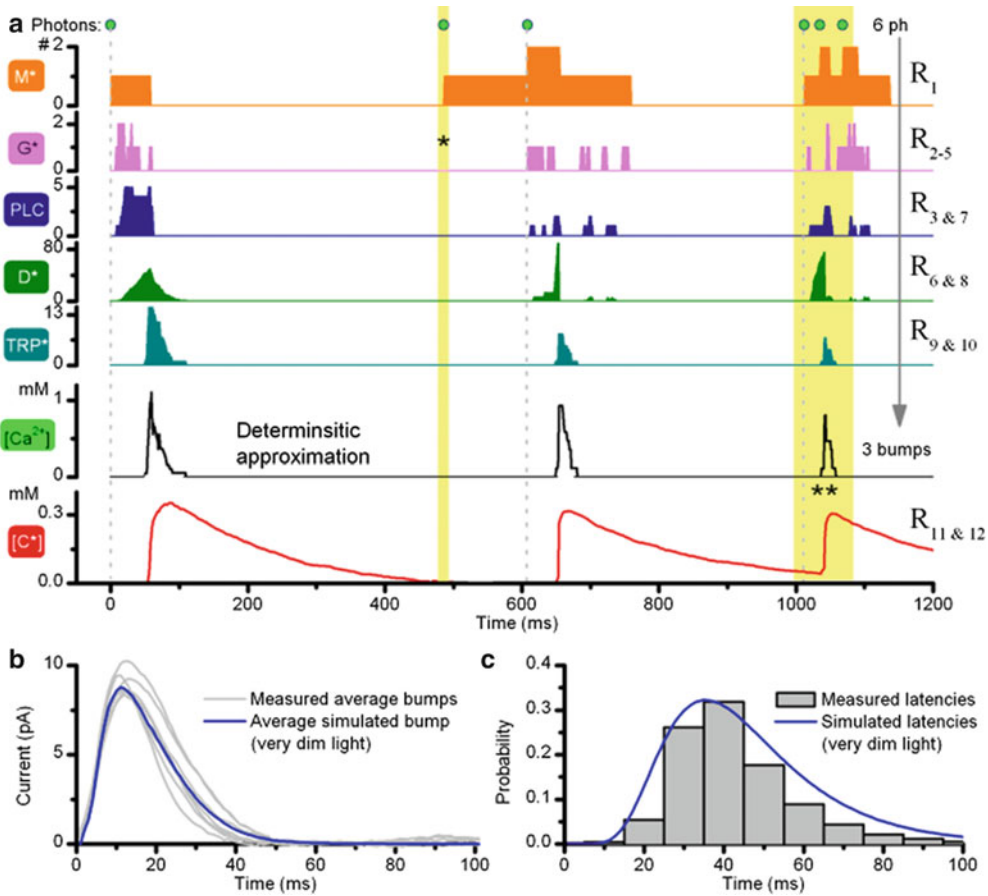
and accelerating response speed (Hardie and Postma 2008).

Biophysical models (Pumir et al. 2008; Song et al. 2012) indicate that as soon as a bump is generated, the negative feedback holds the microvillus in a state of inhibition during which it cannot respond to light. This refractory period represents a balance between the positive and negative feedbacks. It ends when the positive feedbacks outgrow the relaxing negative feedbacks and ultimately set the maximum sample

rate (bump production rate) of the microvillus (Hochstrate and Hamdorf 1990; Scott et al. 1997; Mishra et al. 2007; Liu et al. 2008).

How Changes in Sampling Result in Adapting Macroscopic Responses?

Adaptation in macroscopic response (Fig. 5a) to continuous light is mostly caused by reduction in the (i) number and (ii) size of samples over time.

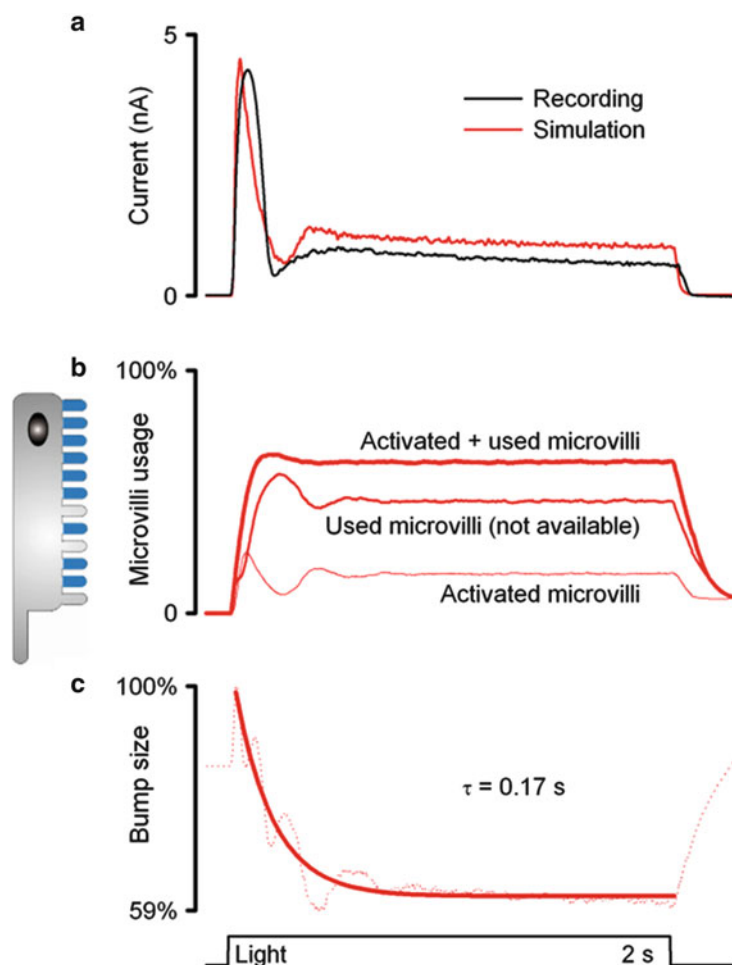


Phototransduction Biophysics, Fig. 4 Phototransduction Biophysics, *Reactions inside a microvillus are modeled in a stochastic framework, with known molecular interactions, using physiologically measured parameters.* (a) Simulations show how a microvillus generates elementary responses (bumps) to captured photons; after a “dead time,” 5–15 TRP channels open, mediating Ca^{2+} and Na^+ influx into the microvillus. Ca^{2+} -dependent feedback (red) provides negative feedback, which prevents new bumps until the feedback is low. * = G^* activation failed;

** = negative feedback blocked two photon activations. $[C^*]$; decay phase is longer than the real refractory period, which represents a balance between the feedbacks; the positive feedback can outgrow the negative one in the middle of $[C^*]$ decay. Thus, a bump can be generated without C^* being zero (e.g., the third bump). (b) Average recorded and simulated bumps are similar. The bump current is given by Eq. 1. (c) Latency distributions of simulated and real bumps are similar. (Adapted from Song et al. 2012)

(i) At the stimulus onset, a large fraction of the microvilli is activated simultaneously but then becomes refractory (Fig. 5b). This leaves a smaller fraction of the microvilli to respond to the next photons in the stimulus until more microvilli become available again. Therefore, the number of activated microvilli (samples) first peaks, followed by a rapid drop before settling to a steady state as photon arrivals and refractory periods balance.

(ii) If all bumps were identical, then the macroscopic current would simply represent the number of activated microvilli at a given photon rate, with a flattened steady-state response. However, real light-induced currents show decaying trends toward lower plateau levels. This is because bumps adapt (Fig. 5c), becoming smaller and briefer with brighter backgrounds (Wong and Knight 1980; Wong et al. 1980, 1982; Juusola and



Phototransduction Biophysics, Fig. 5 Phototransduction Biophysics, Availability of microvilli and their adapting bumps shape responses to light. (a) LIC to a bright pulse recorded from dissociated R1–R6 *Drosophila* photoreceptors (R1–R6 are the six outer photoreceptors in a single ommatidium) during whole-cell patch clamp (black) and a simulated LIC (red) to the same stimuli. LIC is shaped by the number of activated microvilli (b) and negative feedback, which reduces the size of the bumps they produce (c). (b) Output of 30,000 microvilli modeled, showing the fractions of used (refractory) and activated microvilli and their sums in the model simulations to

reproduce (a). (c) Dotted line shows the ratio of the normalized LIC (a) and the number of activated microvilli (b), which represents the effect of a reduction in bump waveform on LIC as a function of time (whereas the refractory period affects microvilli usage). Bump size begins to diminish already after the first bumps, which shape the initial transient response. Time course of bump adaptation is approximated by a single exponential. In (a), most differences between the traces are due to a fixed (light adapted) refractory period distribution, which was used in the simulation

Hardie 2001b). This global negative feedback likely stems from Ca^{2+} -dependent inhibition due to light-induced calcium spread between microvilli via the cell body (Hardie 1996; Postma et al. 1999; Hardie and Postma 2008). This attenuates bump waveforms by progressively strengthening the negative feedback to multiple targets. Furthermore,

the resulting membrane voltage increase also compresses responses by reducing the electromotive force for the light-induced current across all microvilli (Song et al. 2012).

Thus, experiments and simulations suggest that reduction both in the number of samples (activated microvilli) and in their size (bump

waveforms) largely accounts for adaptation in the macroscopic response.

What Governs the Rate of Information Transfer of Macroscopic Responses?

The signal-to-noise ratio and rate of information transfer increase with the average sampling rate, which is the average number of samples per unit time. Thus, the more samples that make up the macroscopic response to a given light pattern, the higher is its rate of information transfer (Fig. 6). However, with more photons being counted by a photoreceptor at brightening stimulation, information about naturalistic light patterns in its responses first increases and then approaches a constant rate. This is because:

- (i) When more microvilli are in refractory state, more photons fail to generate bumps. As quantum efficiency drops, the equilibrium between used and available microvilli approaches a constant (maximum) bump production rate (sample rate).
- (ii) Once global calcium and voltage feedbacks saturate, they cannot make bumps any smaller and briefer with increasing brightness.
- (iii) After initial acceleration from the dark-adapted state, bump latency distribution remains practically invariable in different light-adaptation states (Juusola and Hardie 2001b).

Therefore, when sample rate modulation (i) and sample integration dynamics (ii and iii) of the macroscopic voltage responses settle (at intensities $>10^5$ photons/s in *Drosophila* R1–R6 photoreceptors; Fig. 6a–d), allocation of visual information in the photoreceptor's amplitude and frequency range becomes nearly invariable (Faivre and Juusola 2008; Song et al. 2012). Correspondingly, stochastic simulation closely predicts measured responses and rates of information transfer (Zheng et al. 2006, 2009; Gonzalez-Bellido et al. 2011; Song et al. 2012). Notably, when the microvilli usage reaches a mid-point (~50% level) (Fig. 6e), the information rate encoded by the macroscopic responses to natural

light intensity time series saturates (Song et al. 2012). This is presumably because sample rate modulation to light increments and decrements – which in the macroscopic response code for the number of different stimulus patterns (Juusola and de Polavieja 2003) – saturate.

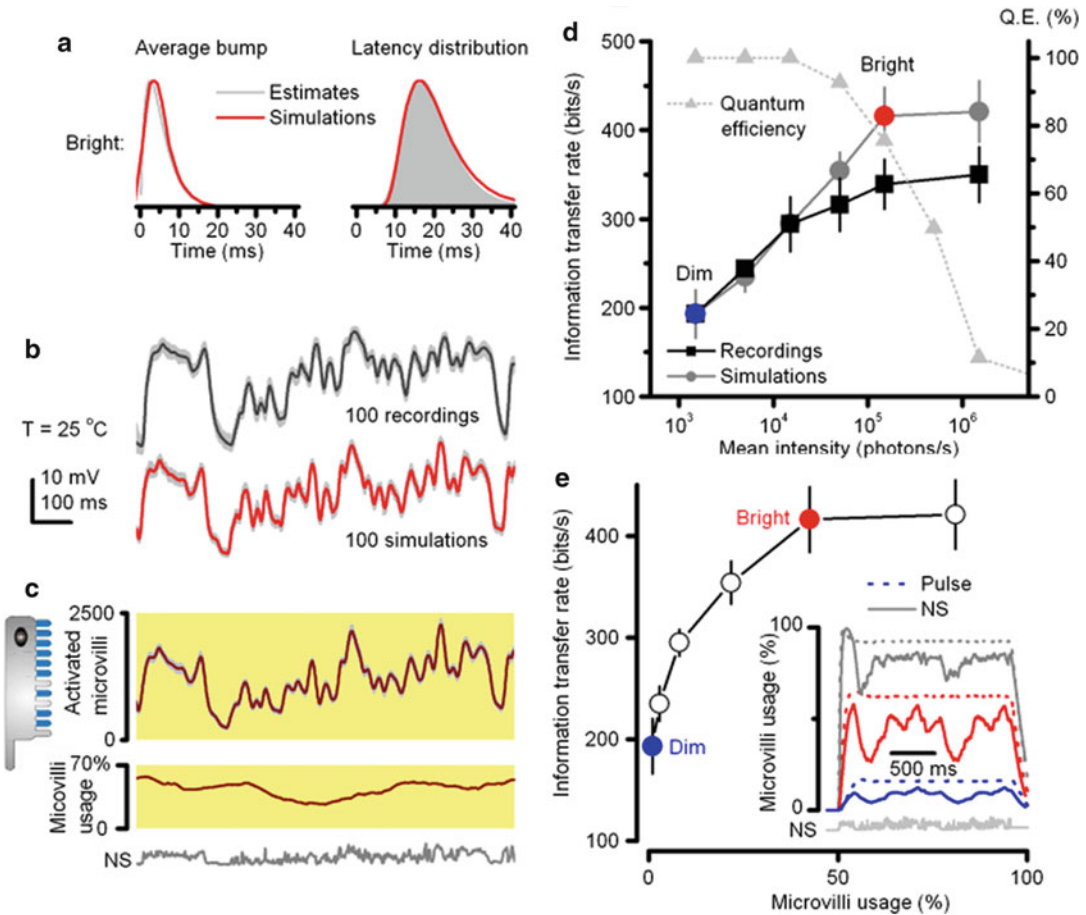
Bump size, if invariable, does not affect the rate of information transfer – as long as the bumps are briefer than the stimulus changes they encode. Thus, like any other filter, a fixed bump waveform affects signal and noise equally (data processing theorem; Shannon 1948; Juusola and de Polavieja 2003; Song et al. 2012). But varying bump size adds noise; when this variation is adaptive (memory based), less noise is added (Song et al. 2012).

What Are the Coding Benefits of Global Feedbacks?

In bright light, global calcium and voltage feedbacks reduce bump amplitudes and durations, enabling more evenly encoded macroscopic responses that can utilize a smaller voltage range. This likely reduces a photoreceptor's energy consumption (Laughlin et al. 1998).

Together with the stochastic latency and refractory period distributions, the bump waveform regulates the size (gain) and speed (frequency range) of macroscopic responses (Juusola and Hardie 2001b; Faivre and Juusola 2008; Song et al. 2012). In very dim conditions, quantum efficiency is near 100% and the influence of global feedbacks is minimal. This leads to generation of large variable bumps with broad timing jitter, integrating macroscopic responses of high sensitivity. In bright conditions, conversely, quantum efficiency is $<1\%$ and global feedbacks are maximal. The outcome is smaller, less variable, and better synchronized bumps, which integrate to a macroscopic response of lower sensitivity. However, in large part due to the low-frequency dominated spectra of natural images ($1/f$), the macroscopic response waveforms to dim or bright natural light intensity time series are very similar (Faivre and Juusola 2008; Song et al. 2012).

In diurnal insect photoreceptors that have been tested both in dark- and light-adapted conditions



Phototransduction Biophysics, Fig. 6 Phototransduction Biophysics. In a fully light-adapted state, sample (bump) rate changes define the rate of information transfer of macroscopic responses. (a) Stochastic microvilli models can be set to use the corresponding average bump waveforms and latency distributions, estimated from the white-noise contrast experiments at different light levels, by refixing two model parameters: n_s (Eq. 7) for the bump shape and l_a (Eq. 8) for the latency distribution. (b) 100 superimposed responses (light gray) and the average signal to a repeated bright naturalistic stimulus (NS), and the corresponding simulations. (c) The NS activates microvilli stochastically with appropriate dynamics and statistics. Owing to largely low-frequency input ($1/f$ statistics), the number of activated microvilli is mostly responsible for the corresponding response waveforms (b). This encoding uses only a fraction of 30,000 microvilli (maximally $\sim 68\%$ for the repeated NS) because the NS contains long relatively dim periods, allowing refractory microvilli to return to the pool of available ones during stimulation. (d) Information transfer rate of photoreceptors (black)

and the model (gray) to the same NS at six different light levels. Recordings' lower information transfer at three brightest intensities can be attributed to damage, experimental noise, and intracellular pupil, which progressively filter out photons. At dim intensities, the effect of experimental noise and adaptation may be compensated by the synaptic network introducing new information from neighboring photoreceptors. Quantum efficiency (QE) of simulated photoreceptor output drops with brightening of the NS, while the information transfer approaches a constant rate. (e) Information transfer reaches maximum when about 50% of microvilli are in continuous use and is maintained, despite steep falloff in quantum efficiency (QE) at the brightest intensities (d). Inset: during a very bright NS, because of its $1/f$ statistics that contain interspersed darker periods, proportionally more microvilli recover than during light pulses (dotted lines) of equal mean intensity. A very bright pulse (10^6 photon/s) activates $\sim 99\%$ of microvilli at the beginning of stimulation, and their usage remains high throughout the pulse. Error bars show SD (Adapted from Song et al. 2012)

(Juusola and Weckström 1993; Juusola and Hardie 2001a, b; Faivre and Juusola 2008; Gonzalez-Bellido et al. 2011), the bandwidths of their membranes show higher cutoff frequencies than those of their light-induced currents. Thus, the global voltage feedback compresses – by reducing the electromotive drive of light-induced current (Song et al. 2012) – the responses without much influencing the frequency allocation of the transmitted information (Shannon 1948; Juusola and de Polavieja 2003).

In summary, global feedbacks perform important energy-efficient normalization processes. These enable variable samples and counts to add up to similarly shaped macroscopic voltage responses for natural light changes in different illumination conditions, paving the way for perceptually invariant neural representations of visual objects.

What Are the Benefits and Costs of Adaptive Stochastic Sampling?

Stochastic sampling is not only an elegant light-adaptation strategy but may also represent a novel, generic solution to the temporal aliasing problem. It scatters high-frequency information into broadband noise rather than generating the false patterns produced by regular sampling (Leneman 1966). Thus, variable sampling times and sample sizes prevent distortions or artifacts in reconstruction of macroscopic responses from the original (continuous) light patterns. Similarly, topological disorder of photoreceptors in retinae likely provides anti-aliased sampling of spatial (Yellott 1982) and chromatic (Wardill et al. 2012) information from visual scenes. Intrinsic biophysical heterogeneity in neuron populations can further increase information content and robustness of their collective spatiotemporal signal (Heimonen et al. 2006; Padmanabhan and Urban 2010).

The trade-off of stochastic sampling is broadband noise (Leneman 1966; Dippe and Wold 1985). However, in fly photoreceptors – due to

global feedbacks that carry memory of the past events – such noise is reduced by adapting the sample sizes to the ongoing light stimulation. This accounts for about 10% improvement in the rate of information transfer, in comparison to sampling the bumps randomly from the same distribution (Song et al. 2012). Noise is further reduced when signals from neurons converge, e.g., when macroscopic responses of photoreceptors, which sample light from the same point, are pooled in synaptic transmission to interneurons (Zheng et al. 2006).

Specifically in fly photoreceptors, adaptive stochastic sampling has been shown to (Song et al. 2012):

- Resist saturation – It is hard to knock out all microvilli at once, as there are always some returning to the pool of available ones in any one moment.
- Improve the signal-to-noise ratio of macroscopic responses, in comparison to corresponding estimates that are sampled randomly (without memory) from the same bump waveform distribution.
- Reduce oscillations in macroscopic responses to sudden stimulus changes.
- Utilize microvilli and the amplitude range of photoreceptor output more evenly. Notably, a macroscopic response, in which every voltage level is utilized equally often, would have the highest information content (Shannon 1948; Zheng et al. 2009).
- Promote equalizing of contrast information transfer in different light conditions.
- Evoke similarly shaped responses in different light conditions.
- Enhance responses to novel stimuli (Juusola and de Polavieja 2003). Events which generate the largest changes in microvilli activation (sample rate modulation bump increments or decrements) with respect to the ongoing average are represented by macroscopic responses with the highest information content (Song et al. 2012).

Photoreceptor Structure Defines Its Encoding Performance

Models of different fly photoreceptors indicate that their structures and biophysical makeup are intrinsically linked to the neural signaling they carry out (Song et al. 2012). Thus, differently shaped photoreceptors of different species presumably evolved to match the visual requirements of their lifestyle. A photoreceptor's maximum information transfer rate cannot be increased beyond its structural limits, hardwired in the maximum number microvilli and in their maximum bump production rate (Fig. 7). Photoreceptors with the most and fastest microvilli in principle provide the best vision. However, this comes at a price: more microvilli increase plasma membrane's capacitance and potentially its time constant. The larger (slower) time constant can only be offset by larger conductances, ultimately consuming more ATP (Laughlin et al. 1998; Fain et al. 2010).

Appealing analogy: Sir Francis Galton realized that the mean of variable samples, reported independently by honest observers, provides the best estimate of the witnessed event (Galton 1907). In fly photoreceptors, the observers are the tens of thousands of microvilli. Each of them has either encountered photons recently or not. A microvillus that absorbs a photon casts an independent vote on how important (surprising) that event is, given the past light history. Accordingly, the weighted average of all the sampled simultaneous votes (macroscopic response) provides a reliable (non-aliased) neural estimate of the ongoing light signal. This information matches the visual requirements of the animal, as embedded in its hardwired photoreceptor structures and stochastic phototransduction biophysics (Gonzalez-Bellido et al. 2011; Song et al. 2012).

Biophysical Photoreceptor Model

A biophysical model of a *Drosophila* photoreceptor that can generate realistic responses to time series of light intensities contains four modules (Song et al. 2012):

- (i) Random Photon Absorption Model: regulates photon absorptions in each microvillus, following Poisson statistics.
- (ii) Stochastic Bump Model: stochastic biochemical reactions inside a microvillus capture and transduce the energy of photons to variable bumps or failures.
- (iii) Summation Model: bumps from 30,000 microvilli integrate to the macroscopic light-induced current (LIC) response.
- (iv) Hodgkin-Huxley (HH) Model of the photoreceptor plasma membrane: transduces LIC into a voltage response.

This modeling approach is robust and does not require full knowledge of all molecular players and dynamics in the phototransduction process. From a computational viewpoint, the exactness of the simulated molecular interactions is not important. As long as the photoreceptor model contains the right number of microvilli, each of which is a semiautonomous sampling unit, and their stochastic bump dynamics (average waveforms, latency distribution, and refractory period) approximate those in the real recordings, it will sample and process information much like a real photoreceptor (Song et al. 2012).

Random Photon Absorption Model

- Input: the number of photons absorbed by the rhabdomere in each 1 ms time interval
- Output: the number of photons absorbed by each microvillus

With photon absorptions following Poisson statistics (Hochstrate and Hamdorf 1990), variable numbers of photons are absorbed by each microvillus in the rhabdomere. Because the bump/photon ratio in each microvillus changes with the number of photons it absorbs, this model is needed for generating a realistic light input for each microvillus.

Key assumptions:

- Each microvillus absorbs photons independently with all microvilli having the same

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Fig. 7 Phototransduction Biophysics,

Photoreceptor models of adaptive sampling behave like real photoreceptors. (a–c)

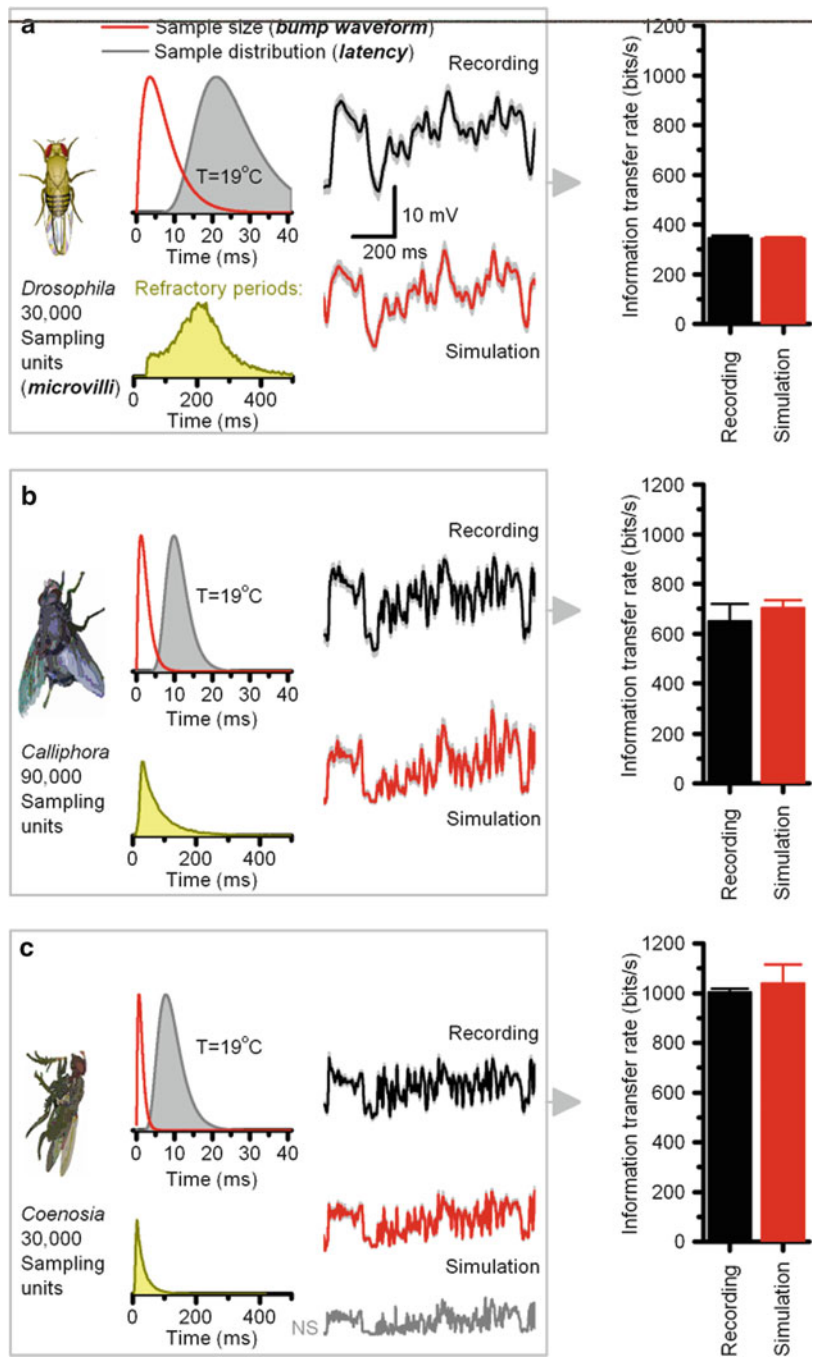
Outputs of *Drosophila*, *Calliphora*, and *Coenosia* photoreceptors, respectively, were simulated by stochastic models. The microvilli numbers were fixed to match those of the real cells, and their average bump waveforms (dark red) and latency distributions (gray)

were approximated from *in vivo* recordings by adjusting the negative feedback strength within their microvilli, by refixing two global negative feedback parameters: n_s and la . These photoreceptor models' voltage responses (red)

to the repeated presentations of a naturalistic stimulus (NS) pattern behave as their real counterparts (black).

Lower insets show the corresponding refractory periods (inter-bump intervals, yellow), generated by the microvilli of the models to the NS. Information transfer rates (right) of the simulated responses follow those of the real recordings.

(Adapted from Song et al. 2012)



absorption probability. These assumptions eliminate the role of rhabdomere topology, simplifying calculations. In rhabdomeres, microvilli taper, with their photon absorption probabilities at the bottom being likely less

than those at the top. Nonetheless, because simulations pair well with the experimental results, probabilistic scaling of the photon flux (through the tapering microvilli) is not critical.

As there are $\sim 30,000$ microvilli in a *Drosophila* photoreceptor rhabdomere, if the light input contains N_{ph} photons in the given time interval (1 ms), the average number of photons a single microvillus can absorb is $\lambda_M = N_{ph}/30,000$. Following Poisson statistics, the fraction of microvilli that absorb k photons is $p(k) = \lambda_M^k e^{-\lambda_M} / k!$. Therefore, $30,000 \times p(k)$ microvilli can be uniformly drawn to absorb k photons at one time point, where $k < k_n$; k_n is the smallest number that satisfies $p(k_n) < 1/30,000$. This procedure iterates along the light time series with each microvillus obtaining an absorbed photon series to stimulate its phototransduction cascade.

Stochastic Bump Model

- Input: the number of photons absorbed by each microvillus
- Output: variable bumps generated by each microvillus

Stochastic phototransduction cascade models simulate known enzymatic reactions (Pumir et al. 2008; Song et al. 2012), generating variable bumps (samples) to absorbed photons. Bump series to sequential photon absorptions are needed for investigating continuous adaptation processes. Despite the many model parameters, adaptation can be regulated by two master parameters: n_s in Eq. 7 for bump shape and la in Eq. 8 for bump latency distribution. The model also includes a representation of $[Ca^{2+}]$ dynamics.

To account for the intrinsic variability in the reactions, where several molecular interactions occur at low numbers, the quantum bump model uses a stochastic simulation framework based on the Gillespie algorithm (Gillespie 1976).

Key assumptions:

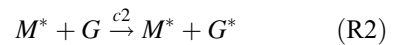
- Because spontaneous bumps are very rare (Hardie and Postma 2008), reactions are assumed to be silent in the dark-adapted state.
- A well-mixed chemical system is assumed for simplicity. All the reaction pathways are decomposed into M unidirectional elementary

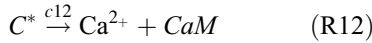
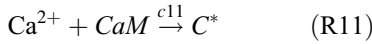
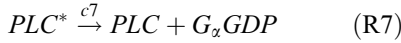
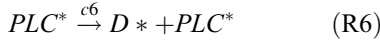
reaction steps R_μ . Each of these reaction steps is characterized by a momentarily defined stochastic reaction constant, c_μ , where $c_\mu \delta t$ ($\mu = 1, 2, \dots, M$) denotes the average probability that a particular combination of R_μ reactant molecules will react accordingly in the next infinitesimal time interval δt .

If h_μ is the total number of R_μ reactant pairs, then $a_\mu \delta t = c_\mu h_\mu \delta t$ is the average probability that reaction R_μ will occur during δt . By considering a discrete infinitesimal time interval, $(t, t + dt)$, during which 0 or 1 reaction occurs, dt and R_μ can be determined independently. When R_μ is chosen, the state vector $\mathbf{X}$ is updated with a state transition vector, $\mathbf{V}_\mu$. The procedure iterates until a termination criterion is satisfied, e.g., if the current simulation time, t , is larger than a preset value.

The molecules are counted when there are only a few in each microvillus. Otherwise, concentrations are used, calculated using the microvillus volume. In the equations or reactions, X is the number of molecules; X^* is the active state of X , and X_T the total number of corresponding molecules/channels inside a single microvillus. $[X]$ is the concentration; $[X]_i$ is intracellular concentration and $[X]_o$ the extracellular concentration. Rates of activation are denoted by κ and rates of deactivation by γ . Positive and negative feedbacks are f_p and f_n , respectively, and the local feedback strength parameter is h .

The signaling pathway is decomposed into a set of unidirectional reactions, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, and R12 (indicated by arrows in Fig. 3, right side), each of which contains only unimolecular or bimolecular reactants:





Because the input is the number of absorbed photons, photon-activated rhodopsin (metarhodopsin, M^*) is incremented by 1 if one photon is absorbed in a microvillus.

In the unidirectional reactions:

- [R1](#) is the inactivation of metarhodopsin (M^*) by arrestin binding; ϕ indicates any reaction product, whose kinetics is not modeled. G-proteins can exist in multiple states. For simplicity, only the cycle through three states is modeled: $G_{\alpha}G_{\beta\gamma}GDP$ (G), $G_{\alpha}GTP$ (G^*), and $G_{\alpha}GTP-PLC$ (PLC^*).
- [R2](#) is the activation of G into G^* by M^* .
- In [R3](#), G^* binds to PLC and becomes an active G-protein-PLC complex (PLC^*).
- [R4](#) and [R5](#) represent the recycling process of G-proteins. [R4](#) is the conversion from $G_{\alpha}GTP$ to $G_{\alpha}GDP$ by GTPase activity of G^* , supposedly catalyzed by PLC^* . $G_{\alpha}GDP$ then rebinds to $G_{\beta\gamma}$ before it can be reactivated ([R5](#)).
- PLC^* hydrolyzes PIP_2 into DAG and IP_3 , generating the unknown excitation messengers for TRP/TRPL channels. In [R6](#), because of this

ambiguity, PLC^* is modeled to activate the supposed excitation messenger D^* directly.

- D^* excites TRP/TRPL channels T to their open states (T^*) in [R9](#) and is degraded in [R8](#).
- [R10](#) is the process of closing the open TRP/TRPL channels.
- [R11](#) is the binding of Ca^{2+} , which enters the microvillus through the open TRP/TRPL channels, to Calmodulin C^* . [R11](#) is a simplified first-order representation of the Ca^{2+} binding process, where in reality, 4 calcium ions bind to CaM to form C^* .
- [R12](#) is the release of Ca^{2+} from Calmodulin.
- Ca^{2+} -bound Calmodulin constitutes the feedback intermediate for regulating the reactions [R1](#), [R2](#), [R3](#), [R4](#), [R5](#), [R6](#), [R7](#), [R8](#), [R9](#), and [R10](#).

In these reactions and under voltage-clamped conditions, the light-induced current, I_{in} , is the product of T^* (the output for the phototransduction cascade) and I_{T^*} (the average single-channel current conducted by an open TRP/TRPL channel).

Assuming that, apart from Ca^{2+} , the molecular components cannot enter or leave the microvillus, the following mass balance equations hold:

$$T^* + T = T_T \quad (1)$$

$$CaM + C^* = C_T \quad (2)$$

$$PLC^* + PLC = PLC_T \quad (3)$$

$$G^*GDP + G + G^* + PLC^* = G_T \quad (4)$$

Using these mass balance equations, the number of state variables can be reduced and the state vector, $\mathbf{X}$, defined as

$$\mathbf{X} = [M^*; G; G^*; PLC^*; D^*; C^*; T^*] \quad (5)$$

The details of how the state transition matrix, $\mathbf{V}$, the number of reactant pairs, $\mathbf{h}$, and the stochastic reaction constant vector, $\mathbf{c}_{1 \times 12}$, are defined and calculated for each reaction, [R1](#), [R2](#), [R3](#), [R4](#), [R5](#), [R6](#), [R7](#), [R8](#), [R9](#), [R10](#), [R11](#), and [R12](#), are explained in Song et al. (2012).

Calcium Dynamics Ca^{2+} is an essential feedback signal in the phototransduction cascade. Ideally, Ca^{2+} should be included as one of the state variables. However, because Ca^{2+} changes up to 1000-fold during a bump, its dynamics is not included in the state vector (Eq. 5) but approximated by a deterministic approach (Fig. 4a) (Song et al. 2012). Otherwise, simulations via the Gillespie algorithm would become impractically slow.

Computations can be streamlined by using hybrid techniques (Resat et al. 2001; Haseltine and Rawlings 2002; Rao and Arkin 2003; Puchalka and Kierzek 2004; Salis and Kaznessis 2005). In general, Ca^{2+} dynamics is simulated by deterministic methods as a balance between net Ca^{2+} influx, Ca^{2+} uptake by calcium buffer, and Ca^{2+} diffusion to the cell body. The net Ca^{2+} influx (pA) is the difference between Ca^{2+} influx and Ca^{2+} extrusion through $\text{Na}^+/\text{Ca}^{2+}$ exchanger, where Ca^{2+} influx is estimated to constitute 40% of the total ion influx. Ca^{2+} extrusion through $\text{Na}^+/\text{Ca}^{2+}$ exchanger can be calculated from a simplified format of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger model (Luo and Rudy 1994), given that the extracellular ionic concentrations are fixed and the cell is voltage clamped. To update Ca^{2+} quantities in the stochastic simulation framework, Ca^{2+} dynamics are assumed to be so fast that the quantities can be approximated by the steady-state values. Song et al. (2012) give the formulation of this approach and explain how to update Ca^{2+} dynamics in the simulations.

Positive feedback (indicated by green dotted lines in Fig. 3): f_p is formulated as a Hill function of $[\text{Ca}^{2+}]_i$ inside a microvillus:

$$f_p([\text{Ca}^{2+}]_i) = \frac{([\text{Ca}^{2+}]_i/K_p)^{m_p}}{1 + ([\text{Ca}^{2+}]_i/K_p)^{m_p}} \quad (6)$$

where K_p is the dissociation constant, i.e., $[\text{Ca}^{2+}]_i$, that provides half occupancy of Ca^{2+} binding sites for the channels and m_p is the Hill coefficient, describing the cooperativity of Ca^{2+} in exciting the channels.

Negative feedback (indicated by red dotted arrows in Fig. 3): f_n is formulated as proportional to a Hill function of $[\text{C}^*]_i$:

$$f_n([\text{C}^*]_i) = n_s \times \frac{([\text{C}^*]_i/K_n)^{m_n}}{1 + ([\text{C}^*]_i/K_n)^{m_n}} \quad (7)$$

where n_s denotes a global negative feedback strength parameter. This is one of the most important parameters in the model; it is the only parameter that is used to regulate the bump shape in our simulations (Fig. 7), whereas all the other kinetic parameters are fixed. K_n is the dissociation constant and m_n is the Hill coefficient for $[\text{C}^*]_i$. In reality, the affinity of $[\text{C}^*]_i$ might vary for different feedback targets, leading to different parameter values for K_n and m_n . However, for simplicity, it is assumed that the whole pool of available C^* binding sites have the same affinity properties and local feedback strengths are parameterized by h_* . This simplification provides a practical initial approximation, in the absence of more complete mechanistic knowledge concerning the different underlying processes. The related parameters (h_* , etc.) are listed in Song et al. (2012).

With the definitions of $\mathbf{V}$, $\mathbf{c}$, and $\mathbf{h}$, the time increment dt , during which the next reaction R_μ occurs, is determined as

$$dt = \frac{1}{la + a_s} \ln \left(\frac{1}{r_1} \right) \quad (8)$$

where r_1 is a uniformly distributed random number and a_s is the dot product between $\mathbf{c}$ and $\mathbf{h} \left(a_s = \sum_{\mu=1}^{\mu=M} c_\mu h_\mu \right)$. Apart from the parameter n_s in Eq. 7, la (or latency width regulator) is the only other critically important parameter in our model, affecting the latency distribution (Fig. 7). R_μ can be chosen so that Eq. 9 satisfies

$$\sum_{v=1}^{\mu-1} a_v < r_2 a_s \leq \sum_{v=1}^{\mu} a_v \quad (9)$$

where r_2 is a uniformly distributed random number and $a_v = c_v h_v$.

Simulating the Phototransduction Model The stochastic bump model can accommodate complex time series of photon inputs. When a new photon input arrives, the Gillespie algorithm is stopped and the molecule numbers are updated. As described above (Fig. 4), simulations clarify why a single microvillus can only produce one bump at a time, regardless of its photon input (see above) and how bumps from a single microvillus adapt, depending on its memory state of the photon input history.

The simulated bump series can be quantified by three bump parameters, namely, bump waveform (i.e., its amplitude and duration), latency distribution, and refractory period distribution (Fig. 7). These bump parameters shape the macroscopic LIC (Juusola and Hardie 2001a, b; Song et al. 2012).

Integration of Light-Induced Current (LIC)

- Input: variable current bumps generated by each microvillus
- Output: macroscopic light-induced current response

Macroscopic LIC of the rhabdomere is integrated from the current bumps of up to 30,000 microvilli (Figs. 2 and 3).

$$LIC = \sum_{N=1}^{N=30,000} I_{in}^N \quad (10)$$

Key assumptions:

- How different microvilli cooperate in producing the LIC is unclear. However, it is assumed that their phototransduction cascades are independent and the macroscopic LIC represents the summation of bumps (Eq. 10). This assumption is valid in dim-to-medium light conditions, where experimentally obtained bump statistics indicate a one-to-one photons-to-bumps relationship (Henderson et al. 2000).

Regulating Bump Waveform and Latency Distribution Statistics Simulations can be made to match to those of recordings by single parameter adjustments. The average bump waveform can be regulated by a single “master” parameter, n_s (Eq. 7), and the average bump latency distribution by another single parameter, la (Eq. 8). n_s and la can be fixed in simulations to produce natural-like bump variations for each light-adaptation state (Figs. 6 and 7). n_s affects mostly the bump shape, whereas la affects mostly the bump latency (Song et al. 2012). Both of these parameters have little effect on the bump refractory period when the bump statistics were within the physiological range for *Drosophila* (Song et al. 2012).

HH Model of Photoreceptor Plasma Membrane

- Input: macroscopic light-induced current response
- Output: macroscopic light-induced voltage response

LICs can be converted to voltage responses by a Hodgkin-Huxley (HH) type of *Drosophila* photoreceptor cell membrane model. This incorporates voltage-gated fast inactivating Shaker and slow delayed rectifier, Shab, K^+ conductances (Hardie 1991; Hardie et al. 1991), and K^+ and Cl^- leaks. It also includes a slowly activating, non-inactivating voltage-gated K^+ conductances and the “window current” representing partial failure of Shaker channel inactivation (−11%). The model lacks further modulation of Shab channels, which are probably located on the microvillar plasma membrane, via phosphoinositide depletion (Krause et al. 2008) and the fast delayed rectifier (Shal current). The conductance for Cl^- leak can be used to regulate the resting potential (Niven et al. 2003; Vähäsöyrinki et al. 2006). The light-dependent conductance is not included, because the phototransduction cascade model provides the functional equivalence to this conductance.

Global Feedback Mechanisms To replicate the effect of slow global feedbacks, such as

intracellular accumulation or diffusion of Ca^{2+} , a global feedback strength parameter can be implemented in the phototransduction cascade model (n_s in Eq. 7). In the simplest case, by changing n_s exponentially (Eq. 11), the model reproduces the slow light-adaptation trends (exponential decay to plateau) in the LIC responses to light pulses (Fig. 5):

$$n_s = n_{s0} + A_{n_s} - A_{n_s} \exp(-t/\tau_{n_s}) \quad (11)$$

where n_{s0} denotes the initial condition for n_s , $n_{s0} + A_{n_s}$ is the value for n_s at, $t \rightarrow \infty$ and τ_{n_s} is the time constant of n_s dynamics. These parameters for n_s at different light levels can be found in Song et al. (2012).

Owing to the model structure, the voltage regulation of the TRP/TRPL channels' driving force can be implemented as a global feedback mechanism. This procedure reveals the interplay between the light-sensitive and light-insensitive membrane, when the photoreceptor is encoding vast changes in light intensity.

Specifically, I_{in} , formulation from Eqs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 can be modified:

$$I_{in}^N = (T^*N)(g_{TRP})(TRP_{rev} - V_m) \quad (12)$$

where T^*N is the number of opened TRP/TRPL channels in the N th microvillus, g_{TRP} is the single TRP channel conductance, TRP_{rev} is TRP channel reversal potential, and V_m is the membrane voltage. g_{TRP} can be formulated according to Eq. 13:

$$g_{TRP} = 8 \times \begin{cases} 1 & \text{if } TRP_{rev} > V_m \\ 0 & \text{otherwise} \end{cases} \quad (13)$$

In this way, TRP/TRPL channels are either fully closed or fully opened, with a single-channel conductance of 8 pS in the open state. TRP_{rev} is set to 0 mV (Hardie and Postma 2008).

From Eq. 12, as membrane voltage (V_m) increases, the bumps (I_{in}^N) shrinks accordingly, reducing the overall macroscopic LIC response

(Eq. 10). Since the phototransduction cascades and the membrane are modeled separately in two compartments, the cell membrane voltage (V_m) is obtained by injecting LIC into the Hodgkin-Huxley-type cell body model

$$V_m = HH(LIC) \quad (14)$$

where HH is a function representing the cell membrane model.

The iteration process is conducted between these two model compartments (Eqs. 10, 11, 12, and 13) to obtain realistic macroscopic LIC s and voltage responses. Thus, the calculation of I_{in}^N in Eq. 12 requires membrane potential feedback, V_m , which is initialized at the resting potential (-70 mV). As a result, I_{in}^N in every microvillus is larger than the true value, and hence LIC_0 obtained in Eq. 10 is larger than the true value of LIC . Accordingly, LIC_0 charges a too large voltage response V_{m1} . To obtain a more realistic LIC , V_{m1} is fed back to Eq. 12; but as a result, LIC_1 can be smaller than the true value (i.e., the obtained values oscillate). Hence, an iterative simulation procedure between rhabdomere and the cell body is conducted to acquire the converged LIC and V_m . Here, it is assumed that the voltage feedback only affects the amount of current influx through the opened TRP/TRPL channels but not the dynamics of the phototransduction; T^*N is not changing in each microvillus.

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Phototransduction Cascade

► [Phototransduction Biophysics](#)

Phototransduction Mechanisms

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Phrenic Nerve Pacing

► [Peripheral Nerve Interface Applications, Respiratory Pacing](#)

Physical Sectioning Microscopy

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Synonyms

[Serial sectioning microscopy](#)

Definition

Physical sectioning microscopy is a technique for three-dimensional (3D) imaging of large biological tissue volumes. As the name suggests, the technique involves physically cutting or ablating tissue to expose successively deeper parts of the tissue volume while imaging the freshly exposed tissue. The approach is in contrast with optical sectioning (e.g., confocal or multiphoton imaging), where volume imaging is performed on small intact tissue volumes, by means of systematically varying the focal plane. The main advantage of physical sectioning over optical sectioning is that it is able to image larger volumes without deterioration in the signal-to-noise ratio, and thus it is ideal for imaging whole organs such as the brain. Another important advantage of physical sectioning is that the axial resolution (in the depth direction) can be at least an order of magnitude higher than optical sectioning.

Detailed Description

The recent surge of interest in quantitative investigation of the brain as a whole has led to a rapid technological development in 3D volume imaging methods. Existing 3D imaging methods that depend on optical sectioning such as confocal microscopy or multiphoton microscopy were deemed inadequate to address the depth and volume requirements posed by whole brain imaging

(latest methods such as light sheet microscopy may be able to overcome some of these limitations). Noninvasive imaging methods based on magnetic resonance (MR) or X-ray were not up to the task, since they either lacked the means to label neurons or offered insufficient spatial resolution, or both.

For large volume brain imaging, physical sectioning (or serial sectioning) is an obvious alternative to optical sectioning or MRI/X-ray (see, e.g., the BigBrain project where a whole human brain was cut into 20µm thin sections and imaged; Amunts et al. 2013). In fact, physical sectioning has been used successfully in the past; however,

Physical Sectioning Microscopy, Table 1 Comparison of representative physical sectioning microscopy techniques

	Sectioning	Post-sectioning preparation	Time of imaging (imaged part)	Imaging modalities	Limiting factors	References
Array tomography	Microtome (linear)	Pasted on glass slides	Post-sectioning (slide). Repeated staining/imaging possible	Fluorescence, SEM	Diffraction limited (fluorescence), imaging slow (fluorescence), imaging very slow (SEM), volume (manual steps)	Micheva and Smith (2007)
KESM	Microtome (linear)	None	During sectioning (slice, at the knife's edge)	LM	Diffraction limited	Mayerich et al. (2008); Choe et al. (2008); Chung et al. (2011) (cf. Li et al. 2010)
SBF-SEM	Microtome (linear)	None	Immediately after sectioning (block face)	SEM	Volume, imaging very slow	Denk and Horstmann (2004)
ATLUM	Microtome (lathe)	Pasted on a spool of carbon-coated tape and later transferred to wafer	After transferring to the wafer (slice)	TEM	Imaging very slow	Hayworth et al. (2006)
Serial two-photon tomography	Microtome (linear)	None	Immediately after sectioning (block face)	Fluorescence	Diffraction limited, imaging slow	Ragan et al. (2012)
3D polarized light microscopy	Microtome (linear)	Pasted on glass slides	Post-sectioning (slide)	Polarized light	Resolution of around 100 µm × 100 µm	Axer et al. (2011)
All optical histology	Femto second laser	None	Immediately after ablation (block face)	Fluorescence	Diffraction limited, imaging slow	Tsai et al. (2003)
FIB-SEM	Focused Ion beam	None	Immediately after ablation (block face)	SEM	Volume, sectioning very slow. Imaging very slow	Hayles et al. (2007)

Abbreviations: *SEM* scanning electron microscopy, *LM* light microscopy, *TEM* transmission electron microscopy

the sectioning and imaging process was largely manual, and thus it required a tremendous amount of effort just to process small amounts of tissue (see, e.g., White et al. 1986). Here, we will discuss automated approaches for physical sectioning imaging.

Means of Physical Sectioning

Currently there are two major means of physical sectioning used in 3D microscopy: One is the use of microtomes (knives typically made of diamond), and the other is the use of focused ion beams (FIB) or femtosecond lasers. Both are equally effective, but depending on the imaging modality one or the other may be more suitable. Microtomes can be used to generate ultrathin sections that can be immediately imaged or preserved for subsequent imaging, while FIB or femtosecond lasers can only be used for immediate block-face imaging since the affected top layer of the tissue will be destroyed by the milling process. The sectioning or milling thickness typically ranges from tens of nanometers to hundreds of nanometers.

A Brief Survey of Physical Sectioning Microscopy Techniques

Physical sectioning has been successfully used with different imaging modalities, such as light and fluorescence microscopy and even with electron microscopy. Here, we discuss representative examples only and defer more detailed discussions to existing reviews (see, e.g., Choe et al. 2008; Chung et al. 2011; Wilt et al. 2009).

Representative techniques that use microtome-based serial sectioning include array tomography (Micheva and Smith 2007), knife-edge scanning microscopy (KESM, Mayerich et al. 2008), serial block-face scanning electron microscopy (SBF-SEM, Denk and Horstmann 2004), Automatic Tape-Collecting Lathe Ultramicrotome (ATLUM, Hayworth et al. 2006), serial two-photon tomography (Ragan et al. 2012), and 3D

polarized light microscopy (3D-PLI, Axer et al. 2011). Representative approaches using lasers or ion beams for ablation include All Optical Histology (Tsai et al. 2003) and Focused Ion Beam Scanning Electron Microscopy (FIB-SEM, Hayles et al. 2006). Note that Serial Two-Photon Tomography and All Optical Histology are hybrid approaches that combine physical sectioning and optical sectioning.

Table 1 below summarizes the characteristics and capabilities of the representative approaches listed above. Note that each approach has limiting factors, so no single approach is sufficient.

In summary, physical sectioning microscopy enables high-resolution 3D imaging of large volumes of biological tissue, allowing multi-scale quantitative investigation of the anatomical properties of whole organs such as the brain.

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Physiology and Computational Principles of Muscle Force Generation

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Definition

Muscle force generation refers to the process in which skeletal muscle, in response to neural stimuli, converts metabolic energy into active force that pulls on the bones through intermediate connective tissue.

Detailed Description

Introduction

The control problems that must be solved by the sensorimotor nervous system are determined by the complex mechanical properties of the musculoskeletal system and the even more complex and nonlinear physiological properties of muscles. Various commercial software products have been available to model musculoskeletal mechanics, but realistic models of muscle physiology are still under development. Both force generation and energy expenditure depend on both the commands from the nervous system and the kinematics of muscle length and velocity. Computational models of these processes provide the substrate upon which computational models of sensorimotor control must operate to demonstrate their feasibility.

Computational models are always approximations and usually simplifications of reality. It is usually both necessary and desirable to leave out known complexities if they do not significantly impact the particular behavior to which the model will be applied. The model presented here includes the most accurate representations currently available for the force-generating processes of individual motor units. Most previous and current research has used models that are considerably simpler, sometimes with clear justification but often from lack of consideration of relevant processes, parameters, and effects. The computational model presented here is embedded in free-ware for modeling complete, arbitrary musculoskeletal systems, including their mechanical dynamics, muscles and proprioceptors, and interactions with external objects (MSMS – MusculoSkeletal Modeling Software – available from <http://mddf.usc.edu>). The construction of a particular model configuration and specification of its parameters, however, must come from the researcher after due consideration of the purposes of the model.

Relevant Physiology

Each muscle is controlled by a group of motoneurons known as a motor pool or motor nucleus. All motoneurons in such a pool generally receive the

same drive signals, although there are some exceptions (Loeb and Richmond 1989). Each motoneuron along with all of its muscle fibers is defined as a motor unit, whose recruitment and firing rate in response to the same drive varies substantially depending on the size and impedance of the motoneuron (Henneman and Mendell 1981). The force generated by a given motor unit at a given rate of firing depends on the total cross-sectional area of the muscle fibers in the unit.

The force production and corresponding energy consumption of each motor unit depend mainly on its length, velocity, and firing rate. Because muscle fibers within a motor unit generally have the same contractile properties, they can be lumped into one mathematical entity whose force generating capacity is proportional to the total cross-sectional area of its fibers and whose energy consumption is proportional to their volume. All of the muscle fibers in all of the motor units of a given muscle tend to move together, experiencing the same sarcomere lengths and velocities. Because of this homogeneity, most of the experimental phenomena related to contraction of whole muscle can be explained by processes occurring at the sarcomere level.

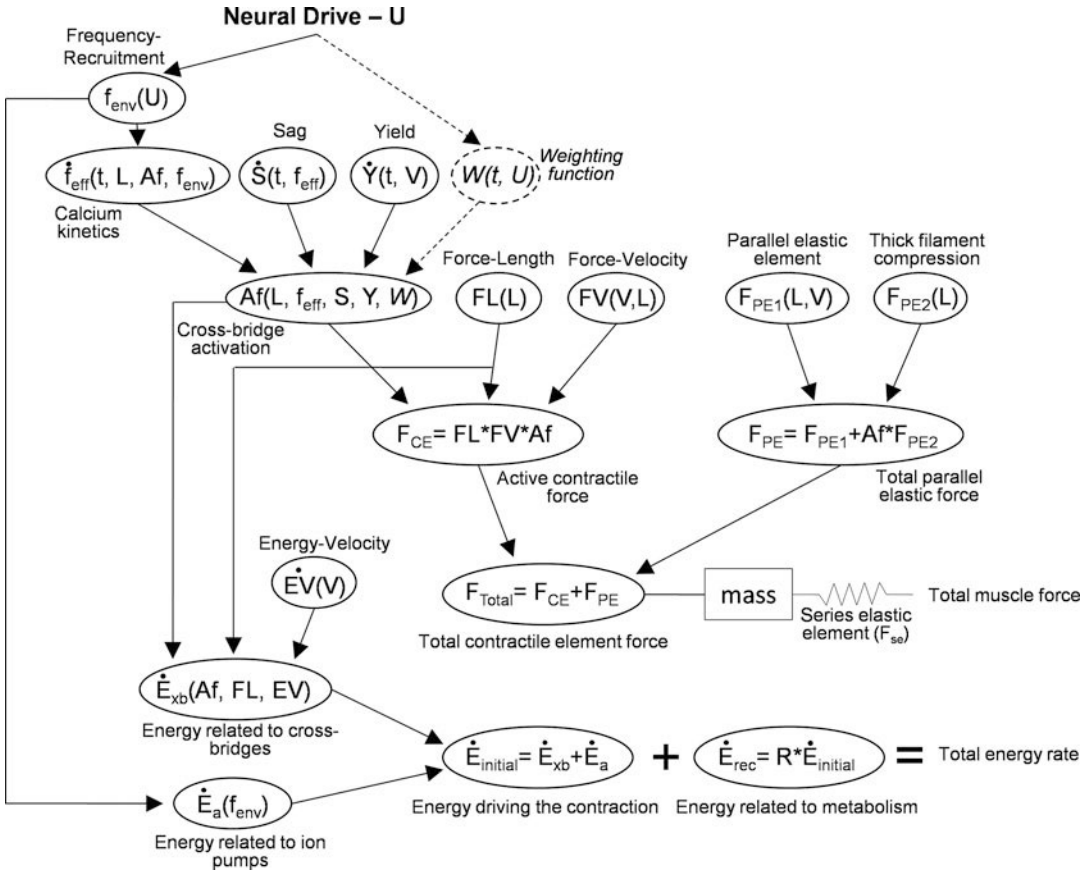
The sarcomere is the basic unit of the contraction apparatus. It is demarcated at its ends by thin Z-plates from which a matrix of thin filaments of actin projects in each direction. These interdigitate with a matrix of thick filaments of myosin that are held in the center of the sarcomere by strands of the highly elastic connectin filaments that tether the thick filaments to the Z-plates. In order for muscles to contract, protrusions from myosin called myosin heads must first be cocked to a relatively high-strain configuration and then attached to neighboring binding sites on the actin. The resulting crossbridges act like springs that pull on the actin. The metabolic energy required to cock the myosin head is provided directly by ATP molecules that are present in the sarcoplasm. In order for myosin heads to attach to neighboring binding sites, a regulatory protein called tropomyosin that normally occludes actin binding sites must undergo a conformational change. This occurs indirectly through binding of calcium to troponin, a relatively smaller

molecule that is bound to tropomyosin at regular intervals along its length. When calcium binds to troponin, a local conformational change is induced that exposes nearby actin binding sites so that the cocked myosin heads can attach to form crossbridges.

The normally relaxed state of inactive muscle is achieved by ATP-powered pumping of the calcium out of the sarcoplasm and into a network of vesicles called longitudinal tubules, preventing crossbridge formation. When the muscle is activated, calcium is released from cisterns in these longitudinal tubules in response to action potentials elicited in the muscle fibers as a result of a chemical synapse with the motor axons. These action potentials propagate along the cell membrane and its invaginations deep into the muscle fiber called transverse tubules. The ATP molecules that cock the myosin heads and drive the ion pumps must be replenished eventually via catabolism of glucose occurring both in the sarcoplasm (glycolytic) and within mitochondria (oxidative), consuming additional energy. The model of muscle presented here attempts to represent each of these structures and processes as explicit terms in the set of equations that comprise the model. A model of the energetics based on these processes can be found in Tsianos et al. (2012) and is embedded in MSMS (see above).

Structure of the Model

The model is an assembly of sub-models, each characterizing a major physiological process underlying muscle contraction (Fig. 1). Modeling physiological processes independently as opposed to the aggregate behavior avoids overfitting data to specific preparations and therefore improves the likelihood that the model will be valid under untested conditions. The data driving the model originate from experiments on mammalian muscle that were designed to isolate specific processes that were then quantified. These include a wide variety of preparations with various muscle fiber architectures, but the model parameters have been normalized to dimensionless variables that depend on the constant structures of the sarcomeres, which are highly similar across all mammalian skeletal muscles.



Physiology and Computational Principles of Muscle Force Generation, Fig. 1 Model overview. Independently modeled physiological processes and their

contribution to muscle force production and energy consumption. (Figure from Tsianos et al. 2012, Fig. 11)

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The physiological properties of muscle can change over time. In the short term, force generation may increase or decrease as a result of chemical changes associated with potentiation and fatigue, respectively. In the longer term, muscle morphology and physiology may change as a result of trophic responses to patterns of use such as exercise and injury. All of these effects tend to be specific to the various muscle fiber types, making it important to develop muscle models that reflect the subpopulations of fiber types and the relative recruitment of the motoneurons that control them. The one-to-one correspondence of the model's terms and coefficients to physiological processes makes it relatively straightforward to extend it to include unaccounted aspects of muscle contraction and

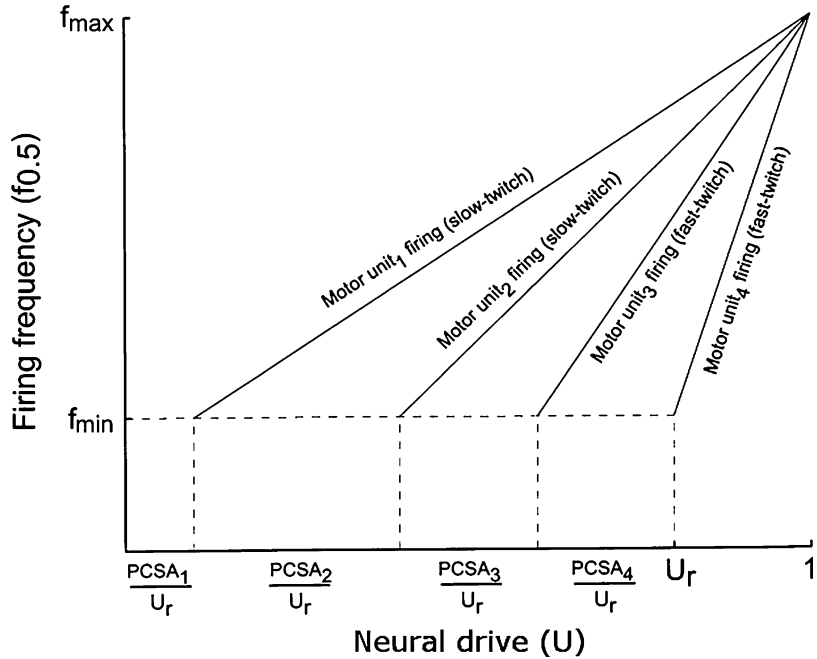
to adjust its coefficients to model changes over time. Unfortunately, quantitative models of most of these time-varying processes have yet to be developed or validated.

Active Force

Frequency Recruitment As the net excitatory synaptic drive increases to a pool of motoneurons, they tend to be recruited in a fixed order from those innervating slow-twitch muscle fibers to those innervating fast-twitch muscle fibers. Increasing the drive past the threshold of a given motoneuron results in higher firing rates. This monotonic relationship can be approximated by a line whose slope depends on the recruitment threshold of the motor unit (see Fig. 2).

Physiology and Computational Principles of Muscle Force Generation, Fig. 2

Motor unit recruitment and modulation. The plot emphasizes the relatively higher recruitment threshold of larger motor units (e.g., *fast* vs. *slow twitch*) and their firing rate modulation until the common drive (U) saturates the firing rate of all motor units. (Figure from Cheng et al. 2000, Fig. 2)



$$f_{env_i} = f_{min} + \left(\frac{1 - U_{MU_i}^{th}}{f_{max} - f_{min}} \right) * U$$

Note that the firing rate is normalized to $f_{0.5}$ (frequency at which the motor unit produces half of its maximal isometric force) because motor units tend to fire between $1/2f_{0.5}$ and $2f_{0.5}$, the range over which muscle activation is most steeply modulated.

Calcium Kinetics and Crossbridge Activation

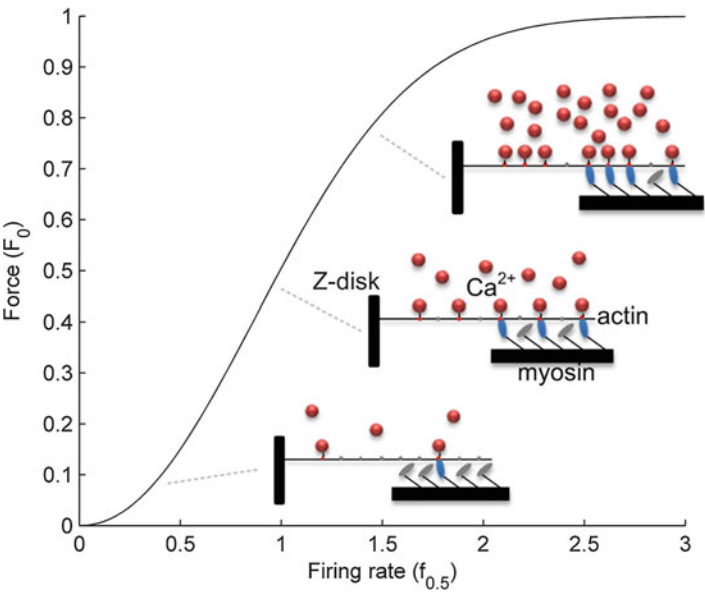
(f_{eff} , A_f) The sigmoidal relationship between motoneuron firing rate and activation of the contractile apparatus arises from the release, diffusion, and reuptake of calcium (see Fig. 3). At low pulse rates, the calcium released by each pulse is completely cleared before the next pulse, resulting in small, discrete twitches. As pulse rate increases, the calcium released by each pulse starts to accumulate to higher concentrations, allowing the calcium to diffuse further and expose more crossbridge binding sites. Eventually, the calcium concentration in all parts of the muscle fiber becomes sufficient to expose all binding sites and activation plateaus even if firing rate continues to increase. This is called a tetanic contraction.

The equation below captures the effects of firing rate on crossbridge activation. Y corresponds to yielding behavior exhibited by slow-twitch fibers and Sag observed in fast-twitch fibers. Both phenomena affect crossbridge activation through hypothesized mechanisms discussed in the corresponding sections. Note that equation parameter n_f is length dependent. The shape of the sigmoid relationship is defined by a_f , n_{f0} , and n_{f1} constants, some of which are fiber-type dependent. For a complete definition of all model parameters, see Tsianos et al. (2012).

$$A_f(f_{eff}, L_{ce}, V_{ce}) = 1 - \exp \left[- \left(\frac{Y S f_{eff}}{a_f n_f} \right)^{n_f} \right] n_f$$

$$= n_{f0} + n_{f1} \left(\frac{1}{L_{ce}} - 1 \right)$$

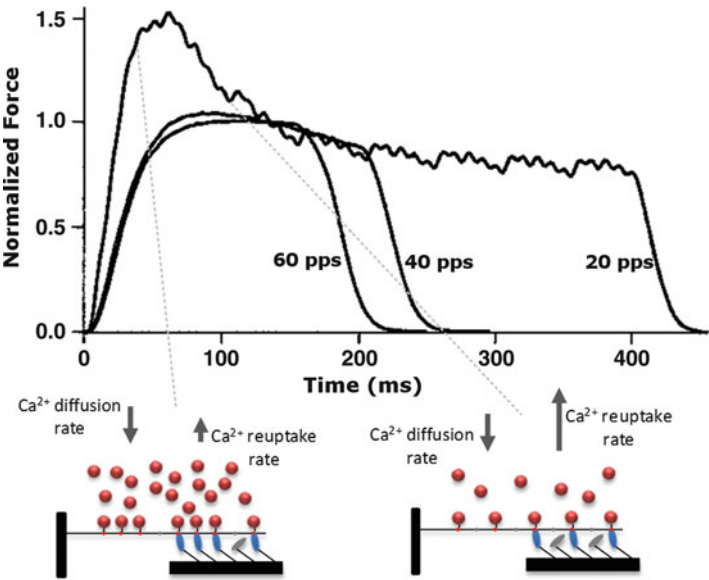
Sag (S) When fast-twitch muscle is excited isometrically with a constant drive, its force output increases initially to some maximal level and then decreases gradually (Fig. 4). This is thought to occur due to an increase in the rate of calcium reuptake, which effectively reduces the concentration of calcium in the sarcoplasm and hence the number of crossbridges that can form.

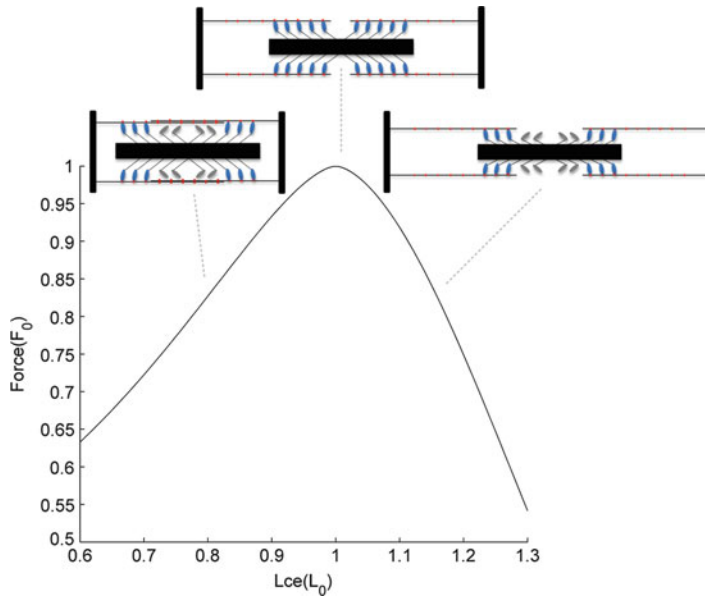


Physiology and Computational Principles of Muscle Force Generation, Fig. 3 Calcium kinetics and crossbridge activation. The effects of firing rate on isometric force output of muscle are shown from zero to tetanic activation. Overlaid graphics highlight underlying processes at the sarcomere level that give rise to the behavior. Only a small portion of the sarcomere is shown here due to symmetry. Thick horizontal bars represent thick filaments and thin horizontal lines represent thin filaments. Vertical

bars correspond to Z-disks. The small red spheres are calcium ions whose bond with actin sites is indicated by short black lines that link them and a small red dot overlaid on top of the actin (gray dots indicate inactive binding sites). If a crossbridge is formed, then the small ovals in the figure representing myosin heads are colored blue and are in a cocked configuration (large angle with respect to their neck region). (Figure from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 3)

Physiology and Computational Principles of Muscle Force Generation, Fig. 4 Sag. Experimental data depicting the Sag phenomenon in response to constant stimulation for several frequencies. The graphics on the bottom portion illustrate the effect of increasing the rate of calcium reuptake on calcium concentration and crossbridge formation (Top plot from Brown and Loeb 2000, Fig. 3a. Bottom schematic from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 4)





Physiology and Computational Principles of Muscle Force Generation, Fig. 5 Force-length relationship. Muscle force dependence on length is shown for tetanically stimulated muscle with minimal motion of its myofilaments. Overlaid graphics depict myofilament overlap and effects on crossbridge formation for different lengths.

This phenomenon can be modeled by a time-varying scaling factor applied to f_{eff} , which is directly related to the calcium present in the sarcoplasm (Brown and Loeb 2000).

$$S(t, f_{\text{eff}}) = \frac{a_s - S(t)}{T_s}$$

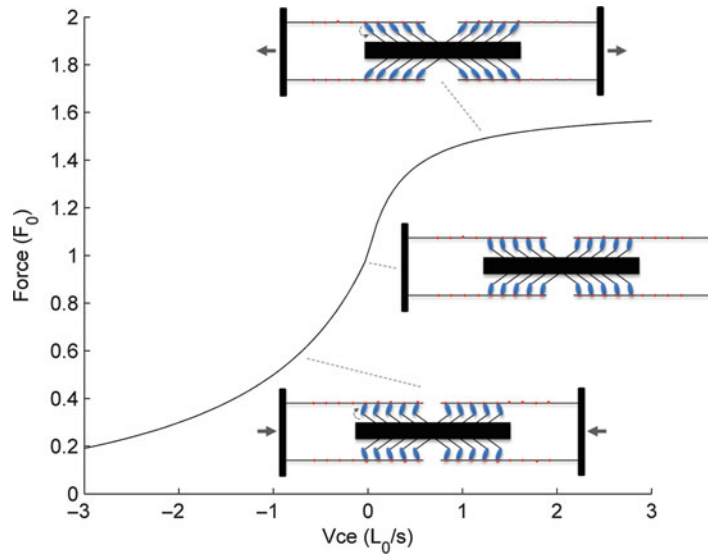
Force-Length (FL) The amount of active force a muscle produces during maximal isometric contractions (i.e., muscle length held constant during the contraction) depends on the length at which it is fixed (Fig. 5). It produces large forces at intermediate lengths and relatively smaller forces at either shorter or longer lengths (Scott et al. 1996).

At some intermediate length, typically referred to as optimal length, overlap between thin filaments and myosin heads is maximal. Therefore, the number of crossbridges that could form and the contractile force are also maximal. Myofilament overlap is less at longer lengths, so the number of potential

crossbridges and force is also smaller. Muscle force decreases at incrementally longer lengths until the point at which no more crossbridges can form and muscle can no longer produce active force. At relatively shorter lengths, thin filaments start to slide past each other (i.e., double overlap), which is thought to sterically hinder the formation of crossbridges, thereby reducing the amount of force that can be produced.

The force-length relationship, as well as all other relationships in the model, is normalized so that it generalizes across a wide range of muscle morphometries. The force corresponding to optimal length is by definition maximal, so, clearly, normalizing all force profiles to maximal isometric force under tetanic conditions provides a useful reference point. The equation capturing the normalized relationship is shown below.

$$FL(L_{ce}) = \exp\left(-\left|\frac{L_{ce}^\beta - 1}{\omega}\right|^\rho\right)$$



Physiology and Computational Principles of Muscle Force Generation, Fig. 6 Force-velocity relationship. Dependence on muscle force output on the velocity of stretch ($V > 0$) and shortening ($V < 0$) for tetanic stimulation at optimal muscle length. The graphics illustrate the hypothesized mechanisms for force enhancement relative to isometric in the lengthening case and depression in the

shortening case. Note that in reality myosin heads do not move synchronously as shown in the figure because they are subject to thermodynamic noise and other stochastic events; the graphic illustrates their configuration on average. (Figure from Tsianos and Loeb, *Muscle Physiology and Modeling*, article in Scholarpedia, Fig. 6)

ω , β , and ρ are constants that define the exact shape of the inverted U and are all fiber-type dependent.

Force-Velocity (FV) Maximally stimulated muscle at a particular length produces different levels of force depending on the rate at which it is shortening or lengthening. Relative to the isometric condition, muscle produces less force while shortening and more force while lengthening (Fig. 6; Scott et al. 1996).

Shortening muscle is accompanied by motion of the attached crossbridges toward relatively less

strained configurations. Larger rates of shortening increase the probability that a given crossbridge will be in a low-strain configuration; therefore, the force generated by the entire population is lower overall. By contrast, crossbridges in lengthening muscle become relatively more stretched and generate more tension until they are forcibly ripped away from the actin binding sites.

The equations below account for the discontinuous effects of the two, separate mechanisms by which velocity affects force generation:

$$FV(V_{ce}, L_{ce}) = \begin{cases} (V_{\max} - V_{ce}) = V_{\max} + (c_{v0} + c_{v1}L_{ce})V_{ce}, & V_{ce} \leq 0 \\ b_v - (a_{v0} + a_{v1}L_{ce} + a_{v2}L_{ce}^2)V_{ce}/(b_v + V_{ce}), & V_{ce} > 0 \end{cases}$$

c_{v0} , c_{v1} , and $V_{\max}$ are constants that define the shortening end of the relationship and depend on fiber type. $V_{\max}$ corresponds to the maximum

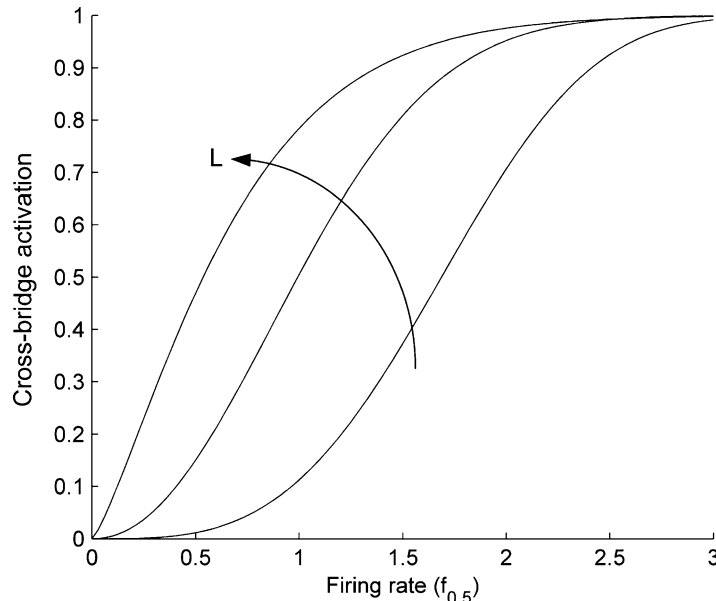
velocity of shortening that the muscle fiber can undergo. The lengthening portion of the relationship is defined by fiber-type-dependent constants

b_v , a_{v0} , a_{v1} , and a_{v2} . Note that the force-velocity relationship also depends on muscle length. See “**Potentialiation**” for a detailed description of this phenomenon as well as a mechanistic explanation. **Interactions Among Length, Velocity, and Activation**

Length Dependency of Calcium Kinetics - Changing length of the sarcomeres has effects on the calcium kinetics that govern activation. The cisterns from which the calcium is released appear to be tethered to the Z-plates at a location that is near the middle of the actin-myosin overlap when the muscle is at optimal length. At longer lengths, calcium has to diffuse over longer distances to get to the actin binding sites, which takes more time. Thus the rise times of the activation are longer (see Brown et al. 1999; Brown and Loeb 2000).

Length Dependency of Crossbridge Dynamics - Changing length of the sarcomeres has effects on the rate of attachment of crossbridges to activated and exposed binding sites on the actin. Because a

muscle fiber does not gain or lose volume as it changes length, the fiber must have a larger diameter when it is at a shorter length. The hexagonally packed lattice of myofilaments in each sarcomere will then be more widely spaced, changing the distance between the myosin heads and the thin filaments where they must bind to form crossbridges. The heads are located on the ends of hinged arms containing myosin light chains, which are canted away from the longitudinal axis of the thick filament. When the sarcomere is at a long length, the myosin heads barely fit between the thick and thin filaments, so they are close to and can bind rapidly to form crossbridges. At short lengths, the myosin heads are less favorably disposed and their binding may also be affected adversely by the double overlap of the thin filaments. These effects are particularly large at lower levels of activation, where activated binding sites are more scarce on the thin filaments. The net result is shown in Fig. 7, which is based on data and models first described in Brown et al. (1999).



Physiology and Computational Principles of Muscle Force Generation, Fig. 7 Length dependence of crossbridge activation. Crossbridge activation is measured as the percentage of maximal force generated for a given amount of myofilament overlap (i.e., effects of myofilament overlap are removed from muscle force). Muscle

length is fixed at three different values. In general, a larger portion of the available contractile machinery is activated for the same firing rate when the muscle is stretched. The *middle curve* corresponds to optimal length. (Figure from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 7)

The precise slope of this relationship, i.e., the sensitivity of force to firing rate, is affected by additional factors. A low firing rate activates only a small portion of the binding sites on the actin filaments. An incremental increase in the firing rate results in a relatively larger increase in the number of crossbridges formed. This is probably due to a relatively larger amount of exposed binding sites per active troponin molecule; this mechanism is known as cooperativity (Gordon et al. 2000; Loeb et al. 2002). Activation of troponin induces a local conformational change in tropomyosin, exposing neighboring binding sites on the actin. When more troponin molecules are activated along tropomyosin, a more global conformational change could be occurring, thus freeing up more actin binding sites. Crossbridge formation may also facilitate exposure of binding sites by inducing relative motion between actin and tropomyosin.

Potentialiation

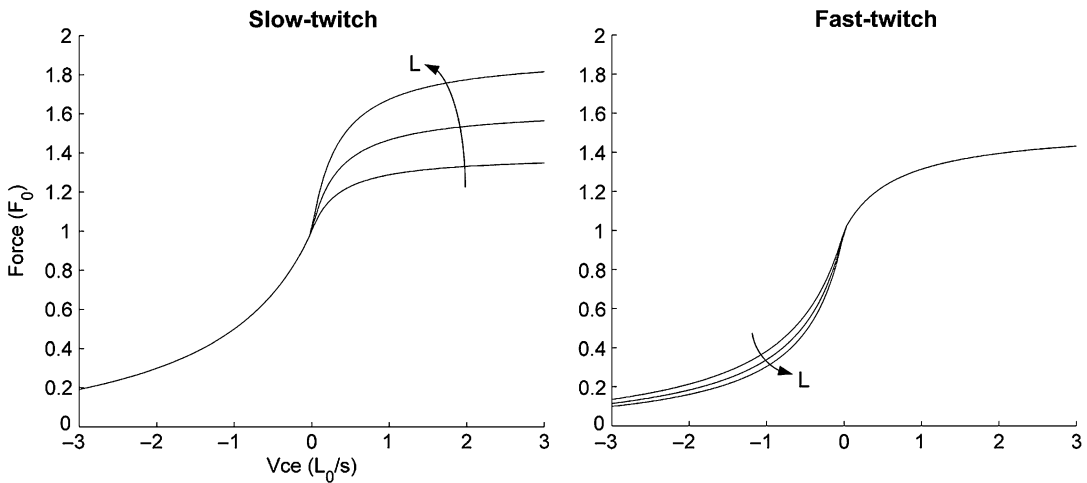
It was originally observed that the force generated by a single twitch of a fast-twitch muscle was much larger after a brief tetanic contraction than before. In fact, the potentiated state tends to prevail for minutes after a few, brief trains of stimulation at physiological rates, suggesting that the normal operating state of fast-twitch muscle is the potentiated state and that the conditions observed after a long period of quiescence reflect a dispotentiated state (see Brown and Loeb 1998). Furthermore, the dispotentiated state exhibits rather odd behavior such as a pronounced rightward shift in the shape of the force-length curve at subtetanic frequencies. For these reasons, the model of the fast-twitch muscle fibers presented here captures their behavior in the fully potentiated state.

Potentiation and dispotentiation phenomena appear to be related mainly to the effects of myofilament lattice spacing described above, but see also Smith et al. (2013). During dispotentiation, the light chain becomes dephosphorylated and the cant angle becomes smaller, leaving the myosin heads further from the thin filaments. The effect is greater at short lengths when the lattice spacing is large. This adversely affects the kinetics of crossbridge formation in general but more so at low firing rates when exposed binding sites are more sparsely distributed.

After a few cycles of calcium release in an active muscle, the short chains become fully phosphorylated and the cant angle increases so as to position the myosin heads more favorably at short and optimal muscle lengths. At longer lengths and narrower lattice spacings, the myosin heads probably remain favorably positioned because they cannot get by the closely spaced thin filaments. The force-length relationship thus returns to the simple inverted U with maximum at optimal myofilament overlap regardless of the firing rate. Slow-twitch muscle appears to lack such a dephosphorylation process and so behaves always as if fully potentiated. The function of the dispotentiation remains obscure but may be related to minimizing “stiction,” which arises when stray crossbridges in an inactive muscle form spontaneously and resist passive stretching by antagonist muscles.

The effects of sarcomere length on myofilament lattice spacing give rise to length dependencies of the force-velocity relationship that are different for slow- and fast-twitch muscle (Fig. 8). For slow-twitch muscle, the force-velocity relationship depends on length only for the lengthening condition, while fast-twitch muscle exhibits a dependency for the shortening condition. In lengthening slow-twitch muscle, smaller spacing between myosin heads and binding sites would result in a higher probability of crossbridge formation, thus leading to higher forces produced for the same velocity of stretch. This effect is also observed in dispotentiated fast-twitch muscle, but not in the potentiated state, because the reduction of interfilament spacing resulting from potentiation is thought to mask the effects of length changes (Brown and Loeb 1999). In shortening fast-twitch muscle, it is thought that smaller interfilament spacing at longer lengths increases the probability that a given crossbridge remains attached, thus making it more likely that it occupies relatively low-strain, low force configurations. Crossbridges in slow-twitch muscle stay attached for longer periods of time, which may mask the effects of length on the rate of detachment hypothesized for fast-twitch muscle.

Yield (Y) When slow-twitch muscle is sub-maximally stimulated at constant length and then



Physiology and Computational Principles of Muscle Force Generation, Fig. 8 Length dependence of force-velocity. Force-velocity curves depicting a substantial length dependency of slow-twitch muscle in the

lengthening state (*left*) and fast-twitch muscle in the shortening state (*right*). See text for details. (Figure from Tsianos and Loeb, *Muscle Physiology and Modeling*, article in Scholarpedia, Fig. 8)

stretched *or* shortened, its force output declines (Joyce et al. 1969). This effect intensifies for lower stimulation frequencies, as shown in Fig. 9. The mechanism for this phenomenon has been hypothesized to be a reduction in the number of crossbridges attached. As muscle length changes past the stroke length of the attached crossbridges, myosin heads detach from their binding sites and must reattach to continue to produce force. The rate at which slow-twitch myosin heads can attach appears to be relatively slow compared to the rate at which binding sites slide past them, therefore making it difficult for crossbridges to reform and produce force. At lower frequencies of stimulation, relatively few binding sites are available on the helical actin, making it less likely that they will be in an appropriate orientation and distance from myosin heads for binding. By applying a time-varying scaling factor to the effective firing rate parameter, the model is able to capture this effect well (Fig. 9).

$$Y(t) = \frac{1 - c_Y \left[1 - \exp \left(-\frac{|V_Z|}{V_Y} \right) \right] - Y(t)}{T_Y}$$

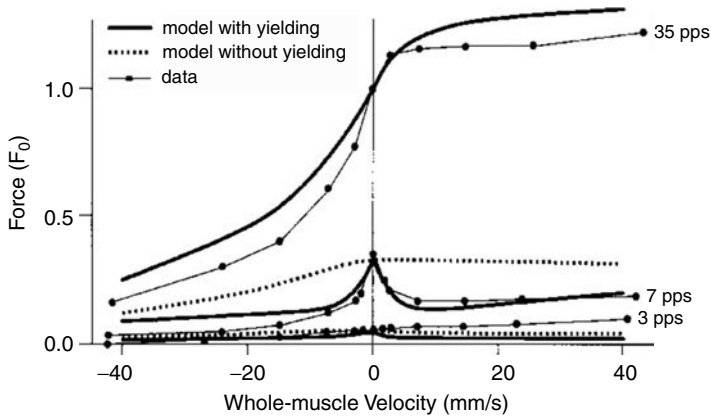
c_Y and V_Y are constants that define the intensity of the yielding effect and T_Y defines its time course.

Passive Elastic Elements

Muscle is comprised of many elastic components that generate passive forces in response to tensile or compressive strain. The aggregate force of these components may be substantial relative to the active force depending on the muscle's condition of use.

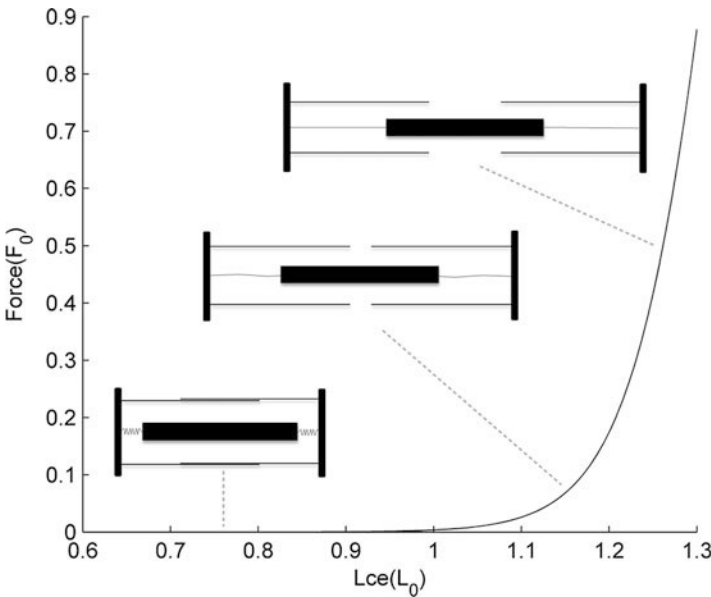
Parallel Elastic Element (F_{pe1}) Inactive muscle is under tension for about half of its anatomical range of lengths. Its passive tensile force rises exponentially over a relatively low range of lengths followed by a steep linear increase that persists all the way until maximal anatomical length (Fig. 10). The quantitative relationship for a particular muscle depends mainly on its maximal isometric force and maximal anatomical length. It is negligible over most of the range and peaks at less than 10% of F_0 at maximal anatomical length.

In frogs, this passive tension appears to arise primarily from stretching of the springlike connectin myofilaments that tether the myosin molecules to the Z-disks (Magid and Law 1985). The contribution of intermediate filaments like desmin that interconnect myofibrils within a muscle fiber has been shown to be negligible over the physiological range of sarcomere lengths (Wang



Physiology and Computational Principles of Muscle Force Generation, Fig. 9 Yielding. Plot of force-velocity relationships of slow-twitch muscle for various frequencies of stimulation. As opposed to tetanic stimulation, the force-velocity relationships for submaximal firing

rates are marked by a sharper decline in force in both shortening and lengthening states relative to isometric. Experimental data and model predictions, with and without accounting for yielding, are shown. (Figure from Brown et al. 1999, Fig. 10b)



Physiology and Computational Principles of Muscle Force Generation, Fig. 10 Parallel elastic force. Passive muscle force is plotted over a representative muscle's range of motion. In general, muscles with larger anatomical ranges of motion produce less passive force at the same length (relative to optimal), that is, their passive force-length curve shifts to the right. As depicted by the

superimposed schematics, some of this force results from stretching an elastic element in the sarcomere called connectin that links the thick filament to the Z-disks, but see text for the role of endomysial connective tissue. Myosin heads and actin binding sites are omitted for clarity. (Figure from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 10)

et al. 1993). Compared to frogs, mammalian muscles have variable but considerably more endomysial collagen surrounding each muscle fiber.

This may account for substantial variation in their passive force curves, which can be substantially shifted to the left or right with respect to the

optimal sarcomere length defined by myofilament overlap (Brown et al. 1996a). This requires introduction of an additional morphometric parameter into the muscle model, $L_{\max}$, which is based on the maximal anatomical length experienced by the muscle when attached to the skeleton. Below is the equation capturing the effect of this property on the entire passive force-length relationship.

$$F_{pe1}(L_{ce}, V_{ce}) = c_1 k_1 \ln \left\{ \exp \left[\frac{L_{ce}/L_{ce}^{\max} - L_{r1}}{k_1} \right] + 1 \right\} + \eta V_{ce}$$

c_1 , k_1 , and L_{r1} are constants defining the precise shape of the curve. Linear damping was also incorporated into the equation with constant coefficient, η , to account for the small amount of damping observed experimentally, which also contributes to the mathematical stability of the model.

Thick Filament Compression (F_{pe2}) At very short lengths, muscles generate passive force that opposes the force of contraction. This force is negligible for long lengths but starts to increase exponentially from $0.7 L_0$ until the minimum physiological length where net contractile force goes to zero (see Fig. 11; Brown et al. 1996b).

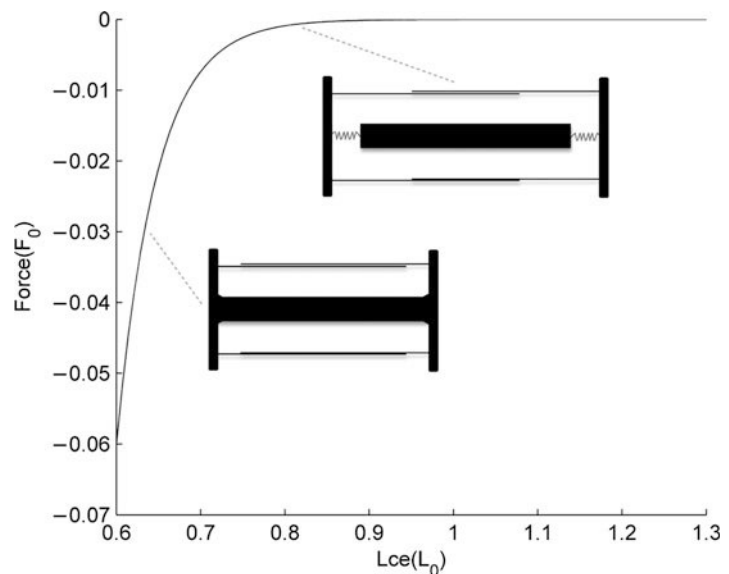
The steady-state force produced by tetanically stimulated muscle decreases at a fairly constant

rate for the range of lengths from L_0 to $0.7L_0$, reflecting steric interference between the overlapped thin filaments. At this relatively small length, however, the slope steepens abruptly and remains steep until the length at which net muscle force is zero. Assuming that the effects of double overlap on crossbridge formation are the same over the entire range of lengths in which it occurs, the number of crossbridges, hence force, should decrease proportionally with decreasing length. The abrupt change in force appears to reflect a collision between the myosin filament and the Z-disk, which would generate a reaction force opposing the force of contraction. The extent of compression of the myosin filament onto the Z-disk would be less for submaximal contractions because the number of crossbridges generating force would be relatively smaller. Thus it is important to model this effect separately from the force-length relationship, which affects force generation equally at all activation levels. The equation below computes the force at the muscle level as a function of length that opposes the force of contraction.

$$F_{pe2}(L_{ce}) = c_2 \{ \exp [k_2(L_{ce} - L_{r2})] - 1 \}$$

Constants c_2 , k_2 , and L_{r2} define the exact shape of the relationship depicted in Fig. 11.

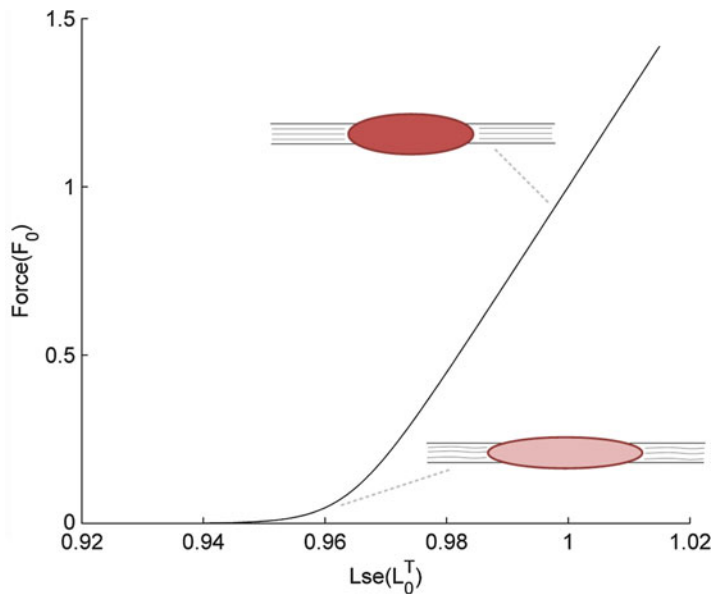
Physiology and Computational Principles of Muscle Force Generation, Fig. 11 Thick filament compression. Plot shows the parallel passive force of muscle opposing the contractile force as a function of fascicle length. The schematics illustrate the hypothesis that this force arises due to compression of the thick filament as the Z-disks are pulled even closer together at short muscle lengths. (Figure from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 11)



Series Elastic Element (Tendon + Aponeurosis; F_{se}) Muscles exert forces on bone segments through intermediate connective tissue, comprised mostly of aponeurosis and tendon. This serially connected tissue affects the muscle's motion, which modulates force output substantially. Clearly, the length of a muscle for a particular joint configuration depends on the length of the series elastic element because together they must span the entire path from the origin to the insertion site of the musculotendon. The portion of the path that is occupied by muscle depends not only on the resting length of the series elastic element but also on its elasticity, which determines how much it will stretch when it is pulled by the attached muscle. If a muscle is activated and then deactivated under isometric conditions as defined at the origin and insertion, the sarcomeres may experience large changes in length and especially velocity that will affect their force-generating ability. Note that the series elastic element is a nonlinear spring (see below and Fig. 12),

which undergoes a substantial portion of its ultimate strain at relatively low stresses, i.e., at low levels of muscle recruitment. Under dynamic conditions of activation and kinematics, the muscle fibers may actually move out of phase with the musculotendon (Zajac et al. 1981). This has important implications for the ability of muscle spindles to encode musculotendon length, hence joint position (Hoffer et al. 1992; Scott and Loeb 1994; Mileusnic et al. 2006).

The magnitude of the effects described above depends on the ratio of the lengths of the muscle fascicles to the connective tissue in series with them. Highly pinnate muscles have short muscle fibers oriented obliquely between fascial planes called aponeuroses that merge with the external tendon. Proximally, the aponeurosis has a thin sheetlike structure with a large surface area to accommodate insertion of a large number of fibers while more distally its shape gradually becomes thicker and smaller in surface area. It has been shown experimentally that for a wide range of



Physiology and Computational Principles of Muscle Force Generation, Fig. 12 Series elastic tendon/aponeurosis force. Force generated by elastic tissue that is in series with muscle as a function of its length. The schematic shows that for a given musculotendon length and low muscle activation (*bottom*), the tendon will be relatively slack and therefore produce little restoring force. At higher

activation levels (*top*), the muscle pulls more on the tendon and causes a larger restoring force. The stiffness is also greater in this case, denoted by the increased slope of the relationship, because the tendon becomes tauter at these higher force levels. (Figure from Tsianos and Loeb, Muscle Physiology and Modeling, article in Scholarpedia, Fig. 12)

muscle forces, aponeurosis and tendon strain are the same (Scott and Loeb 1995). The fact that the gradual thickening of the aponeurosis is paralleled by an increase in the number of fibers that exert force on it suggests that the stresses are fairly constant along its entire length. Because the stress and strain experienced by the aponeurosis and tendon are roughly the same, then presumably their material properties are similar and they can be lumped into a single element. The absolute thickness and strength of this connective tissue element is presumably controlled by trophic factors that depend on the maximal tensile forces that it experiences. The model assumes that tendon force scales with muscle cross-sectional area, or equivalently it scales with F_0 , and strain is measured with respect to tendon length at F_0 (L_0^T), permitting a generic relationship to be derived (see Fig. 12). This has been confirmed using several force-length relationships of the tendon/aponeurosis obtained experimentally (Brown et al. 1996b). L_0^T is a good normalization factor because it can be determined more reliably as opposed to the more commonly used tendon slack length. The equation that defines this relationship is shown below.

$$F_{se}(L_{se}) = c^T k^T \ln \left\{ \exp \left[\frac{L_{se} - L_r^T}{k^T} \right] + 1 \right\}$$

Constants c^T , k^T , and L_r^T define the precise form of the relationship shown in Fig. 12.

Parameters Needed to Model Specific Muscles

Musculotendons are comprised of the same basic elements, such as sarcomeres for contractile elements and collagen for passive elements, whose structural organization and properties lead to substantially different behavior on the whole musculotendon level. Knowledge of musculotendon morphometry and fiber-type-specific properties of sarcomeres is crucial for tailoring the generic relationships that comprise the model to the specific muscle of interest. The general physiological models above all employ normalization to dimensionless parameters (Topp et al. 1986) and so must be converted into real physical units (e.g., cm, N) by morphometric

parameters of the musculoskeletal system to be modeled.

Optimal Fascicle Length (L_0)

As mentioned in “Relevant Physiology,” sarcomeres have roughly the same dimensions and experience the same range of length changes during a contraction. Longer muscle, therefore, has more sarcomeres in series. This means that a given change in muscle length of a longer muscle is accompanied by relatively smaller length changes at the sarcomere level, hence a smaller change in myofilament overlap and force produced. Because the dimensionless force-length relationship applies to behavior at the sarcomere level, it must be scaled by the length of the muscle to account for this architectural effect on the behavior of the whole muscle. The morphometric parameter used for this purpose is optimal fascicle length, which is the distance between the aponeurosis sites measured along the orientation of the muscle fibers, measured at the length for which the muscle produces its maximal isometric force. Fascicle length is measured instead of muscle belly length because muscle fibers in many muscles are oriented obliquely with respect to the long axis of the muscle belly.

Muscle Mass (m)

The amount of force that a muscle can produce depends on the total number of myofilaments arranged in parallel. Because myofilaments are densely packed through muscle fibers, this number is proportional to the physiological cross-sectional area (PCSA) of the muscle fibers. Because those fibers may be arranged in a pinnate form, the anatomical cross section of the muscle may not be perpendicular to all the muscle fibers and so would not reflect their true cross-sectional area. More reliable measurements can be made of the mass of the muscle, which can be converted to its volume by dividing by density. This volume must be the product of the length of the contractile elements (L_{ce}), which can be measured reliably by dissecting fascicles from the muscle, assuming that they are of uniform length (common) and at optimal length L_0 (any discrepancy can be

detected and corrected by observing sarcomere length under a microscope).

$$PCSA = \frac{m}{\rho L_{ce}}$$

Specific tension, ε , or maximal isometric force produced per unit of cross-sectional area (Spector et al. 1980; Lucas et al. 1987), has been shown to be the same across different fiber types (31.8 N/cm^2) and can be used to estimate maximal isometric force (F_0) using the following equation:

$$F_0 = \varepsilon * PCSA$$

Muscle fascicle length in the equation is set to L_0 , because ε is defined at that length. The modeled muscle's F_0 is used to scale the dimensionless relationships to obtain force output in absolute units.

Fiber Composition

Although maximal isometric force per unit area is roughly the same for different muscle fiber types, there are substantial differences in their contractile properties. Fiber types differ in terms of kinematic modulation of force output, rise and fall dynamics of contraction, and especially energy consumption. The recruitment order of motor units also depends on their fiber type. It is therefore important that different fiber types are modeled independently and that the fiber composition of the modeled muscle is known accurately.

Determining fiber composition is often challenging because of the many classifications of fiber types and because of the difficulty in measuring the attributes that distinguish them. Fibers differ mainly in terms of their myosin isoforms (namely, the myosin light and heavy chains) and the size of their sarcoplasmic reticulum and transverse tubule system that together influence force generation under dynamic conditions. There are also large differences in mitochondrial content and blood supply, which affect the metabolic cost of muscle contraction as well as the fiber's susceptibility to fatigue. All of these tend to covary in healthy muscle fibers but may become

heterogenous in muscle fibers that are diseased or undergoing trophic changes as a result of abnormal or rapidly changing usage patterns. Because differences in myosin heavy chain isoform and mitochondrial content have the largest physiological effects, they are used most commonly to classify fiber types. Slow-twitch (type 1) fibers have a different distribution of myosin heavy-chain isoforms than fast-twitch (type 2) fibers that leads to slower crossbridge kinetics, as evidenced by the relatively slow rate at which they hydrolyze ATP. Type 1 fibers and some type 2 fibers (namely, type 2a) have a high volume fraction of mitochondria, which can be assessed indirectly by measuring the concentrations of enzymes such as succinate dehydrogenase, for example, which is normally present in the mitochondria. These histochemical approaches require a tissue sample, which could be too invasive to obtain from humans. It is also worth noting that the results may be biased depending on the location in which it is obtained. Fast-twitch fibers tend to reside in the outer portion in muscle, so if a single sample is obtained from this location, the measurement would underestimate the percentage of slow-twitch muscle. There are also noninvasive methods for measuring fiber composition such as magnetic resonance spectroscopy, but to date they are relatively less accurate.

Characteristic Firing Rate of Muscle Fiber Type ($f_{0.5}$)

Muscles typically fire at rates ranging from $0.5f_{0.5}$ to $2f_{0.5}$, where $f_{0.5}$ is the firing rate at which muscle produces half of its maximal isometric force when its length is held at L_0 . $f_{0.5}$ is an important parameter because crossbridge activation relationships of different muscles that are normalized by this value become congruent, and therefore a generic relationship can be obtained. This is useful because only this parameter is needed to construct the entire crossbridge activation relationship for an arbitrary muscle to a high degree of accuracy. The actual firing rate behavior of motor units has been difficult to record, particularly at the higher levels of recruitment, so this useful normalization remains contentious.

Tendon + Aponeurosis Length (L_0^T)

The tendon plus aponeurosis is composed of tightly packed strands of collagen that are oriented in parallel with the long axis of the musculotendon. As in muscle, the amount a tendon can stretch depends on its length and the amount of force it generates in response to a stretch depends on its cross-sectional area. Longer tendons are composed of more collagen molecules arranged in series, each having similar material properties and dimensions, i.e., experiencing the same change in length in response to the same force. Longer tendons can therefore experience larger changes in length and will produce lower forces in response to the same stretch. The generic relationship of the series elastic element reflects the material properties of the constituent collagen fibers and should be scaled by the length of the tendon plus aponeurosis to be modeled. The length should be measured when muscle is exerting maximal isometric force on the tendon (L_0^T). If only the slack length of the tendon is known, then L_0^T can be estimated as 105% of tendon slack length.

Maximum Musculotendon Path Length ($L_{\max}^{MT}$)

As mentioned in "Parallel Elastic Element," the amount of passive force generated by muscle at a particular length correlates with its maximal anatomical length. Maximal anatomical length is defined as the maximal length a muscle can have across all anatomical configurations of the joints it crosses. This can be estimated by first measuring maximal anatomical length of the musculotendon and subtracting the length corresponding to the tendon (L_0^T).

Pinnation Angle

Muscle fibers of many muscles are oriented obliquely with respect to the tendon, and so not all of the force that they generate is transmitted to the bone segments. It is reduced by the cosine of the pinnation angle, with the remainder of the contractile force producing hydrostatic compression of the muscle. Even for relatively large pinnation angles, however, this loss in total force transmission in isometric muscle is relatively low (Scott and Winter 1991), so this model

does not account for this effect and does not require specification of pinnation angle. Modeling the effects of pinnation angle would be important for the relatively uncommon scenario in which it is large and changes rapidly by large amounts throughout a contraction, as it would alter the kinematics of the muscle fascicles, which in turn have a strong influence on force production.

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Physiology and Function of Cochlear Efferents

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Synonyms

[Final neurons of the descending auditory system](#); [Medial and lateral efferents](#); [Olivocochlear bundle](#); [Olivocochlear efferents](#)

Definition

Cochlear efferents are neurons that originate in the brainstem and terminate in the cochlea.

Detailed Description

Anatomy

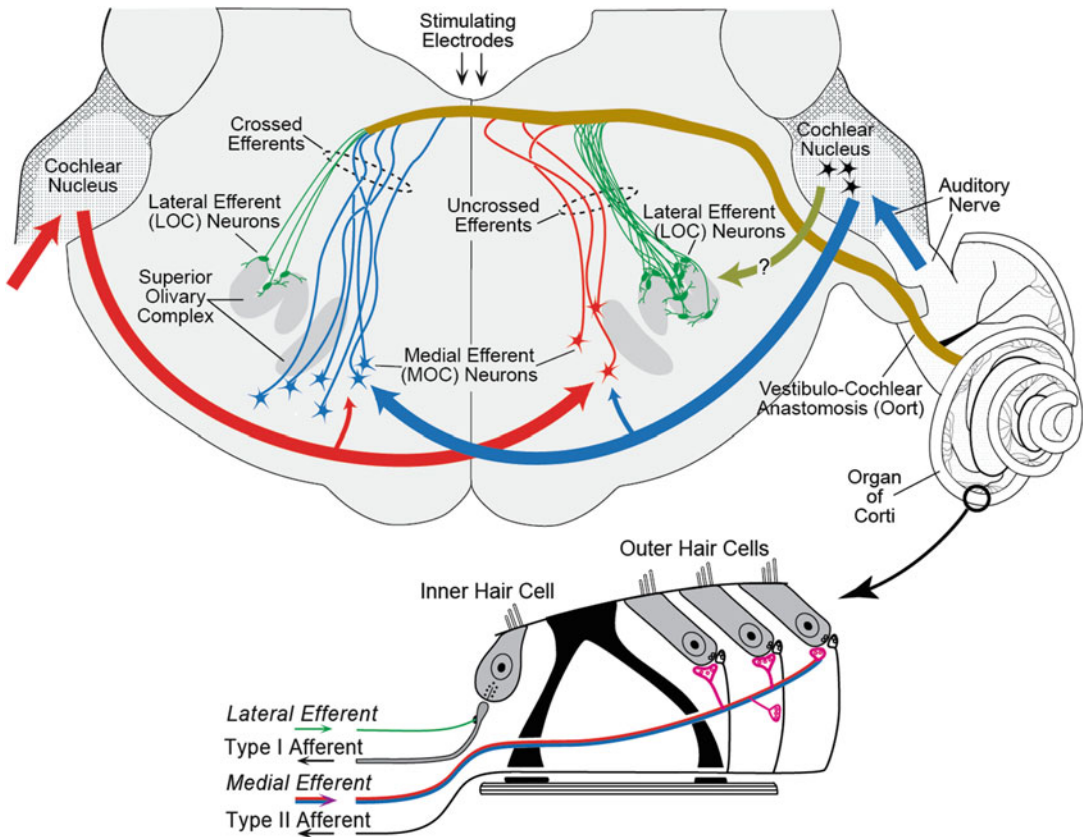
In mammals, the final descending auditory pathways to the cochlea originate in the brainstem superior olivary complex and are called “olivocochlear efferents.” They are divided into two subsystems: the medial olivocochlear (MOC) and lateral olivocochlear (LOC) efferents (Fig. 1). MOC efferents originate in the medial part of the superior olivary complex and terminate mainly on outer hair cells (OHCs). LOC efferents originate in the lateral part of the superior olivary complex and terminate mainly on the peripheral processes (dendrites) of auditory nerve fibers under inner hair cells (IHCs) (Fig. 1, bottom). Efferent fibers also have branches that innervate other structures. Both MOC and LOC neurons receive inputs from other brain areas including higher auditory centers (not shown in Fig. 1).

In many species there are approximately twice as many MOC fibers that cross the midline and innervate the contralateral cochlea compared to the MOC fibers that are uncrossed and innervate the ipsilateral cochlea. In contrast, almost

all LOC fibers are uncrossed. An important difference is that MOC fibers are large and myelinated whereas LOC fibers are small and unmyelinated. One consequence of this is that electrical recordings have been made from the large MOC fibers (which showed that they respond to sound), but recordings have not been made from the small LOC fibers. Also, myelinated fibers are relatively easy to electrically stimulate, so electrical stimulation of MOC fibers has revealed what they do in the cochlea. In contrast, unmyelinated fibers have much

higher thresholds for electrical stimulation, and there are no similar direct stimulation studies that show what LOC fibers do in the cochlea.

MOC fibers are the effector neurons in a brainstem reflex pathway (Fig. 1, red, blue, and gold). The pathway starts with auditory nerve fibers that innervate neurons in the cochlear nucleus. Certain cochlear nucleus neurons (planar multipolar cells) send axons that cross the midline and innervate MOC neurons on the opposite side. These neurons form excitatory synapses on MOC neurons and appear to be the main



Physiology and Function of Cochlear Efferents, Fig. 1 An anatomical schematic of the olivocochlear (OC) reflexes to the right cochlea. *Top*: an outline of a transverse brainstem section showing the lateral OC (LOC green) and medial OC (MOC blue and red) neurons. Blue and red show the ipsilateral and contralateral MOC reflex pathways, respectively, until they join the olivocochlear bundle (OCB gold). Both MOC and LOC fibers form the OCB, which has crossed and uncrossed components. The OCB is accessible to stimulating

electrodes near the fourth ventricle (*at top*). *Bottom*: the afferent and efferent innervation to the organ of Corti: (1) olivocochlear lateral efferent fibers that synapse on Type I afferent fibers, (2) auditory nerve (AN) Type I afferent fibers that innervate inner hair cells, (3) olivocochlear medial efferent fibers to outer hair cells, and (4) AN Type II afferent fibers that form reciprocal synapses on OHCs and receive synapses from MOC fibers. (Modified after Fig. 8.1 of Guinan (1996) by permission of Springer-Verlag)

drive for the MOC acoustic reflexes that feed back to the cochlea. Since the dominant pathway from CN neurons to MOC neurons is crossed, the uncrossed MOC fibers carry the contralateral MOC reflex, and the crossed MOC fibers carry the ipsilateral MOC reflex (which crosses the midline twice). There is also evidence for a minor pathway from the cochlear nucleus to the MOC neurons on the same side which may account for most MOC neurons showing binaural properties, i.e., although MOC neurons are mainly excited by sound in one cochlea, sound in the opposite cochlea can also change the response (most often adding additional excitation).

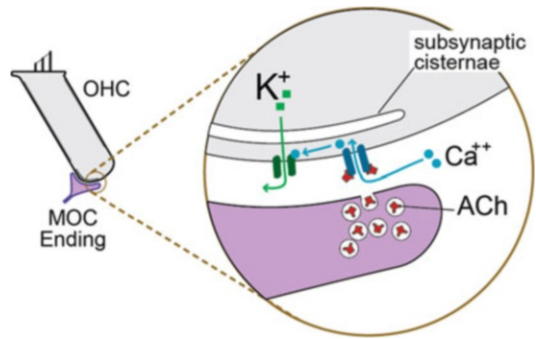
In responses to tones, MOC fibers have V-shaped tuning curves much like those of auditory nerve fibers but somewhat wider. An individual MOC fiber innervates a place along the cochlea that has a best frequency similar to the MOC fiber's best frequency, i.e., the innervation is tonotopic. Although it has not been demonstrated physiologically or anatomically, it seems likely that MOC neurons in the brainstem are also tonotopically arranged.

Neurochemistry

The main neurotransmitter of olivocochlear efferents is acetylcholine (ACh), the same neurotransmitter found in peripheral nerve-muscle junctions. The MOC-OHC synapse is unusual in that it uses $\alpha 9$ - $\alpha 10$ ACh receptors and acts through a Ca^{++} -activated potassium channel (see Fig. 2). LOC-AN synapses use ACh but also have several other neurotransmitters and neuromodulators. Some LOC-AN synapses use the neurotransmitter dopamine. Little detail is known about LOC-AN synapses, but there is evidence that some may be excitatory and some inhibitory, actions which most likely reflect the two neurotransmitters, ACh and dopamine.

MOC Fast Inhibition

The most-studied effect of MOC fibers is a fast (time constant tens to hundreds of ms) inhibition of cochlear amplification (the process by which outer hair cells increase basilar membrane motion in response to low-level sounds). Since MOC action lowers cochlear amplification, a higher



Physiology and Function of Cochlear Efferents, Fig. 2 A schematic of a medial olivocochlear (MOC) synapse (purple) on an outer hair cell (OHC gray). The MOC terminal releases acetylcholine (ACh red) molecules which attach to $\alpha 9$ - $\alpha 10$ ACh receptors (dark blue) on the OHC. The $\alpha 9$ - $\alpha 10$ ACh receptors allow calcium ions (Ca^{++} blue circles) to enter the OHC, and these activate nearby Ca^{++} -activated potassium channels (dark green). These allow potassium ions (K^{+} green squares) to exit the OHC which hyperpolarizes the OHC and shunts OHC receptor currents, thereby reducing OHC motility and cochlear amplification

sound level is needed to achieve a given response level. The result is to shift responses toward higher sound levels; this effect that can be seen both in basilar membrane (Fig. 3a) and auditory nerve (Fig. 3c) responses to tones. Cochlear amplification, and therefore MOC inhibition, is largest in responses at the local best frequency (Fig. 3b, d). While most MOC effects can be explained by the reduction of cochlear amplification of basilar membrane responses, some cannot, e.g., inhibition at high sound levels or on the edges of tuning curves (Fig. 3e, f).

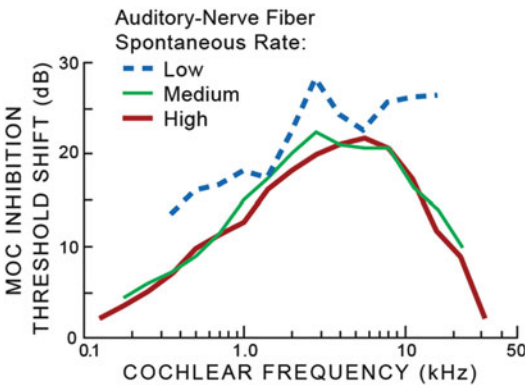
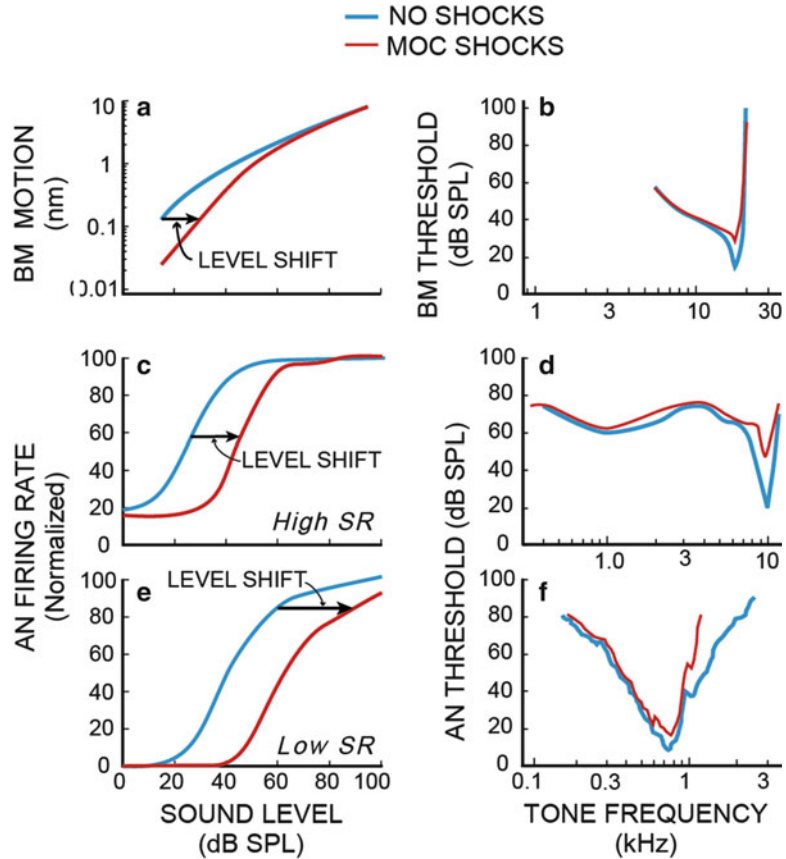
MOC innervation of the cochlea peaks in the mid-basal turn, and when MOC fibers are stimulated electrically, the largest MOC inhibition is seen in the corresponding frequency region (Fig. 4). The profile of MOC effect versus frequency in Fig. 4 is for cats. The corresponding pattern in humans is expected to be shifted 1–1.5 octaves lower in frequency due to human hearing covering a lower frequency range than cats.

MOC Slow Inhibition

When MOC fibers are stimulated over tens of seconds, an inhibition builds up that is called the MOC “slow effect” (Fig. 5). MOC fast and slow

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Fig. 3 MOC fast effects on basilar membrane (BM) motion and auditory nerve (AN) firing. *Left:* MOC inhibition shifts level functions to higher sound levels. *Right:* MOC inhibition usually has the greatest effect at the most sensitive frequency (b, d), but sometimes has the greatest effect at the edge of tuning curves (f). MOC activity was elicited by brainstem shocks. (a, b) Schematized from the data of Cooper and Guinan (2006). (c, e) Schematized from the data of Guinan and Stankovic (1996). (d) Schematized from the data of Guinan and Gifford (1988) and (f) from the data of Guinan and Gifford (1988) published as Fig. 3.3F from Guinan (2011) with permission from Springer Science+Business Media



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Fig. 4 MOC inhibition produced by electrical stimulation of medial efferent fibers in cats. MOC inhibition was measured as the threshold shift at an auditory nerve fiber's best frequency (cochlear frequency). Fibers were divided into low, medium, and high spontaneous rate groups. Each point shows the average over an octave band (adjacent points overlap data). In cats, medial efferent innervation peaks at about the 8 kHz region and has a profile along the cochlea like the inhibition of high and medium SR fibers. (Data from the work of Guinan and Gifford (1988))

effects inhibit both basilar membrane motion and auditory nerve fiber responses. However, basilar membrane responses are changed in opposite phase directions during fast and slow MOC effects, which shows that fast and slow effects originate predominantly from different mechanisms within the outer hair cells. MOC fast inhibition appears to be due to the hyperpolarization of OHCs and the shunting of OHC receptor currents produced by the MOC-OHC synapse's activation of Ca^{++} -activated potassium channels (Fig. 2). Application of ACh to isolated OHCs causes a slow decrease in OHC stiffness. The similarity of the slow time courses of the OHC stiffness change and the MOC slow effect suggests that the MOC slow effect is due to the change in OHC stiffness.

MOC Effects in Humans

All of the data shown above are from animals, and the MOC effects are from MOC activity produced

by electric shocks. In humans, you cannot excite the MOC efferents by shocks or record from auditory nerve fibers, but you can excite efferents by sound and record MOC effects by the change in otoacoustic emissions (OAEs). OAEs are sounds produced within the cochlea as a byproduct of cochlear amplification that travel backward through the middle ear and can be measured in the ear canal by a sensitive microphone. Since OAEs depend on cochlear amplification, and MOC activity turns down cochlear amplification, MOC activity reduces the amplitude of OAEs. Thus, the change in OAE amplitude can provide a measure of the MOC effect within the cochlea. OAE measurements are noninvasive and can be done in humans.

Activation of MOC efferents to one ear can be produced by sound in either or both ears (Fig. 6). This is consistent with the innervation pattern shown in Fig. 1 in that a given cochlea (the right cochlea in Fig. 1) receives sound-driven inputs from both ears. With sound in both ears, the MOC response is roughly the sum of the contributions from both sides (at least when the noise is the same in both ears).

The MOC-induced change takes time to build up and decay (Fig. 6). Across subjects the onset and decay time constants were 277 ± 62 and 159 ± 54 ms for contralateral broadband noise.

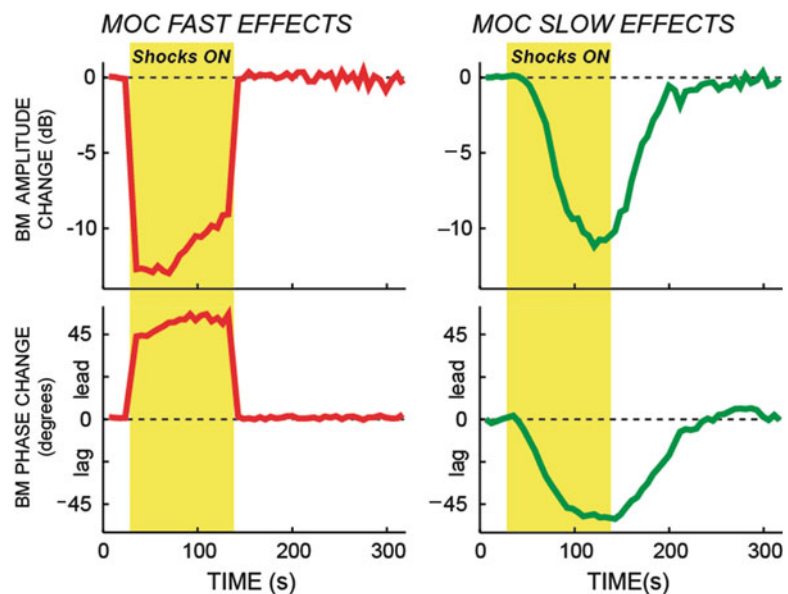
The onset and offset both started after delays of ~ 25 ms from the start or end of a noise burst. Little difference in time course was found for ipsilateral, contralateral, or bilateral elicitors. Considering the overall speed of the reflex, it seems best suited to operate on sound changes that last for 100 s of milliseconds. MOC reflex inhibition is too slow to act at a syllable by syllable rate on responses to speech.

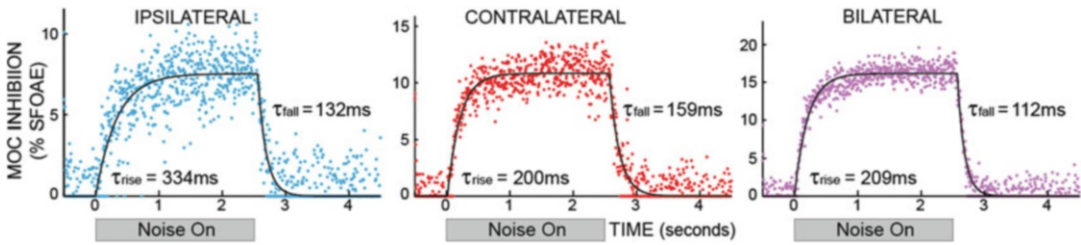
MOC activation is a strong function of the bandwidth of elicitor sounds (Fig. 7). Broadband noise is the strongest elicitor; elicitor strength decreases as bandwidth decreases. This is true for ipsilateral, contralateral, and bilateral sounds. Note that since the overall elicitor level was kept constant as the elicitor bandwidth was increased, the energy density at each frequency decreases as bandwidth increases. These results indicate that the MOC reflex that affects one place on the cochlea summates excitation over almost the whole cochlea.

From experiments in animals, the ipsilateral reflex was expected to be twice as strong as the contralateral reflex. This is what was found for $\frac{1}{2}$ octave bands of noise (Fig. 7, red and blue points at the bottom left in each panel), but for broadband noise, the ipsilateral and contralateral reflexes elicited MOC inhibitions of similar strengths (Fig. 7, red and blue points at the right in each

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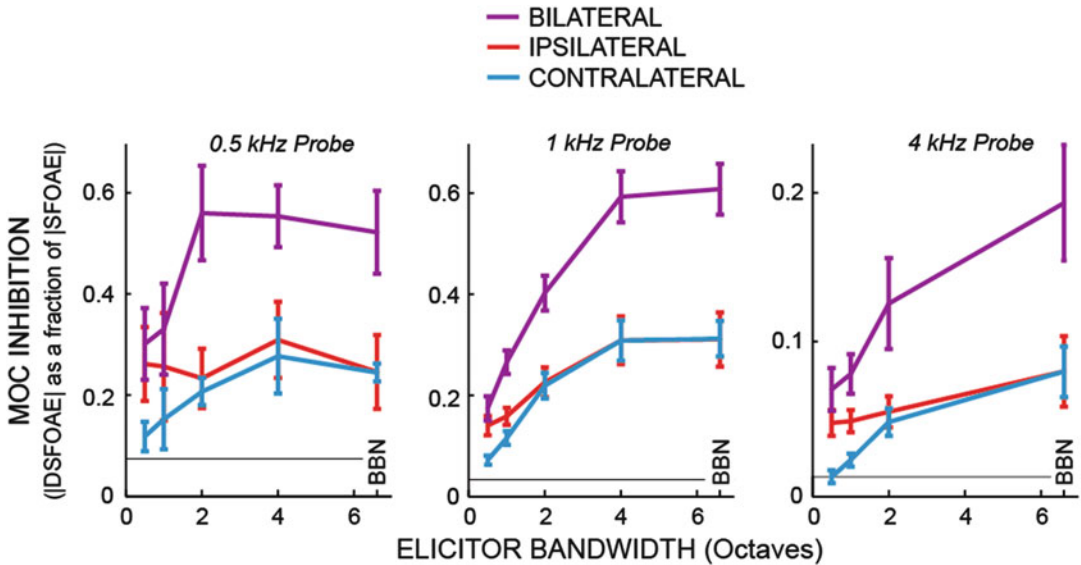
Fig. 5 MOC fast and slow effects both inhibit (i.e., reduce) basilar membrane (BM) motion (*top*), but they produce phase changes in opposite directions (*bottom*). The yellow areas show the period of MOC stimulation. Data at *left* and *right* obtained simultaneously. (From the data of Cooper and Guinan (2003))





Physiology and Function of Cochlear Efferents, Fig. 6 Representative MOC response magnitudes as a function of time from ipsilateral, contralateral, and bilateral elicitors from one ear of one subject. The elicitors were 50 dB SPL wide-band (0.1–10 kHz) noises with a 2.1 octave notch centered on the 40 dB SPL, 1 kHz probe tone. Points are data. Lines represent single exponential fits to the data with rise and fall time constants, τ_{rise} and τ_{fall} , shown in each plot. Each MOC response magnitude

was corrected for the measured noise, i.e., was estimated as the square root of (the magnitude of the change in the stimulus frequency otoacoustic emission ($|\Delta\text{SFOAE}|$) squared, minus the variance of the noise). The MOC response magnitude was set to zero when the noise variance was greater than $|\Delta\text{SFOAE}|$ squared. Responses were normalized by the magnitude of the SFOAE before the noise onset. (Unpublished data of Backus and Guinan (2006))



Physiology and Function of Cochlear Efferents, Fig. 7 MOC inhibition as a function of reflex elicitor bandwidth in humans. 60 dB SPL noise-band elicitors were centered on the frequency of the 40 dB SPL probe tones. The index of MOC inhibition was the magnitude of the change in the stimulus frequency otoacoustic emission $|\Delta\text{SFOAE}|$ normalized to the magnitude of the SFOAE

before the elicitor onset ($|\text{SFOAE}|$). To avoid interaction within the cochlea of the elicitor and probe responses, the MOC inhibition was measured in a 100 ms window starting 50 ms after the elicitor terminated. Error bars are standard errors of the mean. Horizontal lines: Solid mean noise-floor, BBN broadband noise (0.1–10 kHz, or 6.67 octaves). (From the data of Lilaonitkul and Guinan (2009))

panel). The crossed/uncrossed innervation ratio is not known for humans because determining this requires invasive experiments. However, from Fig. 7 it appears that sound bandwidth matters as much as the innervation ratio. Presumably, sound

bandwidth influences the way in which signals from the two ears are summated in the brainstem.

Another way in which the human and animal data differ is in their pattern across frequency. The typical result for shock-evoked MOC effects in

anesthetized cats and guinea pigs is a broad pattern of inhibition of auditory nerve responses that peaks near 8 kHz (Fig. 4). Translated to the frequency range of humans, this would be a peak near 4 kHz. Since shocks excite MOC fibers of all frequencies, the most comparable measurements in humans are those from broadband noise (e.g., the right-most points in Fig. 7). Taking note of the different vertical scale used at 4 kHz in Fig. 7, there is less MOC effect at 4 kHz than at 0.5 and 1 kHz. It has been a consistent finding that sound-evoked MOC effects measured in awake humans by changes in a variety of different otoacoustic emissions peak near 1 kHz. There are many differences in the techniques and conditions between the animal and human experiments, but the exact origin of the frequency of maximal MOC effect is not known.

The pattern of MOC inhibition across frequency depends on both the frequency of the sound that evokes the MOC activity and the place in the cochlea at which the MOC effects are measured (Fig. 8). For ipsilateral elicitors, the MOC inhibition occurs over a broad range but peaks near the frequency of the elicitor. In contrast, for contralateral elicitors, the largest MOC effects are elicited by sounds near 1 kHz no matter whether they are measured with low-, medium-, or high-frequency probes. Binaural

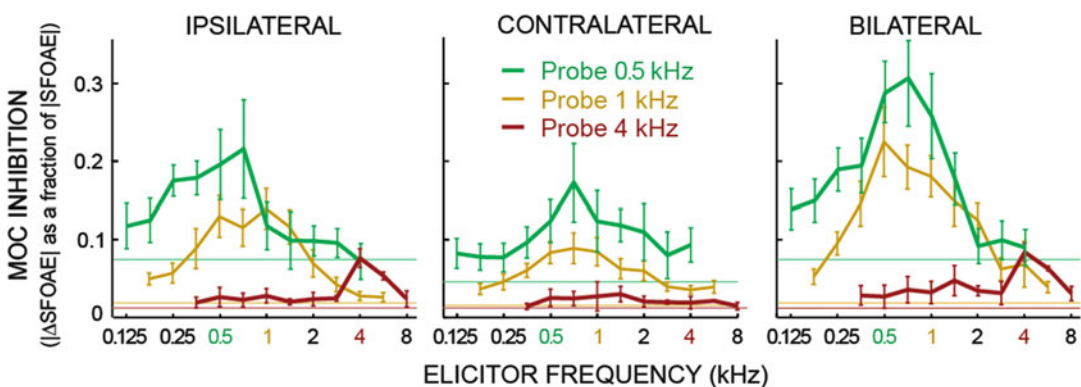
sounds elicit effects with intermediate frequency specificity. For bilateral sound, the magnitude of the MOC effect is typically close to the sum of the separate ipsilateral and contralateral MOC effects.

The strength of the MOC reflex varies across subjects. In a study of 25 subjects with good hearing and with MOC effects averaged long enough to get a statistically significant measurement in each subject, the MOC strength varied over a 5 to 1 range. Whatever benefit MOC inhibition has for hearing, it appears to vary across subjects (Fig. 9).

The Role of Efferents in Hearing

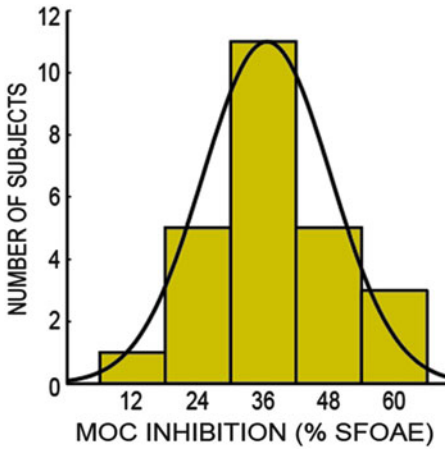
There may be many benefits of efferent activity but there is enough evidence to conclude that the following two efferent roles are important: (1) prevention of damage due to loud sounds and (2) helping to distinguish relevant sounds in background noise.

Animal experiments have shown that MOC efferents help to prevent hearing damage due to traumatic sound levels. When exposed to the same traumatizing sounds, guinea pigs with strong MOC reflexes had lower *permanent* threshold shifts than guinea pigs with weak MOC reflexes (Fig. 10). Other experiments have shown that exciting MOC efferents with shocks reduces temporary threshold shifts (TTSs). Both of these show effects of MOC efferents. Recent



Physiology and Function of Cochlear Efferents, Fig. 8 The MOC inhibition elicited by a $\frac{1}{2}$ octave band of noise depends on the frequency of the noise and of the probe tone. The noise bands were 60 dB SPL and the probe tones were 40 dB SPL. The index of MOC inhibition was the magnitude of the change in the stimulus frequency

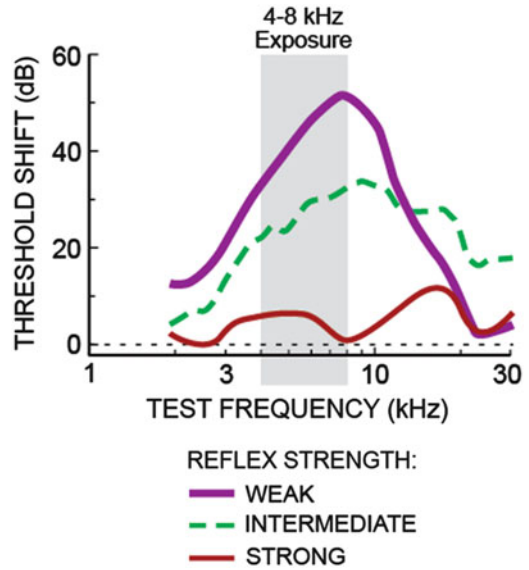
otoacoustic emission $|\Delta SFOAE|$ (measured in a 100 ms window starting 50 ms after the elicitor terminated) normalized by the magnitude of the SFOAE before the elicitor onset ($|SFOAE|$). Error bars are standard errors of the mean. Solid line noise-floor mean, color coded as in the key. (From the data of Lilaonitkul and Guinan (2012))



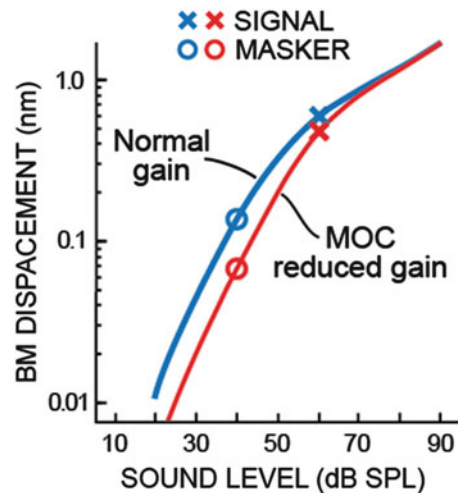
Physiology and Function of Cochlear Efferents, Fig. 9 MOC inhibition varies widely across subjects ($n = 25$, mean = 37%, SD = 12%). MOC inhibition measured by the change in stimulus frequency otoacoustic emissions from a 40 dB SPL probe tone near 1 kHz. A 60 dB SPL contralateral wide-band noise elicited MOC activity. The line is a Gaussian fit to the data. (From the data of Backus and Guinan (2007))

experiments have shown that sounds that produce TTSs (probably due to damage in different cochlear structures than the TTSs noted above) can lead to long-term, permanent loss of auditory nerve fibers. This loss of auditory nerve fibers appears to come about because loud sounds cause an excessive release of neurotransmitter by inner hair cells which produces an excessive, indeed excitotoxic, flow of ions into the dendrites of auditory nerve fibers, which causes them to swell, burst, and degenerate. LOC efferents synapse on these auditory nerve fiber dendrites, and it seems likely that a major role of the LOC efferents is to reduce/prevent such damage. However, there is not, as yet, direct evidence that LOC fibers actually reduce or prevent the degeneration of AN fibers after acoustic trauma.

Many experiments have been done to look for efferent benefits in perceptual tasks. The most convincing evidence of an efferent perceptual benefit comes from animal experiments in which efferents were cut and their ability to localize sounds in noise decreased. In humans, a wide variety of experiments have been done trying to correlate increased MOC activity (measured with



Physiology and Function of Cochlear Efferents, Fig. 10 Strong MOC reflexes help to reduce noise-induced hearing damage. Permanent threshold shifts from 12 guinea pigs grouped by each animal's preexposure MOC reflex strength. Threshold shifts measured from auditory nerve compound action potentials. (Schematized from Fig. 5b of Maison and Liberman (2000))

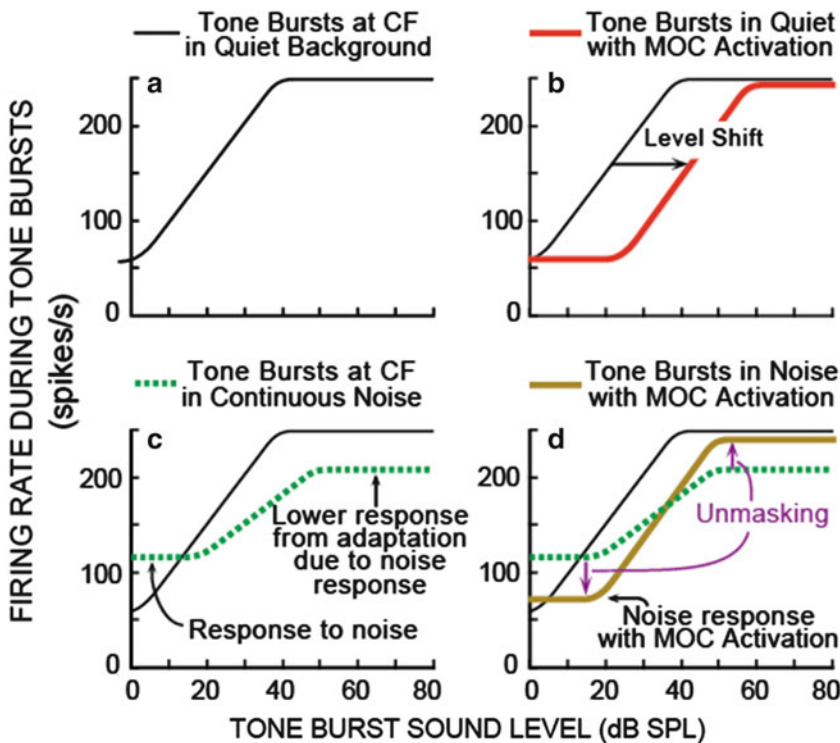


Physiology and Function of Cochlear Efferents, Fig. 11 MOC stimulation can increase the signal-to-noise ratio of a signal relative to a masker. Lines show basilar membrane (BM) response with (thin red) and without (thick blue) MOC stimulation. The BM motion response to the higher-level signal (X) is reduced less than the response to the lower-level masker (O). (BM responses based on unpublished data of Cooper and Guinan)

otoacoustic emissions) with better performance in tasks involving the discrimination of a signal in noise. Both positive and negative results have been reported, even in tasks that look superficially similar. Overall, the data argue that MOC activity provides perceptual benefits, but the conditions under which a benefit is produced and the extent of that benefit are not yet clear.

Despite the lack of clarity in just how much perceptual benefit MOC efferents produce, there are two clearly understood mechanisms by which MOC efferents may produce such a benefit. For a moderate-level sound in a low-level noise, MOC efferents may increase the signal-to-noise ratio in the mechanical response of the basilar membrane. This increase in signal-to-noise ratio is produced because MOC efferents reduce the gain of cochlear amplification more at low sound levels than at high sound levels (Fig. 11).

Another mechanism by which MOC efferents may reduce noise masking (i.e., produce “unmasking”) takes place when there is a transient signal of interest in a background noise. In a silent background, MOC activity reduces cochlear amplification and shifts auditory nerve fiber responses to brief tone bursts to higher levels with little change fiber’s firing rate dynamic range (Fig. 12b). A background noise compresses this dynamic range by causing ongoing firing of the fiber which decreases the dynamic range available to signal-added low-level tone bursts – Fig. 12c. This background firing depletes the inner hair cell supply of vesicles which decreases the dynamic range at high tone levels (Fig. 12c). The net result is that a smaller change in output firing rate can be produced by a change in tone-burst sound level, i.e., the noise masks small changes in tone-burst level. Efferent stimulation



Physiology and Function of Cochlear Efferents, Fig. 12 MOC unmasking of auditory nerve fiber responses. Each panel shows rate versus level functions for a single auditory nerve fiber with sound conditions

coded by line styles as shown at the top of each panel. See text for further explanation. (Modified after Fig. 8.10 of Guinan (1996))

reduces the fiber response to the noise, which reduces the depletion of vesicles, with the net effect to be a partial restoration of the auditory nerve fiber's dynamic range, i.e., efferent unmasking (Fig. 12d).

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Physiome Repository

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Definition

Physiome Repository (<http://models.physiomeproject.org>) is an online repository of mostly publicly available models and their associated data. Although models encoded in CellML are currently best supported, content in any format can be stored, retrieved, shared, and version controlled in the Physiome Repository (e.g., MATLAB m-files, C code, SBML, or NeuroML).

Detailed Description

The Physiome Repository originated as a generalization of the CellML model repository (Lloyd et al. 2008) to enable archiving, exchange, and collaborative development of computational models throughout the Physiome Project. Due to this history, models encoded in the CellML format still form the majority of the Physiome Repository content, with over 500 models currently publicly available. The software infrastructure underlying the repository is the Physiome Model Repository (PMR) software (Yu et al. 2011). The PMR software has specific support for CellML and FieldML, but it allows any electronic file to be

deposited, retrieved, and version controlled. As described later in this entry, the PMR software can also easily be extended to provide specific support for other model or data formats. The PMR software is an open-source software, and most content in the repository is freely available under a creative commons license. It also supports restricted access modes allowing the user who deposits the content to grant specific permissions (e.g., read/write) to specific users.

Revision Control

A key feature of the Physiome Repository is revision control, which relies on integration with the Mercurial distributed version control system (DVCS) (<http://mercurial.selenic.com/>). The CellML and FieldML model formats enable modularity by allowing models to be decomposed into multiple files. This feature is often used in other model and data formats as well. Within a set of related files, it is important to keep the files consistent with one another, which is achieved using the PMR software's revision control features. These allow files to be grouped into "workspaces," each of which is a version-controlled folder along with its contents and sub-folders. The set of related files in a workspace can be retrieved in the state that they were at for any recorded revision in the history. Revision control also assists with data provenance, recording who made each change, and the reason, captured each time a user commits a change to the version control system and manually enters a comment describing the reason. The use of a DVCS enables version-controlled collaboration between multiple users allowing model development to take place independent of the Physiome Repository but preserving the version history when these changes are "pushed" back into the Physiome Repository.

Model Presentation

"Exposures" are used to highlight specific revisions of a workspace, for example, when a

particular revision represents the state of a model at the time of a research publication about the model or has been vetted by a user performing the role of a curator. Importantly, exposures create a persistent URI, which unambiguously identifies a specific version of a workspace and provides the basis for uniquely locating all resources relevant to that exposure. Furthermore, for data formats that have customized exposure plug-ins, the user is able to select enhanced options that control the generation of user-friendly web pages for the model during the exposure creation process. For example, for each CellML model exposure, the mathematical equations for that model are displayed, as well as descriptive text about the model, and an associated diagram, as well as the equivalent computer program code which is automatically generated for the CellML model in a selection of programming languages (MATLAB, Python, C, and Fortran).

Underlying Software

The PMR software is constructed on top of a content management framework called Zope (<http://www.zope.org/>), with all content management aspects surrounding the handling of models and related data using the content management system called Plone (<http://plone.org/>), which is also built on top of Zope. Each feature of the PMR software is constructed as a set of plug-ins on top of the Zope/Plone system. These plug-ins provide the core functionality of the Physiome Repository: collaborative development and data exchange. Support for additional model and data formats, or alternative DVCSs, can be achieved by creating the required plug-ins.

Cross-References

- [CellML](#)
- [FieldML](#)
- [NeuroML](#)

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PhysioNet

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Definition

PhysioNet (<http://physionet.org/>) is a resource for research and education that provides free access to numerous large collections of recorded physiologic signals and time series and related open-source software for exploration and analysis of them, in support of basic, clinical, and applied research in medicine, physiology, public health, biomedical engineering and computing, and medical instrument design and evaluation. Although best known for its critical care, ECG, and cardiovascular data collections, PhysioNet curates a wide variety of data collected and contributed by neuroscientists, clinical neurologists, and researchers in allied disciplines.

Detailed Description

PhysioNet has three major components.

PhysioBank holds more than 60 open-access data collections as of 2013, containing physiologic signals and time series collected from roughly 36,000 human subjects and amounting to more than 4 TB in all. The recordings include cardiopulmonary, neural, and other biomedical signals from healthy volunteers of all ages as well as patient cohorts with conditions

including epilepsy, neurodegenerative diseases, sleep and gait disorders, congestive heart failure, sudden cardiac death, organ failure, trauma, and more.

PhysioToolkit includes software components for data visualization, interactive waveform annotation, data mining, importing and exporting data, deidentification, signal and time series analysis (including QRS and BP pulse detectors, derivation of respiration from the ECG signal, atrial fibrillation detection, apnea detection, IPFM tachometry of heart rate, standard and novel measures of heart rate variability, cardiac output estimation, and T-wave alternans detection and quantification), linear and nonlinear filters, signal averaging, frequency domain analysis of evenly and unevenly sampled time series, detrended fluctuation analysis, multiscale entropy, information-based similarity classification, multifractal analysis of time series, sample entropy, lumped parameter models of the heart and circulation for research and education, and realistic ECG waveform generators, as well as libraries of functions to provide uniform access to PhysioBank-compatible data either from local files or directly from Web servers for user-written software in C, C++, Fortran, Java, MATLAB, Octave, Perl, and Python. All PhysioToolkit software is available in source form under the GNU General Public License (GPL).

PhysioNetWorks is an online laboratory that provides workspaces for researchers to develop contributions that will be made publicly available via PhysioNet when complete. Unlike other areas of PhysioNet, these workspaces are password protected. During the active phase of research, data can be deposited securely; shared with selected collaborators; analyzed, annotated, and indexed using software provided by PhysioNet or by the research team; and documented. When the development is complete (often when the major results of the study are published), the project's contributions are reviewed and posted in PhysioNet's public archives; data go to PhysioBank and open-source software to PhysioToolkit.

Background

PhysioNet was founded in 1999 (Goldberger et al. 2000) by a team of researchers and clinicians headed by Ary L. Goldberger (a professor of medicine at Harvard Medical School and a cardiologist at Boston's Beth Israel Deaconess Medical Center) and Roger G. Mark (a professor of electrical engineering and computer science at MIT, former cochair of the Harvard-MIT Division of Health Science and Technology, and a physician). Mark, Goldberger, and their colleagues are long-time collaborators whose research throughout the previous 20 years had led them to create a series of meticulously characterized data sets, beginning with the MIT-BIH Arrhythmia Database (Moody and Mark 2001), which they had shared with several hundred interested researchers and medical instrument developers via digital tapes and CD-ROMs. The advent of the World Wide Web and widely available high-speed networking offered an opportunity for data sharing on a far larger scale. With support from the US National Institutes of Health (initially via the now-defunct National Center for Research Resources and, since 2006, from the National Institute of Biomedical Imaging and Bioengineering and the National Institute of General Medical Sciences), PhysioNet was established as the outreach component of the Research Resource for Complex Physiologic Signals (Moody et al. 2001, 2011).

Activities

Eleven data sets contributed by the PhysioNet team established PhysioBank. The software they had developed for exploring and analyzing these data sets became the core of PhysioToolkit. By late 2013, their collaborators and many other researchers had donated over 50 more data collections and numerous software packages, and over 60 PhysioNetWorks projects were developing additional data and software resources.

The PhysioNet team's strong support of open data formats, open-source software, and unrestricted access to PhysioNet's content led to the early development of an exportable infrastructure composed entirely of open-source

components. This choice was made to encourage replication of PhysioNet and led to development of a worldwide network of volunteer-operated PhysioNet mirror sites within a few years. These sites provide fast local access to PhysioNet's content and Web services to their maintainers and their colleagues, especially from locations where network connections to the master servers at MIT may be unreliable or slow.

The PhysioNet/CinC Challenge, an annual series of open engineering challenges, was inaugurated for the IEEE EMBS-sponsored conference, *Computers in Cardiology* (now *Computing in Cardiology*, or CinC), which was hosted by the PhysioNet team at MIT in September, 2000. The challenge topic is chosen each year to focus on an unsolved or poorly solved problem that can be addressed using data provided via PhysioNet. The challenges lower the barrier to participation by researchers and students who would otherwise lack access to relevant data and by focusing attention on achievable solutions that can be evaluated and compared objectively using freely available reference data. Challenge topics have included detecting sleep apnea from the ECG (Moody et al. 2000; Penzel et al. 2002); predicting the onset and spontaneous termination of atrial fibrillation; predicting acute hypotensive episodes in intensive care unit patients (Moody and Lehman 2009); developing robust methods for filling gaps in multiparameter physiologic data (including ECG signals, continuous blood pressure waveforms, and respiration), with applications in detection of clinically important events and in reduction of false alarms in the ICU (Moody 2010); predicting mortality of ICU patients (Silva et al. 2012); and noninvasive fetal ECG (Silva et al. 2013), among others.

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fundamental quality of a visual stimulus. It is very important to remember that pitch is a subjective quality that is constructed in the brain of a listener, not a physical quality of a sound wave. This subjective quality makes precise definitions troublesome. The American National Standards Institute defined pitch as “that attribute of sound which allows sounds to be ordered on a scale from high to low.” However, this definition is problematic because it remains mute about who or what is supposed to do the ordering, and as we shall see, there can be more than one “up” direction. Perhaps a more useful operational definition is to think of pitch as that property which carries melody in music. With that definition in mind, sounds can be assigned a **pitch value** which could be specified in terms of the corresponding “musical note” (e.g., A4) or equivalently in terms of the corresponding fundamental frequency (e.g., 440 Hz).

Note that just as the color of a visual stimulus can be faint or pale or indistinct, the pitch of an auditory stimulus can similarly be unclear. Some sounds have no discernible pitch at all (white noise, clicks); others have more or less clear pitches. **Pitch salience** (or pitch strength) might be thought of as equivalent to color saturation. Consider a rushing noise with faint whistling component as an example of a sound with low pitch salience. Furthermore, even salient pitches can be unclear due to possible **pitch ambiguity**.

Piriform Cortex

► [Olfactory](#) [Cortical](#) [Associative](#) [Memory](#)
[Models](#)

Pitch Perception, Models

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Definition

Pitch is a fundamental perceptual quality of an acoustic stimulus, perhaps not unlike color is a

Detailed Description

Which Attributes of Sound Determine Its Pitch?

Whether or not a sound has a salient pitch appears to depend chiefly on its **periodicity**. Sounds are periodic if the sound wave exhibits a motif that repeats. Sine waves or regular click trains are good examples. In nature, periodic sounds often arise as ► [Pulse-Resonance Sounds](#). The repeated motif must roughly be between 33 and 0.25 ms long. The sound’s fundamental frequency corresponds to the inverse of this motif length, resulting in pitch values between 30 and 4,000 Hz. Fundamental frequencies below this range lead to the perception of a beating rhythm rather

than a constant pitch. At fundamental frequencies above this range, sounds still sound pitchy, but pitch discrimination thresholds increase substantially. Also, the motif must be repeated at high fidelity. If the repeat is only approximate (as in narrow band noise), the pitch salience declines. If the sound wave is self-similar over several time delays, the pitch can become ambiguous.

This emphasis on periodicity suggests that determining the pitch of a sound wave should be done using a **time domain analysis** of the waveform. For example, one could calculate the **auto-correlation** function of the sound wave, and indeed some electronic tuners operate in this manner to calculate the fundamental frequency of a musical sound. For periodic sounds, the autocorrelation function will exhibit prominent peaks at time intervals which predict the perceived pitch rather well. However, **frequency domain analysis** can also work because strictly periodic sounds (consisting of a very faithfully repeated waveform motif) necessarily exhibit Fourier spectra with prominent peaks at frequencies which are harmonics (integer multiples) of the sound's fundamental frequency. In other words, the spectra of periodic sounds exhibit **harmonic structure**, and it should in principle be possible to predict the pitch a sound evokes from the position or spacing of harmonic peaks.

Both autocorrelation and frequency domain analysis can also be used in an attempt to explain the phenomenon of **pitch equivalence**. Many musical instruments traditionally produce notes with fundamental frequencies spaced at “semitone” intervals, where a semitone corresponds to 1/12th of an octave, and one octave is a doubling or the fundamental frequency. Notes separated by one or several octaves tend to be perceived as in some sense “equivalent” (they have the same “pitch chroma”), and one instrument playing, say, the note A3 (with a fundamental of 220 Hz), could be said to play “in unison” with another that plays A5 (two octaves higher, at 880 Hz). This perceptual equivalence is perhaps less surprising if one realizes that although the waveforms of these two sounds may look very different, they will have many peaks in common when analyzed with either an autocorrelation of a frequency spectrum.

Timing and Place Theories of Pitch

The fact that either frequency or time domain cues could be used to inform pitch judgment led to competing **place theories** and **timing theories** of pitch (Licklider 1951). Place theories propose that the brain analyzes travelling wave peaks on the basilar membrane of the cochlea to infer harmonic structure. Timing theories propose that the brain might analyze inter-spike intervals of phase-locked auditory nerve fiber responses to achieve something akin to an autocorrelation analysis. Several observations are difficult to account for in place theories, including the pitch of **missing fundamental stimuli**, sound level dependence of cochlear travelling wave peaks, and limited resolution of the cochlear frequency place code leading to “unresolved harmonics.” While these difficulties have led to timing theories being perhaps more popular, so far there is no good physiological evidence for either place- or timing-based analysis in the auditory brainstem. Also, it is of course possible that both time and place information contribute to pitch percepts, just as interaural time and level differences contribute to source direction percepts. Indeed, it is possible that place and timing cues contribute to pitch perception in different ways, as suggested from recent work in cochlear implant patients. With cochlear implants, it is possible to stimulate one place on the cochlea with pulses of varying rates or to stimulate various places at the same rate. Interestingly, cochlear implantees will report that the evoked sound percepts sound “higher” either if the location of the cochlear stimulation moves toward the base while the stimulation rate is held constant or if the stimulation rate is increased but the location is held constant. So both place and rate influence the reported “pitch,” but multi-dimensional scaling analysis of sound similarity ratings suggests that “place pitch” and “periodicity pitch” may correspond to different “up” directions in “perceptual space” (Chen et al. 2005). This may seem bizarre, but it is important to remember that the manner in which perceptual data are collected is not always unambiguous. For example, a very widely used method in psychophysics is the two alternative forced-choice

(2afc) test. Subjects are presented with two sounds and must decide which one “sounds higher” to them – often without much further instruction as to what “higher” means or without feedback. Also, in these tests, subjects are not allowed to answer “I cannot tell – they sound more or less the same.” Instead, they are instructed to guess if they are uncertain. In such a setting, if you present subjects with the two words “soon” and “seen,” both sung as the same note, and forced them to decide which sounds higher even though their fundamental frequency was the same, most would indicate “seen” as “sounding higher” than “soon.” This is a natural choice given that the vowel/ee/comprises higher-frequency formants than the vowel/oo/. But/ee/at $F_0 = 110$ Hz is “higher” than/oo/at 110 Hz in the sense that its “spectral centroid” is higher while the fundamental is the same, while/ee/at $F_0 = 220$ Hz is “higher” than/ee/at $F_0 = 110$ Hz in the sense that the fundamental, and hence the harmonic structure, is higher, while the spectral centroid is the same. These differences manifest as quite distinct perceptual qualities, but this important qualitative difference can easily be lost in 2afc experiments based solely on pairwise comparisons. (Readers can experience this themselves at <http://auditoryneuroscience.com/topics/two-formant-artificial-vowels>).

Presumed Neural Coding for Pitch by Neurons in the Central Auditory System

Since periodicity is an important cue for pitch, many neurophysiologists have studied periodicity tuning among auditory neurons in the brainstem, midbrain, and cortex as a possible substrate for pitch representations. A number of studies have suggested that the periodicity of tuned neurons may form topographically ordered “periodotopic maps” in the inferior colliculus (Schreiner and Langner 1988; Baumann et al. 2011) or cortex (Schulze et al. 2002), with a periodotopic map running orthogonal to the tonotopic axis. The idea of a periodotopic or pitch map in the brain is attractive, as such a structure might serve to

physically separate out different sound sources according to pitch cues. However, data collected by other researchers (Nelken et al. 2008) does not support the idea of periodotopic maps, and while a topographic pitch map is an appealing idea for human observers who would find such a map easy to read, it might provide little benefit to downstream neural networks which would read out such a map through a tangle of heavily divergent and convergent connections.

Whether the central nervous system uses topographic maps to represent pitch is not the only question that remains controversial. Whether topographically organized or not, many researchers have argued that the auditory cortex in particular may have subfields that are dedicated to processing or representing (or perhaps more accurately, creating the percept of) pitch (Griffiths et al. 1998). Some authors have even gone as far as declaring that they identified “pitch neurons” in a narrowly circumscribed “pitch area” in the marmoset cortex (Bendor and Wang 2005), and while their study documented some very interesting periodicity tuning properties in cortical neurons, it remains unclear whether these neurons play any role in forming or signalling subjective pitch percepts. Indeed, other studies which have tried to elucidate whether sensitivity to pitch cues is indeed confined to dedicated neural populations or rather coexists as a **widely distributed representation** intermingled among sensitivity to other auditory attributes such as timbre or sound source direction have found more evidence for the latter than the former (Bizley et al. 2009; Walker et al. 2011), and one of the very few studies that has attempted to link electrophysiological responses in the cortex to subjective pitch judgments for complex sounds similarly found pitch-related responses to be quite widely distributed over large parts of the auditory cortex (Bizley et al. 2013).

Neurocomputational Models of Pitch Perception

Modelling the neural processing of pitch perception has a long history. As mentioned above,

thinking about pitch processing has been dominated by “place theories” which try to discover harmonic structure in the spectral representation of the sounds and “timing theories” which are based on an analysis of the autocorrelation of the sounds. Both these approaches have given rise to many neurocomputational modelling approaches. An extensive review is beyond the scope of this article (interested readers are referred to de Cheveigne 2005), but we might mention “harmonic sieve” pitch template matching (e.g., Shamma and Klein 2000) as a representative example of a place-coded approach, while “summary autocorrelation models” (e.g., Meddis and Hewitt 1991) are representative of a time-coded methods. Of course, time- and place-based methods are not necessarily mutually exclusive, and as early as the 1950s, Licklider proposed a “duplex model” combining both place coding and temporal coding elements. The numerous models that have been proposed vary greatly in their complexity, in their attempts to incorporate “physiological realism,” and in their ability to account for the wide range of pitch-related perceptual phenomena, such as pitch ambiguity in inharmonic sounds, or the apparent ability of the auditory system to extract pitch information on varying time scales. The latter is an interesting case in point. Intuitively, the reader may appreciate that any pitch extraction algorithm may be able to determine pitch with greater accuracy if it can operate over long time scales and thus average over a larger sound sample. However, if the sounds to be analyzed change very rapidly, then algorithms integrating over long time periods will be too sluggish. There is a trade-off to be made between precision and speed, and some of the most sophisticated models developed to date (Balaguer-Ballester et al. 2009) incorporate top-down elements which adapt the time constants of the pitch extraction algorithm to the temporal dynamics of the sound. The development of ever more sophisticated models continues to this day.

Cross-References

► [Pulse-Resonance Sounds](#)

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Further Reading

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Polarization Vision

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Definition

Polarization vision is the ability of animals to detect the oscillation plane of the electric field vector of light (*E*-vector) and use it for behavioral responses. This ability is widespread across animal taxa but is particularly prominent within invertebrates, especially arthropods. Polarized light can be either used implicitly for enhancing image contrast and for adding another dimension to the color vision system, or it can be explicitly used as a separate vision channel for communication purposes and for encoding global directions for an internal compass. Polarized light in nature is produced either by reflection at shiny surfaces or by scattering (e.g., in the atmosphere) of unpolarized sunlight. This results in the presence of polarized light in many different habitats, including underwater. The most prominent source of polarized light is the skylight polarization pattern, which contains information about the position of the sun in the sky and is thus used for navigation purposes. In insects, *E*-vectors are detected through specialized regions of the compound eyes. Neurons downstream of the involved photoreceptors respond to changes in *E*-vectors with modulations of their action potential frequency, so that each neuron is tuned to one particular *E*-vector. Over the last decade, an extensive, conserved network of such neurons has been uncovered in the brains of locusts, crickets, and monarch butterflies, spanning many processing stages, from the photoreceptors to the motor control centers in the thorax. At the boundary of sensory processing and motor planning, a brain region called the central complex plays an integral part in polarized-light processing. It comprises an ordered array of neurons that use polarized-light information to encode a representation of the azimuthal space surrounding the animal. How this

network is proposed to process polarized-light information, integrates it with other sensory modalities, and transforms sensory signals into motor commands that guide behavior is the main focus of this entry. To put this neuronal network into the context in which it has to function in the natural world, results obtained from behavioral experiments in a variety of species are discussed as well.

Detailed Description

One of the defining features of higher animals is their ability to actively move through their environment in order to search for food, escape from predation, or find mating partners. To achieve these behaviors, an animal has to be able to use the available sensory cues to extract information about its current direction of movement and its position relative to other objects in the surrounding space. Visual information plays a dominant role in many animals for guidance of orientation behavior. One cue that can be used by many insects is polarized light. Like color and brightness, the plane of polarization (oscillation direction of the electric field vector (*E*-vector)) is a fundamental feature of light and contains information that can be utilized for guiding behavior. Like bright or colorful objects, objects that emit light with particular *E*-vector orientations may be attractive or repulsive for an animal. This can be used for finding ovipositing sites (e.g., in butterflies) (Kelber et al. 2001; Kelber 1999), for intraspecific communication signals (e.g., in marine invertebrates like mantis shrimp, fiddler crabs, or cephalopods) (Marshall et al. 1999; Chiou et al. 2008), or for detecting suitable habitats (e.g., bodies of water found through polarized light by the back swimmer) (Schwind 1991). Additionally, sunlight scattered in the upper atmosphere, i.e., the blue skylight, contains *E*-vector information that is directly linked to the position of the sun. For animals that exhibit complex behaviors such as central place foraging (returning to a nest after extended foraging trips) or long-distance navigation (e.g., migration to overwintering grounds), the information provided by the position of the

sun provides a global frame of reference and can therefore be used to improve the accuracy of these orientation behaviors (Wehner 1984; Horváth and Varjú 2004).

Behavioral experiments with ants and bees (particularly in the desert ant *Cataglyphis* and the honeybee *Apis mellifera*) have revealed that polarized light is indeed used to infer the position of the sun and guide the animal back to the nest after foraging trips (Wehner and Labhart 2006). In the monarch butterfly, polarized light can also be used to help maintaining a southeasterly flight bearing during the spectacular mass migration of this species from northeastern North America to Central Mexico (Reppert et al. 2004; Merlin et al. 2012). In many other insects, adjustment of flight/walking direction in response to artificial polarized-light stimuli has been described as well (desert locust, Mappes and Homberg 2004; field cricket, Brunner and Labhart 1987; several fly species, Philipsborn and Labhart 1990; Wolf et al. 1980). Interestingly, in nocturnal dung beetles, even the faint polarization pattern around the moon is used for maintaining a straight course when navigating away from a pile of dung with a freshly made dung ball (Dacke et al. 2003).

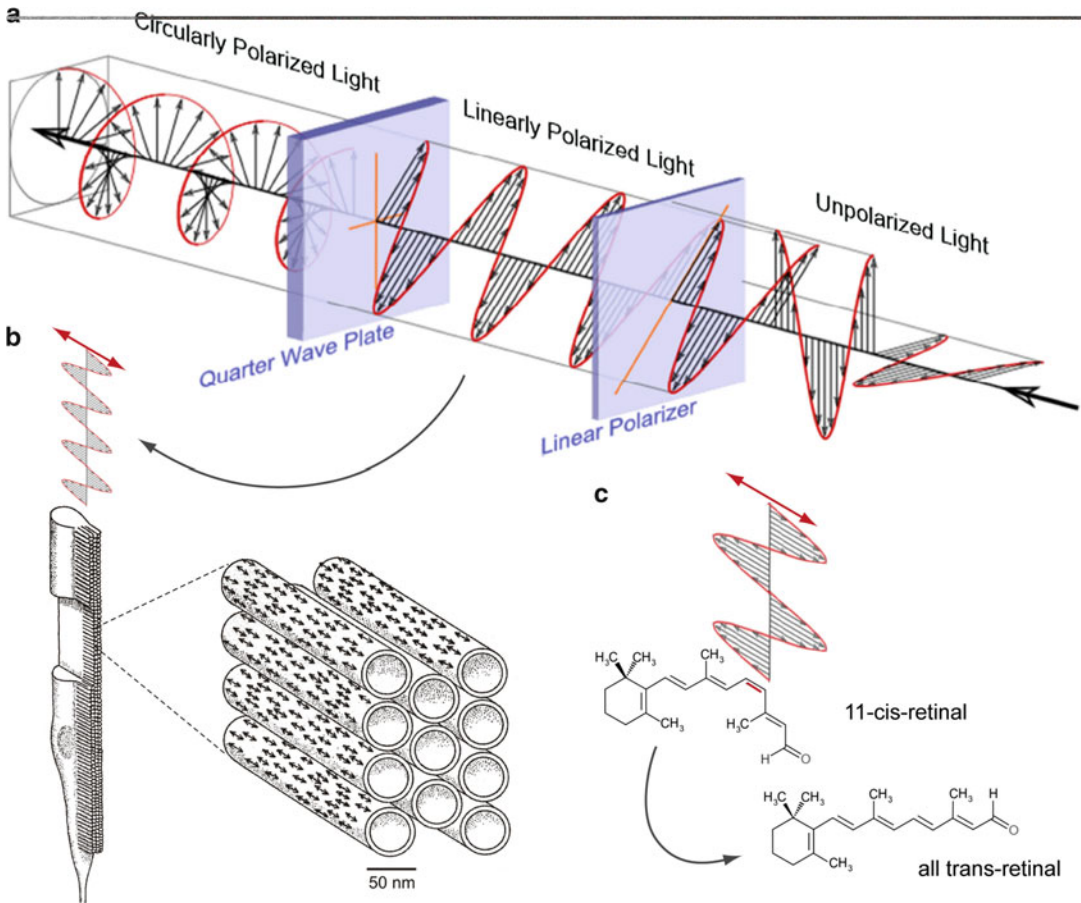
Although the characteristics of the behavioral responses to polarized light have been studied in great detail in ants and bees, little is known about how this information is processed in the brains of these insects. Nevertheless, computational principles about how polarized light is processed to produce the observed behavior have indirectly been concluded from clever behavioral experiments. These indirect findings now remain to be confirmed by direct physiological evidence from polarization-sensitive neurons in the brains of these species. Recently, however, such data has been collected from species that are less well understood behaviorally but much more accessible for electrophysiological experiments: the field cricket, the desert locust, and the monarch butterfly (Homberg et al. 2011). The extensive dataset resulting from the work in these three species provides insight into how polarized light is detected, processed, integrated with other sensory modalities, and finally sent to the motor centers of the nervous system to ultimately guide behavior.

These findings are likely relevant across a wide range of insects and might underly the well-studied behavior of bees and ants as well. The characteristics of the involved neurons and the computational principles revealed by studying the network they comprise are therefore the major focus of this entry.

Polarized Light in Nature

Light is an electromagnetic wave and consists of an electric and a magnetic field vector oscillating orthogonally to each other. Both vectors oscillate perpendicular to the propagation direction of the light beam. Light emitted by the sun is unpolarized. That means that the electric field vectors (*E*-vectors) oscillate randomly in all directions. As the *E*-vectors exhibit axial symmetry, the range of all possible *E*-vector orientations is 180°. Linearly polarized light comprises *E*-vectors all oscillating in the same direction (Fig. 1a). When linearly polarized light is passed through a quarter wave retarder, it becomes circularly polarized light. This form of light can be viewed as consisting of two oscillations with *E*-vector orientations orthogonal to each other and out of phase by a quarter of their wavelength (Fig. 1a). When the observer faces the light beam, the tip of the resulting *E*-vector therefore moves along a circular path. In cases in which the two *E*-vector components are out of phase by a different value, the *E*-vector moves along an elliptical path, producing elliptically polarized light. Linearly polarized light is produced when both *E*-vector components are in phase. Aside from the plane of oscillation, the second important characteristic of polarized light is the degree of polarization, i.e., the ratio of polarized to unpolarized light within a beam of light (between 0% and 100%).

In nature, linearly polarized light is produced from sunlight either by scattering or by reflection at shiny, dielectric surfaces. In air, polarized light thus results from reflections at shiny leaves, animal fur, and water surfaces or by scattering of sunlight by molecules of the atmosphere (Horváth and Varjú 2004). While polarized light

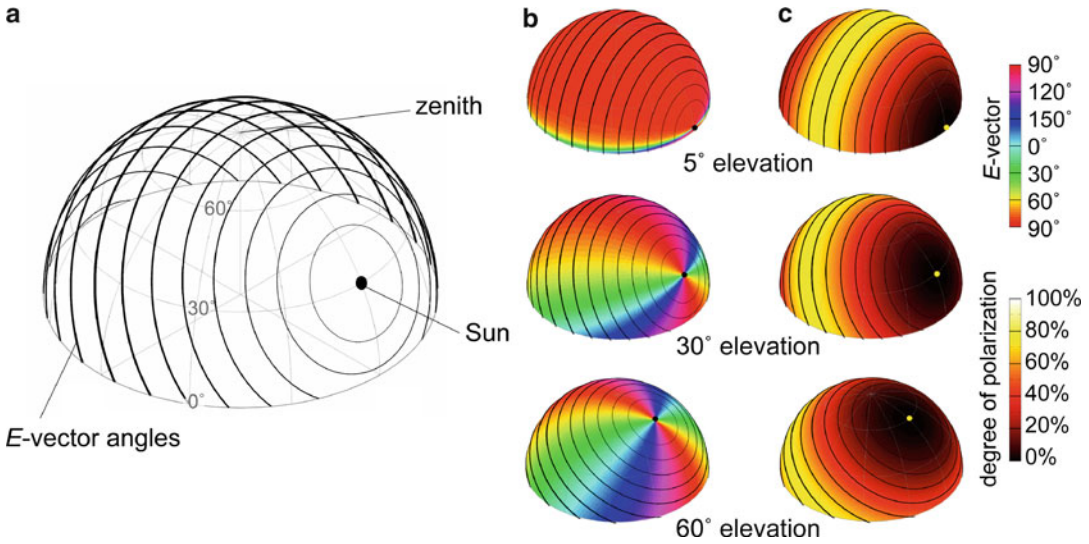


Polarization Vision, Fig. 1 The nature of polarized light and the principle of detecting polarized light in insect photoreceptors. (a) Schematic illustration of the transformation of unpolarized light (right; all planes of oscillation occur) to linearly polarized light (middle; only one oscillation direction occurs) and finally to circularly polarized light (left; direction of oscillation rotates over time). (b) Schematic drawing of an insect photoreceptor and its preferred plane of polarization. Parallel microvilli unilaterally protruding from the cell body form the rhabdomere. Photopigments are embedded in the microvilli membranes (enlargement) and preferentially absorb incoming light

oscillating in one particular plane (indicated by *double arrows*) (Modified from Wehner 1976). (c) Light waves oscillating in parallel to the excitable double bond (between carbon 11 and 12, red) are preferentially absorbed by the photoactive chromophore 11-*cis*-retinal. This photoconversion results in formation of all-*trans*-retinal and to the activation of a downstream signal transduction cascade. The position of retinal is fixed in space by the surrounding protein component of rhodopsin (opsin; not shown) and thus provides the molecular basis for polarization vision

resulting from reflections at water surfaces is dominated by horizontal *E*-vector orientations, polarization in the sky forms a characteristic *E*-vector pattern (Fig. 2). In this pattern, the *E*-vectors are arranged in concentric circles around the sun, with the highest degree of polarization located 90° away from the sun, reaching 75% under optimal conditions. Light close to the sun (and the “antisun” in the opposite sky

hemisphere) is unpolarized. As the *E*-vector pattern in the sky is directly linked to the position of the sun and follows its apparent movement across the sky over the course of the day, it can be used to localize the sun even when only a small patch of blue sky is visible (Fig. 2b, c). A similar *E*-vector pattern is present around the moon, albeit several orders of magnitude dimmer. The fact that the position of the sun can be inferred from viewing



Polarization Vision, Fig. 2 Polarization pattern of the sky. (a) Schematic representation of skylight *E*-vector pattern. Orientation of lines illustrates *E*-vector angles, while the thickness of the lines represents degree of polarization. (b) *E*-vector orientation for different solar elevations. Note that at low elevations, *E*-vectors are oriented in parallel

throughout the sky. At the zenith, the *E*-vector orientation is always perpendicular to the solar azimuth. (c) Degree of polarization for different solar elevations. Note that at high solar elevations, areas of high degrees of polarizations can only be found close to the horizon

E-vectors of the blue sky is exploited by animals for compass navigation and orientation and comprises the best-understood function of polarized-light vision (Wehner and Labhart 2006; Merlin et al. 2012; Wehner 2001).

Other than in air, polarized light is also present within bodies of water (Cronin and Marshall 2011). Here, the difference in refractive indices of air and water results in the compression of the 180° dome of sky into an angle of 97.2° when viewed from under the water surface. This region is called Snell's window and contains the skylight polarization pattern similarly to above the water surface. Outside this critical angle, polarized light is produced by scattering of sunlight by the water itself and results in mostly horizontally oriented *E*-vectors. The degree of polarization underwater rarely exceeds 50%.

Concepts Deducted from Behavioral Data

Behavioral responses to polarized light have been investigated in many species and have revealed

details about how animals, particularly invertebrates, process polarized-light cues. Most work has been carried out in those insects, in which polarized light is used for navigation purposes. The ability of these animals to detect and respond to changing *E*-vectors was shown in experiments, during which a rotating polarizer was placed above a tethered animal during flight or walking behavior. In response to the rotating polarizer, crickets (Brunner and Labhart 1987), houseflies (Philipsborn and Labhart 1990), fruit flies (Wolf et al. 1980), and locusts (Mappes and Homberg 2004) try to align their body length axis with a particular *E*-vector. This results in approximately sinusoidal changes of their (fictive) forward movement direction in phase with the rotating polarizer, a behavior called polarotaxis. Importantly, this polarotactic behavior is abolished (done in locusts and crickets), when a small part of the compound eye, the dorsal rim area (DRA), is painted over but is left intact, when the complete compound eye except for the DRA is covered. These data show that at the level of the eyes, the DRA of these insects is both sufficient and necessary for generating orientation responses

based on *E*-vector information and confirms much earlier data from similar experiments in freely moving bees and ants (Wehner and Strasser 1985; Duelli 1975). In locusts, such experiments have been combined with surgical brain lesions and revealed that the anterior optic tract is necessary for processing the polarized-light information needed for polarotaxis in the brain (Mappes and Homberg 2007). In crickets, polarotactic behavior was further used to delineate the spectral range of polarization vision, its absolute sensitivity, and its reliability under low degrees of polarization. These studies revealed that these insects are using blue light for detecting *E*-vectors and can reliably respond to polarized light under very dim conditions (below light levels of a moonless night) (Herzmann and Labhart 1989). Additionally, even at degrees of polarization as low as 7%, crickets are able to perform polarotactic behavior (Henze and Labhart 2007). The preferred *E*-vector angles in locusts and crickets cover a wide range, are variable between individuals, and even change between trials. This indicates that polarotaxis is not merely a stereotypical alignment response resembling activity maxima or minima in the eye's *E*-vector detection system but that the animals have the ability to actively maintain an orientation matching the angle of any *E*-vector.

Responses to natural skylight polarization patterns have been tested in tethered preparations of monarch butterflies (Reppert et al. 2004; Stalleicken et al. 2005) and the fruit fly *Drosophila* (Weir and Dickinson 2012). Both species were placed in flight simulators with a clear view of the sky, and the skylight polarization pattern was changed by 90° either by rotating the simulator (*Drosophila*), using a liquid crystal device (*Drosophila*), or by inserting and rotating a polarizer sheet above the animal (monarch). In both species, the rotation of the skylight polarization pattern resulted in an adjustment of the flight orientation in the predicted direction in at least a subset of the tested animals. While the population of tested monarch butterflies was oriented in a common direction (in tune with their southwesterly migratory direction), the straight flight segments of the flies did not show such a common orientation (Reppert et al. 2004; Weir and

Dickinson 2012). By using appropriate filters, it was shown that the ultraviolet (UV) range of the spectrum is necessary and sufficient for the monarch butterfly (Sauman et al. 2005). UV light is also sufficient for *E*-vector responses in *Drosophila*, but the behavior can additionally be elicited with blue light (Weir and Dickinson 2012). Similar responses to longer wavelengths have also been documented in an assay that uses a population alignment response to artificial *E*-vectors in *Drosophila*. Whereas dorsally presented light only elicited a response in the UV range, ventrally presented light was additionally efficient at blue and green wavelengths (Wernet et al. 2011). This data therefore also revealed that the DRA cannot be the only eye region involved in detecting polarized light at least in *Drosophila*.

Detection of polarized light in the ventral visual field has also been described in insects that seek water bodies for habitat selection or reproduction. When flying, these animals (e.g., back swimmers, female horseflies, water beetles) are strongly attracted to surfaces emitting horizontally polarized light, whereas other *E*-vector orientations are not attractive (Schwind 1984, 1991; Horváth and Varjú 2004). Naturally, water surfaces are the dominant source of horizontally polarized light, but these insects are easily tricked into landing on man-made polarizing surfaces, illustrating that it is indeed the horizontal *E*-vectors that provide the attraction.

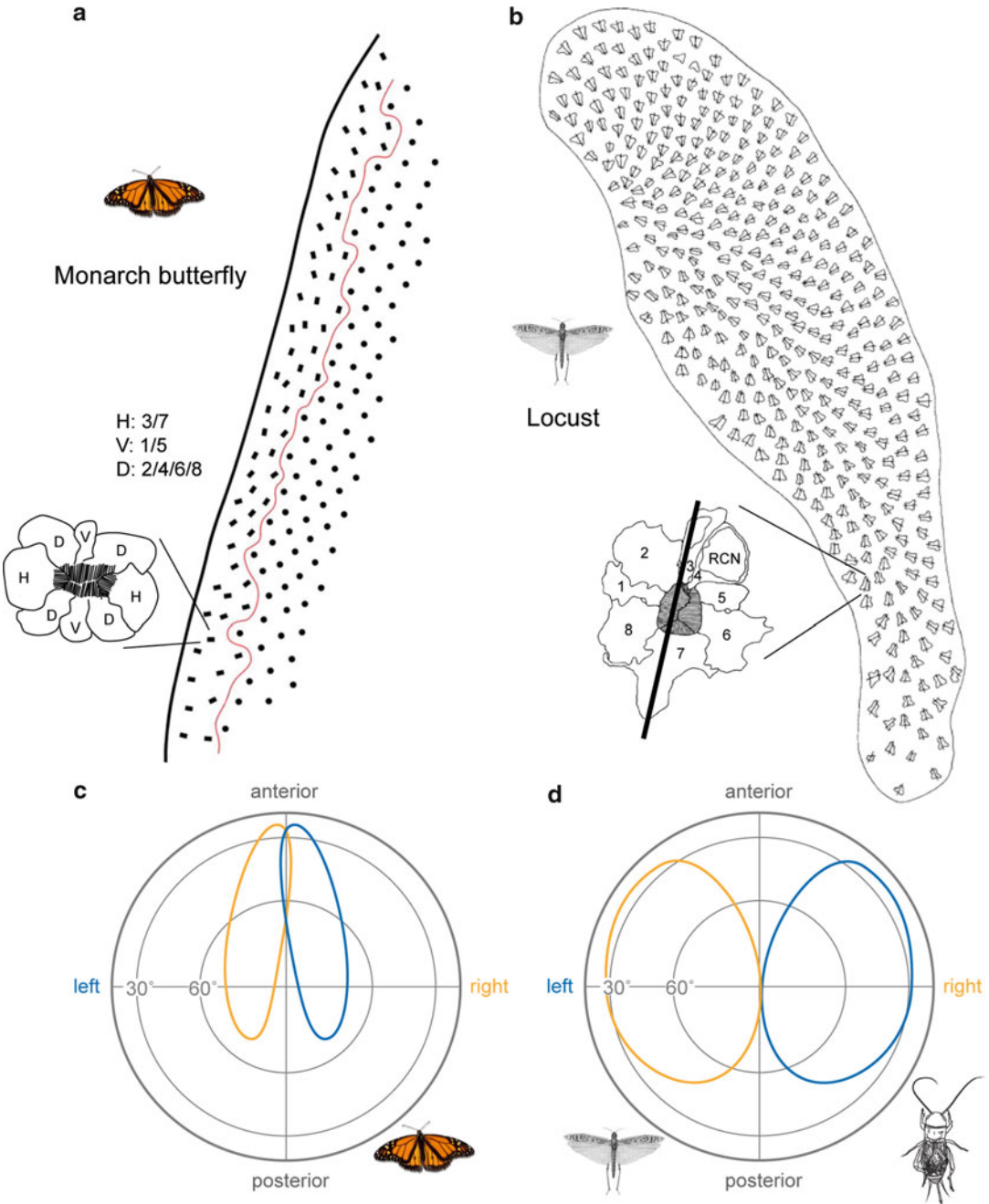
Underwater, stomatopod crustaceans (mantis shrimps) are the most extensively studied invertebrates in relation to polarization vision (Marshall et al. 1999; Marshall 1988; Marshall and Cronin 2011). In learning experiments (simple choice experiments with food reward), it was shown that these animals have the ability not only to detect linearly polarized light but also to respond to circularly polarized light (Marshall et al. 1999; Chiou et al. 2008). Both forms of polarized light are reflected by body parts of mantis shrimps, and this system is thus thought to serve intraspecific communication purposes. Due to the uniform background of mostly horizontally polarized light underwater, linear polarization vision is also suited to enhance contrast and possibly to facilitate prey detection in these habitats.

The best-studied models for polarization vision, however, are the honeybee and the desert ant. Both species are central place foragers and exhibit a behavior called path integration, i.e., they return to their nest in a straight line after a complicated foraging trip. To achieve this, they have to monitor both the distance traveled on the outbound journey and all changes in direction. This information is used to continuously update their homing vector. For monitoring directional changes, bees and ants use the sun and the sun-derived polarization pattern of the sky (Wehner 1984, 1989, 2003). Over several decades, an extensive set of complex behavioral experiments, particularly in bees, has led to knowledge about the internal representation of the sky and how this information is used. In one of the most crucial experiments, bees were trained to learn the route to a feeder in the vicinity of their hive, while the animals could see the complete skylight polarization pattern. When the bees tried to communicate the azimuthal position of the feeder to their nestmates (by performing the waggle dance), only a single *E*-vector was present. The communicated azimuth thus allowed to determine where in the sky the bee estimated the position of the presented *E*-vector (Rossel and Wehner 1982, 1984). Discrepancies between the real azimuth of the feeder and the recalled azimuth communicated under test conditions led to the reconstruction of a proposed internal representation of the skylight polarization pattern in the brain of the bee. If the bee had comprehensive knowledge of the skylight polarization pattern, it would not make any errors under these testing conditions. As errors occur, the bee's internal representation of the sky must be a simplified version of the real world. The anatomical layout of the DRA (see below) was proposed to be the physical substrate of this representation and thus to act as a matched filter that could be aligned with the skylight polarization pattern (Wehner 1989). When this matched filter is rotated under the sky, temporal comparison of the pooled DRA output would be suited to identify the symmetry plane of the sky and thus allow to locate a specific azimuth relative to this symmetry plane. Due to the involved scanning behavior, this method was termed the

scanning hypothesis. Indeed, such behavior can be observed in desert ants intermittently throughout a foraging trip (Wehner 1989). Interestingly, some species of dung beetles also perform a rotational "dance" before choosing a movement direction (Baird et al. 2012). These insects use the polarization pattern of the sun or the moon to roll a freshly made dung ball in a straight line away from a dung pile in order to avoid competition. Overall, the scanning method is an elegant explanation to account for systematic errors present in the bee's navigational system and would enable the animal to obtain directional information in a very simple way. In principle, one neuron that encodes the pooled DRA output with its action potential frequency would be sufficient. Conclusive models that culminate in a hypothetical array of compass neurons have been based on elaborations of this theory (Wehner and Labhart 2006; Wehner 2001; Sakura et al. 2008) and await to be reconciled with the complex neurophysiological data from other insects (see below). Whether the ommatidial array of the DRA is indeed the physical substrate of a matched filter of the sky, or if such a filter is implemented in later stages of the brain, remains to be shown through neurophysiological studies. The complex system of polarization-sensitive neurons in the brains of other insect species, combined with the different shapes and ommatidial arrangement in the DRA across species (see below), however, leaves some doubt as to whether the scanning method is indeed implemented in such a straightforward way in all insects, despite the stunning elegance and simplicity of the proposed idea.

Detection of Polarized Light

In animal eyes, light is absorbed by rhodopsin molecules, which consist of a protein component (opsin) and the photosensitive molecule retinal. As retinal absorbs light preferentially if the plane of oscillation is aligned in parallel with the excitable double bond of the molecule, all rhodopsins are inherently sensitive to the *E*-vector orientation (plane of oscillation) of linearly polarized light (Fig. 1c). However, this only translates into



Polarization Vision, Fig. 3 The dorsal rim area (DRA) of insects is specialized for detecting polarized light. (a) DRA of the monarch butterfly. Shown is the distribution of microvilli orientations of the horizontal retinula cells (H), which results in a fanlike arrangement of preferred *E*-vectors along the length of the DRA. The inset depicts a single ommatidium with the characteristic two blocks of orthogonally oriented microvilli (Modified from Labhart et al. 2009). (b) Structure of the DRA of the desert locust.

Note that the DRA is much wider in the locust compared to the monarch butterfly and that in the monarch, horizontal ommatidial orientations dominate in the anterior and posterior parts of the DRA, while vertical orientations dominate in the medial part of the DRA. In the locust, all regions of the DRA comprise a wide variety of ommatidial orientations (Modified from Homberg and Paech 2002). (c) Estimated receptive fields of the right (yellow) and left (blue) DRA of the monarch butterfly projected onto a

polarization-sensitive photoreceptors, if the rhodopsin molecules are aligned in parallel to one another. Partially, such alignment automatically arises in all rhabdomeric photoreceptors of invertebrates, as the photopigments are embedded in the membranes of the microvilli, i.e., elongated, tubelike structures that protrude unilaterally from the cell body of the receptor cell (Fig. 1b; Horváth and Varjú 2004; Roberts et al. 2011). Even if rhodopsin molecules were randomly oriented within these membranes, the receptor would still be twice as sensitive to *E*-vectors oriented in parallel to the microvilli than to *E*-vectors perpendicular to them (i.e., it would have a polarization sensitivity (PS) of 2; Moody and Parriss 1961), provided that all microvilli of that receptor cell are themselves aligned in parallel to one another. As measured PS-values are much higher in the DRA of insects (up to 40 in crickets; Labhart et al. 1984), photopigments must be actively aligned within the microvilli membranes. Mechanisms of how such alignment could be achieved by tethering the components of the phototransduction pathway to elements of the cytoskeleton have been suggested but remain hypothetical (Roberts et al. 2011).

At the level of the ommatidia, i.e., the individual facets of an insect's compound eye, several mechanisms have been revealed that can increase (or actively reduce) the inherent polarization sensitivity of receptor cells. When detecting light, the animal is faced with the problem of having to identify whether a photoreceptor has absorbed many photons because the incoming light was very bright, of optimal spectral composition, or of optimal *E*-vector orientation. Eliminating polarization sensitivity is relatively easily achieved by twisting the photoreceptor (and the orientation of the microvilli) along the length axis

of the receptor cell (Wehner et al. 1975). A photoreceptor twist has indeed been observed in the retina of many insects and is thought to eliminate interference between color vision and (accidental) *E*-vector detection (Wehner and Bernard 1993). However, separating the *E*-vector information from spectral and intensity information cannot be achieved by one single receptor cell. To render the ommatidial output insensitive to spectral and intensity information and to enhance PS, a region of the insect compound eye has been dedicated to polarization vision, the dorsal rim area (DRA). Here, in each ommatidium, two groups of untwisted photoreceptors have evolved with microvilli orientations orthogonal to one another (Fig. 3a, b, insets; Labhart and Meyer 1999; Blum and Labhart 2000; Homberg and Paech 2002; Labhart et al. 2009). Additionally, both groups of photoreceptors express identical opsins, i.e., they possess the same spectral sensitivity (Labhart and Meyer 1999). In most insects, UV opsins are expressed in the DRA (flies (Wernet et al. 2003), monarch butterflies (Sauman et al. 2005; Stalleicken et al. 2006), bees (Labhart 1980), ants (Labhart 1986), dung beetles (Dacke et al. 2002)), while in locusts (Eggers et al. 1993) and crickets (Labhart et al. 1984; Henze et al. 2012), blue opsins carry out the task of perceiving polarized light. Green opsins have also been observed in the DRA of some insects (cockchafers, Labhart et al. 1992; dung beetles, Dacke et al. 2002). If the output of these orthogonal groups of receptors is subtracted from each other, the resulting information in the post-synaptic neuron will be independent of color and intensity, as both receptor groups are equally affected by changes of these parameters and only differ in their sensitivity to the *E*-vector orientation of the incoming light. Additionally, the

Polarization Vision, Fig. 3 (continued) zenithal view of the sky. (d) As (c), but for locusts and crickets. Note that the region of sky viewed by monarch butterflies on the one hand and locusts and crickets on the other hand is dictated by the anatomical layout of the DRA and thus differs substantially between the two groups. Long, elongated DRAs can be also found in flies, while broad, flat DRAs

are also found in cockchafers and dung beetles. Bees and ants appear to have DRAs with intermediate properties (C/D are based on data from Blum and Labhart 2000; Homberg and Paech 2002; Labhart et al. 2009; Stalleicken et al. 2006). *Abbreviations:* *V* vertical retinula cells, *D* diagonal retinula cells, *RCN* nucleus of retinula cell, numbers of retinula cells (photoreceptors R1–R8)

postsynaptic neuron would show a behavior called polarization opponency, as it is inhibited by one group of photoreceptors but excited by the second one. Although the anatomy of DRA ommatidia across insects strongly suggests such mechanisms, to date no electrophysiological recordings from their target cells in the lamina or medulla have been performed to directly prove this model.

The orthogonal blocks of untwisted microvilli described above are found in the DRA across insects. Additionally, many species possess other specializations that either enhance the sensitivity to polarized light or increase the overall sensitivity at the expense of spatial resolution (reviewed in Labhart and Meyer 1999). Examples of such specializations are shortened rhabdoms, which reduce the problem of self screening. Widened rhabdoms are also present in many species and result in increased sensitivity and sampling over larger visual angles, i.e., widened receptive fields. The lack of screening pigments in the DRA of some insects also dramatically increases the receptive fields of individual photoreceptors. In crickets, this results in receptive fields of ca. 20° (compared to 6° in the rest of the eye). Degraded optics and light-scattering devices in the optical path act as a low-pass filter for incoming light in the DRA of many insects and are thought to render these ommatidia insensitive to local variations in *E*-vector information, e.g., in partly cloudy skies.

The DRA as a whole exhibits further specializations, particularly suited for detecting the polarization pattern of the sky. All DRAs studied to date show a fanlike arrangement of ommatidial orientations (i.e., the orientation of their principal microvilli orientations) that enable the detection of all possible *E*-vectors within the DRA at any given time (Fig. 3a, b; Blum and Labhart 2000; Homberg and Paech 2002; Labhart et al. 1992, 2009). In principle, two types of DRAs exist. The first one is found, for example, in locusts and crickets and is characterized by a wide but short shape (Fig. 3b). The optical axes of its ommatidia are directed to the contralateral sky hemisphere and cover a large portion of the sky (Fig. 3d). The individual photoreceptors have large receptive

fields that overlap substantially between neighboring ommatidia (Blum and Labhart 2000; Homberg and Paech 2002). Due to the fanlike arrangement of preference angles, each region of the DRA is suited to detect all possible *E*-vectors. The second type of DRA is found, for example, in monarch butterflies (and in an even more extreme form in flies) (Fig. 3a). It is only very few rows of ommatidia wide but extends over a large range from posterior to anterior along the medial rim of the compound eye. Its ommatidia possess receptive fields generally not dramatically increased in size relative to the remainder of the eye. They are also directed contralaterally but only cover a narrow stripe of sky parallel to the body length axis of the animal (Fig. 3c; Labhart et al. 2009; Henze 2009). As the fanlike arrangement of the preference angles becomes stretched out along the DRA and individual ommatidia do not possess overlapping receptive fields, parts of the DRA directed towards the anterior sky are tuned to different *E*-vectors than parts of the DRA directed towards the zenith. This means that although both types of DRA are specialized for detecting the skylight polarization pattern, they transmit quite different information to the processing centers of the brain, even when facing identical skylight situations.

As mentioned earlier, polarized skylight is the major source of polarized light in nature, but not the only one. In animals using polarized light to detect water surfaces, ventral regions of the eye have evolved specializations similar to the DRA of other insects (e.g., in the back swimmer *Notonecta glauca*; Schwind 1983). Recently, data has accumulated suggesting that ventral polarization vision is more widespread than previously thought. Behavioral experiments in *Drosophila* have shown that ventrally presented polarized light is well suited to elicit orientation responses, which are likely mediated by a group of untwisted photoreceptors in the ventral retina (Wernet et al. 2011). Anatomical data from polarization-sensitive optic lobe neurons in the locust have revealed branching patterns that correlate with the location of the DRA as well as an unknown ventral eye region (el Jundi et al. 2011). At last, opsin expression studies in the cricket

show blue-sensitive opsins in the DRA and in a ventrally directed band of ommatidia (Henze et al. 2012).

Polarization vision in marine crustaceans, in particular stomatopods (mantis shrimp), has been extensively studied as well (Marshall and Cronin 2011). In these animals, ommatidia sensitive to linearly polarized light are present in the dorsal and ventral eye hemispheres. Additionally, two rows of ommatidia along the equator of the eye are suited to detect circularly polarized light, a feature so far unique in the animal world (Chiou et al. 2008; Kleinlogel and Marshall 2006; Marshall et al. 2007). These ommatidia use the rhabdom of one distal photoreceptor as quarter wave retarder within the light path of the remaining receptors. In this way, it transforms circularly polarized light into linearly polarized light that is in turn detectable by the crossed microvilli arrangement in the underlying receptor cells (Chiou et al. 2008).

Polarized-Light Processing in the Brain of Insects

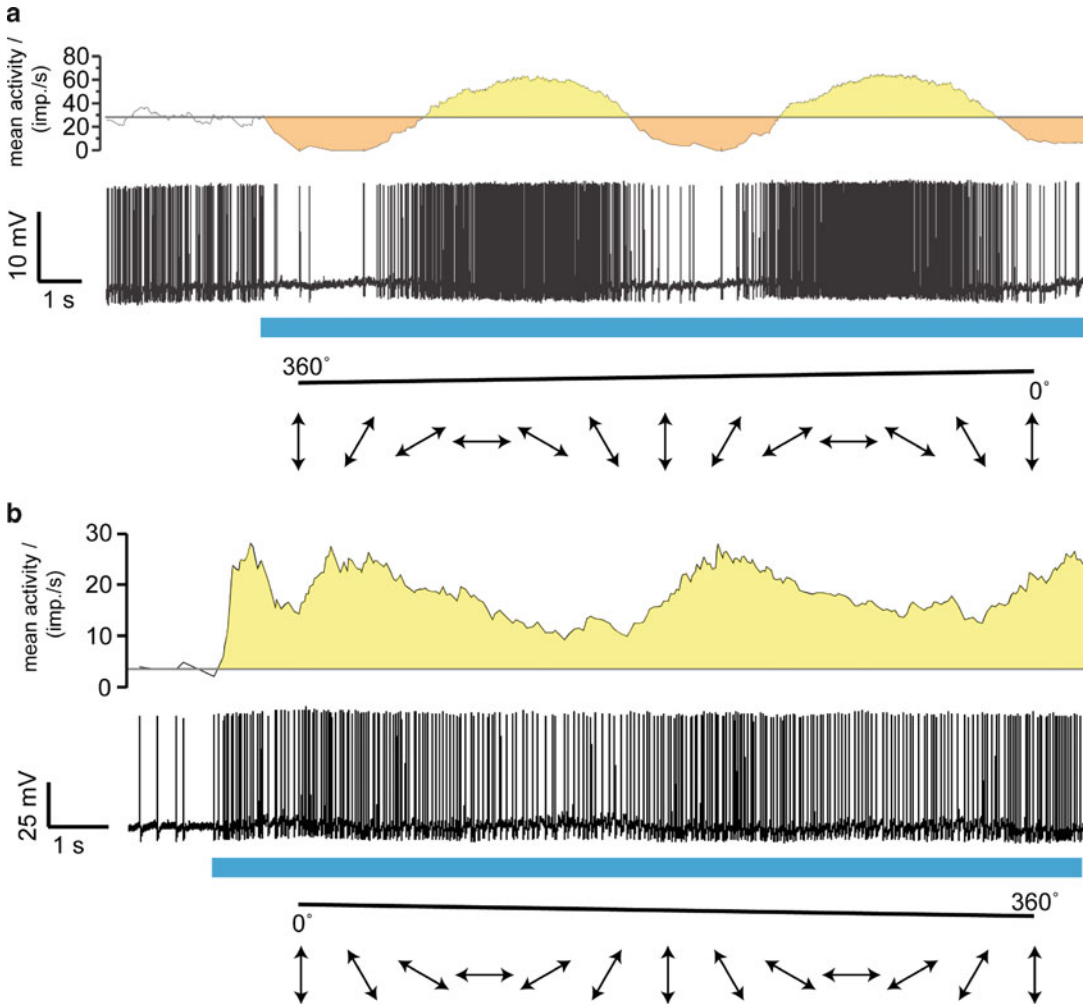
Although most behavioral work in relation to polarized-light perception in the context of orientation and navigation has been carried out in honeybees and ants, virtually all knowledge about how this information is processed in the insect brain results from work in the desert locust, the field cricket, and the monarch butterfly (Merlin et al. 2012; Homberg et al. 2011; Labhart and Meyer 2002). In these species, intracellular recordings from anatomically identified neurons have been performed for over two decades, and over 30 types of neurons sensitive to polarized light have been identified. Together, they form a network, spanning almost all processing stages from the photoreceptors of the DRA to the neurons descending to the motor centers of the thorax.

To understand how this network processes information and transforms sensory input into motor commands that guide orientation behavior, one has to understand the physiological response characteristics of the involved neurons, their anatomical characteristics, and the neural connections

between the individual elements of the system. Much progress has been recently made in describing response characteristics of individual neurons of this “POL network,” as well as in understanding the detailed morphology of all major neuron types involved in processing polarized-light information. Although many neural connections are implied by the anatomical features of the involved neurons and are supported by indirect physiological data, very few neural connections have been verified in this network so far.

Individual neurons respond to different *E*-vectors with changes of their action potential frequency. When the animal is stimulated with a continuously rotating polarizer from the zenith, such neurons show approximately sinusoidal modulations of their mean firing rate (Fig. 4; Labhart 1988; Vitzthum et al. 2002; Heinze and Reppert 2011). Due to the axial symmetry of polarized light, two *E*-vectors elicit peak activity ($\Phi_{\max}$ -value) during each 360° rotation of the polarizer, with the peaks being separated by 180°. Minimal activity occurs at *E*-vectors orthogonal to $\Phi_{\max}$ ($\Phi_{\min}$ -value). The amplitude of modulation is a measure for the strength of the response. It can be quantified as a single number, the R-value. The larger this value, the stronger are the activity fluctuations during the rotation of the polarizer (Labhart 1996; Kinoshita et al. 2007; Heinze et al. 2009).

Depending on the relation of background firing rate and maximal and minimal activity during polarized-light stimulation, responses can be either purely excitatory (Fig. 4b), purely inhibitory, or both. The latter case, i.e., excitation near the $\Phi_{\max}$ -value and inhibition near the $\Phi_{\min}$ -value, is called polarization opponency and is a feature shared by many polarization-sensitive neurons in the brains of all examined insect species (Fig. 4a). Polarization opponency implies that at least one inhibitory neuron and one excitatory neuron with opposite *E*-vector tunings converge on the polarization opponent cell (Labhart 1988). Alternatively, polarization opponency can theoretically also be achieved by purely inhibitory input, if rebound excitation occurs between well-spaced bouts of inhibitory transmitter release events (Pfeiffer et al. 2011).



Polarization Vision, Fig. 4 Neuronal response to polarized light. When stimulated with a rotating polarizer from the zenith, the different E -vector angles elicit a sinusoidal change in spiking frequency. (a) The *top trace* shows the mean frequency (sliding average) of the spike train shown in the *lower trace*. Relative to its background firing rate (gray line in *top trace*), the depicted neuron of the anterior optic tubercle (TuTu1) from the locust is inhibited at the activity trough ($\Phi_{\min}$) and excited at peak activity ($\Phi_{\max}$),

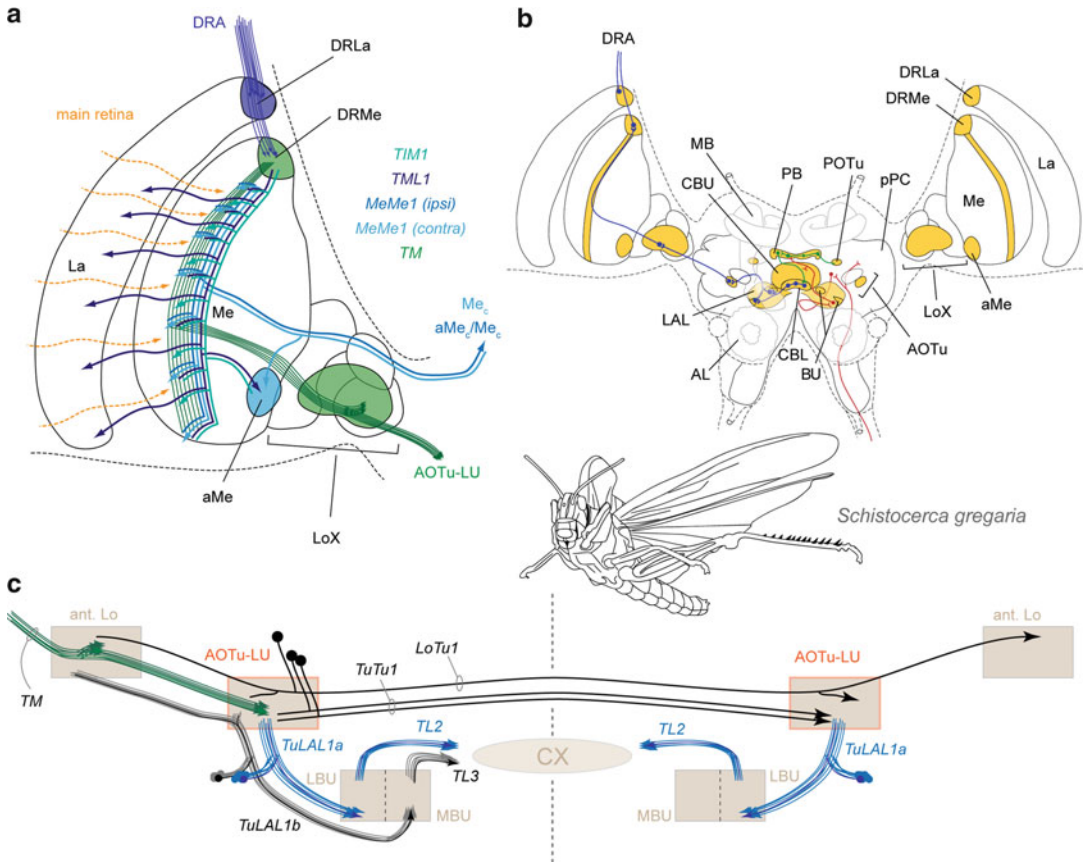
i.e., it exhibits polarization opponency. The *blue bar* illustrated the presence of polarized light, while the *black ramp* illustrates the rotation of the polarizer. The *double arrows* indicate the E -vector orientation (Modified from Pfeiffer et al. 2005). (b) As (a), but for a LoTu1 neuron. This type of neuron does not show polarization opponency but is exclusively excited by all E -vector orientations (Data kind courtesy of B. el Jundi)

Optic Lobe

Beneath the retina of an insect compound eye lies a series of three retinotopically organized brain regions together referred to as the optic lobe. Located on either side of the central brain, they are the first processing stages of all visual information from the eyes. From distal to proximal,

these neuropil regions are called the lamina, the medulla, and the lobula complex. Dependent on the species, the lobula complex can consist of only one neuropil, of two neuropils (lobula and lobula plate), or of several neuropils (e.g., four in the locust) (Fig. 5a).

The axons of the photoreceptors from the DRA terminate in specialized dorsal rim areas of the



Polarization Vision, Fig. 5 Polarization vision pathway in the brain of the locust. (a) Schematic representation of polarization-sensitive neurons of the locust optic lobe. Photoreceptors from the dorsal rim area (DRA) of the compound eye terminate in the dorsal rim lamina (DRLa) and the dorsal rim medulla (DRMe). From there, a set of transmedulla neurons (TM) is proposed to transfer the information to the lobula and the anterior optic tubercle (AOTu). TM cells are suited to integrate input from the main retina (orange) as well. Several types of large, polarization-sensitive tangential neuron possess overlapping branches in the same layer as TM neurons, providing connections to the contralateral medulla (Me_c), the ipsilateral lamina (La) and medulla (Me), and the accessory medulla of both hemispheres (aMe , aMe_c). (Based on data from el Jundi et al. 2011). (b) Schematic overview of the locust brain with neuropils involved in processing polarized-light information highlighted in yellow. Input pathways are shown on the right side of the brain (as seen by the animal), while output pathways are shown

on the left side. Proposed pre- and postsynaptic endings of cells are indicated by filled circles and open half circles, respectively. (c) Schematic representation of the polarization vision pathway in the central brain of the locust, emphasizing all neurons associated with the AOTu. Neurons with proven bilateral input are highlighted in blue. Intertubercle neurons ($LoTu1$ and $TuTu1$) occur only once or twice per hemisphere, while $TuLAL$ neurons and tangential neurons of the central complex (TL) occur in many individuals. Neuron names are indicated by italic lettering. Abbreviations: LoX lobula complex, $AOTu-UU$ upper unit of the anterior optic tubercle, $AOTu-LU$ lower unit of the anterior optic tubercle, *ant. Lo* anterior lobula, LBU lateral bulb, MBU medial bulb, CX central complex, CBU upper division of the central body, CBL lower division of the central body, PB protocerebral bridge, LAL lateral accessory lobe, AL antennal lobe, MB mushroom body, $POTu$ posterior optic tubercle, pPC posterior protocerebrum, *ipsi* ipsilateral, *contra* contralateral. Italic abbreviations: names of neuron types

lamina and the medulla in the locust and cricket, while all receptors found to date in the monarch butterfly could be traced to the medulla (Sauman et al. 2005; Blum and Labhart 2000; Homberg and

Paech 2002). The neurons directly postsynaptic to the photoreceptors are unknown, but anatomical data from locusts and bumblebees suggests that transmedulla neurons arborizing in the dorsal rim

medulla and in one layer of the main medulla transfer information about polarized light to the lobula and further on to the central brain (Fig. 5a; Pfeiffer and Kinoshita 2012; Homberg et al. 2003). All physiologically characterized polarization-sensitive neurons of the optic lobe are tangential neurons with arborization trees covering large portions of the medulla. These cells are either restricted to one optic lobe or cross the midline of the brain and provide a substrate for information flow to the medulla of the contralateral hemisphere. Interestingly, all of these neuron types in the locust have branches restricted to the same layer of the medulla, suggesting that this layer is dedicated to processing polarized-light information (Fig. 5a; el Jundi et al. 2011).

All of the cells described above respond to stimulation with a rotating polarizer from the zenith with sinusoidal modulations of their firing frequency. In fact, the first polarization-sensitive neurons recorded from any insect brain belonged to a group of neurons connecting the medullae of both brain hemispheres in the optic lobes of the cricket (Labhart 1988). These so-called POL1 neurons have been extensively studied and are characterized by polarization opponency, large, contralaterally located receptive fields, and a tightly defined $\Phi_{\max}$ -value. Interestingly, when the population of POL1 neurons from one brain hemisphere is analyzed, three distinct tuning classes of these cells can be distinguished (with respect to the body length axis and plotted clockwise: 10° , 60° , and 130° for neurons with their soma located in the left brain hemisphere (Labhart et al. 2001)). The neurons of the contralateral hemisphere are tuned to mirror symmetrical $\Phi_{\max}$ -values. Therefore, three individual POL1 neurons likely exist in each optic lobe. These cells do not respond to unpolarized light but are extremely sensitive to polarized light down to intensities below that of a moonless night (Labhart et al. 2001). Additionally, the responses are robust even at degrees of polarization as low as 5% (Labhart 1996).

Aside from the cricket, polarization-sensitive neurons of the optic lobe have been also reported in the cockroach *Leucophaea maderae* (Loesel and Homberg 2001) and the ant *Cataglyphis*

(Labhart 2000) but have been studied in detail only in the desert locust (el Jundi et al. 2011; Homberg and Würden 1997; el Jundi and Homberg 2010). Here, five types of neurons have been described. Unlike in the cricket, most of the locust neurons (four out of five) do not show polarization opponency, but responses are purely excitatory. When stimulated from the zenith, all examined cells receive input from the ipsilateral eye only. The lateral extent of the receptive fields of three of the cell types has been described as well. In two cases (MeMe1 and TIM1 cells), it matches the data from the cricket. For one cell type (TML1 cell), however, the receptive field is located in the ipsilateral sky hemisphere. Together with the exclusively ipsilateral input, this suggests that this neuron type receives its polarized-light information from the main retina, as the ipsilateral DRA is directed towards the contralateral sky hemisphere (el Jundi et al. 2011). When the distributions of *E*-vector tunings are compared to the cricket POL1 data, no matching triple-peaked distribution exists for any of the examined locust neuron types. Nevertheless, the tunings of TIM1 and MeMe1 cells are each clustered around one single value, each of which approximately matches one of the three tuning classes described in the cricket (after values have been transformed to the cricket coordinate system: TIM1 = 67° and MeMe1 = 20°) (el Jundi et al. 2011). This suggests that there are differences in *E*-vector coding even between closely related species and that the tasks performed by one cell type in the cricket optic lobe might be distributed among several types of neuron in the locust.

At last, the cricket POL1 neurons as well as several of the described cell types of the locust possess processes in a small neuropil of the optic lobe called the accessory medulla (Fig. 5a; el Jundi et al. 2011; Homberg and Würden 1997; el Jundi and Homberg 2010; Labhart and Petzold 1993). As this neuropil has been implicated in a circadian function in several insect species (it is the seat of the internal clock in *Drosophila* and the cockroach), these neurons may provide an interface between circadian timing information and polarized-light-based compass information (Homberg et al. 2011).

Anterior Optic Tubercle

The first region of the central brain involved in the processing of polarized light is the anterior optic tubercle (AOTu). This neuropil exists in all insects studied and comprises either two subunits (one large and one small, e.g., in locusts; Homberg et al. 2003) or one large and several small subunits (e.g., in the monarch butterfly; Heinze and Reppert 2012). Polarization-sensitive neurons have so far been exclusively identified in the small subunits (Fig. 5b, c). Although not characterized physiologically, the combined population of transmedulla neurons (see above) likely provides polarization-sensitive input to the AOTu from the optic lobe. Within the AOTu, two classes of neurons have been shown to respond to polarized light: first, cell types connecting the AOTus of both brain hemispheres (intertubercle neurons) and, second, cell types that project from the AOTu to small neuropils called the bulbs (lateral bulb [formerly: lateral triangle] and medial bulb [formerly median olive] in locusts) (Fig. 5c). The latter provide the output of the AOTu. Intertubercle neurons (named LoTu1 and TuTu1) have been intensely studied in the locust (Kinoshita et al. 2007; Pfeiffer et al. 2005, 2011; Pfeiffer and Homberg 2007; el Jundi and Homberg 2012), while the output neurons (TuLAL1a/b) have been studied in the locust as well as the monarch butterfly (Heinze and Reppert 2011).

All of these neurons respond to rotating *E*-vectors with sinusoidal modulations of their spiking activity. While most cell types exhibit polarization opponency, responses of LoTu1 cells are exclusively excitatory (Pfeiffer et al. 2005). The *E*-vector tunings of LoTu1 neurons (one per hemisphere) and TuTu1 neurons (two per hemisphere) are fixed to specific values in each cell type. These values are mirror symmetrical with respect to the midline in neurons of the contralateral hemisphere. In TuLAL cells on the other hand, many different tunings occur both in the locust and in the monarch, suggesting that the population of these neurons (ca. 60 per hemisphere in the locust) could cover all possible *E*-vectors (Pfeiffer et al. 2005). Intertubercle

neurons receive input almost exclusively from the ipsilateral eye and possess relatively large receptive fields centered in the contralateral sky hemisphere at ca. 60° elevation, in tune with the orientation of the DRA (el Jundi and Homberg 2012). The receptive fields of TuLAL neurons are smaller and more variable between individual recordings. They are generally also directed contralaterally, indicating that each individual cell covers a small patch of sky viewed by the ipsilateral DRA. The tuning of each TuLAL cell would be expected to match the average microvilli orientation of the ommatidia converging on it. Although examined only in one recording, binocular input has been revealed in one TuLAL1a neuron of the locust, indicating interhemispheric information exchange already in early stages of the polarization vision pathway (Fig. 5c; el Jundi and Homberg 2012). As the described results were obtained in studies with laboratory-raised locusts, additional experiments were performed on locusts that had been raised with clear view of the sky. Surprisingly the distinct tunings of intertubercle cells are not present in those animals. Rather, all possible *E*-vector tunings occur across recordings. Interestingly, these values follow a predictable curve, when plotted against the time of day. This finding of the daytime-dependent adjustment of *E*-vector tunings of AOTu cells has been observed in locusts and monarch butterflies and is part of a mechanism referred to as elevation compensation (see below) (Heinze and Reppert 2011; Pfeiffer and Homberg 2007). This raises interesting questions about how the $\Phi_{\max}$ -values of these cells are generated and indicates that the polarization vision pathway is subject to experience dependent plasticity.

In the locust, these cells, in particular the two types of intertubercle neurons, have been also examined with respect to their responses to different intensities of polarized light, as well as to different degrees of polarization. TuLAL and TuTu neurons are largely intensity independent, i.e., they maintain their full response strength over several orders of magnitude of light intensities (Kinoshita et al. 2007; el Jundi and Homberg 2012). Below a threshold, the response quickly breaks down, leading to an all-or-nothing

response curve that is not suited to encode the stimulus intensity. Different from this behavior is the LoTu1 neuron, which shows a uniquely bell-shaped intensity-response curve. The rising slope is much shallower compared to the other cell types, indicating that *E*-vector responses of LoTu1 neurons are not intensity independent. Additionally, these cells are inhibited when stimulated with very bright polarized light (midday conditions). This suggests that these cells could play a role in adjusting the gain of the polarization vision channel in response to different illumination situations, e.g., shut down the system during midday when solar elevation is high and polarized-light information in the receptive field of the DRA is not reliable due to low degrees of polarization (el Jundi and Homberg 2012).

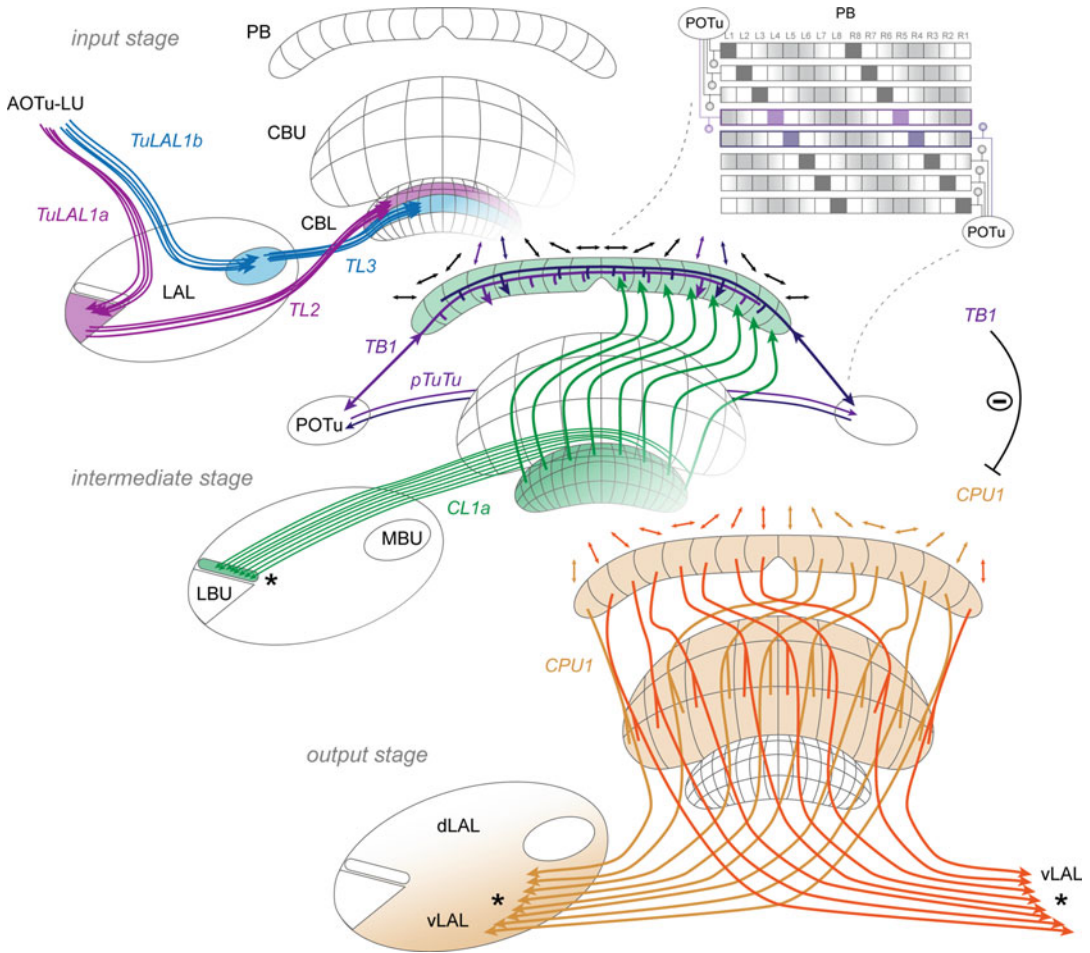
Interestingly, when stimulated with unpolarized light from the zenith, LoTu1 neurons are inhibited, while responses to rotating *E*-vectors from the same direction are purely excitatory (Pfeiffer et al. 2005, 2011). As unpolarized light is merely a blend of polarized light of all possible *E*-vector orientations, this behavior seems paradox. When the degree of polarization of the stimulation light was reduced from 100% to lower values and finally to unpolarized light, the purely excitatory response first turned into a polarization opponent response (containing excitation and inhibition), then to a purely inhibitory frequency modulation, and finally to near total inhibition. This means that the mean activity during the stimulation, as well as the response strength, was reduced when the degree of polarization was decreased. The reduced response strength can be intuitively explained by a more noisy input at lower degrees of polarization. To explain the reduced overall firing in the same situations, a model was developed, in which bouts of inhibitory transmitter release by photoreceptors lead to inhibition combined with rebound excitation in the postsynaptic cells (Pfeiffer et al. 2011).

Central Complex

The polarized-light information carried by the AOTu projection neurons (TuLAL neurons) is

directly transmitted to input neurons of the central complex (TL neurons). The synapses between these neurons are located in the bulbs, small neuropil regions with a characteristic microglomerular appearance. This organization results from highly specialized, very large synaptic complexes between the described cells (Träger et al. 2008). These remarkable synapses resemble similar structures in the auditory pathway of vertebrates that are essential for ensuring precise timing of action potentials when comparing signals originating from both ears. It has therefore been suggested that these synapses might play a similar role for accurately timing binocular integration of inputs from either eye in the polarization vision pathway of insects, e.g., to establish a robust estimate of body orientation during fast rotational movements of the animal. Although these synapses have not yet been studied physiologically, their conserved occurrence across many insects (e.g., locusts, monarch butterflies, flies, bees) suggests that they are essential for the processing of skylight compass cues before this information reaches the central complex (Pfeiffer and Kinoshita 2012; Träger et al. 2008; Heinze et al. 2013; Seelig and Jayaraman 2013).

The central complex is a midline spanning group of neuropils and consists of three major subunits: the protocerebral bridge (PB), the upper division of the central body (CBU; fan-shaped body in flies), and the lower division of the central body (CBL; ellipsoid body in flies). These regions are characterized by a regular neuroarchitecture of vertical columns (usually eight per hemisphere) and orthogonally intersecting layers (in the central body) (Fig. 6; Heinze and Reppert 2012; Heinze and Homberg 2008; Hanesch et al. 1989; Williams 1975; Lin et al. 2013). The layers are predominantly produced by neurons that connect external protocerebral regions with the central body. These so-called tangential neurons are thought to provide the major input to the central complex and occur in many different types in the CBU (Heinze et al. 2013; Hanesch et al. 1989; Young and Armstrong 2010). In the CBL, much fewer of these cells exist, which receive input almost exclusively from the bulbs and respond robustly



Polarization Vision, Fig. 6 Processing of polarized-light information in the central complex (CX) of the desert locust. The majority of cell types shown are also conserved in the monarch butterfly. From *top to bottom*, the input stage, the intermediate stage, and the output stage of the CX polarization-sensitive neuronal network are schematically illustrated. Note that only information reaching the CX from the left side is shown for simplicity. Two parallel pathways from the lower unit of the anterior optic tubercle (AOTu-LU) terminate in individual layers of the lower division of the central body (CBL) after passing through the lateral bulb (LBU) and medial bulb (MBU). CL1a neurons are suited to carry this information from the CBL to the contralateral hemisphere of the protocerebral bridge (PB). These neurons also provide a first output to an unnamed compartment of the lateral accessory lobe (LAL) near the LT (anterior loblet in the monarch butterfly). Within the PB, TB1 neurons are likely postsynaptic to CL1a cells and are suited to bilaterally integrate polarized-light information from both hemispheres. These cells provide output to one PB column in each hemisphere and additionally project to the posterior optic tubercle (POTu), where intertubercle neurons (*pTuTu*) potentially

provide a closed loop between TB1 neurons of both hemispheres. The *inset* on the *top right* illustrates the unique arborization pattern of TB1 neurons in the PB (Modified from Heinze and Homberg 2007). Each row represents an individual neuron, gray squares indicate columns filled with proposed input fibers, and black squares indicate columns filled with proposed output fibers. The potentially complex interplay of CL1a, TB1, and *pTuTu* neurons is likely involved in creating the systematic representation of zenithal *E*-vector tunings observed in TB1 cells (*double arrows*). TB1 cells likely possess inhibitory synapses onto CPU1 output neurons. These cells project from the PB to the contralateral LAL (ventral shell) and also comprise a systematic representation of *E*-vectors in the PB, which is out of phase with the TB1-representation by 90°. CPU1 cells additionally receive input from the upper division of the central body (CBU) and are thus suited to integrate behaviorally relevant aspects of the sensory world represented in the CBU with information about body orientation represented in the *E*-vector map of the PB. The asterisks highlight the converging output sites of the CX polarization-sensitive neuronal network

to zenithal polarized-light stimulation (Sakura et al. 2008; Vitzthum et al. 2002; Heinze and Reppert 2011). Detailed comparisons between the monarch butterfly and the desert locust have shown that this group of neurons is anatomically and functionally highly conserved and, together with TuLAL cells, constitutes two parallel, non-redundant input pathways from the AOTu to the CBL (Fig. 6, top; Heinze et al. 2013; Müller et al. 1997). Due to the large evolutionary distance between these species, this high degree of conservation is remarkable but is also reflected in the later stages of the polarization vision network. As the tangential neurons together are combined into the input stage of the central complex, the other polarization-sensitive neurons of the central complex have been grouped into an intermediate processing stage (CL1, TB1 neurons; Fig. 6 middle) and the proposed output stage (CPU1 neurons; Fig. 6 bottom), based on anatomical and physiological features of the cells.

The tangential neurons of the CBL likely pass their information to a specific set of columnar neurons (CL1). Columnar cells generally are the second major class of central-complex neurons. They possess small arborization trees (covering the width of one column) in the PB and connect these columns to corresponding regions of the CBU or the CBL, while additionally providing output axons to brain areas called the lateral accessory lobes (LAL), neuropils lying on either side of the central complex. Columnar neurons occur in isomorphic sets of 16 cells (one per column) and interconnect the PB and the central body via complex heterolateral projection schemes, suggesting complex patterns of interhemispheric information flow (Heinze et al. 2013; Heinze and Homberg 2008; Hanesch et al. 1989; Lin et al. 2013). The polarization-sensitive CL1 cells are conserved in all examined insects and occur in two subtypes, which, based on the anatomical distribution of proposed input and output fibers, provide a substrate for bidirectional information flow between columns of the CBL and the PB (Heinze et al. 2013; Hanesch et al. 1989; Heinze and Homberg 2009). In tangential input cells as well as in CL1 neurons, the *E*-vector tuning resulting from stimulation with rotating polarizers shown from the

zenith cannot be related to the cell's morphology. This is different in the neuron type presumably postsynaptic to CL1 cells. These neurons are multicolumnar cells of the PB (TB neurons) with a tangentially oriented main neurite spanning the length of the PB and, at least in locusts and monarchs, a connection to the posterior optic tubercle, a small neuropil at the back of the brain (Heinze et al. 2013; Lin et al. 2013; Heinze and Homberg 2007). Within the PB, proposed output fibers are present in two columns, one on either side of the midline at a distance of eight columns. The remaining columns are filled with proposed input fibers with the exception of the columns directly adjacent to the output domains, which remain empty (Fig. 6 middle). These neurons are therefore suited to integrate inputs from wide, bilateral areas of the PB and direct their output to two fixed columns on corresponding sites in either PB hemisphere. As these cells exist in an isomorphic set of eight individual neurons, the position of their output fibers can be correlated to physiological parameters of the neuronal responses. When this was done for the zenithal *E*-vector tuning of the neurons, it was revealed that each TB neuron is tuned to a specific *E*-vector angle according to its anatomical position along the PB. Moreover, this ordered array of tunings spans 180° per hemisphere, i.e., all possible *E*-vectors are represented exactly twice along the whole PB (Fig. 6; Heinze and Homberg 2007). As zenithal *E*-vectors are directly linked to the azimuth position of the sun, this array of neurons indirectly encodes the solar azimuth and is thus suited to act as an internal sun compass. Whether the double representation of 180° of zenithal *E*-vectors is a true representation of 360° of azimuthal space cannot be easily resolved by polarized-light stimulation alone, due to the inherent axial symmetry of *E*-vectors. However, data from the locust show that the *E*-vector tuning within the receptive fields of these cells is not constant but changes systematically in a way that could result in a matched filter for the polarization pattern of the sky (Heinze et al. 2009). The polarization pattern as a whole is therefore thought to elicit stronger responses in one half of the PB when the sun is in one sky hemisphere, while the

other half of the PB would respond stronger when the sun is in the opposite hemisphere, even though the *E*-vectors in the zenith are identical in both situations.

How this maplike representation of *E*-vectors is generated remains one of the major questions in the field. Likely, the complex interplay of CL1 neurons and TB1 neurons plays an important role, as both neuron types appear to be highly conserved across many insect species. Additionally in the locust, neurons that interconnect the posterior optic tubercles (el Jundi and Homberg 2010) have been suggested to provide a closed loop between TB1 neurons from both hemispheres and thus might be suited to refine or stabilize the *E*-vector map found in the PB (Fig. 6; U. Homberg, personal communication).

Most likely, TB neurons synapse onto several types of columnar neuron with input fibers in single columns of the PB (Heinze et al. 2013; Lin et al. 2013; Heinze and Homberg 2007). The most prominent example of such a neuron is a cell type called CPU1 neuron (Fig. 6 bottom). This cell type receives input not only from the PB but also from columnar domains within the CBU, while it provides output to large areas of the contralateral LAL. These neurons exhibit a strong correlation between their *E*-vector tuning and the position of their input arborization. As opposed to TB1 neurons, the systematic representation of *E*-vectors is shifted by 90°. This means that for a given column in the PB, the *E*-vector eliciting maximal excitation in TB1 neurons leads to minimal excitation (maximal inhibition) in the columnar neurons, suggesting an inhibitory connection between the two cell types (Fig. 6; Heinze and Homberg 2007).

Two additional potential output pathways for polarized-light information from the central complex exist. The first one has only been described in the locust and comprises two types of columnar PB cells projecting to small regions of the LAL close to the lateral and medial bulbs (Heinze and Homberg 2007, 2008). The second pathway involves the axonal projections of CL1 neurons to a different sub-compartment of the LAL (Fig. 6 middle). While this pathway is not very prominent in the locust, it is much more developed in the

monarch butterfly (larger axon diameters, wider projections fields, and more numerous terminals). Importantly, this pathway potentially bypasses the PB and could thus provide a direct link between the input neurons of the CBL and downstream targets in the LAL (Homberg et al. 2011; Heinze and Reppert 2011; Heinze et al. 2013; Heinze and Homberg 2009).

All of the described neurons respond to rotating *E*-vectors presented from the zenith with sinusoidal modulations of their action potential frequency. Despite the fact that these responses appear very similar, systematic differences between the physiology of neurons from different processing stages have been described (Heinze et al. 2009). In general, input stage neurons of the central complex have relatively small, contralaterally centered receptive fields, low background activity, low background variability, and high signal to noise ratios. The neurons of later processing stages, particularly the proposed output neurons, possess large, zenith-centered receptive fields and exhibit high background activity, high background variability, and lower signal to noise ratio. CL1 neurons, which have been proposed to link the input and output cells, show intermediate characteristics with respect to all of the described response features. These systematic changes in neuronal physiology suggest that input stage polarization-sensitive cells are specialized for this modality, while the output stage neurons are not maximally driven by polarized light alone and likely receive converging input from other sensory modalities (Heinze et al. 2009; Rosner and Homberg 2013). The proposed direction of information flow in output neurons has been further substantiated by direct observations of graded postsynaptic potentials only when these cells were recorded from the PB, while no such potentials were observed when the same cell types were recorded from their proposed output sites in the LAL (Heinze et al. 2009). The increasing size of the receptive fields suggests that neurons at later processing stages integrate signals from many input stage neurons with small receptive fields to eventually generate a position-invariant head direction signal that can be used to guide directed behavior.

At last, the complexity of the described polarization vision network of the central complex is further increased by the existence of neurons that respond to polarized light in a context-dependent way. These so-called conditional polarization-sensitive neurons have been described in the locust and comprise several types of columnar neurons with input in the PB and output projections to bilateral regions of the LAL or the contralateral nodulus (Heinze and Homberg 2009). In some recordings, these cells respond to polarized light similarly to all other described neurons, whereas in other recordings they remain unaffected by this stimulus, despite the fact that responses to unpolarized light in the frontal visual field remain present. Therefore, these cells appear to be recruited to the central-complex polarization vision network in a context-dependent way. The conditions that lead to this switch in response characteristics remain unknown. Also, whether similar neurons exist in other insects than the locust remains to be shown. However, as all the involved cell types have been described anatomically in many insect species, it seems not unlikely that the observed neuronal response characteristics could be a commonly shared feature across insects.

Beyond the Central Complex

The major output from the central-complex polarization vision network converges in a large region of the LALs defined by the target area of CPU1 neurons. In the locust, this region corresponds to the ventral shell of the LAL, while in the monarch butterfly it corresponds to the dorsal LAL (Heinze et al. 2013; Heinze and Homberg 2008). Polarization-sensitive neurons downstream of this area have been identified only in the desert locust. Two cell types are suited to integrate the converging output from the central complex with large input arborizations covering the whole projection area of CPU1 cells (Heinze and Homberg 2009). The first cell projects to the contralateral LAL, while the second type projects to large bilateral regions in the posterior protocerebrum, a region in which neurons descending from the

brain receive their input. As the latter neuron has been anatomically identified in the monarch butterfly as well, this neural pathway might be conserved in many insects (Heinze and Reppert 2011). Interestingly, neurons interconnecting the LALs of both brain hemispheres have been implicated in controlling steering movements during pheromone responses in moths (Iwano et al. 2010). One can speculate that similar cell types might also be involved in generating motor commands during behavioral responses to polarized-light stimulation (Merlin et al. 2012).

To induce behavioral responses of the animal, the polarized-light information has to reach the motor centers of the thorax. Indeed, such polarization-sensitive descending neurons have been identified in the locust (Träger and Homberg 2011). Two types of neuron possess their proposed input fibers in the posterior protocerebrum and descend either through the ipsilateral or the contralateral neck connective to target the subesophageal and thoracic ganglia. These cells respond to rotating polarized-light stimuli presented from the zenith with sinusoidal modulations of their firing frequency. These responses are considerably weaker and more variable compared to neurons from the central complex. However, this may be expected in cells separated from the sensory periphery by many synapses and suggests that they integrate many different sensory modalities. This is supported by strong, direction-dependent motion sensitivity in these neurons (Träger and Homberg 2011). Additionally, increased variability and lower signal to noise ratio were also observed in later processing stages of the central-complex polarization vision network (Heinze et al. 2009). Surprisingly, much stronger *E*-vector-dependent responses were observed in a type of neuron connecting the subesophageal ganglion to the prothoracic ganglion (Träger and Homberg 2011). Either these cells receive input from an unknown polarization-sensitive pathway or there is substantial local processing of information received from the known descending neurons within the ventral nerve cord that sharpens the tuning curves.

Overall, despite some gaps in understanding, combined data from the locust, the cricket, and the

monarch butterfly have led to the identification of a neural network involved in the processing of polarized light that spans most processing stages from the photoreceptors of the retina to neurons descending to the motor centers of the thorax. The significant challenge lying ahead is to verify the proposed links between these neural elements in order to combine them to a comprehensive network that performs the computations needed to explain an animal's behavior in response to polarized-light stimuli.

Integration of Polarized Light and Unpolarized Light

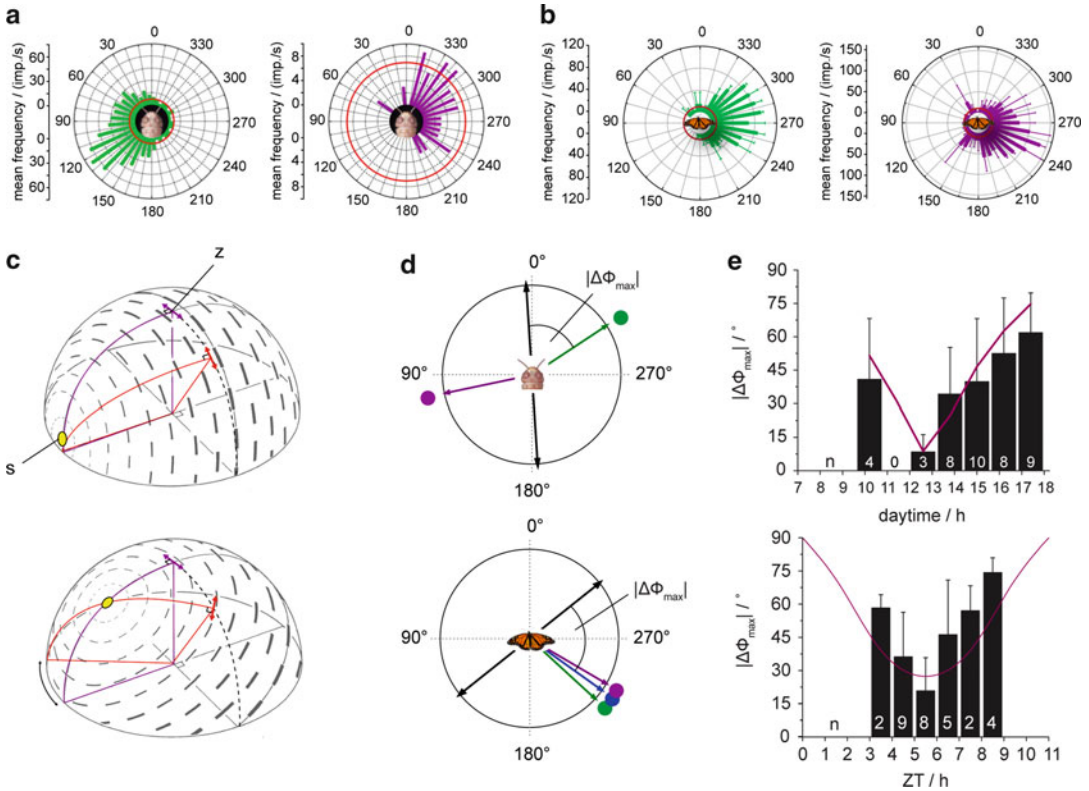
Polarized light is not the only orientation-relevant skylight compass cue. In fact, the sun itself is the most prominent feature of the sky and is indeed the primary source of information used for navigation, e.g., in the monarch butterfly (Reppert et al. 2004, 2010; Stalleicken et al. 2005; Froy et al. 2003). For choosing a reliable direction of travel, only the solar azimuth, i.e., the horizontal position of the sun, but not the solar elevation contains useful information. As the sun is often obscured behind clouds or other features of the visual scene, it is highly desirable for a navigating animal to extract the information about solar azimuth from indirect skylight cues, i.e., the skylight polarization pattern, the skylight spectral gradient, and the intensity gradient of the sky. The nervous system is thus faced with the challenge of integrating all these cues and combining them into a consistent representation of solar azimuth. By using more than one cue, the internal compass is expected to become more reliable and less prone to noise and interference in any of the individual channels.

The finding that polarization-sensitive neurons of the insect brain also respond to unpolarized light suggests that indeed information from other skylight cues is processed by the same neural substrate. The stimulus used most extensively is an unpolarized-light spot that is moved around the animal at a constant elevation of 30–45° (el Jundi et al. 2011; Heinze and Reppert 2011; Pfeiffer and Homberg 2007). This stimulus was applied in

recordings from locusts and monarch butterflies and was shown across different colors, ranging from ultraviolet to green. In principle, many polarization-sensitive neurons were maximally excited when the light spot passed through a specific azimuth value, while the light spot led to an inhibition of the spiking rate or to no response when it was present in the opposite direction (Fig. 7a, b). The resulting tuning curve with respect to the azimuth position of the stimulus is referred to as azimuth tuning of the cell.

When following the polarized-light information through the locust brain, unpolarized light is integrated with polarized light already in neurons of the optic lobe. Virtually all neurons with a defined $\Phi_{\max}$ -value for *E*-vectors also possess a reliable azimuth tuning (el Jundi et al. 2011). This tuning is independent of the color of the stimulus, so that green and UV stimulations result in identical or very similar tunings. This suggests that these cells encode the azimuth of the brightest point in the sky, i.e., the sun. Although it remains unknown where this information about solar azimuth is combined with information from the DRA, likely candidate cells have been anatomically described in the locust and in the bumblebee (el Jundi et al. 2011; Pfeiffer and Kinoshita 2012; Homberg et al. 2003). These transmedulla neurons possess input fibers in the dorsal rim of the medulla and additionally have one long input neurite passing vertically through the medulla, potentially enabling these cells to integrate information from all ommatidia that face one particular azimuth.

The population of the recorded optic lobe neurons showed that these cells exhibit fixed *E*-vector tunings that depend on the cell type. With respect to the azimuth tuning, the situation is more complex. Here, locusts that had been raised in the laboratory with no view of the sky possessed neurons with random azimuth tunings, while neurons from locusts that had been raised with a clear view of the sky showed identical tuning across all cells (tuned to the ipsilateral side, 90°) (el Jundi et al. 2011). This finding reveals that the tunings of these cell types are not static but rather depend on the experience of the animal. It also poses the question as to how both sources of information are



Polarization Vision, Fig. 7 Integration of polarized and unpolarized-light stimuli in neurons of the locust and the monarch butterfly. (a) Neuronal response of a neuron of the anterior optic tubercle (AOTu) of the locust to an unpolarized-light spot moving around the animal at constant elevation (45°). *Left*, green light; *right*, ultraviolet (UV) light. Shown are *circular plots* of mean spiking activity (bin size 20°) against the azimuth position of the stimulus. The *red line* indicates the background activity of the neuron (Modified from Pfeiffer and Homberg 2007). (b) As A, but for an AOTu neuron of the monarch butterfly. Other than in the locust, the neuron is tuned to identical azimuth values for green and UV light (Modified from Heinze and Reppert 2011). (c) Schematic representation of the skylight polarization pattern emphasizing the relation of *E*-vectors outside the zenith and solar azimuth at different solar elevations. *Top*: when the sun is close to the horizon, all *E*-vectors in the sky are oriented approximately in parallel, leading to a 90° relation between the solar azimuth and all *E*-vectors in the sky. *Bottom*: at higher solar elevations, this 90° relation is only given along the solar meridian (including the zenith (*z*), *violet*). Outside the solar meridian (*red*), assuming such a 90° relation leads to a significant error (*double arrow*), as the angle between the solar azimuth and the *E*-vector becomes smaller with increasing solar elevation (i.e., during midday) (Reprinted from Heinze and Reppert 2011). (d) *E*-vector

tuning and azimuth tuning to unpolarized-light spots moving around the animal for an AOTu neuron of the locust (*top*) and the monarch butterfly (*bottom*). The absolute difference between the green azimuth tuning and the *E*-vector tuning is defined as $\Delta\Phi_{\max}$ -value in locusts, while the difference between the *E*-vector tuning and the mean azimuth tuning to all tested colors is defined as the $\Delta\Phi_{\max}$ -value in the monarch butterfly (Modified from Merlin et al. 2012). (e) *Top*: $\Delta\Phi_{\max}$ -values of AOTu neurons plotted against the time of recording (bins of 72°) in the locust. The numbers in the bars represent the number of recorded neurons included in each bin. The data are fitted with a function (*red*) that describes the angular difference between solar azimuth and *E*-vector orientation for individual points of the sky over the course of the day. The fit is calculated for August 1 (within the rearing period of the used animals) and 60° elevation above the horizon according to the optical axis of the DRA. The fit line is calculated for the coordinates of the Tropic of Cancer (23.4°N), which lies in the natural habitat of the locusts. *Bottom*: As the *top* panel, but data for neurons recorded from the bulbs of the monarch butterfly (AOTu neurons and TL neurons) and plotted against zeitgeber time (0 = lights on [=sunrise]). The line represents the mean perceived *E*-vector in the region of sky viewed by the dorsal rim of the monarch over the course of the day, calculated for the location and date of capture of the used animals.

integrated into a consistent representation of solar azimuth.

Similar results have also been obtained from the monarch butterfly in neurons of the AOTu and tangential neurons of the CBL. These cells are tuned to an identical azimuth value of unpolarized green, blue, and UV light, located on the contralateral side of the animal (270° azimuth) for all recorded neurons (Fig. 7b; Heinze and Reppert 2011).

In the locust, neurons of the AOTu exhibit a different behavior. These cells are excited by green light from one direction, while they are inhibited by UV light at that azimuth (Fig. 7a). This color opponency is not suited to encode the brightest spot of the sky but rather the skylight spectral gradient (Kinoshita et al. 2007; Pfeiffer and Homberg 2007). Across the sky, the ratio of green light to UV light varies systematically and is defined by the angular distance of the observed spot of sky to the sun. In short, the closer a spot of sky is towards the sun, the more long wavelength light is present in the light received from that spot. The color opponent neurons of the locust polarization vision pathway consequently would be activated when the locust faces the solar hemisphere (given the preferred azimuth of the cell lies ahead of the animal), while it would be inhibited when facing the antisolar hemisphere. As the zenithal *E*-vectors are identical in both situations, this mechanism could be used to resolve the inherent ambiguity in the polarized-light signal resulting from the axial symmetry of *E*-vectors. How these response properties emerge from the potentially presynaptic optic lobe neurons without color opponency remains unknown.

Despite the differences between the monarch butterfly and the locust in the response characteristics of AOTu neurons (solar azimuth tuning

vs. spectral gradient encoding), both species share a remarkable aspect of their neural responses. In the described neurons, the *E*-vector tuning is adjusted with respect to the azimuth tuning of the same cell in a daytime-dependent way (Heinze and Reppert 2011; Pfeiffer and Homberg 2007). Given that polarized light was always shown from the zenith in these experiments, combined with the fact that zenithal *E*-vectors of the sky are always perpendicular to the solar azimuth, one would expect a fixed 90° relation between *E*-vector tuning and azimuth tuning of a particular neuron (Fig. 7c). However, when one analyzes the population of neurons in both the monarch butterfly and the locust, all possible difference angles between *E*-vector tuning and azimuth tuning can be observed. Plotted against the time of day, the data reveals that large values (close to 90°) are only found in the morning and evening, while small values are found during midday (Fig. 7e). This surprising behavior can be explained by considering that the DRA of the animals does not look exclusively into the zenith. The relation between *E*-vectors and the solar azimuth outside the zenith depends strongly on the solar elevation, which itself is a function of the time of day (Fig. 7c). Modeling of skylight parameters has shown that the angular distance between the mean perceived *E*-vector across the DRA of the monarch butterfly and the solar azimuth precisely matches the measured difference angles of the recorded neurons across the day, particularly when the place and time of capture of the animals is taken into account (Heinze and Reppert 2011) (Fig. 7e bottom). Similarly in the locust, fitting the recorded difference angles to a function that describes this parameter in the sky leads to the closest fit for the point of sky in the center of the locust DRA, especially when

Polarization Vision, Fig. 7 (continued) Data are binned in 1 h bins. Note that in both species, the angular difference between azimuth and *E*-vector tuning is large in the evening and mornings (at *low* solar elevations) and small around noon (at *high* solar elevations). Thus, the *E*-vector

tuning of the neurons changes over the course of the day to match the skylight situation in the region of sky viewed by each species' dorsal rim area, a process called elevation compensation (Modified from Merlin et al. 2012)

skylight parameters from the natural habitat of the locust were used (Pfeiffer and Homberg 2007) (Fig. 7e top). These findings highlight that the integration of unpolarized and polarized skylight cues is achieved by adjusting the *E*-vector tuning over the course of the day so that it always encodes the identical solar azimuth value that is also encoded by the information obtained from viewing the sun directly. This process is referred to as elevation compensation and leads to a consistent representation of the solar azimuth in both species at the input stage to the central complex, despite the fact that the information reaching the brain is strongly dependent on the different layout of the DRA.

Within the central complex, responses to the azimuth of unpolarized light have been reported in the monarch butterfly and are comparable to early stage neurons of the AOTu (Heinze and Reppert 2011). Due to the limited number of recordings, no information about the systematic representation of azimuth tunings exists for this brain region. Additionally, many types of polarization-sensitive neurons of the central complex in the locust have recently been shown to exhibit sensitivity to looming objects and to small moving objects, suggesting that integration of behaviorally relevant object information is integrated with compass information in these cells (Rosner and Homberg 2013).

Surprisingly, in the cricket no responses to unpolarized light in polarization-sensitive neurons have been revealed to date. However, no systematic analysis of azimuth-dependent responses has been carried out, so that the possibility of similar neural mechanisms for integrating solar azimuth and celestial *E*-vectors remains open.

Polarized Light as Global Frame of Reference for Insect Orientation?

Two of the three species studied most extensively with respect to the neural basis of polarized-light vision are long-distance migratory insects (desert locust, monarch butterfly), while the third (field cricket) is a central place forager. As most aspects

of the neural network that have so far been described appear to be highly conserved between even not closely related insect species, polarized-light vision is likely a fundamental feature of the navigation system of insects with highly developed orientation behavior.

However, skylight compass cues like polarized light all by themselves do not provide the animal with any useful information, as long as they are not combined with features of the environment that are either attractive or repulsive, i.e., need to be approached (e.g., food, mating partners, nest) or avoided (e.g., predators). Additionally, whether features are attractive or repulsive depends on the behavioral context. For example, the nest of a central place forager is only attractive on the inbound journey after a foraging trip. Hence, modulating factors, like the motivational state of the animal or the current time of day, have to be integrated when transforming sensory signals into motor commands. An animal constantly has to evaluate whether its current heading matches its desired direction of movement and translate any discrepancy into compensatory movements. If the behavior of the animal contains prolonged straight segments or involves a central point to which it has to return, a global frame of reference is of great value for ensuring accuracy (Lambert et al. 2011). It is in this context in which the sun and other celestial features (e.g., polarized skylight) can provide most valuable orientation cues.

The described neurons that encode both unpolarized and polarized skylight cues are not suited to mediate perception of either individual cue but are much more suited to encode body orientation with respect to the solar azimuth. In the later processing stages of the central complex, this information is then used to generate an ordered representation of azimuthal space, for which polarized skylight is likely only one of many contributing factors. One might speculate that this azimuth representation provides the frame of reference in which behaviorally relevant features of the environment are associated with directional information. This process of combining a “where” pathway (azimuth representation) with a “what” pathway (behaviorally relevant aspects of the sensory world) could provide the basis for generating

motor commands within the computational network of the insect central complex. With its exceptionally rich supply of neuromodulatory substances (Nässel and Homberg 2006; Kahsai and Winther 2011), the central complex is also a promising region for integrating the animal's motivational state necessary for generating appropriate behavior.

Polarization Vision Beyond Arthropods?

Given the substantial progress in understanding the neural mechanisms involved in polarized-light vision in arthropods, especially in insects, the question arises as to what is known about polarization vision in other animals. With regard to other invertebrates, polarization vision is well studied in cephalopods, such as squids, cuttlefish, and octopus (Horváth and Varjú 2004). Like in arthropods, the retina of the cephalopod's camera-type eye contains orthogonally arranged blocks of highly aligned microvilli, which theoretically allow intensity-independent encoding of *E*-vector orientations of polarized light, if polarization opponent processing occurs further downstream (Shashar et al. 2002). Behaviorally, these animals have been shown to use polarized light for intra-specific communication and prey detection and to mediate escape responses (Pignatelli et al. 2011). However, despite electrophysiological recordings from photoreceptors, virtually nothing is known about the neural basis of these behaviors.

In vertebrates, there is behavioral evidence for polarization sensitivity from all taxa, i.e., fish, reptilians, amphibians, birds, and mammals (reviewed in (Horváth and Varjú 2004)). Most systematically studied have been innate and conditioned orientation responses in fishes (Hawryshyn 2010), while recent work in birds has uncovered an important role of polarized light in calibrating the magnetic compass (Muheim 2011). Unlike invertebrates, vertebrates detect light with ciliary photoreceptors that do not contain microvilli. Rather, they are composed of stacks of radially symmetrical disks, in which rhodopsin pigments can rotate freely. Thus, unlike microvilli-based (rhabdomeric) photoreceptors,

ciliary photoreceptors are not intrinsically sensitive to polarized light. This requires intricate specializations of these receptors if polarization sensitivity is to be achieved. In fishes and birds, the so-called double cones have been implicated in mediating polarization vision. These receptors consist of pairs of cones tightly associated with one another. In salmonid fishes, the membrane separating the two cones is tilted at the apical end of their inner segments. This tilted membrane has been suggested to serve as a dichroic mirror that reflects light onto neighboring cones, which are hence illuminated transversely, not axially. At transverse illumination, the receptors are highly sensitive to *E*-vectors oscillating in parallel to the diameter of the disks, whereas they cannot be excited by orthogonally oriented *E*-vectors (Horváth and Varjú 2004; Hawryshyn 2010). Additionally, individual cones of the gold fish have been shown to exhibit weak polarization sensitivity even under axial illumination, albeit through an unknown mechanism (Roberts and Needham 2007). These receptors could thus mediate polarization sensitivity without the involvement of double cones. In birds, reflections in oil droplets in double cones have been proposed to serve a similar role in reflecting incoming axial light from the main cone onto its accessory cone and hence provide transverse illumination suited for *E*-vector detection (Muheim 2011). In reptiles and amphibians, polarization sensitivity has been revealed in several species by behavioral experiments (Horváth and Varjú 2004). Other than in birds and fishes, the retinal photoreceptors of the eyes are likely not involved in mediating this task. Indeed, extraocular photoreceptors in the pineal organ have been shown to be required for *E*-vector-dependent orientation responses (Beltrami et al. 2010). Finally, humans can be trained to perceive a visual effect induced by linearly polarized light, the Haidinger brush. This effect comprises *E*-vector-dependent color perception via an unknown retinal mechanism and suggests that polarization vision is also possible among mammals (Horváth and Varjú 2004).

Overall, compared to invertebrates, the field of polarization vision remains in its infancy in vertebrates. However, as the principles of how

E-vectors might be detected in the different vertebrate orders become increasingly well understood, the neural principles underlying polarized-light-induced behaviors may be elucidated in the not too distant future in at least some of the studied species.

Cross-References

- [Collision Avoidance Models, Visually Guided](#)
- [Connectome, *Drosophila*](#)
- [Computation with Population Codes](#)
- [Optic Flow Processing](#)
- [Phototransduction Biophysics](#)
- [Visual Motion Detection in *Drosophila*](#)
- [Visual Processing in Free Flight](#)

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Policy Gradient Methods

► [Reinforcement Learning in Cortical Networks](#)

Polypeptide and Protein Modeling for Drug Design

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Synonyms

[Computational modeling](#); [Computational structural biology](#); [Structure-aided drug design](#)

Definition

Modeling of polypeptides and proteins, often referred to as biomolecular or molecular modeling, encompasses the use of theoretical models and computational methods to model the structure and dynamics of molecules of biological interest such as peptides, proteins and small organic molecules (ligands).

The aims of protein and peptide modeling for drug design include: (i) modeling the three-dimensional structure of proteins of current or potential drug targets; (ii) identifying and characterizing the structural dynamics associated with the function of a particular protein or peptide; and (iii) predicting the structure and molecular interactions of protein-ligand complexes. This knowledge underpins structure-based and rational drug design. It can aid in the design and optimization of drug molecules by shedding light on their mode of action, specificity and selectivity.

Detailed Description

Background

The number of protein structures solved experimentally and deposited in the Protein Data Bank (PDB) has risen exponentially since its inception in the 1970s (RSCB Protein Data Bank [2013](#)). This has been accompanied by a rapid growth in computational power and continuous improvements in modeling algorithms, greatly enhancing the complexity, size and diversity of the proteins that can be simulated. Together, the experimental and computational breakthroughs initiated in the 1970s have contributed enormously to our knowledge of protein structure and structural conservation within protein superfamilies. In 2013, the contribution of computational modeling to our understanding of protein structure and biochemical function was recognized by the award of the Nobel Prize in Chemistry to three of the founders of the field, Martin Karplus et al. (2013). Computational modeling techniques lie at the core of fields such as protein folding and dynamics, structure-based drug design and computer-aided drug design.

The majority of drugs targeting the central nervous system modulate the action of one or more neurotransmitters involved in synaptic transmission. Thus the most common drug targets fall into the category of cell surface receptors, such as metabotropic and G-coupled protein receptors (GPCRs), transporters and ion channels (Cross and Yocca [2012](#); Hefti [2004](#); Squire et al. [2008](#)). In fact, drugs targeting GPCRs account for over 50 % of all clinical drugs (Schushan and Ben-Tal [2010](#)). Despite their clinical significance, solving the experimental structure of transmembrane proteins remains challenging. In 2013, the PDB contained >94,500 structures, of which only 1954 are transmembrane proteins (RSCB Protein Data Bank [2013](#); Kozma et al. [2013](#)). This gap between the availability of structural models and the need for high-resolution structures of membrane proteins is a major obstacle in the design of drugs targeted for a specific protein or protein isoform. In many cases, both the protein dynamics and the precise details of the drug binding site is unknown. This makes it difficult to identify the

molecular interactions that govern the specificity of the drug. Furthermore, the existence of multiple subtypes or isoforms of many of these proteins, each with distinct physiologic functions, makes isoform selectivity crucial for drug efficacy. Computational modeling techniques offer a means to understand structure-function relationships of these critical proteins.

The Underlying Principles Behind Protein and Peptide Modeling Techniques

Computational modeling is used to address a myriad of question relevant to drug design. Examples include: predicting the structure of a protein from its amino acid sequence or from the structures of homologues; elucidating the relationship between protein structure and biological function; understanding how protein motion is associated with drug binding; determining the molecular basis of the drug-protein interactions that govern drug selectivity and potency; and understanding how drug binding modulates protein function. The most suitable modeling approach for a particular problem depends on the level of structural and biochemical information available and the question to be addressed. Figure 1 gives an overview of commonly used techniques that will be discussed here.

Simulation techniques for the modeling of proteins, peptides and drugs can be classified into three broad categories based on the underlying theory or principle: knowledge or rule based methods; potential energy methods; and quantum mechanical methods (Goodfellow 2008). More recent approaches combine two or more of these categories to improve the quality of the models obtained (Goodfellow 2008). For example, computational approaches that investigate protein dynamics, or protein–ligand interactions (such as molecular dynamics and docking techniques) are primarily based on potential energy methods, while structure prediction methods often combine an initial knowledge-based method with a potential energy method to further refine the model. Methods based on a purely quantum mechanical

approach are not feasible for molecules of more than 50 atoms due to current computational limitations. As most proteins and peptides are larger than this, quantum mechanical approaches will not be discussed here.

Knowledge Based Methods

Knowledge based methods for protein and peptide modeling use comparative statistical analysis to predict the structure of the amino acid sequence of the target protein from (i) the sequence of homologous proteins of known structure; or (ii) a database of protein structures (Rangwala 2010). The accuracy of this approach relies on the current knowledge of protein structures and the evolutionary relationship between the proteins.

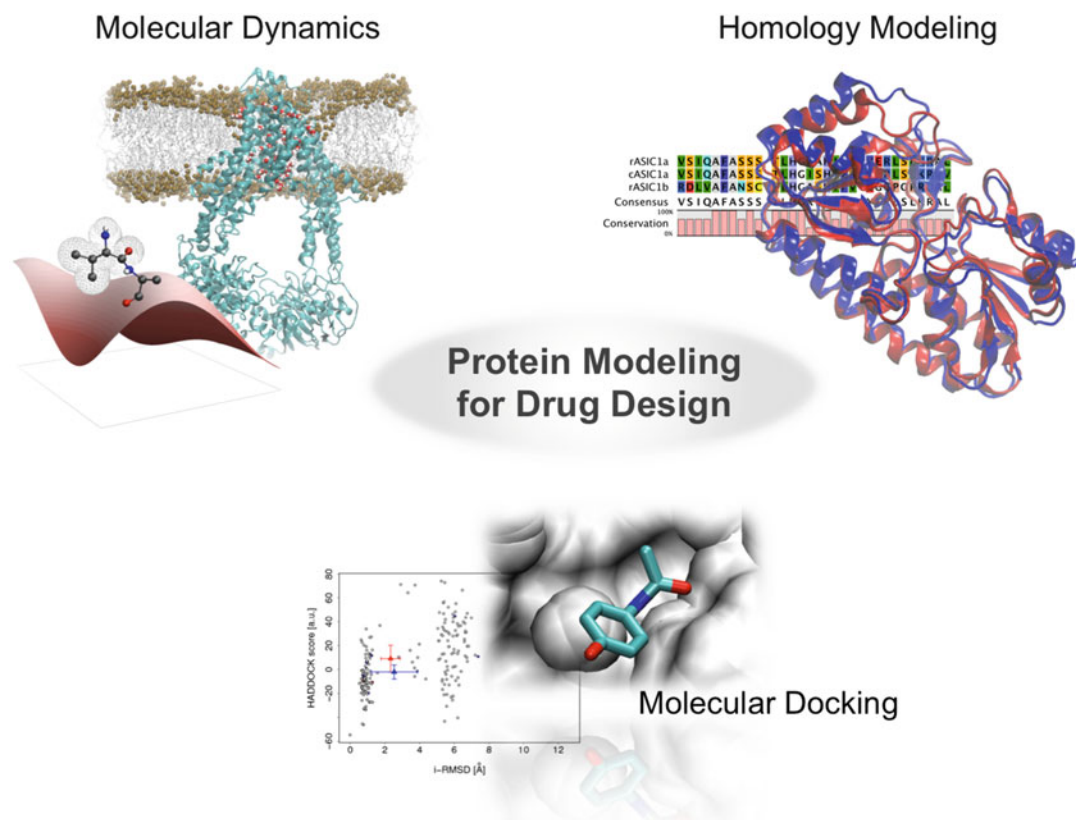
Potential Energy Methods

Potential energy (PE) methods, are based on (i) a description of the fundamental parts of the system (usually atoms), (ii) a mathematical description of the interactions between the atoms; (iii) a starting configuration such as the coordinates of each atom in the system; and (iv) an algorithm to carry out the desired computational steps by evolving the system in time and space (Goodfellow 2008; Jensen 2007).

Most PE methods used for modeling polypeptides and proteins utilize a so-called molecular mechanics (MM) approach in which a system is described as a collection of spheres (representing one or more atoms), connected by bonds in the form of harmonic springs. Both the bonded and non-bonded interactions between all pairs of atoms are described by simple mathematical expressions, referred to as the forcefield, the general form of which is described in Eq. 1:

$$E_{\text{total}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}} + E_{\text{electrostatic}} + E_{\text{vanderWall}} \quad (1)$$

where E is the potential energy. The underlying principle of MM assumes that the potential energy of the molecular system can be described as a function of the atom's position in space. The forcefield allows the change of energy in the system to be calculated as the atomic positions



Polypeptide and Protein Modeling for Drug Design, Fig. 1 An overview of the main techniques used to model proteins and peptides for drug design. The main aims of these techniques is to (i) model the three-dimensional structure of proteins of current or potential drug targets; (ii) identifying and characterizing the structural dynamics associated with the function of a particular protein or peptide; and (iii) predicting the structure and molecular interactions of protein-ligand complexes. In the absence of an experimentally determined protein structure,

homology modeling techniques can be used to predict the structure of a given protein from the sequence similarity to homologues of known structure. Docking simulations can be used to predict the interaction of drugs, ligands or other proteins with the protein of interest. From a high-resolution experimentally determined protein structure, the conformational dynamics within the protein and dynamic binding of drug molecules can be elucidated using molecular dynamics simulation techniques

P

change. The conformation of a protein or peptide is optimized with respect to its energy, as the assumption of the potential energy concept is that the minimization of the potential energy will give the optimal geometry of the protein or ligand. MM becomes particularly powerful when combined with algorithms that propagate the system in time or space (Jensen 2007; Náray-Szabó et al. 2012; Nowak 2012). These algorithms either propagate possible conformations of the protein to sample its conformational space, or examine how the system evolves over time.

Energy minimization and Monte Carlo algorithms are used to propagate the system in conformational space. Energy minimization algorithms (also referred to as geometry or energy optimization) calculate the gradient of the potential energy and evolve the protein in the direction of the minimum potential energy. Monte Carlo algorithms (named after the Monte Carlo casino) rely on repeated random sampling of an initial amino acid conformation to find the statistically most probable end state for the given initial conditions. These algorithms are particularly important for

finding stable, minimum energy conformations of a protein, for example, the local and global energy minima in protein folding or ligand binding pathways. They cannot give information about the timescales of these processes.

Langevin (or stochastic) dynamics and molecular dynamics use algorithms to examine the time-evolution of the system, but differ in the underlying equation of motion. Molecular dynamics is based on Newton's equation of motion:

$$m_i a_i = F_i(r) \quad (2)$$

where m_i , a_i and $F_i(r)$ are the mass, acceleration and force on the i th atom. Stochastic dynamics is based on the Langevin equation:

$$m_i a_i = F_i(r) - m_i \gamma_i(t) + \eta_i(t) \quad (3)$$

where the additional terms, $m_i \gamma_i(t)$ and $\eta_i(t)$ are the random force and frictional force on the i th atom that arise from molecular collisions due to the thermal motion of the atoms. By incorporating these forces, Langevin dynamics model the effects of water and other solvents without including them explicitly in the simulations. In contrast to algorithms that propagate the protein system in conformational space, algorithms that give the time evolution of the system provide information about the dynamics of the system and the timescale at which these occur. One of the major limitations of these algorithms is they often evolve to a local energy minima which is stable over the timescale (ns to μ s) of the simulation. Because of this limitation, time-evolution algorithms cannot currently sample the entire range of conformations that a protein system will adopt in a physiological environment.

Protein Structure Prediction

Homology Modeling

Proteins derived from a common ancestor are homologues and display a conserved amino acid sequence and three-dimensional structure. The extent of the sequence and structural conservation depends on the evolutionary distance

between the homologues. Homology or comparative modeling exploits these similarities to construct a structural model of the target protein based on the experimental structure of one or more homologues, referred to as the modeling template or templates. Conservation of protein folds between homologues guides the modeling, which follows four steps: fold recognition and template selection; target-template alignment; model building; and model assessment (Zvelebil and Baum 2008).

The reliability of the homology model is critically dependent on the accuracy of the sequence alignment between the homologues, and the resolution of the experimental structure of the homologue used as the modeling template. Single residue shifts in the alignment of the sequences can result in register shifts across large regions of the protein, seriously affecting the predictions of binding site residues and ligand coordination (Náray-Szabó et al. 2012; Zvelebil and Baum 2008). This is particularly relevant for the structure of transmembrane proteins such as channels, transporters and receptors. The general role of these proteins is to selectively allow the passage of a hydrophilic or charged moiety across a hydrophobic lipid bilayer. To facilitate this process, transmembrane proteins possess highly ordered secondary structures in which the exterior of the protein is a hydrophobic shell that shields a substrate-selective hydrophilic core from the lipid environment. Most channels and membrane transport proteins are composed of interacting α -helices. Here a residue shift of a single amino acid in one helix may alter the prediction of the entire interaction interface between two or more helices, and shift the orientation of binding site residues within an α -helix by 100° .

The sequence identity between the target and template proteins gives a limit to the confidence placed on the homology of the two proteins. 90 % of the proteins with sequence identities of >30 % are structural homologues, while for pairs of proteins with sequence identities of <20 %, less than 10 % were structural homologues (Rost 1999; Zvelebil and Baum 2008). Aligned proteins with sequence identities ranging from 30 % to 20 % represent the transition zone from a

high-confidence prediction of homology to a low-confidence prediction. This region is referred to as the “twilight zone” for homology modeling (Rost 1999). It should be noted that in transmembrane proteins, substitutions between hydrophobic residues are generally well tolerated, while the amino acid composition of the substrate-selective regions of the protein are tuned for the substrate of interest. For this reason, transmembrane proteins from the same family or superfamily often have sequence identities that lie within this twilight zone, increasing the possibility of alignment errors in homology modeling.

Modeling by Fold Recognition

In many cases, the three-dimensional structure of a protein is more highly conserved than the amino acid sequence. Threading or fold recognition approaches attempt to find a conserved structure that is compatible with the sequence of the target protein. The target sequence is “threaded” onto each protein in a database of experimentally determined protein structures and a scoring function is used to determine which structure best accommodates the target sequence. A high score indicates the structure is compatible with the target sequence and it is assumed that the target

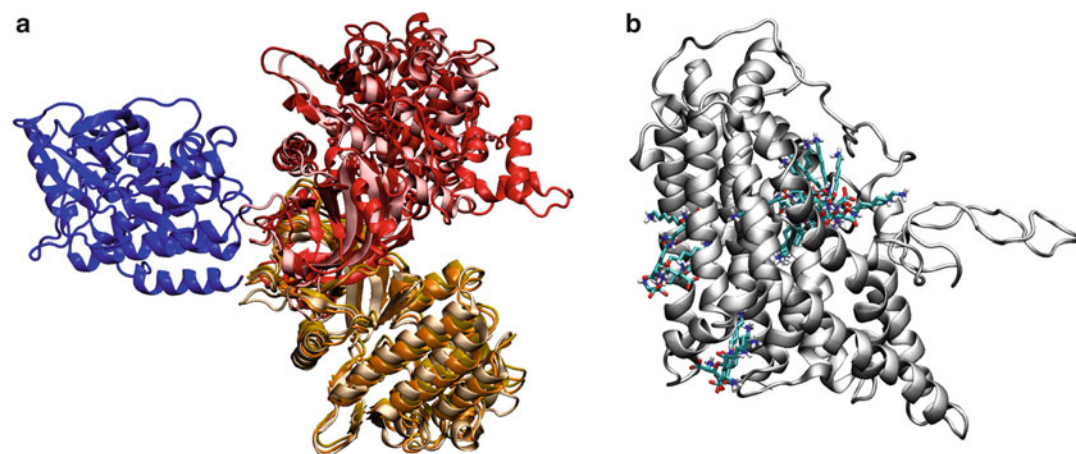
sequence folds in the same manner (Zvelebil and Baum 2008).

Probabilistic Modeling of Protein Interactions

Molecular Docking Techniques

In the case of drug–protein, peptide–protein or protein–protein interactions, computational docking approaches predict an interaction interface between the protein and ligand, which may represent a stable binding mode. Molecular docking essentially involves two steps: (i) generation of a large number of possible configurations of the protein–ligand complex (binding poses); and (ii) scoring of configurations with the aim to distinguish possible protein–ligand configurations from those not physically possible (Xu et al. 2007). A set of example results from a docking simulation is shown in Fig. 2.

Docking methods vary significantly in the degree to which they account for the flexibility of the protein and the ligand. The majority of docking algorithms implement a rigid body approach, in which the internal flexibility of both the protein and the ligand is not considered.



Polypeptide and Protein Modeling for Drug Design, Fig. 2 Molecular docking conformations of protein–protein and protein–ligand docking simulations. Multiple poses of (a) a pseudokinase domain (colored from orange to red) docked onto a kinase domain (blue); and (b) an

inhibitor molecule (CPK coloring, *licorice*) docked onto a homology model of a human homologue of LeuT (grey ribbons). Note the extended loops in the model correspond to amino acid insertions not present in the LeuT crystal structure

More sophisticated approaches allow flexibility of the protein side chain or backbone atoms. The choice of method is essentially a trade-off between accuracy and speed. Rigid body methods are fast and robust and can be applied for virtual screening of a large number of potential ligands, albeit at low accuracy. More sophisticated flexible docking methods allow optimization of the protein-ligand complex. These methods are much slower, but provide greater accuracy (Xu et al. 2007). Recent data driven approaches use experimental information such as NMR chemical shift perturbation or mutagenesis data as internal constraints to drive the docking algorithm (Xu et al. 2007).

Scoring Functions are Used to Assess the Quality of Modeled Structures and Interactions

Scoring functions are an important concept used for assessing the quality of structural models predicted by either potential energy or knowledge-based methods. Scoring functions are approximate mathematical methods that give an empirical score that represents the mathematical quality of the model. A favorable score should be interpreted in light of the experimental results. It does not necessarily imply that the homology model or docked complex represents the physiological state. Instead, it may simply reflect a well-optimized mathematical solution.

Scoring functions for knowledge-based methods provide a measure of the structural environment of the model. Knowledge-based scoring functions are based on mathematical functions that consider inter-residue distances, such as side chain packing, solvation potential or solvent accessibility, and the fit of the sequence into a given protein solvent accessible surface (Zvelebil and Baum 2008). In contrast, scoring functions for potential energy methods are based on steric fit (or hindrance) of the molecular interactions derived from the van der Waals interactions between adjacent atoms, the energetics of the torsional angles for the covalent interactions, and electrostatic potential energy of the interaction (Baron et al. 2012; Náray-Szabó et al. 2012).

Modeling Time-Dependent Protein Dynamics

Molecular Dynamics Simulation Techniques

The function of most proteins is intrinsically linked to dynamic structural changes. Classical molecular dynamics (MD) simulation techniques have been used to model conformational changes of proteins and peptides on ns to μ s timescales. While many biologically important conformational changes, such as protein folding, occur over longer (μ s to ms) timescales, MD simulations are able to capture rapidly induced conformational changes, such as those involved in the process of ligand binding (10–500 ns). Recent advances in algorithm and hardware design, together with the implementation of so-called coarse-grained forcefields have extended the possible simulation times to simulate the conformational dynamics of processes such as channel gating (500 ns to 5 μ s). MD simulations are the most computationally intensive of the techniques discussed here. However, they are currently the only method (computational or experimental) that characterizes the structural dynamics and molecular interactions in atomic detail, while fully accounting for the flexibility of the protein and ligand in a physiologically relevant environment. MD simulations provide an accurate method of studying the molecular interactions involved in ligand binding; the conformational changes induced in the protein or the ligand during the formation of a stable complex; and the correlation of ligand orientation and protein conformations (Shirts 2012).

In general terms, molecular dynamics (MD) is a computer simulation of the dynamics of a set of particles under the influence of a physical force that can be described by classical physics (Alder and Wainwright 1959; Rahman 1964). Historically, MD simulations have been widely applied to problems involving a potential energy field, such as the gravitational potentials of astrophysics and cosmology (von Hoerner 1960, 1963; Rahman 1964). In the 1970s MD simulations were first coupled to molecular mechanics (MM) forcefields to investigate protein dynamics.

In MD simulations of biomolecular systems, Newtonian mechanics is used to generate a series

of time-dependent conformations of the protein system from a starting conformation (usually an experimentally determined structure) and a set of initial velocities. The potential energy of the system is described as a function of the atoms' position using a molecular mechanics (MM) forcefield. The change in energy and the forces acting on each atom are calculated at each step in the simulation. The time-dependent structural, dynamic and thermodynamic properties of the system can be calculated from the MD trajectories. As discussed earlier, one major limitation of classical MD is the limited sampling of the conformational space of the protein (or protein–ligand) system due to time-dependent trapping in local potential energy minima. Since the 1990s a number of enhanced sampling methods have been developed to address these limitations (Lorenz and Doltsinis 2012; Náray-Szabó et al. 2012; Nowak 2012).

Free Energy Calculations

One powerful application of MD simulation techniques is the estimation of the change in free energy on the binding of a drug to its target protein. This can, in principle, be directly related to the experimentally determined binding affinity. A series of methods have been developed to effectively sample the intermediate states in the transition between the ligand free in solution and the formation of the protein–ligand complex. The two most commonly used methods are free energy perturbation (FEP) and thermodynamic integration (TI). In FEP, the difference in energy between the dissociated ligand in solution and the ligand-bound complex is used to derive a thermodynamic cycle from which the binding free energy of the ligand can be calculated. In TI, the free energy difference is determined by defining a thermodynamic path between the bound and free state of the ligand. The path chosen is a simplified (mostly one-dimensional) version of the true diffusive path of the ligand binding to the protein.

The two methods have different applications. FEP methods are generally applied to small ligands or drugs with buried binding sites. Highly charged ligands can be problematic in FEP calculations due to their large solvation free energies.

TI methods are more applicable for drugs or ligands that have a surface-accessible binding mode or binding site (Gumbart et al. 2012; Jensen 2007; Shirts 2012). Independent of the method used, the task of accurately predicting the absolute binding free energies remains “a daunting computational endeavor” (Gumbart et al. 2012) and is among the most challenging types of biomolecular simulations (Shirts 2012).

Current Successes and Future Directions

The field of rational or computer-aided drug design is built on the premise that knowing the molecular structure and dynamics of a ligand binding site will enable the design of an optimized ligand molecule that can act as a more effective drug. Structural knowledge of the protein of interest and its dynamics are an essential pre-requisite for this process. Currently, the structure and dynamics of the human protein is unknown for the majority of drug targets. As experimental and modeling techniques improve, highly specific clinical drugs with minimal cross-reactivity (and side effects) are becoming a reality. The carbonic anhydrase inhibitor and anti-glaucoma drug dorzolamide was the first drug approved for clinical use that was developed by computer-aided drug design. Dorzolamide was approved for clinical use in 1995. It was rapidly followed by HIV protease inhibitors (De Lucca et al. 1997; Greer et al. 1994) and the cancer chemotherapeutic agent and tyrosine kinase inhibitor, imatinib (gleevec) (Druker and Lydon 2000). Current drugs developed by computer-aided drug design target 5-HT₃ and acetylcholine receptor agonists, G-protein coupled receptors such as CCR5 and NK1, proton pumps and TRP channels.

Summary

As computational power and modeling algorithms continue to improve, computational modeling is becoming an increasingly important investigative tool. As our experimental knowledge of protein structure increases, so too does the application of

computational modeling in elucidating the molecular details of drug binding and the mechanism by which drugs modulate protein structure and function.

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Pooling Models

- [Peripheral Vision, Models of](#)

Population Density Model

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Synonyms

[Ensemble density model](#); [Mean field model](#)

Definition

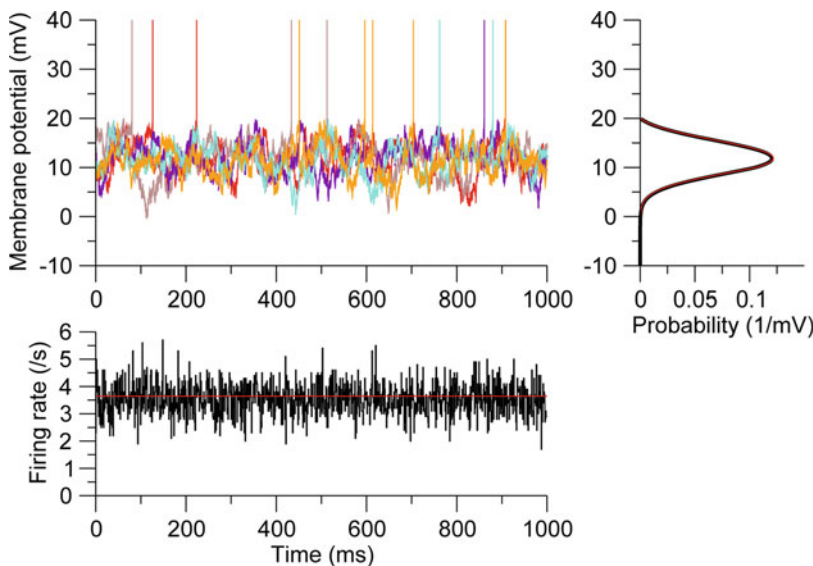
Population density models are reduced descriptions of neuronal ensembles, which consist in characterizing them by the instantaneous distribution of some neuronal variables over the population. The simplest and most useful form only uses the neuron membrane potentials. The distribution of membrane potentials and its dynamical evolution can be exactly computed in different cases, for noninteracting neurons submitted to time-varying stochastic inputs. This provides the basis for the most interesting application of population density models, namely, the quantitative description of the dynamics of networks of coupled spiking neurons. The approach has in particular been used to analyze neural rhythms.

Detailed Description

Cognitive phenomena depend on the concerted activity of large populations of neurons. Understanding the dynamics of such systems has been

one of the major goals of theoretical neuroscience. Various methods have been developed to tackle this problem. These methods range from numerical simulations of large networks of spiking neurons to phenomenological “firing rate”, or “neural mass” models, in which whole populations of neurons are described by a single (or a small number of) ordinary differential equation(s), which describes the temporal evolution of the average firing rate of the population.

An intermediate and very fruitful approach consists in using a population density approach: the stochastic differential equations describing the neurons are converted in a master equation describing the probability density of the variables describing such neurons. This approach has several advantages compared to numerical simulations: in some simple models, the master equation can be solved explicitly, which gives closed form expressions for the probability density and the associated firing rate (see Fig. 1 for an illustration of the approach). In cases where exact solutions do not exist, the master equation (typically a partial differential equation, such as a Fokker-Planck equation) can be solved



Population Density Model, Fig. 1 Population density approach versus numerical simulations for a population of uncoupled leaky integrate-and-fire neurons. (a) Membrane potential of five neurons, from a simulation of a population of 10,000 neurons with stationary input ($\mu = 12.5$ mV, $\sigma = 5$ mV). Spikes are added by hand to better visualize spike

timings. (b) Probability distribution of the membrane potential (black, computed from the simulation; red, computed from the FP equation, Eq. 9). (c) Instantaneous average firing rate of the population (black, computed from the simulation in 1 ms time bins; red, computed from the FP equation, Eq. 10)

numerically, and precise estimates of the quantities of interest can be obtained much faster than using numerical simulations. Finally, this approach can be used to derive a “firing-rate” model from a population of spiking neurons, therefore building a bridge between these two modeling approaches.

In the neuronal context, population density methods (PDMs) were pioneered by Bruce Knight at the beginning of the 1970s (Knight 1972), following earlier work on simplified stochastic single neuron models (Gerstein and Mandelbrot 1964; Stein 1965). This approach was then extensively used in the 1990s (Abbott and van Vreeswijk 1993; Treves 1993; Brunel and Hakim 1999) to investigate properties of networks of spiking neurons, such as synchronization and oscillations. Initially limited to networks of integrate-and-fire neurons, it has been extended to several variants that incorporate more biophysical features of real neurons (Casti et al. 2002; Fourcaud-Trocmé et al. 2003; Brunel and Latham 2003; Richardson 2007). In this entry, we will first describe the PDM for ensembles of independent, non-connected neurons, before moving to networks. Throughout the whole entry, we focus on analytical methods; for numerical methods of integration of population density equations, see, e.g., Omurtag et al. (2000), Nykamp and Tranchina (2000), Haskell et al. (2001), and Caceres et al. (2011).

Ensemble of Independent Neurons

The most widely used model at the network level is the leaky integrate-and-fire (LIF) neuron (Lapicque 1907; Brunel and van Rossum 2007). Its simplicity makes it particularly suitable for population density approaches. We will review in this section studies of LIF neurons with different types of noise sources, before moving to several generalizations.

LIF Neurons with Independent White Noise Sources

The LIF neuron is characterized by a membrane potential $V(t)$, the subthreshold dynamics ($V < V_T$)

of which obeys the simple first-order differential equation

$$C \frac{dV}{dt} = -g_L(V - V_L) + I_{syn}(t), \quad (1)$$

where C is the capacitance, g_L the leak conductance, V_L the leak (resting) potential, and $I_{syn}(t)$ the synaptic input currents.

This equation is often rewritten as

$$\tau_m \frac{dV}{dt} = -V + \tilde{I}_{syn}(t), \quad (2)$$

where $\tau_m = C/g_L$ is the membrane time constant and $\tilde{I}_{syn}(t)$ are synaptic inputs in membrane potential units.

In the LIF model, spikes are emitted whenever $V = V_T$; the voltage is then reset to $V = V_r$ after an absolute refractory period of duration τ_{rp} . This simple spike-and-reset mechanism replaces Na and K currents in more realistic models using the Hodgkin-Huxley formalism.

The LIF model can be further simplified by removing the leak term or making leak voltage independent and implementing a lower bound on voltage. In the first case, this leads to the “perfect” (PIF) or “simplified” (SIF) integrate-and-fire neuron (Knight 1972; Fourcaud and Brunel 2002) and, in the second case, to the “constant leakage integrate-and-fire neuron with floor” (CLIFF) (Fusi and Mattia 1999; Rauch et al. 2003).

In vivo, neurons in the central nervous systems receive highly irregular inputs, leading to large fluctuations of their membrane potentials. This motivates the study of stochastic models for the synaptic currents. A model of interest is a LIF neuron with Poisson inputs

$$\tau V = -V + I(t),$$

where $I(t)$ is a Poisson process with (possibly time-dependent) rate v_{in}

$$I(t) = J\tau \sum_k \delta(t - t_k), \quad (3)$$

where J is the amplitude of postsynaptic potentials (PSPs) elicited by single spikes and t_k are the times of presynaptic spikes.

A second model of interest is derived from the first through a diffusion approximation. When J is small, and τv is large, $I(t)$ can be approximated by

$$I(t) = J\tau \sum_k \delta(t - t_k) \approx \mu(t) + \sigma(t)\sqrt{\tau}\eta(t), \quad (4)$$

where $\mu = Jv_m\tau$, $\sigma^2 = J^2v_m\tau$, and $\eta(t)$ is a white noise ($\langle\eta(t)\rangle = 0$, $\langle\eta(t)\eta(t')\rangle = \delta(t - t')$).

With such a stochastic input, the voltage becomes an Ornstein-Uhlenbeck (OU) process, which obeys a Langevin equation

$$\tau \frac{dV}{dt} = -V + \mu + \sigma\sqrt{\rho}\eta(t). \quad (5)$$

A discretized version of Eq. 5 becomes in the limit $dt/\tau \rightarrow 0$

$$V(t + dt) = V(t)(1 - dt/\tau) + \mu dt/\tau + \sqrt{(dt/\tau)}\sigma Z(t).$$

A population of neurons with independent noise terms can be described by the probability density of the voltage $P(V, t)$, which is described by Fokker-Planck equation (see, e.g., Risken 1984; Gardiner 1986, and entry on ► “Fokker-Planck Equation”):

$$\tau_m \frac{\partial P(V, t)}{\partial t} = \frac{\sigma^2(t)}{2} \frac{\partial^2 P(V, t)}{\partial V^2} + \frac{\partial}{\partial V} \times [(V - \mu(t))P(V, t)], \quad (6)$$

which can be rewritten as a continuity equation,

$$\frac{\partial P}{\partial t} + \frac{\partial j}{\partial V} = 0,$$

where j is the probability flux. The boundary conditions link the density P with the instantaneous firing probability v :

- At threshold V_t , the probability flux at V_t defines the instantaneous firing probability $v(t)$, leading to the boundary 1

$$P(V_t, t) = 0, \quad \frac{\partial P}{\partial V}(V_t, t) = -\frac{2v(t)\tau_m}{\sigma^2(t)}. \quad (7)$$

- At reset potential V_r , what comes out at V_t must come back at V_r :

$$\begin{aligned} P(V_r^-, t) &= P(V_r^+, t), \quad \frac{\partial P}{\partial V}(V_r^-, t) - \frac{\partial P}{\partial V}(V_r^+, t) \\ &= -\frac{2v(t)\tau_m}{\sigma^2(t)}. \end{aligned} \quad (8)$$

Note that in the above equations, the refractory period τ_{rp} has been set to zero. These equations can be easily generalized to nonzero τ_{rp} (Brunel 2000b).

This Fokker-Planck equation can be solved numerically for arbitrary time-dependent inputs or solved analytically in the following two cases:

Time-Independent Input Statistics

For constant $\mu = \mu_0$ and $\sigma = \sigma_0$, Eqs. 6, 7, and 8 yield

$$\begin{aligned} P_0(V) &= \frac{2v_0\tau_m}{\sigma} \exp\left(-\frac{(V - \mu_0)^2}{\sigma^2}\right) \\ &\quad \int_{\frac{V - \mu_0}{\sigma}}^{\frac{V_r - \mu_0}{\sigma}} \exp(u^2)\Theta(u - V_r)du \\ v_0 &= \frac{1}{\tau_m\sqrt{\pi} \int_{\frac{V_r - \mu_0}{\sigma}}^{\frac{V_r - \mu_0}{\sigma}} \exp(u^2)[1 + \text{erf}(u)]}, \end{aligned} \quad (9)$$

which were, to our knowledge, first derived by Siegert for general OU processes (Siegert 1951) and then applied to the neuronal context by Ricciardi (Ricciardi 1977). In the case of a non-zero refractory period τ_{rp} , the “Siegert-Ricciardi” formula becomes

$$v_0 = \frac{1}{\tau_{rp} + \tau_m\sqrt{\pi} \int_{\frac{V_r - \mu_0}{\sigma}}^{\frac{V_r - \mu_0}{\sigma}} \exp(u^2)[1 + \text{erf}(u)]}. \quad (10)$$

The “static transfer function” $v_0 = \Phi(\mu, \sigma)$ is shown as a function of μ for various values of σ in Fig. 2a and as a function of σ for various values of μ in Fig. 2b.

Time-Varying Input Statistics: Linear Response and Spike-Rate Response Function

Solving Eqs. 6, 7, and 8 analytically is much harder when μ and σ are time dependent. A possible solution is to apply a perturbative approach. The idea is to consider a small amplitude temporal modulation of the inputs, $\mu(t) = \mu_0 + \varepsilon\mu_1(t)$, where ε is a small parameter. One can then write

$$P(V, t) = P_0(V) + \varepsilon P_1(V, t) + O(\varepsilon^2) \quad (11)$$

$$v(t) = v_0 + \varepsilon v_1(t) + O(\varepsilon^2), \quad (12)$$

insert Eqs. 11 and 12 in Eq. 6, and expand the resulting equation in ε . The zeroth-order term in ε in that equation yields the stationary solution, Eqs. 9 and 10. The first-order term can be solved by Fourier transform, by writing the input modulation as a superposition of harmonic oscillations

$$\mu_1(t) = \sum_{\omega} [\tilde{\mu}_1(\omega) \exp(i\omega t) + \tilde{\mu}_1^*(\omega) \exp(-i\omega t)], \quad (13)$$

where we have denoted complex conjugation by the star symbol. This leads to an inhomogeneous 2nd-order ODE for $\tilde{P}_1(V, \omega)$, whose boundary conditions involve $v_1(\omega)$. $\tilde{v}_1(\omega)$ describes the amplitude and phase shift of the instantaneous firing rate, when the input oscillates in time with frequency ω . The calculation shows that $v_1(\omega)$ is proportional to the input modulation $\tilde{\mu}_1^*(\omega)$,

$$v_1(\omega) = \tilde{R}_{LIF}(\omega) \tilde{\mu}_1(\omega). \quad (14)$$

The coefficient of proportionality $\tilde{R}_{LIF}(\omega)$ is the linear firing-rate response. It determines how an input modulation at a frequency ω is amplified (or attenuated) by the LIF neuron. The linear firing-rate response $\tilde{R}_{LIF}(\omega)$ is displayed in Fig. 2c–e. The amplitude of $\tilde{R}_{LIF}(\omega)$ shows strong resonances at frequencies that are integer

multiples of the baseline firing rate, for small noise and large firing rates. Otherwise, the response is the one of a low-pass filter, with an attenuation at high frequencies that decay as $1/\sqrt{\omega}$.

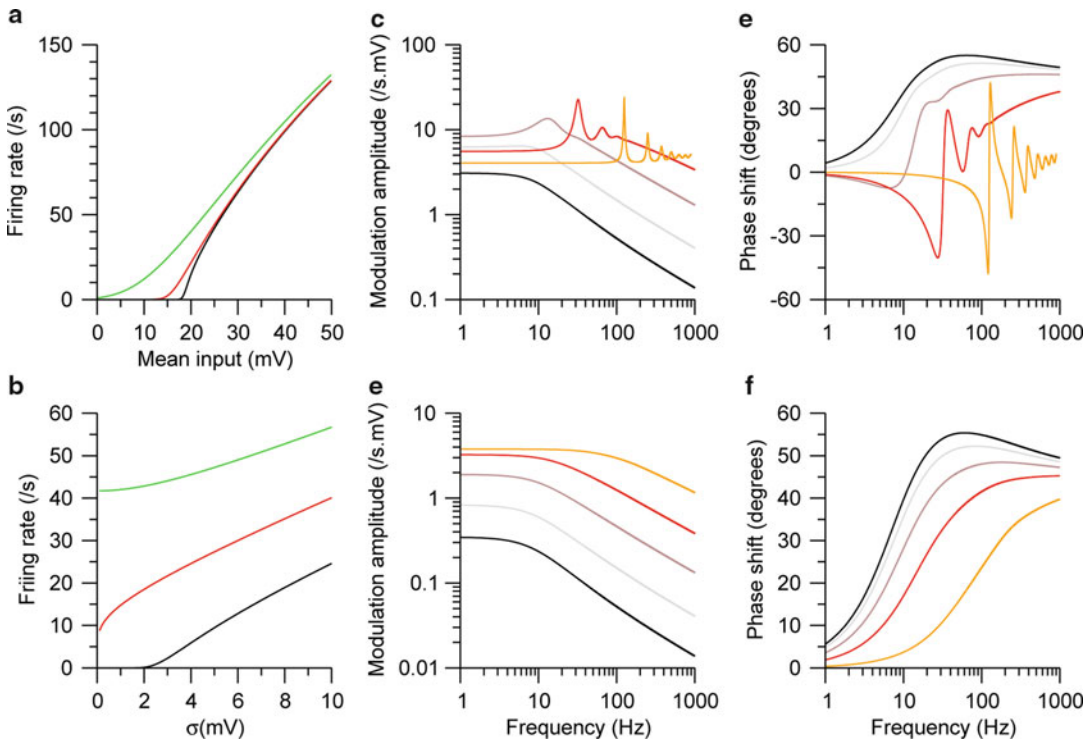
A second strategy is to use an expansion in eigenfunctions of the Fokker-Planck operator (Risken 1984; Knight et al. 2000; Mattia and Del Giudice 2002; Mattia and Del Giudice 2004; Ostojic and Brunel 2011). This approach has the advantage that it is not limited to time-dependent inputs with small amplitude.

LIF Neurons with More Realistic Noise Models

As already discussed, a large part of the fluctuations in neurons of the CNS in vivo originate from the bombardment of spikes from presynaptic neurons, which generate fluctuating synaptic conductances. As discussed above, the resulting total synaptic current is often modeled as additive white noise. However, synaptic currents differ substantially from white noise in at least three respects: (i) they are the sum of a discrete number of individual events and hence can be better described by a filtered point process; (ii) the currents are voltage-dependent, and therefore, noise has a multiplicative component; and (iii) individual synaptic currents have a finite decay time, which leads to finite correlation time constants. Several groups have consequently investigated how to incorporate these more realistic features in the PDM.

Shot Noise

Spike trains have long been modeled as point processes, and it has been argued that the statistics of firing of neurons in many parts of the brain (in particular, in the cortex) bear similarities to a simple Poisson process (in particular, the CV of cortical neurons in vivo is typically close to 1) (Softky 1993; Shadlen and Newsome 1994). Consequently, several authors considered synaptic inputs as Poisson processes (Stein 1965; Richardson and Gerstner 2005; Richardson and



Population Density Model, Fig. 2 LIF transfer functions. (a) Static transfer function, Eq. 10: Firing rate as a function of μ for $\sigma = 1$ mV (black), 3 mV (red), 10 mV (green). (b) Static transfer function, Eq. 10: Firing rate as a function of σ , for $\mu = 15$ mV (black), 20 mV (red), 25 mV (green). (c) Amplitude of firing-rate modulation, as a function of frequency of input modulation, for $\sigma = 1$ mV and $v_0 = 1$ (black), 3 (gray), 10 (brown), 30 (red), 100 (orange). Note the strong resonances at integer multiples of the firing rate, which are present for large-enough firing rates, and the $1/\sqrt{f}$ decay at high frequency.

(d) Amplitude of firing-rate modulation, as a function of frequency of input modulation, for $\sigma = 10$ mV, and same values of the firing rates as in C. Note that the resonances are no longer present, due to strong noise, but the high-frequency behavior is qualitatively unchanged. (e) Phase shift of firing-rate modulation, as a function of frequency of input modulation (same parameters as in c). (f) Phase shift of firing-rate modulation, as a function of frequency of input modulation (same parameters as in d)

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Swarbrick 2010; Helias et al. 2011). The membrane potential fluctuations are therefore described by a shot noise, with instantaneous jumps in the membrane potential occurring at random times. The master equation describing the temporal evolution of the distribution of membrane potential becomes a partial differential-difference equation, which can be solved analytically when the distribution of EPSP amplitudes is exponentially distributed (Richardson and Swarbrick 2010). Using these calculations, it was shown that the diffusion approximation is very good for small PSP amplitudes (<1 mV), but that significant deviations appear for larger PSP amplitudes.

Multiplicative Noise

Another feature of synaptic currents is their voltage dependence. Synaptic currents are induced by ion flow through receptor channels upon binding of neurotransmitter and are therefore dependent on the membrane potential of the cell. This dependence can be described by a linear “driving force” which vanishes at the associated reversal potential, which is close to 0 mV for excitatory glutamatergic synapses and -80 mV for inhibitory GABAergic synapses. This leads to a multiplicative noise, i.e., to a voltage-dependent σ in Eq. 6. The resulting equation can still be solved in the stationary case, and analytical results can also

be obtained for the linear firing-rate response (Richardson 2004, 2007; Richardson and Gerstner 2005).

Temporally Correlated Noise

Synaptic currents $I(t)$ have finite temporal width, and this is often modeled using a first-order equation

$$\tau_s \frac{dI(t)}{dt} = -I + J\tau_m \sum_k \delta(t - t_k),$$

where τ_s is the synaptic time constant. Instead of being delta functions, PSCs are now described by instantaneous jumps followed by an exponential decay with a time constant τ_s .

In the diffusion limit, this leads to a system of two differential equations:

$$\tau_m \frac{dV}{dt} = -V + I_{syn}(t). \quad (15)$$

$$\tau_s \frac{dI_{syn}}{dt} = -I_{syn}(t) + \mu + \sigma\sqrt{\tau_m}. \quad (16)$$

The system is therefore described by a 2D FP equation, which can only be solved in asymptotic limits, as in the limits of short ($\tau_s \ll \tau_m$) and long ($\tau_s \gg \tau_m$) synaptic time constant (Brunel and Sergi 1998; Brunel et al. 2001; Fourcaud and Brunel 2002; Moreno and Parga 2004).

More Realistic Neurons

The LIF model has been criticized because it lacks many of the features of real neurons: (i) spike generation dynamics, (ii) voltage-gated currents active in the subthreshold range (iii) currents leading to firing-rate adaptation, and (iv) finally, spatial structure. To incorporate such features, a common strategy is to use the Hodgkin-Huxley formalism to describe the dynamics of voltage-gated channels (to account for features i–iii) and/or compartmental models to describe the spatial structure of the model (to account for

iv). However, the resulting models are quite complex and therefore not suited for analytical studies or population density approaches.

Another strategy is to devise simplified models in the spirit of the LIF model, which strive to keep simplicity, yet exhibit more realistic features than the LIF. We now address briefly models that tackle issues (i–iii) discussed above.

Nonlinear IF Neurons

A simple extension of the LIF that describes in a simple fashion the dynamics of spike generation is to add a suitable nonlinearity to the voltage dynamics. Such models can be described by the equation

$$\tau_m \frac{dV}{dt} = -V + \psi(V) + I_{syn}(t), \quad (17)$$

where $\psi(V)$ is a nonlinear function of voltage (Fourcaud-Trocmé et al. 2003). With a suitable choice of $\psi(V)$ (in particular, it has to be supra-linear at large V), the membrane potential diverges to infinity in finite time if the synaptic inputs exceed some threshold. The time of divergence to infinity defines spike timing (it is also possible to define for practical purposes a large but finite voltage threshold). Then, as in the LIF model, the voltage is reset to some potential V_r after a refractory period τ_{rp} .

This model introduces two modifications to the standard FP equation for the LIF: (i) one has to introduce the function $\psi(V)$ in the drift term, which becomes $\partial_v[(V - \psi(V))P(V, t)]$; the boundary condition for the threshold becomes a boundary condition at $V = \infty$:

$$v(V) = \frac{1}{\tau_m} \lim_{V \rightarrow \infty} \psi(V)P(V, t).$$

Several choices for the function $\psi(V)$ have been proposed: in particular, quadratic (Ermentrout and Kopell 1986; Ermentrout 1996; Gutkin and Ermentrout 1998; Latham et al. 2000), quartic (Touboul 2008), or exponential functions (Fourcaud-Trocmé et al. 2003). Fourcaud-Trocmé

et al. (2003) found that an exponential nonlinearity is the choice that best approximates the dynamics of neuron models with fast sodium current described by the Hodgkin-Huxley formalism – in particular the WB (Wang and Buzsáki 1996) model. Badel et al. showed that the exponential nonlinearity fits very well-effective I-V curves of both pyramidal cells and fast-spiking interneurons in the cortex (Badel et al. 2008a, b). For both reasons, the EIF neuron is nowadays thought to be the best choice among the family of nonlinear integrate-and-fire neurons.

A Fokker-Planck formalism has been used to derive the static transfer functions of both QIF and EIF neurons (Brunel and Latham 2003; Fourcaud-Trocmé et al. 2003) and the high-frequency behavior of their dynamical transfer function (Fourcaud-Trocmé et al. 2003; Richardson 2007). A simple and efficient numerical method has been developed to obtain these quantities from the Fokker-Planck equation (Richardson 2007). A notable difference with LIF neurons is that spike response function decays at high frequency as $1/f$ (resp. $1/f^2$) for EIF (resp. QIF) neurons, while it decays as $1/\sqrt{f}$ for LIF neurons (see Fig. 2).

Two-Variable Models

An extension of the basic LIF model that leads to richer subthreshold dynamics consists in adding a second variable coupled to the voltage:

$$\tau_m \frac{dV}{dt} = -V + \gamma W + I_{syn}(t). \quad (18)$$

$$\tau' \frac{dW}{dt} = -W + V. \quad (19)$$

These equations can be derived from models using the Hodgkin-Huxley formalism through a linearization around a stable subthreshold potential (see, e.g., Richardson et al. (2003)). The W variable is related to the activation (or inactivation) variable of a current that contributes to the dynamics in the subthreshold range (typical examples are the mixed cationic

H current or various types of potassium currents). This additional variable can lead to subthreshold resonance, provided γ is negative and large enough. The model described by Eqs. 18 and 19 and equipped with a firing threshold and reset has been termed generalized integrate-and-fire (GIF) by Richardson et al. (2003). The resonate-and-fire model of Izhikevich (2001) is a special case of the GIF model. Population density methods have been applied to determine both static and dynamical response properties of this model (Richardson et al. 2003; Brunel et al. 2003).

Another extension of the basic LIF model is to add again a second variable, but which unlike Eqs. 18 and 19 does not depend on the voltage but rather purely on spikes:

$$\tau_m \frac{dV}{dt} = -V + \gamma W + I_{syn}(t). \quad (20)$$

$$\tau' \frac{dW}{dt} = -W. \quad (21)$$

When a spike is emitted by the neuron, the W variable makes a jump, $W \rightarrow W + 1$. This model can describe the phenomenon of “firing-rate adaptation” whereby the firing rate of a neuron steadily decreases upon injection of a constant current. This model is sometimes called “adaptive LIF” model, or LIF model with adaptation.

The two-dimensional models described so far have linear subthreshold dynamics. Other models have introduced nonlinearities in the subthreshold dynamics. In order to reproduce the basic features of the bursting behavior of thalamocortical relay neurons, Smith et al. (2000) introduced an integrate-and-fire-or-burst model by adding an additional slow variable to the basic integrate-and-fire model:

$$\begin{aligned} c \frac{dV}{dt} &= -g_L(V - E_L) - g_T \Theta(V - V_h) h(V - E_T) + I_{syn}(t) \\ \frac{dh}{dt} &= \begin{cases} -h/\tau_h^- & (V > V_h) \\ (1-h)/\tau_h^+ & (V < V_h) \end{cases}, \end{aligned} \quad (22)$$

where the Heaviside function $\Theta(V - V_h)$ represents an instantaneous idealization of the fast activation of the low-threshold calcium

current I_T , while the slow variable h represents the inactivation of the low-threshold calcium. The dynamics of h is governed by Eq. 22: it relaxes to zero with time constant τ_h^- – when the voltage is above V_h , while it relaxes to unity with a slower time constant τ_h^+ when the voltage is below V_h . This model captures the qualitative features of bursting dynamics of thalamic relay cells. In particular, when a current step is applied to the model, the response depends drastically on the initial membrane potential: (i) If V is initially below V_h , the model generates a single burst of spikes. This is due to the fact that initially $h = 1$; when the voltage is depolarized to a value large than V_h , the I_T current provides a strong depolarization that generates the burst. The burst is terminated because of the decay of the variable h to zero with time constant τ_h^- . (ii) If V is initially above V_h , then $h = 0$ – hence, the I_T current remains inactivated and the dynamics is identical to an LIF neuron. The dynamics of a population of such neurons were subsequently studied by Casti et al. (2002).

Izhikevich (2003) and Brette and Gerstner (2005) have proposed two-variable models that include a nonlinearity in the voltage equation (quadratic in Izhikevich and exponential in Brette and Gerstner). These models are able to reproduce a wide variety of electrophysiological behaviors, depending on parameters (Touboul 2008; Naud et al. 2008). Another model was introduced by Badel et al. (2008b) to fit quantitatively electrophysiological data: an EIF model with a dynamical threshold V_T , which increases after each spike and relaxes exponentially in between spikes. Finally, Richardson (2009) proposed a generalized exponential model (GEM): a two-variable model in which the voltage obeys EIF dynamics, with a second variable which depends on the voltage in a nonlinear fashion. He then generalized the method developed in Richardson (2007) to compute static and dynamical response functions, in the limit in which the second variable evolves on a much slower time scale than the voltage.

From Ensemble of Spiking Neurons to Rate Models

Population density methods provide a way to capture accurately the dynamics of the mean instantaneous firing rate of a population of neurons. A long-standing question in theoretical neuroscience is whether this dynamics can be approximated by a system of a small number of ordinary differential equations (ODEs; in other words, a rate or neural mass model) (Ermentrout 1994; Shriki et al. 2003). Two main possible approximation schemes have been devised. In the case when there is a slow synaptic time constant, the instantaneous firing rate can be computed for a given value of the synaptic current, and the dynamics of the system is then given by a simple ODE describing the temporal evolution of the slow synaptic variable (Ermentrout 1994). In the case when the network is composed of EIF neurons, a rate model approximation can be derived analytically based on the specific properties of the linear firing-rate response of this model (in particular, the decay in $1/f$ at high frequency), which is shown to describe accurately the dynamics of the instantaneous firing rate of the network (Ostojic and Brunel 2011).

Ensembles of Connected Neurons

One of the most interesting aspects of the population density approach is that it offers a way to analyze quantitatively the dynamics of ensembles of connected neurons. It allows one to relate the firing properties of a network (rate of spike emission, presence of global oscillations, frequency of these oscillations) to the biophysical characteristics of single neurons (ionic channel content, membrane impedance, mechanism of action potential generation, neuronal geometry) and of their synaptic connections (rise and decay time of synaptic currents, reversal potential, presence and characteristics of electrical connections). The main and classical idea is not to take into account the precise realization of the

network connectivity but rather to replace the specific presynaptic neurons that influence a given neuron by random members of the same class. This neglect of pair correlations constitutes the central tenet of “mean-field” theories in statistical mechanics that date back at least to Boltzmann’s derivation of his kinetic equation (Lifshitz and Pitaevskii 1981) and to Curie and Weiss theory of ferromagnetism (Lifshitz and Pitaevskii 1980). In the simplest case of a homogeneous network, all neurons are considered to belong to the same class. In more complicated cases, one can group in different classes neurons of different types, e.g., excitatory or inhibitory, or neurons which differ in electrophysiological properties (ionic channel content) or inputs (synaptic strengths or numbers). This approximation allows one to use the population density approach for independent neurons, as described in the previous section, Ensembles of Independent Neurons, in a “self-consistent” way. Namely, the characteristics of the inputs of one neuron of a given class, which influence its dynamical behavior, depend themselves on the dynamics of the neurons in the different classes. Therefore, the dynamics of the different classes of neurons should all be determined at once. Before describing this procedure in a more detailed way, we briefly recall the basic elements in the mathematical description of a neuronal network.

Mathematical Description of a Neuronal Network

The dynamics of a neuronal network depends on the characteristics of the different neurons in the network as well as on the specific connectivity of the network. Even when one considers electrophysiologically compact neurons and restricts oneself to the single-compartment models described in the previous sections (LIF, nonlinear IF, two-variable models), the network dynamics is described by an ensemble of equations of the following type:

$$\begin{aligned}\tau \frac{dV_i}{dt} &= F_i(V_i, W_i^\alpha) + I_i^{(s)}(t) \rightarrow \\ \frac{dW_i^\alpha}{dt} &= G_i^\alpha(V_i, W_i^\alpha).\end{aligned}\quad (23)$$

In Eq. 23, V_i is the membrane potential of neuron i and W_i^α is the set of supplementary (gate) variables in the considered model when there are some. In contrast to the case of uncoupled neurons, the synaptic current $I_i^{(s)}(t)$ comes in part from the inputs that neuron i receives from other neurons in the network. This couples the dynamics of different neurons in the network and renders the set of Eq. 23 difficult to analyze. Population density approaches provide a very useful way to tackle this problem.

The coupling between neurons at synapses influences the network dynamics and it needs to be precisely described. Let us denote by $J_{ij}s(t - t_k)$ the unitary synaptic current received by neuron i when its presynaptic neuron j emits a spike at time t_k ($J_{ij} > 0$ if neuron j is excitatory, while $J_{ij} < 0$ if neuron j is inhibitory). Then, the full synaptic current $I_i^{(s)}(t)$ in neuron i is obtained as the sum of synaptic currents created by all presynaptic spikes, i.e., spikes emitted at times t_j^k in the presynaptic neuron j :

$$I_i^{(s)}(t) = \sum_j J_{ij} \sum_k S(t - t_j^k). \quad (24)$$

Similar to neurons, synaptic currents can be described with various levels of complexity, as already discussed in the previous section. The simplest models use the so-called “current-based” description of synaptic inputs, in which the current is independent of the voltage. A more accurate description, discussed in the section “Multiplicative Noise”, takes a voltage-dependent $J \propto g(V - V_{rev})$ where g is the synaptic conductance and V_{rev} is the corresponding reversal potential – the “conductance-based” description.

In the crudest approximation, similar to that of Eq. 3, the time course of the synaptic current is forgotten. One simply takes

$$S(t) = \tau \delta(t - D), \quad (25)$$

where the time D accounts in an approximate way for the delay between spike emission in the pre-synaptic neuron and depolarization of the post-synaptic neuron. However, synaptic currents have finite temporal width, as pointed out in the section “Temporally Correlated Noise”. Thus, in a more accurate description, the time course of the post-synaptic current elicited by a single spike can be modeled by a delayed difference of exponentials. When a spike is emitted at time $t = 0$, the current is zero until $t = D$, where D is the delay, or latency, of the synaptic connection. Then, the current is described by

$$S(t) = \frac{\tau}{\tau_r - \tau_d} \left[\exp\left(-\frac{(t-D)}{\tau_d}\right) - \exp\left(-\frac{(t-D)}{\tau_r}\right) \right] H(t-D), \quad (26)$$

where $\tau_r < \tau_d$ describe the rise and decay times of the current, respectively, and H is the Heaviside function ($H(x) = 1$ for $x > 0$ and $H(x) = 0$, otherwise). This can be equivalently described by the system of differential equations

$$\begin{aligned} \tau_d \frac{dS}{dt} &= -S + X \\ \tau_r \frac{dX}{dt} &= -X + \tau \delta(t - D). \end{aligned}$$

Typical values for the time constants are $D \sim 1$ ms; τ_r and τ_d vary widely depending on receptor type, but are $\tau_r < 1$ ms and $\tau_d \sim 2$ –10 ms for the fast (AMPA and GABA_A) receptor-mediated synaptic responses (note that the synaptic current rise was taken to be instantaneous in section “Temporally Correlated Noise”).

For simplicity, we will mostly consider in this brief review networks with a fixed connectivity and time-independent synaptic strengths J_{ij} . It should however be noted that synapses in the CNS undergo plasticity at various time scales. In particular, short-term depression and facilitation (on time scales of 100 s of ms) potentially play an important role in several dynamical phenomena. Very few

investigations using population density methods have however included plastic synapses (Romani et al. 2006).

Standard Coupling Regime and Mean-Field Approximation: The Simplest Case of a Homogeneous Neuronal Population

The case of a network consisting of a single homogeneous population of LIF model neurons provides a simple example of the self-consistent population density approach.

Thus, we consider a network of N identical LIF neurons, with each neuron receiving inputs from a large number C of randomly chosen other neurons in the network ($C \sim 10,000$ is a typical number for neurons in the CNS). We suppose that the neurons receive as well inputs from neurons outside the network and we describe these, as in Eq. 4, by their mean μ_{ext} and their fluctuations $\sigma_{ext} \sqrt{\tau} \eta_i(t)$, $i = 1, \dots, N$, where $\eta_i(t)$ is a white noise that we suppose uncorrelated on different neurons ($\langle \eta_i(t) \eta_j(t') \rangle = \delta_{ij} \delta(t - t')$). In this model, the membrane potential of neuron i obeys

$$\tau \frac{dV_i}{dt} = -V_i + I_i^{(s)}(t) + \mu_{ext} + \sigma_{ext} \sqrt{\tau} \eta_i(t). \quad (27)$$

In Eq. 27, $I_i^{(s)}(t)$ describes the total synaptic current received by neuron i . It is the sum over all presynaptic neurons j and over all their emitted spikes at times t_j^k of the unitary synaptic currents $J_{ij} S(t - t_j^k)$:

$$I_i^{(s)}(t) = \sum_j J_{ij} \sum_k S(t - t_j^k). \quad (28)$$

For $I_i^{(s)}(t)$ to remain of reasonable amplitude when C is large, each synapse of neuron i should be of strength $\sim 1/C$. When pair correlations between spike emissions are negligible, or neglected in a mean-field approximation, the sum of this large number of weak synaptic currents gives a total synaptic current which depends on the mean rate $v(t)$ of spike emission by the

presynaptic neurons and has negligible fluctuations¹:

$$I_i^{(s)}(t) = CJ \int^t S(t-t')v(t')dt'. \quad (29)$$

The synaptic current (29) only depends on the total number C of synaptic connections received by neuron i and not on the precise network connectivity. In the considered random homogeneous network, each neuron statistically behaves in the same way. This stochastic dynamics can be described by the previous Eq. 6:

$$\tau_m \frac{\partial P(V,t)}{\partial t} = \frac{\sigma_{ext}^2}{2} \frac{\partial^2 P(V,t)}{\partial V^2} + \frac{\partial}{\partial V} \times [(V - \mu(t))P(V,t)]. \quad (30)$$

The difference between the present Eq. 30 and the previous Eq. 6 is that in Eq. 30, the current $\mu(t)$ is not entirely prescribed by the external drive but also depends through the synaptic current on the coupling between the neurons in the network:

$$\mu(t) = \mu_{ext} + CJ \int^t s(t-t')v(t')dt'. \quad (31)$$

The current $\mu(t)$ depends on the instantaneous discharge rate of the neurons in the network, which itself depends on the solution of Eq. 30 (see Eq. 7). Therefore, Eqs. 30 and 31 should be solved simultaneously to determine the network characteristics. We provide several examples of how this is done in the following.

Steady-State Firing Rates

We begin by considering a network that is in a stationary state, namely, with the spike emission rate $v(t)$ independent of time, $v(t) = v_0$. Such a stationary state is sometimes called an *asynchronous state*. How is v_0 determined as a function of

the connection strength J , the number of synapses C , the neuron membrane time constant, or other parameters?

In a time-independent situation, the current drive $\mu(t)$ (Eq. 31) is constant in time, $\mu(t) = \mu_0$. It is simply given as a function of the neuron spike emission rate v_0 by

$$\mu_0 = \mu_{ext} + CJv_0 \quad (32)$$

When this is used in the FPE (30) to obtain the neuron discharge rate, one obtains, as for uncoupled neurons, the Siegert-Ricciardi formula (10):

$$v_0 = \frac{1}{\tau_{ip} + \tau_m \sqrt{\pi} \int_{\frac{V_r - v_{ext} - CJv_0}{\sigma_{ext}}}^{\frac{\sigma_{ext}}{V_r - v_{ext} - CJv_0}} \exp(u^2)[1 + \text{erf}(u)] du}. \quad (33)$$

In contrast to the usual Siegert-Ricciardi formula (10), v_0 appears on both sides of Eq. 33. The spike emission rate v_0 should thus be obtained as a root of the nonlinear Eq. 33. For inhibitory neurons ($J < 0$), it is easy to see, for instance, graphically, that Eq. 33 has a unique root. In contrast, for an excitatory network, no solution exists for J large enough when individual neurons have no refractory period. This reflects the fact that the neuron discharge rate diverges to infinity in this case. Introducing a finite refractory period $\tau_{rp} > 0$ leads to saturation of the rates. In this case, there exists an interval of values of μ_{ext} for which three solutions to Eq. 33 exist, provided J is large enough (Amit and Brunel 1997; Brunel 2000b).

Linear Stability Analysis and Emergence of Oscillations

Besides steady-state firing rates, the main interest of the population density approach is to analyze the dynamics of network of neurons. We illustrate the idea on the simple example of the recurrent network of inhibitory neurons considered above (see Brunel and Hakim 1999; Brunel and Wang 2003; Brunel and Hansel 2006 for more details). When the dynamics is stationary at the network

¹ The important case of excitation-inhibition balance in a multi-population network, which allows for stronger synapses and fluctuations in the noise variance, is discussed in section “Strong Coupling Regime.”

level, the neuron discharge rate is determined by Eq. 33. However, such an asynchronous state can be unstable. For some neuronal and/or synaptic parameters, the neurons can synchronize their discharges and produce a global oscillatory rhythm or more complex dynamics. A simple test consists in investigating whether a small collective fluctuation grows or decays. The analysis proceeds similarly to the previously considered case of an external time-dependent input with the difference that the time dependence of the input is generated by the network itself and has therefore to be determined self-consistently. We consider a time-dependent input current $\mu(t) = \mu_0 + \mu_1(t)$. Linearization of Eq. 30 and solution of the resulting linear equations then relate the modulation of the firing rate of the neurons of the network to the modulated input. At the linear level, it is sufficient to consider perturbations that evolve in an exponential way since the dynamical evolution of a general perturbation can be reconstructed by superposition of those. One can thus focus on input and firing-rate modulations, $\mu_1(t) = \tilde{\mu}_1(\lambda) \exp(\lambda t) + \tilde{\mu}_1^*(\lambda) \exp(\lambda^* t)$ and $v_1(t) = \tilde{v}_1(\lambda) \exp(\lambda t) + \tilde{v}_1^*(\lambda) \exp(\lambda^* t)$. Solving the linear evolution equation shows that the firing rate modulation is given by the product of the neuronal firing rate response and the input modulation,

$$v_1(\lambda) = \tilde{R}_{LIF}(\lambda) \tilde{\mu}_1(\lambda). \quad (34)$$

Up to this stage, there are no differences with the previous treatment of an external input current. Thus, how is the dynamics of μ_1 self-generated? In a recurrent network, the input-modulated current in a given neuron is actually the synaptic current that results from the spikes in its presynaptic neurons. The two are therefore related by the synaptic dynamics as described by Eq. 31. For exponentially modulated time courses, this relation simply reads

$$\tilde{\mu}_1(\lambda) = CJS(\lambda)v_1(\lambda). \quad (35)$$

Comparison between Eq. 34 provides the equation that determines the values of the growth/decay exponent λ , namely, the dynamics, in the linear regime, of a (small) perturbation

$$CJS(\lambda)R_{LIF}(\lambda) = 1 \quad (36)$$

For a synaptic current described by Eq. 26, the function $S(\lambda)$ depends on the synaptic rise and decay times, τ_r and τ_d , as well as on the delay D :

$$S(\lambda) = \frac{\tau \exp(-\lambda D)}{(1 + \lambda \tau_r)(1 + \lambda \tau_d)}. \quad (37)$$

Even without a detailed analysis, one can see how information about the dynamics can be extracted from Eq. 36. For instance, taking its modulus and assuming that $|R_{LIF}(\lambda)|$ is bounded (which is true for $\sigma > 0$), one sees that for small $|J|$, Eq. 36 can be satisfied only when the synaptic function compensates for the smallness of $|J|$. That happens only for $\text{Re}(\lambda) < 0$ when the modulus of the exponential term can become larger than 1 or when λ is close to $-1/\tau_r$ or $-1/\tau_d$ so that the denominator in Eq. 37 is small. Thus, for small-enough synaptic strengths, the network stationary state is found to be linearly stable. This can change as $|J|$ increases. At the critical synaptic strength J_c at which the real part of an eigenvalue changes from negative to positive, $\text{Re}(\lambda) = 0$ and Eq. 36 should have a purely imaginary solution $\lambda = i\omega$. This happens for an inhibitory network ($J < 0$) and signals the spontaneous appearance of oscillations in the discharge rate of the network, namely, a neural rhythm at the frequency ω . By taking the argument of Eq. 36, ω is found to obey

$$\pi = \omega D + \arctan(\omega \tau_r) + \arctan(\omega \tau_d) - \arg[R_{LIF}(\omega)], \quad (38)$$

where the π on the left-hand side come from the inhibitory character of the synaptic current. The oscillation frequency ω is mostly determined by the synaptic constant. The observed fast (200 Hz) cerebellar rhythm has been proposed by de Solages et al. (2008) to be a physiological realization of this kind of fast oscillation driven by recurrent inhibition. The population density formalism has similarly been used to analyze the dynamics of a variety of other networks. We briefly review some of the obtained results in the following section.

Networks Analyzed by the Population Density Approach

Electrically Coupled Neurons

Chemical synapses of different types play a major role in information transmission in the nervous system. We have briefly summarized above how excitatory and inhibitory transmission can be modeled. Electrical coupling mediated by gap junctions between cells is also widespread. In particular, specific electrical coupling has been found between interneurons of the same type (Galarreta and Hestrin 1999; Gibson et al. 1999). This has motivated several theoretical analyses to try and gain a better understanding of electrically connected neural assemblies. Population density models are particularly appropriate to address this issue.

At the simplest level, electrical coupling is simply taken to be an electrical conductance between the two coupled cells. The current in cell i coming with its coupling with cell j is then

$$I_i = G_e(V_j - V_i). \quad (39)$$

A spike in cell j then produced a filtered “spikelet” current injection in cell i . An effective way of accounting for this phenomenon has been proposed for LIF neurons since spike shape is not explicitly described in this simplified electrophysiological model (Lewis and Rinzel 2003). The fast part of the spikelet is taken to be a δ -function depolarization in neuron i which accompanies every spike in cell j very similar to the simplified description of chemical transmission by Eq. 25. Equation 39 is implemented as such at all other times. Reset after a spike or spike after hyperpolarization (AHP) in more realistic descriptions in neuron j can produce in the model as in reality a hyperpolarizing current in cell j , as is not always well appreciated. The population density model based on this simplified description allows one to better understand the effect of these two opposite effects of depolarization by fast spike transmission and hyperpolarization due to AHP transmission. In both cases, a transition from a stationary steady state to a synchronized oscillation is found for large-enough coupling conductances and

low-enough noise. But the transition to synchrony itself has a different character. Interestingly when hyperpolarization dominates over depolarization, the oscillatory state and the stationary state are found to coexist in a window of parameters. The network is bistable between these two different states and its history determines whether it oscillates or not (Ostojic et al. 2009).

Excitatory-Inhibitory Networks

Most networks of the central nervous system are composed of excitatory and inhibitory neurons. Population density models have proven of great help in extracting some general dynamical characteristics of networks of interacting excitatory and inhibitory neurons. Using a self-consistent approach similar to that described above for a single neuronal population with recurrent coupling, one obtains instead of Eq. 36 (Brunel and Wang 2003; Geisler et al. 2005; Ledoux and Brunel 2011):

$$\begin{aligned} & 1 - C_{II}J_{II}R_I(\omega)S_I(\omega) \\ & \times [1 - C_{EE}J_{EE}R_E(\omega)S_E(\omega)] \\ & = C_{EI}C_{IE}J_{EI}J_{IE}R_I(\omega)R_E(\omega)S_E(\omega)S_I(\omega), \end{aligned} \quad (40)$$

where $J_{EE} > 0$, $J_{II} < 0$, $J_{IE} > 0$, and $J_{EI} > 0$, respectively, measure the strength of the recurrent and mutual interactions between the excitatory (E) and inhibitory (I) populations. Instabilities and oscillations can be driven in networks of this kind by the recurrent inhibition between inhibitory interneurons, as in a single population, but also through a two-population inhibitory loop in which excitatory neurons drive inhibitory neurons which in return inhibit them. The frequency of the emergent oscillations therefore depends on the strength of the respective interactions.

In the case where the recurrent interactions within the populations can be neglected, taking the imaginary part of Eq. 40 gives the relation which determines the frequency of the oscillations in the network close to the instability threshold:

$$\begin{aligned} & \Phi_{RE}(\omega) + \Phi_{SE}(\omega) + \Phi_{RI}(\omega) + \Phi_{SI}(\omega) \\ & = \pi. \end{aligned} \quad (41)$$

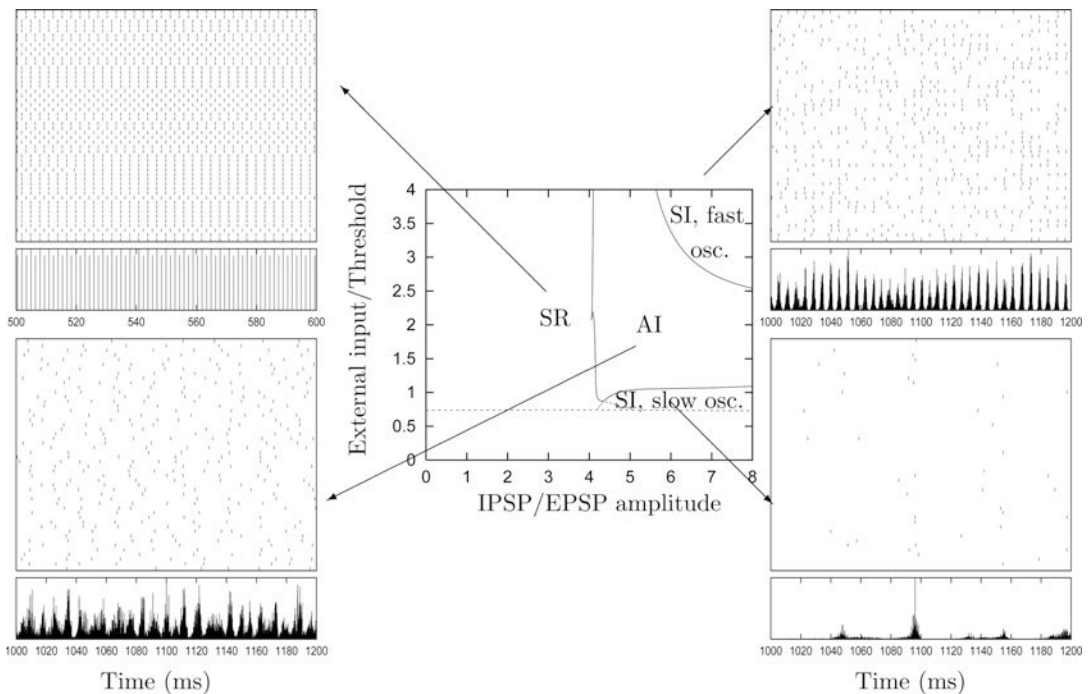
The phases $\Phi_{RE}(\omega)$ and $\Phi_{RI}(\omega)$ are the phases of the firing-rate response of the excitatory (E) and inhibitory (I) neurons, and $\Phi_{SE}(\omega)$ and $\Phi_{SI}(\omega)$ the phase shift induced by excitatory (E) and inhibitory (I) synaptic transmission. When the synaptic phase shifts dominate, Eq. 41 reduces to

$$\Phi_{SE}(\omega) + \Phi_{SI}(\omega) = \pi. \quad (42)$$

Given that $\Phi_{SE} > 0$, this allows one to conclude that oscillations produced by the two-population loop are of lower frequency than those produced by the direct inhibition of interneurons among

themselves, as could intuitively be expected from the longer delay in the feedback inhibition. Typical values for the synaptic transmission kinetics lead one to expect that the 150–250 Hz frequency range of pure I-I inhibition-driven oscillation, as observed for the fast cerebellar observation, lowers to the 60 Hz gamma range for E-I driven oscillations.

In the general case, oscillations in the E-I networks can arise from a combination of the two outlined mechanisms. Examples of such population oscillations are illustrated in Fig. 3.



Population Density Model, Fig. 3 Different dynamical regimes of a sparsely connected neuronal network of excitatory and inhibitory leaky integrate-and-fire neurons. Central panel shows the boundaries of the region in which the asynchronous state is stable as a function of inhibition/excitation balance and external inputs. This region is confined to the inhibition-dominated network, in which mean inputs to neurons are below threshold due to the strong feedback inhibition and spiking is due to fluctuations. This asynchronous irregular (AI) state is therefore characterized by strongly irregular single-cell firing. The three solid lines are instability lines of the asynchronous state. Crossing these lines leads to three types of states in which the global population activity oscillates in time: a synchronous

irregular (SI) state with a fast population oscillation for strong inhibition and strong external inputs, a synchronous irregular (SI) state with slower population oscillations for lower external inputs, and finally, a synchronous regular (SR) state present when excitation dominates the feedback (Adapted from Brunel 2000a, b). Side panels indicate representative simulations in each of these four regions. Each pair of panels displays a raster plot of a subset of 50 neurons (spike times indicated by a vertical bar), and the global activity of the network, as a function of time. Note the large finite size effects, leading to strong fluctuations around the average rate in the AI state and to phase and amplitude fluctuations of the global oscillation in the SI states

Neurons with Heterogeneous Properties

We have described above how the population density approach can be used for two neuronal populations. It can further be generalized to multiple populations. This has in fact served to examine the dynamical consequence of the widely observed heterogeneity in neuronal populations. A heterogeneous population is viewed in this context as an assembly of different populations with continuously varying parameters which could, for instance, be the neuron firing frequencies or the synaptic properties. This is particularly important in the case of neural rhythms, since the synchronization of oscillators is well known to be strongly sensitive to heterogeneity and mismatch in frequencies. Neural rhythms which emerge from stochastically firing neurons are based on a quite different mechanism. It has been shown both in simulations and with population density analyses that, in contrast to classical oscillators, neural heterogeneity does not have a strong impact on the emergence of neural rhythms, although the threshold synaptic strength for their emergence does increase (Brunel and Hakim 1999).

Strong Coupling Regime

In vivo recordings show that neuron membrane potentials display strong fluctuations, as already emphasized. This has been taken into account in the above description by supposing that each neuron in the network is subjected to noise coming from external inputs to the network (as quantified, e.g., by σ_{ext} in Eq. 27). This does not appear fully satisfactory since, in a large network, part of the fluctuating inputs should arise from the drive coming from the neurons of the network themselves. It has been realized that this actually provides strong constraints on the network design (van Vreeswijk and Sompolinsky 1996; Amit and Brunel 1997). Let us consider a network with N_E excitatory neurons and N_I inhibitory neurons in which each neuron receives C_E excitatory and C_I inhibitory synapses from within the network as well as inputs from outside the network.

For simplicity, we first consider instantaneous synapses with weight J_E and $-J_I$, respectively, for excitatory and inhibitory synapses. We suppose that neurons fire in a Poissonian way, respectively, at rates v_E and v_I for the excitatory and inhibitory neurons and operate in the diffusion limit explained above (Eq. 4) where individual synaptic weights small but many inputs are received during the neuron integration time τ . In this case, neurons in the network receive a mean input,

$$\mu = [C_E J_E v_E - C_I J_I v_I] \tau + \mu_{ext} \quad (43)$$

with fluctuations of amplitude

$$\begin{aligned} \sigma^2 &= \sigma_{in}^2 + \sigma_{ext}^2 \text{ with } \sigma_{in}^2 \\ &= C_E J_E^2 v_E \tau + C_I J_I^2 v_I \tau, \end{aligned} \quad (44)$$

where the notations of Eq. 4 have been used. Neurons receive many synaptic contacts. In the previous sections, we have supposed that $J_E \sim 1/C_E$ and $J_I \sim 1/C_I$ so that the mean input μ remains finite in the limit where C_E and C_I are large. However, this implies also that the fluctuations of the network input are negligible ($\sigma_{in}^2 \sim 1/C$). Equation 44 shows that one should have the synaptic weights J of order $1/\sqrt{C}$ in order to have fluctuating internal inputs of finite amplitude. However, in this case, the mean input amplitude $|\mu|$ remains of reasonable amplitude only when the mean excitatory and inhibitory drives almost compensate each other, $C_E J_E v_E \sim C_I J_I v_I$, that is, when the network is in a so-called balanced state. This regime is naturally attained when the inhibition is sufficiently strong for the mean input current received by a neuron to remain under the threshold current required to induce spiking (van Vreeswijk and Sompolinsky 1996; Amit and Brunel 1997). Different experimental data indeed support the fact that neuronal networks work in this regime (Shu et al. 2003; Haider et al. 2006).

In the balanced state, the amplitude of the input fluctuations is not imposed but depends itself on the network state (since σ_{in} depends on the neuron firing rates). Within the framework of the

population density model, the network is described by an FPE like Eq. 30 in which σ^2 depends on the neuron firing rates and thus on time in a nonstationary dynamical regime. In the weakly coupled regime, the dynamics can be analyzed as previously described by the firing-rate response which characterizes the spiking output of a neuron subjected to a modulated current. This single function is no longer sufficient in the strong coupling regime and an equally important role is played to the firing response of a neuron to an oscillatory modulation of the noise amplitude in its input (Brunel and Hakim 1999; Brunel 2000b; Lindner and Schimansky-Geier 2001; Silberberg et al. 2004). While this allows one to extend the analysis to the strong coupling regime for instantaneous synapses, a precise analysis becomes much more involved for synapses with finite kinetics.

Deterministic Networks and the Population Density Approach

In recent years, a series of studies have investigated the dynamics of sparsely connected networks with no external noise (Zillmer et al. 2006, 2009; Jahnke et al. 2008, 2009; Monteforte and Wolf 2010, 2012). Interestingly, these networks typically exhibit highly irregular activity, in spite of the fact that the dynamics is purely deterministic. Zillmer et al. (2009) studied this phenomenon in networks of inhibitory LIF neurons with delta function synapses and found that the irregular dynamics is in fact a transient phenomenon. However, the duration of the transient dynamics increases exponentially with system size. This means that in practice, for realistic network sizes, the periodic attractor state is never reached. It was also found that the mean firing rate in such networks is well described by mean-field theory. Jahnke et al. (2008) showed analytically that any dynamical trajectory in such networks is stable. However, stability holds only for very small perturbations – any finite perturbations lead in the large N limit to a divergence between the perturbed and unperturbed trajectories. These phenomena are consistent with “stable

chaos” that was observed in coupled map lattices (Politi et al. 1993). Later studies showed however that adding a decay time constant of PSCs (Jahnke et al. 2009; Zillmer et al. 2009), excitatory neurons (Jahnke et al. 2009), or a more realistic spike generation mechanism (Monteforte and Wolf 2010) leads to truly chaotic dynamics. Therefore, chaotic dynamics seem to be the most common type of dynamics seen in deterministic randomly connected networks of excitatory and inhibitory neurons.

Conclusion

Population density methods have allowed theorists to characterize the dynamics of networks of simplified leaky integrate-and-fire neurons. In particular, these methods have uncovered different types of states in which these networks can settle: asynchronous states, in which the population firing rate is constant in time and correlations between neurons vanish in the large N limit, and synchronous states, in which population activity oscillates in time, with a frequency that can be related to synaptic and neuronal characteristics. The characteristics of these states bear striking similarities with in vivo recordings: asynchronous irregular states reproduce many of the landmark observations of background activity in the cortex (highly irregular activity of single neurons at low rates, wide distributions of firing rates, weak correlations between neurons), while synchronous irregular states share several characteristics of fast oscillations that are observed in many cortical areas.

So far, population density approaches have been limited to simplified single neuron models and highly simplified unstructured network architectures. Furthermore, even in these contexts, it has been mainly used to compute the stability boundaries of stationary regimes and the characteristics of the emerging oscillatory regimes at the linear or weakly nonlinear level. An important challenge for future years will be to extend this framework to more complex single neuron models, to more structured network architectures, and to fully nonlinear dynamical regimes.

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Population Encoding/Decoding

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Definition

Sensory information, percepts, thoughts, and motor commands are thought to be carried out by spatiotemporal patterns of action potentials (spikes) in neuronal populations in the brain. Classical examples of neural encoding are the tuning of V1 neurons to oriented lines and the tuning of MT and M1 neurons to movement direction (Abbott and Dayan 2001). In addition, neural computation is thought to be instantiated by operations on these spatiotemporal spiking patterns. The problem of neural population encoding and decoding is addressed here from the perspective of reading out information about sensory stimuli and behavioral variables from spike trains simultaneously recorded from neuronal ensembles.

Detailed Description

Probabilistic Population Encoding and Decoding

Consider a sensory stimulus or behavioral variable (e.g., hand movement kinematics) $x_{1:t}$, during a discrete time period $\{1, 2, \dots, t\}$, $x_t \in \mathbb{R}^p$,

encoded by the spiking activity $y_{1:t} = \{y_{1:t}^i\}_{i=1}^N$ of N neurons; $y_t^i \in \{0, 1\}$ denotes whether the i th neuron has spiked or not in a small enough time interval of size Δ indexed by t . Given observed population spike trains $y_{1:t}$, what is the state x_t ? In the probabilistic Bayesian inference and stochastic state-space framework adopted here, this population decoding question is answered by computing the posterior probability density

$$\begin{aligned} p(x_t|y_{1:t}) &= \frac{p(y_{1:t}|x_t)}{\mathbb{P}(y_{1:t})} \\ &= \frac{\mathbb{P}(y_t|\mathcal{H}_t, x_t)p(x_t|\mathcal{H}_t)}{\mathbb{P}(y_t|\mathcal{H}_t)}, \end{aligned} \quad (1)$$

where $\mathbb{P}$ denotes probability and $\mathcal{H}_t = y_{1:t-1}$ is the population spiking history up to (but not including) time t . It is clear from Eq. 1 that the decoding problem $p(x_t|y_{1:t})$ is intrinsically related to a population encoding and neural dynamics model specified by $\mathbb{P}(y_t|\mathcal{H}_t, x_t)$. (For notational convenience, we let x and neuronal spiking to be instantaneously related.) We also note that the framework for population encoding/decoding adopted here can be extended to the broader problem of probabilistic inference and computation with spiking neuron networks.

Population Encoding and Neural Dynamics: $\mathbb{P}(y_t|\mathcal{H}_t, x_t)$

We assume that, conditioned on spiking history $\mathcal{H}_t$ and covariates x_t , the joint probability factorizes as

$$\mathbb{P}(y_t|\mathcal{H}_t, x_t) = \prod_{i=1}^N \mathbb{P}(y_t^i|\mathcal{H}_t, x_t). \quad (2)$$

The population encoding problem thus becomes the estimation of a probabilistic encoding model that captures both the intrinsic neural network dynamics (i.e., collective dynamics reflected in spiking history effects of the entire ensemble activity; Truccolo et al. (2010)) and the effects of x_t on the spiking probability for each observed single neuron. The encoding model can be expressed in terms of the conditional intensity function λ_t^i , i.e., the instantaneous spiking rate conditioned on

population spiking history $\mathcal{H}_t$ and on x_t , such that (Truccolo et al. 2005; Daley and Vere-Jones 2003)

$$\mathbb{P}(y_t^i | \mathcal{H}_t, x_t) = \exp \{ y_t^i \log (\lambda_t^i \Delta) - \lambda_t^i \Delta \} + o(\Delta), \quad (3)$$

where $o(\Delta)$ is a function satisfying $\lim_{\Delta \rightarrow 0} o(\Delta)/\Delta = 0$. Parametric and nonparametric models for the conditional intensity can be estimated from the data based on the discrete-time point process likelihood function derived from Eq. 3. The distribution in this case belongs to the exponential family with canonical parameter

$$\log (\lambda_t^i \Delta) = F_i(\mathcal{H}_t, x_t). \quad (4)$$

Simple but versatile approximations to $F_i(\mathcal{H}_t, x_t)$ can be obtained by generalized linear models (GLMs). For example, a conditional intensity function model for a primary motor cortex neuron that incorporates history effects and tuning to hand velocity x_t can be written as

$$\log (\lambda_t^i \Delta) = \mu_i + \sum_{j=1}^N \sum_{k=1}^q \alpha_k^{ij} y_{t-k}^j + \beta_i^T x_t, \quad (5)$$

where q specifies the extent of the history effects being taken into account and T denotes the transpose operation. Truccolo et al. (2005), Truccolo and Donoghue (2007), Truccolo (2010) provide a detailed treatment of parametric and nonparametric modeling of neural point processes based on and beyond GLMs. Effects of unobserved variables on spiking activity can be incorporated via latent variable models (e.g., Lawhern et al. (2010)), and violations of the assumed factorization in Eq. 2 due to unaccounted instantaneous correlations can be addressed according to Kelly and Kass (2012).

Population Decoding: $p(x_t | y_{1:t})$

In order to compute the posterior Eq. 1 recursively and to incorporate prior knowledge about the temporal evolution of x_t , a Markov state-space model

$$x_t \sim p(x_t | x_{t-1}), \quad (6)$$

$$y_t^i \sim \mathbb{P}(y_t^i | \mathcal{H}_t, x_t), \quad (7)$$

can be adopted. In this case, $p(x_t | \mathcal{H}_t)$ in Eq. 1 can be computed via the Chapman-Kolmogorov equation such that the posterior density then depends recursively on its previous step

$$p(x_t | y_{1:t}) = \frac{\mathbb{P}(y_t | \mathcal{H}_t, x_t)}{\mathbb{P}(y_t | \mathcal{H}_t)} \int p(x_t | x_{t-1}) p(x_{t-1} | y_{1:t-1}) dx_{t-1}. \quad (8)$$

Exact posterior computation can be attempted via numerical integration (for low-dimensional x_t) or via sequential Monte Carlo methods such as particle filters (Doucet et al. 2001). For practical applications, first- and second-order (fully exponential) Laplace approximations are very useful and can be easily implemented (Eden et al. 2004; Truccolo et al. 2005; Koyama et al. 2010). Consider the first-order Laplace approximation

$$p(x_t | y_{1:t}) \approx \mathcal{N}(x_{t|t}, W_{t|t}) \quad (9)$$

where

$$X_{t|t} = E[x_t | y_t, \mathcal{H}_t], \quad (10)$$

$$W_{t|t} = \text{var}[x_t | y_t, \mathcal{H}_t], \quad (11)$$

are the posterior mean and variance, respectively. Further, if the state transition probability $p(x_t | x_{t-1})$ is approximated according to an autoregressive process

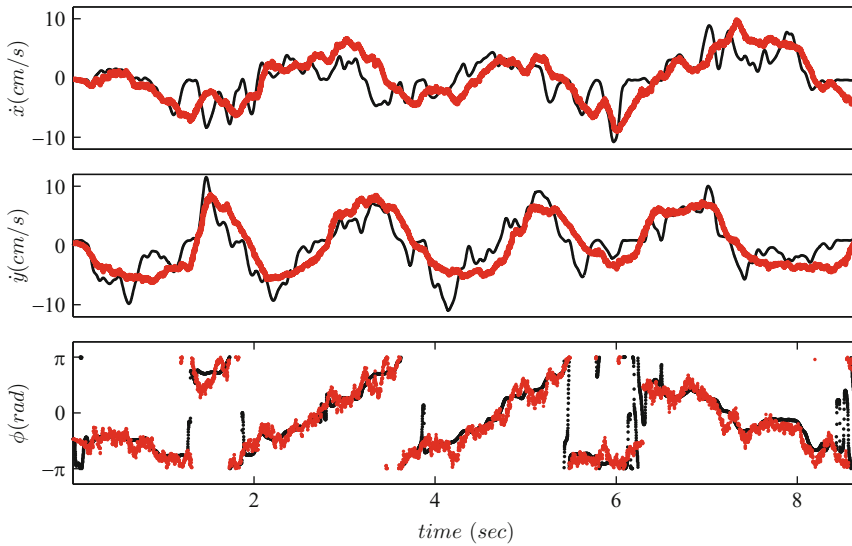
$$x_t = Ax_{t-1} + \varepsilon_t, \quad (12)$$

where $\{\varepsilon_t\}$ are independent $\varepsilon_t \sim \mathcal{N}(0, Q)$, $x_0 \sim \mathcal{N}(\mu_0, W_0)$, then the posterior mean and variance under the Laplace approximation can be easily computed via the following stochastic state-space point process forward filter:

One-step prediction equations

$$x_{t|t-1} = Ax_{t-1|t-1}, \quad (13)$$

$$W_{t|t-1} = AW_{t-1|t-1}A^T + Q; \quad (14)$$



Population Encoding/Decoding, Fig. 1 Decoding of hand velocity from a population of monkey M1 neurons via the stochastic state-space point process filter. Decoded

hand velocities (horizontal and vertical coordinates) and decoded direction of the velocity vectors are shown in *red* (Modified with permission from Truccolo et al. (2005))

Posterior variance and mean equations

$$W_{t|t}^{-1} = W_{t|t-1}^{-1} + \sum_{i=1}^N \left[\left(\frac{\partial \log \lambda_t^i}{\partial x_t} \right)^T [\lambda_t^i \Delta] \left(\frac{\partial \log \lambda_t^i}{\partial x_t} \right) - (y_t^i - \lambda_t^i \Delta) \frac{\partial^2 \log \lambda_t^i}{\partial x_t \partial x_t^T} \right]_{x_{t|t-1}}, \quad (15)$$

$$x_{t|t} = x_{t|t-1} + W_{t|t} \sum_{i=1}^N \left[\left(\frac{\partial \log \lambda_t^i}{\partial x_t} \right)^T (y_t^i - \lambda_t^i \Delta) \right]_{x_{t|t-1}}. \quad (16)$$

Parameters for the state-space model can be estimated from a training dataset via maximum likelihood estimation related methods or, in the case of unobserved x_t , via expectation-maximization or other latent state-space estimation methods. Despite the Laplace approximation to the posterior, the point process nature of the observed spiking activity is preserved. Figure 1 provides a decoding example. Detailed derivations and extensions of the above stochastic

state-space point process filter for population decoding and other applications are presented in Eden et al. (2004), Truccolo (2010), Paninski et al. (2010), and Koyama et al. (2010).

Cross-References

- [Bayesian Inference with Spiking Neurons](#)
- [Brain-Machine Interface: Overview](#)
- [Generalized Linear Models for Point Process Analyses of Neural Spiking Activity](#)
- [Neural Coding](#)
- [Neural Decoding](#)
- [Neuronal Population Vector](#)
- [State-Space Models for the Analysis of Neural Spike Train and Behavioral Data](#)

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Population Vector

► Neuronal Population Vector

Posterior Root Stimulation

► Finite Element Models of Transcutaneous Spinal Cord Stimulation

Postinhibitory Rebound and Facilitation

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Definition

Postinhibitory rebound (PIR) and postinhibitory facilitation (PIF) are both phenomena that modify the intrinsic excitability of a neuron or a network resulting in an enhanced or patterned spike output. In a single neuron, the PIR represents evoking one or more spikes in response to the cessation of a prolonged hyperpolarizing current step. However, the response can also occur for a hyperpolarizing stimulus that is temporally brief. The PIF in a single neuron represents the phenomenon of evoking a spike when a late arriving subthreshold excitatory input is assisted by an early inhibitory input. The inhibitory input causes a reduction of spike threshold at the time of arrival of the subthreshold excitation.

Detailed Description

Rebound is a somewhat generic term that indicates the overshoot of a membrane potential above its resting level, and not necessarily a spike. The excitable property of an inhibitory stimulus applied to a neuron was identified more than a century ago by Sherrington (1913) who termed it “post-inhibitory exaltation” when a skeletal muscle showed spontaneous contractions at the cessation of a reflex inhibition. The term post-inhibitory rebound was coined by Granit (1956) and is often also termed rebound facilitation or anodal break response. In the modern usage, post-inhibitory rebound still represents the basic qualitative observations reported by Sherrington – eliciting a single or a group of spikes following the action of either a steady inhibitory current or a brief pulse of synaptic or current input. The PIR is responsible, for example, for setting up of

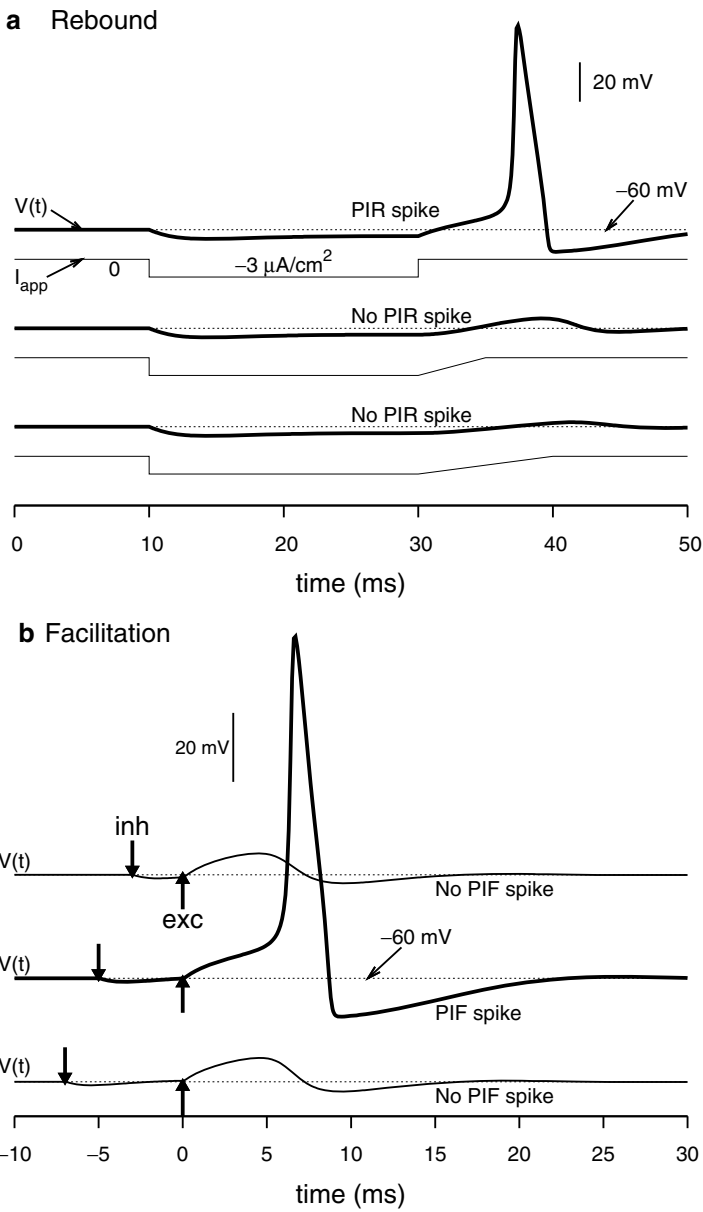
rhythmic pattern generation (Friesen 1994; Wang and Rinzel 1992) between neurons coupled with mutual inhibition.

The condition for eliciting PIR in a one-compartment neuron model is illustrated in Fig. 1a that shows the voltage $[V(t)]$ responses of the well-known Hodgkin-Huxley model, which rests at -60 mV in the absence of any input, to a step of hyperpolarizing current I_{app} . At the end of the hyperpolarizing current, if the release of the

current step is fast or instant, a spike is elicited; this is the PIR phenomenon. But if the release is gradual, only a brief overshoot of the membrane potential is seen, and not a spike. A spike might also be elicited even if the hyperpolarizing input pulse were very brief. Thus, a neuron may indeed have two thresholds for eliciting a spike, one for depolarizing current pulse and the other for hyperpolarizing current pulse. But in mathematical two-dimensional reduced models of neurons,

Postinhibitory Rebound and Facilitation,

Fig. 1 Demonstrating the eliciting of action potentials in a one-compartment Hodgkin-Huxley model by using postinhibitory rebound (a) and postinhibitory facilitation (b) mechanisms



these two thresholds could be seen as part of a single curve or manifold, which is called the threshold separatrix by FitzHugh (1955), whose placement around the rest state is curved and thus a neuron's ability to cross the threshold in eliciting a PIR spike depends on the response of the internal gating variables and the nature of the input itself (i.e., the magnitude and its time constant) (Dodla et al. 2006; Dodla and Wilson 2010). All neurons or neuronal models may not have the PIR property. Physiologically PIR may be realized under many different circumstances but could mainly be attributed to the deinactivation of a fast inward current or removal of the slow outward current (Jones and Thompson 2001). Examination of the time constants of the gating variables of the Hodgkin-Huxley model neuron reveals that, at hyperpolarized voltages, the activation and inactivation of sodium channel become faster while the potassium channel activation becomes even slower. Thus, upon sudden release from the hyperpolarizing step, the sodium channels have the ability to induce a spike before the action of the potassium channels. But a gradual release from the step (see Fig. 1a) will cause the potassium channels defeat the rush of sodium channels and prevent a spike.

Postinhibitory facilitation is closely related to the mechanism of the PIR and was first conceived to address the tuning curve asymmetry of auditory neurons (Dodla et al. 2006) that receive precisely timed but stochastic inhibitory and excitatory synaptic inputs (Brand et al. 2002). It can also be demonstrated in a variety of models including reduced two-dimensional models (Dodla et al. 2006; Dodla and Rinzel 2006). But this phenomenon is indeed related to the observation of modulating excitability of a neuron following an inhibitory stimulus (Luk and Aihara 2000) and the tighter temporal placement of action potentials when an inhibitory stimulus precedes an excitatory stimulus (Baufreton et al. 2005). At a single-neuron level, the PIF spike is elicited when a brief inhibitory stimulus precedes a brief subthreshold excitatory stimulus in a precise time window (Fig. 1b). If the excitatory stimulus arrives either too late or too early, the spike cannot

be elicited. The width of this facilitation window could be several milliseconds and depends on the decay time constant of the inhibitory input and the level of the subthreshold excitation. If the subthreshold excitation is close to the spike threshold, the window broadens significantly. But the neuron does not have to be a linear resonator (Izhikevich 2001), nor does the membrane voltage have to be near the closest approach to the spike threshold. Simulations reveal that facilitation is favored by fast inhibition (Dodla et al. 2006). Such fast but stochastic inhibitory stimuli when combined with stochastic excitatory stimuli could lead to an enhancement of firing rate (Dodla and Rinzel 2006) or even set coherent network oscillations in a mutually inhibitory network that is driven by random excitatory input.

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Post-tetanic potentiation

- [Short-Term Synaptic Plasticity in Central Pattern Generators](#)

Power-Law Distributed Patterns

- [Neuronal Avalanches](#)

Pre-Botzinger Complex Rhythm Generation

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Definition

The pre-Botzinger complex (preBötC) in mammals is a small area of the ventrolateral medulla which generates stable neuronal rhythmic output in phase with the inspiratory muscles of the diaphragm. This rhythmic activity is generated in isolation from the rest of the respiratory column by approximately a thousand bilaterally distributed neurons. Damage to the preBötC results in an inability to breathe and eventual death.

Detailed Description

Respiration is a physiological process of supplying tissues with oxygen and removing carbon dioxide. In mammals, expansion and contraction

of the lungs provide movement of air between the atmosphere and lung alveoli, where oxygen is exchanged with carbon dioxide. Coordinated movements of the diaphragm muscles generate the regular breathing pattern. First, contraction of the muscles during the inspiratory movement pulls the lower surfaces of the lung downward. Then, during expiration, the diaphragm relaxes and abdominal structures compress the lungs. Rhythmic contraction and relaxation of the muscles of the diaphragm during breathing is controlled by neuronal signals from the several areas of the brain stem. The minimal neural structure whose neural output is correlated with the contraction of inspiratory muscles is a small area of the ventrolateral medulla, called the pre-Botzinger complex (preBötC).

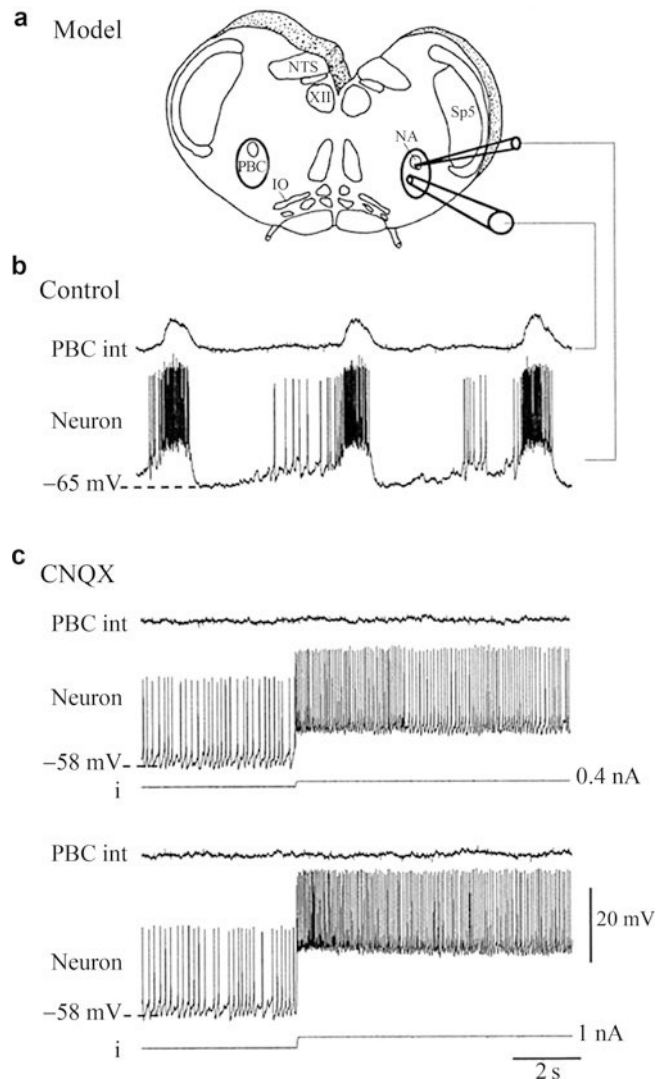
The important role of the preBötC in inspiratory rhythm generation was established in a series of experiments by Smith and colleagues (Smith et al. 1991). By extracting parts of the respiratory column, they discovered that removal of the preBötC results in complete cessation of rhythmic activity. When the preBötC is isolated in a brain stem slice preparation (Fig. 1a), it generates rhythmic neuronal activity in phase with the activity of inspiratory motoneurons (Fig. 1b).

Rhythmic activity in the preBötC depends on excitatory synaptic connections between the neurons, because blocking excitatory synapses ceases the inspiratory rhythm (Fig. 1c). However, some of the preBötC neurons (5–20%) remain rhythmic in isolation (Del Negro et al. 2005; Mellen and Mishra 2010). The role of intrinsically bursting neurons, known as *endogenous bursters* or *pacemakers*, is a hotly debated topic and there have been a number of theories proposed over the years about their role in respiratory rhythm generation.

Two endogenous bursting mechanisms have been described in preBötC neurons (Thoby-Brisson and Ramirez 2001). One type of bursting is mediated by Ca^{2+} (Fig. 2a) and therefore can be suppressed by the application of cadmium (Cd, which is a blocker of a wide range of Ca^{2+} channels.) This type of endogenous bursting neuron is often referred to as a *Cd-sensitive pacemaker*, *Ca-sensitive burster*, or *calcium burster*. Later it was shown that the calcium dependence in this

Pre-Bötzinger Complex Rhythm Generation,

Fig. 1 Experimental model and intracellular recordings from a typical inspiratory neuron. (a) Schematic representation of a brain stem slice preparation obtained from mice. This slice contains the pre-Bötzinger complex (PBC) (b and c) extracellular population activity from the PBC recorded and integrated (PBC int: integrated traces) with simultaneous intracellular recording obtained from an inspiratory neuron under control conditions (b) and after blockade of glutamatergic synapses with 20 μ M of (CNQX, c). Depolarizing current injections (*top*: 0.4 nA; *bottom*: 1 nA) did not trigger bursting activity in the neuron in CNQX (Thoby-Brisson and Ramirez 2001, Fig. 1. Reprinted with permission)



endogenous burster was associated with a calcium-activated nonspecific cationic current (I_{CaN}) (Peña et al. 2004; Del Negro et al. 2005). The second type of endogenous burster remains rhythmic in the presence Cd but ceases its rhythmic output in the presence of any blocker of the persistent sodium current (Fig. 2b). This type of bursting neuron is often called a *Cd-insensitive pacemaker*, *Ca²⁺-insensitive burster*, or *persistent Na⁺ burster*.

Over the last 20+ years, a number of models have been proposed to understand the rhythmic activity of the preBötC and more specifically the endogenous bursting of individual preBötC

neurons. In this entry, four models of preBötC rhythmic activity generation will be discussed chronologically. For convenience, the models will be referred by the name of the first author and the year of first publication.

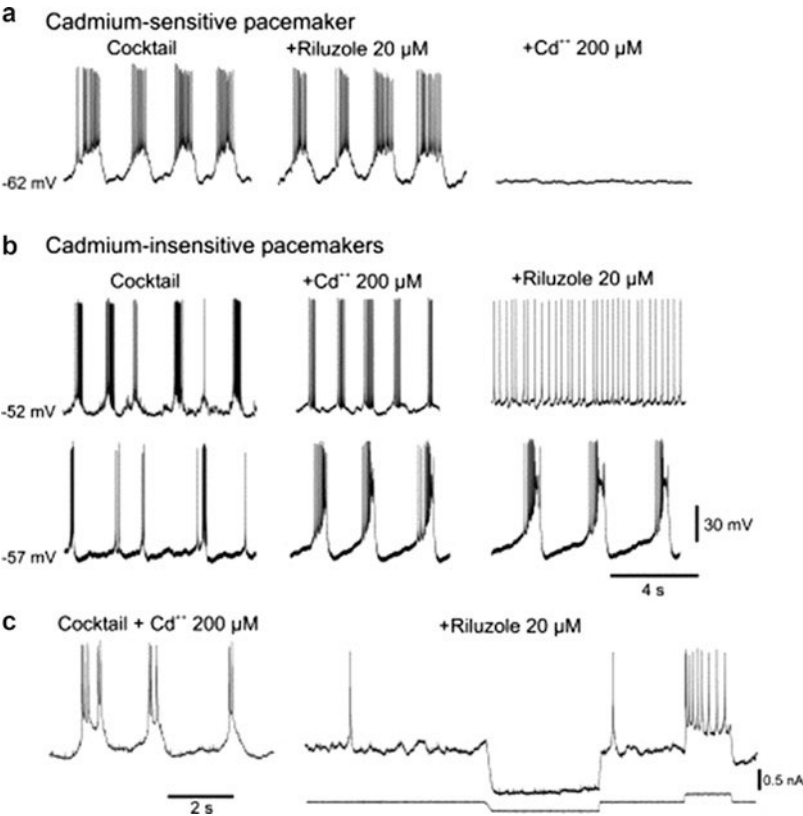
Persistent Na⁺ Bursting Mechanism (Butera 1999 Model)

After the original identification of endogenous bursters, the ionic mechanism underlying rhythmic electrical activity of preBötC neurons remained unknown. To identify a potential mechanism for

Pre-Botzinger Complex
Rhythm Generation,

Fig. 2 Two types of
endogenous bursters
(pacemakers) in preBötC.

(a) A Cd-sensitive
pacemaker continues
bursting in riluzole
(persistent sodium blocker)
but ceases in 200 μ M Cd
(Ca blocker). (b)
Cd-insensitive pacemakers
can be riluzole-sensitive or
insensitive. (Top) This
pacemaker continues to
burst in Cd but in riluzole
fires tonically. (Bottom)
Another pacemaker
continues to generate bursts
in Cd and riluzole. (c) No
burst activity is produced in
a riluzole-sensitive
pacemaker neuron in the
presence of riluzole even if
a step of positive current is
applied (Peña et al. 2004,
Fig. 3. Reprinted with
permission)



Pre-Botzinger Complex Rhythm Generation, Table 1 Equations for Butera model

Variable	Equations	Eq. #
Voltage across the cell membrane	$C_m \frac{dV}{dt} = -I_{Na} - I_{NaP} - I_K - I_L - I_{ton} - I_{syn}$	1
Activation of fast Na ⁺ current	$\frac{dn}{dt} = \frac{n_{\infty}(V) - n}{\tau_n(V)}$	2
Inactivation of persistent Na ⁺ current	$\frac{dh}{dt} = \frac{h_{\infty}(V) - h}{\tau_h(V)}$	3
Synaptic activity	$\frac{ds}{dt} = \frac{(1-s)s_{\infty} - k_{syn}n}{\tau_s(V)}$	4

intrinsic bursting, Butera and colleagues published a mathematical model (Tables 1, 2, and 3) proposing inactivation of a persistent Na⁺ current as an intrinsic burst mechanism (Butera et al. 1999b). Comparing the model with experiments, the authors concluded that the persistent Na⁺ bursting mechanism is compatible with experimental data. Later, this model was confirmed by electrophysiological experiments. The range of values for the conductances of the persistent Na⁺ current (g_{NaP}) was measured in later experiments (Purvis et al. 2007).

The model contains the essential spiking currents: fast inward Na⁺ (I_{Na}), outward delayed rectifying K⁺ (I_K), persistent Na⁺ current (I_{NaP}), and passive leak (I_{leak}). Since inactivation of persistent sodium is several orders of magnitude slower than other currents, its slow decrease provides burst termination mechanism.

The Single Cell Model

The Butera 1999 model (Fig. 3) consists of a fast inward Na⁺ (I_{Na}), an outward delayed rectifying K⁺ (I_K), persistent Na⁺ (I_{NaP}), and passive leak

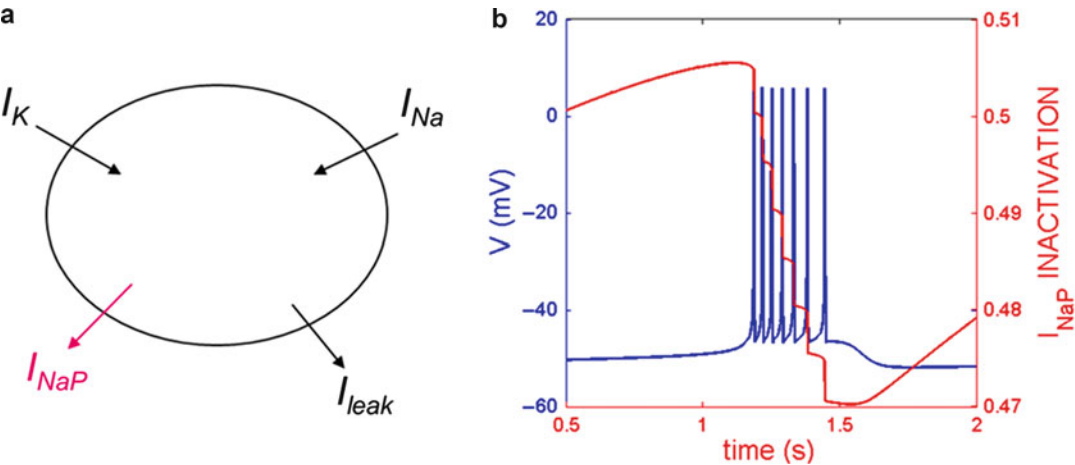
Pre-Botzinger Complex Rhythm Generation, Table 2 Equations for current in Butera 1999 model. The parameter g represents the maximal conductance of

the appropriate current (Na , NaP , K , $Leak$, or $tonic$), while n and h are activation and inactivation variables, respectively

Current	Equations	Eq. #
Inward fast Na^+	$I_{Na} = g_{Na} m \infty^3 (1 - n)(V - V_{Na})$	5
Persistent Na^+	$I_{NaP} = g_{NaP} p \infty h(V - V_{Na})$	6
Delayed rectifying K^+	$I_k = g_k n^4 (V - V_k)$	7
Leak	$I_L = g_l (V - V_L)$	8
Tonic	$I_{ton} = g_{ton} (V - V_{Na})$	9
Synaptic	$I_{syn,j} = \left(\sum_{i=1}^n G_{syn} S_i \right) (V_j - V_{syn})$	10

Pre-Botzinger Complex Rhythm Generation, Table 3 The functions in Butera1999 model. Here, x represents either m , n , h , p , or s . See Fig. 4 for graphs of functions

Function	Equation	Eq. #
Activation/inactivation function	$x_{\infty}(V) = \frac{1}{1 + \exp\left(\frac{V - V_x}{s_x}\right)}$	11
Voltage dependent time constant	$\tau_x(V) = \frac{\tau_x}{\cosh\left(\frac{V - V_x}{2s_x}\right)}$	12



Pre-Botzinger Complex Rhythm Generation, Fig. 3 Schematic diagram of Butera 1999 model. (a) Diagram of ionic current in the model. (b) The bursting dynamics in the model depend on inactivation of persistent sodium current (I_{NaP}). When the membrane voltage

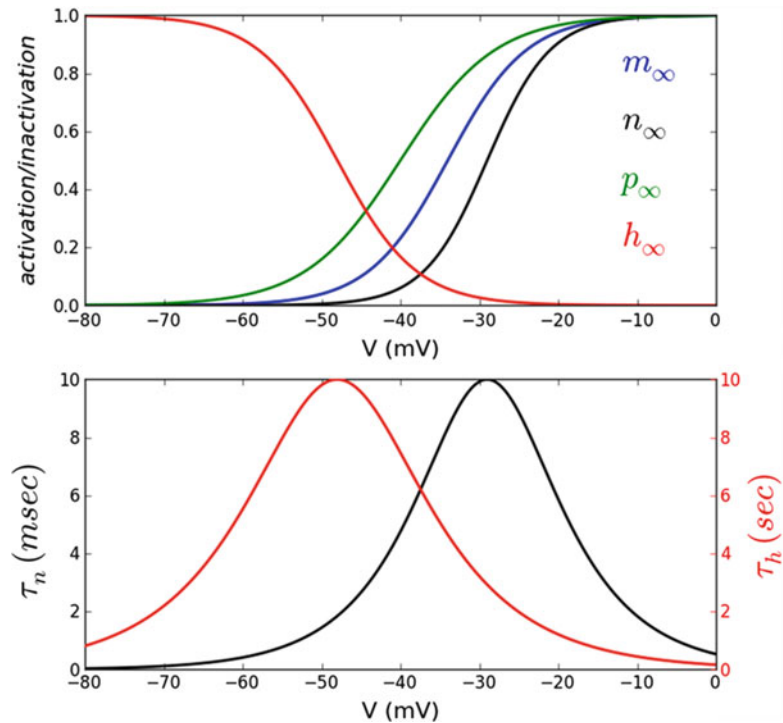
reaches its threshold, a series of action potentials are generated by a fast sodium current (I_{Na}) and a delayed rectifier potassium current (I_K). The burst is then terminated by the slow inactivation of I_{NaP}

(I_{leak}) currents. The bursting in the model depends on the inactivation dynamics of the persistent Na^+ current. When I_{NaP} is fully de-inactivated, the cell is above the spiking threshold and action potentials are produced through the interaction of I_{Na} and I_K . Since the time constant of persistent Na^+ is

significantly higher than the time constant of fast Na^+ current (Fig. 4, low panel), I_{NaP} slowly inactivates during the burst (Fig. 3b, red trace) and repolarizes the cell below the spiking threshold. The frequency and duration of the burst are regulated by the maximum value of the persistent

Pre-Botzinger Complex Rhythm Generation,

Fig. 4 Gating characteristics of components of Butera 1999 model. *Top panel:* activation/inactivation curves. *Bottom panel:* voltage-dependent time constants for fast and persistent sodium currents



Na⁺ conductance (g_{NaP}). If g_{NaP} is low (Fig. 5, top panel), the cell remains below the spiking threshold with constant membrane potential. An increase in g_{NaP} depolarizes the cell above the spiking threshold and induces bursting (Fig. 5, two middle panels). The frequency and duration of the bursting depend on the g_{NaP} (compare two middle panels in Fig. 5). Further increase in g_{NaP} leads to continuous spiking (Fig. 5, bottom panel).

However, the effect of g_{NaP} depends on the overall excitability of the preBötC network, which can be altered by the concentrations of extracellular ions or by application of excitatory neuromodulators. In vivo experiments in preBötC brain stem slices demonstrated that the frequency of bursting depends on K⁺ concentration. Reducing K⁺ decreases the burst frequency, and conversely, raising K⁺ increases the burst frequency. Since leak current in preBötC is carried out mostly by K⁺ ions, the application of K⁺ in Butera 1999 model can be simulated by manipulation of reversal potential for the leak current (V_L), with more hyperpolarized V_L representing low K⁺ concentration and more depolarized V_L representing high K⁺. The model reproduces

experimental data on K⁺ application with a higher level of V_L increasing the burst frequency and lower level of V_L decreasing burst frequency (Butera et al. 1999b).

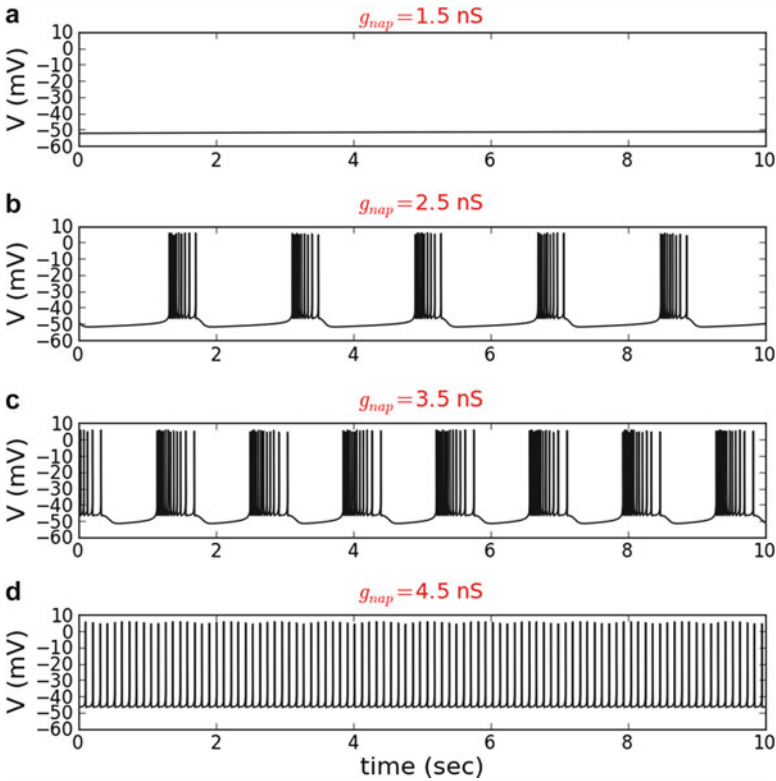
The model predicts that the combination of excitability (V_L) and persistent Na⁺ conductance (g_{NaP}) determines the pattern of electrical activity in a model cell (Fig. 6). For low excitability (low V_L), a progressive increase in g_{NaP} induces a transition from silence to bursting to tonic firing (Fig. 6). In highly excitable conditions (high V_L), no bursting behavior can be achieved and increase in g_{NaP} induces a transition from silence directly to tonic firing (Fig. 6, $V_L > -56$ mV). The prediction that the combination of excitability and persistent Na⁺ conductance determines the degree of bursting was later confirmed experimentally (Purvis et al. 2007).

The Network Model

The preBötC generates rhythmic output only if excitatory synaptic connections among the preBötC neurons are intact; experimentally, it is found that blocking excitatory connections completely abolish the preBötC rhythm. In

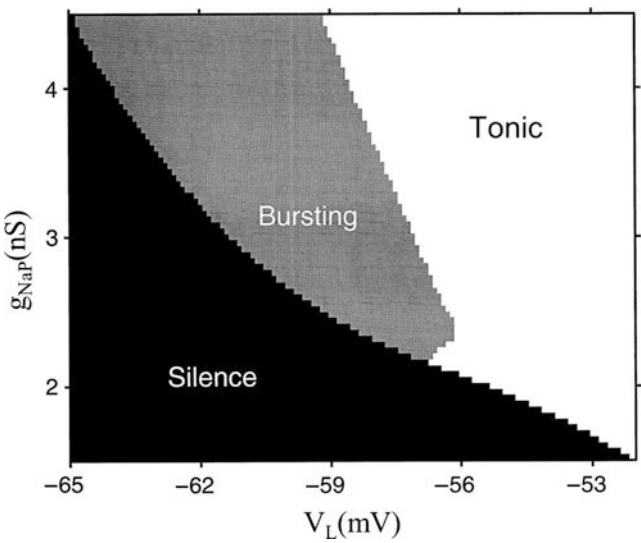
Pre-Botzinger Complex Rhythm Generation,

Fig. 5 Conductance of persistent sodium current guides transition from silence to bursting and then to tonic spiking. (a) For low values of g_{NaP} the model cell is silent. (b) Increase in g_{NaP} induces transition from silence to bursting. (c) Increase in g_{NaP} increases both burst frequency and burst duration. (d) Further increase in g_{NaP} induces transition from bursting to tonic spiking



Pre-Botzinger Complex Rhythm Generation,

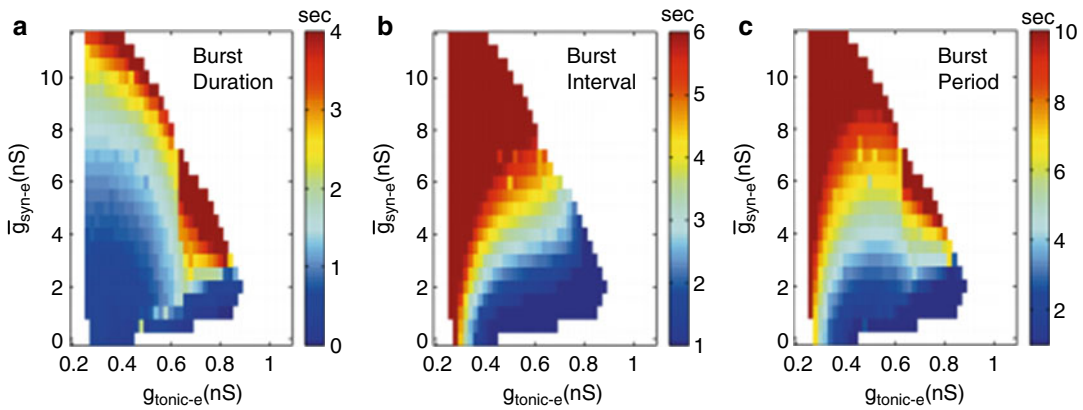
Fig. 6 Intrinsic modes of single-cell activity in Butera model as a function of g_{NaP} and V_L (Butera et al. 1999a, Fig. 7. Reprinted with permission)



addition, tonic excitatory input to the preBötC, provided by excitatory neuromodulators, modifies the rhythmic output of the network. The effects of synaptic excitatory connections and tonic drive on a network constructed from Butera 1999 model

neurons were studied in networks of different sizes (Butera et al. 1999b).

A pair of bursting neurons generates a stable synchronous bursting rhythm when connected through excitatory synapses. The combination of



Pre-Botzinger Complex Rhythm Generation, Fig. 7 Effects of g_{tonic} and g_{syn} on the dynamics of bursting and beating of pairs of coupled cells. Plots are of burst duration (a), burst interval (b), and burst period (c). Colored areas indicate regions of dynamic activity being quantified. The range of shaded values for each diagram is indicated by the associated range bar for each figure.

Units are indicated at the top of each range bar. Color values were scaled to parameter ranges that most accurately revealed trends in the data, and values beyond the minimum or maximum of the range of values used for coloring were clipped at those values (Butera et al. 1999b, Fig. 2. Reprinted with permission)

excitatory synaptic coupling and tonic drive determines the mode of activity (silence, bursting, or tonic). An increase in synaptic coupling increases the burst duration, burst interval, and burst period; however, this effect depends on the tonic drive (Fig. 7). The range of synaptic strengths for which rhythmic output can be achieved is narrowed with larger excitatory tonic drive. These findings are also observed in larger networks of bursting neurons.

However, intrinsically bursting cells constitute only a small fraction of preBötC neurons: a large portion of the neurons are either silent or tonic (note: tonic may also be referred to as *spiking* or *beating*). A realistic distribution of intrinsic firing properties in the Butera 1999 model can be achieved by assigning a distribution of g_{NaP} values (Fig. 6). In a heterogeneous network of silent, bursting, and tonic cells, coupling the cells through excitatory synaptic connections induces rhythmic network output similar to experimental recordings of the preBötC mean field potential. This rhythm disappears if the strength of the excitatory connections is reduced. The network model predicts that the combination of excitatory synaptic coupling and common tonic drive accounts for the synchronization, frequency control, patterns of inspiratory cell activity,

synaptic interactions, and network activity found in vitro (Fig. 8).

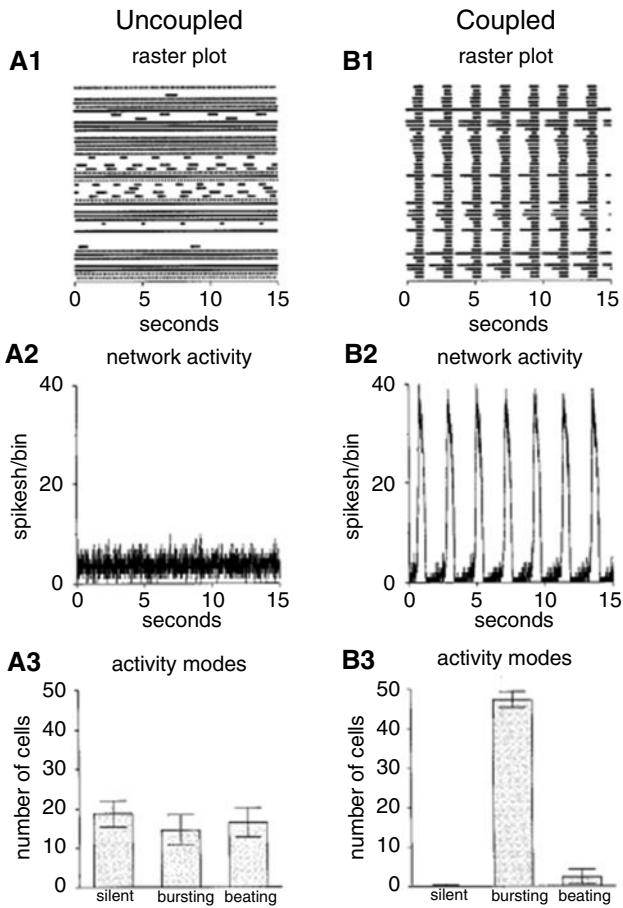
Bursting Mechanism Based on I_{CaN} and Na/K Pumps (Rubin 2009 Model)

Since intrinsic bursters are rare in the preBötC (Del Negro et al. 2005), it has been hypothesized that rhythmic output does not rely on intrinsic neuronal activity, but is a result of emergent network properties. This theory, called the *group-pacemaker hypothesis*, stated that periodic inspiratory bursts are generated by intrinsic currents, which are dormant in isolated cells, but activated by synaptic activity (Rekling and Feldman 1998; Mironov 2008; Del Negro and Hayes 2008). Ca^{2+} -activated nonspecific cation current (I_{CaN}) is one potential candidate to satisfy the group-pacemaker hypothesis. Activated by the stimulation of postsynaptic metabotropic glutamate receptors (mGluRs), I_{CaN} produces a depolarizing burst potential in preBötC neurons (Pace et al. 2007).

To explore a rhythmogenic mechanism based on the group-pacemaker hypothesis, Rubin and colleagues (Rubin et al. 2009) proposed a preBötC rhythm generation model

Pre-Botzinger Complex Rhythm Generation,

Fig. 8 Effects of excitatory coupling on synchronization of a heterogeneous population of 50 bursting neurons. Raster plots illustrate spike times of the population of the 50 cells before (**A1**) and after (**B1**) coupling. Network activity (**A2** and **B2**) is defined by calculating histograms of spike times across the population (bin size: 510 ms). *Bar plots* illustrate the number of cells in a population whose dynamics are defined as silent, bursting, or beating before (**A3**) and after (**B3**) coupling. Results are pooled from 50 simulations (Butera et al. 1999b, Fig. 3. Reprinted with permission)



Pre-Botzinger Complex Rhythm Generation, Table 4 Equations of Rubin 2009 model. The components of modified Rubin 2009 model are highlighted in gray

Variable	Equations	Eq. #
Voltage across the cell membrane	$C_m \frac{dV}{dt} = -I_{Na} - I_k - I_L - I_{CaN} - I_{pump} - I_{syn} - I_{NaP}$	13
Activation of fast Na^+ current	Same as Butera 1999	2
Na^+ concentration	$\frac{d[Na]}{dt} = \alpha(-I_{CaN} - I_{pump})$	14
Intracellular Ca^{2+} concentration	$\frac{d[Ca]}{dt} = \varepsilon([IP_3]s - K_{Ca}([Ca] - [Ca]_{\infty}))$	15
Synaptic activity	Same as Butera 1999	4

(Tables 4, 5, and 6) based on activation of I_{CaN} by synaptic activity (Fig. 9). It has been shown experimentally that activation of synaptic AMPA receptors by glutamate triggers a small influx of calcium (Pace and Del Negro 2008). In addition, glutamate binding to mGluRs can induce G protein activation that leads to synthesis of inositol 1,4,5-trisphosphate (IP_3) and subsequent

release of intracellular Ca^{2+} . In both cases, an increase in intracellular Ca^{2+} activates I_{CaN} (Pace et al. 2007).

The Single Self-Coupled Model

Although the authors conducted the majority of their analysis in one model neuron, the model is self-coupled and therefore represents the activity of

Pre-Botzinger Complex Rhythm Generation, Table 5 Currents of Rubin 2009 model. The component of modified Rubin 2009 model is highlighted in gray

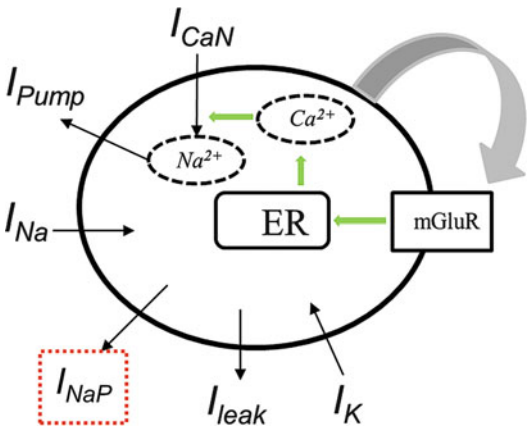
Current	Equation	Eq. #
Inward fast Na ⁺	Same as Butera, 1999	1.5
Delayed rectifying K ⁺	Same as Butera, 1999	1.7
Leak	Same as Butera, 1999	1.8
Persistent Na ⁺	Same as Butera, 1999	1.6
Ca ²⁺ -activated nonspecific cation current	$I_{CaN} = \frac{g_{CaN}(V - V_{CaN})}{1 + \exp\left(\frac{[Ca] - K_{CaN}}{\sigma_{CaN}}\right)}$	2.4
Current through the pumps	$I_{pump} = r_{pump}(\Phi([Na]) - \Phi([Na])_{\infty})$	2.5
Synaptic	Same as Butera, 1999	1.10

Pre-Botzinger Complex Rhythm Generation, Table 6 Functions of Rubin 2009 model

Function	Equations	Eq. #
Activation/inactivation function	Same as Butera 1999	11
Voltage dependent time constant	Same as Butera 1999	12
Activation function of sodium pump	$\Phi([Na]) = \frac{[Na]^3}{[Na]^3 + K_{Na}^3}$	18

a small, synaptically coupled network. In the model, recurrent synaptic excitation stimulates I_{CaN} by activation of IP₃-dependent release of intracellular Ca²⁺ (Fig. 10, top and middle panels). Depolarization due to I_{CaN} also causes voltage-dependent spike inactivation (*depolarizing block*), which reduces synaptic excitation and thus decreases postsynaptic Ca²⁺ accumulation. The influx of Na⁺, through the ion channel associated with I_{CaN} , stimulates the activity of Na/K pumps, repolarizing the cell and terminating the burst (Fig. 10, bottom panel). The recovery of spiking activity initiates a new burst cycle. Since in this case, (i) a synaptic input activates a postsynaptic burst-generating conductance (namely, I_{CaN}) and (ii) the rhythm generation depends on synaptic components rather than on endogenous bursting components, this rhythm-generating mechanism fits the *group-pacemaker* hypothesis.

The disadvantage of the original Rubin 2009 model was its limited implementation of I_{NaP} . Since I_{NaP} was identified in the majority of pre-BötC neurons (Del Negro et al. 2001; Purvis et al. 2007), it is likely that the interaction of I_{NaP} and

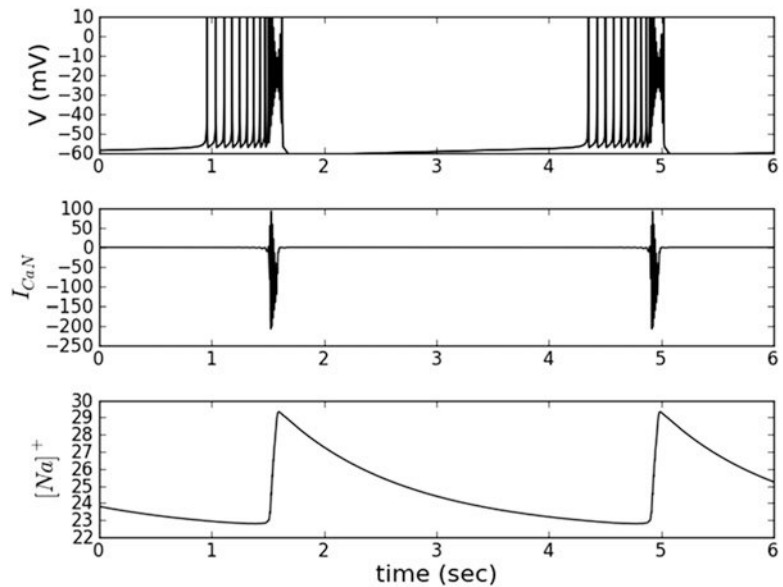


Pre-Botzinger Complex Rhythm Generation, Fig. 9 Schematic diagram of Rubin 2009 model. Self-coupled model neurons have a spike-generating mechanism consisting of fast Na + (I_{Na}), delayed rectifier K + (I_K), and leak (I_L) currents. Synaptic activity of the cell stimulates mGluR and releases intracellular Ca²⁺, which activates I_{CaN} . The influx of Na + through I_{CaN} activates an outward current mediated by Na/K ATPase (I_{pump}). Interaction of I_{NaP} and I_{CaN} was included in a modified model, which is indicated in *red dashed outline*

I_{CaN} produces the cellular activity that underlies the bursting rhythm. The model was modified (Dunmyre et al. 2011), and the combined effect of I_{NaP} and I_{CaN} was analyzed by varying their conductances. It has been found that the modified model exhibits a variety of activity patterns, including quiescence, tonic activity, square-wave bursting, depolarized bursting, and a mixture of square-wave and depolarized bursting, which matches well with the activity observed in experimental preparations (Fig. 11).

Pre-Botzinger Complex Rhythm Generation,

Fig. 10 Bursting in the model in Rubin 2009 model. The burst is initiated by depolarizing spiking currents (*top panel*). The depolarizing block during the burst is a result of increase in I_{CaN} (*middle trace*). The activation of Na/K pumps by increase in Na⁺ concentration (*bottom panel*) terminates the burst



Bursting Mechanism Based on Ca^{2+} Oscillations (Toporikova 2011 Model)

The frequency of breathing is controlled by the release of neuromodulators (often referred to as the *neuromodulatory tone*). In preBötC, the neuromodulatory tone is predominantly excitatory, through release of substance P (SP), serotonin (5-HT), norepinephrine (NA), and other neuromodulators. Some of these, such as SP and 5-HT, are released from the nearby Raphe nucleus which is preserved in a brain slice preparation. Although application of these neuromodulators in vitro excites activity of individual preBötC neurons, the extent of this effect varies from neuron to neuron. Some neuromodulators dynamically modulate the intrinsic properties of preBötC neurons and convert non-bursting cells into endogenous bursters. For example, it has been found that application of 5-HT can induce intrinsic bursting activity in non-bursting inspiratory neurons (Peña et al. 2004; Ptak et al. 2009). However, the same neuromodulator can have a different effect on Ca-sensitive and Ca-insensitive bursters (Ben-Mabrouk and Tryba 2010; Peña and Ramirez 2004). Interestingly, a large fraction of excitatory neuromodulators in the preBötC activate receptors coupled to the Gq protein pathway.

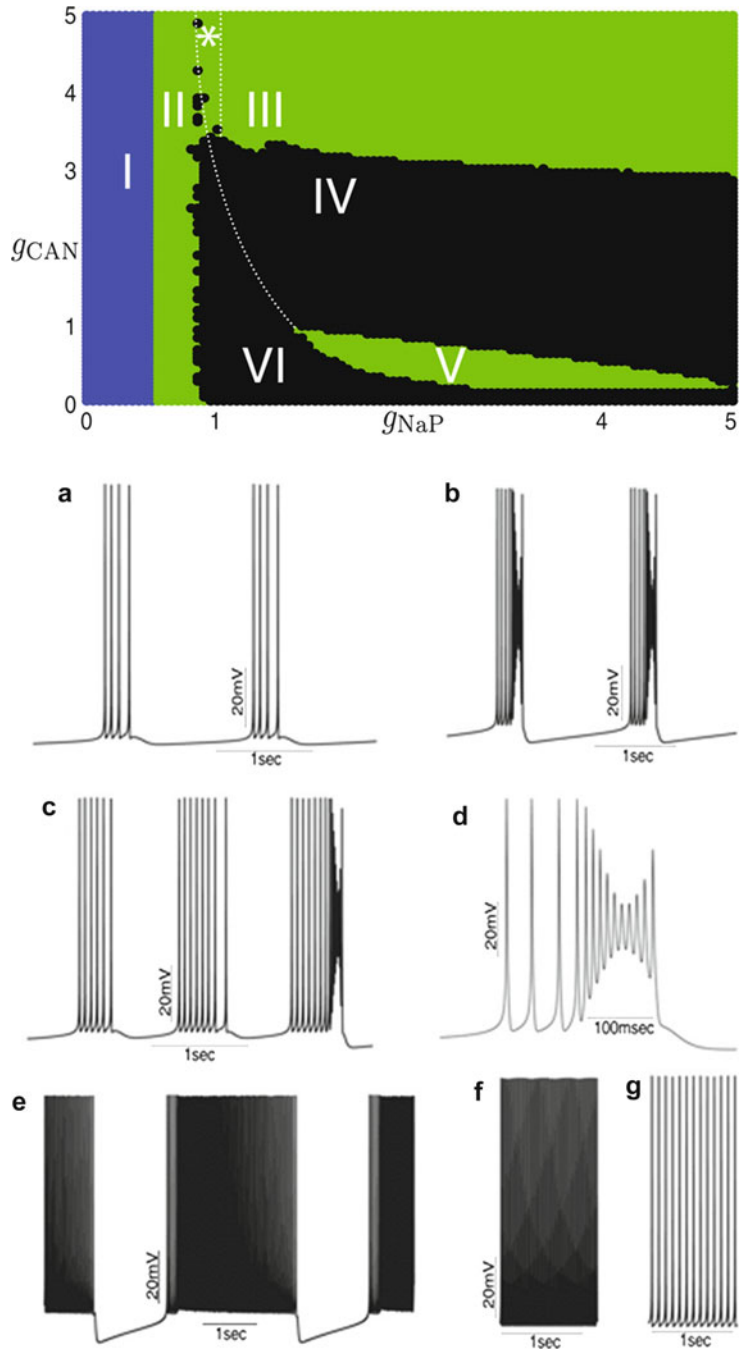
To reconcile the existence of two different types of intrinsic bursters and include the effect of neuromodulators on different cell types in the preBötC, the Toporikova 2011 model was proposed (Tables 7, 8, and 9). The authors hypothesized that Ca-dependent bursting was a result of rhythmic Ca^{2+} release from the endoplasmic reticulum (ER), the cell's Ca^{2+} store (Fig. 12). Depending on the capacity of the intracellular Ca^{2+} store and the value of the persistent Na^+ conductance, the model can reproduce Ca-dependent and/or Ca-independent bursting. The model also can reproduce dynamic changes in intrinsic cell properties during the application of neuromodulators (Toporikova and Butera 2011).

The Single Cell Model

The Toporikova 2011 model neuron has somatic and dendritic compartments, connected through an axial resistance. For the somatic compartment, the authors used a Butera 1999 model. The model hypothesizes that Ca^{2+} oscillations occur in the dendritic compartment (Mironov 2008). The neuromodulator binds to a G_q -coupled receptor and activates release of IP_3 , which binds to its receptor on the surface of the ER and induces Ca^{2+} release from the ER. The resulting increase in Ca^{2+} activates I_{CaN} and depolarizes the dendrite. The depolarizing potential then moves to

Pre-Botzinger Complex Rhythm Generation,

Fig. 11 Partition of (g_{NaP}, g_{CaN}) parameter space based on the dynamics of the unified model. *Blue dots* represent quiescent solutions. *Black dots* represent tonic activity. *Green dots* represent bursting activity, either of depolarized block bursting or square-wave bursting type. Panel (a) corresponds to region II, (b) to region III, and (c) to region*, while panel (d) shows the typical structure of a depolarized block burst from region III or region*. Panel (e) shows activity from region V, (f) from region IV, and (g) from region VI (Dunmyre et al. 2011. Reproduced with permission)



the soma where it activates essential spiking currents. The flux of Ca^{2+} from the ER into the cytosol is regulated by the activity of the IP_3 receptor. The flux from the cytosol back to the ER is controlled by the activity of ATPase SERCA pumps.

The Ca-sensitive and Ca-insensitive bursting types in the Toporikova 2011 model are characterized by different values of the parameters $[Ca]_{tot}$ and g_{NaP} (Fig. 13). The parameter $[Ca]_{tot}$ represents the capacity of the ER (for Ca^{2+} storage) and is determined by dendritic morphology.

Pre-Botzinger Complex Rhythm Generation, Table 7 Equations of Toporikova 2011 model. The components of the network model (Toporikova and Butera 2013) are highlighted in gray

Variable	Equations	Eq. #
Somatic voltage	$C_m S \frac{dV_s}{dt} = -I_{Na} - I_{NaP} - I_K - I_K - I_{DS} - I_{syn}$	3.1
Dendritic voltage	$C_m D \frac{dV_D}{dt} = -I_{CaN} - I_{SD}$	3.2
Activation of somatic fast Na ⁺ current	Same as Butera 1999	1.2
Inactivation of somatic persistent Na ⁺ current	Same as Butera 1999	1.3
Intracellular Ca ²⁺ concentration	$\frac{d[Ca]}{dt} = f_i(J_{ERIN} - J_{EROUT})$	3.3
IP ₃ channel gating	$\frac{dl}{dt} = A(K_d - l([Ca] + K_d))$	3.4
Synaptic activity	Same as Butera 1999	1.4
Concentration of excitatory neuromodulator	$\frac{d[NT]}{dt} = \frac{K_{ionic} - K_{syn} g_{syn} \sum_{j=1}^N s_j - K_{deg}[NT]}{\tau_{NT}}$	3.5

Pre-Botzinger Complex Rhythm Generation, Table 8 Currents in Toporikova 2011 model. The components of the network model (Toporikova and Butera 2013) are highlighted in gray

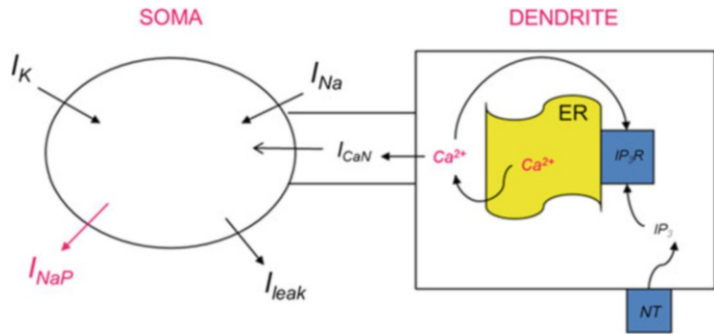
Current	Equations	Eq. #
Inward fast Na ⁺	Same as Butera 1999	1.5
Persistent Na ⁺	Same as Butera 1999	1.6
Delayed rectifying K ⁺	Same as Butera 1999	1.7
Leak	Same as Butera 1999	1.8
Somato-dendritic	$I_{SD} = \frac{g_c}{k}(V_D - V_S)$	3.6
Dendrito-somatic	$I_{DS} = \frac{g_c}{1-k}(V_D - V_S)$	3.7
Ca ²⁺ -activated nonspecific cation current	$I_{CaN} = g_{CaN} \frac{V_D - V_{Na}}{1 + \frac{K_{CaN}}{[Ca]}}$	3.8
Synaptic current	Same as Butera 1999	1.10

The model can reproduce the experiments on application of blockers of either I_{CaN} or I_{NaP}. If there are no Ca²⁺ oscillations and persistent Na⁺ is in the bursting range, the bursting is Ca-insensitive (Fig. 12a, green star). The bursting activity in this regime is prevented by blocking I_{NaP}; however, blocking Ca²⁺ does not affect the rhythmic activity (Fig. 13b). When Ca²⁺ is in the oscillatory regime, but g_{NaP} is in the sub-oscillatory range, the bursting is Ca-sensitive (Fig. 13a, blue star). The bursting activity in this regime is prevented by blocking Ca²⁺; however, blocking I_{NaP} does not affect the rhythmic activity (Fig. 12d). Lastly, when both g_{NaP} and [Ca]_{tot} are in the bursting regime (Fig. 13a, red star), the bursting is insensitive to blocking either I_{NaP} or Ca²⁺ (Fig. 13c).

Pre-Botzinger Complex Rhythm Generation, Table 9 Equations of Toporikova 2011 model. The components of the network model (Toporikova and Butera 2013) are highlighted in gray

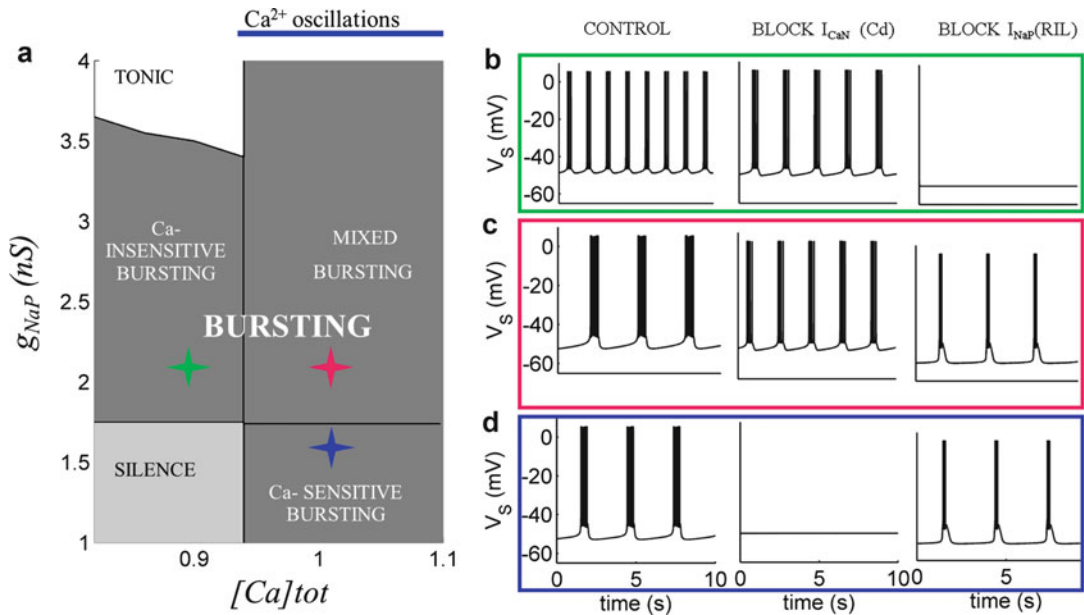
Function	Equations	Eq. #
Activation/inactivation function	Same as Butera 1999	1.11
Voltage dependent time constant	Same as Butera 1999	1.12
Flux of Ca ²⁺ from ER into the cytosol	$J_{ERIN} = (L_{IP3R} + P_{IP3R}\alpha^3)([Ca]_{ER} - [Ca])$	3.9
IP ₃ R gating function	$\alpha = \frac{[IP3][Ca]}{([IP3] + K_i)([Ca] + K_a)}$	3.10
Flux of Ca ²⁺ from the cytosol the ER	$J_{EROUT} = V_{SERCA} \frac{[Ca]^2}{K_{SERCA}^2 + [Ca]^2}$	3.11
ER Ca ²⁺ concentration	$[Ca]_{ER} = \frac{[Ca]_{tot} - [Ca]}{\sigma}$	3.12
IP ₃ concentration	$[IP3] = \alpha[NT]$	3.13

Calcium oscillations in the two-compartment model also depend on the concentration of bath-applied excitatory neuromodulators, which activate the G_q protein pathway and induce IP₃ release. The variable [NT] in the model represents the concentration of such neuromodulators, presumably SP or 5-HT. The authors investigated electrical activity in the model to show that the presence of Ca²⁺ oscillations is nonlinearly dependent on the values of [NT] and [Ca]_{tot} (Fig. 14a). For example, Ca²⁺ oscillations in the model can be generated at low levels of [Ca]_{tot}, if



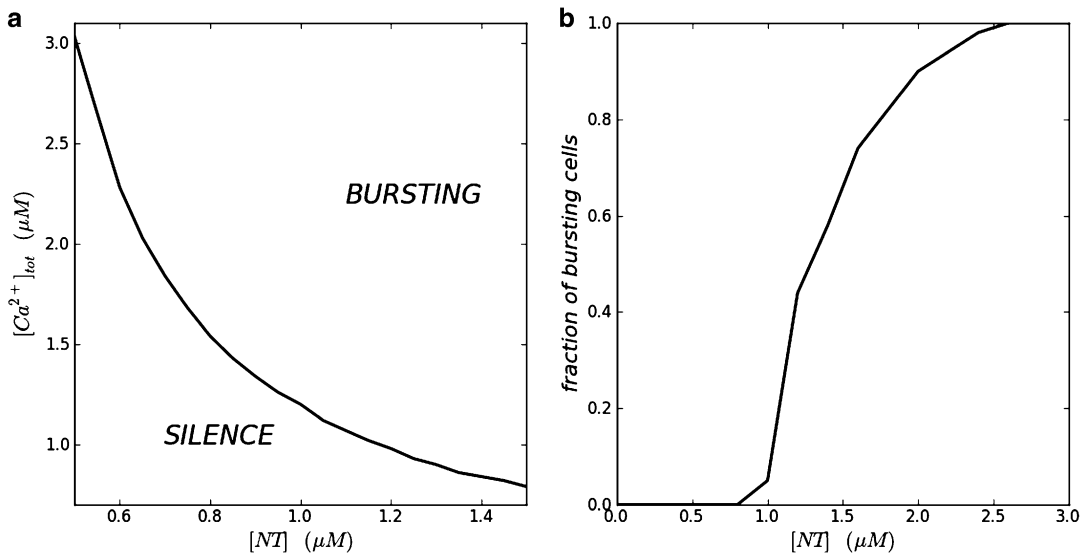
Pre-Botzinger Complex Rhythm Generation, Fig. 12 Schematic diagram of Toporikova 2011 model. The bursting mechanism in somatic compartment is based on persistent sodium current inactivation, while dendritic compartment does not have its own spike-generating currents. Instead, dendritic compartment produces a depolarizing potential following intracellular Ca^{2+} oscillations. An increase in the intracellular Ca^{2+} concentration activates I_{CaN} and depolarizes the cell. When the Ca^{2+} concentration decreases, I_{CaN} inactivates and the cell repolarizes to its resting potential. Calcium oscillations in our

model are dependent on neuromodulator (NT) binding to Gq-protein-coupled receptor. The activation of Gq-protein-coupled receptors leads to an increase in $[\text{IP}_3]$, which binds to its receptor (IP_3R) on the surface of the endoplasmic reticulum (ER) and initiates a Ca^{2+} flux into the cytosol. This Ca^{2+} flux is terminated by the slow inactivation of IP_3R by Ca^{2+} . As a result, intracellular Ca^{2+} decreases as the SERCA pumps bring Ca^{2+} back to the ER. This cycle repeats as IP_3R inactivation is removed at low Ca^{2+} concentration



Pre-Botzinger Complex Rhythm Generation, Fig. 13 The type of endogenous bursting activity is determined by values of parameters for persistent sodium conductance (g_{NaP}) and total amount of ER Ca^{2+} . (a) The range of parameters for different types of electrical activity in the model. White color represents tonic spiking, light gray is silence, and dark gray is bursting. The bursting regime is divided into Ca-sensitive, Ca-insensitive, and mixed types. Stars show representative values chosen for simulations

(b) sub-oscillatory Ca^{2+} regime and g_{NaP} in bursting regime (green star in panel a); the model cell is rhythmic if I_{NaP} is blocked, but blocking of I_{CaN} eliminates bursting. (c) When Ca^{2+} is in the oscillatory regime and g_{NaP} is above the bursting threshold (red star in panel a), the cell produces bursting if either I_{NaP} or I_{CaN} is blocked. (d) If Ca is in oscillatory regime but g_{NaP} is below bursting threshold (blue star in panel a), the model cell remains rhythmic when I_{CaN} is blocked, but bursting ceases if I_{NaP} is blocked



Pre-Botzinger Complex Rhythm Generation, Fig. 14 Bursting in the two-compartment model depends on the choice of parameters. (a) Dendritic bursting regime depends on neuromodulatory tone, $[NT]$, and total Ca^{2+}

concentration in the ER ($[Ca]_{tot}$). (b) A fraction of Ca -dependent bursters in heterogeneous population of cells increases with increase in neuromodulatory tone

$[NT]$ is sufficiently large. These results are consistent with the experimental data on inducing bursting activity in non-bursting inspiratory neurons by application of 5-HT (Peña and Ramirez 2004; Ptak et al. 2009). As a result, the model predicts that in a population of cells with a heterogeneous distribution of bursting properties, the application of excitatory neuromodulators increases the fraction of Ca -sensitive endogenous bursters (Fig. 14b).

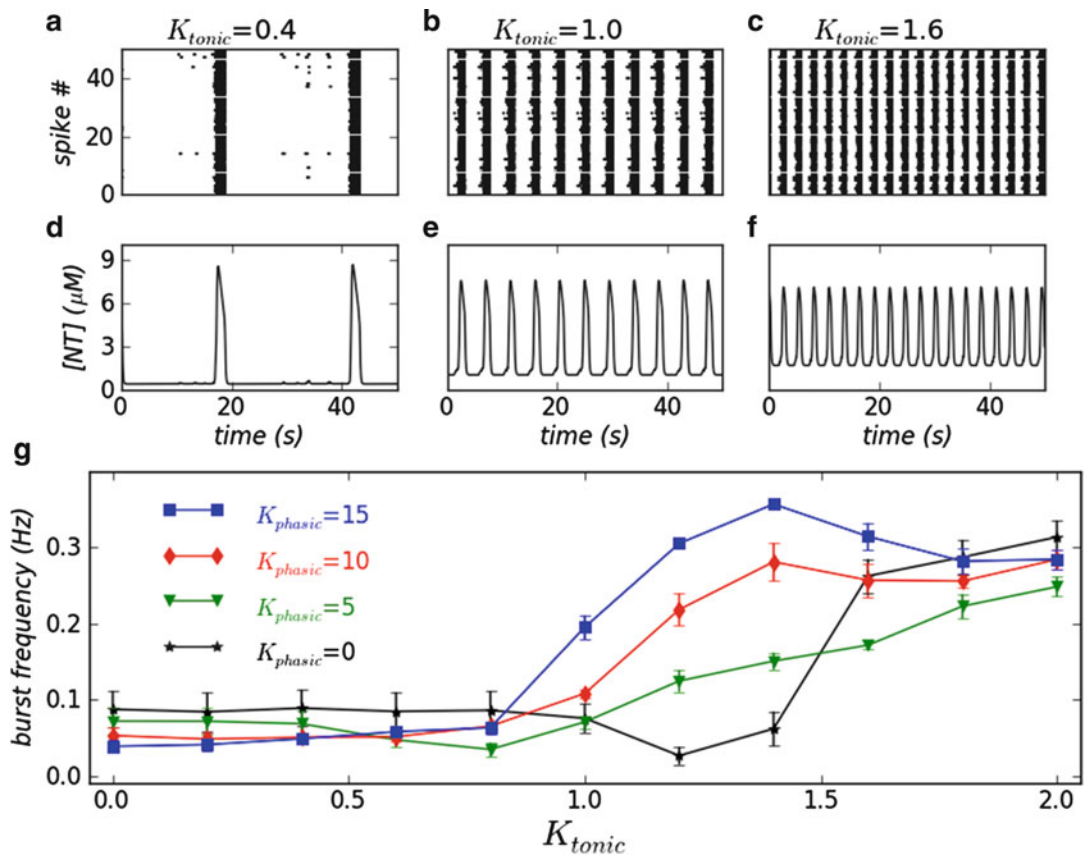
The Network Model

Although the Toporikova 2011 single cell model explains the coexistence of two types of intrinsic bursting in the preBötC cell, it can generate a stable network rhythm only in a very narrow range of neuromodulatory tones. This can be contrasted with an *in vivo* respiratory network, which generates a stable rhythm in a wide range of neuromodulatory tones. To determine the condition for stable rhythm generation in a network with a realistic distribution of intrinsic properties, the authors investigated different connectivities between the preBötC and the Raphe nucleus, which produces a large fraction of the neuromodulators affecting the respiratory rhythm

(Toporikova and Butera 2013). It has been found that a network which includes positive feedback between the Raphe nucleus and the preBötC can produce stable rhythmic output in a wide range of neuromodulatory tones (Fig. 15g). The model also predicts that a brief increase in the release of neuromodulators by the Raphe nucleus induces simultaneous Ca^{2+} oscillations in preBötC neurons (Fig. 15a–f).

Bursting Mechanism Based on Combination of Persistent Na^+ , Na/K Pumps, and Ca^{2+} (Jasinski 2013 Model)

Although experimental studies in rodent brain stem slices containing the preBötC identified that both I_{CaN} and I_{NaP} potentially contribute to the generation of the rhythm, the contribution of each of these mechanisms to rhythmic bursting remains unresolved. The model of Jasinski et al. 2013 (Tables 10, 11, and 12) evaluates the roles of intrinsic Na^+ -dependent and Ca^{2+} -dependent bursting in the generation of rhythmic activity in preBötC (Jasinski et al. 2013). The model explicitly simulates several aspects of the neuron



Pre-Botzinger Complex Rhythm Generation, Fig. 15 Effect of neuromodulatory tone on frequency modulation in a 50-cell network with positive feedback between preBötC and Raphe. The strength of positive feedback is represented by parameter K_{phasic} . The neuromodulatory tone is represented by a parameter K_{tonic} . (a–c) A raster plot of a representative network simulation with positive feedback ($K_{phasic} = 15$). Network frequency increases with an increase in neuromodulatory tone. (a) In low ($K_{tonic} = 0.4$) neuromodulatory tone, the frequency is low. (b) In medium ($K_{tonic} = 1$) neuromodulatory tone, the frequency increases. (c) In high neuromodulatory tone

($K_{tonic} = 1.6$), the burst frequency increases further and the burst shape remains representative of preBötC neurons. (d–f) Concentration of excitatory neuromodulator ([NT]) in the same simulations as (a–c). The rise in [NT] coincides with increases in spiking activity of the network. (g) Burst frequency responses to neuromodulatory tone for four different strengths of positive feedback (K_{phasic}). The network with strong connection between preBötC and Raphe ($K_{phasic} = 15$, blue trace) shows the largest range of frequencies in response to progressive increase in neuromodulatory tone

Pre-Botzinger Complex Rhythm Generation, Table 10 Equations of Jasinski 2013 model

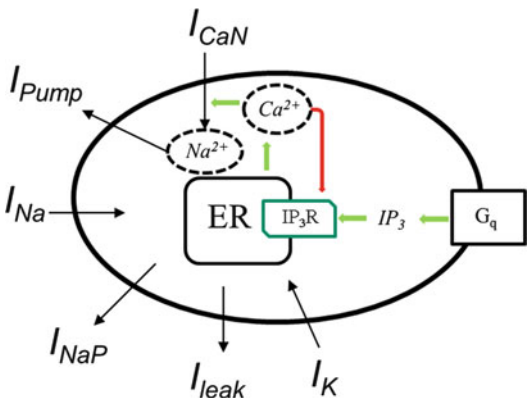
Variable	Equations	Eq. #
Voltage across the cell membrane	$C_m \frac{dV}{dt} = -I_{Na} - I_k - I_{NaP} - I_L - I_{CaN} - I_{pump} - I_{syn}$	32
Activation of fast Na^+ current	Same as Butera 1999	2
Activation of persistent Na^+ current	Same as Butera 1999	3
Activation of voltage-gated Ca^{2+} current	$\frac{dm}{dt} = \frac{m_{\infty}(V) - m}{\tau_m(V)}$	33
Inactivation of voltage-gated Ca^{2+} current	$\frac{dp}{dt} = \frac{p_{\infty}(V) - p}{\tau_p(V)}$	34
Na + concentration	$\frac{d[Na]}{dt} = \alpha_{Na}(-I_{Na} - I_{NaP} - I_{CaN} - 3I_{pump})$	35
Intracellular Ca^{2+} concentration	Same as Toporikova 2011	21
Total Ca^{2+} concentration	$\frac{d[Ca]_{tot}}{dt} = \frac{\alpha_{Ca} I_{Ca} - [Ca]}{Ca}$	36

Pre-Botzinger Complex Rhythm Generation, Table 11 Equations of Jasinski 2013 model. The components of the network model are highlighted in gray

Current	Equations	Eq. #
Inward fast Na^+	Same as Butera 1999	1.5
Persistent Na^+	Same as Butera 1999	1.6
Delayed rectifying K^+	Same as Butera 1999	1.7
Leak	Same as Butera 1999	1.8
Current through the pumps	Same as Rubin 2009	2.5
Voltage gated Ca^{2+} current	$I_{Ca} = g_{Ca} m p (V - V_{Ca})$	4.6
Ca^{2+} -activated nonspecific cation current	Same as Toporikova 2011	3.8
Synaptic	$I_{syn,i} = g_{syn} \sum_{j=1}^N w_{ji} \sum_{t_{ij} < t} \exp\left(-\frac{t-t_{ij}}{\tau_{syn}}\right)$	4.7

Pre-Botzinger Complex Rhythm Generation, Table 12 Functions in Jasinski 2013 model

Function	Equations	Eq. #
Activation/inactivation function	Same as Butera 1999	11
Voltage dependent time constant	Same as Butera 1999	12
Flux of Ca^{2+} from ER into the cytosol	Same as Toporikova 2011	27
IP_3 gating function	Same as Toporikova 2011	28
Flux of Ca^{2+} from the cytosol the ER	Same as Toporikova 2011	29
ER Ca^{2+} concentration	Same as Toporikova 2011	30
Activation function for sodium pump	Same as Rubin 2009	18



Pre-Botzinger Complex Rhythm Generation, Fig. 16 Schematic diagram of Jasinski 2013 model.

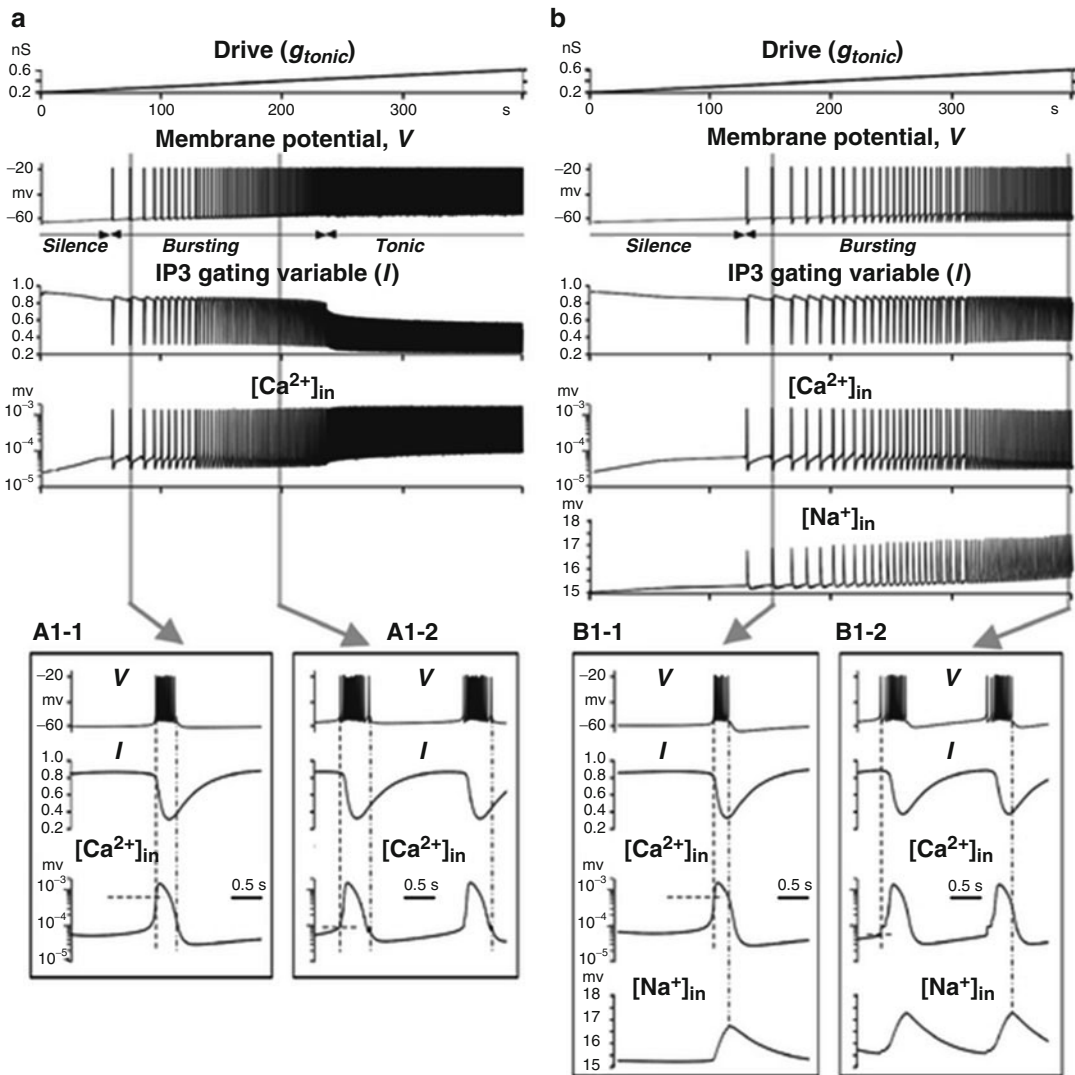
The model has essential spiking currents (I_{Na} , I_K , and I_L), essential bursting currents (I_{CaN} and I_{NaP}), and balance of Ca^{2+} and Na^+ ions. Depending on choice of parameters for conductances of persistent sodium current (g_{NaP}) and voltage-gated Ca^{2+} current (g_{Ca}), the model can reproduce Ca-dependent or Ca-independent (NaP) bursting. Combination of Ca^{2+} influx through voltage-gated Ca^{2+} channels and activation Ca^{2+} release through IP_3 -dependent pathway, mediates Ca-dependent bursting in the model. The Ca-dependent burst can be terminated by either inactivation of IP_3R by Ca^{2+} or by activity of Na/K pumps by the influx of Na through ICaN

dynamics, synaptic interactions, ionotropic and metabotropic synaptic mechanisms, intracellular Ca^{2+} release, and the Na/K pump and examines their effects on network rhythmic bursting. The model predicts that the rhythmic preBötC activity is state-dependent and can operate in either an I_{NaP} -dependent regime or an I_{CaN} -dependent regime or both (Fig. 16).

The Single Cell Model

The goal of the model is to explore the effect of Na^+ - and Ca^{2+} -dependent bursting mechanisms at different levels of the tonic drive. The single cell model includes essential spiking currents as well as balanced equations for Na^+ and Ca^{2+} . The Ca^{2+} can either be released from the ER or enter through a voltage-gated Ca^{2+} channel during the

action potential. The authors explored the two different mechanisms for Ca-dependent bursting. The first mechanism is based on Ca^{2+} oscillations (similar to Toporikova 2011) with burst termination through inactivation of IP_3R by Ca^{2+} . The second mechanism is based on Ca^{2+} entrance through voltage-gated Ca^{2+} channels; in this case, the burst is terminated through the activity of Na/K pumps induced by I_{CaN} (similar to Rubin



Pre-Botzinger Complex Rhythm Generation, Fig. 17 Simulation of I_{Ca} -dependent and I_{CaN} -dependent bursting by the use of two single-neuron models with different burst-terminating mechanisms. In the first model (a), burst termination was based on Ca^{2+} -dependent IP3R inactivation (see the traces for IP3R gating variable I and

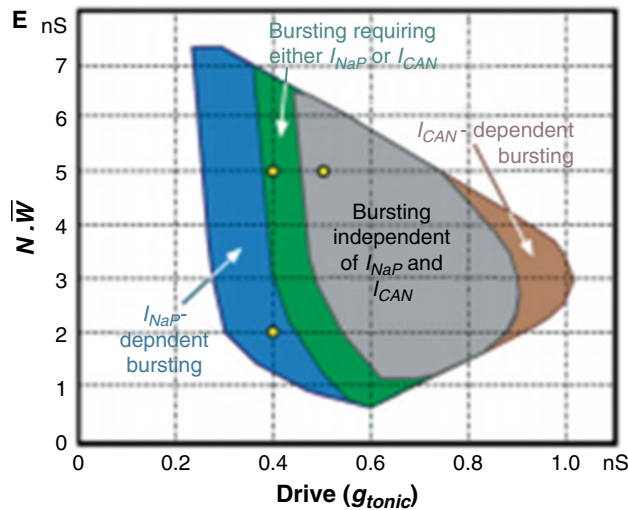
$[Ca^{2+}]_{in}$). In the second model (b), there were two burst-terminating mechanisms: one based on Ca^{2+} -dependent IP3R inactivation (as in the first model) and the other based on intracellular Na^+ accumulation (see $[Na^+]_{in}$ in traces) and subsequent activation of the Na/K pump (Jasinski et al. 2013, Fig. 3. Reprinted with permission)

2009). The authors refer to these two Ca^{2+} mechanism as I_{Ca} -dependent and I_{CaN} -dependent, respectively (Fig. 17). It was found that the distribution of parameters determines the type of bursting in a given cell and also that the bursting mechanisms can dynamically change with the applied tonic drive. Such a mechanism would be beneficial for a preBötC network, where

neuromodulatory tone and input from other brain areas change dramatically within short time intervals.

The Network Model

The authors also simulated a network of excitatory-connected neurons by hypothesizing a heterogeneous distribution of synaptic weights



Pre-Botzinger Complex Rhythm Generation, Fig. 18 Synaptic excitability and tonic drive can modulate the type of bursting in the model network. The region for I_{NaP} -dependent population bursting is shown in blue; the region in which population bursting may be based on either I_{NaP} or I_{CaN} is shown in green; the region in which

population bursting may exist without both of these currents is shown in gray; an additional region (brown) represents unstable Ca-dependent and I_{CaN} -dependent bursting (Jasinski et al. 2013, Fig. 8. Reprinted with permission)

and intrinsic properties of individual neurons. It is assumed that each spike of neuron j triggers a postsynaptic current in neuron i at time t_{kj} . This current increases the excitatory synaptic conductance in neuron i by w_{ji} , which represent the weight of synaptic connection from neuron j to neuron i . The synaptic excitation decays with synaptic constant τ_{syn} . The authors found that in a network with heterogeneous distribution of parameters (assuming normal distributions around an average value), the combination of tonic and synaptic drive determines the bursting type. The model shows that in heterogeneous populations of excitatory-connected neurons, rhythmic network bursting can depend on I_{NaP} and/or I_{CaN} or be independent of both. This finding implies that the involvement of each mechanism might depend on the neuronal excitability, the strength of synaptic interactions, and the distribution of I_{NaP} and I_{CaN} (Fig. 18).

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Predictive Coding

Michael Spratling

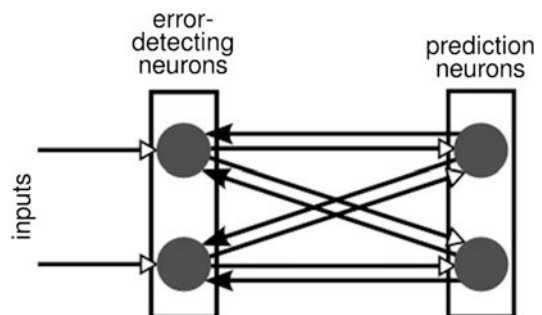
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Definition

Predictive coding is both a technique for efficient information encoding and a method for performing perceptual inference. It is commonly used to model information processing in the cerebral cortex.

Detailed Description

Predictive coding models of cortical function are typically implemented as hierarchical neural networks. Such networks contain alternating populations of “error-detecting” neurons and “prediction” neurons. Figure 1 shows the connectivity between a single pair of adjacent populations in such a hierarchy, for a very simplified case where there are only two neurons in each population. The inputs come from the thalamus or are the outputs of prediction neurons at preceding stages in the hierarchy. The activity of the prediction neurons encodes hypotheses about the causes underlying the inputs to the preceding population of error-detecting neurons. The activity of the error-detecting neurons encodes the discrepancy



Predictive Coding, Fig. 1 Connectivity between adjacent pairs of neural populations in a predictive coding hierarchy

(or residual error) between the expected inputs (reconstructed from the predictions) and the actual inputs. The activations of both the prediction neurons and the error-detecting neurons are updated via an iterative process to find the combination of prediction neuron responses that best explain the inputs (in terms of minimizing the residual error) and to encode this error.

The weights from the error-detecting neurons to an individual prediction neuron determine the pattern of input activations which that particular prediction neuron represents. The strength of activation of that prediction neuron encodes the degree of belief that this specific pattern of inputs is present in the current stimulus. The full range of possible patterns that the network can represent are defined by the weights of all the prediction neurons. If these weights are represented by a matrix, W , then the rows of W (which correspond to the weights targeting individual prediction neurons) comprise “basis vectors” or “elementary components” or “codebook entries” or “atoms.” W as a whole represents a “dictionary” or “codebook” of possible representations or a model of the external world. The feedback weights, connecting the prediction neurons to the error-detecting neurons, are typically chosen to be the transpose of the feedforward weights (i.e., W^T). This means that the feedforward weight connecting a specific error-detecting neuron to a specific prediction neuron is equal to the reciprocal feedback weight connecting the same prediction neuron to the same error-detecting neuron. The feedback weights are used to reconstruct the expected inputs, based on the current prediction neuron responses. If prediction neuron responses are represented by the vector y , then this reconstruction is:

$$r = W^T y \quad (1)$$

The reconstruction thus takes the form of a linear generative model. In other words, the input is reconstructed using a linear superposition of dictionary elements where the contribution of each dictionary element is weighted by the coefficients, y .

Many other algorithms employ linear generate models and hence are closely related to predictive

coding. For example, many methods in signal processing and pattern recognition seek to approximate an input signal, x , as a linear combination of basis vectors selected from a dictionary, W^T , in proportion to a set of coefficients, y . Well-known examples include vector quantization (VQ), principal components analysis (PCA), independent components analysis (ICA), and nonnegative matrix factorization (NMF). In signal processing linear predictive coding is used to encode a temporal sequence of signals using a linear combination of signals from the recent past; hence, the dictionary is composed of previous signals and may change through time. Sparse coding (Olshausen and Field 1996) is also closely related, as it employs a linear generative model, but one in which y is constrained to contain only a few nonzero elements, so as to represent the input using a sparse set of coefficients. Unlike predictive coding these related methods are not hierarchical; however, algorithms that employ a hierarchy of generative models, and which are also therefore closely related to predictive coding, include the Helmholtz machine, the restricted ► “Boltzmann Machine,” stacked auto-encoders, and deep learning architectures in general (Arel et al. 2010).

The linear reconstruction of the inputs is compared to the actual inputs (x) in order to calculate the residual error. This calculation is performed by the error-detecting neurons and is encoded in the responses of these neurons (represented by the vector e). Two methods of calculating the error have been suggested. The more common method uses subtraction (Rao and Ballard 1999), such that

$$e = x - r \quad (2)$$

If the predictions are accurate, then the reconstructed input will equal the actual input and the error will be zero. Elements of the input vector which are not correctly predicted will result in positive or negative values in the corresponding elements of e . An alternative method uses element-wise division (Spratling 2008), such that

$$e = x/r \quad (3)$$

In this case, elements of the input that are accurately represented by the predictions will

have a value of one, and elements of the input that are not correctly predicted will result in values of e greater or less than one.

The aim of predictive coding is to find the combination of prediction neuron activations that minimize the residual error. Hence, the error-detecting neuron activations are used to calculate new prediction neuron responses with the aim of improving the predictions and subsequently reducing the error. At each iteration, the prediction neuron activations are updated as follows:

$$y \leftarrow ay + bWe \quad (4)$$

or

$$y \leftarrow y.We \quad (5)$$

where Eq. 4 is used if Eq. 2 has been used to calculate the residual errors and Eq. 5 is used if Eq. 3 has been used to calculate the residual errors. a and b are scalar parameters.

In either case, errors that are large (positive values from Eq. 2 or values greater than one from Eq. 3) correspond to elements of the input that are underrepresented in the reconstruction, and the above equation leads to an increase in the responses of prediction neurons that represent those elements of the input. Similarly, elements of the input that are overrepresented in the reconstruction, giving rise to errors that are negative (Eq. 2) or less than one (Eq. 3), reduce the responses of prediction neurons that represent those elements of the input.

While we can think of the weights, W , as defining the pattern of input activations that each prediction neuron represents, or the receptive fields (RFs) of each neuron, the prediction neurons do not behave as linear feature detectors, or linear filters, for these input patterns. If multiple prediction neurons all receive nonzero connections from the current active subset of inputs, then in the linear case each of those prediction neurons would respond in proportion to the overlap between the stimulus and that neuron's RF (i.e., $y = Wx$). In contrast, in predictive coding the activation dynamics described above cause the

prediction neurons to interact in a mutually suppressive and nonlinear manner to determine the subset of those predictions which can best explain the input pattern. This interactive process can be thought of as a form of perceptual inference in which the prediction neuron responses represent hypotheses and the inputs provide evidence in support of those hypotheses. If a prediction neuron (or subset of prediction neurons) is able to explain the input, then the evidence supporting alternative hypotheses is "explained away" (Lochmann and Deneve 2011) and the prediction neurons representing those alternative hypotheses do not respond. This perceptual inference process can also be thought of in terms for competition between the prediction neurons. Each prediction neuron effectively tries to block other prediction neurons from responding to the inputs which it represents, such that prediction neurons with overlapping RFs compete for the right to represent active inputs.

If the input remains constant, at the end of several iterations of Eqs. 1, 2, and 4 or of Eqs. 1, 3, and 5, the prediction neuron responses will typically reach a steady state where the active prediction neurons represent the linear combination of dictionary elements that can best explain the input. In the longer term, the dictionary elements (i.e., the weights W) can be adjusted to provide a better set of elementary components with which to encode the input space. Like the updating of the prediction neuron responses, this learning process is also error driven, such that

$\Delta W = fn(ye)$ if Eq. 2 has been used to calculate the residual errors

$\Delta W = fn(y(e - 1))$ if Eq. 3 has been used to calculate the residual errors.

The above description has been concerned with the interactions between pairs of error-detecting and prediction neuron populations. In a hierarchical predictive coding model, there will be multiple such pairs, and the activity in one pair will be influenced by the subsequent pair, higher up the hierarchy. For example, Eq. 4 will become $y \leftarrow ay + bWe - ce^*$ where e^* is the activation of the subsequent population of error-detecting neurons in the hierarchy and c is a scalar parameter. Alternatively, Eq. 5 will become

$y \leftarrow y.We + dW^*y^*$ where W^* and y^* are the weights and prediction neuron responses of the subsequent stage in the hierarchy and d is a scalar parameter. In either case prediction neuron responses at one stage in the hierarchy can enhance the responses of neurons representing corresponding predictions at the preceding stage.

Predictive coding is an abstract, functional model which explores the computational principles by which the cortex operates, rather than the biophysical mechanisms by which these computations may be implemented (Spatling 2011). It is therefore difficult to relate specific aspects of the model to individual components of cortical physiology. However, the most common interpretation is that cortical feedback connections carry predictions and that these act on regions at preceding stages along an information processing pathway in order to calculate the residual error which is then propagated via cortical feedforward connections (Rao and Ballard 1999; Friston 2005). Under this interpretation, pyramidal cells in the superficial layers of primary visual cortex (V1) would correspond to error-detecting neurons and some aspects of V1 complex cell behavior can be modeled by error-detecting neurons in a suitable predictive coding model (Rao and Ballard 1999). An alternative interpretation proposes that the calculation of the residual error is performed by connections intrinsic to each cortical region and hence that both cortical feedforward and feedback pathways carry predictions (Spatling 2008). Under this interpretation, pyramidal cells in the superficial layers of primary visual cortex would correspond to prediction neurons. Many properties of orientation-tuned cells in V1 can be simulated by the prediction neurons in a suitable predictive coding model (Spatling 2010, 2011).

Predictive coding has also been proposed as a model of retinal information processing (Srinivasan et al. 1982). Retinal circuitry is believed to predict the local intensity values expected at a particular spatial location (as the average intensity of all neighboring locations) and to subtract this prediction from the actual intensity. The signal generated following subtraction of the predicted information has a smaller dynamic range than the raw intensity values and

hence can be transmitted with greater accuracy using a limited range of firing rates. By removing predictable information for the transmitted data, the retina can be considered to perform redundancy reduction (the removal of statistical dependencies between neighboring pixel values) as proposed by Barlow (2001).

Cross-References

- [Bayesian Inference with Spiking Neurons](#)
- [Boltzmann Machine](#)
- [Cortical Function, Normative Models of](#)
- [Hierarchical Models of the Visual System](#)

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Preference Mapping

- [Choice Behavior](#)

Preparatory Set

- [Decision-Making, Motor Planning](#)

Pressure-Difference Receiver

- [Internally Coupled Ears \(ICE\): Biophysical Consequences and Underlying Mechanisms](#)

Pressure-Gradient Receiver

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Probabilistic Models of Cognition

- [Cognition, Bayesian Models of](#)

Propagator, Axonal

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Synonyms

[Equivalent partial differential equations \(PDEs\); Green's function, axonal](#)

Definition

The axonal propagator is an operator that is applied to the initial state of a neural field variable and predicts the spatiotemporal spread of neural activity as a function of axonal distribution. It is most commonly represented as an integral operator over the axonal distribution function and the associated time delay via signal transmission. The axonal propagator is used to mathematically capture the connectivity across neuronal ensembles and derive the evolution equations of network activity.

Detailed Description

Historical Remarks

Beurle (1956) and Griffith (1963, 1965) were among the first to formulate spatially continuous evolution equations for neural fields. Wilson and Cowan (1972, 1973) and Nunez (1974) extended the neural field populations to include excitatory and inhibitory populations, refractoriness, and signal transmission delays. For specific axonal distributions, Amari (1977) obtained detailed results on pattern formation phenomena when neglecting the time delays of the axonal propagator. Jirsa and Haken (1996) generalized the expression of the axonal propagator, unified various neural field formulations, and derived its partial-differential-equation (PDE) equivalent for translationally invariant axonal distributions.

Later developments include extensions to translationally variant (Jirsa and Kelso 2000) and patchy propagators (Robinson 2006), propagators with axonal velocity distributions (Bojak and Liley 2010), and applications to large-scale brain dynamics as observed, among others, in anesthesia, gamma oscillations, epilepsy, sleep, resting state, and event-related potentials.

Mathematical Definition

Let $\psi(x, t) \in \mathbb{R}^N$ be the neural field capturing the activity of an N -dimensional neuronal population at location x and time t . The spatial domain of the neural field is denoted by Γ , which is typically a one- or two-dimensional space. The evolution in space and time of the neural field can then be described by

$$\dot{\psi}(x, t) = N(\psi(x, t)) + \int_{\Gamma} G(x, y, t - t' - \tau(x, y)) S(\psi(y, t')) dy dt'$$

where the dot designates the first time derivative, $N(\psi(x, t))$ is the local nonlinear dynamics of the neuronal population at location x , $S(\psi(y, t'))$ is the nonlinear transfer function of the neural activity generated at location y and past time point t' where $t' < t$, and $\int_{\Gamma} \int_{\Gamma} dy dt' G(x, y, t - t' - \tau(x, y))$ is the

axonal propagator. The integral kernel of the propagator factorizes into two functions, the axon distribution function $W(x, y)$ and the associated time-delayed Dirac delta function $\delta(t - t' - \tau(x, y))$, providing $G(x, y, t - t' - \tau(x, y)) = W(x, y)\delta(t - t' - \tau(x, y))$. The integral kernel G is also known as Green's function.

Equivalent Partial-Differential-Equation (PDE) Approach

Under the condition of translational invariance in physical space, $W(x, y) = W(|x - y|)$, the Volterra integral formulation of the neural field equation can be transformed into a fully equivalent PDE formulation (Jirsa and Haken 1996).

Derivation (Jirsa and Haken 1996)

With the integral kernel $W(|x - y|)\delta\left(t - t' - \frac{|x - y|}{v}\right)$ of the axonal propagator and linearization of the local dynamics around the equilibrium point, $N(\psi(x, t)) = -\frac{1}{\tau_0}\psi(x, t)$, the linear neural field equation reads

$$\dot{\psi}(x, t) = -\frac{1}{\tau_0}\psi(x, t) + \int_{\Gamma} W(|x - y|)\delta\left(t - t' - \frac{|x - y|}{v}\right) S(\psi(y, t')) dy dt' \quad (1)$$

Transforming into Fourier space, $(x, t) \rightarrow (k, \omega)$, the neural field equation reads then

$$i\omega\psi(\omega, k) = -\frac{1}{\tau_0}\psi(\omega, k) + G(\omega, k)S(\omega, k)$$

If the local dynamics is sufficiently fast as compared to the time scale characteristic for the axonal propagator, then the time derivative on the left-hand side of the equation can be adiabatically ignored. The expressions of neural field equation can be rearranged as $\psi(\omega, k) = G(\omega, k)S(\omega, k)$ where we set $\tau_0 = 1$ for simplicity. Splitting $G(\omega, k)$ into numerator and denominator, $G(\omega, k) = \frac{P(\omega, k)}{Q(\omega, k)}$, we obtain $Q(\omega, k)\psi(\omega, k) = P(\omega, k)S(\omega, k)$.

The expressions $Q(\omega, k)$ and $P(\omega, k)$ are completely determined by the axonal propagator, in particular the properties of the axonal and delay distributions. We perform another Fourier transformation back into physical space-time and make the following identifications: $(ik, i\omega) \rightarrow \left(\frac{\partial}{\partial x}, -\frac{\partial}{\partial t}\right)$ where the latter denote the partial derivatives with respect to space and time, respectively. Then, the above neural field equation can be expressed through the equivalent PDE formulation

$$\sum_{i,j} q_{ij} \frac{\partial^i}{\partial t^i} \frac{\partial^j}{\partial x^j} \psi(x, t) = \sum_{i,j} p_{ij} \frac{\partial^i}{\partial t^i} \frac{\partial^j}{\partial x^j} S(\psi(x, t)) \quad (2)$$

where q_{ij}, p_{ij} are constant coefficients.

Special Cases in 1D and 2D with Exponential Distributions

For the special 1D case of exponential distribution of axonal fiber length, $W(|x - y|) = \frac{1}{2\sigma} \exp(-|x - y|/\sigma)$, where $x, y \in \mathbb{R}$, the corresponding PDE is the Jirsa-Haken equation:

$$\left(\frac{\partial^2}{\partial t^2} + 2\omega_0 \frac{\partial}{\partial t} + \left(1 - v^2 \frac{\partial^2}{\partial x^2} \right) \right) \psi(x, t) = \omega_0 \left(\omega_0 + \frac{\partial}{\partial t} \right) S(\psi(x, t))$$

with $\omega_0 = \frac{v}{\sigma}$.

For the special 2D case of exponential distribution of axonal fiber length, $W(|x - y|) = \frac{1}{2\pi\sigma^2} \exp(-|x - y|/\sigma)$, where $x, y \in \mathbb{R}^2$, the corresponding PDE reads

$$\left(\frac{\partial^2}{\partial t^2} + 2\omega_0 \frac{\partial}{\partial t} + \left(1 - v^2 \frac{\partial^2}{\partial x^2} \right) \right)^{3/2} \psi(x, t) = \omega_0^2 \left(\omega_0 + \frac{\partial}{\partial t} \right) S(\psi(x, t))$$

with $\omega_0 = \frac{v}{\sigma}$.

Expansions

Axonal and velocity distributions shape Green's function of the axonal propagator and have been addressed for various configurations. For short fiber lengths the integral kernel in (1) can be expanded into a Taylor series and truncated for higher orders (Jirsa 2009), which is equivalent to a truncation of the order of differentials in (2). Equivalently, in Fourier space, the expressions of the neural field equation and the axonal propagator can be rearranged as $G(\omega, k) - {}^1\psi(\omega, k) = S(\omega, k)$ and expanded via a slow-wave approximation giving the same results (Jirsa 2009). Distributions of short-range excitatory and longer-range inhibitory fibers result in a Mexican hat distribution function of the axonal propagator, which then causes the following PDE:

$$\frac{\partial}{\partial t} \psi(x, t) = N(\psi(x, t)) + D_1 \frac{\partial^2}{\partial x^2} \psi(x, t) - D_2 \left(\frac{\partial^2}{\partial x^2} \right)^2 \psi(x, t)$$

resembling essential features of pattern formation dynamics as known from the Swift-Hohenberg equation. The latter is known to give rise to self-sustained spatial patterns thought to be involved in working memory. Other modifications of the axonal propagator include periodic modulations of the integral kernel mimicking connectivity properties such as are seen in the visual cortex (Robinson 2006), enabling the generation of features including orientation preference and wave number selectivity. Bojak and Liley (2010) extended the axonal propagator to include axonal velocity distributions and suggested that longer fibers tend to have higher transmission speeds.

Applications

Initial applications focused on the approximation of symmetric axonal distributions, resulting in translationally invariant axonal propagators. Jirsa and Haken (1996, 1997) discussed sensorimotor coordination phenomena in their original work. Using a modified Bessel function of 2nd kind in the propagator, Robinson et al. (1997) derived the Jirsa-Haken equation and added a corticothalamic circuit with time delay to explain spectral features of spontaneous activity. Later work expanded these results in much detail (Breakspear et al. 2003; Freyer et al. 2011; Wright and Liley 1995, 1996, Liley et al. 1999; Robinson et al. 2001b), as well as other applications including evoked potentials (Robinson et al. 2001a), anesthesia (Bojak and Liley 2005; Hutt 2013), and epilepsy (Breakspear et al. 2006). Independent of any neurobiological motivation, researchers have also explored the pattern-forming capacities of neural fields for artificially designed axonal propagators to study generic principles of spatiotemporal pattern formation and computation (Laing 2005). It was noted early on that the translationally invariant symmetry imposed on the axonal propagator will constrain the possible range of dynamic solutions (Jirsa et al. 2002) and further extensions will be needed accommodating the translational variance of the axonal propagator, $G(x, y, t - t' - \tau(x, y)) \neq G(|x - y|, t - t' - \tau(x, y))$. Such extensions are nowadays at the core of

connectome-based modeling efforts (see Deco et al. (2011, 2013) for reviews) and are integrated in modern neuroinformatics efforts as pioneered by Bojak et al. (2010, 2011) and The Virtual Brain (Sanz Leon et al. 2013).

Cross-References

- [Amari Model](#)
- [Anesthesia, Neural Population Models of](#)
- [Collations of Connectivity Data on the Macaque Brain \(CoCoMac\)](#)
- [Dynamic Causal Modelling with Neural Population Models](#)
- [Epilepsy, Neural Population Models of](#)
- [Gap Junctions, Neural Population Models and](#)
- [Human Connectome Project](#)
- [Mesoscopic Anatomy and Neural Population Models](#)
- [Multiscale Brain Connectivity](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Model](#)
- [Neuroimaging, Neural Population Models for](#)
- [Pattern Formation in Neural Population Models](#)
- [Synaptic Connectivity in Neural Population Models](#)
- [Synaptic Dynamics: Overview](#)
- [Wilson-Cowan Model](#)

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information about the limb's actual position (Sober and Sabes 2003). Any discrepancy between the two signals can be used to adjust the motor command to correct the course of the limb trajectory. The importance of proprioception in movement is especially apparent in patients with impaired proprioception; these patients tend to display highly uncoordinated movements despite having an intact motor system. The movements of these patients are slow, jerky, and usually inaccurate (Sacks 1985). If the proprioceptive impairment is temporary and the sense is able to be restored, movements become normal again.

Proprioceptors

There are several types of proprioceptive receptors (Fig. 1), located in the muscles, in the skin, and in the joint capsules. Muscle proprioceptors, which are thought to be the primary contributors to proprioception, come in two types: muscle

Proprioception

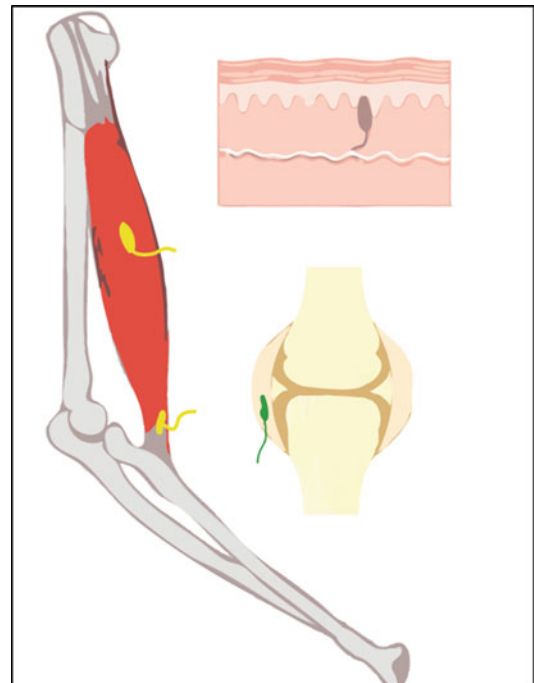
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Definition

Proprioception is the awareness of the position and movements of one's body.

Detailed Description

Proprioception refers to the sense of one's body, in particular, the position of body parts relative to each other, as well as their movements through space. Proprioception plays an important role in the planning and execution of actions. Indeed, during goal-directed motor behavior, the estimation of the limb's position derived from the signals in motor cortex is compared with proprioceptive



Proprioception, Fig. 1 Proprioceptors can be found in the muscles (*left*), in the skin (*top*), or in the joint capsules (*bottom*)

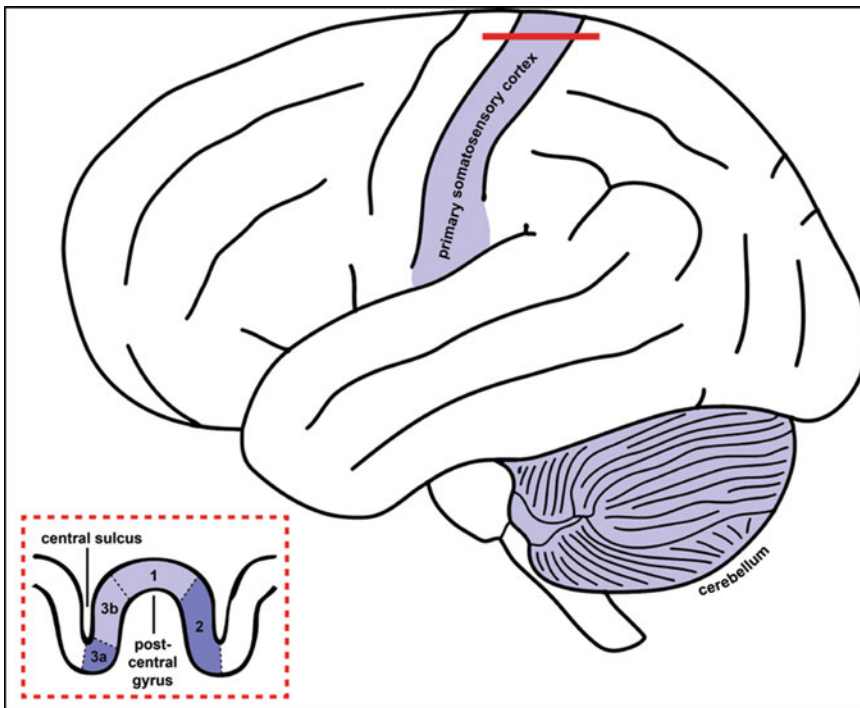
spindles and Golgi tendon organs. Muscle spindles convey information about the rate of change in a muscle's length. They are innervated by gamma motor neurons which, upon activation, can modify the sensitivity of the muscle spindles. Golgi tendon organs signal muscle force generated by muscle contraction. The information signaled from muscle proprioceptors can be integrated to determine the position of the limbs (Goodwin et al. 1972; McCloskey et al. 1983).

One population of receptors in the skin is sensitive to skin stretch and has been implicated in proprioception (Wheeler et al. 2010). Indeed, when we flex a joint – say, the elbow – the skin on the outer aspect of the joint becomes tauter and stretch receptors that innervate that skin become activated. Conversely, when we extend that joint, those stretch receptors become less activated. Signals from these stretch receptors can then be used to infer joint position and movements. Another type of proprioceptor, the joint capsule receptor, signals joint positions during movement or static postures. However, these receptors typically fire

only at the extreme ends of the joint's range and may only be involved in providing a signal geared toward preventing overextension of the joint (Clark and Burgess 1989). Signals originating from either skin or joint capsule proprioceptors probably play a secondary role to that of muscle proprioceptors, as when the former are removed, proprioception is only slightly degraded (Edin and Johansson 1995; Goodwin et al. 1972).

Pathway

Information about the limb's position and movements is signaled from the proprioceptors and is carried to the brain by long, pseudo-unipolar afferents. These afferents relay the signals into and up the ipsilateral dorsal column of the spinal cord. These axons synapse onto the dorsal column nuclei in the brainstem. Projections from these nuclei cross the midline at the medulla oblongata and synapse onto the contralateral ventral posterior lateral nucleus of the thalamus. From the



Proprioception, Fig. 2 Primary somatosensory cortex (S1) and the cerebellum receive proprioceptive signals

thalamus, the signals are then projected to cortex. Proprioceptive signals are also used to maintain postural stability during sitting, standing, simple gait tasks, or other movements or postures that do not require volitional control (Johnson et al. 2008). These signals also travel up the dorsal column of the spinal cord through the brainstem but terminate in the ipsilateral cerebellum.

Proprioception in the Brain

Proprioceptive neurons in the thalamus project to areas 3a and 2 in primary somatosensory cortex (S1) (Fig. 2). Area 3a is located in the rostral bank and fundus of the central sulcus and borders both primary motor cortex (area 4) and area 3b, an area in S1 which receives primarily cutaneous input. Area 3a is implicated in sensorimotor integration given its proximity to and its dense reciprocal connections with motor cortex. In contrast, area 2 is located in the caudal region of the postcentral gyrus and receives both proprioceptive and cutaneous input, the latter most likely via projections from areas 3b and 1, two primarily cutaneous areas. Area 2 is thought to play a role in combining both cutaneous and proprioceptive inputs to achieve a three-dimensional percept of the position of the limbs and what those limbs are contacting. The cerebellum mediates aspects of proprioception required for the coordination and timing of movement.

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Further Reading

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Proprioceptive Feedback to Central Pattern Generators

► Sensory Input to Central Pattern Generators

Proprioceptor Models

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Definition

Charles Sherrington coined the term “proprioception” to describe the sensing of the body’s own movements (Sherrington 1907). He included receptors of the vestibular apparatus as well as receptors in deep tissues such as muscles in his definition. Proprioceptive signals are an important component of feedback to the CNS for the control of posture and movement. Input to the spinal cord from proprioceptors influences the activity of muscles via reflex connections to motoneurons. It is also conveyed to structures in the brainstem, midbrain, cerebrum, and cerebellum involved in motor control. Neuromechanical models

incorporating proprioceptive feedback have become increasingly influential in the understanding of the neural control of movement.

Detailed Description

In 1834, Charles Bell proposed that mammalian muscles contain sensory receptors that mediated both a “muscle sense” underlying the subconscious control of movement (Bell 1834) and the conscious sensation of position and movement of limbs, later termed “kinesthesia” (Bastian 1888). Bastian argued that not only muscle receptors but also cutaneous receptors contribute to kinesthesia (Bastian 1888).

Proprioception in Invertebrates

Several important aspects of our understanding of motor control have come from studies of invertebrates. Invertebrates have sensory receptors that in some cases bear an uncanny resemblance to mammalian proprioceptors. For example, crustacean thoracicocoxal muscle receptor organs have two types of sensory afferents, as do mammalian muscle spindles (Bush 1981). Furthermore, their sensitivity is controlled by two types of efferent motoneurons, similar to the fusimotor neurons that control the sensitivity of mammalian muscle spindle afferents. Neuromechanical models of sensory inputs and muscle responses in invertebrates have been reviewed elsewhere (Pearson et al. 2006; Zill et al. 2012). This entry will focus on models of proprioception in mammals.

Properties of Mammalian Proprioceptors

In mammals, proprioception is mediated by muscle spindles (Hulliger 1984), Golgi tendon organs (Proske and Gregory 2002), joint receptors (Johansson et al. 1991), and skin receptors (Zehr and Stein 1999). The human upper extremity contains about 4000 muscle spindles, 2500 Golgi tendon organs, and a few hundred joint receptors

(Barker et al. 1962; Hulliger 1984; Voss 1971). Cutaneous receptors far outnumber those in muscles, tendons, and joints: the human hand alone has around 17,000 myelinated cutaneous afferents (Johansson and Vallbo 1979). However, only a small proportion of these respond to skin stretch around joints, thus providing proprioceptive information.

Muscle Spindles

Nearly all mammalian muscles contain fusiform receptors called muscle spindles (Hulliger 1984; Prochazka 1996). The average number of spindles in a muscle is roughly $38 \times (\text{cube root of mass in grams})$ (Banks and Stacey 1988; Hulliger et al. 1985; Prochazka 1996). Thus, a 64 g muscle contains about 152 spindles. A typical muscle spindle is 0.5–10 mm long and consists of 6–10 “intrafusal” muscle fibers attached at each end to the surrounding “extrafusal” muscle fibers. Intrafusal muscle fibers do not contribute significantly to the force developed by the muscle’s extrafusal fibers. Their only role is to control the stretch sensitivity and offset firing rate (“bias”) of the spindle’s sensory afferents.

The muscle spindle has a central noncontractile sensory region innervated by one or two group Ia afferent axons, each terminating in a primary sensory ending and up to five group II afferents terminating in secondary sensory endings. Each spindle is also innervated by 10–12 γ -fusimotor axons and often by a β -skeletofusimotor axon, which also innervates extrafusal muscle fibers.

In the absence of fusimotor activity, group Ia and II afferents respond to changes in muscle length and velocity. There is a continuum from the smallest diameter group II afferents with low velocity sensitivity to the largest diameter Ia afferents with high velocity sensitivity. Group Ia and II afferents both have nonlinear aspects of response, e.g., sensitivity to small-amplitude length changes that is much larger than that to large-amplitude length changes, a power-law dependence of Ia firing on velocity, stretch sensitivity that depends on mean muscle length, history-dependent initial burst responses, a decline in velocity-sensitive response during shortening that is greater than the increase during lengthening, creep (a slow

decline in firing after a stretch during γ_d action), and competition (occlusion) between effects on Ia firing of different γ efferents (Hulliger 1984; Prochazka 1996). These nonlinearities pose problems for modeling.

Most mammalian muscle spindles contain three types of intrafusal muscle fiber: a dynamic bag₁ (DB1 or b₁), a static bag₂ (SB2 or b₂), and 2–11 chain (c) fibers. The dynamic b₁ fiber is selectively activated by dynamic fusimotor (γ_d) or β_d skeletofusimotor axons, though b₂ and chain fibers may sometimes be co-activated (Emonet-Denand et al. 1977). The b₂ and chain fibers are activated by static fusimotor (γ_s) or skeletofusimotor (β_s) axons. More details of intrafusal and fusimotor subdivisions in different species are available elsewhere (Matthews 2011).

By contracting and stiffening b₁ intrafusal muscle fibers, γ_d action imparts more stretch to the sensory region, increasing Ia afferent stretch sensitivity (“gain”) up to fivefold, except when muscle displacements are so small that some intrafusal cross-bridges remain attached. γ_d action also causes a small increase in Ia offset firing (bias) (Emonet-Denand et al. 1977). The phase of responses to sinusoidal stretching is little changed, i.e., gain is increased in the absence of a change in phase, which is important from a modeling point of view. Strong γ_s action adds a large bias to both Ia and II afferent firing rates, attenuates Ia stretch sensitivity by up to 50 %, but increases group II afferent gain up to twofold. Paradoxically, weak γ_s action can *increase* rather than decrease Ia gain (Hulliger et al. 1985). The terms dynamic and static fusimotor action are in fact misleading, in that both types alter mainly the gain and offset rather than the dynamics of group Ia and II responses to stretch. An interactive animation of some of these interactions is available online (Kowalczewski and Prochazka 2006).

There is still considerable disagreement on the way the CNS uses γ -motoneurons to control the offset and gain of muscle spindles during voluntary movement, which is a major problem for modelers. This will be discussed again below.

Golgi Tendon Organs (GTOs)

These are encapsulated structures 0.2–1 mm long, usually located at musculotendinous junctions (Barker 1974). There are about 80% as many GTOs in a typical limb muscle as spindles. Their sensory endings, which become group Ib afferent axons, are entwined among the tendinous strands of 10–20 motor units, a given motor unit affecting 1–6 tendon organs (Jami 1992; Proske 1981). Unlike spindles, GTOs do not have a mechanism akin to fusimotor action to modulate their sensitivity. Ib afferents can have a high threshold to stretch of the inactive muscle but respond sensitively to force actively generated by the motor units with which they are associated (Houk and Henneman 1967; Stephens et al. 1975).

Though individual tendon organ afferents signal increasing muscle force with steps in firing rate corresponding to the progressive recruitment of motor units, when the firing of several Ib afferents is summed, the net ensemble firing rate is monotonically related to whole muscle force (Prochazka and Gorassini 1998a).

Recently, it was shown that the inclusion of signals from Ib afferents along with those from spindle afferents improved the discrimination of different muscle stretches (Bergenheim et al. 1996). In a study of human grasp (Dimitriou and Edin 2008), the decoding of velocity by muscle spindle afferents was improved by including the firing rates of tendon organ afferents. Because tendons lengthen during muscle contraction, muscle spindles “see” a distorted version of muscle length changes, so tendon organ information could be used to correct for this in proprioception (Kistemaker et al. 2013).

Cutaneous Receptors

Slowly adapting type II and III cutaneous receptors located over or near limb joints respond to the stretching of skin during movement, their firing rates correlating well with a weighted sum of joint angle and joint angular velocity (Aimonetti et al. 2007; Clark et al. 1979; Edin 2001; Edin and Johansson 1995). In fact their signals may be more closely related to joint rotations than those of muscle spindle afferents, which as we have seen above are affected by tendon strain and

fusimotor efferent activity, which varies during active movement in ways that are not fully understood (Aimonetti et al. 2012). Stimulating cutaneous afferents can produce movement illusions (Collins and Prochazka 1996; Edin and Johansson 1995), and anesthetizing them reduces kinesthetic acuity (Lowrey et al. 2010), suggesting an important role in proprioception and kinesthesia.

Joint Receptors

Stretch receptors in joint capsules were initially assumed to signal joint rotation over the full range of motion (Boyd and Roberts 1953) until two research groups reported that most joint receptors were unresponsive in the midrange (Burgess and Clark 1969; Tracey 1979). Subsequent work indicated that at least some joint receptors do signal over the full range of motion (Carli et al. 1979; Ferrell 1980; Ferrell et al. 1987; Godwin-Austen 1969; Lund and Matthews 1981; Zalkind 1971), though some of these may have been muscle spindles or tendon organs in nearby muscles (Clark et al. 1985; Gregory et al. 1989; McIntyre et al. 1978). Loading of the joint capsule may be necessary to sensitize joint receptors enough to confer midrange responsiveness on them (Grigg and Greenspan 1977). Most joint afferents have group II conduction velocities (Burgess and Clark 1969), and their reflex connections with α -motoneurons are polysynaptic and relatively weak (Johansson et al. 1991). They may have a special role in inhibiting muscles when joints are damaged (Iles et al. 1990).

Models of Proprioceptors

Muscle Spindle Models

Numerous muscle spindle models have appeared in the literature (summarized in Table 1). It has been claimed that these models fall into one of two categories: early “black box” models comprising input–output functions fitted to experimentally obtained Ia or II afferent responses to length changes and later “structural models” based on the mechanical interaction between the sensory transducer component of the spindle and the intrafusal muscle component (Lin and Crago

2002b; Mileusnic et al. 2006; Schaafsma et al. 1991). This is a little unfair, as sensory transducer properties and the role of intrafusal mechanics were in fact taken into account in the development of even the earliest spindle models (Chen and Poppele 1978; Crowe 1968). The progression of modeling should rather be described as a series of refinements in which fusimotor action and various nonlinearities associated with different components of the spindle were progressively included, resulting in better fits to experimental data but also in an increase in the number of free parameters.

The first spindle models were linear transfer functions developed to fit the passive responses of Ia afferents to triangular and sinusoidal length changes and to sudden increments and decrements in fusimotor stimulation (Andersson et al. 1968; Crowe 1968; Lennerstrand 1968). Ia firing rate was modeled adding length and velocity terms. The Andersson model added a second length term, the gain of which depended on velocity (Table 1 top row). Andersson’s fusimotor response model (not shown in Table 1) comprised a single-pole low-pass filter and an impulse generator. Matthews and Stein published a simplified version of these models, a single-zero high-pass filter with a turning point of 1.5 Hz (Matthews and Stein 1969). Further refinements of the transfer function models were introduced by Poppele’s group, with the addition of poles and zeroes that took into account slower adaptive components of Ia afferent response (Chen and Poppele 1978; Poppele and Bowman 1970; Table 1). Interestingly, whereas an additional term, $(s + 4)$, was required to fit the small-amplitude Ia model to large-amplitude data (Table 1), the linear transfer function developed for group II afferents fitted the empirical data for both small and large amplitudes of stretch (Poppele and Bowman 1970). A slightly different Ia model was published by Terzuolo’s group (Chen and Poppele 1978; Rosenthal et al. 1970). The fits of these Ia models to empirical frequency response data were not compared head-to-head, but their Bode plots are quite similar.

The nonlinearities mentioned above were discussed by all of these authors, particularly the dependence of Ia stretch sensitivity on muscle

Proprioceptor Models, Table 1 Models of the mammalian muscle spindle

Source	Equation	Definitions	Fusimotor action	Comments
Crowe (1968)	Spindle group Ia $r(s) = \frac{E_2 + V_2 s}{E_1 + E_2 + V_2 s} x(s)$	r: firing rate	γ_d modeled by increasing V_2 (velocity sensitivity) γ_s modeled by increasing E_2 (bias)	Developed on the basis of prior experiments with P.B.C. Matthews
		s: Laplace operator		
		E_1, E_2 : elastic moduli		
		V_2 : viscosity x : length		
Andersson et al. (1968); Lennerstrand (1968)	Spindle group Ia $r(s) - r_0 = k\Delta x + \frac{gs}{1+st} \Delta x + h\Delta x$	$r(s)$: firing rate	Modeled by increasing k, g, and h	Because T, the time constant of developing the velocity response to the onset of a ramp, is ~0.2 s, the second term could be viewed as a simple velocity response
		r_0 : firing rate at x_0		
		k, g: length and velocity gains		
		Δx : length increment		
		T: time constant h: velocity-dependent length gain		
Matthews and Stein (1969)	Spindle group Ia $r(s) = kx(s + 10)$	r: firing rate	Scaled by k	Simplified version of the Crowe and Andersson models. Small amplitude
		x: muscle length		
		k: gain		
Rudjord (1970)	Spindle group Ia $r(s) = \frac{kx(1+a_1s+a_2s^2+a_3s^3)}{1+b_1s+b_2s^2+b_3s^3}$	r: firing rate	Scaled by k	Frequency domain
		x: muscle length		Mechanical model
		a_1 – a_3 , b_1 – b_3 : parameters		>20 parameters
Poppele and Bowman (1970)	Spindle group Ia $r(s) = \frac{k_1xs(s+0.44)(s+11.3)(s+44)}{(s+0.04)(s+0.82)}$	r: firing rate	Scaled by k_1 and k_2	Frequency domain
		k_1, k_2 : gains		No offset term
	Spindle group II $r(s) = \frac{k_2xs(s+0.44)(s+11.3)}{(s+0.82)}$	x: muscle length		Small amplitude
Rosenthal et al. (1970)	Spindle group Ia $r(s) = \frac{kx(s+0.44)(s+0.17)(s+11.3)(s+200)^2}{(s+0.82)(s+2.7)}$	r: firing rate	Scaled by k	Modification of the Poppele model
		k: gain		
		x: muscle length		
Chen and Poppele (1978)	Spindle group Ia $r(s) = \frac{kxs(s+0.4)(s+4)(s+44)}{(s+0.04)(s+0.8)}$	r: firing rate	Scaled by k	Frequency domain
		k: gain		No offset term
		x: muscle length		Large-amplitude stretch
Holm et al. (1981), Schafer (1973)	$r(t) = kv(t)^n$	r: firing rate, time t	Scaled by k	Time domain
		k: gain (12.6 $\pm$ 10.5)		r is a power function of velocity
		v(t): muscle velocity		No offset term

(continued)

Proprioceptor Models, Table 1 (continued)

Source	Equation	Definitions	Fusimotor action	Comments
		n: 0.56 ± 0.17		Large-amplitude stretch
Houk et al. (1981)	Spindle group Ia and II	r: firing rate, time t	Scaled by k	Time domain
	$r(t) - r_0 = k(x - x_1)v^n$	r_0 : firing rate at x_0		Power function of velocity scaled by length
		x, v: muscle length, velocity		Large-amplitude stretch
		x_1 : extrapolated length		Ia and II afferents modeled by the same equation but with different parameters
		v: muscle velocity		
		k: gain		
		n: 0.21 to 0.39		
Hasan (1983)	Spindle group Ia and II	r: firing rate, time t	γ_d and γ_s action simulated by trial-and-error setting of parameters a, b, c, h	Ia and II afferents modeled by the same equation but with different parameters.
	$r(t) = h(\mu + p\mu)$	x: muscle length		Nonlinear relationship requiring numerical solution, e.g., with MATLAB/Simulink
	where $\mu = \frac{(x-c)(1+v^{0.3})}{b+v^{0.3}}$			
	and $V = \left(\frac{\bar{x}-\bar{\mu}}{a}\right)^{0.3}$	$\bar{x}$: muscle velocity		
	and $\bar{\mu} = \bar{x} + \frac{a(b\bar{\mu}-x+c)^3}{(\bar{\mu}-x+c)^3}$	μ : velocity-dependent strain of sensory region		
	and $\bar{\mu} = \bar{x} + a\left(\frac{b\bar{\mu}-x+c}{\bar{\mu}-x+c}\right)^3$	a, b, c, h, p: parameters		
Schaafsma et al. (1991)	Complex model not completely specified in the reference	N/A	γ_d and γ_s action simulated by trial-and-error setting of parameters	Mechanical interaction between muscular and sensory portions of two types of intrafusal fiber
Prochazka (1999)	Spindle group Ia:	r: firing rate, time t	γ_s biasing action modeled by EMG term. γ_d modeled by gain factors a and b	Modified version of Schafer and Houk models
	$r(t) = av^n + bx(t) + c + d(EMG(t))$	x, v: muscle length, velocity		Tested on Ia afferent firing rates in normal locomotion and ramp-and-hold stretches
		b: length gain		
		c: offset rate		
		d: % maximal EMG		
		n: 0.5 or 0.6		

(continued)

Proprioceptor Models, Table 1 (continued)

Source	Equation	Definitions	Fusimotor action	Comments
Lin and Crago (2002b)	Spindle group Ia and II, complex model not completely specified in the reference	N/A	Three types of intrafusal fiber with individual Hill-type models	89 parameters
Maltenfort and Burke (2003)	$r(t) = r_p + \Delta r_\gamma$	r: firing rate, time t	Occlusion between γ_s and γ_d action included in additional equations	Based on the Andersson and Lennerstrand models
	$r_p = (S_p(v_f) + S_{ss})x + Q_p(v_f)$	r_p : passive Ia response		Power-law relationship between velocity gain parameters Q and velocity
	$\Delta r_\gamma = (S_{v,g}(\gamma, v_f) + S_{ss,g}(\gamma))x + Q_g(\gamma, v_f) + B(\gamma)$	x: muscle length		
		Δr_γ : Ia rate due to γ		
		$S_p(v_f)$: length gain f(v)		
		v_f : filtered velocity		
		S_{ss} : passive length gain		
		Q_p : passive velocity gain		
		$S_{v,g}$: length gain f (γ, v_f)		
		$S_{ss,g}$: length gain f (γ)		
		Q_g : velocity gain f(γ)		
Mileusnic et al. (2006)	Complex model not completely specified in the reference	N/A	Partial occlusion between γ_s and γ_d action included	Power-law relationship of Ia rate and velocity. Tendon strain during active movement included

velocity, the high stretch sensitivity to very small muscle length changes (<2% muscle strain), and the initial burst response at the onset of large ramp stretches. These latter two behaviors are related and have been attributed to the formation of stable cross-bridges in resting intrafusal muscle fibers that are then ruptured when muscle strain exceeds 2% (Morgan et al. 1984). They are not present in cyclical movements or during fusimotor drive, and yet much attention was paid to them in some of the later, more complex models.

In a study in which six of the simpler models were compared (Prochazka and Gorassini 1998b), the linear transfer function models performed reasonably well when tested on simulated Ia responses to slow ramp-and-hold stretches like those used by Lennerstrand et al. However,

when tested on Ia firing rates recorded in normal locomotor movements, the r^2 values obtained with the Matthews and Stein model were in the range 0.41–0.58, which was well below the range 0.83–0.94 achieved by the more recent models tested.

One of the reasons the later models performed better was that some of them incorporated a power-law relationship between muscle velocity and Ia firing rate (the peak muscle velocities in the locomotor data were much higher than those in the acute experiments upon which linear models had been based). A nonlinear Ia response to stretch velocity had been noted in the late 1960s (Matthews 1963), and a power-law relationship was proposed in the early 1970s (Schafer 1973), but it was not until the work of Houk and

colleagues a decade later that it became generally accepted. Schafer and colleagues reported a mean value of 0.56 of the exponent in their power-law function (see Table 1), and this produced better fits to the data in awake animals (Prochazka and Gorassini 1998b) than the value 0.3 proposed later (Houk et al. 1981). A simple way of thinking of Schafer's relationship is that the Ia response to length changes is approximately proportional to the square root of muscle velocity. The Schafer model does not include an offset term, and this omission was remedied by Houk and colleagues (Hasan 1983; Houk et al. 1981), who also proposed a scaling of the velocity response by muscle length.

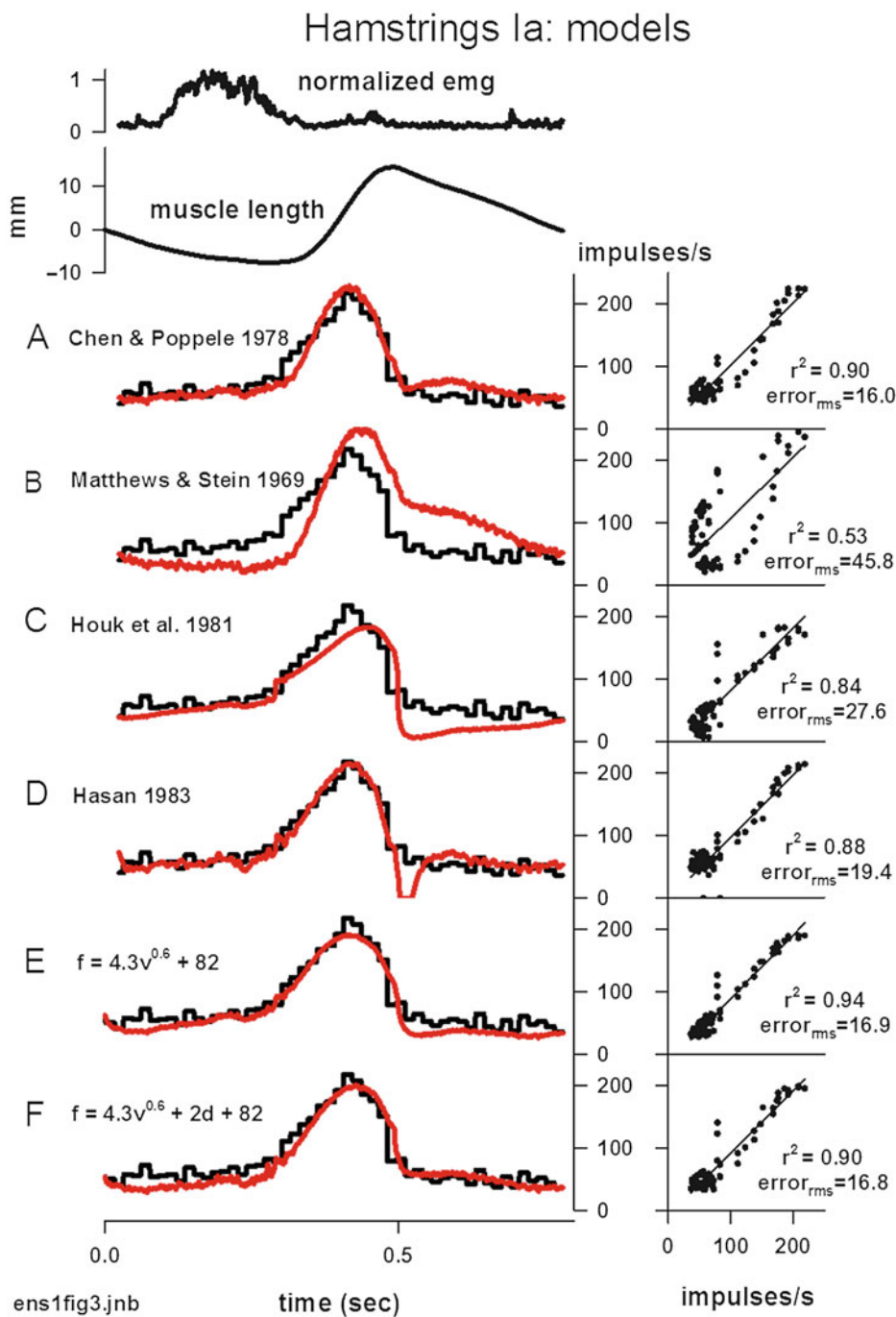
Hasan's model, based on biomechanical considerations, incorporated nonlinear elements, including a velocity^{0.3} term. The main new feature here was a term that modeled the initial burst response of Ia afferents to ramp stretches, but as pointed out above, this behavior only occurs in muscle stretches that start from rest and is inappropriate for rhythmical movements. The Houk and Hasan Ia models performed well in the tests on the normal locomotor data but only after the velocity exponent was changed from 0.3 to 0.6 (Schafer 1973), after the models were adjusted to cope with negative velocities (i.e., muscle shortening), and after parameter values had been selected by trial and error, in particular to reduce the initial burst component. The modified Hasan model overemphasized the fall in Ia firing rate when muscle velocity changed from positive to negative, a situation for which the original model had admittedly not been developed. Fusimotor action was not explicitly included in either of these models, though it was pointed out that this could be done by altering parameters.

The next development was a neuromechanically based model that included separate inputs to intrafusal muscles from static and dynamic fusimotor neurons (Schaafsma et al. 1991). It also included a stiction component that produced initial burst responses. An all-or-nothing competition between the two fusimotor inputs during lengthening and shortening (complete occlusion) was assumed. The model

had over 20 parameters, which, when adjusted appropriately, resulted in reasonable fits to data from acute experiments, but in the absence of tests on data from normal movements or quantitative comparisons with other models, it is difficult to judge the relative merits of this model. Implementing it with commercially available software was found to be a challenge (Maltenfort and Burke 2003).

As mentioned, some of the above models were compared in a study of afferent recordings obtained during voluntary locomotion in normal cats (Prochazka and Gorassini 1998b). The best fits were obtained with a fairly simple nonlinear model based on those of Schafer, Houk, and Hasan (Table 1; Fig. 1). This model assumed a constant level of γ_d action and a modest amount of γ_s action linked to muscle activation (represented by the rectified, smoothed electromyographic activity of the receptor-bearing muscle). Though this model may be adequate for neuromechanical models of locomotion, it may not generalize to other types of movement in which γ_d and γ_s activity may be elevated or vary phasically over a large range.

In 2002, a very detailed neuromechanical model of the muscle spindle was developed (Lin and Crago 2002b). This model took into account all of the nonlinearities mentioned above and ran in the widely used MATLAB/Simulink software environment. In defense of the complexity of the model and its large number of parameters (89), the authors argued that compared to previous simpler models, it was likely to be more accurate under a wide range of conditions, it could more easily be modified as knowledge was gained, and since the parameters did not vary with operating conditions, parameter estimates could be drawn from a wider pool of data rather than from one organism. The model was incorporated along with a Golgi tendon organ model into an analysis of the stretch reflex. Several features of empirically observed stretch reflexes were accurately simulated, including linearization effects and the dependence on operating force and initial muscle length. The model did not accurately predict the reflex responses at higher stretch velocities, evidently



Proprioceptor Models, Fig. 1 Comparison of the predictions of six models of muscle spindle Ia afferent responses. The target Ia firing rate (black trace repeated in panels A–F) was computed from individual firing rates of an ensemble of nine hamstrings Ia afferents recorded during locomotion in the normal cat. Top to bottom: Mean

muscle activity (EMG), muscle origin-to-insertion length, fitted firing profiles A–F: red lines superimposed on the target ensemble data. Right column: linear regressions of the target firing rate versus the firing rate predicted from the length signal by each model (From Prochazka and Gorassini (1998b))

due to failure of the extrafusal muscle model. Interestingly, underdamped “ringing” responses occurred in the simulated Ia, II, and Ib afferents and α -motoneurons, which might have resulted from exaggerated initial bursts, or too high a reflex loop gain.

In 2003, Maltenfort and Burke (2003) added explicit fusimotor action to the early transfer function models (Andersson et al. 1968; Crowe 1968; Lennerstrand 1968). A power-law relationship related firing rate to muscle velocity. The main aim of the study was to explore the positive feedback effect of β skeletofusimotor in stretch reflexes. In reflex simulations, it was found that β skeletofusimotor action produced significant increments in Ia afferent firing. This could either amplify existing γ drive or compensate for insufficient γ bias for the task at hand. The Maltenfort and Burke model has not been compared quantitatively with other models. It does have the advantage of relative simplicity. The omission of stiction effects in this model may paradoxically make it more suitable than some of its more complex competitors for modeling the neuromechanical control of movement.

The most recent model (Mileusnic et al. 2006) incorporates all of the known nonlinearities and also takes into account the fact that muscle spindles do not “see” all of the changes in muscle length that occur during voluntary movement, because stretching of the tendons in series with muscle accounts for some part of the changes in muscle length. The model has over 20 parameters, and because some of the equations did not have analytical solutions, stepwise simulations were performed in a MATLAB/Simulink environment. One of the strengths of this work is that the model was tested not only on data obtained in acute experiments but also on recordings from afferents and γ -motoneurons obtained in decerebrate cats walking on a treadmill (Taylor et al. 2000). With the appropriate handcrafting of parameters, the decerebrate data were well fitted. The very large fluctuations in γ activity that seem to characterize decerebrate locomotion provided a good test bed for the simulations. An interesting result in this study was that a velocity exponent of 0.3, as

suggested by Houk et al. (1981), gave better fits than the 0.5–0.6 values in other studies (Prochazka and Gorassini 1998b; Schafer 1973). It was pointed out by Mileusnic et al. that their model could in principle allow γ activity occurring in normal behaviors to be deduced from recordings from spindle group II afferents and, with some caveats, from spindle Ia afferents as well.

Golgi Tendon Organ Models

Few individual Ib afferents fire at a zero force level (Houk et al. 1971). Their firing rate jumps when a force threshold is reached, this threshold varying widely between Ib afferents in the same muscle. Individual Ib afferents are more sensitive to changes in muscle force when motor units with muscle fibers inserting into their receptor capsule are active (Jansen and Rudjord 1964). This results in steplike increases in firing rate with the progressive recruitment of each associated motor unit. When two motor units engaging a Ib afferent are stimulated together, the net rate of discharge is less than the sum of individual responses (Gregory et al. 1985). In acute experiments in which motor units were electrically activated, individual Ib firing rates saturated at high force levels, but when motor units were recruited physiologically during reflex contractions, the relationship between individual Ib firing rate and muscle force was remarkably linear (Crago et al. 1982).

As in the case of muscle spindle afferents, ensemble responses smooth out some of the nonlinear responses of individual Ib afferents. In the Crago et al. study, the firing rates of 19 individual Ib afferents were summed. The combined firing rate had a near-zero force threshold, and recruitment steps were absent. On the other hand, the aggregated firing rate saturated at high force levels even though most of the contributing Ib afferents had responded linearly. This is because more of the afferents were recruited at lower forces than at higher forces, and so their onset firing rates summed more at the lower end of the force range. This resulted in a logarithmic relationship between ensemble Ib firing rate and force (Lin and Crago 2002a; Table 2), though a recent model

Proprioceptor Models, Table 2 Models of GTOs and cutaneous afferents

Source	Equation	Definitions	Comments
Houk and Simon (1967)	$r(s) = \frac{kF(s+0.15)(s+1.45)(s+16)}{(s+0.2)(s+2)(s+37)}$	r: firing rate	Ensemble model
		s: Laplace operator	Frequency domain
		F: whole muscle force	No offset term
		k: gain (4N)	
Roberts et al. (1971)	$r(s) = \frac{kF(s+0.44)(s+1.7)(s+11.3)(s+126)^2}{(s+0.82)(s+2.7)} e^{-0.002s}$	r: firing rate	Ensemble model
		s: Laplace operator	Frequency domain
		F: whole muscle force	No offset term
		k: gain	Includes conduction delay
Anderson (1974)	$r(s) = \frac{F(s+0.63)(s+3.14)(s+25.1)(s+628)^2}{(s+0.82)(s+2)(s+3.88)} e^{-0.002s}$	r: firing rate	Ensemble model
		F: whole muscle force	No gain term
			No offset term
			Takes into account dependence of response on carrier frequency
Lin and Crago (2002a)	$r(s) = \frac{G_g \ln\left(\frac{F}{G_f} + 1\right)(s+0.15)(s+1.45)}{(s+0.2)(s+2)}$	r: firing rate	Ensemble model
		F: whole muscle force	Combines transfer function truncated from Houk and Simon (1967) with logarithmic static response term
		G_g : gain (60impulses/s)	
		G_f : gain (4)	
Mileusnic and Loeb (2006)	GTO Ib model	s: Laplace operator	
Edin (2001)	Cutaneous slowly adapting receptor model, joint angle	N/A	Individual receptor model
			Takes into account all nonlinearities in prior studies
			MATLAB/Simulink software platform
Edin (2004)	Cutaneous slowly and rapidly adapting FA receptor model, skin strain	r: firing rate, time t	Human neurography data
		ω : joint angle velocity	SAI, SAII, and SAIII receptors near the knee joint
		ω : joint angle	Response to active flexion-extension movements of the knee
		a, b: gains	
	$r(t) = a\omega + b\alpha + c$	c: offset (spontaneous rate)	
	$r(t) = av^n + c$	v: velocity of skin strain	SAI, SAII, SAIII, and FAI receptors
		a: gain	Refers to response during dynamic phase of a stretch causing strain velocity v
		n: exponent, <1	
		c: offset	

(continued)

Proprioceptor Models, Table 2 (continued)

Source	Equation	Definitions	Comments
Edin (1992, 2004), Knibestol (1975)	$r(t) = a\omega^n + b\alpha^m + c$	r: firing rate, time t	The static sensitivity term $b\alpha^m$ is derived from Knibestol (1975), with confirmatory data in Edin (1992). Skin strain is nonlinearly related to joint angle, possibly also with a power-law relationship (Edin 1992; Fig. 2)
		ω : joint angle velocity	
		α : joint angle	
		a, b: gains	
		c: offset (spontaneous rate)	
		n: velocity exponent, <1	
		m: exponent, <1	

suggested a power-law relationship (Mileusnic and Loeb 2009, Fig. 9).

Regarding the dynamics of Ib responses to time-varying forces, several transfer functions have been proposed (Table 2; Anderson 1974; Houk and Simon 1967; Roberts et al. 1971). These transfer functions all provided good fits to empirical data, though no quantitative comparisons were published. A slightly modified version of the Anderson transfer function gave a good fit to the firing profile of a Ib afferent recorded during imposed stretches in a conscious cat, in which the force applied had been monitored (Appenteng and Prochazka 1984). In another study, muscle force was reconstructed from the ensemble Ib firing rate recorded during voluntary locomotion, by using the inverse of the Houk and Simon model (Prochazka 1999). Interestingly, the form of the Ib transfer functions is similar to that of the transfer functions developed for muscle spindle group Ia and II endings (Poppele and Bowman 1970). This indicates that the transduction process in GTO receptor endings is similar to that in receptor endings in the muscle spindle, in spite of their very different morphology. Another similarity with spindle II afferents is that Ib afferents tend to fire fairly regularly, except at low levels of active force, when unfused twitch contractions of newly recruited motor units summate and “beat,” causing characteristic bursts of Ib firing (Jami 1992). In a recent model of the stretch

reflex, two of the terms in the Houk and Simon model were discarded, and the logarithmic non-linearity mentioned above was added (Lin and Crago 2002a; Table 2). This model of ensemble Ib firing is the most current and probably the most useful in relation to neuromechanical modeling of reflex and voluntary movement.

Modelers more interested in the specifics of the firing of individual Ib afferents are referred to a recent mechanical model that takes into account the types of motor units acting on a GTO, the order of their recruitment, adaptation of the sensory endings to the time course, and combination of motor unit inputs, occlusion between transduction regions, and other nonlinearities mentioned above (Mileusnic and Loeb 2006, 2009).

Cutaneous Receptor Models

The cutaneous receptors best suited to signal joint angle are slowly adapting type II receptors (SAII) which respond to stretching of the skin, in some cases several centimeters from the point of maximal skin strain (Edin 2001, 2004; Horch et al. 1977). Slowly adapting type I receptors (SAI) respond more locally, fire less regularly, and adapt more rapidly. Finally, there are at least four kinds of hair follicle and glabrous skin receptors which respond to dynamic components of hair deflection or skin stretch (Willis and Coggeshall 1991). Skin stress and strain over and near moving joints is directional, and the location and

orientation of cutaneous receptors determine their “preferred direction of firing,” i.e., the direction of skin strain and joint movement to which they respond best (Aimonetti et al. 2007; Edin 1992).

Mechanical analysis suggested that SA receptor firing recorded during skin indentation in monkeys was correlated with skin strain (Phillips and Johnson 1981). However, *in vitro* studies of patches of innervated rat skin indicated that SAI afferents respond to stress, rather than strain, at least under circumstances in which these variables were independent (Grigg and Del Prete 2002). During phasic joint movements, it seems reasonable to assume a covariation of stress and strain. Viscoelastic behavior such as “creep” could make these variables diverge in maintained positions of a limb.

In human studies in which recordings were obtained from cutaneous afferents with the use of percutaneous needle electrodes, SA afferents responded to skin indentation in a nonlinear manner, the static response being best fitted by a power function (Knibestol 1975). In a later human neurography study, ramp-and-hold stretching of the skin was imposed by a displacement servo with caliper-like prongs (Edin 1992, 2004). This provided a more direct measure of strain. A detailed quantitative analysis of the static and dynamic responses of the cutaneous afferents was performed. Slowly adapting type II afferents (SAII) and to some extent SAIII afferents responded both rapidly and consistently at low strain velocities; at higher velocities, SAI and fast-adapting FAI afferents were recruited at longer latencies. Good fits were obtained for both SA and FA afferents when their responses were modeled by a simple power function of velocity ($r^2 > 0.9$ for 95 % of the units) (Table 2). The exponent of the power function varied between afferents but was generally less than 1, which is reminiscent of the Schafer and Houk models of muscle spindle afferents.

In an analysis of the firing rates of SA cutaneous receptors of the human knee, good fits were obtained with a linear combination of joint angle and joint angle velocity (Edin 2001; Table 2; Fig. 2). However, a previous study had shown a nonlinear relationship with joint angle, possibly

also following a power law (Edin 1992; Fig. 2), and a later study showed a power-law relationship with angular velocity (Edin 2004). The equation in the last row of Table 1 is proposed here, to take these nonlinearities into account. Regarding the gain and offset terms, these are provided in the original publications. It was pointed out that the larger the joint, the larger the skin strain, and therefore presumably the larger the sensitivity of cutaneous receptors to joint rotation (Edin and Johansson 1995).

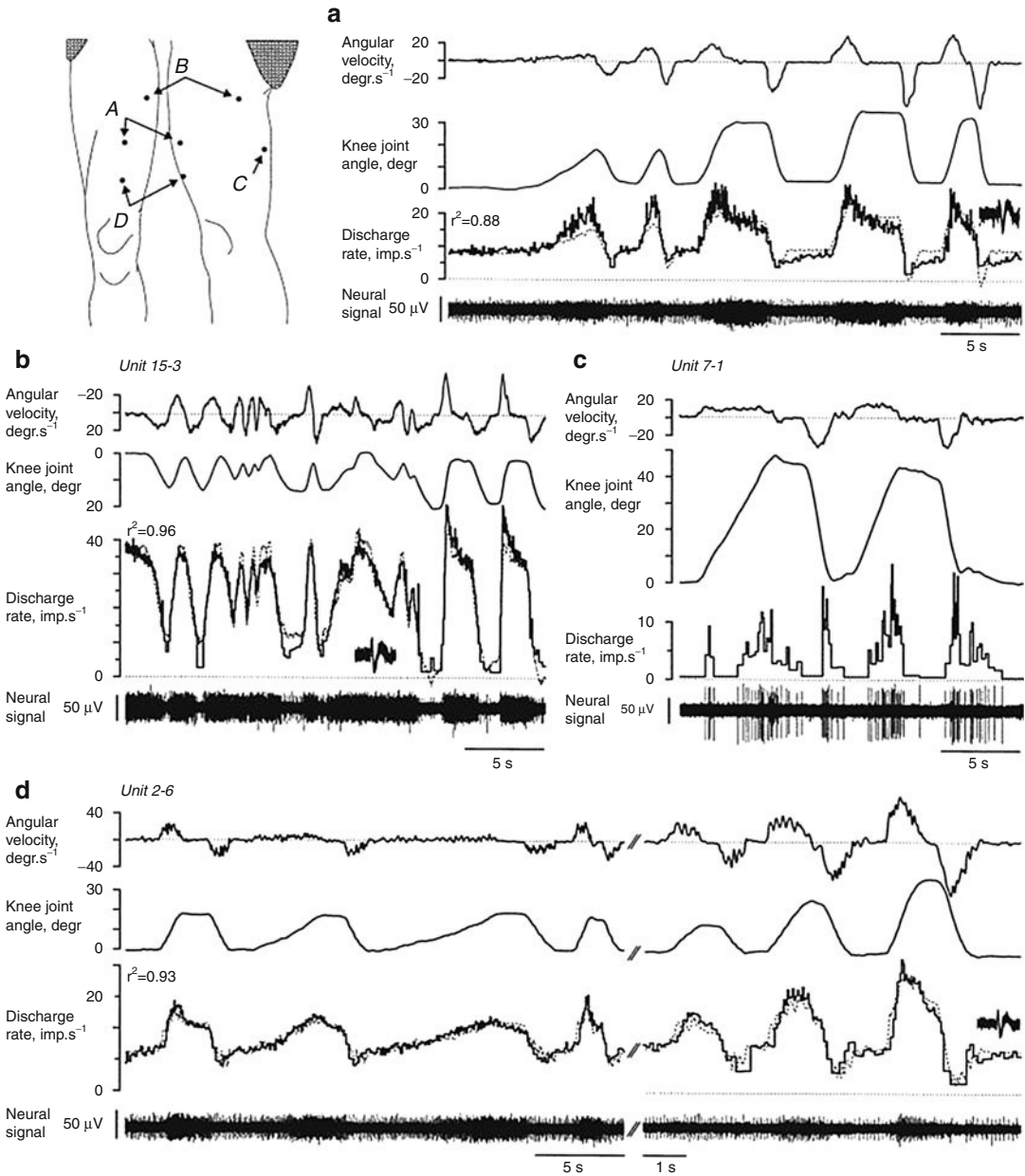
Joint Receptor Models

As discussed above, there is no consensus on the response properties of joint receptors, some researchers claiming that they are incapable of signaling joint rotation except at the extremes and others disputing this. Under these circumstances, the only useful data relevant to modeling is the fact that joint receptors are slowly adapting and have response properties similar to SA cutaneous receptors. One approach that could be taken would be to assume that their contribution to proprioception would be similar to that of SA cutaneous receptors (Williams 1981).

General Comments: Which Models to Choose?

In the simpler spindle models, fusimotor action mediated via intrafusal muscles is represented by just one or two parameters: gain and offset, the assumption being that these are the two main effects of fusimotion on spindle afferent responses. The later models have parameters representing up to three types of fusimotor action, but because there is conflicting evidence on the way in which the CNS controls fusimotor neurons in normal movements, it is unclear whether these additional parameters lead to better predictions of afferent firing in awake animals and humans.

Unfortunately, so far, the performance of different muscle spindle models has only been compared head-to-head in a single study, and this was restricted to some of the simpler models (Prochazka and Gorassini 1998b). Consequently, the only quantitative criterion upon which the



Proprioceptor Models, Fig. 2 Knee joint movements and associated firing rate of four SA III cutaneous afferents (a–d) recorded by neurography during voluntary knee flexion and extension. Schematic shows location of the receptors. The instantaneous discharge rates of the

receptors were fitted by a model comprising a linear combination of knee angle and angular velocity (dotted lines superimposed on the recorded discharge rate) (From Edin (2001))

more complex models can be compared with each other and with the simpler models is the reported variance accounted for (r^2) in fitting the available

data on afferent responses to length changes and fusimotor stimulation. Qualitative evaluation of specific features of response can be useful, e.g.,

the initial burst in Ia afferents at the onset of stretch or occlusion of fusimotor action in ascending and descending phases of a stretch. In light of the complexities, the reported r^2 values of fits to experimental data for most of the models have been surprisingly good, generally exceeding 0.8 and in some cases 0.9.

This raises the question of the intended purpose of the model. Complex structural models are well suited to modeling fusimotor action and non-linear responses and to describing the contributions of the different internal elements of individual receptors. However, if the focus is more on the ensemble afferent input to the CNS, features such as initial bursts can be misleading, because they tend to occur asynchronously in different afferents. CNS neurons that receive synaptic inputs from first-order afferents integrate the inputs from many receptors. This “washes out” asynchronous responses of individual receptors. Simpler models that do not attempt to replicate such transients may therefore paradoxically be more suitable for such applications, and of course they have the added advantage of simplicity. Another major issue is the lack of consensus in the literature regarding the way in which fusimotor activity is modulated in conscious animals and humans. If the activity of both types of fusimotor neurons remains fairly constant for movements of a given type or if there is a predictable relationship between their activity and another variable such as α -motoneuronal activity (which can be measured with electromyography), the net fusimotor effect can be modeled to some extent by adjusting the gain and bias terms of the simpler models and, in theory, more accurately by adjusting parameters in the complex models. If fusimotor activity is highly modulated, detailed parameter adjustments may succeed in the more complex models (e.g., as shown in Mileusnic et al. (2006)) but only if the individual time courses of γ_d and γ_s activity are known.

Regarding the accuracy that is actually required of a model, again this depends on the task at hand. For example, the gain of displacement and force feedback in spinal stretch reflexes is probably quite low. Open-loop gains of spindle

feedback of more than 1 or 2 tend to cause instability because of the sluggish responses of load-moving muscles (Prochazka et al. 1997a, b). Because of the low gain, such reflexes probably contribute quite modestly to load compensation (Prochazka et al. 2002), and therefore, r^2 values of 0.9 in predicting ensemble afferent signals may suffice to characterize their contribution (i.e., a higher accuracy would make very little difference to the overall performance of the overall neuromechanical model). On the other hand, the fine-tuning of locomotor phase transitions (from swing to stance and back) relies on accurate information on the position and velocity of a limb (Markin et al. 2010; Prochazka and Yakovenko 2007b), so here, a higher accuracy of the ensemble afferent input is desirable.

Models may be used in the future to infer movements and forces from ensemble firing rates recorded from dorsal root electrodes and to use these inferences to control muscle stimulators in real time. This inverse approach gave reasonably good estimates of muscle length and force from Ia and Ib ensemble firing rates reconstructed from individual recordings during locomotion (Prochazka 1999; Prochazka and Gorassini 1998b). Joint angles were estimated in real time from microelectrode array recordings of ensembles of muscle and skin afferents (Weber et al. 2007, 2011).

To what extent have the models been used in neuromechanical studies? Transfer function models of muscle spindles and GTOs have been used by several groups to analyze stretch reflexes (Poppo and Terzuolo 1968; Roberts et al. 1971; Rosenthal et al. 1970). Power-law function models have been used in several studies of reflexes and locomotion (Markin et al. 2010; Spardy et al. 2011a, b) (Dideriksen et al. 2011; Hatz et al. 2012; Prochazka and Sorensen 2009; Prochazka and Yakovenko 2007a, b; Shim and Husbands 2012; Stienen et al. 2007; Yakovenko et al. 2004; Zhang et al. 2009). Structural models have been used less often, partly because of their complexity and partly because they are more recent (Song et al. 2008a, b; Williams and Constandinou 2013).

Cross-References

- [Control of Breathing, Integration of Adaptive Reflexes](#)
- [Neural Decoding](#)
- [Proprioception](#)
- [Sensory Input to Central Pattern Generators](#)
- [Spinal and Neuromechanical Integration: Overview](#)

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Prosthetic Device

► Visual Prosthesis, Optic Nerve Approaches

Prosthetic Vision, Assessment

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Synonyms

Functional vision; Ultralow vision assessment; Visual function

Definition

As early-generation visual prostheses offer only modest increases in visual acuity, it is vital that a thorough assessment of pre- and postoperative function is completed. Assessment of prosthetic vision is multimodal and requires both clinical measures (visual acuity, visual fields) and functional vision measures (orientation and mobility, activities of daily living).

Detailed Definition

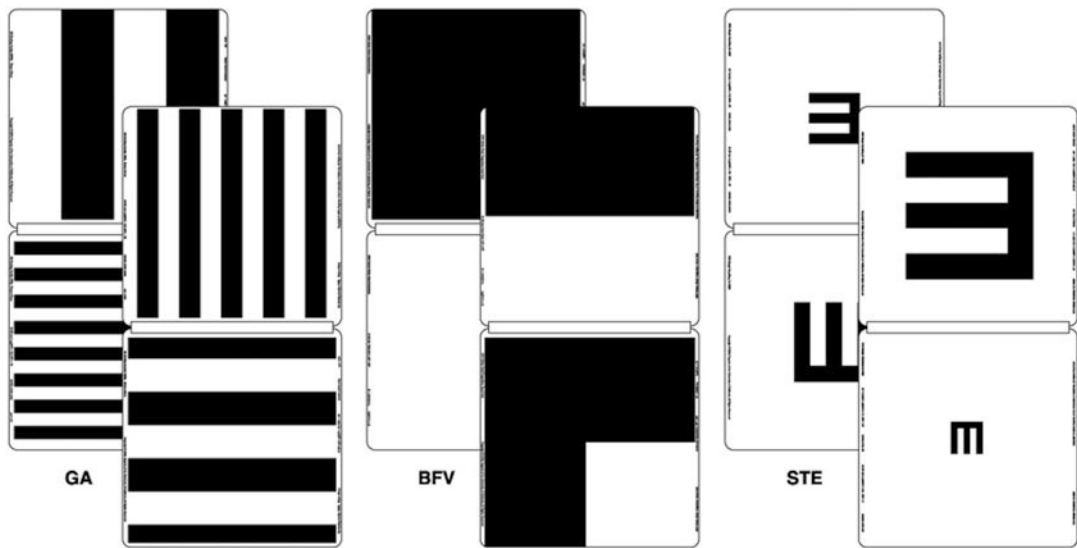
Assessment of prosthetic vision is challenging, as prosthesis recipients have very poor preoperative vision (less than 20/4000 or logMAR 2.3), and in early-generation devices, the improvements in vision are small. The majority of recipients of these early-generation prosthetic devices have a condition called retinitis pigmentosa (RP), and it is common for their visual performance to fluctuate significantly in differing light conditions. Due to these factors, a detailed and multimodal assessment of prosthetic vision is indicated and requires both clinical and functional vision measures.

Clinical Vision Measures

The main two clinical vision tests that are completed on prosthesis recipients are visual acuity and visual fields. Acuity gives a measure of a person's ability to see letter optotypes and gratings, as well as black-white discrimination and basic light perception. As the level of acuity experienced by the early implant recipients is very low, novel acuity tests have been developed to enable quantification of trace levels of function (Bach 1996; Bach et al. 2010; Bailey et al. 2012) (Fig. 1).

Functional Vision Measures

Due to the variability of results and difficulties in obtaining accurate clinical measures, it is important that assessments of prosthetic vision include functional vision testing. This includes orientation and mobility (O&M), which is a measure of how



Prosthetic Vision, Assessment, Fig. 1 Example of a novel visual acuity test developed for people with ultralow vision (less than 20/4000): the Berkeley Rudimentary Vision Test, which includes grating acuity (GA), basic functional vision (BFV), and single tumbling E letter optotypes (STE) (Image courtesy of Professor Ian Bailey, University of California – Berkeley). Visual field assessment for these patients requires a skilled examiner, as

people with RP often exhibit small and variable islands of residual vision. The most common method of assessing visual fields in recipients of visual prostheses is Goldmann manual kinetic perimetry (Bittner et al. 2011), in which a small illuminated target is moved slowly from the perimeter of the visual field until the patient reports seeing it. This enables the examiner to plot a map of any residual islands of vision (Fig. 2)

well a person can orientate themselves and move safely around an environment. O&M assessments can be simple, such as identifying a light in the room, through to complex tasks such as walking through a maze dotted with obstacles. In clinical trials of visual prostheses to date, O&M tasks have included following a line on the floor and identifying a black door on a white wall (Humayun et al. 2012).

The other key aspect in functional vision assessment is the testing of activities of daily living (ADLs). ADLs are tasks which are required for self-care and independent living and are considered to be key life skills. Examples of general ADLs are tasks such as cooking, getting dressed, and bathing. In relation to prosthetic vision assessment, researchers use ADL tasks which are vision-dependent, such as identifying common household objects and sorting light- from dark-colored laundry (Fig. 3).

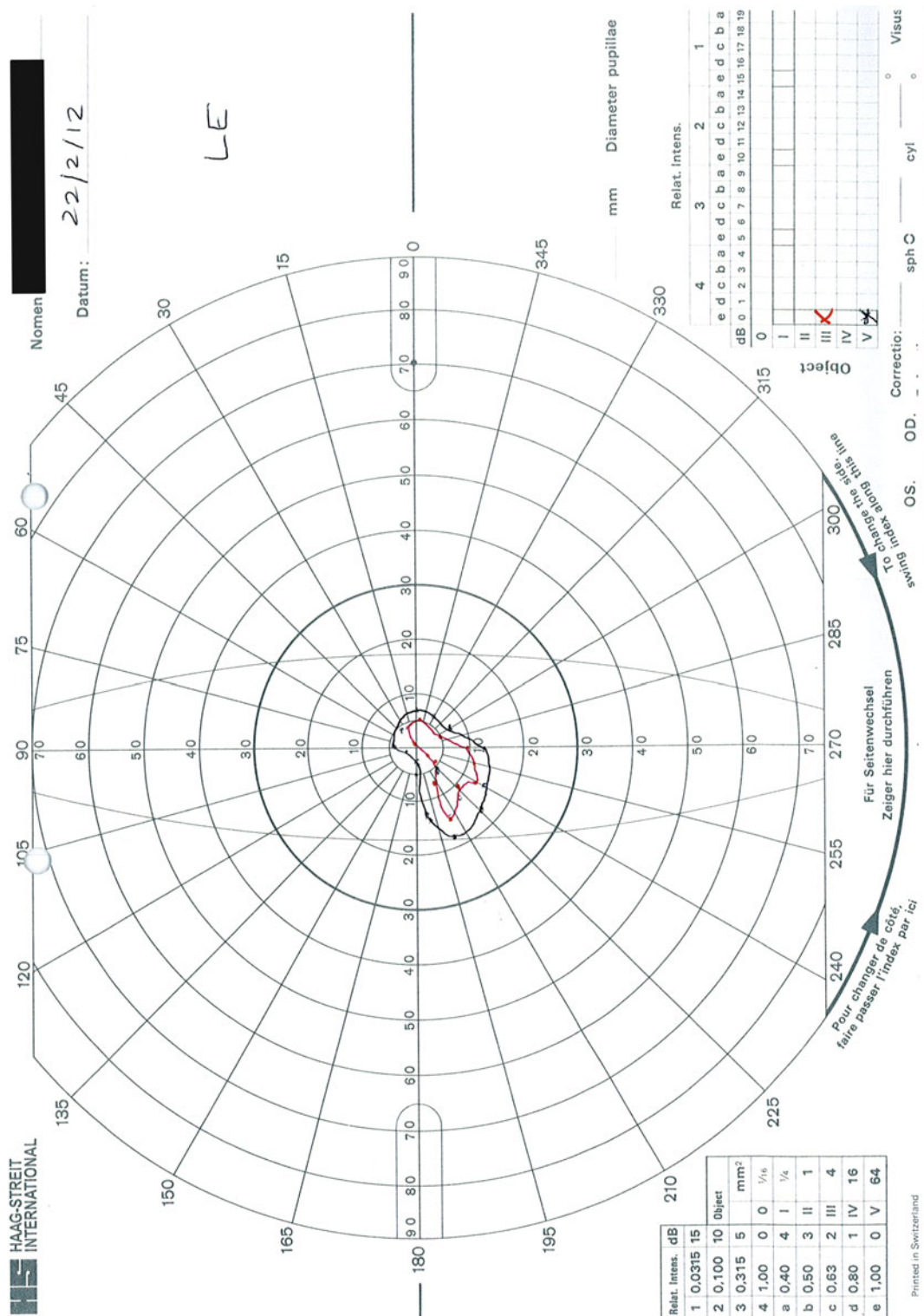
Electrophysiology

Another method of assessing prosthetic vision is using electrophysiological methods.

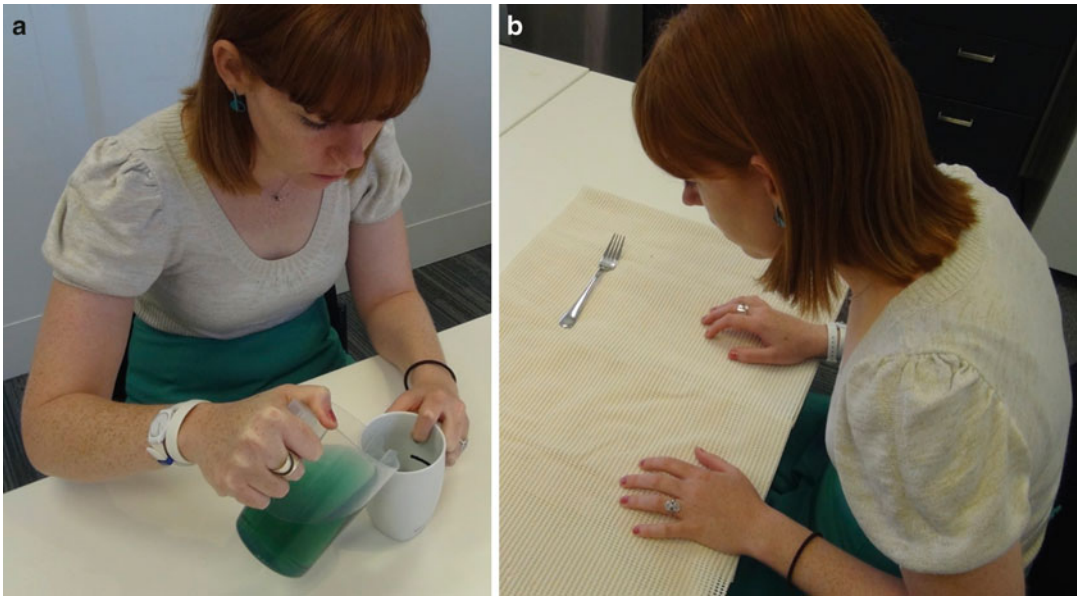
Electroretinography (ERG) is a technique for measuring retinal responses to flashes of light and can give an indication of preoperative retinal function. Tests such as full-field stimulus threshold (FST) have been used to quantitatively measure levels of light perception in patients both pre- and postoperatively.

Methodology of Prosthetic Vision Assessments

Due to the fact that people with vision impairment often are able to compensate for their vision loss with other techniques (such as hearing, touch, and echolocation), it is important that the assessment of prosthetic vision includes adequate control scenarios. In visual prostheses that use an external camera, vision assessments can be made with the device on and device off (as a control). However, some devices do not have this ability and so require patients to be blindfolded during the control experiments.



Prosthetic Vision, Assessment, Fig. 2 A Goldmann perimetric plot, showing a small central island of residual vision in an otherwise blind visual field. The red and black lines represent different stimuli used in the test



Prosthetic Vision, Assessment, Fig. 3 Examples of activities of daily living: pouring a glass of water (a) and identifying common household objects (b)

To date, there has been no consensus into the methodology and reporting of assessments of prosthetic vision. It is hoped that this will eventuate in the coming years and result in generation of internationally accepted protocols for prosthetic vision testing.

Cross-References

- [Prosthetic Vision, Perceptual Effects](#)
- [Retinal Disease and Remodeling](#)
- [Retinal/Visual Interfaces \(Models, Theory, Techniques\): Overview](#)

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Prosthetic Vision, Perceptual Effects

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Synonyms

Artificial vision; Bionic vision; Perceptual correlates; Subjective experience; Visual sensations of visual prostheses

Definition

Perceptual effects of prosthetic vision refer to the subjective experiences elicited by the use of a visual prosthetic device.

Detailed Description

General Appearance of Electrically Elicited Percepts

Visual prostheses that have been tested in human clinical trials are, as yet, invariably based on implanted devices that electrically stimulate the visual system. Most studies have focused on retinal implants, as opposed to cortical, optic nerve, and thalamic implants. Electrical point stimulation of visual nervous tissue can elicit localized flashes of light called phosphenes. Phosphenes generated by retinal stimulation are typically perceived as circular, oval, or ring-shaped spots of light (Rizzo 3rd et al. 2003; De Balthasar et al. 2008), but a variety of other shapes have been reported (Keserü et al. 2012). Typically they are white or yellow (Humayun et al. 2003), although other colors (Klauke et al. 2011) and “dark phosphenes” (i.e., darker than background) (Humayun et al. 2003; De Balthasar et al. 2008) have been reported as well. Dependent on stimulation

parameters, the angular subtense of phosphenes generally ranges from the size of a match head to a small coin viewed at arm’s length (Humayun et al. 2003; Rizzo 3rd et al. 2003).

Effects of Stimulus Parameters

Present-day implant systems encode light intensity by varying current level. The dependence of phosphene brightness on stimulus level can be described by a simple saturating power function (Humayun et al. 1996; Greenwald et al. 2009), and as many as 10 intensity levels may be distinguishable (Humayun et al. 2003). Increasing stimulus amplitude also increases current spread from the electrode, however, thereby impacting phosphene size (Humayun et al. 1996, 2003; De Balthasar et al. 2008; Nanduri et al. 2008, 2012; Wilke et al. 2011). Because of this, amplitude modulation may substantially decrease spatial resolution (Behrend et al. 2011). In contrast, pulse rate modulation has been shown to affect brightness while having little impact on phosphene size and may therefore be a more suitable approach for controlling phosphene brightness (Nanduri et al. 2012).

Single-point stimulation at different locations on the retina generally results in topographically organized phosphenes that roughly correspond to the retinotopic map (Rizzo 3rd et al. 2003; Humayun et al. 1996), e.g., stimuli applied in the upper-left hemisphere of the retina are perceived in the lower right of the field of view. Hence, by mapping images onto a retinal electrode grid, meaningful shapes can theoretically be presented to the implant wearer.

A particularly vexing issue in present-day retinal implants is the effect of fading, in which the brightness and size of phosphenes decline over time. Fading may occur within seconds after the onset of a train of stimulus pulses (Perez Fornos et al. 2012) but can take as long as 10 min to reach its full effect (Stronks et al. 2013). One way to reduce fading is to use low stimulation rates of 1–20 Hz. However, low stimulation rates of

1–5 Hz may result in unstable percepts (Stingl et al. 2013), since the flicker fusion frequency during single-electrode stimulation may be as high as 40–50 Hz (Humayun et al. 1999; Horsager et al. 2010). Hence, reduction of fading by adjusting the stimulation rate may cause a trade-off with perceptual image stability and intensity.

Performance of Visual Prosthesis Wearers

The Argus[®] II, alpha-IMS, and EPIRET3 clinical trials have shown that nearly 100 % of retinal-implant wearers benefit from their device when performing relatively simple tasks (e.g., identifying the orientation of a line, localizing a high-contrast target). 50–60 % benefit on more complex tasks (e.g., perceiving the direction of motion or “maze tracing”) (Humayun et al. 1999; Yanai et al. 2007; Klauke et al. 2011; Zrenner et al. 2011; Barry and Dagnelie 2012; Stingl et al. 2013). About 40–50 % of retinal-implant wearers can perceive large-print letters (in the order of 40° visual angle), while approximately 10–20 % are able to read short words (Zrenner et al. 2011; Da Cruz et al. 2013; Stingl et al. 2013). Single-letter recognition can take anywhere between 6 s and 3.5 min (Da Cruz et al. 2013). The drop in performance on more complex tasks can be attributed to many factors, of which spatiotemporal interactions between electrodes, retinal degeneration and remodeling, and a suboptimal tissue-electrode interface are among the most important (Marc et al. 2003; Horsager et al. 2010; Horsager et al. 2011).

Among the different implant systems tested to date, between-subject variability on standardized visual acuity tests is substantial. As much as 75 % of the subjects may not be capable of performing such tests (Da Cruz et al. 2013). For those who can, however, visual acuities as good as 20/546 have been reported (Stingl et al. 2013), a level classified as “profound vision loss.” This modest level of vision should be considered a huge achievement, since these patients were all classified as “functionally blind” before implantation.

Argus II subjects show significantly improved performance in orientation and mobility, including a task where they locate and walk to a high-contrast door and a task in which they follow a high-contrast line on the floor with different angles in it (Humayun et al. 2012). Hence, retinal implants can allow people previously unable to navigate without a guide dog or white cane to orient and navigate independently (Dorn et al. 2012).

Cross-References

- [Prosthetic Vision, Assessment](#)
- [Retinal Disease and Remodeling](#)
- [Retinal/Visual Interfaces \(Models, Theory, Techniques\): Overview](#)
- [Visual Prosthesis, Cortical Devices](#)
- [Visual Prosthesis, Epiretinal Devices](#)
- [Visual Prosthesis, Subretinal Devices](#)

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Protein Kinase A, Models of

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Definition

An enzyme that phosphorylates proteins on either serine or threonine (a member of the serine/threonine kinase family) which is activated by cAMP.

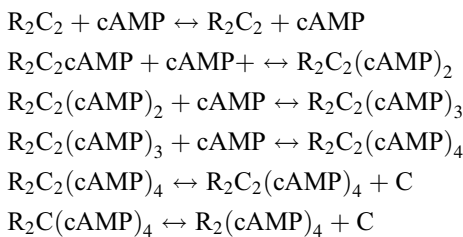
Detailed Description

PKA is an abbreviation of protein kinase A, also known as cyclic adenosine monophosphate (cAMP)-dependent protein kinase (EC 2.7.11.11).

The studies of Krebs and Fischer (Krebs and Fischer 1956; Krebs et al. 1959) laid the foundation for protein phosphorylation as a mechanism for regulation, and PKA, discovered in the 1960s (Walsh et al. 1968), is viewed as a model kinase in the family of eukaryotic protein kinases (Taylor et al. 1993). PKA and PKA-dependent phosphorylation is also one of the key processes that regulate and engage in signaling pathways leading to synaptic plasticity (Nguyen and Woo 2003) and underlying learning and memory.

In the inactive state, PKA is composed of two regulatory (R) subunits (Gill and Garren 1969) forming a dimer and two catalytic (C) subunits. In fact, there are four different regulatory subunit isoforms (RI α , RI β , RII α , RII β). All four isoforms have a similar domain structure comprised of an amino-terminal dimerization/docking domain, two cAMP-binding domains at the carboxyl terminus (designated Site A and Site B, respectively; Doskeland 1978), and a linker region containing the primary docking/inhibitory site for the catalytic (C) subunit. The holoenzyme (R₂C₂) is activated by cAMP, which binds to the R-subunit; after which, the C-subunits dissociate from the inhibitory domains of the R-subunit dimer and these C-subunits are intrinsically active (Ogreid and Doskeland 1981, 1982; Herberg et al. 1996). The C-subunit is also inhibited by PKI (protein kinase inhibitor), a naturally occurring, high affinity inhibitor peptide (Walsh et al. 1990).

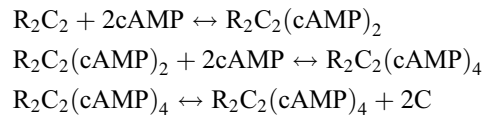
Based on the four cAMP-binding steps and the two C-subunit dissociation steps, Bhalla and Iyengar (1999) introduced a four-step cAMP-binding model with two-step PKAc dissociation:



The model and its rate constants were based on (Doskeland and Ogreid 1984; Ogreid and Doskeland 1981; Hasler et al. 1992; Smith et al. 1981) and can be found in the author's web

repository. This PKA model was incorporated into a model of four signaling pathways (Bhalla 2004a, b) which investigated effects of diffusion and scattering on information flow through four protein kinase regulatory pathways and investigated bistability, thresholding, and pattern selectivity in kinase regulatory pathways.

Though there are four cAMP-binding sites, Ogreid and Doskeland (1982) showed that protein kinase activity and cAMP binding comprise two nearly linearly coupled processes that are positively cooperative with a Hill coefficient of 1.7 (Zawadzki and Taylor 2004). Swillens (1983) discussed kinetic schemes that would fit data presented by Ogreid and Doskeland (1982) and allow minimal molecular requirements. Swillens (1983) then simplified a reaction diagram consisting of 15 holoenzyme states in order to obtain a minimal reaction scheme that fit the data from Ogreid and Doskeland (1982). Four possible reaction schemes were presented and fitted. One of these reaction diagrams, a two-step binding model, was used in (Kim et al. 2010). After binding four molecules of cAMP, the two catalytic subunits (C) dissociate from the regulatory subunit dimer (R):



The rate constants governing these biochemical reactions were fit to data in (Ogreid and Doskeland 1982; Zawadzki and Taylor 2004). This model explored why the requirement for PKA is limited to a long lasting form of long-term-potential (L-LTP) induced using spaced stimuli, but not massed stimuli. Simulations showed spaced stimulation activates more PKA than massed stimulation and made a key experimental prediction that L-LTP is PKA-dependent for intervals larger than 60 s. This prediction was confirmed experimentally (Kim et al. 2010). In a later paper (Kim et al. 2011), a two-step dissociation of R₂C₂(cAMP)₄ was added, based on the observation by Johnson et al. (1993) that the molecule R₂C₂(cAMP)₄ "opens up" and that binding of substrate stabilizes dissociation of the

C-subunit from the R_2 dimer. This PKA model was included in a multi-compartmental stochastic reaction–diffusion model. Simulations showed that PKA anchoring both near the source of cAMP and near specific targets enhance PKA activity; however, anchoring both near the source of cAMP dominates. Both models can be found in ModelDB database.

Graupner and Brunel (2007) presented a spike-timing dependent synaptic plasticity (STDP) model comprised of a biochemical model of the CaMKII autophosphorylation and the protein-signaling cascade governing CaMKII dephosphorylation, which included PKA. The activity of PKA by calcium–calmodulin activation of adenylyl cyclase was modeled using a Hill equation to condense several bimolecular and enzyme reaction steps:

$$v_{PKA} = k_{PKA}^0 + \frac{k_{PKA}}{1 + \frac{K_{PKA}}{C}},$$

where C is calcium–calmodulin concentration, k_{PKA}^0 is minimum PKA activity, k_{PKA} is maximum PKA activity, K_{PKA} is PKA half activity concentration, and n_{PKA} is PKA Hill coefficient. The model can be found in ModelDB database.

Due to its importance in synaptic plasticity, PKA activation has been incorporated into several other models (Zhabotinsky 2000; Lisman and Zhabotinsky 2001; Miller et al. 2005) as a parameter.

Cross-References

- [Bimolecular Reactions, Modeling of](#)
- [Enzyme Kinetics, Modeling of](#)
- [Spike-Timing Dependent Plasticity \(STDP\), Biophysical Models](#)
- [Stochastic Simulators](#)

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Protein Kinase C, Models of

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Definition

Protein kinase C is a class of protein kinases with 11 isozymes grouped into three

subclasses (Newton 2001). The protein kinase C isozymes in the typical group are activated by calcium, diacylglycerol (DAG), and arachidonic acid (AA). The isozymes in the novel group are activated by DAG and AA, but not calcium. The atypical group of isozymes are insensitive to both DAG and calcium. Most models of PKC activity describe binding of calcium and one or two lipids to the PKC holoenzyme.

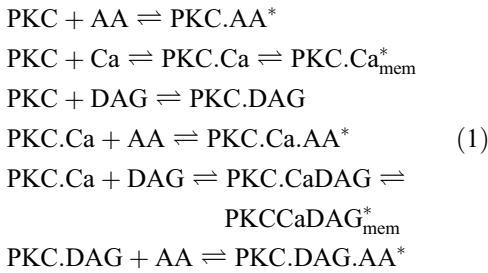
Detailed Description

All of the protein kinase C isozymes have a similar catalytic domain, and most of the isozymes have two additional domains important for PKC activation: the C2 domain that binds two to three calcium ions and the C1 domain that binds lipids. One additional PKC isozyme is called PKM ζ . This is the constitutively active, catalytic domain of typical PKC. This molecule is normally at low levels, and it is “activated” either by cleavage of typical PKC forms or by synthesis.

Most, though not all, models of PKC activity are of typical PKC. These models differ by the reaction scheme describing PKC activation and also in the interaction of PKC with other signaling pathways. In addition, most PKC models are components of signaling pathways within the cerebellum, in part because PKC has demonstrated importance for long-term depression of excitatory synapses onto cerebellar Purkinje cells.

Conventional PKC: Bhalla Model

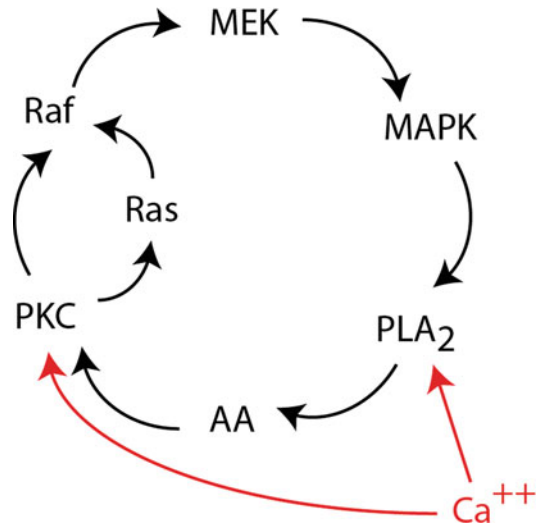
The first model of PKC activation in neurons was developed by Bhalla and Iyengar (1999), based on experiments showing that PKC is activated synergistically by calcium, DAG, and AA. In their model, AA could bind to any form of PKC (whether or not calcium or DAG was bound), and any order of binding was allowed:



Also, all bound forms of PKC were active, though an additional translocation to the membrane was required for forms not bound to AA. Calcium was not required for PKC activity; however, the PKC ligands acted synergistically, so that a much higher concentration of DAG and AA was required when acting alone. This model was originally implemented in Kinetikit (Bhalla and Iyengar 1999) and has been used in many signaling pathway networks.

This model was originally implemented in a feedback loop with MAPK and phospholipase A₂ (PLA₂) as illustrated in Fig. 1. Active PKC phosphorylates the small GTP binding protein Ras. PKC phosphorylation enhances the activity of the kinase Raf and PKC phosphorylation of RasGTP enhances its ability to activate Raf. Raf activates MAPK by phosphorylating MEK, which phosphorylates MAPK. The latter phosphorylates PLA₂, leading to higher production of AA, thus completing the feedback loop (Bhalla and Iyengar 1999). Simulations showed that this feedback loop exhibits bistability, a property important for long-term memory. Simpler models of PKC activation that omit the DAG binding also exhibit interesting dynamics when part of the same MAPK-PLA₂ feedback loop (Ajay and Bhalla 2007).

This reaction scheme also was used in several models of signaling pathways underlying LTD in cerebellar Purkinje cells. The amplitude of the synaptic response to parallel fiber input is controlled by the phosphorylation state of the AMPA receptors, and this amplitude is decreased (LTD) in response to paired climbing fiber and parallel fiber stimulation. In the first cerebellar LTD model (Kuroda et al. 2001), PKC phosphorylates AMPA receptors, whereas protein phosphatase



Protein Kinase C, Models of, Fig. 1 Positive feedback loop formed by PKC interacting with MAPK. PKC enhances activation of the monomeric GTP binding protein Ras, and activation of the kinase Raf, which phosphorylates MEK, which phosphorylates MAPK. Among its targets, MAPK phosphorylates phospholipase A₂ (PLA₂), which enhances production of AA, thereby further activating PKC. The feedback loop can be initiated by calcium acting on two molecules in the loop

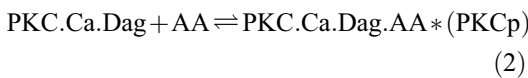
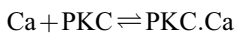
2A dephosphorylates both MEK and AMPA receptors. Simulations showed that the initial phase of AMPA phosphorylation corresponded to the initial phase of PKC activation, which was independent of the MAPK loop. However, the intermediate phase of AMPA phosphorylation depended on the prolonged PKC activation provided by the MAPK loop. A combination of simulations and experiments evaluated whether the feedback loop could explain various characteristics of calcium dependence of cerebellar LTD, such as threshold behavior, cooperativity, and saturation. Indeed, once spatial gradients of calcium were taken into account, this feedback loop explained the sigmoidal relationship between calcium and LTD observed experimentally (Tanaka et al. 2007).

The feedback loop also has been incorporated into a signaling pathway model investigating hippocampal LTP (Kikuchi et al. 2003). This model included the dynamic regulation of protein phosphatase 2A by activated calcium

calmodulin-dependent protein kinase II (CaMKII) and was implemented in ECell. Simulations demonstrated that the additional reactions involving PP2A and CaMKII eliminate the need for PKC in producing LTP. Also this PKC feedback loop model, though with different rate constants, was used in a model of serotonin receptor activation of MAPK (Chang et al. 2009) via the HT1A receptor activation of MAPK through the guanine exchange factor mSos and the HT1A/HT2A receptor activation of MAPK through PKC.

Conventional PKC: Other Models

Kotaleski et al. (2002) developed an alternative model of PKC activation by calcium, diacylglycerol, and arachidonic acid. Imaging of translocation of both full length and various fragments of a GFP-tagged conventional PKC isoform (Oancea and Meyer 1998) suggests that calcium ions must bind first in order to expose the DAG binding site and that AA binding is required for a persistently active form. This led to a sequential model of PKC activation:



This model was used in a model of LTD in cerebellar Purkinje cells and illustrated that PKC activation was sensitive to timing of parallel fiber and climbing fiber activation. Interestingly, the main source of timing sensitivity was not due to PKC binding order, but was due to temporal sensitivity of IP₃-induced calcium release.

This model also was used in a spatial model of LTD in the medium spiny neurons of the striatum (Kim et al. 2013). Simulations demonstrated that the translocation of PKC from the cytosol to the membrane could be explained as a passive process that resulted from binding of the calcium bound PKC to the DAG in the membrane.

More recently, the Bhalla model of PKC has been updated (Antunes and De Schutter 2012) based on recent evidence of multiple calcium

binding sites: one high affinity site (1 μM) and another two sites which affinity ranges from 4 to 22 μM (Torrecillas et al. 2004). Binding of three calcium ions promotes PKC binding to membrane phospholipids, and arachidonic acid acts synergistically with calcium to promote translocation and binding to membrane phospholipids such as DAG, though this latter binding step was not modeled explicitly. This updated model was implemented within the MAPK/PLA₂ feedback loop and simulated stochastically to investigate threshold behavior and sigmoid response characteristics of cerebellar LTD.

Other PKC Isozymes

There are only a few models of other forms of PKC. There is one model of novel PKC, which is sensitive to DAG, but not calcium (Dupont et al. 2011). This model was used to investigate calcium oscillations caused by stimulation of the type 5 metabotropic glutamate receptor (mGluR5). The overall goal of that study was to develop a minimal model which could explain experimental results of calcium oscillations. Consequently, PKC activation was a sigmoid function of DAG concentration, with maximal rate of K_{act} and half activation of K_{DAG} :

$$\frac{d\text{PKC}}{dt} = K_{\text{act}} \cdot \frac{D}{D + K_{\text{DAG}}} \cdot (1 - \text{PKC}) - K_{\text{deact}} \cdot \text{PKC} \quad (3)$$

The DAG to activate PKC was produced by the activated mGluR5 receptor, and the activated PKC in turn phosphorylated the mGlu5 receptor which caused cessation of DAG and IP₃ production. Simulations show that this negative feedback loop produces calcium oscillations due to the periodic IP₃ production and thus is an alternative mechanism to that typically modeled in response to constant IP₃.

Two models of PKM ζ have been developed to investigate mechanisms underlying the persistence and maintenance of synaptic plasticity. One model added PKM ζ to the Bhalla PKC-MAPK/PLA₂ feedback loop model to

investigate mechanisms underlying the late phase and consolidation phase of cerebellar LTD (Ogasawara and Kawato 2009). In this model, the PKM ζ is activated initially by MAPK; then the PKM ζ activates itself by inducing its own translation. Simulations show how the PKM ζ positive feedback loop supports the late phase of LTD and memory consolidation, which is disrupted by protein synthesis inhibitors.

A second model of PKM ζ investigated its role in synaptic tagging and capture (Sajikumar et al. 2005), which describes the observation that strong stimulation in the hippocampus is needed to produce a protein synthesis-dependent, long-lasting LTP or LTD, but that a weak stimulation is converted to a long-lasting LTP or LTD if given within 30 min or so of the strong stimulation. In this two-compartment model (Smolen et al. 2012), synthesis of PKM ζ in the dendrite required phosphorylation of (unknown) targets by both CaMKII and MAPK. PKM ζ can diffuse into the spine compartment to cause LTP. Model simulations showed that LTP maintenance was caused by bistability in PKM ζ activity in the spine compartment.

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PSICS: The Parallel Stochastic Ion Channel Simulator

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Definition

PSICS (www.psics.org, Cannon et al. 2010) is a simulator for computing the behavior of neuron models in which the membrane ion channels are

expressed as kinetic schemes. It can operate in the stochastic regime where each channel is treated as an independent entity or in the deterministic regime where a population of channels is lumped together as a single continuous process. For extended cells, channels are given precise positions on the membrane before any spatial discretization is performed so exactly the same model can be computed at different spatial and temporal resolutions and with the various channel populations computed stochastically or deterministically. This enables a range of questions to be addressed concerning the influence of channel stochasticity and spatial discretization on the behavior of neurons.

Detailed Description

PSICS operates as a sequential processor taking a declarative model description as input and mapping it through a series of processing and computation stages to produce a self-contained set of data tables, images, logs, and XML files linked by an HTML index file as output. The input files must specify the model, the simulation to be performed, and the quantities to be recorded. There are no command line options and it does not have a graphical user interface. The complete input specification is packaged up as a zip file as part of the output results set so that any PSICS computation can be reproduced from its results set.

The main stages of a PSICS simulation are:

- Model instantiation. Each ion channel is given an exact position on the membrane.
- Discretization. The 3-D morphology is divided into sections by perpendicular cuts across straight sections of the structure. Cuts are not made at branch points.
- Tabulation of kinetic schemes. For each channel type, the finite-time step transition matrix is tabulated over a grid of membrane potentials.
- Serialization. The transition matrices, element dimensions, numbers of channels of each type per element, stimulation parameters, and recording configuration are written out as a single space and newline delimited ASCII file.

- Execution. A separate process reads just this ASCII file and performs the specified calculations, comprising mainly channel population updates and membrane potential diffusion.
- Output and rendering. The results of the execution step are used to generate any figures specified in the initial model specification, and these are combined into a single web page incorporating the model description, figures, and raw output.

For all but the shortest simulations, the execution step is the dominant computational cost. Two implementations are provided for this stage: one written in Java and the other in highly optimized Fortran. All other steps are implemented in Java. For stochastic calculations of a population of channels on an isopotential element, PSICS exploits the interchangeability of channels in the same state. Rather than storing the state of every channel, it is sufficient to know how many channels there are in each possible state. Furthermore, at most membrane potentials, the overwhelmingly most likely outcome for any channel over one time step is that it will be in the same state at the end of the step as it was at the beginning. PSICS exploits this observation to allow approximate stochastic population updates with far fewer random numbers and operations than would be required if every channel is treated independently. A range of heuristics and fitting functions is used to ensure the statistical properties are within the required tolerance over a range of population sizes and transition probabilities.

Cross-References

- [Hodgkin-Huxley Model](#)
- [Markov Models of Ion Channels](#)
- [neuroConstruct](#)
- [NeuroML](#)

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PSTH

► Estimation of Neuronal Firing Rate

Pulse-Coupled Oscillators

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Definition

Pulse-coupled oscillators are intrinsically rhythmic circuit elements (oscillators) that are coupled via instantaneous interactions. Pulse (or pulsatile) coupling is only approximate because real world pulses cannot exert their effects instantaneously. Instead, a finite amount of time must elapse in order to produce an effect. However, the theoretical results for pulse-coupled oscillators generally apply to cases in which the input pulse exerts its effects during a time window of finite duration, provided that this duration is short compared to the period of the oscillation.

Detailed Description

This article focuses on neural oscillators, or intrinsically rhythmic nerve cells (neurons). Neurons are well suited to an analysis based on pulse coupling because they communicate via action potentials, also called spikes, which are all or nothing electrical signals that trigger a cascade of events leading to a somewhat slower, graded response in the target neuron. Coherent oscillations in networks of neurons are thought to coordinate the flow of information necessary for cognitive processing (Wang 2010). Phase locking implies a consistent phasic relationship between periodic events. Phase locking between spikes and a periodic drive or between spikes in mutually coupled oscillators can be investigated using pulse-coupled oscillator theory. These phasic

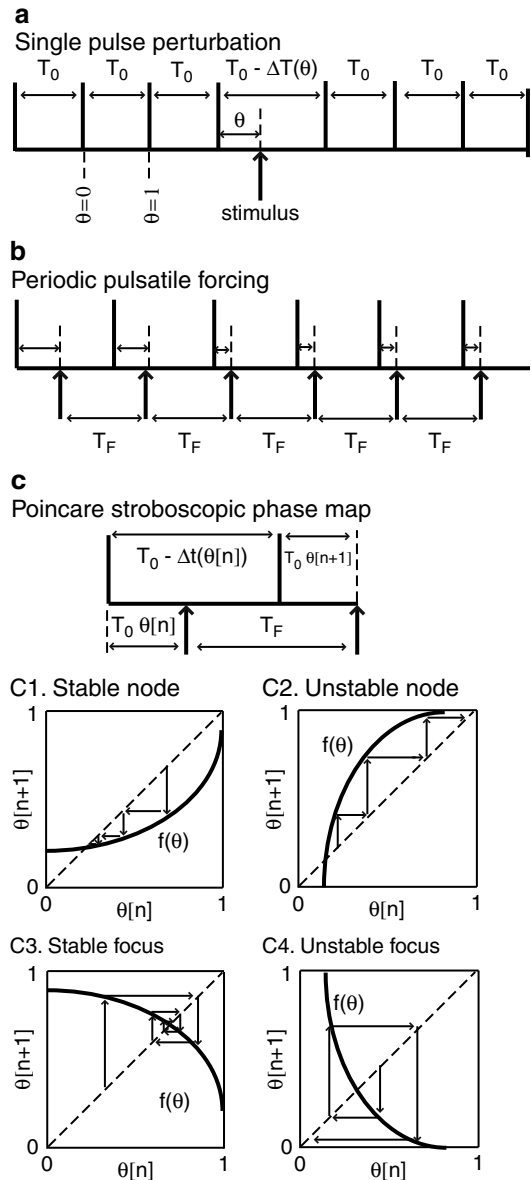
relationships may be utilized for information processing (Buzsaki 2006). Other oscillatory systems, such as fireflies emitting a pulse of light (Pikovsky et al. 2001) or central pattern generating circuits comprised of bursting neurons (Canavier 2005), have also been analyzed using the same pulse-coupled methods. Phase locking in central pattern generators may be important for coordination of rhythmic motor activity (Glass and Mackey 1988).

Networks of coupled oscillators can be studied analytically using simple integrate-and-fire networks or by numerical simulations of specific networks; both of these methods produce results that are model dependent. Model-independent results can only be obtained by assuming rather severe limitations in the case of weak coupling or pulsatile coupling (Ermentrout and Chow 2002; Izhikevich 2007). The model-independent nature of the results obtained from pulsatile coupling stems from the assumption that the oscillators involved are limit cycle oscillators (Winfree 2001; Glass and Mackey 1988). In mathematical terms, the periodic trajectory in a multi-dimensional state space must be a stable limit cycle, that is, a closed, periodic trajectory to which all nearby trajectories in a nonlinear dynamical system are attracted in the limit of long times. This article focuses on the model-independent results that can be obtained using pulsatile coupling when the effect of that pulsatile coupling on the component oscillators is not constrained to any particular form. However, very influential results that were obtained for a particular form of pulsatile coupling between generalized integrate-and-fire model oscillators will also be presented because of the historical importance of the analytically tractable integrate-and-fire models.

Event Maps

The analytical approach to pulse-coupled oscillators in general consists of constructing a map of events, meaning that the timing of previous events is used to calculate the timing of future events. The emission of a pulse by one oscillator and its

receipt by another are the critical events in map construction. If conduction delays between oscillators are ignored, the difference in elapsed time between the time of emission and the time of receipt is considered to be small and neglected. The intrinsic rhythmicity of an oscillator is necessary for this analysis. In addition, a threshold event that precipitates emission of a pulse by each oscillator in order to influence the other oscillators is required. Uncoupled oscillators emit pulses, which we will call spikes without loss of generality, at regular intervals given by the free running period T_0 . Therefore, for a single uncoupled oscillator (Fig. 1a), the time of the next spike can be obtained by adding the cycle period T_0 to the time at which the previous spike occurred. Each cycle of the free running cycle is presumed to be identical, so the time elapsed since the previous spike at the time the stimulus is applied corresponds to a unique point in the cycle, called the phase θ . The phase in Fig. 1 is the elapsed time normalized by the cycle period and ranges from zero to one, but other choices for normalization are possible. If an oscillator receives a pulsatile stimulus during a particular cycle (Fig. 1a, arrow), then the perturbed cycle length is shortened by an amount $\Delta T(\theta)$ that depends upon the time elapsed since the previous spike (if the period is lengthened the convention adopted here is that $\Delta T(\theta)$ is negative). The effect of the coupling depends upon the phase at which pulses are received, and this dependence is quantified as a phase-resetting curve of arbitrary shape (Glass and Mackey 1988; Schultheiss et al. 2012). The main assumption of pulse-coupling theory is that only the cycle that contains the perturbation is altered in duration and that the free running rhythm is reestablished immediately after the spike following the perturbation (Winfree 2001; Glass and Mackey 1988). For the coupling to be effectively pulsatile, the attraction to this limit cycle must be strong enough for each oscillator to ensure that the effects of perturbations decay quickly. So if the inputs are delivered too often, or the attraction to the limit cycle is too weak, or the stimulus is too strong, an analysis based on pulsatile coupling and event maps can fail (Izhikevich 2007).



Pulse-Coupled Oscillators, Fig. 1 Periodically forced oscillator. (a). Schematic for measurement of pulsatile phase-resetting $\Delta T(\theta)$ as a function of phase θ . This quantity is often normalized as $\Delta T(\theta)/T_0$. (b). Schematic representation of periodic pulsatile forcing. (c). Derivation of phase map. C1–C4, four possible trajectories near a fixed point in which the map intersects the identity diagonal

Event Map for Periodic Pulsatile Forcing

An event map can be formulated for periodic forcing of an oscillator. In the example given in

Fig. 1b, a pulsatile stimulus is applied repetitively at forcing intervals T_F . In this example, the elapsed time since the previous spike at the time an input is received converges to a steady value such that the forced oscillator becomes phase locked to the periodic stimulus. The forcing stimulus provides a reference point for stroboscopically sampling the forced oscillator. A potentially huge reduction in the dimensionality of the system is achieved by sampling a scalar quantity, the phase of the forced oscillator, each time that a forcing pulsatile stimulus is applied. A map that gives the phase of the oscillator at the time of one input in terms of the phase at the previous input can be constructed based on the algebraic relationships evident in the diagram at the top of Fig. 1c. This diagram assumes a one-to-one ratio of input stimuli to oscillator spikes. Forcing at a 1:M ratio can be analyzed by assuming M unperturbed oscillator periods between input stimuli rather than just one (Rinzel and Ermentrout 1998).

For the one-to-one ratio shown, the key observation is that the sum of the perturbed cycle ($T_0 - \Delta T(\theta[n])$) and the elapsed time ($T_0\theta[n+1]$) to the stimulus on cycle $n+1$ represents the same time interval as the sum of the elapsed time ($T_0\theta[n]$) to the stimulus on cycle n and the forcing period (T_F). Therefore, subtracting $T_0 - \Delta T(\theta[n])$ from both sides of the equality and dividing through by T_0 produces the event map $\theta[n+1] = f(\theta[n]) = \theta[n] + T_F/T_0 - 1 + \Delta(\theta[n])$, where $\Delta(\theta[n])$ is the normalized phase-resetting $\Delta T(\theta[n])/T_0$ (Glass and Mackey 1988) and $f(\theta[n])$ is the map from the phase on one cycle of forcing to that on the next. Note that there are two components to the map: the resetting term that occurs at the time of the pulse ($\Delta T(\theta[n])/T_0$) and the detuning term ($T_F/T_0 - 1$) that accounts for the change in phase (modulo one) that occurs during a forcing period. The dependence of the “old” phase prior to a pulse and the “new” phase immediately after a pulse is given by the phase transition curve (Glass and Mackey 1988). The map can also be written in terms of the “new” phases after the pulse (Pikovsky et al. 2001, p. 64), rather than the “old” before the pulse as shown above. Both maps are Poincare phase maps on a circle (Izhikevich 2007; Pikovsky et al. 2001; Winfree

2001), since the phases 0 and 1 represent the same point.

Poincare maps offer an important advantage in the study of dynamical systems, in that the stability of a periodic orbit in a system of differential equations reduces to the problem of the stability of the corresponding fixed point of the map (Wiggins 1990, Chap. 1). The forced oscillator phase locks to the stimulus if $\theta[n+1] = \theta[n] = f(\theta[n])$, which occurs when $f(\theta)$ intersects the diagonal (dashed line in Fig. 1c1–4). For simplicity of notation, we will omit the indexing of the phases in the remainder of the map descriptions. The map is iterated graphically by starting at a value of θ on the diagonal, moving vertically to the $f(\theta)$ curve to find the next value of θ , then returning to the diagonal horizontally and repeating. Linearizing the map shows that a periodic locking is stable if the absolute value of the slope of $f(\theta)$ is less than one. This is clear from the schematic drawings in Fig. 1c. For a stable node (Fig. 1c1), $0 < f'(\theta) < 1$, and the phase monotonically converges to its steady value as in Fig. 1b. For a stable focus (Fig. 1c3), $0 > f'(\theta) > -1$, and the phase alternately increases and decreases until it reaches its steady value. For an unstable node (Fig. 1c2), $f'(\theta) > 1$, and the phase monotonically diverges in the vicinity of the intersection. For an unstable focus (Fig. 1c4), $f'(\theta) < -1$, and the phase alternately increases and decreases as it diverges in the vicinity of the intersection. The stability criterion can equivalently be written in terms of the phase-resetting curve (Rinzel and Ermentrout 1998) so that $-2 < \Delta'(\theta) < 0$ at the fixed point guarantees stability.

Event Map for Two Pulse-Coupled Oscillators

An event-based map can also be constructed for two pulse-coupled oscillators firing in alternation (Ermentrout and Terman 2010, pp. 193–194; Pikovsky et al. 2001, Chap. 8). For the case of two pulse-coupled intrinsic oscillators with no external forcing, the stroboscopic Poincare sampling occurs at the time of each internally generated threshold event. The assumption of identical,

identically coupled oscillators allows the double iteration (Fig. 2) of a single event map (Pikovsky et al. 2001, Chap. 8) in terms of the phases and the phase-resetting Δ normalized by the intrinsic period T_0 . Time can be removed from the map since both oscillators have the same intrinsic period. Figure 2a schematically shows the timing of threshold events (spikes) in two coupled

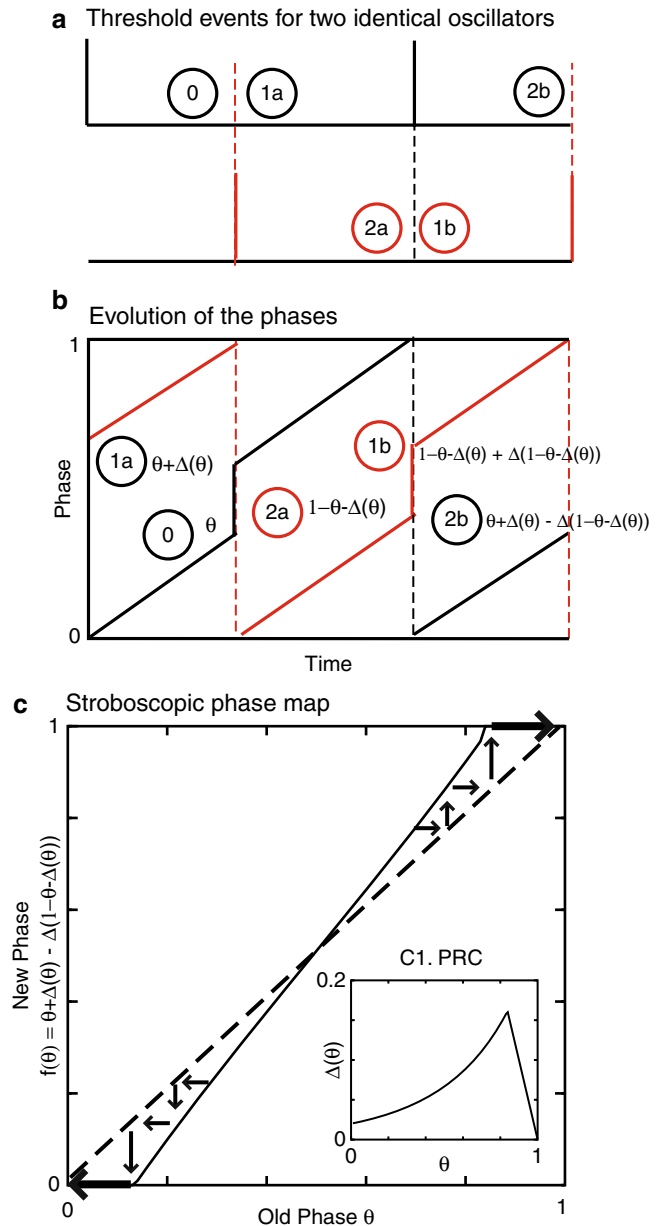
oscillators that lead to the emission of a pulse that affects the other oscillator. Figure 2b shows the presumed time course of the phases. The phase increases at a constant velocity between threshold events. When the phase in one neuron reaches one, its phase is reset to zero, and the phase of the other oscillator is instantaneously incremented or decremented as a result of the pulse coupling.

Pulse-Coupled

Oscillators, Fig. 2

Two identical pulse-coupled oscillators. (a). Schematic representation of spike times. (b). Schematic update of phases between pulses and as a result of input pulses. (c).

Stroboscopic phase map for pulse-coupled leaky integrate-and-fire neurons, whose PRC is given in the inset. Arrows show that the intersection of the smooth part of the map with the diagonal is unstable, and synchrony at phases 0 and 1 is globally attracting



There are two steps in constructing the event-based map, updating the phases (1) immediately after a pulse and (2) during the interval until the next pulse in the other neuron. Figure 2a, b shows the double iteration of the map starting at the phase just prior to a spike in the red neuron.

This event stroboscopically samples the phase θ of the black neuron at the point just prior to the pulse, indicated schematically with a black circle containing the label 0. The phase is updated to the phase just after the pulse is received ($\theta + \Delta(\theta)$) by adding the resetting appropriate for the phase at which the pulse is received. This first step in the first iteration is schematically indicated by a black circle containing the label 1a. Since the red neuron had a phase of zero at the time just after the pulse, the normalized interval ($1 - \theta - \Delta(\theta)$) that remains until the next spike in the black neuron occurs becomes the phase just before the next pulse is received in the red neuron. This second step in the first iteration is indicated schematically by the red circle containing the label 2a. This iteration can be described by the intermediate mapping $h(\theta) = (1 - \theta - \Delta(\theta))$. Since the two neurons are identical and identically coupled, the same two steps are repeated for a second iteration. The dependence of the phase of the reference oscillator on one cycle as a function of its phase on the previous cycle is $f(\theta)$, where $f(\theta) = h(h(\theta))$. Thus, the phase $\theta[n + 1]$ just prior to a pulse received by the black neuron can be written in terms of the phase $\theta[n]$ just prior to the previous pulse as follows: $\theta[n + 1] = f(\theta[n]) = \theta + \Delta(\theta) - \Delta(1 - \theta - \Delta(\theta))$. Therefore, a map analogous to those shown in Fig. 1c can be constructed for two identical pulse-coupled oscillators as shown in Fig. 2c. Sometimes this map is constructed using time rather than phase and called a spike time difference map (Canavier and Achuthan 2012). The derivation for the map in Fig. 1c was given in terms of the algebraic relationships between time intervals, whereas the map in Fig. 2c was derived explicitly applying the map to the presumed time course of the phases, but the two approaches are equivalent, and either can be applied. Again, $|f'(\theta)| < 0$ is required at the intersection of $f(\theta[n])$ with the diagonal in order for the fixed point at that intersection to be stable.

Applying the chain rule shows that the following quantity written in terms of the slope of the phase-resetting curve $(1 + \Delta'(\theta))(1 + \Delta'(1 - \theta - \Delta(\theta)))$ must have an absolute value less than one for stability.

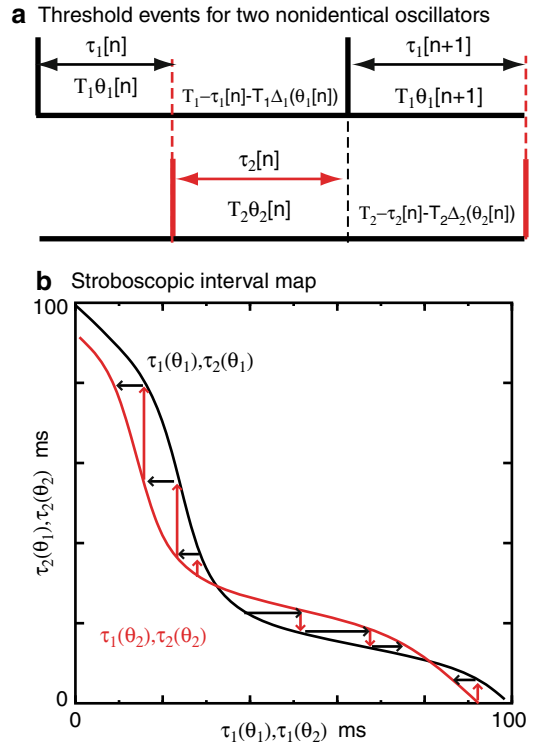
The map $f(\theta)$ in Fig. 2c is shown for the case of two identical pulse-coupled leaky integrate-and-fire oscillators with the phase-resetting curve for the pulses shown in the inset. In this case the map $f(\theta)$ has a monotonically increasing portion. Any fixed point in this interval is given by the intersection with the diagonal (dashed line) and is unstable because the slope is greater than one. The flat portion of the map indicated by the thick arrows at the top and bottom results from the form of the pulse coupling: if one oscillator fires a sufficient short interval before the other, it causes the other oscillator to fire at the same time and they remain synchronized. The map in Fig. 2c makes the assumption that one neuron never fires two consecutive spikes before the other neuron has a chance to fire. More complicated maps can be constructed for other scenarios (Canavier and Achuthan 2010).

One method for obtaining general results is to use an analytically tractable model, like a leaky integrate-and-fire model; such a model has an observable (usually membrane potential) that increases monotonically between threshold events and is reset to its minimum value after reaching its threshold value. A very influential treatment of the two-oscillator problem by Mirollo and Strogatz is described in Pikovsky et al. (2001) as well as in Ermentrout and Terman (2010). This approach generalizes the leaky integrate-and-fire model, in which v is the only observable variable. They assume that the time evolution of v on each cycle is a function $g(\theta)$ of the elapsed time, which in this case is proportional to the phase (θ), and that the function $g(\theta)$ is monotonically increasing $g'(\theta) > 0$ and concave $g''(\theta) < 0$. The pulse coupling has the form that a pulse in one oscillator increases v in the other oscillator either to $v + \varepsilon$ or to the firing threshold, whichever is less.

Under these assumptions, it can be shown directly that there is a single unstable attractor and that it repels all trajectories that do not lie on

this fixed point toward synchrony. For two identical oscillators, it is enough to show that the slope of just one iteration of the previously derived map $h(\theta) = (1 - \theta - \Delta(\theta))$ has an absolute value greater than one due to the symmetry. The phase at the point labeled 1a in Fig. 2b, just after the black neuron receives an input is $g^{-1}(v + \varepsilon)$, where g^{-1} is the inverse function and v is the voltage just prior to the pulse. Then the phase at the point labeled 2a for the phase in the red neuron just prior to the next spike in the black neuron is $h(\theta) = 1 - g^{-1}(g(\theta) + \varepsilon)$. The derivative $h'(\theta) = -g'(\theta) g'^{-1}(g(\theta) + \varepsilon)$, which can be rewritten as $h'(\theta) = -g'^{-1}(g(\theta) + \varepsilon)/g'(\theta)$, taking advantage of the fact that the two functions are inverses. The fact that $g''(\theta) < 0$ implies that $g'^{-1}(\theta) > 0$, so it follows that the absolute value slope of $h(\theta)$ and therefore of $f(\theta)$ is greater than one everywhere on the smoothly varying segment, and therefore any intersection with the diagonal in the monotonically increasing portion of the map is unstable as indicated. The pulse-coupled leaky integrate-and-fire model satisfies their assumptions; therefore, the Mirollo and Strogatz results apply as shown schematically in Fig. 2c. Since it is also true that $h'(\theta) = -1 - \Delta'(\theta)$ on the continuous segment, the proof is exactly equivalent to showing that the smoothly varying portion of the PRC is monotonically increasing ($\Delta'(\theta) > 0$). The flat portion of the map that synchronizes immediately is due to the second segment of the PRC that is linear with a slope equal to -1 . The shape of the map guarantees that there is but a single intersection of the smoothly varying portion with the diagonal.

For two nonidentical oscillators, symmetry is broken, but a single map still captures the dynamics. The intrinsic periods T_1 and T_2 , the stroboscopically sampled phases θ_1 and θ_2 , and the normalized phase-resetting curves Δ_1 and Δ_2 are subscripted to indicate that they may be different for the two neurons. Since the oscillators have different frequencies, we must explicitly keep track of time intervals and not just phases. The information in the phase-resetting curve is not sufficient; we need the information from the spike time resetting curve that preserves the time interval information. Figure 3a shows the



Pulse-Coupled Oscillators, Fig. 3 Two nonidentical oscillators. (a) Schematic showing firing intervals τ . (b) Stroboscopic map of the firing intervals shows the intersection at the lower right is stable

derivation from Ermentrout and Terman (2010) of the map for two nonidentical pulse-coupled oscillators. The interval between the firing of the first neuron (black) and the second (red) is designated τ_1 , whereas the firing interval between the second and first neuron is τ_1 . In the drawing the firing intervals and stroboscopically sampled phases are indexed by cycle number. These intervals can be calculated in two ways: based on the phase in the non-firing neuron at the end of the interval, as in $\tau_1[n+1] = T_1 \theta_1[n]$ and $\tau_2[n] = T_2 \theta_2[n]$. Alternatively, the intervals can be calculated based on the phase at which the firing neuron previously received an input, as in $\tau_1[n+1] = T_2 - T_2 \theta_2[n] - T_2 \Delta_2(\theta_2[n])$ and $\tau_2[n] = T_1 - T_1 \theta_1[n] - T_1 \Delta_1(\theta_1[n])$. After substitution, the interval map is $\tau_1[n+1] = T_2 - T_1 + \tau_1[n] + T_1 \Delta_1(\tau_1[n]/T_1) - T_2 \Delta_2(1 - \tau_1[n]/T_2 - \Delta_1(\tau_1[n]/T_2))$, and a one-dimensional map similar to the

one in Fig. 2c can be constructed in which the intersections with the diagonal give the fixed point. An alternate map construction is given in Fig. 3b that shows the intervals in both neurons rather than just one, using the fact that each interval can be calculated either in terms of the previous phase in the one neuron $\tau_j = T_i - T_i \theta_i - T_i \Delta_i(\theta_i)$ or in terms of the current phase in the other $\tau_j = T_j \theta_j$. The black curve calculates the intervals using the phase in the black neuron, and the red curve calculates the intervals using the phase in the red neuron. The intersections of the two curves are the fixed points of the map which correspond to phase-locked period modes of the two-oscillator system. If the frequencies of the oscillators are sufficiently different, there will be no intersection and no one-to-one phase-locked mode. The arrows show the stroboscopic sampling: the leftmost intersection is unstable, but the rightmost intersection is stable. The stability criterion can be obtained by taking the derivative with respect to phase of the map given above for $\tau_1[n+1]$ in terms of $\tau_1[n]$. The resultant criterion is that $-1 < (1 + \Delta_1'(\theta_1))(1 + \Delta_2'(\theta_2)) < 1$, the same as for two identical oscillators except the relationship between the two phases θ_1 and θ_2 is slightly more complicated than in the homogeneous case.

More Complicated Systems

We have shown in detail pulse-coupled maps for one-to-one forcing of a single oscillator or one-to-one phase locking between two oscillators. These methods are generalizable to many more complicated cases (for a review, see Canavier and Achuthan 2010, 2012). For example, including conduction delays in a circuit of two pulse-coupled oscillators can change not only the phasic relationships between the oscillators but also the stability criterion. They can be extended to M:N locking in two-neuron networks. Pulse-coupling methods have also been applied to study more complex architectures, such as globally coupled synchronous networks and multiple clusters of synchronous neurons within networks, chains, rings, and hubs.

The Fully Synchronous State of Mirollo and Strogatz

The reason the Mirollo and Strogatz approach was so influential was because it could be extended to an N neuron network to show the global attractiveness of the fully synchronous state of a network of all-to-all identical, identically pulse-coupled oscillators under their assumptions. An $N - 1$ dimensional map (Guckenheimer and Holmes 1983, Chap. 1) was constructed for an N neuron network of identical, identically all-to-all coupled neurons by indexing the oscillators by the time until the next spike in that oscillator, which rotated in a predictable manner on each cycle and did not require a map for the currently spiking oscillator. The all-to-all coupling assures that each neuron receives the same inputs as every other neuron. The map uses the same general approach shown in Fig. 2 with the same two steps in the reverse order. After any oscillator fires, the phase of every oscillator is updated by the interval until the next oscillator indexed $N - 1$ in the rotation fires, then the phase of every oscillator is updated by the phase resetting produced by that event such for each oscillator i . This produces the set of maps $h(\theta_i) = g(g^{-1}(\theta_i + 1 - \theta_{N-1}) + \epsilon)$. The predictability of the firing order resulted from the assumption of a common intrinsic frequency and the monotonically increasing $g(\theta)$ and the form of the coupling. Under these assumptions, if the phase of an oscillator is less than that of another before they receive a common input, it is still less (or equal) after the two oscillators receive a common input. The $N - 1$ dimensional map is only defined for sequential firing patterns, and Mirollo and Strogatz proved in a manner analogous to the two-neuron case that any fixed point of this map must be unstable. However, there are other possible firing patterns because the phases of two oscillators can become equal if the firing of one oscillator brings another to threshold; after the spike, both oscillators are reset to a phase of zero. From that point forward, the two oscillators, which have the same frequency, receive exactly the same input and therefore have identical dynamics for all time. This event is called an absorption. Therefore, they

must also show that no firing patterns with partial absorptions can persist. The map was redefined after each absorption: neurons that have been synchronized are considered to coalesce into a single oscillator with a greater pulse strength. Thus, the number of independent oscillators is reduced. The proof does not depend on the pulse strengths being equal but instead only requires at least one pulse strength to be nonzero to destabilize the sequential state comprised of the redefined set of oscillators. Therefore, all sequential states in which some but not all neurons fire together are unstable, and global synchrony is therefore globally attracting.

The Fully Synchronous State of Goel and Ermentrout

The globally attracting, global synchrony described above is very dependent on the form assumed for the voltage waveform and the pulsatile resetting. Goel and Ermentrout used the same methodology to construct return maps for networks of all-to-all connected oscillators with identical frequencies; however, they made no assumptions regarding the voltage waveform or the precise form of the pulsatile coupling. For two neurons, the stability of synchrony can be determined by evaluating the criterion for stability in an alternating firing pattern at the phases just after (phase = 0^+) and just before (phase = 1^-) a spike, so that synchrony is stable if $-1 < (1 + \Delta'(0^+))(1 + \Delta'(1^-)) < 1$. The slopes of the phase-resetting curves are often not the same just after a spike and just before a spike for a variety of reasons, hence the right limit at a phase of 0 and the left limit at a phase of 1. This concept was extended to N all-to-all coupled neurons as follows. The phase transition function $F(\theta)$ was defined (Glass and Mackey 1988) as the phase after a pulse as a function of the phase immediately before a pulse: $F(\theta) = \theta + \Delta(\theta)$. They required $F(\theta)$ to be monotonically increasing in order to ensure the preservation of the sequential firing order. They excluded the possibility that a pulse could immediately bring an oscillator to threshold, meaning that

absorptions were excluded or at least assumed to occur all at once or not at all. These assumptions put the problem of global synchrony in a much different context than Mirollo and Strogatz, because the map of the alternating firing pattern was not applied to sequential firing patterns that repelled trajectories toward global synchrony. Instead the map was considered as a perturbation from global synchrony, and if the perturbation can be shown to die out, then global synchrony was considered stable. The issue of whether stability is globally attracting is not addressed by this methodology.

The map was constructed based on the PRCs, using the steps shown in 2a and 2b of Fig. 2b, with a rotating frame of reference so that the phase of each neuron was updated between pulses using the time until the next neuron to fire will reach threshold, then updated again by the phase resetting due to the most recent pulse. The neurons were indexed in the order in which they will fire next, so the indexes were also updated after each spike. The stability of the coupled map system was determined by linearizing about the fixed point and calculating the eigenvalues of the system. For a system in which the slopes at 0 and 1 are the same, then the stability criterion reduced to $-1 < F'(0) < 1$, or $-2 < \Delta'(0) < 0$, but $F'(0)$ was already assumed to be greater than zero because of the assumption that it is monotonically increasing. On the other hand, if the slope is discontinuous, then the stability criterion requires all permutations of $F'(0)^L F'(1)^{N-L}$ to have an absolute value less than 1. The stability of synchrony can depend on network size. A more general approach would consider perturbations with arbitrary numbers of neurons forming synchronized clusters, as in Mirollo and Strogatz.

Direct Extension of Two-Neuron Method for Synchrony

The Mirollo and Strogatz approach allowed for the possibility that a group of oscillators have a stronger effect on other oscillators than a single oscillator. They also neglected any effect of

coupling within a group of synchronized oscillators. Extending the two-neuron stability criterion for synchrony to groups of arbitrary size within an all-to-all N neuron network results in the set of criteria $-1 < (1 + \Delta_L'(0^+))(1 + (\Delta_{N-L}'(1-))) < 1$ for $L = 1$ to $N - 1$, where the subscript refers to the phase resetting due to groups of L and $N - L$ synchronized neurons, respectively (Achuthan and Canavier 2009). There is clearly an effect of network size in these criteria as well, and in that study, that perturbing a single neuron was likely to be the most destabilizing perturbation.

Applying Pulse-Coupled Maps to Real Neural Systems

There are two basic ways in which the pulse-coupling assumptions are violated by physical systems: (1) multiple input pulses that are not sufficiently separated from each other or (2) input pulses that have effects that continue beyond the next pulse emitted by the receiving oscillator. Also, it is likely that strong pulses do not sum linearly. In an N neuron network, an individual neuron may receive pulses from many other neurons. If they are spaced together closely in time, the neuron may not be able to recover from one pulse before the next is received, violating the pulse-coupling assumptions. In a physical system, the effects of two sequential pulses that are applied with diminishing separation must converge to the effect of two simultaneous pulses, but if the two pulses do not add linearly, a discontinuity appears in the pulse-coupled approximation. A second way that the assumption can be violated is if a single pulse affects not only the duration of the cycle in which it is received but the next cycle as well. This can happen if there is insufficient time to recover to the limit cycle before the neuron spikes. Also, real inputs are not Dirac delta functions with no width but instead have a finite duration. Therefore, pulses applied near the end of one cycle may bleed over into the next. The effect on the next cycle has been called second-order resetting and complicates stability criteria by requiring higher dimensional maps (Canavier and Achuthan 2010, 2012). If the resetting at zero phase is

nonzero, the presence of second-order resetting can cause the first-order resetting, or the effect on the cycle that contains the pulse, to appear discontinuous, that is, to have different values at phases of 0 and 1. Finally, the map approaches described assume a particular firing pattern, then analyze that pattern only. More generally, pulse-coupled maps (Canavier and Achuthan 2010, 2012) can be constructed by simply polling all oscillators and updating the phases based on the time till the next threshold event, but this general map is not analytically tractable. Despite these limitations, pulse-coupled maps have been used to explain synchrony within local networks of neuron as well as between distal brain regions (Ermentrout and Terman 2010).

Cross-References

- [Phase Response Curve, Measurement and Shape of General](#)
- [Spike Time Response Curve](#)
- [Weak Coupling Theory](#)

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Pulse-Resonance Sounds

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Synonyms

Animal calls; Engine purr; Musical tones; Speech sounds

Definition

Pulse-resonance sounds are the sounds that animals use to communicate at a distance, to declare

their territories, and to attract mates (Fitch and Reby 2001). They form the basis of most of the calls produced by vertebrates (fish, frogs, birds, and mammals). The tones of orchestral instruments are pulse-resonance sounds (Fletcher and Rossing 1998) and the internal combustion engine produces a form of pulse-resonance sound. Pulse-resonance sounds are ubiquitous in the world around us and they are the interesting sounds of everyday life (Patterson et al. 2008). They are acoustically distinct from the inanimate sounds produced by turbulent air and water (wind and rain).

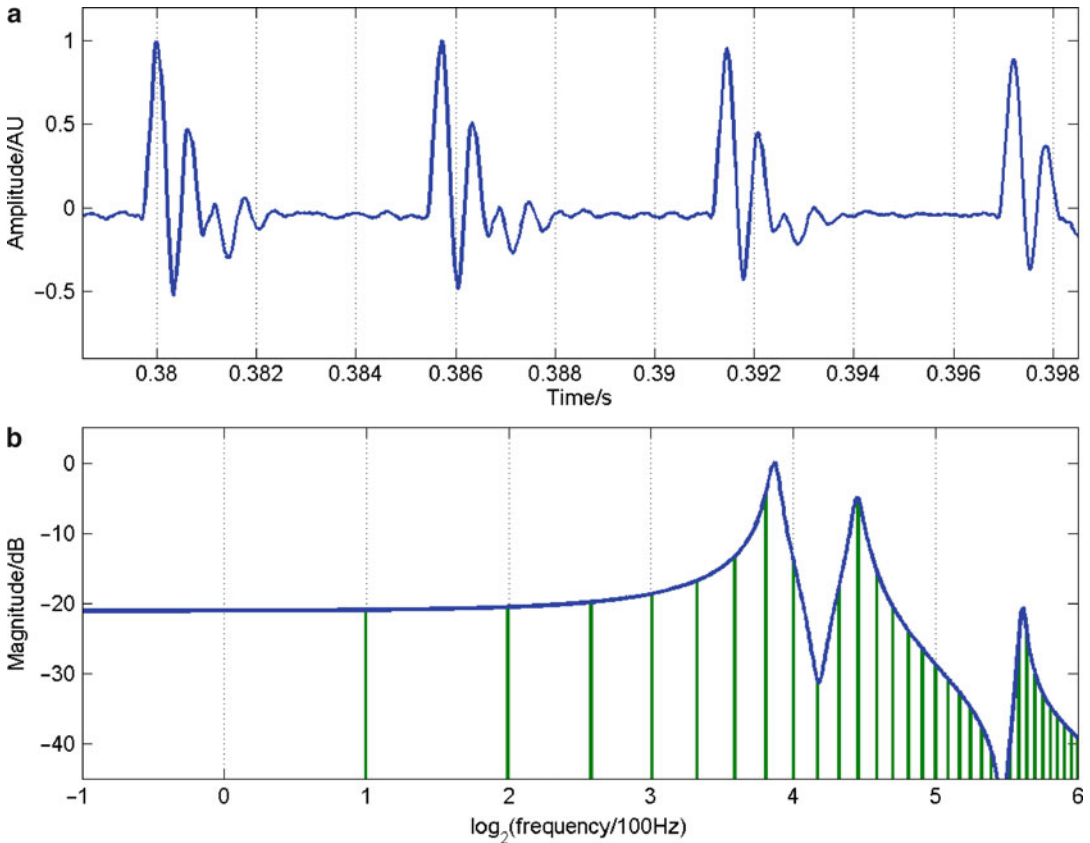
Detailed Description

The vowels of speech are pulse-resonance sounds and the waveforms of the vowels illustrate the properties of these sounds. Figure 1 shows the waveform (a) and the magnitude spectrum (b) of an /a/ vowel. It sounds like the vowel in the word “paw” and in this case it sounds like it was spoken by a child. Note that the period of the sound is very short (5 ms); six cycles of this sound would occur in less than the time of a single frame of a standard video. So the waveform in this figure presents the microstructure of the sound.

Under this temporal microscopic, we see that the sound is composed of a regular stream of acoustic pulses, each of which is accompanied by a resonance. It is this pairing of pulses with resonances and the mechanical implications for how the sounds are produced that gives them the name *pulse-resonance sounds* (Patterson et al. 2008).

Pulse-Resonance Sounds and Source-Filter Systems

The mechanisms in animals and musical instruments that produce pulse-resonance sounds are referred to in engineering terms as *source-filter systems* (Fant 1970). In mammals, the *source* of the regular stream of pulses is the glottis in the larynx at the bottom of the throat; the pulse shape is effectively invariant and so the information



Pulse-Resonance Sounds, Fig. 1 The waveform (a) and magnitude spectrum (b) of a short segment of an /a/ vowel. It sounds like the vowel in “paw” as spoken by a child

associated with the stream of pulses is primarily the *glottal-pulse rate* (GPR) (the reciprocal of the period of the wave). The GPR determines the fundamental, F_0 , of the series of spectral harmonics that carry the energy of the sound (the set of vertical green lines in Fig. 1b). The spacing of the harmonics decreases as harmonic number increases because the spectrum is plotted on a logarithmic frequency axis. The frequency unit is octaves relative to 100 Hz, and so, 1 is 200 Hz (the reciprocal of 5 ms). The GPR determines the sequence of pitches we hear when a person sings a song; when GPR and the pitch of the voice increase, F_0 and the entire set of harmonics move, as a unit, to the right along this logarithmic frequency axis.

In mammals, the *filter* is the vocal tract between the larynx and the lips; the vocal cavities of this filter impose resonances on the glottal

pulses which appear as peaks in the magnitude spectrum. Collectively, the resonances impose a shape on the envelope of the frequency spectrum (the blue line in Fig. 1b), and this *envelope shape* is what determines vowel type (/a/, /e/, /i/, /o/, /u/, etc.). In speech research, the peaks in the spectral envelope are referred to as “formants,” and the position of the spectral envelope along the frequency axis is expressed in terms of the geometric mean formant frequency (MFF) (e.g., Assmann and Nearey 2008; Irino et al. 2012).

The Size Information in Pulse-Resonance Sounds

It is a general principle of mechanical vibration that larger/heavier things vibrate more slowly than smaller/lighter things. The sources and the filters

in the bodies of animals developed, evolutionarily, from preexisting body parts. As a result, as an individual matures, the source and the filter increase in size. For example, in mammals, the components of the vocal tract that compose the filter are tubes that connect the openings of the mouth and nose to the lungs and the stomach. These tubes are essential for life and they have to increase in length as the body of an individual matures and the nose and mouth move further and further away from the lungs and stomach. In humans, vocal tract length increases almost linearly with height from age three (Fitch and Giedd 1999; Turner et al. 2009, Fig. 4).

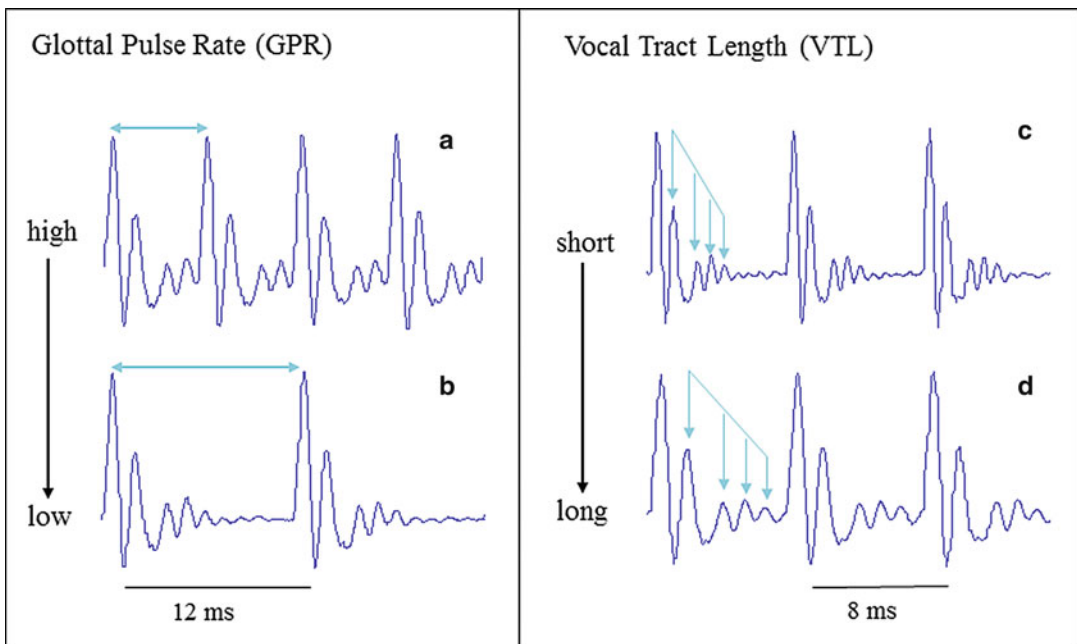
The effects of source size and filter size on the waveform of a vowel are illustrated in Fig. 2. The shape of the resonance is the same in each cycle of all four waves. In the left column, one person has spoken two versions of /a/ using a high (a) and a low (b) GPR; the pulse rate determines the pitch of the voice. The resonances have the same form since it is the same person speaking the same vowel. In the right column, a short person (c) and a tall person (d) have spoken versions of

/a/ on the same pitch. The pulse rate and the shape of the resonance are the same, but the rate at which the resonance proceeds within the glottal cycle is slower in the lower panel. This person has the longer vocal tract and so their resonances ring longer.

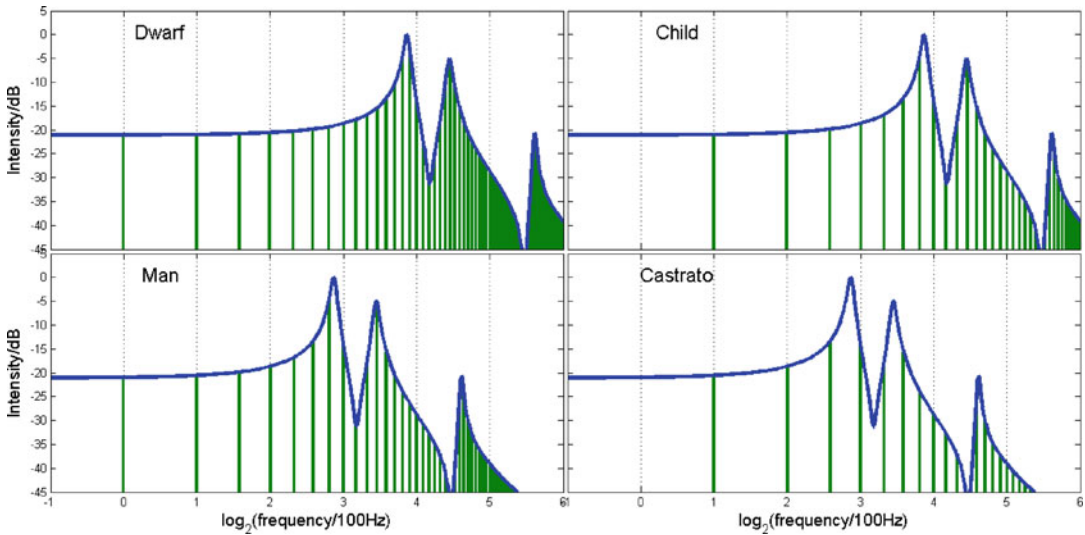
In signal processing terms, changes in the size variables cause dilation in the waveform of a pulse-resonance sound. Changes in F0 cause dilation in the period of the pulse stream; changes in MFF cause dilation in the period of the resonance. Note, however, that the two size variables are mathematically independent, within the constraint that the pitch period has to be sufficiently long to permit the resonance to run for a reasonable proportion of its natural duration.

The Role of Size Information in Speaker Perception

The effect of size on the magnitude spectrum of a vowel is illustrated schematically in Fig. 3. The spectrum used to illustrate the /a/ vowel of a child in Fig. 1 is shown in the upper right-hand panel of the figure. The size information appears in the



Pulse-Resonance Sounds, Fig. 2 Left panel: Two /a/ vowels spoken by one person on low and high pitch. Right panel: Two /a/ vowels spoken by different people, one with a short and one with a long vocal tract



Pulse-Resonance Sounds, Fig. 3 Magnitude spectra for an /a/ vowel as spoken by four different people, a child, a man, a male dwarf, and a castrato. The harmonics are

shifted one octave toward the origin in the *left* column; the spectral envelope is shifted one octave toward the origin in the *lower* row

position variables, F0 and GPR. The GPR and MFF are both relatively high in the upper right-hand panel, and it is this combination of GPR and MFF that produces the sound of a child's voice. As a child matures into an adult, the GPR and the MFF both decrease, and the average decrease for males and females is approximately one octave for both MFF and GPR (Lee et al. 1999).

In Fig. 3, the GPR in the panels of the left-hand column is one octave below that in the panels of the right-hand column; the set of harmonics (green) is shifted, as a unit, one octave toward the origin, on this logarithmic frequency scale. Similarly, in the panels of the lower row, the spectral envelope is shifted, as a unit, one octave toward the origin on this logarithmic frequency scale, and the MFF in the lower row is one octave below that in the upper row. The logarithmic frequency scale converts the dilation of the waveform into a frequency shift in the magnitude spectrum. In the lower left-hand panel, the voice has a combination of a relatively low GPR and a relatively low MFF, and this combination of GPR and MFF produces the sound of a man's voice.

Although, the descent of F0 and MFF is highly correlated in normal human development, the two size variables are acoustically independent to a

large degree, and occasionally, the ratio of F0 to MFF can be considerably larger or smaller than normal. The effects are most pronounced in males where a sex-related release of hormones at puberty causes the vocal folds of males to grow and add weight which in turn causes F0 to decrease disproportionately in males. In the nineteenth century, the hormone release was occasionally inhibited artificially in choir boys to prevent the normal pitch break at puberty. As the boy increased in stature and MFF decreased as normal, the voice developed an *unusually large F0-to-MFF ratio* because the F0 did not decrease disproportionately. The situation is illustrated in the lower right-hand panel of Fig. 3, and it explains the distinctive singing voice referred to as a "castrato." Today, counter tenors produce a somewhat similar effect by singing in falsetto voice, that is, they temporarily inflate the F0-to-MFF ratio by artificially increasing their pitch while singing. An *unusually small F0-to-MFF ratio* arises when the hormones that induce normal body growth are not produced in sufficient amounts; growth in stature is restricted and with it the decrease in MFF that accompanies the normal increase in vocal tract length. Nevertheless, the sex-related increase in vocal fold size still occurs and F0 drops by the

normal amount at puberty. This explains the distinctive voice of the dwarf, where the pitch is unusually low for the vocal tract length.

Before the age of puberty, as girls grow in stature, F0 and MFF both decrease but they do so in a way that preserves the F0-to-MFF ratio (Turner et al. 2009, Fig. 13). Near the time of puberty, girls have a growth spurt, but even during this phase, the F0-to-MFF ratio remains effectively the same, with the result that women have almost the same F0-to-MFF ratio as girls (and boys). The ratio is larger than it is for men because F0 is disproportionately low in men. In any event, it is the F0-to-MFF ratio that primarily distinguishes the voices of women and children from the voices of men.

In summary, when a person is speaking, the F0 and MFF are largely responsible for communicating the size of the speaker and, in adults, the ratio of F0 to MFF provides an important cue as to whether the speaker is a man or a woman. The message of the communication is conveyed by the shape of the spectral envelope which is largely independent of the size variables, F0 and MFF.

Background and Research on Pulse-Resonance Sounds

The remainder of this entry provides a little background information on the mathematics underlying pulse-resonance sounds and some recent research projects that it has spawned. The paragraphs are intended to provide the reader with leads they might want to follow up rather than a working knowledge of each topic.

Background Mathematics

About 20 years ago, sections of the signal processing community began to suspect that the traditional time-frequency representation of sound (the spectrogram) was probably not the best representation for automatic speech recognition, and Cohen (1993) suggested an alternative time-scale representation of sound. The mathematics of acoustic scale suggested that it should be possible to construct a scale-invariant representation of

speech sounds. This was important because when a traditional automatic speech recognition (ASR) system is trained on the speech of one person, the system does not generalize well to the speech of people who differ in size. It was argued that if the spectrogram of the traditional ASR system was replaced by a scale-invariant representation of speech, it would facilitate both the learning and recognition stages of ASR. Umesh et al. (1999) illustrated the potential of the time-scale representation for ASR.

The Auditory Representation of Acoustic Scale

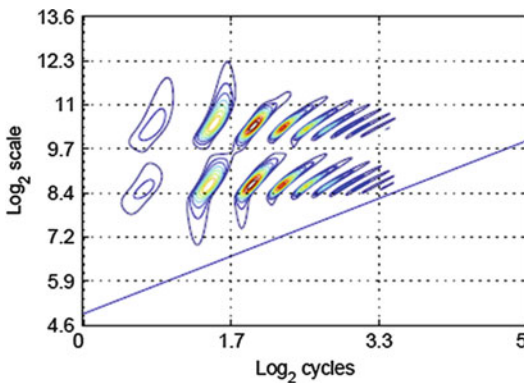
The mathematics of acoustic scale prompted Irino and Patterson (1997, 2002, 2006) to revise their computational model of auditory processing and show how the auditory system might construct a scale-invariant representation of pulse-resonance sounds. In their model, the spectral analysis performed by the cochlea is simulated by an auditory *wavelet transform* rather than a windowed Fourier transform. It is referred to as a dynamic, compressive gammachirp filterbank (Irino and Patterson 2006). The frequency/scale dimension of the wavelet transform is quasi-logarithmic which gives the auditory image a normalized scale dimension by default. The initial stages of neural processing are simulated by “strobed” temporal integration (STI) – a process that stabilizes the repeating neural pattern produced in the auditory nerve by successive cycles of a vowel (Patterson 1994). The resulting two-dimensional representation of sound is referred to as an auditory image. The STI calculation is a simplified version of autocorrelation which Licklider (1951) suggested as a neural mechanism for pitch extraction more than 60 years ago. STI has the advantage of preserving the temporal asymmetry of pulse-resonance sounds which means that it can be used to explain aspects of timbre perception that autocorrelation cannot (Patterson and Irino 2013).

Irino and Patterson (2002) showed that the temporal dimension of the auditory image could be normalized by converting the units of the time-like dimension into cycles of the impulse response of the auditory filter (on a channel-by-channel

basis). Mathematically, the processes that generate the auditory image are a form of stabilized, wavelet-Mellin transform (SWMT), and the representation it produces is scale-shift *invariant*. It is, however, somewhat complex and it has not been successfully applied to ASR as yet.

A Scale-Shift Covariant Auditory Image

A more intuitive version of the normalized auditory image that is scale-shift *covariant* has since been developed (Patterson et al. 2007). The auditory image of a synthetic two-formant /a/ vowel is presented in Fig. 4 to illustrate the form and value of scale-shift covariance. The two formants have the same mathematical form (a simple damped resonance), and they simulate the action of the throat and mouth cavities of the vocal tract. The only difference between them is that one cavity is smaller than the other. In the scale-shift covariant auditory image (Fig. 4), the two resonators produce the same pattern of activity and the cavity size information is coded separately as the vertical position of the pattern. The representation is covariant, rather than invariant, because the size information remains in the auditory image. The combined distribution produced by the pair of formants represents the vowel-type information, which in this example is /a/. There are figures showing the form of the vowel information at earlier stages of processing in Patterson et al. (2007). In those representations,



Pulse-Resonance Sounds, Fig. 4 The /a/ vowel of a man as it appears in the scale-shift covariant version of the auditory image

the upper vowel pattern is shorter than the lower vowel pattern and it is somewhat twisted relative to the lower pattern.

When speaker with a different size speaks the same /a/ vowel, the change in vocal tract length causes proportionate changes in vocal cavity length, and the complete vowel-type distribution moves vertically in the auditory image without changing shape – up for a shorter VTL and down for a longer VTL. The blue diagonal shows the period of the vowel which is the pitch information in the auditory image (the transformation from time-like units to cycles causes it to rotate from its vertical orientation in earlier representations). When the size of the speaker changes, the associated change in vocal cord size causes the diagonal to move vertically in the image without changing its angle, and the shift is independent of both the shape and position of the vowel-type distribution. The diagonal also restricts the vowel-type distribution to the part of the space above the diagonal. In the voices of tall women, the diagonal can encroach on the vowel-type distribution and limit the extent of the first formant in the cycles dimension.

Terminology of Acoustic Scale

In the most recent version of the terminology (Patterson et al. 2010), the rate of oscillation of a vocal resonance (or a set of vocal resonances) is referred to as the “acoustic scale of the filter element of the sound” (S_f), and the pulse rate is referred to as the “acoustic scale of the source element of the sound” (S_s) (Patterson and Irino 2013). The values of these acoustic variables describe the size, or scale, of acoustic features in the waveform, and they describe the position of their counterparts in the magnitude spectrum (when plotted on a log-frequency axis).

Research on Pulse-Resonance Sounds

There are two software packages that allow one to manipulate the S_f and S_s of natural speech sounds, so that utterances recorded by a man could be transformed to sound like those of a woman or a child and vice versa; their names are

STRAIGHT (Kawahara et al. 1999) and PRAAT (Boersma 2001). They made it possible to record the speech sounds of one individual and then synthesize populations of speakers with widely varying vocal characteristics who were all speaking the same set of utterances with the same accent and the same prosodic details. These speaker sets were used to perform behavioral experiments on the perception of S_f and S_s separately and in combination.

The Robustness of Speech Perception to Variation in S_f and S_s

The initial experiments were designed to provide quantitative evidence for what everyone intuitively knows, namely, that speech perception is singularly robust to changes in the S_f and S_s values of communication sounds. We have no difficulty whatsoever understanding when a child and an adult have spoken the same speech sounds (vowels, syllables, or words), despite substantial differences in the S_f and S_s values of the sounds. Indeed, we can recognize speech sounds when the S_f and S_s of the voice have been scaled well beyond the range of normal experience and when the combination of S_f and S_s values is not one that occurs in the normal population (Smith et al. 2005; Assmann and Nearey 2008). The recognition performance of humans stands in marked contrast to that of machines; if an ASR system is trained on a man's voice, it is unlikely to work for a woman, let alone a child.

The behavioral experiments with scaled speech sounds also showed that listeners can specify the size and sex of speakers from random samples of their speech sounds (Smith and Patterson 2005). Discrimination experiments were performed with sequences of vowels, syllables, and words to determine the just noticeable difference (JND) for changes in S_f which listener's hear as a change in speaker size. The JND is defined as the change in S_f required to support 76 % correct identification of which of two speakers is the smaller (or larger). The results are surprisingly simple: The JND for S_f was about 8 % with vowel sounds

(Smith et al. 2005), 5 % with syllables (Ives et al. 2005), and 5 % with words (Irino et al. 2012), and these values are roughly the same over a wide region of the $S_f - S_s$ plane, that is, for voices with very different combinations of S_f and S_s . For comparison, the JND for noise level (loudness) is about 10 % and the JND for light level (brightness) is about 15 %. The experiment of Irino et al. (2012) also compared discrimination performance for voiced words with that for whispered words and showed that the JND for whispered words is also 5 % provided the words are clearly audible.

In short, the experiments support the hypothesis that the auditory system automatically normalizes communication sounds for S_f and S_s to segregate the message from the vocal characteristics.

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PyNN: A Python API for Neural Network Modelling

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Definition

PyNN is an application programming interface (API) for describing and simulating neuronal network models in the Python programming language. Numerical solution of the model equations is performed by a “backend” simulator, which as of PyNN version 0.7 can be any of NEURON (Hines and Carnevale 1997), NEST (Gewaltig and Diesmann 2007), Brian (Goodman and Brette 2008), or PCSIM (Pecevski et al. 2009). Alternatively, the backend can be a neuromorphic hardware system (Bruderle et al. 2009; Galluppi et al. 2010). PyNN thus provides a simulator-independent method for describing spiking neuronal network models. Data generated by the backend simulator is reformatted by PyNN into a standard format, and thus PyNN can also be used as a base platform on which to build simulator-independent data analysis and visualization tools.

Detailed Description

The PyNN API allows the construction and simulation of neuronal network models in a simulator-independent way, i.e., the same Python script can be used to perform simulations on any of the supported backend simulators or hardware devices. The results are expected to be quantitatively the same within certain limits determined by the choice of numerical algorithms made by different simulators. PyNN provides a limited number of standardized neuron and synapse models (including synaptic plasticity) that are each available in at least two of the supported

p-Value

► Significance Evaluation

simulators. At the present time, all of the neuron models are point neuron models such as the integrate-and-fire family of models or single-compartment Hodgkin-Huxley models. Multi-compartment models are not yet supported in a simulator-independent way, although they can be used with those simulators that support them. Arbitrary network structure and connectivity may be expressed with the API. PyNN provides a library of commonly used connectivity patterns, but user-defined patterns are straightforward to write.

The implementation of PyNN is made much simpler by the widespread adoption of Python as an interface language for neuronal network simulators (Davison et al. 2009). For each supported backend simulator, the PyNN API is implemented in terms of the native Python API of that simulator. For simulators that do not provide a Python interface, PyNN can generate code in the language used by that simulator. The same approach can be used for other simulator-independent model description languages such as NeuroML (Gleeson et al. 2010).

PyNN is open-source software, developed by an informal community and distributed under the CeCILL license. An automated test suite and continuous integration software are used to verify correct behavior and minimize bugs. The project homepage is at <http://neuralensemble.org/PyNN>. This page contains links to detailed documentation, to the version control repository, and to the bug tracker.

Cross-References

- [Brian Spiking Neural Network Simulator](#)
- [Integrate and Fire Models, Deterministic](#)

- [MOOSE, the Multiscale Object-Oriented Simulation Environment](#)
- [NEST: the Neural Simulation Tool](#)
- [neuroConstruct](#)
- [NeuroML](#)
- [Neuromorphic Hardware, Large-Scale](#)
- [NEURON Simulation Environment](#)
- [NineML](#)

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Further Reading

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Q

Q Current

► [Hyperpolarization-Activated Cyclic Nucleotide Gated Channels](#)

dependence of maximum channel conductance on temperature.

Detailed Description

Mathematical Definition

The Q_{10} of a process is defined as

$$Q_{10} = \frac{\text{Rate of process at temperature } T + 10^{\circ}\text{C}}{\text{Rate of process at temperature } T}$$

Usage

If the rate r of a process at temperature T is known, the rate at another temperature T_1 can be estimated using

$$r(T_1) = r(T)Q_{10}^{(T_1-T)/10}$$

For example, in a model of an ion channel in the formalism used by Hodgkin and Huxley (1952), the opening and closing rate coefficients of a particular gating particle at temperature T might be $\alpha(T)$ and $\beta(T)$. To scale these to temperature T_1 , the following relations can be used:

$$\begin{aligned}\alpha(T_1) &= \alpha(T)Q_{10}^{(T_1-T)/10} \text{ and } \beta(T_1) \\ &= \beta(T)Q_{10}^{(T_1-T)/10}\end{aligned}\quad (1)$$

Q10: The Effect of Temperature on Ion Channel Kinetics

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Synonyms

[Temperature coefficient](#)

Definition

The Q_{10} is a measure of the degree to which a biological process depends on temperature. It is defined as the ratio between the rate of a biological process at two temperatures separated by 10°C . In the context of ion channels, it can be applied to the temperature dependence of the rate of channel opening and closing and to the

If the ion channel kinetics are expressed in terms of the time constant $\tau = 1/(\alpha + \beta)$, the transformation is

$$\tau(T_1) = \tau(T)Q_{10}^{(T_1-T)/10} \quad (2)$$

Measurement and Validity

The Q_{10} can be measured empirically at a particular base temperature T . As described later, the Q_{10} is expected to vary depending on the base temperature used for the measurement. There are more theoretically based ways than the Q_{10} for adjusting for temperature in complex models of ion channels (Sterratt et al. 2011). However, the Q_{10} can be a practical approximation to relate measurements at one temperature to measurements or models at other temperatures.

Typical Values

The rate of opening and closing of ion channels typically has a Q_{10} in the range 2.4–4 (Hille 2001). The maximum conductance of an ion channel varies with temperature with a Q_{10} in the range 1.2–1.5 (Hodgkin et al. 1952; Hille 2001).

Physical Basis

According to the Arrhenius equation, a chemical reaction has an associated activation energy ΔE and the rate $r(T)$ of the reaction at temperature T (in kelvins) is given by

$$r(T) = A \exp\left(-\frac{\Delta E}{k_B T}\right) \quad (3)$$

where k_B is Boltzmann's constant and A is a constant of proportionality. According to the definition of the Q_{10} , this gives

$$Q_{10} = \frac{r(T+10)}{r(T)} \quad (4)$$

$$= \exp\left(-\frac{\Delta E}{k_B(T+10)} + \frac{\Delta E}{k_B T}\right) \quad (5)$$

$$= \exp\left(\frac{\Delta E}{k_B} \left(\frac{10}{T(T+10)}\right)\right) \quad (6)$$

Thus, the Q_{10} is expected to depend on the measurement temperature. However, this dependence is small for the temperature ranges within which ion channels operate. For example, if the Q_{10} of a reaction calculated from rates at 5 °C and 15 °C is found to be 3, the Q_{10} calculated at 27 °C and 37 °C would be 2.57, a reduction of 14%. This can be shown by rearranging Eq. 6 to obtain $\Delta E/k_B$:

$$\frac{\Delta E}{k_B} = \ln Q_{10}^{5-15} \frac{T(T+10)}{10} \quad (7)$$

where $T = 5$ °C is the lower measurement temperature, and then substituting this value of $\Delta E/k_B$ back into Eq. 6 with $T = 27$ °C.

Cross-References

- [Hodgkin-Huxley Model](#)
- [Markov Models of Ion Channels](#)
- [Thermodynamic Models of Ion Channels](#)

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Quadratic Integrate and Fire Model

- [Integrate and Fire Models, Deterministic](#)

Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities

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Definition

Quadratization of biophysical (conductance-based) models having a parabolic-like voltage nullcline in the subthreshold voltage regime refers to the process by which these models are substituted by “caricature” models having a strictly parabolic voltage nullcline and a linear nullcline for the recovery variable. We refer to the latter as quadratic or parabolic models. The parabolic-like and strictly parabolic voltage nullclines coincide at their extrema (minima or maxima) and are well approximated by each other in vicinities of these extrema whose sizes depend on the model parameters. Quadratic models are simplified by a change of variables that translates these extrema to the origin of the phase-plane diagram. A further simplification (parameter reduction) can be achieved by nondimensionalizing the quadratic models. This procedure can be extended to three-dimensional models having a parabolic-cylinder-like shaped voltage nullsurface and to models having time-dependent inputs and synaptic currents.

Detailed Description

Introduction

Reduced models of neuronal activity often involve a detailed description of the subthreshold

dynamics supplemented with artificial spikes (Izhikevich 2006; Ermentrout and Terman 2010; Borgers 2017). One classification of the different types of mathematical descriptions of the neuronal subthreshold dynamics consists of two groups: biophysical and phenomenological. Biophysical models include the description of the interplay of the ionic currents that operate in the subthreshold voltage regime in terms of electric circuit parameters such as capacitances, conductances, and reversal potentials, among others. These models can be thought of as conductance-based models of Hodgkin-Huxley (HH) type (Hodgkin and Huxley 1952) where the spiking currents (transient sodium and delayed-rectifier potassium) have been removed (Lapicque 1907; Ermentrout and Terman 2010; Gerstner et al. 2014; Rotstein et al. 2006; Smith et al. 2000; Izhikevich 2006). Phenomenological models, on the other hand, consist of heuristic dynamic equations that include idealized versions of the types of nonlinearities (e.g., parabolic, cubic) and time constants that are assumed to be present in the system. The parameters have no explicit connection to the neuronal biophysics, but these models can be used to understand the neuronal dynamic mechanisms in terms of relatively simple sets of equations and the geometry of the phase-plane diagrams. In both types of models, the parameters can be fitted to match the observed experimental patterns. However, the results of using phenomenological models lack a biophysical interpretation in the absence of an explicit link to the biophysical models.

In the so-called leaky integrate-and-fire (IF) model, the subthreshold dynamics are linear and one-dimensional. The quadratic and exponential IF models have also one-dimensional subthreshold dynamics and include the said type of nonlinearities for the evolution of the equation for V (Latham et al. 2000; Hansel and Mato 2001; Fourcaud-Trocme et al. 2003). Models with two-dimensional dynamics can be obtained by adding a recovery variable (w) with linear dynamics to the models mentioned above, giving rise to the linear resonate-and-fire models (Izhikevich 2001) and the nonlinear adaptive quadratic (Izhikevich 2003) and exponential (Brette and Gerstner 2005)

IF models. More complex models with three-dimensional subthreshold dynamics that include two recovery variables mimicking ionic currents with slow dynamics have been used to a lesser extent (e.g., hyperpolarization-activated mixed sodium-potassium, T-type calcium, adaptive) (Rotstein et al. 2006; Smith et al. 2000).

Phenomenological models of quadratic IF type with strictly parabolic V -nullclines in the subthreshold regime (Izhikevich 2003) have been frequently used as ad-hoc models to investigate the dynamics of neurons in a variety of systems. The lack of an explicit connection with the neuronal biophysics limits the scope of these studies as well as network studies that combine the two modeling approaches (phenomenological and biophysical) for different neuron types in the same circuits (Tikidji-Hamburyan et al. 2015; David et al. 2015). For example, phenomenological models cannot capture the effects of changes in the biophysical conditions (e.g., ionic currents levels, synaptic connectivity) on the resulting patterns. These models also fail to capture the existence of patterns with equal attribute values (e.g., firing frequency) generated by neurons with different biophysical properties (Prinz et al. 2004; Rotstein et al. 2016) or the effects of these types of heterogeneous neurons on the network patterns in which they are embedded. These issues are not unique for models of adaptive quadratic IF models, but they are shared by all phenomenological models. Linearization of conductance-based models (Richardson et al. 2003; Koch 1999) provides explicit formulas for the parameters in the linearized models in terms of the biophysical parameters (Izhikevich 2001; Rotstein 2013, 2014a), but linear models fail to capture important dynamic effects (Rotstein 2015).

In this entry, we present a systematic reduction of biophysical (conductance-based) models with parabolic-like V -nullclines (nullsurfaces) to phenomenological models with strictly parabolic V -nullclines (nullsurfaces) and linear nullclines (nullsurfaces) for the recovery variable(s). We refer to these reduced models as parabolic or quadratic and to the reduction process as

quadratization. The approach presented here extends the concept of linearization to include second order derivatives in voltage and captures the quadratic nonlinearities in close vicinities of the extrema of the parabolic-like nullclines for the underlying two-dimensional system. It is different from the approach discussed in Izhikevich (2006) where a phenomenological quadratic model is presented ad hoc and no explicit formulas that link its parameters with the biophysical parameters are provided. Although the phenomenological parameters can be approximated by using the steady-state $I - V$ relation, this needs to be measured experimentally or computed numerically. Our approach allows for a biophysical straightforward biophysical interpretation of the results using the quadratic model.

We focus on two- and three-dimensional models having one or two voltage-dependent gating variables, respectively (each of which correspond to an ionic current) and an additional gating variable with fast dynamics (slave to voltage). The system consisting of the voltage equation together with an equation for one of the gating variables (x_1) is thought to be the “main” system. The second gating variable (x_2), typically slower, is considered to have a modulatory effect in the sense that the projections of the V -nullsurface onto planes parallel to the V - x_1 plane remain parabolic-like in the subthreshold regime. We also include a time-dependent input current and a synaptic current in order to make the reduction amenable for network models, although we do not discuss these models here.

After an appropriate translation, the minimum of the strictly parabolic V -nullcline is located at the origin of the phase-plane diagram. The strictly parabolic V -nullcline is concave up. If the parabolic-like V -nullcline is concave-down, then the quadratization process includes an inversion of the V -nullcline. An additional simplification (nondimensionalization) reduces the number of parameters further, but it changes the definitions of the time and the dependent variables. Importantly, the units of the variables in the quadratic model are different from their original units. This approach produces formulas that relate the parameters of the quadratic model with the biophysical

parameters. This is necessary for the biophysical interpretation of the results using caricature models.

The quadratization procedure described in this entry assumes that the V -nullcline (nullsurface) is parabolic-like (parabolic-cylinder-like shaped) in the subthreshold voltage regime. This is often overlooked when phenomenological models of quadratic IF type with strictly parabolic V -nullclines are used. In fact, the neuronal subthreshold dynamics are often governed by other types of nonlinearities such as cubic-like ones (Rotstein 2017, 2014b; Remme et al. 2012). Whether the subthreshold dynamics have parabolic- or cubic-like nonlinearities may not be apparent from the identity of the participating ionic currents in the biophysical models (Izhikevich 2006; Rotstein 2017). As shown in previous work, models with the same combination of ionic currents may give rise to different types of nonlinearities (parabolic- and cubic-like) in the subthreshold regime (Rotstein 2017).

We discuss additional limitations of the quadratization procedure and the use of quadratic models later in this entry.

Models

Conductance-Based Models

We use conductance-based models of Hodgkin-Huxley type (Hodgkin and Huxley 1952) to describe the neuronal subthreshold dynamics. Our formulation allows for various combinations of ionic currents that have been shown to underlie the generation of subthreshold resonance, including persistent sodium (I_{Nap}), h- (I_h) and slow potassium currents (I_{Ks}) (Acker et al. 2003; Schreiber et al. 2004; Rotstein et al. 2006; Izhikevich 2006) (see below). However, we do not include the spiking currents (transient sodium and delayed-rectifier potassium). The onset of spikes is described by the models we use. In order to describe the spiking dynamics either these currents have to be included or spikes have to be added manually after their onset.

For generality, in our description we use non-specific ionic currents. We discuss specific model

examples later in this section. The current-balance equation is given by

$$C \frac{dV}{dt} = I_L - I_1 - I_2 - I_3 + I_{app} + A_{in} I(t) - I_{syn}, \quad (1)$$

where V is the membrane potential (mV), t is time (msec), C is the membrane capacitance ($\mu(\text{farad})/\text{cm}^2$), I_{app} is the applied bias (DC) current ($\mu(\text{ampere})/\text{cm}^2$), $I(t)$ is a time-dependent input current with amplitude A_{in} ($\mu\text{A}/\text{cm}^2$), $I_L = G_L (V - E_L)$ is the leak current, I_j ($j = 1, 2, 3$) are ionic currents, and I_{syn} is a synaptic current. The ionic currents we consider here are of the form

$$I_j = G_j x_j (V - E_j) \quad (2)$$

where x_j are the gating variables, G_j the maximal conductances (mS/cm^2), and E_j the reversal potentials (mV).

All gating variables x obey a first order differential equation of the form

$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)} \quad (3)$$

where $x_\infty(V)$ and $\tau_x(V)$ are the voltage-dependent activation/inactivation curves and time-scales, respectively.

The synaptic current we consider has the form.

$$I_{syn} = G_s s(t) (V - E_s) \quad (4)$$

where $s(t)$ is the synaptic function, G_s the maximal synaptic conductance, and E_s the synaptic reversal potential.

The ionic currents we consider here (Eq. 2) are restricted to have a single gating variable x and to be linear in x . In addition, in this entry we focus on two-dimensional models having two dynamic gating variables (x_1 and x_2) and an additional gating variable evolving on a fast time scale for which the adiabatic approximation $x_3 = x_{3,\infty}(V)$ is justified. Additional fast currents can be included without significantly changing the formalism.

Models of Quadratic Type

The models of quadratic type we use in this entry have the form

$$\frac{dv}{dt} = \sigma av^2 - w + \hat{A}_{in} I(t) - g_s s(t) (v - \hat{E}_s) \quad (5)$$

$$\frac{dw}{dt} = \epsilon [\alpha v - w - z], \quad (6)$$

$$\frac{dz}{dt} = \epsilon \eta [-\gamma v - z + \lambda]. \quad (7)$$

For two-dimensional biophysical models, the geometric model reduces to Eqs. 5 and 6 with z substituted by λ .

$$\frac{dv}{dt} = \sigma av^2 - w + \hat{A}_{in} I(t) - g_s s(t) (v - \hat{E}_s), \quad (8)$$

$$\frac{dw}{dt} = \epsilon [\alpha v - w - \lambda]. \quad (9)$$

Collectively, we refer to the parameters $a, \alpha, \gamma, \lambda$, and σ as the geometric parameters since they control the geometry of the phase-space diagram: α and γ control the slope of the w and z nullsurfaces, respectively, λ controls the relative displacement between the v - and the z nullsurfaces (or between the v - and w nullclines in the two-dimensional case). The parameter a is assumed to be positive. The product σ controls the curvature of the parabolic V -nullcline. The concavity sign is captured by $\sigma = \pm 1$. By an appropriate change of variables when $\sigma = -1$ (concave down parabolic v -nullcline), the model can be transformed into one having a concave up parabolic v -nullcline.

The dynamic parameters ϵ and η represent the time scale separation between the variables v and w_1 , and between the variables w_1 and w_2 , respectively. For simplicity we assume that $\eta < 1$.

The geometric and dynamic parameters and the parameters $\hat{A}_{in}$, g_s , and $\hat{E}_s$ can be expressed in terms of the biophysical parameters in Eqs. 1, 2, 3, and 4. We provide these expressions below and

briefly explain the quadratization procedure that brings the biophysical model (1), (2), (3), and (4) into the quadratic model (5), (6), and (7).

The units of the variables and parameters in Eqs. 5, 6, and 7 are $[v] = \text{mV}$, $[w] = \text{mV/msec}$, $[z] = \text{mV/msec}$, $[\epsilon] = 1/\text{msec}$, $[\eta] = 1$, $[a] = 1/(\text{msec mV})$, $[\alpha] = 1/\text{msec}$, $[\gamma] = 1/\text{msec}$, $[\lambda] = \text{mV/msec}$, $[\hat{A}_{in}] = \text{mV/msec}$, $[g_s] = 1/\text{msec}$, and $[\hat{E}_s] = \text{mV}$. Some of these variables and parameters involve the capacitance C . When it is assumed to be $C = 1$ and not included in the definitions of the variables and parameters, $[w] = \text{mS mV/cm}^2$, $[z] = \text{mS mV/cm}^2$, $[a] = \text{mS}/(\text{cm}^2 \text{mV})$, $[\alpha] = \text{mS}/\text{cm}^2$, $[\gamma] = \text{mS}/\text{cm}^2$, $[\lambda] = \text{mS mV/cm}^2$, $[\hat{A}_{in}] = \mu\text{A}/\text{cm}^2$, and $[g_s] = \text{mS}/\text{cm}^2$.

Dimensionless Models of Quadratic Type

System (5), (6), and (7) can be put in dimensionless form with the consequent reduction in the number of parameters

$$\frac{d\bar{v}}{d\bar{t}} = \sigma \bar{v}^2 - \bar{w} + \bar{A}_{in} I(\alpha^{-1} \bar{t}) - \bar{g}_s s(\alpha^{-1} \bar{t}) (\bar{v} - \bar{E}_s) \quad (10)$$

$$\frac{d\bar{w}}{d\bar{t}} = \bar{\epsilon} [\bar{\alpha} \bar{v} - \bar{w} - \bar{z}], \quad (11)$$

$$\frac{d\bar{z}}{d\bar{t}} = \bar{\epsilon} \eta [-\bar{\gamma} \bar{v} - \bar{z} + \bar{\lambda}], \quad (12)$$

by a nondimensionalization process, where

$$\bar{t} = \alpha t, \quad \bar{v} = \frac{a}{\alpha} v, \quad \bar{w} = \frac{a}{\alpha^2} w, \quad \bar{z} = \frac{a}{\alpha^2} z, \quad (13)$$

$$\bar{\epsilon} = \frac{\epsilon}{\alpha}, \quad \bar{\gamma} = \frac{\gamma}{\alpha}, \quad \bar{\lambda} = \frac{\lambda a}{\alpha^2}, \quad (14)$$

$$\bar{A}_{in} = \frac{\hat{A}_{in} a}{\alpha^2}, \quad \bar{g}_s = \frac{g_s}{\alpha}, \quad \bar{E}_s = \frac{\hat{E}_s a}{\alpha}. \quad (15)$$

Quadratization Procedure

We assume that $\tau_1 < \tau_2$ (x_2 is slower than x_1). We also assume that the projection of the

V -nullsurface onto the planes parallel to the V - x_1 plane (constant values of x_2) are parabolic-like functions. In other words, we assume that the presence of the variable x_2 does not qualitatively change the shape of the parabolic-like V -nullcline of the two-dimensional system (for $x_2 = 0$), but it can only produce parabolic-like deformations, raise it and shift it down as in Rotstein et al. (2006). The case $\tau_2 = \tau_1$ is excluded because the system can be reduced to a quasi-two-dimensional (Rotstein 2017).

As a starting point, we identify the minimum ($V_{min}, x_{1,min}, 0$) or maximum ($V_{max}, x_{1,max}, 0$) of the parabolic-like V -nullcline (for $x_2 = 0$). We refer to them indistinctly as $(V_e, x_{1,e}, x_{2,e})$. We define

$$\begin{aligned} u &= V - V_e, \\ w &= \frac{x_1 - x_{1,e}}{x'_{1,\infty}(V_e)}, \\ w_2 &= \frac{x_2 - x_{2,e}}{x'_{2,\infty}(V_e)}. \end{aligned} \quad (16)$$

We then expand the right-hand sides of Eqs. 1 and 3 around $(V_e, x_{1,e}, x_{2,e})$ up to the first order in x_1 and x_2 and up to the second order in V . This yields

$$\begin{aligned} C \frac{du}{dt} &= F_e - g_L u + \sigma g_c u^2 - g_1 w_1 \\ &\quad - g_2 w_2 + A_{in} I(t) \\ &\quad - G_s s(t) (u + V_e - E_s) \end{aligned} \quad (17)$$

and

$$\bar{\tau}_j \frac{dw_j}{dt} = (1 - \xi_j)u - w_j + \beta_j, \quad j = 1, 2, \quad (18)$$

where

$$\begin{aligned} F(V, x_1, x_2) &= I_{app} - G_L(V - E_L) \\ &\quad - G_1 x_1(V - E_1) \\ &\quad - G_2 x_2(V - E_2) \\ &\quad - G_3 x_{3,\infty}(V) (V - E_3), \end{aligned} \quad (19)$$

$$F_e = F(V_e, x_{1,e}, x_{2,e}), \quad (20)$$

$$g_L = G_L + G_1 x_{1,e} + G_2 x_{2,e} + G_3 x_{3,\infty}(V_e) + g_3, \quad (21)$$

$$g_j = G_j(V_e - E_j)x'_{j,\infty}(V_e), \quad j = 1, 2, 3 \quad (22)$$

$$\begin{aligned} \sigma g_c &= \frac{1}{2} \frac{\partial^2 F}{\partial V^2} \\ &= - \frac{G_3 x''_{3,\infty}(V_e) (V_e - E_3) + 2G_3 x'_{3,\infty}(V_e)}{2} \end{aligned} \quad (23)$$

and

$$\begin{aligned} \beta_j &= \frac{x_{j,\infty}(V_e) - x_{j,e}}{x'_{j,\infty}(V_e)} \quad \xi_j = \beta_j \frac{\tau'_j(V_e)}{\tau_j(V_e)}, \\ \bar{\tau}_j &= \tau_j(V_e), \quad j = 1, 2. \end{aligned} \quad (24)$$

In Eq. 23 $g_c > 0$ and the concavity of the original V -nullcline is captured by the sign of $\sigma = \pm 1$. Next, we define

$$v = u - \frac{g_L}{2\sigma g_c}. \quad (25)$$

Substituting into Eqs. 17 and 18 yields

$$\begin{aligned} C \frac{dv}{dt} &= F_e - \frac{g_L^2}{4\sigma g_c} + \sigma g_c v^2 - g_1 w_1 \\ &\quad - g_2 w_2 + A_{in} I(t) \\ &\quad - G_s s(t) \left[v + V_e + \frac{g_L}{2\sigma g_c} - E_s \right], \end{aligned} \quad (26)$$

$$\begin{aligned} \bar{\tau}_j \frac{dw_j}{dt} &= (1 - \xi_j)v \\ &\quad + \beta_j + (1 - \xi_j) \frac{g_L}{2\sigma g_c} - w_j, \\ j &= 1, 2. \end{aligned} \quad (27)$$

Subsequently, we define

$$w = \frac{g_1}{C} w_1 + \frac{g_2}{C} w_2 - \frac{F_e}{C} + \frac{g_L^2}{4\sigma g_c C}. \quad (28)$$

Substituting into Eqs. 26 and 27 we obtain

$$\begin{aligned} \frac{dv}{dt} = & \sigma av^2 - w + \hat{A}_{in} I(t) \\ & - g_s s(t) \left(v - \hat{E}_s \right), \end{aligned} \quad (29)$$

$$\frac{dw_1}{dt} = \epsilon \left[\beta_1 + (1 - \xi_1) \frac{g_L}{2\sigma g_c} + (1 - \xi_1)v - w_1 \right], \quad (30)$$

$$\frac{dw_2}{dt} = \epsilon \eta \left[\beta_2 + (1 - \xi_2) \frac{g_L}{2\sigma g_c} + (1 - \xi_2)v - w_2 \right], \quad (31)$$

where

$$\hat{A}_{in} = \frac{A_{in}}{C}, \quad g_s = \frac{G_s}{C}, \quad \hat{E}_s = E_s - V_e - \frac{g_L}{2\sigma g_c}, \quad (32)$$

$$\epsilon = \frac{1}{\tau_1}, \quad \eta = \frac{\hat{\tau}_1}{\hat{\tau}_2}, \quad a = \frac{g_c}{C}. \quad (33)$$

By differentiating both sides of Eq. 28 with respect to t , substituting Eqs. 30 and 31 and rearranging terms we obtain Eq. 6 where

$$\alpha = \frac{g_1(1 - \xi_1) + g_2\eta(1 - \xi_2)}{C} \quad (34)$$

and

$$\begin{aligned} z = & -\frac{g_2(1 - \eta)}{C} w_2 + \frac{F_e}{C} - \frac{g_L^2}{4\sigma g_c C} \\ & - \frac{g_1\beta_1 + g_2\eta\beta_2}{C} \\ & - \frac{g_1(1 - \xi_1) + g_2\eta(1 - \xi_2)}{2\sigma g_c C} g_L. \end{aligned} \quad (35)$$

By differentiating both sides of Eq. 35 with respect to t , substituting Eq. 31 and rearranging terms we obtain Eq. 7 where

$$\gamma = \frac{g_2(1 - \eta)(1 - \xi_2)}{C}, \quad (36)$$

and

$$\begin{aligned} \lambda = & -\frac{g_2(1 - \eta)}{C} \left[\beta_2 + (1 - \xi_2) \frac{g_L}{2\sigma g_c} \right] \\ & + \frac{F_e}{C} - \frac{g_L^2}{4\sigma g_c C} - \frac{g_1\beta_1 + g_2\eta\beta_2}{C} \\ & - \frac{g_1(1 - \xi_1) + g_2\eta(1 - \xi_2)}{2\sigma g_c C} g_L. \end{aligned} \quad (37)$$

For $g_2 = 0$, substituting into Eqs. 35, 36, and 37 yields $\gamma = 0$ and $z = \lambda$.

Two Examples: $I_{Nap} + I_h$ and $I_{Nap} + I_{Ks}$ Models

We present two two-dimensional and autonomous ($G_2 = G_s = A_{in} = 0$ and $g_2 = g_s = \hat{A}_{in} = 0$) examples: the $I_{Nap} + I_h$ and $I_{Nap} + I_{Ks}$ models (Rotstein 2017, 2015) adapted from Acker et al. (2003) and Rotstein et al. (2006).

The $I_{Nap} + I_h$ involves the interaction between a persistent sodium ($I_{Nap} = I_3$) and a hyperpolarization-activated (or h-) ($I_h = I_1$) currents, where $I_{Nap} = G_p p_\infty(V) (V - E_{Na})$ and $I_h = G_h r(V - E_h)$. The $I_{Nap} + I_{Ks}$ model involves the interaction between a persistent sodium ($I_{Nap} = I_3$) and slow potassium ($I_{Ks} = I_1$) currents, where $I_{Nap} = G_p p_\infty(V) (V - E_{Na})$ and $I_{Ks} = G_q q(V - E_k)$. We use the same I_{Nap} in both models. The activation and inactivation curves we used are given by the following functions (see Fig. 1)

$$p_\infty(V) = 1 / \left(1 + e^{-(V+38)/6.5} \right), \quad (38)$$

$$r_\infty(V) = 1 / \left(1 + e^{(V+79.2)/9.78} \right), \quad (39)$$

$$q_\infty(V) = 1 / \left(1 + e^{-(V+40)/5.5} \right). \quad (40)$$

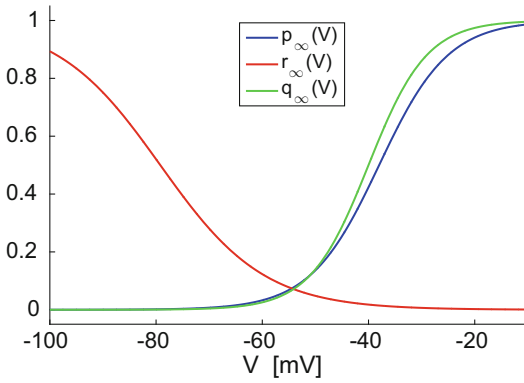
We used the following time constants $\tau_i(V) = \tau_q(V) = 80$. The nullclines for both models are shown in Fig. 2.

Fig. 3 shows the quadratic approximations for both models in neighborhoods of the knee of the corresponding V -nullclines (subthreshold regime) and the linearization of the corresponding

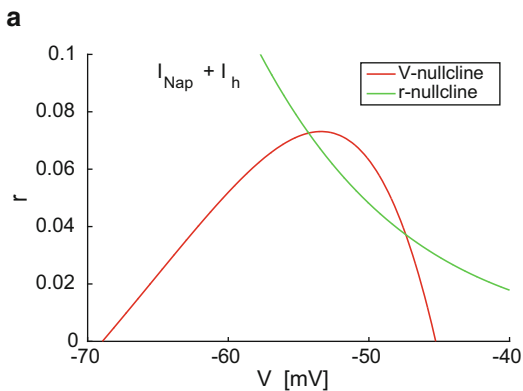
x_1 -nullclines (r - and q -nullclines, respectively). In Fig. 4, we illustrate that the biophysical and quadratic approximations are in good agreement by comparing the results of using the $I_{Nap} + I_h$ model.

Other Related Quadratic Model Formulations

The subthreshold dynamics in the model proposed in Izhikevich (2006) (see also (Izhikevich 2003, 2010)) is given by



Quadratzation: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities, Fig. 1 Activation/inactivation curves for the $I_{Nap} + I_h$ and $I_{Nap} + I_{Ks}$ models. The function $p_\infty(V)$, $r_\infty(V)$, and $q_\infty(V)$ are given by Eqs. 38, 39, and 40



Quadratzation: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities, Fig. 2 Phase-plane diagram for the 2D biophysical $I_{Nap} + I_h$ and $I_{Nap} + I_{Ks}$ models. (a) $I_{Nap} + I_h$ model. (b) $I_{Nap} + I_{Ks}$ model. The activation and inactivation curves are as in

$$C \frac{dv}{dt} = k(v - v_r)(v - v_t) - u + I_{app}, \quad (41)$$

$$\frac{du}{dt} = \epsilon [b(v - v_r) - u], \quad (42)$$

where v is the membrane potential, u is the recovery variable, and the parameters v_r and v_t are the resting membrane potential and the instantaneous threshold potential, respectively.

Equations 41 and 42 can be transformed to Eqs. 8 and 9 with $\hat{A}_{in} = g_s = 0$ by defining the new variables

$$\hat{v} = v - \frac{v_r + v_t}{2} \quad (43)$$

and

$$w = \frac{1}{C} \left[u - I_{app} - k v_r v_t + \frac{k}{4} (v_r + v_t)^2 \right], \quad (44)$$

substituting into Eqs. 41 and 42, rearranging terms, dropping the “hat” sign from $\hat{v}$ and calling

$$a = \frac{k}{C}, \quad \alpha = \frac{b}{C}, \quad (45)$$

and

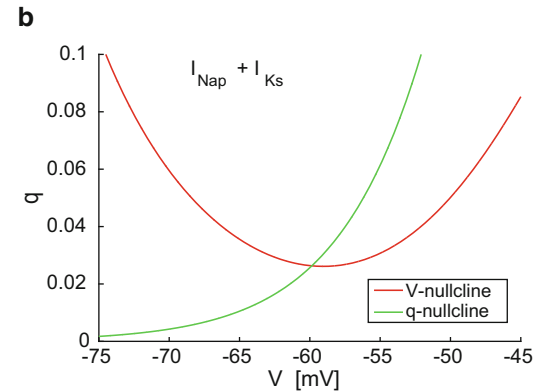
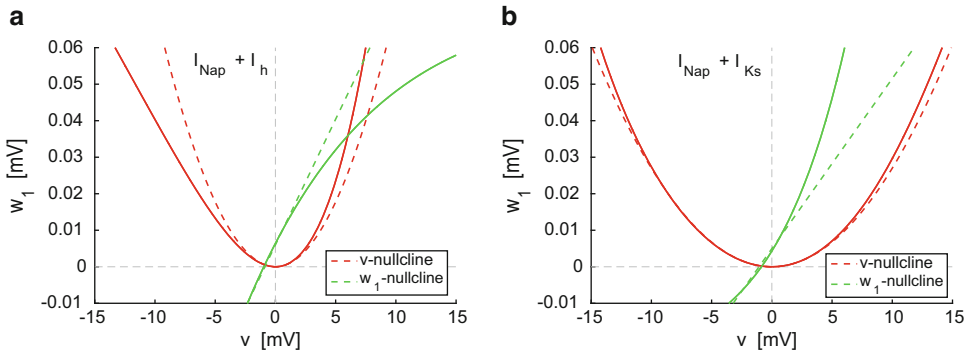
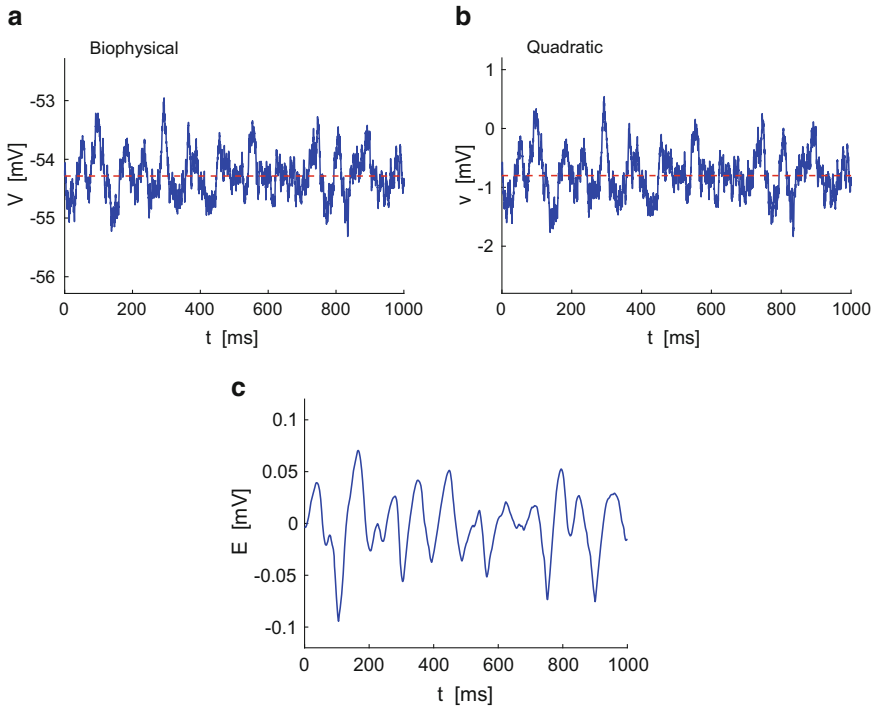


Fig. 1. We used the following parameter values (a): $C = 1$, $G_L = 0.5$, $G_h = 1.5$, $G_p = 0.5$, $E_L = -65$, $E_{Na} = 55$, $E_h = -20$, $I_{app} = -2.5$. (b): $C = 1$, $G_L = 0.1$, $G_q = 1$, $E_L = -54$, $E_{Na} = 55$, $E_K = -90$, $I_{app} = -0.6$



Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities, Fig. 3 Superimposed phase-plane diagram for the 2D biophysical and parabolic (quadratized) $I_{Nap} + I_h$ and $I_{Nap} + I_{Ks}$ models. (a) $I_{Nap} + I_h$ model. (b) $I_{Nap} + I_{Ks}$

model. The *solid and dashed curves* are the nullclines for the biophysical (as in Fig. 2) and parabolic (quadratized) models, respectively. We used the same parameter values as in Fig. 2



Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities, Fig. 4 Comparison between the voltage time courses for the biophysical $I_{Nap} + I_h$ model and the quadratic approximation, respectively, in the presence of additive white noise. We used the same parameter values as in Fig. 3a (and Fig. 2a). (a) Graph of $V(t)$ for the biophysical model. The *dashed-red line* represents the stable fixed-point V . The difference between the average value of V and V is $\langle V - \bar{V} \rangle =$

$\langle V - \bar{V} \rangle \sim 0.029$ and the variance is $\text{Var}(V) \sim 0.1762$. (b) Graph of $v(t)$ for the quadratic model. The *dashed-red line* represents the stable fixed-point v . The difference between the average value of V and V is $\langle v - \bar{v} \rangle \sim 0.02$ and the variance is $\text{Var}(v) \sim 0.1857$. (c) Graph of the error $E(t)$, defined as $E(t) = (V(t) - \bar{V}) - (v(t) - \bar{v})$. $\langle E \rangle \sim -1.3 \times 10^{-13}$ and $\text{Var}(E) \sim 0.0012$. The statistics for $V(t)$, $v(t)$, and $E(t)$ have been computed over a time interval of 10 s

$$\lambda = \frac{1}{C} \times \left[I_{app} + k v_r v_t - \frac{k}{4} (v_r + v_t)^2 - b \frac{v_t - v_r}{2} \right] \quad (46)$$

This transformation allows to interpret the parameters in Eqs. 41 and 42 in terms of the biophysical parameters.

Limitations and Additional Comments

The quadratic models (5), (6), and (7) and (10), (11), and (12) provide a good approximation to the original biophysical models (1) and (2) for a range of voltage values close enough to the knee of the V -nullcline. The parabolic-like and strictly parabolic V -nullclines (for $x_2 = 0$) coincide at their extrema (minima or maxima) and are well approximated by each other in vicinities of these extrema whose sizes depend on the model parameters. This requires the fixed-point to be close to the extremum (minimum or maximum) of the parabolic-like V -nullcline. Away from these ranges of values of V , but still within the subthreshold voltage regime, there may be significant differences between the parabolic-like and strictly parabolic nullclines. We emphasize the need to check the validity of the use of quadratic models in these regions where the approximations are no longer mathematically valid. One possible solution is to include higher order terms in the expansion of the right-hand side of Eq. 1. However, this increases the complexity of the process given the need to include mixed derivatives. While in some cases the differences between the quadratic model approximation and the original biophysical models may be negligible, in other cases it may be qualitatively important. For example, two-dimensional quadratic models cannot exhibit supercritical Hopf bifurcations (Touboul 2008; Krupa and Szmolyan 2001) nor the associated supercritical canard phenomenon (Krupa and Szmolyan

2001) that requires cubic nonlinearities (Rotstein et al. 2012).

In the quadratic models, the recovery variable nullclines (nullsurfaces) are linear. This may create dynamic differences between the biophysical and phenomenological models. For example, the linear and parabolic nullclines may intersect twice in the subthreshold regime, while the original nullclines do not. This is more likely to happen in models with concave-up parabolic-like nullclines (e.g., Fig. 3b) than in models with concave-down parabolic-like nullclines (e.g., Fig. 3a). As before, one possible solution is to include second order terms in the expansion of the right-hand side of Eq. 3.

When the fixed-point of the biophysical model is not close enough to the extremum of the V -nullcline, the biophysical model is quasi-linear in the subthreshold regime. However, the parabolic-like nonlinearities may still play a role in the global subthreshold dynamics and should not be disregarded. One possible approach in these cases is to linearize Eq. 3 around the fixed-point and not around the extremum of the parabolic-like V -nullcline.

The use of the dimensionless model (10), (11), and (12) involves the rescaling of t and v in addition to the other variables. This makes the comparison among results for different parameter values more difficult and less straightforward, since both v and t may be used in the computation of some attributes. This is particularly important when one investigates the response of neurons to external inputs or network effects. In the latter case, it is important to take into account that the synaptic effective synaptic decay times of excitation and inhibition are affected by the rescaling parameters.

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Quasi-active Approximation of Nonlinear Dendritic Cables

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Definition

The quasi-active approximation of a dendritic cable is a linearized description of a cable with voltage-dependent membrane conductances. It is an extension of classical passive cable theory relying on linearization of the voltage-dependent conductances around a reference membrane potential (typically the resting potential). The current thereby acquires a linear current–voltage relationship but still has an activation time constant associated with it that determines its gating dynamics. This approximation accurately describes the frequency-dependent filtering of the nonlinear cable for sufficiently small voltage deflections around the reference potential.

Detailed Description

The use of linearized descriptions of voltage-dependent membrane conductances in *point neuron* models has a rich history, e.g., Hodgkin and Huxley (1952) already used this to analyze the subthreshold (oscillatory) response of the *space-clamped* squid giant axon. However, the first use of such methods in a (not space-clamped) cable dates back to Sabah and Leibovic (1969), also to analyze subthreshold responses of the squid giant axon. The study by Koch (1984) is the first to apply the linearized description specifically to dendrites and study how membrane currents affect dendritic input filtering. Koch introduced the term *quasi-active* cable in this work, and while he used this term to denote only dendritic cables that show band-pass filtering, the term has since been used (as we do here) more generally for any linearized cable that retains the dynamics of voltage-

dependent membrane currents, independent of whether this leads to band-pass or low-pass filtering.

Derivation of the Quasi-active Description of a Nonlinear Dendritic Cable

We consider an infinite dendritic cable with a single voltage-dependent conductance. Let $V(x, t)$ denote the membrane potential (in mV) along the cable at position x (in cm) and time t (in s). The passive properties of the cable are determined by membrane time constant τ (in s) and space constant λ (in cm). The cable expresses a voltage-dependent conductance with a single gating variable $w(x, t)$, which has activation function $w_\infty(V)$ and time constant $\tau_w(V)$ (in s). The equations governing $V(x, t)$ and $w(x, t)$ are

$$\begin{aligned} \tau \frac{\partial V(x, t)}{\partial t} &= \lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - (V(x, t) - E_L) \\ &\quad - \frac{\bar{g}_w}{g_L} w(x, t) (V(x, t) - E_w) \\ \tau_w(V(x, t)) \frac{dw(x, t)}{dt} &= w_\infty(V(x, t)) - w(x, t) \end{aligned} \quad (1)$$

with leak conductance g_L (in S/cm²), leak reversal potential E_L , peak conductance of the active current $\bar{g}_w$ (in S/cm²), and reversal potential of the active current E_w .

To obtain the quasi-active approximation of the nonlinear cable, Eq. 1 is linearized about membrane potential V_R . We define the variables $U(x, t) \equiv V(x, t) - V_R$ and $m(x, t) \equiv (w(x, t) - w_\infty(V_R)) / \frac{d}{dV} w_\infty(V_R)$ and employ a Taylor series expansion of Eq. 1. After dropping the higher-order terms, we obtain the linear equations describing the quasi-active cable:

$$\begin{aligned} \hat{\tau} \frac{\partial U(x, t)}{\partial t} &= \hat{\lambda}^2 \frac{\partial^2 U(x, t)}{\partial x^2} - U(x, t) + \phi m(x, t) \\ \tau_w \frac{dm(x, t)}{dt} &= U(x, t) - m(x, t) \end{aligned} \quad (2)$$

where the membrane time constant and space constant are both corrected to include the contribution of the active conductance: $\hat{\tau} = \tau / \left(1 + \frac{g_w}{g_l} w_\infty(V_R)\right)$ and $\hat{\lambda} = \lambda / \sqrt{1 + \frac{g_w}{g_l} w_\infty(V_R)}$ and where $\tau_w = \tau_w(V_R)$ and

$$\phi = \frac{\bar{g}_w(E_w - V_R) \frac{dw_\infty(V_R)}{dV}}{g_l + \bar{g}_w w_\infty(V_R)} \quad (3)$$

The dimensionless parameter ϕ is central in characterizing the effect of the active membrane current and denotes the strength of the feedback that the current provides. Its sign defines whether the current functions as a positive or a negative feedback (or is passive when $\phi = 0$). The system is unstable when a regenerative current is too strong ($\phi > 1$).

Note that many studies use an alternative formulation of these equations and describe the effect of the linearized active current as a phenomenological inductance (or capacitance):

$$\begin{aligned} \hat{\tau} \frac{\partial U(x,t)}{\partial t} &= \hat{\lambda}^2 \frac{\partial^2 U(x,t)}{\partial x^2} - U(x,t) - \frac{I_w(t)}{g_l + \bar{g}_w w_\infty(V_R)} \\ L_w \frac{dI_w(x,t)}{dt} &= U(x,t) - r_w I_w(x,t) \end{aligned} \quad (4)$$

with active membrane current I_w (in mA/cm²), inductance $L_w = r_w \tau_w$ (in H cm²), and resistance $r_w = [\bar{g}_w(V_R - E_w) \frac{d}{dV} w_\infty(V_R)]^{-1}$ (in ohm cm²).

Use of the Quasi-active Cable Description

Impulse Response Function

Since the quasi-active description of a cable is linear, we can determine its response to an arbitrary external input using the cable's impulse response function or Green's function. This function can be obtained by first writing the Fourier transform of Eq. 2:

$$\frac{d^2 \tilde{U}(x, \omega)}{dx^2} = \frac{b^2(\omega)}{\hat{\lambda}^2} \tilde{U}(x, \omega) \quad (5)$$

where $\tilde{U}(x, \omega)$ is the Fourier transform of $U(x, t)$ with respect to time, $\omega = 2\pi f$ with frequency f (in Hz), and

$$b(\omega) = \sqrt{1 - \frac{\phi}{1 + \omega^2 \tau_w^2} + i\omega \left(\hat{\tau} + \frac{\phi \tau_w}{1 + \omega^2 \tau_w^2} \right)} \quad (6)$$

Note that the fraction $\frac{b^2(\omega)}{\hat{\lambda}^2}$ in Eq. 5 is also referred to as the propagation constant $\gamma^2(\omega)$. Solving the second-order ODE Eq. 5 when a δ -current impulse is injected at the origin of the infinite cable gives the Fourier transform of the impulse response function, that is, the transfer function:

$$\tilde{K}(x, \omega) = \frac{\hat{R}_\infty}{b(\omega)} e^{-b(\omega)x/\hat{\lambda}} \quad (7)$$

where $\hat{R}_\infty$ is the input resistance (in ohm) of a passive infinite cable, which includes the contribution of the active current to the resting conductance (but does not take into account the dynamics of the active current): $\hat{R}_\infty = \sqrt{R_a / (g_l + \bar{g}_w w_\infty(V_R))} \pi^2 d^3$ with intracellular resistivity R_a (in ohm cm) and cable diameter d (in cm). Note that we defined the transfer function in units of ohm and hence $\tilde{K}(x, \omega)$ is the transfer impedance (or input impedance when $x = 0$).

The response at location x to input current $I(t)$ at the origin can now be obtained by convolving the input with the impulse response function. Since it is not feasible to determine the inverse Fourier transform of $\tilde{K}(x, \omega)$, we make use of the convolution theorem:

$$\begin{aligned} V(x, t) &= K(x, t) * I(t) \\ &= \mathcal{F}^{-1} \left\{ \tilde{K}(x, \omega) \cdot \tilde{I}(\omega) \right\} \end{aligned} \quad (8)$$

where $*$ is the convolution operator and $\mathcal{F}^{-1}\{z\}$ denotes the inverse Fourier transform of z .

Frequency-Dependent Response of Quasi-active Cable

Having obtained the transfer function Eq. 7, we can describe the frequency-dependent input filtering by the quasi-active cable (Fig. 1). The amplitude of the signal at location x resulting from a

sinusoidal input current with frequency ω at the origin is

$$|\tilde{K}(x, \omega)| = \frac{\hat{R}_\infty}{|b(\omega)|} e^{-\operatorname{Re}\{b(\omega)\}x/\hat{\lambda}} \quad (9)$$

where $|z|$ is the modulus and $\operatorname{Re}\{z\}$ is the real part of the complex number z . Thus, a sinusoidal signal decays exponentially along the quasi-active cable with frequency-dependent space constant $\hat{\lambda}/\operatorname{Re}\{b(\omega)\}$ (Fig. 1a). Hence, the steady state voltage attenuation to a step current decays with space constant $\hat{\lambda}/\sqrt{1-\phi}$, which shows that the space constant is decreased by restorative currents and increased by regenerative currents.

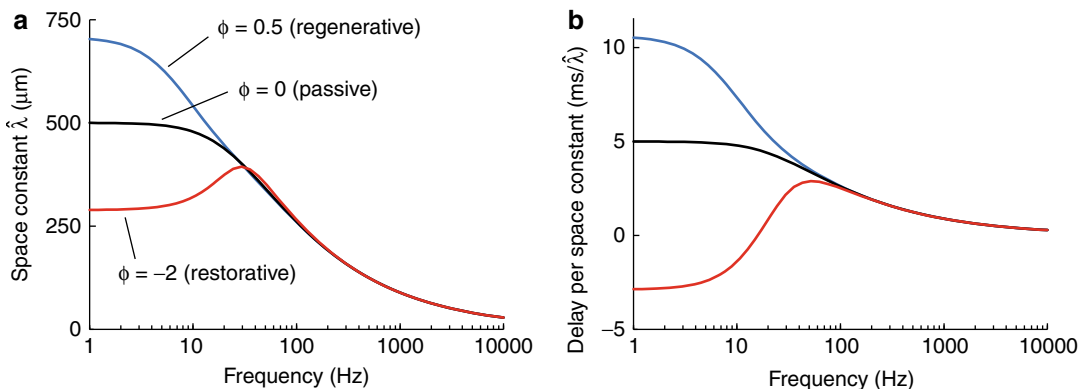
The phase shift of the response at location x relative to the phase of the injected current is

$$\arg\{\tilde{K}(x, \omega)\} = \arctan \frac{\operatorname{Im}\{b(\omega)\}}{\operatorname{Re}\{b(\omega)\}} + \operatorname{Im}\{b(\omega)\} \frac{x}{\hat{\lambda}} \quad (10)$$

where $\arg\{z\}$ is the argument and $\operatorname{Im}\{z\}$ is the imaginary part of the complex number z . Thus, the phase shift or delay (in s) of the steady state response to a sinusoidal signal changes linearly along the cable with slope $\operatorname{Im}\{b(\omega)\}/\lambda\omega$ (Fig. 1b).

Advantages and Limitations of Approach

The linear quasi-active approximation naturally does not capture the full dynamics of a cable with nonlinear voltage-dependent membrane conductances. The approximation is mathematically valid for small-amplitude voltage fluctuations around a fixed mean membrane potential; however, in practice those fluctuations can be quite large (10–20 mV), mostly depending on how well the membrane current in question can be approximated by a linear current–voltage relationship over the voltage range of interest. In any case, the quasi-active description of dendritic cables serves as a solid reference to understand how voltage-dependent membrane currents affect input integration in dendrites, and with this method the linear versus nonlinear effects of such currents can be identified. The description reduces the system to the essential parameters and thereby highlights that there are effectively two types of currents: regenerative currents (such as the persistent sodium current) and restorative currents (such as the hyperpolarization-activated inward h-type current; see also Hutcheon and Yarom 2000). Compared to a passive cable, regenerative currents



Quasi-active Approximation of Nonlinear Dendritic Cables, Fig. 1 Frequency-dependent filtering in a quasi-active cable. (a): Frequency-dependent space constant of a cable with an additional current that is regenerative ($\phi = 0.5$), passive ($\phi = 0$), or restorative ($\phi = -2$). The cable has passive space constant $\hat{\lambda} = 500\mu\text{m}$ and membrane time constant $\hat{\tau} = 10\text{ms}$. The active current has activation time constant $\tau_w = 10\text{ms}$. Note that in a cable with a

restorative current, the space constant can have a local maximum at a nonzero frequency. (b): Frequency-dependent delay per space constant of the steady state response to a sinusoidal signal for the same conditions as in a. Note that in a cable with a restorative current, the delay can be zero (i.e., synchronous response of the entire cable) or even negative (i.e., the response at the input site lags behind the neighboring cable)

make the cable electrotonically more compact (less voltage attenuation) and slow down the membrane response, whereas restorative currents increase the electrotonic length of the cable (stronger voltage attenuation) and lead to a faster membrane response (see Koch 1984; Remme and Rinzel 2011). Naturally, the quasi-active approximation can also be applied to cables with multiple voltage-dependent currents and/or currents that have multiple gating variables (see Coombes et al. 2007; Remme and Rinzel 2011). Finally, the approximation also allows one to use other linear methods, for example, the sum-over-trips method, which is used to compute the voltage response of a branched dendritic tree to current input (Coombes et al. 2007).

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R

Radioactive Isotope

- [Radiopharmaceuticals in Molecular Imaging](#)

Radioindicator

- [Radiopharmaceuticals in Molecular Imaging](#)

Radioisotope

- [Radiopharmaceuticals in Molecular Imaging](#)

Radiolabeled Molecular Imaging Probe

- [Radiopharmaceuticals in Molecular Imaging](#)

Radiopharmaceutical

- [Radiopharmaceuticals in Molecular Imaging](#)

Radiopharmaceuticals in Molecular Imaging

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Synonyms

[Nuclear medicine](#), [molecular imaging](#); [Radioactive isotope](#); [Radioindicator](#); [Radioisotope](#); [Radiolabeled molecular imaging probe](#); [Radiopharmaceutical](#); [Radiotracer](#)

Definition

Molecular imaging (MI) is a biomedical research discipline enabling the visualization, characterization, and quantification of biological processes taking place at the cellular and subcellular levels within intact living subjects including patients. MI typically includes two- or three-dimensional imaging as well as quantification over time. The MI techniques may include radiotracer imaging/nuclear medicine (such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), optical imaging, ultrasound, and others.

Radiopharmaceuticals are drug molecules (containing radioactive atoms or radioisotopes) useful for noninvasive imaging studies or radionuclide therapy.

Nuclear medicine (PET and SPECT) uses radiopharmaceuticals as molecular imaging probes that produce signals by means of radioactive decay.

Detailed Description

Elements and Atoms

Everything in this universe is made up of *matter* and *energy*. Matter is anything that has *mass* and occupies space. In contrast, light and heat are forms of energy. All matter in nature is made up of pure substances, known as chemical elements, which are the building blocks of all types of matter. The modern periodic table of elements lists 114 confirmed elements. The first 98 elements exist naturally although some are found only in trace amounts and were initially discovered by synthesis. Of the 98 elements that occur naturally, 84 are primordial. The other 14 elements occur only in decay chains of primordial elements.

From the point of view of chemistry, the smallest unit of an element is the atom of an element representing the chemical identity of that element. The atom consists of a dense central nucleus surrounded by a cloud of negatively charged electrons. The atomic nucleus contains a mix of positively charged protons and electrically neutral neutrons (except in the case of hydrogen-1, which is the only stable nuclide with no neutrons). An atom is classified according to the number of protons and neutrons in its nucleus: the number of protons (*atomic number*, Z) determines the chemical element, while the total number of protons and neutrons (*mass number*, A) determines the isotope (or nuclide) of the element. The electrons of an atom are bound to the nucleus by the electromagnetic force. Likewise, a group of atoms can remain bound to each other by chemical bonds based on the same force, forming a molecule.

Isotopes and Radioisotopes

An isotope and/or nuclide is specified by the name of the particular element (this indicates the Z implicitly). An element may have several isotopes with the same Z , but different A . Most naturally occurring isotopes are stable, while some isotopes undergo spontaneous radioactive decay or transmutation and are therefore described as radioisotopes or radionuclides. Of the known chemical elements, 80 elements have at least one stable nuclide. For example, carbon has two stable isotopes (^{12}C , ^{13}C) and two important radioactive isotopes (^{11}C , ^{14}C). The most important elements and their useful radioisotopes for developing PET and SPECT radiopharmaceuticals are shown in Table 1.

Radioactivity

Radioactive decay, also known as nuclear decay or radioactivity, is the state, property, or process of being radioactive with a spontaneous emission of a stream of particles or electromagnetic rays by unstable atomic nuclei.

Radioactive decay is the process by which a nucleus of an unstable atom loses energy by emitting radiation in order to become a more stable atom.

Types of Radioactive Decay

The stability of an atomic nucleus depends on the neutron/proton (n/p) ratio. There are many different types of radioactive decay depending on whether the nuclide is neutron deficient or neutron rich. The radioactive decay processes, however, falls into two categories: those in which both the parent and the daughter radionuclides have the same mass number (isobaric decay) and those that involve change in mass number (A) of a radionuclide. The five major kinds of radioactive decay are shown in Table 2. Neutron-rich radionuclide generally undergoes β^- decay and increases the atomic number ($Z + 1$). In contrast, the neutron-deficient radionuclide may decay by positron (β^+) emission or by an electron capture (*EC* or *K capture*). In either case, the daughter radionuclide will have one less proton ($Z-1$).

Radiopharmaceuticals in Molecular Imaging, Table 1 Important elements and their useful radioisotopes for PET and SPECT

Element	Atomic number	Stable isotope	Natural abundance (%)	Useful radioisotopes	Decay mode
Carbon	6	^{12}C	98.9	^{11}C	β^+
		^{13}C	1.10		
Nitrogen	7	^{14}N	99.634	^{13}N	β^+
		^{15}N	0.366		
Oxygen	8	^{16}O	99.762	^{15}O	β^+
		^{17}O	0.038		
		^{18}O	0.200		
Fluorine	9	^{19}F	100	^{18}F	β^+
Copper	29	^{63}Cu	69.17	^{62}Cu	β^+
		^{65}Cu	30.83	^{64}Cu	β^+ , β^- , EC
				^{67}Cu	β^- , γ
Gallium	31	^{69}Ga	60.1	^{66}Ga	β^+ , EC, γ
		^{71}Ga	39.9	^{67}Ga	EC, γ
				^{68}Ga	β^+ , EC, γ
				^{72}Ga	β^- , γ
Bromine	35	^{79}Br	50.69	^{75}Br	β^+ , EC
		^{81}Br	40.31	^{77}Br	EC, γ
Rubidium	37	^{85}Rb	72.165	^{82}Rb	β^+
		^{87}Rb	27.845		
Yttrium	39	^{89}Y	100	^{86}Y	β^+ , EC, γ
				^{87}Y	EC, γ
Zirconium	40	^{90}Zr	51.45	^{89}Zr	β^+ , γ
		^{91}Zr	11.22		
		^{92}Zr	17.15		
		^{94}Zr	17.38		
		^{96}Zr	2.80		
Technetium	43	—	—	$^{94\text{m}}\text{Tc}$	β^+
				$^{99\text{m}}\text{Tc}$	IT, γ
Indium	49	^{113}In	4.3	^{111}In	EC, γ
		^{115}In	95.7		
Iodine	53	^{127}I	100	^{123}I	EC, γ
				^{124}I	β^+ , EC, γ
				^{131}I	β^- , γ

Radiopharmaceuticals in Molecular Imaging, Table 2 Types of radioactive decay

Decay mode	Reason for instability of parent nucleus	Transformation	Example	N/P ratio change
Alpha decay	Too large	${}_Z^AX \rightarrow {}_Z - 2^{A-4}Y + {}_2^4\alpha$	${}_{88}^{226}\text{Ra} \rightarrow {}_{88}^{226}\text{Rn} + {}_2^4\alpha$	Increases
Beta decay	Neutron rich	${}_Z^AX \rightarrow {}_{Z+1}^AY + e^-$	${}_6^{14}\text{C} \rightarrow {}_7^{14}\text{N} + e^- + \nu$	Decreases
Positron emission	Neutron deficient	${}_Z^AX \rightarrow {}_{Z-1}^AY + e^+$	${}_6^{11}\text{C} \rightarrow {}_5^{11}\text{B} + e^+ + \nu$	Increases
Electron capture	Neutron deficient	${}_Z^AX + e^- \rightarrow {}_{Z-1}^AY$	${}_{49}^{111}\text{In} + e^- \rightarrow {}_{49}^{111}\text{Cd}$	Increases
Isomeric transition	Excess energy	${}_Z^AX^* \rightarrow {}_Z^AY + \gamma$	${}_{43}^{99\text{m}}\text{Tc}^* \rightarrow {}_{43}^{99}\text{Tc} + \gamma$	No change

Alpha decay is generally seen in high atomic number elements such as ^{238}U and ^{226}Ra . The radionuclide ejects an α particle or a He nucleus (2 protons and 2 neutrons) is converted into a nuclide with a lower atomic number ($Z-2$). Two radionuclides of an element that differ only in the energy content are called *isomers* and the metastable states (half-life $>10^{-12}$ s) are called isomeric states (designated with letter *m* next to A). *Isomeric transition* involves emission of gamma (γ) photons from a radionuclide in metastable state.

Radioactive Decay Equations

Radioactive decay or transformation is a statistical process that obeys the laws of chance. No cause-effect relationship is involved in the decay of any radionuclide, only a certain probability per unit time. The activity (**A**) of a sample of any radionuclide is the rate at which the nuclei of its constituent atoms (**N**) decay. Also the activity (**A**) or the disintegration rate of a radionuclide at any time is proportional to the total number of radioactive atoms present at that time. Mathematically, rate of decay (**A**) is given by

$$A = -\frac{dN}{dt} \propto N \quad (1)$$

$$N = N_0 e^{-\lambda t} \quad (2)$$

$$A = -\frac{dN}{dt} \lambda N \quad (3)$$

$$A_t = A_0 e^{-\lambda t} \quad (4)$$

In the above equations, *N* is the number of radioactive atoms, and λ is the *decay constant* (or proportionality constant) that is defined as the probability of disintegration per unit time. The Eqs. 3 and 4 represent *exponential decay* of any radionuclide and the factor $e^{-\lambda t}$ is known as the *decay factor*, the fraction of original activity A_0 remaining after time *t*.

Units of Activity

The SI unit of radioactivity is named after Becquerel

$$1 \text{ Becquerel} = 1\text{Bq} = 1 \text{ decay/s} \quad (5)$$

The traditional unit of activity is the Curie (Ci), originally defined as the activity of one gram of radium, ^{226}Ra .

Curie is now defined as

$$1 \text{ Curie} = 1 \text{ Ci} = 3.7 \times 10^{10} \text{ dps} \\ = 37 \text{ GBq} \quad (6)$$

$$1 \text{ milliCurie} = 1 \text{ mCi} = 3.7 \times 10^7 \text{ dps} \\ = 37 \text{ MBq} \quad (7)$$

$$1 \text{ milliCurie} = 1 \mu\text{Ci} = 3.7 \times 10^4 \text{ dps} \\ = 37 \text{ MBq} \quad (8)$$

Half-Life and Average Life Time

Every radionuclide has a characteristic half-life ($T_{1/2}$), which is the time required for the activity to decay to 50% of its original value. That is, A_0 is reduced to $A_0/2$ in one half-life, $A_0/2^2$ in 2 half-lives, and $A_0/2^n$ in *n* half-lives. The activity **A** of a radionuclide at any time *t* is given by

$$A_t = \frac{A_0}{2^n} = \frac{A_0}{2^{(t/T_{1/2})}} \quad (9)$$

$$T_{1/2} = \frac{\ln(0.2)}{\lambda} = \frac{0.693}{\lambda} \quad (10)$$

In a given sample of radionuclide, all atoms do not decay with the same half-life; some atoms may have shorter and some atoms may have longer life span than one half-life. The average or mean life (τ) of a radionuclide is therefore defined as the average of all individual life times of that the atoms in a sample of radionuclide experience. The mean life is related to decay constant and half-life:

$$\tau = \frac{1}{\lambda} = \frac{T_{1/2}}{0.693} = 1.44 T_{1/2} \quad (11)$$

Specific Activity (SA)

The SA of a radioactive sample is defined as its activity per unit mass or the ratio of activity (**A**) to the total mass (**m**) of the element present. SA (**A/m**) has units of Ci/g, Ci/mmol, or GBq/mmol, etc. When stable isotopes of an element are present

along with the radioactive isotope, then the stable isotopes are called *carrier*. The radioactivity of the sample is said to be with carrier and the SA of such a radioisotope is low since the total mass of the element includes the mass of radioisotope and also that of carrier. A radioactive sample that does not contain carrier is called *carrier-free*. The highest possible SA of a radionuclide is its carrier-free SA (CFSA). It is also known as the theoretical SA and not necessarily achieved practically by radionuclide production methods. For a number of radioisotopes, the CFSA are shown in the Table 3. CFSA can be calculated since there is a well-defined activity–mass relationship based on the following mathematical relationships:

- Knowing the activity (Ci or GBq, etc.) and λ , the number of atoms (N) in a sample of radioactivity can be determined based on activity law, $A = \lambda N$.
- Based on N, the mass (g or moles) of a radioisotope can be determined since one mole (gram atomic weight) of any element contains 6.022×10^{23} atoms (Avogadro’s number).

Radionuclide Production: Nuclear Reactions

When two nuclei come close together, a *nuclear reaction* can occur that results in *nuclear*

transformation, the conversion of one element to another. In a nuclear reaction, when the atoms of a stable element (target) are bombarded by a subatomic particle (projectile), the nucleus of the stable atom absorbs the subatomic particle. The resultant *compound nucleus* is very unstable and excited. The compound nuclei have life times in the order of 10^{-16} s or so. The compound nucleus may decay in one or more ways, depending on its neutron/proton ratio and excitation energy. It may quickly decompose by emitting some radiation (subatomic particle and/or gamma radiation) to form an unstable product radionuclide. The general equation for a nuclear reaction can be written as follows:

$$T(P,R)Y \tag{12}$$

where *T* represents the target nuclide; *P* is the projectile, the incident, or the bombarding particle; *R* represents the radiation (subatomic particle or γ photons) emitted by the compound nucleus; and finally *Y* represents the product unstable radionuclide. The *P* and *R* in parenthesis, written as (*P, R*), represent the nuclear reaction. A number of reactions such as (*p, n*), (*p, α*), and (*d, α*) are some of the common nuclear reactions used to produce artificial radioisotopes in a cyclotron.

Radiopharmaceuticals in Molecular Imaging, Table 3 Radionuclides for PET and SPECT: half-life and specific activity (SA)^a

Radionuclides for PET			Radionuclides for SPECT		
Nuclide	T _{1/2} (min)	SA (Ci/ μ mol)	Nuclide	T _{1/2} (min)	SA (Ci/ μ mol)
¹⁵ O	2.07	91,730			
¹²² I	3.62	51,912			
⁶² Cu	9.76	19,310			
¹³ N	10.0	18,900			
¹¹ C	20.4	9220			
^{94m} Tc	52.0	3614	^{99m} Tc	360	522
⁶⁸ Ga	68.3	2766			
⁷⁷ Br	96.0	1960			
¹⁸ F	110	1708			
⁶⁶ Ga	567	331	⁶⁷ Ga	4320	40
⁶⁴ Cu	768	245			
⁸⁶ Y	884	213	¹¹¹ In	4020	47
⁸⁹ Zr	4709	39.9			
¹²⁴ I	6048	31.0	¹²³ I	780	237

^aMaximum theoretical SA

Radiopharmaceuticals in Molecular Imaging, Table 4 Nuclear reactions for the production of the most common radionuclides

Radio isotope	Nuclear reaction	Yield	Product chemical
		mCi/μA	
¹⁸ F	¹⁸ O (p, n) ¹⁸ F	110	¹⁸ F [−]
¹⁸ F	²⁰ Ne (d, α) ¹⁸ F	51	¹⁸ F ₂
¹¹ C	¹⁴ N (p, α) ¹¹ C	40	¹¹ CO ₂
¹³ N	¹⁶ O (p, α) ¹³ N	7	¹³ NH ₄ ⁺
¹⁵ O	¹⁴ N (d, n) ¹⁵ O	50	O ₂
¹⁵ O	¹⁵ N (p, n) ¹⁵ O	47	O ₂
⁶⁴ Cu	⁶⁴ Ni (p, n) ⁶⁴ Cu	73	⁶⁴ CuCl ₂
⁸⁶ Y	⁸⁶ Sr (p, n) ⁸⁶ Y		⁸⁶ YCl ₃
⁸⁹ Zr	⁸⁹ Y (p, n) ⁸⁹ Zr		⁸⁹ Zr oxalate
¹¹¹ In	¹¹¹ Cd (p, n) ¹¹¹ In		¹¹¹ In chloride
¹²³ I	¹²⁴ Xe (p, 2n) ¹²³ Cs (T _{1/2} = 5.9 min) → ¹²³ Xe	73	¹²³ I as NaI
	¹²³ Xe (T _{1/2} = 2.08 h) → ¹²³ I		
¹²⁴ I	¹²⁴ Te(p, n) ¹²⁴ I	73	¹²⁴ I as NaI
	¹²⁴ Te(d, 2n) ¹²⁴ I		

The most widely used particle accelerator is the *medical cyclotron*, which is capable of accelerating protons to low and medium energy levels (10–20 MeV) needed for the production of PET radionuclides (Ruth 2003; Schlyer 2003). Certain cyclotrons also have a deuteron (proton + neutron) beam capability. The commercial cyclotrons with higher-energy proton beams (>30 MeV) are needed to produce proton-rich radionuclides that decay by electron capture. The most important nuclear reactions used in the production of radionuclides are summarized in Table 4.

Radionuclide Generators

When a sample of radioactivity consists of a pair of parent and daughter radionuclides, the daughter is continuously produced by the decay of the parent, and at the same time, the daughter activity is also decaying. The *Bateman equation* (Eq. 13) describes the parent–daughter relationship and provides an estimate of A_d:

$$A_{d(t)} = A_{p(t_0)} \frac{\lambda_d}{\lambda_d - \lambda_p} (e^{-\lambda_p t} - e^{-\lambda_d t}) + A_{d(t_0)} e^{-\lambda_d t} \tag{13}$$

At equilibrium, the parent and daughter activities appear to decay with the same rate, even if the two nuclides have different half-lives. Two

different equilibrium conditions (secular and transient), however, may exist depending on how short lived the daughter radionuclide compared to the parent. If the parent is short lived compared to the parent, then there is no equilibrium at all. If the parent and daughter nuclides are two different elements, they can be separated chemically and the daughter radioactivity can be obtained in high SA. Such a parent–daughter radionuclide pair is ideal to build a generator system to produce daughter radionuclide, when needed (Welch and McCarthy 2000). The *radionuclide generator* is a device to separate the daughter radionuclide from the parent radionuclide. All kinds of physico-chemical separation methods (such as distillation, liquid/liquid extraction) may be used. A chromatographic method based on an inorganic or resin adsorbent material, however, is the most practical method for routine clinical utility. Three important generator systems (Table 5) are available to produce radionuclides of clinical interest.

Radiopharmaceuticals

Radioactivity Versus Chemistry

Radioactivity is a process involving primarily the decay of an unstable nucleus of an element, whereas all the chemical reactions of an element

Radiopharmaceuticals in Molecular Imaging, Table 5 Radionuclide generators

Parent				Daughter			Generator	
Nuclide	T _{1/2}	Decay	NR	Nuclide	T _{1/2}	Decay	Column	Eluent
⁹⁹ Mo	66 h	β [−]	²³⁵ U fission	^{99m} Tc	6 h	IT	Al ₂ O ₃	0.9% saline
⁶⁸ Ge	271 day	EC	⁶⁹ Ga(p, 2n) ⁶⁸ Ge	⁶⁸ Ga	68 min	β ⁺	TiO ₂	1 N HCl
⁶² Zn	9.3 h	EC, β ⁺	⁶³ Cu(p, 2n) ⁶² Zn	⁶² Cu	9.7 min	β ⁺	Dowex	2 N HCl

involve the outermost orbital electrons. Atoms of different isotopes of an element, both stable and radioactive, will have similar chemistry regardless of the radioactive emissions from an unstable nucleus. Similarly, the chemistry of an atom does not affect in any way the radioactive decay characteristics of an atom. The *tracer principle* in nuclear medicine is based on the fact that the chemistry and physiological behavior of radioisotopes of an element are identical to the corresponding naturally occurring stable isotopes of that element.

Radiotracer and Radiopharmaceutical

A radiotracer can be defined as a specific radio-labeled molecule (or probe) that resembles or traces the *in vivo* behavior of a natural molecule and can be used to provide information about a specific biological process. The degree of similarity between radiotracer and the natural substance, however, may vary depending on the particular radiotracer. For example, [¹¹C]glucose and [¹⁴C]glucose are true tracers of glucose since they are chemically identical to natural glucose, while [¹⁸F]fluorodeoxyglucose (FDG), an analog of glucose, also traces glucose, but does not behave identically to glucose since it is chemically different. One of the most important characteristics of a true radiotracer, however, is the ability to study the components of a homeostatic system without disturbing their function. Occasionally, the term *radioligand* is also used in the context of imaging studies. Radioligand can be defined as any radio-labeled molecule that can bind with another molecule or substance (binder) in a predictable way under controlled conditions. For example, [¹¹C]raclopride is a radioligand that binds specifically to dopamine D₂ receptors, while [¹⁸F]FDG is a radiotracer to image glucose metabolism.

All radiolabeled compounds or substances used for the purpose of diagnosis or therapy have been defined as *radioactive drugs* or *radiopharmaceuticals* by the US Food and Drug Administration (FDA). Diagnostic radiopharmaceuticals, however, are administered in trace amounts (<100 μg) and, typically, do not induce any physiological response or pharmacological effect in patients. In addition, FDA adopted the same regulations for radiolabeled compounds (or nuclear medicine imaging probes) as those in existence for traditional drugs (pharmaceuticals). As a result, the term radiopharmaceutical has become the official FDA categorization for all radioindicators and radiotracers used for diagnosis and therapy. Although, the field of nuclear medicine evolved into a more sophisticated molecular imaging technology, the FDA continues to extend the usage of the term radiopharmaceuticals to include the novel radiolabeled molecular imaging probes (RMIPs) also. From a regulatory point of view, however, a radiopharmaceutical must also be sterile, pyrogen-free, safe for human use, and efficacious for a specific indication.

Choice of Radionuclide

A number of radionuclides that emit either a β⁺ or a γ photon are available (Table 6) for radiopharmaceuticals for PET or SPECT. These radionuclides basically belong to four groups of chemical elements: organic elements (C, N, and O), halogens (F, Br, and I), metals (Ga and In), and transition metals (such as Cu, Y, Zr, and Tc). Only certain elements (I, Ga, Cu) have radioisotopes useful to develop radiopharmaceuticals for both PET and SPECT. The organic radionuclides that decay by positron emission are ¹¹C, ¹³N, and ¹⁵O. These three radionuclides are isotopes of

Radiopharmaceuticals in Molecular Imaging, Table 6 Radionuclides useful for developing PET and SPECT radiopharmaceuticals

Elements	For PET				For SPECT		
	Radionuclide	T _{1/2}	Positron (β^+)		Radionuclide	T _{1/2}	γ energy (MeV)
			E (MeV)	Branching			
Organic elements	¹¹ C	20.39 min	0.960	99.759			
	¹³ N	9.967 min	1.198	99.8			
	¹⁵ O	2.041 min	1.732	99.9			
Halogens	¹⁸ F	109.728 min	0.633	96.86			
	⁷⁵ Br	96.7 min	1.74	75.5			
	⁷⁶ Br	16.2 h	1.31	54			
	¹²⁴ I	4.2 day	1.535	23	¹²³ I	13.27 h	0.159 (83%)
Metals			2.138		¹³¹ I	8.04 day	0.364 (81%)
	⁶⁶ Ga	9.45 h	4.153	56	⁶⁷ Ga	78.2 h	0.093 (39%)
	⁶⁸ Ga	68.3 min	1.898	90			0.184 (21%)
Transition metals	^{110m} In	69 min	2.25	62	¹¹¹ In	67.2 h	0.173 (90%), 0.247 (94%)
	⁶² Cu	9.76 min	2.910	98.0	⁶⁷ Cu	61.83 h	0.185, 0.92
	⁶⁴ Cu	12.7 h	0.653	17.52			
	⁸⁶ Y	14.74 h	3.150	33.0			
	⁸⁹ Zr	78.4 h	0.897	23.0			
	^{94m} Tc	52 min	2.470	72.0	^{99m} Tc	6.01 h	0.140 (99.99%)

natural elements that are part of the majority of biochemicals and drugs. Among the halogens, fluorine atom is the only one that closely mimics the hydrogen atom in size (Park et al. 2001). The van der Waals' radii of fluorine and hydrogen are very similar, 1.35 and 1.2 Å, respectively. As a result, one can expect that in any given organic molecule, C–F bond closely mimics the biological behavior of C–H bond. In addition, fluorine atom is also the most electronegative of all halogens. As a result, fluorine atom introduces a polarity more akin to a hydroxyl substituent in a molecule. The other halogens are bigger in size and are less electronegative compared to fluorine. As a result, labeling a biochemical with bromine or iodine radioisotopes would alter the biological behavior of the molecule. However, halogen atoms in drug molecules are quite common, and sometimes, the halogen-containing drug molecules may have even greater affinity for a receptor or an enzyme in vivo than the non-halogenated molecules (Park et al. 2001). In the last 2 decades, several

radiotracers were developed based on ¹²³I for SPECT imaging studies of brain. Organic molecules containing aromatic ring can be labeled easily with radioisotopes of iodine. As a result, ¹²³I and ¹²⁴I will play a major role in the development of molecular imaging probes. Among the metals, Ga, In, and Y are trivalent and have similar chemistries. The transition metals such as Cu, Sc, Zr, and Tc have complex coordination chemistries. The radionuclides of all these metals (⁶⁸Ga, ⁶⁴Cu, ⁸⁶Y, ⁸⁹Zr, ¹¹¹In, and ^{99m}Tc) can be used to label small molecules, peptides, and proteins using bifunctional chelating agents.

Radionuclide: Positron (β^+) Versus Gamma (γ) Emission

A positron ejected by a radionuclide travels a very short distance in a tissue, dissipating its kinetic energy in collisions with electrons, and finally combines with an electron to form a positronium, a state which lasts for a very short time (10^{-10} s), and the subsequent positron–electron annihilation

results in the emission of two 511 KeV photons, 180° apart. A PET scanner is designed to detect this pair of annihilation photons almost simultaneously based on a process known as annihilation coincidence detection (ACD). Positron-emitting radionuclides differ in the energy of emitted positrons. For example, the energy of positrons emitted by ^{18}F ($E_{\text{max}} = 0.63$ MeV) is almost 1/7th compared to that of a positron emitted by ^{66}Ga ($E_{\text{max}} = 4.153$ MeV). Positron range is the direct distance traveled by positron from the decaying atom to the exact location of annihilation event. Positron range is a function of the energy of positron (Table 6). The mean positron range may vary from 1 to 4–6 mm depending on the radionuclide. The error due to positron range may be significant, and therefore, positron range limits the ultimate resolution attainable by PET. In addition, the number of positrons emitted (the branching ratio) also changes among different positron emitters (97.86% for ^{18}F compared to 17.5% for ^{64}Cu). It is very important to appreciate that SPECT technique inherently offers no limitation in spatial resolution since γ photons are emitted directly by the nucleus of a SPECT radionuclide ($^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I). The abundance of γ emission from SPECT radionuclides is more than adequate (>80%). Molecular imaging by PET technique, however, is inherently quantitative, while SPECT offers relatively poor resolution (8–10 mm) and is semiquantitative.

Radiochemistry: Synthesis of Radiopharmaceuticals

Radiolabeling is the chemical reaction during which the radionuclide is incorporated in the desired molecule. The position of a radionuclide in a radiopharmaceutical must be carefully selected so that the presence of radionuclide at that position preserves the overall chemical and pharmacological properties of the parent unlabeled molecule. In addition the position of radiolabel must also preserve the metabolic stability of the radiotracer during the time course of an imaging study. In addition, specific activity, stereospecificity, lipophilicity, and plasma protein binding are all important in the overall design of any radiopharmaceutical. Depending on the type

of radioisotope chosen and the method used to radiolabel a specific molecular imaging probe, three different methods may be utilized in the synthesis of radiopharmaceuticals:

1. *Isotope exchange*: A radiopharmaceutical may be prepared by direct exchange (isotopic substitution) of one or more stable atoms of an element in a molecule with one or more radioisotopes of the same element. The radiolabeled molecule and the unlabeled molecule are chemically identical and behave in vivo in a similar manner. In the preparation of ^{11}C -labeled radiotracers, the Stable ^{12}C atom is replaced by ^{11}C radionuclide. The preparation of ^{11}C compounds, however, may involve multistep alkylation reactions. The method of isotope exchange radiolabeling is generally used to prepare radioiodinated radiopharmaceuticals in which the Stable ^{127}I atom is replaced by ^{123}I or ^{124}I tom.
2. *Introduction of a foreign element*: A radiopharmaceutical may be prepared by the introduction of a foreign element or radionuclide in a parent molecular imaging probe. Most of the radiopharmaceuticals are prepared based on this method. The radiotracer may not be chemically identical to unlabeled molecule and may have different in vivo behavior. For example, preparation of [^{18}F]FDG involves the introduction of ^{18}F atom in deoxyglucose molecule. Also in the preparation of radioiodinated peptides and hormones, ^{123}I or ^{124}I is added to the parent molecules that do not contain natural stable iodine atom.
3. *Metal chelation*: This method also introduces a foreign element (radiometal such as $^{99\text{m}}\text{Tc}$, ^{64}Cu , ^{68}Ga , and ^{111}In) into an organic molecule known as chelating agent. One or more atoms (such as O, N, and S) in the chelating agent donate a pair of electrons to the foreign metal atom to form coordinate covalent bonds. As a result, the chemical and biological properties of the radiometal-chelate complex are different compared to the chelating agent. Certain peptides and proteins such as monoclonal antibodies can be labeled with radiometals based on the metal chelation method described

above. This technique, however, requires conjugation of a bifunctional chelate (BFC) to the peptide or protein first and then subsequent chelation of the radiometal by the BFC molecule. In general, radiometals are not directly incorporated into the peptide or protein molecule. However, proteins like transferring may have specific binding sites to metals like iron and gallium.

In this chapter on radiopharmaceuticals for neuroimaging studies, an overview of the most common chemical approaches for the synthesis of PET and SPECT radiotracers are discussed with special emphasis on the most recent developments and trends. The major emphasis, however, is on PET radionuclides, especially ^{11}C and ^{18}F .

^{11}C -Labeled Radiopharmaceuticals

Carbon is one of the main constituents in most molecules of biological importance. Hence, labeling with ^{11}C will result in radiotracers indistinguishable from their non-labeled counterparts. There are several disadvantages of using ^{11}C radionuclide. Because of its short half-life (20 min), the synthesis of ^{11}C -labeled radiotracer, purification, and quality control testing has to be performed very rapidly (in <1 h) in order to have optimal specific activity for receptor imaging studies. Also because of short half-life, commercial distribution of ^{11}C radiotracers by commercial radiopharmacies is not very difficult and can only be done at academic research facilities. $[^{11}\text{C}]\text{CO}$ was the first radiotracer used in human subjects to investigate the fixation of CO by red blood cells. Several reviews discussed extensively the

chemistry and potential application of ^{11}C -labeled radiotracers (Antoni and Långström 2005; Dollé 2013; Långström et al. 2013).

The most commonly used method of ^{11}C production is based on the nuclear reaction, $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$, in which the natural nitrogen gas is used as the target. With trace amounts of oxygen in the target (<1%), the $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CO}$ are formed. With relatively higher proton energies (>13 MeV), longer irradiation times (>30 min), and higher beam currents (>30 μA), the most predominant ^{11}C precursor generated is $[^{11}\text{C}]\text{CO}_2$ gas. In the presence of hydrogen (5%) in the target, $[^{11}\text{C}]\text{methane}$ (CH_4) and $[^{11}\text{C}]\text{hydrogen cyanide}$ (HCN) can be produced in the target by a recoil synthesis, but due to radiolysis, $[^{11}\text{C}]\text{CH}_4$ is the main precursor available for processing. The theoretical SA of ^{11}C is 9.22 Ci/nmol. The contamination of the target and the gas lines with Stable ^{12}C is unavoidable. As a consequence, the practical SA of ^{11}C precursors achieved from typical production in a cyclotron target varies from 0.01 to 0.1 Ci/nmol depending on a number of factors.

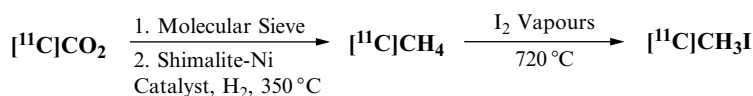
$[^{11}\text{C}]\text{Methyl iodide}$ (CH_3I) is the precursor of choice for introducing ^{11}C into organic molecules. Two methods are used for the synthesis of $[^{11}\text{C}]\text{CH}_3\text{I}$ (Fig. 1). In a “liquid-phase” synthesis, $[^{11}\text{C}]\text{CO}_2$ is first reduced using lithium aluminum hydride (LiAlH_4) to methanol $[^{11}\text{C}]\text{CH}_3\text{OH}$, which then reacts with hydroiodic acid (HI) to generate methyl iodide. In a “gas-phase” synthesis, $[^{11}\text{C}]\text{CH}_4$ gas (either from the target directly or produced from $[^{11}\text{C}]\text{CO}_2$) reacts with iodine vapors generating methyl iodide. Commercial automated synthesis modules are available to synthesize $[^{11}\text{C}]\text{CH}_3\text{I}$. *GE MicroLab* and *GE TracerLab FXc Pro* modules were designed to generate methyl iodide based on the gas-phase method

Radiopharmaceuticals in Molecular Imaging,
Fig. 1 Synthesis of $[^{11}\text{C}]$
methyl iodide

A. Liquid Phase



B. Gas Phase

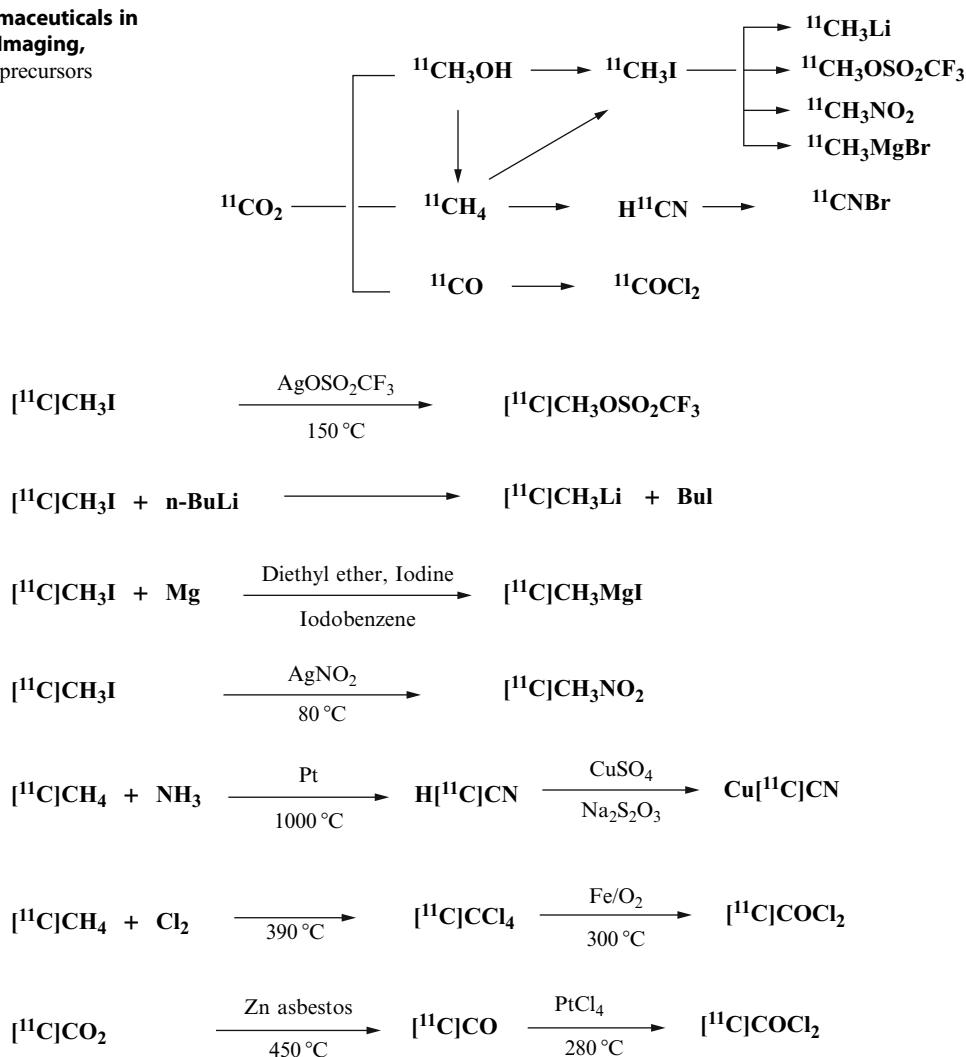


while *Bioscan MeI-Plus* was designed based on the liquid-phase method. [^{11}C]CH $_3$ I can also be used to prepare a number of secondary ^{11}C precursors (Fig. 2) such as methyl triflate, ($\text{CH}_3\text{OSO}_2\text{CF}_3$) methyl lithium, nitromethane, and methyl magnesium iodide or bromide. Starting with [^{11}C]methane, precursors such as hydrogen cyanide, cupric cyanide, carbon tetrachloride, and phosgene can be prepared (Antoni and Långström 2005; Li and Conti 2010). Synthesis of several ^{11}C precursors is shown in Figs. 2 and 3.

In the last three decades, a number of ^{11}C -labeled molecular imaging probes of significant clinical interest have been developed. Historically several different approaches have been developed for the production of ^{11}C -labeled radiotracers, but the most practical approaches have been based on either (a) organic synthetic methods or (b) enzyme catalysis (Antoni and Långström 2005). The methods based on organic synthesis typically involve alkylations of C, N, O, and S nucleophiles with [^{11}C]methyl iodide or methyl triflate. The alkylation

Radiopharmaceuticals in Molecular Imaging,

Fig. 2 ^{11}C precursors



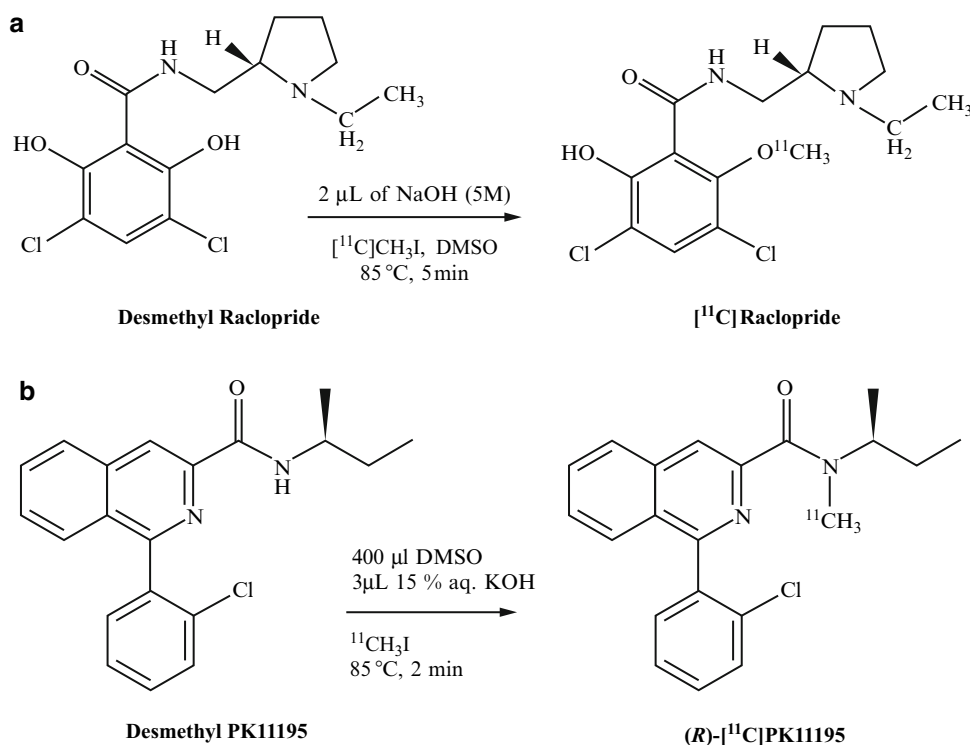
Radiopharmaceuticals in Molecular Imaging, Fig. 3 Synthesis of ^{11}C precursors

reactions require an organic precursor, also known as *nor* compound (a molecule of interest without a methyl group on a specific C, N, O, or S atom). If a molecule of interest has several reactive groups, the organic precursors must have protective groups that can be easily de-protected by hydrolysis following methylation to generate the final drug product. This is the most common synthetic approach used in the routine production of ^{11}C -labeled radiopharmaceuticals.

Several methods for carrying out ^{11}C methylations either in solution or on solid support have been reported in the literature. When methylations are carried out in solution, solvents like DMSO, DMF, acetone, and acetonitrile are generally used. In many cases, a base is needed for deprotonation. Commonly used bases are K_2CO_3 , TBOH, NaOH, and NaH. In general, the precursor is dissolved in the appropriate solvent in the presence of a base. The ^{11}C -methylating agent (methyl

iodide or methyl triflate) is bubbled through the solution and incubated at 70–120 °C. Following HPLC purification the ^{11}C -labeled radiotracer is dissolved in an appropriate isotonic buffer and sterilized by membrane filtration. Representative PET tracers made from this category of reactions are listed in Fig. 4. Methylations on a solid support are very convenient for automation purposes. The precursor is coated on a solid support, such as an HPLC loop or a solid-phase extraction cartridge. The ^{11}C -methylating agent is passed through the solid support. The product is eluted from the support by a solvent or HPLC mobile phase.

$^{11}\text{CO}_2$ has been converted to organometallic Grignard reagents to form $[^{11}\text{C}]$ carboxymagnesium halides and then transformed into $[^{11}\text{C}]$ carboxylic acids. Moreover, enzyme-catalyzed chemical transformations have been employed for the introduction of ^{11}C in amino acids.



Radiopharmaceuticals in Molecular Imaging, Fig. 4 Synthesis of ^{11}C -labeled radiopharmaceuticals

¹⁸F-Labeled Radiopharmaceuticals

¹⁸F is the most often used radionuclide for diagnostic PET imaging since the decay properties of ¹⁸F provide significant advantages. As discussed earlier, labeling a molecule with ¹⁸F in place of a hydrogen atom often does not change its size or shape, and generally metabolically stable compounds are obtained. ¹⁸F appears to be an ideal radionuclide for developing PET radiopharmaceutical in the following reasons:

- Low β^+ energy (0.64 MeV) with a short range in tissue (~2.0 mm) and provides high-resolution images.
- Can be produced in high SA (20–50 Ci/ μ mole).
- Can be produced in large amounts (>10 Ci) in a cyclotron.
- Fluorine is the most electronegative and can react with many organic and inorganic chemicals.
- It can react as an electrophile or a nucleophile chemical species.
- Relatively high labeling yields (20–70%) in the synthesis of ¹⁸F-PET tracers.
- Acceptable radiation dosimetry for multiple studies in a patient.
- The physical $T_{1/2}$ (110 min) allows for transport from the production site to the PET centers.

The design and synthesis of ¹⁸F-labeled radiopharmaceuticals of clinical interest has been extensively reviewed previously in several publications (Vallabhajosula 2009; Li and Conti 2010). Some of the basic principles of ¹⁸F chemistry are briefly described below.

Radiofluorination

In addition to the two primary ¹⁸F precursors (fluoride and fluorine gas), several secondary precursors have been developed to radiolabel a number of organic molecules (Fig. 5). Fluoride ion needs to be activated (discussed below) prior to fluorination reactions. Metal fluorides (such as K¹⁸F, Cs¹⁸F) and tetra-n-butyl ammonium fluoride (nBu₄N¹⁸F) are the most widely used ¹⁸F precursors in nucleophilic fluorination reactions, while [¹⁸F]CH₃COOF (acetyl hypofluorite) is the most common precursor in the electrophilic reactions. The main synthetic strategies could be divided into two categories: (1) direct fluorination (the ¹⁸F isotope is introduced “directly” into the target molecule of interest) and (2) indirect fluorination (the ¹⁸F isotope is introduced through ¹⁸F prosthetic groups, which usually requires a multi-step synthetic approach).

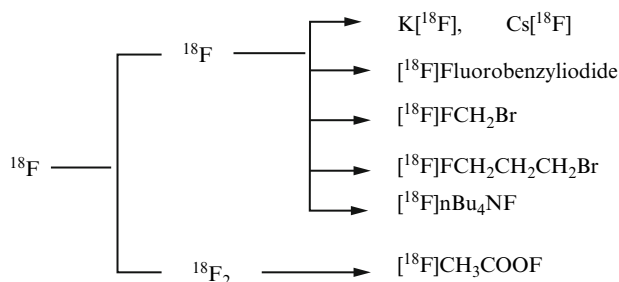
Nucleophilic Fluorination Reactions

The most successful approach for preparing high SA ¹⁸F radiotracers is based on nucleophilic fluorination reactions. Synthesis of ¹⁸F radiotracers using fluoride ion utilize 2 general types of chemical reactions: (a) aliphatic nucleophilic substitution or substitution nucleophilic bimolecular (S_N2) and (b) aromatic nucleophilic substitution (S_NAr). In aliphatic S_N2 reactions, the fluoride ion attacks and binds to the carbon atom of the substrate at 180° opposite to a leaving group (Fig. 6) that is a weak base (such as iodide, bromide, triflate, tosylate, nosylate, mesylate, etc.). S_NAr nucleophilic reactions were designed to

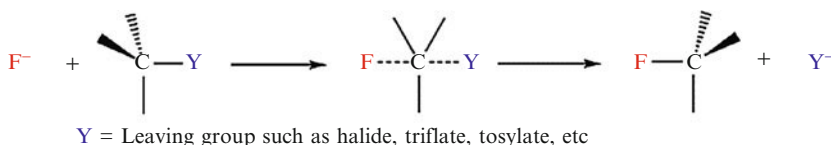
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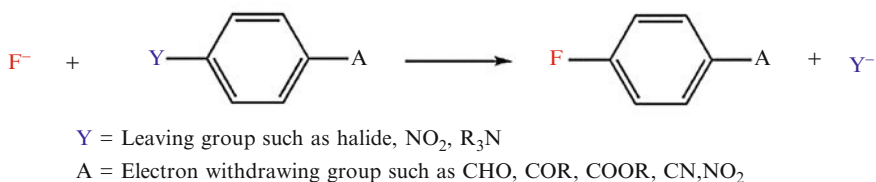
Fig. 5 ¹⁸F precursors



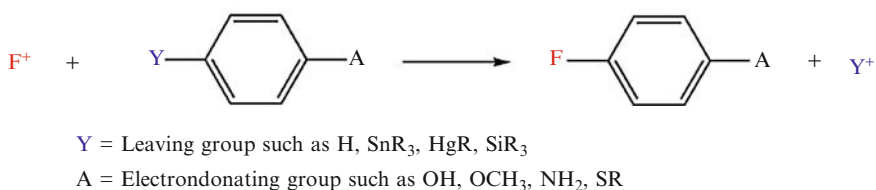
1. Aliphatic Nucleophilic Substitution (S_N2)



2. Aromatic Nucleophilic Substitution (S_NAr)



3. Electrophilic fluorination



Radiopharmaceuticals in Molecular Imaging, Fig. 6 Fluorination reactions

incorporate ^{18}F atom directly into the aromatic ring as well as into prosthetic groups containing aromatic ring of a molecule. In these reactions, the leaving group is activated by the electron-withdrawing groups *ortho* and/or *para* to the leaving group, such as halide, NO_2 , and R_3N^+ . The fluoride ion in aqueous solution is very unreactive and has to be activated to increase its solubility and lipophilicity. ^{18}F fluoride ion is generally activated by complexing with a metal or positively charged ion. When alkali metal halides (K^{18}F , Cs^{18}F , Rb^{18}F) are used, it is essential to have the metal to be coordinated by cryptands and polyaminoethers (such as Kryptofix 2.2.2) so that the free fluoride can show very good reactivity. Instead of alkali metal halides, a variety of tetraalkylammonium ^{18}F fluorides have also been used but show low stability at higher temperature. These reactions generally take place in basic or neutral conditions in the presence of an appropriate dipolar

aprotic solvent (such as acetonitrile, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF)) in which the reactants show good solubility. Sometimes, ^{18}F fluoride ion is first converted to another reactive species such as alkyl halides (such as ^{18}F fluorobromoethane, ^{18}F fluorobromopropane) and benzylic halides. A number of ^{18}F radiopharmaceuticals such as ^{18}F FDG and ^{18}F fallypride can all be prepared using commercially available precursors.

Electrophilic Fluorination Reactions

The reaction of ^{18}F F_2 with precursors is accomplished by addition to double bonds or to aromatic rings. The ^{18}F F_2 precursor has only one of the atoms as ^{18}F while the other is Stable ^{19}F atom. Therefore, the labeling yield are always $<50\%$. Since fluorine is a nonselective electrophile, and acts as an oxidizing agent, it is frequently

converted into [^{18}F]acetyl hypofluorite, a milder and much less reactive agent with greater solubility than elemental fluorine. With these precursors, direct electrophilic fluorinations are not necessarily regioselective and the ^{18}F atom can attack any of the C–C double bond in the molecule. Therefore, these precursors are used only in rare situations where nucleophilic reactions are not appropriate. However, regioselective electrophilic fluorodemetalation reactions were developed to take advantage of reactive electrophiles in the preparation of ^{18}F -PET tracers. Electrophilic fluorination reactions (Fig. 6) are facilitated by the presence of electron-donating groups (such as OH, OCH_3 , NH_2 , etc.) and appropriate leaving groups (such as H, SnR_3 , SiR_3 , and HgR) in the precursor molecule. Selectivity can further be increased by using the fluorodemetalation reaction, in which preferentially a trialkyltin group is substituted by electrophilic ^{18}F .

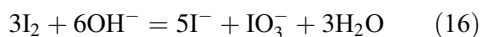
Organic Precursors for ^{18}F Labeling

The synthesis of ^{18}F -labeled PET tracer is a multi-step process and it is ideal to introduce ^{18}F in the last step to reduce synthesis time. In the design of a PET tracer, the most important step is the synthesis of an appropriate precursor of the desired radiotracer, which will facilitate ^{18}F labeling. As discussed above, the ^{18}F reactions require an appropriate leaving group, in the precursor molecule. In addition, the molecules to be labeled may have a number of functional groups (such as OH, COOH , NH_2), which may react and interfere with the labeling of radioisotope in a specific position in a molecule. Therefore, in order to facilitate regioselective labeling of substrates, organic precursors have to be synthesized first with protective groups attached to functional groups. It is very important that the protective groups are very stable during labeling procedure and can be removed rapidly and easily under conditions favorable to maintain the stability of the radiolabeled molecule. A number of precursors for ^{18}F labeling have been developed over the years and are now commercially available. Several examples of precursors with appropriate leaving groups and

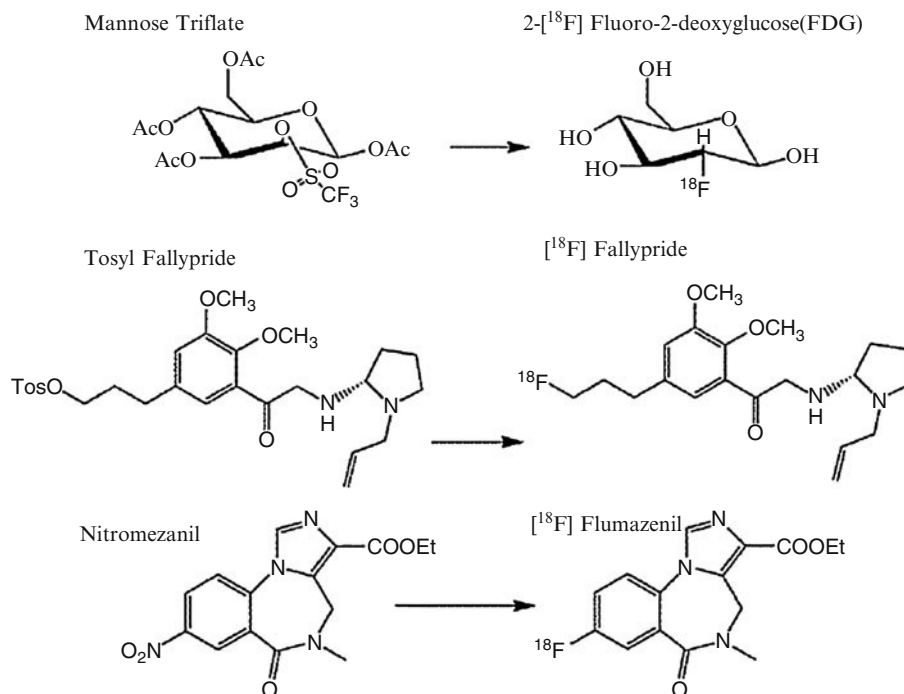
protective groups developed for the synthesis of ^{18}F -labeled radiotracers such as [^{18}F]FDG, [^{18}F]fallypride, and [^{18}F]flumazenil are shown in Fig. 7. In case of [^{18}F]FDG, the precursor is mannose triflate, in which the 4 hydroxyl groups of deoxyglucose are protected by adding acetate (Ac) groups. Also, in order to facilitate ^{18}F labeling, a leaving group, trifluoromethane sulfonate (TFMS), is added to the carbon in the second position. In case of [^{18}F]fallypride, the precursor is tosyl fallypride, in which the leaving tosyl group is added to the alkyl side chain. The precursor for the synthesis of [^{18}F]flumazenil is nitromezanil in which the nitro group (NO_2) in the aromatic ring is substituted by the reactive [^{18}F]fluoride ion.

Radioiodination

Unlike fluorine, iodine can exist in several oxidation states. The free molecular iodine (I_2) has the structure of I^+-I^- in aqueous solution. But the electrophilic species (I^+) does not exist as a free species, but forms complexes with nucleophilic entities such as water or pyridine. The reactions with water can be written as follows:



The hydrated iodonium ion, H_2OI^+ , and the hypoiodous acid, HOI, are believed to be the highly reactive electrophilic species. In an iodination reaction, iodination occurs by (a) electrophilic substitution of a hydrogen ion by an iodonium ion in a molecule of interest or (b) nucleophilic substitution (isotope exchange) where a radioactive iodine atom exchanges with a stable iodine atom that is already present in the molecule. In the preparation of radioiodinated compounds, the radioiodine is preferentially attached to a carbon atom, in a vinylic or aromatic moiety, in which the carbon–iodine bond strength



Radiopharmaceuticals in Molecular Imaging, Fig. 7 Precursors for ^{18}F -labeled radiopharmaceuticals

is higher. Therefore, the radioiodination is often implemented by electrophilic or nucleophilic aromatic substitution. Electrophilic labeling reactions can often be performed fast and under mild reaction conditions. The electrophilic species (HO^*I , $\text{H}_2\text{O}^*\text{I}$) generated from radioiodide and the oxidant react directly with the aromatic moiety of the compound to be labeled. Most frequently used oxidizing agents are peracetic acid and the N-chloro compounds, such as chloramine-T, iodogen, and succinimides. The labeling of small organic molecules, peracetic acid, is often preferred due to its mild oxidizing properties. Electrophilic substitutions can often be carried out on a non-derivatized substrate. However, in case of low reactivity or lack of regioselectivity, radioiodo destannylation has become more and more the method of choice. The method of choice in nucleophilic radioiodination is the well-established Cu(I)-catalyzed halogen-halogen exchange reaction in an acidic, aqueous medium. The exchange reactions can be either isotopic exchange ($^*\text{I}/\text{I}$) or non-isotopic exchange

($^*\text{I}/\text{Br}$), which specifically enables the synthesis of a high SA radiopharmaceuticals. A nucleophilic exchange can be successfully applied on activated (presence of electron-deficient substituents, e.g., carbonyl group) or non-activated (e.g., alkyl group) aromatic compounds. However, in organic media, electron-donating substituents are also well tolerated. The advantages and disadvantages of different radioiodination techniques were recently reviewed (Kabalka and Mereddy 2004; Eersels et al. 2005).

Labeling of Biomolecules with Radiometals

The majority of diagnostic SPECT radiopharmaceuticals currently available in nuclear medicine are either radiometal complexes or target-specific biomolecules labeled with metallic radionuclides, such as $^{99\text{m}}\text{Tc}$, ^{67}Ga , and ^{111}In . Metallic radionuclides, such as ^{68}Ga , ^{64}Cu , and ^{89}Zr , are potentially useful to radiolabel biomolecules for PET.

Different radiometals have significant difference in their coordination chemistry. Since the radio-metal chelate can have a significant impact on biological properties, the biodistribution of a target-specific metallic radiopharmaceutical can be systematically changed either by modifying the coordination environment around the radio-metal with a variety of chelators or by the use of various coligands if the radiometal chelate contains two or more ligands.

Both gallium and indium are group IIIB metals and the most prevalent oxidation state in aqueous solution is +3. Due to their high charge density, these two metals prefer hard donors, such as amine-N and carboxylate-O atoms. However, hydrolysis of Ga(III) around physiological pH range remains a significant challenge during radiolabeling (Wadas et al. 2010). The bifunctional chelates (BFC) to develop target-specific radiotracers are polydentate acyclic and macrocyclic chelators such as DTPA, DOTA, and NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid). To develop ^{68}Ga -labeled radiopharmaceuticals, NOTA is ideal since the thermodynamic stability constant of Ga-NOTA ($\log K = 30.98$) is much higher than that of Ga-DOTA ($\log K = 21.33$).

Copper is a first-row transition metal and its chemistry in aqueous solution is restricted to two oxidation states: Cu(I) and Cu(II). Cu complexes remain stable in aqueous solution only when chelators contain soft donors, such as phosphine-P and thioether-S. The coordination geometry for Cu(I) complexes is almost always tetrahedron and the coordination number is 4, 5, or 6 depending on denticity of the chelator. The design of BFCs for copper radionuclides has been focused on macrocyclic chelators that are able to form Cu(II) complexes with both high thermodynamic stability and kinetic inertness.

Molecular Imaging

Molecular imaging is generally defined as the ability to visualize and quantitatively measure the function of biological and cellular processes in vivo. In addition, molecular imaging aims to integrate patient-specific and disease-specific

molecular information derived from diagnostic imaging studies. The members of the Molecular Imaging Center of Excellence (MICoE) Standard Definitions Task Force recently developed the following standard definitions and terms (Mankoff 2007):

- Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems.
- Molecular imaging agents as “probes used to visualize, characterize, and measure biological processes in living systems. Both endogenous molecules and exogenous probes can be molecular imaging agents.”

The main advantage of in vivo molecular imaging is its ability to characterize diseased tissues without invasive biopsies or surgical procedures. The goal of molecular neuroimaging is the noninvasive visualization and quantification of molecular entities in brain and its correlation to pathophysiological events. Nuclear medicine (PET and SPECT), with the radiolabeled target specific molecular imaging probes (radiopharmaceuticals), can be considered presently as the most sensitive technique for in vivo imaging of the ligand–receptor interactions with picomolar to femtomolar sensitivity. The ultimate goal of brain PET radiotracers is the noninvasive localization and quantification of neuronal metabolism, protein function, neurotransmitter–neuroreceptor interaction, and abnormal protein accumulation in order to get further insight into the mechanisms of molecular pathophysiology associated with various neuropsychiatric diseases and to facilitate the design of diagnostic biomarkers and to speed up the development of new therapeutics. Several hundred radiotracers are listed at the “Molecular Imaging and Contrast Agent Database” (MICAD). A number of radiopharmaceuticals useful for PET and SPECT imaging studies of brain are summarized in Tables 7, 8, and 9.

The brain function is directly related to neural signaling and transmission of electrical activity via chemical and electrical synapses. Neurotransmitters are endogenous chemicals (amino acids,

Radiopharmaceuticals in Molecular Imaging, Table 7 Radiopharmaceuticals for molecular imaging studies of brain

Molecular target		Radiopharmaceuticals for		
Category	Target	PET		SPECT
		^{11}C	^{18}F	^{123}I
Enzymes	<i>Hexokinase</i>	$[^{11}\text{C}]\text{d-glucose}$	2- $[^{18}\text{F}]\text{Fluoro-2-deoxyglucose}$	
	<i>Choline kinase</i>	$[^{11}\text{C}]\text{Choline}$	$[^{18}\text{F}]\text{Fluorocholine}$	
	<i>Thymidine kinase-1</i>	2- $[^{11}\text{C}]\text{Thymidine}$	3'-Deoxy-3'- $[^{18}\text{F}]\text{fluorothymidine}$	
	<i>Acetyl-CoA synthetase</i>	$[^{11}\text{C}]\text{Acetate}$	$[^{18}\text{F}]\text{Fluoroacetate}$	
	<i>Cyclooxygenase and peroxidase</i>	$[^{11}\text{C}]\text{Arachidonic acid}$	20- $[^{18}\text{F}]\text{Arachidonic acid}$	
	<i>Aromatase</i>	$[^{11}\text{C}]\text{Vorzole}$		
	<i>Monoamine oxidase (MAO) MAO-1</i>	$[^{11}\text{C}]\text{Harmine}$ $[^{11}\text{C}]\text{Chlorgyline}$		
	<i>MAO-2</i>	$[^{11}\text{C}]\text{Deprenyl-d2}$		
	<i>Fatty acid amide hydrolase (FAAH)</i>	$[^{11}\text{C}]\text{CURB}$	$[^{18}\text{F}]\text{-PF-04457845}$	
	<i>Phosphodiesterases (PDE) PDE-4</i>	$[^{11}\text{C}]\text{-(R)-rolipram}$		
	<i>PDE-10A</i>	$[^{11}\text{C}]\text{MP-10}$	$[^{18}\text{F}]\text{MN1659}$	
	<i>Adenylate cyclase</i>	$[^{11}\text{C}]\text{Forskolin}$		
	<i>Acetylcholine esterase (AChE)</i>	$[^{11}\text{C}]\text{MP4A}$ $[^{11}\text{C}]\text{PMP}$		$^{123}\text{I-IBVM}$
	<i>Aromatic amino acid decarboxylase (AAAD)</i>		6- $[^{18}\text{F}]\text{-l-DOPA (FDOPA)}$	
	<i>AAAD and 5-HTP decarboxylase</i>	$[^{11}\text{C}]\text{5-Hydroxy-tryptophan (5-HTP)}$		
	<i>Tryptophan hydroxylase</i>	$\alpha\text{-}[^{11}\text{C}]\text{-l-methyl-tryptophan}$		
Transporters	Dopamine transporter (DAT)	$[^{11}\text{C}]\text{PE2I}$	$[^{18}\text{F}]\text{FP-CIT}$	$[^{123}\text{I}]\text{FP-CIT (DaTscan)}$
		$[^{11}\text{C}]\text{Methylphenidate}$	$[^{18}\text{F}]\text{FE-PE2I}$	$[^{123}\text{I}]\text{CIT (Dopascan)}$
			$[^{18}\text{F}]\text{FECNT}$	$[^{123}\text{I}]\text{Altropane}$ $[^{123}\text{I}]\text{PE2I}$
	Serotonin transporter (SERT)	$[^{11}\text{C}]\text{DASB}$		$[^{123}\text{I}]\text{-}\beta\text{-CIT}$
		$[^{11}\text{C}]\text{MADAM}$		$[^{123}\text{I}]\text{mZIENT}$
		$[^{11}\text{C}]\text{AFM}$		
		$[^{11}\text{C}]\text{HOHMADAM}$		
	Norepinephrine transporter (NET)	$[^{11}\text{C}]\text{MeNER-d}_2$	$[^{18}\text{F}]\text{FMeNER-d}_2$	$[^{123}\text{I}]\text{INER}$ $[^{123}\text{I}]\text{MIBG}$
	Glycine transporter (Gly-T ₁)	$[^{11}\text{C}]\text{CFpyPB}$	$[^{18}\text{F}]\text{CFPyPB}$	
		$[^{11}\text{C}]\text{GSK 931145}$		
		$[^{11}\text{C}]\text{RO5013853}$		
	VMAT2	$[^{11}\text{C}]\text{DTBZ}$	$[^{18}\text{F}]\text{Florbenazine}$	
		$[^{11}\text{C}]\text{MTBZ}$	$[^{18}\text{F}]\text{AV-133}$	
			$[^{18}\text{F}]\text{FP-DTBZ}$	

(continued)

Radiopharmaceuticals in Molecular Imaging, Table 7 (continued)

Molecular target		Radiopharmaceuticals for		
Amino acids	Facilitated transport	L-[¹¹ C]leucine,	[¹⁸ F]Fluorotyrosine	¹²³ I-Iodo- α -methyl-tyrosine (IMT)
		S-[¹¹ C]methyl-L-methionine	[¹⁸ F]Fluoro- α -methyltyrosine	
		L-[¹¹ C]tyrosine,	3-[¹⁸ F]Fluoro-cyclobutane-1-carboxylic acid [FACBC]	

Radiopharmaceuticals in Molecular Imaging, Table 8 Radiopharmaceuticals for molecular imaging studies of brain

Molecular target		Radiopharmaceuticals for		
Category	Target	PET		SPECT
		¹¹ C	¹⁸ F	¹²³ I
Dopamine receptors	Dopamine D2/D3	[¹¹ C]Raclopride	[¹⁸ F]Fallypride	[¹²³ I]IBZM [¹²³ I]Epidepride
		[¹¹ C]FLB 457		
		[¹¹ C]MNPA (agonist)		
		[¹¹ C](+)-PHNO (agonist)		
		[¹¹ C]NPA (agonist)		
	Dopamine D1	[¹¹ C]NNC 112 [¹¹ C]Sch 23390		
Serotonin receptors	5-HT _{1A}	[Carbonyl- ¹¹ C]WAY	[¹⁸ F]FCWAY	
		[Carbonyl- ¹¹ C]DWAY	[¹⁸ F]MefWAY	
		[¹¹ C]CUMI-101 or [¹¹ C]MMP (agonist)	[¹⁸ F]MPPF	
	5-HT _{1B}	[¹¹ C]AZ10419369 [¹¹ C]P943		
	5-HT _{2A}	[¹¹ C]MDL 1000907	[¹⁸ F]Altanserin [¹⁸ F]Altanserin-D2	
	5-HT ₄ 5-HT ₆	[¹¹ C]SB-207145 [¹¹ C]GSK-215083		
Cholinergic receptors	Nicotinic ACh $\alpha_4\beta_2$ receptors		2-[¹⁸ F]F-A-85380 2-[¹⁸ F]FA 6-[¹⁸ F]FA [¹⁸ F]Nifene (agonist)	[¹²³ I]5IA
	Nicotinic ACh α_7 receptors	[¹¹ C]CHIBA-1001		
	Muscarinic cholinergic M ₂ receptors		[¹⁸ F]FP-TZTP	
Opioid receptors	δ opioid receptors (DOR)	[¹¹ C]Methylnaltrindole		
	μ opioid receptors	[¹¹ C]Diprenorphine	[¹⁸ F]Fluoroethyl-diprenorphine	
		[¹¹ C]Carfentanil (agonist)		

(continued)

Radiopharmaceuticals in Molecular Imaging, Table 8 (continued)

Molecular target		Radiopharmaceuticals for		
Glutamate receptors	mGluR ₁	[¹¹ C]ITMM	[¹⁸ F]FITM	
	mGluR ₅	[¹¹ C]SP 203 [¹¹ C]ABP688	[¹⁸ F]SP 203 [¹⁸ F]F-FPEB	
	N-methyl-d-aspartate (NMDA) receptor	[¹¹ C]Flumazenil (FMZ)	[¹⁸ F]FFMZ	¹²³ I-Iomezenil
		[¹¹ C]Ro15 4513		
Adenosine receptors	A1 receptors	[¹⁸ F]CPFPX		
	A2 receptors	[¹¹ C]SCH442416		[¹²³ I]MNI420
Histamine receptors	H1 receptors	[¹¹ C]Doxepin		
	H3 receptors	[¹¹ C]GSK189254	[¹⁸ F]FMH3	
		[¹¹ C]GR 103545		
Cannabinoid receptors	CB1 receptor	[¹¹ C]MePPEP	[¹⁸ F]FEMMEP-d2	
		[¹¹ C]OMAR	[¹⁸ F]MK-9470	
		[¹¹ C]SD5024		
Neurokinin receptor	NK ₁ receptor		[¹⁸ F]SPA-RQ	
			[¹⁸ F]MK-0999	
			[¹⁸ F]FE-SPA-RQ	
NOP receptor	NOP receptor	[¹¹ C]NOP-1A		

amines, peptides) that transmit signals from a neuron to a target cell (or another neuron) across a synapse. A neuroreceptor is a membrane receptor protein that is activated by a neurotransmitter. Glutamate is excitatory while GABA is inhibitory at the receptor site. Major neurotransmitter–receptor systems are summarized in Table 10. Neurotransmitters are at the foundation of many psychiatric and neurological disorders, and imbalances in neurotransmission are associated with movement disorders, depression, insomnia, anxiety, behavioral disorders, memory disorders, and many other neurological functions. Because neurotransmitters play an integral role in these disease states, they are prime targets for treating disorders of the nervous system and mental health concerns. In order to optimize the individualized patient treatment based on targeted molecular therapies, selection of appropriate patients for specific drugs needs noninvasive molecular imaging techniques that can quantitatively assess the functional status and the underlying neurotransmitter and/or neuroreceptor abnormalities associated with a specific neuropsychiatric disease or disorders. The major contributions of molecular neuroimaging studies are summarized below:

Neuronal Metabolism

The changes in electrical activity of neurons (excitation or inhibition) have been indirectly attributed to the alterations in the regional cerebral blood flow (rCBF) or local cerebral metabolic rate for glucose (LCMRglc). The functional coupling of rCBF and LCMRglc has been well established in normal human brain and certain neurological diseases. [¹⁵O]water-PET has been the gold standard to assess regional cerebral blood flow (rCBF). The deoxyglucose technique, by employing autoradiography using radiolabeled deoxyglucose ([¹⁴C]DG), opened the way to measure regional cerebral glucose metabolism. The development of [¹⁸F]FDG-PET added a major dimension to the investigation of brain function. FDG is transported into the cell, phosphorylated and, unlike glucose, cannot be metabolized further, and remains trapped within the cytoplasm. Therefore, PET provides insight into energy metabolism in vivo by quantifying glucose consumption, cerebral perfusion, and oxygen consumption. In neuroscience research, this allows the study of neural activity, as well as disease processes, based on the brain's metabolism and

Radiopharmaceuticals in Molecular Imaging, Table 9 Radiopharmaceuticals for molecular imaging studies of brain

Molecular target		Radiopharmaceuticals for		
Category	Target	PET		SPECT
		^{11}C	^{18}F	^{123}I
Activated microglia and macrophages	Translocator protein (TSPO) or peripheral benzodiazepine receptor (PBR)	$^{[11]\text{C}}(\text{R})\text{-PK 11195}$	$^{[18]\text{F}}\text{DPA-714}$	$^{[123]\text{I}}\text{CLINDE}$
		$^{[11]\text{C}}\text{PBR28}$	$^{[18]\text{F}}\text{FEPPA}$	
		$^{[11]\text{C}}\text{DAA1106}$	$^{[18]\text{F}}\text{PBR111}$	
		$^{[11]\text{C}}\text{DPA-713}$	$^{[18]\text{F}}\text{FEDAA1106}$	
		$^{[11]\text{C}}\text{SSR180575}$		
Activated astroglia	MAO-B	$^{[11]\text{C}}\text{-l-deuterodeprenyl (DDP)}$		
Aggregated protein	β -amyloid ($\text{A}\beta$) plaques	$^{[11]\text{C}}\text{PiB}$	$^{[18]\text{F}}\text{-3'-F-PiB (flutemetamol)}$	$^{[123]\text{I}}\text{IMPY}$
		$^{[11]\text{C}}\text{AZD2184}$	$^{[18]\text{F}}\text{AV-45 (florbetapir)}$	
		$^{[18]\text{F}}\text{NAV-4694 (AZD 4694)}$	$^{[18]\text{F}}\text{AV-1 (florbetaben)}$	
			$^{[18]\text{F}}\text{NAV-4694 (AZD 4694)}$	
			$^{[18]\text{F}}\text{FBM}$	
			$^{[18]\text{F}}\text{-SMIBR-W372}$	
			$^{[18]\text{F}}\text{MK3328}$	
	$\text{A}\beta$ and α -synuclein fibrils		$^{[18]\text{F}}\text{BF-227}$	
	Neurofibrillary tangles (NFTs) and aggregated tau (τ) proteins (PHF)		$^{[18]\text{F}}\text{FDDNP}$	
			$^{[18]\text{F}}\text{THK-523}$	
			$^{[18]\text{F}}\text{THK-5105}$	
			$^{[18]\text{F}}\text{T807}$	

function. FDG-PET is indicated the detection of epileptogenic foci and the differential diagnosis of various dementias.

Brain Receptors and Transporters

The design, synthesis, and development of molecular neuroimaging radiopharmaceuticals in the assessment of neurotransmission are some of the most active areas of molecular imaging research. Several review articles have discussed the development of receptor binding radiopharmaceuticals and their potential clinical applications (Fowler et al. 2003; Heiss and Herholz 2006; Zimmer and Luxen 2012). The estimation of neuroreceptor occupancy is one of the most

powerful examples of the utility of molecular imaging in CNS drug development and for personalized patient therapy. The potential value of neuroreceptor imaging based on PET was first demonstrated in 1983 using dopamine D_2 receptor ligand $^{[11]\text{C}}\text{N-methylspiperone}$ (Wagner et al. 1983). A primary goal of brain neuroreceptor imaging is to visualize the receptors and involved in neurophysiological and pathological processes. The outcome measures are the density of receptors and the binding affinity of the radioligand binding to the receptor. For PET ligands with high specific radioactivity, the maximum bound/free (B/F) ratio will be equivalent to the receptor concentration/ligand affinity (Bmax/Kd). Brain imaging typically identifies neurotransmitters at three locations in the neurotransmitter pathway:

Radiopharmaceuticals in Molecular Imaging, Table 10 Important neurotransmitters and receptors in brain

Neurotransmitter	Function	Neuroreceptors	Potential role in disease
Dopamine (DA)	Mediation of movement, cognition, and emotion	DA D ₁ to D ₅ receptors	PD, AD, schizophrenia, Huntington's disease
5-Hydroxytryptamine (5-HT or serotonin)	Regulation and modulation of sleep, affective and personality behaviors, and pain	5-HT ₁ to 5-HT ₇ receptors	Depression, anxiety, schizophrenia, obsessive-compulsive disorder, eating disorders
Acetyl choline (ACh)	Mediates complex functions, such as attention, memory, cognition, and consciousness	ACh nicotinic and muscarinic receptors	AD, PD, schizophrenia, Huntington's disease
Norepinephrine (noradrenaline)	Stimulates sympathetic nervous system responsible for fight-or-flight response	Adrenergic (α_2) receptors	AD, movement disorders, and depression. Age-related changes in arousal, mood, and memory
Endorphins	Play an important role in the regulation of analgesia, shock, appetite, thermoregulation, and cardiovascular, mental, and endocrine function	Opiate delta (δ), mu (μ), and kappa (κ) receptors	PD, epilepsy, depression, drug abuse, epilepsy, Tourette's syndrome
Glutamate	Responsible for postsynaptic excitation and are important for neural communication, memory formation, learning, and regulation	Ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs)	Several neurodegenerative diseases. Anxiety, depression, schizophrenia, and drug addiction or withdrawal
N-methyl-d-aspartate (NMDA)	A selective agonist of NMDA critical in synaptic plasticity, a cellular mechanism for learning and memory	The NMDAR is a specific type of iGluR	
γ -Amino butyric acid (GABA)	The chief inhibitory neurotransmitter	GABA _A is the target for benzodiazepines and is known as central benzodiazepine receptor (CBR)	Alzheimer's disease, epilepsy, or cerebral ischemia
Glycine	Modulates the neuroexcitatory activity of the NMDA receptor	Glycine binding site on NMDA receptor	Neuropsychiatric ailments, such as schizophrenia and related disorders
Histamine	Regulates the synthesis and release of histamine itself and other neurotransmitters such as noradrenalin, dopamine, and acetylcholine	Histamine H ₃ receptor	Involved in the development of schizophrenia, epilepsy, ADHD, and AD
Adenosine	In the brain, regulate the release of dopamine and glutamate. Also has a sedative effect	Adenosine (A ₁ , A _{2A}) receptors	Epilepsy, ischemic cerebral stroke, movement disorders, sleep disorders, and psychiatric disorders
Cannabinoid receptors	Endocannabinoids and hallucinogens (such as marijuana) can mimic or block actions of neurotransmitters and interfere with normal functions	CB1 receptors expressed on presynaptic terminals	Range of neuropsychiatric and neurodegenerative disorders

(continued)

Radiopharmaceuticals in Molecular Imaging, Table 10 (continued)

Neurotransmitter	Function	Neuroreceptors	Potential role in disease
Substance P	Modulatory roles in mood, anxiety/stress responses, reward, nociception, emetogenesis, motor control, and neurogenesis	Neurokinin (NK ₁) receptor	Depression. Treatment of emesis, associated with cancer chemotherapy
Nociceptin/orphanin FQ peptide	Regulation of pain, anxiety and depression, drug abuse, feeding, learning/memory, and motor activity	NOP receptor (an opioid receptor)	Treatment of chronic pain

the presynaptic neuron, the postsynaptic neuron, and the intraneuronal metabolism. For example, [¹¹C]PE2i-PET or DaTscan-SPECT provides a measure of dopamine transporter (DAT) density on presynaptic neuron membranes, [¹¹C]raclopride-PET or ¹²³I-IBZM-SPECT measures D2 receptor density on the postsynaptic dopaminergic neuron, and [¹⁸F]FDOPA, the radiolabeled precursor of dopamine, allows imaging of the dopamine metabolic pathway, at a presynaptic intraneuronal level (Brooks 2010).

Enzymes in the Brain

Biologically important processes in normal brain function and brain disease involve the action of enzymes. High-affinity radiolabeled enzyme inhibitors are now serving as tracers for enzymes, particularly for measuring the abundance of enzymes mediating intracellular signal transduction in the brain, and may offer a rich diversity of potential targets for drug discovery. Several radiotracers under clinical evaluation for some of the important enzymes are summarized in Table 7.

Neurodegenerative Diseases (NDDs) and Aggregated Proteins

One of the most active domains in brain PET imaging is currently the field of neurodegenerative disorders, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) (Någren et al. 2010; Vallabhajosula 2011). Because β-amyloid (Aβ) plaques are the hallmark of Alzheimer’s disease

pathology, a number of radiotracers were developed to measure the brain regional distribution and density of Aβ. [¹¹C]PiB is a sensitive and specific marker for Aβ. Since the short physical half-life of ¹¹C requires that a cyclotron be available on-site, three different ¹⁸F analogs were also developed. Two agents, florbetapir and flutemetamol, were approved by FDA for commercial distribution. NDDs are also characterized by pathological tau (τ) accumulation and are termed “tauopathies,” involving intracellular accumulation of τ protein leading to the so-called neurofibrillary tangles (NFTs) (Goedert et al. 2006). Several new radiotracers such as ¹⁸F-THK5117 and ¹⁸F-T807, specific for PHF-tau, are under clinical investigation.

Neurooncology

Unlike CT and MRI, PET imaging studies in patients with brain tumors give information on the metabolic state and molecular events within the tumor. [¹⁸F]FDG has been the tracer of choice for oncologic PET imaging, based on the increased glucose metabolism of most tumors. However, it has significant limitations for brain tumor imaging due to the normal gray matter uptake of FDG. Neurooncology is a discipline that integrates cancer science and neuroscience. A number of targeted radiopharmaceuticals were developed. Radiotracers such as [¹¹C]choline, [¹¹C]methionine, [¹⁸F]fluoromethyl (or ethyl) tyrosine, and [¹⁸F]fluorothymidine provide significant advantages compared to FDG, for initial diagnosis, tumor grading, and assessment of treatment response (Vallabhajosula 2011).

Neuroinflammation

Classical inflammation response is more and more closely associated with many neurological disorders (e.g., stroke or trauma) when in acute and NDDs when chronic (Cagnin et al. 2007; Glass et al. 2010; Hirsch et al. 2012). A dominant response to all types of CNS injuries is the activation of microglia and astroglia, often referred to as gliosis, at the sites of damage. The inflammatory response in the brain is a double-edged sword. It is a self-defense reaction aimed at eliminating injurious stimuli and restoring tissue integrity. However, inflammation may become a harmful process when it becomes chronic. A major hallmark of microglial activation is the expression of the peripheral benzodiazepine receptor (PBR), also known as the translocator protein. The TSPO expression is nearly absent in resting microglia but rapidly increases during inflammation. This increase in TSPO expression is correlated to the extent of microglial activation. This makes PBR/TSPO a biomarker and an attractive target for the imaging of cerebral inflammation (Ching et al. 2012). (*R*)-[^{11}C]PK11195 is the first nonbenzodiazepine and selective TSPO ligand with nanomolar affinity, and it is the prototypical reference for PBR/TSPO binding. It has been investigated extensively in humans; however, it has low sensitivity and a limited capacity to quantify subtle TSPO expression *in vivo*. Several new TSPO radiotracers with higher affinity, low nonspecific binding, and improved capacities to image and quantify TSPO expression are being evaluated in preclinical models and pilot human studies. Among these new radiotracers, [^{11}C]DPA713, [^{18}F]DPA714, [^{11}C]DAA1106, [^{18}F]FEDAA1106, and [^{11}C]SSR180575 have shown significantly increased binding in the living brain.

Summary

Molecular imaging (MI) is a new biomedical research discipline enabling the visualization, characterization, and quantification of biological processes taking place at the cellular and subcellular levels within intact living subjects including patients. Nuclear medicine (PET and SPECT)

uses radiopharmaceuticals as molecular imaging probes that produce signals by means of radioactive decay. The goal of molecular imaging studies of brain based on PET and SPECT is the noninvasive localization and quantification of neuronal metabolism, protein function, neurotransmitter–neuroreceptor interaction, and abnormal protein accumulation in order to get further insight into the mechanisms of molecular pathophysiology associated with various neuropsychiatric diseases and to facilitate the design of diagnostic biomarkers and to speed up the development of new therapeutics. [^{15}O]Water-PET has been the gold standard to assess the rCBF and [^{18}F]FDG is the most important radiotracer designed to study glucose metabolism. While hundreds of radiotracers were developed for neuroreceptor imaging, ^{123}I -labeled FP-CIT (DaTscan) is the only tracer approved to image presynaptic dopamine receptors in PD. Deposition of protein aggregates (A β and τ protein) with ^{18}F -labeled tracers (florbetapir and flutemetamol) and study of the role of neuroinflammation in NDDs are two major areas of active clinical investigation. The use of imaging biomarkers for the development of drug therapies, a field termed “pharmaco-imaging,” has become more common in recent years. This is particularly advantageous since one can explore brain neurochemistry *in vivo*. There is increasing evidence that PET and SPECT imaging can accelerate the drug development process by revealing early information regarding drug effectiveness and safety for both research and regulatory purposes.

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Radiotracer

► Radiopharmaceuticals in Molecular Imaging

Rational Models of Cognition

► Cognition, Bayesian Models of

Receptive Field Modeling

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Synonyms

Neural Development; RF Modeling

Definition

The mathematical modeling of properties of *sensory* neurons, specifically relating to the patterns that elicit strong neuronal responses.

Detailed Description

The term *receptive field* (RF) refers to any of the following, depending on the context:

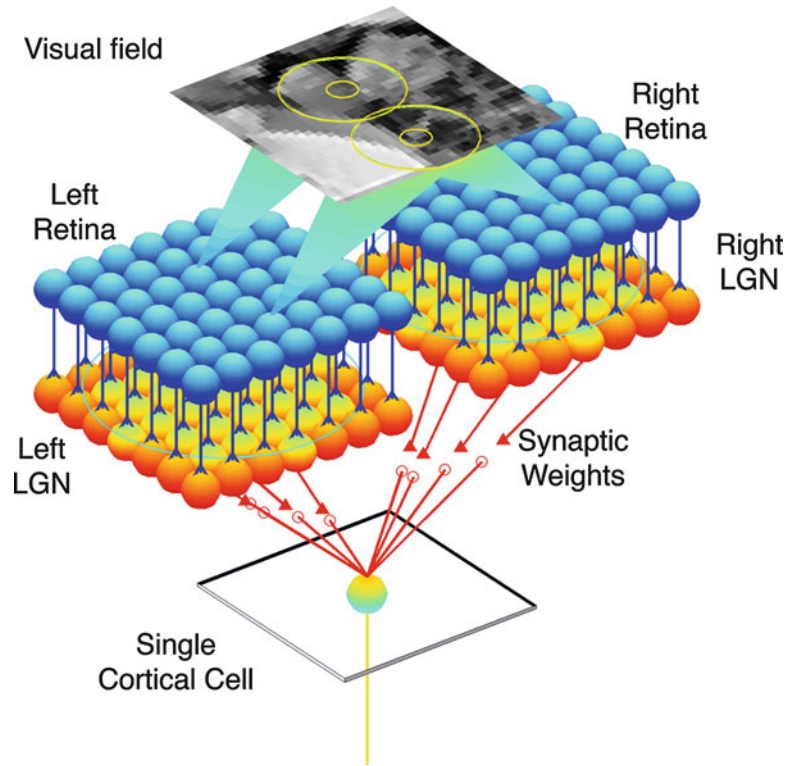
1. The *sensory area* over which sensory neurons give strong responses (e.g., portion of the visual field for visual neurons, frequency range for auditory neurons, etc.)
2. The *input patterns* that elicit those strong responses
3. The pattern of strong and weak *synaptic strengths* that results in the strong responses to the specific patterns
4. The *spatiotemporal* response properties of the sensory neurons, often referred to as a spatiotemporal receptive field

Modeling refers to the *mathematical* modeling of the response properties of the neuron or the development of the pattern of synaptic strengths and/or the neural dynamics that give rise to those response properties. Thus, the models are often specified as a set of differential equations for the parameters of the model, typically the synaptic weights, and include the activities for both the inputs to and outputs from the neurons.

Sensory neurons include neurons organized in a hierarchical structure (shown in Fig. 1 for visual neurons). For the visual system, this includes neurons in the retina, lateral geniculate nucleus (LGN), and visual cortex. For the auditory system it includes the cells in the cochlea, medial geniculate nucleus (MGN), other subcortical areas, and primary auditory cortex. Thus, the concepts motivating receptive field developmental models in one sensory modality can often be applied directly to another sensory modality.

Receptive Field

Modeling, Fig. 1 Visual architecture. Shown is the visual field, approximated here as a two-dimensional projection, to left and right retinal cells. These left and right retinal cells project to the left and right LGN cells, respectively, and finally to a single cortical cell. The *receptive field* can refer either to the area in the visual field (labeled with the yellow circles) that the cell can see or the distribution of the synaptic weights that yield responses within the visual field (labeled with large blue circles)



Kinds of Models

Models of receptive field activity and development fall into a few categories:

1. Mathematical approximation to the response properties of the neurons. In these models, a mathematical form is proposed that matches the response properties of the neurons.
2. Development of the receptive field through an optimization process. In these models, the connection weights (i.e., synaptic strengths) or other neuronal parameters are adjusted to optimize a proposed objective function. Objective functions include measures of sparsity (Rao et al. 2002), independence (Hyvärinen et al. 2001b), and selectivity (Cooper et al. 2004; Blais and Cooper 2008).
3. Detailed models of the *spiking* behavior of neurons. These models include the stochastic nature of the inputs and outputs and often are motivated by concepts in molecular biology

(Yeung et al. 2004; Smith and Lewicki 2006; Gjorgjieva et al. 2011).

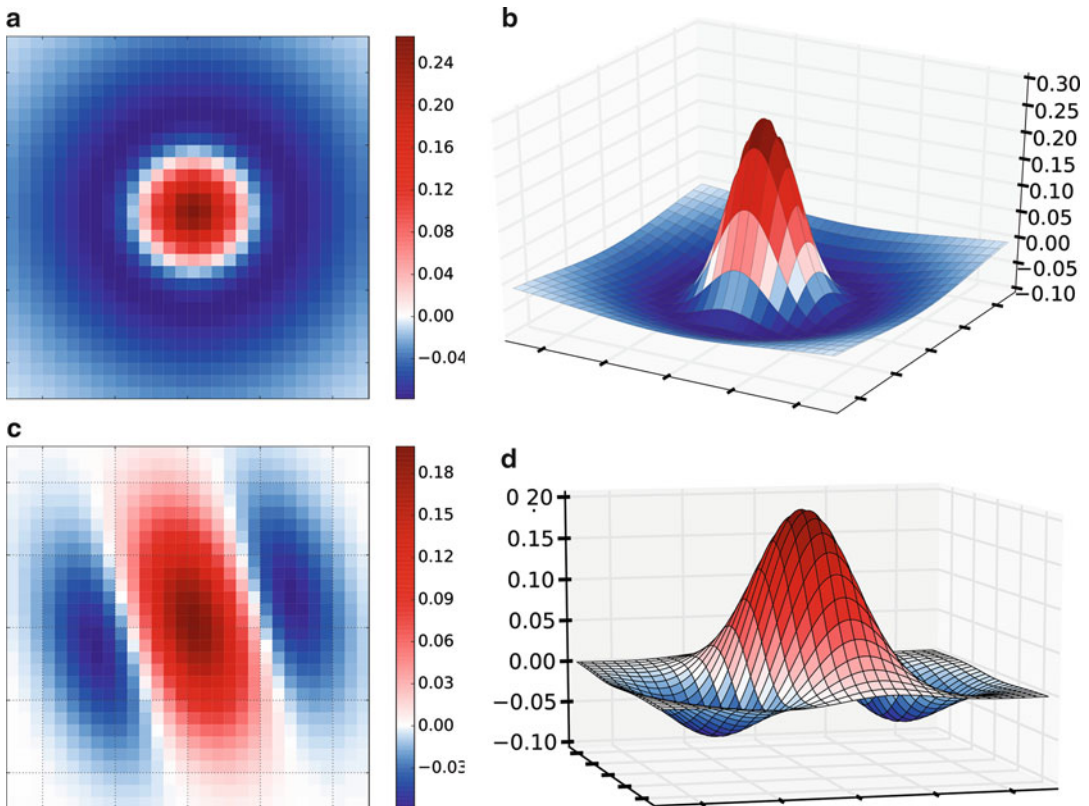
Mathematical Approximations

Mathematical Approximation for Retinal and LGN Receptive Fields

Both retinal neurons and neurons in the LGN have what is referred to as a center-surround receptive field. A spot of light in the center of the visual area elicits a strong response, a uniform illumination over the entire area elicits a weak response, and light illuminating only the area around the center elicits a suppressed response (Alonso and Chen 2009).

The typical functional form used for retinal responses is the so-called center-surround form, mathematically expressed as a difference of Gaussians, depicted graphically in Fig. 2 (Enroth-Cugell and Robson 1966; Rodieck 1965).

LGN cells typically have response properties similar to those of retinal ganglion cells and thus



Receptive Field Modeling, Fig. 2 Representations of receptive fields. Shown are the (a) center-surround retinal/LGN receptive fields and the (b) Gabor-like visual cortical receptive fields

can be modeled with a spatial difference of Gaussians. Temporally, the LGN can be described approximately in terms of lagged and non-lagged populations, differing in their phase lags (Saul and Humphrey 1990). More details reveal that a distribution of delays exists (Wolfe and Palmer 1998).

Mathematical Approximation for Visual Cortical Receptive Fields

So-called simple cells in the visual cortex respond to *bars of light* of a particular orientation in their receptive field and have *binocular* receptive fields (Hubel and Wiesel 1962). The cortical responses can be approximated with a Gabor function (Jones and Palmer 1987), which is a 2D circular Gaussian multiplied by a sinusoidal plane wave (see Fig. 2). Other forms can also be used and may perhaps fit to

the data better but qualitatively have the same form (Stork and Wilson 1990; Rust et al. 2005).

Nonlinear combinations of these simple responses are an approximation to some of the more complex receptive fields of visual neurons (Finn and Ferster 2007; Adelson and Bergen 1985).

Mathematical Approximation for Auditory Cortical Receptive Fields

In auditory cortex, there is considerably more diversity of responses, and thus the response properties are not easily summarized by a simple mathematical approximation. Many of these cells are *frequency tuned*, responding to a narrow band of sound frequencies, but others respond strongly to transient sounds or are intensity tuned (Bear et al. 2007).

Development of Receptive Fields

The essential idea behind models of receptive field development is the learning of structure in the input environment through some form of statistical optimization. Differences between the methods proposed to describe receptive field development can arise from both the particular optimization performed and the statistics of the input environment used to develop the neuronal responses. Common examples of statistical optimization used in receptive field modeling are:

1. Bienenstock, Cooper, Munro (BCM) – maximizing statistical bimodality in the distribution of cortical responses (Bienenstock et al. 1982; Blais et al. 1998; Cooper et al. 2004).
2. Independent Component Analysis (ICA) – maximizing independence between input patterns (van Hateren and Ruderman 1998; Hyvärinen et al. 2001b)
3. Sparse Coding – maximizing sparsity in the distribution of cortical responses (Olshausen and Field 1996; Rao et al. 2002).

Note that these differences are not always clearly distinguishable, such as using ICA to do sparse coding. Further, some of the proposed methods have not just their receptive fields tested by experimental observations but also the underlying mechanisms explored in detail. For a nice survey of the comparison between theory and experiment for the BCM learning rule, see Cooper and Bear 2012.

Examples of input environments used with these methods include:

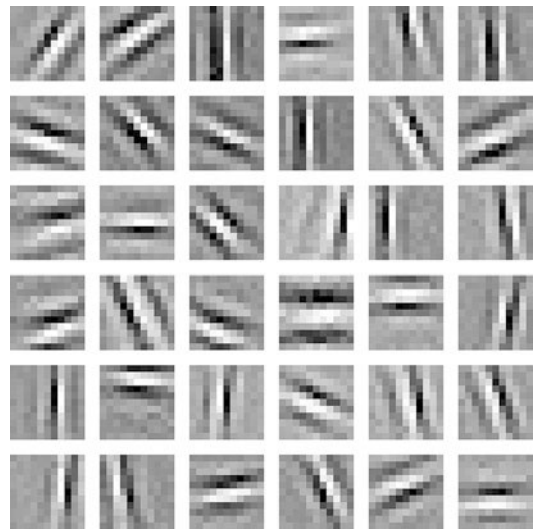
1. Retinal waves for retinal and LGN development (Wong 1999)
2. Natural image input for the development of orientation selective and binocular receptive fields (Blais et al. 1998; Cooper et al. 2004; Hyvärinen et al. 2009).
3. Natural image movies for the development of spatiotemporal receptive fields in visual cortex, resulting in direction selectivity (Hyvärinen et al. 2001b; Blais et al. 2000; Cooper et al. 2004).

4. Natural sounds for the development of frequency-temporal receptive fields in auditory cortex (Smith and Lewicki 2006; Saxe et al. 2011).

A sample of visual cortical receptive fields in natural image input in a model of the visual system is shown in Fig. 3.

Organization of Receptive Fields

Beyond the development of selectivity properties of the receptive fields (e.g., orientation, direction, spatial frequency, temporal frequency, etc.), some models attempt to also capture the distribution and arrangement of these receptive field properties in the cortex. Invariably this includes models of the *interaction* between neurons during development. Thus, models include self-organizing maps (Kohonen 2001), short- and long-range lateral connections (Shouval et al. 2000), topographic ICA (Hyvärinen et al. 2001a), and deep belief networks (Lee et al. 2007).



Receptive Field Modeling, Fig. 3 Sample receptive fields developed from natural image input, using the BCM learning rule (Bienenstock et al. 1982), a method that modifies the synaptic strengths to maximize statistical bimodality in the distribution of cortical responses. Shown are the synaptic values with *white* and *black* denoting strong and weak (or negative/inhibitory) connections, respectively

For a good review in the visual system, see Hyvärinen (2010).

Other Sensory Neurons

Less work has been done in the area of modeling other sensory areas, such as somatosensory (i.e., touch) and olfactory (i.e., smell) systems. Some progress has been made using sparse coding to develop somatosensory receptive fields (Saxe et al. 2011). Part of the challenge in the olfactory system is that the *field* of odor parameters is not well understood, so even the space over which one could establish a receptive field is not well defined.

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Reconstruction of Current Sources

► Current Source Density (CSD) Analysis

Reconstruction, Electron Microscopy

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Definition

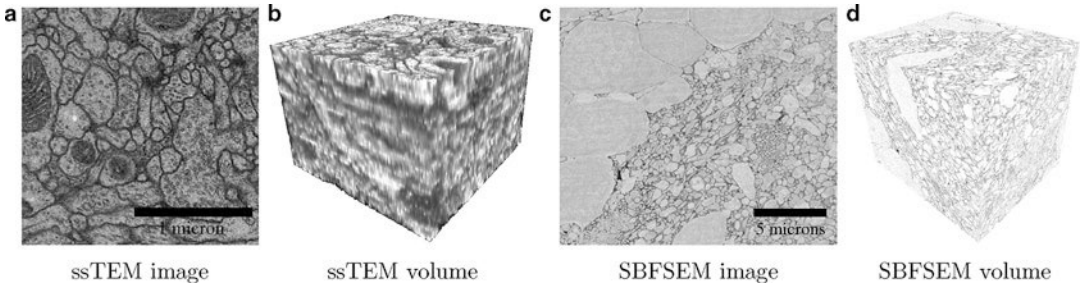
Reconstruction of neural circuits using large volumes of electron microscopy (EM) data is essential for understanding the function and dysfunction of the nervous system. The reconstruction task involves the geometric tracing of each neurite and the identification of the interconnections between neurons in order to obtain a complete wiring diagram of the nervous system, known as the connectome.

Detailed Description

To reconstruct the connectome that reveals synaptic connections, the tissue has to be imaged at a

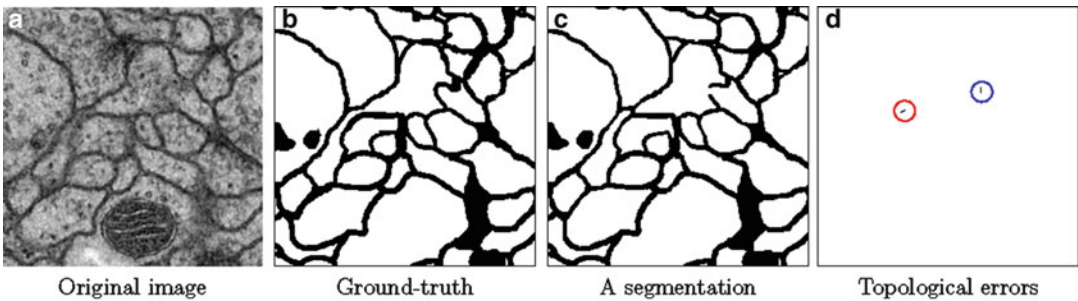
sufficiently high resolution. EM can provide image data at nanometer scale and has been a key source of 3D imaging data for the study of neuroanatomy for years (Macagno et al. 1979; Stevens et al. 1980). For example, the entire nervous system (302 neurons and over 7,000 synaptic connections) of the nematode *Caenorhabditis elegans* was reconstructed (White et al. 1986) using serial section transmission electron microscopy (ssTEM).

Breakthroughs in high-throughput and high-resolution three-dimensional EM imaging instruments have made the acquisition of unprecedented amounts of biological data possible. See ► “Physical Sectioning Microscopy.” These techniques have enabled the acquisition of large-scale data sets and have opened new roads for the connectomic research. However, data produced by these instruments pose significant challenges due to the amount and complexity of information. For example, an SBFSEM data set at a resolution of $10 \times 10 \times 50$ nm, sectioning a $200^3 \mu\text{m}^3$ sample tissue, results in a data set of 1.6×10^{12} voxels (Denk and Horstmann 2004). In Fig. 1, we can see two EM (ssTEM and SBFSEM) image stacks and their sample images. Manual reconstruction of the *C. elegans* connectome took more than a decade. To reconstruct more complex neural circuits, such as *Drosophila* or mouse brains, automation of the reconstruction process is a necessity. One of the main steps in EM reconstruction is image segmentation. It is to partition an image into disjoint regions, each of which shares common characteristics. For EM data, segmentation groups voxels into different sets that represent distinct neurons (Chklovskii et al. 2010), which is a fundamental step toward a full analysis of neuronal morphological models. Such a task poses unique challenges because of the inevitable staining noise, incomplete boundaries, and inhomogeneous staining intensities that can make segmentation and subsequent 3D reconstruction and visualization difficult. Numerous methods have been proposed to automate EM segmentation. They can be grouped into three categories: machine learning-based, semiautomated, and crowdsourcing-based approaches.



Reconstruction, Electron Microscopy, Fig. 1 Sample EM images and image stacks. (a) A sample ssTEM image having a size of 512×512 from a data set of *Drosophila* first-instar larva ventral nerve cord (VNC). The resolution is $4 \times 4 \times 50$ nm/voxel. (b) A publicly available ssTEM data set provided by Cardona et al. 2010. (c) A sample

SBFSEM image having a size of 631×539 from a data set of larval zebrafish tectum. (d) An SBFSEM image stack. Note that cells in both the ssTEM and the SBFSEM images are densely packed. (Courtesy of Stephen J. Smith, Stanford University)



Reconstruction, Electron Microscopy, Fig. 2 Measured warping error of a segmentation against the ground truth. (a) A sample EM image. (b) Manually annotated ground truth. (c) A segmentation to be

evaluated. (d) Measured warping error. In this case, two topological errors, a merge (blue circle, right) and a split (red circle, left), occur due to the boundary ambiguity in the original image

Reconstruction Approaches

Machine learning-based approaches for EM reconstruction involve training classifiers that can perform the segmentation task. The basic idea of machine learning approaches is that humans provide a set of positive and negative examples (i.e., training data) to a machine learning algorithm so that it can learn to perform classification on unseen data. In EM reconstruction, a machine can be trained to learn to distinguish cellular membranes from other objects given manually annotated ground truth. During learning, using the given training examples, the machine learns to perform the classification task by optimizing its parameters through minimization of a cost function, which, for example, can be the measure of disagreements between machine

generated segmentations and manual annotations. After learning, a machine learning algorithm can segment new EM data that was not included in the training. 3D convolutional neural networks, trained to minimize topological errors, have been proven to be an effective method because EM data contains detailed connectivity of neurons and the topological correctness of the reconstruction is critical in EM analysis (Jain et al. 2010). Topological errors can be measured by a *warping error* metric, which is designed specifically for EM data. Figure 2 illustrates the importance of topology. Figure 2a shows part of an ssTEM image and Fig. 2b its ground truth. Compared to the ground truth, the segmentation in Fig. 2c contains two topological errors, one merge and one split, as shown in Fig. 2d. Classifiers based on random forests (Andres et al. 2008), artificial neural

networks (Jurrus et al. 2010), and support vector machine (SVM) (Lucchi et al. 2010) are also widely used in EM reconstruction.

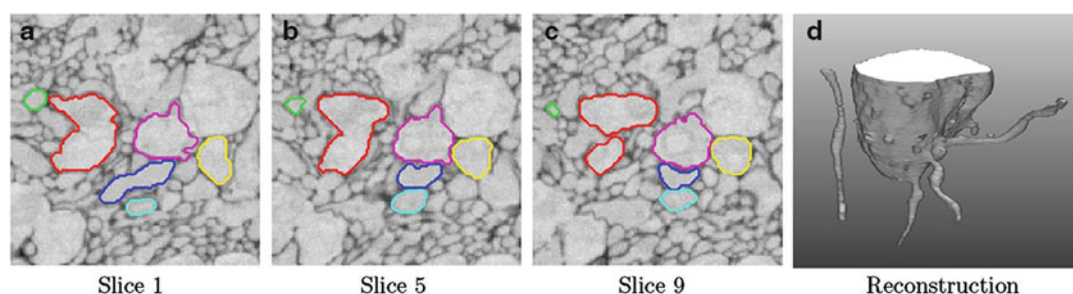
In addition to training a machine to perform membrane detection at the pixel level, another trend is to have a machine actively learning to perform agglomerative segmentation through superpixels (Nunez-Iglesias et al. 2013). Superpixels are small regions having common characteristics. In the process of region agglomeration, the machine determines whether or not two adjacent superpixels should be merged based on a merging criterion. The advantage of performing the segmentation at the superpixel level is that richer features can be incorporated in the learning algorithm, thus improving the segmentation accuracy.

Semiautomated approaches have also gained much attention because of the complexity of EM images. These approaches take as input user-specified seed points or neuronal contours and trace them through successive 2D cross sections to build 3D anatomical structures. The 2D segmentation is commonly posed as an energy minimization problem. To follow the neuronal processes, the 2D contour is propagated from a slice to the next. Such information can serve as a geometric constraint and can be incorporated in a Markov Random Field (MRF) energy functional while delineating the neuronal boundaries of an image (Yang and Choe 2009). Figure 3a–c shows the tracked 2D contours on the selected images using such an approach, and Fig. 3d shows the reconstruction results.

Besides following neuronal processes from user-specified seed points or contours, another semiautomated method employs a multistage approach: 2D segmentation, 3D linkage, and proofreading. The first stage is to segment each 2D section separately, the second is to link the segmentations between adjacent slices to reconstruct 3D neuronal structures, and finally, proofreading ensures the correctness of the reconstruction (Chklovskii et al. 2010). In this reconstruction pipeline, proofreading is a step that requires manually correcting reconstruction errors. Interactive systems, such as Raveler (Chklovskii et al. 2010) and Mojo (Knowles-Barley et al. 2013), are used for such a task. The proofreading systems provide two basic editing operations: merge and split. The merge operation allows the user to connect two disjoint regions, and the split operation allows the user to divide a region into subregions. To reduce annotation time, Mojo uses sparse user scribbles to correct topological errors.

To deal with extremely large volumes of EM data, crowdsourcing-based approaches are used. They employ large number of citizen scientists with the goal of reconstructing a complete connectome. EyeWire, designed as an online game and launched in 2012, aims at mapping the neuron connections in the retina (<http://eyewire.org>). In EyeWire, each player is presented by a small EM volume, and the task is to trace the neurons. Combining the results from all the users builds the complete reconstruction.

R



Reconstruction, Electron Microscopy, Fig. 3 Tracked and segmented 2D contours on selected image slices. The user manually delineates the boundaries of the regions on the first image (a), and the algorithm tracks and segments

the selected regions in the subsequent images (b)–(c). (d) Partly reconstructed 3D structures, where part of a neuron can be seen (Adapted from Yang 2011)

Reconstruction Software Packages

Manual tracing is a labor-intensive task and many reconstruction software packages have been developed to aid in manual reconstruction. These software packages provide user interfaces to assist users in processing, analyzing, and visualizing serial EM images. This leads to reduction in annotation time. For EM reconstruction, the software packages include tools for users to align image volumes, trace neurons, and visualize 3D reconstructions. *Reconstruct* is one such software package for large volumes of serial EM images (Fiala 2005). Most packages use volume annotation method to reconstruct neuronal processes. This requires correct delineation of the cell boundary. Skeleton annotation, in which the user places markers at the center of the neurons, takes less human effort. KNOSSOS (Briggman et al. 2011; Helmstaedter et al. 2011) provides a skeletonization mode to make manual tracing more efficient. In combination with a machine learning approach for neuronal membrane detection, crowdsourced manual annotation using KNOSSOS has mapped the mouse inner plexiform layer of 950 neurons in the retina (Helmstaedter et al. 2013). Other software packages, such as TrakEM2 (Cardona et al. 2012) and NeRV (Jurrus et al. 2013), also have been developed for manual EM reconstruction. Different from the software packages that reconstruct neural circuits from raw EM images, VolRoverN (Edwards et al. 2013) takes as input existing contour tracings produced by other software tools and focuses on accurate surface reconstructions. Models of these surface reconstructions can be used for simulation of neuronal dynamics. Identification of the presynaptic and postsynaptic connectivity is crucial in connectomic research. Elegance (Xu et al. 2013) provides tools for synapse annotation and produces a connectivity matrix, including synaptic strengths, for analysis of the network function.

Cross-References

► [Physical Sectioning Microscopy](#)

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Reconstruction, Techniques and Validation

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Definition

Reconstruction algorithms are used to build a geometric model of neurons, describing their

morphology, from two-dimensional and three-dimensional images. Validation methods are used to determine the accuracy of the resulting models. Both reconstruction and validation are active areas of research, where proposed algorithms must address several complex problems, including (a) the use of a wide range of imaging modalities used to collect data, (b) the complex topological structure of interconnected branches within the neurons, and (c) automation for large data sets. Several methods have been proposed for addressing these issues; however, current reconstruction algorithms can be broadly placed into four categories: semiautomated software packages, local exploration, global processing, and crowdsourcing-based approaches.

Detailed Description

Neuronal reconstructions provide geometric representations of cell and network morphology that can be used to perform quantitative analysis and simulation (e.g., of multicompartmental models). Depending on the features required, this representation can take the form of either a detailed three-dimensional surface or a cylinder-based representation (Ascoli et al. 2001). Surface representations are generally created from high-resolution serial electron microscopy (EM) images and used to analyze cellular ultrastructure, including spine shape and receptor density. Cylinder-based representations are more commonly used to describe the morphology of dendritic trees and axonal arbors where each segment in the processes is fitted with a cylinder. The multicompartmental models used in computational simulations of neurophysiology (e.g., using NEURON or GENESIS (Bower and Beeman 1998; Carnevale and Hines 2009)) are generally created from cylinder-based representations.

Reconstruction

While a significant amount of research has been directed toward automated methods, semi-automated techniques are still widely used.

These methods focus on creating optimized user interfaces for labeling cellular structures and tracing neuronal processes. These methods are most commonly used in serial EM, due to the complexity of these images. Traditional methods rely on a user specifying neuronal boundaries in a 2D cross section of a 3D data set (Fiala 2005), while automated methods are also actively being developed (Mishchenko et al. 2010). Segmented regions are then used to build 3D explicit model of the cell surface. For large-scale data sets, faster reconstruction can be achieved by specifying the centerlines of cellular processes in order to build a cylinder-based representation (Helmstaedter et al. 2011).

Alternatively, local exploration relies on traversing a process starting from user-specified seed points. For each seed point, the local region around the process is analyzed to determine its size and trajectory. This allows the neuronal processes to be traced outward and limits the amount of image data to the relevant regions near the neuron (Luisi et al. 2011; Meijering 2010). This provides a significant computational advantage for sparse data sets, where individual neurons are labeled in isolation. These techniques usually create a cylinder-based representation of the cell. Localized exploration is among the most popular methods for reconstructing light microscopy data (Halavi et al. 2012).

The development of fully automated global reconstruction techniques is an active area of research. A significant amount of work has been proposed regarding the use of supervised machine learning to perform segmentation, particularly in serial EM data sets (Jain et al. 2010b).

Finally, crowdsourcing has proven to be quite effective for large-scale, complete reconstruction (Giuly et al. 2013; Seung and Burnes 2012). In this approach, the reconstruction task is broken down into tiny subtasks that are distributed to a large population of volunteer users who mechanically solve the subtasks typically posed as an entertaining online game. Pooling together the solutions to the subtasks from the users produces the desired reconstruction.

Validation

Validation methods are used to determine the robustness of segmentation algorithms by comparing automated results to a known ground truth. These methods are useful for comparing reconstruction algorithms on known data sets, as well as training new classifiers using supervised learning techniques. Quantitative validation of automated reconstructions is a particularly challenging problem, due to the unique structure of neurons and the explicit representation of most models.

Implicit representations of the neuronal model can be constructed and compared to a ground truth using cluster analysis metrics, including the Rand error and variation of information (Meila 2003). Initial efforts extended these existing methods to neuronal models using *warping error* (Jain et al. 2010a). This implicit metric is used to compare segmentation results in serial slices of EM data and is particularly sensitive to topological errors, which can significantly affect connectivity between multiple neurons in serial EM images.

Explicit validation metrics have also been proposed for comparing cylinder-based models more commonly used for whole-neuron or multiple-neuron reconstructions. These methods extend metrics used for surface comparisons, such as quadric error metrics and the Hausdorff distance (Luebke et al. 2002). One of the first techniques to directly address the problem of large-scale validation of neuron tracing is the DIADEM metric, which was used to quantify the performance of segmentation algorithms submitted to the DIADEM Challenge (Liu 2011). This method first identifies points where the neuronal process branches or terminates, creating a mapping between these nodes in the ground truth and test case. The lengths of segments connecting these points are then computed and compared.

While the DIADEM metric can be used to effectively compare the topological structure of neuronal trees, the application of validation methods to connectomics research generally requires the comparison of connected networks, which do not necessarily exhibit treelike properties. In addition, comparing the lengths of segments between branch points does not

necessarily guarantee that a process exhibits the correct shape. A more complete solution to this problem requires a thorough comparison of the network shape and connectivity (Mayerich et al. 2012). This converges to a graph isomorphism problem, which is known to be NP-complete.

Finally, synthetic neuronal morphology generator tools such as TREES toolbox, NETMORPH, neuroConstruct (Gleeson et al. 2007), NeuGen (Eberhard et al. 2006), and I-Neuron (see Cuntz et al. 2011 for a review) can be used to generate digital phantoms for automated ground-truth generation and validation.

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Recording the Peripheral Nervous System

► [Peripheral Nerve Interface Applications, EMG/ENG](#)

Recurrent Brain-Computer Interfaces

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Synonyms

[Bidirectional brain-machine interface](#); [Brain-machine-brain interface](#); [Closed-loop neuroprosthesis](#)

Definition

A recurrent brain-computer interface (or rBCI) exchanges information directly with the nervous system in a bidirectional manner, bypassing sensory and motor modalities. These devices can both sense neural activity (usually by amplifying and processing electrical potentials) and influence it (by electrical or other stimulation methods). Applications include neuroprostheses to replace lost function and neuromodulation devices to renormalize function following neurological injury or disease.

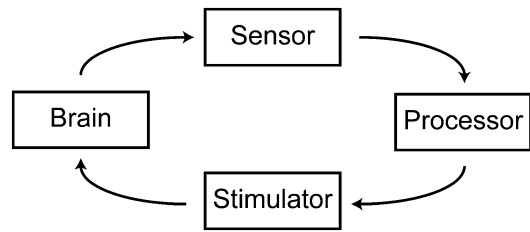
Detailed Description

History

The earliest recurrent brain-computer interface was the “stimoceiver” built and used by the Spanish physiologist Jose Delgado (Delgado et al. 1968; Horgan 2005) at Yale University. He believed that this wireless device, which combined electrical recording and stimulation of the brain, could be used for treatment of neurological conditions including depression, schizophrenia, and epilepsy. About 25 patients were implanted with the device from 1952 to 1974 after which Delgado returned to Spain in part due to controversy over potentially unethical applications of “mind control.” Around the same time Giles Brindley, working at the MRC Neurological Prostheses Unit in London, proposed using electrical activity recorded from the motor cortex to control an implanted stimulator and thus restore movement to spinal cord-injured patients (Craggs 1975). The clinical success of deep brain stimulation as well as recent advances in brain-machine interface technologies including high-density electrode implants and low-power microelectronics has led to renewed interest in rBCI applications in recent years (e.g., Rouse et al. 2011; Morrell 2011).

System Components

Recurrent brain-computer interfaces generally comprise three components (Fig. 1). A *sensor*



Recurrent Brain-Computer Interfaces, Fig. 1 Components of a recurrent brain-computer interface

transduces neural activity, usually by recording electrical signals on one or more electrodes positioned on the scalp or inside the brain. A *processor* detects relevant features in the recorded signals, for example, action potential discharges relating to motor intentions, the phase and amplitude of ongoing neural oscillations, or abnormal brain events such as seizures. These features are used to determine the timing, frequency, and/or intensity of a *stimulator* which delivers signals back to the nervous system. Since information travels in a loop from the brain to the device and back again, such an arrangement is often called “closed-loop” neurostimulation. Note, however, that the term “closed loop” can also be used to describe the operation of a brain-computer interface under conditions where feedback is provided to the user through visual or other sensory modalities. A system in which signals from the motor cortex control the movement of an avatar and feedback is provided through stimulation of the sensory cortex has been described as a brain-machine-brain interface (O’Doherty et al. 2011). rBCIs may be implemented by noninvasive technologies such as electroencephalography and transcranial magnetic stimulation or invasive approaches using implanted microelectrodes. If the processor is implemented in wearable or implanted electronics, an rBCI may operate autonomously delivering closed-loop stimulation continuously without the need for external communication. One technical problem with rBCIs that use electrical stimulation is the contamination of recordings by stimulus artifacts if the recording is adjacent to where stimulation is delivered. Therefore, other nonelectrical means for stimulating neurons such

as optogenetic techniques that use light-sensitive ion channels may prove particularly advantageous for rBCIs (Witt et al. 2013).

Theory of Operation

At its simplest, an rBCI can act as an artificial connection between two parts of the nervous system which may replace or augment a physiological connection (e.g., between the brain and the spinal cord). In more sophisticated implementations, additional processing may be performed between the input and the output so as to perform some useful computation and potentially replace a lost cognitive function (Berger et al. 2005). Long-term operation of an rBCI may result in several secondary changes as a result of known neuroplasticity mechanisms. First, operant conditioning may optimize upstream inputs into the device so as to produce a beneficial or rewarding output (e.g., if stimulation is delivered to a reward center). Second, associative or Hebbian plasticity mechanisms such as spike timing-dependent plasticity may strengthen physiological connections between recording and stimulation sites (Jackson et al. 2006). Third, stimulus-induced activity may strengthen downstream connectivity through long-term potentiation. It has been argued that these three changes may act synergistically to retrain injured pathways during rehabilitation (Jackson and Zimmermann 2012).

Alternatively, the operation of an rBCI may be considered in the framework of dynamical systems. Through recurrent connections between the brain and device, the resulting coupled system may exhibit different attractor dynamics, for example, undesired oscillatory states may become unstable. Such an approach may have application to disorders characterized by abnormal network dynamics, for example, Parkinson's disease and epilepsy (Marceglia et al. 2007; Witt et al. 2013).

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Recurrent Network Models, Reservoir Computing

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Synonyms

Echo state networks; Liquid computing; Liquid state machines; State-dependent networks; Temporal recurrent neural networks

Definition

Reservoir computing (RC) is a general concept for computation and learning on temporal input streams with dynamical systems. Time can either be continuous or discrete. We will here use continuous time for the general definition. An input-driven dynamical system (the *reservoir*) provides a nonlinearly transformed and temporally integrated representation of the input stream in terms of its internal state. This representation is utilized by a *readout* which maps internal states to outputs of the system. The output of the readout can be fed back into the reservoir. The reservoir is typically a recurrent neural network, but other dynamical systems have been employed in the RC spirit recently. The readout function is adapted through some learning procedure. Originally, this training was supervised and the reservoir was not adapted. Today, many extensions of the original idea include unsupervised or reward-based readout training and unsupervised reservoir adaptation. This is in contrast to traditional recurrent neural network training where the whole network is trained in a supervised manner.

More formally, a *RC system* computes a mapping from a K -dimensional input stream $\mathbf{u}(\cdot)$ to a L -dimensional output stream $\mathbf{y}(\cdot)$. It consists of an N -dimensional dynamical system with internal state (*reservoir state*) $\mathbf{x}(t)$ and a memoryless readout function f . The reservoir state at time t , $\mathbf{x}(t)$, depends on the preceding inputs $\mathbf{u}(s)$ for $s \leq t$. In mathematical terms, the state $\mathbf{x}(t)$ is the current output of some operator or filter $\mathcal{F}$ that maps the functions $\mathbf{u}$ onto functions $\mathbf{x}$ (note that in the case of readout feedback, the dependence of $\mathbf{x}$ on the output $\mathbf{y}$ can be incorporated in the filter $\mathcal{F}$). The memoryless readout function f provides a mapping from the vector $\mathbf{x}(t)$ to the output $\mathbf{y}(t)$.

Detailed Description

The theoretical concept of RC was introduced independently in the context of theoretical/computational neuroscience as liquid state machines (LSMs; Maass et al. 2002) and in the context of

recurrent artificial neural networks as echo state networks (ESNs; Jaeger 2001). Earlier implementations of the idea are temporal recurrent neural networks (Dominey 1995) and state-dependent networks (Buonomano and Merzenich 1995).

Liquid State Machines

In LSMs, the reservoir is called the *liquid* and the reservoir state is the *liquid state*. The liquid is a recurrent network of spiking neurons. The liquid state at time t , $\mathbf{x}(t)$, is obtained by filtering of the network spikes. Usually, a linear filter with exponential decay is used, mimicking the membrane potential of cortical readout neurons.

Typically, synaptic connections involve short-term plasticity such as short-term facilitation and short-term depression. The prolonged time constants of these processes provide additional temporal integration power. Each readout unit computes a pseudo-linear function of the system state

$$\mathbf{y}(t) = g(\mathbf{W}^{\text{out}}\mathbf{x}(t) + \mathbf{b}). \quad (1)$$

Here, the output activation function (usually the identity or a sigmoid) g is applied component-wise, $\mathbf{W}^{\text{out}}$ is the $L \times N$ matrix of output weights, and $\mathbf{b}$ is the L -dimensional vector of bias values. Training proceeds as in ESNs; see below.

LSMs were introduced as a model for computation and learning in cortical microcircuits. One major incentive was to explain how complex but stereotypic cortical microcircuits can process spatiotemporal information in order to perform a wide spectrum of tasks. In this context, the cortical microcircuit is seen as the liquid, and projection neurons in layers 2/3 and 5 implement the readout neurons. The LSM model possesses a number of advantageous features that were in contrast to most other models for cortical computation at that time:

- LSMs map temporal input streams onto temporal output streams instead of static patterns.

- LSMs perform anytime computations, i.e., the result of a computation can be probed at any time, with usually better results as more information is integrated in the liquid over time.
- Diverse network components (diverse types of neurons and diverse dynamics of synaptic connections) as found in cortical circuits in general improve the computational power of LSMs.
- The LSM hypothesis circumvents the problem of neural coding – circuit states are good if they are useful for the task.
- No precise circuitry is needed in order to perform useful computations, instead a specific functionality is acquired through learning. In particular, the liquid is usually a randomly connected spiking neural network.

2. Run the network on the training input $\mathbf{u}$ and collect the reservoir states $\mathbf{x}(1), \dots, \mathbf{x}(T)$. If feedback is required, use (possibly a noisy version of) the target output $\mathbf{y}^*(1), \dots, \mathbf{y}^*(T)$ for the feedback in Eq. 2. This procedure is called *teacher forcing*.
3. Compute the optimal output weights $\mathbf{W}^{\text{out}}$.

For a linear readout, the readout weights $\mathbf{W}^{\text{out}}$ are typically determined by regularized least squares. Various variants for readout training as well as for adaptation of the reservoir have been proposed (Lukoševičius and Jaeger 2009). Recently, it has been shown that supervised learning can often be replaced by reward-based learning (Hoerzer et al. 2012).

Echo State Networks

In an ESN, the reservoir is a recurrent artificial neural network consisting of randomly connected neurons. Consider an ESN with N reservoir neurons, a K -dimensional input $\mathbf{u}$, and L outputs $\mathbf{y}$. The reservoir state $\mathbf{x}$ of a standard discrete-time reservoir in an ESN evolves according to

$$\mathbf{x}(t+1) = \sigma(\mathbf{W}\mathbf{x}(t) + \mathbf{W}^{\text{in}}\mathbf{u}(t+1) + \mathbf{W}^{\text{fb}}\mathbf{y}(t)), \quad (2)$$

where σ is a sigmoid function (usually the tanh), $\mathbf{W}$ is the $N \times N$ matrix of recurrent weights, $\mathbf{W}^{\text{in}}$ is the $N \times K$ matrix of weights from input units to reservoir neurons, and $\mathbf{W}^{\text{fb}}$ is the $N \times L$ matrix of weights from output units to reservoir neurons. Some tasks may not require feedback from the readout units to the reservoir. In ESNs, the readout is a pseudo-linear function of the *extended system state*, that is, the vector $(x_1(t), \dots, x_N(t), u_1(t), \dots, u_K(t))^T$.

For supervised training, a training set is given that consists of a sequence of inputs $\mathbf{u}(1), \mathbf{u}(2), \dots, \mathbf{u}(T)$ and target outputs $\mathbf{y}^*(1), \mathbf{y}^*(2), \dots, \mathbf{y}^*(T)$. Training proceeds in the following steps (Lukoševičius et al. 2012):

1. Generate a random reservoir by choosing weight matrices $\mathbf{W}$, $\mathbf{W}^{\text{in}}$, and $\mathbf{W}^{\text{fb}}$.

Theory

Maass et al. (2002) presented a universal approximation theorem for LSMs without readout feedback based on two properties:

- The *separation property* addresses the amount of separation between the trajectories of liquid states that are caused by two different input streams.
- The *approximation property* addresses the capability of the readout to distinguish and transform different liquid states into given target outputs.

The theorem states that any time-invariant fading memory filter can be approximated to any degree of precision by an LSM if the liquid possesses the separation property and if the class of functions from which the readout map is drawn satisfies the approximation property. Informally, a filter has fading memory if the most significant bits of its current output depend just on the most significant bits of the values of its input function from some finite time window into the past (Boyd and Chua 1985).

The computational power of an LSM increases significantly if readout feedback is incorporated. In this case (and in the absence of noise), it can carry out any conceivable digital or analog

computation on time-varying inputs (Maass et al. 2007).

Not every reservoir can be used for reservoir computing. In the case of an ESN, the reservoir needs to have the *echo state property* (ESP; Jaeger 2001). Intuitively, the ESP states that the reservoir will asymptotically wash out any information from initial conditions. An easy to check sufficient condition for the ESP can be derived for tanh reservoir neurons. If the largest singular value of W is below 1, then the reservoir has the ESP. On the other hand, if the spectral radius of W is above 1, then the network does not have the ESP for zero input. These conditions imply that in order to satisfy the ESP, one simply has to scale the network weights.

Applications

LSMs have become an important theoretical concept for understanding complex brain networks (Buonomano and Maass 2009; Destexhe and Contreras 2006; Rigotti et al. 2013; Nikolic et al. 2009).

The dynamics of recurrent spiking networks is in general harder to tune because of a much sharper phase transition between the ordered and chaotic regime (Buesing et al. 2010). Therefore, ESNs are often preferred over LSMs in engineering applications (see, e.g., Lukoševičius et al. (2012) for a review). Although the general emphasis is on engineering, ESNs were also used to model biological neuronal networks.

Temporal recurrent networks were introduced by Peter F. Dominey (1995) to model corticostriatal circuits. Dominey was probably the first who explicitly spelled out the RC principle. State-dependent networks were introduced by Buonomano and Merzenich (1995) to model temporal processing in cortical circuits.

RC applications outside the field of neural networks include analog electronics, atomic switch networks based on nanowires, optoelectronic, and optical systems (see Lukoševičius et al. (2012)).

Scholarpedia
Echo State Networks

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Further Reading Webpages

Reservoir Computing. <http://reservoir-computing.org>

Recurrent Neural Network

► [Hopfield Network](#)

Reduced Morphology Models

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Synonyms

Simplified conductance-based models

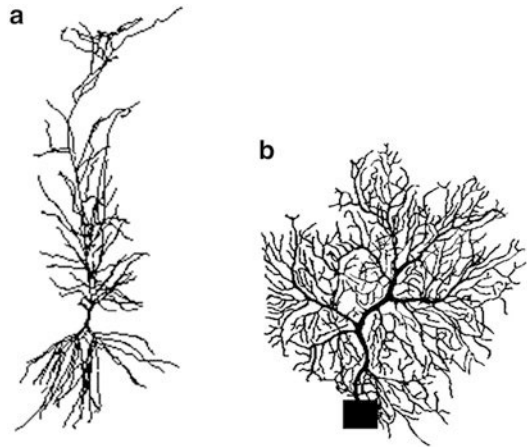
Definition

Reduced morphology models are simplified computational models obtained by collapsing the dendritic tree of a detailed neuron model, in such a way to preserve as much as possible the original membrane dynamics.

Detailed Description

Morphologically detailed neuron models are based on 3D anatomical cell reconstructions and describe how the spatial dendritic structure of a neuron together with the kinetic properties and distributions of ion channels and synaptic inputs contributes to the dynamics and functionality of a neuron. These *compartmental neuron models* are usually composed of hundreds of dendritic branches (Fig. 1) with nonlinear membrane properties.

Mathematically, they are described by thousands of coupled nonlinear partial and ordinary differential equations. The high dimensionality and intricate system structure impede the mathematical understanding of their emergent properties, and detailed investigations of the parameter space and simulations, using this kind of implementation in large networks, are rarely carried out because the computational cost dramatically



Reduced Morphology Models, Fig. 1 Typical 3D reconstruction of a hippocampal CA1 pyramidal neuron (a) and of a Purkinje cell (b). Both reconstructions were downloaded from the public neuromorpho.org database (cell c70863 and e4cb2a2, respectively)

increases with network size. These problems have prompted the need for a suitable reduction of a realistic neuron into a much simpler computational model, since the individual neuron dynamics and its role within a network are a fundamental problem for *Computational Neuroscience*. The design of a reduction method requires a delicate balance between incorporating sufficient details to account for the complex single-cell dynamics and reducing this complexity in such a way to implement a computationally efficient model. Systematic approaches to build simplified models with electric behavior equivalent to a detailed representation started with the concept of *equivalent cylinder* introduced by Rall (Rall 1959, 1964; Rall and Rinzel 1973; Rinzel and Rall 1974; Rall et al. 1995). The pioneering idea of Rall consisted in collapsing an idealized branching dendritic tree into a mathematically equivalent single cylinder with the same total membrane area and electrotonic structure. However, this method requires specific mathematical assumptions: (i) all dendrites must end at the same electrotonic distance from soma; (ii) the specific membrane resistance R_m and capacitance C_m , as well as the specific axial internal resistivity R_i , must be uniform throughout the structure; and (iii) branch point diameter must follow the $3/2$

power rule. These conditions are not satisfied for the great majority of real neurons, and, moreover, the method does not apply to cells with non-uniform active kinetic and synaptic properties.

Building up on Rall's seminal works, various alternative reduction methods have been suggested. Here we will discuss the two main approaches: theoretical or heuristic methods.

Theoretical Methods

In these cases, the reduction of a dendritic neuron tree into an *equivalent branched or unbranched cable* (i.e., a single or multicylinders with variable diameters) can be mathematically derived from theoretical grounds.

Clements and Redman (Clements 1986; Clements and Redman 1989) introduced a method to collapse a dendritic tree into an unbranched electrotonic cable in which the compartments can have unequal diameters. This method assumes that *all points on the dendritic tree at a given electrotonic distance from the soma will be at the same potential at all times*. The method thus cannot be applied to real neuron cells with nonuniform active kinetic and synaptic properties.

In Schierwagen (1994), the reduction to an equivalent cable can be derived only for passive dendritic trees fulfilling certain symmetry conditions.

Ohme and Schierwagen (1998), extending Rall's 3/2 power rule, developed a mathematical method to reduce branching neuronal trees with active ion channels into an equivalent cable model (see Fig. 2).

However, their main result (*Equivalent Cable Theorem*) applies only to ideal neuronal trees fulfilling special geometrical and electrical conditions such as:

1. For all dendritic segments, the membrane time constants must be uniform and independent of the segments.
2. All terminal nodes must have the same electrotonic distance from the soma.

3. The voltage functions are equal in all parallel segment domains (see the grey-labelled regions in Fig. 3).
4. All segments must be of the same geometric type, and nodes must satisfy an additional condition (Eq. 14 in Ohme and Schierwagen 1998).
5. At each node all (nonvanishing) current functions must be distributed among all locations at the same electrotonic distance from the soma corresponding to the weights of their parent segments.

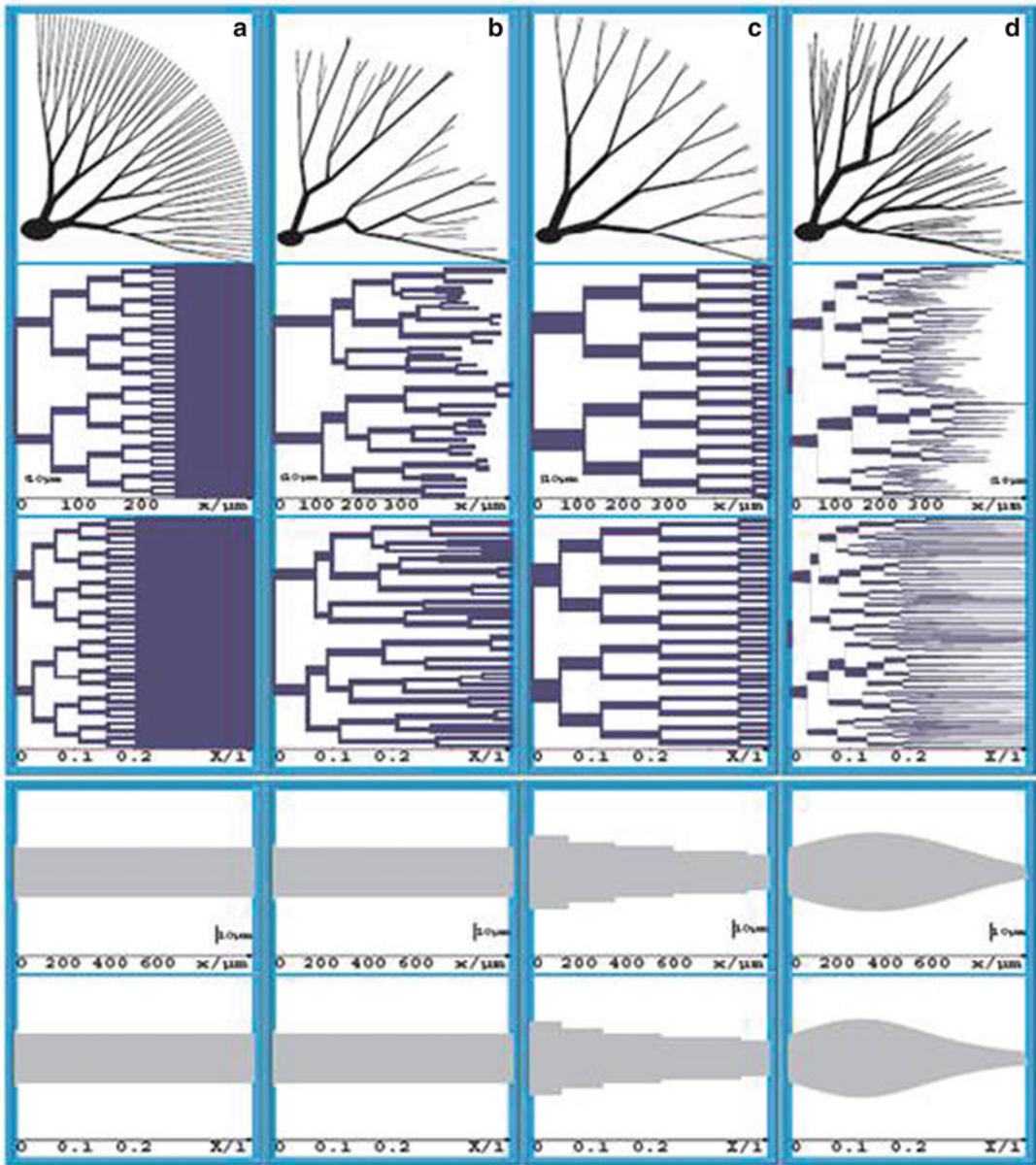
These conditions prevent the use of the method for real neurons. An additional adaptation of specific cell parameters of the reduced cable leads to a procedure that is computationally more expensive than the heuristic method proposed by Bush and Sejnowski (1993; see next section).

Finally, in Evans (2000), the exact solution of a multiple equivalent cylinder cable model for passive neurones was derived. Relaxing certain symmetry conditions necessary for the Rall equivalent cylinder reduction, the model consists of one or more tapering equivalent cylinders (belonging to a class of six specific forms) connected to a uniformly polarized soma. Following this approach, in Evans (2005), an analytical solution of the cable equation with synaptic reversal potentials for a pair of electrotonically coupled passive neurons was considered. In this approach, the synaptic inputs were modeled as a conductance change.

Heuristic Reduction Methods

Empirical methods to create reduced models follow two main approaches: (i) implementing the generic electrophysiological properties of a given neuron population with single- or multi-compartment conductance-based models and (ii) devising rules to reduce a full morphological and biophysical model into a simpler one.

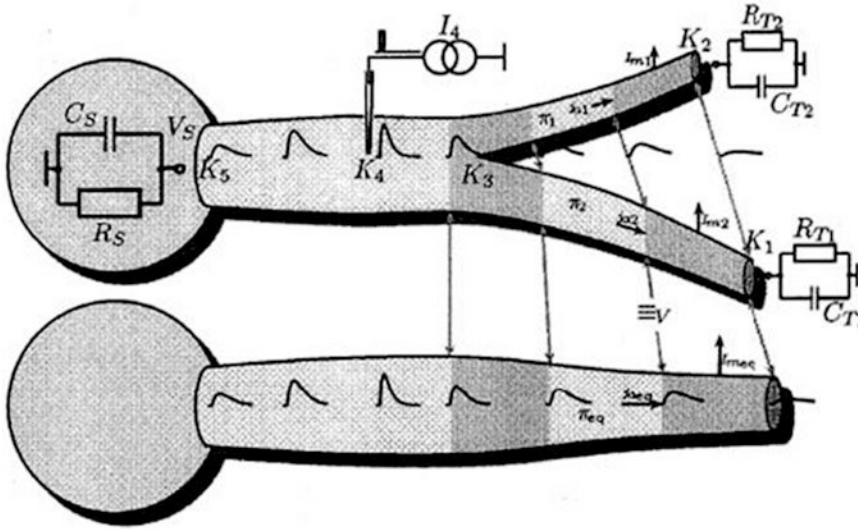
In the first approach, Hodgkin-Huxley-type models (Hodgkin and Huxley 1952) are arranged to reproduce the intrinsic electrophysiological properties of a generic neuron belonging to a



Reduced Morphology Models, Fig. 2 Schematic representation of different types of neuronal trees and their equivalent cable representation (see Ohme and Schierwagen 1998 for details)

given population as observed from the soma, neglecting the neuron's dendritic structure. This facilitates a more detailed mathematical investigation of the equations, such as bifurcation and phase-plane analysis (see, for instance, Bianchi et al. 2012), which can give useful information on critical model parameters. Multi-compartmental models are instead based on a set

of ad hoc rules that, inspired by the principles of cable theory, implement a full dendritic tree with a few compartments mapping the electric and synaptic properties into a reduced model. This kind of implementation was introduced in the 1990s by Traub et al. (1991), with an empirical 19-compartment model of hippocampal *CA3* pyramidal neurons, followed by a further



Reduced Morphology Models, Fig. 3 A simple neuronal tree and its equivalent cable (Ohme and Schierwagen 1998)

reduction to a two-compartment model (Fig. 4a) by Pinsky and Rinzel (1994). The same strategy was adopted by Davison et al. (2000) for *olfactory bulb mitral cells* (Fig. 4b), who devised a systems of current balance equations for four specific compartments (soma, tuft, primary and secondary dendrite) that included the HH-like equations for the ionic channels. In this case, a rescaling factor and model parameters were determined using the *downhill simplex algorithm* to fit the simplified models with the full model, using two criteria for evaluating goodness of fit (the so-called *fit-to-shape* and *fit-to-time*). The resulting reduced four-compartment model ran 75 times faster than the full model.

The second approach, based on conserving the electrotonic properties of a specific morphology, was originally proposed by Stratford et al. (1989) (the *cartoon model* consisting of 24 compartments) and Bush and Sejnowski (1993) for a deep cortical pyramidal neuron. The cell's morphology was reduced to eight to nine compartments (see Fig. 5) in such a way to preserve the axial resistance of the original model. In this method, all dendrites belonging to a specific functional region (i.e., preterminal and terminal basal dendrites, distal apical and apical dendrites), with approximately the same origin and (electrotonic) length, are collapsed into a single

equivalent cylinder with radius ρ^{eq} and length L^{eq} determined as

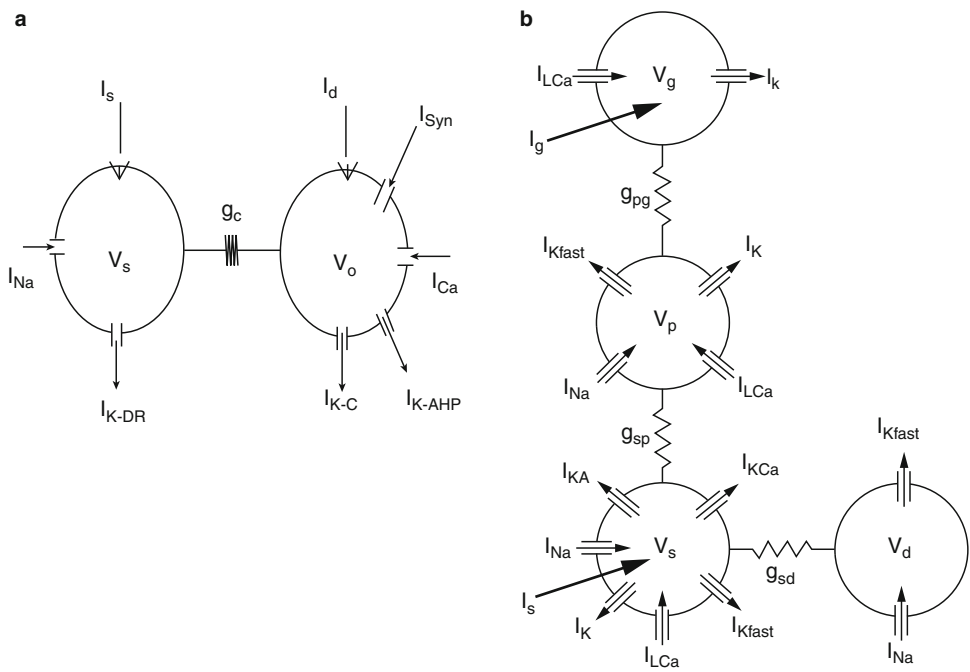
$$\rho^{eq} = \sqrt{\sum_i \rho_i^2}, \quad L^{eq} = \frac{1}{N} \sqrt{\sum_i L_i}, \quad (1)$$

where ρ_i and L_i are the radius and the length of the i th dendrite. Since this results in the surface area of the reduced model being lower than in the full model, it required a fine-tuning procedure to find the specific membrane resistance (R_m^{eq}), the specific membrane capacitance (C_m^{eq}), and active properties to obtain the same input resistance of the full model. The reduced models ran approximately five times faster in simulations that included a full set of voltage- and ligand-gated conductances.

A modification of this method to generate simplified representations of thalamocortical (TC) relay cells was proposed in Destexhe et al. (1998). It consisted of merging dendritic branches into equivalent cylinders with radius as in Eq. 1 but length weighted by their respective diameters (ρ_i):

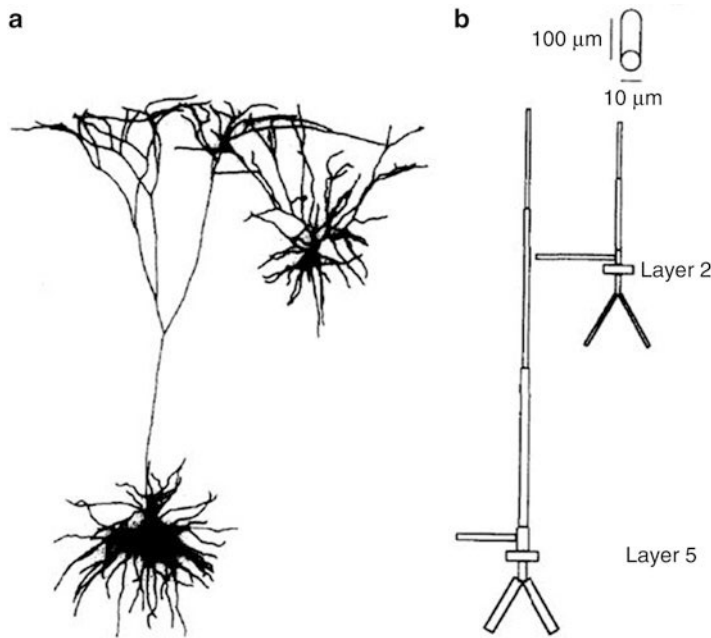
$$L^{eq} = \frac{\sum_i L_i \rho_i}{\sum_i \rho_i}. \quad (2)$$

More recent studies (Destexhe 2001; Tobin et al. 2006) have employed reduction methods



Reduced Morphology Models, Fig. 4 (a) Two-compartment model (Pinsky and Rinzel 1994); (b) four-compartment model showing ion channels and points of stimulation (Davison et al. 2000)

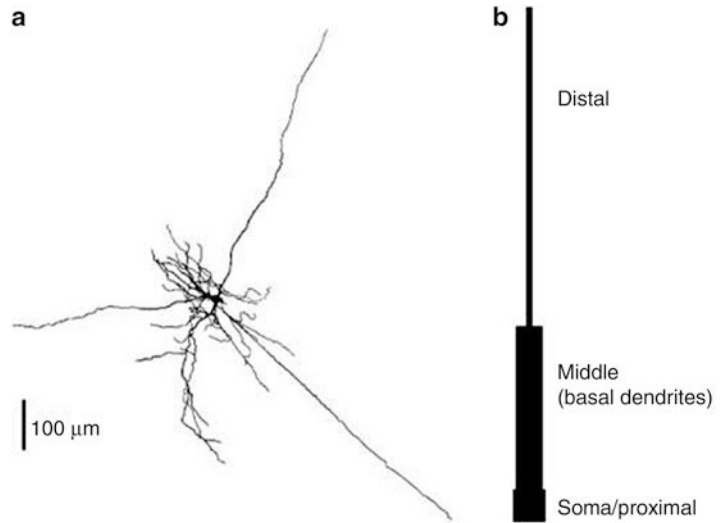
Reduced Morphology Models, Fig. 5 (a) HRP-filled layer 5 (left) and layer 2 (right) pyramidal cells; (b) their reduced models (Bush and Sejnowski 1993)



preserving the total surface area and somatic input resistance of the full model while ignoring its specific axial resistance. In Destexhe (2001), to

reduce the complexity of detailed models, the author identify different functional regions in the dendritic morphology based on the distribution of

Reduced Morphology Models, Fig. 6 (a) Layer VI pyramidal cell from cat parietal cortex; (b) simplified three-compartment model (Destexhe 2001)



synapses in the cell (Fig. 6). The axial resistances of the reduced model are adjusted by a fitting procedure, matching the passive responses and voltage attenuation of the simplified and detailed models.

The reduced model has thus the same membrane area, input resistance, time constant, and voltage attenuation as the detailed model. Similarly, in Tobin et al. (2006) a *leech heart interneuron* was divided into functional regions corresponding to distinct anatomical and physiological roles (Fig. 7). The reduction method included active properties and preserved the surface area of each functional region. However, to improve the correspondence between the reduced and full active models, the axial resistance of several compartments had to be adjusted by fitting procedures.

In Brown et al. (2011) a *preserved path* reduction method was proposed, in which an explicit unreduced path between the soma and a single spine was retained, while reducing the rest of a Purkinje cell morphology (Fig. 8). In this way, the reduction method allows to preserve the essential features of activity in both the soma and a remote dendritic spine. In particular, the length and the radius for each equivalent cylinder are determined taking into account the branching geometries of the cells, i.e.,

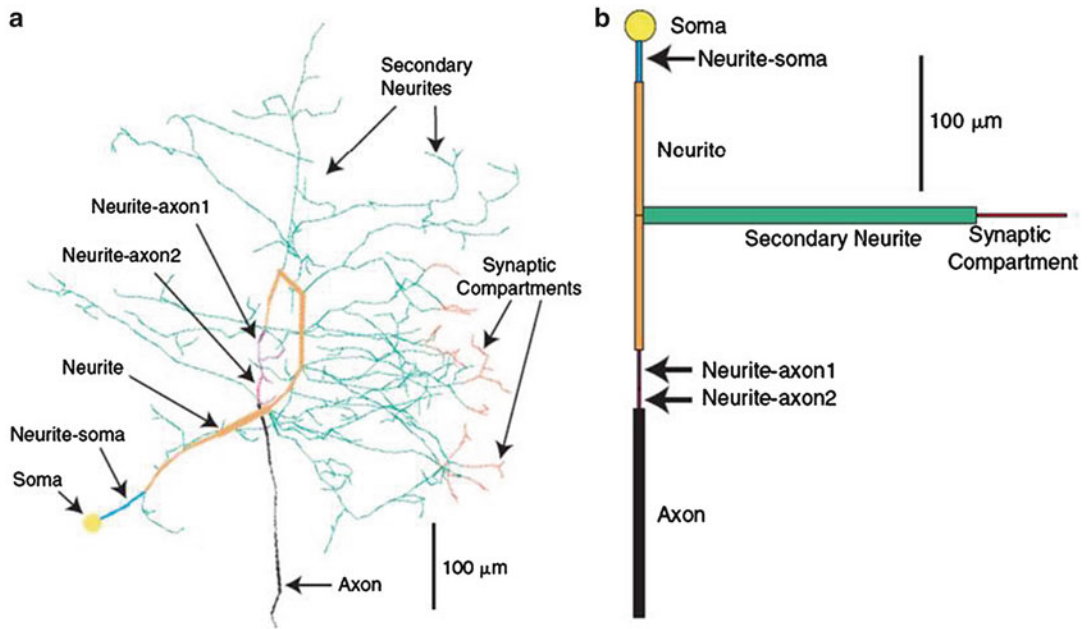
$$L^{eq} = L_\alpha - L_\omega, \rho^{eq} = \sqrt{\sum_{seqbr} \rho_{seq} \rho_{br}}, \quad (3)$$

where L_α and L_ω are the anatomic distances to the soma of the closest and farthest dendrites in the cluster, and the quantities ρ_{seq} and ρ_{br} are chosen as the average radius of all the dendrites in the cluster if the dendrites are sequential (seq) or as in Eq. 1 if the dendrites are branched, respectively, i.e.,

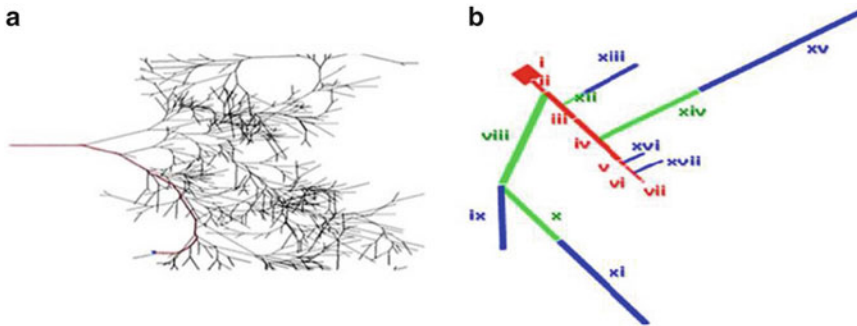
$$\rho_{seq} = \frac{1}{N} \sum_i \rho_i, \rho_{br} = \sqrt{\sum_i \rho_i^2}. \quad (4)$$

The procedure conserved axial resistivity, and an iterative procedure was needed to adjust passive and active properties with scaling factors representing the ratio between the surface areas of the dendrites in the full model and the corresponding equivalent cylinders in the reduced version.

The major problem with all the above methods is that none of them take explicitly into account synaptic input locations or non-uniform distribution of ionic conductances. Furthermore, it has been shown (Hendrickson et al. 2011) that for branched neurons in the presence of dendritic synaptic inputs, these methods do not provide significant accuracy (Fig. 9d) or



Reduced Morphology Models, Fig. 7 (a) An oscillator leech heart interneuron; (b) reduced model (Tobin et al. 2006)



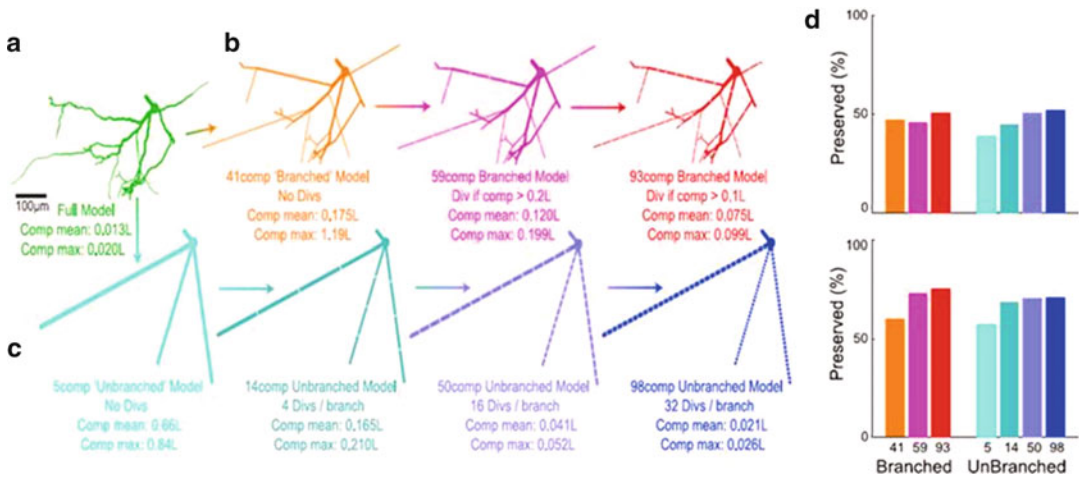
Reduced Morphology Models, Fig. 8 (a) Purkinje neuron; (b) reduced model. Preserved electronic path is highlighted in red. The rest of the neuron is reduced to equivalent cylinders (green, smooth; blue, spiny; Brown et al. 2011)

reduction in the number of compartments. In this work, reduced models were created by collapsing the dendritic tree of a full morphological model of a *globus pallidus* neuron (GP, Fig. 9a) in such a way to preserve the total surface area (TSA), electrotonic length (L), and the passive and active parameters. The TSA and L for a given group of dendrites were used to calculate the length L^{eq} and radius ρ^{eq} of the corresponding reduced model compartment using the following two equations:

$$TSA = 2 \pi \rho^{eq} L, L^{eq} = \sqrt{\frac{2R_a}{R_m \rho^{eq}}}. \quad (5)$$

where R_a is the specific axial resistance and R_m is the specific membrane resistance. To test different reduction factors, dendritic subtrees were progressively collapsed (*branched models*) up to a single compartment (*unbranched models*) (Fig. 9b, c).

More general reduction methods using the *iterative rational Krylov algorithm* (Kellems et al. 2009) or a *proper orthogonal decomposition*,



Reduced Morphology Models, Fig. 9 (a) GP neuron; (b) “branched”; (c) “unbranched”; (d) spike time preservation during asynchronous (*top*) and synchronous (*bottom*) synaptic inputs (Hendrickson et al. 2011)

and *direct empirical interpolation methods* (Kellems et al. 2010), have been proposed. In these works, the authors applied a reduction technique to generic passive, quasi-active, and active dendritic tree and reproduce the transmembrane potential at the soma without sacrificing the spatial distribution of inputs. In Kellems et al. (2009), the reduction method reproduced only the sub-threshold dynamics by considering the quasi-active version of the full model, whereas in Kellems et al. (2010) the reduction technique preserves the spatial location of synaptic inputs while reproducing the global voltage dynamics, including both subthreshold and spiking behaviors. These two techniques allow for up to ≈ 15 -fold speedup in simulation time (Fig. 10 for the kinetics and nonuniform channel density from Migliore et al. 1999), but they need a sufficiently rich set of *snapshots* of the voltage dynamics to reproduce the full range of neuronal behavior. This in turn appears to require a setup procedure for every morphology and synaptic configuration that need to be reduced.

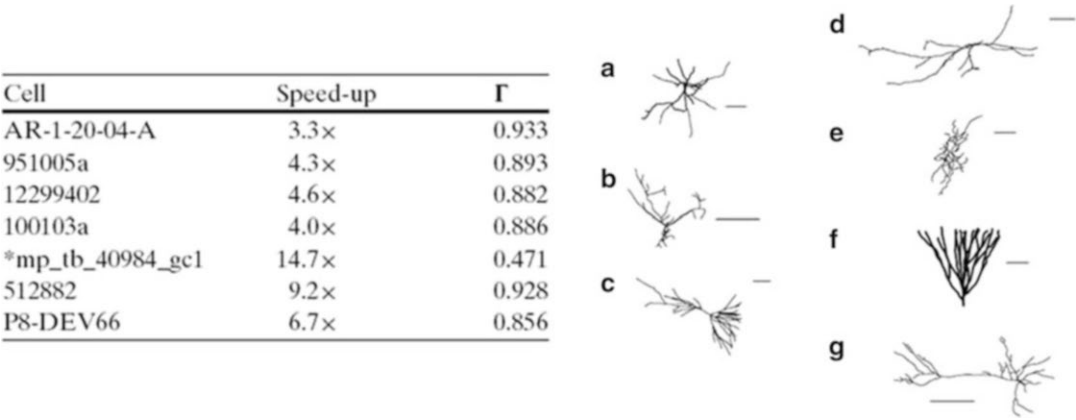
In conclusion, although all these methods are often sufficient to take qualitatively into account the somatodendritic interactions that govern spiking or bursting, they present several drawbacks:

- (a) Overall poor results in terms of run time reduction that can be achieved in order to maintain a

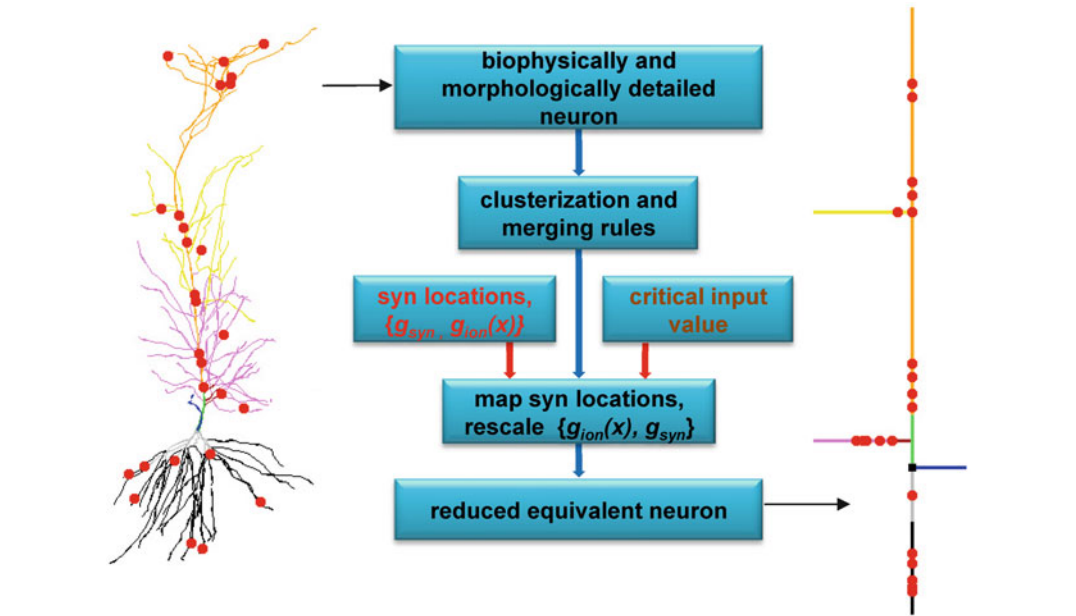
relatively good somatic trace accuracy (Brown et al. 2011; Bush and Sejnowski 1993)

- (b) The need, in many cases, of optimization techniques and fine-tuning procedures carried out independently on each neuron that must be reduced (Bush and Sejnowski 1993; Destexhe et al. 1998; Destexhe 2001; Tobin et al. 2006.
- (c) A limited field of application, restricted in most cases to passive dendritic trees and/or without taking into account synaptic input location (Destexhe et al. 1998; Destexhe 2001; Tobin et al. 2006; Brown et al. 2011.

Recently, in Marasco et al. (2012), it has been shown how all these problems can be solved by using a fast and accurate reduction method to simplify models of complex neurons with an arbitrary distribution of active properties, synaptic inputs, and dendritic trees. The new empirical method, tested on a set of hippocampal pyramidal CA1 neurons, was able to map any morphologically and biophysically accurate model of these kind of neurons into equivalent models that can run up to >40 times faster, while maintaining the same average I/O properties. In contrast with all previously published reduction techniques, this method is able to include arbitrary distributions of synaptic inputs and active dendritic conductances without any fitting or parameter tuning procedures (Fig. 11).



Reduced Morphology Models, Fig. 10 Performance of the reduced models in Kellems et al. (2010). (a) projection interneuron AR-1-20-04-A, (b) CA3 hippocampal interneuron 951005a, (c) CA3 hippocampal pyramidal cell 12299402, (d) CA1 hippocampal interneuron 100103a from the stratum oriens, (e) retinal ganglion cell mp_tb_40984_gc1, (f) hippocampal cell 512882 from the dentate gyrus, and (g) pyramidal cell P8-DEV66 from the cerebral cortex. Scale bars on all cells represent 100 μm



Reduced Morphology Models, Fig. 11 Schematic representation of a method to reduce the computational complexity of realistic neuron models (Marasco et al. 2012)

The details of the method are illustrated below. For CA1 neurons, a given morphology is first reduced to nine compartments (see Fig. 11), by clustering dendrites belonging to different functional regions (i.e., soma, axon, apical trunk, apical dendrites (oblique, distal), basal dendrites

(proximal, distal)). The length L^{eq} for each equivalent cylinder is chosen as the sum of the dendrites' length if the dendrites are sequential (seq) or as the average length weighted by their respective areas (S_i) if the dendrites are branched (br), i.e.,

$$L^{eq} = \frac{\sum_{seq, br} S_h L_h}{\sum_{seq, br} S_h}, \quad (6)$$

where

$$L_{seq} = \sum_i L_i, L_{br} = \frac{\sum_i S_i L_i}{\sum_i S_i}. \quad (7)$$

The radius ρ^{eq} for each equivalent compartment is chosen taking into account the axial resistance of the ensemble of dendritic segments it represents (cluster), i.e.,

$$\rho^{eq} = \sqrt{\sum_{seq, br} \rho_h^2}, \quad (8)$$

where

$$\begin{aligned} \rho_{seq} &= \sqrt{\sum_{seq, br} \frac{R_a L_{seq}}{\pi r_{a,seq}}}, r_{a,seq} = \sum_i r_{a,i}, \\ \rho_{br} &= \sqrt{\sum_i \rho_i^2}, \end{aligned} \quad (9)$$

where R_a is the specific axial resistance of each dendrite in the cluster and $r_{a,i}$ is the axial resistance of the i th dendrite.

The specific axial resistance in the equivalent compartment R_a^{eq} is defined as

$$R_a^{eq} = \frac{\pi(\rho^{eq})^2 r_a^{eq}}{L^{eq}}, \quad (10)$$

where

$$\begin{aligned} r_a^{eq} &= \frac{\sum_{seq, br} r_{a,h}}{H}, r_{a,br} = \frac{\prod_i r_{a,i}}{\sum_i r_{a,i}}, \\ \rho_{br} &= \sqrt{\sum_i \rho_i^2}, \end{aligned} \quad (11)$$

and H is the total number of the dendrites in the cluster.

Owing to Eqs. 6, 8, and 10, the membrane area and the axial resistance of the neuron are not conserved in the reduced model; then, a scaling factor ($fact_s^{eq}$) is defined as follows:

$$fact_s^{eq} = \begin{cases} \frac{1}{S^{eq}} \sum_i W_i S_i, & \text{if there are no synaptic inputs,} \\ \frac{1}{S^{eq}} \sum_i S_i, & \text{otherwise,} \end{cases} \quad (12)$$

where S^{eq} is the surface area of the equivalent compartment and $w_i = 1$ if in the i th dendrite there is at least one synapse and 0 otherwise. This factor is used to scale the specific membrane capacitance (C_m), the specific membrane resistance (R_m), and ion channel peak conductance ($\dot{g}_{ionic}$) (see Eqs. 17 and 18). Note that in this way the method takes into account synaptic input location without any fitting or tuning procedures.

To take into account the effect of the i th synaptic input on cluster C of the full model, the *axial path resistance* $r_{i,PATH}$ was used to reposition the input as follows:

$$r_{i,PATH} = \sum_{h=1}^j r_{a,h}, \quad (13)$$

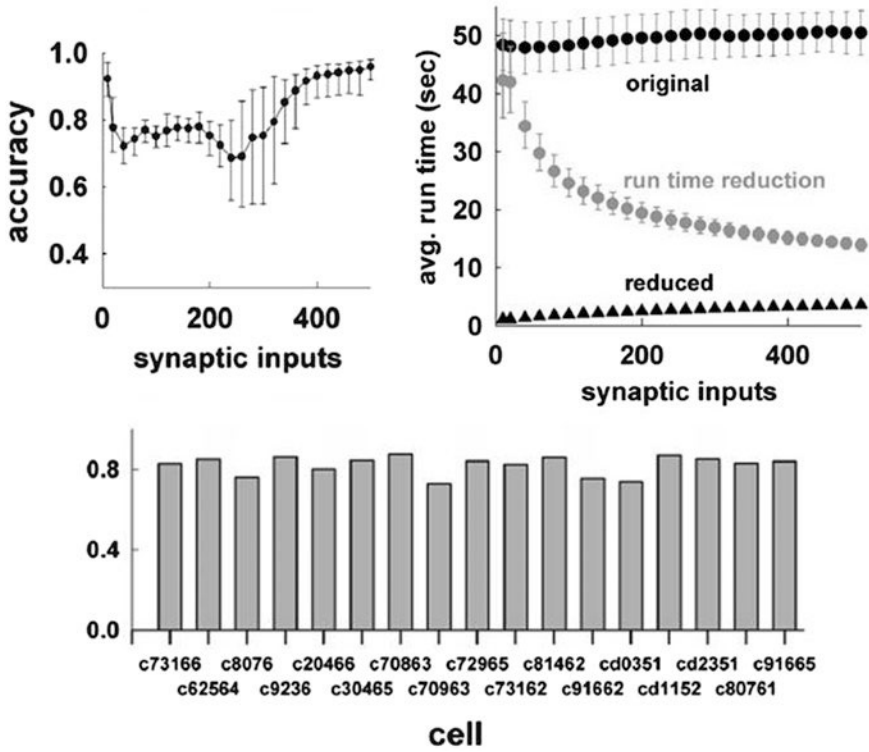
where $r_{a,h}$ is the axial resistance of the h th segment of the *path* consisting of the unique sequence of j segments leading from the soma to the dendrite on which the i th synapse is positioned.

Let $r_{\max}$ and $r_{\min}$ be the maximum and the minimum axial path resistance of cluster C and suppose that this cluster is modeled with a single compartment C', consisting on n' segments (see Eq. 6 in Marasco et al. 2012), in the reduced model. Then, the segment s_i of C' where to place the i th synapse is defined by its axial path resistance $r_{i,PATH}^{eq}$ in such a way that

$$r_{i,PATH}^{eq} \in \left[r_{\min}^{eq} + \sum_{h=1}^{S_i-1} r_{a,h}^{eq}, r_{\min}^{eq} + \sum_{h=1}^{S_i} r_{a,h}^{eq} \right], \quad (14)$$

where

$$r_{\min}^{eq} = \sum_{h=1}^k r_{a,h}^{eq}, r_{\max}^{eq} = \sum_{h=1}^{k+n'} r_{a,h}^{eq} \quad (15)$$



Reduced Morphology Models, Fig. 12 (Top, left) average accuracy obtained for all cells; (top, right) average run time reduction; (bottom) average accuracy for each cell (Marasco et al. 2012)

and k represents the number of segments from the soma to compartment C' and $r_{a,h}^{eq}$ is the axial resistance of the h th segment of C' .

Finally, the passive parameters, the peak conductances of ion channels, and the synaptic inputs are scaled as

$$C_m^{eq} = fact_s^{eq} C_m, R_m^{eq} = \frac{R_m}{fact_s^{eq}}, \quad (17)$$

$$\begin{aligned} \bar{g}_{ionic}^{eq} &= fact_s^{eq} \bar{g}_{ionic}, \\ g_{i,max}^{eq} &= fact_{g_{max}} \frac{r_{i,PATH}^{eq}}{r_{i,PATH}} g_{i,max}, \end{aligned} \quad (18)$$

where $g_{i,max}$ is the original peak conductance of the i th synapse of the full neuron and $fact_{g_{max}}$ is a factor which depends on specific electrophysiological properties of CA1 neurons.

The results (Marasco et al. 2012) showed the accurate mapping of the somatic dynamics of the full models, with a 13–50-fold reduction of the run times (Fig. 12).

An improved version of this method, clustering the compartments according to their Strahler's number, was extended also to Purkinje cells (Marasco et al. 2013). This allows the complete generalization of the method to any type of neuron implemented with any kind of conductance-based model, with arbitrary dendritic distribution of ion channels and synaptic inputs and no need to explicitly take into account special electrophysiological neuron properties. Using this method for Purkinje cells, we demonstrate how run times can be reduced up to 200-fold, while accurately taking into account the effects of arbitrarily located and activated synaptic inputs.

Cross-References

- [Cable Equation](#)
- [Cable Theory: Overview](#)
- [Multiscale Modeling of Purkinje Cells](#)
- [Neuronal Model Reduction](#)

- [Spatial Temporal Spike Pattern Analysis](#)
- [Spike Train Analysis: Overview](#)

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Further Reading

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Reflex

- [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Regulated Exocytosis

► [Biophysical Models of Calcium-Dependent Exocytosis](#)

Regulator

► [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Reinforcement Learning in Cortical Networks

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Synonyms

[Policy gradient methods](#); [Reward-based learning](#); [Temporal difference \(TD\) learning](#); [Trial-and-error learning](#)

Definition

Reinforcement learning represents a basic paradigm of learning in artificial intelligence and biology. The paradigm considers an agent (robot, human, animal) that acts in a typically stochastic environment and receives rewards when reaching certain states. The agent's goal is to maximize the expected reward by choosing the optimal action at any given state. In a cortical implementation, the states are defined by sensory stimuli that feed into a neuronal network, and after the network activity is settled, an action is read out. Learning consists in adapting the synaptic connection strengths into and within the neuronal network based on a (typically binary) feedback about the

appropriateness of the chosen action. Policy gradient and temporal difference learning are two methods for deriving synaptic plasticity rules that maximize the expected reward in response to the stimuli.

Detailed Description

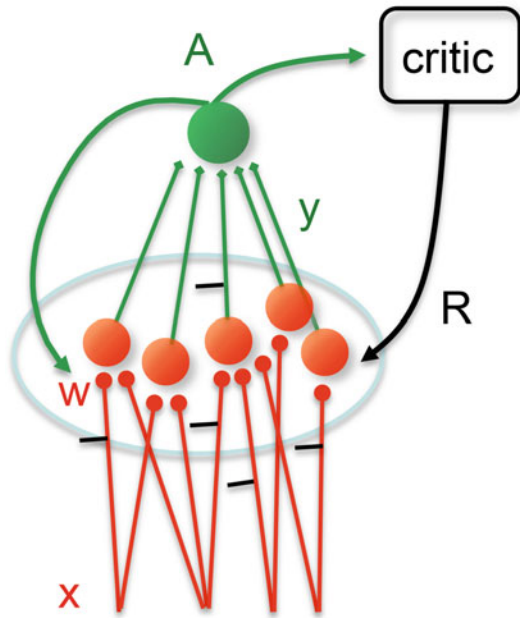
Different methods are considered for adapting the synaptic weights w in order to maximize the expected reward $\langle R \rangle$. In general, the weight adaptation has the form

$$\Delta w = R \cdot p \text{ PI} \quad (1)$$

where $R = \pm 1$ encodes the reward received upon the chosen action, and PI represents the plasticity induction the synapse was calculating based on the pre- and postsynaptic activity. To prevent a systematic drift of the synaptic weights that is not caused by the covariation of reward and plasticity induction, either the average reward or the average plasticity induction must vanish, $\langle R \rangle = 0$ or $\langle \text{PI} \rangle = 0$.

Reinforcement learning can be divided in these two, not mutually exclusive, classes of assuming that (A) $\langle \text{PI} \rangle = 0$ or (B) $\langle R \rangle = 0$. The first class encompasses *policy gradient* methods while the other, wider class, encompasses *temporal difference* (TD) methods. Policy gradient methods assume less structure as they postulate the required property ($\langle \text{PI} \rangle = 0$) on the same synapse of the action selection module that is adapted by the plasticity. TD methods also involve the adaptation of an internal critique since they have to assure that the required property on the modulation signal ($\langle R \rangle = 0$) eventually holds after learning.

(A) Policy Gradient Methods In the simplest biologically plausible form, actions are represented by the activity of a population of neurons. Each neuron in the population is synaptically driven by feedforward input encoding the current stimulus (Fig. 1). The synaptic strengths are adapted according to the gradient of the expected reward across possible actions. Various learning rules emerge from the different methods of estimating this gradient.



Reinforcement Learning in Cortical Networks, Fig. 1 Population reinforcement learning adapts the synaptic strengths w to the population neurons based on 4 ingredients: the presynaptic activity x , the postsynaptic activity y , the action A encoded in the population activity, and the reward signal R received in response to the action; see Urbanczik and Senn (2009)

In formal terms, sensory stimuli define an input x , e.g., a spike train, that is fed to the network characterized by the synaptic strengths w . This network generates an output y , say again a spike trains, that depends on the synaptic weights w and the input x . Based on y , an action A is selected (Fig. 1). The action is eventually rewarded by a typically binary signal $R(x, A) = \pm 1$ that is fed back to the network where it modulates synaptic plasticity by a global factor. The stimulus presentation, the network activity, and the action selection may have stochastic components. The probability function $P_w(A|x)$ that specifies how likely action A is selected upon input x is referred to as action policy. A policy gradient method considers the expected reward

$$\langle R \rangle = \sum_{x,A} P(x) P_w(A|x) R(x,A) \quad (2)$$

and adapts the synaptic connection strengths w along the reward gradient, i.e., such that the expected weight change satisfies $\langle \Delta w \rangle = \eta \frac{d\langle R \rangle}{dw}$ with some small but positive learning rate η (Williams 1992).

Hedonistic Synapse In the current form, the change in synaptic strength depends on how w affects the likelihood $P_w(A|x)$. But this information may not be available at the single synapse. According to the hedonistic synapse model (Seung 2003), a synapse is only assumed to have access to the very local information of whether there was a release or not ($r_t = 1$ or 0) at time t in response to a presynaptic spike, and x_t itself encodes the presence or absence of a presynaptic spike. We can then write $P_w(A|x) = \sum_r P(A|r) P_w(r|x)$, where $P_w(r|x)$ is parameterized by the variable w and the sum is taken across release trains r . Plugging this into (2) and taking the derivative we obtain

$$\begin{aligned} \frac{d\langle R \rangle}{dw} &= \sum_{r,x,A} P_w(x,r,A) R(x,A) \\ &\quad \times \frac{d}{dw} \log P_w(r|x). \end{aligned} \quad (3)$$

Sampling this gradient leads to updates of w after taking action A in response to the presynaptic spike train,

$$\Delta w = \eta R \frac{d}{dw} \log P_w(r|x). \quad (4)$$

Note that in any case $\langle \frac{d}{dw} \log P_w(r|x) \rangle_r = \sum_r \frac{d}{dw} P_w(r|x) = 0$ because $\sum_r P_w(r|x) = 1$ and hence $\langle \text{PI} \rangle = 0$ as described after Eq. 1.

To obtain an online rule from (4) one low-pass filters $\frac{d}{dw} \log P_w(r_t|x_t)$ to get an eligibility trace that is then multiplied by R to calculate the synaptic update (Seung 2003). If for simplicity we consider a single time interval for a presynaptic spike to occur and an action to be taken, the rule (5) becomes

$$\Delta w = \eta R(r - p)x, \quad (5)$$

where $p = P_w(r = 1 | x = 1)$ is the probability of release that is parametrized by a sigmoidal function of w , $p = 1/(1 + e^{-w})$. In the general case, the plasticity induction $PI = (r - p)x$ is low-pass filtered with a time constant that reflects the delay of the reward (see *Online learning* below).

Spike Reinforcement Since there is only little correlation between specific synaptic releases and rewards given for actions, a more efficient way to estimate the gradient $\frac{d(R)}{dw}$ is to consider the dependence of A on y , as expressed by $P_w(A|x) = \sum_y P(A|y)P_w(y|x)$. Plugging this again into (2) and taking the derivative, we get for the sampled version

$$\Delta w = \eta R \frac{d}{dw} \log P_w(y|x). \quad (6)$$

To illustrate learning rule (6), we can again interpret x and y ($= 1$ or 0) to encode the presence or absence of a spike in a given interval, with the probability p for $y = 1$ being again a sigmoidal function of $u = \sum_i w_i x_i$. Analogously to (5) we obtain the rule $\Delta w = \eta R (y - p)x$ (Williams 1992). Alternatively, x and y may encode firing rates with $y = \phi(u) + \xi$, where $\phi(u)$ is a nonnegative increasing function and ξ some Gaussian noise. We then calculate $\frac{d}{dw} \log P_w(y|x) \propto (y - \phi(u))\phi'(u)x$, and the learning rule becomes

$$\Delta w = \eta R (y - \phi(u))\phi'(u)x. \quad (7)$$

This synaptic plasticity rule depends on 3 factors, (i) the reward, (ii) the postsynaptic quantities (here considered as a single factor), and (iii) the presynaptic activity. For spiking neurons, the corresponding learning rule has been introduced by Xie and Seung (2004) and has been further studied by Pfister et al. (2006); Florian (2007); Frémaux et al. (2010).

Node Perturbation In the framework of spiking neurons, the exploration of the neuronal state space is driven by the intrinsic noise present in the individual neuron's spiking mechanism. A more efficient exploration can be achieved if the noise enters from an external source and can therefore be explicitly tuned. This idea leads to RL based on node perturbation (Fiete and Seung 2006). In the simple coding scenario considered above, node perturbation is formally equivalent to (7), and, with $\xi = y - \phi$, it can be rewritten as

$$\Delta w = \eta R \xi \phi' x. \quad (8)$$

Yet, node perturbation can also be generalized to conductance-based neurons driven by regular “student” input and “exploration” input, and, as before, the plasticity induction $PI = \xi \phi' x$ can again be replaced by a low-pass filtering to comply with delayed reward (Fiete and Seung 2006).

Population Reinforcement When assuming that a synapse has access to the downstream information involved in choosing action A , e.g., via global neuromodulators, the gradient can be well estimated by directly calculating the derivative of (2) with respect to w . The sampling version of this rule is then

$$\Delta w = \eta R \frac{d}{dw} \log P_w(A|x). \quad (9)$$

The action can itself be binary and, e.g., depend on whether the majority of the population neurons did or did not spike in response to the stimulus (Friedrich et al. 2011) or it can be continuous and, e.g., depend on the average population firing rate (Friedrich et al. 2014).

To give an example, we consider a population of N neurons with outputs $y_i = \phi(u_i) + \xi_i$ for $i = 1 \dots N$ that are obtained by an increasing function $\phi(u_i)$ of the weighted input, $u_i = \sum_j w_{ij} x_j$, plus some independent Gaussian noise ξ_i of mean 0. For simplicity we assume ϕ to increase from -1 to $+1$ with $\phi(0) = 0$ and consider binary actions $A = 1$ or $A = -1$ that are taken

stochastically based on the population activity $\mathcal{A} = \frac{1}{\sqrt{N}} \sum_i y_i$ with $P(A = 1 | \mathcal{A}) = (1 + \tanh \mathcal{A})/2$ being a sigmoidal function of $\mathcal{A}$. Neglecting again the indices, the learning rule (9) can then be evaluated to (see Friedrich et al. (2014), Eq. 21 therein)

$$\Delta w = \eta R(A - \tanh \mathcal{A}) \phi'(u) x. \quad (10)$$

Note the formal similarity to (5) and (7) where in the latter the “exploration term” ($y - \phi(u)$) is now replaced by $(A - \tanh \mathcal{A})$. The population reinforcement learning rule (10), however, is composed of 4 factors that originate from 4 different consecutive biological processing stages: (i) the presynaptic activity, (ii) a postsynaptic quantity, (iii) the population activity with the corresponding action, and (iv) the reward. Explicit expressions for (7) and (10) in the case of spiking neurons are given in *spike-timing-dependent plasticity, learning rules*.

Online Learning To obtain online learning rules, one considers an ongoing stimulus x_t that may, e.g., define spike trains up to a discrete time step t . Actions A_t can be taken each moment t , and a reward signal R_t is potentially always present, although it is typically sparse. To express the weight change at each time step t , one considers the so-called synaptic eligibility trace e_t . In the case of the rule (9), this is defined as a low-pass filtering of the instantaneous plasticity induction $\text{PI}_t = \frac{d}{dw} \log P_w(A_t | x_t)$, i.e., $e_{t+1} = \gamma e_t + \text{PI}_t$, with some discount factor $\gamma \in [0, 1)$. Here, the derivative of the log likelihood is evaluated as in (10), with the individual factors each being low-pass filtered to obtain a fully online rule. The final rule then becomes

$$\Delta w_t = \eta R_t e_t. \quad (11)$$

By low-pass filtering the corresponding instantaneous plasticity induction terms PI_t occurring in (5), (7), and (8) (compare with the general form of

Δw given in Eq. 1), one analogously obtains the online version for these rules.

Assuming that the states x_t are sampled from a partially observable Markov decision process (POMDP), the online learning rule (11) can be shown to maximize the expected discounted future reward

$$V_t = \sum_{k=0}^{\infty} \gamma^k \langle R_{t+k} \rangle \quad (12)$$

for each time step t , see Baxter and Bartlett (2001), Theorem 5, for the general case, and Friedrich et al. (2011), Supporting Information, for population learning.

Phenomenological R-STDP Models The gradient-based learning rules discussed so far prevent a systematic weight drift by assuring that the plasticity induction in average vanishes, $\langle \text{PI} \rangle = 0$. This was also assumed in reward-modulated spike-timing dependent plasticity (R-STDP, Izhikevich (2007)). Nevertheless, when considering specific (*in vitro*) data on plasticity induction, one will typically have $\langle \text{PI} \rangle \neq 0$ in Eq. 1 (Sjöström and Gerstner 2010). It is therefore plausible that the reward signal itself in average vanishes. One strategy to achieve this is to subtract the mean reward from the modulating factor such that the learning rule, now reading as $\Delta w = (R - \langle R \rangle) \cdot \text{PI}$, is again unbiased. This leads to the concept of actor-critic learning where a stimulus-specific internal critique adapts the global modulation signal of the plasticity induction to prevent drifts even for individual stimuli. When the LTD part in the STDP window is suppressed and the remaining R-STDP bias is corrected, the learning speed for standard association tasks comes close to the one for gradient-based spike reinforcement (Frémaux et al. 2010).

An elegant solution to solve the reward-bias problem is to assume that the internal reward signal is shaped by a temporal kernel that sums up to zero across time, $\int R_t dt = 0$, and hence a positive internal reward signal must be followed or preceded by a negative one (Legenstein et al.

2008). What appears as a computational trick is reminiscent to the observed relieve from pain in fruit flies (Tanimoto et al. 2004) or the reward baseline adaptation in rodents (Schultz et al. 1997). Along similar lines, pairing reward with differential Hebbian plasticity was also shown to be bias-free and asymptotically equivalent to temporal difference learning (Kolodziejcki et al. 2009).

(B) Temporal Difference (TD) Learning TD methods represent a class of learning rules where the modulatory feedback signal on the level of the synapse is again unbiased. These methods consider a learning scenario where an agent navigates through different states to eventually reach a final rewarding state.

The actor-critic version of TD learning is to calculate a value for each state and to use the value updates to also train the action selection network (Fig. 2). The value of a state x is defined as the expected discounted future rewards when being in that state at time t (Sutton and Barto 1998),

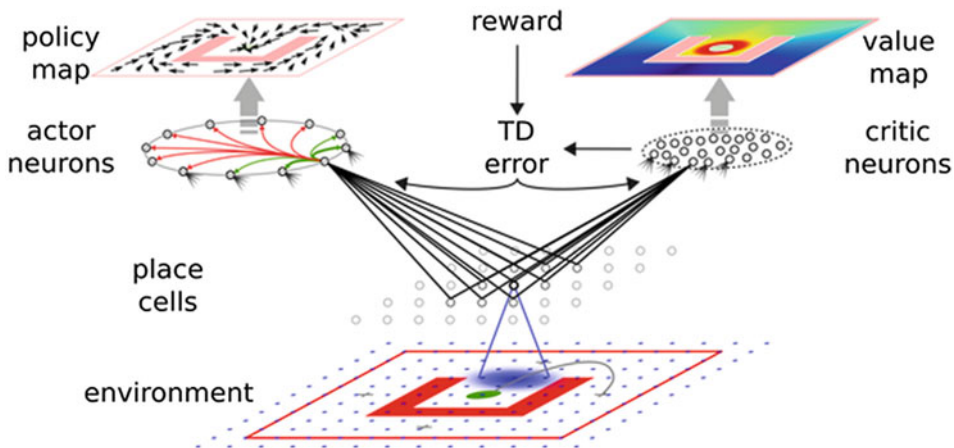
$$V^\pi(x_t) = \sum_{k=0}^{\infty} \gamma^k \langle R_{t+k} \rangle \quad (13)$$

where γ denotes the discounting factor and the expectation $\langle \cdot \rangle$ is taken over all future actions according to a fixed policy π , see Sutton and Barto (1998). While this definition involves future rewards, an online version would again need to estimate the quantity based on only past experiences. It is therefore interesting to note that (13) can be rewritten in a recursive way as $V^\pi(x_t) = \langle R_t \rangle + \gamma V^\pi(x_{t+1})$.

The value function $V^\pi(x_t)$ is assumed to be represented (and approximated) by the activity $V_w(x_t)$ of a given neuron, where w denotes the strength of synapses converging to that neuron and x_t is the input to the network. The synaptic strengths can be adapted online by gradient descent on the error function $E = \langle V(x) - V_w(x) \rangle^2$ with respect to w , where the expectation is over the states x (Sutton and Barto 1998; Frémaux et al. 2013). The weight change at time t is therefore given by

$$\Delta w_t = \eta (V^\pi(x_t) - V_w(x_t)) \frac{dV_w(x_t)}{dw}. \quad (14)$$

Since the true value $V(x_t)$ is not known to the network, it can be approximated as $V^\pi(x_t) \approx R(t) +$



Reinforcement Learning in Cortical Networks, Fig. 2 Actor-critic network for navigation. Based on the current position information, the action network chooses action A that moves the agent towards the neighboring position closest to the site of reward delivery (inside the U-shaped obstacle). The critic network calculates the TD

error δ_t based on the values V and the reward signal R_t . The synaptic strengths w_A and w_V of the action selection and the value representation network, respectively, are both adapted by a TD learning rule. Figure adapted from Frémaux et al. (2013)

$\gamma V_w(x_{t+1})$ by using the recursive definition of $V^\pi(x_t)$. This leads to the learning rule

$$\Delta w_t = \eta \delta_t \frac{dV_w(x_t)}{dw}, \quad (15)$$

where δ_t is called the temporal difference (TD) error and is given by

$$\delta_t = R_t + \gamma V_w(x_{t+1}) - V_w(x_t). \quad (16)$$

If the network that encodes the value $V_w(x)$ consists of a single neuron, say $V_w(x) = \phi(u)$ with $u = wx$, then the synaptic learning rule can be expressed as

$$\Delta w_t = \eta \delta_t \phi'(u) x_t. \quad (17)$$

As compared to the policy gradient rules above, the TD learning rule (17) is obtained by replacing the reward R in Eq. 1 with the TD- δ . Since this δ converges to zero during learning, any systematic weight drift is also suppressed.

As with all reinforcement learning, exploration of the state space is needed to find states associated with more reward or higher values. In policy gradient methods the exploration is enforced by some noise on the synapse, the neuron or the population level (or even at the level of the stimulus selection, see Vladimirov et al. 2009). In TD methods, exploration enters by a noisy action selection and hence, as compared to rules (7) or (8), the noise is implicitly present in the δ .

TD learning in the form of actor-critic has been implemented in spiking neuronal networks (Di Castro et al. 2009; Potjans et al. 2009; Potjans et al. 2011; Frémaux et al. 2013). In these implementations, separate networks for the value representation and the action selection are considered, and the synaptic strengths w in both networks are adapted based on the temporal difference δ_t (Fig. 2). An alternative to this actor-critic learning is to learn values for state-action pairs (“Q-values”) and choose actions based on these values, for instance using the softmax

policy “SARSA”; see Sutton and Barto (1998)). Because the evaluation of a value for a state-action pair in a standard neuronal implementation requires to actually choose that action, however, value evaluation in order to decide for a single next action cannot be implemented in this straightforward form.

Policy Gradient versus TD Methods Both, online policy gradient and TD learning, maximize the discounted future reward as expressed by (12) and (13). But while policy gradient methods do not require specific structures on the network or the task, TD methods do so. First, TD learning assumes an internal representation of states x . Second, the definition of the TD error involves two subsequent states, and hence, value learning requires to sample all the corresponding transitions. Third, to assign values to a state, it is implicitly assumed that the history of reaching that state does not influence future rewards. In fact, TD learning assumes that the underlying decision process is Markovian.

Gradient-based learning does not assume an internal representation of states to which values would be assigned. Neither does gradient-based learning assume Markovianity of the underlying decision process for convergence. When this decision process is not Markovian, TD learning can fail in both ways, by either choosing inappropriate actions while correctly estimating values or by incorrectly estimating the values themselves (Friedrich et al. 2011). Yet, when the decision process is Markovian, TD learning becomes faster than policy gradient learning (Frémaux et al. 2013). Note that a decision process can always be made Markovian by expanding the state-space representation and including hidden states to which again values need to be assigned. To model how the brain can create such hidden states, however, remains a challenge (Dayan and Niv 2008).

Cortical Implementations Due to their conceptual simplicity, policy gradient methods may be implemented in any cortical network that is engaged in stimulus-response associations and that receives feedback via some global

neuromodulator. TD learning was related to basal ganglia where specific networks were suggested to represent values (Daw et al. 2006; Wunderlich et al. 2012), and dopamine activity was suggested to represent the TD error δ_t (Schultz et al. 1997).

Both policy gradient and TD learning are considered as model-free, although TD learning makes use of some information about the underlying model. If more information is included such as state-transition probabilities, the learning can again become faster as less sampling is required to explore the reward function. TD learning methods and their extensions have in particular been proven successful in interpreting human cortical activity during decision-making tasks (for a review, see *Reward-Based Learning, Model-Based, and Model-Free*).

Cross-References

- Basal Ganglia: Decision-Making
- Decision-Making Tasks
- Reward-Based Learning, Model-Based and Model-Free
- Spike-Timing Dependent Plasticity, Learning Rules

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Relation to Unit Activity

- [Local Field Potential, Relationship to Unit Activity](#)

Relative Motion

- [Optic Flow Processing](#)

Resistivity, Axial

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Synonyms

Cytoplasmic resistivity; Intracellular resistivity; R_i (Units: Ω Cm); Specific intracellular (or cytoplasmic) resistance

Definition

The axial resistivity, R_i , is a measure of the Ohmic resistance of the intracellular medium of a neuronal process (e.g., axon or dendrite). R_i is defined as the resistance of the medium contained within a fixed-radius cylinder of unit length and unit cross-sectional area, measured between the flat ends of the cylinder. The most commonly used units are Ω cm, in which case the dimensions of the cylinder are in cm. For neurons, R_i is typically on the order of 100 Ω cm.

Detailed Description

Explanation of the Units

R_i is a specific property of the intracellular medium that should not depend on the dimensions of the cylinder across which it is measured. If the length of the unit cylinder is increased to length L cm, then the total resistance, R_T , measured from one end of the cylinder to the other increases to $R_i L$, because current needs to flow through a greater length of resistive medium. On the other hand, if the radius of the cylinder is increased to a cm, the cross-sectional area of the cylinder becomes πa^2 and R_T decreases to $R_i / \pi a^2$. Intuitively, this is because a larger cross-sectional area provides more parallel pathways for current to flow through the resistive medium, reducing the total resistance. Hence, combining changes to both dimensions of the cylinder, the total resistance R_T (Ω) is given by

$$R_T = R_i L / \pi a^2$$

Because L and a have units of cm, in order to get the correct units of Ω for R_T , the axial resistivity R_i must have the units Ω cm.

Determinants of R_i

It is generally thought that R_i is determined by the presence of mobile ions, mainly monovalent cations (dominated by K^+), that can move freely through the aqueous gel that forms the cytoplasm (Jack et al. 1983). Free diffusion of intracellular ions ensures that R_i is purely Ohmic, as has been confirmed in classic experiments in axons (Hodgkin and Rushton 1946; Hodgkin and Keynes 1953). For technical reasons, R_i is difficult to measure accurately in neurons, leading to variable estimates, particularly in dendrites (Major et al. 1994; Stuart and Spruston 1998; Roth and Häusser 2001). Neuronal modeling typically uses values of R_i in the range 50–400 Ω cm. Recent work has hinted that R_i may be nonuniform and activity-dependent, perhaps because of the plugging of the lumen by the accumulation of

intracellular organelles (Bloodgood and Sabatini 2005; Bekkers 2011).

Applications of R_i

R_i is one of the three fundamental electrical parameters that occur in linear cable theory, the other two being R_m (specific membrane resistance; units $\Omega \text{ cm}^2$) and C_m (specific membrane capacitance; units $\mu\text{F}/\text{cm}^2$). In computational neuroscience, it is usually assumed that intracellular current flow is purely axial, that is, there is negligible radial current. This is achieved if the radius (a) of the cylinder is small compared to its length and if $R_m \gg R_i$. Both of these conditions are generally satisfied in neurons. R_i , together with R_m , appears in an important parameter in linear cable theory, the space constant (or length constant) λ , given by $\lambda = \sqrt{aR_m/2R_i}$. The space constant is a measure of how far current can flow axially without leaking out across the membrane. Intuitively, λ is inversely related to R_i because a lower R_i means it is easier for current to flow axially than to leak out.

Cross-References

- [Cable Equation](#)
- [Electrotonic Length, Formulas and Estimates](#)
- [Space \(Length\) Constant, Lambda, in Neuronal Signaling](#)

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Resistivity/Conductivity of Extracellular Medium

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Synonyms

[Tissue conductivity](#); [Tissue impedance](#); [Tissue resistivity](#)

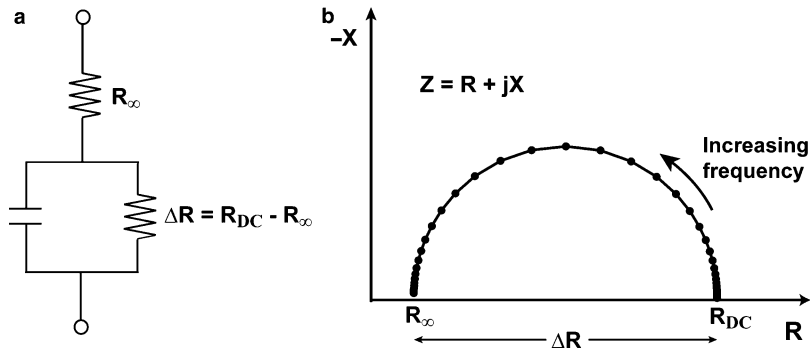
Definition

The electrical properties of neural tissue describe how an applied electric field (e.g., biopotentials or electrical stimulation) propagates through the tissue. The complex nature of neural tissue leads to frequency-dependent, inhomogeneous, and anisotropic electrical properties within the tissue.

Detailed Description

Introduction

Electrical properties of neural tissue can be described in terms of electrical impedance. Electrical impedance describes the opposition to the flow



Resistivity/Conductivity of Extracellular Medium, Fig. 1 *Frequency-dependent impedance of biological tissue.* (a) The impedance of biological tissues typically display resistive and capacitive properties. The circuit model in (a) represents a simplified model that has been used to characterize the impedance of biological tissue. R_{DC} represents the resistance that would be measured with direct currents, while R_{∞} represents the resistance that would be measured at extremely high frequencies (frequency $\rightarrow \infty$). (b) The resistive and capacitive properties of biological tissue produce a frequency-dependent tissue impedance. (b) Shows a standard impedance

spectrum that can be measured in biological tissue with each point representing the impedance measured at a specific frequency. The abscissa represents the real part of the impedance (i.e., resistance) while the ordinate represents the negative imaginary part of the impedance (i.e., reactance/capacitance). Tissue impedance spectrum can typically be fit to a semicircle. The example in (b) represents a spectrum with the center of the semicircle along the abscissa; however, the complex frequency-dependent properties of tissue typically cause the center of this semicircle to be shifted below the abscissa. (see McAdams and Jossinet 1995; Foster and Schwan 1996)

of an electrical current through the tissue. Electrical impedance can be a complex quantity with both real (i.e., resistive) and imaginary (i.e., reactive) components. While several studies only consider the resistive component of neural tissue, neural tissue often displays frequency-dependent electrical properties in which it is often useful to consider both the resistive and the reactive components (Fig. 1). The electrical properties and corresponding paths ions travel through the neural tissue are determined by the composition and structure of the tissue. Adequate knowledge of these electrical properties is required to understand the origin of recorded biopotentials and the effects of electrical stimulation on neural tissue.

Frequency-Dependent Behavior

Characterization of the electrical properties of biological tissues has been an intense area of study for well over a century. The main investigative tool has been electrical impedance measurements of tissue samples performed at a wide range of frequencies (Fig. 1). These impedance measurements have shown a clear reactive (i.e., capacitive)

component of biological tissue as well as frequency-dependent changes in both the resistive and reactive components of the tissue impedance. Experiments suggest that at low frequencies, ionic currents largely flow around cells through the extracellular space due to the capacitive nature of cell membranes. At high frequencies, the ionic currents can travel through cell membranes. This process, first described by Höber, is known as the beta dispersion and is largely attributed to the charging of cellular membranes (McAdams and Jossinet 1995; Foster and Schwan 1996). The term, dispersion, describes this dependence of the tissue's permittivity (i.e., capacitance) on the frequency of the applied electric field. Experimental measurements have clearly demonstrated the existence of several dispersions, such as α , β , and γ , at low radio and microwave frequencies, respectively. Detailed descriptions of the dispersions observed in biological tissues are available (see Foster and Schwan 1996). Several publications containing compilations of experimental impedance data for numerous tissue types over a wide range of frequencies are also available (Ranck 1963; Ranck and BeMent 1965; Geddes and Baker 1967; Gabriel et al. 1996a, b).

Volume Conduction of Biopotentials

The frequency-dependent electrical properties of biological tissues have potential implications for both neural stimulation and recording applications. Nervous tissue is a complex environment consisting of a high density of cells and extracellular matrix materials bathed in an electrolyte-rich solution. This environment produces complex paths in which ions can travel.

One of the main reasons for the frequency-dependent electrical properties of biological tissues is the lipid bilayer structure of cell membranes. The capacitive component of cell membranes arises from charge separation that is possible across this lipid bilayer (Sperelakis 2012). Cell membranes also contain ion channels that allow for a resistive component to their impedance. Thus, the impedance of an individual cell is often represented by a parallel combination of resistance and capacitance (Sperelakis 2012). However, at sufficiently low frequencies, the cell membrane is a poor conductor relative to the surrounding electrolyte, and currents are largely limited to the extracellular space (Foster and Schwan 1996).

Although the frequency-dependent electrical properties of neural tissue have clearly been demonstrated, it is less certain how these frequency dependencies affect the volume conduction of biopotentials. There is a significant amount of theoretical and experimental evidence suggesting that the electrical properties of tissue produce a low-pass filtering effect of biopotentials (i.e., attenuation of high-frequency information) due to the capacitive nature of biological tissue (Bedard and Destexhe 2012). There are several possible biophysical properties that could produce this low-pass filtering: inhomogeneities in the biological media, polarization of passive cell membranes (i.e., glia) surrounding a particular neuron, diffusion of ions, and neuron geometry (Linden et al. 2010; Bedard and Destexhe 2012).

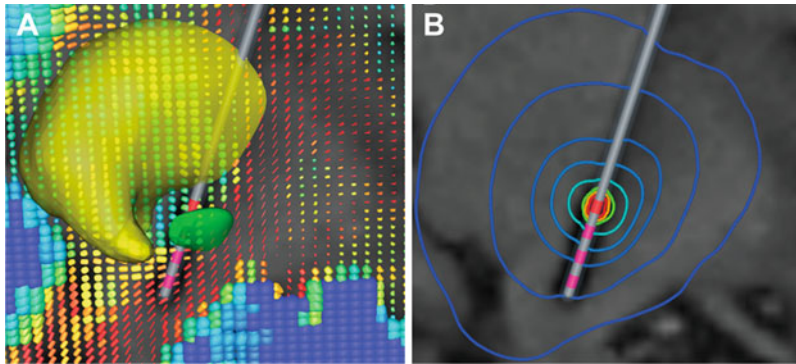
Quasi-Static Approximation

Contradictory evidence also exists suggesting frequency-independent volume conduction of

biopotentials (Plonsey and Heppner 1967; Logothetis et al. 2007; Bosetti et al. 2008; Kajikawa and Schroeder 2011). Frequency-independent signal propagation suggests that the resistivity of the tissue dominates and the tissue can be assumed to behave “quasi-statically” (Plonsey and Heppner 1967). By ignoring capacitive, inductive, and wave propagation effects, the quasi-static approximation leads to a major simplification in Maxwell’s equations for use in the analysis and modeling of biological signals (Plonsey and Heppner 1967). Applications exploiting the quasi-static approximation include theoretical analysis of neural stimulation (e.g., deep brain stimulation, transcranial direct current stimulation), theoretical analysis of neural recordings (e.g., action potential recordings, local field potential recordings), and inverse solution/source localization methods (e.g., current-source density analysis) (Mitzdorf 1985; Moffitt and McIntyre 2005; Miranda et al. 2006; Nunez and Srinivasan 2006; Bosetti et al. 2008; Chaturvedi et al. 2010; Lempka et al. 2011; Buzsaki et al. 2012; Lempka and McIntyre 2013).

Tissue Inhomogeneities/Anisotropies

It is also important to note that the structure of the nervous system can produce significant inhomogeneities and anisotropies in its electrical properties. For example, gray and white matter display significant differences in resistivity (Geddes and Baker 1967). The structural organization of white matter produces a high degree of anisotropy (i.e., directionally dependent tissue impedance). Ionic currents traveling parallel to the orientation of the axons experience a lower resistivity relative to the ion currents traveling perpendicular to the axons (Ranck and BeMent 1965). The development of diffusion-weighted magnetic resonance imaging (MRI) has allowed for estimation of the tissue conductivity tensor from the water self-diffusion tensor (Tuch et al. 2001). This discovery has allowed for the development of volume conductor models incorporating detailed tissue inhomogeneities and



Resistivity/Conductivity of Extracellular Medium, Fig. 2 *Tissue anisotropies and inhomogeneities.* The complex structure of neural tissue often results in various anisotropies and inhomogeneities that affect its conductivity profile. It is now possible to use diffusion-weighted MRI to estimate these complexities. The images above illustrate a model of deep brain stimulation (DBS) (yellow volume = thalamus; green volume = subthalamic nucleus) (see Chaturvedi et al. 2010). (a) Individual tensors are displayed as ellipsoids with the color representing the fractional anisotropy (blue = 0; red = 1) and the shape describing both the direction and magnitude of water

diffusion (spherical = isotropic; cylindrical = anisotropic). The red cylindrical tensors show a high degree of anisotropy that is typical of white matter and correspond to the internal capsule. The spherical blue tensors are typical of gray matter. (b) Isolines illustrating the theoretical voltage distribution generated during stimulation from a DBS electrode (blue = low voltage, red = high voltage). This image shows that the complex tissue structure of the brain may lead to an asymmetric voltage distribution during electrical stimulation. (Reproduced from Chaturvedi et al. (2010) with permission from Elsevier)

anisotropies (Fig. 2) (McIntyre et al. 2004; Chaturvedi et al. 2010).

Significance/Implications/Conclusion

The structure and organization of nervous tissue produce complex electrical properties that need to be considered in neural stimulation and recording applications. Inhomogeneous and anisotropic properties can affect the degree and direction of volume conduction. It is also not always clear if potentials propagate through neural tissue in a frequency-dependent or quasi-static manner. Characterization of the electrical properties of biological tissue still remains an active area of research, and only with an adequate knowledge of these properties can we understand the origin of biopotentials and the effects of electrical stimulation on neural tissue.

Cross-References

► [Local Field Potentials: Interaction with the Extracellular Medium](#)

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Respiratory Electrical Stimulation

- [Peripheral Nerve Interface Applications, Respiratory Pacing](#)

Response Planning

- [Decision-Making, Motor Planning](#)

Response Selection

- [Decision-Making, Motor Planning](#)

Retina Chip

- [Visual Prosthesis, Subretinal Devices](#)

Retinal Chip

- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)

Retinal Disease and Remodeling

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Definition

Retinal remodeling is a collection of pathologic changes in the structure and function of the neural retina triggered by photoreceptor degenerations.

Detailed Description

Diseases That Cause Retinal Remodeling

Retinal remodeling is initiated by inherited gene defects and gene-risk coupled environmental stressors that lead to photoreceptor degeneration (Jones et al. 2003, 2012; Marc et al. 2003), e.g.,

retinitis pigmentosa (RP) and macular degeneration (AMD). Over 100 gene loci are associated with RP-like degenerations (Daiger and Sullivan 2013). Most RP-like degenerations directly affect rods, leaving many cones intact. Rod death can, however, trigger extensive bystander killing of cones. These different effects have been classified as *cone sparing* and *cone decimating* (Marc et al. 2007). After photoreceptor death, the surviving retina progressively changes form and signaling properties. Remodeling progression depends on the nature of the primary degeneration. Recessive RP often triggers rapid remodeling. Slower autosomal dominant RP may take a year or two to deplete photoreceptors and trigger remodeling in experimental animals and many years in humans. Decades of advanced RP or AMD generate severely remodeled zones in humans (Jones et al. 2003, 2012).

Remodeling Phases

Remodeling occurs in phases (Marc et al. 2003, 2007). In phase I, stressed photoreceptors retract or extend their synaptic terminals, disrupting connectivity with their target bipolar and horizontal cells. In phase II, photoreceptor cell death and ablation of the outer nuclear layer lead to extensive bipolar cell remodeling. In cone-decimating disease, all bipolar cells retract their dendrites. In cone-sparing disease, rod bipolar cells retract their dendrites from dying rods and attempt to establish sparse connections with survivor cones. After the cones die, phase III remodeling ensures with (1) glial hypertrophy and formation of a dense (non-scar) distal seal: a barrier to transport between the surviving retina and the retinal pigmented epithelium (RPE); (2) de novo neuritogenesis by survivor neurons; (3) evolution of synaptic microneuromas throughout the retina, thus scrambling networks; (4) pathologic migration of neurons to ectopic sites and occasional emigration into the choroidal space; (5) progressive neuronal cell death, with bipolar cells dying more rapidly than amacrine or ganglion cells; (6) retinal invasion and encapsulation of retinal vessels by the RPE; and (7) alterations in glial and neuronal gene expression. Most aspects of phase III are prevented in cone-sparing pathologies. Cone

survival appears key to maintaining the dendritic arbors of cone bipolar cells. However, even in cone-sparing disease, rod bipolar cells display massive dendritic remodeling, retargeting to cones, with concomitant reprogramming of their normal metabotropic ON glutamate receptors to ionotropic OFF glutamate receptors (Marc et al. 2007).

Mechanisms and Physiology of Remodeling

The mechanisms of remodeling are not yet well understood. Similar to rewiring after brain trauma, retinoic acid receptor (RAR) pathways appear necessary for de novo neuritogenesis. All elements of retinoic acid synthesis and signaling pathways are expressed in the degenerating retina, and RAR signaling inhibitors may prevent neuritogenesis (Lin et al. 2011). The mechanisms driving new synapse formation and cell migration are unknown. As the strength of photoreceptor signaling decreases in phase II, network signal-to-noise ratios decrease, with extensive light-independent spiking in retinal ganglion cells (Margolis et al. 2008). This appears partly due to spread of corruptive signals via gap junctions (Toychiev et al. 2013). Spontaneous retinal self-signaling persists well into phase III, after total loss of photoreceptors (Marc et al. 2007).

Consequences

Remodeling corrupts retinal networks, impacting the outcomes of prospective interventions such as induced pluripotent stem cell implants, fetal tissue transplants, and gene, optogenetic, photochemical, or retinal prosthetic chip therapies (Jones et al. 2012; Marc et al. 2005). There is no evidence that remodeling is interrupted by any intervention.

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Retinal Network Models

► Computational Models of Neural Retina

Retinal Neurophysiology

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Definition

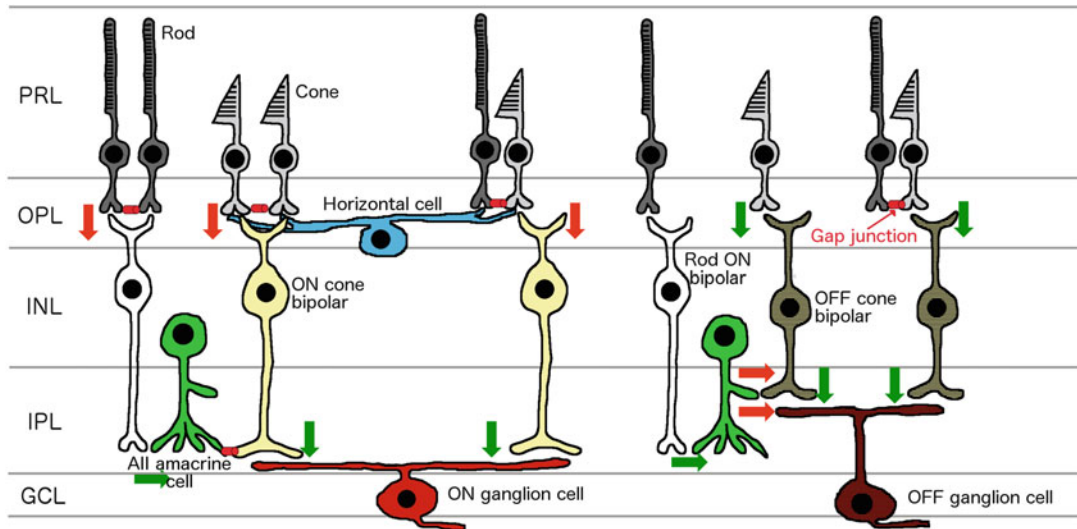
Vision is a complex, computationally demanding, perceptual task that begins at the retina, a layered sheet of tissue, 200–300 μm thick, that lines the

posterior part of the eye. The cornea and lens of the eye focus light rays onto the retina, leading to the activation of photoreceptors located in the back of the retina. The photoreceptors are one of the five major classes of neurons in the retina, the other four being bipolar cells, horizontal cells, amacrine cells, and ganglion cells, the output neurons of the retina. Within each class of neuron, there are a number of different types based on morphological and/or functional criteria, and current estimates are that in all there are more than 60 different cell types in the mammalian retina (Masland 2012).

Detailed Description

The photoreceptor layer (PRL), shown in Fig. 1, comprises two classes of photoreceptor, rods and cones. Rods are highly sensitive and primarily operate under low light conditions. Cones are less sensitive, but highly adaptive, operating over a vast range of light intensities. The human retina contains three types of cone (but only one type of rod), short (S), middle (M), and long (L) wavelength cones that are maximally sensitive to light of varying wavelengths (420 nm, 530 nm, and 560 nm, respectively) allowing for trichromatic color vision.

Photoreceptors convey their light information to bipolar cells of which there are 10–12 types. This signal transfer occurs in the outer plexiform layer (OPL) where this signal can also be modulated by laterally situated horizontal cells. Two main functional classes of bipolar cells exist in the mammalian retina: those that depolarize in response to a “light on” signal from photoreceptors, ON bipolars, and those that hyperpolarize, OFF bipolars. This organization is thought to function to make small changes in irradiance more conspicuous and to segment contrast polarity (increasing or decreasing irradiance) for the purposes of perception (Westheimer 2007). Bipolar cells (and photoreceptors) generally encode light information by graded changes in membrane potential rather than produce action potentials (Morgans 2000). This means light intensities can be reported, at this early stage of light signaling, continuously in an analogue fashion, before the



Retinal Neurophysiology, Fig. 1 Light pathways through the retina. Light hyperpolarizes both rod and cone photoreceptors. They transfer this signal via either a sign-conserving (green arrow) or sign-inverting (red arrow) chemical synapse. Cone signals pass to depolarizing ON or hyperpolarizing OFF bipolar cells and then to ON and OFF ganglion cells, respectively.

Rod signals are passed to depolarizing ON rod bipolar cells to All amacrine cells where they subsequently enter the cone circuitry via gap junctions (red tube) to cone ON bipolars or to cone OFF bipolars via inhibitory synapses. Alternatively, rod signals can be passed directly to cones via rod/cone gap junctions where they enter the cone circuitry at an earlier stage

signal is processed by the retinal circuitry and digitally encoded into a train of action potentials in the retinal ganglion cells (RGCs).

Cone photoreceptors form synapses with both ON and OFF bipolar cells, whereas rods primarily form synapses only with ON rod bipolars (Wässle and Boycott 1991). Figure 1 summarizes the flow of light information from rods and cones to RGCs. Both ON and OFF cone bipolar cells synapse directly onto RGCs in different layers of the inner plexiform layer (IPL) where they contact respective ON and OFF (or small bistratifying ON/OFF) retinal ganglion cells (RGCs). OFF bipolar cell to OFF RGC connections occur in the “OFF” lamina closest to the INL, and ON connections occur in the “ON” lamina, closer to the ganglion cell layer (GCL) (Hartveit 1997). Rod bipolar cells generally do not synapse directly onto ganglion cells; instead, they synapse onto a specific type of amacrine cell, the AII amacrine (Sharpe and Stockman 1999). These cells have been shown to subsequently infiltrate the main cone circuitry by exciting ON cone bipolar cells through electrical gap junctions and

inhibiting OFF cone bipolar cells through glycinergic synapses (Kolb and Famiglietti 1974; Muller et al. 1988). Gap junctions also exist between rods and cones (and between rod/rod and cone/cone), providing another avenue for rod signals to reach RGCs (Sterling and Demb 2004). Other types of amacrine cells are generally situated in the IPL and are orientated horizontally. This allows these cells to greatly influence the transfer of information from bipolar cells to ganglion cells.

The output from the retina is via retinal ganglion cells (RGCs) that form the innermost neural layer of the retina. The axons of RGCs leave the eye as the optic nerve and convey visual information to the brain regions in the form of action potentials. In the primate retina, there are more than 15 morphologically distinct RGCs; however, two types make up the greatest proportion of RGCs: parasol RGCs (alpha cells are the homologue in cat retina) make up about 5% of all ganglion cells, and midget RGCs (beta cells are the homologue in cat retina), about 70–80% of all ganglion cells (Dacey 2004; Wässle 2004). The

receptive field of RGCs shows a concentric organization whereby the central region of the receptive field is enclosed by an antagonistic surround: producing RGCs with an ON center/OFF surround and OFF center and ON surround, depending on their pattern of connectivity with bipolar cells in the IPL. This classical description of the RGC receptive field organization has recently been shown to be much more dynamic than previously thought (see Masland 2012). In addition to the ON/OFF response classification, many midget RGCs also display a chromatic contrast sensitivity, with the receptive field centers and surrounds receiving input from either M or L cones/bipolar cells, underpinning the red/green opponent pathway. The small bistratified RGCs receive chromatic input from S cones and a combined M + L cone input, underpinning the blue/yellow opponent pathway (Martin 1998). The midget RGCs respond best to higher spatial frequencies and lower temporal frequencies and display high chromatic contrast sensitivity. Parasol RGCs on the other hand are most responsive to lower spatial frequencies, to higher temporal frequencies, and to differences in retinal luminance. Midget, parasol, and small bistratified RGCs make up approximately 80% of the RGC population in the primate retina. The function of many of the RGCs that make up the remaining 20% remains largely unknown. One such RGC type that constitutes less than 1% of RGCs in the primate retina (Dacey et al. 2005) is intrinsically light sensitive and has been shown only recently to contain the photopigment melanopsin (Berson 2003). These RGCs are thought to play a significant role in circadian rhythms and the pupillary light reflex, as well as a variety of other non-image-forming functions, and are now thought to contribute to perceptual vision (Lucas 2013).

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Retinal Prosthesis

- [Vision Prosthesis](#)
- [Visual Prosthesis, Epiretinal Devices](#)
- [Visual Prosthesis, Subretinal Devices](#)

Retinal Waves, Models of

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Definition

The developing retina displays spontaneous activity characterized by correlated, propagating activity

patterns (Wong 1999; Blankenship and Feller 2010). Retinal waves are hypothesized to provide cues for the development of retinal receptive fields and projections from the retina to higher visual brain areas (Sernagor et al. 2001; Torborg and Feller 2005). Several computational models have been developed to simulate retinal waves, which have helped to shed light on the mechanisms involved in their generation (Godfrey and Eglen 2009). Two different approaches have been used in these models; they simulate networks either as cellular automata or using biophysical neurons models. These models also provide tools for generating synthetic activity to investigate the role of retinal waves in models of visual system development.

Detailed Description

Since their discovery in 1988 (Galli and Maffei 1988; Wong et al. 1993), there has been intensive research into the mechanisms underlying retinal waves using both experimental and computational approaches. Retinal waves undergo several major developmental changes. Each stage has a different pharmacological profile, indicating that the network activity is supported by different pathways and transmitter systems (Blankenship and Feller 2010). Efforts to model retinal waves have so far exclusively focused on acetylcholine-dependent waves during early developmental stages because these are experimentally the best understood.

Refractoriness as a Central Mechanism

The first key insight came from a model by Feller et al. (1997) and Butts et al. (1999). This work was based on the following four assumptions, which were subsequently each confirmed experimentally:

1. Waves are initiated by cell-autonomous, spontaneous activity in cholinergic amacrine cells.
2. Neural activity propagates laterally in a recurrently connected network of amacrine cells through excitatory synapses (Fig. 1a).
3. Activity drives amacrine cells into a long-lasting refractory state, which restricts the

propagation of subsequent wave into regions of non-refractory neurons (Fig. 1b–d).

4. Retinal ganglion cells read out the wave activity from the starburst amacrine cells and transmit it to higher areas in the visual system (Fig. 1a)

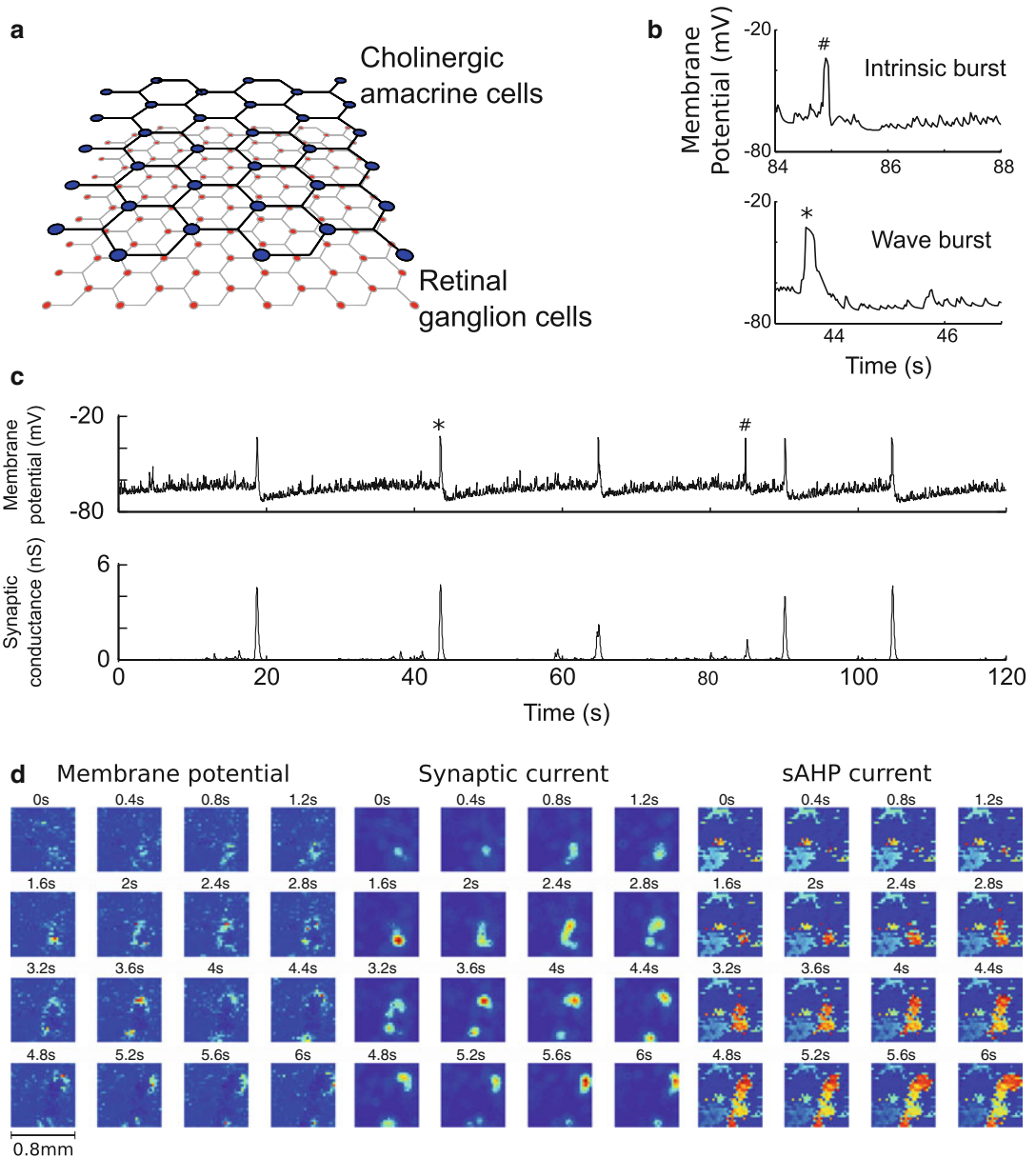
This model, implemented as a cellular automaton with simple threshold units, produces propagating, wavelike activity patterns in the simulated ganglion cell layer replicating several properties of retinal waves. In particular, it was able to reproduce the two hallmark properties of cholinergic waves: subsequent waves are nonoverlapping, and the whole retina is uniformly covered by waves over time. The model could be tuned such that the simulated wave size and frequency distributions closely matched those recorded from the ferret retina with calcium imaging.

Butts and Feller showed that a refractory mechanism is sufficient to control the spatiotemporal propagation of activity in this otherwise purely excitatory recurrent network. Only non-refractory regions on the retina can be invaded by an active wave, so the recent history of activity limits the spreading of activity. This prediction is consistent with later data from patch clamp recordings from starburst amacrine cells showing that a slow after-hyperpolarization (sAHP, Fig. 1b) conductance constitutes a strong, cell-intrinsic refractory mechanism (Zheng et al. 2006).

A problematic assumption in this model was that ganglion cells had to filter the more random amacrine cell activity to produce spatiotemporally compact waves, while paired recordings later demonstrated that amacrine and ganglion cell activities are tightly correlated (Zheng et al. 2006). This indicates that the spatiotemporal properties of cholinergic waves are already present in the amacrine cell network.

Activity-Dependent Refractoriness

The fact that the main properties of retinal waves are already present in the network of cholinergic amacrine cells and are primarily inherited by



Retinal Waves, Models of, Fig. 1 Illustration of simulated cholinergic retinal waves with the model by Hennig et al. (2009). (a), Schematic view of the network architecture generating retinal waves. Neural activity is spontaneously generated in cholinergic amacrine cells and propagates laterally across the network. Retinal ganglion cells receive excitatory input from amacrine cells and read out their activity. (b), Spontaneous events (top) and events triggered by synaptic input during waves (bottom) cause large Ca^{2+} spikes in amacrine cells. These spikes subsequently activate a slow afterhyperpolarization conductance, which puts neurons into a long-lasting refractory state.

Wave events cause a stronger activation, which recovers more slowly than intrinsic, spontaneous spikes. (c), Simulated network activity exhibits a mix of synaptically driven spikes and spontaneous intrinsic events. The former synchronize the network through strong synaptic currents (bottom), while the latter desynchronize the network through refractoriness. (d), A simulated wave event. Propagation of activity is seen in the membrane potential (left) and the synaptic currents (middle). The activity leaves a trail of refractory neurons. Also visible are other refractory regions from preceding activity, which cannot be invaded by the current wave

ganglion cells was addressed in a more recent model by Godfrey and Swindale (2007). It was again implemented as a cellular automaton, and it incorporated new findings on cholinergic amacrine cell physiology (Zheng et al. 2006). While overall very similar to the model by Feller et al. (1997), it was assumed that the duration of the refractory state of amacrine cells depends on the amount of synaptic input received (Fig. 1b). Stronger input then causes stronger activation of the refractory mechanism, and a linear relaxation function ensures that such differences in activation result in pronounced differences in recovery time. As a result, the refractory state of amacrine cells in the center of waves lasts longer than near wave boundaries, introducing a further dependence on the previous history of excitation. This model could reproduce typical wave size and frequency distributions from a range of species, as measured by calcium imaging, without requiring the filtering of amacrine cell activity by the ganglion cells. It also suggested that the network producing retinal waves may have chaotic dynamics.

Between Local and Global Functional Connectedness

To better reproduce data from patch clamp recordings (Zheng et al. 2006), a study by Hennig et al. (2009) provided a biophysically plausible model of retinal waves. Cholinergic amacrine cells were implemented as Morris-Lecar-type models that produce prolonged calcium channel-mediated bursts in response to depolarization (Fig. 1b–d). Bursts are then triggered either by a cell-intrinsic noise source or by multiple sources of synaptic input from neighboring neurons. Importantly, in this model only the latter events cause sufficient transmitter release and then also trigger bursts in connected neurons.

This model also placed a refractory mechanism, implemented as a calcium-dependent sAHP conductance, at the heart of the regulation of propagating activity (Fig. 1b). Critically, it was assumed that the sAHP was activated on two different time scales, which

reproduced an activity-dependent refractoriness similar to that in the Godfrey and Swindale (2007) model. Simulations showed that this multi-scale refractory mechanism can desynchronize network activity while maintaining spatially correlated activity typical for cholinergic retinal waves.

Thus, the network can be set up to operate either in a highly correlated regime, where most waves spread across the whole retina, or in a strongly decorrelated regime, where activity can only propagate over small distances. The transition point between these two states corresponds to a continuous (second-order) percolation phase transition, where wave sizes and durations assume power law distributions (Ódor 2004). An analysis of multielectrode array recordings of waves from turtle and mouse retina indicated that cholinergic retinal waves indeed show the scale-free properties that characterize the network state near the phase transition.

The idea that retinal waves may result from dynamics close to a percolation phase transition was also formulated by Albert et al. (2008), who showed that such patterns can be used to train receptive fields similar to those found in visual cortex. This behavior resembles neural avalanches observed in a range of preparations (Plenz and Thiagarajan 2007; Beggs and Timme 2012). A common feature of this form of activity is that it contains events on all length scales, which are unbiased with respect to scale or sequence and as such resemble lower-order natural image statistics.

Summary

The existing models of cholinergic retinal waves provide satisfactory explanations for the mechanisms responsible for their generation and propagation. More recent experimental work should make it possible to implement models for other developmental stages, such as early waves mediated by gap junctions and late waves that depend on extrasynaptic glutamate diffusion (Blankenship and Feller 2010). In particular for the latter, the precise mechanisms and network connectivity are still under investigation, and models can help to

uncover these factors. It is also worth noting that the mechanisms investigated in these models are based on fairly generic properties of neurons and therefore potentially also relevant in other areas of the nervous system, which also show spontaneous activity during development (Blankenship and Feller 2010).

Cross-References

- [Computational Models of Neural Retina](#)
- [Cortical Maps, Activity-Dependent Development](#)
- [Retinal Neurophysiology](#)
- [Retinotopic Development, Models of](#)
- [Spontaneous Activity, Models of](#)

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Retinocollicular Development

- [Retinotopic Development, Models of](#)

Retinogeniculate Development

- [Retinotopic Development, Models of](#)

Retinotopic Development, Models of

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Synonyms

[Neural map formation](#); [Retinocollicular development](#); [Retinogeniculate development](#); [Topographic map formation](#)

Definition

Axons of neighboring retinal ganglion cells (RGCs) coming from the eye normally terminate in neighboring parts of target brain regions, such as the optic tectum of amphibians or the superior colliculus (SC) and lateral geniculate nucleus of

mammals. This orderly arrangement of connections is termed a retinotopic map. Theoretical models of retinotopic map formation help us understand how these connections develop in early life and how maps might reform after surgical or experimental manipulations.

Detailed Description

What Is a Retinotopic Map?

A projection of connections is termed a topographic map when neighboring neurons in the source region project to neighboring regions in the target. Topographic maps are found in many sensory systems. Perhaps the most-studied topographic map is the projection from the retina to primary targets in the brain, which ensures that the overall layout of the visual image is preserved as it is sent to the brain (Fig. 1). Topographic maps in the visual system are often termed retinotopic maps.

In principle a topographic map can emerge through *local* interactions between neighboring neurons (Willshaw and von der Malsburg 1976). However, local mechanisms alone cannot generate the *global* order observed in maps, whereby one region of the retina consistently projects to the

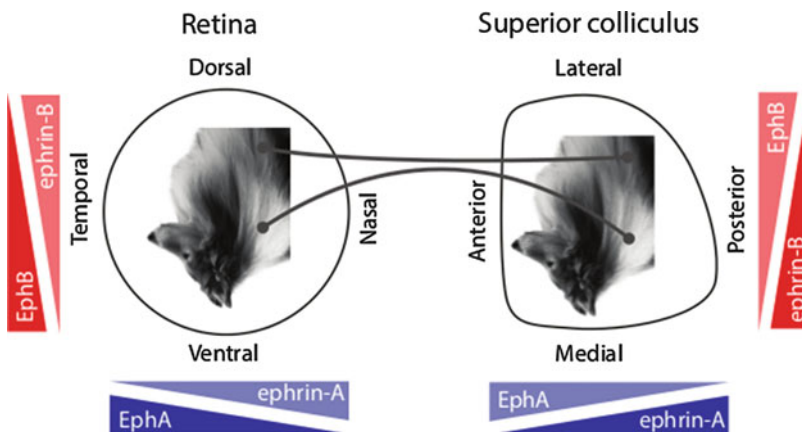
same region of the target in different animals. For example, in mouse, neurons in the temporal retina consistently project to anterior SC (Fig. 1). Hence, retinotopic maps contain both local and global order.

Mechanisms of Map Formation

Here I describe three key mechanisms proposed to drive the formation of retinotopic maps (Cang and Feldheim 2013).

Molecular Gradients

Early experiments into regrowth of retinal axons following surgical manipulations suggested that RGCs tended to regrow to predefined target locations (Sperry 1963). Sperry therefore proposed that neurons in the retina and target had unique molecular labels that encoded this preference (Sperry 1963). The abilities of such molecular labels to establish retinotopic maps were established computationally by von der Malsburg and Willshaw (1977), long before any molecular cues had been discovered. The first molecular cues identified were the Eph receptor and ephrin ligand families (Drescher et al. 1997). These proteins are distributed across the retina in a graded fashion (Fig. 1) such that neighboring neurons in the retina or target express similar



Retinotopic Development, Models of, Fig. 1 The retinotopic map in the mouse ensures that the retinal image is preserved as it projects to the superior colliculus (SC). *Dark red* and *blue* triangles denote the relative expression levels of Ephs and ephrins in the retina

and SC (see “Molecular Gradients”). Lighter triangles indicate counter-gradients. (Figure adapted from Sterratt and Hjorth (2013) with permission from Cambridge University Press)

levels of these proteins, and there is a consistent bias (e.g., EphA receptor is always highest in the temporal retina).

The mouse visual pathway contains two gradient families, the A system and the B system, across the two axes of the retina and target. The A system is repulsive: temporal RGCs have high levels of EphA and terminate in anterior SC, where ephrin-A levels are lowest. Nasal RGCs have low levels of EphA and terminate in posterior SC, where ephrin-A levels are highest. By contrast, the EphB system is attractive, such that the ventral retina (with high levels of EphB) projects to medial SC (with high levels of ephrin-B). Cross talk between A and B systems, counter-gradients (Fig. 1), and other proteins may also contribute to map formation (Cang and Feldheim 2013). Molecular gradients thus provide both local order (neighboring neurons express similar protein levels) and global order (gradient directions are consistent between animals). A recent computational modeling study has evaluated different hypotheses by which these gradients might contribute to map formation (Triplett et al. 2011).

Spontaneous Neuronal Activity

The pioneering model of Willshaw and von der Malsburg (1976) proposed that correlated activity in neighboring RGCs could provide appropriate cues for the development of ordered maps. Experimental evidence for such patterned activity came 14 years later (Maffei and Galli-Resta 1990). Early in postnatal development, before the retina is visually responsive, RGCs generate spontaneous neuronal activity. These activity patterns are often termed “retinal waves” as the activity propagates across the retina (Wong 1999). Correlated RGC activity induces correlated activity in mouse target regions (Siegel et al. 2012; Ackman et al. 2012). Hebbian-based activity-dependent refinement can adapt initially weak synapses between RGCs and SC neurons to ensure that (1) SC neurons receive inputs from coactive neighboring RGCs and (2) neighboring SC neurons receive inputs from neighboring RGCs. Activity-based refinement generates local, but not global, order (Willshaw and von der Malsburg 1976).

Competition for Resources

A third key mechanism is that of competition for limited resources. For example, SC neurons can receive only a finite amount of inputs, and RGC axons can make only a limited amount of contacts. Competition comes in many forms, which can be described by a class of mathematical structures (van Ooyen 2001). The importance of competition in map formation can be tested by altering neuronal numbers in either the retina or target. Reducing retinal cell numbers affects the maps generated in mouse, but does not alter zebrafish RGC projections (Triplett et al. 2011). Competition can also be used instead of counter-gradients to generate maps (Sterratt 2013).

Future Directions

Many computational models have been proposed for the formation of retinotopic maps (Goodhill and Xu 2005; Goodhill 2007) and show how retinotopic order might interact with the development of other map properties, such as ocular dominance or orientation preference (Swindale 1996). Recent experimental advances in mouse genetics and imaging have generated more quantitative descriptions of retinotopic maps that should help us discriminate which mechanisms are important for map formation. Our recent unpublished work suggests that no single model can yet account for all quantitative data on retinotopic map formation in mouse. It is therefore likely that new models are still needed to account for modern experimental results.

Cross-References

- Cortical Maps, Activity-Dependent Development
- Cortical Maps, Intrinsic Processes
- Hebbian Learning
- Learning Rules: Overview
- Retinal Waves, Models of
- Somatosensory Cortex: Organization
- Spike-Timing Dependent Plasticity, Learning Rules
- Topographica

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Reverse Correlation

► Spike Triggered Average

Reward-Based Learning

► Reinforcement Learning in Cortical Networks

Reward-Based Learning, Model-Based and Model-Free

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Definition

Reinforcement learning (RL) techniques are a set of solutions for optimal long-term action choice

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such that actions take into account both immediate and delayed consequences. They fall into two broad classes: model-based and model-free approaches. Model-based approaches assume an explicit model of the environment and the agent. The model describes the consequences of actions and the associated returns. From this, optimal policies can be inferred. Psychologically, model-based descriptions apply to goal-directed decisions, in which choices reflect current preferences over outcomes. Model-free approaches forget any explicit knowledge of the dynamics of the environment or the consequences of actions and evaluate how good actions are through trial-and-error learning. Model-free values underlie habitual and Pavlovian conditioned responses that are emitted reflexively when faced with certain stimuli. While model-based techniques have substantial computational demands, model-free techniques require extensive experience.

Detailed Description

Theory

Reinforcement Learning

Formally, reinforcement learning (RL; Sutton and Barto 1998) describes a type of solution to Markov decision process (MDP) problems, which are defined by a tuple $\mathcal{S}, \mathcal{A}, \mathcal{T}, \mathcal{R}, \pi$:

- $\mathcal{S}$: a set of states $s \in \mathcal{S}$.
- $\mathcal{A}$: a set of actions $a \in \mathcal{A}$.
- $\mathcal{T}(s'|s, a)$: the transition function maps each state-action pairs to a distribution over successor states s' , with $s, s' \in \mathcal{S}; a \in \mathcal{A}$ and $\sum_{s'} \mathcal{T}(s'|s, a) = 1$.
- $\mathcal{R}(s, a, s') \rightarrow r$: the reinforcement function mapping state-action-successor state triples to a scalar return r .

The goal is to determine a policy $a \leftarrow \pi(s)$ that maps each state to the action maximizing the total expected future return of actions a in state s .

$$\begin{aligned} a^* &\leftarrow \operatorname{argmax}_a Q(s, a) \text{ where } Q(s, a) \\ &= \mathbb{E} \left[\sum_{t'=0}^{\infty} r_{t'} | s, a \right] \end{aligned} \quad (1)$$

where the sum over the future returns results from the fact that choices lead both to immediate returns but also have longer-term consequences.

The sum in Eq. 1 may not be finite. For this reason, it is often replaced by the discounted total expected reward $\mathbb{E} \left[\sum_{t'=0}^{\infty} \gamma^{t'} r_{t'} | s, a \right]$ with the discount factor $0 \leq \gamma \leq 1$. The discount factor sets the relative importance of immediate and future rewards: $\gamma = 0$ means that only the next reward is considered, whereas $\gamma = 1$ considers all rewards to have equal importance no matter how far in the future they occur.

Model-Based RL

Model-based RL assumes knowledge of the transition matrix $\mathcal{T}$, the reward function $\mathcal{R}$, and the state and action spaces $\mathcal{S}, \mathcal{A}$ which define the model of the world. This means that the expectation in Eq. 1 can be written explicitly in terms of $\mathcal{T}$ and $\mathcal{R}$ as the *Bellman equation* (Bellman 1957):

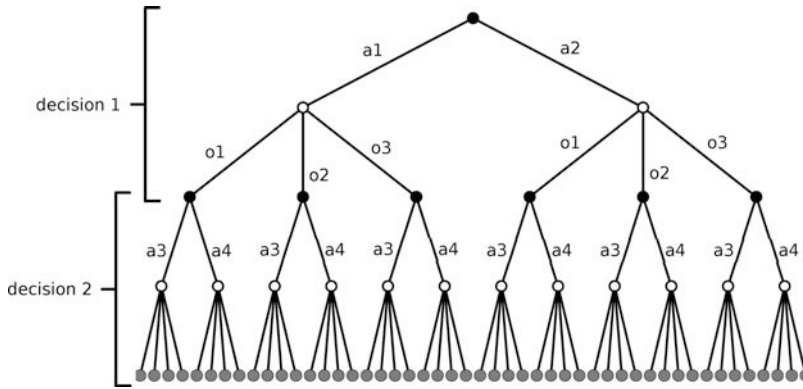
$$Q(s, a) = \sum_{s'} \mathcal{T}_{ss'}^a [\mathcal{R}(s, a, s') + V(s')] \quad (2)$$

$$\text{with } V(s') = \max_{a'} Q(s', a') \quad (3)$$

The Q value is the long-run expected return for taking action a in state s . The optimal policy maps each state to the action with the highest Q value:

$$\pi^*(s) \leftarrow \operatorname{argmax}_a Q(s, a). \quad (4)$$

Equation 3 represents a recursive definition of a decision tree of width w (determined by the number of actions $|\mathcal{A}|$ and the size of the state-space reached by these actions). The computational cost of simple tree search is $O(w^d)$ where d is the depth of the tree (see Fig. 1 for an example). Although dynamic programming methods such as policy iteration reduce this cost to $O(|\mathcal{S}|^3)$, this is still computationally prohibitive



Reward-Based Learning, Model-Based and Model-Free, Fig. 1 Example decision tree. The problem consists of first choosing between actions a1 and a2, each of which has three possible outcomes, followed by choosing between actions a3 and a4, each of which has another three possible outcomes that might depend on which

action/outcome preceded them. Actions are shown in solid black and outcomes as empty circles. Optimal action choice requires evaluation of all the branches. In this simple problem, with a sequence of two choices, each leading to three possible outcomes, the tree has width $w = 6$, depth $d = 2$, and $w^d = 36$ branches. (Adapted from Huys 2007)

for most real-life problems and additionally difficult to implement neurally as it involves matrix inversion. Psychological and neurobiological accounts of model-based RL thus emphasize sequential evaluations of decision trees.

Model-Free RL

Model-free RL methods apply to situations where agents do not know $\mathcal{T}$ and $\mathcal{R}$ where the decision trees are too complex to evaluate. They approximate the expectations in Eq. 1 by sampling from the world. *Temporal difference reinforcement learning (TDRL)* constructs estimates of state or state-action values from these samples by bootstrapping. To achieve this, the total future reward is written as the sum of the immediate reward plus the average value of the successor state:

$$\begin{aligned} \mathcal{V}^*(s) &= \mathbb{E} \left[\sum_{t=0}^{\infty} r_t | s \right] = \mathbb{E} \left[r_0 + \sum_{t=1}^{\infty} r_t | s \right] \\ &= \mathbb{E} [r_0 + \mathcal{V}^*(s') | s] \\ &= \mathbb{E} [r_0 | s] + \mathbb{E} [\mathcal{V}^*(s') | s] \end{aligned} \quad (5)$$

For approximate values $\mathcal{V}$, Eq. 5 does not hold:

$$\widehat{\mathcal{V}}(s) \neq \mathbb{E} [r_0 | s] + \mathbb{E} [\widehat{\mathcal{V}}(s') | s] \quad (6)$$

Letting the difference between the two sides be δ_t , one can arrive at correct values by iterative updates

$$\widehat{\mathcal{V}}_{i+1}(s) \leftarrow \widehat{\mathcal{V}}_i(s) + \epsilon \delta_V \quad (7)$$

with $0 \leq \epsilon \leq 1$.

TDRL combines such iterative updates with sampling. Instead of evaluating the expectations, it assumes that agents can repeatedly generate actions from their (suboptimal) policy at $a_t \sim \pi(s_t)$ and on the t 'th such interaction obtains state and reward samples from the world:

$$s_{t+1} \sim \mathcal{T}(s | s_t, a_t) \quad (8)$$

$$r_t \sim \mathcal{R}(s_t, a_t, s_{t+1}) \quad (9)$$

These samples are used to approximate the expectations, letting

$$\delta_t = r_t + \widehat{\mathcal{V}}_t(s_{t+1}) - \widehat{\mathcal{V}}_t(s_t) \quad (10)$$

$$\widehat{\mathcal{V}}_{t+1}(s_t) \leftarrow \widehat{\mathcal{V}}_t(s_t) + \epsilon \delta_t \quad (11)$$

A similar approach can be applied to learning state-action values (Watkins and Dayan 1992). Thus, while model-based RL methods

prospectively predict the consequences of actions based on an understanding of the structure of the world, model-free methods retrospectively approximate these based on past experience. Nevertheless, under certain situations, model-free methods have strong convergence guarantees (Bertsekas and Tsitsiklis 1996; Sutton and Barto 1998; Puterman 2005). Policies π are often in turn formalized as parametric functions of the value functions $\mathcal{V}$ or Q themselves, although this may break certain guarantees (Bertsekas and Tsitsiklis 1996).

One biologically important variation of a reinforcement learning algorithm is the **Actor-Critic** (Barto et al. 1983). The Critic uses TD to estimate the value $\mathcal{V}_t(s)$ for states, while the Actor maintains the policy used to select actions. After each action a_t , the Critic calculates the prediction error and sends it to the Actor. A positive prediction error indicates that the action improved the potential for future rewards, and the tendency to select the action should be increased. An example of using the prediction error is to select actions based on the Gibbs softmax method

$$\pi_t(s, a) = \frac{e^{p_t(s, a)}}{\sum_{a'} e^{p_t(s, a')}} \quad (12)$$

where $p_t(s, a)$ defines the “propensity” to take action a in state s . These propensities are updated by the prediction error $p_t(s, a) \leftarrow p_{t-1}(s, a) + \epsilon \delta_t$.

Sampling and Computational Costs

The algorithms discussed so far suffer either from catastrophic computational requirements or from equally drastic dependence on extensive sampling in realistic environments. Solutions to these drawbacks fall into four general categories: (1) subdivision into smaller subtasks (possibly each having their own subgoal; cf. Dietterich 1999; Sutton et al. 1999); (2) pruning of the decision tree (cf. Knuth and Moore 1975; Huys et al. 2012); (3) approximations (e.g., neural networks for function approximation, Sutton and Barto 1998; or (4) structured representations (Boutillier et al. 1995) and sampling techniques (Kearns and Singh 2002; Kocsis and Szepesvari 2006).

A fourth approach, the successor representation (Dayan 1993), involves rewriting Eq. 5 by observing that the total expected future rewards involve repeatedly summing over the same reward but weighted by the probability of reaching that state-action pair:

$$\begin{aligned} \mathcal{V}^\pi(s) = & \sum_a \sum_{s'} \pi(a|s) \mathcal{T}_{ss'}^a \mathcal{R}_{ss'}^a \\ & + \sum_a \pi(a|s) \sum_{s'} \mathcal{T}_{ss'}^a \sum_{a'} \pi(a'|s') \sum_{s''} \mathcal{T}_{s's''}^{a'} \mathcal{R}_{s's''}^{a'} \\ & + \dots \end{aligned} \quad (13)$$

Letting $[\mathbf{P}]_{as, s'} = \sum_a \pi(a|s) \mathcal{T}_{ss'}^a$ be the effective transitions when following policy π , we can rewrite this as

$$\begin{aligned} \mathbf{V}^\pi &= \mathbf{R} + \mathbf{P}\mathbf{R} + \mathbf{P}^2\mathbf{R} + \dots \\ &= (\mathbf{I} - \mathbf{P})^{-1}\mathbf{R} \end{aligned} \quad (14)$$

where $[\mathbf{R}]_s$ is the first sum in Eq. 13 above. That is, the values of the states are linear in the immediate rewards $\mathbf{R}$, with the weights given by $\mathbf{I} + \mathbf{P} + \mathbf{P}^2 + \mathbf{P}^3 + \dots = (\mathbf{I} - \mathbf{P})^{-1}$, which is the total time spent in each state-action pair.

The strengths of model-based and model-free computations can also be combined to offset their mutual weaknesses. In Dyna-Q (Sutton 1990), samples as in Eq. 9 are generated from the agent’s internal estimates of $\mathcal{T}$ and $\mathcal{R}$ to updating model-free values. Conversely, model-free state values can be substituted for subtrees to reduce the size of decision trees (e.g., Campbell et al. 2002).

If the states $\mathcal{S}$ are not fully observable, the problem becomes a partially observable MDP (Kaelbling et al. 1998), which presents substantial additional complexities.

Behavior

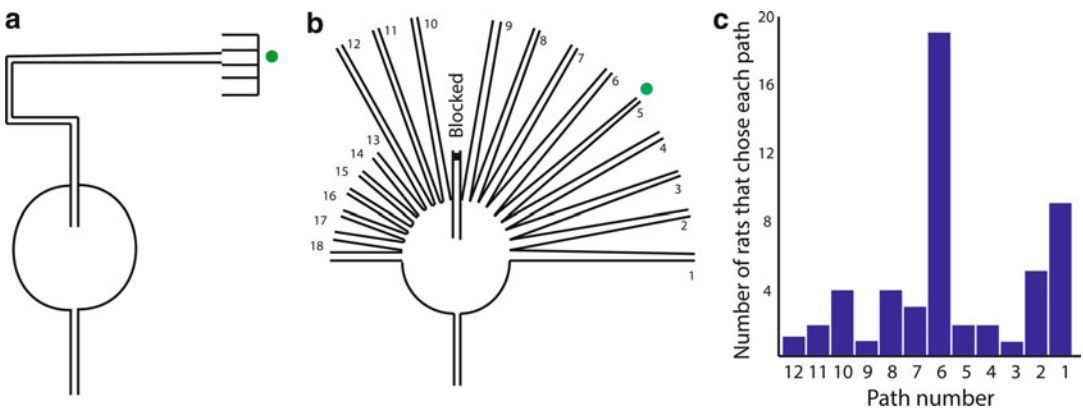
Model-based and model-free accounts of behavior were held to be incompatible for much of the last century (Hull 1943; Tolman 1948). However, key signatures of both systems can be discerned within individual animals’ (Balleine and Dickinson 1994; Killcross and Coutureau 2003; Yin et al. 2004, 2005) and humans’ (Valentin et al.

2007; Daw et al. 2011) behavior and neurobiology. These signatures reflect central differences in their utilization of information. For a discussion, see Daw et al. (2005), Dayan and Berridge (2014), and Huys et al. (2014). This is also evidence for the use of the successor representation in humans (Russek et al. 2017; Momennejad et al. 2017).

In instrumental paradigms, particular actions a are reinforced in the presence of certain stimuli or in situations s . These experiments are modelled using $Q(a, s)$ values. In Pavlovian paradigms, stimuli s lead to reinforcements independent of subjects' actions. These paradigms are modelled using stimulus values $\mathcal{V}(s)$. Importantly, there can be model-based and model-free versions of both, leading to a quartet of values $\mathcal{V}^{\text{MF}}(s)$, $\mathcal{V}^{\text{MB}}(s)$, $Q^{\text{MF}}(s, a)$ and $Q^{\text{MB}}(s, a)$. Both model-free values $\mathcal{V}^{\text{MF}}(s)$ and $Q^{\text{MF}}(s, a)$ are *scalar* representations that change *slowly*. These two features account for its key behavioral signatures (Fig. 2).

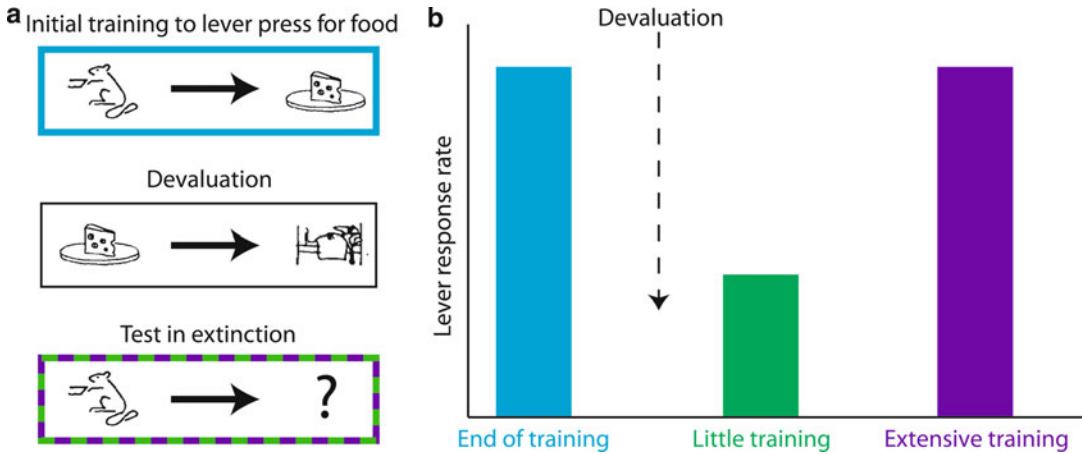
The consequences of the *scalar* nature of model-free values are most clearly seen in Pavlovian scenarios, where $\mathcal{V}^{\text{MF}}(s)$ reflect only the magnitude of reinforcements but not other aspects such as whether an action was rewarded by food or water. One paradigmatic example is blocking experiments (Kamin 1969). In these, learning the reward association of a stimulus “B” in a compound “AB” is prevented if “A” already fully predicts the reward. Then the reward is fully

predicted; no prediction error occurs. Hence, model-free values are not updated and hence no learning occurs. Thus, if the model-free system makes no prediction about certain aspects of stimuli, then shifts in these aspects should not lead to learning. In transreinforcer blocking, animals treat a reward reduction and delivery of a shock punishment as equivalent (Dickinson and Dearing 1979), arguing for a linear and unitary representation of rewards and punishments as encapsulated in the single value r in Eq. 11. In Pavlovian unblocking, animals similarly can show an insensitivity toward shifts between rewards of equal magnitude but different modality (e.g., water and food; McDannald et al. 2011), showing that only the reward value, but not its other sensory features, is encoded. As a scalar value, model-free values can, however, replace reinforcements and be approached (if positive; Dayan et al. 2006) or avoided (if negative; Guitart-Masip et al. 2011). In conditioned reinforcement experiments, behavior is motivated by stimuli associated with the rewards (i.e., having positive model-free value $\mathcal{V}^{\text{MF}}(s)$) even in the absence of the rewards themselves (Bouton 2006). This can be captured by Actor-Critic models (Barto et al. 1983). By the same argument, model-free state or stimulus values $\mathcal{V}^{\text{MF}}(s)$ can also influence the vigor with which ongoing actions are performed (Pavlovian-instrumental transfer; Huys et al. 2011). These



Reward-Based Learning, Model-Based and Model-Free, Fig. 2 Early experiment used to argue that rats can build and use spatial representations. Figure after Tolman (1948). (a) Rats were first trained to find a food source located below the green point (a light). (b) After training,

the rats were placed in the same starting position at the bottom of the maze but found their usual route blocked. Instead, they now had multiple alternative arms they could run down. (c) Histogram of arm the rats chose to run down first



Reward-Based Learning, Model-Based and Model-Free, Fig. 3 Devaluation experiments. (a) Animals are first reinforced to press a lever for a particular food for either a brief period of time or for a long period. This food is then devalued, either by satiation or by pairing with illness. Animals are then given the opportunity to press the lever again, though in the absence of any food

outcomes (in extinction). (b) After brief initial training, animals will refuse to press the lever (green bar), but after extensive training, they will press the lever (purple bar) at the same rate as at the end of training (blue bar) despite refusing to consume the food if given the opportunity. (Figure adapted from Balleine and Dickinson 1994)

three features are also central to the notion of incentive value (McClure et al. 2003).

Model-free values change slowly over time as they rely on iterative updating (Eqs. 7 and 11). The consequences of this have been mainly examined in instrumental settings (though see Schoenbaum et al. 2009; Robinson and Berridge 2013 for Pavlovian examples). The paradigmatic example is outcome devaluation (Fig. 3). On the very first trial after the devaluation, the model-free system would have had no opportunity to update the $Q^{\text{MF}}(s, a)$ values via prediction errors δ and hence would predict continued responding. Conversely, by considering the now undesired outcome of actions, model-based evaluation should lead to a reduction in lever pressing on the very first trial after the devaluation. Accounts of the shift from early model-based and goal-directed to later model-free and habitual behavior rely on their statistical properties (Daw et al. 2005) or the tradeoff between the cost of cognition and the value of improved choices (Keramati et al. 2011).

Neurobiology

The component of model-free learning best understood is the representation of the temporal

prediction error δ . Interpreting earlier work by Schultz and Romo (1990) and Montague et al. (1996) pointed out that the phasic firing of dopaminergic midbrain neurons corresponds closely to the positive portion of the prediction error δ . This has been extensively validated with single-electrode recordings (even in humans; Zaghoul et al. 2009), functional neuroimaging (D'Ardenne et al. 2008), cyclic voltammetry (Day et al. 2007), with optogenetic manipulations (Steinberg et al. 2013) and in diseases of the dopamine neurons (Frank et al. 2004). This is true both in Pavlovian (Waelti et al. 2001; Flagel et al. 2011) and instrumental scenarios (Morris et al. 2006; Roesch et al. 2007). These phasic prediction errors are not just a linear reflection of the magnitude and probability of the expected reward (Tobler et al. 2005; Bayer and Glimcher 2005) but also of the summed long-term future rewards (Schultz et al. 1997; Enomoto et al. 2011). Dopamine neurons have a low-firing baseline and therefore appear to represent the negative portion of the prediction errors δ by the length of the pause in firing (Bayer et al. 2007). Phasic firing covaries with the development of behavioral responses (Waelti et al. 2001; Flagel et al. 2011) and can causally drive learning

(Steinberg et al. 2013; Saunders et al. 2018). Furthermore, pharmacological manipulations of dopamine alter the behavioral expression of model-free vs model-based behaviors (Nelson and Killcross 2006; Wunderlich et al. 2012).

In comparison, the neural location where prediction errors are summated into model-free values is much less well understood, although multiple parts of the affective neural circuitry appear to be involved, from the ventral (Cardinal et al. 2002; Corbit and Balleine 2011; McDannald et al. 2011) and dorsal portions of the striatum (Yin et al. 2004, 2005), the ventromedial prefrontal cortex (Killcross and Coutureau 2003; Smith and Graybiel 2013), to the amygdala (Corbit and Balleine 2005).

Similarly, the neural bases of the model-based system are also poorly understood. Depending on the nature of the structure represented in $\mathcal{T}$, different neural substrates will be required. Hence, there is a priori no reason to expect a unitary representation of a single model-based system. However, particular features of the system can probably be pinpointed. For instance, learning about a stimulus-stimulus transition matrix recruits the posterior parietal cortex (Gläscher et al. 2010), while model-based expectations of stimulus value involve the ventromedial prefrontal cortex (Hampton et al. 2006; Schoenbaum et al. 2009). Recordings from spatial navigation tasks in the rodent hippocampus are so far unique in yielding direct neural evidence of the implementation of sequential tree search (Johnson and Redish 2007; Pfeiffer and Foster 2013).

Psychopathology

Given the representation of a key model-free component by dopaminergic neurons, pathological excesses of dopamine have been suggested to involve a shift from model-based toward model-free decision-making (Redish et al. 2008; Robbins et al. 2012; Huys et al. 2014). This has been clearly demonstrated in laboratory animals (Dickinson et al. 2000; Nelson and Killcross 2006), though data in humans has been less clear-cut (Voon et al. 2015; Sebold et al. 2017; Nebe et al. 2017). Similar arguments have been made about other disorders with a striatal component, particularly obsessive-

compulsive disorders (Gillan et al. 2011, 2016), and models incorporating additional neurobiological details about the striatum can account for some of the choice patterns seen in Parkinson's disease, ADHD, and Tourette's (Maia and Frank 2011).

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RF Modeling

► Receptive Field Modeling

Rhythm Generation in Embryonic Chick Spinal Cord

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Definition

Early in development, vertebrate neural networks become spontaneously active in the absence of sensory inputs. Their activity is episodic and differs from the activity that will take place in the fully mature, functional network. In the isolated chick spinal cord preparation, episodic activity starts at embryonic day (E) 4 and lasts about 10 days. At E4, it is characterized by one short bout of synchronous activity along the ventral spinal cord occurring every 2 min. By E10, episodes can last over a minute and are comprised of several cycles of activity. Many different developing networks also produce episodic activity; this activity plays an important role in the maturity of the synaptic networks in which it is expressed (Blankenship and Feller 2010; O'Donovan 1999).

Detailed Description

Spontaneous network activity was first observed behaviorally as embryonic motility (Preyer 1937). This spinally generated activity occurs in bouts separated by periods of quiescence. Experimental isolation of the chick spinal cord for experimental studies was an important step in understanding the mechanisms that generate spontaneous episodic activity. The activity produced by the spinal cord *in vitro* resembles the activity observed *in ovo* but is more regular (Fig. 1).

In the functionally mature spinal cord of lamprey and *Xenopus* embryos, highly organized motor circuits (► [Rhythm Generation in Young *Xenopus* Tadpoles](#)) produce rhythmic activity

patterns thanks to “pacemaker” (oscillatory) neurons or reciprocal synaptic inhibition between groups of neurons. In the embryonic chick spinal cord, however, no particular circuit architecture is necessary to generate rhythmic episodes (Ho and O'Donovan 1993). Episodic activity is not dependent on pacemaker cells, and synaptic connections are all functionally excitatory at these early stages of development (Chub and O'Donovan 1998). This purely excitatory connectivity generates episodes of activity, which are thought to terminate due to an activity-dependent decrease in synaptic strength, which then recovers in the interepisode interval (Fedirchuk et al. 1999). The model described below shows that excitatory connectivity with slow synaptic depression can reproduce realistic episodic activity.

A Model of the Mean Network Activity

Because connectivity pattern appears to be unimportant, and because neurons are all active together, we only consider the average network activity, a (Fig. 2).

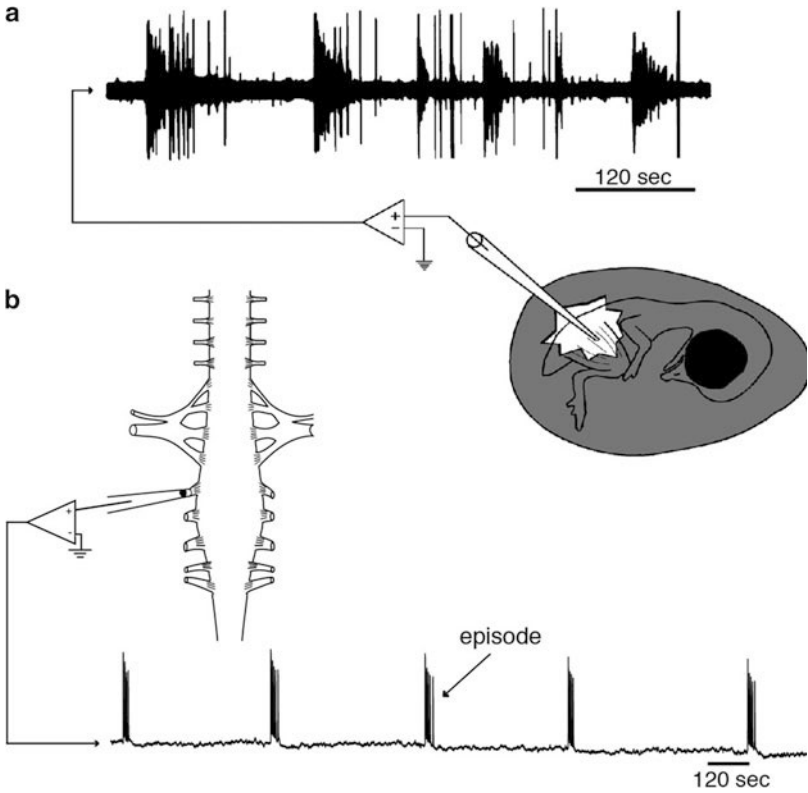
The equation describing the variations of activity is

$$\tau \frac{da}{dt} = -a + a_{\infty}(w s a - \theta_0)$$

where a_{∞} is a sigmoidal input/output function, continuously increasing from 0 (all neurons are silent) to 1 (all neurons are active). Parameter w measures network connectivity and θ_0 represents the amount of input necessary to make half the neurons active. This equation means that activity will reach a_{∞} with a time constant τ_a that sets the timescale for network integration of synaptic inputs. The term $w s a$ represents positive feedback with gain $w s$, due to the excitatory connections that inject activity back as input to the network (Fig. 2). Finally, s is a slow variable (timescale minutes) that represents activity-dependent synaptic depression. When activity is high, s decreases so the positive feedback gain is reduced. Variations of s are described by

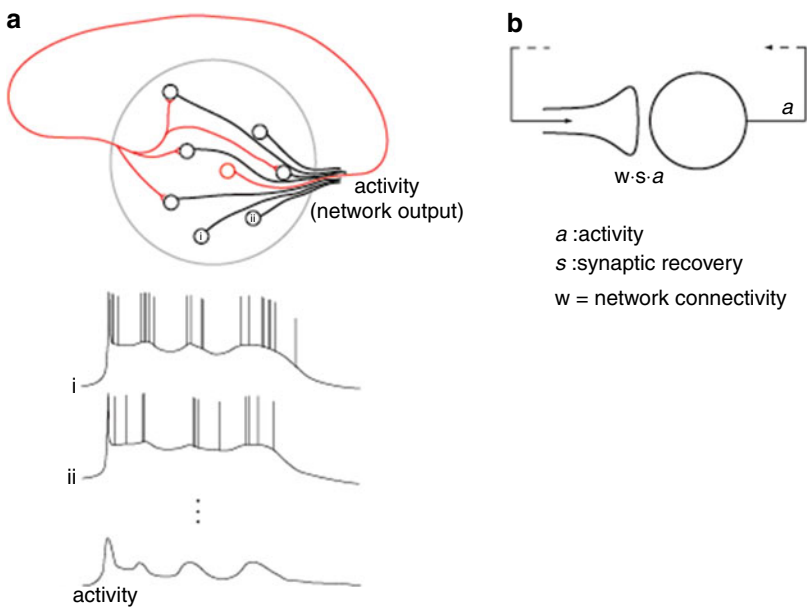
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Fig. 1 Spontaneous motor activity in developing chick. **(a)** Electrical activity recorded in ovo from a muscle. The activity occurs in bouts. **(b)** Electrical activity recorded from an E8 spinal cord *in vitro*. Activity episodes occur regularly



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Fig. 2 Model structure. **(a)** Neurons are active together, but with different spike times, so their averaged activity (*bottom trace*) is a good indicator of global activity. **(b)** Activity as network output is injected back into the network due to the recurrent connectivity (shown in **a**). The gain of this positive feedback loop is $w s$



$$\tau_s \frac{ds}{dt} = -s + s_\infty(a)$$

where s_∞ is a decreasing function of a and $\tau_s \gg \tau_a$. One synaptic depression process operating on the minute timescale of s is the extrusion of Cl^- ions from neuronal somas and dendrites during episodes of activity (Chub and O'Donovan 2001; Marchetti et al. 2005). Cl^- extrusion weakens synaptic strength by decreasing postsynaptic excitatory currents.

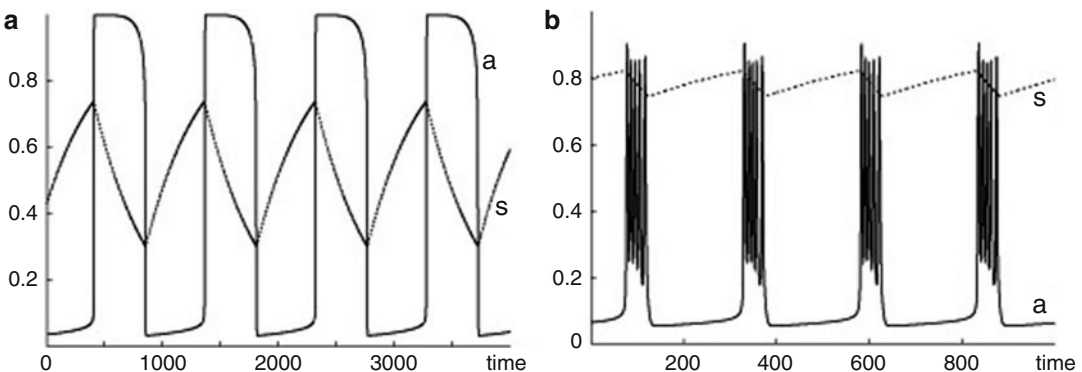
The model described by these two equations can produce episodic activity with slow oscillations of s controlling the transitions between high and low activity. When activity is high, synapses depress so s goes down, until it becomes too low to sustain activity. The network then becomes silent, allowing synapses to recover. When s becomes high enough, activity jumps up to a high level and the cycle continues (Fig. 3a).

Rapid cycling during an episode can be modeled by adding another synaptic depression variable, d , that varies on a timescale of hundreds of milliseconds – slower than a , but much faster than s . Synaptic depression on this timescale may represent neurotransmitter depletion at synaptic terminals. The full model with both fast and slow synaptic depression produces spontaneous episodes of rhythmic activity as shown Fig. 3b (Tabak et al. 2000).

Models Based on Individual Spiking Neurons

The model described above captures essential features of spontaneous episodic activity, on the network scale and on a coarse-grained timescale. Episodic activity in excitatory networks with synaptic depression has also been investigated with network models that incorporate many neurons connected to each other (Tsodyks et al. 2000; Vladimirovski et al. 2008; Wiedemann and Luthi 2003). These models allow observing the activity of individual neurons in the network and incorporate the effects of stochastic spike timing. Connecting all the individual neurons produces “population spikes,” or bursts, during which most neurons are active, separated by periods of quiescence. One common feature of these models is that the neurons in the networks have different excitability levels. Some spike spontaneously most of the time, while most are silent unless they receive sufficient synaptic inputs. This heterogeneity of neuronal properties allows the network to produce robust episodic activity.

Excitatory network models with some form of activity-dependent negative feedback (synaptic depression or neuronal refractoriness) also describe episodic activity in other developing networks, such as the retina (Butts et al. 1999), or population bursts in hyperexcitable hippocampal networks (Staley et al. 1998).



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Fig. 3 Episodic activity generated by the model. **(a)** The model generates periods of high activity during which synapses slowly depress (s decreases). After the activity

stops, synapses recover (s increases) until the next episode begins. **(b)** With an additional, fast, synaptic depression variable, rhythmic cycling occurs during the episodes of activity

Model Achievements

The models have demonstrated that rhythmic episodes of activity can be generated according to a simple mechanism requiring only excitatory connections and activity-dependent depression. They also explain two important sets of data.

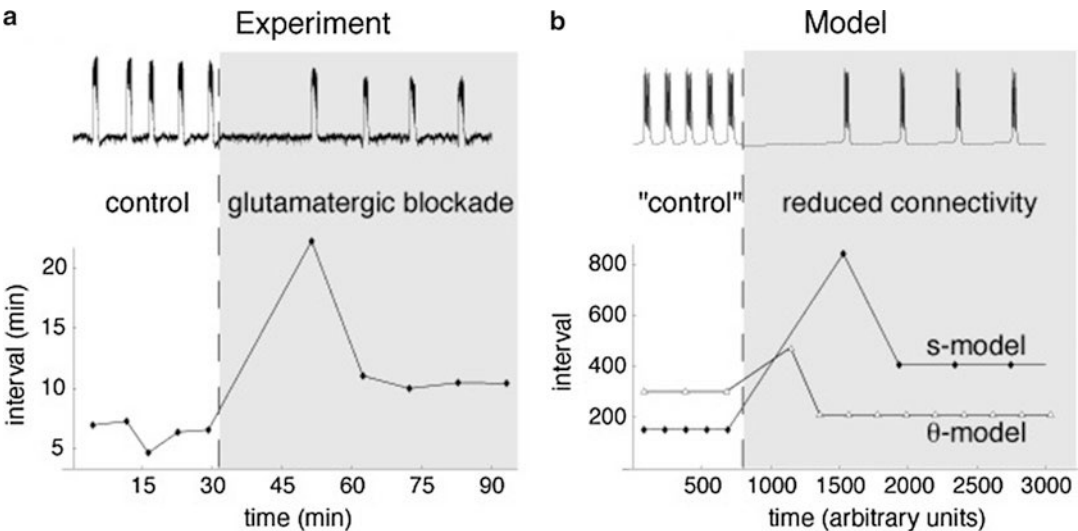
Blocking excitatory neurotransmission abolishes activity in most neural networks. In the embryonic spinal cord, pharmacological blockers of receptors for the neurotransmitters acetylcholine and glutamate abolish spontaneous activity for up to 3 h, but after this delay activity reappears with similar characteristics as before pharmacological block (Chub and O'Donovan 1998). Why does activity recover in the presence of the synaptic blockers?

This can be explained with our mean activity model, where parameter w represents the total synaptic connectivity comprising glutamatergic, cholinergic, and GABAergic/glycinergic synapses. Blocking glutamatergic synapses is equivalent to decreasing w . If we decrease w by a small amount, the model also stops generating activity for a long period, but eventually activity reappears as it was before decreasing w (Fig. 4). When w is

decreased, the gain of the positive feedback loop, $w s$, decreases too, so the model can no longer be active. During the long period of inactivity, s increases to higher than normal level and compensates for the decreased w . Activity thus resumes with $w s$ operating at its normal range thanks to s operating at a higher level. This suggests that the GABAergic/glycinergic connections become stronger to compensate the block of the glutamatergic connections.

This model prediction was confirmed experimentally when it was shown that GABAergic responses were larger after glutamatergic blockade (Tabak et al. 2001). Therefore, the synaptic depression process responsible for the episodic nature of the activity also provides the plasticity that allows this activity to be robust to disruptions in synaptic connectivity. Such homeostatic plasticity has since been further investigated in the developing chick spinal cord in ovo (Gonzalez-Islas and Wenner 2006; Wilhelm and Wenner 2008).

One surprising experimental finding that also results from synaptic depression controlling the occurrence of activity episodes is that the duration of an episode strongly depends on the length of the *preceding* silent interval, but does not affect

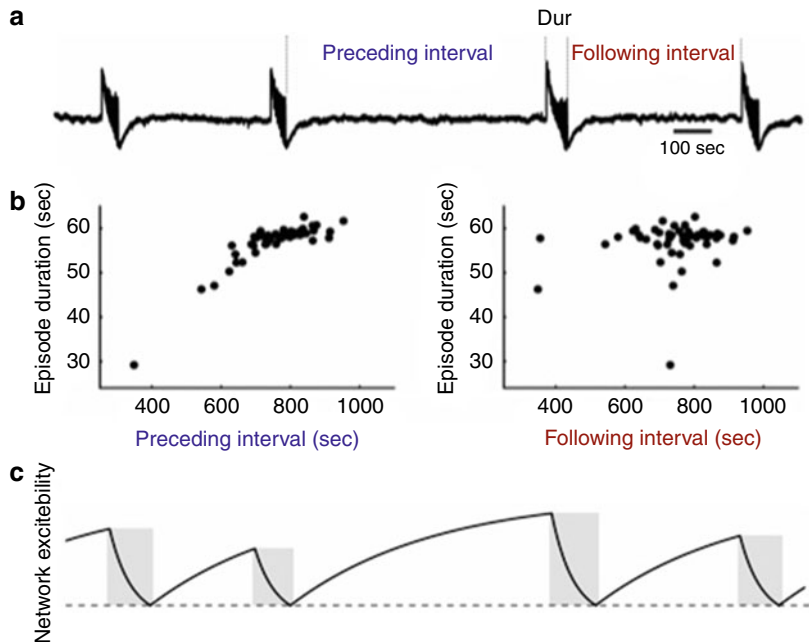


Rhythm Generation in Embryonic Chick Spinal Cord, Fig. 4 Blockade experiment. **(a)** Upper trace, blocking glutamatergic synaptic transmission stops the activity for a long period of time, but then the activity resumes with similar characteristics as control activity. Lower panel

shows the interepisode intervals. **(b)** Model behavior when the connectivity parameter w is decreased to mimic glutamatergic blockade. As in the experiments, activity eventually resumes and interepisode intervals are slightly longer than control intervals

Rhythm Generation in Embryonic Chick Spinal Cord,

Fig. 5 Correlation pattern in spontaneous activity. (a) Spontaneous activity recorded from an E10 chick spinal cord. (b) There is a clear correlation between episode duration and the length of the preceding, but not following, interepisode interval. (c) This suggests that network excitability at episode onset is variable but always reaches the same value at episode termination



the length of the *following* interval (Fig. 5; Tabak et al. 2001). This suggests that the network is always in the same state at the end of an episode. Such pattern has also been found in many developing or hyperexcitable networks (O'Donovan 1999).

The models based on a heterogeneous population of spiking neurons produce the same strong correlation between episode duration and the preceding, but not following, interval. This correlation pattern is not affected if we change the average number of connections in the network or the properties of the single cells, demonstrating that it is a robust feature of excitatory networks with synaptic depression (Tabak et al. 2010). That such robust correlation pattern can be obtained using simple network models and the fact that many developing networks produce this pattern provide evidence that neural networks that differ widely, such as the spinal cord and the retina, operate using similar principles early in their development.

Cross-References

► [Rhythm Generation in Young *Xenopus* Tadpoles](#)

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Rhythm Generation in Young *Xenopus* Tadpoles

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Synonyms

[Behavior of just-hatched frog tadpoles and the neuronal networks underlying it](#)

Definition

Just after they hatch from the egg, tadpoles of the frog *Xenopus* can swim when touched and make stronger struggling movements when

held. They provide one of the simplest organisms where the networks' underlying behavior can be studied. Models of swimming networks rely on the interaction of pacemaker and network rhythm generation based on reciprocal inhibition and rebound. The network can be reconfigured during continuous stimulation when some neurons active during swimming become silent and new neurons are recruited, so the network generates the slower struggling pattern.

Detailed Description

Background

The spinal cord of the adult mammal has proved very difficult to investigate and understand. This is the reason to look for simpler, related systems which might be more accessible. The hatchling frog tadpole is a vertebrate like us, but its nervous system has only just begun to generate the behavior needed for survival. The inspiration for studying it came from the simple network diagrams in a book by George Coghill (1929) on the development of the brain and behavior of tiger salamander tadpoles. I chose *Xenopus* to study the sensory systems controlling behavior (Roberts 1969) because tadpoles can be obtained throughout the year. They have two main responses (Roberts et al. 2010): when touched, they bend their trunk and swim away (15–25 Hz with head-to-tail waves) and when grasped by a predator, they struggle violently (5–10 Hz with tail-to-head waves). The neurons controlling responses have been studied in immobilized tadpoles, first with sharp microelectrodes and dye filling and more recently using whole-cell recordings with neurobiotin. The skin is stimulated electrically to evoke responses monitored with electrodes on the motor nerves going to the trunk muscles. This work has led to a remarkably detailed picture of the anatomy and physiology of the ten or so types of neuron in the spinal cord and hindbrain which control the tadpole's responses to skin stimulation. This entry outlines modeling studies of the tadpole networks.

Modeling Swimming

From an early stage in the investigation, network modeling was used to evaluate ideas about how swimming was generated. The pattern of spinal neuron firing during swimming is very simple with each neuron type firing only once on each cycle. There was no evidence of any neurons firing at high rates to produce a steady excitatory drive to turn on swimming. However, the *Xenopus* tadpole was the place where long-duration, NMDAR-mediated glutamate excitation was first discovered (Dale and Roberts 1985). This led to the hypothesis that rhythmic activity is sustained after a brief stimulus by feedback excitation on each cycle from the excitatory neurons driving swimming. These neurons fire a single spike, but their excitation has a time course longer than the swim cycle period and so can sum from cycle to cycle to sustain rhythmic firing (Roberts et al. 1984). The second hypothesis was that the basic alternating swimming rhythm is produced by a post-inhibitory rebound mechanism (Perkel and Mulloney 1974) similar to that found in the swimming network of the marine snail *Clione* (Satterlie 1985). In the tadpole, such rebound firing did not occur at rest but could lead to firing in neurons held depolarized by the slow NMDA component of glutamate excitation and receiving mid-cycle reciprocal inhibition from glycinergic neurons on the opposite side of the spinal cord (Soffe 1990). Modeling showed that networks, where the excitatory neurons had appropriate properties based on the evidence from recordings, could generate swimming based on post-inhibitory rebound (Roberts 1989; Roberts and Tunstall 1990; Tabak and Moore 1998).

Whole-cell recordings from spinal neurons led to new ideas about the role of the spinal excitatory neurons active during swimming. Dale proposed that these neurons acted as pacemakers to drive swimming and that the single firing responses to current injections seen with sharp microelectrodes were artifacts resulting from damage-induced leak currents (Aiken et al. 2003; Dale 1995a, b, 2003). However, later in situ whole-cell recordings showed that this was not the case and built up a very complete picture of the

neurons and synaptic connections underlying swimming (Li 2011; Wolf et al. 1998). This allowed evidence-based modeling of the swimming network and confirmed that the post-inhibitory rebound mechanism could produce stable rhythm (Sautois et al. 2007). The large number of paired recordings also suggested that synaptic contacts could be made probabilistically and modeling showed that networks built on this principle could swim (Li et al. 2007a). A crucial discovery was that the excitatory neurons driving swimming were switched into pacemaker mode when their mutual synapses activated NMDARs (Li et al. 2010). This finding could explain the rhythm generation found in a single isolated side of the CNS and reconcile the earlier proposals made by Dale (1995a). Our current modeling is investigating the significance of these pacemaker properties in the population of electrically coupled excitatory neurons.

During swimming motor activity starts in the rostral trunk and spreads toward the tail, and recordings have shown that there is a head-to-tail gradient in the excitation and inhibition underlying swimming (Tunstall and Roberts 1991, 1994; Zhao et al. 1998). The tadpole like other biological networks has long-range axonal coupling so cannot be treated as a series of oscillators with nearest neighbor coupling. Modeling has shown that gradients in synapse numbers can be generated when neurons with relatively short axons are unevenly distributed along the nervous system (Wolf et al. 2009): with more neurons near the head, there are more synapses. Gradients in synapse numbers can lead to head-to-tail propagation of activity during swimming. The detailed synaptic mechanisms coupling activity longitudinally have been investigated (Tunstall et al. 2002).

Modeling Struggling

Struggling is a slower pattern of activity where motor neurons fire bursts of spikes like those seen during locomotion in most larger animals. Unlike swimming, this means that burst termination mechanisms are required. Struggling occurs when the tadpole is grasped or during continuous skin stimulation (at 25–40 Hz) (Soffe 1991) and involves the recruitment of additional reciprocal

inhibitory neurons and motoneurons (Soffe 1993). Whole-cell recordings with neurobiotin injections later revealed new types of neurons only recruited during struggling (Li et al. 2007b), but when the network was modeled, alternating bursting was unstable. This led to the discovery that reciprocal inhibition was antifacilitated at struggling intra-burst frequencies. When this process was included in the model as a burst termination mechanism, stable struggling activity could be obtained. The mechanisms for tail-to-head propagation of the struggling wave have not yet been elucidated.

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Rhythm Perception: Pulse and Meter

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Synonyms

Beat, Dynamic attending, Metrical structure, Neural oscillation, Neural resonance, Rhythmic entrainment

Definition

Pulse and *meter* are perceptual/attentional responses to patterns of timing and stress in acoustic rhythms. Pulse corresponds to the perception of periodicity, while meter corresponds to the perception of alternating strong and weak beats. Pulse and meter are thought to arise as cortical rhythms entrain to acoustic rhythms, influencing temporal expectancy and attention. Computational models of pulse and meter as neural resonance to acoustic rhythms are based on theoretical models of neural oscillation.

Detailed Description

Musical rhythm is of considerable interest as a model system for the study of rhythmic communication. In music, rhythms are often perceived to have a pulse or basic beat in the approximate range of 0.5–4 Hz (London 2004). Meter corresponds to the percept of alternating strong and weak beats (Lerdahl and Jackendoff 1983) and, metrical structures include the pulse frequency, slower beat frequencies (<2 Hz) that group pulse cycles and higher beat frequencies that subdivide the pulse (4–8 Hz) (London 2004). Metrical structures are stereotypical patterns that can be described in terms of phase and frequency relationships among multiple frequency components. Frequency relationships are theoretically restricted to harmonics (e.g., 1:2, 1:3),

subharmonics (e.g., 2:1 and 3:1), and other simple integer ratios (e.g., 3:2, 4:3) (London 2004). Rhythmic patterns also group into phrase structures (see Fig. 1). Speech is generally hierarchical as well syllables (4–8 Hz) assemble into lexical and phrasal units at slower timescales (<4 Hz) (Giraud and Poeppel 2012). However, the fundamental temporal structures of speech are more flexible and less well understood than those of music.

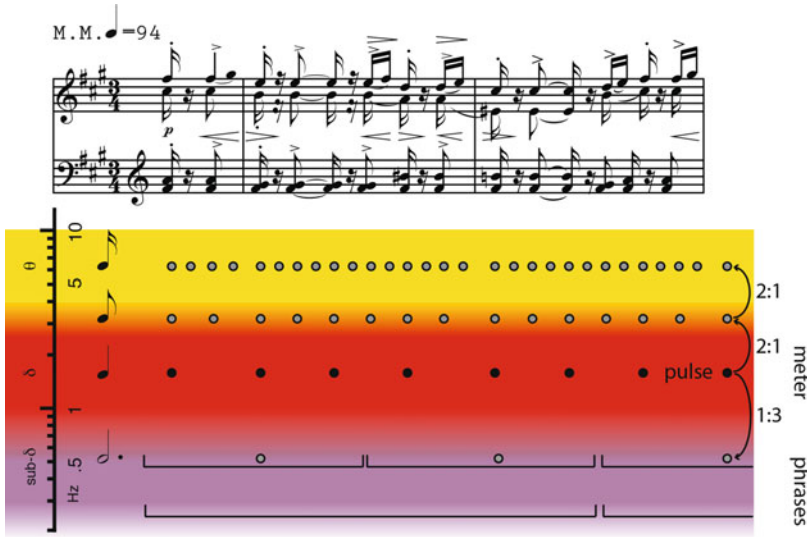
Neural Resonance

Pulse and meter are believed to arise as endogenous cortical rhythms entrain to acoustic rhythms. Entrainment of cortical rhythms to music and speech is thought to engage neurodynamic mechanisms of temporal prediction and attention (Large and Jones 1999) and segregate incoming information (Ghitza 2011). Auditory cortical rhythms, for example, nest hierarchically (Lakatos et al. 2005) and are entrained by music and speech rhythms. Acoustic stimulation in the range of musical pulse synchronizes cortical rhythms in the delta band (e.g., Will and Berg 2007; Nozaradan et al. 2011), and stimulation with spoken syllables synchronizes cortical rhythms in the theta band (e.g., Luo and Poeppel 2007). In general, the neural resonance theory of pulse and meter holds that neural oscillations in distributed cortical and subcortical areas entrain to the rhythms of auditory sequences (Large 2008).

Models of Pulse and Meter

Generic models of neural oscillation are often used for modeling pulse and meter because they make predictions that hold under a rather general set of assumptions. Equation 1, for example, is a generic model that can be derived from the Wilson-Cowan model of neural oscillation (Aronson et al. 1990; Large et al. 2010):

$$\frac{dz}{dt} = z(\alpha + i\omega + (\beta + i\delta)|z|^2) + c s(t) + \text{h.o.t.} \quad (1)$$



Rhythm Perception: Pulse and Meter, Fig. 1 Musical rhythm, pulse, meter, and grouping. Piano score of Isaac Albeniz's *Iberia II, Triana*, annotated with pulse (black dots), metrical structure (all dots), and phrasing (brackets). Pulse frequencies overlap with cortical

oscillations in the delta range, while other metrical frequencies extend into theta and sub-delta ranges. Frequency relationships among metrical levels are restricted to harmonics, subharmonics, and other integer ratios

This differential equation is two dimensional, because z is a complex variable, having real ($Re(z)$) and imaginary ($Im(z)$) parts. It has both real (α , β) and imaginary (ω , δ) parameters as well, whose meanings are described next. In neural oscillator models of pulse and meter, the system is driven by a temporal sequence, $s(t)$, of event onsets as illustrated in Fig. 2a.

When this system is driven with an external rhythm, an oscillation may arise (e.g., Fig. 3a) and entrain to the stimulus. To study this behavior, Eq. 1 is rewritten in polar coordinates, by setting $r = e^{i\phi}$ (Fig. 3b), revealing the dynamics of amplitude, r , and phase, ϕ , individually:

$$\begin{aligned} \frac{dr}{dt} &= r(\alpha + \beta r^2) + cs(t) \cos \phi + \text{h.o.t.} \\ \frac{d\phi}{dt} &= \omega + \delta r^2 - c \frac{s(t)}{r} \sin \phi + \text{h.o.t.} \end{aligned} \quad (2)$$

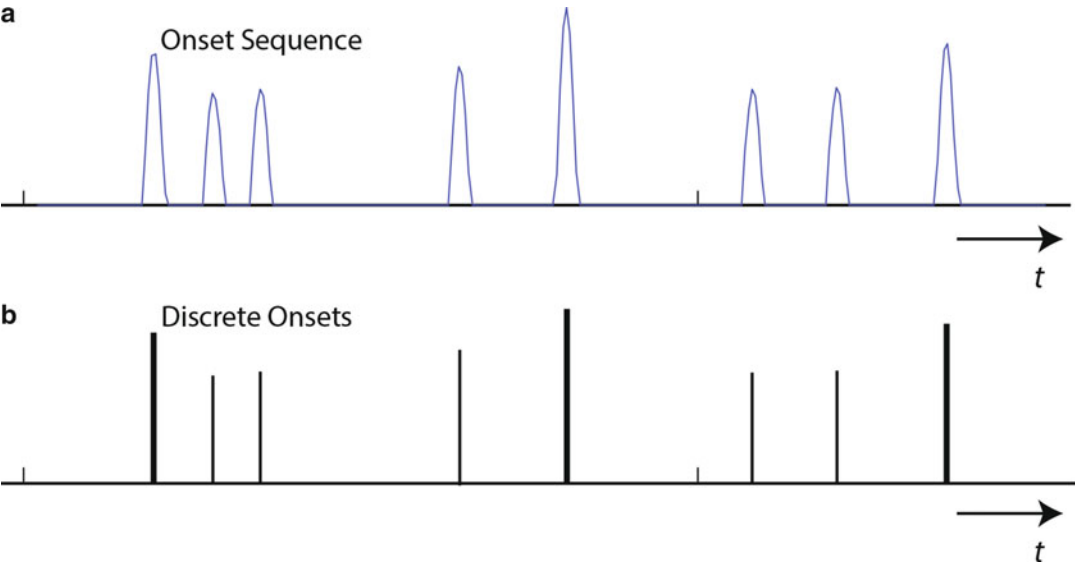
The parameters relate directly to the amplitude and phase of the oscillation. They are α , the bifurcation parameter; β , the nonlinear saturation parameter; ω , the natural frequency ($\omega = 2\pi f$, f in Hz); and δ , a detuning parameter (for details, see Large (2008)). The connection strength, c ,

captures the influence of the stimulus on the oscillator.

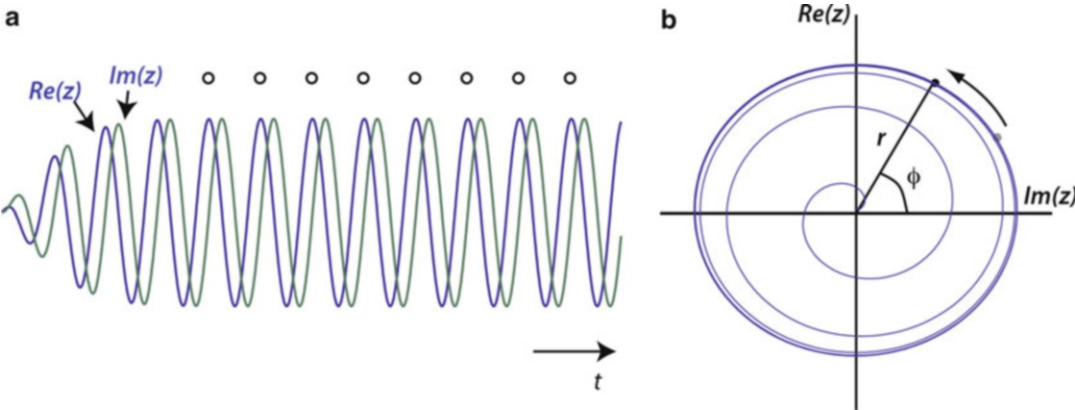
Neurodynamic models assume that neural oscillations in the range of musical pulse entrain to the stimulus sequence, as do oscillations at higher and lower metrical frequencies. Entrainment in integer-ratio-structured patterns is based on mode-locking, a generalization of phase-locking in which a periodic stimulus interacts with an intrinsic oscillatory dynamics of a neuron or neural circuit, causing k cycles of an oscillation to lock to m cycles of the stimulus, where k and m are integers (in phase-locking $k = m = 1$). In Eqs. 1 and 2, mode-locking neural dynamics are captured in the higher-order terms (h.o.t.). For an expansion of higher-order terms that captures mode-locking, see Large et al. (2010). This article explains mode-locking using a discrete-time model, next.

Discrete-Time Models

If a neural oscillator spontaneously generates an oscillation with a stable limit cycle amplitude, and



Rhythm Perception: Pulse and Meter, Fig. 2 Driving rhythms. Input to a neural oscillator model of pulse/meter is assumed to be a temporal sequence of event onsets. (a) Continuous-time onset sequence (Eq. 1, $s(t)$). (b) Discrete-time representation (Eq. 5, t_n)



Rhythm Perception: Pulse and Meter, Fig. 3 Canonical neural oscillation. (a) When stimulated at an appropriate frequency, a neural oscillation arises and entrains to a musical rhythm. The point in the cycle when $Re(z) = 0$ is usually assumed to correspond to an individual beat or pulse (see Fig. 1). (b) The oscillation can also be understood in terms of amplitude, r , and phase, ϕ

the stimulus is not too strong, then we can ignore amplitude and work entirely in the phase dimension (Pikovsky et al. 2001). We consider the phase equation of the system above, ignoring frequency detuning and higher-order terms:

$$\frac{d\phi}{dt} = \omega - c s(t) \sin \phi \tag{3}$$

Next, assume the stimulus to be a periodic series of discrete impulses with fixed period, T_0 (T_0 (sec) = $1/f_0$ (Hz); note also, $\omega_0 = 2\pi f_0$). Then the above phase equation can be integrated to create the discrete-time (stroboscopic) mapping.

$$\phi_{n+1} = \phi_n + \omega T_0 - c \sin \phi_n \tag{4}$$

known as a circle map (Pikovsky et al. 2001; Glass 2001). Formally, one should also apply the operation modulo 2π to the right-hand side, but it is omitted here for simplicity of presentation. Once this transformation has been accomplished, ϕ represents relative phase, the phase of the oscillator when an input event occurs. The discrete-time model exhibits phase-locking and mode-locking properties that make it useful for describing structural aspects of pulse and meter (Large and Kolen 1994; McAuley 1995).

Phase-Locking and Mode-Locking

Figure 4 shows resonance regions called Arnol'd tongues, based on simulation of Eq. 4 (cf., Glass 2001). Figure 4 illustrates that a neural oscillator locks to stimuli near its own frequency and to integer-ratio-related frequencies. Importantly, oscillations lock at frequencies that are not present in the stimulus. The most stable response is found at the stimulus frequency (i.e., 1:1 phase-locking), but mode locks are also observed at harmonics (e.g., 2:1), subharmonics (e.g., 1:2 and 1:3), and integer multiples (e.g., 3:2). At low coupling strengths, mode-locking regions are small; they

increase with coupling strength. Phase- and mode-locking capture many aspects of pulse and meter that have been directly observed in experiments (Large 2008).

Discrete-Time Models of Pulse

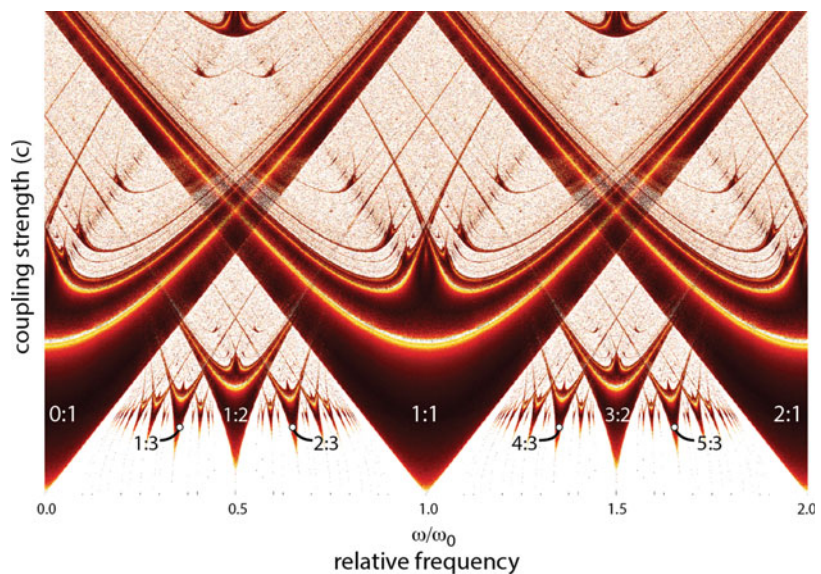
To create a discrete-time model that can handle complex musical rhythms, it is assumed that a sequence of event onsets (Fig. 2a) may be described as temporally discrete impulses (Fig. 2b). Such data is readily collected in the laboratory in the form of MIDI recordings of musical performances and retains the most basic information about event timing. The key insight is to replace the fixed period, T_0 , of a discrete map with the succession of event times in a music performance:

$$\phi_{n+1} = \phi_n + \omega(t_{n+1} - t_n) - cF(\phi_n) \quad (5)$$

This formulation was conceived as a model of temporal expectation by Large and Kolen (1994) and as a model of dynamic attending (Large and Jones 1999). According to McAuley (1995), the basic theoretical insight is to model the perception of time as phase. Related models, termed adaptive

Rhythm Perception: Pulse and Meter,

Fig. 4 Mode-locking regions for Eq. 4. Arnol'd tongues show where mode locks occur, depending on the parameter c and the relative frequency, ω/ω_0 ($\omega_0 = 2\pi/T_0$). A few of the larger, more stable mode locks are labeled



oscillators, include adaptation of oscillation frequency (or equivalently, period).

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Rhythmic Entrainment

- [Rhythm Perception: Pulse and Meter](#)

Ri (Units: Ω Cm)

- [Resistivity, Axial](#)

Robinson Model

- [Down Under Neural Population Models](#)

Role of Delayed Feedback in Human Balancing

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Definition

The destabilizing effect of reaction delay to balancing tasks is demonstrated using the pendulum-cart (inverted pendulum) model associated with delayed proportional-derivative (PD) feedback.

Detailed Description

Stabilization of unstable equilibria and orbits by means of feedback control is a highly important task in engineering and science. It is more efficient to start quick movements from an unstable position than from a stable one, while the energy

demand of the control process is relatively small. Maintaining balance is also a vital ability for humans: falls are leading causes of accidental death and morbidity in the elderly, which provides a strong motivation to understand the nature of mechanisms that maintain human balance, why these mechanisms fail, and how risks for falling can be minimized. The primary causes that deteriorate the performance of feedback control systems are reaction delay and sensory uncertainties.

Here, the basic model of balancing is presented, where the control law is a delayed proportional-derivative (PD) feedback. It is shown how the feedback delay deteriorates the stability properties of the control process. A model of stick balancing on the fingertip is investigated, but the underlying mathematical model is similar to postural sway, too.

Mechanical Model

Experiments on stick balancing on the fingertip (Milton et al. 2016) show that in most of the cases (72% for novice stick balancer and 84% for experienced stick balancers), stick falls in the AP direction, which can be explained by the necessity of depth perception for the estimation of the spatial angular position of the stick. Balancing trials also show that the movements of the arm of the stick balancer are confined to the elbow and shoulder while the wrist and finger are held rigid and moved horizontally (Cabrera and Milton 2004;

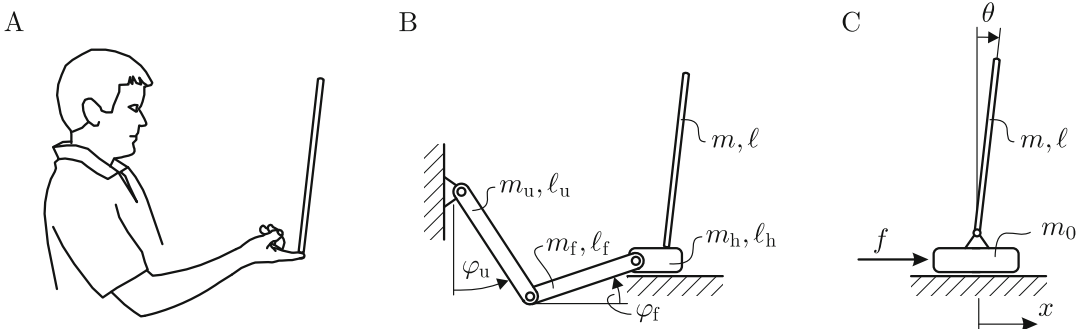
Lee et al. 2012; Milton et al. 2016). These observations imply that stick balancing on the fingertip in the AP direction can be modeled as a pendulum-cart system moved by a slider crank linkage, which models the human arm mechanism as shown in Fig. 1. This model can be reduced to a simple pendulum-cart system with an equivalent mass m_0 of the cart, which involves the inertia and the mass of the arm segments.

The equivalence of the models shown in panels B and C in Fig. 1 is to be established based on the equivalence of their kinetic energy. The kinetic energy of the arm mechanism can be given as

$$E_{\text{kin,arm}} = \frac{1}{2}m_u v_u^2 + \frac{1}{2}J_u \dot{\varphi}_u^2 + \frac{1}{2}m_f v_f^2 + \frac{1}{2}J_f \dot{\varphi}_f^2 + \frac{1}{2}m_h v_h^2, \quad (1)$$

where v_u , v_f , and v_h are the velocities of the center of gravity of the upper arm, forearm, and hand, respectively, and J_u and J_f are the moment of inertia with respect to the normal line via the center of gravity of the upper arm and the forearm. Assuming homogeneous arm segments, we have $J_u = \frac{1}{12}m_u \ell_u^2$ and $J_f = \frac{1}{12}m_f \ell_f^2$. The mass of the stick is negligible compared to the mass of the arm-hand mechanism (cart), and then the kinetic energy of the pendulum-cart model is

$$E_{\text{kin,car}} = \frac{1}{2}m_0 \dot{x}^2, \quad (2)$$



Role of Delayed Feedback in Human Balancing, Fig. 1 (a) Subject balancing stick on fingertip. (b) Slider crank model of the arm used to estimate the equivalent

mass of the cart for the pendulum-cart model. (c) Pendulum-cart model for stick balancing with equivalent mass

Role of Delayed Feedback in Human Balancing,
Table 1 Arm segment parameters taken from de Leva (1996)

Segment	Mass	Length (ℓ)
Upper arm	$m_u = 1.775$ kg	$\ell_u = 0.2874$ m
Forearm	$m_f = 1.015$ kg	$\ell_f = 0.2666$ m
Hand	$m_h = 0.395$ kg	$\ell_h = 0.0821$ m

where x is the displacement of the cart and $\dot{x}$ is its derivative with respect to time (i.e., the cart's velocity).

Using the equations $E_{\text{kin,arm}} = E_{\text{kin,cart}}$, $v_h = \dot{x}$ and the relations between the velocities v_u , v_f , and v_h and the angular velocities $\dot{\varphi}_u$ and $\dot{\varphi}_f$, one can calculate the equivalent mass m_0 of the cart. The parameters of the mechanism are set according to the average human arm segment as listed in Table 1 (de Leva 1996). Assuming $\varphi_u \approx 20$ deg, and $\varphi_u \approx 10$ deg. for the arm segment positions during stick balancing, the mass of the cart is obtained to be $m_0 = 2.46$ kg.

The pendulum-cart system can be modeled by a two-degree-of-freedom system governed by

$$\begin{pmatrix} \frac{1}{3}m\ell^2 & \frac{1}{2}m\ell\cos\theta \\ \frac{1}{2}m\ell\cos\theta & m+m_0 \end{pmatrix} \begin{pmatrix} \ddot{\theta} \\ \ddot{x} \end{pmatrix} + \begin{pmatrix} -\frac{1}{2}mg\ell\sin\theta \\ -\frac{1}{2}m\ell\dot{\theta}^2\sin\theta \end{pmatrix} = \begin{pmatrix} 0 \\ f(t) \end{pmatrix}, \quad (3)$$

where θ is the vertical displacement angle of the stick; m and m_0 are the mass of the stick and cart, respectively; ℓ is the length of the stick; $\ddot{x}$ is the acceleration of the cart (fingertip); and $f(t)$ describes the control force exerted at the fingertip. The linearized equation of motion is

$$\begin{pmatrix} \frac{1}{3}m\ell^2 & \frac{1}{2}m\ell \\ \frac{1}{2}m\ell & m+m_0 \end{pmatrix} \begin{pmatrix} \ddot{\theta} \\ \ddot{x} \end{pmatrix} + \begin{pmatrix} -\frac{1}{2}mg\ell & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \theta \\ x \end{pmatrix} = \begin{pmatrix} 0 \\ f(t) \end{pmatrix}. \quad (4)$$

If the control force does not depend on x and $\dot{x}$, then x is a cyclic coordinate, which can be eliminated and the equation of motion can be reduced to

$$\ddot{\theta}(t) - \frac{6g}{c\ell}\theta(t) = -\frac{6}{(m+m_0)c\ell}f(t), \quad (5)$$

where the parameter $c = 4 - 3m/(m+m_0)$ is equal to 1 when $m_0 = 0$ and to ~ 4 when $m_0 \gg m$. The coefficient $6g/c\ell$ is often called system parameter since $\omega_n = \sqrt{6g/c\ell}$ is the angular natural frequency of the free pendulum hung downward. The corresponding oscillation period is

$$T = 2\pi\sqrt{\frac{c\ell}{6g}}. \quad (6)$$

The control force f is assumed to be a locally linear function of the angular position θ and the angular velocity $\dot{\theta}$ in the form

$$f(t) = K_p\theta(t-\tau) + K_d\dot{\theta}(t-\tau) + \text{h.o.t.}, \quad (7)$$

where K_p is the proportional gain, K_d is the derivative gain, τ is the reaction delay, and h.o.t. stands for the higher-order terms not modeled here. It shall be mentioned that the displacement x and its derivative $\dot{x}$ are not involved in the control law. This means that there is no limitation to translational motion in the model. However, in real experiments, there is a limitation, namely, the arm length when the subjects are performing the balancing task sitting on a chair or the length of the cart track when balancing a pendulum-cart system.

Finally the governing equation can be written in the simple form

$$\ddot{\theta}(t) - a\theta(t) = -k_p\theta(t-\tau) - k_d\dot{\theta}(t-\tau), \quad (8)$$

where

$$a = \frac{6g}{c\ell}, \quad (9)$$

$$k_p = \frac{6K_p}{(m+m_0)c\ell}, \quad (10)$$

$$k_d = \frac{6K_d}{(m + m_0)c\ell}. \quad (11)$$

Stability and Stabilizability

Stability properties can be given after the analysis of the characteristic roots λ (Insperger and Stepan 2011; Stepan 1989). For this, the characteristic function reads

$$D(\lambda) = \lambda^2 - a + k_p e^{-\lambda\tau} + k_d \lambda e^{-\lambda\tau}. \quad (12)$$

According to the D-subdivision method (Stepan 1989), substitution of $\lambda = \gamma \pm i\omega$, $\omega \geq 0$, into $D(\lambda) = 0$, decomposition into real and imaginary part, and setting $\gamma = 0$ give the D-curves in the form

$$\text{if } \omega = 0: k_p = a, \quad k_d \in \mathbb{R}, \quad (13)$$

$$\begin{aligned} \text{if } \omega \neq 0: k_p &= (\omega^2 + a) \cos(\omega\tau), \\ k_d &= \frac{\omega^2 - a}{\omega} \sin(\omega\tau). \end{aligned} \quad (14)$$

The D-curve $k_p = -a_0$ given by (13) is associated with a real critical characteristic exponent $\lambda = 0$. The D-curve given by (14) is associated with a complex conjugate pair of characteristic exponents of the form $\lambda = \pm i\omega$. In (14) $\omega \in [0, \infty)$ can be treated as a running parameter. For a fixed a , these curves cut the parameter plane (k_p, k_d) into infinitely many domains. In each of these

domains, the number of unstable characteristic roots is fixed. The stable domain (with zero unstable root) is the one attached to the point $(k_p, k_d) = (a, a\tau)$ (Insperger and Stepan 2011).

A series of stability diagrams are shown in Fig. 2 for balancing a stick of length $\ell = 0.25$ m with different reaction delays. It can be seen that the stable region shrinks with the reaction delay, and at a critical value τ_{crit} , it disappears. This means that if $\tau > \tau_{\text{crit}}$, then stabilization by delayed PD feedback is not possible. In case of a stick of length $\ell = 0.25$ m, one requires faster reactions than 184 ms.

It can be shown that the stable region disappears when the tangent of the parametric curve (14) at $\omega = 0$ becomes vertical. Analytical calculations give

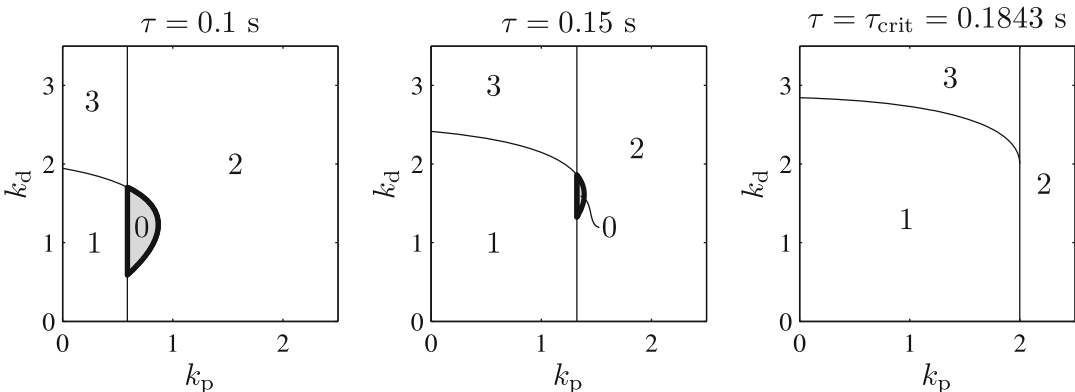
$$\tau_{\text{crit}} = \sqrt{\frac{2}{a}}, \quad (15)$$

which can be reformulated as

$$\tau_{\text{crit}} = \frac{T}{\pi\sqrt{2}}, \quad (16)$$

where T is the period of the small oscillations of the structure hung at its downward position (Stepan 2009).

The same relation can be phrased in terms of the critical length. The critical length l_{crit} is a length of the pendulum that can be balanced by a



Role of Delayed Feedback in Human Balancing, Fig. 2 Number of unstable characteristic exponents for (8) with length $\ell = 0.25$ m and with different feedback delays τ

PD feedback with reaction delay τ . Substituting (9) into (15) gives

$$l_{\text{crit}} = \frac{3}{c} g \tau^2. \quad (17)$$

When balancing a stick made of wood on the fingertip, then typically $m \ll m_0$; hence $c \approx 4$. An average human reaction delay is somewhere between 200 and 250 ms. This gives that humans typically cannot balance sticks of length shorter than 30 ~ 46 cm, which agrees with the experimental observations (Milton et al. 2016).

Discussion

In the above analysis, delayed PD feedback was assumed. However, many other types of control concepts are investigated in the literature as possible candidate for the human control process. A trivial extension of PD feedback is the application of an integral term, hence PID feedback (Maurer and Peterka 2005). Addition of the I term however does not help in the stabilization process, i.e., the critical delay for a PID control is obtained when the integral gain is zero (Lehotzky 2017). When the acceleration is also fed back (PDA feedback), then the critical delay is increased by a factor of $\sqrt{2}$, which means that the critical length is reduced to half of that of the PD feedback (Insperger et al. 2013; Sieber and Krauskopf 2005). Delay compensation, when an internal model is able to predict the consequences of the control commands over the delay period, is also an often used control concept, which in control theory is called predictor feedback (Krstic 2009; Milton et al. 2016), while in the neuroscience literature, it is called forward model (Mehta and Schaal 2002). When the internal model is perfectly accurate, then the delay can be totally compensated. In theory, there is no limit to the size of the critical delay in this case. However, the internal model and its performance are never perfect, which introduces modeling error in the control process that presents further limitations to the balancing abilities. Other types of control concepts, such as intermittent predictive control

(Gawthrop et al. 2013), event-driven intermittent controller (Yoshikawa et al. 2016), and act-and-wait (Insperger 2006) or drift-and-act controllers (Milton et al. 2009) are also often used to model and explain human balancing performance.

Cross-References

- [Intermittent Control of Movement and Balance](#)
- [Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the](#)

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Role of Descending Pathways in Extrinsic to Intrinsic Coordinate Transformation

► [Coordinate Transformations, Role of Spinal Circuitry in](#)

S

SBML

- [Systems Biology Markup Language \(SBML\)](#)

Scale-Invariant Patterns

- [Neuronal Avalanches](#)

Segmental Control

- [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Self-Organizing Maps

- [Cortical Maps, Activity-Dependent Development](#)

SenseLab: Integration of Multidisciplinary Neuroscience Data

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Definition

The SenseLab project involves novel informatics approaches to constructing databases and Web-enabled applications for collecting, modeling, analyzing, and sharing neuroscience information. The emphasis of SenseLab (<http://senselab.org>) is

on building experimental data into integrated, multidisciplinary models of neurons and neural systems in order to gain insight into the neural basis of behavior. SenseLab is also part of the ► “Neuroscience Information Framework (NIF)” project and the International Neuroinformatics Coordinating Facility (INCF).

Detailed Description

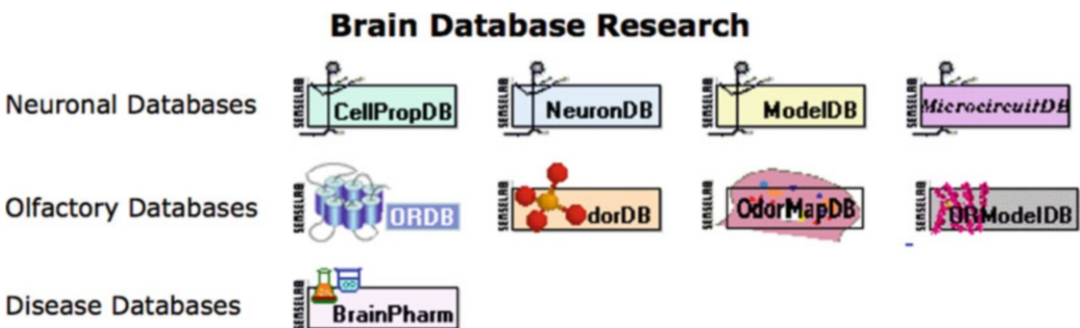
SenseLab was founded in 1993 as part of the original Human Brain Project sponsored by the National Institutes of Health, National Science Foundation, and several other government funding agencies in the United States, which began the development of neuroinformatics tools in support of neuroscience research. Using the olfactory system as a model, SenseLab has built a suite of nine databases (see Fig. 1) to support research across multiple disciplines and at multiple scales of time and space. We test the validity and value of each database for its usefulness for our own research on synaptic organization and sensory processing and seek to develop principles for general application to other neural systems, as summarized in *The Synaptic Organization of the Brain* (Shepherd 2004) and *Handbook of Brain Microcircuits* (Shepherd and Grillner 2010).

SenseLab is built on three foundations. First is the informatics expertise provided by the Yale Center for Medical Informatics (<http://ycmi.med.yale.edu>). This was one of the first such centers in the United States, formed by Dr. Perry Miller in

the 1980s, and has enabled SenseLab to have state-of-the-art informatics as an integral part of our approach by providing the digital infrastructure for the experimental data and for the online databases. This has enabled the different SenseLab databases to be developed in a tightly interoperational framework.

Second are databases for neuroscience data and computational models. The aim is to provide curated published models to enable computational neuroscientists efficiently to run published models to check them and use them to apply to their own research. The importance of computational models for integrating neuroscience data was envisaged in the original Human Brain Project (see Pechura and Martin 1991). This approach is being supported by four interoperational databases, starting with a simple neuron inventory and working up through canonical neurons to neuron models and finally microcircuit models. This sequence starts with **CellPropDB**, a database of currents, neurotransmitter receptors, and neurotransmitters expressed in 30 types of neurons that can be searched across neurons (in parallel to Neurolex Neuron in the NIF). **NeuronDB** expands this to expression in different parts of the dendrites and axons of canonical neuron representations, enabling properties to be searched across neuronal compartments.

The quantitative integration of these properties occurs in the models contained in **ModelDB**. The modeling methods were introduced in neuroscience by Wilfrid Rall, with the first applications to brain neurons in the olfactory bulb (Rall and



SenseLab: Integration of Multidisciplinary Neuroscience Data, Fig. 1 Suite of databases in SenseLab

Shepherd 1968). Current studies rely widely on the modeling environment NEURON (Hines and Carnevale 2014). Dr. Michael Hines brought the NEURON simulation environment to SenseLab in 1995. ModelDB contains fully curated published models running in NEURON and over 50 other modeling programs, with functionality for searching for specific properties. The total number of entries is currently 801 models. Recently, **MicrocircuitDB** has been introduced to cover multineuronal circuits within specific brain regions. It currently contains 180 models for microcircuits in 24 brain regions.

In addition to these general neuron databases, SenseLab also supports research in the olfactory system with an extensive archive of properties related to the olfactory receptors. This is a particularly challenging task given that these receptors are the largest family in the genome (Buck and Axel 1991). The olfactory receptor database (**ORDB**) serves this function with information related to over 14,000 chemosensory genes and proteins. A recent addition is **ModelORDB** for molecular models of olfactory ligand–olfactory receptor interactions, closely related to **OdorDB**, which contains data on the odor molecules that have been shown to interact with the olfactory receptors. These interactions generate activity in the receptor cells which set up different activity patterns representing different odors in the olfactory glomeruli of the olfactory bulb. **OdorMapDB** contains experimental data from functional imaging of these activity patterns, which are believed to be critical for the neural basis of olfactory perception.

A final database still under construction covers the domain of brain pharmacology (**BrainPharmDB**), which expands the information for normal function contained in the other databases to neurological disorders.

The third foundation of SenseLab is integration of our own research data, by developing computational models based on state-of-the-art computational techniques. Currently, we are applying the Rall approach to analyzing the lateral inhibitory network formed by mitral and granule cells in the olfactory bulb. Studies led by Michael Hines and Michele Migliore are constructing

models which accurately represent experimental data on the differential distribution of olfactory inputs in the olfactory glomerular layer (Yu et al. 2013). We are introducing a new generation of three-dimensional models of the overlapping dendritic trees of mitral and granule cells (Migliore et al. 2013). This approach is being applied to experimental data from our own lab as well as in collaboration with other experimental labs.

SenseLab's current activities also include major contributions to neuroinformatics through participation in the Neuroscience Information Framework (NIF), the International Neuroinformatics Coordinating Facility (INCF), the Blue Brain Project (<http://bluebrain.epfl.ch/>), and the Human Brain Project (<http://humanbrainproject.eu/>). This work has included developing **DISCO**, an automated resource discovery, registration, and interoperation framework designed to facilitate data integration among Internet resources for the NIF, and **Neurolex Neuron** as an inventory of basic properties characterizing different types of neurons (see <http://neuinfo.org>).

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Sensorimotor Control of Balance

► [Neuromechanics of Postural Control](#)

Sensorimotor Control of Posture

► [Neuromechanics of Postural Control](#)

Sensory Coding, Efficiency

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Definition

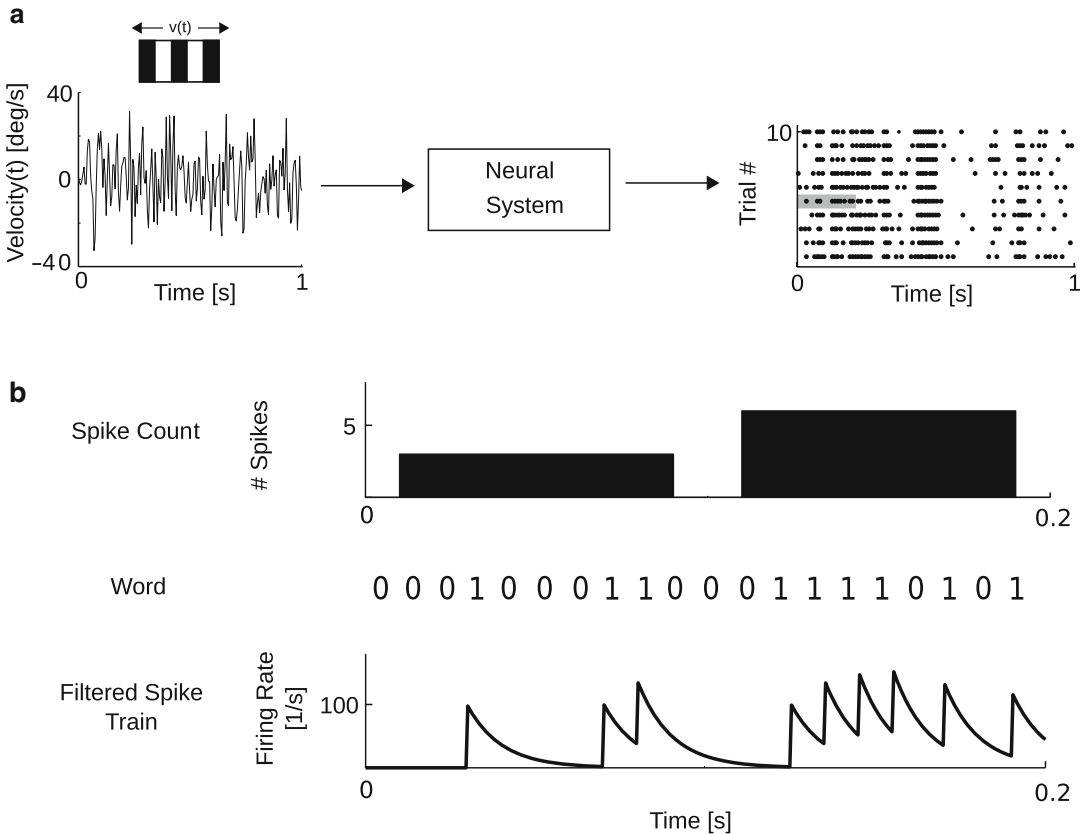
If a neuron's spikes are highly informative about an ensemble of stimuli, then the generated code is called efficient. The efficient coding hypothesis states that the highest levels of efficiency are reached when the ensemble of stimuli encoded by sensory neurons captures important aspects of an animal's natural environment. This notion of efficiency has been employed to explain various properties of sensory neurons including their stimulus–response functions, gain, and connectivity. Specifically, research on insect systems has shown that the stimulus–response function of many insect sensory neurons matches behaviorally relevant stimuli, while the neural gain is adjusted to the current stimulus statistics and behavioral state.

Detailed Description

To probe the properties of sensory neurons, neurophysiologists present various stimuli (e.g., gratings with different orientations for visual neurons or tones with different frequencies for auditory neurons), while recording the neural responses. Information theory provides a theoretical framework to study how much and what information a recorded neural response carries about the presented stimulus. Early influential studies focused on how single neurons in insects efficiently encode stimuli (Laughlin 1981; Bialek et al. 1991; Van Hateren 1992). In this context, a sensory neuron is defined as efficient, if its response is highly informative about behaviorally important stimuli. The efficiency of the neural code served as a first principle explaining various properties of sensory neurons including their tuning, gain, and adaptive features. More recent studies in insects have furthermore explored how changes in the behavioral state of the animal affect the efficiency of sensory processing (Maimon et al. 2010; Chiappe et al. 2010; Jung et al. 2011). Here, we will discuss concepts that have been proven important for the understanding of experimental results from invertebrate systems. Especially insect studies provided many insights on how single neurons efficiently encode stimuli. For completeness, we briefly discuss efficient coding in neural populations, even though most work on population coding has been done for mammalian systems.

Neural Codes

Most sensory neurons respond to sensory stimuli with series of action potentials, also called spike trains. These responses are usually quantified with respect to different “neural codes,” as shown in Fig. 1. The most common codes are (1) spike count or firing rate codes, in which the number of spikes within a given time window is counted; (2) spike timing codes or words, in which a spike train is binned in very short time windows, and thereby converted into a sequence of zeros (no spike) and ones (spike); and (3) time-varying rate codes, in which a spike train is filtered, e.g.,



Sensory Coding, Efficiency, Fig. 1 Neural codes. **(a)** Sensory neurons transform external stimuli into neural responses. In the example, a white-noise velocity stimulus (*left*) is presented to the identified motion-sensitive neuron H1 in the visual system of the blowfly. The velocity stimulus determines the speed $v(t)$ at which a vertical grating within the receptive field of H1 moves along the horizontal axis (see inset). Positive values represent rightward motion; negative values correspond to leftward motion. The stimulus is processed by the visual system including H1, yielding a sequence of action potentials fired by H1.

The responses of H1 elicited by the stimulus are represented on the *right*. Each row corresponds to one repetition of the stimulus, and each dot represents the time point of a single spike. **(b)** Three common schemes to quantify the neural response. The 200 ms long response by H1 indicated by the *gray box* in **(a)** is represented in three different ways: as the number of spikes within two 100 ms windows (“spike count”), as a series of zeros and ones, obtained by discretizing the spike train into 10 ms bins (“word”), and as a spike train filtered with an exponential kernel

with an exponential filter with a given decay time constant (similar to a postsynaptic potential). This type of filtered spike train interpolates between the spike count and spike timing codes. For very short time constants (1–2 ms), the code resembles a spike timing code; for very long time constants (100 s of milliseconds), the code resembles a spike count code. Especially in insects, one also finds quite often neurons with a graded voltage response, or neurons that mix such graded responses with small spikes (or spikelets) (Borst and Haag 2002). In these cases, the definition of

the neural code has to be tailored towards the properties of the specific neuron.

For all practical purposes, both the presented stimuli s and the measured responses r are often discretized and enumerated. Importantly, the mapping of a stimulus onto a neural response is usually corrupted by noise. As shown in Fig. 1a for the motion-sensitive neuron H1 in the blowfly, each presentation of the same stimulus yields a slightly different spike pattern. This variability in the neural response can be quantified by the distribution $p(r|s)$, i.e., the probability of observing response r ,

given that the stimulus was s . This distribution quantifies the noise in the transmission of the stimulus s to the responses r . If the distribution is peaked around a single stimulus value, the neuron's response is reliable; if the distribution is broad, the neuron's response is unreliable.

The noise in the neural response, here defined as trial-to-trial fluctuations elicited by the repeated representation of the same stimulus, can arise from multiple sources (Faisal et al. 2008), including the stimulus itself. External stimuli are noisy in nature. For example, the binding of olfactory molecules to taste receptors is affected by thermal noise. Vision is based on the absorption of photons which is a highly stochastic process. A further prominent source of noise stems from stochastic events in the molecular transduction machinery of sensory neurons, as, e.g., the synthesis and degradation of proteins. So-called electrical noise is generated by random openings and closings of voltage- and ligand-gated ion channels. Moreover, the biochemical communication between neurons is afflicted by noise arising from stochastic events in synaptic mechanisms (as the docking of vesicles to the membrane, the number of available vesicles, their exact locations, etc.).

The Efficiency of Neural Codes

Once the mapping between a set of sensory stimuli and the responses of a neuron has been determined, the neural efficiency can be quantified. Common measures of efficiency are the quality and precision of representation or the amount of transmitted information.

Reconstruction Quality and Precision

One particularly straightforward way of measuring the efficiency of a neural code is to try to reconstruct the original stimulus from the neural response and then simply measure the mean squared error between the original and the reconstructed stimulus. This method requires a specification of how such a reconstruction should be done. One simple method is to assume that the

original stimulus information can be read out by a linear filtering operation of the spike train. If we denote the original, time-varying stimulus by s_t , where t is a time index, and the reconstructed stimulus by $\hat{s}_t$, then a normalized measure for the efficiency of the neural code is given by the coding fraction (Gabbiani and Metzner 1999)

$$\varepsilon = 1 - \frac{\sum_{t=1}^N (s_t - \hat{s}_t)^2}{\sum_{t=1}^N s_t^2}, \quad (1)$$

where we assumed that the stimulus s_t has mean zero. This measure takes a value of zero if the reconstruction fails completely and a value of one if the reconstruction perfectly recovers the original stimulus. An important caveat is that one can only attempt to reconstruct the part of a stimulus that is represented by the neuron. Stimuli that a neuron does not respond to, e.g., because they are outside of the neuron's receptive field, or below a neuron's threshold, cannot be reconstructed (Bialek et al. 1991; Machens et al. 2001).

In a realistic experimental setting, the coding fraction ε is always smaller than one, i.e., the stimulus cannot be exactly reconstructed from the observed neural response. First, the reconstruction algorithm or estimator may be incorrect, e.g., it could be biased. Second, the transmission from the stimulus to the response is affected by noise. Given an unbiased estimator, how precisely can the stimulus be reconstructed from the response? Intuitively, the reconstruction is directly related to the shape of the likelihood function $p(r|s)$ describing the probability to observe the response r given the stimulus s . The reconstruction will be the better, the more the response distribution $p(r|s)$ varies with s , and the less $p(r|s)$ is spread out for a given value of s . For an unbiased estimator $\hat{s}$ of s , the variance of $\hat{s}$, σ_s^2 , is bounded from below by the Cramer-Rao bound

$$\sigma_s^2 \geq \frac{1}{I(s)} \quad (2)$$

where $I(s)$ denotes the Fisher information

$$I(s) = \left\langle -\frac{\partial^2 \ln P(r|s)}{\partial s^2} \right\rangle, \quad (3)$$

with $\langle \cdot \rangle$ denoting the expectation value over r for a given s . The Fisher information has become a theoretically important quantity in the study of population coding (Brunel and Nadal 1998), but has not been widely applied in the analysis of insect model systems.

Mutual Information

The reconstruction error is based on an explicit reconstruction of the original stimulus and thereby makes implicit assumptions about how the stimulus information is embedded in the neural response. A different measure that is free of these assumptions is the mutual information, which is conventionally measured in bits.

If the mapping between the stimuli s and the responses r is deterministic, then the information conveyed by the neural response is given by the entropy of the response distribution. In general, the entropy of a distribution measures how spread or peaked a distribution is. The response entropy is given by

$$H(R) = - \sum_{i=1}^N p(r_i) \log_2 p(r_i), \quad (4)$$

where each r_i , with $i = 1 \dots N$, denotes one of the possible responses. To ensure that a response r_i that is not observed, i.e., $p(r_i) = 0$, does not contribute to the entropy, it is assumed that $0 \log_2 0 = 0$. Intuitively, the response entropy increases with the number of responses encoded by the neuron. The entropy is zero, $H(R) = 0$ bits, if the neuron generates only a single response, say $r = r_0$, irrespective of the stimulus. In this case, the response is completely predictable, and the neuron thus conveys no information about the stimuli. On the other hand, the response entropy is maximal if each response symbol is observed equally often. In this case, the response is completely unpredictable, $H(R) = \log_2 N$ bits, and the neuron transmits the maximum information possible.

In real neurons, the mapping between stimuli s and responses r is usually stochastic, in which

case the neural response becomes less predictable from the stimulus. To compute the actual information conveyed, this undesirable effect needs to be measured and subtracted from the response entropy. The so-called noise entropy measures how much the response fluctuates for a given stimulus s and is evaluated as

$$H(R|s) = - \sum_{i=1}^N p(r_i|s) \log_2 p(r_i|s) \quad (5)$$

The mutual information is defined as the difference between the response entropy and the average noise entropy so that

$$I(R; S) = H(R) - \langle H(R|s) \rangle \quad (6)$$

where the angular brackets denote averaging over all stimuli s . Note that if $H(R|S) = 0$ bits, i.e., the mapping between stimulus and response is noise-free, the mutual information equals the response entropy.

The efficiency of a neural code is often quantified either directly as the mutual information, $I(R; S)$ (Borst and Theunissen 1999), or as the ratio

$$\varepsilon = \frac{I(R; S)}{H(R)} \quad (7)$$

(Rieke et al. 1997). The closer ε to one, the smaller the noise, and the more the neuron makes use of its full capacity to encode information about the stimulus.

The Efficient Coding Hypothesis

The efficient coding hypothesis states that neural systems strive to employ their full information capacity in response to natural stimuli. The natural stimuli encountered by animals are often characterized by high redundancy, meaning that parts of an image or a sound can often be predicted by knowing the rest of the image (or the sound). The task of a sensory representation is then to eliminate this redundancy. If the response entropy is maximized, the neural responses by themselves

are unpredictable, and all redundancy has been removed. If at the same time, the noise entropy is minimal, then the responses are also highly informative about the stimulus (see Eq. 6). The original formulation of the efficient coding hypothesis relied on mutual information as the key quantity to measure efficiency (Attneave 1954; Barlow 1961). However, in many instances, it has proven fruitful to assume a specific neural code, then reconstruct the original stimulus, and use the quality of this stimulus reconstruction to evaluate efficiency (Bialek et al. 1991; Rieke et al. 1997). The efficient coding hypothesis has been successfully applied both to invertebrate systems (Rieke et al. 1997; Borst and Theunissen 1999; Fairhall et al. 2001; Machens et al. 2001, 2005), mostly focusing on single neurons, and to vertebrate systems (Olshausen and Field 1996; Simoncelli and Olshausen 2001; Smith and Lewicki 2006), mostly focusing on populations of neurons. Here we focus on invertebrate systems.

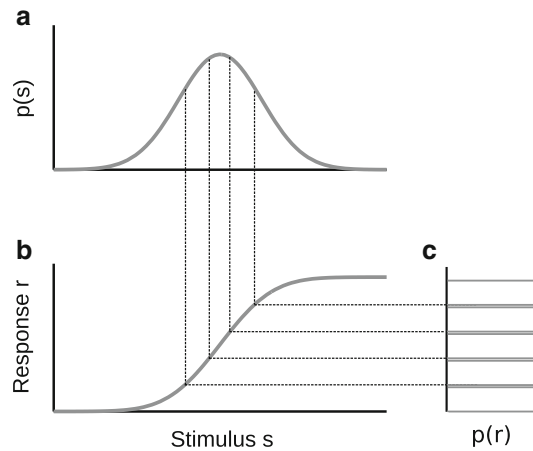
Consequences and Experimental Evidence

Stimulus–Response Function of Single Neurons

In the simplest case, the stimulus s and response r are one dimensional (e.g., sound intensity or luminance of a stimulus, and firing rate or voltage response of a single neuron). The so-called input–output or stimulus–response function f maps the stimulus s onto the response r , i.e., $r = f(s)$. How should the stimulus–response function be shaped to maximize the efficiency of a sensory system?

In the limit of relatively small noise or response variability, the question can be answered precisely by resorting to probability densities and differential entropies (Laughlin 1981). The stimulus–response function should then be the cumulative probability function of the stimulus distribution $p(s)$, or

$$r = f(s) \propto \int_{-\infty}^s p(s') ds', \quad (8)$$

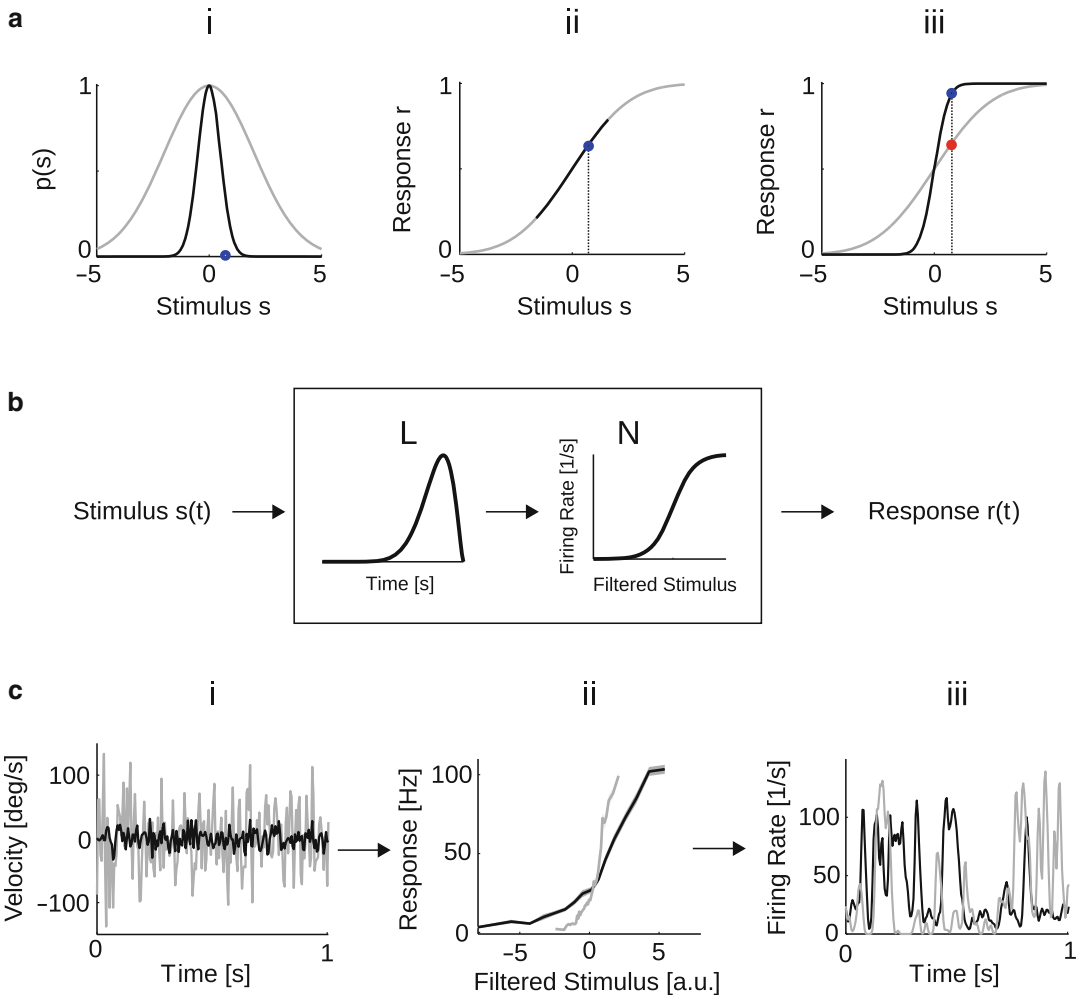


Sensory Coding, Efficiency, Fig. 2 Optimal stimulus–response function for a single neuron. (a) The stimuli represented by the sensory neuron follow the distribution $p(s)$. (b) The sensory system transforms the stimulus s to the neural response r carrying information about s . (c) According to the efficient coding hypothesis, the neural code is most efficient, if each response r occurs with equal probability $p(r)$. This is the case, if the stimulus–response function is proportional to the integral of the stimulus distribution $p(s)$

because in this case, all responses are equally likely. This so-called histogram equalization maximizes the response entropy and thereby the mutual information in the noise-free case (see explanations above and Fig. 2). Evidence that the input–output function of sensory neurons is indeed matched to the stimulus statistics has been provided for the large monopolar cells in the visual system of the blowfly (Laughlin 1981). The voltage of these neurons is sensitive to luminance contrasts. Measuring the contrast distribution within typical habitats of the fly revealed that the input–output function of the monopolar cells is indeed very close to the integrated stimulus distribution.

Adaptation of Stimulus–Response Functions in Single Neurons

The distribution of stimuli experienced by an animal will vary over time. Typically, the “local” distribution of stimuli encountered over a shorter time interval will differ from the “global” distribution of stimuli encountered over long stretches of time (Wark et al. 2007).



Sensory Coding, Efficiency, Fig. 3 Gain control and efficient coding. (a) Two local stimulus distributions differing in their standard deviation (a i). a ii and a iii illustrate two different coding schemes: For each local distribution, the stimulus s is represented by the same, fixed input-output function (a ii). Contrarily in a iii, the input-output function adjusts its gain to the current stimulus statistics such that each local distribution is efficiently encoded by the neural response. (b) Linear-nonlinear models are frequently applied to characterize sensory neurons. In this model, the stimulus is first convolved with a linear filter (L). The filter output is then fed through a static

nonlinearity (N) yielding a prediction of the instantaneous firing rate. The static nonlinearity can be viewed as the time-averaged stimulus-response function of the neuron. (c) The H1 neuron adjusts its gain to the statistics of the presented white-noise stimulus. In this example, two white-noise stimuli differing in their standard deviation have been presented to H1 (c i). Increasing the standard deviation of the stimulus leads to a decrease of the slope (gain) of H1's input-output function (c ii). Consequently, H1 represents both stimuli with its full response range (c iii)

A simple example is the distribution of light intensities or contrasts, which change strongly throughout the day or with the weather. For illustration, Fig. 3ai shows two different local stimulus distributions which differ in their standard deviation.

An “efficient” sensory neuron can deal with this problem in two possible ways, as illustrated in Fig. 3a. In the first solution (Fig. 3aii), the input-output function of the neuron is fixed and proportional to the global stimulus distribution. The neuron will be efficient for the global

distribution, but inefficient for any local distribution. In the second solution (Fig. 3a_{iii}), the input-output function of the neuron changes with the local stimulus distribution such that it is proportional to the integral of the current distribution. It will now be efficient for the local distribution, but inefficient for the global distribution. Given that neural responses are usually corrupted by noise, the two solutions represent trade-offs. In the first coding scheme, the local stimulus distributions are mapped onto a rather small response range (Fig. 3a_{ii}), and many of the smaller stimulus changes may be lost in the response noise. In the second coding scheme, the responses become ambiguous across different local stimulus ensembles, and the respective global information is lost (Fig. 3a_{iii}). In practice, some of the ambiguities can often be avoided if the neuron's responses can vary on different time scales. In the fly, for instance, the motion-sensitive neuron H1 changes its gain instantaneously when the variance of the presented stimulus ensemble is changed, yet the mean firing rate changes only slowly. Hence, the slow changes of the mean firing rate allow the sensory system to track slow changes in the encountered stimulus distribution (Fairhall et al. 2001).

Various studies demonstrated that sensory neurons adjust their input-output function to the local stimulus distribution (Fairhall et al. 2001; Brenner et al. 2000; Borst 2003; Borst et al. 2005; Weber et al. 2010; Rinberg and Davidowitz 2000; Geffen et al. 2009; Laughlin 1981). As an example from the fly, responses of the motion-sensitive neuron H1 to varying stimuli are shown in Fig. 3c. Here, two sets of motion stimuli that differ in the standard deviation of their velocities have been presented to the fly (Fig. 3c_i). To analyze the neuron's input-output function, a so-called linear-nonlinear (LN) model was fitted to the neural responses (see Fig. 3b). In this model, the time-varying stimulus is first convolved with a linear filter, and the filtered stimulus is then fed through a static nonlinearity, which models the neuron's input-output function. As shown in Fig. 3c_{ii}, the gain of the input-output function, as given by its slope at half maximum, is larger for the velocity profile with smaller standard deviation. Hence, the neuron is sensitive to small changes in the

stimulus. Contrarily, if the gain is small, similar stimulus values elicit similar responses. Since the gain of H1 is adjusted to the statistics of the applied velocity distribution, both stimuli are represented with H1's full response range: While the variance of both stimuli strongly differs, both response profiles in Fig. 3c_{iii} exhibit a similar variance. Thus, both stimulus distributions are efficiently represented with H1's full dynamic response range.

Maximization of Information Rates in Single Neurons

The stimulus-response functions considered above operate with spike counts or firing rates and therefore do not fully capture the inherent capacity of spike trains. The information present in a neural spike train can be measured by using the mutual information, either indirectly (e.g., by assessing the quality of a reconstruction Bialek et al. 1991; Theunissen and Miller 1991) or by binning spike trains into words and computing the mutual information between the spike timing code and the stimulus (Strong et al. 1998). In practice, these computations usually require large amounts of data since the number of stimulus and response symbols increases exponentially with the number of neurons or the length of time windows. Additionally, estimating mutual information is prone to systematic errors (or biases) if the amount of data is insufficient (Strong et al. 1998; Paninski 2003).

For single neurons, such estimates of the mutual information have usually been possible and have been computed in many systems (Rieke et al. 1997; Borst and Theunissen 1999). In turn, the information rates of different stimulus ensembles can be compared. In cockroaches, for instance, the information rates of wind-sensitive neurons change with the overall shape of the wind spectrum. If the wind spectrum shape is similar to that of an approaching predator, such as a spider, information rates are maximized (Rinberg and Davidowitz 2000). Consequently, the sensory neurons are tuned to a subspace of behaviorally relevant stimuli that convey information about predators.

In the grasshopper auditory system, information rates are maximized when the spectrum of the sounds approaches the frequencies common in grasshopper communication calls (Machens et al. 2001). Using these measures of information rates, the efficient coding hypothesis can also be inverted: Knowing the input–output function of a neuron allows one to deduce the distribution of the optimally represented stimuli. This approach has been applied to grasshopper auditory receptor neurons (Machens et al. 2005). Instead of being tuned for the average distribution of natural stimuli, the investigated neurons have been found to be optimized for behaviorally important subensembles of natural sounds, which are related to grasshopper sounds. These studies demonstrate that sensory neurons rather encode a behaviorally relevant subspace of stimuli than the distribution of all naturally occurring stimuli.

Information rates can also be used to test a system's efficiency with respect to its biophysical parameters such as the connection weights between two neurons. Using a combination of data analysis and modeling, it was shown that the coupling strength between two global motion-sensitive neurons in the blowfly, Vi and H1, is information-theoretically optimal: Changing its value, either experimentally or in simulations, led to a decrease of the information carried by the spikes (Weber et al. 2012).

Efficiency of Neural Populations

Many studies of sensory coding in insect systems have focused on single neurons. While the insect nervous system knows many instances where single neurons represent actual information bottlenecks, most information is still processed in (small) neural populations. What does the efficient coding hypothesis predict about neural populations?

In general, the efficiency of a population code can be evaluated with the same criteria as the efficiency of a single neuron. If the efficiency is measured through the mutual information, then one important aspect of an efficient code is that the response distributions of all neurons need to be statistically independent of each

other. For a population with M neurons, an efficient code therefore requires that $p(r_1, \dots, r_M) = \prod_{k=1}^M p(r_k)$. A neural population code that fulfills this condition is called a factorial code. This requirement is often difficult to fulfill. A weaker condition is that the response distributions of each neuron pair are decorrelated.

These considerations illustrate the importance of redundancy reduction as an integral part of the efficient coding hypothesis. Statistically independent or decorrelated representations will generally have a much lower degree of redundancy than the original stimulus input. The efficient coding of neural populations has been extensively investigated in various vertebrate systems (Simoncelli and Olshausen 2001; Simoncelli 2003), with only some studies on insect sensory systems (Broome et al. 2006; Geffen et al. 2009; Olsen et al. 2010). Similar to neural populations in vertebrate systems, neural populations in insects decorrelate their responses. This has been demonstrated in the olfactory system of the fly (Olsen and Wilson 2008; Olsen et al. 2010). In the antennal lobe, the second stage of olfactory processing, the so-called projection neurons receive input from the presynaptic olfactory receptor neurons (ORNs). ORNs expressing the same odorant receptor project to the same glomerulus. Different glomeruli within the antennal lobe are interconnected by inhibitory interneurons. The size of the inhibition mediated by the interneurons scales with the strength of the feedforward input from the ORNs to a glomerulus. Interestingly, the interglomerular inhibition acts at the presynaptic locus of synapses connecting the ORNs to PNs. Hence, lateral presynaptic inhibition between glomeruli mediates a gain control mechanism which accounts for variations in the strength of odorant signals (Olsen and Wilson 2008). Second, modeling of the projection neuron responses revealed that the lateral inhibition decorrelates the population response (Olsen et al. 2010).

State-Dependent Efficient Coding

Sensory neurons adjust various properties such as their gain or connectivity to match the current behaviorally important stimulus ensemble.

However, the relevance of a particular stimulus set might depend on the behavioral state of the animal. For instance, animals that are hungry show a stronger attraction to food stimuli, than animals that are full (Sengupta 2013). This type of behavioral modulation and its implications on sensory processing have been studied in fruit flies. When flies are starved, olfactory receptor neurons express higher levels of a receptor for neuropeptide F. An increased level of neuropeptide F receptors leads to a facilitation of the synapse between the olfactory receptor neurons and secondary olfactory neurons. Hence, starvation enhances the strength of synapses in the olfactory system and, thus, causes an increased sensitivity to food odors (Root et al. 2011).

Apart from hunger, an animal's locomotion state also influences the response properties of its sensory neurons, as has recently been demonstrated for flying and walking flies (Maimon et al. 2010; Chiappe et al. 2010; Jung et al. 2011). Generally, the gain of motion-sensitive lobula plate neurons in walking or flying flies is strongly increased compared to stationary animals. This gain modulation is caused by increased inputs from presynaptic elements (Maimon et al. 2010). Assuming that increased synaptic inputs correlate with an increased energy consumption, the fly's visual system seems to tightly control its resources depending on the organism's needs. During flight, visual motion stimuli might be more relevant than during a quiescent state such that the overall activity can be lowered when the fly is not flying. Moreover, since the statistics of velocities is predictably different during flight, the gain increase might be interpreted as an adjustment of the neurons' coding properties to the velocity distribution encountered during flight.

In line with this hypothesis, flying and walking induce a pronounced shift in the velocity tuning curve of lobula plate neurons. When moving, the velocity tuning is shifted towards higher speeds. This effect is likely mediated by the neuromodulator octopamine. Direct application of the octopamine agonist CDM induces a similar shift in the tuning (Jung et al. 2011). Moreover, CDM causes an increase in the baseline firing rate similar to that observed for flying or walking flies. Additionally, CDM application enhanced the

information rate (Longden and Krapp 2009, 2010). Hence, the release of a neuromodulator can adjust the coding properties of sensory neurons to the current locomotor state.

Assuming that the relevance of particular stimuli changes with the behavioral state, these results can be reconciled with the efficient coding hypothesis: Sensory neurons regulate their properties to efficiently encode what is currently behaviorally important.

Outlook

Many insect sensory neurons seem to be adjusted to the currently prevailing stimulus statistics and to the behavioral state of the animal. A large set of studies has furthermore elucidated the adaptation of sensory neurons to the ever-changing stimulus statistics of their environment. Most of these studies have been performed in "passive" animals that were not interacting with their environment. In contrast, the dependency of sensory processing on an animal's internal state or its current behavior has been less well studied. In the future, experimental work may give more insight into the biophysical mechanisms and circuits that underlie these state-driven changes in the tuning of sensory neurons. Furthermore, theoretical concepts may help to explain these changes from a normative point of view. For instance, is the state dependency of sensory neurons, such as the gain decreases in fly visual neurons during immobility, due to a necessity to save metabolic energy? Or is the state dependency fully explained by sensory adaptation to the animal's internal expectations, such as the expected distribution of motion stimuli during immobility or flight? We believe that addressing these types of questions will help us to more thoroughly understand sensory processing in animals that interact actively with their environment.

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Sensory Drive to Rhythmic Neuronal Networks

► Sensory Input to Central Pattern Generators

Sensory Input to Central Pattern Generators

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Synonyms

[Afferent feedback to neural oscillators](#); [Afferent input to rhythm generating networks](#); [Proprioceptive feedback to central pattern generators](#); [Sensory drive to rhythmic neuronal networks](#); [Sensory modulation of central pattern generators](#)

Definition

A central pattern generator (CPG) is an assembly of neurons (neuronal network) that produces rhythmic activity without requiring phasic input signals and often drives the motor system and rhythmic muscle movements. Sensory feedback to a CPG circuit is the return signal from the sensory system in response to this rhythmic muscle movement, which conveys a continuous measurement of the output behavior to the CPG.

Detailed Description

Individual neural networks, such as CPGs, can generate rhythmic output patterns even in the absence of any phasic input. They drive vital behaviors such as breathing, swallowing, and chewing, as well as locomotion and saccadic eye movements, and often continue to function even in isolated nervous system (i.e., in vitro) preparations (Marder and Calabrese 1996; Grillner et al. 2005; Dickinson 2006; Gordon and Whelan 2006; Isa and Sparks 2006; Kiehn 2006; Katz and Hooper 2007; Chevallier et al. 2008; Doi and Ramirez 2008; Berkowitz et al. 2010; El Manira et al. 2010; Büschges et al. 2011; Harris-Warrick 2011; Marder 2012). Given the improved accessibility for neuronal manipulations in vitro, it is

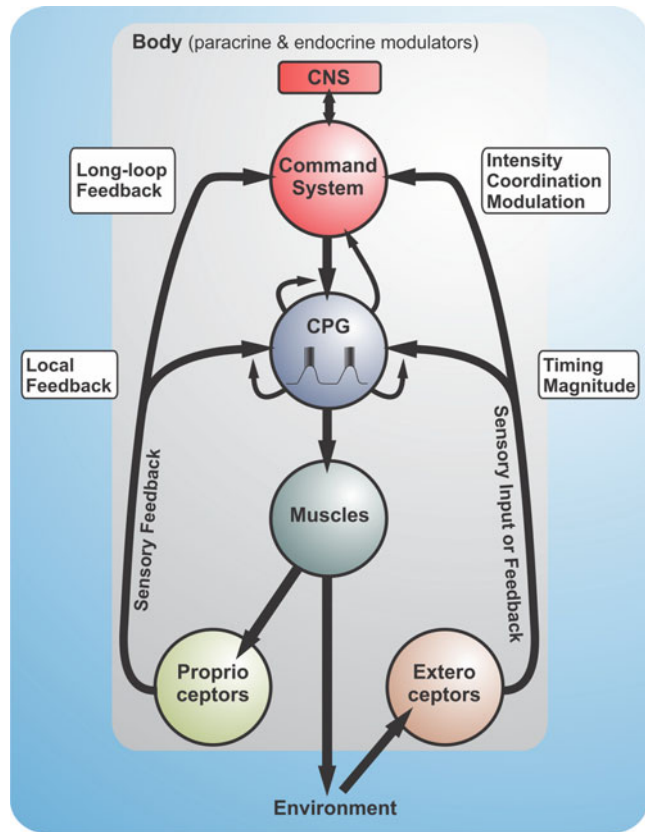
not surprising that most insights into the rhythm generating mechanisms of CPGs have been derived from this condition, and hence using preparations deprived of sensory information. In vivo, however, numerous additional influences have access to the CPG circuit from other CNS regions, circulating hormones, and sensory systems (Fig. 1). In particular for driving motor behaviors, CPGs receive constant feedback from peripheral sense organs, including proprioceptors. While CPGs may also contribute to cognitive functions (e.g., theta and gamma rhythms in the hippocampus; Grillner et al. 2005), this essay focuses on CPGs underlying motor pattern generation because the influence of sensory feedback is particularly obvious in these CPGs.

Sensory Feedback Versus Sensory Input

Sensory feedback differs from *sensory input* in that it provides the CPG with a continuous readout of the consequences of CPG activity on the resulting behavior. Typically, the sense organs providing *sensory feedback* to CPGs are proprioceptive, that is, they continuously measure the response of the muscles to the rhythmic motor output and thus show phasic activity patterns. Exteroceptive sense organs, in contrast, typically provide *sensory input*, rather than *feedback*, about changes in external conditions. They are not necessarily related to CPG activity, although in some cases they can be. To demonstrate this difference, imagine eating an almond chocolate truffle. You take a first bite from the soft chocolate layer of the truffle and your periodontal mechanoreceptors (peripheral receptors that signal information about tooth load; Bonte et al. 1993) will initially encounter little resistance and will thus either be inactive or continuously active at a low level and hence provide *sensory input*. As you encounter the almond with your second bite this changes dramatically and the periodontal mechanoreceptors now register a strong mechanical load, and they do so whenever your teeth meet the almond, in phase with the chewing pattern, providing a signal that chewing strength needs to be increased. In other words, they now provide *sensory feedback* that is directly related to the motor output. In contrast, typical proprioceptors, such as

Sensory Input to Central Pattern Generators,

Fig. 1 Schematic overview of sensory input to a CPG. For simplicity, the motor neurons are not shown separately. The CPG receives input from proprioceptive and exteroceptive pathways. This input either directly affects the CPG (local feedback) and/or is mediated via upstream control neurons (long-loop feedback). Local feedback mainly determines the magnitude and timing of CPG activity, while long-loop feedback has modulatory effects, regulates intensity and coordinates CPG activity with other motor acts. CPG activity itself can modulate incoming sensory feedback, for example, via presynaptic inhibition of the afferent pathways. *CNS* central nervous system



muscle spindles that mainly measure the stretch of muscles, provide phasic *feedback* at all times, even in the unlikely event that the manufacturer of the chocolate truffle forgot to put in the almond.

Sensory *input*, due to its (partial) independence of CPG activity, often initiates or modulates the intensity of the motor pattern on a longer time scale, adapts CPG activity to external conditions and coordinates it with other motor acts to maintain equilibrium during behavior (Grillner 2003; Dickinson 2006; Stein 2009; Blitz and Nusbaum 2011; Harris-Warrick 2011; Marder 2012). Many actions of sensory input pathways are mediated via intercalated interneurons that process many different sensory modalities and often exert modulatory influences on the CPG circuits.

Local Sensory Feedback

The role of local sensory feedback on CPG activity has been particularly well studied. CPGs are often located close to the musculoskeletal system

they control and they receive local feedback from that system (via proprioceptive pathways, or, in some cases, directly from dendrites of CPG motor neurons; Garcia-Crescioni et al. 2010). Local sensory feedback typically modifies and adapts CPG activity on a short time scale (Pearson 2004) by altering magnitude and relative timing of muscle activity. Conceptually, local sensory feedback to a CPG serves at least three main functions:

1. *Corrective input*: It can provide a corrective signal to adapt CPG patterns to deal with environmental perturbations. Corrective feedback is necessary in an unpredictable environment, for instance, to reinforce CPG activities that drive fin or body movements during swimming in rough water or to adjust wing beat in a turbulent air stream.
2. *Timing*: It can contribute to CPG activity in an *ongoing* fashion, during unperturbed motor pattern production, by providing timing cues

about the biomechanical state of the moving body part(s). During walking in cats and insects, for example, phase transitions are facilitated by sensory feedback that depends on the biomechanical state of the leg (Büschges 2005). This sensory feedback ensures that a certain phase of the movement (e.g., the swing phase) is not initiated until the appropriate biomechanical state of the leg (the posterior extreme position) has been achieved. It provides information about limb and appendage position in space and thus allows for adapting and planning of movements.

3. *Stability*: By ensuring that the timing and force output of a motor pattern is appropriate for the task at hand, local sensory feedback can also lead to a stabilization of the motor pattern. The tegula, a wing proprioceptor in locusts, for example, is excited during wing depression and hence provides feedback about the position of the wing and facilitates phase transitions (Wolf 1993). In addition, however, the tegula acts to stabilize the flight rhythm: If its nerve is stimulated with a relatively weak shock, activating only a few of the tegula's sensory neurons, the flight rhythm speeds up (Ausborn et al. 2007). If it is stimulated strongly, the pattern slows. This example nicely demonstrates that proprioceptors can have a pivotal influence on the pattern generating machinery in vivo: they work together with the CPG to ensure that the behavioral output is continuously adjusted to maintain functioning and stability of the desired pattern.

Due to these essential functions of local sensory feedback, in most systems behaviorally appropriate motor pattern generation requires both CPG activity and sensory feedback, with sensory and central mechanisms being integrated to produce a robust rhythmic activity pattern that can be rapidly adjusted to cope with unpredictable environmental disturbances.

Sensory Gating and Phase Dependent Modulation of Sensory Feedback

As is likely true for all aspects of neural signaling, the effect of sensory feedback on CPG activity is

modified by many influences. For instance, it can vary with the phase of the motor pattern at which it is given.

For example, during stick insect walking, the influence of the campaniform sensilla, which measure load of the leg, always supports phase transitions from swing to stance phase (Akay et al. 2007). Functionally, this makes sense: when load is high this means that the leg must be on the ground and stance phase should commence. Interestingly, the effect of the load receptors on the protractor and retractor muscles that move the leg forward and backward changes in sign with a switch from forward to backward walking. During forward walking, a transition from protractors to retractors is facilitated, while during backward walking transitions from retractor to protractor activity are elicited.

Another example, also from the walking system, is the phase-dependence of local sensory feedback. A perturbation that occurs during the swing phase of the leg (e.g., when the foot hits a step when climbing up a stairway) usually results in the leg being lifted to enable it to reach the next step. During the stance phase, the same stimulus causes a further descending of the leg to increase force between foot and ground, which enhances stability. Such reflex reversals have been observed in many motor systems (Skorupski and Sillar 1986; Bässler 1993; Burrows 1996), but the neuronal basis for this switch in sign is not well understood.

There are two principle possibilities for how such a reflex reversal can be achieved (Hooper 2000): (1) a differential (phase-dependent) routing of sensory feedback to different CPG neurons; and (2) a varying response by the CPG network to sensory feedback due to how the network integrates the input during different phases of the pattern. In locusts, for example, the sensory feedback from the femoral chordotonal organ, which measures the position of the femur-tibia joint during walking, is gated with the phase of the walking motor pattern, disabling feedback during certain phases of this pattern (Wolf and Burrows 1995). The underlying mechanism is a phase-dependent presynaptic inhibition of the sensory terminals and a concomitant decrease in

transmitter output. While sensory activity remains unchanged, sensory transmission to the CNS is impaired. Since presynaptic inhibition is typically strongest whenever sensory activity is high, it reduces the overall amount of sensory feedback, and, quite peculiarly, it also diminishes *expected* sensory feedback at certain phases of the CPG pattern. Presynaptic inhibition could thus be one mechanism that underlies the reafference principle, which tries to explain the fact that self-initiated motions do not interfere with the perception of constancy [proposed by von Holst and Mittelstädt (1950)]. One way to achieve this goal is via an efference copy of the motor signal (in this case the CPG output) which provides the input to a forward internal model. This model is then used to generate the predicted sensory feedback that estimates the sensory consequences of the motor command. This signal is sent to the periphery, where it (presynaptically) inhibits any proprioceptor response to the CPG-generated movement which could interfere with the execution of the motor task. Differences in the actual from the predicted sensory activity are then sent back to the CPG as an error signal to adapt the motor output. While the pathways that elicit the presynaptic inhibition are still somewhat nebulous, it has been demonstrated that proprioceptors can presynaptically inhibit the terminals of neurons from other proprioceptive sense organs (Stein and Schmitz 1999). Since proprioceptors typically show phasic activity, this could contribute to the gating of sensory feedback at specific phases of the motor pattern.

While CPG activity can affect transmitter release from sensory neurons (Wolf and Burrows 1995), so far there are no indications that CPGs can directly modulate sensory spike activity. However, CPGs may indirectly affect sensory spike activity via feedback onto modulatory neurons that not only control CPG activity, but also release neuromodulatory substances in a paracrine fashion. Neuromodulators, in turn, affect both muscle contraction and sensory activity, which makes it possible for CPGs to interfere with sensory spike activity, at least in principle (Städle et al. 2018). The activity of the anterior gastric receptor (AGR) in the stomatogastric nervous

system of crustaceans, for example, can switch from spiking to bursting, depending on the modulatory conditions present (Birmingham et al. 1999). While in spiking mode, AGR encodes both rapid and slow stimuli and thus reports cycle-by-cycle muscle movements that are driven by the CPG. In bursting mode, however, only persistent stimuli are detected and thus average levels of muscle tension are reported. This example demonstrates that the same proprioceptor can provide feedback about different qualities of the CPG output.

Context or Task-Dependent Modulation of Sensory Feedback

While phase-dependent modulation affects sensory feedback on a cycle-by-cycle basis, sensory feedback can also be subject to long-term modulation, either via the actions of neuromodulators released from neurons (paracrine, as stated in the previous paragraph) or the endocrine system (hormones) that modify the sensory response itself (Birmingham 2001) or via a modulation of the response of the CPG network to sensory input. In the stomatogastric nervous system of crustaceans, for example, changes of a few Hertz in the tonic activity of the AGR muscle proprioceptor modify the response of the gastric mill (chewing) CPG network to sensory input from mechanoreceptors in the stomach (Daur et al. 2009). Magnitude and timing of the gastric mill motor pattern elicited by the mechanoreceptive input correlate with the tonic spike activity of the muscle receptor, which means that the state of the system and its response to incoming sensory input is modified.

What Drives Rhythmic Behavior In Vivo: Sensory Feedback or CPG Activity?

Discussion regarding whether the CPG or the sensory feedback drives the actual behavior of an animal in vivo is as old as the discovery of CPG circuits. There is no universal answer, because their relative impact appears to differ from system to system. Büschges et al. (2011) draw the conclusion that, although clearly affected by sensory feedback, CPGs that drive locomotor movements in homogeneous media

such as air (flying) or water (swimming) often continue to be rhythmically active even when isolated from sensory feedback. In contrast, CPGs that drive locomotion in heterogeneous environments, such as terrestrial locomotion, typically lack rhythmic activity in isolation from local sensory feedback. This distinction, however, does not necessarily mean that sensory feedback does not shape the rhythmic movement. In locust flight, for example, the CPG can be activated in isolation and will show a stable flight pattern, but in vivo several sense organs, including the tegula, provide feedback to the CPG and dominate the motor pattern. The frequency of the rhythm, however, increases by a factor of two, which is why in this system sensory feedback is seen as a major contributor to the functional motor pattern (Ausborn et al. 2007).

While in this example there would be no flight pattern without CPG activity, theoretical approaches have proposed that sensory feedback itself could act as an oscillator if provided with the adequate properties, such as delay lines and gain (Cruse 2002). For example, a network with negative sensory feedback will produce stable oscillations if the open-loop gain is equal or larger than 1 at a frequency where the phase-shift is 180° (Nyquist criterion). It should be noted though that for nonlinear systems such as neural networks more complex stability criteria such as Lyapunov or the circle criterion, might be necessary. Networks with positive feedback, on the other hand, need a high-pass filter or related mechanism that reduces the positive feedback to create stable oscillations (Bässler 1986). In both cases, the oscillations would be driven entirely by sensory feedback and might not even require a central oscillatory network. In such a case, the system would be called a chain reflex (because a system that *must* be driven by sensory input is defined as a reflex). In fact, a chain reflex may not be distinguishable from a CPG in vivo (Bässler 1986). If we consider a relaxation oscillator as a pattern generating circuit (e.g., a half-center circuit with reciprocal inhibition, as is found in many systems), the frequency of the oscillations would depend on the endogenous excitation of the loop

and its internal characteristics (gain and time constant of the fatigue of the positive feedback). Sensory feedback could affect oscillation frequency either by affecting the intrinsic characteristics or by modifying the excitation state of the network. Even in the easiest situation of a simple addition of excitation to the oscillator neurons by the sensory feedback, the timing cues for switching between oscillation states would depend on the sensory feedback, and the CPG would only be responsible for managing the actual switch between phases. If the endogenous excitation in such a relaxation oscillator network would fall below the threshold for oscillations, the sensory feedback could substitute for the lack of endogenous excitation and elicit oscillations. Per definition, this would then be a chain reflex.

Even if the CPG consists of a negative feedback loop (such as serial inhibition in a network with an odd number of neurons), sensory feedback would drive the frequency of the oscillation. In such a system, the CPG oscillation frequency depends on the amplitude and phase-frequency oscillations of the open-loop system. If sensory feedback is added to the system, the eigenfrequency stays the same and the sensory input will be damped and superimposed on the inherent (CPG) oscillations (Cruse 2009). The resulting frequency will thus be a superposition of central and sensory oscillations. Sensory feedback, however, will entrain the central oscillations within a given range. Thus, the CPG represents a band-pass filter for the sensory oscillation. In the passband, the timing cues of the oscillations are determined by the sensory feedback. In summary, determining whether the CPG or sensory feedback dominates the behavior of the oscillatory system in vivo, although of pivotal importance for understanding the dynamics of motor systems, continues to challenge studies of CPG function.

Long Loop Sensory Feedback and Long Lasting Effects of Sensory Feedback

While one role of sensory feedback is to allow the CPG to deal with environmental perturbations (corrective input), certain motor pattern characteristics such as phase relationships must be

maintained to guarantee functional and behavioral homeostasis. Sensory changes from one part of the pattern, for example, might require compensatory changes in other parts. Thus, the effects of local sensory feedback might have widespread and possibly long-lasting effects.

Sensory pathways also affect CPGs indirectly, by influencing the neurons that control the CPGs. In the locomotor systems of cats and lampreys, for example, supraspinal networks in the brainstem receive sensory input from many modalities, including proprioceptive feedback (Rossignol et al. 2006). While in general these upstream neurons are involved in pattern initiation, modulation, and selection, the uniquely identifiable reticulospinal Mauthner and Müller cells in lampreys display movement related activities that appear to be elicited by ascending feedback from the CPGs (Antri et al. 2009; Buchanan 2011). This is similar to modulatory projection neurons that control the CPGs in the stomatogastric nervous system (Blitz and Nusbaum 2012). Here, ascending feedback from CPG neurons impose a rhythmic activity pattern onto these modulatory neurons. In both cases, neurons outside of the CPG have access to the timing of the CPG and they are affected by sensory input. In the stomatogastric nervous system, phasic sensory feedback affects the very set of projection neurons that shows CPG timing (Hedrich et al. 2009), which allows for a long-loop sensory control of CPG activity. In lobsters, for example, the phasing of CPG activity can reverse activity if the proprioceptive AGR neuron exceeds a certain threshold (Combes et al. 1999), due to the bistable intrinsic properties of modulatory projection neurons that process sensory feedback from AGR.

Open-Loop Versus Closed-Loop Sensorimotor Interactions

Even if sensory feedback only exerts short-acting effects, compensatory changes in the motor pattern may occur and induce global, long-lasting changes in the CPG pattern, because the activity changes of the neurons targeted by sensory feedback may induce changes in a chain of followers. Yet, relatively little is known about such holistic

sensorimotor interactions. This is mostly due to the fact that while sensory feedback has been studied in many motor circuits, this was typically done in open-loop conditions, that is, with emphasis on how sensory signals alter motor output (rather than interact with it), or on information flow toward that output. The dynamical components determined by the interaction of motor and sensory activities, however, can create emergent properties that govern the functional characteristics of the system. While already a standard for investigating movement or behavior in general (e.g., fly and bee flight: Dickinson 2005; Fry et al. 2008; Mronz and Lehmann 2008; Sareen et al. 2011; Srinivasan 2011; monkey motor control and vision: Nicolelis 2003), the idiosyncratic dynamics created by the sensorimotor interaction have only rarely been elucidated at the level of the nervous system.

One reason for the discrepancy between closed-loop behavioral and open-loop nervous system studies is the unfortunate fact that sensory structures, and thus also sensory feedback, are typically not available in experiments performed in isolation from the body. The functional and circuit properties as well as the cellular characteristics of CPG networks, however, are only known in great detail because of their accessibility in isolated preparations. In contrast, in systems with well-characterized behavior and sensory structures, the underlying neural network is usually not well-described. One way to circumvent this problem is to provide artificial sensory feedback that depends on the motor output, in real-time, to the isolated CPG circuit. Thus far, in the few instances in which such closed-loop experiments have been performed (Bässler and Nothof 1994; Ausborn et al. 2007; Smarandache et al. 2008; Ausborn et al. 2009), it is clear that sensorimotor interactions pivotally shape the motor output. Given the fact that sensory feedback also affects the upstream neural structures that control the motor circuits, it seems reasonable to assume that sensory feedback in closed-loop conditions will have an impact on the motor pattern that goes beyond simple influences on timing and magnitude. Rather, emergent properties of sensorimotor interactions are to be expected.

Indirect and Long-Term Influences of Sensory Feedback

While the immediate influences on timing and magnitude of sensory feedback are well-studied, sensory feedback also has long-term influences on CPG activity.

1. Development of vital rhythmic activities: It is still unclear whether sensory feedback is needed during early nervous system development (Suster and Bate 2002). A lack of feedback, however, leads to dysplasia or coordination problems later in life.
2. Stability and robustness of the motor pattern during the life span of the animal. While motor circuits must be flexible in order to respond to changes in the environment or the body conditions, they must also generate stable patterns and be robust against perturbations. Emergent properties of sensorimotor interactions may well supply the basis for stability and robustness and may even help to select the adequate motor pattern, biasing the system towards specific patterns. In particular when environmental or neuromodulatory conditions change, robustness must be present. Failures of this control may be fatal (e.g., sudden infant death syndrome).
3. Recovery from injury. Continuous CPG activity requires CNS input and removal of this input causes a failure of the motor pattern. While there is some evidence that continuous entrainment of the motor patterns via sensory feedback supports recovery (e.g., after spinal cord injury; Rossignol and Frigon 2011; Mehrholz et al. 2012), it is far from clear what mechanisms drive recovery. Emergent properties during sensorimotor interactions might support recovery, in particular if neuromodulatory neurons (long-loop sensory influences) are involved. Sensory feedback could in this case replace the missing endogenous excitation of the CPG network.

In summary, while CPGs generate rhythmic activity patterns that have similarities to the behavioral patterns, sensory feedback pivotally shapes the CPG output. While the short-term and

direct actions of sensory feedback on CPG activity are well-described, their long-term actions and sensorimotor interactions in closed-loop conditions are a focus of current studies.

Cross-References

- ▶ [Bursting in Neurons and Small Networks](#)
- ▶ [Comparative Analysis of Half-Center Central Pattern Generators \(CPGs\)](#)
- ▶ [Computational Analysis of Rodent Spinal CPG](#)
- ▶ [Computational Models of Mammalian Respiratory CPG](#)
- ▶ [Control of Aquatic and Terrestrial Gaits in Salamander](#)
- ▶ [Control of Locomotion and Scratching in Turtles](#)
- ▶ [Coupled Oscillations in Neural Control of Breathing](#)
- ▶ [Gap Junctions in Small Networks](#)
- ▶ [Invertebrate Pattern Generation: Overview](#)
- ▶ [Invertebrate Sensory Systems: Overview](#)
- ▶ [Locomotor Pattern Generation in the Rodent Spinal Cord](#)
- ▶ [Multistability Arising from Synaptic Dynamics](#)
- ▶ [Multistability of Coupled Neuronal Oscillators](#)
- ▶ [Neuromodulation in Small Networks](#)
- ▶ [Pre-Botzinger Complex Rhythm Generation](#)
- ▶ [Rhythm Generation in Embryonic Chick Spinal Cord](#)
- ▶ [Rhythm Generation in Young *Xenopus* Tadpoles](#)
- ▶ [Short-Term Synaptic Plasticity in Central Pattern Generators](#)
- ▶ [Spinal and Neuromechanical Integration: Overview](#)
- ▶ [Stability and Homeostasis in Small Network Central Pattern Generators](#)
- ▶ [Two-Level Model of Mammalian Locomotor CPG](#)
- ▶ [Vertebrate Pattern Generation: Overview](#)

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Further Reading

Scholarpedia Articles on Central Pattern Generators and Sensory Feedback

- Motor coordination. http://www.scholarpedia.org/article/Motor_coordination
- Periodic orbits and dynamical systems. http://www.scholarpedia.org/article/Periodic_orbit
- The spinal cord. http://www.scholarpedia.org/article/Spinal_cord
- The stomatogastric ganglion. http://www.scholarpedia.org/article/Stomatogastric_ganglion
- The Tritonia swim network. http://www.scholarpedia.org/article/Tritonia_swim_network

Facebook Pages on Central Pattern Generators

- <https://www.facebook.com/pages/Central-pattern-generator/138633789494277?nr>

Wikipedia Articles on Central Pattern Generators and Feedback

- Central pattern generation. http://en.wikipedia.org/wiki/Central_pattern_generator
- Feedback. <http://en.wikipedia.org/wiki/Feedback>
- Locomotion and the spinal cord. http://en.wikipedia.org/wiki/Spinal_Locomotion
- Neural oscillations. http://en.wikipedia.org/wiki/Neural_oscillation
- The efference copy. http://en.wikipedia.org/wiki/Efference_copy
- The scratch reflex. http://en.wikipedia.org/wiki/Scratch_reflex

Sensory Modulation of Central Pattern Generators

- [Sensory Input to Central Pattern Generators](#)

Sensory Stimulation

- [Peripheral Nerve Interface Applications, Sensory Restoration](#)

Serial Sectioning Microscopy

- [Physical Sectioning Microscopy](#)

Serpentine Receptors

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Servo Control

- [Spinal Cord, Integrated \(Non CPG\) Models of](#)

Seven-Transmembrane Domain Receptors

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

SFC

- [Spike Triggered Average](#)

Shaking Palsy

- [Parkinson's Disease: Deep Brain Stimulation](#)

3D Shape Perception, Models of

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Definition

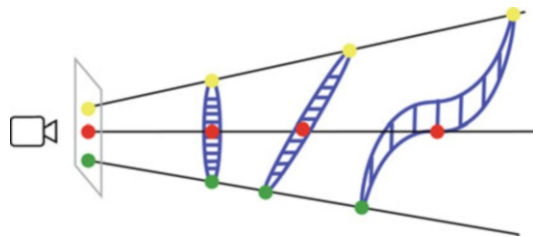
A 3D shape percept is the psychophysical response induced from a visual stimulus. The

percept is the result of (partially) unknown neural processes within the visual system. Psychophysical tests of performance have mainly involved humans, and most relevant neurophysiological research (to date) has been performed on primates. The challenges are that (i) many different visual areas can be involved in producing a shape percept; and (ii) a single image rarely constrains the potential shape possibilities to a unique percept. Therefore, the visual system (and our computational models) must exploit assumptions to restrict the range and type of solutions. Since most models seek to return a single and, to some extent, veridical 3D shape percept, understanding both the assumptions needed and the mechanisms of computation are key components of research.

Detailed Description

An Ill-posed Inverse Problem

When a 3D object must be recovered from a single image of the object, the inverse problem is ill-posed. This is because the image (e.g., photograph or retinal image) is a result of a projection of the 3D world onto the camera sensor or retina. A projection (see Figure 1) identifies all the points along a single ray with a single image point. Once this projection has occurred, the information about the depth of the true 3D point has been lost. Thus, imaging of different shapes can result



3D Shape Perception, Models of, Fig. 1 Ill-posedness, or the ambiguity inherent in recovering 3D shape from a projection. Each of the three cartoon surfaces sketched in blue can be described (in a low resolution manner) by a collection of three points in depth (yellow, red, green) along perspective rays emanating from the camera. Each point can be arbitrarily far along the ray; there is only hope to recover their depth if assumptions are made about how the image (e.g., the color of the points) is related to the surface depth

in precisely the same image (Belhumeur and Kriegman 1998).

In order to combat this ill-posedness, our brain (and our algorithms) must use assumptions regarding the original surface. These assumptions codify regularities about the surface and the environment in which it was imaged. For example, in shape from shading (Horn and Brooks 1989), a common assumption is that the object is smooth and the image intensity value corresponds to the interaction between the object's normal field and the light sources. In shape from texture (Witkin 1981), the image may be understood to result from foreshortened texture elements. In both of these cases, these assumptions (and additional ones) may allow for surface shape to be recovered. However, there is a tension between the severity of the assumptions—e.g., Lambertian reflectance—and relevance in the natural world. This brings us to the second major difficulty:

The Diversity of Image Cues

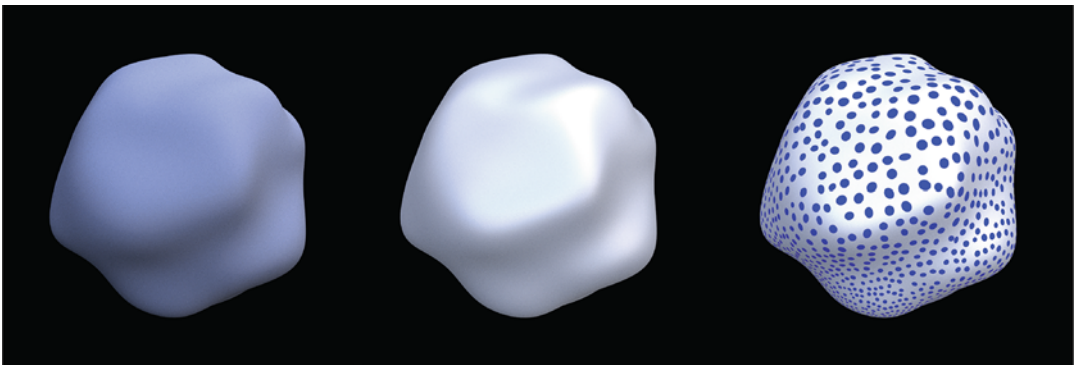
3D percepts derive from an incredible diversity of image cues. Images of the same 3D shape can differ greatly, depending on the type of material (i.e., its bidirectional reflectance distribution function, or BRDF), cue, or environment. In Figure 2, we illustrate this point by showing a shape with three different cues: diffuse shading, specular shading, and texture. In each of these cases, the values of image intensity from corresponding

surface points may differ drastically. Thus, the relationship between individual intensities and surface shape is heavily dependent on the type of cue, which is unknown a priori. Even more remarkable is that the visual system achieves a degree of *shape constancy*, meaning that the same shape can be recognized when seen from novel views, with novel materials, and in novel environments. Although our abilities are impressive, we emphasize that constancy is neither perfect nor quantitatively invariant across individuals, although informally it might seem so.

Given only an image, how does the human visual system efficiently understand the surface shape while also interpreting the cue? What are the neural representations of 3D objects? Does the visual system “memorize” an object as a collection of 2D images collected from different views or does it achieve some type of 3D representation? To what extent does the visual system achieve shape constancy, and how does this vary with viewpoint, lighting, and material? These are some of the questions involved in understanding 3D shape perception.

Research into 3D Perception

The literature is filled with many computational studies, models, and algorithms for reconstructing a 3D shape from an input image(s). Perhaps the earliest one, which set the stage for much of the modern research, is Ernst Mach's work in the



3D Shape Perception, Models of, Fig. 2 An example of three different images of the same object from same viewpoint but rendered from different image cues. Left: An object under diffuse shading. Center: A specular shaded

object. Right: A textured and shaded object. A sufficient model of 3D shape perception should be able to handle these different cues. (Figure courtesy Shivam Nadimpalli)

middle of the nineteenth century (see the translations in Mach (1965)), which formulated the problem as a differential equation, discussed the difficulty in solving it, and assessed the phenomenology of human performance.

Nevertheless, although the problem is inherently interdisciplinary, the perception of 3D shape has been investigated (roughly independently) within several different fields, including neuroscience, psychology/psychophysics, and computer vision, and the interactions between them have ranged from weak to occasionally intensive. Psychologists take a large-scale, almost black-box approach, and study how the full visual system could work as a whole; they seek to understand the relationship between input and output representations. Their interest (and the models) is largely phenomenological; they wish to understand performance and behavioral limits and answer the question: “what do we see?”

From the perspective of neuroscientists, vision is a problem whose solution requires a deep understanding of the individual neurons, how they are connected, and what is their preferred stimulus. They investigate the local circuitry and the role of different cortical areas. Neuroscientists look inside the black-box to study the mechanisms involved. They wish to understand: “how do we see?”

Computer scientists seek algorithms for useful tasks such as visual categorization and scene understanding. Some motivation is application driven (e.g., biomedical applications); some is algorithm driven (e.g., regularization), and some is inspired by either human capability (e.g., autonomous vehicles) or neurophysiological insight. Thus, like neuroscientists, some computer scientists are interested in the architecture behind the computations. They build applications for constrained domains (e.g., shape-from-shading and shape-from-motion) and wish to answer: “how can machines see?”

Clearly the different approaches are interrelated, and the cross pollination is important. We will review certain key points in this complex research program in roughly chronological order, starting with models that were under the purview of psychology. More recently, innovations in

cellular recording have allowed researchers to gather electrophysiological data to support certain theories. We will conclude with descriptions of related computer vision algorithms. These different threads through our dialogue remain tangled, to some extent, which highlights the interdisciplinary nature of the problem.

Psychology and Psychophysics

In psychology, there have been numerous studies considering the priors and models the brain uses in the perception of 3D objects. This is often done in two ways: with computational models simulating the process and psychophysical experiments.

Psychological research consists, for starters, of psychophysical experiments. A visual stimulus is shown to a subject, after which the subject performs a task related to their perception of the stimulus. The difficulty is finding tasks that isolate and inform a single property; this allows meaningful conclusions to be drawn from the task performance. Often psychophysical experiments are used to advocate for or against the computational models that are much too general to test via intracellular recordings. Below, we describe several major themes running through modern investigations into 3D shape perception.

Intuitively, perhaps the easiest route from 2D to 3D is with multiple images in space (namely, stereo) or multiple images in time (structure from motion). Both of these were actively pursued; see Howard and Rogers (1995) and Kolars (2013), respectively, for reviews; we shall only occasionally discuss these here. Rather, the concentration will be on shape inferences from a single, time-invariant image.

Invariants and Affordance

Gibson’s “ecological” approach to explaining 3D shape constancy was through an emphasis on “invariants”. Gibson believed that 3D shapes were perceived veridically (contrary to some of his contemporaries), and he posited that this was due to physical invariants in the 2D image that directly corresponded to the true 3D shape (Gibson 1979). For example, Gibson was the first to test how textures lead to perception of surface slant (Gibson and Cornsweet 1952). He

proposed that perception was based on the spatial gradients in the textures and the necessary inverse to shear these spatial gradients back into an isotropic texture. This was an early example of an inverse optics approach. It was built on foundations established by the Gestalt psychologists (Metzger 1936) and it stimulated much work that came later.

Unlike computational theorists, Gibson believed that the visual system “directly” perceived these invariants, and by computing only on them, was able to achieve some degree of shape constancy. He may have been the first to attempt computationally to “extract informative variables from raw light” (Warren 2012), but see Ullman (1980) for a critique.

The Gibson school also addressed motion (Cutting 1986), but it was in this context that more computational research started to accelerate (Ullman 1979). This push-and-pull between phenomenological observations and computational concreteness continues to the current period and underlines the interdisciplinary nature of the problem.

Computational Modules

Marr synthesized much work on 3D perception (Marr 1982), and “made it clear that a computational model is critical” (Pizlo 2008). He attempted to understand the computational tasks needed to turn early information into surface orientations and then a 3D model.

His ideas elucidated a computational framework for vision that focused on “taking slant into account.” Following Horn (discussed later), he believed that 3D shape perception is based on the local 3D surface orientation. Following work in software engineering (Brooks Jr 1995), he sought to split the 3D vision problem up into a sequence of modular problems, each with increasingly symbolic representations. The symbolic emphasis built on influences from AI and cognitive science (Pylyshyn 1986), integrated with research in image processing (Rosenfeld and Kak 1982). The first stage was extracting important lines and edges from the image and using these to construct a “primal sketch.” (This followed directly in the lines of Gestalt

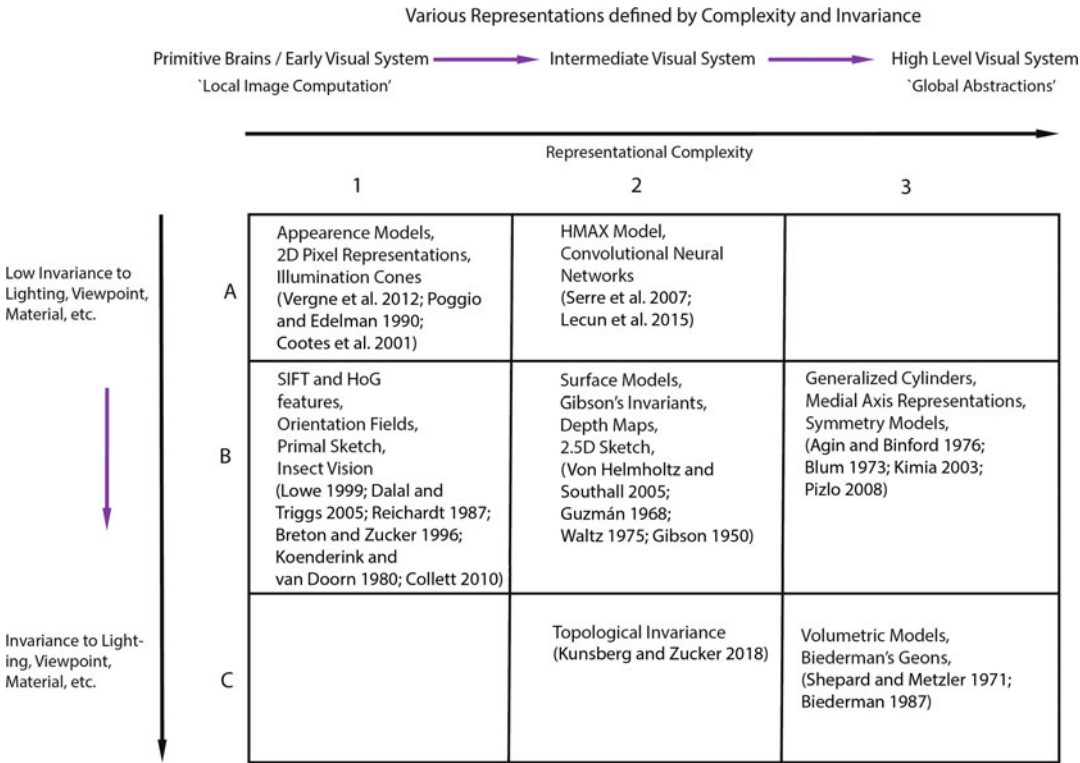
psychology (Koffka 1955) and perceptual organization.) These edges and lines could then be interpreted as depth or orientation cues, called a “2.5D sketch,” in a viewer-centered frame. The 2.5D sketch could then be attributed to surface primitives and eventually be converted into an object-centric 3D volumetric structure based on generalized cylinders (discussed below). This viewpoint was very influential and led to many investigations attempting to perform one of these steps; see Fig. 3 boxes 1B and 2B.

Marr and many contemporaries believed that the local surface orientation was an important surface feature that could be observed from the image and then integrated into a 3D shape representation. Several investigators, e.g., (Stevens 1983; Witkin 1980; Koenderink and Van Doorn 1980a; Koenderink et al. 1992; Koenderink 1984), expanded on this idea. Koenderink et al. introduced the gauge-figure experiments for detecting local perceived surface orientation (Koenderink et al. 1992). Marr’s ideas (insistence on slant and depth fields) eventually came into conflict with the requirement for 3D primitives. Later ideas by Biederman, expanded on below, rather considered 2D projected features of a set of volumetric primitives.

Although compelling, many of Marr’s ideas on object recognition were eventually superseded. Marr assumed that the goal of the visual system was to acquire a general purpose, Euclidean, representation of the world. But psychophysics experiments began to show that the visual system rarely achieves such a veridical solution, and his computational ideas were unable to handle real-world noise. However, his convincing prose and beautiful demonstrations shaped the field for a decade or more.

Volumetric Primitives

It is clear that neurons in the visual system form a hierarchy (Hubel 1988). Hierarchical systems are efficient as they start with simple parts and construct more complex “objects” from the simple parts, and computation is limited as the representation becomes more abstract. Thus it is natural to ask the question: “What are the primitives (beginning elements) the brain uses to understand



3D Shape Perception, Models of, Fig. 3 A diagram of different theories for the visual system. Across the columns, we change the level of abstraction. For example, the first column considers models based directly on image pixels and appropriate for computations in the early visual system. The third column consists of computations on higher areas of the visual system which are conjectured to

involve 3D volumetric understanding. Across the rows, we have placed theories according to increasing robustness to changes in “world properties.” The first row consists of structures that may be brittle when, e.g., illumination direction is changed, whereas the third row contains structures that may be invariant

and categorize 3D objects?” There have been many theories that attempt to model complex 3D objects through compositions of primitive 3D objects. However, the primitives need to be chosen carefully as they need to have explanatory power while also being recognizable from their 2D retinal images. (This line of research is a generalization of medial axis representations for 2D shapes (Siddiqi and Pizer 2008). Importantly, the medial axis shares much in common with the (projected) main axis for generalized cylinders.) A powerful choice for these primitives is simple volumetric 3D shapes with small numbers of parameters. It is necessary that they are distinguishable from image features, regardless of the viewpoint. (See Figure 3, 3rd column.) Importantly, such models underline the transition from

local features, such as edges or surface curvatures, to global descriptors. Their psychophysical origins may date from the Johansson biological motion demonstrations (Johansson 1973) and the 3D rotation experiments by Shepard Metzler (1971), but had their direct origins in a computer vision approach, namely Binford’s generalized cones (Binford 1971). This influential model showed that combinations of generalized cones could model a large variety of objects. It continued with Biederman’s (1987) “recognition-by-components” theory, in which 3D perception was modeled via combinations of simple geometric components called *geons*. For example, a flashlight can be represented as a cylinder attached to a flared cone and a small rectangular solid (the switch). These geons were chosen by

informally considering nonaccidental properties and still have an important legacy in visual psychophysics and design (Norman 2002). However, Biederman's approach needs salient contours and established figure/ground organization which, at the time, were not directly computable from an image. Later, Dickinson et al. (1992), among others, expanded on these ideas by building a working algorithm operating on simple images without figure/ground organization and returning correct interpretations and decompositions of the image parts into the volumetric 3D primitives. Although there was progress, "real images do not allow unambiguous recognition of parts" (Pizlo 2008). This research direction eventually foundered because of this pragmatic computational issue and, as of 10 years ago, "today's systems focus on 2D configurations of local image-based features rather than on 3D configurations of shape-based volumetric features" (Pizlo 2008). (We shall discuss more recent computational approaches shortly.)

The geon concept remains a driving force conceptually and an anchor for thinking about shape. It also spawned a fascinating debate about invariances over viewpoint and lighting, which played out directly against appearance models.

Appearance Models

By the early 1990s, practical shortcomings in the above theories were becoming pressing, so researchers began to reexamine the assumption that perceptual representations were, in fact, "3D." Perhaps the visual system simply "memorizes" a collection of 2D views of an object? Could this still explain shape constancy?

Influential papers by Ullman (1989) and Poggio and Edelman (1990) suggested alternate theories, called appearance models (see Fig. 3), for object recognition. In Ullman (1989), it was suggested that object recognition could be obtained from a novel view by considering it as a linear combination of images learned in previous views. In Poggio and Edelman (1990), a network of radial basis functions was trained to map images from one viewpoint into a "standard" viewpoint. This allowed for comparison and thus

object recognition. Both of the above methods hypothesized that 3D shape perception was nothing more a collection of 2D images with perhaps an alignment or extrapolation mechanism, an idea favored in insect vision (Collett 2010) and deployed today in face recognition and related problems.

Importantly, the appearance model's collections of views were associated with learning, and geons were interpreted as fixed. This leads to testable hypotheses (Bülthoff and Edelman 1992), which favored these new theories against those that used 3D model alignment. However, this association of 2D views with learning versus fixed 3D representations had other issues regarding invariance; we shall return to these in the last section. Nevertheless, algorithms for object recognition have largely focused on extracting and recognizing 2D features from the image. This is more convenient computationally, although recent psychophysical experiments by Pizlo, Todd, and others (Pizlo 2008; Fleming et al. 2011; Farley Norman et al. 1995) show that 3D structure is still reliably inferred from ill-posed 2D images. In this way, the computer vision community and the 3D perception community have split: while the computer vision scientists mainly use 2D image features for their purposes, many vision scientists still believe the brain computes 3D structures.

Bayesian Models

Computational difficulties with the modular and the appearance approaches were brought to the forefront by phenomenological approaches that considered the interaction between lighting, depth, surfaces, and viewer position simultaneously. Convincing demonstrations (Yuille and Kersten 2006) forced a retreat from Lambertian models and forced the field to confront the difficulties of natural images. Popular Bayesian methods introduced a massive search for priors, providing a mechanism for relating structure in the world to that manner in which we recover it. Such approaches suggest that we are wired to see what we expect to see (Knill and Richards 1996), which brings us to neuroscience.

Neuroscience and Neurobiology

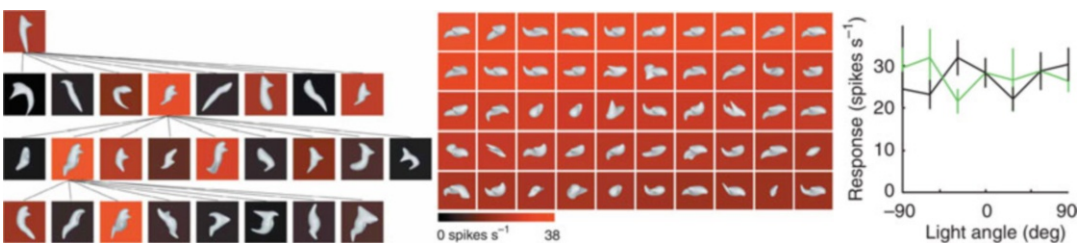
The fundamental goal for neuroscientists studying 3D perception is to understand the neural circuitry and mechanisms that allow the visual system to perceive the 3D world with such accuracy and flexibility. To this end, they have studied neural representations, often through intracellular recordings in V4 (the fourth visual area), inferotemporal cortex, and other visual areas. Simply explained, “awake and behaving” primates are trained to fixate while viewing images on a computer monitor. Electrodes (and now imaging) report the activity in targeted visual areas. By carefully choosing and modifying the type of stimulus, they attempt to capture a cell’s preferred stimulus; such preferred stimuli are then used as evidence for certain perceptual theories.

We already mentioned the hierarchy of Hubel and Wiesel, but their work also provided the usual starting point for theories of image representation in the visual system. In (Hubel 1988), they argued there are two types of cells in V1: the first type are simple cells tuned to sinusoidal gratings and often modeled with Gabor filters. The second type, complex cells, has a larger retinotopic tuning that “pool” over the simple cells. The complex cells become spatially invariant, to a small extent, whereas the simple cells have spatial selectivity. These results inform the initial theories for 2D representations of images in the brain. The logical next step would be to search for cells tuned to a representation for 3D surfaces. Much work has been expended to understand stereo (Cormack

et al. 2017) and motion (Britten et al. 1992) in this regard.

The debate above, between appearance models and volumetric models, was also addressed physiologically. We highlight two notable studies; one from each side. The first is Logothetis et al. (1995), where inferotemporal (IT) neurons were found in monkeys that responded selectively to specific views of unfamiliar objects. The discharge rate of these neurons were bell-shaped functions of orientation centered around their preferred view. The finding was interpreted as supporting theories (such as the appearance models described above) where a 3D object recognition system was encoded via a population of neurons tuned to different views.

The second impressive study investigating the preferred stimulus of IT neurons is Yamane et al. (2008). See Figure 4. They found results that agreed more with the volumetric primitive approach. By carefully modulating a 3D rendered shaded stimulus through a genetic algorithm, they found preferred 3D stimuli for a collection of IT neurons. Remarkably, these IT neurons responded invariably even when the light source, x-y position, and object depth were changed. The IT neurons stopped responding when the shading was removed, implying that the 2D boundary stimulus did not suffice. This suggested that these neurons were tuned to the 3D shape cues expressed via shading or disparity, rather than 2D features in the retinal projection. Importantly, the response was nonlinear with respect to the 3D primitives that



3D Shape Perception, Models of, Fig. 4 Figures from (Yamane et al. 2008). In this work, Yamane et al. identified preferred stimulus from IT (inferotemporal) neurons in macaque monkeys. The preferred stimuli were found via a genetic algorithm and shown to have similar 3D structure. The redness of the image corresponds to the neuron’s preference. Left: An example of modifying a 2D image of a

3D stimulus in a part-based fashion to search for the neuron’s preferred stimuli. Center: The preferred stimuli found for one IT neuron. Note the commonality in the 3D structure across the stimuli. Right: A light source invariance was found for several stimuli. Changing the direction of the light source (and thus the image of the 3D object) did not change the response of the neuron

composed the stimuli; this means the neurons required several 3D features in specific relative positions and orientations in order to respond positively.

An early and more complete review of neurophysiological studies on visual recognition can be found in Logothetis and Sheinberg (1996). Closer to this review are neurophysiological studies of shape and the inferotemporal area of visual cortex (Tanaka 1996). We now summarize other research in the field of computer vision that is relevant to 3D shape perception.

Computer Vision

In computer vision, there are often two competing goals. The first is application driven and involves specialized techniques for targeted areas, such as fMRI or facial image analysis. Studies of this type typically have little, or no, connection to biological information processing. The second goal is to build algorithms that are “as good as a human” in computing the 3D shape from images, although not necessarily requiring that models are biologically plausible (computable under the brain’s constraints and according to properties observed in the experiments described above). Rather, in computer vision, the incentive is higher performance on benchmark datasets collected, e.g., in support of autonomous driving. “Models” may then be only broadly interpreted to mean algorithms that could be weakly inspired by known properties of the visual system’s mechanisms. Such inspired properties include ideas like hierarchical units, spatial pooling, multiscale representations, and Bayesian priors. Below we describe efforts of this nature; we will first describe some earlier image reconstruction approaches and then discuss multiview approaches.

Differential Equation Approaches

The first major effort in computing shape from a single image was the work of Horn (1970) in the 1970s. Like Mach earlier, he focused on understanding the inverse process for Lambertian shaded images. His reflectance map approach translated the problem into a partial differential equation (PDE) which, like Mach, he solved via the method of characteristic strips.

The logic behind the PDE approach is that, for Lambertian shading, the brightness at a point relates to the projection of the surface normal onto the light source position. Therefore, a change in brightness (derivative with respect to the image) relates to a change in normal (a type of curvature).

Central to the PDE approach are boundary conditions; for example, a curve along which the solution is known. Although there is substantial psychophysical evidence that boundaries matter substantially (Ramachandran 1988), uniqueness and stability remain elusive in general (Deift and Sylvester 1981).

The PDE work led to other classical approaches (Horn 1986; Horn and Brooks 1989), often posing the problem as one of cost function minimization (regularization (Poggio et al. 1985)) rather than a propagation: one defines various penalty terms based on the surfaces desired and cues expected. These penalty terms may correspond to surface smoothness, constant albedo, boundary constraints, etc. The defining characteristics of the model are then the choice and justification of these penalty terms. Many penalty terms have been suggested for a vast array of image cues, including shaded (Horn and Brooks 1989; Barron and Malik 2012; Zhang et al. 1999), textured (Witkin 1981), symmetrical (Pizlo 2008), and polyhedral surfaces (Pizlo 2008). One of the benefits of regularization is that it sidesteps the issue of solution uniqueness and only attempts to find some local minimum. Related to the cost function approach is the Bayesian approach.

Bayesian Approach

The classical regularization approaches were mainly deterministic and did not explicitly take into account noise. Bayesian approaches that more explicitly built noise into the models gained traction in the 1990s. The assumptions about the natural world from the deterministic approaches can more generally be described as Bayesian “priors.” However, there is a philosophical tradeoff between the “firm” computational theory of constraints, e.g., as described by Marr, and the statistical machinery of the Bayesian framework. With the deterministic approaches, there is a firm

basis on which the intermediate stages of the model can be interpreted. This understanding is less viable with Bayesian approaches. Second, a priori constraints in deterministic problems restrict the domain of the solution (Poggio et al. 1985); “they are not used like priors to refine the solution” (Pizlo et al. 2014).

One example, the framework of Bayesian graphical models, has been successful in recovering 3D shape from an image. In the Markov Random Field framework (Geman and Graffigne 1986), the goal may be to solve for the latent variables of a graph network which together define the depth function of the unknown surface (Saxena et al. 2005). The known variables are local image properties, and the potentials involve similar constraints to the penalty terms used above.

Deep Learning

Recently, deep learning has been applied to reconstructing 3D shape from a single image (Liu et al. 2015; Eigen et al. 2014). The results involve training convolutional neural networks (CNNs) on large public datasets. Although very promising for applications, the deep learning results on shape-from-shading do not inform or validate theories of perception. Understanding the visual system’s abilities is only loosely tied to training these deep networks, because of the need for labeled training examples. However, some have argued that there are relationships between deep networks and object recognition (Yamins and Dicarlo 2016) and others have been inspired by research into human perception, such as Marr’s 2.5D sketch theory (Marr 1982), in building deep architectures (Wu et al. 2017).

Multi-image Reconstruction

Although we only mentioned stereo at the beginning of this review, it has achieved a substantial level of success in computer vision. 3D reconstruction becomes easier if several images of the same object are available, either from different positions or under different controlled lightings. In this case, the problem is different philosophically as it becomes well-posed or even over-posed. The issue becomes one of using and

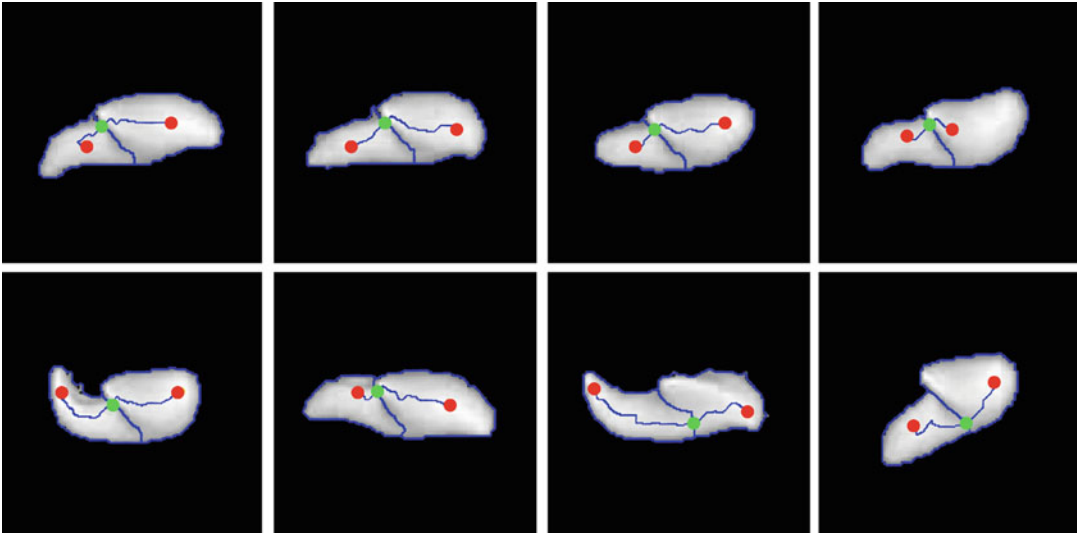
combining the correct matching information across the abundant data. The most common example is binocular (stereo) vision, where there is a pair of calibrated images as input. In this case, the use of epipolar geometry will define the depth map provided a correspondence matching problem can be solved (Longuet-Higgins 1981; Scharstein and Szeliski 2002; Li and Zucker 2010).

Other work in multi-image reconstruction is structure from motion (to compute camera parameters) (Tomasi and Kanade 1992), optical flow (Barron et al. 1994), and multi-view stereo (Seitz et al. 2006).

Recent Integrative Shape Perception Theories

Several threads can be pulled from the studies reviewed above, and their historical evolution. Perhaps the main tendency in shape inference is to isolate one aspect of the problem and then develop a rich theory of it. This could be the dependence on a single – and simple – lighting model (e.g., Lambertian); the assumption of known parameters (e.g., light source position); or assumed factors (material properties or albedo). The other extreme is to work with “natural” images, e.g., office scenes, and exploit expectations about their overall properties (e.g., tables are flat). Both threads have advantages, but both suffer shortcomings. There are two possibilities for progress: enlarge the threads to integrate different requirements into theories. We now mention an example of each of these.

Recent work has attempted to enlarge these threads to include drastically different rendering models and shape properties. Building on shading isophotes (Koenderink and Van Doorn 1980b) and flows (Breton and Zucker 1996), Fleming et al. (2011, 2004) have investigated the use of orientation fields as the underlying framework for 3D perception in specular shading. Vergne et al. expanded on that work by showing how deformations of the orientation field can modify 3D image perceptions (Vergne et al. 2012). Such approaches integrate information about photonics (isophotes), visual cortex (flows), and non-standard rendering models (specularity). Regarding different properties, Pizlo et al. (2014) and colleagues study the



3D Shape Perception, Models of, Fig. 5 In Kunsberg and Zucker (2018), it is proposed to describe important surface features via the Morse-Smale complex of the image. Parts of this structure are robust with respect to illumination conditions and other rendering changes. Here, we show the first eight preferred stimuli from Fig. 4 and how the Morse-Smale complex of the image gives a consistent segmentation of those surfaces into two

“lobes.” The red and green points represent maxima and saddle points of the image, while the blue curves represent separatrices. Note a common separatrix (blue curve) is always aligned in the “southeast” direction. This may explain: (i) the similarity between the preferred stimuli and (ii) the light source invariance (Kunsberg and Zucker 2018) found for those stimuli

implications of hard symmetry constraints. By carefully defining “3D shape” to be fundamentally based on symmetry, they have explained a body of conflicting research on shape constancy (Pizlo 2008; Dickinson and Pizlo 2013).

Two other significant directions are derived from mathematical and psychophysical consideration. First, shape inferences are global, so local (e.g., differential geometric) techniques are questionable. Second, psychophysically it has been determined that shape percepts are qualitatively but not quantitatively identical; see, e.g., shape constancy psychophysical results in Mooney and Anderson (2014), Khang et al. (2007), Faisman and Langer (2013), Sun and Schofield (2012), and Koenderink et al. (2015). In light of these points, Kunsberg and Zucker (2018) have proposed using topological image features of the orientation flow (described by the Morse-Smale complex) to extract a relevant surface segmentation into “bumps” and “valleys.” Their motivation is that a qualitative representation more accurately models the lighting invariance that is commonly

part of our subjective experience. This is also seen explicitly in the electrophysiological results from the Connor lab (Yamane et al. 2008). Inspired by image invariants from Gibson’s approach and volumetric primitives from Biederman’s theories, Kunsberg sought a 3D representation based on 2D image curves with an invariance to rendering functions. By focusing on the invariant features of the image, the visual system may be able to extract weak (nonmetric) yet intuitive 3D relationships without needing to identify the precise cue. See Figure 5.

Summary

Although shape inferences have been studied experimentally, formally and computationally for more than a century, many conundrums remain. How does the visual system infer shape from translucent objects (Kim et al. 2014)? How can it compute shape from shading “on a cloudy day” (Langer and Zucker 1994)? What about metallic and specular objects (Fleming et al. 2004; Todd and Norman 2018; Adato et al.

2010)? Are there multiple “modes” that it can access for different cases (Sun and Schofield 2012)? Or perhaps the goal of the visual system is not to perceive veridically (Koenderink 2011; Hoffman et al. 2015).

Fortunately, there is an active research community in 3D perception attempting to understand the above questions and find a unifying framework for shape constancy. Understanding 3D perception would not only be a scientific triumph but would also lead to breakthroughs in many computer vision and industrial applications. It would contribute to artistic understanding and rendering applications such as computer graphics. Most importantly, we would understand one of the most intriguing abilities of our visual system: how we can interact with, navigate through, and generally understand the 3D world in which we live with such reliability even though the retinal patterns we are given are so disparate and under-constrained.

Cross-References

- [Cognition, Bayesian Models of](#)
- [Hierarchical Models of the Visual System](#)
- [Large-Scale Neural Networks: Vision](#)
- [Perception, Bayesian Models of](#)

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Short-Term Plasticity, Biophysical Models

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Definition

Short-term plasticity refers to changes in synaptic efficacy in response to presynaptic spiking that persist for a few seconds at most but more often decay over a timescale of a few hundred milliseconds. There are two primary types of short-term

plasticity: short-term depression and short-term facilitation. Short-term depression is a reduction in synaptic efficacy that is often, but not always, caused by a transient depletion of neurotransmitter vesicles. Short-term facilitation is an increase in synaptic efficacy often caused by a transient increase in the number of vesicles released by presynaptic action potentials. The detailed biophysical mechanisms underlying synaptic facilitation are discussed in Facilitation, Biophysical Models, and we therefore focus on more phenomenological models of facilitation here.

Detailed Description

Stochastic Models of Short-Term Depression Arising from Neurotransmitter Depletion

Short-term depression is often believed to arise primarily from the depletion of neurotransmitter vesicles, and therefore a large proportion of short-term depression models rely solely on the mechanism of vesicle depletion. It should be noted, though, that some synapses exhibit short-term depression that is inconsistent with vesicle depletion alone (Branco and Staras 2009; Zucker and Regehr 2002; Wong et al. 2003; Xu and Wu 2005).

We begin by describing a model of short-term depression that takes into account the stochastic nature of vesicle release and recovery. The model was introduced in Vere-Jones (1966), and various formulations of it have since been used extensively (Senn et al. 2001; Zador 1998; Wang 1999; Matveev and Wang 2000; Fuhrmann et al. 2002; Goldman et al. 2002; Goldman 2004; de la Rocha and Parga 2005; Pfister et al. 2010; Rosenbaum et al. 2012, 2013, 2014; Reich and Rosenbaum 2013). A presynaptic neuron makes M functional contacts onto a postsynaptic neuron, and each functional contact contains N_0 release sites that can each dock at most one vesicle, so that the maximum number of docked vesicles is $M \times N_0$. Of course, the model can easily be extended to allow heterogeneity in the number of release sites at each contact. Here, the term “functional contact” (hereafter, simply “contact”) refers to a group of vesicle release sites where the grouping

is chosen so that release sites at different contacts release vesicles independently from one another, but release sites on the same contact are not necessarily independent. Functional contacts need not necessarily correspond to anatomical contacts in a one-to-one fashion. The most widely assumed dependence between release sites arises from the “univesicular hypothesis” which states that each contact can release at most one vesicle in response to a single presynaptic spike. If this constraint is to be met, then release sites at the same contact cannot be independent.

Since release sites at different contacts are independent, we need only specify the probability distribution of the number of vesicles released by a presynaptic spike at each contact. A widely used rule (Vere-Jones 1966; Wang 1999; Matveev and Wang 2000; Goldman et al. 2002; de la Rocha and Parga 2005; Rosenbaum et al. 2014) that is consistent with the univesicular hypothesis states one vesicle is released at a particular contact with probability $1 - (1 - p)^n$; otherwise, no vesicles are released. Here p is a number between 0 and 1, and $n \in [0, N_0]$ is a dynamical variable representing the number of docked vesicles at the contact in question at the moment when the presynaptic spike occurs. When $n = 0$, the release probability is zero, as expected. When $n = 1$, the release probability is p . In general, the probability of release increases with the number of docked vesicles.

While the rule above is straightforward to simulate numerically, it is difficult to treat analytically due to the non-independence of release sites. Some analytical tractability can be gained by assuming that the release of a vesicle at each release site is independent. This is equivalent to assuming that each functional contact has exactly one release site (i.e., making the substitutions, $M = M \times N_0$ and $N_0 = 1$). In this widely used version of the model (Zador 1998; Matveev and Wang 2000; Fuhrmann et al. 2002; Goldman 2004; Pfister et al. 2010; Rosenbaum et al. 2012, 2013; McDonnell et al. 2013; Reich and Rosenbaum 2013), each presynaptic spike releases each docked vesicle independently with probability p . Thus, the number of vesicles released by a presynaptic spike is a binomial

random variable with parameters n and p , where n is the number of docked vesicles when the spike arrives.

When a vesicle is released at a contact, the number of docked vesicles at that contact is decremented. The waiting time until a released vesicle is recovered is an exponentially distributed random variable with mean τ_u . Equivalently, it is the waiting time for the first event in a Poisson process with rate $1/\tau_u$. Due to the memoryless property of Poisson processes, this rule allows the modeler to keep track of only the *number* of docked vesicles at each contact and ignore the time at which empty release sites became empty. In particular, the probability that one empty release site is filled during the time interval $(t, t + dt)$, i.e., that the number of releasable vesicles is incremented during that time interval, is given by $(N_0 - n)dt + o(dt)$, where n is the number of docked vesicles at that release site and $o(dt)/dt \rightarrow 0$ as $dt \rightarrow 0$.

Each released vesicle induces a change in conductance of the postsynaptic neuron's membrane. This is often modeled by setting the postsynaptic conductance to $g(t) = \sum_j w_j \alpha(t - t_j)$, where t_j is the time of the j th presynaptic spike, w_j is the number of vesicles released by the j th spike, and $\alpha(t)$ is a stereotyped synaptic conductance waveform representing the change in postsynaptic conductance elicited by the release of a single vesicle. In general, $w_j \in [0, M \times N_0]$ but $w_j \in [0, M]$ whenever the univesicular hypothesis is satisfied.

Pseudo-code for implementing this and similar models of stochastic vesicle dynamics is provided in McDonnell et al. (2013) along with a review and discussion of some effects of stochastic vesicle dynamics on neural coding and the statistics of the synaptic response.

Deterministic Models of Short-Term Facilitation and Depression

The stochastic model of short-term depression discussed above can be difficult to analyze mathematically, and it can also be difficult to fit the model's parameters to data. Moreover, the model assumes that short-term depression is due solely to the depletion of neurotransmitter vesicles even though other factors sometimes play a role.

Finally, the model does not account for the effects of short-term facilitation on synaptic efficacy.

These difficulties are partly overcome by a deterministic model in which synaptic efficacy is treated as an abstract, continuous variable that is modified by each presynaptic spike. This model is mostly agnostic to the precise mechanisms responsible for changes in synaptic efficacy, but it can accurately reproduce experimental data after the model parameters are fit to the data using statistical fitting algorithms. Due to its amenability to mathematical analysis and its ability to reproduce experimental data, this deterministic model and its variations are widely used in both theoretical and experimental studies (Tsodyks and Markram 1997; Varela et al. 1997; Tsodyks et al. 1998; Markram et al. 1998; Chance et al. 1998; Maas and Zador 1999; Fuhrmann et al. 2002; Hanson and Jaeger 2002; Cook et al. 2003; Grande and Spain 2005; Rothman et al. 2009; Lindner et al. 2009; Merkel and Lindner 2010; Pfister et al. 2010; Rosenbaum et al. 2012; Scott et al. 2012; Mohan et al. 2013).

We describe the model as presented in Varela et al. (1997) and then discuss some common variations of the model. The efficacy of a synapse is defined by $A(t) = A_0 F(t) D_1(t) D_2(t) D_3(t)$, where A_0 is a constant representing a baseline efficacy, $F(t)$ is a dynamic variable representing facilitation, and each $D_k(t)$ is a dynamic variable representing depression.

Immediately after each presynaptic spike, each depression variable is updated according to the rule $D_k \leftarrow D_k d_k$ for $k = 1, 2, 3$, where each d_k is a number between 0 and 1 representing the amount of depression evoked by each spike. Between presynaptic spikes, the depression variables decay exponentially back to their maximal values, which can be normalized to one without loss of generality, so that $\tau_{Dk} \frac{dD_k}{dt} = 1 - D_k$, where τ_{Dk} is the timescale of recovery for the k th depression variable.

Similarly, the facilitation variable is updated after each presynaptic spike according to $F \leftarrow F + f$, and the evolution between spikes is defined by $\tau_F \frac{dF}{dt} = 1 - F$.

The postsynaptic conductance (or current for current-based modeling) can then be written in

terms of the synaptic efficacy as $g(t) = \sum_j A(t_j) \alpha(t - t_j)$, where $\alpha(t)$ is a stereotyped waveform and t_j is the time of the j th presynaptic spike.

This model is commonly modified by changing the number of facilitation or depression variables. A common variation uses only one facilitation and one depression variable so that $A(t) = A_0 F(t) D(t)$. Some synapses exhibit short-term depression but not facilitation, in which case the facilitation variable can be removed completely and we can simply write $A(t) = A_0 D(t)$. These two variations of the model are amenable to mathematical analysis (Lindner et al. 2009; Merkel and Lindner 2010; Rosenbaum et al. 2012).

In the form of the model described above, the depression variables are updated multiplicatively, while the facilitation variable is updated additively. Updating facilitation multiplicatively can cause synaptic efficacy to grow unrealistically large at high presynaptic rates (Varela et al. 1997), but a saturating multiplicative update rule was applied in Hanson and Jaeger (2002) and accurately captured recorded data. In other variations of the model, updates to the depression variables depend on the value of the facilitation variables, for example, in Lindner et al. (2009) and Merkel and Lindner (2010), the update rule for the depression is given by, $D_k \leftarrow (1 - F) D_k$.

It should be noted that the deterministic model with one depression variable and no facilitation variables is equivalent to the mean field of the stochastic model of short-term depression with $N_0 = 1$. Specifically, if the stochastic model is simulated over several trials with the same presynaptic spike train, then the trial average of the postsynaptic conductance it produces is proportional to the postsynaptic conductance produced by one trial of the deterministic model driven by the same presynaptic spike train whenever $\tau_u = \tau_D$ and $p_r = d$.

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Short-Term Synaptic Facilitation

► Facilitation, Biophysical Models

Short-Term Synaptic Plasticity in Central Pattern Generators

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Synonyms

[Augmentation](#); [Depression](#); [Enhancement](#); [Facilitation](#); [Post-tetanic Potentiation](#)

Definition

Short-term synaptic plasticity (STP) is a transient (milliseconds to minutes) activity-dependent change in the amplitude of the postsynaptic current in response to presynaptic activity. Central pattern generators (CPGs) are neural networks in the central nervous system capable of producing coordinated rhythmic output without rhythmic input from sensory organs or from higher control centers.

Detailed Description

Short-term synaptic plasticity (STP) is a transient (milliseconds to minutes) activity-dependent change in the amplitude (strength) of the postsynaptic current in response to presynaptic activity. It has clear implications for neural signaling and has been studied for several decades. Much of the modeling work has focused on the events in the presynaptic terminal and primarily on the role of Ca^{2+} in synaptic release of neurotransmitters (Zucker and Regehr 2002; Fioravante and Regehr 2011). However, postsynaptic effects such as saturation of postsynaptic receptors can also contribute to STP (Hennig 2013; Xu-Friedman and Regehr 2004). A complete understanding of

short-term synaptic plasticity requires knowing how the pre- and postsynaptic neurons interact to alter synaptic strength.

The contribution of short-term synaptic plasticity to network-level output has probably been best examined in studies of central pattern generator (CPG) networks. CPG networks produce rhythmic patterned outputs without patterned input and are best understood in the analysis of rhythmic motor activities such as locomotion and respiration. For instance, the CPG underlying the inspiratory phase of respiration is located in the pre-Bötzinger complex found within the ventrolateral medulla of the mammalian brain (Grillner 2003). Identified CPG circuits are known to govern locomotion in invertebrates, including leeches, mollusks, and crustaceans (Arshavsky Yu et al. 1993; Ayers 2004; Friesen and Kristan 2007). Additionally, locomotion in mammals is believed to be governed by CPG networks in the spinal cord (MacKay-Lyons 2002). The understanding of CPGs in producing motor behaviors has been greatly advanced through the use of computational models (Butera et al. 1999; Tabak et al. 2000; Oh et al. 2012; Vavoulis et al. 2007; Sherwood et al. 2011).

Almost all synapses are regulated by a variety of short- or long-term activity-dependent processes that alter the strength of the synapse. Depending on the behavioral needs, CPGs alter their rhythmic activity patterns by changing the cycle frequency and the relative activity phases of the participating neurons. Synapses in CPG networks are naturally subject to short-term activity-dependent modifications due to the rhythmic nature of the network output. This review examines the mechanisms and consequences of short-term changes in synaptic strength within CPGs. Although both pre- and postsynaptic mechanisms have been implicated in short-term plasticity, the majority of known STP effects are presynaptic (Wadiche and Jahr 2001).

Neurobiology of Central Pattern Generators

CPG networks often involve neurons that produce bursting oscillations. Bursting refers to an interval

of rapid firing of spikes, bookended by intervals of quiescence. Bursting activity in neurons is often the result of a slow-wave oscillation in the membrane potential which, on the depolarized portion, crosses spike threshold. The slow-wave oscillations that underlie bursting activity result from the interaction of low-threshold-activated inward currents and slow voltage- or Ca^{2+} -gated outward currents.

In cases where the mechanisms underlying rhythm generation have been described, CPG oscillations have been shown to arise in one of two ways: either through the activity of endogenously oscillatory (pacemaker) neurons or through the synaptic interactions of neurons within a network (Goldin-Meadow et al. 2001). Pacemaker neurons produce oscillations when they are synaptically isolated from the network. However, these oscillations may be conditional upon the presence of the appropriate neuromodulatory substances. Although pacemaker neurons can be the rhythm-generating kernel of a CPG network, the proper output of the CPG usually requires the synaptic interaction of the pacemaker neurons with non-oscillatory (follower) neurons whose activity is important in producing the proper output pattern.

In contrast to pacemaker-driven CPGs, network oscillators produce rhythmic output through synaptic interactions of pairs or groups of neurons, which may not be oscillatory when synaptically isolated. The most prominent example of such network oscillations is half-center oscillators that drive the activities of antagonistic muscles. First proposed by T. Graham-Brown in the early 1900s, half-center oscillators are responsible for producing rhythmic behavior in these types of networks (Brostoff et al. 2008). Half-center oscillators are driven by neurons (or neuron groups) that are antagonistic in their activity. The two groups of neurons are rhythmically active but activity in one group inhibits the activity of the other. In the first classification of half-center oscillators by Wang and Rinzel, they demonstrated that the transition between the two halves of the half-center oscillation can occur through one of two distinct mechanisms: escape and release. In escape mode, the inhibited neurons transition to

active mode due to their own intrinsic properties. In contrast, in release mode, the active neurons terminated their activity due to their intrinsic properties and thereby release the inhibited neuron which rebounds from inhibition to produce activity (Wang and Rinzel 1992). The frequency and relative phases of the two halves of the half-center are controlled by the intrinsic properties of the neurons as well as the strength and dynamics of the reciprocal synapses. The extent to which intrinsic versus synaptic properties control the half-center oscillations can be used to further divide these networks into intrinsic or synaptic (Skinner et al. 1994). In biological systems, the transitions between the two halves of the half-center oscillator are often through a combination of escape and release mechanisms (Nadim et al. 1995).

Invertebrate CPG studies provided crucial results for the understanding of the mechanisms of neural network connectivity and CPG functions. The ease of accessibility of many of the invertebrate networks has allowed for a mapping of the synaptic connectivity and therefore the identification of the CPG circuits. Additionally, in many invertebrate networks, the voltage-gated ionic currents of the component neurons and the short-term dynamics of the synapses have been characterized. Examples of well-studied invertebrate CPG networks include those underlying tritonia swimming, feeding in crustaceans, and leech heartbeat (Marder and Calabrese 1996).

CPGs have also been the subject of intensive research in vertebrate systems, in particular, lamprey swimming, salamander locomotion, and rodent models of respiration. Lampreys are primitive fish whose spinal cords are easily dissected and are capable of producing fictive locomotion *in vitro*. As such, this preparation has become the best studied example of rhythmic locomotor activity in vertebrates (Grillner 2003). Salamanders offer an insight into the switching of two different types of locomotor modalities: swimming or stepping. Of particular interest is the stepping gait, in which the body makes an S-shape wave with coordinate movement of the limbs (Ijspeert et al. 2007). This stepping gait can either be fast or slow, but salamanders prefer the

faster trotting gait. When trotting, diagonal limbs are in phase while opposite limbs are out of phase. Both the switching between swimming and stepping, as well as the simulation of stepping, have been modeled and studied (Ijspeert et al. 2007) but the full understanding of the behaviors has been elusive.

The medullar pre-Bötzinger complex contains the CPG responsible for the genesis of breathing in mammals (Smith et al. 1991). The pre-Bötzinger complex controls the inspiratory phase of breathing through the activity of a set of pacemaker neurons that are state dependent. In particular, there are two subsets of pacemaker neurons within the system which have been characterized based on their pharmacological properties. During normoxia, respiratory rhythm generation is driven through a heterogeneous population of pacemaker neurons, while during hypoxia the respiratory rhythm is driven by only one type of pacemaker (Pena et al. 2004). The pacemaker groups and the properties of the network have been the subject of many computational models (Butera et al. 1999; Del Negro et al. 2002a, b; Cordovez et al. 2010).

Molecular Mechanisms of Neurotransmitter Release

Presynaptic Machinery Responsible for Neurotransmitter Release

Neurotransmitter release is achieved through the interplay of a variety of proteins associated with the presynaptic terminal. Once transmitter-filled vesicles are transported to the synaptic terminal, they dock and are primed for release. This process involves the attachment of vesicles to the membrane through the SNARE complex, a set of interacting proteins found on the vesicle and cytoplasmic membranes (Jahn and Fasshauer 2012). Only primed vesicles can fuse with the membrane and release neurotransmitter into the presynaptic cleft through the process of exocytosis, triggered by the interaction of Ca^{2+} with the SNARE complex. Depolarization of the presynaptic terminal, usually due to the arrival of an action potential, activates voltage-gated Ca^{2+} channels (VGCCs) and results in a rapid increase of the local

concentration of Ca^{2+} , which then binds to synaptotagmin, causing the vesicle membrane to fuse with the plasma membrane (Mehta et al. 1996). The SNARE complex is a helical protein complex composed of the v-SNARE protein synaptobrevin (also known as vesicle-associated membrane protein [VAMP-2]) and the t-SNARE (“target” SNARE) proteins localized to the presynaptic plasma membrane, SNAP-25 (synaptosome-associated protein of 25 kDa), and syntaxin. Apart from its interaction with v-SNARE, t-SNARE proteins syntaxin also directly interact with the Ca^{2+} channels to promote vesicular fusion (Stanley 1997). Finally, synaptic function also requires the interaction of SNARE proteins with Munc-18, which has been found to allow for syntaxin and SNAP-25 to form a complex that serves as an intermediate in the exocytic pathway (Zilly et al. 2006). The three SNARE proteins, syntaxin, SNAP-25, and synaptobrevin, have been found to be the minimal set of proteins required for fusion (Sudhof 2012).

Pools of Neurotransmitters: Ready or Not

The presynaptic terminal may contain hundreds of neurotransmitter vesicles; however, only a fraction of these, the readily releasable pool (RRP), are docked at the active zones of the membrane awaiting release. The remaining vesicles are divided between the reserve pool, the vesicles that are ready to be moved to the docking position, and the non-recycling pool (Regehr 2012).

Short-term synaptic plasticity is affected by the size of the RRP. The number of vesicles in the RRP varies across species and measuring it could be difficult due to the replenishment from the reserve pool. Earlier studies estimated the range of the RRP to vary from 7 to 130 depending on the type and location of synapse (Rosenmund and Stevens 1996; Xu-Friedman et al. 2001; Zucker and Regehr 2002). However, that number can average as high as 1700 as measured in the mouse neuromuscular junction (Ruiz et al. 2011) and is also high at special high-throughput synapses such as calyx of Held, which contains hundreds of active zones (Schneggenburger et al. 2002). More recent studies have found those numbers to be much smaller than originally estimated.

For instance, at certain GABAergic synapses within the cerebellum, the number of vesicles was found to be maximally 4 (Trigo et al. 2012). The size of the RRP may be regulated by a variety of factors, including the actions of the Na^+/K^+ ATPase pump (Taruno et al. 2012).

Postsynaptic Factors Influence Short-Term Plasticity

While many studies have concentrated on the presynaptic mechanism of short-term plasticity, postsynaptic factors also contribute to changes in the synaptic transmission strength. The postsynaptic response depends on the amount of transmitter release from the presynaptic neuron, kinetics of the receptor, and other factors. Postsynaptic Ca^{2+} contributes significantly to post-tetanic potentiation in sensory-motor neurons of Aplysia, by facilitating the induction of plasticity at neighboring neurons (Schaffhausen et al. 2001). Additionally, when postsynaptic receptors are saturated, this may limit responses by the cell, as shown at the climbing fiber synapse (Wadiche and Jahr 2001). Desensitization of postsynaptic receptors can cause a temporary decrease in synaptic responses (Xu-Friedman and Regehr 2004). Additionally, saturation of the postsynaptic receptors may have a significant impact on recovery from depression (Foster et al. 2002).

The Role of Ca^{2+} in Neurotransmitter Release
 Ca^{2+} entry through VGCCs in the presynaptic terminal results in vesicle fusion and the release of neurotransmitters. Synaptic strength is dependent on Ca^{2+} levels in the presynaptic active zone. This is believed to be partially due to Ca^{2+} interaction with multiple low-affinity binding sites on synaptotagmin, several of which have to be bound to trigger vesicle fusion (Felmy et al. 2003). If Ca^{2+} binds one or more sites, it increases the probability of release upon subsequent depolarization of the presynaptic membrane. Elevated amounts of local Ca^{2+} , however, are transient and highly sensitive to the distance from the VGCCs and the site of release. Local Ca^{2+} concentrations are also affected by Ca^{2+} -binding proteins that exist in the presynaptic bouton (Regehr 2012). Not all Ca^{2+} that enters the presynaptic

cell, however, binds to the docked vesicles: it diffuses away from the active site, is rapidly buffered (Burrone et al. 2002; Burnashev and Rozov 2005), or is actively pumped out of the presynaptic terminal (Regehr 2012). The residual Ca^{2+} is then gradually removed from the presynaptic bouton (Scott and Rusakov 2006). Ca^{2+} diffusion in the presynaptic terminal has been extensively studied and modeled (Simon and Llinas 1985; Zucker and Fogelson 1986; Bertram et al. 1999; Matveev et al. 2004).

Multiple Forms of Synaptic Plasticity Coexist at a Synapse

The interactions of different types of synaptic plasticity found at most synapses allows for an alteration in synaptic strength. Short-term depression, facilitation, augmentation, and post-tetanic potentiation can coexist at the synapse; however, the dominance of each of the mechanisms at a given time point is controlled by the activity of the presynaptic neuron.

Short-term plasticity is often measured using a paired-pulse protocol. The presynaptic neuron is stimulated with a square pulse two to five times with an appropriately chosen interpulse interval. The postsynaptic response is then measured for each stimulus and the ratio of the postsynaptic response to the presynaptic response becomes the measure of short-term plasticity. If the ratio is greater than 1, the response is deemed facilitatory, and when it is less than 1 then it is deemed depressing. This method has been used in a variety of systems including different CPGs such as the pre-Bötzinger complex, the pyloric network of the stomatogastric system, and leech feeding behavior.

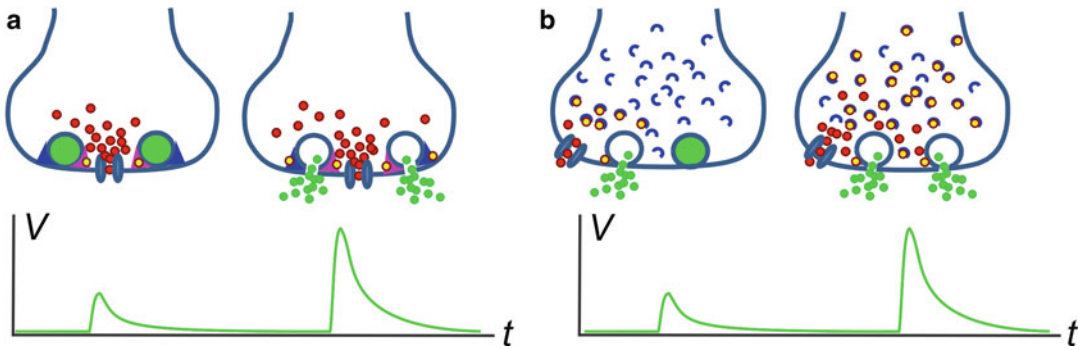
Facilitation

Synaptic facilitation is a type of short-term plasticity where the amount of neurotransmitter released is increased during a sequence of action potentials reaching the synaptic bouton. This increase leads to a prolonged effect of the neurotransmitter on the postsynaptic membrane. This type of short-term plasticity occurs at the fastest

time scale and is measured using a paired-pulse protocol. Facilitation is subdivided into two different stages: F1 facilitation which lasts tens of milliseconds and F2 facilitation which lasts hundreds of milliseconds (Zucker and Regehr 2002).

Many ideas were put forward to explain presynaptic facilitation (Regehr 2012). The simplest hypothesis states that the arrival of the action potential at the presynaptic bouton evokes a rise in local Ca^{2+} which triggers neurotransmitter release and which then persists at a lower concentration in the presynaptic bouton. Since such low residual Ca^{2+} concentration is insufficient by itself to trigger low-affinity vesicle release gates, this hypothesis requires the residual Ca^{2+} to act at a high-affinity presynaptic Ca^{2+} sensor other than synaptotagmin. Further, such a high-affinity second sensor should be located farther from the channel in order to prevent its rapid saturation; for this reason, this model is sometimes referred to as the two-site model of synaptic facilitation (Matveev et al. 2002) (Fig. 1a). A second possibility is that this second, high-affinity Ca^{2+} binding site possesses slower Ca^{2+} kinetics, allowing its Ca^{2+} -bound state to outlive the Ca^{2+} residual signal. This mechanism is often referred to as the bound residual Ca^{2+} mechanism of synaptic facilitation (Matveev et al. 2006) and was historically the first facilitation model proposed in the pioneering studies by Katz and Miledi (1968), who called such bound Ca^{2+} the “active” Ca^{2+} (Bornschein et al. 2013; Isope 2013). Finally, it is also possible that this additional slower Ca^{2+} binding process may represent Ca^{2+} -dependent vesicle priming or other Ca^{2+} -dependent process upstream of vesicle (Pan and Zucker 2009).

The action of endogenous Ca^{2+} buffers has been proposed as an alternative mechanism of synaptic facilitation. Both fast, high-affinity Ca^{2+} buffers and those that slowly bind Ca^{2+} can influence facilitation. Ca^{2+} binding proteins reduce the concentration of local Ca^{2+} at the release site (Regehr 2012). However, high-affinity Ca^{2+} buffers bind Ca^{2+} at the presynaptic bouton when concentrations are sufficiently high, which leaves them unable to bind additional Ca^{2+} . As a result, the additional Ca^{2+} that enters and is not bound by buffers will reach the release site. In this



Short-Term Synaptic Plasticity in Central Pattern Generators, Fig. 1 *Models of facilitation (a) Residual-free Ca^{2+} accumulation: the two-site model of synaptic facilitation.* Exocytosis requires simultaneous binding of Ca^{2+} (red circles) to a low-affinity sensor located within the channel nanodomains (magenta at the vesicle base) and more remotely located low-affinity sensors (blue on the far side of the vesicle). The accumulation of free residual Ca^{2+} is small but more significant far from the channel, allowing for a significant increase in the binding of remote Ca^{2+} sensor from the first stimulus to the second and, therefore,

more transmitter release and a larger postsynaptic response (*bottom traces*). (b) *Facilitation by saturation of high-affinity buffer.* The postsynaptic response (*bottom trace*) to the first presynaptic stimulus is small, because most of the free Ca^{2+} ions entering the presynaptic site are bound (yellow circles) by the Ca^{2+} buffer molecules (blue crescents) before they reach the vesicles. However, the postsynaptic response to the second presynaptic stimulus will be large because there are fewer free buffer molecules around, thus increasing the probability of Ca^{2+} ions reaching the targets for exocytosis

manner, local buffer saturation can contribute to paired-pulse facilitation (Burnashev and Rozov 2005; Matveev et al. 2006; Neher 1998) (Fig. 1b). Slow Ca^{2+} binding proteins can also influence facilitation. By controlling the concentration of residual Ca^{2+} and accelerating its decay in the presynaptic bouton, slow endogenous buffers act like the slow buffer EGTA (Atluri and Regehr 1996), which then provides a mechanism to control the rate of Ca^{2+} decay, thereby influencing facilitation rates (Regehr 2012). However, the contribution of both fast and slow buffers to facilitation is still a matter of debate (Bornschein et al. 2013).

An important example of a CPG where synaptic facilitation has been observed and studied both experimentally and using computational modeling is the lamprey swim CPG. In control conditions, activity-dependent plasticity does not contribute to the patterning of network activity. However, Kozlov et al. found that substance P can lead to an activity-dependent facilitation during repetitive activation of the inhibitory cross caudal interneurons (CCINs) in the lamprey swim CPG (Parker and Grillner 1999; Kozlov et al. 2001). This is accomplished through control of the

release of the neuromodulators from the presynaptic side as well as postsynaptic modulation of different ionic conductances (Kozlov et al. 2001). In order to examine the activity-dependent facilitation in this system, they used a compartmentalized Hodgkin-Huxley model neuron with the synaptic activation modeled as a leaky integrator and synapse activation summing input spike events of constant duration. Their study aimed to elucidate the two alternate modes of activity within the lamprey spinal locomotor network, showing that facilitation has a strong effect on frequency regulation in this CPG (Kozlov et al. 2001).

Facilitation has also been observed in the crustacean stomatogastric nervous system, specifically in the synapses of the pyloric CPG. The synapse from the lateral pyloric (LP) neuron to the pyloric dilator (PD) neurons is the sole chemical feedback to the pacemaker group and exhibits short-term depression. This synapse possesses both a graded and spike-mediated component (Zhao et al. 2011). However, the presence of the endogenously released neuromodulatory peptide proctolin switches the dynamics of this synapse from depression to facilitation. The mechanism of

this switch was investigated in the modeling study of Oh et al. (2012), who proposed that the low-voltage-activated Ca^{2+} current possesses both fast and slow kinetic components and that proctolin adjusts the activation rate of the slow component, leading to an accumulation of local Ca^{2+} in response to low-voltage presynaptic stimuli, resulting in synaptic facilitation (Oh et al. 2012).

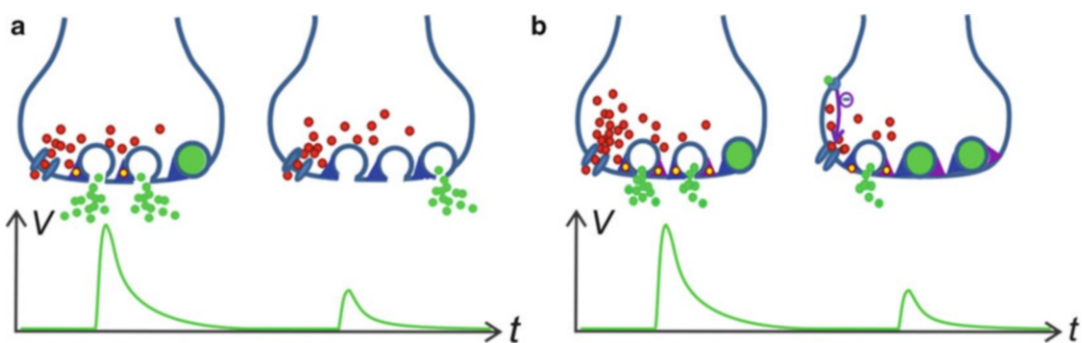
Depression

At many synapses, elevated activity or repeated stimulation leads to a decrease in synaptic strength. As is the case for facilitation, multiple mechanisms can contribute to synaptic depression (Zucker and Regehr 2002; Regehr 2012). Depression is believed to be caused in large part by the reversible depletion of available synaptic resources, mainly the release-ready pool of vesicles (RRP; Fig. 2a). Such vesicle depletion is an example of use-dependent synaptic depression, with higher levels of use associated with larger degree of synaptic depression (Markram et al. 1998). Reducing the level of synaptic transmission relieves use-dependent synaptic depression, while at high sustained synaptic activity, the replenishment of the RRP from the reserve vesicle pool cannot keep up with the depletion of the RRP (Zucker and Regehr 2002; Regehr 2012). Therefore, the extent to which depletion occurs is

dependent on the number of vesicles in the RRP at each active zone and the number of vesicles that are released by an action potential. This depletion model accounts for the properties of the paired-pulse depression that is seen in many different types of synapses. According to the depletion model, the more vesicles released with the initial stimulus, the fewer will be released by the second and subsequent pulses. Depression by vesicle depletion is particularly pronounced following high-frequency tetanic stimulation, which strongly depletes the RRP so that the subsequent recovery may take tens of seconds, rather than seconds.

Another mechanism of activity-dependent depression involves inhibition of the response caused by the vesicle fusion with the active zone. Vesicle fusion may transiently disrupt the morphology of the active zone and may inhibit the time it takes for membrane proteins to clear the active zone. This mechanism is supported by experimental evidence that blocking endocytosis can increase synaptic depression during pulse trains (Regehr 2012).

Other depression mechanisms may depend on the intensity of stimulation rather than amount of neurotransmitter released. This is true, for instance, in the case of inactivation of Ca^{2+} channels that has been found to account for depression



Short-Term Synaptic Plasticity in Central Pattern Generators, Fig. 2 Models of depression (a) **Synaptic depression by vesicle depletion.** The postsynaptic response (bottom panel) to the second presynaptic stimulus is greater compared to the response to the first presynaptic stimulus because of the reduction in the number of available neurotransmitter-filled vesicles (green circles). (b) **Ca^{2+} channel inactivation/presynaptic modulation.**

Presynaptic Ca^{2+} channel opening probability may decrease during the presynaptic stimulus train, due to one of two mechanisms: (i) inactivation of presynaptic voltage-dependent Ca^{2+} channels or (ii) activation of presynaptic metabotropic receptors that modulate the gating of presynaptic Ca^{2+} channels (e.g., through G-protein-regulated pathways). Reduction in the presynaptic Ca^{2+} current leads to a reduction in the vesicle release rate

at some synapses (Bertram et al. 2003). Presynaptic recordings from the calyx of Held have shown that high-frequency stimulation reduces Ca^{2+} entry. Decreased Ca^{2+} entry was found at frequencies greater than 30 Hz and depletion was found when the stimulus was in excess of 100 Hz (Xu and Wu 2005).

Also on the presynaptic side, depression can arise through the activation of metabotropic presynaptic receptors activated by modulatory substances released from the activated presynaptic terminals, postsynaptic cells, or neighboring cells (Fig. 2b). Metabotropic receptors may be selective either for the neurotransmitter released by the terminal itself (autoreceptor-mediated depression), for retrograde messengers (e.g., endocannabinoid receptors), or for neuromodulatory substances projecting from elsewhere in the nervous system (neuromodulatory receptors). Depression may also arise from postsynaptic mechanisms such as postsynaptic receptor desensitization, which in fact represents another form of use-dependent synaptic depression. Another mechanism of synaptic depression was demonstrated in the developing spinal cord (Tabak et al. 2000, 2001). In this system, GABA is functionally excitatory because intracellular Cl^- is high. During an episode of activity, Cl^- ions leave the neurons so the GABA reversal potential becomes more negative. This mechanism seems quite important for the episodic activity in the developing spinal cord.

Regulation of and recovery from depression are also important factors in short-term synaptic plasticity. Bassoon, a large presynaptic protein present at the active zone, has been found to minimize depression by replenishing vesicles at release sites (Hallermann et al. 2010; Regehr 2012). When Bassoon is experimentally removed, synaptic depression is enhanced. Rab3-interacting molecules (RIM) are vital components of the active zone (Kaeser et al. 2011), serving two critical functions: priming of synaptic vesicles and tethering of Ca^{2+} channels to the active zone (Kaeser 2011; Kaeser et al. 2011). RIM proteins have been implicated in influencing depression: when they are removed, depression is dramatically alleviated (Calakos et al. 2004; Sudhof 2012).

The role of synaptic depression in CPG networks has been studied in great detail. For instance, synaptic depression has been determined to be pivotal in the maintenance of phase relationships within CPGs (Mamiya et al. 2003; Manor et al. 2003). Depression of synapses of the pyloric network leads to synaptic weakening during fast rhythmic behavior while allowing the synapses to remain strong during a slow rhythm (Marder et al. 2005). Manor et al. examined the effect of synaptic depression using a model of an oscillator neuron and a follower neuron coupled with an inhibitory synapse from the oscillator to the follower (Manor et al. 2003). An important result from their study was that depression in inhibitory synapses always promotes a constant relative phase between the pre- and postsynaptic neurons in an oscillatory network. The strength of a depressing synapse in an oscillatory network is dependent on the cycle frequency: the faster the oscillation, the more depression and therefore the weaker the synapse. This frequency dependence implies that synaptic inhibition gets weaker if the network operates at a faster pace, thus reducing the latency between the pre- and postsynaptic neuron activity. Because relative phase is defined as latency over period, this simple observation implies that a depressing synapse will always promote phase constancy (as opposed to a constant latency) compared to a synapse that is nondepressing.

In order to maintain stability, a network may reconfigure itself to produce different patterning behaviors. Li et al. explored the mechanisms by which sensory activity led to the selection and generation of swimming and struggling in *Xenopus* tadpoles (Li et al. 2007). In *Xenopus* tadpoles, two different behaviors can be triggered: struggling, which is elicited if the animal is held or pinned against a silicone-gel-lined Petri dish and involves strong head-to-tail bends, and swimming, which is elicited if the animal is touched lightly and involves low-amplitude bends (Kahn and Roberts 1982; Li et al. 2007). In immobilized tadpoles, stimulation of the skin causes a switch of the struggling CPG by reconfiguration of the locomotor network. This switch is thought to be caused by a context-dependent short-term

depression of the reciprocally inhibitory synapses between two CPG neurons, the commissural interneurons (cINs). When synaptic depression was included in these synapses in a model network, activation of the network at higher firing frequencies characteristic of struggling led to robust bursting activity. In contrast, when the network was activated at lower firing rates, depression was not active and the network output resembled more the swimming behavior which involves a single spike per cycle (Li et al. 2007). Thus, as shown in this system, synaptic depression of reciprocal inhibition may play a key role in one behavior (struggling) but be mostly absent in another (swimming).

Synaptic depression was also proposed as the principal mechanism of rhythmogenesis in the developing chick spinal cord (Tabak et al. 2000). These studies proposed that synaptic depression accumulates during the active burst phase of the rhythm, ultimately terminating the active phase, and that the recovery from depression during the inactive state allows the bursting activity to resume in the next cycle of activity. Within certain networks, rhythm generation may depend on specific types of synaptic depression which are more complex than simple vesicle depletion. For example, this is the case in the group pacemaker model of rhythmic activity in the pre-Bötzinger complex developed by Rubin et al. (2009) based on a Hodgkin-Huxley style conductance-based model of spiking activity. In this model, glutamatergic synapses and short-term depression of excitatory transmission have roles in the rhythmogenesis of a particular type of pacemaker group within the pre-Bötzinger complex. A network-wide burst is generated through recurrent synaptic excitation that initiates the postsynaptic Ca^{2+} -activated non-specific cation current (I_{CAN}). The depolarization due to I_{CAN} causes a voltage-dependent spike inactivation, diminishing recurrent excitation and therefore attenuating the postsynaptic accumulation of Ca^{2+} . The burst is then terminated through activity-dependent outward currents, resulting in a quiescent state in the network. A new cycle is then initiated when sporadic spiking activity rekindles excitatory interactions (Rubin et al. 2009).

Augmentation and Post-Tetanic Potentiation

While facilitation has been shown to last no more than hundreds of milliseconds, two other forms of potentiating short-term synaptic plasticity, last tens of seconds to minutes in duration. Augmentation and post-tetanic potentiation (PTP) are related forms of synaptic plasticity that are observed after sustained high-frequency stimulation (Zucker and Regehr 2002; Regehr 2012). Augmentation is an increase in the synaptic potential amplitude that is produced by repetitive stimulation which has been found to act by potentiating vesicle fusion (Zucker and Regehr 2002). Post-tetanic potentiation is a common form of short-term plasticity that leads to an increase in synaptic strength for several minutes after increased stimulation. PTP is closely related to augmentation and lasts tens of seconds to minutes in duration and increases with the presence of additional or sustained stimuli.

Augmentation was originally described in the frog neuromuscular junction and now has been observed in many synapses, including in mammalian cortex (Regehr 2012). Augmentation increases during a stimulus train, but decays slower than facilitation with a time constant of 5–8 s. The decay of augmentation has been shown to be insensitive to stimulation duration and frequency. Additionally, augmentation shares other properties with facilitation. Augmentation is dependent on the buildup of Ca^{2+} in the presynaptic terminals during spike trains, after the development of a significant level of facilitation. Several mechanisms are believed to contribute to augmentation and PTP, including action potential broadening, increase in quantal size, and changes in the RRP (Zucker and Regehr 2002).

Several functional roles of augmentation and PTP in synaptic plasticity have been suggested. Augmentation is believed to be a counteracting mechanism against depression during times of high levels of neural activity (Deng and Klyachko 2011). Furthermore, it has been shown that transmitter release is sustained during trains of stimuli by increasing the release probability of vesicles within the RRP. In addition to maintaining transmitter release during high-frequency stimulation, augmentation has been found to directly

counteract depression in hippocampal excitatory synapses (Deng and Klyachko 2011). The mechanisms for both augmentation and PTP have been studied and debated for many years. Early studies proposed the accumulation of residual Ca^{2+} as a primary mechanism, but more recent results have implicated both PKC activation and CaM kinase II activity (Hennig 2013). However, very few studies have concentrated on these phenomena in CPGs.

In the crustacean STG, the gastric mill network is responsible for movement of muscles that control chewing within the foregut. Stein et al. characterized the temporal dynamics of the gm6 gastric mill muscle and explored the response of this muscle to different patterns of input during the gastric mill CPG activity (Stein et al. 2006). Using train stimulations of various frequencies, they found that augmentation increased the amplitude of the EJPs at certain frequencies while not at others. During the ongoing gastric mill rhythm, augmentation contributed to the response of the muscle as well as muscle force.

Outlook

Theoretical models have contributed greatly to the advancement in understanding of synaptic transmission and short-term plasticity in CPGs. In concert with experimental data, studies of both vertebrates and invertebrate CPGs have provided insight and mechanisms by which neural circuits reconfigure in order to generate different patterns to alter behavior. Many of the models discussed capture the processes involved in short-term synaptic release in a relatively simple way. Additionally, many studies on the effects of short-term synaptic plasticity on CPG activity suggest that neuromodulators play an important role in the network behavior through their effects on synaptic properties. As CPG circuits continue to be mapped, it will be essentially to gain insight about mechanisms which cause switches in behavior, changes in synaptic strength, and remodeling of the circuits in general. The mutual relationship between computational modeling and experimental studies will continue to be important for the understanding of the role of STP in CPG function.

Cross-References

- ▶ [Biophysical Models of Calcium-Dependent Exocytosis](#)
- ▶ [Rhythm Generation in Embryonic Chick Spinal Cord](#)

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Signaling Pathways, Modeling of

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Synonyms

[Kinetic modeling](#)

Definition

The use of models to study the dynamical behavior of a biological (sub)system described as a set of biochemical reactions and diffusion. Here, the evolution in time for quantities such as protein concentrations or amount of enzyme activation is typically described using ordinary differential equations. The evolution in time of second messengers is typically described using partial differential equations. Alternatively, stochastic methods can be used to determine evolution in time of all molecules in a simulation.

Detailed Description

The development of quantitative models at multiple spatial and temporal scales is necessary for integrating the knowledge obtained from diverse experimental approaches into a coherent picture. Such models represent current knowledge in a compact and standardized way and constitute a tool for guiding experiments and generating predictions.

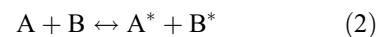
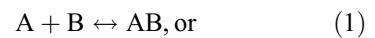
Modeling of intracellular signaling within the field of computational neuroscience is typically done to better understand how events on the subcellular level affect, or even may explain, higher-level phenomena. For example, subcellular mechanisms underlying synaptic long-term potentiation (LTP) and long-term depression (LTD) could be investigated in models of receptor-induced cascades of signaling molecules activated during typical experimental protocols. Commonly modeled LTP or LTD systems begin with the activation of transmembrane receptors or the influx of calcium and include the activation of kinases and/or phosphatases and their phosphoprotein targets (see, e.g., Kotaleski and Blackwell 2010).

Dynamical modeling of signaling pathways is required because steady states are rarely achieved. Most of the time activation of signaling pathways is transient, and thus, the response of the system is transient. Intracellular signaling pathways may reach a steady state solution if the activation is kept constant, but sometimes such systems can show oscillations or behave as a bistable (or even multistable) biochemical switch.

How to Represent the Reactions in the Signaling Pathway?

Signaling pathways are represented as cascades of biochemical reactions, together with the diffusion of a subset of the molecular species. It is not plausible to include every reaction known to occur in neurons or cells; thus, the modeled pathway includes those components, such as enzymes, proteins, calcium ions, etc., judged to be relevant for the research question. The identification of critical components and how they interact or react typically are based on experimental data. Such data is often qualitative, but quantitative data are required for model development. Once the relevant molecules and reactions have been identified, the system can be specified and simulated. Two general approaches to the simulations are *stochastic* and *deterministic*. When using a deterministic approach, the system of biochemical reactions are described using a system of ordinary differential equations, which describe the rate of change in the concentrations/amounts of each component. The rate of change is based on the concentrations of all other reactants involved in a reaction. In addition, the *diffusion* of molecules is represented using discretized versions of partial differential equations. Various software packages that include numerical integrators can then be used to simulate the dynamics of the system if initial conditions and reaction rate parameters are provided.

To capture the individual steps in a signaling pathway, bimolecular and enzymatic reactions as well as protein modifications need to be included. Simple biochemical reactions, where one reacting substance (A) binds to another one (B) to form a product (AB) or to modify each other (A^* , B^*), can be represented as



Here, it is assumed that in both these cases, the reaction can be reversed. The speed of the forward and backward reactions is described by corresponding reaction rate parameters, k_f and k_b .

The “ $A + B \leftrightarrow AB$ ” system in Eq. 1, for example, is modeled deterministically using the following first-order differential equations:

$$\begin{aligned} d[A]/dt &= d[B]/dt \\ &= -k_f \cdot [A] \cdot [B] + k_b \cdot [AB] \text{ and } \end{aligned} \quad (3a)$$

$$d[AB]/dt = k_f \cdot [A] \cdot [B] - k_b \cdot [AB], \quad (3b)$$

where $[A]$, $[B]$, and $[AB]$ stand for the concentrations (e.g., measured in μM) of the corresponding reactants or products. The k_f and k_b rate parameters have here units of $\text{concentration}^{-1} \text{time}^{-1}$ and time^{-1} , respectively. The units for concentration of molecules must match the units of the rate constants. One additional set of values are required: given the initial concentrations for A , B , and AB , one can numerically integrate the behavior of the system over time.

When the system Eq. 1 above has reached steady state, ss , so that all time derivatives of the concentrations are zero, then

$$k_b/k_f = [A_{ss}] \cdot [B_{ss}]/[AB_{ss}], \quad (4)$$

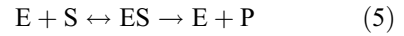
where k_b/k_f defines the dissociation constant, K_D , which thus can be estimated from the steady state concentrations of the involved species. (Note that sometimes the affinity constant, $K_A = 1/K_D$, is given instead.) Measures of K_D are provided in the biochemical literature more frequently than individual rate constants, because to estimate k_b and k_f individually requires data on the dynamics in the system, which are difficult experiments to perform.

The above approach assumes *mass action kinetics* which states that the rate of a reaction is the product of a rate constant (k) times the concentrations of the reacting species. This approach can be used to describe the behavior of both reversible and irreversible reactions, also when these reactions are part of reaction cascades, such as simple enzymatic reactions, as explained below. A similar framework, $A \leftrightarrow A^*$, can also represent the exchange of mass through diffusion between different compartments (dendritic spines, dendritic shaft, or different subvolumes within a spine or a dendrite). The rate by which the species move between

compartments can be represented by the diffusion coefficient adjusted for the volume and contact areas of the adjacent compartments.

Mass action kinetics grew out of the work by Guldberg and Waage (reviewed by Lund 1965) who investigated, and tried to find laws for, how the velocity of chemical reactions could be described. This law describes how fast the molecules in a well-stirred solution collide and interact on average (and thus, stochastic interactions between individual species molecules are ignored).

Enzymatic reactions can be modeled as a cascade of biochemical reactions with the approach above. Enzymes speed up the rate by which the substrate of the enzyme is transformed into a product. The underlying reactions are assumed to be captured by the following scheme, which in the simplest case assumes a nonreversible catalytic step, a scheme developed successively in the early twentieth century by Michaelis and Menten (1913) and Briggs and Haldane (1925):



In the first step, described as above by a k_f and k_b rate parameter, the enzyme (E) binds to the substrate (S) in an enzyme-substrate compound (ES). The second reaction step, where the enzyme is catalyzing the formation of the product, is controlled by the catalytic rate parameter, k_{cat} . Again, given some initial conditions and some values on the rate parameters, k_f , k_b , and k_{cat} , these two reaction steps can be modeled *deterministically* using first-order differential equations of the form

$$\begin{aligned} d[E]/dt &= -k_f \cdot [E] \cdot [S] + k_b \cdot [ES] + k_{cat} \\ &\quad \cdot [ES] \end{aligned} \quad (6a)$$

$$d[S]/dt = -k_f \cdot [E] \cdot [S] + k_b \cdot [ES] \quad (6b)$$

$$\begin{aligned} d[ES]/dt &= k_f \cdot [E] \cdot [S] - k_b \cdot [ES] - k_{cat} \\ &\quad \cdot [ES] \end{aligned} \quad (6c)$$

$$d[P]/dt = k_{cat} \cdot [ES] \quad (6d)$$

A common example is the reaction catalyzed by a kinase, which phosphorylates a substrate,

$S + \text{ATP} \rightarrow P + \text{ADP}$, where the substrate, S , is a protein to be phosphorylated, P . This simple, one-step reaction assumes that ATP is constant (and sufficiently high that it is not rate limiting) and all substrate molecules have formed a complex with the enzyme. Then, the reaction rate is captured by the k_{cat} rate constant above. In theory, an enzymatic reaction must be reversible since an enzyme just speeds up the reaction, but does not change the steady state, which is decided by the thermodynamics constraints. Thus, if the product is accumulating in high enough amounts, a reversible reaction may need to be accounted for. Whether this needs to be represented in a model depends on the equilibrium constants for the enzymatic reactions considered.

Enzymatic reactions are sometimes modeled deterministically using the *Michaelis-Menten kinetics*. With this simplification, the variations in $[E]$ and $[ES]$ are discarded from Eq. 6a–6d and instead assumed to be constant, i.e., $d[ES]/dt = 0$, as during steady state conditions. Since the amounts of the substrate and product change over time, this assumption requires that the substrate be present in sufficient amount, else the amount of $[ES]$ will change over time. Whether the enzymatic reaction can be simplified to the Michaelis-Menten (MM) formalism or needs to be modeled explicitly using Eq. 6 depends therefore on the particular system modeled.

When modeling a set of signaling pathways as a cascade of biochemical reactions, the product of one reaction is usually the substrate of a subsequent reaction. Alternatively, active enzymes are often the product of a reaction. Frequently, enzyme and bimolecular reactions alternate. For example, first a ligand binds to a receptor; second, the ligand receptor complex is an enzyme; third, product of the enzyme reaction binds to and activates another enzyme, etc. When the product of the enzyme is a diffusible molecule, it is often called a second messenger. The diffusion and degradation of the second messenger must be modeled carefully to correctly represent its spatial and temporal dynamics.

When searching for parameter values in the literature for the various enzymatic reactions to

be represented in the model, usually only k_{cat} (or more often V_{max} which is k_{cat} total amount of enzyme) and the concentration of substrate when the production of product is half-maximal, K_M , is reported. Thus, the k_f , k_b , and k_{cat} in the equations above need to be mapped onto K_M , and it can be shown that $(k_b + k_{\text{cat}})/k_f = K_M$. This, however, means that we only have two measured values but three parameters to set. Thus, when k_b is not known explicitly, it needs to be set, e.g., as $4 \cdot k_{\text{cat}}$ as motivated in Bhalla and Iyengar (1999). Under the assumption that $d[ES]/dt = 0$, and setting $[E] = [E_{\text{total}}] - [ES]$, then

$$d[P]/dt = k_{\text{cat}} \cdot [E_{\text{total}}] \cdot [S]/(K_M + [S]) \quad (7)$$

Whether the Michaelis-Menten (MM) representation, Eq. 7, and the explicit formulation above, Eqs. 6a–6d, give similar results or not depends on to what extent the assumptions underlying the MM formalism are fulfilled. In, e.g., Ramakrishnan and Bhalla (2008), there is one example of a minimal biochemical system that can behave as a switch when the system is modeled using the MM formalism, but not when the explicit formulation above is used.

Limitations

Although the above deterministic approaches are commonly used within the computational neuroscience field (Manninen et al. 2010), several factors should be considered when representing a signaling pathway with a set of ordinary differential equations, assuming well-stirred solutions. For example, receptor-induced cascades involved in synaptic plasticity typically are localized in dendritic spines, and compartmentalization with regard to functions of different molecules might be common. Also proteins are heterogeneously distributed in different parts of the cytosol and membrane, and some molecules are anchored, while others might diffuse freely. Modeling these reactions across different compartments requires diffusion. If reacting or diffusing species are present in small quantities, then reactions and diffusion occur stochastically, in which case they

cannot be modeled deterministically, and stochastic approaches must be used.

One overall challenge when building models of signaling pathways is the estimation of the reaction rate constants and amounts of the different molecular species. Biochemical estimates of model parameters can, for instance, be obtained through “test tube” experiments. However, the conditions in real cells might vary significantly from those in the experiments.

Although one often talks about a signaling pathway, it should be realized that such a reaction cascade is most likely embedded in a larger signaling network and that many interactions from other parts of the bigger system are left out. This also makes it difficult to validate pathways models, e.g., a pathway leading from a certain G-protein-coupled receptor to the activation of an enzyme, if those pathways are present in different cell types. Although the reaction rates between the pathway’s individual components are assumed to be similar, differences in the left-out interacting network might affect effective concentrations of enzymes and substrates through sequestration effects, for example, through the competition for available pools of enzymes and substrates.

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Significance Evaluation

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Synonyms

[Hypothesis testing](#); [p-value](#); [Statistical significance](#)

Definition

Broadly speaking: assigning a numerical score to the “unusualness” of data relative to a specific theory. In this entry: computing a p-value for a statistical hypothesis test with emphasis on spike-train resampling.

Detailed Description

Deciding whether the patterns observed in experimental data support or challenge existing theories is a recurring theme in data analysis. Assigning a numerical score, or *significance*, is a central part of the decision process. *Hypothesis testing* is the classical statistical approach with *p-values* being the most common (but not the exclusive) method of communicating statistical significance. This entry is about basic statistical hypothesis testing with a focus on the connection between hypothesis testing and the so-called resampling methods that are gaining widespread popularity in the statistical analysis of neural firing patterns.

A comprehensive statistical analysis rarely stops with hypothesis testing. Parameter

estimation and confidence intervals are often more useful statistical tools. This entry, however, focuses exclusively on hypothesis testing and, in particular, on p-values. (Bayes factors and more generic model selection tools are not discussed.) Although hypothesis testing may not be the ending point of data analysis, it is often an insightful starting point and typically requires simpler statistical models and methods than a more complete analysis.

Statistical Versus Scientific Significance

Statistical significance should never be equated with scientific or experimental significance. Although establishing statistical significance may be an important prerequisite for establishing scientific significance, the latter requires additional analyses, interpretations, and, quite often, experiments. Statistical significance tries to quantify how unusual the data appear with respect to a given statistical model. If the statistical model is not appropriate for the experimental question or if the measured effect is too small to be of scientific importance, then statistical significance, no matter how striking, may have little or no scientific significance. This entry is about *statistical significance* only.

Hypothesis Testing and p-Values

Hypothesis testing begins with a null hypothesis H_0 which can be viewed as a collection of hypothesized probability distributions for the data. Often, H_0 is specified in two steps. The first step involves various underlying *modeling assumptions*, such as the data consist of n independent coin flips with a common probability θ of observing a head on each flip. The second step involves additional restrictions within this basic modeling paradigm, such as the probability, θ , is exactly one-half, which might be written as

$$H_0 : \theta = 0.5.$$

Or, for another example, the null hypothesis might be that the coin is biased towards heads, namely,

$$H_0 : \theta > 0.5.$$

When interpreting the conclusions of a hypothesis test, it is important to inspect both the obviously stated null hypothesis (such as $\theta = 0.5$) and the sometimes not-so-obvious modeling assumptions (such as independent coin flips or constant θ) for their fidelity to the scientific questions at hand.

In most cases, a hypothesis test also comes equipped with a *p-value*. A p-value is any function of the data, say $p(X)$, where X is the data, with the property that

$$\begin{aligned} \text{Prob}(p(X) \leq \alpha) &\leq \alpha \text{ for all } 0 \leq \alpha \\ &\leq 1 \text{ whenever } X \text{ satisfies } H_0, \end{aligned} \quad (1)$$

where $\text{Prob}(A)$ denotes the probability of the event A – in this case, the event that the p-value is at least as small as the number α . Loosely speaking, if the null hypothesis is true, then it is unusual to see a small p-value. For instance, the probability of seeing a p-value less than 0.1 is at most 10% when H_0 is true.

Sometimes, we redundantly say that a p-value is *valid* to emphasize that it has property (1) and to distinguish it from other objects, such as approximations of p-values, that might be (mis-)interpreted as p-values or mistakenly called p-values, even though they are not valid p-values. For any given null hypothesis, there will be many potential ways to create a p-value. It is extremely important to decide which type of p-value will be used before observing the data; otherwise, the “p-value” will lose its validity and will not satisfy property (1) – it will no longer be a p-value! (See section “[Choice of \$T\$ and the Alternative Hypothesis](#)”.)

P-values are particularly useful for communicating statistical significance, because they have a common interpretation regarding type I error rates. A *type I error* occurs when we reject a null hypothesis even though it is true. P-values have the nice property that if we pick a threshold, say 0.05, and reject null hypotheses whenever the corresponding p-values are 0.05 or less, then our

type I error rate is at most 5%. Similarly, if we use a threshold of 0.01, then our type I error rate is at most 1%. In light of these formal guarantees, it is commonplace for smaller p-values to be interpreted as stronger statistical evidence against the null hypothesis than larger p-values.

When the null hypothesis is true, p-values tend to not be small. For a p-value to be useful, however, it should also have good *power*, meaning that it does tend to be small when the null hypothesis is false and some competing alternative hypothesis is true instead. The *alternative hypothesis* is a different collection of hypothesized probability distributions for the data that is distinct from the collection defined by H_0 . A *type II error* occurs when the alternative hypothesis is true, but we do not reject the null hypothesis (because the p-value was too large). Type I and type II errors are in opposition to one another. For a given type of p-value, we can lower the type I error rate only by raising the type II error rate. Using a p-value threshold of 0.01 will lead to less type I errors, but more type II errors, than using a p-value threshold of 0.05.

A rejection of the null hypothesis should not lead to unscrutinized acceptance of the alternative hypothesis. The alternative hypothesis may also be a poor description of the data, perhaps even more so. Similarly, a failure to reject the null hypothesis does not mean that the null hypothesis is a better description of the data than the alternative. It simply means that the statistical evidence is insufficient to rule out the null hypothesis (for the type I error rates that we are willing to tolerate).

A full discussion of p-values and their connections to other common concepts in hypothesis testing, such as power, critical region, size, and level, is beyond the scope of this entry. Any introductory statistics textbook is likely to have a thorough exposition of these and other hypothesis testing concepts. Casella and Berger (2002) is an intermediate-level reference. Lehmann and Romano (2005) is an advanced, comprehensive source. Kass et al. (2014) is an accessible reference aimed for the neuroscience community.

Construction of p-Values

Here, we will focus on a special type of p-value that is particularly relevant for resampling methods in neurostatistics. Let T be any function of the data and let P be a special probability distribution for the data, both of which will be discussed later. Here, T is called the *test statistic* and P is called the *null distribution*. For any potential data set x , define.

$$p(x) = \text{Prob}(T(Y) \geq T(x)) \text{ when } Y \text{ has distribution } P. \quad (2)$$

In words, $p(x)$ gives the probability that a random data set Y would have a test statistic T at least as large as x has, if Y was chosen according to the null distribution P . (When computing the probability, only Y is random; x is held fixed. See section “[Heuristic Resampling](#)” for additional intuition.) In certain special cases, using Eq. 2 to define $p(X)$ creates a p-value, meaning that it satisfies property (1) for an appropriate null hypothesis. For instance, if the null hypothesis is simply that the data have distribution P , then $p(X)$ is a p-value for this null hypothesis. In many cases, p-values cannot be created using Eq. 2, but a discussion of these cases is beyond the scope of this entry.

Example 1

Let $X = (X_1, \dots, X_n)$ be a sequence of n independent coin flips with common probability θ of heads. Let $T = \# \text{heads}$. Let P correspond to the case $\theta = 0.5$ and let the null hypothesis be the same, namely, $H_0: \theta = 0.5$. Using Eq. 2 in this case gives

$$\begin{aligned} p(x) &= \text{Prob}(T(Y) \geq T(x)) \\ &= \sum_{k=T(x)}^n \text{Prob}(T(Y) = k) \\ &= \sum_{k=T(x)}^n \binom{n}{k} 0.5^n, \end{aligned}$$

where $\binom{n}{k} = n!/(k!(n-k)!)$ is the number of distinct ways to have k heads in a sequence of n coin flips and where the computation is done for Y having probability distribution P . Then $p(X)$ is a p-value for H_0 . (To compute $p(X)$, we substitute the observed value of X for the variable x on the right side of the derived formula for $p(x)$ above.) If we observe 7 heads in 10 flips, then the p-value is 0.172. If we had decided to reject H_0 when the p-value was less than 0.2, then we would reject. If instead we had chosen a threshold of 0.1, then we would not reject. This p-value is designed to be used when we anticipate that the coin might favor heads in cases where the null is false. For example, if we observe 3 heads in 10 flips, then the p-value is 0.945 and we would normally not reject, even though there is a sense in which 3 heads and 7 heads are equally extreme observations for a fair coin. By changing the test statistic, T , we could create a p-value that was more symmetric in its behavior or one that tended to be small for large numbers of tails. The choice depends on the scientific context and on the desired error performance. Finally, we note that the original p-value is also a p-value for the null hypothesis $H_0: \theta \leq 0.5$, illustrating that this method of constructing p-values based on a single null distribution P can sometimes be used even when the null hypothesis includes many distributions.

This method in Eq. 2 of constructing a p-value based on a test statistic T and a null distribution P maps closely onto what is normally done with resampling methods in neuroscience. Within this context, there are several important issues:

- Choice of the null hypothesis H_0
- Choice of the null distribution P
- Choice of the test statistic T
- Computation of the p-value $p(X)$
- Adjustments for multiple hypothesis tests.

We will discuss each of these in the remainder of this entry.

Choice of H_0 and P

The choice of the null hypothesis, including the choice of the underlying statistical model, is arguably the most important choice among the items listed in the previous paragraph. The null hypothesis needs to be appropriate for the scientific question and the available data. Despite its centrality, there is little to say here about H_0 , because it is so context dependent. Perhaps the best guidance is to *always clearly state the complete statistical model and the null hypothesis*. Only when H_0 is clearly stated can one interpret the conclusion of a hypothesis test and judge its scientific relevance.

Given H_0 , the next step is to choose a null distribution P under which a p-value can be computed. If H_0 is a *simple null hypothesis*, meaning that it consists of a single hypothesized probability distribution for the data, then we can take P to be this unique distribution specified by H_0 . If H_0 is a *composite null hypothesis*, meaning that it consists of many possible probability distributions for the data, then it may be difficult to find an appropriate P or one may not even exist. Example 1 above illustrates both a simple null hypothesis ($H_0: \theta = 0.5$) and a composite null hypothesis ($H_0: \theta \leq 0.5$) and a corresponding null distribution P (which happens to be the same for each, in this case).

Example 2

Let $X' = (X'_1, \dots, X'_n)$ be a sequence of n independent coin flips with a fixed, but unknown, common probability v' of heads. Let $X'' = (X''_1, \dots, X''_n)$ be another sequence of n independent coin flips with a fixed, but unknown, common probability v'' of heads. In this case, the data are $X = (X', X'')$. The null hypothesis H_0 is that X' and X'' are independent. H_0 is a composite null hypothesis because v' and v'' are not specified by H_0 and are unknown. The unknown parameters $v = (v', v'')$ are often called *nuisance parameters*, because they are necessary to specify the probability distribution but are otherwise unrelated to the target

statistical question – in this case, a question about independence.

Let $T = T(X) = \#\{i: X'_i = X''_i = \text{heads}\} = \#$ aligned heads, which we might expect to be large if X' and X'' are positively correlated. The distribution of T depends heavily on the unknown parameters v and is not uniquely specified if these parameters are not known. Hence, a null distribution P for computing p-values is not apparent. For example, T could be large because the sequences are correlated or because v' and v'' are both large, resulting in many heads, some of which are likely to align by chance. Bootstrap approximation and conditional inference are two common approaches for specifying a null distribution P in situations like this with nuisance parameters. Each is considered below in the continuation of this example.

This example is stereotypical of early frameworks for testing for synchronization between two simultaneously recorded neural spike trains, modeled by X' and X'' , with heads denoting a spike (an action potential) in a small time bin and tails denoting no-spike. The unknown parameters v' and v'' are often called the theoretical firing rates of the respective neurons, and $N(X')$ and $N(X'')$ correspond to the observed spike counts, where $N = \#$ heads. T is the number of precisely synchronous spikes. This simple framework is no longer thought to be appropriate, particularly when recording *in vivo*, because, among other things, the underlying modeling assumption that v' and v'' are constant in time is usually a very poor description of the data. More recent approaches improve on this simple framework both by mak-

ing the underlying modeling assumptions more believable and by aligning the null hypotheses more closely with the scientific questions of interest (Amarasingham et al. 2012; Harrison et al. 2013, ► “Surrogate Data for Evaluation of Spike Correlation” in this encyclopedia).

Bootstrap Approximation

Consider a composite null hypothesis H_0 that would admit a null distribution if we happened to know the value of some nuisance parameter v . The null distribution might be different for each v , say $P = P_v$, which, using Eq. 2, would give rise to a different p-value for each v , say $p(X) = p_v(X)$. One possibility is to use the observed data to obtain an estimate $\hat{v}$ for v and then use the approximate p-value $p_{\hat{v}}(X)$ in place of the true p-value $p_v(X)$. It is an approximate p-value, because the true unknown value of v is replaced with an approximation $\hat{v}$ estimated from data. Usually, Eq. 1 will not hold exactly for an approximate p-value.

Example 2 Part II: Bootstrap Approximation

Continuing Example 2, suppose for the moment that we happen to know the true values of v' and v'' . Then the null hypothesis becomes a simple null hypothesis, namely, that X' and X'' are sequences of independent coin flips with probability of heads given by the known values of v' and v'' , respectively. Using Eq. 2 gives

$$\begin{aligned} p_v(x) &= p(x) = \text{Prob}(T(Y) \geq T(X)) \\ &= \sum_{i=0}^n \sum_{j=0}^n \sum_{k=T(x)}^n \text{Prob}(N(Y') = i, N(Y'') = j, T(Y) = k) \\ &= \sum_{i=0}^n \sum_{j=0}^n \sum_{k=T(x)}^n \binom{n}{i} \binom{n}{j} \binom{n-i}{j-k} (v')^i (1-v')^{n-i} (v'')^j (1-v'')^{n-j}, \end{aligned} \quad (3)$$

where $x = (x', x'')$, where $N = \#$ heads, where we take $\binom{a}{b} = 0$ if $a < b$ or $b < 0$, and where

the computation is done for $Y = (Y', Y'')$ satisfying the null hypothesis for parameters $v = (v', v'')$. The

specific formula for this p-value is not the main point. The key observation is that we could compute $p(X)$, at least in principle, if we knew the values of the test statistic $T = T(X)$ and the parameters v . For instance, if $n = 10$, $v' = 0.3$, $v'' = 0.5$, and we observe $T = 5$, then the p-value is 0.0099. Note that we have emphasized this dependence on the parameters by writing

$$p(x) = p_v(x).$$

But what if v' and v'' are unknown, as originally stipulated in Example 2? One possibility is to estimate their values from the observed data, pretend that their estimated values are correct, and then use the p-value derived above for the case where the parameters are known. If $\hat{v} = (\hat{v}', \hat{v}'')$ are the estimated values, then we would use the approximate p-value

$$p_{\hat{v}}(X)$$

as given by Eq. 3. For instance, if $n = 10$ and we observe $N(X') = 5$ and $N(X'') = 6$, then we might estimate $\hat{v}' = 0.5$ and $\hat{v}'' = 0.6$ (these are the maximum likelihood estimates). If we additionally observe $T = 5$, then the approximate p-value is 0.1503. It is only an approximate p-value, because the true v' and v'' are replaced by estimates from the data. As n gets large, the approximation will improve and the approximate p-value will come closer and closer to being a true p-value in the sense of Eq. 1.

The substitution of the unknown nuisance parameters with their estimates from the data is sometimes called the *substitution method* (or *substitution principle*). Here we use the term *bootstrap approximation*, because it is the first and most important step in bootstrap and because this type of substitution arises almost exclusively in connection with bootstrap in resampling methods for neuroscience. Bootstrap approximations are easy to use and easy to misuse. In Example 2 part II above, the null hypothesis only had two nuisance parameters that needed to be estimated from the data. A more modern example from neuroscience

might have hundreds or thousands or even infinitely many nuisance parameters. Estimating a large number of parameters from data is fraught with difficulty and the estimation errors are essentially guaranteed to be large in some respects. For bootstrap approximations to work well in these situations, the p-value itself must be fairly insensitive to certain types of large approximation errors. Even in cases with only a single nuisance parameter, bootstrap approximations can fail (meaning that they perform poorly no matter how much data is available), usually in cases where the p-value in Eq. 2 is unusually sensitive to tiny changes in the nuisance parameter. There is a substantial literature about both the theoretical properties of bootstrap approximations and their practical use (Davison and Hinkley 1997).

Conditional Inference

Consider a composite null hypothesis H_0 that would admit a null distribution if we happened to condition on the value c of some statistic C , which we call a *conditioning statistic* (and is different from the test statistic). The null distribution might be different for different values of c , say $P = P^c$, which, using Eq. 2, would give rise to a different p-value for each c , say $p(X) = p^c(X)$. Since we can directly observe $c = C(X)$, however, this causes no difficulties, and $p^{C(X)}(X)$ is a valid p-value for the null hypothesis. The most common situation where we can use conditioning to create a null distribution is when $\text{Prob}(X = x | C(X) = c)$ is the same function of x and c regardless of the specific distribution of X , as long as X satisfies the null hypothesis. In this case, we can take $P^c(x) = \text{Prob}(X = x | C(X) = c)$.

Example 2 Part III: Conditional Inference

Continuing Example 2, if we use the conditioning statistic $C(X) = (N(X'), N(X''))$, which is the total number of heads for each of the two coins and assume the null hypothesis is true, then the conditional distribution of the data given the conditioning statistic is.

$$\begin{aligned}
& \text{Prob}(X = x | C(X) = c) \\
&= \frac{\text{Prob}(X' = x', X'' = x'', N(X') = c', N(X'') = c'')}{\text{Prob}(N(X') = c', N(X'') = c'')} \\
&= \frac{\left[\prod_{i=1}^n (v')^{x'_i} (1 - v')^{1-x'_i} (v'')^{x''_i} (1 - v'')^{1-x''_i} \right] I(N(X') = c') I(N(X'') = c'')}{\binom{n}{c'} (v')^{c'} (1 - v')^{n-c'} \binom{n}{c''} (v'')^{c''} (1 - v'')^{n-c''}} \\
&= \frac{I(N(X') = c') I(N(X'') = c'')}{\binom{n}{c'} \binom{n}{c''}},
\end{aligned} \tag{4}$$

where $x = (x, x')$, where $c = (c, c')$, and where I denotes the indicator function having $I(A) = 1$ if A is true and $I(A) = 0$ if A is false. In words, it says that if the two coins are independent, then the conditional distribution of the arrangement of heads and tails, given the number of heads for each coin, does not depend on the unknown probability of heads for each coin. Furthermore, the common conditional distribution is *uniform* meaning that all possible arrangements of heads and tails are equally likely, subject to having the correct numbers of heads. Since this conditional distribution does not depend on the unknown nuisance parameters v' and v'' , we can use it as a null distribution for the null hypothesis of independence, namely,

$$\begin{aligned}
P(x) &= P^c(x) \\
&= \frac{I(N(X') = c') I(N(X'') = c'')}{\binom{n}{c'} \binom{n}{c''}}.
\end{aligned} \tag{5}$$

The (conditional) null distribution in Eq. 5 does not depend on the unknown parameters v' and v'' , but it does depend on the observed number of heads c' and c'' . This presents no difficulties, though, since we can directly observe these values from data. Using the test statistic $T = \# \text{aligned heads}$ as before and using Eq. 2 to compute the p-value give

$$\begin{aligned}
p^c(x) &= \sum_{k=T(x)}^n \text{Prob}(T(Y) = k) \\
&= \sum_{k=T(x)}^n \frac{\binom{n}{c'} \binom{c'}{k} \binom{n-c'}{c''-k}}{\binom{n}{c'} \binom{n}{c''}},
\end{aligned} \tag{6}$$

where we take $\binom{a}{b} = 0$ if $a < b$ or $b < 0$ and where $Y = (Y', Y'')$ has the joint pmf P^c given in Eq. 5. Again, the specific form of the p-value is not the main point. We can observe $c = (c', c'') = (N(X'), N(X''))$ and, at least in principle, compute the valid p-value $p^c(X)$. For instance, if $n = 10$ and we observe $N(X') = 5$, $N(X'') = 6$ and $T(X) = 5$, then the p-value is 0.0238.

Conditional inference creates a null distribution without needing to use a bootstrap approximation. This can be an advantage in settings with many nuisance parameters, where the bootstrap approximation may be poor. Conditional inference can also be robust to modeling assumptions about the conditioning statistic, C , which is desirable in many contexts. Conditional inference is more limited than bootstrap approximation, however, since many examples do not have an appropriate conditioning statistic, C . The two approaches can also be combined if conditioning still leaves some unknown parameters that need to be estimated.

It is important to note that bootstrap approximation and conditional inference usually lead to

different types of p-values. For example, the same data at the ends of Example 2 parts II and III gives an approximate p-value of 0.1503 using a bootstrap approximation and a p-value of 0.0238 using conditional inference. The difference between the two is not a result of approximation errors from the bootstrap approximation. Rather, the two methods lead to fundamentally different types of p-values. Both control the type-I error rate in the usual way (only approximately so for bootstrap), but each will have different type-II error profiles. One is not necessarily better than the other. The bootstrap approximate p-value is larger in this case because it accounts for the fact that T could be large by seeing an unusually large number of heads, whereas conditional inference uses knowledge about the observed number of heads and notes that T is unusually large (in fact, it is as large as possible) given the number of heads. The scientific context will dictate which of these is preferable.

Heuristic Resampling

The intuition behind the p-value in Eq. 2 is straightforward. If we repeatedly generate surrogate data sets Y according to some probability distribution P and see what fraction of them gives test statistics that are at least as extreme as the original data (if we did this infinitely many times, then the fraction would match the p-value formula), then we can gauge how unusual the original data are with respect to P . There are many examples in the literature where this intuition is implemented directly with some choice of P that makes intuitive sense, but that has not been derived directly from a well-formulated null hypothesis. These heuristic procedures can lead to revealing exploratory analyses, but the “p-values” obtained from them are rarely valid p-values for any null hypothesis. A “rejection” is particularly difficult to interpret, since there is no clear null hypothesis that is being rejected and since the numerical value of the “p-value” cannot be interpreted in the usual manner in terms of type-I error rates. Whenever possible, it is preferable to develop a proper null hypothesis and communicate the results with a valid p-value.

Choice of T and the Alternative Hypothesis

Much like the choice of H_0 , the choice of T is critical but also highly problem-dependent. The choice of T is closely related to the concept of an alternative hypothesis. In most cases, investigators not only formulate a null hypothesis, but they also have rough expectations about how the data will appear if the null hypothesis is false. For example, when testing the null hypothesis of independence between two spike trains, in some settings, one might expect that a lack of independence will manifest itself as an abundance of synchronous spiking at some time scale. Usually T is chosen to capture this anticipated departure from the null behavior. The more precisely the alternative hypothesis is formulated, the more precisely T can be tailored to detect differences between the null and alternative hypotheses in the data.

Perhaps the most important guidance is *to avoid unscrutinized acceptance of the alternative hypothesis* after rejecting the null hypothesis. Usually, the alternative hypothesis is only one of many ways for the null hypothesis to be wrong. Careful choice of T can help ensure that the alternative hypothesis is detected, if it happens to be true, but for any choice of T , there are often many other distributions (not in the null or alternative hypotheses) that are also well detected. For example, suppose we reject the null hypothesis of independence between two spike trains using a test statistic that involves precise (millisecond-precision) synchronous spiking. While it is true that we can conclude that the neurons are dependent (this is the rejection of the null hypothesis), we should be careful not to immediately assume the existence of processes that create fine-precision spike timing (which would be acceptance of some specific alternative hypothesis that we have in mind, usually the one that motivated our choice of test statistic). There are many ways to be dependent that may create excess amounts of precise synchrony without involving precise spike timing.

Another important point is that *changing T changes the p -value and its properties*. Consequently, T cannot be chosen after inspecting the data or the resulting p -value will not be valid (cf., Kriegeskorte et al. 2009). Simple choices of T are easier to interpret and also less likely to raise concerns that T was tailored to the data.

Multiple Hypothesis Tests

Many experiments lead to multiple hypothesis tests. These could be different null hypotheses and/or different p -values for the same null hypothesis but tailored to different alternative hypotheses (typically created by using different test statistics). For example, when testing for differences between experimental conditions, there may be different hypothesis tests for each of many different spike trains, or different brain regions, or different time intervals. There are two key issues to keep in mind when performing multiple hypothesis tests.

First, *the pattern of accepted and rejected hypotheses may not correspond to the underlying pattern of true and false null hypotheses*. There are many influences on the *power* of a test to detect violations of the null hypothesis, including the amount and quality of the data, the strength of the signal, the appropriateness of the test statistic, and so on. The pattern of rejections may reflect underlying fluctuations in power resulting from processes that are scientifically unrelated to those which are being studied by the hypothesis tests. For example, rejecting a null hypothesis of independence between spike trains in one experimental condition, but not another, is not necessarily strong evidence that the dependence structure has changed across conditions. Perhaps the firing rates changed across conditions and this influenced the power of the hypothesis test to detect dependence?

Second, *large numbers of hypothesis tests will lead to some false rejections unless p -values are adjusted for multiple tests*. For example, suppose that we simultaneously record spike trains from 100 neurons in each of two experimental conditions and then, for each neuron separately, construct a p -value to test whether the neuron's

response distribution differed across conditions. If we reject the null hypothesis of no difference across conditions whenever a p -value is less than 0.05, then (assuming the p -values are not overly conservative) we can expect roughly 5 rejections even if all 100 null hypotheses are true. If, further, the p -values are not overly correlated, then the probability of at least one false rejection among these 100 tests is close to one. The basic interpretation of a p -value has apparently been diluted by performing multiple hypothesis tests.

There is a vast and active literature about methods for adjusting p -values so that they maintain various interpretations in the presence of multiple tests (Farcomeni 2008; Nichols and Hayasaka 2003). A common approach is to adjust p -values so that they control the *family-wise error rate (FWER)*, which is the probability of one or more false rejections among all hypothesis tests in the family (regardless of the actual pattern of true and false null hypotheses). Defining this formally requires some care. Let $H_0^{(1)}, \dots, H_0^{(h)}$ be the collection of h null hypotheses and let $V \subseteq \{1, \dots, h\}$ denote the (unknown) indices of the true null hypotheses. We say that $p^{(1)}(X), \dots, p^{(h)}(X)$ are FWER-adjusted p -values for these null hypotheses if

$$\begin{aligned} \text{Prob}\left(p^{(k)}(X) \leq \alpha \text{ for one or more } k \in V\right) \\ \leq \alpha \text{ for all } 0 \leq \alpha \leq 1, \end{aligned}$$

for every possible distribution of X . Now, if we only reject those null hypotheses where the adjusted p -values are 0.05 or less, then our probability of falsely rejecting even a single true null hypothesis is at most 0.05. The Bonferroni correction is the simplest method to create FWER-adjusted p -values. Beginning with a collection of p -values, $p^{(1)}, \dots, p^{(h)}$, we simply multiply the original p -values by the number of tests, h , to get the adjusted p -values, i.e.,

$$p^{(k)}(x) = hp^{(k)}(x) \quad (k = 1, \dots, h)$$

Although the Bonferroni correction appropriately controls the type-I error rates (in the sense of FWER), it can have poor type-II error rate

performance. In particular, if the number of tests is large, then unadjusted p-values must be very small in order to reject using the Bonferroni-adjusted p-values. There exist improvements to the Bonferroni correction that provide the same FWER guarantees.

For situations with very large numbers of tests, controlling the FWER may be a too stringent goal, and statisticians have defined a variety of more relaxed criteria. For example, the *false discovery rate* (FDR) is the expected proportion of rejections that are false rejections (defining the proportion to be zero if there are no rejections), and methods that control the FDR bound this expected proportion. Loosely speaking, controlling the FDR allows there to be some false rejections, but hopefully not too many. Like the Bonferroni procedure for FWER, there are simple procedures for controlling the FDR, such as the Benjamini-Hochberg-Yekutieli correction, that require only a collection of unadjusted p-values.

Procedures for adjusting for multiple hypothesis tests require the original, uncorrected p-values to be actual *valid* p-values in the sense of Eq. 1. Using multiple testing adjustments on approximate p-values (such as approximate p-values resulting from bootstrap or from asymptotic approximations) requires great care. Multiple testing adjustments tend to amplify approximation errors, and errors that are insignificant for single hypothesis tests can easily corrupt multiple testing interpretations. For example, uncorrected p-values of 10^{-5} and 10^{-10} are essentially equivalent if we are testing a single null hypothesis at level 0.05, and a procedure that could approximate p-values to within 10^{-5} would be more than adequate for most purposes. But if this is one of a million different p-values, then 10^{-5} and 10^{-10} are quite different – only the latter would be unusual to see somewhere among the million p-values (consider a Bonferroni correction with $h = 10^6$) – and even tiny approximation errors could drastically alter our final conclusions.

Monte Carlo Approximation of p-Values

The examples above are special in that the p-values have a simple closed-form expression

that is easy to compute. In many practical settings, there may be no practical methods for exactly computing the p-value in Eq. 2: $p(x) = \text{Prob}(T(Y) \geq T(x))$ when Y has distribution P . It is easy to approximate the p-value, however, as long as we can sample from the null distribution P . Loosely speaking, if we generate many random observations from P , then the p-value is closely approximated by the fraction of those observations that have test statistics at least as large as the original data. This is called *Monte Carlo* approximation. Furthermore, we can engineer our Monte Carlo p-value to actually be a valid p-value in sense of Eq. 1. As mentioned in section “Multiple Hypothesis Test”, using valid p-values is especially important in the context of multiple hypothesis testing.

Let $Y^{(1)}, \dots, Y^{(m)}$ be a random sample from the null distribution P . (Using superscripts to index the observations in the Monte Carlo sample will be convenient later.) The Monte Carlo p-value is

$$\begin{aligned} \hat{p}(x) &= \hat{p}(x; Y^{(1)}, \dots, Y^{(m)}) \\ &= \frac{\#\{k : T(Y^{(k)}) \geq T(x)\} + 1}{m + 1}. \end{aligned} \quad (7)$$

Without the 1 in the numerator and denominator, this is simply the fraction of the $Y^{(k)}$'s with $T(Y^{(k)}) \geq T(x)$. Including the 1 is like including a copy of x among the $Y^{(k)}$'s when computing this fraction, and it ensures that $\hat{p}(X; Y^{(1)}, \dots, Y^{(m)})$ is a valid p-value for the original null hypothesis. Validity means that the type I error is controlled appropriately. As the Monte Carlo sample size, m , gets large, $\hat{p}(X)$ will be a better and better approximation of the target p-value, $p(X)$. Consequently, for large m , both p and $\hat{p}$ control the type II error in similar ways.

Example 2 Part IV: Monte Carlo p-Values

Revisiting Example 2, look again at the bootstrap approximate p-value formula in Eq. 3 and the conditional inference p-value formula in Eq. 6. What if these formulas were not available or too difficult to compute? Monte Carlo approximation is often a good alternative.

Consider first the bootstrap approximation from Example 2 part II. We first estimate the unknown nuisance parameters from the observed data using $\hat{v} = (\hat{v}', \hat{v}'')$, and we hold these parameters fixed throughout the rest of the procedure. Now, we artificially generate a random data set that satisfies the null hypothesis using the parameters $\hat{v}$. There is no ambiguity about which distribution to use for the random data set, because once the nuisance parameters are specified, the null hypothesis contains only a single distribution $P = P_{\hat{v}}$. For this example, to generate a random data set $Y = (Y', Y'')$, we first sample $Y' = (Y_1', \dots, Y_n')$ independently from a coin with probability of heads $\hat{v}'$. Then, independently from Y' , we sample $Y'' = (Y_1'', \dots, Y_n'')$ independently from a coin with probability of heads $\hat{v}''$. $Y = (Y', Y'')$ is a single random data set from the (bootstrap approximate) null distribution P . Let us call this data set $Y^{(1)}$. Now, using the same $\hat{v}$, we independently repeat this procedure many times to get a collection of Monte Carlo data sets $Y^{(1)}, \dots, Y^{(m)}$, which is a random sample of size m from the (bootstrap approximate) null distribution $P = P_{\hat{v}}$. We can compare the observed number of aligned heads $T(X)$ to the collection of numbers of aligned heads from the Monte Carlo data $T(Y^{(1)}), \dots, T(Y^{(m)})$ to get a Monte p-value $\hat{p}(X)$, as defined in Eq. 7. For large m , $\hat{p}(X) \approx p_{\hat{v}}(X)$ from Eq. 3 (with v replaced by $\hat{v}$). Note that $\hat{p}(X)$ would itself be a valid p-value if the Monte Carlo sample came from P_v , but it does not. It comes from $P_{\hat{v}}$ which, if our bootstrap approximation is good, will be very close to P_v . The combination of a bootstrap approximation and Monte Carlo approximation is called **bootstrap**, and in this case, it would be called *parametric bootstrap hypothesis testing* – parametric, because our bootstrap approximation involves the estimation of a fixed and finite number of parameters (in this case, two parameters: v' , v''). It is important to remember that the bootstrap approximation is the key approximation in bootstrap. Monte Carlo approximation is only done for computational convenience, and usually m can be chosen sufficiently large that the Monte Carlo approximation error is negligible.

Now consider conditional inference from Example 2 part III. We first observe the numbers of heads $c = C(X) = (N(X'), N(X'')) = (c', c'')$ coming from the two coins in the original data, and we define the null conditional distribution $P = P^c$ as in Eq. 5. To generate a random data set $Y = (Y', Y'')$ from P , we first generate $Y' = (Y_1', \dots, Y_n')$ by choosing c' of flips to be heads, $n - c'$ of the flips to be tails, and uniformly shuffling the order, so that each of the $\binom{n}{c'}$ possibilities is equally likely. Another way of thinking about this is to randomly and uniformly shuffle the order of the flips in the original sequence X' , which automatically has c' heads. Then we independently do the same thing for $Y'' = (Y_1'', \dots, Y_n'')$, but using c'' heads and $n - c''$ tails. Calling this shuffled data set $Y^{(1)} = Y$, we can repeat this process independently, each time using the same $c = (c', c'')$, to get a Monte Carlo random sample $Y^{(1)}, \dots, Y^{(m)}$ from the null conditional distribution P . Exactly like the bootstrap sample, we compute $\hat{p}(X)$ using Eq. 7. For large m , $\hat{p}(X) \approx p^c(X)$. Furthermore, $\hat{p}(X)$ is itself a valid p-value.

Example 3: Permutation Tests

Let S_k denote the spike train data collected on trial k and let $E_k \in \{1, 2\}$ denote which of two experimental conditions was in effect during trial k . The complete data set of n trials (each of the same duration) is $X = (S, E)$, where $S = (S_1, \dots, S_n)$ and $E = (E_1, \dots, E_n)$. We assume that $E_1, \dots, E_n$ are *exchangeable*, which means that every possible ordering of experimental conditions was, in principle, equally likely to occur. (Usually, this is easy to ensure as part of the overall experimental design.) We want to test whether the experimental condition is related to the spiking data. The formal null hypothesis is that S and E are independent, that is, the experimental condition has no effect on spiking. We conjecture that if the null hypothesis is false (i.e., if there is a difference across conditions), then it will be reflected in the distribution of total spike counts over a trial, namely, $N(S_k) = \#$ spikes in $S_k = \#$ spikes on trial k . In particular, we

expect the average spike count in condition 1 to be different from the average spike count in condition 2, quantified by the absolute difference:

$$T(X) = T(S, E) = \left| \frac{\sum_{k:E_k=1} N(S_k)}{\#\{k : E_k = 1\}} - \frac{\sum_{k:E_k=2} N(S_k)}{\#\{k : E_k = 2\}} \right|.$$

This will be our test statistic.

The null hypothesis of independence is a very large composite null hypothesis. Without further assumptions, there are infinitely many nuisance parameters needed to specify the distribution of S . We will use conditional inference to specify a unique null distribution P . Let $D = D(E) = \#\{k: E_k = 1\}$ be the number of trials in experimental condition 1. Our conditioning statistic will be $C = C(X) = (S, D)$, that is, we will condition on all of the spike train data, including the order of the trials, and we will also condition on the number of trials in experimental condition 1 (and, consequently, the number of trials in experimental condition 2, which is $n - D$). The only uncertainty remaining is the ordering of E , that is, the pairing of experimental condition with trial. Under the null hypothesis of independence (and assuming E was constructed to be exchangeable), then every possible ordering of E is equally likely. The null conditional distribution is just the uniform distribution over all possible $\binom{n}{D}$ pairings of trials with condition labels. Since this conditional distribution is the same for all possible distributions in the null hypothesis, we can use it as our null distribution without needing to estimate any nuisance parameters or to introduce additional modeling assumptions. To sample from this distribution, we simply shuffle, or permute, the experimental condition labels relative to the trials. We can do this many times, each time computing the test statistic T . (Note that T will change because we are changing which trials are assigned to the different experimental conditions.) Equation 7 gives a valid Monte Carlo p-value for this hypothesis test, which is called a Monte Carlo *permutation test*.

Example 4: Trial Shuffling

This is similar to Example 3, except that now E_k is spike train data from another neuron recorded simultaneously with S_k . The null hypothesis is still independence – in this case, independence between neurons. We change the test statistic to be the absolute correlation coefficient (Pearson's r) between spike counts:

$$T(X) = T(S, E) = |\text{corr} - \text{coef}((N(S_k), N(E_k)) : k = 1, \dots, n)|.$$

To create a unique null distribution, we condition on all of S , as before, and we condition on all of E except for the specific order of the trials in E . The null hypothesis of independence, combined with the assumption that E is exchangeable, gives the uniform conditional null distribution over the ordering of the trials for E . To sample from this null distribution, we simply shuffle the order of E 's trials. Monte Carlo p-values are computed in the usual way.

Scientifically, interpreting a rejected null hypothesis in this case requires some care. For instance, unlike Example 3, where we could design E to be exchangeable, here we must assume that E is exchangeable. In some experiments, this may not be true. For example, if the neurons are modifying their response functions over trials (because of, say, habituation or learning or fatigue or metabolic changes), then trials are not exchangeable. When this modification affects both neurons, then it may be detectable using the correlation coefficient test statistic. It likely depends on the experimental context whether this type of co-modulation reflects the underlying mechanisms the investigator was intending to detect with a test of independence. This final caution holds more generally. There are many mechanisms, including experimental artifacts, such as misaligned trials, that can create dependence between spike trains. With sufficient data and an appropriate test statistic, trial shuffling can detect these dependencies, but it cannot determine which mechanisms created the dependencies.

Summary

The perspective of this entry is that spike train resampling is best viewed as Monte Carlo hypothesis testing. More specifically, the procedure of using surrogate data created by resampling spike trains for the purpose of evaluating the significance of patterns observed in the data is best viewed as Monte Carlo sampling from a null hypothesis that admits a unique null distribution for the purpose of numerically approximating a p-value. The key concepts underlying this view are reviewed above, along with some standard guidance about the use and misuse of hypothesis testing. The entry ► [“Surrogate Data for Evaluation of Spike Correlation”](#) in this encyclopedia describes many of the commonly used methods for resampling spike trains.

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Decision-Making, Threshold](#)
- [Estimation of Neuronal Firing Rate](#)
- [Neural Coding](#)
- [Neural Decoding](#)
- [Population Encoding/Decoding](#)
- [Spatial Temporal Spike Pattern Analysis](#)
- [Spike Train Analysis: Overview](#)
- [Statistical Analysis of Neuroimaging Data](#)
- [Surrogate Data for Evaluation of Spike Correlation](#)
- [Unitary Event Analysis](#)

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Silicon Cochleas

- [Neuromorphic Sensors, Cochlea](#)

Simple-to-Complex Hierarchies

- [Hierarchical Models of the Visual System](#)

Simplified Conductance-Based Models

- [Reduced Morphology Models](#)

Simulation Experiment Description Markup Language (SED-ML)

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Definition

The Simulation Experiment Description Markup Language is an XML-based exchange format for

the encoding of simulation experiments mainly in the field of computational biology. It stores the simulation recipe, including the models used in the experiment, the pre- and post-processing procedures, and the instructions for how to generate the simulation output.

Detailed Description

Overview

The Simulation Experiment Description Markup Language (SED-ML) encodes simulation setups in XML. Thereby it provides a means to exchange simulation descriptions in standard format. SED-ML respects the Minimum Information Guidelines for Simulation Experiments (Minimum Information About a Simulation Experiment, MIASE (Waltemath et al. 2011a)). Following these recommendations, the first version of SED-ML has been published in March 2011 (Waltemath et al. 2011b). It covers the description of time-course simulations and consists of five major building blocks:

1. The **Model** entity contains references to the models used in the simulation experiment and pre-processing procedures on these models before simulation. Models must be in standard representation formats (e.g., SBML, CellML, NeuroML). Examples for pre-processing are, e.g., changing the value of an observable, computing the change of a value using mathematics, or general changes on any XML element of the model representation.
2. The **Simulation** entity contains all information about the simulation settings and the steps taken during simulation, e.g., the particular type of simulation and the algorithm used for the execution of the simulation.
3. The **Task** entity applies one of the defined simulations on one of the referenced models at a time.
4. The **DataGenerator** entity encodes post-processing procedures which need to be

applied to the simulation result before output, e.g., normalization of data.

5. The **Output** entity specifies the simulation output, e.g., the particular plots to be shown.

Structure of SED-ML

Model Elements

The SED-ML model elements define the identity and location of the model(s) to be simulated and specify the model's native encoding format. The location is to be given as a Uniform Resource Identifier (URI), which enables software interpreting SED-ML to retrieve the model. In case of a relative URI, the base is the location of the referring SED-ML file. The SED-ML archive format can furthermore be used to share model and simulation descriptions together (see the specification (Waltemath et al. 2011b)). In addition to defining the source model's location and encoding, SED-ML model elements can also list changes to be applied to a model before simulation. Such changes could be altering attribute values (e.g., a parameter value in an SBML model or the `initial_value` of a CellML variable) or changing the model structure. Attribute values may undergo a simple substitution or more complex calculation using content MathML 2.0 (<http://www.w3.org/Math/>). The model structure may be changed by adding or removing XML elements.

Simulation Elements

The SED-ML simulation elements define the simulation algorithms to be used in the experiment and their configuration. Simulation algorithms are specified using terms from the Kinetic Simulation Algorithm Ontology (KiSAO, <http://biomodels.net/kisao/>). KiSAO classifies and characterizes kinetic simulation algorithms. Furthermore, configuration details of the simulation can be described in SED-ML, such as the start and end times or the number of time points to output. The current implementation supports the description of time-course simulation setups. Extensions towards further experiment types are already being discussed and will be available

in the next versions, including the description of steady-state analyses and nested simulations, such as parameter scans.

Task Elements

The SED-ML task elements apply a particular simulation algorithm to a specific model. Because simulations and models are described independently, they can be combined in diverse ways. Tasks allow for this flexibility. For example, a simulation can be applied to different versions of a model with varying parameterization.

DataGenerator Elements

The SED-ML dataGenerators define transformations of raw simulation output (as generated by a task) into the desired numerical form. They can simply be references to a model variable but may also be defined through complex mathematical expressions encoded using content MathML. Some variables used in an experiment are not explicitly defined in the model, but may be implicitly contained and can be addressed using SED-ML-specific constructs. The SED-ML website provides a mapping of these SED-ML symbols onto possibly existing concepts in the individual languages.

Output Elements

The SED-ML output elements describe how numerical data from the data generators are grouped together. SED-ML allows to generate 2D and 3D plots or sets of unrelated arrays.

SED-ML Development

SED-ML is a community-driven project that is part of the COmputational Modeling in Biology NEtwork (COMBINE, <http://co.mbine.org>). SED-ML development is coordinated by five elected editors. Format extensions are discussed on the SED-ML mailing list and on annual meetings. Simulation descriptions in SED-ML are currently provided for SBML and CellML models.

The adoption of SED-ML for NeuroML models is ongoing.

Software Support

SED-ML files can be created and read using software libraries and tools (Waltemath et al. 2011c). The libSedML (<http://libsedml.sf.net/>) is a set of .NET libraries for reading, validating, and writing SED-ML descriptions, along with all necessary utility functions for resolving models and XPath expressions. The libSedMLScript, which is part of libSedML, provides a script-based language for defining SED-ML experiments. Alternatively, jlibsedml (<http://sourceforge.net/projects/jlibsedml/>) is a Java library for creating, manipulating, validating, and working with SED-ML documents. The jlibsedml application programming interface (API) follows a similar organization to that of libSBML, a successful and popular library for manipulation of SBML documents. SProS (the SED-ML Processing Service) is an API for creating, reading, and manipulating SED-ML documents. It is integrated in the CellML API. Future versions of SProS will also provide support for running simulations described in SED-ML and involving CellML models (using the simulation facilities already present in the CellML API).

An up-to-date list of software supporting SED-ML is available from the Showcases on the SED-ML web page (<http://sed-ml.org>).

Cross-References

- [CellML](#)
- [neuroConstruct](#)
- [NeuroML](#)
- [Systems Biology Markup Language \(SBML\)](#)

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Further Readings

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SK Channels (KCa2.x)

► Calcium-Dependent Potassium Channels

Skill Acquisition in Stick Balancing

► Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights

Sleep, Neural Population Models of

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Definition

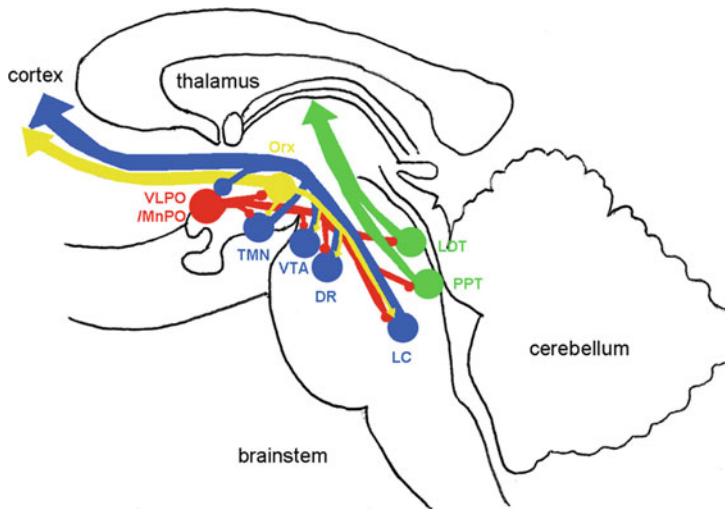
A neural population model of sleep is a mathematical model of neural populations that regulate the timing and expression of sleep/wake patterns. Specific circuits and nuclei have been identified in the mammalian brainstem and hypothalamus that play a key role in modulating the brain's overall arousal state with a circadian (daily) rhythm. These neural populations have been the focus of most sleep modeling.

Detailed Description

Sleep is an arousal state characterized by physical inactivity, reduced sensitivity to environmental stimuli, and a range of characteristic physiological changes, including changes to the EEG associated with rapid eye movement (REM) and non-REM (NREM) sleep in mammals. Sleep is regulated by a variety of physiological and biochemical processes (Krueger et al. 2008; Saper et al. 2010), including specific neural populations in the brainstem and hypothalamus. Various mathematical models have now been developed, providing a conduit between the underlying physiology and the sleep/wake dynamics observed at the behavioral level.

The Sleep/Wake Switch

The arousal states of sleep and wakefulness typically manifest as global patterns of brain activity; notable exceptions to this rule are unihemispheric



Sleep, Neural Population Models of, Fig. 1 The brain's overall arousal state is modulated by ascending projections to the cortex and thalamus from nuclei in the brainstem and hypothalamus. These include (i) wake-promoting nuclei that release monoaminergic neurotransmitters (blue), the tuberomammillary nucleus (TMN), the ventral tegmental area (VTA), the dorsal raphe (DR), and the locus coeruleus (LC); (ii) wake-promoting and REM sleep-promoting nuclei that release acetylcholine (green), the laterodorsal tegmentum (LDT) and the

pedunculopontine tegmentum (PPT); and (iii) wake-promoting neurons in the lateral hypothalamus (yellow) that release orexin (Orx). These nuclei are all GABAergic inhibited by sleep-promoting neurons (red) in the ventrolateral preoptic area (VLPO) and median preoptic area (MnPO). Excitatory (pointed arrows) and inhibitory (rounded arrows) interactions between nuclei are indicated. Mutual inhibition between sleep-promoting and wake-promoting nuclei forms the basis for the sleep/wake switch

sleep (sleeping with one brain hemisphere) and local sleep (emergence of sleep-like activity patterns in overworked neural assemblies while the rest of the brain is awake), which demonstrate that sleep can in principle be regulated on more local scales. Global synchronization of sleep and wake states across brain regions is achieved by control systems in the brainstem and hypothalamus. As shown in Fig. 1, a group of monoaminergic, cholinergic, and orexinergic neural populations projects diffusely to the cortex and thalamus. The coherent activation of these populations modulates corticothalamic activity, so as to promote and sustain wakefulness.

A population of sleep-promoting neurons in the ventrolateral preoptic area (VLPO) and median preoptic area (MnPO) of the hypothalamus GABAergicly inhibits the wake-promoting monoaminergic, cholinergic, and orexinergic neural populations. Interestingly, the wake-promoting monoaminergic populations in turn inhibit the sleep-promoting VLPO/MnPO populations. This

mutual inhibition between sleep-promoting and wake-promoting neural populations provides a basis for a switch-like system, with stable sleep and wake states, and relatively rapid transitions between states (Saper et al. 2010). This system is called the *sleep/wake switch*.

Sleep-Regulatory Processes

Prior to the recent detailed mapping of sleep-regulatory circuits in the brain, mathematical models of sleep were developed. In the absence of physiological data, these models were phenomenological rather than physiological. The most influential of these models was the two-process model of sleep (Daan et al. 1984), which provided the conceptual basis for most subsequent models of sleep and human performance (Van Dongen 2004). The two-process model assumes that sleep can be understood in terms of two key sleep-regulatory processes: the circadian process

and the sleep homeostatic process. The circadian process represents an approximately 24-h biological rhythm in sleepiness and alertness, typically described by a periodic function or nonlinear oscillator. The sleep homeostatic process represents the increasing need to sleep the longer one is awake and the dissipation of this need the longer one is asleep, typically described by exponentially saturating functions.

The physiological basis for the circadian process has now been well elucidated. Circadian rhythms are generated endogenously on a molecular level by virtually all mammalian cells. These cellular rhythms are synchronized by a master circadian clock that resides in the suprachiasmatic nucleus (SCN) of the hypothalamus. SCN neurons act as tightly coupled circadian pacemaker cells, sending a robust circadian signal to many other brain regions. The SCN receives direct input from the retina, allowing it to entrain to the daily light/dark cycle (Foster and Kreitzman 2005).

The physiological basis for the sleep homeostatic process is still not well understood, but evidence points towards the accumulation of certain sleep-promoting factors in the brain during wakefulness. These substances include adenosine, nitric oxide, TNF- α , Interleukin-1, and prostaglandin D2 (Krueger et al. 2008).

Both the circadian and sleep homeostatic processes have been found to act on the neural populations in the sleep/wake switch (Pace-Schott and Hobson 2002). The SCN has multiple relays to both the sleep-promoting and wake-promoting neural populations. The sleep-promoting factor adenosine has also been found to have effects on the VLPO. The sleep/wake switch therefore provides a neural basis for the integration of the circadian and sleep homeostatic processes.

Neural Population Models of Sleep

In order to test the theoretical value of the sleep/wake switch theory of sleep regulation, and to link the dynamics of underlying neural systems to behavioral manifestations, various mathematical models of the neural populations in the sleep/wake switch have recently been developed

(Tamakawa et al. 2006; Phillips and Robinson 2007; Behn et al. 2007; Behn and Booth 2010; Rempe et al. 2010; Kumar et al. 2012; Sedigh-Sarvestani et al. 2012). These models have included different levels of detail in terms of the neural populations included, as well as slightly different mathematical formalisms, including neural mass, single neuron, and neural mass/neurotransmitter concentration implementations. Central to all of these models is mutual inhibition between sleep-promoting and wake-promoting neural populations, i.e., the sleep/wake switch.

Here, we present a simplified mathematical description of the core dynamics of these neural population models of the sleep/wake switch. We base our equations on the Phillips–Robinson model, since it is the simplest and most widely used of the models (Robinson et al. 2011).

We model two neural populations: a wake-promoting population (subscript w) and a sleep-promoting population (subscript s). Each population has a mean firing rate, Q_j , and a mean cell body voltage relative to resting, V_j . We assume that the firing rate is a sigmoidal function of voltage, $Q_j = S(V_j)$. We also assume that the postsynaptic effects on voltage for each population are proportional to the presynaptic firing rates. The dynamics can then be represented by a pair of coupled first-order differential equations,

$$\begin{aligned}\tau_w dV_w/dt + V_w &= v_{ws}Q_s + A, \tau_s dV_s/dt + V_s \\ &= v_{sw}Q_w + D(t),\end{aligned}$$

where τ_j is a time constant for the saturation time constant; $v_{ws} < 0$ and $v_{sw} < 0$ represent the strengths of the inhibitory synaptic connections between the two populations; A represents any constant net input to the wake-promoting population; and $D(t)$ represents the net drive to the sleep-promoting population from circadian and sleep homeostatic processes. In general, the circadian and sleep homeostatic processes could also have a direct effect on the wake-promoting population. Here, we consider the most simple case for analysis.

The dynamics of the neural populations occur on a timescale of milliseconds to minutes (determined by the τ_j parameters), whereas $D(t)$

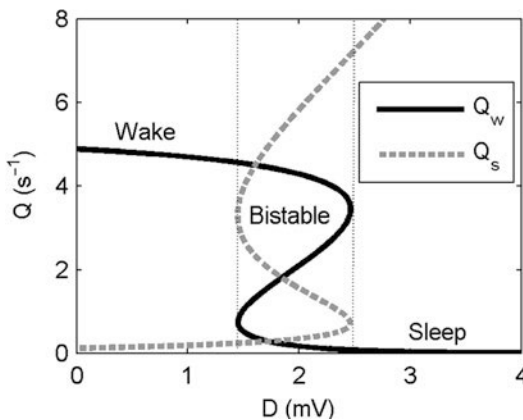
varies on a daily timescale by definition. A timescale separation can therefore be performed, treating D as approximately constant on timescales relevant to neural dynamics (Fulcher et al. 2008). The system dynamics can then be summarized by the reduced manifold of equilibrium values for various fixed values of D , as shown in Fig. 2.

For reasonable parameter values, the reduced system has two stable states, corresponding to sleep and wake. For a certain intermediate range of values for D , the system is bistable. As D oscillates with a period of ~ 24 h, the system is dragged back and forth across the bistable region, resulting in daily transitions between sleep and wake. The model exhibits hysteresis, because the thresholds for sleep-to-wake and wake-to-sleep transitions are different, as shown in Fig. 2.

This hysteresis behavior describes the most basic, reduced dynamics of most neural population

models of the sleep/wake switch. Interestingly, these physiologically based models recapitulate the basic assumptions of the phenomenological two-process model: two separate thresholds for sleep-to-wake and wake-to-sleep transitions (Phillips and Robinson 2008; Rempé et al. 2010). In other words, these models provide a physiological justification for the two-process model, as well as providing new insights by explicitly modeling the underlying physiological dynamics.

Neural population models of the sleep/wake switch have been highly successful in reproducing and predicting many aspects of human sleep and circadian rhythms (Robinson et al. 2011). In addition, mathematical models have been developed to describe how modulation of the corticothalamic system can give rise to the neural activity patterns associated with sleep and wakefulness, as well as transitions between arousal states (Robinson et al. 2002; Hill and Tononi 2005; Steyn-Ross et al. 2005; Deco et al. 2013). Linking corticothalamic and subcortical models poses a significant theoretical and numerical challenge due to their inherently different spatiotemporal scales, but such models are on the horizon (Robinson et al. 2010).



Sleep, Neural Population Models of, Fig. 2 If the sleep drive, D , is assumed to be slowly varying, the model dynamics can be visually summarized in terms of the equilibrium values for the wake-promoting population firing rate, Q_w , and the sleep-promoting population firing rate, Q_s . When the drive for sleep is low, the model has a stable wake state, with high Q_w and low Q_s . When the drive for sleep is high, the model has a stable sleep state with low Q_w and high Q_s . For an intermediate range of drive values, the model is bistable, with stable sleep and wake states. Saddle node bifurcations occur at critical thresholds (dotted lines). The stable wake and sleep branches are linked by an unstable equilibrium branch within the bistable zone. As D slowly oscillates on a daily timescale, the model therefore undergoes hysteresis as it is dragged across the thresholds where sleep and wake states become unstable

Recent Findings

Neural population models of the sleep/wake switch have been highly successful in reproducing and predicting many aspects of human sleep and circadian rhythms. Specifically, models of the sleep/wake switch have been used to understand the physiological mechanisms that underlie interindividual (Phillips et al. 2010a; Robinson et al. 2011) and interspecies (Phillips et al. 2010b, 2013) differences in sleep timing and duration. They have been used to reproduce normal human sleep (Phillips and Robinson 2007) and mouse sleep (Behn et al. 2007), as well as the effects of neurotransmitter microinjections (Behn and Booth 2010). They have also been applied to predicting human performance, including the effects of sleep deprivation (Fulcher et al. 2010) and caffeine on subjective fatigue (Puckeridge et al. 2010) and the effects of shiftwork on performance (Postnova et al. 2012).

Given the current uncertainty regarding the physiological mechanisms that underlie the REM/REM sleep cycle, neural population models have also been used to probe the possible dynamics of the system. This has led to concrete hypotheses regarding physiological mechanisms and circuits that could potentially generate the REM/NREM sleep cycle (Rempe et al. 2010; Behn and Booth 2012; Behn et al. 2013). Sleep/wake switch models have also recently been applied to reproducing the desynchronization of sleep/wake cycles from the circadian process that can occur when individuals are completely isolated from environmental time cues and are free to self-select their sleep/wake timings (Phillips et al. 2011; Gleit et al. 2013).

In addition, mathematical models have been developed to describe how modulation of the corticothalamic system can give rise to the neural activity patterns associated with sleep and wakefulness, as well as transitions between arousal states (Robinson et al. 2002; Hill and Tononi 2005; Steyn-Ross et al. 2005; Deco et al. 2013). Linking corticothalamic and subcortical models poses a significant theoretical and numerical challenge due to their inherently different spatiotemporal scales, but such models are on the horizon (Robinson et al. 2010).

Cross-References

- ▶ [Anesthesia, Neural Population Models of](#)
- ▶ [Bifurcations, Neural Population Models and](#)
- ▶ [Down Under Neural Population Models](#)
- ▶ [Neural Population Model](#)
- ▶ [Neuroimaging, Neural Population Models for](#)
- ▶ [Phase Response Curves: Overview](#)
- ▶ [Wilson-Cowan Model](#)

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Scholarpedia

- Neurobiology of sleep and wakefulness
- Sleep homeostasis

Wikipedia

- Circadian rhythm
- Neuroscience of sleep
- Sleep
- Suprachiasmatic nucleus

Slow Feature Analysis

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Definition

Slow feature analysis (SFA) is an unsupervised learning algorithm for extracting slowly varying features from a multidimensional input signal in time. It is not based on low-pass filtering, i.e., temporal averaging, but combines input components of single time steps into temporally stable features. SFA can be used for nonlinear dimensionality reduction and learning of invariant representations. Algorithmically, it is closely related to principal component analysis (PCA).

Detailed Description

Slowness Principle

The slowness principle is based on the observation that different representations of a sensorial input vary on different time scales. For instance, a zebra grazing in the savanna is a scene that changes slowly. This scene is represented in the eyes of an observer in terms of activities of retinal receptors, which, due to the black-and-white stripes of the zebra, change quickly between high and low values whenever the zebra moves or the gaze of the observer changes. However, in higher brain areas of the observer, there is a high-level representation of the zebra grazing, which changes slowly again. This difference in time scales is true for most dynamic scenes. The slowness principle therefore states that high-level representations can be learned from the receptor

activities simply by extracting features that vary slowly over time (without using the trivial option of low-pass filtering).

The idea of the slowness principle has probably first been mentioned by Geoffrey Hinton in 1989; early algorithms were presented by Peter Földiák and by Graeme Mitchison, both in 1991; slow feature analysis (SFA) has first been introduced by Laurenz Wiskott in 1998; see (Wiskott et al. 2011) for references.

Slow Feature Analysis

Most learning algorithms based on the slowness principle are online learning rules, i.e., they improve the extracted features incrementally with each time step of the training data. Slow feature analysis (SFA) (Wiskott et al. 2011) in contrast is an algorithm that takes all training data into account at once.

SFA first uses PCA to normalize the input signal such that it has zero mean and unit variance in all directions, which is also known as whitening or sphering. It then calculates the time derivative (in the discrete case the difference between successive time points) of the whitened signal and uses PCA again to find the directions of smallest variance, which are the directions of slowest variation and correspond to the slow features to be extracted.

As SFA is based on PCA, it is basically a linear algorithm. However, one typically applies a pre-defined set of nonlinear functions to the input signal first, which is known as nonlinear expansion, and then applies SFA to this expanded input signal. Thus, SFA learns linear combinations of fixed nonlinear functions, which results in nonlinear functions to extract features from the input.

It has been shown analytically that SFA is closely related to spike-timing-dependent plasticity (STDP) (Sprekeler et al. 2007).

Applications in Computational Neuroscience

SFA has been developed for learning invariant representations of moving objects in a feedforward model of the visual system. It has been shown that a hierarchical network of SFA nodes extracts features from a video signal of moving objects that permit invariant object

recognition with a simple classifier and also extraction of positional and pose information with linear regression (Wiskott et al. 2011). Interestingly, on the first SFA layer units share many properties with complex cells in the primary visual cortex, such as phase invariance, orientation selectivity, and frequency tuning. One also finds end- and side-inhibited units there. Complex cell-like units emerge also if learning is based on simulated retinal waves rather than moving objects (Dähne et al. 2014).

If combined with independent component analysis, an SFA network trained with input from a simulated rat running around in a static environment develops units that behave like place cells and others that behave like head-direction cells in the hippocampal formation of rats (Wiskott et al. 2011). Place cells fire if a rat is at a particular location independently of its head direction; head-direction cells fire if a rat is oriented in a particular direction independently of its location. SFA can extract location and head direction because these variables vary slowly compared to individual pixel values of the visual input sequence as the rat runs through the environment.

SFA has also been used for technical applications (Escalante-B and Wiskott 2012).

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Slow Oscillation

► [Delta Rhythms: Models and Physiology](#)

Slow Oscillations and Epilepsy: Network Models

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Definition

Network models are very useful tools to investigate the genesis of oscillatory behavior such as epileptic seizures. During many types of seizures, the brain produces oscillatory spike-and-wave discharges, which are particularly prominent for absence seizures. It was found that the thalamocortical mechanisms leading to spindle oscillations and their large-scale synchrony can explain spike-and-wave oscillations, if the excitability of the cerebral cortex is augmented. These pathological oscillations can be reproduced by network models involving the reciprocal interaction between thalamus and cortex.

Detailed Description

Introduction

Many types of epileptic seizures display very synchronized oscillations producing a typical electroencephalogram (EEG) pattern consisting of one or several sharp deflections (“spikes”) followed by a surface-positive “wave.” Spike-and-wave patterns of similar characteristics are also seen in a number of experimental models in cats, rats, mice, and monkeys, as well as in many other types of epilepsies. In some of these experimental models, it was shown that the critical regions involved are the thalamus and neocortex and that the genesis of spike-and-wave activity shares common mechanisms with sleep spindle oscillations, which are generated in the thalamus. Computational models have explored mechanisms for such spike-and-wave activity, as reviewed here.

The Cellular Bases of Spike-and-Wave Discharges in Cortex

Computational models have first explored the cellular pattern needed to generate spike-and-wave EEG or local-field potentials. Using a simple biophysical model of cortical network with excitatory and inhibitory neurons (Destexhe 1998), it was found that spike-and-wave LFP patterns can be generated if all cells fire in synchrony (“spike” component), followed by a hyperpolarization mediated by K^+ conductances (“wave” component). The synchronized discharge during the “spike” was indeed found in many different experimental models of seizures (reviewed in Destexhe 2013), while the hyperpolarization during the “wave” remains poorly studied. Intracellular recordings during spike-and-wave seizures showed that the “wave” is correlated by hyperpolarization, which was interpreted as due to a mixture of disfacilitation and K^+ currents (Neckelmann et al. 2000). The model suggests that this slow K^+ conductance can be due to two different mechanisms: either it can be generated by the slow voltage-dependent K^+ conductances responsible for spike-frequency adaptation in pyramidal neurons. In this case, the strong firing during the “spike” maximally activates these adapting currents, which then produce the slow hyperpolarization. Another possible origin is synaptic; the strong firing may massively activate the slow type of GABAergic inhibition, acting on $GABA_B$ receptors, which also cause a slow activation of K^+ channels.

Hypersynchronized Slow Oscillations in the Thalamus

Many experimental evidences show that thalamic circuits are implicated in seizure generation (reviewed in Gloor and Fariello 1988; Crunelli and Leresche 2002). It was found that if convulsants are applied to the thalamus *in vitro*, blocking $GABA_A$ receptors, they induce the production of a slow and synchronized oscillation at around 3 Hz and are dependent on $GABA_B$ receptors (von Krosigk et al. 1993). Although it is tempting to associate the origin of the seizure and the spike-and-wave oscillation to the thalamus, it is not the case, because this slow oscillation was shown to

be different from spike-and-wave oscillations *in vivo* (Steriade and Contreras 1998). This slow oscillation was simulated by network models of thalamic circuits (Destexhe et al. 1993, 1996; Golomb et al. 1996) and was due to the mutual interaction between thalamic relay and reticular neurons, involving GABA_B receptors.

Model of Spike-and-Wave Discharges in the Thalamocortical System

Experimentally, it was shown that the cerebral cortex is the key to the induction of seizures. In cats, different experimental manipulations of cortical excitability lead to spike-and-wave seizures, but the *physiologically intact* thalamus is necessary (Gloor and Fariello 1988). In rat models of absence seizures, a focus of increased excitability was found in cortex (Meeren et al. 2002; Polack et al. 2007), but the thalamus was also necessary for seizure generation (Vergnes and Marescaux 1992). These results were replicated by computational models of thalamic and cortical networks, endowed with the different receptor type present as well as the intrinsic cellular properties of thalamic and cortical cells (Destexhe 1998, 1999). This model is explained below.

The main hypothesis explored by this model was that seizure generation uses the oscillatory-generating mechanisms present in the thalamus but with an over-excitable cortex. In “control” conditions, the network model generates spindle oscillations. As shown in detail in another entry (► “Spindle Oscillations: Models”), spindle oscillations are generated by thalamic circuits and can be modeled by thalamic networks. In the thalamocortical system, the cortex plays an essential role in synchronizing the thalamic-generated oscillations, as also described in detail in another entry (► “Corticothalamic Feedback: Large-Scale Synchrony”). In this case, the models established that the most efficient way for the cortex to control the thalamic oscillation and organize its large-scale synchrony is to evoke strong inhibition in the thalamus (Destexhe et al. 1998).

This “inhibitory dominant” character of the corticothalamic interaction is fundamental to explain seizures. While this cortically evoked thalamic inhibition is mostly mediated by GABA_A

receptors in normal conditions, it may be different in pathological conditions. If the cortex is hyper-excitable, the exaggerated corticothalamic feedback will be strong enough to activate GABA_B receptors (due to their nonlinear activation properties – see Destexhe and Sejnowski 1995). This activation of slow GABA_B inhibition will “force” the thalamus, although physiologically intact, to oscillate at a slower and more synchronized frequency around 3 Hz (Destexhe 1998).

This mechanism was tested by simulating networks of thalamic and cortical cells, with the different receptor types present, and the system was able to generate hypersynchronized oscillations at 3 Hz when solely the cortex was affected (its excitability was augmented by diminishing intracortical inhibition). Remarkably, this model generated 2–3 Hz oscillations with spike-and-wave patterns in the calculated LFPs (Destexhe 1998).

A very similar mechanism was found for faster oscillation frequencies typically observed in rodents (Destexhe 1999). In this case, the total conductance of GABA_B inhibition in the thalamus had to be weaker, preventing the thalamus to oscillate at 3 Hz. Thus, this model predicts that the ~3 Hz spike-and-wave of cats, monkey, and man and the ~8 Hz spike-and-wave seizures of rats and mice have a common cellular mechanism but different respective conductances of GABA_A and GABA_B receptor-mediated inhibition in the thalamus. This prediction still awaits to be tested.

Testing the Mechanism in Thalamic Slices

The main prediction of this thalamocortical model of seizures is that a too-strong corticothalamic feedback should be able to switch the *intact* thalamus to oscillate at 3 Hz (Destexhe 1998), a frequency which is not normally seen in the physiologically intact thalamus. This prediction was tested in thalamic slices, where the corticothalamic fibers can be stimulated electrically. It was found by two independent studies (Bal et al. 2000; Blumenfeld and McCormick 2000) that, indeed, strong stimulation of corticothalamic fibers can “force” the thalamus to oscillate at 3 Hz and that this forcing is dependent on GABA_B receptors. It was also shown that

the “forced” 3 Hz oscillations are more synchronized than the natural 10 Hz spindle rhythm produced by the same thalamic circuits. These findings are all in agreement with the predictions of the model and therefore support the view that 3 Hz hypersynchronized oscillations can be generated by the thalamus subject to a hyperexcitable cortex.

Discussion

In conclusion, computational models have provided a plausible explanation for a number of contrasting experimental results. First, the thalamus can produce a slow oscillation around 3 Hz, where GABA_B receptors are important, but this oscillation is not the primary cause for ~3 Hz spike-and-wave discharges seen in epileptic seizures. The model can reproduce the experiments showing that the disinhibited thalamus does not produce spike-and-wave in cortex.

Second, seizures can be generated by a hyperexcitable cortex, but the intact thalamus is necessary. The generation of seizures depends on an interaction between cortex and thalamus. An essential ingredient in this interaction is that the corticothalamic feedback must be very efficient in evoking inhibition in the thalamus. If this is the case, the models show that a hyperexcitable cortex will generate a feedback strong enough to recruit GABA_B receptors in the thalamus and “force” the slow oscillatory mode (although the thalamus is physiologically intact).

If these ingredients are assembled in a thalamocortical model, ~3 Hz spike-and-wave oscillations can be generated if the cortex alone is made hyperexcitable, but the thalamus is kept physiologically intact (Destexhe 1998). This thalamocortical mechanism is dependent on the presence of GABA_B receptors in the thalamus, which are responsible for the ~3 Hz oscillation of the entire system. If the thalamus has weak GABA_B-mediated inhibition, then the hyperexcitable system oscillates at a faster frequency, around 8 Hz, as found in rodents. Thus, the models predict that a common mechanism underlies absence seizures in all mammals but that the

exact oscillation frequency will be dependent on the balance between GABA_A and GABA_B receptors in the thalamus (Destexhe 1999).

Finally, this model is compatible with the finding that a focus in cerebral cortex is associated to absence seizures in rats (Meeren et al. 2002). It was found that deep (layers 5–6) cortical neurons are hyperexcitable and seem to lead the discharges during ictal activity (Polack et al. 2007). As layer 6 neurons project to thalamus, this finding is consistent with the idea that an excessive corticothalamic feedback may be a primary cause for absence seizures.

Cross-References

- [Corticothalamic Feedback: Large-Scale Synchrony](#)
- [Spindle Oscillations: Models](#)

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Slow Oscillations: Models

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Synonyms

[Up and down state models](#)

Definition

Several computational models have been proposed to describe the generation of spontaneous slow oscillations, or up and down state dynamics, in neuronal circuits of the cerebral cortex. Most models rely on strong excitatory feedback to generate reverberatory dynamics in the up state, which are then quenched by some negative feedback mechanism to form down states. The specific mechanisms responsible for triggering the transitions between up and down states distinguish these models. In addition, some models have been proposed that emphasize the role of thalamocortical loops in generating this spontaneous activity.

Detailed Description

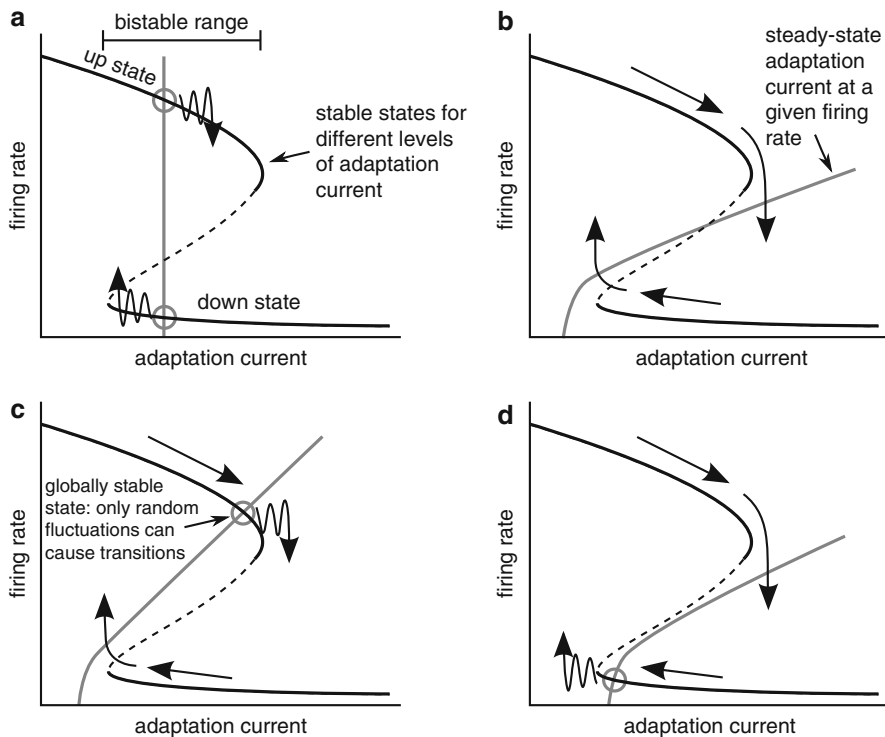
During non-REM sleep and under most anesthetics, cortical network dynamics exhibit slow oscillations or up and down state switching (see ► [“Slow Oscillations: Physiology”](#)). This pattern of activity has been the subject of numerous computational models, which have formulated quantitative accounts of the possible mechanisms that participate in their generation.

The models contemplate two main mechanisms to ignite up states. One set of models proposes that down states end as a result of the recovery of a fatigue mechanism accumulated during up states, such as some activity-dependent potassium current (Compte et al. 2003; Destexhe 2009), or short-term synaptic depression (Mejias et al. 2010). Spontaneously active excitatory neurons, possibly in specific layers (Destexhe 2009), are then responsible for starting a new up state. This links down state duration to the time constant of recovery of such fatigue mechanism. On the other hand, up states could be started by input fluctuations that impose a transition from a stable down state to the up state. Mechanistically, these fluctuations could be due to spontaneous synaptic release (Timofeev et al. 2000; Holcman and Tsodyks 2006; Mejias et al. 2010) or to external fluctuating inputs (Kepecs and Raghavachari 2007; Hughes et al. 2002; Mattia and Sanchez-

Vives 2012). Down state duration in these scenarios is highly variable.

Similarly, the extinction of up states has also been modeled through either deterministic or stochastic processes. Mechanisms relying on activity-dependent negative feedback bring the up state deterministically to the point of sudden transition to the down state (Fig. 1b, d). Such negative feedback can be due to activity-dependent potassium currents (Compte et al. 2003; Hill and Tononi 2005), short-term synaptic depression (Holcman and Tsodyks 2006), short-term synaptic facilitation to interneurons (Melamed et al. 2008), or slow

GABA_B feedback inhibition (Parga and Abbott 2007). On the other hand, endogenous fluctuations can also induce transitions from the up to the down state (Fig. 1a, c), in the form of stochastic inputs nonlinearly gated by NMDA receptors (Kepecs and Raghavachari 2007) or as a result of the stochastic dynamics of the firing rate in small populations (Mattia and Sanchez-Vives 2012). Note, however, that these recurrent networks impose complex interdependencies between all these mechanisms: as an example, short-term depression promotes up-to-down transitions on its own (Holcman and Tsodyks 2006), but prevents them when



Slow Oscillations: Models, Fig. 1 Mechanistic scenarios for up and down state switching in a bistable recurrent network with adaptation currents. (a) For fixed values of the adaptation current, the recurrent network stabilizes at firing rates that trace a cubic nullcline with a stable upper branch (up states) and a stable lower branch (down states). Unstable solutions are marked with a *dashed line*. In a range of values of adaptation (bistable range), the system features bistability between the two states. For very weak or absent adaptation dynamics, the systems sit at a fixed value of adaptation current (*gray line*) giving rise to two stable states. In this scenario, transitions between states can only occur if external fluctuations arrive that impose a

change of state (*wiggled arrows*). (b) For strong adaptation, the nullcline defining the values of adaptation current that are steadily maintained at a given neuronal firing rate (*gray line*) does not intersect the network stability nullcline (*black cubic line*), and the system cycles periodically between up and down states. (c) Weaker adaptation makes the adaptation nullcline intersect the network nullcline in the upper branch and up states become stable. Only strong fluctuations will induce an up-to-down transition. (d) Starting from the condition in b, a slight hyperpolarization to all neurons in the network makes the down state stable, and down-to-up transitions now depend on strong episodic fluctuations

combined with adaptation currents (Benita et al. 2012).

All the models proposed share a common mechanistic substrate: up and down dynamics emerge from an underlying bistability between these states that gets perturbed by additional slow or episodic mechanisms. This general dynamic picture can be illustrated graphically for a network with recurrent excitation and slow rate adaptation mechanisms (Fig. 1; Latham et al. 2000), from which it can be generalized to other mechanisms. The bistability condition implies that two stable states are accessible for a range of values for the adaptation current (bistable range, Fig. 1a). Thus, for a fixed level of adaptation (gray line in Fig. 1a), only random occasional fluctuations in excitability can impose a transition between the stable states (Fig. 1a). Adaptation mechanisms, however, can modify the system so that it no longer has stable fixed points but exhibits an oscillatory behavior. During this oscillation the network shows slow drifts along the up and down branches as adaptation builds up and decays, respectively (Fig. 1b). Depending on the magnitude of adaptation and the level of external drive to the network, transitions may occur deterministically due to the slow dynamics of adaptation (Fig. 1b, down-to-up in Fig. 1c and up-to-down in Fig. 1d), or they may be induced by episodic fluctuations that trigger transitions to escape from a stable state (Fig. 1a, up-to-down in Fig. 1c and down-to-up in Fig. 1d).

The mechanism by which bistability is achieved in the cortical network is generally assumed to be excitatory synaptic reverberation within the local circuit (Timofeev et al. 2000; Compte et al. 2003; Bazhenov et al. 2002; Hill and Tononi 2005; Holcman and Tsodyks 2006; Melamed et al. 2008; Mejias et al. 2010; Mattia and Sanchez-Vives 2012). Indeed, the bistable range of the cubic nullcline in Fig. 1 grows larger with stronger recurrent connections. This is consistent with the strong and dense connectivity in cortical circuits and explains parsimoniously the sensitivity of up states to excitatory synaptic blockers and the resilience of up-and-down membrane voltage dynamics to the hyperpolarization of individual neurons. Alternative mechanisms

for such bistability are nonlinearities in NMDA receptors (Kepecs and Raghavachari 2007) or interactions between intrinsic ionic channels in individual neurons (Hughes et al. 2002; Parga and Abbott 2007). Also, intrinsic mechanisms such as persistent sodium currents have been invoked to achieve and maintain reverberatory activity in the up state (Timofeev et al. 2000; Bazhenov et al. 2002; Hill and Tononi 2005).

Several mechanisms have been proposed to explain that firing rates during up states remain low despite strong excitatory feedback in the network. Here, the most common mechanism invoked is inhibitory feedback from the local microcircuitry. A strong coupling with a local inhibitory population can control firing rates while recurrent excitation maintains up states. Consistent with this, blockers of inhibitory synaptic transmission increase the firing rates in up states (Sanchez-Vives et al. 2010). It has been argued that short-term synaptic depression can also counteract strong excitation and maintain low firing rates in up states (Holcman and Tsodyks 2006).

Finally, computational models have also addressed the role of the thalamocortical loop in slow oscillations. While thalamocortical neurons can modulate cortically generated slow oscillations (Bazhenov et al. 2002; Hill and Tononi 2005), some computational studies attribute an active role of thalamocortical neurons in maintaining these dynamics. In particular, intrinsic oscillatory mechanisms in thalamocortical neurons may take part in up state initiation in cortical networks (Hughes et al. 2002).

Cross-References

► [Slow Oscillations: Physiology](#)

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Slow Oscillations: Physiology

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Synonyms

Slow waves; Up and down states

Definition

Slow oscillations are the coordinated activity of large populations of neurons consisting of an alternation of active periods (Up states) and silent periods (Down states). These oscillations occur with a slow frequency (≤ 1 Hz) in the corticothalamocortical network during slow-wave sleep and deep anesthesia, and they spontaneously occur also in cortical slices. This rhythmic activity emerges in the cortical network when there are no other driving inputs, and it can be considered its default activity. During the active periods, or Up states, neocortical neurons (both excitatory and inhibitory) are depolarized, receive barrages of synaptic inputs, and fire action potentials. During Down states neurons remain hyperpolarized and the synaptic activity is almost nonexistent. This “on-and-off” synaptic activity results in a bimodal distribution of the membrane potential values, an intracellular signature of slow oscillations. During the active or Up states, the activity expresses coherent oscillations at high frequencies in the beta (15–30 Hz) and gamma (30–90 Hz) range.

Detailed Description

Background

Slow waves during quiescent sleep have been recorded since the early days of electroencephalogram (EEG) in the 1930s. However, the first detailed characterization of the cortical slow oscillation was published by Steriade and collaborators in 1993 (Steriade et al. 1993a, b, c). In these studies, the frequency of the slow oscillation was described to be between 0.2 and 0.5 Hz, and generally below 1 Hz in the cat.

Origin

Slow oscillations are prominent in the corticothalamocortical loop, and they originate in the cortical recurrent connectivity. The initial observation that slow oscillations persisted in the cortex after destruction of the connected thalamus (Steriade et al. 1993c) while the opposite was not true (Timofeev and Steriade 1996)

was strongly suggestive of their cortical origin. The fact that cortical slices *in vitro* spontaneously generate slow oscillations highly similar to the ones in the whole brain is also a strong evidence in favor of their cortical origin (Sanchez-Vives and McCormick 2000; McCormick et al. 2003). *In vivo* cortical slabs (Timofeev et al. 2000), disconnected from the surrounding tissue, can as well generate slow oscillations. However, the cortex is reciprocally connected to subcortical structures, and the emergent pattern recorded *in vivo* is shaped as a result of this interaction. The interaction with the thalamus is especially relevant, since it also displays slow oscillations coordinated with the cortical ones (Steriade et al. 1993b; Crunelli and Hughes 2010). Detailed analysis has revealed that the inactivation of the thalamus results in a decreased frequency of the cortical slow oscillations (David et al. 2013).

Mechanisms of Initiation of the Up States

Simultaneous recordings from different cortical layers provide a layer profile of activation during Up states. Cortical recordings from different species (cats, ferrets, rodents) both *in vivo* and *in vitro* agree on the leading role of infragranular layers – in particular layer 5 – in the initiation of Up states (Sanchez-Vives and McCormick 2000; Sakata and Harris 2009; Chauvette et al. 2010). Layer 5 neurons not only lead Up states, but also have a more intense and longer discharge during each Up state, while layer 2/3 neurons display a weaker and shorter firing (Sanchez-Vives and McCormick 2000; Sakata and Harris 2009). Furthermore, optogenetic activation of layer 5 – but not of layer 2/3 neurons – is enough to initiate Up states and entrain slow oscillations (Beltramini et al. 2012; Stroh et al. 2013).

Different mechanisms have been proposed for layer 5 neurons to initiate the firing that by reverberation in close loops results in the initiation of new waves. A larger intrinsic excitability of layer 5 neurons drives them to start firing during Down states (Sanchez-Vives and McCormick 2000; Compte et al. 2003; Sakata and Harris 2009), stochastic release of synaptic vesicles (Timofeev

et al. 2000) and specific pacemaker cells (Le Bon-Jego and Yuste 2007).

Only in human cortex Up states are reported to start in supragranular layers (Cserscsa et al. 2010), a critical difference in cortical function that requires further study.

Excitatory/Inhibitory Balance During Up States

A key element in the balance and control of either spontaneous emergent or evoked cortical activity is the relation between excitation and inhibition. Both excitatory and inhibitory neurons fire during Up states (Steriade et al. 1993c). Conductance measurements during Up states reveal that the weights of excitation and inhibition are well balanced *in vivo* (Haider et al. 2006) and similarly *in vitro* (Shu et al. 2003) as argued theoretically (Compte et al. 2003). Changes in excitatory and inhibitory conductance *in vitro* reveal that both increase and decrease at the beginning/end of Up states occur in close association with each other (Shu et al. 2003). The timing of individual excitatory and inhibitory synaptic events also reveals a remarkable coincidence in the accumulation of both excitatory and inhibitory synaptic events during the rise of an Up state both *in vitro* and *in vivo*, although it is 1.4 times faster *in vivo* (Compte et al. 2009). A similar coincidence also occurs at the termination of the Up state. Such interlocking in time of excitation and inhibition is also found in simultaneous recordings of nearby pairs of cortical neurons (Okun and Lampl 2008).

Both the excitatory and the inhibitory synaptic conductances are high at the beginning of the Up state, and they tend to progressively decrease, but their ratio remains constant and close to 1 in anesthetized and *in vitro* preparations (Shu et al. 2003; Haider et al. 2006). Other studies report that the inhibitory conductance is much larger than the excitatory conductance during Up states in natural sleep (Rudolph et al. 2007).

Mechanisms of Termination of the Up States

Several mechanisms have been proposed that could account for the termination of Up states.

They include arrival of excitation (Shu et al. 2003; Haider et al. 2006), synaptic depression (Bazhenov et al. 2002), thalamic disfacilitation (Contreras et al. 1996), activation of K^+ currents (Sanchez-Vives and McCormick 2000; Compte et al. 2003), or extracellular K^+ dynamics (Frohlich et al. 2006). The time course of the slow afterhyperpolarization observed in intracellular recordings during Down states (e.g., Fig. 7c in Sanchez-Vives and McCormick 2000; Contreras et al. 1996) suggests that slow K^+ currents can be contributing to the termination of Up states and maintenance of Down states. Different mechanisms involving K^+ currents have been proposed, including ATP-dependent K^+ current (Cunningham et al. 2006), GABA_B receptor-mediated responses (Mann et al. 2009), and Ca^{2+} - and Na^+ -dependent K^+ currents (Sanchez-Vives and McCormick 2000). Slow K^+ -mediated afterhyperpolarizations are blocked by neurotransmitters (acetylcholine, noradrenaline) that control the transition from sleep to awake (Schwindt et al. 1988; Brumberg et al. 2000), providing a mechanism for stopping the bistability when entering the awake state.

Propagation

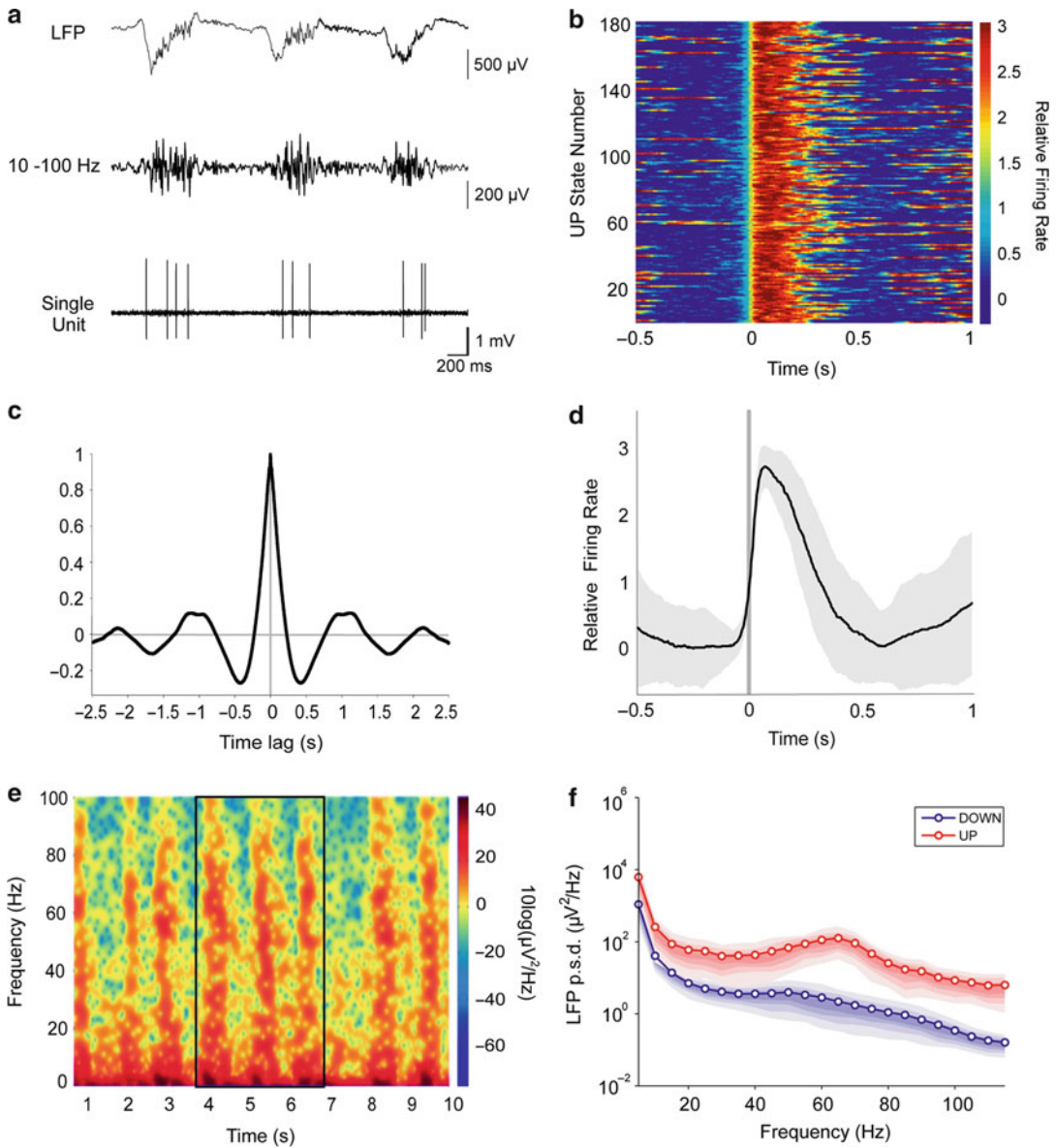
Slow waves propagate along the cortical network. Propagation occurs both in vivo during slow-wave sleep or anesthesia and also in the cortex in vitro. During wave propagation, infragranular layers lead the front of the wave, although columnar interactions between supragranular and infragranular layers are required for maintaining correct propagation speed (Wester and Contreras 2012). The propagation is continuous, and locally generated Up states can be recorded along the propagation in all cortical layers. The reported values of the propagation speed vary across species and conditions: 1.2–7 m/s in humans during slow-wave sleep (Massimini et al. 2004), 100 mm/s in the anesthetized cat (Steriade et al. 1993c), around 30 mm/s in the anesthetized mouse (Ruiz-Mejias et al. 2011; Stroh et al. 2013), and 10 mm/s in the neocortical slices in vitro (Sanchez-Vives and

McCormick 2000). In paleocortex in vitro, such as the olfactory cortex, propagation is an order of magnitude faster (114 mm/s) (Sanchez-Vives et al. 2008). Cortical inhibition slows down propagation (Trevelyan et al. 2007), and the gradual blockade of GABA_A-mediated inhibition progressively increases the propagation speed (Sanchez-Vives et al. 2011). Once the wave is transformed into an epileptiform discharge due to inhibition removal, propagation speed increases by one order of magnitude (Sanchez-Vives et al. 2011).

Fast Rhythms During Up States

During Up states the in vivo network activity is temporally structured in fast oscillations in the beta (15–30 Hz) and gamma (30–90 Hz) range (Steriade et al. 1996; Hasenstaub et al. 2005; Ruiz-Mejias et al. 2011). Inhibitory synaptic potentials carry the great majority of power in this high-frequency range, often synchronously inhibiting nearby pyramidal cells (Hasenstaub et al. 2005).

The emergent activity of the cortical network in vitro can also be synchronized in these high frequencies as a result of pharmacological activation, typically with cholinergic or metabotropic agonists, kainate, or electrical tetanic stimulation of the tissue (Buhl et al. 1998; Cunningham et al. 2003; Hasenstaub et al. 2005; Traub et al. 2005). Although these neuromodulators potently modulate high frequencies, robust beta/gamma oscillations emerge already during physiological network function in vitro in the absence of externally applied neuromodulatory agents and without any particular stimulation pattern (Compte et al. 2008). The systematic comparison across different cortical areas of beta and gamma power in the mouse in vivo reveals that prefrontal cortex Up-state activity presents significantly stronger fluctuations than in motor, somatosensory, and visual cortex, in particular in the gamma range (one order of magnitude larger power) (Ruiz-Mejias et al. 2011; Fig. 1).



Slow Oscillations: Physiology, Fig. 1 Slow oscillations and fast frequencies during Up states. **(a)** Slow oscillations in the mouse prefrontal cortex under ketamine anesthesia. *Upper trace:* Unfiltered LFP (local field potential). *Middle trace:* Filtered LFP between 10 and 100 Hz. *Lower trace:* Single-unit recording obtained in the vicinity of the LFP recording (<200 μm apart). For details see Ruiz-Mejias et al. 2011. **(b)** Raster plot of the relative firing rate in the local population (color scale) obtained from 200 s recording and corresponding to 180 Up states. Up states are

aligned at the onset. For methodological details see Reig et al. 2010. **(c)** Waveform autocorrelation of the same 200 s period of LFP shown in B. **(d)** Waveform average of the raster plot in b. Gray shade correspond to the SD. **(e)** Spectrogram of the same LFP recording. The central three Up states in the black box correspond to the traces illustrated in a. **(f)** Power spectral density plots of the LFP during Up and Down states, where a resonant peak appears in the gamma band during Up states

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Further Reading

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Slow Waves

- [Slow Oscillations: Physiology](#)

Slowness of Movement Model

- [Basal Ganglia: Bradykinesia Models](#)

Slow-Wave Oscillation (SWO)

- [Delta Rhythms: Models and Physiology](#)

Smoluchowski Equation

- [Fokker-Planck Equation](#)

Sodium Channels

Dominique Engel

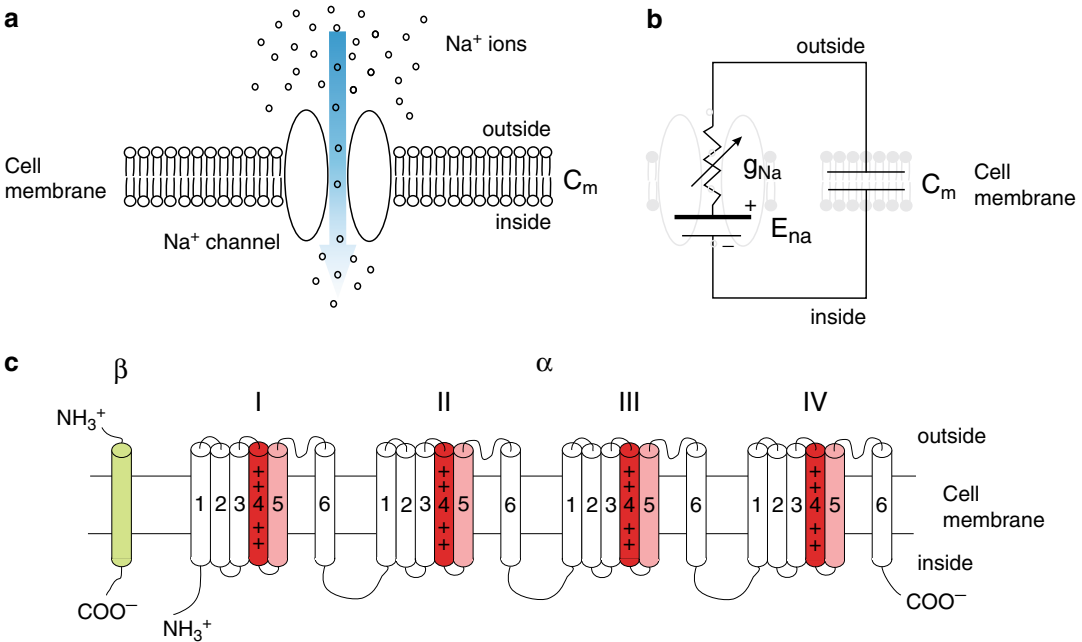
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Synonyms

[Na⁺ channels](#); [Voltage-gated Na⁺ channels](#)

Definition

Sodium channels are proteins enched in the cell membrane of both excitable and nonexcitable cells. They are in general composed of two different types of proteins, termed subunits, an alpha (α) and two beta (β) subunits. The arrangement of the α subunit across the cell's membrane enables the formation of an aqueous tunnel termed channel linking the cells interior and the extracellular space. Changes in the transmembrane voltage govern channel gating. When the channel is open, almost exclusively sodium (Na⁺) ions flow through the channel (Fig. 1a). The Na⁺ ion flow through the channel can be blocked by tetrodotoxin (TTX), a specific and widely used puffer fish toxin.



Sodium Channels, Fig. 1 Structure and function of sodium channels. (a) Schematic representation of a sodium channel enmeshed in the plasmic membrane of a cell. When the membrane potential is close to rest, Na⁺ ions are flowing inside the cell due to the driving force of Na⁺ ($V_m - E_{Na}$). (b) Conductance model for sodium channels. E_{Na} is the equilibrium potential for Na⁺ represented by the

battery and g_{Na} is the variable conductance of Na⁺ channels which depends on time and potential represented by the arrow. C_m is the capacitance of the membrane. (c) Transmembrane organization of the α and β subunits of the sodium channel. (Modified from Catterall (2001) with permission)

Functional properties of sodium channels can be translated into an electrical conductance model consisting of a battery in series with a resistor and an arrow indicating a time- and voltage-dependent conductance (Johnston and Wu 1995; Hille 2001; Fig. 1b).

Detailed Description

Structure and Function of Sodium Channels

Sodium channels are proteins enmeshed in the cell membrane of different excitable cell types including neurons of the central and peripheral nervous system and muscle cells including skeletal, smooth, and cardiac muscle cells but also in various nonexcitable cells (Black and Waxman 2013). They are composed of a principal alpha subunit responsible for the formation of the pore and beta auxiliary subunits implicated in the

regulation of channel function (Johnston and Wu 1995; Hammond 2001; Catterall 2012; Fig. 1c). The alpha subunit exists in distinct isoforms (Table 1) and consists of a long chain of about 2000 amino acids arranged in four repetitions of a specific sequence of amino acids termed homologous domain (I, II, III, and IV). Within each domain, the sequence forms six transmembrane segments (S1–S6). The four homologous domains are presumably arranged across the membrane to form a central pore bordered by S6 segments. S4 segments are important for the gating as they are composed by positively charged amino acids and thereby are believed to represent the voltage sensor of the channel (Johnston and Wu 1995; Hammond 2001; Hille 2001; Catterall 2012). In neurons, sodium channels are present generally in each subcellular compartment (soma, axon, and dendrites). But a nonhomogeneous distribution of the channels may exist in the different neuronal

Sodium Channels, Table 1 Mammalian sodium channel properties

Conventional name	Original name	Corresponding gene	TTX sensitivity	Predominant location
Na _v 1.1	Type I, rat I, Scn1a	SCN1A	Yes	CNS, PNS
Na _v 1.2	Type II, rat II,	SCN2A	Yes	CNS
Na _v 1.3	Type III, rat III	SCN3A	Yes	Embryonic CNS
Na _v 1.4	SkM, μ 1	SCN4A	Yes	skeletal muscle
Na _v 1.5	SkM2, rH1, H1	SCN5A	No	Heart muscle
Na _v 1.6	Type IV, NaCh6, Na6, Scn8a	SCN8A	Yes	CNS, PNS, axons
Na _v 1.7	PN1, hNE, Nas	SCN9A	Yes	PNS, Schwann cells
Na _v 1.8	SNS, PN3, NaNG	SCN10A	No	PNS, sensory neurons
Na _v 1.9	SNS2, NaN, SCN12A	SCN11A	No	PNS
Na _x	Nav2.1, Nav2.2	SCN6A	No	Heart, uterus, glia
	Nav2.3, SCL11, NaG	SCN7A	No	PNS smooth muscle

CNS central nervous system, PNS peripheral nervous system, TTX tetrodotoxin (specific blocker of sodium channels). A more detailed description of the diversity of Na⁺ channels is reviewed in (Goldin 2002). A detailed analysis of the localization of Na⁺ channels is reviewed in (Vacher et al. 2008)

compartments (Magee 2008; Vacher et al. 2008). The function of Na⁺ channels in excitable cells is to permit an entry of positive charges into the cell in order to depolarize the membrane and to generate action potentials (APs). Na⁺ channel permeability is essential for the initiation and the propagation of APs in excitable cells, and their open probability increases largely during the upstroke of APs. Na⁺ channels mentioned above and in the two following paragraphs have fast activation and inactivation and are therefore termed transient Na⁺ channels. Two additional Na⁺ currents may be expressed by excitable cells, termed “resurgent” and “persistent,” passing current during membrane potential repolarization after brief depolarizations (Cruz et al. 2011) and passing noninactivating current, respectively (Kiss 2008). Dysfunctions of sodium channels (sodium “channelopathies”) cause a variety of diseases among which are epileptic syndromes and muscle diseases (Waxman 2001; Savio-Galimberti et al. 2012).

Patch-Clamp Recordings of Single-Channel and Macroscopic Sodium Currents

The development of the patch-clamp technique gave the opportunity to measure directly the unitary Na⁺ current flowing through a single

sodium channel (Sakmann and Neher 1995). Unitary Na⁺ currents have a typical rectangular time course representing transitions between open and closed states of the channel. Unitary currents are therefore all-or-none events, and their peak amplitude is voltage-dependent according to Ohm’s law:

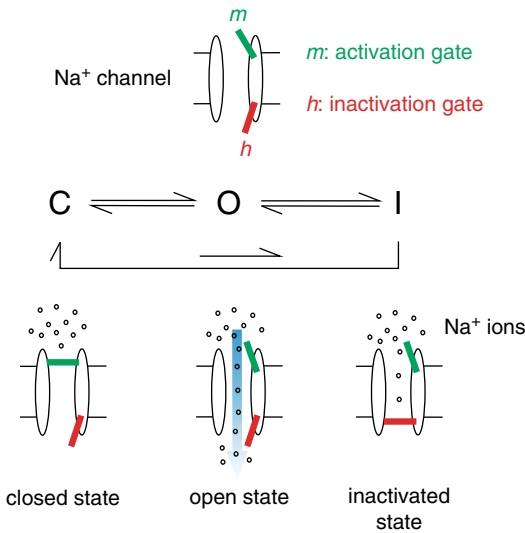
$$i_{Na} = \gamma_{Na}(V_m - E_{Na})$$

where i_{Na} is the unitary Na⁺ current, γ_{Na} is the single-channel conductance, V_m is the membrane potential, and E_{Na} is the reversal potential of Na⁺ ions.

The summation of a large number of unitary Na⁺ currents results in a macroscopic Na⁺ current which corresponds nearly to the “whole-cell” current recorded in a cell. Unitary and macroscopic Na⁺ currents are proportional and related by the following equation:

$$I_{Na} = N \ p_{(t)} i_{Na}$$

where I_{Na} is the macroscopic current, N is the number of Na⁺ channels, and $p_{(t)}$ is the open probability at a time t . Mechanistically, the behavior of Na⁺ channels is characterized by transitions between three distinct states, an open state (O), a



Sodium Channels, Fig. 2 Conformational states in the Hodgkin Huxley formalism. Sequence of transitions of sodium channels through C, O and I states illustrated with the movement of the gating particles (*m* and *h*)

closed state (C), and an inactivated state (I). Transitions are illustrated by the scheme in Fig. 2.

Typically, the sodium channel switches from C to O on depolarization and rapidly back from O to C with repolarization when the depolarization time is very short. On sustained depolarization, the sodium channel closes more slowly and switches from O to I. The latter transition is termed inactivation and corresponds to a refractory state of the channel characterized by a non-passing ion state (Ulbricht 2005; Catterall et al. 2012). The probability of the Na⁺ channels being open increases with depolarization and the duration of the open state varies around a mean value termed mean open time. To be able to reopen after inactivation, sodium channels need to transit through the C state for a certain period of time, and this is achieved with membrane hyperpolarization (Hammond 2001). With fundamental work published in 1952, Hodgkin and Huxley interpreted the transitions between the conformational states of sodium channels with the movement of activation (*m*) and inactivation (*h*) gates regulating the permeability of the channel (Fig. 2; Johnston and Wu 1995; Koch 1999). In the Hodgkin–Huxley (HH) formalism, permeability

changes are described by ionic conductance which is voltage- and time-dependent:

$$g_{\text{Na}} = \bar{g}_{\text{Na}} m^3 h$$

from which the right side of the equation can be implemented in the equation describing the macroscopic Na⁺ current:

$$I_{\text{Na}} = \bar{g}_{\text{Na}} m^3 h (V_m - E_{\text{Na}})$$

where $\bar{g}_{\text{Na}}$ (g_{Na} “bar”) is the maximal value of the conductance and *m*, *h* represent the fraction of two distinct type of gating particles in the inside of the membrane.

Modeling Sodium Channel Conductance to Estimate Membrane Potential Changes

A detailed functional analysis of sodium channel properties is fundamental to understand the generation of APs in excitable cells. With their pioneer study, Hodgkin and Huxley proposed a quantitative model describing the permeability of sodium channels in terms of ionic conductance changes using experimental data. With this model, they could also predict the time course of APs. Without any knowledge about the structure of an ion channel, they predicted that sodium channels are gated by gating variables which are dependent on time and voltage and postulated that the transitions between open and closed states obey first-order kinetics (Johnston and Wu 1995; Destexhe and Huguenard 2001; Hille 2001; Koch 1999). While the HH formalism has still a large influence to describe channel functional properties and to predict AP time course, it is a macroscopic approximation (Catterall et al. 2012) and may have some limitations. For instance, the HH formalism is unable to describe the abrupt onset of APs of cortical neurons (Naundorf et al. 2006).

Alternatively, the gating of sodium channels in stochastic Markov models is described by transitions through a series of distinct conformational states. These models assume that the transitions between conformational states are memoryless and depend only on the current state (Destexhe and Huguenard 2001; Kispersky and White

2008). Markov models are thereby more precise to describe conformational changes of single channels (Destexhe and Huguenard 2001).

Cross-Reference

► Hodgkin-Huxley Model

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Software for Neuroimaging Data Analysis

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Definition

Software is defined by as “a plan specification composed of a series of instructions that can be interpreted by or directly executed by a processing unit.” We define Software for Neuroimaging Data Analysis as software whose primary goal is to support the extraction of information, and ultimately knowledge, from data acquired by an imaging device used on the brain (of human or animal subjects).

Detailed Description

Introduction

Tell us what you think about neuroimaging software, and we will tell you who you are. To some,

using software to analyze data is little more than a technical step that stands between data acquisition and publishing. Doctoral students, postdocs, or technical assistants only need to operate the appropriate software, i.e., the script to run or the right sequence of buttons to press. To others, choosing, adapting, running, or developing the right software code is critical and requires investing significant time and resources.

Data analysis is one of the most time-consuming parts of neuroimaging research. While it can take, in general, months to acquire a small to medium dataset, it often takes years before the data are fully analyzed. It is not rare that specific software or methods have to be developed for a specific question or dataset. Data are typically reanalyzed several times in different ways, using different inputs or software options, influencing the interpretation or the type I error rate (Simmons et al. 2011). With the perspective of efficiency, if most of the time is spent on data analysis, sharpening these tools should be a priority. In addition, errors are ubiquitous in data analysis, and software bugs or misuses are a major contributor to this (Donoho 2010). To take a classic example, a source of error was (and probably still is) the handling of the left versus right hemisphere identification in neuroimaging data, which very likely led to many erroneous publications. Finally, software tools are strongly influencing – and limiting – the type of questions that are put to the data. These factors should place a thorough understanding of one’s analysis software in a predominant place in the research process.

While no neuroimaging research would be done without software, few articles are dedicated to the description of their development and capability. Partly, this is due to the nature of the software description that does not lend itself very well to a static written description; this is better seen through example of use and documentation. Partly, this reflects the somewhat distorted nature of the publication process in neuroimaging (as well as in other scientific fields) that puts too much emphasis on the interpretation (the “story”) and less on the facts (and, inherent to the scientific process, how these were obtained). Donoho famously paraphrased Claerbout ([https://en.](https://en.wikipedia.org/wiki/Jon_Claerbout)

[wikipedia.org/wiki/Jon_Claerbout](https://en.wikipedia.org/wiki/Jon_Claerbout)) stating that *“an article about computational science in a scientific publication is not the scholarship itself, it’s merely scholarship advertisement. The actual scholarship is the complete software development environment and the complete set of instructions which generated the figures”* (Donoho et al. 2009). There is little doubt that neuroimaging is a computational science and that Donoho and Claerbout’s point applies to our field.

In this encyclopedia entry, we lay out the neuroimaging software analysis landscape in section “Detailed Description,” then consider the problems we face currently in section “3,” and suggest directions for solutions in section “4.” We last review some of the future challenges in this field. There will be no attempt to make an even non-exhaustive list of the software currently in use in neuroimaging although we cite some software to illustrate our text. Our purpose is to reflect and inform on some sociological aspects of the brain imaging field related to data analysis software which are likely less ephemeral than current software. We will use examples that are related to the research community from MRI (magnetic resonance imaging) and more rarely EEG-MEG (electro- and magnetoencephalography), but most of the ideas can be extrapolated to other brain imaging modalities (positron-emission tomography, near-infrared spectroscopy, etc.).

Emergence Mechanisms and Taxonomy

We start by reviewing a few mechanisms by which neuroimaging software emerge. We take a few examples to illustrate these mechanisms and then propose a few major criteria for software classification.

Emergence Mechanisms

A Data Analysis Method Developed in a Lab This mechanism is simple and often observed. A good method to analyze data has been developed in a lab and has produced interesting results and led to (possibly high-profile) publications. Other researchers in the same lab, or in other labs, would like to use the same

technique, but it is not easily recoded because of its mathematical or algorithmic complexity. There is a pressure to share the software with colleagues attracted by the technique, as well as reward since ensuing collaborations will lead to authorship for the developer. More rarely, the author believes that scientific work requires that colleagues can check and reproduce one's work. The software may get used locally for a while and then distributed under more or less lenient terms of use and license.

This mechanism is close to what happens for SPM, for instance, started by Karl Friston (Ashburner 2012). SPM is an interesting example because of its predominance in positron-emission tomography and functional magnetic resonance imaging data analysis for a long time. The early distribution of the code, the fact that the software was solving for both spatial normalization and the multiple comparison statistical aspects, and the use of a high-level language (Matlab) were key aspects of its success. To some degree, this is also the story of software such as Brainstorm, MLE, fieldtrip, or others in the EEG-MEG field (see the special issue of Baillet et al. 2011).

The Methodological Lab Development Receptacle More a communal than a single researcher enterprise, laboratories which are mainly dedicated to developing methods are almost systematically developing the software tools to consolidate their research. This often takes the form of a software library, maintained so that research work can build on the previous methods without having to restart coding from scratch with every new student. But many groups have also developed full-fledged applications to demonstrate their research to a wider, more application-oriented community. For instance, the Oxford group, led by S. Smith, was predominantly developing methods to analyze MRI and fMRI data and developed FLS (Jenkinson et al. 2012) to propose an alternative to SPM. It took a few years for the software to establish itself as a valid alternative, but key methodological components and a coding language that did not require buying a license (Matlab can be a significant

budget for a lab) and led to faster execution were important aspects of the initial success. Later, FSL developed methods in diffusion imaging, while SPM developed the “Dynamical Causal Models” techniques, differentiating the two software suites for some applications. Many other examples can be found, such as the Montreal Neurological Institute (MNI) Brain Imaging Center (MNI Software Tools n.d.).

The Commercial Enterprise The transformation of a research software to a commercial product is not an easy enterprise, given the competition of freely available tools. BrainVoyager (Goebel 1996) is a remarkable example of success in this category. The incentive here is clearly to generate revenues, as well as having the means to easily incorporate a new method in one's preferred and controlled environment. BrainVoyager has in particular good visualization components as well as an interface adapted to end users which made for some of its success. More commercial software are used for EEG because of its strong link to the medical community (e.g., Besa <http://www.besa.de>).

Software Evolution Most software platforms that have been around for numerous years undergo an evolution in the set of functions that they perform. SPM started in support of PET imaging and evolved to handle functional and anatomical MRI, EEG, and MEG and more over the years. FreeSurfer (Fischl 2012) initially handles cortical surface extraction and quantification and evolved to include intersubject registration and subcortical segmentation, as well as adapt to numerous cortical parcellations schemes. These developments clearly follow the laboratories scientific directions, but students who are responsible for developing part of the code eventually leave the laboratories and this often lead to code base difficult to refactor and maintain.

One key for the success of all these tools is they are developed by or closely associated with a neuroscience/brain imaging laboratory that publicize the software through publications, talks, or teaching.

What's the Difference? Taxonomy of Software

While criteria for classifications are numerous and often nonindependent, we briefly review four possible criteria.

Application Domain and Scope This is probably the clearest and easiest of these criteria. Eight large categories dominate: (i) anatomical structures, (ii) diffusion imaging, (iii) functional (time-domain) data (PET or fMRI), (iv) electric and magnetic encephalography, (v) visualization tools, (vi) infrastructure software such as pipelining and databasing systems, and (vii) other more specialized software such as imaging genetics, PET modeling, etc. Many of the most used neuroimaging packages include several components, for instance, some visualization aspects and some scripting or pipelining capabilities. Other categories continue to emerge, such as the software for the connectome (e.g., Gray 2011) or “brain reading” (e.g., MVP <http://www.pympva.org/>).

Intended Users Part of the neuroimaging community has trained in psychology, neuroscience, or medicine; others may be trained in computer science, physics, or statistics. Some of software are clearly targeting the former part of the community (e.g., Toussaint et al. 2007), with easy installation and graphical interfaces, while others are at the stage of libraries and require programming skills to be used (e.g., the nipy suites: www.nipy.org).

Code Openness and Licensing These aspects are also critical for adoption in particular by method-oriented researchers. Many of the research software are open source with GPL-/BSD-/MIT-/CECIL-like licenses (e.g., SPM, many of the MEG tools such as Brainstorm or MNE, Baillet et al. 2011). While the code may be open, only a few however have open-source developing modes, where contributors propose changes through the mechanism of “pull requests” and decisions on whether to include or not a change are discussed on mailing lists. Some have licenses that distinguish the commercial and academic uses such as FSL.

Licensing of software remains a problematic in terms of the proliferation of different licensing terms. While the development of the Creative Commons suite of selectable options is a great advance, much software has been released prior to the development of that licensing strategy, and a majority of the software has been developed by investigators working at various academic institutions with specific intellectual property that have been felt to require university-specific terms. As an example, the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) hosts over 640 neuroimaging resources, and these require the listing of over 120 separate licenses.

Development Language This may not seem a major criterion at first sight for many. However, the readability of the code, its maintainability, and the flexibility with which the code source can be extended and refactored are major aspects for both maintenance and extension of a software platform. A strong attractive aspect of SPM is that it is written in Matlab, a high-level language that is particularly well suited for matrix algebra, which is at the heart of many of the data analysis methods. This makes it possible for a neuroscientist to adapt the code to develop his or her own ideas. Other high-level languages of the kind are Octave (Matlab clone), Python, and R.

The Problems with Software

There are a number of issues that are associated with the current state of brain imaging regarding software for data analysis. We list below these issues from the most practical to the most general/sociological aspects.

Proliferation: Finding the Right Software

The proliferation of myriad software solutions poses a number of practical issues that researchers or practitioners have to face. As an image processing need becomes more mature, more software has been developed to attempt to deal with it, and the user tends to be faced with more options about how to solve this task in their ongoing studies. Let us take individual image registration to a template image to illustrate this. In 1990, you either wrote the software yourself or accessed AIR

(Woods et al. 1992); today, there are over 10 (AIR, FSL (FLIRT, FNIRT), DRAMS (Ou et al. 2011), SPM-LDDMM, ANTS (Avants et al. 2010), Civet (Ad-Dab'bagh et al. 2006), nipy (nipy.org)) different major software solutions to such a task, spanning linear and nonlinear techniques, varying registration cost functions and different degrees of freedom in the fit, etc. (Klein et al. 2009). Where there are multiple “major” software options, you can be sure that there are many more options that have been developed that you just might not know about. This is not limited to the registration problem. For instance, fMRI had more than two decades to investigate various ways of extracting neuroscience or clinical results from data. To name a few, with fMRI, one can work on the cortical surface or on the volume data and apply dozens of preprocessing steps; MEG data can be analyzed using coherency or with evoked potential and led to many tools (Baillet et al. 2011), in diffusion imaging one can extract individual fibers or work with probabilistic models, etc. The complexity is exponentially increasing when data are combined. To add to the issue, software are constantly evolving, augmented with new functionality and debugged.

While the neuroimaging community may already be facing too many choices, the computer science and engineering literature are rife with algorithms and techniques that just are not commonly investigated by most neuroscience researchers. The main reason is that making these algorithms available to a wide audience requires software development skills that are not always available in methodological research teams. The “cost” to develop, distribute, and maintain a large or complex code and user base software is typically high, although underestimated in the research community.

Given multiple options to choose from, how does the investigator find all the options and choose the best option? Equally importantly, what are the practical differences between the different options?

There are many metrics and proxy metrics for “best” software solution for a given task. Ideally, one would like to know that the software is validated and that it produces the “correct” answer in

testing on when the solution is known. This can include simulation data. However simulation data when computationally known “ground truth” is designed into the data very often cannot mimic complete set of nuances of real data. Similarly, the performance of software under different input conditions (signal to noise ratio, contrast to noise ratio, etc.) is an important characteristic. Traditionally, patient and extreme populations are susceptible to more artifacts (motion) than healthy controls, so how well software performs in the presence of some degree of acquisition imperfections is also critical. It is not uncommon to find that the “best” software in perfect conditions may not be the “best” under more practical, real-world scenarios. Software that is designed and deployed with unit testing and that has been validated and profiled relative to all the available software options is to be preferred.

Popularity is a common criterion for selection of the “best” software option for a researcher. The argument is simple: reviewers will not – or rarely – question a method that has been used in published literature. Similarly, many research laboratories have developed a “culture” of using specific platforms; that’s what the current personnel are used to using, so that’s what they pass on to new investigators. Legacy of analyses performed in a specific way can span decades. Popularity can be quantitatively assessed by metrics like download count and number of publications. However, *popularity, correctness, and usefulness are notions that are far from being fully aligned.*

A last important factor is the documentation and available help with the software. All major software have forums and diffusion lists that often are critical for solving a particular question.

Software Testing

Testing whether the outcome of software is producing the right result is no simple task. This is particularly true for software that offer a high-level graphical interface to the user. One specific issue is that there is yet a lack of quality checking tools embedded in the software most commonly used, such that if, for some reason, part of the analysis fails (entry error, implementation bug or

not covering the use case, etc.), it is hard to find if anything went wrong at all, especially if the results “look” all right. One reason for this, in fMRI, is that although the field has more than twenty years of experience, almost any pattern of activity can be explained in a cognitive task.

At the implementation levels, although the outcome of example dataset or simulations is generally checked to provide reasonable results, the software rarely implement unit and integration testing procedure. This makes the code base fragile to any change. There are famous example of bugs in neuroimaging, and one of the most confusing and leading to a large number of erroneous publications was the left versus right issue (neurological vs. radiological display) as some early image formats did not allow code properly for this information. This was corrected in the NIfTI format (as long as the DICOM to NIfTI conversion is correct – which is not a small assumption). Other examples exist where software has implemented an incorrect statistical correction technique, for instance. Until a more careful and principled approach is taken by the developers of neuroimaging software, we are unclear on the error rate. Note that many of the mistakes may not be due to a specific faulty routine or method, but done during collecting and formatting all the auxiliary information (response time, paradigm sequence, etc.) necessary to launch an analysis. The example of the Duke University scandal (and other such examples) should be kept vivid in the mind of the research community, not as an exception but as a situation that can easily occur (Baggerly and Coombes 2009).

Analyses Reproducibility

A critical aspect to neuroimaging analysis lies in their reproducibility. This is a software issue in the sense that some software platforms will make it almost impossible to reproduce an analysis, for instance, when there is no other option than clicking on graphical interfaces, and detailed graphical logging options are not available. Many software platforms, however, do provide some solutions to this with the ability to script the analysis. This is of utmost importance. The

mechanism is simple: if it takes a few days to set up and run an analysis, and if the results “look all right,” there will be a very strong resistance to start over again in case of doubt. This will also prevent experimentators from checking that results are similar with trivial change of parameters. For instance, if changing a filter value by a small amount changes very significantly the results, these results are not robust, and unless there is a clear way to choose this filter value, the scientific community should not trust the findings. Interestingly, this ability also provides scientists with a way of trying out many filter values and selecting the best results, which poses some other issues addressed later in this entry.

Provenance

Even when scriptable, very few software platforms track and report their complete provenance of operation and attach it to the derived data; and those that do, do not necessarily do it in a standard fashion. First, this is important when software goes through major revisions and the nature of the results and methods can evolve substantially. When it comes to comparing the resultant data with other results, even from the same software system, version information (and computer operating system) can influence the results (Gronenschild et al. 2012). Second, when there is doubt on how the data have been generated within a lab, since there is no way to check their provenance, the only solution is to regenerate the results. This happens relatively frequently when a new student or postdoctoral fellow has to work on previously analyzed data. A third point is that if provenance data existed and were included in the supplementary material or better available digitally, reviewers could check the validity of the computations described in articles.

Data Management and Sharing Capacity

Just as shared raw imaging data is becoming increasingly important, so is the sharing of derived results. Most software do not integrate data management and sharing capacity. This prevents researchers to easily collaborate and build on the work of each other with more direct and effective ways than with the publications. The

data organization impacts in part of the effectiveness (and therefore lower cost) of the research performed and in part the rate of error and provenance tracking capacity.

One of the factors that make raw data sharing work is the existence of standards for data description. Image data formats, such as DICOM and NIfTI, are understood by scanner manufacturers and analysis software platforms alike. When it comes to the derived data however, there is yet neither the culture nor the infrastructure (standards or repositories) to promote widespread sharing of derived data. Standards for the representations of common derived results need to be adopted by a broad set of software developers and derived databases in order to fully promote the sharing of derived data.

Software Installation and Interoperability

A final factor that integrates a number of the aforementioned issues relates to promotion and “marketing” of a software system. There is little incentive and mechanisms so far in the community to establish and use a standard application program interface (API) to help software interact easily. *This is because software are rarely developed across laboratories.* Developers have therefore little interest at easing the interactions with other software and often tend to promote their tools even when it is demonstrated that other solutions may lead to better results. As a number of software packages become more mature, and the development and support infrastructure behind them becomes more complex and expensive, the need to develop continued funding to support the infrastructure is magnified. A laboratory may choose to continue developing some software to have some internal cohesion, or because large resources have been invested (“too big to fail”) despite evidence that more adequate solutions exist or more useful scientific results may be obtained with other software. This points to the immaturity of the scientific community which can act in a competing and individualistic mode when efficiency would require collaboration.

A second aspect is that it can be expected that significant improvements in processing methods have been developed by smaller, more transient software efforts, but it can be very hard to compete

with the established providers to distribute the method. This is because groups controlling which methods are to be integrated in most popular software are also the ones developing methods. There will be a strong resistance to implement a “competing” method in an in-house software. Methodological improvements that are embraced by the field may become adopted and incorporated into the major developers’ packages eventually, but these improved methods have to reach a level of adoption that is not easy to obtain given the established tools.

This may be less the case when software are the products of large consortiums (for instance, from the BIRN, INCF, etc.), often also working on standardization of formats or meta-information. Pipelining systems such as nipype are to some extent breaking these barriers, but they require good knowledge of the pipelining system as well as of the individual software.

Solutions

Some solutions to the issues listed in the previous section are emerging in the neuroimaging community. We list the ones that seem most promising.

Neuroimaging Informatics Tools and Resources Clearinghouse

The host of “problems” introduced above is not new or specific to the neuroimaging software community, and “solutions” to many of them are in place. One important tool in the handling of a rich and diverse set software options is an independent “clearinghouse” of information about all of the software relevant to a particular field. As a clearinghouse, such a resource supports the needs of the software developers to make consumers aware of their software’s availability and supports the needs of users to be able to find all the potential software solutions to a particular problem. For the neuroimaging community, such a resource exists in the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC – nitrc.org). Funded by the National Institutes of Health Blueprint for Neuroscience Research in 2006, the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) is the go-to website for neuroinformatics

software, tools, data, and other resources for an ever-broadening set of imaging domains (Kennedy et al. 2009). Starting with structural and functional MRI, NITRC catalogs virtually every resource in the domain to promote discovery and dissemination. The scope of resources covered by NITRC has expanded to include EEG/MEG/eCoG, PET/SPECT, CT, optical imaging tools, and, most recently, imaging genomics and clinical informatics. NITRC provides three types of services: NITRC Resources Repository (NITRC-R), the collaboration environment hub that enables the distribution, enhancement, and adoption of neuroimaging tools and resources (Luo and Kennedy 2009); NITRC Image Repository (NITRC-IR), a curated repository (developed from the XNAT open-source framework, Marcus et al. 2007) of NIfTI-1 and DICOM images searchable by metadata such as handedness, gender, and group; and NITRC Computational Environment (NITRC-CE) and NITRC-CE for Cluster Compute Instances, virtual big-data compute services (using the Amazon EC2 (Amazon. Amazon Elastic Compute Cloud (EC2) n.d.) Cloud and NeuroDebian, Hanke and Halchenko 2011; Halchenko and Hanke 2012) pre-configured with popular neuroimaging software analysis tools using pay-as-you-go compute time on AWS (Amazon. Amazon Web Service (AWS) n.d.) Marketplace.

In addition, as an independent clearinghouse, all providers, commercial and academic, large and small, and mature and in development, can have exposure to the community. NITRC provides a forum where community dialog about best practices, optimal solutions, standards development, etc., can occur in a fashion that transcends the forums and resources of the myriad individual resource providers. As a data host with community engagement, test datasets can be hosted and standard validation and comparison protocols can be run, and dissemination of the comparative results supported.

The International Neuroinformatics Coordinating Facility

The International Neuroinformatics Coordinating Facility (INCF) develops collaborative neuroinformatics infrastructure and promotes the

sharing of data and computing resources to the international research community. The INCF achieves its mission, in part, through the conduct of “Scientific Programs,” which are long-term strategic undertakings to address issues of high importance to the neuroscience community. Each program provides tools for integrating research findings from different labs and multiple experimental techniques. One of these, the **Standards for Data Sharing** program, aims to develop generic standards and tools to facilitate the recording, sharing, and reporting of neuroscience metadata, in order to improve practices for the archiving and sharing of neuroscience data. Metadata define the methods and conditions of data acquisition and subsequent analytical processing. Within data sharing broadly is the NeuroImaging Data SHaring (NI-DASH) task force. NI-DASH focuses on neuroimaging as a testbed for the development of specific tools and standards for data sharing within neuroimaging (Poline et al. 2012).

Along with the development of standards, INCF supports a number of data repositories designed to promote the adoption of the standards as they are developed. INCF XNAT is a neuroimaging archive that is supported by easy-to-use data sharing tools integrated with the delivery of quantitative feedback quality assurance measures to incentivize image data sharing. INCF Dataspace enables the collaboration between researchers through the sharing of a broad set of neuroscience data, including text, images, sounds, movies, models, and simulations.

Open Science and Open-Source Software Development

Open-source collaborative projects have proved that they can lead to very successful software and be major components in research or industry. Mozilla Firefox, LibreOffice, the Linux operating system, major databasing, and communication systems such as MySQL, PostgreSQL, Apache, etc., are only but a few examples of this. The software are developed by large distributed communities, with core team often scattered around the globe. They have along the years developed the tools and the know-how (the cultural rules) to

interact remotely and make the software evolve. They sometimes attract hundreds of developers whose interest may lie in the product itself, or sometimes just in being part of a community that produces useful software (see Raymond 1999 for a description of the open-source development history process).

Can neuroimaging software adopt this model? Contradicting the Betteridge's law (http://en.wikipedia.org/wiki/Betteridge's_law_of_head_lines), we believe that the answer is yes. An interesting example of this is the nipy libraries suite. Nipy started in Montreal with J. Taylor and then in France and in California (www.nipy.org) at the university of Berkeley and at Neurospin and was originally a library for functional MRI statistical analysis. Early on, the main developer (M. Brett) decided to apply the open-source development principles and constructed an adapted environment, using the most efficient collaborative tools (i.e., the git control version system, the github social coding platform, the python language, a suite of unit test with good coverage of the code base, a nightly building of the software, etc.). Although nipy itself has not made it the large brain imaging community, these working principles have fostered the emergence of multiple useful software projects (nibabel, nipy, dipy, nitime, etc.), and other solid projects are following the same principles (scikit-learn/nilearn, MNE, etc.).

Similarly, at the level of applications, a number of open science and software projects are modeled under the principles of open collaboration, meaning that any developer can propose code changes and the major direction of the software are discussed between developers. Neurosynth, Brainspell, and Neurovault are just a few of promising examples.

The New Challenges

The Reproducibility Problem

Neuroimaging is at a critical point in its sociological development. There are a few critical factors for this. First, many studies include a small number of subjects, and therefore the chance that the alternative hypothesis is true is

low even when the statistical test leads to reject the null hypothesis (Button et al. 2012; Ioannidis 2005). In other words, most of the claims are likely to be false because of power issues. Second, there is a strong sociological pressure to publish in the academic environment. It is clear that publication is the main assessment tool for grant attribution and renewal, as well as for granting tenure position. There are, therefore, very few imaging datasets that are acquired and not published, because the flexibility and multiplication of the analyses will almost certainly provide a significant test. The poor state of our knowledge will almost invariably provide a possible explanation for the results. Simmons et al. (2011) assessed a risk of type I error of about 60% if flexible analyses are allowed in psychology. The flexibility of neuroimaging analyses is even larger, alimmented by the publication pressure. Third, mistakes are ubiquitous, even within the most serious and careful individuals and laboratories (e.g., “anatomy of a coding error”; <http://www.russpoldrack.org/2013/02/anatomy-of-coding-error.html>). In this later case, the author provided a great service to the community in presenting the issue.

By combining these three factors, we conclude that there is a very high chance that many neuroimaging results (or neuroimaging genetics) are likely to be false. Clearly some results are reproduced, and meta-analyses are able to extract common results that are likely to be correct and will be found again. But extracting the solid results with large enough sample size – e.g., having the “big enough” data – or replicating across enough studies close enough in their goal remains a critical challenge of this field, and we suspect of others (see, for instance, an example in cancer research by Begley and Ellis 2012). From the above, we clearly see that neuroimaging has not been well served by our current publication paradigm. If one is interested in a result published in a journal, it is most often impossible to replicate the results, assess its validity, and link it to results of the same kind. The result – and the knowledge that we can extract from it – is in effect a sentence in a pdf file. Tools to mine text are being developed – but tools to link the scientific claim to the

data and computation that have led to the claims are mostly to be developed.

The field needs to generate a framework for deploying reproducible and re-executable neuroimage processing workflows to support the full connection between data, processing, results, and published claims so that the inference can persist and be dynamically assessed as the available data evolves over time. In addition to simply being able to re-execute a specifically published analysis (which by itself is significant and important), this will enable vastly new ways of querying data and performing analyses. One can take a publication perspective and from a result in one publication discover other publications that used similar data, found a similar finding, or used a similar analysis method. One can then explore all the parameters of an experiment. The primary authors of a paper may not be able to probe or explore all experimental factors, nor should they; but that does not mean that the stability of results relative to parameter settings, other data sources, is not important to explore. We cannot continue to assume that the one published set of observations from a particular set of data is the only interpretation. This “dynamic” nature needs to be exposed, so that all experimental parameters can be part of the ongoing dialog about what a set of observations mean and how they extend as the data available changes.

Computational Challenges

Virtualization Software deployment and utilization, for both the developer and user, is hampered by the proliferation of operating systems and hardware platforms. This places extra demands on developers to support the many platforms their users may be using and on users to deal with many software installation dependencies that may or may not be compatible with their existing hardware platform. This proliferation of platforms leads to increased variance in the results and provenance of ongoing neuroimaging studies and limiting data integration and aggregation. One major effort designed to alleviate some of these issues is NeuroDebian. The NeuroDebian project (<http://neuro.debian.net>; Halchenko and Hanke

2012) integrates many neuroimaging (and generic computing and neuroscience) software developments in a turnkey platform. Besides preparing, testing, and uploading software for inclusion into official Debian GNU/Linux distribution immediately making those available to millions of users worldwide, NeuroDebian project provides a repository with backport builds of maintained software for all supported Debian and Ubuntu releases making them available on top of existing deployments of their stable and LTS releases. NeuroDebian virtual appliance provides users of other platforms (e.g., Windows or OS X) a seamless solution for deploying complex analysis environments for research, teaching, and collaboration. Integration of software within a uniform software and data deployment platform allows for a seamless installation and maintenance of computing environments staying at the frontier of methodological developments while also allowing for easy instrumentation of existing installations on bare metal, or automated Debian-based deployments locally (VirtualBox <https://virtualbox.org/> and Vagrant <http://www.vagrantup.com/> or Docker <http://www.docker.io/>), or cloud appliances.

Distributed Computation There is still a long way to go in the initiative to enable a comprehensive data sharing infrastructure for the neuroimaging community. Nevertheless, numerous successes in large-scale image data sharing have occurred (i.e., Alzheimer’s Disease Neuroimaging Initiative (Mueller et al. 2005), National Database for Autism Research (Hall et al. 2012), Autism Brain Data Exchange (Di Martino et al. 2013), 1000 Functional Connections (Biswal et al. 2010), INDI http://fcon_1000.projects.nitrc.org/indi/IndiPro.html; Mennes et al. 2013; The ADHD-200 Consortium 2012, etc.). This means that researchers now have access to thousands of publically available neuroimaging cases. This blessing of data is matched with a curse of computation. As the available data grows and the complexities of processing and pooling data in specific domains increase, the demands on the availability of high-performance or large-scale computational resources skyrocket. The era of imaging analysis requiring processing workflows

that operate on thousands of cases is upon us. While many universities are fortunate enough to host local high-performance computational resources, not all investigators have access to such computational resources, and even those that do may or may not have these configured to handle the necessary neuroimaging processing software tools. In addition to local high-performance computing, the emergence of consumer-accessible cloud computing has brought the availability of scalable, on-demand computing to the community. Relatively simple configure of local and cloud-based neuroimaging systems is now easily deployed using such resources as NeuroDebian, VirtualBox, NITRC Computational Environment, and StarCluster. Thus, the acquisition of massive amounts of compute nodes is no longer rate limiting.

More limiting, at the moment, is the logistics and expense of moving the vast data resources to the processors. Now that net input data volumes to the workflows can be on the order of Terabytes, moving (or copying) this data to a local computer system will be intolerably slow (as well as relatively insecure). As data sources begin to reside on cloud-based storage facilities, and mirrored to multiple national and international sites, the financial and temporal pressures to move the computational processing to the cloud “nearby” will increase dramatically. This will usher in a completely new era in the design and financing of modern large-scale neuroimaging computational analysis.

Training and Collaboration As the world of neuroimaging data analysis and software development complexifies, the need for training the new generations of researchers to the new collaborative tools is becoming clear. None will be able to be an expert in all the domains required by brain imaging (image acquisition physics, applied mathematics and statistics for data analysis, software development, and the application field of neuroscience, cognitive neuroscience, neurology, or psychiatry). The only practical solution is to train on how to collaborate efficiently between individuals with complementary expertise. This means learning the common language of

collaboration through Internet, such as version control systems and collaborative development tools. As neuroimaging has become a computational field, we need to respond to the new challenge of training researchers on how to collaborate on computational projects, as well as clarify how acknowledgments and credits are to be handled in groups of individuals originating from multiple institutions and countries. The new “brain imaging” curriculum should have a significant component on this as this critically impacts both the quality and the efficiency of the research performed.

Conclusion

The neuroimaging research community could gain both in efficiency and in correctness by focusing more on its basic tools. In the same way that a common image format facilitates greatly the adoption and use of software tools, common application program interfaces, provenance exchange formats standards, test datasets, and community platforms, linking data to publications and programming training would lead neuroimaging to another level of efficiency. This may have to be the tasks of an emerging research field: the brain imaging neuroinformatics – or brain informatics.

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Somatosensory Cortex: Neural Coding of Motion

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Synonyms

[Aperture problem](#); [Tactile motion](#); [Tactile motion integration](#)

Definition

The tactile perception of motion involves the perception of movement of an object across the skin. Neural processing in the somatosensory cortex transforms the information originating from populations of afferents into a percept of the direction and speed of the tactile motion.

Detailed Description

Two Sources of Tactile Motion Information

The perception of tactile motion is thought to rely on two types of signals at the somatosensory periphery: the sequential activation of slowly adapting type 1 (SA1) (Johansson and Vallbo 1979) and rapidly adapting (RA) afferents (Kirman 1974; Sherrick and Rogers 1966) as an object moves across the skin and the activation of slowly adapting type 2 (SA2) afferents (Olausson et al. 2000) caused by friction-

induced skin stretch resulting from motion (Olausson and Norrsell 1993).

Direction Tuning Emerged in the Primary Somatosensory Cortex

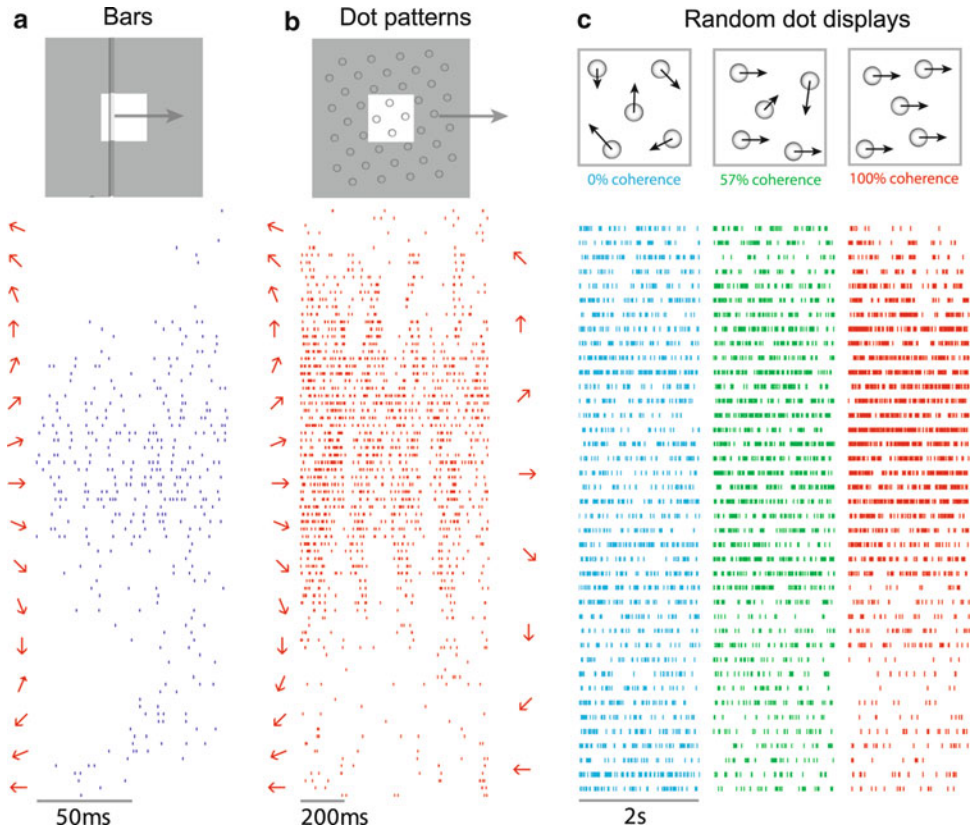
SA1 and RA afferents encode stimulus motion in a pixel-wise manner, and each single afferent exhibits little to no direction tuning (Whitsel et al. 1972; Pei et al. 2010); that is, the responses of these afferents are not modulated by the direction in which an object moves across their receptive field. Direction tuning emerges in primary somatosensory cortex (S1), namely, in areas 3b, 1, and 2 (Werner and Whitsel 1970; Whitsel et al. 1972; Costanzo and Gardner 1980; Warren et al. 1986; Ruiz et al. 1995). The direction tuning of S1 neurons has been hypothesized to be shaped by asymmetrical lateral inhibition in a feedforward neural circuit (Gardner and Costanzo 1980). Specifically, a cortical neuron receives inputs from subcortical neurons with adjacent receptive fields, and each input suppresses the input from an adjacent spatial location. If inhibition along one direction is stronger than along the opposite direction, the neuron would exhibit direction tuning.

Neurons in Primary Somatosensory Cortex Exhibit Shape-Invariant Direction Tuning

The preferred direction (*PD*) of neurons in S1 is invariant across stimulus types (including bars, dot patterns, and random dot displays), amplitudes, and motion speed (Fig. 1) (Pei et al. 2010). That is, they respond most strongly to motion across the skin in a given direction, regardless of the geometric properties of the object scanned across the skin. While neurons in area 3b exhibit some direction tuning, neurons in area 1, which is downstream to area 3b, produce responses that are more strongly dependent on motion direction. The responses of area 1 are highly predictive of the perceived direction of motion, suggesting that this population of neurons plays a causal role in tactile motion perception.

Motion Integration Is Mediated by a Terminator-Mediated Vector Average Model

Plaids, which are constructed by superimposing two moving gratings (Pei et al. 2008), can be



Somatosensory Cortex: Neural Coding of Motion, Fig. 1 Responses of a neuron in area 1 to bars (a), dot patterns (b), and random dot displays (c) presented to the monkey's fingertip. The stimuli are illustrated as insets at the top: for bars and dot patterns, the *white square* shows the 1 × 1 cm area at which the stimuli were presented; the *gray region* illustrates the stimulus extending outside of the stimulation area. To the left of each raster is the direction of

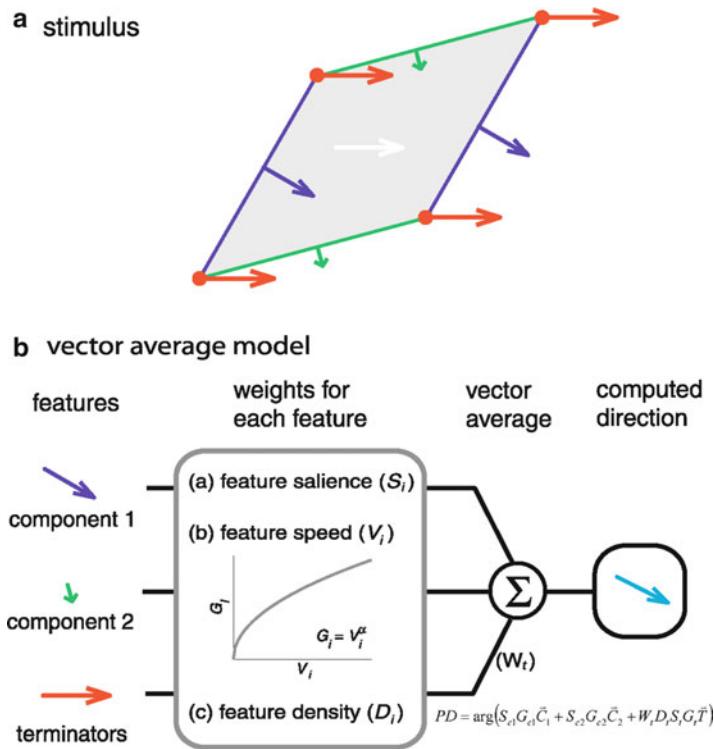
motion of the stimulus. This neuron produced the most robust response to stimuli moving from left to right (with a slight slant outward), regardless of whether the stimuli were bars, dot patterns, or random dot displays. For random dot displays, the tuning response increased with increases in the motion coherence. *Error bars* denote mean ± s.e.m. (Reproduced from Pei et al. (2010) with permission from PLoS Biology (Pei et al. 2010))

used to understand how motion information is integrated across the sensory sheet. Based on the responses to these more complex stimuli, a model for tactile motion integration was developed that predicts both neuronal responses to and the perception of tactile motion across a variety of conditions (Pei et al. 2011). According to the model, the representation of motion is determined by the motion vectors of the component gratings, as well by the intersections of the gratings (which constitute terminators, whose motion direction is unambiguous). Components and terminators are then weighted according to their speeds and amplitudes

account for the *PDs* and combined using a vector average (Fig. 2).

Processing of Motion Speed in the Primary Somatosensory Cortex

Human subjects can scale the perceived speed of tactile motion stimuli (Essick et al. 1988; Bensmaia et al. 2006). The structure of scanned objects is essential for tactile speed perception as evidenced by the fact that speed information is unavailable for smooth surfaces (Depeault et al. 2008). Furthermore, the spatial characteristics of the surfaces – i.e., their texture – influence speed perception. A population of neurons in areas 1 and



Somatosensory Cortex: Neural Coding of Motion, Fig. 2 A terminator-mediated vector average model for tactile motion integration. (a) Breakdown of the stimulus features for input components into the VA model. Green and blue contours and arrows correspond to the component edges and their respective directions of motion; red vertices and arrows correspond to the terminators and their

direction of motion. (b) Computation for the stimulus direction based on the direction of its components. Each feature is weighted according to its density (length of the edges, density of the terminators), its amplitude, and its speed. Weighted unit direction vectors are then summed to compute the perceived direction. (Reproduced from Pei et al. (2011) with permission from Neuron (Pei et al. 2011))

2 exhibit a graded increase in discharge with increasing speed, and their responses are affected by spatial period, suggesting a role in tactile speed scaling (Depeault et al. 2013).

Cross-References

- Somatosensory Cortex: Neural Coding of Shape
- Somatosensory Cortex: Organization

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Somatosensory Cortex: Neural Coding of Shape

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Definition

We appreciate object shape information by touch alone. Spatial feature representations, initially carried by populations of slowly adapting type I afferents (SAIs) in the peripheral nervous system, are centrally encoded by neural populations residing in the somatosensory cortex. Cortical neurons function as spatial filters that select out

specific object features falling within their receptive fields (RFs) on the skin. This neural selectivity, or tuning, changes across a hierarchy of processing stages spanning primary (S1) and secondary somatosensory (S2) cortices (Fig. 1a). While somatosensory neurons at the first cortical processing stage (area 3b in S1) have small receptive fields and respond to simple contour features like oriented bars and edges, neurons at intermediate and later processing stages (area 2 and S2) respond to stimulation of larger skin regions and are selective for more complex spatial features. In individual neurons and across neural populations, spatial tuning evolves in time, reflecting extensive and rapid network processing. Decoding of object shape information requires integrating activity over neural populations tuned for cutaneous and proprioceptive information.

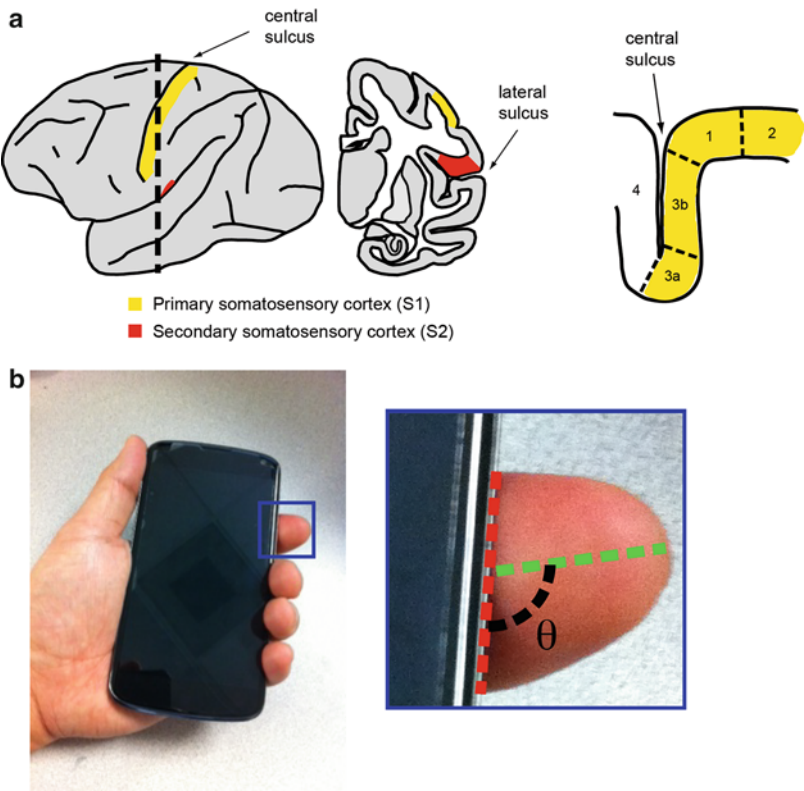
Detailed Description

We rely on our sense of touch to perceive and manipulate objects. Consider the act of holding a smartphone in one hand (Fig. 1b) – although much of the phone’s body is cradled in the palm of your hand, notice how your fingers are deftly positioned around the phone’s frame, allowing you to grip it easily and securely. If you gently adjust and tighten your grip, you may notice how the phone’s frame presses into each individual finger, and you can focus your attention on how the frame passes over your skin along a single edge (Fig. 1b, red dashed line). Shape perception is based in part on this cutaneous information, and importantly, regardless of where your fingers and thumb fall on the phone as you adjust your grip, you maintain a stable perception of the object in your hand. This stable object representation is encoded in the distributed neural activity over shape-sensitive neurons in the somatosensory cortex.

To understand how shape information is represented in the brain, we must consider how this information is initially encoded at the hand. Specialized mechanoreceptors in the skin respond to different cutaneous aspects of object contact

**Somatosensory Cortex:
Neural Coding of Shape,**

Fig. 1 Somatosensory system and shape perception. **(a)** The somatosensory cortical system in primates comprises primary (S1) and secondary (S2) somatosensory cortices. S1 consists of a densely interconnected set of regions: Brodmann areas 1, 2, and 3. **(b)** Tactile shape perception requires the integration of cutaneous and proprioceptive information. The phone's straight edge (red dashed line) is processed within each finger pad and is represented as an oriented edge feature in the activity of cortical neurons



(Johnson 2001). Note that separate afferent populations also carry proprioceptive information about hand conformation, which is necessary for stereognosis (i.e., haptic perception of objects) – this information is integrated with cutaneous shape information in the cortex (see below). Individual afferents display no spatial tuning and only respond when a stimulus impinges the afferent’s small RF. In this manner, a shape’s spatial profile is carried in the total activity over a population of afferents. Of the cutaneous afferents, SA1 fibers carry the most refined spatial information, and the SA1 population activity conveys a low-pass filtered neural image of a tactile stimulus that is isomorphic with respect to the contacted shape. Ultimately, information about object shape must be extracted from a pattern of activation across a two-dimensional sheet of receptors embedded in the skin. The challenge to characterizing somatosensory shape coding, then, is in understanding how cortical neurons process this two-dimensional spatial information conveyed by peripheral afferents.

Spatial Filtering

A large body of neurophysiological evidence implicates area 3b of S1 cortex as the primary cortical recipient of sensory input projecting from the afferent systems, sent via the dorsal column nuclei and the thalamus (Bensmaia and Yau 2011). Area 3b neurons function as linear spatial filters that cover small regions on a single finger pad: A neuron’s RF is a linear approximation of the effects of stimulus elements inside the RF on the neuron’s response. Stimulus contact in any single RF region can result in an increase or decrease in spiking activity, and a neuron’s overall response to each stimulus pattern is given by the sum of the effects of the stimulus elements over all RF regions. This can be formalized as

$$r(t) = b_o + b_1 \cdot 5emx_1(t) + b_2 \cdot 5emx_2(t) + \dots b_ix_i(t) \tag{1}$$

where $r(t)$ is the spiking activity predicted in response to the stimulus pattern at time t , b_0 is

the baseline firing rate, b_i is the effect strength (positive or negative) of a stimulus element in the i th region of the skin, and $x_i(t)$ is the stimulus value in the i th region of the skin (e.g., as in a bitmap, where a value of 1 indicates the presence of a stimulus element and 0 indicates no contact) at time t . The model can be rewritten in matrix form in order to solve for the set of weights defining the linear RF:

$$r = Xb \quad (2)$$

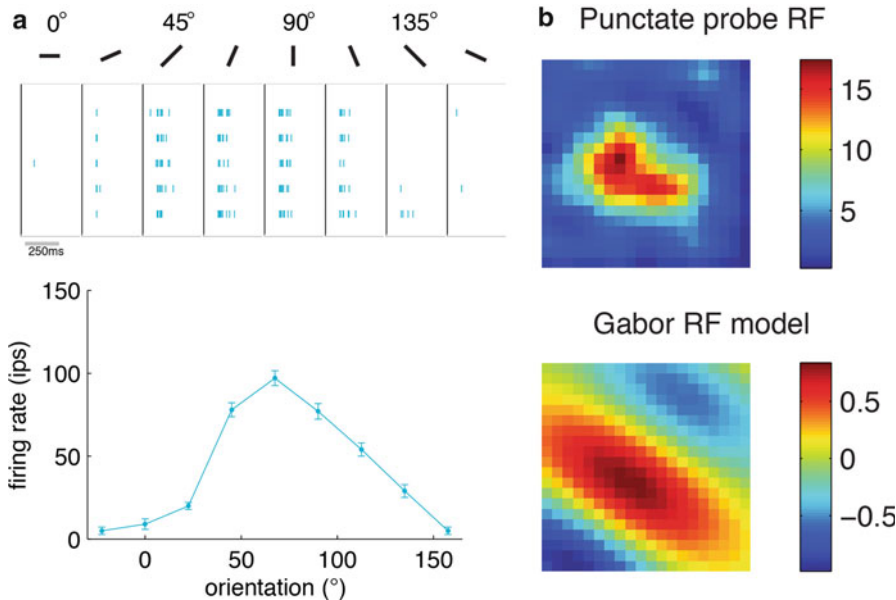
where r is a vector containing firing rates over all response times, X is the stimulus matrix, and b is a vector of weights (plus a constant term) describing the RF. The matrix equation can be solved for b :

$$b = (X^T X)^{-1} X^T r \quad (3)$$

where $X^T X$ is the stimulus autocorrelation matrix (which is an identity matrix when a white noise

stimulus devoid of temporal and spatial correlation is employed). RF maps for cortical neurons recorded from area 3b, derived from linear regression or reverse correlation, display obvious structured organization and typically consist of a central excitatory field flanked by one or more inhibitory fields (DiCarlo et al. 1998).

The shape and arrangement of these RF structures, or kernels, clearly underlie the spatial tuning of area 3b neurons. Specifically, a neuron may respond vigorously to a small bar indented in its RF at a particular orientation, and its response strength will decrease as the bar's orientation deviates from this "preferred" orientation (Fig. 2a). The shape and orientation of the RF structures tend to match that of the "preferred" bar orientation. Because of the clear correspondence between RF composition and spatial selectivity, orientation tuning in area 3b neurons can also be parameterized with two-dimensional Gabor filter RF models (Bensmaia et al. 2008;



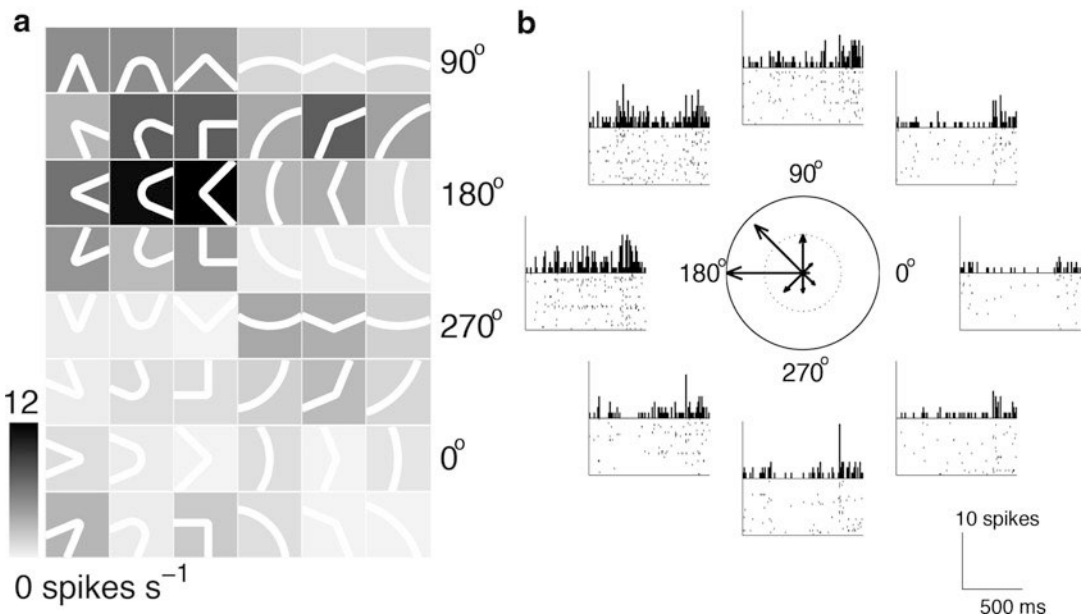
Somatosensory Cortex: Neural Coding of Shape, Fig. 2 Neural coding of bar orientation. (a) *Top*: spiking activity of an example somatosensory neuron to a bar stimulus presented briefly within the neuron's RF at different orientations reveals clear response modulation that is consistent over repeated trials (*rows* in the raster plot). *Bottom*: orientation-tuning curve shows the neuron's response as a function of bar orientation and a clear

preference for bars oriented near 67.5°. (b) *Top*: RF map for a different orientation-tuned cortical neuron computed by averaging responses (*scale bar*) to small punctate probes presented at each RF location. *Bottom*: RF map capturing orientation selectivity with a two-dimensional Gabor function (relative response weight for each pixel given by *scale bar*)

Fig. 2b). Although the neural basis for the linear RF composition is unknown, such organization likely results from the patterned convergence of afferent inputs projecting through the medial lemniscal system. However, cortical response selectivity is likely also shaped by recurrent network interactions among cortical populations (see below).

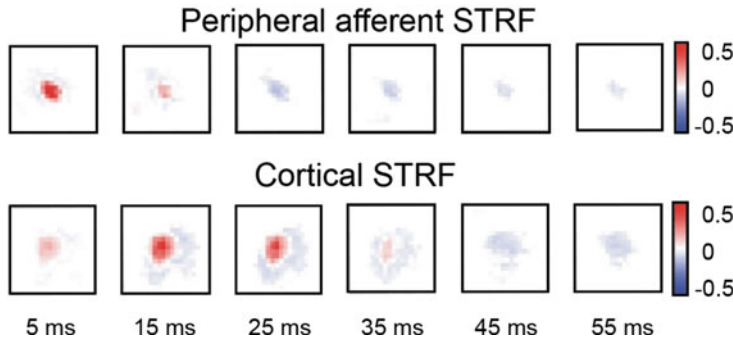
Neural responses become more selective as one ascends the somatosensory processing pathway. As a result, while the responses of afferents and of neurons in area 3b can be accounted for effectively using linear models, the responses of neurons in area 1, the primary recipient of projections from area 3b, cannot. Indeed, neurons in area 1 exhibit many properties that are similar to their counterparts in area 3b (e.g., orientation tuning), but detailed RF comparisons consistently reveal more complex spatial selectivity in area 1. Response properties continue to grow more complex and nonlinear in area 2 (the most caudal S1 region in the postcentral gyrus) and in S2 (located in the superior bank of the lateral sulcus).

RF size increases dramatically to span multiple fingers and even one or both hands in their entirety (in the case of S2 neurons). Linear RF models account for little response variance in most neurons in these populations as shape coding transitions from orientation selectivity to curvature tuning (Yau et al. 2009): Individual neurons respond preferentially to curved and angled contour fragments pointing in narrow direction ranges (Fig. 3). Although these response patterns cannot be approximated with two-dimensional spatial filter models, they can be modeled explicitly with tuning functions in the curvature direction domain. Thus, we can consider transitions in shape coding within the somatosensory system as projections of shape representations from an initial two-dimensional skin-based coordinate space into orientation and curvature feature spaces. Neural computations that transform object information into higher-order contour derivatives (orientation is a first-order spatial derivative; curvature can be defined as the rate of change in orientation along a contour, a second-order



Somatosensory Cortex: Neural Coding of Shape, Fig. 3 Neural coding of contour curvature. (a) Gray scale indicates average spiking activity of a neuron in area 2 responding to contour fragments indented into the skin at different curvature directions. (b) Raster plots and

peri-stimulus time histograms showed curvature responses sorted by direction (rows in a). Central bouquet plot depicts the same neuron's average responses as a function of direction and reveals its strong preference for *leftward* (180°) pointing curves



Somatosensory Cortex: Neural Coding of Shape, Fig. 4 Dynamic spatial response properties. Example spatiotemporal receptive field (STRF) for a peripheral afferent unit (*top*) and a cortical neuron (*bottom*). Pixel color (*scale bar*) indicates response contribution of each RF location

(spikes per second per micrometer). The majority of cortical STRFs in areas 3b and 1 comprise an excitatory center coupled with surround inhibition and trailed by replacing inhibition

derivative) may be especially efficient for building compact and sparse shape representations. In other words, these transformations in shape representations can help minimize the number of active neurons required for coding shape, thereby reducing the metabolic demands related to shape processing.

Position Tolerance

Shape-selective responses in many area 2 and S2 neurons exhibit position consistency: Tuning preferences are maintained even as stimulus features are moved over different RF locations. Although stimulus position changes can result in general response strength modulations, the relative preference for particular ranges of edge orientation or contour curvature direction is preserved regardless of where the stimulus is presented within and across finger pads (Fitzgerald et al. 2006). This position tolerance is computationally demanding and requires nonlinear shape coding mechanisms.

Temporal Dynamics

Shape coding in the somatosensory system is a dynamic process which takes place over tens to hundreds of milliseconds after a stimulus contacts the skin. Dynamic shape coding in the peripheral

afferent system and cortical neurons has been studied by characterizing selectivity using spatiotemporal receptive field (STRF) models, which capture the temporal modulation of neural RFs, in addition to their spatial tuning properties (Fig. 4). (These models are a temporal extension of the spatial filtering models described above.) Cortical neurons display a range of spatiotemporal response patterns, and the most common STRF (in areas 3b and 1) consists of initial excitation, flanked by inhibitory regions (“surround inhibition”) and followed by a long period of (“replacing”) inhibition (Sripati et al. 2006). Because of this composition, the majority of cortical STRFs are space-time inseparable: RFs cannot be decomposed into the product of a spatial kernel (excitatory region) and a temporal kernel (e.g., an exponential response decay or a difference of two exponential decays). (Note that some cortical STRFs lack surround inhibition, like afferent STRFs, making them space-time separable.) Although the neural basis for these dynamic response patterns is still unknown, there is little question that evolution of RF composition depends on rapid intracortical interactions. Importantly, particular aspects of dynamic shape coding, especially the spatiotemporal profile of inhibition, may play a critical role in establishing response properties like invariance to scanning velocity (DiCarlo and Johnson 1999), i.e., a preference for spatial patterns that is consistent across a range of scanning speeds. Moreover, recurrent

network interactions likely also contribute to the dynamic feature selectivity observed in cortical neurons: Orientation selectivity builds gradually in areas 3b and 1, after population spiking activity peaks (Bensmaia et al. 2008), and curvature signaling similarly lags an initial buildup of spiking activity in areas 2 and S2 (Yau et al. 2013). Such response time courses may reflect the role of cortical inhibition in sculpting neural selectivity and sharpening shape representations over time.

Proprioception

Representation of three-dimensional object shape requires the integration of cutaneous and proprioceptive information. Consider again the act of holding and perceiving a smartphone in your hand: All of the cutaneous processing described above only accounts for your ability to perceive the phone's straight and curved boundary edges in contact with your fingers. The exact computation used by somatosensory neurons to combine these cutaneous representations with hand conformation information is unknown, but neuroimaging and neurophysiological evidence implicate neural populations residing in area 2 (Mountcastle 2005). Indeed, area two neurons, while selective for cutaneous stimulus patterns, are additionally sensitive to the three-dimensional arrangement of the hand and fingers (Iwamura and Tanaka 1978). Accordingly, area 2 lesions result in clear haptic object perception deficits (Carlson 1981). There is also evidence that area two responses may be influenced by motor command signals in the context of active object exploration (London and Miller 2013): This proprioceptive feedback (which may be the result of efference copy) from the motor system could serve to gate self-generated sensory signals and to refine shape representations acquired during object manipulations.

Conclusion

Shape representations are carried in population activity of somatosensory cortical neurons. Across different levels of a cortical hierarchy,

shape representations transition from occupying a skin-centered coordinate space to higher-order feature spaces. Response selectivity grows more complex at successively higher processing stages in the somatosensory cortical pathway: Linear responses give way to nonlinear responses. Neural response patterns evolve rapidly in time, reflecting intracortical interactions that sharpen shape representations. In many respects, the principles of shape coding in the somatosensory system resemble those that apply to shape coding in the visual system (although equivalence may be restricted to two-dimensional shape representations). Despite our advancements in understanding neural shape coding in the somatosensory cortex, the computations underlying three-dimensional object representations, which require the integration of cutaneous and proprioceptive information, are not well understood. Similarly, whether and how haptic shape information interacts with other object characteristics like texture and temperature remains to be tested. Finally, the computations underlying the decoding of tactile shape representations for perceptual access and executive functioning remain to be characterized.

Cross-References

- ▶ [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- ▶ [Receptive Field Modeling](#)
- ▶ [Somatosensory Cortex: Organization](#)
- ▶ [Somatosensory System: Overview](#)

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Somatosensory Cortex: Organization

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Detailed Description

History

In 1909, Brodmann published maps of the different regions of cortex in humans and monkeys (Brodmann 1909). He partitioned the postcentral gyrus into three distinct areas based on cytoarchitecture and cell organization. From rostral to caudal, he designated these areas as areas 3, 1, and

2. Later studies showed that Brodmann's area 3 could be functionally and structurally divided into two distinct areas now labeled areas 3a and 3b (Vogt and Vogt 1919). Although all four brain areas are often together designated primary somatosensory cortex (S1) and to an extent respond to cutaneous stimulation, area 3b is most analogous to the other primary sensory cortices given its similarity in inputs and laminar structure. Area 3b is thus S1 proper.

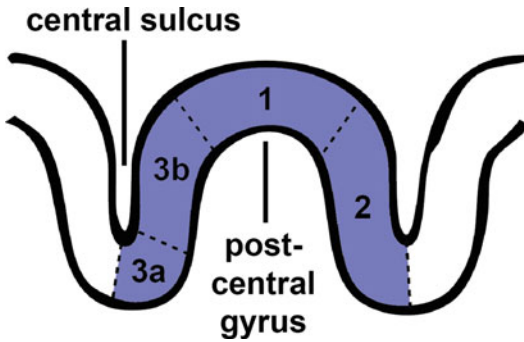
Later, in 1940 Adrian discovered a second brain region, adjacent to S1, which contained representations of the forefoot and hindfoot in cats (Adrian 1940). Adrian initially thought this area to be a cortex dedicated to the cats' special ability to extend and retract their claws; however, Woolsey was able to show that this additional somatosensory area, now known as the secondary somatosensory cortex (S2), is shared by monkeys and other animals (Woolsey 1943).

Structural Organization

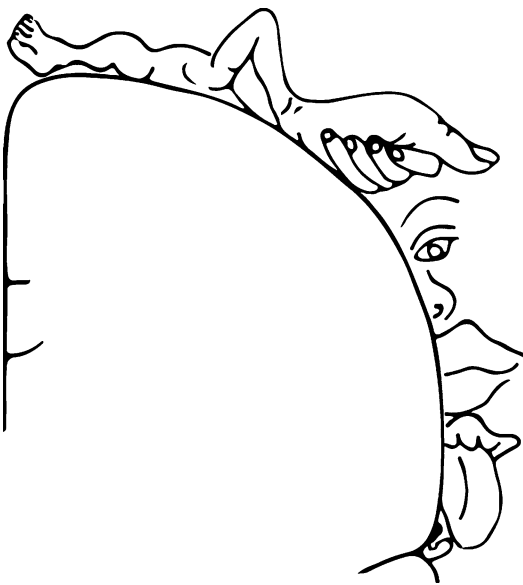
Area 3a is located in the fundus of the central sulcus, contiguous to primary motor cortex (area 4) on the rostral side and to area 3b on the caudal side. Area 3b lies on the rostral bank of the postcentral gyrus and, proceeding caudally, abuts area 1, located at the apex of the postcentral gyrus, followed by area 2, which lies on the apex and sometimes on the caudal bank of the postcentral gyrus (Fig. 1).

Each of the four brain areas comprises a distinct cortical representation of the contralateral body (Kaas et al. 1979) (Fig. 2). The representation of each body part in the cortex is not proportional to its physical size or mass. Instead, the parts of the body with dense innervations (i.e., the hand or face) have larger cortical representations than do parts that are more sparsely innervated (i.e., the back or leg) and likely contribute to a richer sensory representation.

S2 is located in the parietal operculum on the upper bank and ceiling of the lateral sulcus (Woolsey et al. 1979). The structural organization of S2 is not as well characterized as is that of S1 but is thought to comprise at least two distinct cortical representation of the contralateral body (Krubitzer et al. 1995).



Somatosensory Cortex: Organization, Fig. 1 Primary somatosensory cortex comprises four brain areas: areas 3a, 3b, 1, and 2



Somatosensory Cortex: Organization, Fig. 2 A coronal view of primary somatosensory cortex from a single hemisphere of the brain. The size of the body part represents how much cortical volume is devoted to processing that part

Functional Organization

Area 3a, considered a transitional zone between the motor and somatosensory cortices, receives and processes information about muscle stretch, joint movement, and posture from muscle receptors (Yumiya et al. 1974) and possibly other proprioceptors. Area 3a is thought to contribute to the

sense of proprioception, the awareness of the position, and movements of one's body. Its dense reciprocal connections with motor cortex (Zarzecki et al. 1978) suggest a role in the coordination of movements.

Tactile information is processed in areas 3b, 1, and 2 in a hierarchical fashion (Iwamura 1998). Cutaneous signals are first processed in area 3b (via projections from the ventral posterior nucleus of the thalamus) then are further elaborated in areas 1 and 2 (which also receive some thalamic input) before being sent to S2 or other associative areas for further processing. The hierarchical progression is observed in the increasing latencies of the responses to tactile stimuli (Lebedev and Nelson 1996) and in the response properties of neurons. Indeed, receptive fields (RFs) get larger as one ascends the processing pathway from area 3b to 2, and neurons exhibit increasingly complex response properties as one proceeds caudally (Iwamura et al. 1993), such as a selectivity for direction of motion (Pei et al. 2010) or the orientation of edges (Bensmaia et al. 2008). In addition to exhibiting complex cutaneous RFs, neurons in area 2 also receive proprioceptive input, suggesting that this area mediates the integration of cutaneous and proprioceptive information to achieve a three-dimensional percept of objects.

Cutaneous and proprioceptive neurons from S1 then project to S2, which is functionally divided into different fields: anterior, central, and posterior (Fitzgerald et al. 2004). Neurons in the central field are sensitive to cutaneous stimuli with RFs that often span multiple digits (Krubitzer et al. 1995). Some neurons exhibit orientation selectivity over their (large) RFs (Fitzgerald et al. 2006) and even more complex shape tuning properties such as a selectivity for orientation (Yau et al. 2009). In contrast, neurons in the anterior and posterior fields are more sensitive to proprioceptive stimuli than to cutaneous stimuli (Fitzgerald et al. 2004).

In addition to processing cutaneous and proprioceptive stimuli, both S1 and S2 process noxious stimuli (Treede et al. 1999): S1 neurons seem to encode pain intensity while S2 neurons may be involved in signaling the presence of any pain (Timmermann et al. 2001).

Cross-References

- [Proprioception](#)
- [Somatosensory Cortex: Neural Coding of Motion](#)
- [Somatosensory Cortex: Neural Coding of Shape](#)

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Somatosensory Neurons: Spike-Timing

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Synonyms

[Entrainment](#), [First-spike latency](#), [Phase-locking](#), [Temporal coding](#)

Definition

A long-standing controversy in neural coding has been about whether the timing of individual action potentials (spikes) conveys information and is behaviorally relevant or whether information is instead transmitted simply by neurons' firing rates. Both peripheral and cortical somatosensory neurons in primates can exhibit precisely timed action potentials in response to tactile stimuli, and there is a growing consensus that not only is some tactile information exclusively represented by such temporal codes but also that spike timing can shape tactile perception.

Detailed Description

Precisely Timed Responses of Cutaneous Mechanoreceptors to Skin Vibrations

In primates, rapidly adapting (RA) and Pacinian (PC) afferents entrain to medium- and high-frequency vibrations, respectively, in that their action potentials occur precisely within a given phase of each stimulus cycle (Talbot et al. 1968). Such precise timing can also be seen in the responses to diharmonic and noise stimuli (Muniak et al. 2007, see Fig. 1). PC responses are generally more precise than RA responses. Slowly adapting type I (SAI) afferents only respond weakly to vibrations, and their spikes are not precisely

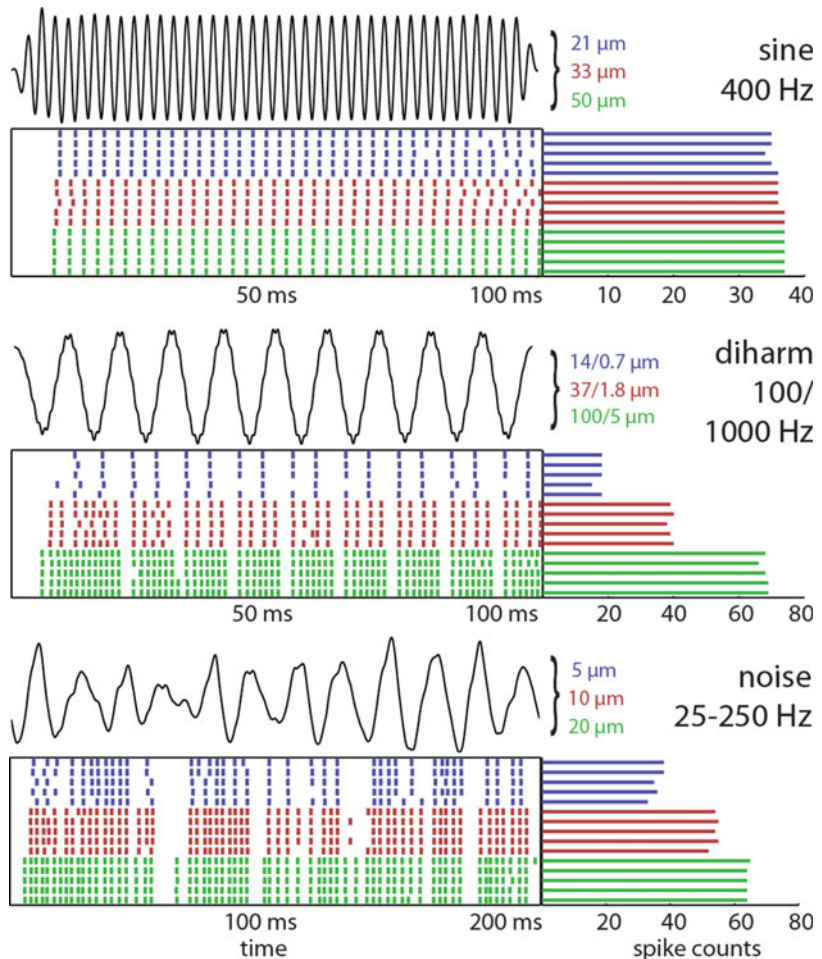
timed. Finally, the temporal patterning has been shown to be behaviorally relevant at a fine temporal resolution, by presenting different stimuli that elicit similar or the same firing rates and then test whether those are perceptually discriminable (Mackevicius et al. 2012). One behavior where skin oscillations are especially relevant is texture perception, where RA and PC afferents respond with precise temporal spiking patterns to texture-elicited skin vibrations (Weber et al. 2013).

Peripheral Responses During Object Manipulation

Another temporal code might be active during object manipulation. When grasping an object,

Somatosensory Neurons: Spike-Timing,

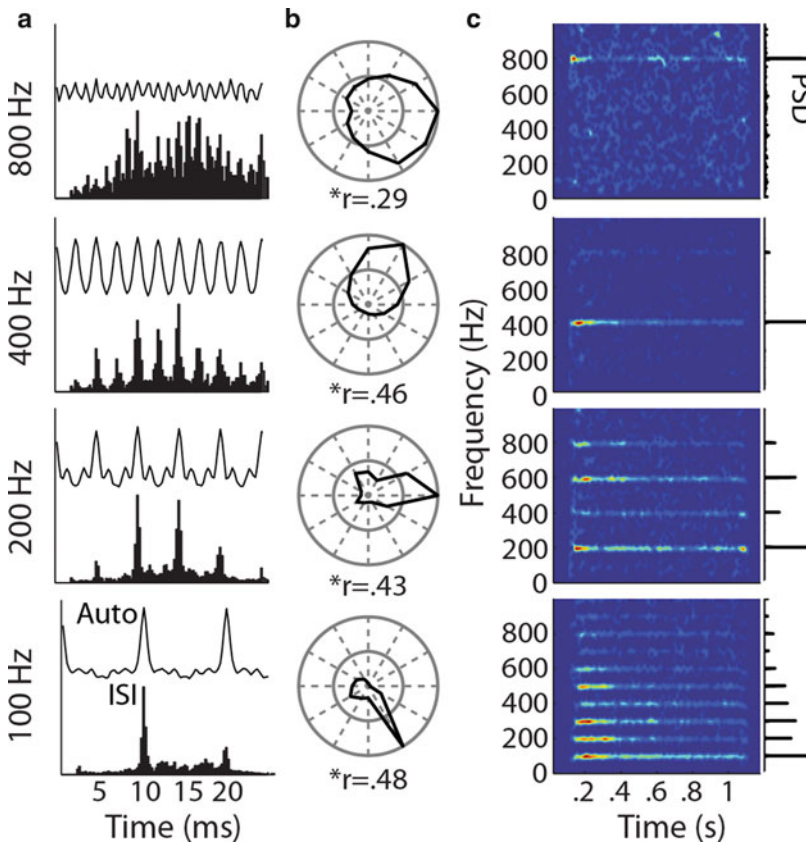
Fig. 1 Responses of a PC afferent to sinusoidal, diharmonic, and bandpass noise stimuli. In each of the three panels, the top trace shows the time-varying position of the vibratory stimulus (with the three amplitudes marked to the right). The raster plots show the responses of a PC afferent to five repeated presentations of the stimulus at the three stimulus amplitudes. The bars to the right indicate the spike counts evoked on each stimulus presentation. While spike counts tend to change with stimulus amplitude, temporal patterning in the afferent response is more consistent across amplitudes. (Adapted from Mackevicius et al. (2012))



one needs to rapidly adapt grip forces depending on object properties to prevent slip or over-grasping. Information about object curvature and similar properties is encoded mostly by SA1 and RA afferents. It has been shown that in addition to firing rates, the first-spike latencies of SA1 and RA afferents are highly informative about object features. A neural code based on first-spike latencies could explain how tactile feedback is rapidly integrated into motor commands (grip force adjustments can occur within 100 ms) (Johansson and Birznieks 2004; Saal et al. 2009).

Spike Timing in Somatosensory Cortex

Whether spike timing matters in primate somatosensory cortex is more controversial. It is often assumed that even though peripheral afferents might exhibit precisely timed spikes, such temporal information might be converted into a rate code on the way to cortex. Thus, most work on somatosensory cortical neurons has focused on characterizing the makeup and extent of spatial receptive fields using firing rates. A notable exception concerns flutter stimuli (low-frequency vibrations in the range of 5–50 Hz), in response to which cortical



Somatosensory Neurons: Spike-Timing, Fig. 2 Temporal patterning in cortical responses to sinusoidal stimulation. (a) Autocorrelations (top) and interspike interval histograms (bottom) for one neuron in area 3b, whose responses are entrained with the stimulus up to 800 Hz. (b) Phase histograms along with vector strength (r) for the same neuron as in (a) showing action potentials tended to occur during a restricted phase of each

stimulus cycle. (c) Spectrograms for the same neuron as in (a), with corresponding power spectral densities (PSD) in the insets to the right. Note that the temporal patterning begins almost immediately and lasts for the duration of the stimulus and that the fundamental frequency in the neural response reflects the frequency of the sinusoid. (Adapted from Harvey et al. (2013))

somatosensory neuron both exhibit entrainment (phase-locking) and modulate their firing rates. However, changes in the perception of flutter stimuli align more closely with changes in the firing rates of cortical neurons rather than changes in their temporal profile, which has led to the conclusion that spike timing plays no role in the perception of flutter stimuli (Luna et al. 2005; Salinas et al. 2000). For high-frequency texture-like vibrations, however, a different picture emerges. For such stimuli, their amplitude is signaled in the slowly time-varying firing rates of cortical neurons, while their frequency content is transmitted by precisely timed action potentials (Harvey et al. 2013, see Fig. 2). Such a code is an instance of multiplexing, where different kinds of information are transmitted by different aspects of the neural response. Interestingly, information about amplitude and frequency is separated so well by these two different codes that some frequencies would be impossible to tell apart without, providing a strong argument that spike timing is indeed behaviorally relevant.

Spike Timing and Attention

Spike timing across a population of neurons can also carry information. Specifically, attention modulates the synchrony of spikes of cortical somatosensory neurons (Steinmetz et al. 2000). Such a mechanism might enhance the saliency of attended stimuli by increasing the number of coincident spikes across the neural population.

Cross-References

- ▶ [Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture](#)
- ▶ [Metric Space Analysis of Neural Information Flow](#)
- ▶ [Neural Coding](#)
- ▶ [Spike Train](#)
- ▶ [Tempotron Learning](#)
- ▶ [Time-Frequency Analysis of Analog Neural Signals](#)

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Somatosensory Prosthesis

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Detailed Description

Our ability to dexterously manipulate objects relies heavily on somatosensory signals from the hand (Johansson and Flanagan 2009). Receptors

embedded in the skin, joints and muscle convey information about the size, shape, and texture of grasped objects, and signal whether these are slipping from our grasp. The sensory experience of our hand also plays an important role in conferring to it embodiment, making it feel a part of us. Without these signals, using our hand to perform even the most rudimentary tasks would be slow, clumsy, and effortful. Given the importance of somatosensation in natural motor behavior, to achieve a clinically viable upper-limb neuroprosthesis will require that this sense be restored.

Sensory Substitution

There are a variety of approaches to conveying useful somatosensory feedback for use in upper-limb neuroprostheses. The least invasive approach consists of substituting lost sensation by mechanically stimulating – with vibratory motors, e.g., – regions of the sensory sheet that are still intact (the face, for example) (Stepp et al. 2012). In both amputees and individuals with upper spinal cord injury – the two patient populations that are targeted with these technologies – mechanical stimulation can be applied to signal movements of the hand and objects contacting it. While sensory substitution does not require surgical intervention, the patient must learn to associate patterns of skin stimulation with hand movements or with object contact, which may require extensive training. Furthermore, given spatial constraints, patients can only be instrumented with a relatively small number of stimulators, so sensory substitution can be used to convey only limited information compared to the high-bandwidth of the intact native hand.

Neural Interfaces

An alternative approach consists of interfacing directly with the nervous system. Indeed, in intact individuals, signals from the hand are carried via nerve fibers that climb up the arm and the spinal cord before they synapse onto neurons in the brainstem (in the dorsal column nuclei). These

secondary afferents then cross the midline and project to the ventroposterior nucleus thalamus, which in turn projects to primary somatosensory cortex. In principle, an interface can be developed to interact with any of these neuronal populations by developing the right type of implantable device (Weber et al. 2012), but the different potential interface sites vary in their accessibility. The neural interface approach consists of eliciting patterns of neuronal activation informative of the state of the limb and of events impinging upon it, typically through electrical stimulation of the neuronal tissue. Let us briefly compare and contrast interfaces with the nerve and with the brain, at the two anatomical extremes of the interface continuum.

Peripheral Interfaces Afferents can be accessed either in the residual nerve (Dhillon and Horch 2005) or in the dorsal root (Hokanson et al. 2011), where all of their cell bodies are located. Only a relatively small number of different types of mechanoreceptive afferents convey proprioceptive and cutaneous information, and the properties of these neurons are both highly stereotyped and well characterized. Furthermore, these neurons are not interconnected, so they essentially convey independent signals to the brain, which greatly simplifies stimulation strategies. The idea, then, is to attempt to reproduce natural patterns of activation in the nerve by strategically injecting small electrical currents into it, ideally through many independently controlled electrodes. The patterns of electrical stimulation can be modulated in space and time to produce naturalistic patterns of afferent activation. A variety of very powerful single input single output models have been developed to convert the output of sensors on the prosthesis into desired patterns of neuronal activation and these patterns can in theory be effected in the nerve through electrical stimulation (Dong et al. 2012; Kim et al. 2009, 2010), while other multi input multi output models have also been explored (Daly et al. 2012; Liu et al. 2011).

Cortical Interfaces A cortical interface has the advantage that it can be applied to patients with upper spinal cord injury, for whom the communication between the nerve and the brain has been

severed. Another desirable feature of cortical interfaces is that sensory systems extract behaviorally relevant information from the relatively unelaborated representation in the nerve through successive stages of processing. Indeed, individual cortical neurons encode more complex stimulus features than do their peripheral counterparts. Furthermore, cortical neurons are organized topographically, such that nearby neurons tend to respond to similar stimulus features. This organizational scheme, largely absent in the nerve, may thus be exploited in attempting to elicit artificial percepts.

There are two general approaches to conveying sensory information through a cortical interface. The first, analogous to its peripheral counterpart, consists of attempting to reproduce naturalistic patterns of neuronal activation through electrical stimulation. To the extent that patterns of activation are naturalistic, the evoked percepts will be verisimilar and thus intuitive, requiring little training on the part of the patient. Within this approach, the functional topography of the brain can be exploited. For example, information about contact location – where is the object contacting the skin? – is important for object manipulation. In intact individuals, where we feel a poke on the skin is determined by which population of neurons gets activated. Thus, information about contact location might be conveyed by stimulating small populations of somatosensory neurons, thereby eliciting a percept that is localized to a small patch of skin (Tabot et al. 2013). In amputees, the sensation is projected to a phantom limb, in tetraplegic patients to their deafferented limb. Now imagine that anytime the prosthetic thumb touches an object, stimulation is triggered through electrodes that are implanted in the thumb representation of somatosensory cortex. The evoked sensation will be projected to the phantom or deafferented thumb, which will lead to an intuitive sense of where contact happened. In fact, studies suggest that, while stimulating the neuronal representation of the thumb will be experienced on the phantom or deafferented thumb, if patients have consistent visual experience of contact with the thumb, paired with sensations experienced on

the native thumb, the sensations will start to be experienced on the prosthesis (Marasco et al. 2011). Artificial touch may thus lead to embodiment of the robotic limb! While some degree of naturalism might be achieved with a brain interface, cortical neurons are embedded in highly complex networks, and electrical stimulation of cortical tissue leads to diffuse activation of neurons with very different response properties despite the spatial organization of the brain (Histed et al. 2009). Producing truly naturalistic patterns of activation through electrical stimulation is therefore an endeavor that is doomed to failure.

With this in mind, the so-called biomimetic approach – the exploitation of existing neuronal representations – may be unnecessary. Another approach to conveying sensory feedback through a cortical interface consists of exploiting the brain's ability to learn. Indeed, the brain is known to be highly adaptable, so it is not unreasonable to hypothesize that if a systematic mapping is created between patterns of sensory activation and patterns of intracortical microstimulation, patients will learn to use this artificial sensory feedback to control the limb. Indeed, animals are able to learn to use completely arbitrary but systematic artificial sensations to guide behavior (Thomson et al. 2013; O'Doherty et al. 2011). However, the space of possible sensations that were tested in these experiments is small relative to the almost infinite space of sensory events associated with the hand and it is unclear whether the adaptation-based approach will scale up sufficiently for use in upper-limb neuroprostheses. Most likely, biomimicry and adaptation will both play critical roles in successful attempts to convey sensory feedback.

Conclusions

Multielectrode arrays have been implanted in the brain of human patients, and algorithms have been developed to decipher how these patients wish to move anthropomorphic robotic arms from signals in the motor parts of their brain (Hochberg et al. 2012; Collinger et al. 2013). In other words, these

patients can control robotic limbs by thought alone. While these studies constitute staggering examples of scientific and technological achievement, the evoked movements are slow and inaccurate, and the neuroprostheses are only viable in a laboratory setting. Given its importance in guiding movement, the incorporation of somatosensory feedback in the next generation of prostheses may bring about a major improvement in the dexterity of these limbs, and perhaps eventually may lead to a clinically viable option to restore sensorimotor function in amputees and tetraplegic patients.

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Sound Localization and Experience-Dependent Plasticity

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Definition

The ability to localize sounds in space, and the way in which such a task is performed, is not fixed. If the physical cues for sound localization are altered, ability is initially disrupted. However, following experience with the new set of cues, a degree of the original performance is regained, accompanied by various changes in auditory processing.

Detailed Description

Localizing sound sources in the external world requires the integration of multiple cues. The

relative time of arrival and sound level across the two ears depend on which side of the head the sound originates from (azimuth) and frequency-dependent filtering by the head and ears that depends on the vertical angle of the sound source (elevation). For a given location these cues correspond, but not uniquely for a given frequency. Thus, information is integrated across different monaural and binaural cues and different frequency ranges. The correspondence of cue values also depends on individual's head and outer ear (pinna) size and shape and the relative state of their hearing at each ear, all of which change with age. Possibly as a consequence, the calibration of these cues in the auditory system is quite flexible. Flexibility may also be an advantage for dealing with different acoustic environments.

Experience-Dependent Changes in Sound Localization Ability

Manipulating of the cues for sound localization by altering the sound input to the ear immediately results in impaired sound localization ability. However, in most cases there is some subsequent recovery of sound localization ability over time.

Occlusion of one ear (typically with a removable ear plug) results in an immediate shift in free field azimuthal sound localization toward locations on the other side. In humans (Kumpik et al. 2010), ferrets (King et al. 2000), and owls (Knudsen 2002), sound localization ability improves over days and weeks of continued occlusion. Performance with the altered cues recovers completely in juveniles and is robust in experiments with adult ferrets and humans but does not occur in adult owls. However, even owls raised with altered cues can learn to localize correctly if normal hearing is reestablished in adulthood. Although differences in timing and level across the two ears are the dominant cues for azimuthal sound localization, in adult humans (Kumpik et al. 2010) and ferrets (Kacelnik et al. 2006), performance improvement in azimuthal sound localization appears to reflect an increased reliance on monaural spectral cues.

Modification of the vertical cues for sound localization also results in adaptation of behavioral responses. Ear molds that modify the elevation-dependent spectral filtering by the pinnae produce immediate deficits in the vertical plane. Performance is almost entirely recovered with experience (Hoffman et al. 1998). Explicit modification of binaural cues (e.g., interaural timing), azimuthal shifts, or nonlinear transforms also results in an immediate drop and subsequent improvement of localization ability, though recovery of unaltered performance is not generally complete and it is not possible to adapt to reversal of the inputs to each ear. Training also produces improvements on unaltered cues (see Wright and Zhang (2006) for a review). The immediate effect of monaural earplugging in adult humans suggests that sound localization in both azimuth and elevation relies on a rapidly updated weighting of all acoustic cues depending on their reliability (Van Wanrooij and Van Opstal 2007).

Reversal of cue manipulations generally results in recovery of the original sound localization behavior with only small aftereffects. Recovery is immediate in most cases in mammals (see Wright and Zhang 2006; Kacelnik et al. 2006) but only gradual in owls raised with monaural occlusion (Knudsen 2002). Improvement is often dependent on explicit training (Kumpik et al. 2010; Kacelnik et al. 2006) and has been observed when cues are only altered during testing sessions (see Wright and Zhang 2006).

Visual manipulations such as prism lenses that disrupt the correspondence between auditory and visual space also induce corrective changes in sound localization behavior (Knudsen 2002; Zwiers et al. 2003).

Mechanisms Underlying Changes in Perceptual Ability

Perceptual changes in sound localization have been shown to be associated with a range of different physiological changes that depend on experimental species and circumstances.

In the superior colliculus of the midbrain, there is a multisensory map of space, which plays an important role in orienting responses toward visual and auditory objects. In owls raised with one ear occluded, or with a visual displacement, a rewiring of the projection from the auditory midbrain (the inferior colliculus) occurs that ensures that spatial maps remained well aligned (Knudsen and Brainard 1991; Knudsen 2002). Realignment of space maps is also seen in the superior colliculus of ferrets raised with abnormal visual or auditory cues (King et al. 2000). However, realignment is not complete and alignment nevertheless improves once normal cues are reinstated. This is consistent with the rapid recovery of behavioral performance, as if the “default” map develops regardless. Even visual deprivation during development still results in a largely normal map. However, pinnae and conchae are required for the auditory space map to develop properly.

In purely auditory regions (inferior colliculus in the midbrain, primary auditory cortex), raising animals with a monaural hearing loss tends to result a change in binaural sensitivity in favor of the unaffected ear (see King et al. 2011). This suggests a shift toward monaural cues, rather than “rebalancing” the binaural cues.

Despite the ability of adult mammals to adapt perceptually in response to monaural occlusion, the auditory-visual space map of the midbrain does not realign in adulthood. However, there is considerable evidence that the auditory cortex and descending pathways in the auditory system are involved. Protracted deactivation of the auditory cortex which can affect sound localization often has a more profound effect on the ability to adapt behaviorally to altered localization cues (Nodal et al. 2012). The descending pathways also appear to mediate adaptation in mammals. Lesions to the descending pathway from the auditory cortex to the midbrain (Bajo et al. 2010) or efferent connections (olivocochlear) from the brainstem to the cochlea (Irving et al. 2011) do not affect normal sound localization but impair the

ability to adapt to monaural occlusion. These data are consistent with the idea that auditory spatial plasticity in adulthood reflects a change in the way different cues are used (choosing reliable ones) rather than change in the way any individual cue is computed. Possibly, the effort required to interpret altered cues places a greater reliance on the cortex and descending pathways.

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Sound Localization in Mammals and Models

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Definition

Models of sound localization for mammals describe or simulate the process of how the mammalian auditory system determines the position and/or spatial extent of one or multiple sound sources from cues it extracts from signals captured at the eardrums.

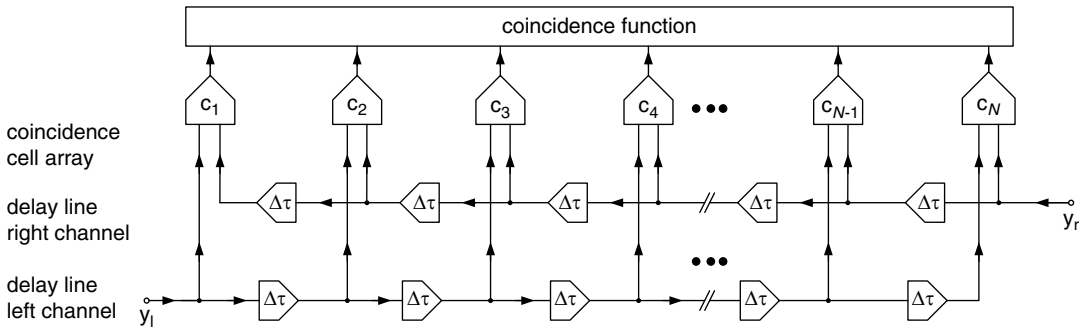
Detailed Description

Historical Overview

The first theories describing how the human auditory system can determine the position of a sound source appeared in the late nineteenth century after W. Thompson (1877), S. P. Thompson (1882), and Steinhauser (1877) discovered that interaural time and level differences occur between both ear signals if a sound source arrives from the side. The focus continued to be on so-called lateralization models, which explain how a sound source is perceived to the left or right based on interaural cues. The first model that describes an actual physiological mechanism of how the central nervous system localizes sound is the Jeffress model, which proposes a combination of delay lines and coincidence detectors to estimate the lateral position of a sound source based on interaural time differences. Within the same time period, better electronic devices enabled psychophysicists to better understand how the auditory system extracts localization cues. Devices like precise sine generators and circuits to produce interaural time and level differences made it possible to measure the performance of the auditory system in greater detail. One milestone was an experiment by Mills

(1958) to demonstrate that the human auditory system cannot lateralize a signal based on the interaural time differences of the left and right signal carriers above 1.5 kHz, correctly assuming that the underlying physiological mechanism can no longer utilize phase locking above this threshold. Other mammals can process interaural time differences (ITDs) of carrier signals at higher frequencies. The gerbil is known to process ITDs up to at least 3.0 kHz (Tolnai et al. 2017). Heffner (2004) and Heffner and Heffner (2018) demonstrated that the highest audible frequency of mammals, measured at 60 dB SPL, negatively correlates with the functional interaural distance, which describes the highest ITD that occurs for this species in their natural habitat (land or water). The functional interaural distance is largely dependent on the species head size, and it is likely that upper frequency threshold for ITD-based phase locking is generally higher for smaller mammals than for larger ones. For frequencies above the phase locking threshold, interaural time differences can be extracted from the signals' envelopes and used by the auditory system – e.g., see Joris and Yin (1995).

Another important factor in the development of localization models was advances in signal processing and communication theory. A milestone was reached when Cherry and Sayers (1956) described a functional localization model using a cross-correlator. In this model, cross-correlation is applied between the left and right ear signals to measure the delay and thus the ITD between both signals. In the late 1970s, computers were powerful enough to develop computational models that predict the lateral position of an auditory event precisely for a given pair of ear signals by simulating the complete pathway from the eardrums to higher stages including band-pass filter banks to mimic the basilar membrane's separation of the signals in bands of approximately a third of an octave wide (auditory bands) and simulating the stochastic processes of hair cells e.g., see Blauert and Cobben (1978). Aside from models simulating the general functionality of the localization process, models exist to simulate the underlying physiological process in greater detail, often simulating the response of a certain cell type



Sound Localization in Mammals and Models, Fig. 1 Coincidence mechanism as first proposed by Jeffress (1948)

measured in electrophysiological animal experiments. The latter are frequently termed pink box models to separate them from the functional black box models. Cai et al. (1998a, b) and Stecker et al. (2005) are good examples of this type of approach.

Understanding the mechanisms of how the auditory system determines the elevation and front/back direction of sound sources was much more difficult than understanding how the auditory system estimates lateral positions due to the complexity of the involved monaural cues. Blauert (1969/1970) was able to demonstrate that auditory systems utilize characteristic, direction-dependent frequency boosts or reductions which occur when the pinnae alter the incoming sound waves. Zakarauskas and Cynader (1993) presented an early localization model based on spectral monaural cues using the second derivative of the frequency spectrum. Later, statistical methods such as a Bayes classifier were used to predict the three-dimensional location of auditory events by analyzing both interaural and monaural cues (e.g., see Hartung 1998 and Nix and Hohmann 2006).

Jeffress Model

The Jeffress model (1948) was the first model to propose a physiological mechanism for mammalian sound localization. The core idea of the Jeffress model is the combination of delay lines and coincidence cells. In this model, two separate delay lines exist for each ear that run parallel. The

signals propagate on each line in opposite direction as shown in Fig. 1. A signal arriving at the left ear, $y_{l(m)}$, with m being the index for time, has to pass the first delay line, $l(m, n)$, from left to right. The variable n is the index for the coincidence detectors at different internal delays. A signal arriving at the right ear, $y_{r(m)}$, travels on the other delay line, $r(m, n)$, in the opposite direction. The discrete implementation of the delay lines can be described as follows:

$$l(m+1, n+1) = l(m, n); 1 \leq n < N \wedge l(m, 1) = y_{l(m)}, \quad (1)$$

$$r(m+1, n-1) = r(m, n); 1 < n \leq N \wedge r(m, N) = y_{r(m)}, \quad (2)$$

with N being the number of implemented coincidence cells. The time, t , and the internal delay, τ , can be easily estimated from the indices, m and n , and the sampling frequency, f_s , as follows: $t = (m-1)/f_s$ and $\tau = (n-(N+1)/2)/f_s$. A coincidence detector, $c(m, n)$, is activated when it receives simultaneous inputs from both delay lines at the positions that it is connected to. Each of the coincidence detectors is adjusted to a different ITD, due to the limited velocity of propagation of the signals on the delay line. For example, a sound source located in the left hemisphere will arrive at the left ear first, and therefore, the signal will travel a greater distance on the delay line than the signal for the right ear before both of them activate the coincidence detector for the corresponding ITD.

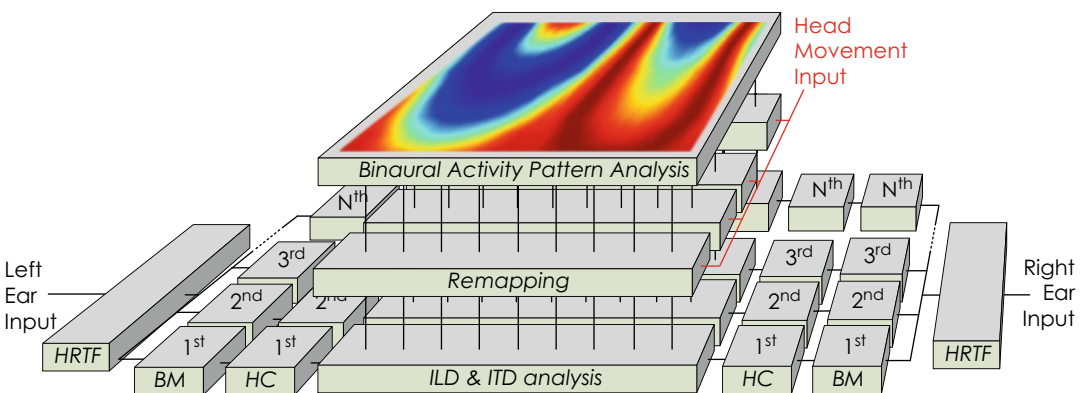
Interaural Cross-Correlation Models

Jeffress himself never specified explicitly how two spikes would coincide. Stern and Colburn (1978) later pointed out that the coincidence model can be considered to be an estimator for the interaural cross-correlation (IACC) function – which had been proposed earlier by Cherry and Sayers (1956) to estimate ITDs. To this end, they assumed that many parallel coincidence detector cells exist which are tuned to the same ITD. Then, the probability that two spikes from two opposite channels will activate a specific coincidence cell is given by the product of the number of spikes in those left and right channels, the interaural delay of which matches the internal delay of the coincidence cell. This product also appears in the running cross-correlation function, which is defined for a discrete system as follows. Note that $l(m', n)$ and $r(m', n)$ have to be determined recursively from Eqs. 1 and 2. The classical continuous form of the running cross-correlation function is

$$\Psi_{y_{lr}}(t, \tau) = \int_{t' = t}^{t + \Delta t} y_l(t' - \tau/2) \cdot y_r(t' + \tau/2) dt',$$

$$\Psi_{y_{lr}}(m, n) = \frac{1}{\Delta m} \sum_{m' = m}^{m + \Delta m} c(m', n) = \frac{1}{\Delta m} \sum_{m' = m}^{m + \Delta m} l(m', n) r(m', n),$$
(3)

with $c(m, n) = l(m, n) r(m, n)$ and the assumption that the amplitudes in the left and right channels are proportional to the number of spikes. In Eq. 3, a rectangular window of the length, Δm , was chosen, within which the cross-correlation function for each time interval is calculated. Often other window shapes, e.g., Hanning window, triangular window, and exponential window, are used. The duration of the time window, $\Delta t = \Delta m / f_s$, can be determined in psychoacoustical experiments measuring binaural sluggishness. Values come out to be on the order of tens to hundreds of milliseconds depending on the listener and measurement method (Grantham and Wightman 1978, 1979; Grantham 1982, 1979; Kollmeier and Gilkey 1990). Sayers and Cherry (1957) used the interaural cross-correlation (IACC) to determine the ITDs, and in 1978, a computational lateralization model based on IACC and the simulation of the auditory periphery was introduced independently in Blauert and Cobben (1978) and Stern and Colburn (1978). The general structure of a common cross-correlation model is shown in Fig. 2. Besides the common cross-correlation function, there are alternative ways to implement the coincidence detectors. Figure 3 shows the results of different implementations, namely, the interaural cross-correlation functions of two



Sound Localization in Mammals and Models, Fig. 2 General model structure of a binaural localization model utilizing head rotations according to Braasch et al. (2013). *HRTF* outer-ear simulation/HRTF filtering, *BM* basilar membrane/band-pass filtering, *HC* hair-cell/half-wave rectification, *ITD* and *ILD analysis* interaural time

difference (ITD) cue extraction/interaural cross-correlation, and interaural level difference (ILD) cue analysis with EI cells; remapping to azimuth angles with head-rotation compensation; binaural activity pattern analysis to estimate the sound-source positions

1-kHz sinusoidal tones with ITDs of 0 and 0.5 ms are depicted. In contrast to the models reported in Blauert and Cobben (1978) and Stern and Colburn (1978), Wolf (1991) assumed that two spikes from opposite channels would always coincide when they pass by each other on the delay lines. In this case, the output of the coincidence function is not the product of the amplitudes in the left and right channel for each delay time, but rather the minimum of those two amplitudes. The signal amplitude, then, correlates with the number of spikes within the time interval of Δt as follows:

$$c_d(m, n) = \min [l(m, n), r(m, n)]. \quad (4)$$

The output characteristics of this algorithm, Fig. 3b, are quite similar to the output characteristics of the cross-correlation algorithm, with the exception that the peaks are slightly narrower at the top. In his original work, Wolf further assumed that two spikes would be canceled out after they coincide. This approach, however, is very sensitive to interaural level differences, and, thus, the

signals in the left and right channels have to be compressed in amplitude beforehand. For this reason, Wolf used a hair-cell model (Duifhuis 1972) to transform the signal level code into a rate code.

The output of Wolf's algorithm is shown in Fig. 3c. In contrast to the cross-correlation algorithm, the peaks are very narrow, and the side peaks have vanished. Lindemann achieved a similar effect a few years earlier by introducing contralateral inhibition elements into his model. The implementation of the inhibition elements is achieved by modifying the computation of the delay lines from Eqs. 1 and 2 to

$$l(m+1, n+1) = l(m, n)[1 - c_s \cdot r(m, n)]; \quad (5)$$

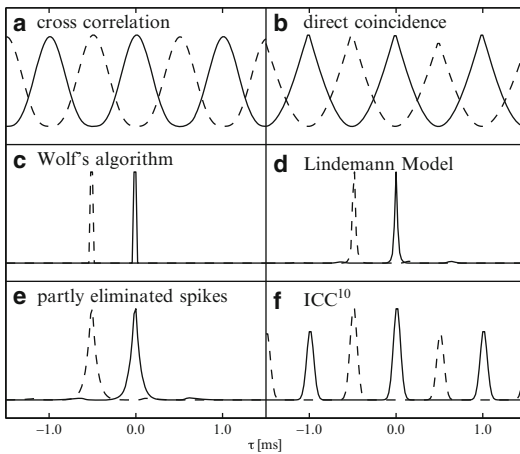
$$0 \leq l(m, n) < 1,$$

$$r(m+1, n-1) = r(m, n)[1 - c_s \cdot l(m, n)];$$

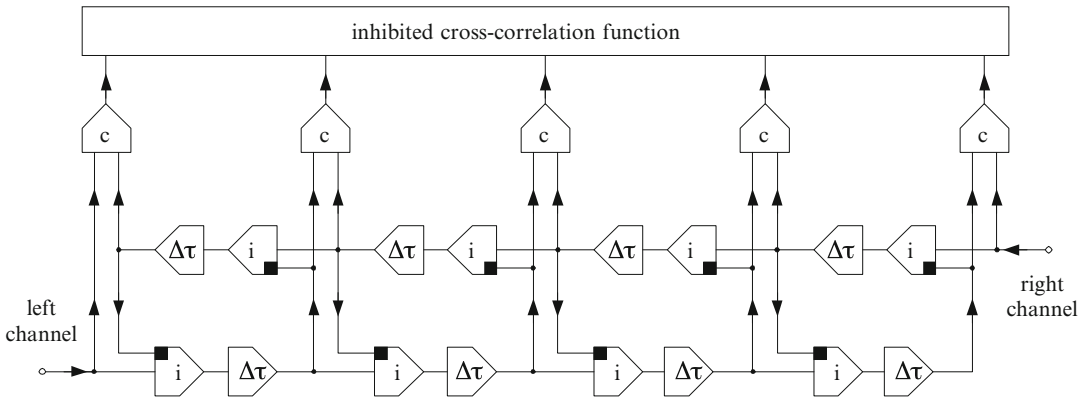
$$0 \leq r(m, n) < 1, \quad (6)$$

with c_s being the static inhibition constant, $0 \leq c_s < 1$. Now the signals in both delay lines inhibit each other before they meet and reduce the amplitude of the signal in the opposite channel at the corresponding delay unit as can be seen in Fig. 4. The side peaks that are found in the plain cross-correlation algorithm in Fig. 3a are eliminated in this way. Wolf's algorithm becomes more similar to Lindemann's algorithm, if only a certain percentage of the spikes is canceled in Fig. 3e. In this case, it is not even necessary to use a probabilistic hair-cell model. If only a smaller amount of the spikes is eliminated, there is, qualitatively spoken, only a little difference in whether the spikes are inhibited/canceled before or after they coincide. It should be noted that the outcome of these inhibitory algorithms is dependent on the ILDs.

In the simulation of binaural hearing, it is sometimes advantageous to reduce the peak widths of the cross-correlation curves when determining the position of the peak. Besides employing an inhibition stage, a peak reduction can be achieved by taking the signal to a power greater than one. Figure 3f shows this procedure



Sound Localization in Mammals and Models, Fig. 3 Examples for the outputs of different coincidence detectors for a 500-Hz sinusoidal signal (a) Cross-correlation algorithm; (b) direct coincidence algorithm, spikes always interact when passing each other; (c) Wolf's algorithm; (d) Lindemann's algorithm; (e) coincidence algorithm with partly eliminated spikes after coincidence; and (f) cross-correlation algorithm taken to the power of 10 (solid lines, 0-ms ITD; dashed lines, 0.5-ms ITD)



Sound Localization in Mammals and Models, Fig. 4 Structure of the Lindemann algorithm

for the power of 10. However, by this approach, the side peaks are hardly reduced. When using the cross-correlation algorithm, not only the position of the cross-correlation peak but also its normalized height – the so-called interaural cross-correlation (IACC) coefficient or interaural coherence (IC) – can be used to gain information about the spaciousness of the environment, e.g., a room. It can be determined by taking the maximum of the normalized cross-correlation function,

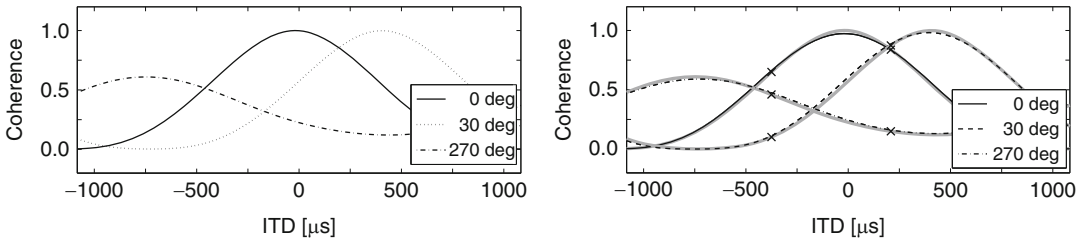
$$\Psi_{y_l, r}(\tau) = \frac{\int_{t=-\infty}^{+\infty} y_l(t) \cdot y_r(t + \tau) dt}{\sqrt{\int_{t=-\infty}^{+\infty} y_l^2(t) dt \cdot \int_{t=-\infty}^{+\infty} y_r^2(t) dt}}, \quad (7)$$

with the internal delay, τ , and the left and right sound pressure signals, $y_l(t)$ and $y_r(t)$. The left panel of Fig. 5 shows an example of an IACC function of a broadband noise signal for three different positions for a frequency band centered at 434 Hz. The peak of the solid cross-correlation function is located at 0 μ s which corresponds to the position at 0°. The peak of the dashed IACC function is located at 400 μ s, which indicates an azimuth of 30°. The height of the peak depicts the coherence, that is, the degree to which both signals are similar when shifted by the corresponding internal delay, τ . In both cases, the signal is fully correlated. In the third example, depicted by a dash-dotted line, the signal is

partly decorrelated as indicated by the lower peak height of 0.6. The peak location at –600 μ s belongs to an azimuth angle of 270°. The cross-correlation coefficient correlates strongly with “spaciousness” – or auditory source width – a psychoacoustical measure for the spatial extent of auditory events and an important parameter for room acousticians (Blauert and Lindemann 1986; Okano et al. 1998). Spaciousness decreases with an increasing correlation coefficient and, therefore, with the height of the cross-correlation peak (Fig. 5).

Two-Channel ITD Models

A few years ago, the Jeffress model and with it the cross-correlation approach were challenged by physiological studies on gerbils and guinea pigs. McAlpine and Grothe (2003) and others (Grothe et al. 2010; McAlpine 2005; McAlpine et al. 2001; Pecka et al. 2008) have shown that the ITD cells for these species are not tuned evenly across the whole physiologically relevant range, but heavily concentrate on two phases of $\pm 45^\circ$. Consequently, their absolute best-ITD values vary with the center frequency that the cells are tuned to. Dietz et al. (2011, 2008) and Pulkki and Hirvonen (2009) developed lateralization models that draw from McAlpine and Grothe’s (2003) findings. It is still under dispute whether the Jeffress delay-line model or the two-channel



Sound Localization in Mammals and Models, Fig. 5 *Left:* Interaural cross-correlation functions for a sound source at three different positions in the horizontal plane. The sound sources at 0° and 30° azimuth are fully correlated; the sound source at 90° is partly decorrelated. *Right:* Interaural cross-correlation functions for a sound source at three different positions in the horizontal plane. The same stimuli as in the left panel are used, but this time, a two-channel model was applied with delay lines for $\pm 45^\circ$. The actually measured values, x_- for the

-45° -phase condition and x_+ for the $+45^\circ$ -phase condition, are shown by the “x” symbols. The simulated IACC curves were compensated for half-wave rectification. The gray curves show the actual IACC curves from the left panel. The normalized cross-correlation curves were estimated using standard trigonometric sine-cosine relationships for magnitude $A = \sqrt{x_-^2 + x_+^2}$ and phase $\phi = \arctan(x_- / x_+)$

model correctly represents the human auditory system, since the human ITD mechanism cannot be studied directly on a neural basis. However, the human auditory system evolved from smaller mammals, and for these, current theories are trending toward two-channel models (Leibold and Grothe 2015). A recent magnetoencephalography (MEG) study confirmed that the cortical representation of ITDs in the human auditory system is very similar to the cortical ITD representation in other mammals (Salminen et al. 2018). For other species, such as owls, a mechanism similar to the one proposed by Jeffress has been confirmed by Carr and Konishi (1990), but it needs to be considered that the mammalian auditory system evolved independently from those of birds and reptiles (Grothe and Pecka 2014). Opponents of the two-channel theory point out that the cross-correlation model has been tested much more rigorously than other ones and is able to predict human performance in great detail (Bernstein and Trahiotis 2002). From a practical standpoint, the result for both approaches is not as different as one might think. For the lower frequency bands, the cross-correlation functions always have a sinusoidal shape, due to the narrow width of the auditory bands – see the right panel of Fig. 5. Consequently, the whole cross-correlation function is more or less defined by two phase values 90° apart.

Models Utilizing Interaural Level Differences

Interaural level differences are the second major localization cue. They occur because of shadowing effects of the head, especially when a sound arrives sideways. For humans ILDs typically reach values of up to ± 30 dB at frequencies around 5 kHz and azimuth angles of $\pm 60^\circ$. At low frequencies, the shadowing effect of the head is not very effective, and ILDs hardly occur, unless the sound sources come very close to the ear canal entrance (Blauert 1997; Brungart and Rabinowitz 1999). This led Lord Rayleigh (1907) to postulate his *duplex theory*, which states that ILDs are the primary localization cue for high frequencies and ITDs for low frequencies. In the latter case, Lord Rayleigh assumed that unequivocal solutions for the ITDs can no longer exist for high frequencies. Then, the wavelength of the incoming sound is much shorter than the width of the head, which determines the physiological range for ITDs of approximately ± 800 μs. Mills (1958) later supported the duplex theory by demonstrating that the auditory system can no longer detect ITDs from the fine structure of signals above 1500 Hz. This effect results from the inability of the human auditory system to phase lock the firing patterns of auditory cells with the waveform of the signal at these frequencies. Meanwhile, however,

it has been shown that the auditory system can extract ITDs at high frequencies from the signals' envelopes (Joris 1996; Joris and Yin 1995), and the original duplex theory had to be revised accordingly. ILDs, denoted as α , can be computed directly from the left and right ear signals – which is typically done for individual frequency bands:

$$\alpha = 10 \log_{10} (P_l) - 10 \log_{10} (P_r), \quad (8)$$

with P_l the power of the left and P_r the power of the right signal. Reed and Blum (1990) introduced a physiologically motivated algorithm to compute ILDs based on the activity, $E(\alpha)$, of an array of excitation/inhibition (EI) cells:

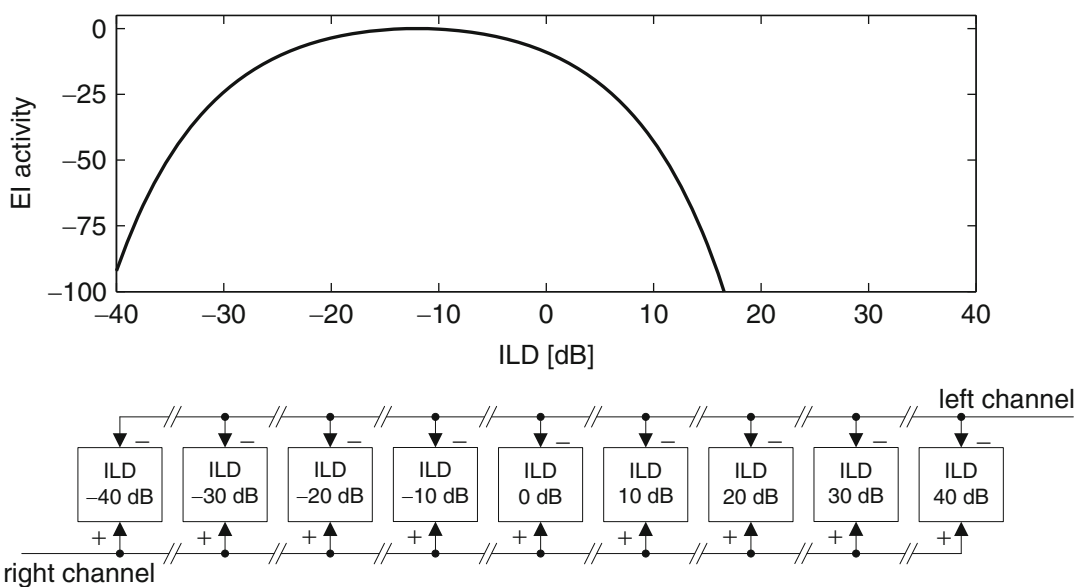
$$E(\alpha) = \exp \left[\left(10^{\alpha/ILD_{\max}} \sqrt{P_l} - 10^{-\alpha/ILD_{\max}} \sqrt{P_r} \right)^2 \right], \quad (9)$$

with P_l and P_r being the power in the left and right channels, respectively, and $ILD_{\max}$ the maximal ILD magnitude that the cells are tuned to. Each cell is tuned to a different ILD. Figure 6 shows an example for a sound with an ILD of -12 dB. The curve depicts how the response of each cell is

reduced the further the applied ILD is away from the value the cell is tuned to.

Lateralization Models

Many models have been established to predict the perceived left/right lateralization of a sound which is presented to a listener through headphones with an ITD or an ILD or both. Usually, those sounds are perceived inside the head on the interaural axis with a distance from the center of the head. This distance, the so-called lateralization, is usually measured on an interval or ratio scale. The simplest implementation of a decision device is to correlate the perceived lateralization with the estimated value of a single cue, e.g., the position of the cross-correlation peak in one frequency band. This is possible, because the laterality, the perceived lateral position, is often found to be nearly proportional to the value of the analyzed cue. The decision device has to be more complex if different cues are to be analyzed or if one cue under consideration is observed in different frequency bands. A very early model that integrates information from different cues, ITDs and ILDs, is the



Sound Localization in Mammals and Models, Fig. 6 Bottom: EI-cell structure. Top: Output of the EI cells for a signal with an ILD of -12 dB

position-variable model of Stern and Colburn (1978). The authors were able to predict the perceived lateralization for a 500-Hz sinusoidal tone for all combinations of ITDs and ILDs. The left panels of Fig. 7 show the results of the position-variable model for three different combinations of ITDs and ILDs. The ITDs are measured using the cross-correlation algorithm of Fig. 7a. Afterward, the cross-correlation curve is multiplied by a delay-weighting function in order to enhance the output for small ITDs; see Fig. 7b. This is done to take into consideration that the number of neural fibers which are tuned to small ITDs is higher than those tuned to large ITDs. The delay-weighting function (Colburn 1977) is shown in Fig. 8, left panel, dotted curve. The influence of the ILDs is represented in a second function of Gaussian shape and constant width of 1778 μs , as depicted in Fig. 7c. The peak position of this second weighting is varied with the ILD of the signal. For this purpose, the signal's ILD, α , is calculated according to Eq. 8 and transferred into a corresponding ITD, τ , using a function which

can be derived from psychoacoustical data as follows:

$$\tau = 0.1\alpha - 3.5 \cdot 10^{-5} \alpha^3 [\text{ms}]. \quad (10)$$

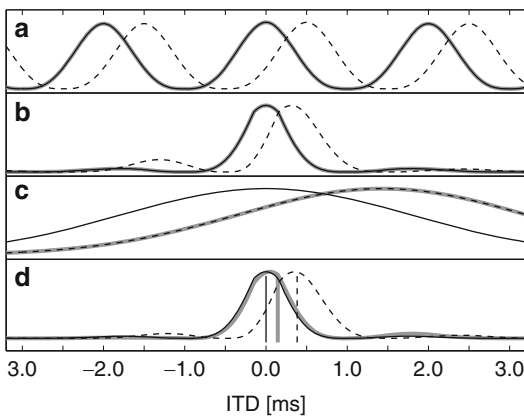
Finally, this function is multiplied with the weighted cross-correlation function from Fig. 7b, and the centroid of the resulting function correlates with the perceived lateralization (Fig. 7d).

Localization in the Horizontal Plane

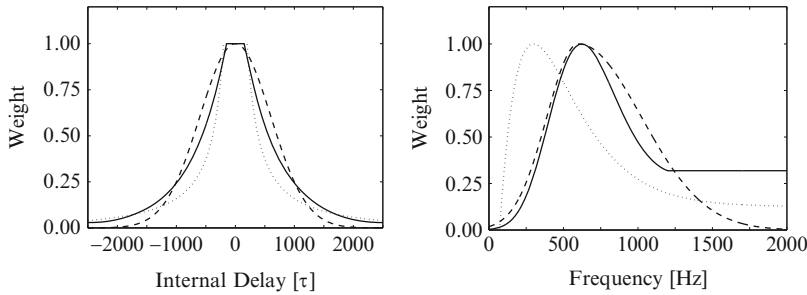
Several methods to calculate sound-source positions from the extracted binaural cues exist. One method of achieving this is to create a database to convert measured binaural cues, namely, ITDs and ILDs, into spherical coordinates. Such a database or map can be derived from a measured catalog of *head-related transfer functions* (HRTFs) of a large number of sound-source directions. Here, the binaural cues are calculated frequency-wise from the left- and right-ear HRTFs of each position. Using this database, the measured binaural cues of a sound source with unknown positions can be mapped to spherical angles. The application of the remapping method to localize a signal in the horizontal plane is discussed in detail in Braasch et al. (2013). Figure 9 shows the results of remapped cross-correlation functions and ILD-based EI cell-array functions for different frequency bands. The results were obtained using a click source signal convolved with HRTFs from a human catalog at 0° elevation.

An ongoing challenge has been to figure out how the auditory system combines the individual cues to determine the location of auditory events – in particular to answer how the auditory system performs tasks to (i) combine different cue types, such as ILDs and ITDs, (ii) integrate information over time, (iii) integrate information over frequency, (iv) discriminate between concurrent sources, and (v) deal with room reflections.

A number of detailed overviews (Stern and Trahiotis 1995; Stern et al. 2006; Braasch 2005) have been written on cue weighting, and only a

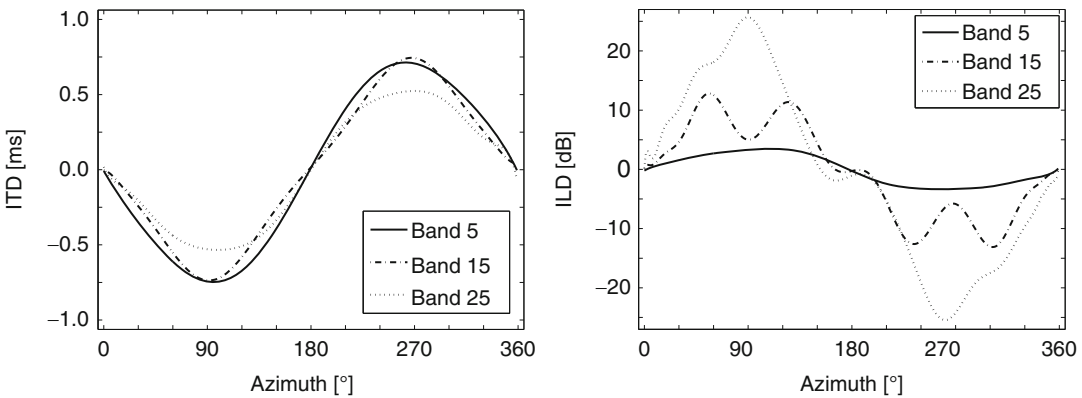


Sound Localization in Mammals and Models, Fig. 7 Results for the position-variable model (Stern and Colburn 1978) for a 500-Hz sinusoidal signal with different combinations of ITD and ILD, namely, 0 ms/0 dB (black solid line), 0 ms/15 dB (gray solid line), and 0.5 ms/15 dB (black dashed line): weighted function of (a) interaural cross-correlation functions, (b) delay-line (a) to emphasize small ITD values, (c) ILD functions, and (d) combined ITD and ILD analysis by multiplying (b) with (c) and calculating the centroid as represented by the vertical lines



Sound Localization in Mammals and Models, Fig. 8 Delay weighting (left panel): Colburn (1977), dotted line; Shackleton et al. (1992), solid line; and Stern and Shear

(1996), dashed line. Frequency weighting (right panel): Raatgever (1980), dotted line; Stern et al. (1988), solid line; and Akeroyd and Summerfield (1999), dashed line

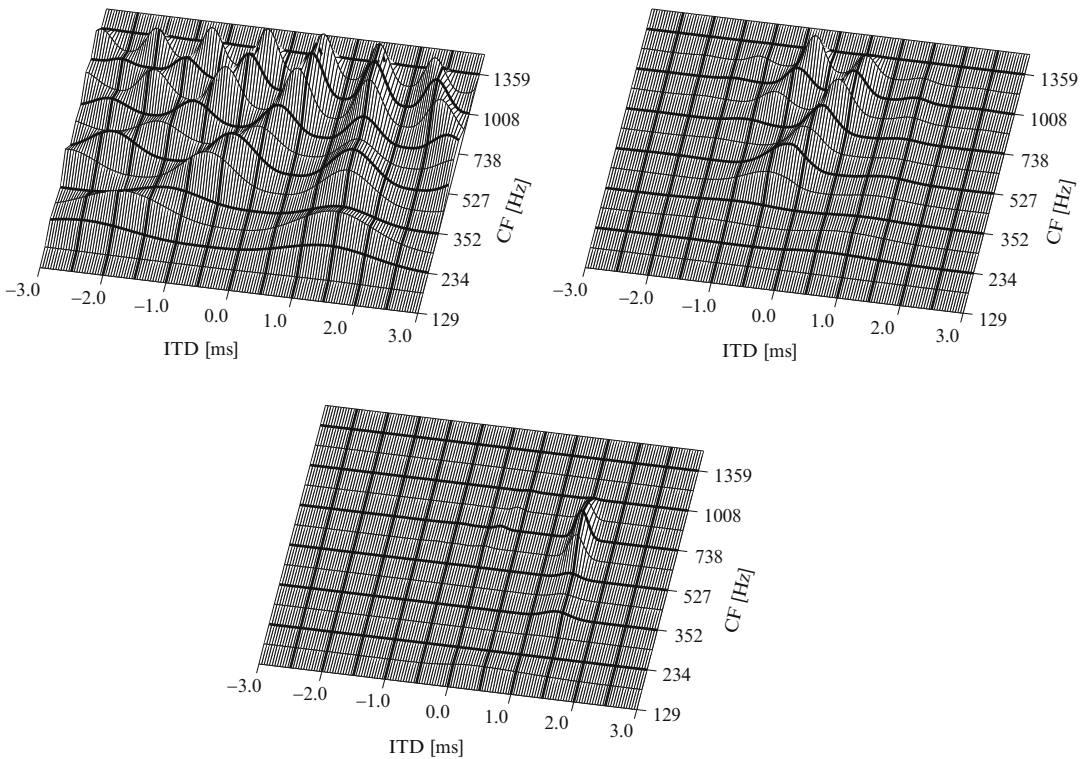


Sound Localization in Mammals and Models, Fig. 9 Left: Interaural time differences. Right: Interaural level differences. Plotted for different frequency bands:

Band 5, $f_c = 234$ Hz (solid line); Band 15, $f_c = 1359$ Hz (dashed line); and Band 25, $f_c = 5238$ Hz (dotted line)

brief introduction will be given here. One big question is how the auditory system weights cues temporally. The two opposing views are that the auditory system primarily focuses on the onset part of the signal versus the belief that the auditory system integrates information over a longer signal duration. Researchers have worked with conflicting cues – such as trade-off between early onset and later ongoing cues – and it is generally agreed upon that the early cues carry a heavier weight (Freyman et al. 1997; Hafter 1997; Zurek 1993). This phenomenon can be simulated with a temporal weighting function. More recently it was suggested that the auditory system does not simply blindly combine these cues but also evaluates the robustness of these cues and discounts unreliable cues. A good example for this approach is a model by Faller and Merimaa

(2004). In their model not only the positions of the cross-correlation peaks are calculated to determine the ITDs but also the coherence – as, for example, determined by the maximum value of the interaural cross-correlation function. Coherent time-frequency segments are considered to be more salient and weighted higher assuming that concurrent sound sources and wall reflections that can produce unreliable cues decorrelate the signal and thus show low coherence. Frequency weighting also applies and, in fact, the duplex theory can be seen as an early model where ITD cues are weighted high at low frequencies, and ILD cues dominate at higher frequencies. Newer models have provided a more detailed view of how ITDs are weighted over frequency. Different curves have been obtained for different sound stimuli (Akeroyd and Summerfield 1999;



Sound Localization in Mammals and Models, Fig. 10 Output of Stern et al.'s model (Stern et al. 1988) to a band-pass noise, 700-Hz center frequency, 1000-Hz bandwidth, 1.5-ms ITD. The *top-left panel* shows the

output without centrality and straightness weighting, the *top-right panel* with centrality weighting only, and the *bottom panel* with centrality and straightness weighting

Raatgever 1980) including straightness and centrality weighting (Stern et al. 1988, see Fig. 10).

Localization Models Using Monaural Cues

A model proposed in 1969–1970 (Blauert 1969/1970) analyzes monaural cues in the median plane as follows. The powers in different frequency bands, the directional bands, are analyzed and compared to each other. Based on the signal's angle of incidence (front, above, or back), the pinnae enhance or deemphasize the power in certain frequency regions, which are the primary localization cues for sound sources within the median plane. Building on this knowledge, Blauert's model uses a comparator to correctly

predict the direction of the auditory event for narrowband signals. Zakarauskas and Cynader (1993) developed an extended model for monaural localization, which is based on the assumption that the slope of a typical sound source's own frequency spectrum only changes gradually with frequency, while the pinnae-induced spectral changes vary more with frequency. The model primarily uses the second-order derivative of the spectrum in frequency to determine the elevation of the sound source – assuming that the sound source itself has a locally constant frequency slope. In this case, an internal, memorized representation of a sound source's characteristic spectrum becomes obsolete. Baumgartner et al. (2013) created a probabilistic localization model that analyzes inter-spectral differences (ISDs) between the internal representations of a perceived sound

and templates calculated for various angles. The model also includes listener-specific calibrations to 17 individual listeners. It had been shown earlier that, for some cases, ISDs can be a better predictor for human localization performance than the second-order derivative of the spectrum (Langendijk and Bronkhorst 2002). By finding the best ISD match between the analyzed sound and the templates, Baumgartner et al.'s model is able to demonstrate similar localization performance as human listeners.

In contrast to models which do not require a reference spectrum of a sound source before it is altered on the pathway from the source to the ear, it is sometimes assumed that listeners use internal representations of a variety of everyday sounds to which the ear signals are compared to in order to estimate the monaural cues. A database with the internal representations of a high number of common sounds has not been implemented in monaural model algorithms so far. Some models exist, however, that use an internal representation of a single reference sound, e.g., for broadband noise (Hartung 1998) and for click trains (Janko et al. 1997).

Three-Dimensional Localization Models

In free field, the signals are filtered by the outer ears, and the auditory events are, thus, usually perceived as externalized in three-dimensional space. One approach to estimate the position of a sound source is to train a neural network to estimate the auditory event from the interaural cues rather than to combine the cues analytically, e.g., Hartung (1998); Janko et al. (1997); Ma et al. (2017); Xu et al. (2019). When applying such a method, the neuronal network has to be trained on test material. The advantage of this procedure is that often very good results are achieved for stimuli that are very similar to the test material. The disadvantages are, however, the long time necessary to train the neural network and that the involved processing cannot easily be described analytically.

The frequency-dependent relationship between binaural cues and the azimuth and

elevation angles can be determined from a catalog of HRTFs which contains the HRTFs for several angles. Spatial maps of these relationships can be set up, using one map per analyzed frequency band. It should be noted at this point that, although neurons that are spatially tuned were found in the inferior colliculus of guinea pigs (Hartung 1998) and in the primary field of the auditory area of the cortex of cats (Middlebrooks and Pettigrew 1981; Imig et al. 1990), a topographical organization of those types of neurons could not be shown yet.

Those types of localization models that analyze both ITDs and ILDs either process both cues in a combined algorithm (e.g., Stern and Colburn 1978) or evaluate both cues separately and combine the results afterward, in order to estimate the position of the sound source (e.g., Janko et al. 1997; Nix and Hohmann 2000, 2006; Hartung 1998). In Janko et al. (1997), it is demonstrated that, for filtered clicks, both the ITDs and ILDs contribute very reliable cues in the left–right dimension, while in the front–back and the up–down dimensions, ILDs are more reliable than ITDs. The findings are based on model simulations using a model that includes a neural network. The network was trained with a back-propagation algorithm on 144 different sound-source positions in the whole sphere, the positions being simulated using HRTFs. The authors could feed the neural network with either ITD cues, ILD cues, or both. Monaural cues could also be processed.

Precedence Effect Models

Dealing with room reflections remains to be one of the biggest challenges in communication acoustics across a large variety of tasks including sound localization, sound-source separation, as well as speech and other sound feature recognition. Typically, models use a simplified room impulse response, often only consisting of a direct sound and a single discrete reflection to simulate the precedence effect. Lindemann (1986a, b) took the following approach to the inhibition of location cues coming from reverberant information. Whenever his contralateral inhibition algorithm

detects a signal at a specific interaural time difference, the mechanism starts to suppress information at all other internal delays or ITDs and thus solely focuses on the direct source signal component. The Lindemann model relies on onset cues to be able to inhibit reflections, but fairly recently, Dizon and Colburn (2006) have shown that the onset of a mixture of an ongoing direct sound and its reflection can be truncated without affecting the precedence effect.

Based on their observation that human test participants can localize the on- and offset-truncated direct sound correctly in the presence of a reflection, Braasch and Blauert (2011) and Braasch (2013) proposed an autocorrelation-based approach. The model reduces the influence of the early specular reflections by autocorrelating the left and right ear signals. Separate autocorrelation functions for the left and right channels determine the delay times between the direct sound source and the reflection in addition to their amplitude ratios. These parameters are then used to steer adaptive deconvolution filters to eliminate each reflection separately. It is known from research on the *apparent source width* of auditory objects that our central nervous system is able to extract information about early reflections (Barron and Marshall 1981), which supports this approach. The model is able to simulate the experiments from Dizon and Colburn's (2006) study, and the revised model is able to predict the lateral positions and delays of early reflections from a running signal (Braasch 2016).

Further, it has been shown that for short test impulses such as clicks, localization dominance can be simulated using a simple cross-correlation algorithm without inhibition stages when a hair-cell model is included in the preprocessing stage (Hartung and Trahiotis 2001). To this end, an adaptive hair-cell model (Meddis et al. 1990) was employed. Parts of the precedence effect are, thus, understood as results of sluggish processing in the auditory periphery. Further models to simulate the adaptive response of the auditory system to click trains, "buildup of the precedence effect," can be found in Zurek (1987) and Djelani (2001).

Localization in Multiple-Sound-Source Scenarios

In general, physiologically motivated computational localization models have difficulties to localize two or more independent sound sources. A number of binaural localization models exist that are specialized to localize a test sound in the presence of distracting sound sources, but these models typically follow more traditional signal processing methods and do not represent the neural mechanism with the same details some of the previously mentioned models do. In one class of models, termed "cocktail-party processors," the information on the location of the sound sources is used to segregate them from each other (e.g., Bodden 1992; Lehn 2000). These algorithms can be used to improve the performance of speech recognition systems (Rateitschek 2000). For further improvement of binaural models, it has been proposed to implement an expert system, which completes the common signal-driven, bottom-up approach (Blauert 1999). The expert system should include explicit knowledge on the auditory scene and on the signals – and their history. This knowledge is to be used to set up hypotheses and to decide if they prove to be true or not. As an example, front-back differentiation can be named. The expert system could actively test whether the hypothesis that the sound source is presented in the front is true or false, by employing "auditory scene analysis (ASA)" cues. It could further analyze the monaural spectrum of the sound source in order to estimate the influence of the room in which the sound source is presented, determine the interaural cues, and even evaluate cues from other modalities, for example, visual cues. The expert system would evaluate the reliability of the cues and weight them according to the outcome of the evaluation. In the future, once the computational power increases furthermore and more knowledge on the auditory system is gained, one can expect that binaural models will become more complex and include the simulation of several binaural phenomena rather than the simulation of only a few specific effects.

Matters become more complicated if it is not clear how many sound sources currently exist.

Then the cues do not only have to be weighted properly but also assigned to the corresponding source. Here one can either take a target + background approach (Nix and Hohmann 2006), where only the target sound parameters are quantified and everything else is treated as noise, or one can attempt to determine the positions of all sound sources involved (Braasch 2002, 2003; Roman and Wang 2008; Deshpande and Braasch 2016; Mi et al. 2016; Zhang and Wang 2017). Often, in models that segregate the individual sounds from a mixture, the positions of the sources are known a priori, such as in Bodden (1993) and Roman et al. (2006).

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Sound Source Identification

► Acoustic Timbre Recognition

Sound Source Separation

► Auditory Perceptual Organization

Space (Length) Constant, Lambda, in Neuronal Signaling

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Definition

The space (length) constant λ with $\lambda = (R_m d / (4R_a))^{1/2}$ is a measure of steady-state voltage decay with distance in a cell. Quantitatively λ is the distance over which the steady-state voltage decays to $1/e$ or 37% of its value at the origin in a semi-infinite cable.

Detailed Description

As given in the definition above, the space constant λ with $\lambda = (R_m d / (4R_a))^{1/2}$ is a measure of steady-state voltage decay in a cell. Quantitatively λ is the distance (usually expressed in cm or μm) over which the steady-state voltage decays to $1/e$ or 37% of its value at the origin in a semi-infinite cable. This can be seen by solving the steady-state cable equation (Rall 1977)

$$\lambda^2 d^2 V / dx^2 - V = 0$$

with boundary conditions of voltage clamp to V_0 at the origin and voltage bounded at $x = \infty$ to get

$$V(x) = V_0 \exp(-x/\lambda)$$

The above equation is useful to describe voltage displacements from rest. A more general solution for voltage decay with distance that includes resting potential explicitly is

$$V(x) = V_{\text{rest}} - (V_{\text{rest}} - V_0) \exp(-x/\lambda)$$

where now V_0 is actual voltage instead of a difference from rest.

The importance of λ is that it determines how spatially separated inputs are integrated (spatial summation). If λ is small, then spatially separated inputs are unlikely to sum because voltage will decay significantly over the distance between the inputs, but if λ is large, inputs will not decay as much with distance allowing summation to occur. Given the formula for λ , spatial summation is more likely to occur when diameter or membrane resistivity is large or axial resistivity is small.

One must be careful not to equate quantitatively the steady-state voltage decrement with distance for the semi-infinite cylinder with voltage decay in finite cylinders. For finite cylinders steady-state voltage decay with distance will depend strongly on both the boundary conditions and the length of the cylinders (see entry ► “Cable Equation”), and for transient inputs voltage decay with distance will be very different. Conductance changes associated with transient inputs may make λ variable in time; depending on the level of background synaptic activity, λ may be large at one moment and small at another causing effective spatial integration to vary widely.

The definition of λ given above is for the special case where extracellular voltage is assumed to be isopotential. In the derivation of the cable equation, a generalized λ is defined as

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}}$$

where r_m is membrane resistance of a unit length of membrane in Ωcm and r_i and r_e are the intracellular and extracellular resistances per unit length in Ω/cm . In single cell models, it is usually appropriate to neglect r_e unless ephaptic interactions are a concern. If we neglect r_e then

$$\lambda = \sqrt{\frac{r_m}{r_i}} \text{ or in terms of specific resistivities}$$

$$\lambda = \sqrt{\frac{R_m d}{4R_a}}$$

Setting r_c to 0 in the above expression for λ leads to another insight when the equation is expressed as $\lambda r_i = r_m/\lambda$. What this equation says is that λ corresponds to the length of the core conductor for which the core resistance (λr_i) equals the resistance (r_m/λ) across the membrane.

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Sparse Coding of Natural Images

► [Independent Component Analysis of Images](#)

Spatial Modeling

► [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Spatial Spectral Analysis

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Definition

Spatial spectral methods are extensions of the well-known Fourier transform in time into the spatial domain. Whereas the basis functions for the Fourier transform are sine and cosine or complex exponentials, the bases used in space often reflect a symmetry of the problem. Common basis sets are plane waves (Cartesian space), Bessel

functions (circular and cylindrical symmetry), and spherical harmonics (sphere). Moreover, basis vectors can be derived from the dataset under consideration that are optimal with respect to certain criteria like mean squared error.

Detailed Description

Spectral methods are best known from the Fourier transform that decomposes a time series into its frequency components. Spectral methods in space are applied to datasets that are recorded at different locations in space like EEG (electroencephalography is recorded with up to several hundred electrodes attached to different locations on the scalp surface), MEG (magnetoencephalography measures the magnetic field created by electric currents inside the brain at the locations of sensors surrounding the head), or even fMRI (functional magnetic resonance imaging, where brain activity is measured at locations inside a 3-dimensional volume).

In general, a spatial pattern that evolves in time is decomposed into a set of functions that depend only on space and corresponding time series representing their amplitudes. To be specific, one can think of an EEG experiment where the electric potential at the scalp surface is recorded at N different locations. Such a dataset can be written as a vector $\mathbf{H}(t)$, where component $H_i(t)$ is the time series from electrode i . On the other hand, for a given time point t , the N components of $\mathbf{H}$ represent a discrete spatial pattern of activity on the scalp surface. If N is sufficiently large, the potential can be described as a continuous function of space and time $H(x, t)$. For the spatially discrete and continuous cases, the decompositions read

$$\begin{aligned}\mathbf{H}(t) &= \sum_{i=1}^M \xi_i(t) \mathbf{v}^{(i)} H(x, t) \\ &= \sum_{i=1}^M \eta_i(t) g^{(i)}(x)\end{aligned}\quad (1)$$

where $\xi_i(t)$ and $\eta_i(t)$ are the time-dependent amplitudes that correspond to the pattern vectors and functions $\mathbf{v}^{(i)}$ and $g^{(i)}(x)$, respectively.

One application of such decompositions is the reduction of the size of the dataset, i.e., the sums are truncated at a value $M \ll N$. How well such a truncated decomposition represents the original data obviously depends on the choice of the basis vectors $\mathbf{v}^{(i)}$ or basis functions $g^{(i)}(x)$.

One of the most popular function sets to describe scalp potentials is the spherical harmonics (Nunez and Srinivasan 2006) given by

$$Y_l^m(\theta, \phi) = \sqrt{\frac{(2l+1)}{4\pi} \frac{(l-m)!}{(l+m)!}} P_l^m(\cos \theta) e^{im\phi} \quad (2)$$

where θ and ϕ are the polar and azimuthal angle, respectively, and P_l^m are the associate Legendre polynomials of degree l and order m . The spherical harmonics are orthogonal and normalized such that

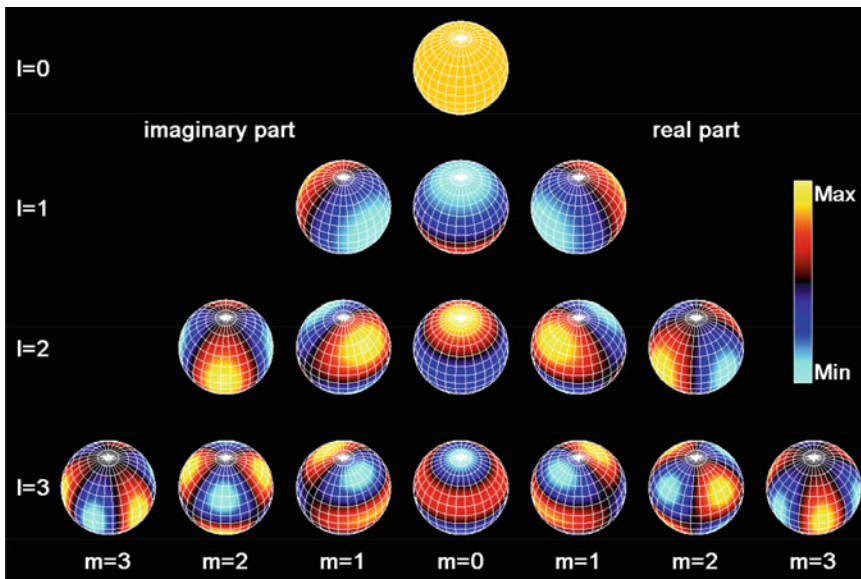
$$\int_0^{2\pi} d\phi \int_0^\pi \sin \theta d\theta Y_l^{m'}(\theta, \phi) Y_l^m(\theta, \phi) = \delta_{ll'} \delta_{mm'} \quad (3)$$

where the asterisk “*” denotes the complex conjugate and δ represents the Kronecker delta.

The spatial patterns on the sphere for $l = 0 \dots 3$ and $m = 0 \dots 3$ are shown in Fig. 1 with the real and imaginary parts of the complex-valued functions on the right and left. The value for m is the number of minima and maxima in the azimuthal direction and Y_0^0 is a constant with a value of $1/4\pi$.

The spherical harmonics in space are closely related to the Fourier series in time as both are the eigenfunctions to an operator (The eigenfunctions of an operator are similar to the eigenvectors of a matrix. The application of a matrix to one of its eigenvectors simply scales the vector and nothing else, $M\mathbf{v} = \lambda\mathbf{v}$, where λ is a scalar, the eigenvalue. In the same way, an operator applied to one of its eigenfunctions results in the same function times a scalar $Of(x) = \lambda f(x)$.) that takes a second derivative. For the Fourier series in sine and cosine or complex exponentials, this takes the form

$$\begin{aligned} \frac{d^2}{dt^2} \cos \omega t &= -\omega^2 \cos \omega t & \frac{d^2}{dt^2} \sin \omega t \\ &= -\omega^2 \sin \omega t & \frac{d^2}{dt^2} e^{i\omega t} = -\omega^2 e^{i\omega t} \end{aligned}$$



Spatial Spectral Analysis, Fig. 1 The spatial patterns for the spherical harmonics with $l = 0 \dots 3$ and $m = 0 \dots 3$ plotted on a sphere with the real parts of the complex-valued functions on the *right* and the imaginary parts on the *left*

In space, in Cartesian coordinates, the Laplace operator, Δ , is simply the sum of the second derivatives, whereas in spherical coordinates, its form is more complicated. Explicitly, on a unit sphere, the angular part, $\Delta_{\theta\phi}$, applied to the spherical harmonics reproduces these functions times a constant

$$\begin{aligned}\Delta_{\theta\phi} &= \frac{1}{\sin\theta} \frac{\partial}{\partial\theta} \sin\theta \frac{\partial}{\partial\theta} \\ &\quad + \frac{1}{\sin^2\theta} \frac{\partial^2}{\partial\phi^2} \Delta_{\theta\phi} Y_l^m(\theta, \phi) \\ &= m(m+1) Y_l^m(\theta, \phi)\end{aligned}$$

In other words, the spherical harmonics $Y_l^m(\theta, \phi)$ are the eigenfunctions to the angular part of the Laplacian in spherical coordinates with eigenvalues $m(m+1)$.

Data-Dependent Basis: PCA

Instead of using a system of predefined basis vectors or functions, there are ways to calculate a basis from the dataset itself that is optimal in a certain sense to the specific data under consideration (Johnson and Wichern 2007, Jolliffe 2002). One such procedure is known as principal component analysis (PCA) (Other names for identical or very similar methods are Karhunen-Loève transform (KLT) or singular value decomposition (SVD)), where the basis is obtained as the eigenvectors $\mathbf{v}^{(i)}$ of the covariance matrix, C . Specifically, assuming a dataset of time series from N electrodes in EEG, the covariance matrix is an $N \times N$ matrix and calculated as

$$C_{ij} = \frac{1}{T} \int_0^T dt \{H_i(t) - H_i\} \{H_j(t) - H_j\} \quad (4)$$

where H_i and H_j are the mean values over time of $H_i(t)$ and $H_j(t)$, respectively. The eigenvalues of C , λ_i are a measure of the contribution of the corresponding eigenvector to the dataset. In many applications 90–95% of the entire variance is represented by a few of the eigenvectors corresponding to the largest eigenvalues. The

time series of the amplitudes for the eigenvectors are obtained as

$$\xi_i(t) = \mathbf{H}(t) \cdot \mathbf{v}^{(i)} = \sum_{n=1}^N H_n(t) v_n^{(i)} \quad (5)$$

As the covariance matrix is real, symmetric, and positive semi-definite, all eigenvalues are real and nonnegative, and the eigenvectors are mutually orthogonal. Moreover, the time series for the amplitudes $\xi_i(t)$ are also orthogonal and fulfill the relation

$$\int_0^T dt \xi_i(t) \xi_j(t) = \lambda_i \delta_{ij} \quad (6)$$

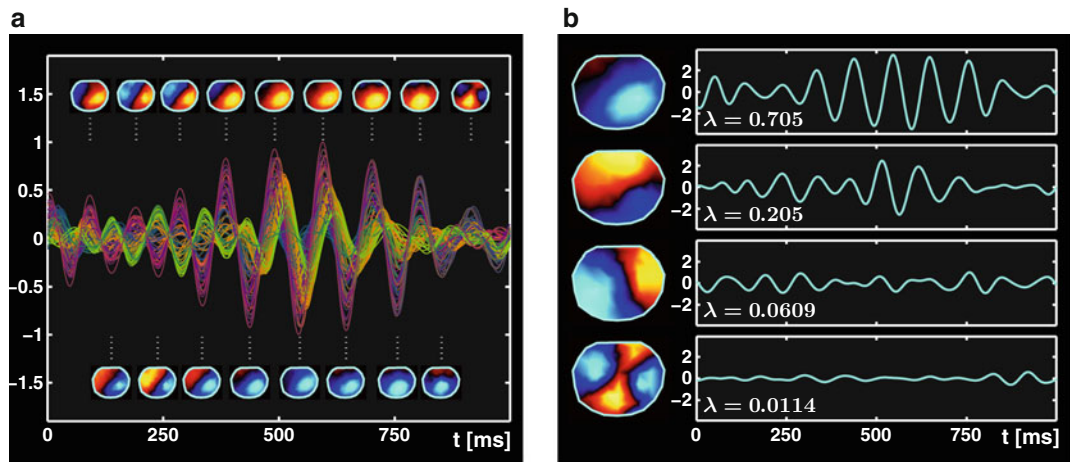
Principal component analysis is optimal in the sense that it minimizes the mean squared error between the dataset and its expansion for all truncation points. This means that if the decomposition is taken up to a point M and $\mathbf{v}^{(m)}$ are the eigenvectors corresponding to the M largest eigenvalues, the error E_M defined as

$$\begin{aligned}E_M &= \sum_{n=1}^N \int_0^T dt \left\{ H_n(t) - \sum_{i=1}^M \xi_i(t) v_n^{(i)} \right\}^2 \\ &= \text{Min} \forall M\end{aligned} \quad (7)$$

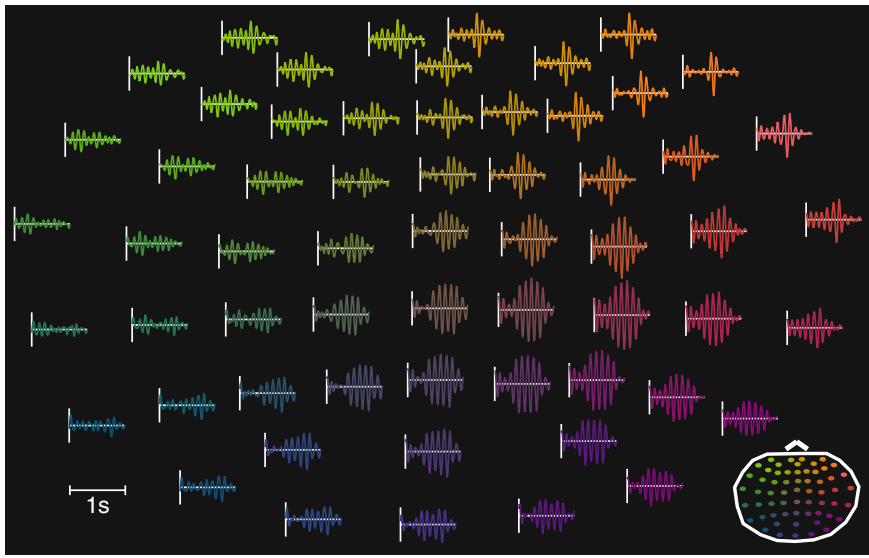
is a minimum independent of M , i.e., there is no set of M basis vectors that carry more of the variance of the dataset than the eigenvectors $\mathbf{v}^{(m)}$ of the covariance matrix.

Explicit Example

A short dataset representing 1 s from an EEG recording using a montage with 60 electrodes is shown in Fig. 2. The time series are arranged and color-coded in a topological layout corresponding to the spatial locations of the electrodes on the scalp surface (also shown in the insert). The same color coding for the time series is used in the butterfly plot in Fig. 3a, which also shows the spatial pattern of the potential at the maxima and minima. This dataset is decomposed by calculating the 60×60 covariance matrix as in Eq. 4,



Spatial Spectral Analysis, Fig. 2 Sample dataset of an EEG recording of 1 s from 60 different locations on the scalp surface as shown in the insert



Spatial Spectral Analysis, Fig. 3 The dataset and its decomposition using PCA. (a) Superposition of the time series (butterfly plot) with the color coding used in Fig. 2 together with topographical plots showing the spatial

patterns at the maxima and minima. (b) Spatial patterns representing the eigenvectors $\mathbf{p}^{(1-4)}$ that correspond to the four largest eigenvalues (left). Time-dependent amplitudes $\xi_{1-4}(t)$ and eigenvalues λ_{1-4} (right)

finding its eigenvalues and eigenvectors, and determining the amplitudes of the spatial patterns according to Eq. 5.

The results are shown in Fig. 3b with the four dominating spatial pattern, i.e., the eigenvectors corresponding to the four largest eigenvalues on the left and their time-dependent amplitudes on the right. The eigenvalues sum up to 0.9823,

which means that more than 98% of the total variance in the original 60-dimensional dataset is covered by these four patterns and their amplitudes.

Summary and Conclusions

Spatial spectral methods, in general, are used to perform a separation of a spatiotemporal signal

into patterns that depend only on space and corresponding time-dependent amplitudes, which may lead to a strong compression of the original dataset while keeping the relevant information. On the other hand, methods like PCA can also be used to detect artifacts (like bad electrodes in EEG) as they may get lumped into an individual pattern and can then be removed from the dataset. Aside from those representing artifacts, one should not attempt to interpret individual spatial patterns obtained by PCA as a manifestation of underlying separate sources because due to the way they are obtained (as eigenvectors of a real, symmetric matrix), they are mutually orthogonal, a constraint that is in general incompatible with activity patterns originating from different sources inside the brain. There are other decomposition techniques like independent component analysis (ICA) where the patterns do not have to be orthogonal but a further discussion of such methods is beyond the scope of this entry.

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Spatial Temporal Spike Pattern Analysis

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Definition

Sequences of events that repeat several times are called *precise spatiotemporal patterns*. The

number of participating events is called the *complexity* of the patterns. The time precision with which the delays are measured is called the *time accuracy* of the pattern.

Examples

Suppose we have three parallel point processes (e.g., times of spiking of three neurons), among them, we find repeatedly an event from process A followed after t_1 seconds by an event from B and after t_2 seconds by an event from C, then the composite event

$$\begin{array}{c} A \\ | \text{ } _ t_1 _ B \\ | \text{ } _ _ t_2 _ _ C \end{array}$$

is called a precise spatiotemporal pattern and may be coded $\langle A, B, C; t_1, t_2 \rangle$. Its *complexity* is 3.

If t_1 and t_2 are taken at infinite resolution, the probability of observing it twice is zero. Therefore, some time accuracy (Δt) is associated with the pattern such that B occurred at $[t_1 \pm \Delta t/2]$ after A and C at $[t_2 \pm \Delta t/2]$ after A. Figure 1 illustrates such a precise spatiotemporal pattern.

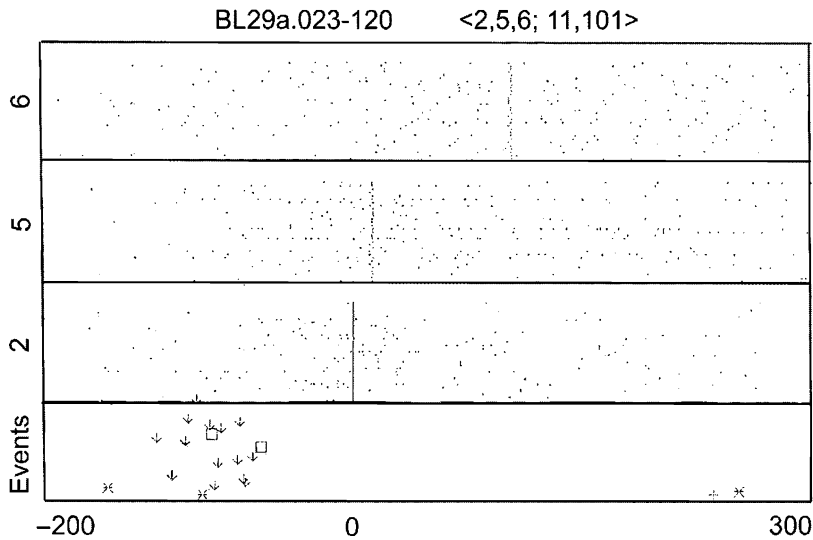
Variations

In some works the value of Δt was varied and allowed to become longer, the longer is the delay t_i . In some works, just the order of events (disregarding the exact time interval between successive events) was also considered as a spatiotemporal pattern.

Detailed Description

History

Numerous publications mentioned observing precise spatiotemporal patterns in neuronal data (see Abeles and Gat 2001 for a partial list). The first ones to make a systematic search for such patterns were Dayhoff and Gerstein (1983a, b), who



Spatial Temporal Spike Pattern Analysis, Fig. 1 Example of a precise spatiotemporal pattern. Dot display of the pattern $\langle 2,5,6; 11, 101 \rangle$ that repeated 31 times. The precision was 3 ms. All dot rasters are aligned on the first spike in the pattern. Recording from the frontal cortex of a monkey performing a localization task of visual and auditory stimuli. The patterns tend to

appear after a visual stimulus (*down pointing arrows*) but are not tightly locked in time to the stimulus. Each neuron fired also other (seemingly random) spikes during and around the time of the patterns. This suggests that the precise timing is a network property (and not due to any internal processes of each of the neurons)

looked for repeating sequences of inter-spike intervals in the recorded activity of a single unit in the cat cortex. The first to systematically search for such patterns in parallel spike trains were Abeles and Gerstein (1988). Both reported significant excess. However, their methods for evaluating significance were criticized (Oram et al. 1999; Baker and Lemon 2000).

Meaning of Finding Precise Patterns

Existence of significant precise spatiotemporal patterns is taken as evidence that there is some mechanism that precisely controls the timing of events in the involved point processes. That relates to the question of how information is coded and transmitted within the cortex. Is it by firing rate, oscillations, precise synchrony, or delayed synchrony (► [Neural Coding](#))? For that the question whether there exists some mechanism that produces precise timing (and can read it) is so important. In a single neuron, precise firing patterns may be produced in a burst of

spikes, and periodic oscillations may be produced by internal pacemaker mechanism or in an oscillating network. The main interest in repeating spatiotemporal patterns is directed to cases that cannot be explained by precise time relations of external events, by intrinsic mechanisms of a single neuron, or by close to periodic oscillations of a network. When the above simple explanations do not apply, then one should assume that the patterns are the expression of some special neural networks that can produce them. The synfire chain model (Abeles 1982) and the polychronization model (Izhikevich 2006) are two such models.

Statistical Significance

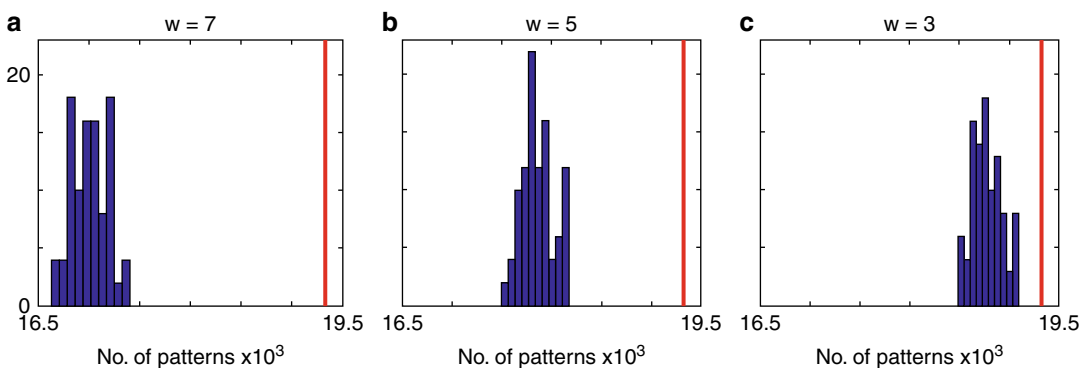
Given enough data and large enough Δt , one expects to see many precise spatiotemporal patterns by chance. How can one decide whether the number of repetitions exceeds chance? Typically, one generates surrogate spike trains and looks for patterns there. If the data contains many more, it is assumed that they are significant. Numerous proposals of surrogates for looking for patterns exist

in the literature including the following: the individual point processes are inhomogeneous Poisson processes (Oram et al. 1999); they behave like gamma processes (Baker and Lemon 2000); two successive intervals in the same point process are not independent (Gerstein 2004); and a particular pattern $\langle A_0, A_1, A_2, \dots, A_n; t_1, t_2, \dots, t_n \rangle$ happens many more times when compared to patterns of the same events with slightly different times $\langle t_1, t_2, \dots, t_n \rangle$ (Abeles and Gat 2001) (► [Surrogate Data for Evaluation of Spike Correlation](#)).

The good way to examine the existence of precise timing was suggested by Geman and Bienenstock (Date et al. 2000; Hastopoulos et al. 2003). According to their suggestion, the null hypothesis is that there is nothing that controls the event timing below some accuracy W . Therefore, randomly teetering the event timing within W seconds should not affect any statistics that is derived from the involved point processes. Thus, one teeters the timing by W and computes the same statistics again and again forming a probability density function of the statistic for teetered data. If the value of the data statistic falls in the tail of this pdf, one can estimate the probability of the time accuracy of the data from the area of the tail. Figure 2 illustrates this process.

In theory, this idea is of limited usefulness. Any variation in the rate of events (e.g., a response of a neuron to a stimulus) will be “smeared” by such teetering. Thus, given enough data, it would be possible to detect significant variations by teetering. However, if the variations are slow relative to the window width W , it would take enormous amount of data to obtain significant differences. One should therefore be careful not to use this method when sharp transients of some property are expected. For example, inter-spike interval histograms may change abruptly from zero (during the refractory period) to some high level. Cross-correlations between pairs of spike trains may show a very sharp peak at zero lag (► [Unitary Event Analysis](#); ► [Correlation Analysis of Parallel Spike Trains](#)). Teetering spike times within W is equivalent to convolving the histogram with a boxcar kernel of width W . If the transition is sharp relative to W , significance may be found. This suggests a way to evaluate how much data would be needed before these effects will be significant.

Therefore, this method should not be used to detect significance for precise spatiotemporal patterns when the same point process participates more than once or when near zero delays between events in two point processes are included. The work of Shmiel et al. (2006) illustrates finding



Spatial Temporal Spike Pattern Analysis, Fig. 2 Distributions of patterns in randomly teetered data. *Red bar*, the number of repeating patterns in the data. *Blue histogram*, the distribution of the number of repeating patterns in data that was randomly teetered 100 times. The data is from the MEG recording of a subject that performed a task of following a musical meter. The

MEG data was converted to current dipoles in the cortex. From these the position of sharp (20 ms) peaks was detected and presented as parallel point processes. Data was sampled at 508/s and the precision was three samples. The teetering windows were 7, 5, and 3 samples from left to right respectively

accurate time relations between two spike trains even when W was 0.5 ms and all possible precautions were taken into considerations.

Cross-References

- ▶ [Correlation Analysis of Parallel Spike Trains](#)
- ▶ [Neural Coding](#)
- ▶ [Surrogate Data for Evaluation of Spike Correlation](#)
- ▶ [Unitary Event Analysis](#)

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Spatiotemporal Energy Models

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Synonyms

[Disparity energy model](#); [Motion energy model](#)

Definition

Spatiotemporal energy models were developed to explain the physiological properties of a class of motion sensitive neurons known as complex direction selective (DS) cells in the primary visual cortex (V1). These models are tuned to respond to energy within the spatiotemporal frequency spectrum of time-varying imagery, particularly to the spectral bands that are associated with specific directions of motion. This is accomplished using quadrature pairs of linear filters that are oriented both in space and in space-time. Spatiotemporal energy models are commonly used as the initial stages of higher-level models of motion, stereopsis, and form processing.

Detailed Description

Fundamental Example

The classical instance of a spatiotemporal energy model is the motion energy (ME) model (Adelson and Bergen 1985). It consists of two linear filters that have a quadrature phase relationship, meaning that one filter is shifted by ninety degrees with respect to the other. For example, if one filter is the product of a cosine function times a Gaussian, the other is the product of a sine times the same Gaussian, as follows:

$$h1(x, y, t) = \cos(f_s x + f_t t) e^{[-1/2(x^2 + y^2)/\sigma^2_s - 1/2t^2/\sigma^2_t]}$$

$$h2(x, y, t) = \sin(f_s x + f_t t) e^{[-1/2(x^2 + y^2)/\sigma^2_s - 1/2t^2/\sigma^2_t]}$$

where f_s , f_t , σ_s , and σ_t set the preferred spatial frequency (SF) and temporal frequency (TF) and the size of the filters in space and time, respectively. The output of the model is the sum of the squares of the two filter outputs.

Conceptual Development

Three insights were essential to the invention of spatiotemporal energy models. The first was that visual neurons could be modeled as linear filters and described in terms of their sensitivities to spatial and temporal frequencies within a sequence of images. By the end of the decade in which Hubel and Wiesel (1962) made the critical discovery that many V1 neurons were selective for the orientation, size, and direction of motion of simple bar stimuli, other experimentalists, in particular those using drifting sinewave grating stimuli, had begun theorizing that the visual system was in fact a spatial frequency analyzer containing independent, narrowband channels (Campbell and Robson 1968; Campbell et al. 1969; Blakemore and Campbell 1969; Maffei and Fiorentini 1973). Ultimately, it was established that responses of simple cells in V1 could, under limited conditions, be well described by the outputs of linear filters (Movshon et al. 1978).

The second essential insight was that visual motion, particularly rigid translation, creates orientation in space-time and that this can be detected by oriented space-time filters (Fahle and Poggio 1981; Watson and Ahumada 1983; Adelson and Bergen 1985). Here, theory preceded experiment, as the first clear demonstrations of spatiotemporal orientation in the responses of V1 neurons appeared several years later (Reid et al. 1987; McLean and Palmer 1989). The third essential insight was the use of the squared outputs of a quadrature pair of filters to demodulate the temporal response to moving stimuli (Adelson and Bergen 1985). This is related to the fact that $\cos^2 + \sin^2$ is a constant, and it allows the ME model to respond to a moving grating with a constant positive response and to a moving bar with a unimodal positive response. This was

important to capture the responses of complex, as opposed to simple, DS neurons.

Related Approaches

A contemporaneous approach to modeling DS neuronal responses began with the fundamentally nonlinear, correlation-style Reichardt motion detector (Reichardt 1957, 1961) and added appropriate linear filters at the front end, resulting in the elaborated Reichardt detector (ERD) model (van Santen and Sperling 1984, 1985). The ERD model has computational steps that are distinct from those of the ME model; nevertheless, in some forms, the final outputs of the two models are mathematically equivalent (Adelson and Bergen 1985). This demonstrates the close link between what are arguably the two historically most important models for direction selective neurons. An alternative approach that contrasts with the energy model was proposed by Watson and Ahumada (1985) in which the temporal modulation of the response, rather than being removed by squaring the outputs of quadrature filters, is retained and used to encode information relevant for downstream velocity estimation.

More recently, the spatiotemporal energy model has been modified and generalized to account for the responses of neurons that are selective for binocular disparity. The first binocular disparity energy (BDE) model (Ohzawa et al. 1990; Ohzawa 1998) was strictly spatial and consisted of separate pairs of quadrature filters for the left and right eyes. The preferred disparity is determined by a parameter that controls the offset of the filters across the two eyes, and the quadrature pair, followed by squaring, maintains the complex cell behavior. The BDE model has been unified with the ME model (Chen et al. 2001) to produce a set of spatiotemporal energy models that can account for both disparity and direction selectivity. These models continue to be the subject of active development as researchers attempt to account more accurately for response properties to an ever increasing set of visual stimuli (Read et al. 2002; Chen

and Qian 2004; Haefner and Cumming 2008; Peng and Shi 2010).

Cross-References

- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [Hierarchical Models of the Visual System](#)
- [Receptive Field Modeling](#)
- [Spectrotemporal Receptive Fields](#)
- [Stereo Vision, Models of](#)

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Specific Intracellular (or Cytoplasmic) Resistance

- [Resistivity, Axial](#)

Spectral Interdependency Methods

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Synonyms

[Coherence and Granger causality spectral analysis](#); [Multivariate spectral analysis](#); [Oscillatory network activity analysis](#)

Definition

Spectral interdependency methods are a means of statistically quantifying the interrelationship between a pair of dynamic processes as a function of frequency or time period of oscillation. The measures of spectral interdependency are derived from the time series recordings of dynamic systems either by using autoregressive modeling (parametric method) or by using direct Fourier or wavelet transforms (nonparametric method). For a pair of multivariate stationary processes (1 and 2), there are three measures that characterize the spectral interdependency between these processes. They are total interdependence ($M_{1,2}$), Granger causality (one-way effect or directional influence from the first process to the second process, $M_{1 \rightarrow 2}$, or from the second to the first, $M_{2 \rightarrow 1}$), and instantaneous causality (measure of reciprocity, $M_{1,2}$). In general, the total interdependence is the sum of directional influences and instantaneous causality frequency by frequency ($M_{1,2} = M_{1 \rightarrow 2} + M_{2 \rightarrow 1} + M_{1,2}$) and is related to coherence (C_{12}) as $M_{1,2} = -\ln(1 - C_{12})$. These measures can also be estimated for nonstationary processes by using moving time-windowed autoregressive modeling or Fourier transformations or wavelet transformations. Coherence and spectral Granger causality are well-accepted measures in neuroscience to characterize frequency-specific interdependence between multiple time series from multisite neurophysiological recordings.

Detailed Description

Many processes in nature, including brain processes, have oscillatory motion, and the time series measurements of their activity are rich in oscillatory content, lending them naturally to spectral analysis. Spectral interdependency methods are used to study the relationship in the frequency domain between multiple processes from their simultaneously recorded time series signals. Consider a pair of zero-mean, stationary processes (1 and 2) in which simultaneously

measured time series at a sampling rate of f_s are represented as 1: $X_1(1), X_1(2), \dots, X_1(t), \dots$ and 2: $X_2(1), X_2(2), \dots, X_2(t), \dots$. The spectral interdependency measures as defined above are derived from the spectral matrix (S) and/or from the transfer function (H) and noise covariance matrix (Σ), which can be estimated by the parametric (Ding et al. 2006) or nonparametric approaches applied to these time series (Dhamala et al. 2008a, b). Brief mathematical derivations and descriptions of these interdependency measures (C_{12} , $M_{1,2}$, $M_{1 \rightarrow 2}$, $M_{2 \rightarrow 1}$, and $M_{1,2}$) are included below.

Directed transfer function (DTF) (Kaminski et al. 2001) and partial directed coherence (PDC) (Baccala and Sameshima 2001) are the accepted alternative measures of directional influence, equivalent to the measures for $M_{1 \rightarrow 2}$ and $M_{2 \rightarrow 1}$ as defined above. DTF is obtained from H and PDC from the Fourier transform of model coefficients in the parametric approach.

Parametric Approach

Jointly, X_1 and X_2 series can be represented as the following bivariate autoregressive (AR) models:

$$\begin{aligned} X_1(t) &= \sum_{j=1}^{\infty} a_{11,j} X_1(t-j) + \sum_{j=1}^{\infty} a_{12,j} X_2(t-j) + \varepsilon(t) \\ X_2(t) &= \sum_{j=1}^{\infty} a_{21,j} X_1(t-j) + \sum_{j=1}^{\infty} a_{22,j} X_2(t-j) + \eta(t), \end{aligned} \quad (1)$$

where ε and η are residual (one-step-ahead prediction) errors and are uncorrelated over time. After Fourier transforming the bivariate AR representation Eq. 1 and applying proper ensemble average, we obtain the following spectral density matrix S as a function of frequency (f):

$$S(f) = H(f) \Sigma H^*(f), \quad (2)$$

where $*$ denotes the matrix adjoint. Here, the noise covariance matrix Σ is computed from the residual errors $\varepsilon(t)$, $\eta(t)$ and the transfer function matrix $H(f)$ is constructed from the matrix inverse of the Fourier transforms of the coefficients as

$$\Sigma = \begin{pmatrix} \text{var}(\varepsilon) & \text{cov}(\varepsilon, \eta) \\ \text{cov}(\varepsilon, \eta) & \text{var}(\eta) \end{pmatrix} \quad (3)$$

$$H_{lm}(f) = \left(\delta_{lm} - \sum_{k=1}^{\infty} a_{lm,k} e^{-i2\pi f k} \right)^{-1},$$

where δ_{lm} is the Kronecker delta function with the matrix element index lm .

Nonparametric Approach

S , H , and Σ can also be estimated by using the nonparametric spectral methods (Dhamala et al. 2008a, b) without explicitly fitting the time series $X_1(t)$ and $X_2(t)$ in autoregressive models. In this approach, S is constructed by Fourier transforming X_1 and X_2 and properly averaging over ensembles usually with multitapers (Mitra and Pesaran 1999):

$$S_{lm} = \langle x_l(f) x_m(f^*) \rangle, \quad (4)$$

where lm is the index for time series and matrix element, $\langle \rangle$ represents averaging over ensemble, and X 's are the direct Fourier transforms of X 's. H and Σ can be derived from the minimum-phase factors of S :

$$H = \psi A_0^{-1} \quad (5)$$

$$\Sigma = A_0 A_0^T,$$

where T stands for matrix transposition, $\psi(e^{i\theta}) = \sum_{k=0}^{\infty} A_k e^{ik\theta}$ defined on the unit circle and $A_k = \frac{1}{2\pi} \int_{-\pi}^{\pi} \psi(e^{i\theta}) e^{-ik\theta} d\theta$.

Spectral Interdependence

The coherence function $C(f)$ is derived from the cross spectra normalized by the product of the individual auto spectra and measures the amount of interdependence (synchrony) as a function of frequency:

$$C(f) = \frac{|S_{12}(f)|^2}{S_{11}(f)S_{22}(f)}. \quad (6)$$

$C(f)$ is sensitive to both amplitude and phase relationships between processes at f and its value ranges from 0 (no interdependence) to 1 (maximum interdependence). $C(f)$ is related to Geweke's measure of total interdependence ($M_{1,2}$) (Ding et al. 2006).

$$M_{1,2}(f) = -\ln(1 - C(f)), \quad (7)$$

whose value ranges from 0 to infinity. The total spectral interdependence ($M_{1,2}$) is equal to the sum of Granger causality or directional influences (one-way effects, $M_{1 \rightarrow 2}$ and $M_{2 \rightarrow 1}$) and instantaneous causality ($M_{1,2}$) (Geweke 1982):

$$M_{1,2} = M_{1 \rightarrow 2} + M_{2 \rightarrow 1} + M_{1,2} \quad (8)$$

Here, directional influences between 1 and 2 are given by (Geweke 1982)

$$M_{1 \rightarrow 2}(f) = \ln \frac{S_{22}(f)}{\tilde{H}_{11}(f) \Sigma_{11} \tilde{H}_{11}(f)} \quad (9)$$

$$M_{2 \rightarrow 1}(f) = \ln \frac{S_{11}(f)}{\tilde{H}_{22}(f) \Sigma_{22} \tilde{H}_{22}(f)},$$

where $\tilde{H}_{11} = H_{11} + \sum_{12}^{12} H_{12}$, $\tilde{H}_{22} = \tilde{H}_{22} + \sum_{22}^{12} H_{21}$, and instantaneous causality $M_{1,2}$ is given by

$$M_{1,2}(f) = -\ln \frac{|S(f)|}{\left(\tilde{H}_{11}(f) \Sigma_{11} \tilde{H}_{11}(f) \right) \left(\tilde{H}_{22}(f) \Sigma_{22} \tilde{H}_{22}(f) \right)}. \quad (10)$$

Granger causality at low frequencies between a pair of cointegrated series depends only on a few statistically interpretable coefficients from the error correction model if Hosoya's spectral decomposition (Hosoya 1991) is used (Granger and Lin 1995).

The time-domain counterparts of these spectral measures in Eq. 8 are obtained by integrating the spectral measures over the entire frequency range as $\frac{2}{f_s} \int_0^{\frac{f_s}{2}} M(f) df$. The integral of total

interdependence measures the total amount of mutual information, and the other integrals are simply the respective time-domain measures of Granger causality.

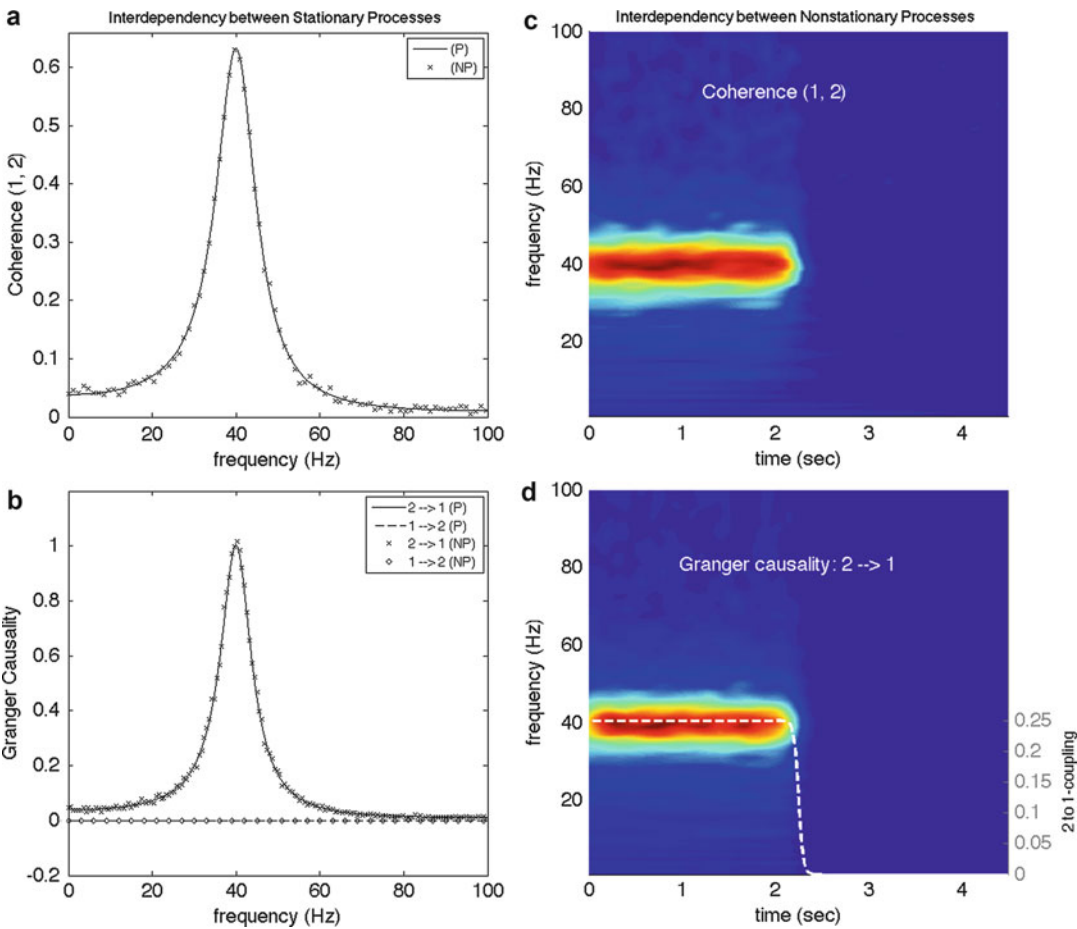
Spectral Interdependency for Nonstationary Processes

The spectral interdependency measures can also be defined for nonstationary processes by treating their time series in sufficiently short windows as locally stationary processes. They can be estimated as a function of time and frequency by using

moving time-windowed autoregressive modeling (Liang et al. 2000), moving time-windowed Fourier transformations (Shiogai et al. 2012), or wavelet transformations (Dhamala et al. 2008a, b).

Numerical Examples

Here, we generate time series (500 trials) from jointly stationary and nonstationary processes and illustrate the estimation of coherence and Granger causality spectra using the parametric (P) and nonparametric (NP) approaches. We consider two interacting autoregressive processes,



Spectral Interdependency Methods, Fig. 1 Coherence (a, c) and Granger causality (b, d) spectra between stationary (a, b) and nonstationary (c, d) processes (1 and 2). Parametric (P) and Fourier transform-based nonparametric (NP) methods are used here to evaluate these quantities

(a, b) between the stationary processes. The wavelet transform-based time-frequency maps of coherence (c) and Granger causality (d) recover the time-varying nature of 2 to 1 coupling (shown on the right y-axis in d)

2: $\{X_2(t)\}$ driving 1: $\{X_1(t)\}$, similar to the network model considered in Dhamala et al. (2008b), where $X_1 = 0.55 X_1(t-1) - 0.8 X_1(t-2) + C(t)X_2(t-1) + \varepsilon(t)$ and $X_2(t) = 0.55 X_2(t-1) - 0.8 X_2(t-2) + \eta(t)$. Here, $(\varepsilon(t), \eta(t))$'s are independent white noise processes with zero means and unit variances, the sampling rate is considered to be 200 Hz, and the coupling strength $C(t)$ remains 0.25 for time t in the stationary condition and slowly changes from 0.25 to 0 around $t = 2$ s in the case of nonstationary processes. P and NP approaches agree well in coherence and Granger causality spectra (Fig. 1a, b). Morlet wavelet transform-based method yields complete time-frequency maps of coherence (Fig. 1c) and Granger causality (Fig. 1d), consistent with the trend of the 2 to 1 coupling as shown on the right side of Fig. 1d.

Extensions of Spectral Interdependency Methods

As an extension of the ordinary coherence described above, block coherence (Nedungadi et al. 2011) can estimate coherence spectra between pairs of nonoverlapping time series. Conditional Granger causality (Geweke 1984; Hosoya 2001) measures directional influences between two processes eliminating the effect of a third process, thereby distinguishing between direct and mediated causality (Ding et al. 2006; Dhamala et al. 2008b). The multivariate version of the spectral Granger causality between two processes makes use of this idea of eliminating the causal effect from all other interrelated processes as an extension of the conditional Granger causality defined for three processes.

Applications in Neuroscience

Spectral interdependency measures have been instrumental in attempts to understand the relationships between oscillatory brain processes at various spatial scales from multisite brain activity recordings. Coherence is widely used in neuroscience (Siegel et al. 2012; Roberts et al. 2013). The

insights provided by this measure have even led to the “neuronal communication through coherence” hypothesis (Fries 2005; Roberts et al. 2013). Spectral Granger causality and equivalent directional measures have been used in a variety of brain signal recordings, such as local field potentials, EEG, MEG, and fMRI, in animals and humans (see Bressler and Seth 2011; Friston et al. 2012 for reviews). Because of the unknown theoretical distributions of coherence and spectral Granger causality, establishing statistical significance in these measures derived from experimental time series requires data resampling (surrogate) methods such as jackknifing (Bokil et al. 2010), bootstrapping, and random permutation (Seth 2010).

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Spectrotemporal Receptive Fields

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Synonyms

Frequency tuning curves; Iso-intensity response curves; Spectrotemporal response fields

Definition

The spectrotemporal response field (STRF) of an auditory neuron is a time-frequency measure of the dynamic responses of an auditory neuron to impulsive energy delivered at various

frequencies. As such, it gives simultaneously two types of information about the neuron. The first is its frequency tuning, or more specifically which frequencies excite the cell best and which inhibit it. The other is the nature of its temporal response, i.e., whether it is sustained in time or is rapidly adapting. This measure is linear and takes the stimulus spectrogram as its input and hence is often found to be useful in predicting responses of a neuron to unseen stimuli.

Detailed Description

The Value of the STRF

A key requirement in the study of sensory nervous systems is the ability to characterize effectively neuronal response selectivity. In the visual system, striving for this objective yielded remarkable progress in understanding the functional organization of the visual cortex and its implications to perception. For instance, the discovery of ordered feature representations of retinal space, color, ocular dominance, orientation, and motion direction in various cortical fields has instigated vast studies into the anatomical bases of this organization, its developmental course, and the changes it undergoes during learning or following injury. In the primary auditory cortex (A1), response selectivity of the neurons (also called their *response fields*) is ordered topographically according to the frequency they are most tuned to, an organization inherited from the cochlea. Beyond their tuning, however, A1 responses and response fields exhibit a bewildering variety of dynamics, frequency bandwidths, response thresholds, and patterns of excitatory and inhibitory regions. All this has been learned over decades of testing with a large variety of acoustic stimuli (tones, clicks, noise, and natural sounds) and response measures (tuning curves, rate-level functions, and binaural maps).

Distinguishing the STRF

A response measure that has proven particularly useful beyond the feature-specific measures

enumerated earlier is the notion of a generalized *spatiotemporal*, or equivalently for the auditory system, the *spectrotemporal response field* (STRF). It is distinguished from other measures by its broader descriptive power (encompassing both dynamics and spectral selectivity) and its relatively noncommittal nature (not requiring too much prior knowledge such as frequency tuning or threshold). In the last two decades, the STRF has become widely employed in all sensory systems (Hochstein and Shapley 1976; De Valois and De Valois 1988; Arun et al. 2006; Aertsen and Johannesma 1981; DeAngelis et al. 1995; Gosselin and Schyns 2002), and especially in the auditory system where it had found its original promise, development, and examination of its value and liability (Arun et al. 2006; Aertsen and Johannesma 1981; de Boer 1967; de Boer and de Jongh 1978). The STRF has primarily been viewed as a linear characterization of the complex stimulus-response transformations seen in sensory neurons. However, there are well-understood limitations of the STRF ability to capture all the essential details of a sensory neuron's response. These stem from the existence of a host of known nonlinearities such as spiking threshold, rate saturation, and synaptic-depression that can complicate the interpretation of the STRF and render its representation stimulus dependent or meaningless. Nevertheless, the utility of the STRF has inspired deeper and broader examination of its constraints and pitfalls and ways to circumvent them (David et al. 2006; Christianson et al. 2008; Atencio et al. 2008; Nagel and Doupe 2008) or even exploit them to learn more about the nonlinearities in the system (Theunissen et al. 2000; Ahrens et al. 2008; Klein et al. 2006).

Using the STRF

The STRF concept has proven valuable in the understanding of auditory cortical processing and its applications in audio systems ranging from speech and speaker recognition to enhancements of speech signals and cochlear implants. Their first valuable contribution has

been to provide an effective summary of the representation of sound features in the primary auditory cortex (Theunissen et al. 2000; Atencio et al. 2008; Shamma et al. 1995). A key finding has been the realization that the huge variety of auditory cortical responses in frequency tuning, dynamics, and other features has inspired models of auditory processing that view the cortex as a “multiscale” spectrotemporal analyzer that decomposes the signal into a rich representation that can be effectively harnessed for a variety of applications (Chi et al. 2006). For example, complex signals such as speech and music can be analyzed in this cortical model to understand how phonetic information is represented (Mesgarani et al. 2008) or how timbres of different musical instruments are encoded (Patil et al. 2012). The uniqueness of the representation of the different types of signals allows us further to separate the speech from interfering noise, to detect the presence of speech compared to no speech (Mesgarani et al. 2005), and to separate multiple speakers (Elhilali and Shamma 2008).

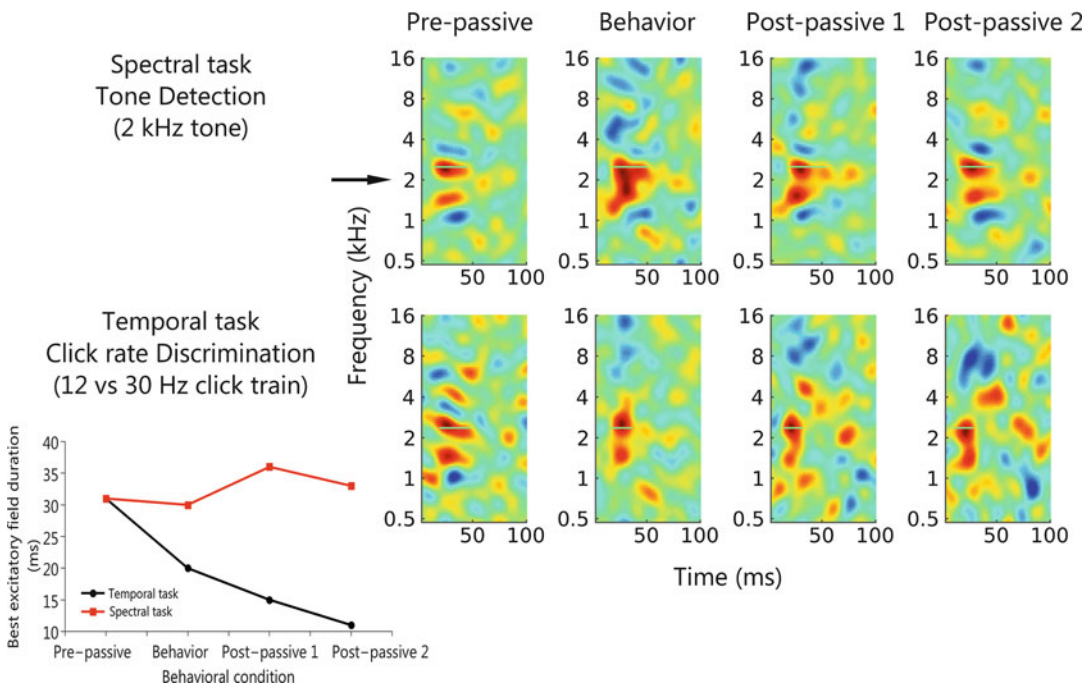
STRF and Plasticity

STRFs have proven valuable in plasticity and developmental studies as a summary of a neuron's response properties *even if incomplete*. The reason is that in many cases, it is not the completeness of the representation that is of interest but rather *how* the (admittedly incomplete) representation changes during behavior or learning. In this role, the STRF has demonstrated a robustness and versatility that was not initially appreciated. For instance, auditory cortical STRFs often provide an estimate of the *relative* sensitivity of a neuron to different frequencies and temporal dynamics. Therefore, when examining the effects of attention and learning, changes in neuronal responsiveness are often unpredictable in their dynamics or spectral configurations or are very small and augment already very noisy responses. The STRF counters both of these challenges. Thus, by virtue of its generalized nature (not being specific to a particular feature or response dimension),

changes in the neuronal sensitivity in one of multiple dimensions can readily be spotted and characterized (Fritz et al. 2003). Furthermore, these response changes are often very difficult to discern or interpret (as spectral or temporal changes) in the firing rates themselves. STRFs by their nature are simultaneous *relative* measures of a neuron's responsiveness to many frequencies and dynamics. Consequently, the effect of attention and learning (and behavior in general) is often seen as changes in the STRF shape that can be readily interpreted as changes in the relative sensitivity of the neuron to different frequencies (Fritz et al. 2005a) or in the temporal parameters of the STRF such as its latency (Fritz et al. 2005b) (Fig. 1).

Forward and Inverse STRF

Another interesting use of the STRFs is in characterizing global response properties of a large population of cells or cortical areas for the purpose of summarizing its representational properties and how that may change due to learning and plasticity. Specifically, in many situations, cortical neurons encode considerable details about the underlying sensory stimuli, and the encoded information is likely to change with stimulus context and behavioral conditions in a manner that is difficult to discern across large sets of single neuron data because of the complexity of cortical receptive fields. STRFs help overcome this problem because they



Spectrotemporal Receptive Fields, Fig. 1 Example of an STRF that showed spectral and temporal task-related plasticity in successive tasks. The spectral task was performed first, with a target tone of 2 kHz. The STRF obtained during spectral task behavior displayed an expansion of both excitatory fields towards the target frequency. The STRF returned to its original pre-passive shape following behavior. Shortly after the spectral task, the animal was presented with the temporal task, in which it had to discriminate reference click trains of 12 Hz from target

click trains presented at 30 Hz. In contrast to the plasticity observed during the spectral task, in the temporal task the excitatory field of the STRF became narrower. This narrowing of the STRF persisted following behavior. Persistent plasticity has also been described previously (Fritz et al. 2003). (From Abstract #377, ARO 2013, *Laminar Recordings of Task-Related Receptive Field Plasticity with Multisite Depth Electrodes in the Primary Auditory Cortex (A1) of the Behaving Ferret*, by Elgueda D., B Englitz, M Locastro, M Elhilali, S Shamma, and J Fritz)

facilitate methods of stimulus *reconstruction* to study how complex sounds are encoded in AI. In such a method, measured STRFs are used to *invert* the responses and hence map population responses to an estimate of the stimulus spectrogram (Mesgarani et al. 2009). This enables one to perform a direct comparison between an original stimulus spectrogram and its reconstruction following learning or from responses during a behavioral paradigm. In fact, by estimating the fidelity of such reconstructions using generalized spectrally and temporally modulated noise stimuli, one can determine the range over which AI neurons can faithfully encode such spectrotemporal features. Finally, contrasting stimulus reconstructions under different behavioral states can reveal a novel view of the rapid changes in spectrotemporal response properties induced by different attentional and motivational states.

Updating the STRF

There is much ongoing research to develop new STRF measurement procedures and structures and to combine them with new methodologies that go beyond the simple ways employed earlier. For instance, generalizing the STRFs to include nonlinear phenomena (Atencio et al. 2008; Christianson et al. 2008; Nagel and Doupe 2008), inhibitory interactions (Schinkel-Bielefeld et al. 2012), and more flexible structures are among the goals being pursued. Also, STRFs are now being regularly estimated with a variety of specialized complex sounds such as bird vocalizations and speech (David et al. 2007; David et al. 2009; Theunissen et al. 2000), measurements that yield STRFs that are tailored to describe more faithfully cortical responses to these sounds. Furthermore, STRFs have now transcended their initial use in single unit recordings and are currently being widely used as a tool to summarize responses in human subjects recorded with fMRI (Zatorre and Belin 2001), MEG (Ding and Simon 2012), EEG (Power et al. 2011), and ECoG (Mesgarani and Chang 2012).

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Spectrotemporal Response Fields

► Spectrotemporal Receptive Fields

Speech Auditory Brainstem Response (sABR)

► Auditory Frequency-Following Responses

Speech Sounds

► Pulse-Resonance Sounds

Speed-Accuracy Tradeoff

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Definition

In many decision tasks, humans and animals cannot simultaneously improve both speed and accuracy of choices (Wickelgren 1977). If subjects are required to be faster, they become less accurate, and conversely, when they are more accurate, they become slower. This inverse relationship between the speed and the accuracy of choices is known as the speed-accuracy trade-off (SAT).

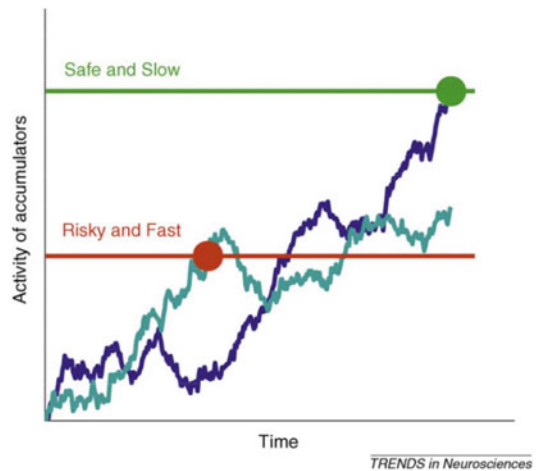
Detailed Description

SAT Results from the Accumulation of Noisy Information

SAT is produced in many models of decision making, but to motivate these models, it is helpful to first briefly review a specific example of a task used for studying the neurobiology of perceptual

decision making. Neural bases of decision making have been studied in a simple task in which a subject is presented with a stimulus consisting of dots moving left or right and on each trial has to make an eye movement in the direction of the movement of the majority of dots. A brain area critical for this task is a part of visual cortex specialized in motion processing (known as V5 or MT), where different neurons are selective for different directions of motion and respond when motion in their preferred direction is present in their receptive field (Britten et al. 1992). These neurons provide information that could be used to make a decision, but the activity of these sensory neurons is noisy due to the noise present in the stimulus and the stochastic nature of neuronal firing. Experimental data suggest that to average out this noise, the output from sensory neurons selective for a particular stimulus is integrated by the frontoparietal neurons selective for a corresponding response (Gold and Shadlen 2007). This is suggested by an observation that the neurons selective for a particular response gradually increase their activity within a trial with a rate that depends on the activity of corresponding sensory neurons. It has been further observed that the movement is initiated whenever the activity of these integrator neurons reaches a certain threshold level (Gold and Shadlen 2007).

Computational models describing the above decision process range from abstract mathematical models, e.g., Ratcliff (1978), to detailed spiking models, e.g., Furman and Wang (2008). The simplest of these models is an abstract race model in which two integrators accumulate independently sensory inputs from two corresponding sources, and the choice is made when the activity of any integrator reaches a threshold (Vickers 1970). The sources of input are noisy, but one of them provides an input with a higher mean, and the choice is considered correct, when the integrator accumulating the information from this source is the first to reach the threshold. The integration process averages out the noise present in the inputs; thus, the longer the period of integration, the higher the probability that the “correct” accumulator wins the race. The ability to trade speed for accuracy in the model arises due to the assumption that subjects are able to vary the distance between the baseline



Speed-Accuracy Tradeoff, Fig. 1 Simulated activity of accumulators in the race model. In the simulation the accumulator corresponding to *dark blue line* received input from a source with a higher mean than the accumulator corresponding to *light blue line*. Green and red lines indicate two possible positions of decision threshold and circles the times when the decision would be made. (Reproduced from Bogacz et al. (2010) with permission from Cell Press)

level of the integrators at the start of the trial and the threshold, as illustrated in Fig. 1. When this baseline to threshold distance is short, the decisions are on average faster but less accurate, whereas when the baseline to threshold distance is long, it takes on average longer to reach the threshold, but the choice is made on the basis of a larger amount of input, so it is more likely to be correct.

Speed Emphasis Increases Baseline Activity

In many computational models, like the race model discussed above, speed and accuracy depend on the baseline to threshold distance: thus, faster choices may be achieved either by lowering the decision threshold or by increasing the initial level of activity of the integrator neurons. Experimental data suggest that the latter mechanism is employed by the brain. Increased baseline with speed emphasis was first suggested by imaging studies that observed higher activity in several decision-related areas before the onset of trials on which participants were required to be fast (Forstmann et al. 2008; Ivanoff et al. 2008;

van Veen et al. 2008). More recently this suggestion was confirmed by a study (Heitz and Schall 2012) in which monkeys were trained to make saccadic choices in three conditions: fast, neutral, and accurate (in the fast condition they were rewarded only if the correct response was made before a certain deadline). Recordings of the activity of neurons from frontal eye field (FEF) in this task revealed that their activity before stimulus onset was indeed higher in the fast than in the neutral condition. Furthermore, a computational model of subcortical neurons receiving input from FEF, which was constrained by the data from the above experiment, suggested that the threshold activity these downstream neurons needed to reach for the response to be initiated was the same for all three conditions (Heitz and Schall 2012).

Control Over Speed and Accuracy

Several detailed theories have been proposed on how the speed and accuracy of choices are controlled in neural decision circuits in cortex (Furman and Wang 2008; Roxin and Ledberg 2008) and basal ganglia (Lo and Wang 2006; Frank et al. 2007; Forstmann et al. 2010). These models describe what inputs or plastic changes in the corticobasal-ganglia circuits could result in the increased baseline activity of cortical integrators with speed emphasis (see previous section), and these theories have been reviewed in more detail by Bogacz et al. (2010). Although these proposed mechanisms are very different from one another, it is conceivable that multiple mechanisms operate in parallel.

Optimal Speed and Accuracy

The selected combination of speed and accuracy of choices influences the reward rate, i.e., the number of rewards per unit of time, in many natural foraging tasks and experimental paradigms. For example, consider a simple paradigm in which on each trial a subject has to judge the direction of movement of the majority of dots (as described earlier) and receives rewards for

correct responses and no penalties for errors, and after each response there is a fixed delay until the beginning of the next trial. In this paradigm the optimal combination of speed and accuracy maximizing the reward rate depends on task parameters (Bogacz et al. 2006). For instance, when the dots move completely randomly, in order to maximize the reward rate, the subject should respond as quickly as possible (as the accuracy cannot be improved by inspecting the stimulus), whereas when substantial fraction of dots move coherently, the subject should take more time to respond more accurately. Experimental evidence suggests that humans indeed adapt their speed and accuracy to improve their reward rate (Simen et al. 2009), especially when given more practice (Balci et al. 2011).

In the above paradigm, if the difficulty of all trials is constant, reward rate is maximized in computational models by setting the baseline to threshold distance to an appropriate constant throughout the trial (Bogacz et al. 2006). However, when the difficulty varies between trials, the distance should change within a trial to maximize reward rate. For example, when a substantial amount of time has elapsed within a trial and the choice has still not been made, the subject may infer that this is a very difficult trial, so it is better to force a decision and move on to the next trial. Methods for estimating the optimal time course of the threshold parameter of decision models have been described (Deneve 2012; Drugowitsch et al. 2012). However, recall that in mathematical models speed and accuracy can be adjusted by varying either the threshold or the baseline level of activity, and experimental data indicate that when difficulty varies between trials, the levels of activity of integrator neurons increase within a trial, eventually forcing a fixed decision threshold to be reached (Churchland et al. 2008).

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Spike Contribution

- [Local Field Potential, Relationship to Unit Activity](#)

Spike Initiation

- [Action Potential Initiation](#)

Spike Metric

- [Spike Train Distance](#)

Spike Rate

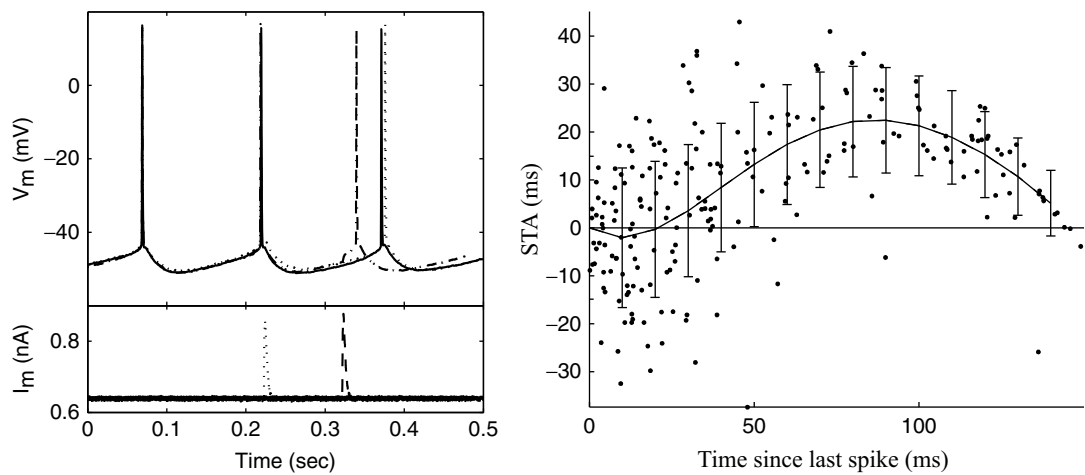
- [Estimation of Neuronal Firing Rate](#)

Spike Time Response Curve

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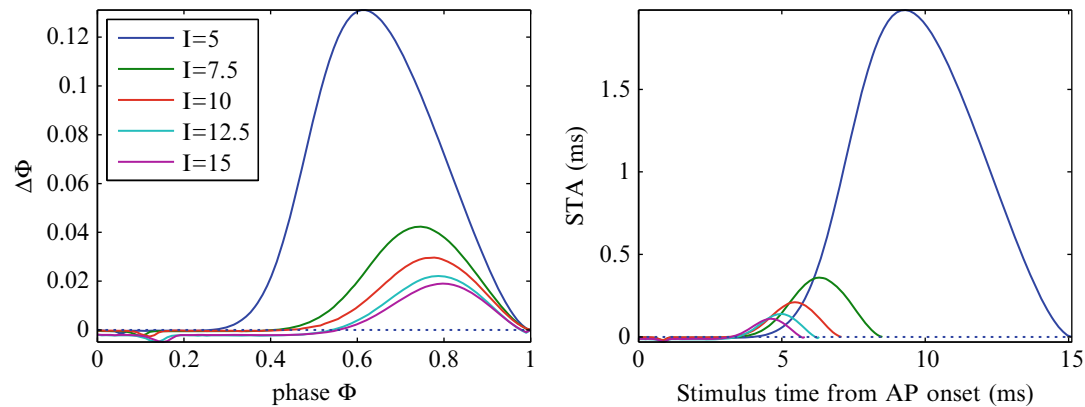
Definition

The spike time response curve (STRC) is a measure of how a stimulus affects the timing of a neuron's action potential. Specifically, in a periodically firing



Spike Time Response Curve, Fig. 1 *Left panel*, a pyramidal neuron in the hippocampus is recorded and stimulated using whole-cell patch clamp. Voltage traces (*top*) and stimulus current (*below*) are plotted from three segments of data. The first interspike interval is unperturbed in all three traces, and interspike intervals are almost identical. In the second interval, a stimulus is applied. The *solid line* shows the unperturbed recording, and the *dotted* and *dashed lines* show recordings where a synaptic-like

stimulus waveform is applied, at a time just after the neuron spikes (*dotted*) and in the *middle* of the period (*dashed*). *Right panel*, the spike time response curve is generated by plotting spike time advance (STA) from the unperturbed interspike interval (150 ms in this case) against the time that the stimulus was applied since the last spike. A polynomial function is fit to the mean and the standard deviation of the data (This figure is modified from Netoff et al. (2005))



Spike Time Response Curve, Fig. 2 Phase response curve compared to STRC. A PRC (*left*) and an STRC (*right*) are measured from a computational model of a neuron at different amounts of applied current. As the

applied current increases, the interspike interval decreases. The PRC is normalized to the change in the unperturbed interspike interval, while the STRC is not. Both graphs represent the same data but with different axes

neuron, the STRC is a measure of the change in the interspike interval given the time of the stimulus pulse since the last action potential. An example of an STRC measured from a pyramidal neuron in the

hippocampus is shown in Fig. 1. The STRC is closely related to the phase response curve (PRC); the difference is that the STRC is not normalized by the period of the neuron.

Detailed Description

An example where the PRC and the STRC provide different information is when comparing stimulus responses at different firing rates of the neuron. Figure 2 shows the same data plotted as a PRC and as an STRC from a model neuron, the $I_{NaP,K}$ model (Izhikevich 2007). As current applied to the neuron increases, the interspike interval shortens. It can be seen at higher current and shorter ISIs, the PRC peak of the PRC shifts to the right. However, when plotted as an STRC, the peak shifts earlier in time. The amplitude of the phase advance is also normalized by the interspike interval. It can be seen that the difference in the peak from the smallest to biggest PRC is about sixfold, while in the STRC, the difference between the smallest peak spike advance and the largest is a twenty-fold difference. As stated above, the STRC retains information about time intervals, whereas the PRC is normalized by the intrinsic period. It is necessary to retain the information about time intervals in order to predict the synchronization properties of periodically driven or reciprocally coupled oscillatory neurons, as described in the entry on ► “Pulse-Coupled Oscillators” (Netoff et al. 2005; Oprisan et al. 2003; Glass and Mackey 1988).

Cross-References

► [Pulse-Coupled Oscillators](#)

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Spike Train

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Definition

A spike train is a sequence of recorded times at which a neuron fires an *action potential*. When the voltage drop across a neural soma or axon membrane is recorded, intermittent pulses of roughly 100 mV over 1–2 ms are observed – these are action potentials or “spikes.” On a behavioral time scale of several hundred milliseconds, each spike may be considered to occur at a single point in time. Sequences of such spike times form spike trains. The total duration of a recorded spike train can range from less than a second to many minutes or even, in chronic recordings, to many days. Spike trains are considered to be the primary mode of information transmission in the nervous system.

Detailed Description

When action potentials are recorded repeatedly from a neuron in response to changing stimuli (or while an organism produces changing behaviors), they maintain a relatively consistent shape. However, the pattern of spike times varies as the stimulus changes. Most prominently, the rate at which spikes occur, the firing rate (FR), varies with conditions. When firing rate is defined in terms of the number of spikes that occur over a time interval of length Δt (such as $\Delta t = 500$ ms), using

$$FR = \frac{\text{number of spikes}}{\Delta t}, \quad (1)$$

this phenomenon of firing rate varying with stimulus is called *rate coding*. While analysis of neural activity in terms of varying firing rates, as defined in Eq. 1, is useful in many contexts, more subtle alterations of the pattern of spike times also occur

and these, too, may convey information. For example, the lengths of gaps between spikes, known as inter-spike intervals (ISIs), often vary substantially across an observed spike train. In principle, a neural communication “code” could carry enormous amounts of information in the specific patterns of spike times, but even in highly controlled in vitro preparations, repeated injection of the same time-varying current can lead to varying spike times, due to the stochastic behavior of ion channels and related sources of noise. Furthermore, synaptic noise is introduced at multiple connections across a neural network. Thus, a good deal of the irregularity of ISIs observed in many parts of the nervous system (especially, in cortex) may be unrelated to any stimulus or behavior. The problem of *neural coding* is to determine the ways that patterns of spike times convey information in particular contexts, possibly extending beyond rate coding. For this purpose, spike trains are subjected to statistical methods of data analysis.

In probability and statistics, irregular sequences of event times are modeled as *point processes*. If we start at time $t = 0$ and let $X_1, X_2, \dots$ be a sequence of random variables representing the ISIs, then the time of the j th spike is given by $S_j = \sum_{i=1}^j X_i$ and the sequence $S_1, S_2, \dots$ forms a point process. In practice, point processes representing spike trains are considered only over some finite interval of time $[0, T]$.

The oldest and most basic model for spike trains is the *integrate-and-fire model*, according to which a neuron is equivalent to an electrical circuit involving a resistor and a capacitor in parallel, together with an input current; the neuron fires whenever the voltage reaches a threshold, then it resets to a fixed resting potential. A component of the input current may be used to represent stochastic synaptic activity. This idea, and many variations on it, is commonly used to generate artificial spike trains in computational studies (Gerstner and Kistler 2002). The resulting spike trains follow point processes and, under simplifying assumptions, can be subjected to theoretical analysis. For example, when excitatory and inhibitory inputs are conceptualized (in the theoretical limit) as Brownian motion, the ISI

distribution may be derived analytically (Tuckwell 1988), and it turns out that certain features of this ISI distribution bear a striking qualitative resemblance to corresponding features of observed spike trains.

Point process representations of spike trains are governed by a theoretical instantaneous firing rate. If we replace the spike count in the numerator of Eq. 1 by its theoretical counterpart, the expected spike count, and then pass to the limit as $\Delta t \rightarrow 0$, we obtain

$$FR(t) = \lim_{\Delta t \rightarrow 0} \frac{P(\text{spike in } (t, t + \Delta t))}{\Delta t}. \quad (2)$$

(For small intervals Δt there is at most 1 spike and the expected count is equal to the probability of spiking.) However, the definition in Eq. 2 omits any mention of both the spiking behavior prior to time t and the experimental context. For instance, immediately after a neuron fires a spike, the probability of the neuron firing again is greatly reduced – this is known as the refractory period. If we write all relevant variables that affect the probability of a neuron firing (including the time of the most recent previous spike) as a vector x_t , we instead obtain the more explicit definition of neural firing rate:

$$FR(t|x_t) = \lim_{\Delta t \rightarrow 0} \frac{P(\text{spike in } (t, t + \Delta t)|x_t)}{\Delta t}. \quad (3)$$

Acknowledging that the numerator of Eq. 3 may involve complicated functions of stimuli, prior spiking patterns, and other variables, a statistical model for spike trains involves two things: (i) a simple, universal formula for the probability density of the spike train in terms of the instantaneous firing rate function defined in Eq. 3 and (ii) a specification of the way the firing rate function depends on the variables x_t (the numerator of Eq. 3). This representation provides a framework that may be called *point process regression* because it relates the specific pattern of spike times, i.e., the spike train, to variables collected as x_t . The full battery of modern statistical machine learning methods may then be applied to the problem of neural coding.

The simplest point process regression models take a special form known in the statistics literature as *generalized linear models* (GLMs). In computational neuroscience the term GLM may refer to any type of point process regression model.

Cross-References

- [Estimation of Neuronal Firing Rate](#)
- [Neural Coding](#)
- [Spike Train Analysis: Overview](#)

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Spike Train Distance

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Synonyms

[Spike metric](#)

Definition

A “spike train distance” is a means for comparing two sequences of stereotyped events. The term “spike metric” refers to a spike train distance that, additionally, has the formal mathematical properties of a metric. Spike train distances have broad application in neuroscience, since the action potentials emitted by a neuron or set of neurons can be regarded as a sequence of stereotyped events; we briefly survey these applications here.

Detailed Description

Spike train distances are rules for assigning a notion of distance, or dissimilarity, to pairs of event sequences. In contrast to most quantitative approaches to the analysis of scientific data, the framework of spike train distances does not make the implicit assumption that the objects of interest (i.e., the event sequences) can be thought of as vectors. In many cases, including the earliest examples of spike train distances (van Rossum 2001; Victor and Purpura 1996, 1997), these distances also satisfy the formal mathematical requirements to be a “metric” (see below). In this case, the event sequences may be considered elements in a “metric space.” A metric space is a topological space that is more general than a vector space. A metric space must have a notion of distance, but it need not have coordinates, nor allow for addition, scalar multiplication, or the measurement of angles.

Two considerations give this general framework a special flavor when applied to neural data. The first consideration is mathematical: for event sequences, it is natural to think of the topology as combining a discrete component with a continuous component. The discrete component is that the number of events in a spike train must be an integer; the continuous component is that each of these events can occur across a continuum of times. The second consideration is biological: much is known about the physiology of neurons and neural circuits, and spike train distances are typically designed with the goal of capturing the

biologically significant aspects of neuronal activity.

As detailed below, two contrasting ideas concerning the biological meaning of a spike train serve as anchor points: (a) the firing events in a spike train might serve primarily as a means to represent an underlying firing rate vs. (b) the times of these firing events might have individual significance, enabling neural computations to be based on coincident firing events across neurons and other aspects of fine temporal structure.

Notation

A spike train – the sequence of action potentials emitted by one or more neurons – is formalized as a sequence of stereotyped events, called spikes, that occur during a fixed observation period $[0, T]$. That is, a spike train A is represented by an ascending sequence of real numbers $t_1^A, \dots, t_{M(A)}^A$ in $[0, T]$, where t_j^A (or simply t_j) is the time of occurrence of the j th spike and $M(A)$ is the total number of spikes (which may be 0).

The above applies to a setting in which all spikes originate from a single neuron or in which the identity of the neurons that generate the individual spikes is not distinguished. It is readily extended to a setting in which the neural activity arises from R different neurons, and the neuron of origin of each event is known: the sequence of times $t_1, \dots, t_{M(A)}$ is associated with a sequence of labels $a_1, \dots, a_{M(A)}$, each drawn from a set of tags $\{1, \dots, R\}$. Thus, spike trains are regarded as a sample drawn from a **point process** (activity of one neuron) or a **labeled point process** (activity of several neurons).

Formal Definition

A spike train distance is a mapping D from the set of spike trains to the nonnegative real numbers that meets the three requirements of a topological **metric**:

Non – negativity: $D(A, B) \geq 0$ and

$$D(A, B) = 0 \text{ only if } A = B \quad (1)$$

$$\text{Symmetry: } D(A, B) = D(B, A) \quad (2)$$

$$\begin{aligned} \text{Triangle inequality: } D(A, C) \\ \leq D(A, B) + D(B, C) \end{aligned} \quad (3)$$

The symmetry property (Eq. 2) and the triangle inequality (Eq. 3) are critical to give the metric the properties that one expects from a distance based on paths between points. Specifically, the symmetry property means that the shortest path between two points does not depend on the direction of travel, and the triangle inequality means that the shortest path between two points (A and C) cannot be any longer than a path that is constrained to stop at a particular intermediate point B . However, the nonnegativity property (Eq. 1) is less crucial and is frequently relaxed to omit the “only if” clause – in which case, D is formally a **pseudometric**. In this case, the space of spike trains can be partitioned into equivalence classes of spike trains that are at distances of zero from each other, and D acts as a metric on these equivalence classes. The “spike count distance,” formalized following Eq. (11), is a simple example of a pseudometric; spike trains with the same number of spikes fall into an equivalence class.

Constructing Spike Train Distances

Spike train distances can be organized into several families. The most straightforward family is based on embedding: spike train distances are defined by mapping the spike trains into a vector space and then adopting the vector space distance. Since the vector space distance is a metric, the resulting spike train distance is also guaranteed to be a metric.

However, spike train distances need not be derived from distances in vector spaces. In cost-based distances, a set of simple transformations of spike trains is specified, along with their (nonnegative) costs. The spike train distance is then defined as the minimal total cost of transforming one spike train into another. Because the distance is defined in terms of a minimum cost

path of transformations, these distances are guaranteed to be metrics. Other families of distances include time-resolved and timescale-independent spike train distances, described below. These constructs, while intuitively distances, do not meet the formal requirements of a metric.

Spike Train Distances Based on Embedding

In the embedding construction, spike trains are first mapped into a **normed vector space** V via a mapping f . Since the vector space norm $\|u\|$ provides a metric on vectors via $D(u, v) = \|u - v\|$, mapping spike trains into vectors yields a metric on the spike trains:

$$D(A, B) = \|f(A) - f(B)\| \quad (4)$$

The nature of the mapping f from the space of spike trains to the vector space is critical. Typically, this mapping respects an additive structure on the spike trains: that is, if $A + B$ denotes the spike train that results from superimposing A and B (with suitable provision made for coincident spikes), then $f(A + B) = f(A) + f(B)$. For such embeddings, then resulting metric is unchanged by parallel translation:

$$D(A + C, B + C) = D(A, B) \quad (5)$$

Spike train distances in this class generally emphasize either the continuous aspect of spike train topology or its discrete aspect. The family of distances introduced by van Rossum (van Rossum 2001) is a prototypical example of the former. We consider first the case of an unlabeled spike train, which here is regarded as a sequence of delta functions. The target vector space consists of scalar functions of time (considered as a continuous variable), and the embedding f consists of a convolution by a kernel function $K(t)$:

$$f(A)(t) = \int_{-\infty}^{\infty} K(t - \tau) \sum_{j=1}^{M(A)} \delta(\tau - t_j^A) d\tau \quad (6)$$

Since the mapping in Eq. (6) from the spike train A to the vector space element $f(A)$ is linear, it follows that the resulting metric, defined by

Eq. (4), is unchanged by parallel translation (as in Eq. 5).

Typically the kernel function K in Eq. (6) includes a parameter that expresses the temporal resolution of the comparison between two spike trains, e.g.,

$$K(t) = \begin{cases} \frac{1}{t_0} e^{-t/t_0} & , t \geq 0. \\ 0, & \text{otherwise} \end{cases} \quad (7)$$

If spikes in train A and train B are matched within this resolution, i.e., if $|t_j^A - t_j^B| \ll t_0$, then the spike train distance between A and B will be small. Gaussians, boxcars, and similar nonnegative windowing functions are also reasonable choices for K . These embedding functions are conventionally used in conjunction with an L^p norm for the target vector space,

$$\|f(A)\| = \left(\int_{-\infty}^{\infty} |f(A)(t)|^p dt \right)^{1/p}, \quad (8)$$

usually with $p = 2$ (the Euclidean norm). Thus, the net result of a linear embedding followed by the vector space norm provides a Euclidean geometry on spike trains.

To extend this kind of spike train distance to the multineuronal setting (R labeled neurons), the target vector space is taken to be vector-valued functions of time (Houghton and Sen 2008), and the norm is the L^2 -norm on the space of vector-valued functions. To define the embedding function f , vectors $\vec{v}_l$ (typically, unit vectors) are assigned to each of the R labels. With this assignment,

$$f(A)(t) = \int_{-\infty}^{\infty} K(t - \tau) \times \sum_{j=1}^{M(A)} \vec{v}_{a(j)} \delta(\tau - t_j^A) d\tau \quad (9)$$

Thus, the j th event, a spike on neuron $a(j)$ at time t_j , is mapped to a bump (the kernel shape) “pointing” in the direction $\vec{v}_{a(j)}$ that has been

assigned to neuron $a(j)$. The angles between the vectors $\vec{v}_i$ correspond to the extent to which the spike train distance is sensitive to the label associated with each spike. An alternative approach is to define multidimensional kernels that spill over from one neuron's spike train to another's (Tezuka 2014, 2018).

In the above examples, the embeddings are linear, and, moreover, time reversal (formally, replacing each t_j with $T - t_{M(A)+1-j}$) has no effect on the resulting distances. Neither of these properties is needed for an embedding to yield a metric; in fact, there are biological motivations to consider distances that derive from embeddings but lack these properties. For example, as a consequence of synaptic facilitation and depression (Sen et al. 1996), the effect of a spike on a post-synaptic neuron depends on how much time has elapsed since the previous spike. This dependence can be incorporated into an embedding function (Brasselet et al. 2011a; Houghton 2009), conferring on it both nonlinearities and time-reversal asymmetries.

Spike train distances based on an embedding can also emphasize their discrete aspect. Specifically, a spike train can be discretized into “bins” of width ΔT (typically chosen to be short enough so that no bin contains more than two spikes) and then regarded as a binary sequence. The Hamming distance between two discretized spike trains (i.e., an L^1 distance in a vector space of dimension $T/\Delta T$) is a spike train distance. The main distinction is that in contrast to the kernel-based distances discussed above, spike trains that have spikes in different bins are regarded as equally distant, regardless of whether or not the times of occurrence of the spikes are close.

Embeddings can also be used to construct measures of spike train **similarity** (i.e., measures that decrease as spike trains become more dissimilar), via the normalized inner product

$$\rho(A, B) = \frac{\langle f(A), f(B) \rangle}{\|f(A)\| \|f(B)\|}, \quad (10)$$

where $\langle u, v \rangle$ is the inner product in the vector space V and $\|v\| = \sqrt{\langle v, v \rangle}$ is the corresponding norm. These similarity measures have an exact

correspondence to a spike train distance, as $\cos^{-1}(\rho(A, B))$ is a metric, namely, the geodesic distance between the unit vectors in the direction of $f(A)$ and $f(B)$ on the unit sphere. The Haas and White measure (Haas and White 2002) uses an exponential kernel for the embedding (Eq. 6); the Schreiber measure (Schreiber et al. 2003) uses a Gaussian kernel. Since these measures are normalized for the spike count of the individual spike trains, they are only sensitive to temporal pattern, and a provision needs to be made for the empty spike train.

Cost-Based Spike Train Distances

While distances constructed via vector space embeddings focus on either the continuous or discrete aspects of the topology of spike trains, cost-based distances attempt to combine these two facets.

The prototypical example was introduced by Victor and Purpura, the “spike time” distance (Victor and Purpura 1997). As is the case for the other distances in this class, the key ingredient is a set of elementary transformations between spike trains, each of which is assigned a cost. Once the elementary transformations have been specified, the distance between two spike trains is the minimal total cost required to transform one spike train into another. That is, the distance $D(A, B)$ is defined as

$$D(A, B) = \min \sum_{k=0}^{K-1} c(X_k, X_{k+1}), \quad (11)$$

where $X_0, \dots, X_K$ is a sequence of spike trains with $X_0 = A$ and $X_K = B$ and each successive spike train linked to the next by an elementary transformation of cost $c(X_k, X_{k+1}) = c(X_{k+1}, X_k)$. For the specific case of the spike time distance, the elementary transformations consist of (i) inserting a spike into a spike train, (ii) deleting a spike from a spike train, and (iii) shifting a spike in time. Inserting or deleting a spike is assigned a cost of 1; shifting a spike by an amount of time Δt is assigned a cost $q|\Delta t|$. The parameter q plays the same role as the parameter $1/t_0$ for the kernel-based distances (Eq. 7): as q increases (or as t_0 decreases), the distance becomes progressively more sensitive to fine timing differences. For

$q = 0$, the distance is entirely insensitive to timing differences (so, formally, it is a pseudometric), since spikes can be moved “for free.” In this limit, the distance which is often called the “spike count distance” is simply the difference in spike counts, $D(A, B) = |M(A) - M(B)|$.

The choice of elementary transformations determines the qualitative nature of the distance. A contrasting example of the spike time distance is the “interspike interval” distance (Victor and Purpura 1997), in which the elementary transformations act on interspike intervals, rather than on the spike times themselves. Since changing the length of one interspike interval shifts the time of all successive spikes, two spike trains can be close in terms of the spike interval distance, but not in terms of the spike time distance. Thus, these distances confer different topologies on the space of spike trains: the topology of the spike time distance is equivalent to that of the van Rossum distance (Eq. 6) with a typical kernel, but the topology of the spike interval distance is not. Additionally, the spike time distance is invariant under parallel translation (adding a common spike train to the spike trains being compared, as in Eq. (5)), while the spike interval distance is not. Cost-based distances are typically non-Euclidean (Aronov and Victor 2004; Dubbs et al. 2010).

Cost-based distances are also applicable to the multineuron setting (Aronov et al. 2003). For the spike time distance, a straightforward approach is to include an elementary transformation that assigns a cost to changing the neuronal label associated with a spike. Parametric variation of this cost changes the character of the distance from one that is sensitive to overall population activity (low cost to change the label) to one that is sensitive to cross-population patterns (high cost to change the label).

For cost-based distances, the overall distance and the costs associated with elementary transformations can be interpreted in terms of a generative model for spike trains (Dauwels et al. 2009). Cost-based distances can also be formulated in terms of “alignments” between spikes, rather than transformations (Dubbs et al. 2010).

The above constructions can be generalized in many ways. To name a few, normalization by spike count can be applied; the costs of each transformation (Victor et al. 2007) or alignment (Dubbs et al. 2010) can be transformed by a power law prior to summation; elementary transformations sensitive to burst structure can be added (Victor and Purpura 1997); and different kinds of elementary transformations can be combined.

Timescale-Independent Spike Train Distances

Complementary to the timescale-dependent approaches, in recent years spike train distances have been proposed which are timescale and thus parameter free since they always adapt to the local firing rate. While not allowing the functional characterization and precision analysis described above, single-valued methods give an objective and comparable estimate of neuronal variability (Chicharro et al. 2011). Measures in this group include the ISI-distance (Kreuz et al. 2007), the SPIKE-distance (Kreuz et al. 2013), and the SPIKE-synchronization (Kreuz et al. 2015).

ISI-Distance and SPIKE-Distance

The ISI-distance D_I and the SPIKE-distance D_S rely on instantaneous values in the sense that in a first step the sequences of discrete spike times are transformed into piecewise-continuous dissimilarity profiles $I(t)$ and $S(t)$. For the ISI-distance (Kreuz et al. 2007), the dissimilarity profile is derived from the interspike intervals, while in the case of the SPIKE-distance (Kreuz et al. 2013), it is extracted from differences between the spike times of the two spike trains. Both distances are then defined as the temporal average of the respective dissimilarity profile, e.g., for the SPIKE-distance

$$D_S = \frac{1}{T} \int_{t=0}^T S(t) dt. \quad (12)$$

The two dissimilarity profiles rely on three piecewise constant quantities which for each neuron ($X = A$ or $X = B$ below) are assigned to every time instant between 0 and T . These are the time of the preceding spike

$$t_P^X(t) = \max(t_i^X | t_i^X \leq t), \quad (13)$$

the time of the following spike

$$t_F^X(t) = \min(t_i^X | t_i^X > t), \quad (14)$$

and the interspike interval

$$z_{ISI}^X(t) = t_F^X(t) - t_P^X(t). \quad (15)$$

The ambiguity regarding the definition of the very first and the very last interspike interval is resolved by means of auxiliary spikes (Kreuz et al. 2015).

ISI-Distance The ISI-distance (Kreuz et al. 2007) is a time-resolved, symmetric, and timescale-adaptive measure of the relative firing rate pattern. It is defined as the normalized ratio between the instantaneous interspike intervals $z_{ISI}^A(t)$ and $z_{ISI}^B(t)$ (Fig. 1a):

$$I(t) = \frac{z_{ISI}^A(t) - z_{ISI}^B(t)}{\max(z_{ISI}^A(t), z_{ISI}^B(t))}. \quad (16)$$

This quantity is 0 when the ISIs in the two spike trains are equal and approaches -1 and 1 , respectively, if the first or the second spike train is much faster than the other. Since both directions of deviation from identical ISIs are equally important, the ISI-distance is calculated by temporal averaging over the absolute values $|I(t)|$ in Eq. (12).

SPIKE-Distance The ISI-distance relies on the relative length of simultaneous interspike intervals and is thus capable to quantify similarities in the neurons' firing rate profiles. However, it is not optimally suited to track synchrony that is mediated by spike timing. This issue is addressed by the SPIKE-distance (Kreuz et al. 2013) which combines the properties of the ISI-distance with a specific focus on spike timing.

The dissimilarity profile of the SPIKE-distance is based on differences between the spike times in

the two spike trains. It is calculated in two steps: first, for each spike, the distance to the nearest spike in the other spike train is calculated. Then, for each time instant, the relevant spike time differences are selected, weighted, and normalized. Here "relevant" means "local," i.e., each time instant is uniquely surrounded by four corner spikes: the preceding spike of the first spike train t_P^A , the following spike of the first spike train t_F^A , the preceding spike of the second spike train t_P^B , and, finally, the following spike of the second spike train t_F^B (Fig. 1b). Each of these corner spikes can be identified with a spike time difference, for example, for the previous spike of the first spike train

$$\Delta t_P^A = \min_k (|t_P^A - t_k^B|) \quad (17)$$

and analogously for t_F^A , t_P^B , and t_F^B .

For each spike train separately, a locally weighted average is employed. The weighting factors ensure that the differences for the closer spike dominate: the weighting factors depend on

$$z_P^A(t) = t - t_P^A(t) \quad (18)$$

and

$$z_F^A(t) = t_F^A(t) - t, \quad (19)$$

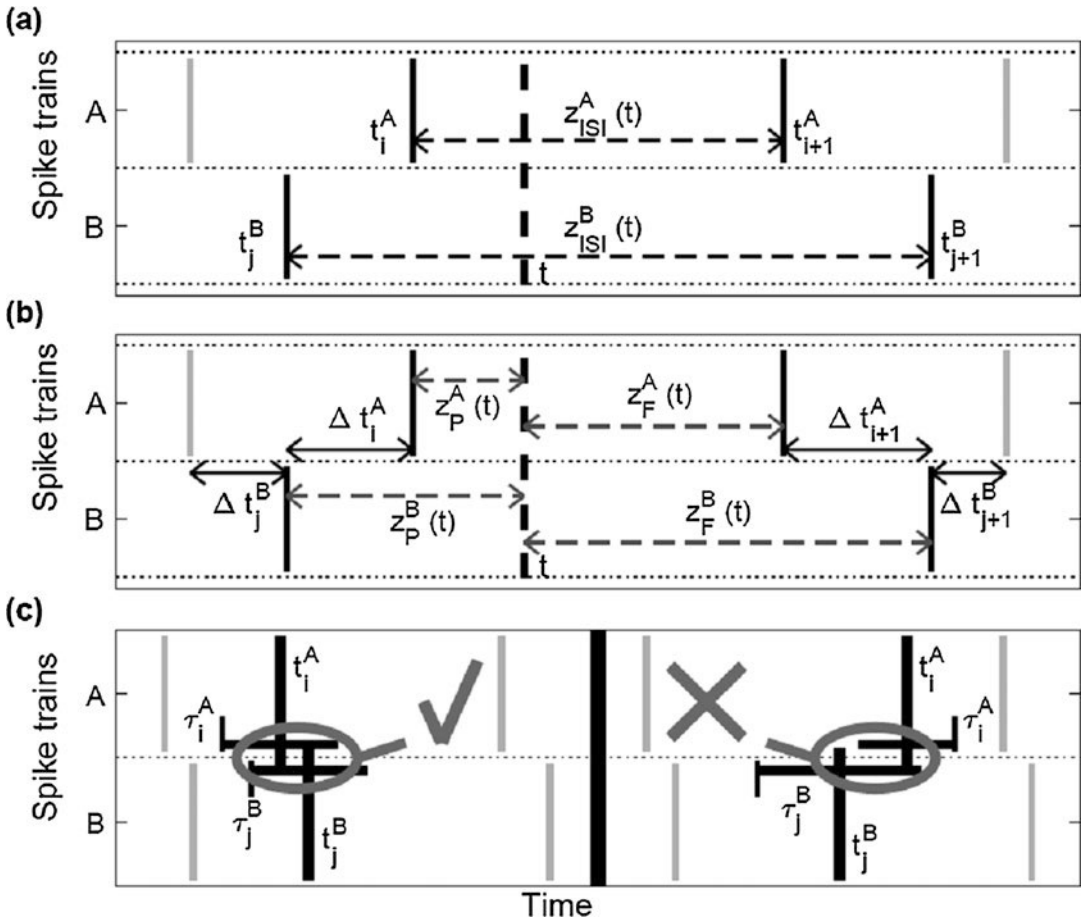
the intervals to the previous and the following spikes for each neuron. The local weighting for the spike time differences of the first spike train reads

$$S_A(t) = \frac{\Delta t_P^A(t) z_F^A(t) + \Delta t_F^A(t) z_P^A(t)}{z_{ISI}^A(t)}. \quad (20)$$

For the second spike train, $S_B(t)$ is obtained analogously.

Averaging over the two spike train contributions and normalizing by the mean interspike interval yield

$$S'(t) = \frac{S_A(t) + S_B(t)}{2 \langle z_{ISI}^X(t) \rangle_{X=A,B}}, \quad (21)$$



Spike Train Distance, Fig. 1 Schematic of the three timescale-independent measures. (a) The variables that define the ISI-distance. The instantaneous interspike intervals are used as estimates of the local firing rate. (b) Additional variables employed in the definition of the SPIKE-distance, which is based on spike time differences. (c) Coincidence criterion for SPIKE-synchronization. The coincidence window of each spike is derived from its two surrounding interspike intervals. The two spikes on the left side are considered coincident since both lie in each other's coincidence windows, while on the right, there is no

coincidence since the spike from the second spike train is outside of the coincidence window from the spike of the first spike train. The quantity $\tau_{ij}^{A,B}$ in the text (Eq. 24) is defined as $\tau_{ij}^{A,B} = \min(\tau_i^A, \tau_j^B)$. (Modified with permission from Fig. 1 of Satuvuori E, Malvestio I, Kreuz T: Measures of spike train synchrony and directionality In: Neuro-Math, Mathematical and Computational Neuroscience: Cell, Network and Data analysis (Springer INdAM series, 2018))

where $\langle z_{ISI}^X(t) \rangle_{X=A,B}$ is the average of the local ISIs of spike trains A and B .

This quantity weights the spike time differences for each spike train according to the relative distance of the corner spike from the time instant under investigation. Averaging over this dissimilarity profile $S'(t)$ according to Eq. (12) yields the rate-independent SPIKE-distance (RI-SPIKE-distance) D_S^{RI} (Satuvuori et al. 2017), which

completely disregards any rate differences between the two spike train and thus focuses purely on spike timing information.

In order to also account for differences in firing rate, in a last step, the two contributions from the two spike trains are locally weighted by their instantaneous interspike intervals. This leads to the dissimilarity profile of the SPIKE-distance

$$S(t) = \frac{S_A(t)z_{ISI}^B(t) + S_B(t)z_{ISI}^A(t)}{2\langle z_{ISI}^X(t) \rangle_{X=A,B}^2} \quad (22)$$

which is thus sensitive to both spike rate and spike timing (Satuvuori and Kreuz 2018).

The dissimilarity profiles of both the ISI-distance and the SPIKE-distance and thus both distances are bounded in the interval $[0, 1]$. For the ISI-distance, the minimum value 0 is obtained for any periodic spike trains with the same period. Thus the ISI-distance is a pseudometric, in which all spike trains with a certain constant interspike interval but overall time shifts form the equivalence classes (Mulansky et al. 2015). On the other hand, for the SPIKE-distance, the value 0 is indeed obtained only for perfectly identical spike trains, but it is possible to construct examples that violate the triangle equality (Mulansky et al. 2015), so the SPIKE-distance is not a metric.

For both distances there exists a straightforward extension to estimate the time-resolved level of dissimilarity within a group of spike trains (Kreuz et al. 2009, 2013). It is the straightforward average over all pairs of spike trains, but in these cases, the averaging can be performed locally, e.g., for the SPIKE-distance:

$$S^a(t) = \frac{1}{M(M-1)/2} \sum_{n=1}^{M-1} \sum_{m=n+1}^M S^{mn}(t). \quad (23)$$

SPIKE-Synchronization

SPIKE-synchronization (Kreuz et al. 2015) acts as coincidence detectors and quantifies the level of synchrony from the number of quasi-simultaneous appearances of spikes. It is a measure of similarity, i.e., for identical spike trains, it yields not its minimum value 0 but its maximum value 1.

The calculation consists of two steps, coincidence detection and a combination of normalization and windowing. The first step builds on the same bivariate and adaptive coincidence detection that was used for event synchronization (Quiroga et al. 2002). The temporal resolution can be adjusted with a coincidence window of fixed size τ , but in the parameter- and timescale-free main variant, the maximum time lag $\tau_{ij}^{A,B}$ up to

which two spikes t_i^A and t_j^B are considered to be synchronous is adapted to the local spike rates according to:

$$\tau_{ij}^{A,B} = \frac{1}{2} \min \left[t_{i+1}^A - t_i^A, t_i^A - t_{i-1}^A, t_{j+1}^B - t_j^B, t_j^B - t_{j-1}^B \right]. \quad (24)$$

The coincidence criterion can be quantified by means of a coincidence indicator

$$C_i^A = \begin{cases} 1 & \text{if } \min_j (|t_i^A - t_j^B|) < \tau_{ij}^{A,B} \\ 0 & \text{otherwise} \end{cases} \quad (25)$$

(and analogously for C_j^B), which assigns to each spike either a one or a zero depending on whether it is part of a coincidence or not (Fig. 1c). Here the minimum function already takes into account that a spike can at most be coincident with one spike in the other spike train. If a spike is exactly in between two spikes from the other spike train, this is not considered a coincidence.

The extension to the case of one group of more than two spike trains is straightforward. After performing bivariate coincidence detection for every pair of spike trains, for each spike of every spike train, a normalized coincidence counter

$$C_i^A = \frac{1}{M-1} \sum_{X \neq A} C_i^{A,X} \quad (26)$$

is obtained by averaging over all $M-1$ bivariate coincidence indicators involving the spike train A . This way for both the bivariate and the multivariate case, we have defined a coincidence counter for each individual spike in every spike train. In order to obtain one combined similarity profile, we pool the spikes of all the spike trains as well as their coincidence counters by introducing one overall spike index j . In case there exist exact matches (perfectly coincident spikes), j counts over all of these spikes. From this discrete set of coincidence counters C_j , the SPIKE-synchronization profile $C(t_j)$ is obtained via $C(t_j) = C(j)$. Finally, SPIKE-synchronization is defined as the average value of this profile

$$S_C = \frac{1}{M_p} \sum_{j=1}^{M_p} C(t_j) \quad (27)$$

with $M_p = \sum_X M(X)$ denoting the total number of spikes in the pooled spike train.

The interpretation is very intuitive: SPIKE-synchronization quantifies the overall fraction of coincidences. It is zero if and only if the spike trains do not contain any coincidences and reaches one if and only if each spike in every spike train has one matching spike in all the other spike trains.

SPIKE-synchronization is complementary to the distances described above. It is a measure of spike matching based on a binary coincidence criterion. If converted from a measure of similarity into a measure of distance (by considering $1 - S_C$), it would remain symmetric, but it would fail to be a metric. This is because of the binariness of the coincidence criterion: there are nonidentical spike trains that would have a distance of zero (violating Eq. (1)), and it is possible to construct violations of the triangle inequality (Eq. 3) (Mulansky et al. 2015). SPIKE-synchronization is complemented by SPIKE-order and spike train order (Kreuz et al. 2017), two indicators that allow to sort spike trains from leader to follower and to quantify the consistency of the temporal leader-follower relationships for both the original and the optimized sorting.

All three of these timescale-independent approaches (the ISI-distance, the SPIKE-distance, and the SPIKE-synchronization) have recently been adapted for data containing multiple timescales by adding a notion of the relative importance of local differences compared to the global timescales (Satuvuori et al. 2017).

Other Timescale-Independent Measures

The modulus- and the max-metric (Rusu and Florian 2014) form another family of metrics which is timescale free as well and can also be turned into a time-resolved profile. Both measures are more sensitive to large-scale temporal structure and less sensitive to spike counts and to fine structure within bursts. The most recent proposal

in this group is spike-contrast, a further timescale-independent and multivariate measure of spike train synchrony (Ciba et al. 2018). It mostly yields very similar results to the SPIKE-distance; however, it is complementary since it does not provide a time-resolved dissimilarity profile but instead a synchrony curve as a function of bin size (one of several parameters).

Other Types of Spike Train Distances

There are several useful spike train distances that do not fall into these major categories. The family of metrics proposed in (Wu and Srivastava 2011) resembles an embedding-based metric in that the spike trains are mapped to functions using a kernel; however, these metrics also allow for time to be warped for one spike train relative to the other to bring them into better alignment. In a manner which is reminiscent of a cost-based metric, this warping is associated with a penalty. This metric facilitates the calculation of a “mean spike train,” something that can also be calculated using an embedding-based metric (Julienne and Houghton 2013).

The Hunter-Milton measure compares spike times in one train with the nearest spike times in the other (Hunter and Milton 2003). A choice of scale parameter is required. Lyttle and Fellous have proposed metrics to specifically assess the similarity of spike trains with either common silent periods or bursts (Lyttle and Fellous 2011). Both metrics can be adapted to the dataset by means of several parameters. Finally, the “coincidence factor,” while not a distance, has also been used to compare discretized spike trains based on a normalized count of coincidences (Jolivet et al. 2008; Kistler et al. 1997).

Applications: Analytical Methods

Spike train distances are the starting point for many analysis and modeling strategies. The distinctive feature of this starting point (i.e., considering spike trains to be event sequences, vs. considering them to be vectors) is that it allows for a much more flexible kind of geometry and focuses on intrinsic relations between spike trains, rather than a coordinate system for them. As we

describe below, this enables a variety of approaches to exploratory data analysis, neural coding, and model testing. We first survey these approaches according to the type of analysis and then describe some examples of these applications in neuroscience and behavior. For earlier reviews, see Houghton and Victor (2011), Victor (2005), and Victor and Purpura (2010).

Dimension Reduction

A main challenge in analyzing neural data is its high dimensionality. Thus, as a first step in exploratory analysis or data visualization, it is often helpful to construct a low-dimensional representation of a dataset that preserves key aspects of its structure. From the spike train distance viewpoint, the central goal is to preserve similarity; thus, the crucial requirement in dimensional reduction is to preserve the metric.

The classical approach to accomplishing this is standard multidimensional scaling (Kruskal and Wish 1978), which can be directly applied to spike metrics. Multidimensional scaling is algebraically related to principal components analysis, but in multidimensional scaling, there is no need to identify coordinates or to conceptualize the spike trains as points in a vector space. When applied to a cost-based distance, multidimensional scaling approach often leads to a representation of the neural responses that recapitulates the geometry of the domain being represented (e.g., spatial phase (Aronov et al. 2003) or sound location (Victor and Purpura 1997)).

The global geometry of cost-based distances is typically non-Euclidean (Aronov and Victor 2004). As a consequence, standard multidimensional scaling can at best approximate these (and perhaps other) spike train distances. One approach to this problem is to apply multidimensional scaling to a monotonic function of the distance (such as d^p for $0 < p < 1$), rather than the raw distances themselves. For a sufficiently small but data-dependent p , these derived distances can be exactly embedded into a Euclidean space. An alternative approach is to seek an embedding that focuses on local geometry: the isomap (Tenenbaum et al. 2000) or local linear

embedding (Roweis and Saul 2000) approaches can be used to expand a locally Euclidean representation to a non-Euclidean manifold. The t-distributed stochastic neighbor embedding (t-SNE) is another such nonlinear dimensional reduction approach, which is particularly suitable for sampled data and also focuses on local geometry. Specifically, combining spike train metrics with t-SNE (van der Maaten and Hinton 2008) has been found to be effective for single-neuron and multineuronal datasets (Vargas-Irwin et al. 2015), as well as for nonneural data – bat biosonar, an acoustic emission that can be considered as a sequence of pulses (Accomando et al. 2018).

Information-Theoretic Analysis

Spike train distances are also the starting point for information-theoretic analyses of neural coding. For example, they can be used as a way to estimate the **mutual information** between a set of stimuli and a set of responses, by determining the extent to which neural responses to a set of stimuli form reliable clusters. The dependence of this estimate on the kind of spike train distance used (e.g., one that is sensitive to spike times, vs. spike intervals, or the degree of temporal precision of the distance) points to the features of the neural response that carries the information (Satuvuori and Kreuz 2018; Victor and Purpura 1997). Spike train distances can also be combined with the Kozachenko-Leonenko estimator (Kozachenko and Leonenko 1987) to provide estimates of mutual information, without the need for explicit clustering (Houghton 2015; Houghton 2019; Shapira and Nelken 2013). It is important to note, however, that these approaches typically yield underestimates of mutual information, since they focus on a single timescale and use a very limited number of parameters to describe the possible relationships between spike trains (Lopes-dos-Santos et al. 2015).

Model Evaluation

Spike train distances provide a way to measure the quality of a neural model, by determining the distance between experimentally observed spike trains and models of them (Kameneva et al. 2015). Extending this idea, a spike time distance can also

be used as a cost function to be minimized by adjusting model parameters (Lynch and Houghton 2015) or as a cost function to drive learning algorithms that shape artificial networks to process temporal patterns (Florian 2012). They can also provide a way to quantify whether a model accounts for neuronal variability, by determining the distances between members of a set of spike trains that represent samples of spontaneous activity or samples of responses to the same stimulus.

Applications to Neuroscience

As spike train metrics are metrics on sequences of events, they can be applied to any problem where the data are sets of event sequences. However, they are primarily designed to express the metric structure of spike trains that is functionally or mechanistically relevant and are most often applied to the analysis of electrophysiological data.

One frequent application is as a tool for quantifying how information is coded in spike trains. In describing the different spike train metrics, it has been noted that they often have a parameter interpolating between a spike count pseudometric and metrics in which the precise timing of individual spikes is very significant. In the case of the embedding metrics, this parameter is the width of the kernel used in the embedding, for example, if the kernel is given by Eq. (7), it is t_0 ; in the case of the cost-based metric, it is q , the cost of moving a spike (see discussion following Eq. (11)). This parameter can be fitted to stimulus-evoked spike train data by choosing the value where the metric-based clustering best matches clustering according to stimulus. This gives an indication of the temporal scale relevant to the coding of information about the stimulus in the spike trains. This approach was used, for example, in analyzing visual responses in V1, V2, and V3 in monkey in Victor and Purpura (1996) and in analyzing auditory responses in zebra finch in Narayan et al. (2006). A related approach is used in Brasselet et al. (2009, 2011b) where a metric analysis combined with a novel definition of mutual information is used to argue for the primacy of the latency of first spike in encoding tactile information in human microneurography data.

In multineuronal spike train metrics, there is often a parameter which specifies how significant the individual neurons are in coding; this parameter interpolates between a population code where the identity of the neuron firing a spike has no effect on the distance and a “labeled line code” where the spike train distance between a pair of multineuron spike trains is effectively the sum of the distances between the individual pairs of spike trains for individual neurons. This was used, for example, in Clemens et al. (2011) to analyze the degree of population coding of auditory information in grasshoppers.

These applications all compare responses by the same neuron, or neurons, across different stimuli. Another application of spike train metrics is the detection of cell assemblies; this involves comparing the spiking responses of different neurons to the same stimulus (Humphries 2011, 2017): roughly, a network is formed whose nodes correspond to neurons and the links to a measure of similarity derived from a spike train metric; assemblies are then identified using community detection algorithms. This approach has been applied to CA3 in hippocampus (Li et al. 2010), to reaching tasks in monkey (Newman et al. 2011), and similar ideas can be applied to recordings of activity in the retina (Cutts and Eglén 2014). In Kreuz et al. (2013), the SPIKE-distance is used to study synchrony between recording sites in data recorded from epilepsy patients. It is demonstrated that during ictal periods, there is an elevated level of neuronal synchrony in the hemisphere containing the seizure focus.

It is important to note that the spike metric framework, by itself, is not a statistical one – a spike metric yields a number that indicates the distance between two specific spike train examples, and not a way of assessing whether this difference is statistically significant. Any assessment of statistical significance requires either a model for spike train variability or experimental assessment of this variability, which is independent of the choice of the metric. With a model of variability or a data-driven assessment of it, standard statistical techniques (either parametric or nonparametric) can be applied.

Computation of Spike Train Distances

Computation of distances based on embeddings is straightforward, as the essential steps are convolution and pairwise multiplication. Houghton and Kreuz (2012) introduced a markage trick which reduces the computational cost for the regular van Rossum metric between two spike trains of similar length, $M(A) \sim M(B)$, to order $M = M(A) + M(B)$ from order M^2 . The same markage trick can also be used for the multineuron extension.

For cost-based distances, dynamic programming algorithms modeled after alignment algorithms for genetic sequences (Needleman and Wunsch 1970; Sellers 1974) provide an efficient way to identify the minimal-cost sequence of transformations in the single-neuron setting and for settings with a small number of neurons. The number of computations is approximately $O(M^2)$ for unlabeled spike trains containing M events and $O(M^{R+1})$ when R neurons (labels) are present. These algorithms extend to enable simultaneous computation of distances for all values of its parameters (cost to move a spike, cost to change a label) (Victor et al. 2007). For the single-neuron scenario and single values of the cost parameter, a graph-theoretic approach based on the “Hungarian” algorithm may provide improved performance (Dubbs et al. 2010). For five or more neurons, an incremental matching algorithm (Diez et al. 2012) is the most efficient approach currently available; the computational complexity (specifically, the number of computations required) scales approximately as M^6 , independent of the number of neurons.

Finally, the calculation of the time-resolved and timescale-independent spike train distances is very straightforward since it involves only simple arithmetic. Computational complexity for the ISI-distance and the SPIKE-distance is $O(M)$; for SPIKE-synchronization, it is $O(M^2)$.

A comprehensive compilation of links to code to calculate spike train distances can be found at <http://wwwold.fi.isc.cnr.it/users/thomas.kreuz/sourcecode.html>. Additionally, software for the cost-based distances may be found at <http://www-users.med.cornell.edu/~jdvicto/pubalgor.html>, <http://www.csse.monash.edu.au/~lloyd/tildeAlgDS/Dynamic/Edit/>, and in the Spike Train Analysis

Toolkit, at <http://neuroanalysis.org/>. The latter site also includes modules for information-theoretic calculations based on these distances.

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Metric Space Analysis of Neural Information Flow](#)
- [Spike Train](#)
- [Spike Train Analysis: Overview](#)

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Further Reading

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Spike Triggered Average

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Synonyms

[Reverse correlation](#); [SFC](#); [Spike-field coherence](#); [STA](#)

Definition

The spike-triggered average (STA) is a measure to relate a continuous signal and a simultaneously recorded spike train. It represents the average signal taken at the times of spike occurrences and with proper normalization is equivalent to the cross-correlation between the continuous signal and the spike train.

Detailed Description

The STA is widely used to study the temporal relationship between a spike train and a simultaneously recorded continuous signal, such as the local field potential (Eckhorn et al. 1988; Gray and Singer 1989; Murthy and Fetz 1996; Fries et al. 2001; Okun et al. 2010; Denker et al. 2011), membrane potential (Matsumura et al. 1996; Lampl et al. 1999; Poulet and Petersen 2008), synaptic conductance (under dynamic clamp, Gauck and Jaeger 2000) and electromyogram (McKiernan et al. 1998). Even non-physiological signals, such as electric stimulation to a single neuron (Mainen and Sejnowski 1995) or visual (Ringach and Shapley 2004) and auditory (Eggermont et al. 1983) stimulation, have been related to a spike train via the STA. In such cases the STA is commonly referred to as reverse correlation.

Here we introduce the STA in relation to the local field potential (LFP). The LFP signal is obtained as a low-frequency component, typically below approximately 100 Hz, of extracellular recordings of neuronal electric activity. Its physiological origin is the transmembrane current of neurons in the vicinity of the recording electrode (Mitzdorf 1985; Nunez and Srinivasan 2006). Theoretical considerations and experimental observations have elucidated that the strongest contribution to the LFP is from the currents caused by postsynaptic potentials, while the influence of action potentials on the LFP is weak (Mitzdorf 1985; Logothetis 2003; Buzsaki et al. 2012). Therefore, the LFP predominantly reflects the synaptic inputs to the local neuronal circuit around the tip of the recording electrode (including the recurrent inputs due to internal processing of the circuit) (Logothetis 2003). This view is further strengthened by the observation that temporal modulations of the (intracellularly recorded) somatic membrane potential of a single cell, which represent net synaptic input to the cell, are tightly correlated with modulations of the (extracellularly recorded) LFP in the vicinity of that same cell (Poulet and Petersen 2008; Okun et al. 2010). Given that spikes are the output of single

neurons, the relationship between simultaneously recorded spikes and LFPs could be interpreted as reflecting the input–output relation of the local brain area [cross-ref: Local Field Potential, Relationship to Unit Activity].

It has been shown in various species and various cortical/subcortical brain regions that LFPs exhibit distinct oscillations in a wide range of frequencies (Buzsaki 2006). Previous studies have identified modulations of these oscillatory activities as reflecting changes in the functional states of perceptual, cognitive, and motor processes in the brain. An important question about the spike-LFP relation would therefore be whether, and if so how, temporal modulations of spiking activity are related to LFP oscillations or, more concretely, how the timings of spike occurrences correlate with the phase of LFP oscillations.

The spike-triggered average (STA) is a commonly used measure for assessing the temporal relation between a spike train and an LFP signal. Assume simultaneous recordings of a spike train, represented as time points t_i ($1 \leq i \leq N$; N , total number of spikes) of spike occurrences, and an LFP signal, represented by $X(t)$, where t is time. For simplicity, also assume that the recording time is sufficiently long. The STA is defined as

$$STA(\tau) = \frac{1}{N} \sum_{i=1}^N X(t_i + \tau), \quad (1)$$

i.e., the average value of $X(t)$ at a given time lag τ in relation to the spike time t_i . This is equivalent to the cross-correlation (with normalization by the number of spikes) between the LFP signal and the spike train:

$$STA(\tau) = \frac{1}{N} \int_{-\infty}^{\infty} X(t + \tau) Y(t) dt,$$

with $Y(t) = \sum_{i=1}^N \delta(t - t_i)$ representing the spike train as a sum of Dirac delta functions $\delta(\cdot)$. Typically the STA is computed for a range of lags τ around the spike times, so that the waveform of the STA as a function of the lag illustrates the average modulation of the LFP around the

occurrences of spikes. The STA obtained in this manner is widely used as a measure of the temporal locking of spikes to oscillatory LFP modulations (Eckhorn et al. 1988; Gray and Singer 1989; Murthy and Fetz 1996; Fries et al. 2001; Okun et al. 2010; Denker et al. 2011).

When spikes occur preferentially at a specific phase of LFP oscillations, the summation in the right-hand side of Eq. 1 accumulates LFP values at similar phases of the oscillation for each lag τ , resulting in the STA having an oscillatory waveform with the preferred phase represented at $\tau = 0$. Thus, the degree of temporal spike-to-LFP locking can be evaluated by the strength of oscillatory modulations of the STA, i.e., the greater the modulation, the stronger the locking. A caveat is, however, that the strength of modulation depends not only on the degree of locking but also on the amplitudes of the oscillatory components of the LFP signal. One way to quantify the degree of locking in spite of this amplitude dependence is to estimate the significance of the oscillatory modulation in the obtained STA by use of a bootstrap method. Commonly used methods include trial shuffling, spike randomization, and spike dithering [cross-ref: Surrogate Data for Evaluation of Spike Correlation]. A proper use of bootstrap significance tests also enables rejection of artificial locking due to non-stationarities in the firing rate of the spike train (Grün 2009; Louis et al. 2010).

The oscillatory power of LFP signals typically shows a strong dependence on frequency. Therefore, the amplitude dependence causes another concern when the LFP signal contains oscillatory components at multiple frequencies and one wishes to compare the strengths of the spike-to-LFP locking at different frequencies. To normalize for the difference in power at different frequencies, it is possible to move from the time domain to the frequency domain. Spike-field coherence (SFC) is a measure derived from the STA through such normalization. It is defined as

$$SFC(f) = |\tilde{STA}(f)|^2 / |\tilde{X}(f)|^2,$$

where

$$\begin{aligned} \tilde{STA}(f) &= \int_{-\infty}^{\infty} STA(\tau) e^{-2\pi i f \tau} d\tau, \tilde{X}(f) \\ &= \int_{-\infty}^{\infty} X(t) e^{-2\pi i f t} dt, \end{aligned}$$

i.e., the power spectrum of the STA normalized by the power spectrum of the LFP signal used to compute the STA (Fries et al. 2002). For each frequency, f , the SFC takes on a value between 0 and 1, which corresponds to independence and to perfect locking, respectively, between the spike train and the corresponding spectral component of the LFP. Owing to the normalization by the LFP power, SFC serves as a proper measure for comparison of the degree of spike-to-LFP locking at different frequencies. Studies have shown that the modulation of SFC is related to various aspects of brain function such as sensory processing (Womelsdorf et al. 2006), attention (Chalk et al. 2010), working memory (Pesaran et al. 2002), and decision making (Pesaran et al. 2008).

Cross-References

- [Auditory-Nerve Response, Afferent Signals](#)
- [Dynamic Clamp Technique](#)
- [Gamma and Theta Oscillations, Hippocampus: Overview](#)
- [Local Field Potential, Relationship to Unit Activity](#)
- [Local Field Potentials: LFP](#)
- [Low Frequency Oscillations \(Anesthesia and Sleep\): Overview](#)
- [Significance Evaluation](#)
- [Spike Train](#)
- [Surrogate Data for Evaluation of Spike Correlation](#)

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Spike-Dependent Synaptic Learning Rules

► Spike-Timing Dependent Plasticity, Learning Rules

Spike-Field Coherence

► Spike Triggered Average

Spike-Frequency Adaptation

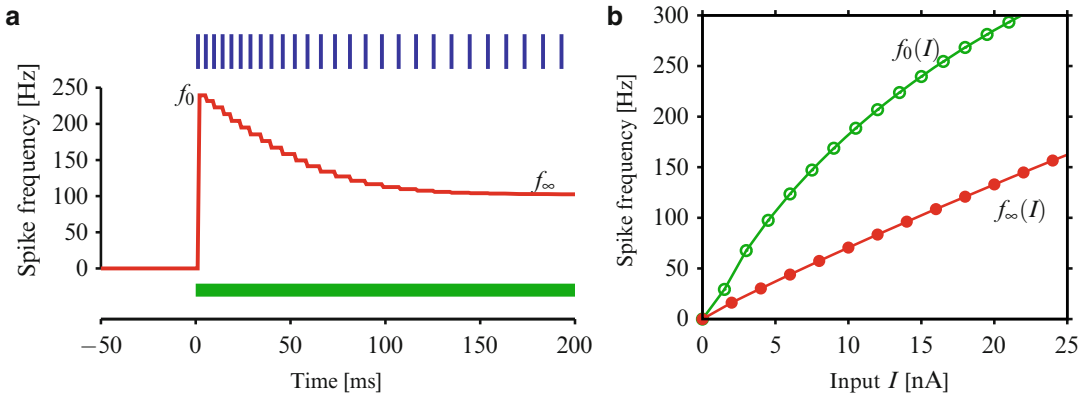
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Definition

When stimulated with a constant stimulus, many neurons initially respond with a high spike



Spike-Frequency Adaptation, Fig. 1 Phenomenon spike-frequency adaptation. (a) Spike train (vertical strokes at the top) of an adapting neuron evoked by the onset of a constant stimulus (green bar at the bottom, $I = 15$ nS). The spike frequency drops from an initially high onset rate, f_0 , in an approximately exponential way down to a lower steady-state rate, f_∞ . (b) Repeating the experiment shown in (a) for various stimulus intensities

I (here an injected current) results in the onset f - I curve $f_0(I)$ and the steady-state f - I curve $f_\infty(I)$. Shown are simulations of a single-compartment conductance-based model with an M-type current (the Ermentrout model; Ermentrout 1998; Benda et al. 2010; with $\dot{g}_{Ca} = 0$, $\dot{g}_{AHP} = 0$, and $\dot{g}_M = 8 \mu\text{S}/\text{cm}^2$, the input current is scaled such that 1 nA equals $1 \mu\text{A}/\text{cm}^2$)

frequency that then decays down to a lower steady-state frequency (Fig. 1a). This dynamics of the spike-frequency response is referred to as “spike-frequency adaptation”. Spike-frequency adaptation is a process that is slower than the dynamics of action-potential generation. Spike-frequency adaptation by this definition is an aspect of the neuron’s super-threshold firing regime, although the mechanisms causing spike-frequency adaptation could also be at work in the neuron’s subthreshold regime.

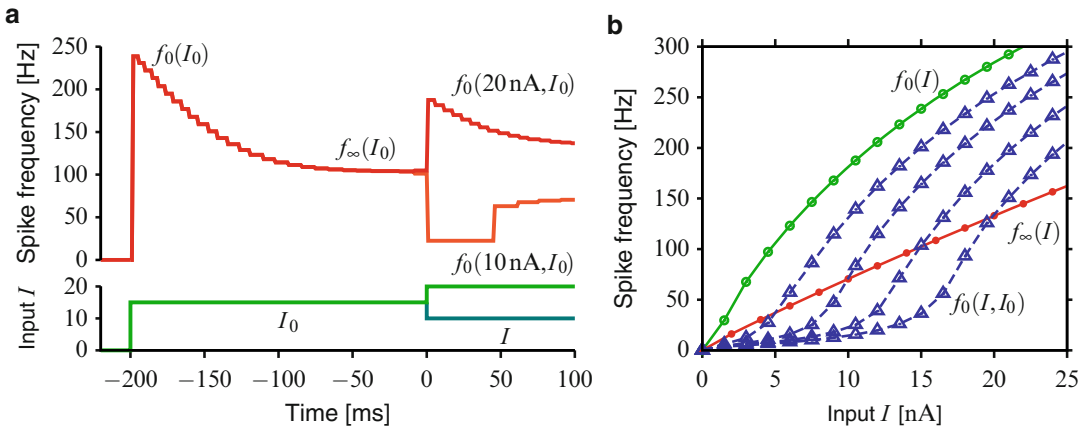
Detailed Description

In the context of spike-frequency adaptation, spike frequency is often measured as the instantaneous rate, i.e., the averaged reciprocal interspike intervals at each time. This measures the inverse period of super-threshold firing. In contrast, the PSTH (peristimulus time histogram (► [Estimation of Neuronal Firing Rate](#))) estimates the probability of a spike at a given time and therefore is also sensitive to variability of the response caused by intrinsic or external noise sources.

Important characteristics of a neuron with spike-frequency adaptation are its f - I curves (spike frequency f versus input strength I).

Because of adaptation, a certain input intensity will not evoke a constant spike frequency. Instead, the initial response in spike frequency to the onset of a constant input will result in the so-called “onset f - I curve” (green curve in Fig. 1b). Later during the constant stimuli, the spike frequency reaches a steady state. Drawn as a function of input intensity, this forms the “steady-state f - I curve”, which usually lies below the onset f - I curve, because the spike frequency adapts from the onset down to the steady state (red curve in Fig. 1b). The third type of f - I curves is the “adapted f - I curves” (Benda and Herz 2003). For these the neuron is first adapted to some adaptation input of fixed intensity and then the onset responses to various test inputs are measured (Fig. 2). The adapted response curves indicate how the neuron being in a certain and fixed adaptation state will initially respond to new stimuli. While each neuron has exactly one onset and one steady-state f - I curve, it has for each adaptation stimulus a different adapted f - I curve.

Simple adaptation currents (see below) will shift the neuron’s adapted f - I curves to higher input intensities. Other (less well-understood) mechanisms like presynaptic inhibition may also tilt the adapted f - I curves (Hildebrandt et al. 2011) or distort it in other ways (see also Fig. 5).



Spike-Frequency Adaptation, Fig. 2 Adapted $f-I$ curves. In addition to the onset and the steady-state $f-I$ curves, the adapted $f-I$ curves provide important information about the adaptation properties of a neuron. (a) In order to measure an adapted $f-I$ curve for a specific adaptation state, the neuron is first adapted to its steady-state response $f_\infty(I_0)$ by stimulating it with a constant adapting stimulus I_0 (here 15 nA). Then, a test stimulus I is applied and the onset response $f_0(I, I_0)$ to this stimulus is measured.

In the figure, the responses (red and orange) to two different test stimuli ($I = 20$ nA in green and $I = 10$ nA in dark cyan) are shown. (b) Each adapting stimulus I_0 results in one adapted $f-I$ curve $f_0(I, I_0)$. Shown are adapted $f-I$ curves for $I_0 = 5, 10, 15, 20$ nA. In this example the adaptation process mainly shifts the adapted $f-I$ curves to the right. All curves together characterize the spike-frequency response of an adapting neuron. Same model neuron as in Fig. 1

Spike-frequency adaptation is related to the classification of neurons into phasic, phasic-tonic, or tonic spiking neurons. Tonic spiking neurons are neurons that keep firing in response to a constant stimulus with an almost constant rate. Many neurons that are classified as tonic spiking, however, still show some weak spike-frequency adaptation. On the other hand, phasic spiking neurons only emit one or several spikes to the onset of the stimulus and then cease spiking. If this onset response consists of several spikes with a decreasing spike frequency, then the phasic response is probably caused by strong spike-frequency adaptation. With less or only a single spike and no clear decrease in spike frequency, this type of response can be that of a type III neuron (► [Excitability: Types I, II, and III](#)). The intermediate phasic-tonic responses exactly match the definition of spike-frequency adaptation.

Mechanisms

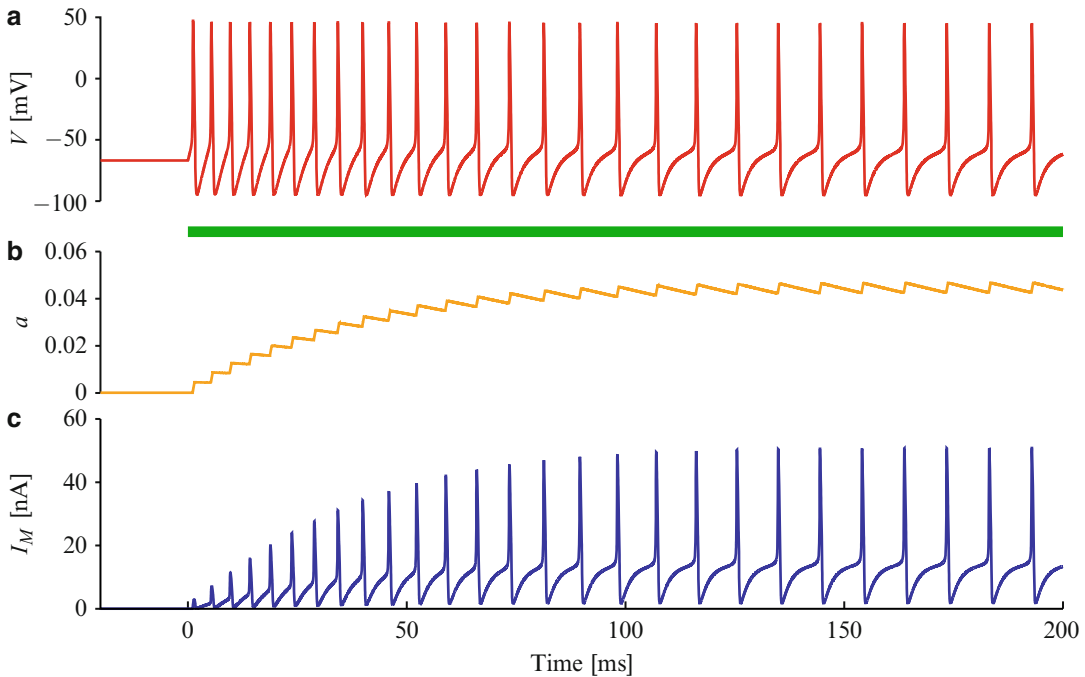
There are many different mechanisms that all cause a neuron to adapt its spike-frequency

response. First, there are adaptation currents – ionic currents (► [Biophysics of Adaptation in a Computational Model of the Leech T Neuron](#)) that act together with the spike-generating currents (“output-driven adaptation”). Second, other mechanisms, such as fatigue of receptor currents, adapt the input a neuron receives (“input-driven adaptation”). And third, there are network effects that also can adapt the neuron’s response in both an input-driven or output-driven way.

Adaptation Currents

There exists a whole zoo of mechanisms based on ionic currents that are all directly or indirectly activated by the action potentials generated by the neuron – the output of the neuron – and have at least one time scale involved that is slower than the dynamics of an action potential.

M-type currents are a simple example (Fig. 3; Brown and Adams 1980). These are voltage-gated potassium currents that are mainly activated at high voltages as they occur during an action potential and that deactivate with a slow time



Spike-Frequency Adaptation, Fig. 3 Dynamics of an adaptation current. (a) The membrane potential V in response to a step input ($I = 15$ nA, indicated by the green bar) simulated with the same model as in Fig. 1. As adaptation progresses the interspike intervals get longer. (b) The gating variable of the M-type current a is

increased by every action potential and decays slowly in between them. This way a slowly builds up during stimulation. (c) The adaptation current, here an M-type current, I_M , gets larger and larger as a increases and inhibits the input. This way it causes the neuron's response to adapt

constant of about 100 ms. If the neuron initially fires with a frequency of say 200 Hz, then the activation of the M-type currents builds up from one action potential to the next, since there is not enough time for the current to completely deactivate between succeeding action potentials. As a potassium current, the activated M-type currents then counteract the input to the neuron and as a consequence the spike frequency is reduced – the neural response adapts.

An important class of adaptation currents are AHP-type currents, calcium-gated potassium currents, that enhance the after hyperpolarization following an action potential (Sah 1996). Here, during each action potential, calcium enters the cell through voltage-gated calcium channels. Depending on the intracellular calcium concentration, the AHP-type currents are activated and as potassium currents inhibit the input to the neuron. Calcium is only slowly removed from the cytosol

and this time scale is then reflected by the resulting spike-frequency adaptation.

Further ionic mechanisms that cause spike-frequency adaptation include sodium-activated potassium channels and slow inactivation of the sodium current (for details see ► [“Biophysics of Adaptation in a Computational Model of the Leech T Neuron”](#)).

Input Adaptation

In receptor neurons the whole transduction process from the physical stimulus to the receptor current can adapt in different ways. These can be mechanisms controlling the sensitivity of the receptor organ, like the pupillary light reflex. Within the receptor neuron itself, the transduction machinery may produce adapting receptor currents due to fatigue (e.g., bleaching of rhodopsin)

or active adaptation to the intensity of the physical stimulus within a second messenger cascade (e.g., in photoreceptors) or by molecular motors (e.g., in mechanical transduction in hair cells (► [Cochlear Inner Hair Cell, Model](#))). All these and many other mechanisms eventually produce an adapting receptor current that then leads to spike-frequency adaptation in the receptor neuron. Gollisch and Herz (2004) demonstrated how to unmask input-driven adaptation from output-driven adaptation in auditory receptor neurons of locusts.

In all other neurons that receive their input through synapses on their dendrite, the input current reaching the site of action-potential generation can also be adapted. The various forms of synaptic dynamics, in particular short-term depression, are potential sources of spike-frequency adaptation. Also various ionic currents on the dendrite (► [Quasi-active Approximation of Nonlinear Dendritic Cables](#)) might potentially adapt the input.

Network Effects

In case the spiking activity of a neuron leads to the activation of recurrent inhibitory synapses, this might cause spike-frequency adaptation in a way quite similar as the adaptation currents (Sutherland et al. 2009). Here, the slow time scale would be introduced by the time scale of the postsynaptic current of the inhibitory synapse, by the delay introduced by wiring, and by the integration dynamics of the neurons participating in this negative feedback loop.

Similar to input-driven adaptation, some forms of feedforward input may also cause spike-frequency adaptation in the target neuron. In its simplest form, the presynaptic neuron already adapts, and thus, the postsynaptic neuron very likely will adapt as well. In addition, the synaptic transmission might adapt through synaptic plasticity (► [Short-Term Plasticity, Biophysical Models](#)) or by presynaptic inhibition, or delayed and slower inhibitory input can adapt the response of the target neuron.

Network and cell-intrinsic adaptation mechanisms shape in specific ways functionally

different response properties of auditory interneurons in locusts (Hildebrandt et al. 2009).

Models of Spike-Frequency Adaptation

There are many ways to model spike-frequency adaptation. In the following overview, we focus on output-driven adaptation, i.e., adaptation currents that are activated by the neuron's output activity (membrane voltage with action potentials). In contrast, input-driven adaptation is activated by the input signal irrespective of the resulting output.

Conductance-Based Models

In conductance-based models like the Hodgkin-Huxley model (► [Short-Term Plasticity, Biophysical Models](#)), any ionic current of a neuron is modeled in detail. This requires exact knowledge of the specific type of adaptation current involved. For example, the M-type current I_M would be modeled as

$$I_M = \dot{g}_M a (V - E_K) \quad (1)$$

$$\tau_a(V) \frac{da}{dt} = a_\infty(V) - a \quad (2)$$

where E_K is the potassium reversal potential, $\dot{g}_M$ is the maximum conductance, and a is the gating variable of this voltage-gated current. $\tau_a(V)$ and $a_\infty(V)$ are the voltage-dependent time constant and activation variable, respectively, that determine the (slow) temporal evolution of the gating variable. $a_\infty(V)$ is a sigmoidal function depending on the membrane potential V that is close to zero at the resting potential and about one during an action potential (Brown and Adams 1980; Benda and Herz 2003).

Integrate-and-Fire Models

As for conductance-based models, any adaptation current can also be simply added to the input of an

integrate-and-fire model. The only difference is that the effect the action potential has on the dynamics of the current has to be modeled explicitly, for example, by increasing a in Eq. 2 by a certain increment whenever there was a spike.

Often, however, a more generalized form of adaptation currents is used in (leaky, quadratic, exponential) integrate-and-fire neurons (Izhikevich 2003; Brette and Gerstner 2005). This has the advantage that the exact nature of the adaptation current in question does not have to be known. First, the electromotoric force $E_K - V$ is often approximated away, so that the gating variable a then becomes the (appropriately scaled) adaptation current A . Second, $a\infty(V)$ is replaced by incrementing A by some appropriate value ΔA whenever an action potential occurs at time t_i . Between the action potentials, A decays exponentially with a fixed adaptation time constant τ_a :

$$I_M \approx A \quad (3)$$

$$\tau_a \frac{dA}{dt} = -A + \Delta A \sum_{i=-\infty}^{\infty} \delta(t - t_i) \quad (4)$$

The adaptation dynamics (4) can be extended by an additional term proportional to V in order to incorporate the fact that some adaptation currents are already activated by subthreshold membrane voltages.

Integrate-and-fire models with a dynamic threshold are another class of adapting neuron models, where the firing threshold is incremented by each action potential and follows a slow dynamics between the action potentials. Although this mechanism also produces spike-frequency adaptation (Liu and Wang 2001), the resulting adapted f - I curves do not only shift to higher inputs, as any adaptation current does, but also reduce their slopes (Benda et al. 2010).

Firing-Rate Models

By simply approximating the neuron's spike generator by its f - I curve $f_0(I)$ and using Kirchhoff's law that ionic currents over the cell's membrane

add up yield the following equation for the spike frequency $f(t)$:

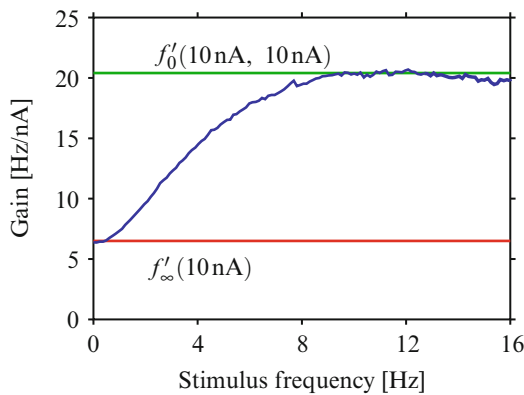
$$f = f_0(I - A) \quad (5)$$

$$\tau_a \frac{dA}{dt} = -A + A_\infty(f) \quad (6)$$

(Benda and Herz 2003). Because the adaptation current acts inhibitory on the input current, it is subtracted from the input. The dynamics for A is the same as for the simplified integrate-and-fire neurons, but it is driven via the term $A_\infty(f)$ by the output spike frequency and not by individual spikes any more. This dependence on the spike frequency arises from averaging over the spike train in time (Wang 1998). This averaging procedure is possible if the spike frequency is higher than the reciprocal adaptation time constant. Only then the adaptation dynamics can be separated from the one of the membrane potential. Choosing $A_\infty(f)$ to be proportional to f often is a reasonable approximation. Then, the only nonlinearity remaining is the neuron's onset f - I curve. By linearizing the onset f - I curve around the current spike frequency, one can easily compute the neuron's filter properties that are introduced by the adaptation process.

Signal Processing

The slow adaptation variable (gating variable of M-type current, intracellular calcium concentration for AHP-type currents, etc.) is a low-pass filtered version of the output spike train (output-driven adaptation, Eqs. 4 or 6) or of the input to the neuron (in the case of input-driven adaptation). Since this low-pass filtered signal is then subtracted from the input current I , this basically (i.e., with linear f - I curves) results in a high-pass filter between the input to the neuron and the resulting output spike frequency. The spike frequency of an adapting neuron thus encodes the high-pass filtered input signal (Fig. 4; Benda and Herz 2003). For example, in electroreceptors, this high-pass filter resulting from adaptation processes enhances the response to fast stimulus



Spike-Frequency Adaptation, Fig. 4 High-pass filter of adapting neurons. Adaptation processes add high-pass filter characteristics to a neuron's transfer function between the input to the neuron (here, e.g., an injected current) and the resulting spike frequency. Shown is the gain, i.e., the amplitude of the modulation of the spike-frequency response divided by the amplitude of the injected current input as a function of the frequency of that input, obtained for the same model neuron as in Fig. 1. As a stimulus a low-pass filtered Gaussian white noise with cutoff frequency at 16 Hz, mean 10 nA, and standard deviation 2 nA was used. The slopes of the steady-state f - I curve (red) at 10 nA and the one of the adapted f - I curve (green) for $I_0 = 10$ nA are plotted for comparison

components in communication signals (Benda et al. 2005).

The gain of the filter at low stimulus frequencies that are below the reciprocal adaptation time constant is given by the slope of the steady-state f - I curve. The gain of stimulus frequencies faster than the reciprocal adaptation time constant is given by the slope of the adapted f - I curves. In the case of purely subtractive adaptation, the latter equals the slope of the onset f - I curve.

It follows that neurons with flat steady-state f - I curves (zero slope) implement perfect intensity invariance (zero gain at low stimulus frequencies), i.e., no matter on what mean intensity a certain input waveform is delivered, the output spike-frequency will always be the same, since the mean intensity is completely filtered out by the adaptation process (Benda and Hennig 2008).

The high-pass filter effect of spike-frequency adaptation considers the linear aspects of spike-frequency adaptation only. At least the steady-state f - I curve is indeed linearized by adaptation

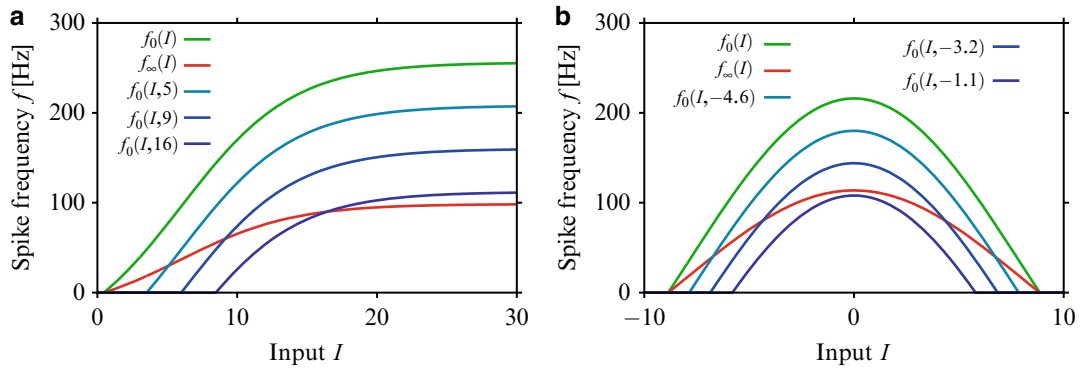
currents (as shown in Ermentrout 1998, and also illustrated in Fig. 1b). In addition, the nonlinear shape of a neuron's f - I curves (e.g., rectification at zero firing rate and saturation) together with the high-pass filter introduces additional aspects. For example, the subtractive shift of the adapted f - I curves to higher input intensities might be accompanied by a reduction in their maximum firing rate and/or by a reduction of their slope (see Fig. 5 for simple examples) and thereby influence the filter properties of a neuron in a nonlinear way.

The various forms of this interplay of adaptation dynamics and the resulting high-pass characteristics with nonlinearities lead to diverse functional consequences. For example, in the auditory system of crickets, the slow calcium dynamics leads to forward masking of weaker stimuli (Sobel and Tank 1994). A collision-detecting neuron in the visual system of locusts responds very selectively to looming stimuli because of spike-frequency adaptation (Peron and Gabbiani 2009).

Adaptation currents can even alter the type of action-potential dynamics (► **Excitability: Types I, II, and III**). A type I neuron where repetitive firing occurs via a saddle-node bifurcation on an invariant cycle can switch into a type II neuron where the resting potential loses stability via a Hopf bifurcation by the activation of an M-type adaptation current (Ermentrout et al. 2001; Prescott et al. 2006).

Multiple Adaptation Time Scales

Usually, spike-frequency adaptation occurs not only on a single but on several time scales. The shortest time scales of spike-frequency adaptation are in the range of 10–100 ms. This at the same time usually also is the strongest adaptation process in the neuron. Additional slower adaptation processes are weaker and have time constants of seconds, 10 s and slower. Adaptation on several time scales could resemble power-law adaptation (Clarke et al. 2013) or logarithmic adaptation (Xu et al. 1996) in contrast to the single adaptation process showing exponential adaptation of the firing rate.



Spike-Frequency Adaptation, Fig. 5 Nonlinearities and adaptation. Simple subtractive adaptation can have unexpected effects when it occurs after a nonlinearity. The examples show two simple scenarios where the firing rate f of a neuron is directly proportional to the input current J , and an adaptation current A acts subtractive on the current, as in Eq. 5: $f = c \cdot (J - A)$, with $c > 0$, and $f = 0$ if $J < A$. The input current, however, depends nonlinearly on some (sensory) input I : $J(I)$. (a) The input nonlinearity is a

sigmoidal function of the sensory input: $J(I) = (1 + \exp.(-(J - 6)/4))^{-1} - 0.2$ ($c = 320$ Hz). This is the case, for example, in auditory or olfactory receptor neurons. Although the adaptation acts subtractive on the input current, the resulting adapted f - I curves appear to be shifted to the right as well as downward. (b) $J(I) = \cos(0.2 I) + 0.2$ ($c = 180$ Hz). This models, for example, an orientation-selective cell in the visual system. Here, the adapted f - I curves appear to be shifted downward

Noise

Adaptation currents are a potential source of ion channel noise. Since these ionic currents are characterized by their slow adaptation dynamics, the resulting channel noise is a colored noise with correlation time given by the adaptation time constant. Such a noise results in positive correlations between successive interspike intervals and in interspike-interval histograms with a sharper peak and heavier tail in comparison to the ones obtained with white noise (Fig. 6d–f; Schwalger et al. 2010).

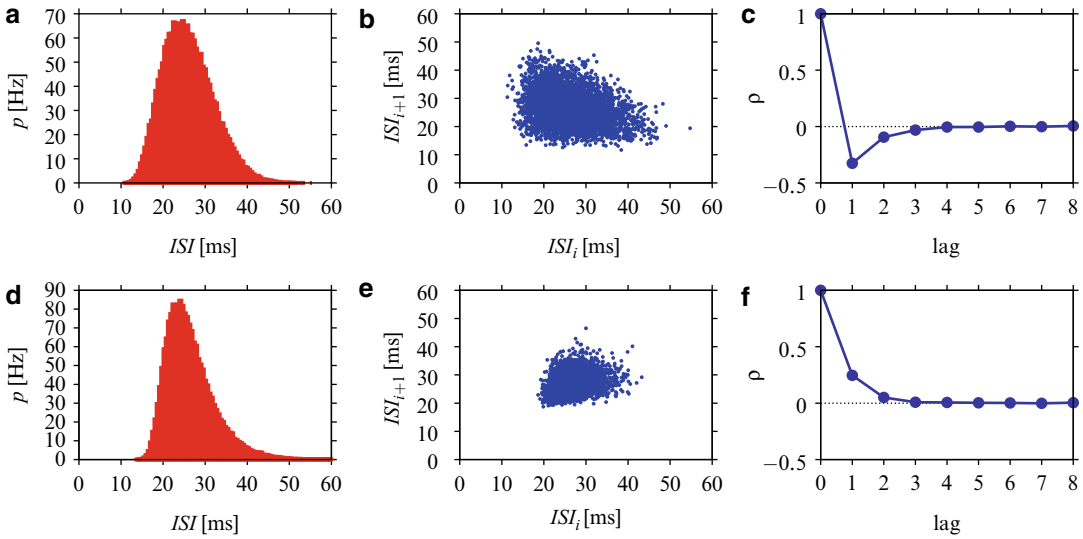
Output-driven adaptation also interacts with white noise, e.g., generated by ion channel noise from fast spike-generating currents. In this case, adaptation introduces negative serial correlations between successive interspike intervals (Fig. 6a–c; Chacron et al. 2000; Benda et al. 2010) that improve information transmission at low frequencies (Chacron et al. 2001). The interspike-interval statistics of auditory receptor neurons in locusts have been shown to be shaped by both white noise sources and colored noise presumably generated by an adaptation current (Fisch et al. 2012).

Rhythmogenesis in Neural Networks

The slow decrease in firing frequency due to adaptation currents provides delayed negative feedback that can result in the production of oscillations by excitatory neural networks. The population activity of an excitatory neural network can be roughly described by its mean firing rate, which varies according to

$$\tau \frac{df}{dt} = f_0(I) - f \quad (7)$$

(Wilson and Cowan 1972). Here, the firing frequency f is averaged spatially (over the population) and temporally (over the synaptic integration time scale). It is assumed that the neurons fire asynchronously. f_0 is the steady-state firing rate that will be reached with a network integration time constant τ . It is similar to the function f_0 in Eq. 5, but is not strictly the firing rate of one neuron, as it also incorporates information about synaptic dynamics, heterogeneity in the neuron population, etc. Because of the recurrent excitatory connectivity, the input I to the network is given by $I = wf$, where f is



Spike-Frequency Adaptation, Fig. 6 Spike-frequency adaptation and noise. (a–c) Interspike-interval (ISI) histogram (a), return map (b), and ISI correlations (c) for the conductance-based model with an M-type adaptation current (same model as in Fig. 1) driven with white noise (mean $I = 10$ nA, noise strength $D = 1$ nA²/Hz). (d–f)

The same measures for colored noise arising from the stochasticity of the adaptation current. Noise strength was scaled to result in the same standard deviation of the ISIs ($D = 30$ nA²/Hz). Note the more peaked shape of the ISI distribution as well as the positive ISI correlations

the output firing rate of the network, and w is a connectivity parameter akin to synaptic weight or the number of connections per neuron. If neurons are adapting, the effective input becomes $I = wf - A$, where A is the average adaptation current in the population. This description is valid as long as adaptation is much slower than network integration ($\tau_a > \tau$).

The population firing rate equilibrates to

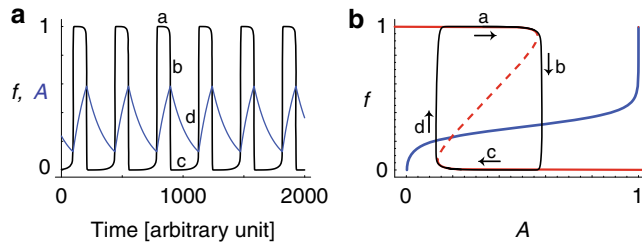
$$f = f_0(wf - A) \quad (8)$$

and A varies according to Eq. 6. Note that Eq. 8 can have two stable solutions over a range of A values. This bistability, due to the fast positive feedback provided by excitatory connections, together with the slow A dynamics produce relaxation oscillations as illustrated in Fig. 7 (Tabak et al. 2000; van Vreeswijk and Hansel 2001; Giugliano et al. 2004; Gigante et al. 2007).

Note that the exact dependence of adaptation on frequency (here given by Eq. 6 and represented as the blue curve in Fig. 7b) may affect the type of bifurcation that occurs between a silent and an oscillatory network as a source of excitation is

increased (Nesse et al. 2008), but it does not change the fundamental mechanism of the oscillations. So the excitatory network can oscillate whether adaptation is input- or output-driven (Nesse et al. 2008). Synaptic adaptation (often called short-term synaptic depression (► [Synaptic Dynamics: Overview](#))) also produces oscillations in excitatory networks, through the same mechanism as the intrinsic adaptation mechanisms described here (Tabak et al. 2000; Tsodyks et al. 2000; Wiedman and Luthi 2003). Note, however, that the two types of adaptation (intrinsic or synaptic) can be distinguished in models (even in firing rate models) as well as in experiments based on the models' predictions (Tabak et al. 2000, 2010; Wiedman and Luthi 2003). Thus, it is important to pay careful attention to what adaptation model is most appropriate in a particular modeling context.

In addition to its rhythmogenic properties in excitatory networks, activity-dependent adaptation facilitates network-based oscillations due to the interaction of excitatory and inhibitory populations (Augustin et al. 2013). The rhythmogenic mechanism based on excitatory



Spike-Frequency Adaptation, Fig. 7 Oscillatory activity in an excitatory network with adaptation. (a) Time courses of f , the average firing rate (black), and A , the average adaptation current (blue) in the population. During an episode of activity ($f \simeq 1$), A is increasing, until activity drops to $\simeq 0$. During the inter-episode interval, A decreases until the network is excitable enough to start a new high-activity episode. (b) The two time courses from (a) describe a closed trajectory in the (A, f) plane. The red curve is the curve of steady states of f , solutions of Eq. 8 at each value of A . There is an interval of A over which there are two stable steady states for f , one high and one low (and

an intermediate, unstable steady state, dashed). The blue curve represents $A \propto(f)$; when the phase point (A, f) is above this curve, A increases; below this curve A decreases, according to Eq. 6. During an episode of network activity (a), f is high so A increases, moving the trajectory to the right. After the point where the high steady state meets the unstable steady state, the only available steady state is at low f . The trajectory jumps down (b), starting the inter-episode interval (c), during which A decreases. When A is low enough, the lower steady state disappears and the trajectory jumps up (d), beginning a new high-activity episode

connectivity and slow activity-dependent adaptation may underlie various types of network activity such as episodic activity in developing networks (Butts et al. 1999; Tabak et al. 2000), respiratory rhythms (Kosmidis et al. 2004), or slow oscillations between up and down states in cortex (Compte et al. 2003).

Cross-References

- [Biophysics of Adaptation in a Computational Model of the Leech T Neuron](#)
- [Cochlear Inner Hair Cell, Model](#)
- [Estimation of Neuronal Firing Rate](#)
- [Excitability: Types I, II, and III](#)
- [Quasi-active Approximation of Nonlinear Dendritic Cables](#)
- [Short-Term Plasticity, Biophysical Models](#)
- [Synaptic Dynamics: Overview](#)

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Spike-Rate Neural Networks

► Large-Scale Neural Networks: Vision

Spike-Timing Dependent Plasticity (STDP), Biophysical Models

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Definition

A biophysical model of spike-timing-dependent plasticity (STDP) is one which converts time

intervals, in a given firing pattern of synaptically coupled pre- and postsynaptic neurons, to modifications of the connecting synapse. This class of STDP model is defined by their mathematical representation of specific biophysical quantities, which have been shown to play a role in the intracellular mechanisms underlying synaptic plasticity.

Detailed Description

Within the STDP framework, models of synaptic plasticity are dependent on the precise relative timing of pre- and postsynaptic spikes and, broadly speaking, utilize one, or a combination, of two modelling approaches. The first group of STDP models use phenomenological modelling to empirically describe the relationship between the model inputs (pre- and postsynaptic spike times) and the model output (synaptic weight modification). There is usually little or no attempt to represent the intracellular machinery governing synaptic plasticity in the model. The second group of STDP models use a *biophysical* modelling approach, which means that they include variables that represent specific biophysical species or quantities. The mathematical relationships between the variables in a biophysical model encapsulate our mechanistic understanding of the biochemical and electrophysiological processes that are being modelled. Predictions from biophysical STDP models can therefore offer insight into the mechanisms governing the induction of synaptic plasticity.

Ca²⁺-Based Models of STDP

The critical trigger for synaptic plasticity is a rise in intracellular Ca²⁺ concentration, [Ca²⁺], since synaptic long-term potentiation (LTP) and depression (LTD) are blocked by pharmacological buffering of Ca²⁺ (Malenka and Bear 2004; Graupner and Brunel 2010). The importance of intracellular Ca²⁺ is reflected in the fact that dynamic cytosolic Ca²⁺ levels, acting as intermediate signals for induction of plasticity, are a common feature of most biophysical models of STDP.

Ca²⁺-based biophysical models of STDP must include a description of the changes in [Ca²⁺] due to pre- and postsynaptic spiking. Ca²⁺ sources may depend on the particular synapse to be modelled but most frequently include influx via NMDA receptors (NMDARs), influx via Ca²⁺-permeable AMPA receptors (AMPA), influx via voltage-gated Ca²⁺ channels (VGCCs), or Ca²⁺ release from intracellular stores. Since most modelling efforts are directed towards understanding NMDAR-dependent plasticity, NMDARs are the primary source of Ca²⁺ in the majority of biophysical STDP models. Entry of extracellular Ca²⁺ via postsynaptic membrane ion channels can be dependent on both the postsynaptic membrane potential and the action of neurotransmitters in the synaptic cleft; therefore, biophysical models of STDP often contain descriptions of electrophysiological cell membrane phenomena and AMPAR/NMDAR ligand gating in response to neuron pair spiking. The sophistication of intracellular Ca²⁺ handling within the model can be further increased by the inclusion of Ca²⁺ buffers or plasma membrane ion pumps.

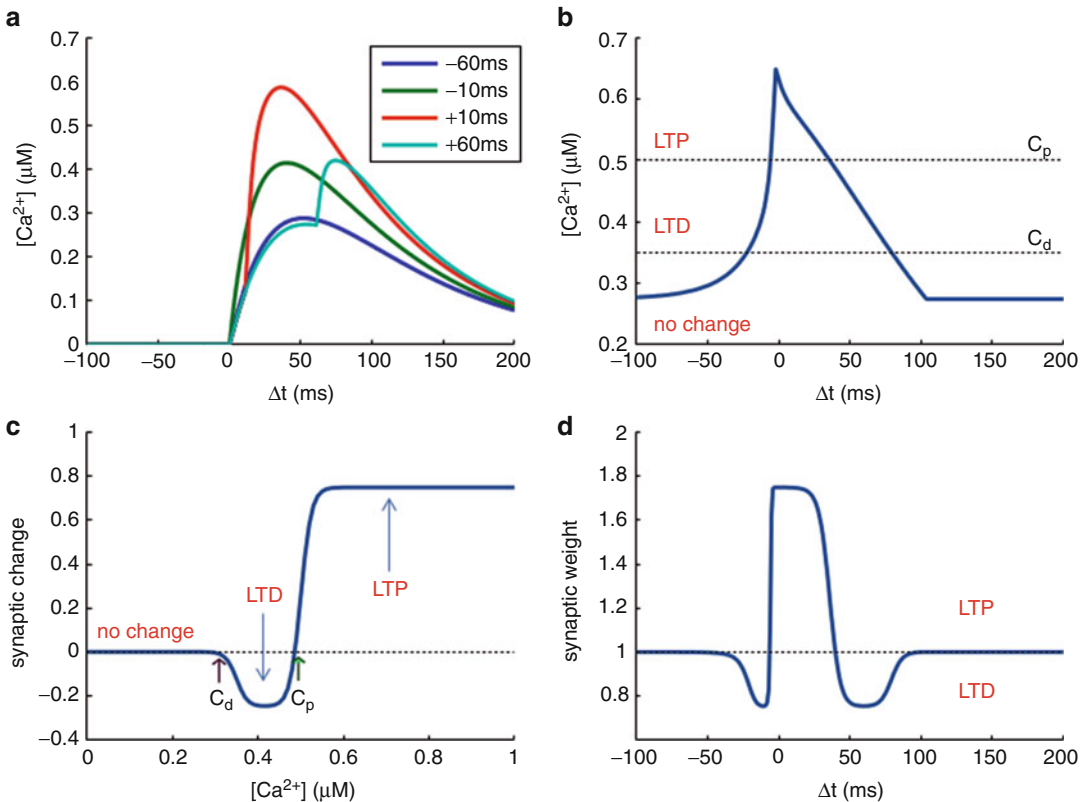
Simplified Intracellular Dynamics

Biophysical STDP models can be categorized according to their method of transposing postsynaptic Ca²⁺ signals into synaptic modifications. In one set of STDP models, simplifications of the forward-connected Ca²⁺-dependent mechanisms underlying synaptic plasticity are used alongside a realistic biophysical treatment of Ca²⁺ dynamics within the postsynaptic neuron. Ca²⁺ signalling networks in these models are reduced to abstract Ca²⁺-signal detection systems or simple algebraic equations, which introduce phenomenological variables relating postsynaptic [Ca²⁺] to synaptic weight changes. These types of STDP models vary in their consideration of the postsynaptic [Ca²⁺] transient, with some using peak magnitude only as their signal (e.g., Shouval et al. 2002; Rackham et al. 2010), while others consider the whole transient (e.g., Rubin et al. 2005). The Ca²⁺ detectors are designed to describe

simplified kinase/phosphatase activity in dephosphorylation/phosphorylation cycles that are critical for synaptic plasticity induction and to capture the essential quality of the Ca^{2+} -control hypothesis, which states that high transient intracellular $[\text{Ca}^{2+}]$ leads to LTP, whereas moderate more prolonged increases in $[\text{Ca}^{2+}]$ result in LTD (Lisman 1989). Examples of models using this approach include Shouval et al. (2002), Abarbanel et al. (2003), Rubin et al. (2005), and Rackham et al. (2010).

The simplest of these models (Shouval et al. 2002, Fig. 1) results in a second LTD

window at large positive STDP time intervals between pre- and postsynaptic spikes, an effect that is not observed in the majority of experimental STDP spike-pair studies. Conflicts with experimental data, such as this, can be remedied by the introduction of further phenomenological variables to “veto” LTD at positive time intervals (Rubin et al. 2005) or by including the stochastic properties of synaptic transmission in the model, a modification which significantly reduces the magnitude of the second LTD window (Shouval and Kalantzis 2005).

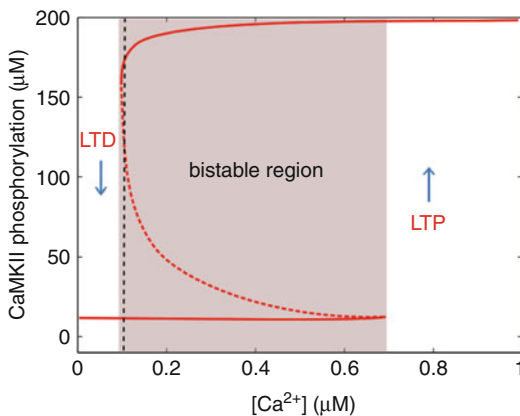


Spike-Timing Dependent Plasticity (STDP), Biophysical Models, Fig. 1 STDP according to Shouval et al. (2002). (a) $[\text{Ca}^{2+}]$ transients as described by Shouval et al. (2002) for four spike pairs. Presynaptic spike occurs at $t = 0$, and postsynaptic spike occurs at time interval as indicated in the legend. The only source of Ca^{2+} in the model is Ca^{2+} influx mediated by NMDARs. (b) Peak predicted $[\text{Ca}^{2+}]$ plotted against the spike-pair time interval. LTP and LTD peak $[\text{Ca}^{2+}]$ -signal threshold values, C_p and C_d , are illustrated showing plasticity outcomes for spike-pair

intervals from -100 ms to 200 ms. (c) The calcium-control hypothesis. Plot shows direction and magnitude of synaptic strength modification with $[\text{Ca}^{2+}]$ signal according to the calcium-control hypothesis (Shouval et al. 2002). LTD is predicted at moderate Ca^{2+} levels, and for large $[\text{Ca}^{2+}]$, LTP is the outcome. (d) STDP curve for spike pairs within range -100 ms to 200 ms as predicted by Shouval et al. (2002). Note the second LTD window at larger positive time intervals, an effect that is not observed in the majority of experimental STDP studies

Modelling Signalling Pathways

A key signalling pathway that has been identified in the mediation of NMDAR-dependent synaptic plasticity is the Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) signalling cascade (Lisman et al. 2002). Phosphorylation of CaMKII is linked with increased synaptic AMPAR number and conductance. Models of the complex CaMKII signalling pathway use Ca^{2+} signals to regulate the phosphorylation state of CaMKII. These models can exhibit a bistable switch-like behavior in the phosphorylation state of CaMKII (Fig. 2). This is due to the combination of a CaMKII autophosphorylation-generated positive-feedback loop in the signalling network and CaMKII activity inhibition by Ca^{2+} /calmodulin-dependent protein phosphatase 1 (PP1). Bistable models result in a synapse that exists in one of two states: a baseline state with synaptic AMPAR conductance magnitude corresponding to low levels of post-synaptic CaMKII phosphorylation and a



Spike-Timing Dependent Plasticity (STDP), Biophysical Models, Fig. 2 Bistable CaMKII switch. Concentration of phosphorylated CaMKII subunits as a function of the intracellular Ca^{2+} level. Stable states are indicated by solid red line, and unstable stationary states are indicated by dashed red line. Shaded region represents the $[\text{Ca}^{2+}]$ window within which both low and high CaMKII phosphorylation states are stable. Baseline $[\text{Ca}^{2+}]$ is indicated with vertical dashed black line showing stability of both high and low CaMKII phosphorylation states allowing maintenance of plasticity at normal intracellular levels of Ca^{2+} . LTP and LTD $[\text{Ca}^{2+}]$ signal windows are shown either side of the bistable region (Figure reproduced from Zhabotinsky (2000))

potentiated state corresponding to the second stable (high) phosphorylation level of CaMKII. The transition between the two states is triggered by intracellular $[\text{Ca}^{2+}]$, with moderate concentrations leading to low CaMKII phosphorylation states and high concentrations causing a transition to the highly phosphorylated state. This behavior corresponds with the Ca^{2+} -control hypothesis. A requirement for the maintenance of plasticity in CaMKII models is that the two CaMKII phosphorylation states must also be stable at baseline intracellular Ca^{2+} levels.

Castellani et al. (2005) is an example of a CaMKII-class, biophysical STDP model, describing induction of plasticity only since bistability is absent from the model. An early mathematical model of the CaMKII system that exhibits bistability in the phosphorylation states of CaMKII is detailed by Lisman and Zhabotinsky (2001). Studies that have used similar CaMKII bistable switching models, with particular application to STDP, include Graupner and Brunel (2007) and Urakubo et al. (2008). A more complicated signalling network is described by Jain and Bhalla (2009), whose model incorporates transcription and protein synthesis for the maintenance of LTP/LTD.

There is still some uncertainty as to whether NMDAR-dependent LTD/LTP is the same process acting in opposing directions or whether NMDAR-dependent LTD induction proceeds via a separate molecular signalling pathway to LTP induction. Models of cerebellar, non-NMDAR-dependent LTD do use a separate signalling pathway, which proceeds in a metabotropic glutamate receptor (mGluR)-dependent manner, ultimately leading to removal of AMPARs from the postsynaptic membrane and, hence, a reduction in synaptic transmission efficiency (Ito 2001).

Modelling Approaches

Over 100 biophysical models for synaptic plasticity exist in publication, most of which bear a resemblance to the models described in the above sections (Manninen et al. 2010). These models can be classified according to the various

methods used to create the model. For instance, many models have deterministic outcomes, while others include the stochasticity inherent in biochemical processes and have variable output. It is also possible to utilize a hybrid approach, incorporating stochastic and deterministic methods within the same model. Furthermore, some models take into account the spatial dependence of plasticity mechanisms since $[Ca^{2+}]$ signalling may be variable over the intracellular region to be modelled, whereas other models compress $[Ca^{2+}]$ signals to their time-dependent component only. Some biophysical STDP models include increased complexity, such that the outputs include spatial resolution of biological signals, and also variability across synapse populations (Manninen et al. 2010).

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Spike-Timing Dependent Plasticity, Learning Rules

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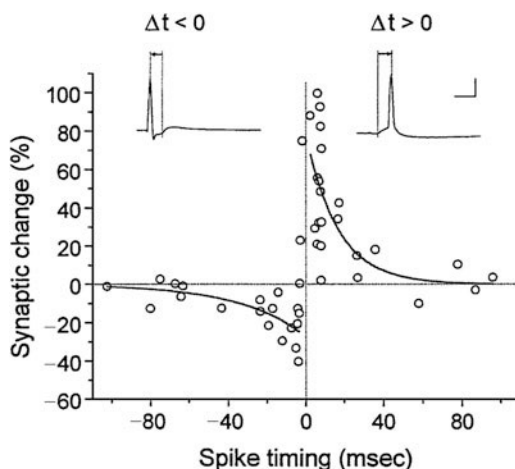
Synonyms

Spike-dependent synaptic learning rules; Spike-timing dependent synaptic plasticity; STDP

Definition

Biological phenomenon. Spike-timing-dependent plasticity (STDP) in its narrow sense refers to the

change in the synaptic strength as a result of repeatedly triggering pairs of action potentials (“spikes”) with a fixed time difference between the pre- and postsynaptic action potentials (Markram et al. 1997; Bi and Poo 1998; Sjostrom et al. 2001). STDP is typically observed for synapses between hippocampal or cortical pyramidal neurons in slices of juvenile rodents, and the spike pairings are repeated 50–100 times with various frequencies, e.g. 1 or 10 Hz. This protocol induces a change in the amplitude of a single excitatory postsynaptic potential (EPSP) which is plotted against the spike time difference $\Delta t = t_{\text{post}} - t_{\text{pre}}$ between the postsynaptic spike and the presynaptic spike (Fig. 1). The change takes in many cases a few minutes to be expressed and lasts at least for the duration of the experiment. Typically, when the presynaptic spike precedes the postsynaptic spike by roughly 10 ms, the synapse is potentiated; if the presynaptic spike follows the postsynaptic spike, the synapse is depressed (for reviews, see Bi and Poo (2001); Senn (2002); Sjostrom et al. (2008); Sjöström and Gerstner (2010)).



Spike-Timing Dependent Plasticity, Learning Rules, Fig. 1 Change of the EPSP amplitudes as a function of the time difference $\Delta t = t_{\text{post}} - t_{\text{pre}}$ between the post- and presynaptic spike. Time constants for LTP and LTD fits are $\tau_{\text{pre}} \approx 17$ ms and $\tau_{\text{post}} \approx 34$ ms, respectively (for an interpretation, see Fig. 2). Pairing protocol: 60 spike pairs at 1 Hz. Inset: postsynaptic action potential, relative to the time of the presynaptic spike (vertical line). Scale bars: 10 ms, 50 mV (Figure from Bi and Poo (2001))

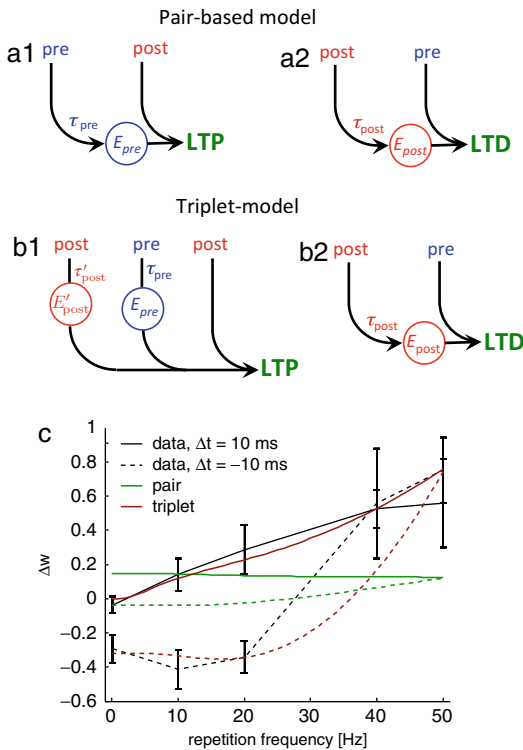
Learning rules. In a computational context, STDP refers to plasticity rules that depend on the timing of pre- and postsynaptic spikes and that are involved in various learning scenarios for neuronal networks. These learning rules either emphasize the link to the biophysics underlying the synaptic modification (Senn et al. 2001; Shouval et al. 2002; Karmarkar and Buonomano 2002; Rubin et al. 2005; Graupner and Brunel 2012), or are minimalistic with respect to a biological implementation (Kempster et al. 2001; Song and Abbott 2001), or are derived from the maximization of a utility function (Pfister et al. 2006; Toyozumi et al. 2007; Florian 2007; Urbanczik and Senn 2009; Friedrich et al. 2011). The learning rules are studied in the context of supervised, unsupervised, or reinforcement learning. When evaluated from the performance point of view, learning rules that are mathematically derived from an optimization principle are superior over STDP rules designed to fit a given set of experimental data (Frémaux et al. 2010). Interestingly, biological plausibility and computational relevance may go together when considering 2-compartment neurons with synapses on a dendritic tree (Urbanczik and Senn 2014).

Detailed Description

STDP models come in different flavors, emphasizing more the phenomenology, the biophysics, or the computational aspects. As learning rules, their primary focus is on doing computations rather than on reproducing synaptic plasticity data. An excellent and comprehensive review to STDP models, starting with the basic pair-based STDP models (Fig. 2a) and including also functional consequences, is found in the Scholarpedia article by Sjöström and Gerstner (2010). Here we highlight the properties of third-order STDP models and focus on gradient rules.

Phenomenological STDP Models

The simplest online model that phenomenologically reproduces the basic STDP curve (Fig. 1)



Spike-Timing Dependent Plasticity, Learning Rules,

Fig. 2 Phenomenological STDP models. (a) Simplest model reproducing Fig. 1. (A1) Each presynaptic spike stepwise increases a presynaptic eligibility trace E_{pre} that otherwise exponentially decays to 0 with time constant τ_{pre} (Eq. 1). LTP is induced by each postsynaptic spike proportionally to the amount of E_{pre} available at that time. (A2) LTD is induced by each presynaptic spike proportionally to E_{post} that low-pass filters the postsynaptic spiking. Note that the post-pre-chain is itself acausal and does not appear in the gradient-based learning schemes represented in the subsequent figures. (b) Triplet rule. (B1) In the triplet model, LTP is induced at the time of the postsynaptic spike and is proportional to the product $E_{pre}E'_{post}$. (B2) In the triplet model, LTD is induced by pairs of spikes as in B1. (c) Weight change as a function of the repetition frequency of the pre-post pairs (solid lines, $t_{post} - t_{pre} = 10$ ms) and the post-pre pairs (dashed lines, $t_{post} - t_{pre} = -10$ ms). The triplet model (brown) fits well the data from (Sjostrom et al. 2001) (black) while the pair-based model (green) cannot

separately induces long-term potentiation (LTP) or long-term depression (LTD), by either a pre-post or post-pre-coincidence detector, respectively. The key feature is that pre- and postsynaptic spikings are each tracked by leaky integrators, the so-called synaptic eligibility traces, while LTP

and LTD are triggered proportionally to these traces at the times of the post- and presynaptic spikes, respectively (Fig. 2a, see also Sjöstrom and Gerstner (2010)).

The triplet model The simple STDP model which depends on pairs of spikes (pre-post and post-pre) correctly predicts the weight change only for a restricted number of protocols. If potentiation is assumed to be governed by triplets of spikes (pre-post-post) instead of pairs of spikes, a much broader class of experimental data can be captured (Pfister and Gerstner 2006). This so-called triplet model can be expressed as a sum of a depression term (Fig. 2B2) and a triplet term where at the time of the postsynaptic spike the weight change is proportional to the product of a postsynaptic and a presynaptic eligibility trace (Fig. 2B1).

The triplet model becomes especially relevant when the repetition frequency of the pre-post pairs increases. The pair-based model predicts a decrease of potentiation as a function of the pairing frequency. But in the visual cortex ($L5 \rightarrow L5$ pyramidal neurons, Sjostrom et al. (2001)), potentiation increases with increasing repetition frequency, and this is well reproduced by the triplet model (Fig. 2c; it is also qualitatively captured by the Senn-Markram-Tsodyks model; see Senn (2002)).

This triplet model has also interesting computational properties. Under the assumption of independent pre- and postsynaptic Poisson firing rate (Pfister and Gerstner 2006), the expected weight change predicted by the triplet model is consistent with the Bienenstock-Cooper-Munro (BCM) learning rule (Bienenstock et al. 1982) which elicits input selectivity, i.e., the output neuron becomes strongly responsive to one given (rate-based) input pattern and much less to all the other ones. Furthermore, if the independent Poisson assumption is relaxed such that output firing rate depends on the presynaptic spike timings, the triplet rule becomes sensitive to third-order spiking correlations in the input, thereby generalizing the BCM learning rule to spiking-correlated patterns (Gjorgjieva et al. 2011).

Extended models A next important extension of STDP models takes account of the modulation

of plasticity by the postsynaptic voltage (Clopath et al. 2010; Clopath and Gerstner 2010). This unifying model is formulated in terms of the postsynaptic voltage time course and presynaptic spikes. It can explain the widest set of STDP experiments, including burst-induced synaptic plasticity and those experiments that reveal the dependence on the postsynaptic voltage, as e.g. in Artola et al. (1990) and Sjostrom et al. (2001). This voltage-dependent model can also be seen as an extension of the triplet model where the postsynaptic eligibility trace in the potentiation term is replaced by a low-pass filter of the postsynaptic voltage. The triplet model, in turn, can be seen as a simplified version of the model by Senn et al. (2001). This latter model also depends on triple events (pre-post-post) for the induction of long-term potentiation, but the pre-post-post ordering is important while in the triplet model both pre-post-post as well as post-pre-post events lead to potentiation.

Biophysical STDP models Another class of STDP models explains the synaptic modifications as a nonlinear function of the postsynaptic calcium concentration. The question whether the postsynaptic calcium alone can capture the characteristic STDP curve of Fig. 1 (see Shouval et al. (2002) versus Karmarkar and Buonomano (2002)) has been affirmed by taking into account the calcium dynamics (Rubin et al. 2005) or additional nonlinearities (Graupner and Brunel 2012). Functionally, these threshold nonlinearities are very similar to the ones imposed on the pre- and postsynaptic eligibility traces introduced in the phenomenological models (Senn et al. 2001; Clopath et al. 2010). Yet, by starting with individual protein kinetics, a biophysical model may explain how these nonlinearities arise (Rubin et al. 2005), see also ► “Spike-Timing Dependent Plasticity (STDP), Biophysical Models.”

Gradient-Based STDP Learning Rules

By their nature, the phenomenological and biophysical STDP models are not directly designed as synaptic learning rules that solve an explicit learning task. When canonical target functions for

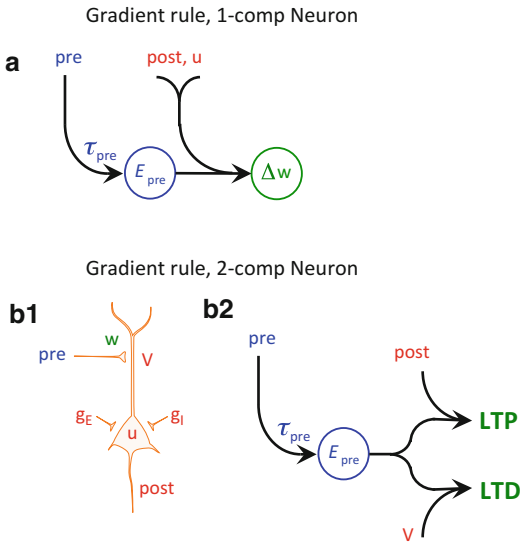
the learning can be defined, such as in the supervised and reinforcement learning scenario, spike-timing-dependent learning rules can be derived from gradient procedures that maximize/minimize these functions. A very convenient neuron model suited for a theory of learning is the escape rate neuron. Indeed since it allows to explicitly quantify the probability for a given postsynaptic spike train as a function of the afferent synaptic strengths w_j , the likelihood of a given spike train is differentiable (w.r.t to w_j) (Pfister et al. 2006). This neuron stochastically emits spikes with instantaneous firing rate $\rho(u)$ that is an increasing function of the instantaneous membrane potential $u(t)$. The latter is itself a sum of the postsynaptic potentials (PSPs) weighted by the synaptic strengths, $u(t) = \sum_j w_j \text{PSP}_j(t)$, optionally subtracted with a reset kernel after a postsynaptic spike.

Supervised learning In the supervised learning scenario, the target function can be defined as a distance between the desired postsynaptic spike train, $S_{\text{post}}^{\text{cl}}(t) = \sum_i \delta(t - t_i^{\text{post}})$, that is clamped as an output to the neuron and the spike trains that would be generated by the neuron itself. If we pick out a specific synapse, the presynaptic eligibility trace $E_{\text{pre}}(t)$ is again obtained by the leaky integration of the presynaptic spike train $S_{\text{pre}}(t) = \sum_i \delta(t - t_i^{\text{pre}})$. Typically, the integration time constant τ_{pre} is equal to the membrane time constant, and hence this trace can also be identified with the postsynaptic potential induced by that synapse, $E_{\text{pre}}(t) = \text{PSP}(t)$. The gradient rule that maximizes the log-likelihood of reproducing the clamped target spike trains is then obtained as (Pfister et al. (2006); see Fig. 3a).

$$E_{\text{pre}}(t) = \int_{-\infty}^t S_{\text{pre}}(\tilde{t}) e^{-\frac{t-\tilde{t}}{\tau_{\text{pre}}}} d\tilde{t} \quad (1)$$

$$\dot{w}(t) = \eta \frac{\rho'}{\rho} \left(S_{\text{post}}^{\text{cl}}(t) - \rho(u(t)) \right) E_{\text{pre}}(t), \quad (2)$$

where η is some small learning rate. Here, $\rho' = \rho'(u(t))$ is the derivative of the escape rate ρ with respect to u , evaluated at t . Interestingly, by expressing Eq. 2 as a sum of a potentiation and a



Spike-Timing Dependent Plasticity, Learning Rules, Fig. 3 Gradient-based SDTP for supervised learning (a, b) and unsupervised learning (b). (a) An optimal learning rule that reproduces the timing of a given (“clamped”) output spike needs to take account of the postsynaptic membrane potential u beside the pre- and postsynaptic spikes (Eqs. 1 and 2). (B1) In a biological version, u is only slightly “nudged” by excitatory and inhibitory conductances g_E and g_I . The strength of synapses on the dendrites is adapted such that the dendritic potential V converges to the nudged somatic potential u . (B2) The corresponding gradient rule yields LTP that does only depend on the pre-post spike timings and LTD that depends only on the presynaptic spike time (captured by E_{pre}) and the local dendritic voltage (V ; see Eqs. 1 and 3)

depression term, we note that potentiation depends on three factors (the postsynaptic spike, the presynaptic eligibility trace, and a nonlinear function of the postsynaptic membrane potential $\rho'(u)/\rho(u)$) and depression on two factors (the presynaptic eligibility trace and $\rho'(u)$). This learning rule is reminiscent of the voltage-triplet rule discussed above (Clopath and Gerstner (2010); see also Brea et al. (2013) for a detailed discussion of the mapping between those two learning rules).

Arguably, clamping the postsynaptic spike train S_{post}^{cl} is biologically unfeasible as it would require that the membrane potential u is ∞ at the time of a target spike and $-\infty$ else, conflicting with the evaluation of ρ and ρ' at the synaptically generated value of u . An alternative is to separate the spike-generating voltage from the synaptically

induced voltage and consider a somatic and dendritic membrane potential, u and V , that are interpreted as a “teacher” (u) and “student” (V) potential, respectively (Fig. 2B1; Urbanczik and Senn (2014)). The soma receives conductance-based synaptic input that represents a teaching signal, and the postsynaptic spike train S_{post} is stochastically generated in the “free” run, i.e., according to a firing intensity $\rho(u)$ that is affected by this teaching input. Without teaching input, the somatic membrane potential is just the attenuated dendritic voltage, $u = \alpha V$, where α represents some dendritic attenuation factor and the instantaneous somatic firing is therefore $\rho(\alpha V)$. But if the somatic teaching input is turned on, the somatic voltage typically differs from the “dendritic prediction,” $u \neq \alpha V$. Learning is driven by the “prediction error” measured in terms of the firing rates, $\rho(u) - \rho(\alpha V)$. It reduces this error by adapting the synaptic strengths of the dendritic “student inputs.” At the synaptic location on the dendrite, the somatic rate $\rho(u)$ can be sampled by the backpropagating spikes S_{post} . The learning rule (Eq. 2) now translates to the biological version

$$\dot{w}(t) = \eta \frac{\rho'}{\rho} (S_{post}(t) - \rho(\alpha V(t))) E_{pre}(t). \quad (3)$$

that can operate all the time, without need for clamping (Fig. 2B2).

Crucially, after learning the teaching input driving, the synaptic plasticity (Eq. 3) can be turned off or on, without affecting the somatic voltage and hence without inducing additional weight changes. This is a consequence of the conductance-based teacher input that itself only changes the membrane potential if it deviates from the reversal potential defined that teaching input (Urbanczik and Senn 2014). The rule shares other interesting biological features. When the backpropagation is hampered, say due to insufficient dendritic depolarization, S_{post} is thinned out at the synaptic site and a putative LTP turns into LTD, as observed for synapses on the distal apical tree of cortical pyramidal neurons (Sjostrom and Häusser 2006). Similarly, when the dendritic depolarization V is enhanced without additional postsynaptic

spikes, LTD dominates as observed for these same cells (Sjostrom et al. 2004).

Unsupervised learning The learning rule (Eq. 2) in the free run is itself not suited for unsupervised learning since averaging $\dot{w}$ across trials cancels out to 0 at each point in time. However, if we consider a 2-dimensional sheet of 2-compartmental neurons as described in Fig. 2b, with Mexican-hat shaped somato-somatic connections, the somatic potential u is nudged away from V^* and the somatic firing in average does not anymore reflect the dendritic drive, $\langle S_{\text{post}} \rangle \neq \rho(V^*)$. In this case, the lateral connectivity induces a soft winner-take-all dynamics in the network that becomes a spike-based self-organizing feature map (Urbanczik and Senn 2014). When the dendrites of these neurons are supplied by spatiotemporal spike patterns via plastic synapses governed by the rule (Eq. 3), the feature map learns to cluster the spike patterns according to their similarity.

Another form of a gradient-based unsupervised learning that maximizes the mutual information between the pre- and postsynaptic spike trains was also shown to share classical STDP features while being able to develop receptive field properties (Toyoizumi et al. 2007). In the unsupervised setting, functional properties have also been shown for phenomenological STDP models in forming auditory maps (Gerstner et al. 1996), cortical columns (Song and Abbott 2001), direction-selective neurons in the visual cortex (Buchs and Senn 2002), or receptive fields similarly as described in the BCM theory (Gjorgjieva et al. 2011).

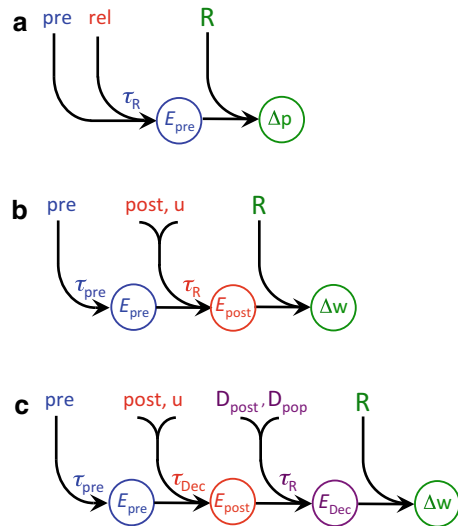
Reinforcement learning In reinforcement learning (RL), the putative synaptic weight changes induced by the pre- and postsynaptic activities are first low-pass filtered, and when a binary reward signal $R = \pm 1$ is applied, the changes accumulated until this time are multiplicatively modulated by R and turned into a real synaptic weight change. The phenomenological STDP model shown in Fig. 2 has also been adapted to this reinforcement learning scenario where it is referred to as R-STDP (Izhikevich 2007; Legenstein et al. 2008). However, R-STDP is shown to be problematic since for each stimulus class the expected reward must be

0 (Frémaux et al. 2010). This is because the integral over the STDP curve (Fig. 1) in general deviates from 0, and hence learning with $\langle R \rangle \neq 0$ would cause a weight drift. This is not the case for Eq. 2 in the free run, nor for Eq. 3 without somatic teaching conductances. These latter rules translate to the RL rule schematized in Fig. 4b:

$$E_{\text{post}}(t) = \int_{-\infty}^t \frac{\rho'}{\rho} (S_{\text{post}}(\tilde{t}) - \rho(u(\tilde{t}))) E_{\text{pre}}(\tilde{t}) e^{-\frac{t-\tilde{t}}{\tau_R}} d\tilde{t} \quad (4)$$

$$\Delta w(T) = \eta R E_{\text{post}}(T), \quad (5)$$

Gradient rules for RL



Spike-Timing Dependent Plasticity, Learning Rules, Fig. 4 Gradient-based SDTP for reinforcement learning (RL). With incorporating downstream quantities into the synaptic plasticity, learning becomes faster. (a) The simplest spike-based RL rule changes the presynaptic release probability p (a proxy for the synaptic strength w) as a function of the presynaptic spike and the release, low-pass filtered with a time constant τ_R corresponding to the typical reward delay (Seung 2003). (b) The same synaptic modifications for supervised learning (Fig. 3) yields RL when low-pass filtered with τ_R and modulated with the delayed reward R (Eqs. 1, 4, and 5). (c) As a decision is made by a population of neurons, synaptic updates should take account of the population decision signal D_{pop} , compare it with the single neuron decision D_{post} , low-pass filter the correlation between the two decision signals with τ_R , and only then implement the resulting weight change modulated by R (Eqs. 1, 6, 7, and 8)

where E_{pre} is given in (Eq. 1) and for the 2-compartmental model, the argument u of ρ and ρ' is replaced by V^* . The rule is shown to perform stochastic gradient ascent on the expected reward and has been studied in different applications (Xie and Seung 2004; Pfister et al. 2006; Florian 2007; Frémaux et al. 2010).

Stochastic gradient rules are not unique since the same gradient can be obtained from different estimators. The rule in Eq. 5, for instance, represents an estimator of the gradient of the expected reward, $\frac{\partial}{\partial w} \langle R \rangle = \langle R \frac{\partial}{\partial} \log P_w(y|x) \rangle$, averaged across stimuli x , network activity y , time and reward. The reward R may depend on quantities downstream of x and y like the decision (or action) D that itself may stochastically depend on y . The reward $R(x, y)$ therefore is a stochastic function of (x, y) with conditional expectation $\langle R|x, y \rangle = \sum_D R(x, D)P(D|x, y)$. For a synapse that has only access to the pre- and postsynaptic activities (components of x and y), the samples $R(x, y)$ have a large variance and so will the samples $R(x, y) \times \frac{\partial}{\partial w} \log P_w(y|x)$ of the gradient estimate have. In contrast, $R(x, D)$ may be a deterministic function (or again a stochastic function with smaller variance) and the samples $R(x, D) \frac{\partial}{\partial w} \log P_w(D|x)$ of the same reward gradient $\frac{\partial}{\partial w} \langle R \rangle$ show a smaller variance. To calculate $\frac{\partial}{\partial w} \log P_w(D|w)$, however, a synapse needs to have access to D (beside the pre- and postsynaptic activities).

Instead of considering $R(x, y)$, the reward can even be seen as a stochastic function of only the presynaptic spikes and the synaptic releases, $R(x, \text{rel})$. This leads to a learning rule where synaptic releases that are correlated with subsequent rewards are made more likely by enhancing the corresponding release probability (Seung 2003). But the variance of this reward gradient estimator can be reduced by taking account of the postsynaptic activity. In this way, more and more downstream information can be taken into account in the synaptic update, leading to learning rules that consider (A) only presynaptic spikes/releases and reward, (B) presynaptic spikes/releases, postsynaptic activity and reward, and (C) presynaptic spikes/releases, postsynaptic activities, single neuron and network decisions, and reward

(Fig. 4). In these gradient estimators, the correlation between the synaptic parameter change and reward is progressively increased the more reward-relevant information the synapse exploits. In the case of only evaluating presynaptic spikes and releases, learning was claimed to mimic song acquisition in the zebra finch (Seung 2003). When additionally evaluating the postsynaptic spikes and the membrane potential, the rule was shown to learn motor trajectories (Frémaux et al. 2010). When further evaluating the population decision the rule was shown to be successful in a complex sequential association task with delayed and scrambled rewards that is even hard to be learned by humans (Friedrich et al. 2011).

In population RL, the synaptic plasticity is modulated by the population decision that ultimately leads to the reward signal (Urbanczik and Senn 2009). The sign of the weight change should depend on whether the decision of the individual postsynaptic neuron D_{post} coincides with population decision D_{pop} formed by the majority of population neurons. These signals intrinsically depend on the neuronal code with which neurons and populations represent the possibly multi-valued decisions and actions (Friedrich et al. 2014). In the simplest case of binary decisions, these signals may be set to 1 or -1 , depending on whether the neuronal or population activity, low-pass filtered by τ_{Dec} , is above or below the corresponding decision threshold (Friedrich et al. 2011). The gradient rule emerging from this reasoning reads as (cf. Fig. 4c)

$$E_{\text{post}}(t) = \int_{-\infty}^t \frac{\rho'}{\rho} (S_{\text{post}}(\tilde{t}) - \rho(u(\tilde{t}))) E_{\text{pre}}(\tilde{t}) e^{-\frac{t-\tilde{t}}{\tau_{\text{Dec}}}} d\tilde{t} \quad (6)$$

$$E_{\text{Dec}}(t) = \int_{-\infty}^t D_{\text{post}}(\tilde{t}) D_{\text{pop}}(\tilde{t}) E_{\text{post}}(\tilde{t}) e^{-\frac{t-\tilde{t}}{\tau_{\text{R}}}} d\tilde{t} \quad (7)$$

$$\Delta w(T) = \eta R E_{\Delta \varepsilon_X}(T). \quad (8)$$

Intracellular recordings from dendrites during plasticity induction protocols have shown that SDTP also depends on dendritic NMDA spikes

(Gordon et al. 2006). This raises the question whether there are spike-timing-dependent plasticity rules that take account of such dendritic spikes as well. There is in fact a class of gradient-based RL rules that incorporate the “triple-spike timing” among the presynaptic, dendritic, and postsynaptic spike sequence, including the dendritic and somatic voltage and the reward modulation, analogously to the four-step cascade schematized in Fig. 4c (Schiess et al. 2012).

Cross-References

- ▶ [Learning Rules: Overview](#)
- ▶ [Long-Term Plasticity, Biophysical Models](#)
- ▶ [Reinforcement Learning in Cortical Networks](#)
- ▶ [Reward-Based Learning, Model-Based and Model-Free](#)
- ▶ [Spike-Timing Dependent Plasticity \(STDP\), Biophysical Models](#)
- ▶ [Tempotron Learning](#)

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Spike-Timing Dependent Synaptic Plasticity

- [Spike-Timing Dependent Plasticity, Learning Rules](#)

Spike-Triggered Average

- [Local Field Potential, Relationship to Unit Activity](#)

Spiking Cochleas

- [Neuromorphic Sensors, Cochlea](#)

Spinal Biomechanics

- [Biomechanical Model of Low Back Pain](#)

Spinal Control of Voluntary Movements

- [Coordinate Transformations, Role of Spinal Circuitry in](#)

Spinal Cord Stimulation

- [Methodologies for the Treatment of Pain](#)
- [Spinal Stimulation for Parkinson Treatment](#)

Spinal Cord, Integrated (Non CPG) Models of

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Synonyms

Adaptive control; Motor control; Motor learning; Reflex; Regulator; Segmental control; Servo control; Voluntary behavior

Definition

Spinal cord refers to the central nervous system (CNS) in vertebrates below the foramen magnum,

between the brainstem and the peripheral nervous system, not including the autonomic ganglia.

Learned sensorimotor behavior refers to all types of voluntary musculoskeletal activation that accomplish a behavioral goal and that utilize sensory feedback during execution, but here excluding cyclical locomotor behaviors known to be generated and controlled autonomously by central pattern generators residing within the spinal cord itself (see “Cross-References”).

Detailed Description

The spinal cord is not part of the brain; together they constitute the central nervous system of vertebrates. The spinal cord alone is capable of controlling complete motor behaviors such as locomotion. It can generate complex sequences of muscle activation and alter them to ambient conditions detected by somatosensory afferents. The well-studied role of the spinal cord in locomotion is covered in other entries (► [“Vertebrate Pattern Generation: Overview”](#)); this article considers whether and how the same spinal circuits contribute to voluntary motor behavior that is ultimately controlled by the brain.

Historical and Methodological Perspective

Several anatomical features of the spinal cord made it an attractive target for the earliest neurophysiological investigations. Its connections to and from the peripheral nervous system of the body are arranged in four laterally and dorsoventrally segregated and highly elongated rows of roots. These are divided and gathered into spinal nerves based on the openings between adjacent vertebrae. These roots and their associated peripheral nerves are readily traced by gross anatomical dissection to various target structures (individual muscles and regions of skin) whose function can be easily observed and manipulated. About 200 years ago, the anatomist Charles Bell and, separately, the physiologist Francois Magendie discovered that the ventral roots conveyed the motor commands to the

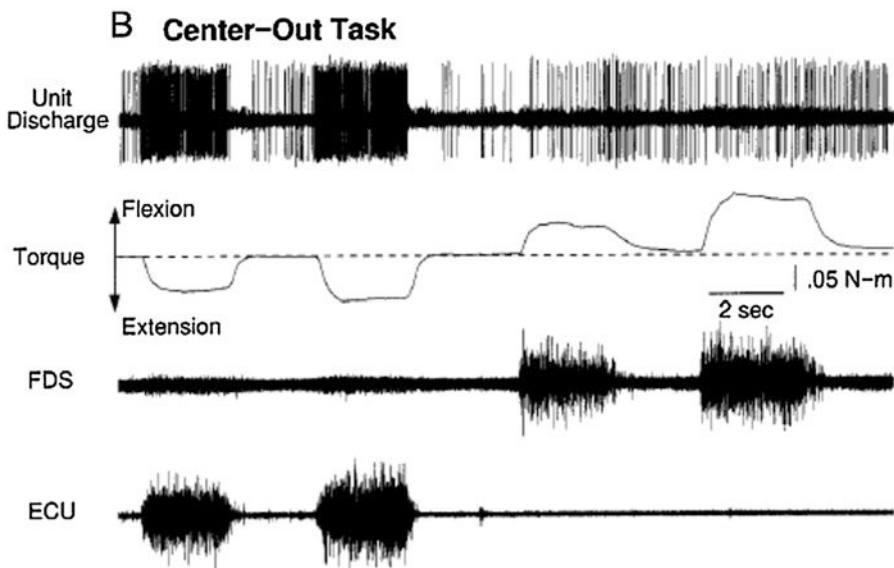
muscles (Bell 1811) while the dorsal roots conveyed only sensory information (Magendie 1822), respectively. This laid a foundation for the interpretation of clinical phenomena such as the knee-jerk reflex, well known to nineteenth-century neurology. At the turn of the twentieth century, Sir Charles Sherrington systematically extended the set of spinal reflexes to include both excitatory and inhibitory responses as well as interlimb effects and suggested that such reflexes constituted the building blocks of spinally mediated behaviors such as locomotion (Sherrington 1910).

As electrophysiological methodology developed during the middle of the twentieth century, it became possible to identify the individual neurons and circuits responsible for behavioral phenomena. The spinal interneurons came to be divided and identified by the nature of the input and output connections by which they were first identified. The newly discovered proprioceptors and spinal interneurons appeared to correspond to the feedback circuits utilized by the emerging field of servo control engineering to stabilize electrical and mechanical systems (including the instrumentation that those electrophysiologists generally had to build for themselves). This suggested that the reflexes might be just the most visible manifestations of continuous servo control, in which the spinal circuitry could simplify the problem of motor control by linearizing the complex mechanical properties of the musculoskeletal system (Houk 1979). It gradually became clear, however, that the actual input and output connections to spinal interneurons and motoneurons were far broader than predicted by servo control. The most local circuits were the easiest to find but the cumulative effects of the more widespread circuits are probably much larger. Furthermore, the strength and even the sign of many spinal reflexes were found to be modulated during both locomotor and voluntary motor behaviors (Burke 1999).

Neurophysiological studies of voluntary behaviors have focused mostly on the cerebral cortex of the brain, correlating neural activity recorded by chronically implanted

microelectrodes with observable kinematics and/or muscle activity in the limb. However, the vast majority of corticospinal projections end on spinal interneurons rather than the motoneurons that activate muscles directly (Rathelot and Strick 2009). These interneurons are vigorously active during learned, voluntary limb movements (see Fig. 1 below from Perlmuter et al. 1998). The threshold nonlinearity of spiking neurons implies that the cortical commands can be seen as enabling reflexive adjustments or, equally, that the ongoing somatosensory feedback enables the commanded behavior. Early attempts to tease this apart relied on the latencies of various responses to strong electrical stimuli, which depend on the physical lengths of the circuits and the conduction velocities of the axons. This can be used to compute the minimal latency of the fastest possible responses such as the monosynaptic stretch reflex, but it does not help with mechanical stimuli whose asynchronous afferent signals may undergo substantial temporospatial integration in the interneurons at every level before any response is seen.

This entry summarizes what is now known about the connectivity of the spinal circuits (for a detailed review, see Pierrot-Deseilligny and Burke 2005). Much of that information comes from histological tracing and electrophysiological studies of the spinal cord of the cat, supplemented by clinical studies of human limb reflexes. There are substantial specializations in other species and other parts of the body such as the axial muscles of the neck and trunk (Richmond and Loeb 1992). This review also considers theories and models regarding how these spinal circuits could contribute to control of learned, voluntary limb movements. Other parts of the brain such as the cerebellum have equally well-developed connections to and from spinal cord (Spanne and Jörntell 2013) compared to the cerebral cortex. Damage to the cerebellum produces different but equally profound sensorimotor disorders, but its role in voluntary behavior is even less well understood. The actual functional relationships between the brain and the spinal cord remain contentious.



Spinal Cord, Integrated (Non CPG) Models of, Fig. 1 Extracellularly recorded spikes from a spinal premotor interneuron recorded as monkey-generated isometric ramp-and-hold torques in flexion and extension at the wrist in order to match a visual cue; *FDS* = EMG from

flexor digitorum superficialis, *ECU* = EMG from extensor carpi ulnaris. Note strong correlation with ECU during extension torques but substantial activity during flexion torques that was not correlated with *FDS* modulation (From Perlmuter et al. 1998)

Basic Components

Somatosensory Afferents

A general review of somatosensation can be found elsewhere; this is a brief summary of the afferents whose modalities and conduction velocities resulted in the naming conventions for the interneurons described below.

- **Spindle Primary Afferents (Ia):** Most muscles contain 20–500 elaborate sense organs attached in parallel with their muscle fibers. These muscle spindles each contain several specialized and separately innervated intrafusal muscle fibers. Each spindle is innervated by one rapidly conducting, primary afferent axon ($A\alpha$) whose local sensory endings consist of spirals wrapped around the middle of each of the intrafusal muscle fibers. These Ia afferents are exquisitely sensitive to stretch of the muscle (and hence of the spindle and its intrafusal muscle fibers). The absolute and relative sensitivities of the Ia afferents to length versus velocity are modulated over a wide dynamic range by centrally controlled activation of their various types of intrafusal muscle fibers (Loeb 1984).
- **Golgi Tendon Organ (GTO) Afferents (Ib):** Most muscles contain 20–200 simple sense organs attached in series with various subsets of their muscle fibers, making them sensitive to active muscle force. Each GTO is innervated by one rapidly conducting primary afferent axon ($A\alpha$). The random sampling of muscle fibers makes the response of a given GTO somewhat idiosyncratic, but the generally orderly recruitment of motor units results in ensemble activity of the Ib afferents that accurately reflects total muscle force (Mileusnic and Loeb 2009).
- **Group II Afferents:** The smaller and slower conducting myelinated axons ($A\beta$) in peripheral nerves are designated as Group II. They include both cutaneous mechanoreceptors with a wide range of sensitivities in both glabrous and hairy skin plus secondary spindle afferents attached to a subset of the intrafusal muscle fibers and sensitive mostly to absolute length.

Some cutaneous stretch sensors contribute to the sense of body posture and motion in combination with the spindle afferents (Gandevia 1996); others are better suited to detecting intermittent contact with external objects.

- **Group III and IV Afferents:** The smallest myelinated ($A\delta$) and unmyelinated (C) sensory nerve fibers innervate a wide range of specialized receptors for strain, temperature, pain, and metabolic products. Their signals are processed locally by dorsal horn interneurons, many of which project to some of the spinal interneurons or their presynaptic inputs. Their slow conduction velocities lead to the presumption that they do not contribute importantly to moment-to-moment coordination but they probably modulate the state of the system in response to fatigue and injury (Martin et al. 2006).
- **Recurrent Motoneuron Collaterals:** Most alpha motoneurons give off collateral branches before leaving the spinal cord en route to the muscles. While not truly sensory, these efference copy signals provide feedback regarding important state variables of the system, contributing to both the reflexive behavior of the spinal cord itself and the ascending information that is conveyed to the brain (Windhorst 1990).

Presynaptic Modulation

An important feature of many spinal circuits is the presence of synaptic triads, in which the synaptic boutons of one neuron (modulator) end on the boutons of another neuron (transmitter) rather than on the cell body or dendrites of the receiver neuron. These presynaptic pathways may exert either depolarizing or hyperpolarizing effects on the resting membrane potential of the transmitter boutons. When a spike arrives at the transmitter bouton, the amplitude of the voltage excursion depends on this resting potential; the amount of transmitter that is released depends strongly on the voltage excursion. A depolarizing presynaptic modulation thus has the effect of inhibiting the efficacy of the transmitter; a hyperpolarizing modulation facilitates the transmitter. The presynaptic inhibitory effects of many cutaneous afferents

have been particularly well described (Rudomin and Schmidt 1999). The monosynaptic stretch reflex is also presynaptically inhibited by descending cortical pathways (Meunier and Pierrot-Deseilligny 1998) and in fatigued muscles (Baudry et al. 2010). The full extent of sources and recipients of presynaptic inhibition and facilitation is not known.

Limb Dynamics

Physiologists look for ways to simplify complex musculoskeletal anatomy and mechanics in order to identify organizing principles of control. By focusing on one axis of motion of one joint (e.g., dorsiflexion/extension of the ankle joint), it is possible to describe all the muscles that create a positive moment as synergists and all that create a negative moment as antagonists. Activation of the muscles in each group will have opposite effects on the joint torque, and motion of the joint in this axis will have opposite effects on the stretch receptors in these two groups of muscles. Unsurprisingly, the reflexes elicited by afferents from synergistic muscles are substantially different and often opposite in sign from those elicited by the same types of afferents from the antagonist muscles (Sherrington 1908). Much of the terminology below reflects this natural reciprocity of function and connectivity.

Unfortunately, most musculoskeletal anatomy and dynamics are not well described by simple reciprocity. Most joints have more than one axis of motion and the majority of mammalian muscles cross more than one joint. The lengths of the muscles and their moment arms on each axis of motion depend on the posture and motion of all the axes of all the joints that they cross. Muscles that are synergists for the restricted motion described above may be undergoing length changes that are opposite in sign and generating torques in other axes that are opposite in sign. Furthermore, a skeleton consisting of a series of linked inertial masses is subject to intersegmental dynamics, sometimes summarized as Coriolis effects. Acceleration induced by a muscle crossing one joint results in angular accelerations at distant joints, similar to the complex sequence of motion

induced by cracking a whip from its proximal end (Zajac and Gordon 1989). The idealized classical circuits described below use the terminology of synergist and antagonist, but most muscles relate to most other muscles via combinations of both types of circuitry (designated as a “partial synergist” relationship). The net effects depend on the gains in the competing pathways, which are strongly modulated by both descending and local pathways, as discussed in Coordination and Regulation.

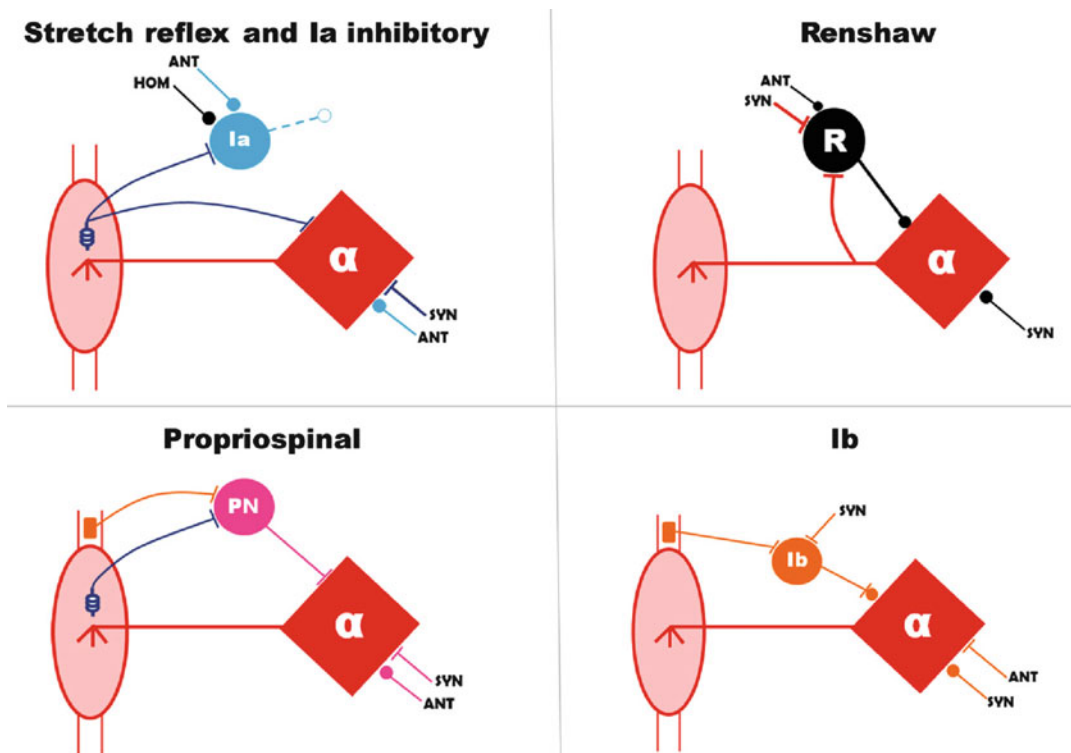
Spinal Circuits

Ia Monosynaptic Stretch Reflex

The tendon jerk reflexes (e.g., knee, ankle) are the fastest and most reliable responses because they involve only one synapse between a rapidly conducting Ia spindle afferent and an alpha motoneuron. The Ia afferents from a given muscle project to most or all of the motoneurons that control that muscle (homonymous projection; HOM in Fig. 2) and to many of the motoneurons of synergist (SYN) muscles (Eccles et al. 1957a). Nevertheless, the strength of the observable response can be substantially modulated by post-synaptic polarization of the receiving pool of motoneurons via other synaptic inputs and by presynaptic inhibition or facilitation of the Ia synapse itself. The brain can learn to change the gain of even this direct connection (Wolpaw 2010).

Ia Inhibitory Interneurons

Spindle Ia afferents excite a class of inhibitory interneurons that project to the motoneurons of antagonist muscles (Eccles and Lundberg 1958). Thus, stretching one muscle tends to inhibit activity that may be occurring in the antagonist muscles and that would otherwise oppose the excitatory stretch reflex described above. It is important to remember that the spindle receptors of both the synergist and antagonist muscles are generally biased by their respective fusimotor efferents so that they are generating continuous activity. Sudden perturbations that give rise to excitatory and inhibitory reflexes are just the



Spinal Cord, Integrated (Non CPG) Models of, Fig. 2 Five classical interneuronal pathways that comprise the model from the perspective of a single muscle. Projections from neural elements associated with self (*HOM*) as well as synergist (*SYN*) and antagonist (*ANT*)

muscles are shown with color codes: Ia inhibitory interneurons are *blue*, Ib inhibitory interneurons are *orange*, and Renshaw inhibitory interneurons are *black* (Illustration from Tsianos et al. 2011)

most obvious manifestation of a continuous push-pull servo control system. These reciprocal circuits work continuously to maintain stable body posture and minimize energetically wasteful cocontraction of mutually antagonistic muscles.

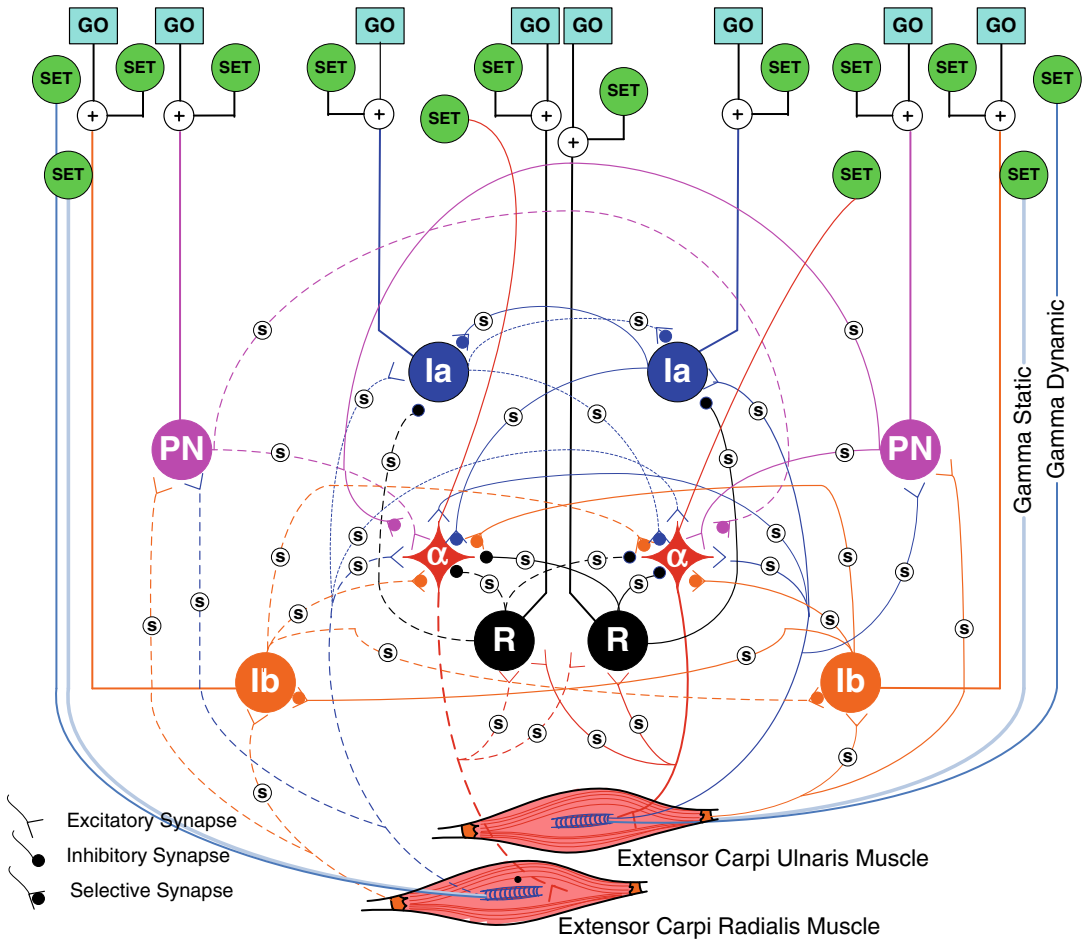
Ib Inhibitory Interneurons

The force-sensitive Golgi tendon organs excite a class of inhibitory interneurons that project to their own and synergist motoneurons (Eccles et al. 1957b). This results in a simple servo controller that tends to stabilize fluctuations in force. The story does not end there, however. The Ib inhibitory interneurons actually receive inputs from a wide range of cutaneous and proprioceptive afferents, and they project widely to both synergistic and antagonistic motoneurons. Furthermore, Ib inhibitory interneurons project to

each other, resulting in disinhibition whereby force feedback can actually result in positive, self-reinforcing feedback loops (McCrea 1986). This complexity is summarized in Fig. 2 (Ib, bottom right) and Fig. 3 with a symbol denoting the selectability of both excitatory and inhibitory effects between the Ib inhibitory interneuron and homonymous alpha motoneuron.

Renshaw Inhibitory Interneurons

The recurrent motoneuron collaterals excite an interneuron that inhibits the homonymous motoneurons and their synergists, in the manner of a servo control governor preventing runaway activation of the muscles. These Renshaw inhibitory interneurons also project to the Ia inhibitory neurons of the same muscle, resulting in a disinhibition of the antagonist motoneurons (Windhorst 1990).



Spinal Cord, Integrated (Non CPG) Models of, Fig. 3 The major proprioceptive feedback circuits between two wrist muscles that are synergists for some tasks (e.g., extension) and antagonists for others (e.g., radioulnar deviation); color code is the same as in Fig. 1.

Tasks were controlled by learning a background pattern of *SET* signals to designated spinal neurons and presynaptic gains (*S* in circles) and a *GO* pattern to initiate the task via only the spinal interneurons (Figure from Raphael et al. 2010)

Propriospinal Excitatory Interneurons

There are clusters of excitatory spinal interneurons located just rostral to both the cervical and lumbar enlargements wherein the limb motor nuclei are located. These interneurons receive direct excitatory projections from both Ia and Ib afferents as well as strong descending control from the brain (Jankowska et al. 1973). They have been implicated in the initiation of voluntary limb movements via their excitatory and inhibitory effects on synergist and antagonist motoneurons, respectively (Lundberg 1992).

Cutaneous Reflex Interneurons

Activity in cutaneous afferents can produce strong and widely distributed excitation and inhibition of motoneurons. The pathways all go through chains of at least two interneurons, however, each of which is subject to modulation by other afferents, other interneurons, and descending signals from the brain. The functional contribution of cutaneous feedback is obvious from studies of dexterous manipulation of objects (Johansson and Flanagan 2009), but specific circuit models are not available.

Spindle Secondary Interneurons (Group II)

The tonic stretch reflex and perhaps some of the knee-jerk reflex may be generated by disynaptic excitation arising from Group II muscle afferents. These same interneurons also receive input from Flexor Reflex Afferents (see below). It has been proposed that these Group II interneurons and others resulting in disynaptic inhibition contribute to voluntary behaviors (Lundberg et al. 1987), but there is little direct evidence as yet.

Flexor Reflex Afferents

Nociceptive cutaneous afferents (Group III = A δ fibers, Group IV = C fibers) give rise to the flexion reflex, consisting of coordinated activation of ipsilateral limb flexors and often accompanied by contralateral limb extension (Anden et al. 1964; Duysens et al. 2013). It is prominent during locomotion, enabling the limb to withdraw from an obstructive or aversive stimulus to get around an obstacle. Specific models of these oligosynaptic circuits are not available.

Commissural Interneurons

Interneurons that project across the midline appear to be useful for interlimb coordination during locomotion (Jankowska 2008). Specific circuit models are not available and their role in learned motor behaviors is unknown.

Central Pattern Generators (CPG)

As discussed elsewhere (McCrea and Rybak 2008), the spinal cord contains reciprocally inhibited groups of interneurons that function as self-sustaining oscillators for cyclical behaviors such as locomotion. Their relatively simple, alternating rhythms are converted into the more subtly phased activation of individual muscles by the interneuronal circuits listed above and perhaps unknown others. Their rhythms can be altered or even reset by somatosensory feedback and descending control. It is unknown whether these CPG circuits are utilized for learned motor behaviors that have similar oscillatory patterns.

Decision and Command Versus Coordination and Regulation

The general notion is that the brain is strategic, deciding what voluntary movement should be executed and when, while the spinal cord is tactical, dealing with the details of apportioning the physical work among various muscles and making reflexive adjustments to cope with local conditions. Most of the theories described below were motivated by the desire to simplify these problems, both so that the process could be understood by researchers and so that the brain could actually solve them. Nevertheless, from the relatively slow rate at which infants develop motor coordination, it is apparent that this is a very hard problem requiring a great deal of adaptive learning by the brain. Simple and intuitive theories may not be consistent with reality.

Fusimotor Servo Control

If the brain plans movements according to the desired trajectory of limb postures, then there has to be a computation to convert that plan into the net drive to each of the muscles required to stay on that trajectory. The complex mechanical dynamics of a multiarticular limb plus the highly nonlinear force-generating properties of muscle make such a calculation difficult, to say the least. Servo control offers a way out of this dilemma. Muscle activation could be commanded (or at least assisted) by first activating fusimotor neurons, thereby turning on muscle spindle afferents, and then allowing the excitatory reflexes from those afferents to turn on the motoneurons until the muscle shortened to the point where the fusimotor effects were negated (Merton 1953).

These ideas have fallen out of favor for two reasons. One is the lack of evidence for sufficiently high gains in these pathways or for fusimotor drive and spindle afferent activity that clearly leads the alpha motoneuron activity. The second is the recognition that the spindle afferents are responsible for much of the senses of posture and kinesthesia (Scott and Loeb 1994), which must be independent of muscle activation. It seems more likely that the fusimotor system is used to optimize the sensitivity of the spindle

afferents to the expected range of voluntary movements, thereby improving rather than degrading these critical senses (Loeb and Marks 1985).

Reciprocal and Equilibrium Control

Another way to solve the above-stated problem of getting a complex musculoskeletal system into the desired posture is to take advantage of the spring-like properties of mutually antagonistic sets of muscles at each joint. Active muscles themselves tend to behave like springs, increasing their force output when stretched and decreasing it when shortened. Simply coactivating mutually antagonistic muscles at different levels necessarily results in various postures (Bizzi et al. 1993); perturbations away from those postures are automatically resisted by the effective mechanical impedance of the system (which includes spring-like terms related to joint angle plus terms related to joint velocity and acceleration (Hogan 1984)). The ability of such a control system to follow dynamic trajectories can be greatly enhanced by including the reciprocal reflexes mediated by spindle afferents, and they can be more subtly modulated by further including fusimotor control. This is the so-called gamma equilibrium-point hypothesis (Feldman 1966; Feldman et al. 1998). A more general model of how the brain could utilize the reciprocally organized spindle feedback was presented by Maier et al. (2005).

While these muscle properties and reflexes certainly affect the properties of the system that the brain must control, they do not by themselves seem to account well for many observed behaviors (Kistemaker et al. 2007). Equilibrium control predicts more inefficient and undesirable cocontraction of muscles than is generally observed. It has difficulty with highly dynamic movements or when the goal is to control force on an object or surface rather than position. Finally, it is difficult to extend these schemes to account for the many multiarticular muscles and for the intersegmental dynamics of limbs.

Inverse Dynamics Models

Presumably the brain generates the command signals to the spinal cord that will result in the desired limb trajectory. If the brain were sending signals

directly to the motoneurons, it could learn an inverse model of the musculoskeletal mechanics and then employ an optimization scheme to compute an effective and efficient pattern of commands (Kawato 1999; Scott and Norman 2003). It would also have to monitor the sensory feedback and compute the necessary adjustments (Scott 2004), suppressing or taking into account any reflexes that would be occurring simultaneously in the autonomous circuits of the spinal cord (and probably other lower centers). But the brain is largely sending signals to the spinal interneurons themselves. In order to compute those commands, the brain would require an inverse model that included also the connectivity of the interneurons plus a forward model of the sensory afferents that project to those interneurons. It is unclear how the brain could learn such a complex model.

Regulator Models

Rather than trying to assign specific roles to each individual reflex or circuit, it may be more productive to look at the emergent properties of the complete spinal cord network. One approach is to ask what sorts of connections between afferents and efferents would be useful for solving typical problems in motor control. Given certain constraints, it is possible to apply an engineering tool for designing a linear quadratic regulator (LQR), which is essentially a matrix of excitatory and inhibitory gains between all possible pairs of input and output signals. The solution minimizes a cost function that reflects both the deviations from the desired state of the system and the expense of efforts to correct such deviations. When such a matrix was computed for maintaining stable standing posture in the hindlimb of a cat, the patterns of connections bore a striking resemblance to the patterns of connectivity in the major known interneuronal circuits listed above (Loeb et al. 1990; He et al. 1991). The matrix computed for a different mechanical state such as when freely moving through space would be substantially different, similar to the changes in reflex gains known to occur for such state changes. The methods used by engineers to compute such LQRs are unlikely to be employed by

the brain, but it is possible that they could be approximated by trial-and-error iteration over the lifetime of the animal.

While LQR analysis provides some insights into the general utility of the spinal cord for responding to perturbations, it does not provide a way to generate the desired states or trajectories in the first place. The general absence of direct cortical drive to the alpha motoneurons and the targeting of that drive onto the interneurons that mediate the reflexes suggest that the brain must plan simultaneously both the nominal behavior and desirable responses to anticipated perturbations (Loeb et al. 1999). The difficulty of computing such plans from inverse models suggests that they must be learned and stored as lookup tables and then replayed whenever the brain is called on to perform a familiar or at least similar task. Given the very large number of different interneuronal drives and synaptic gains in the spinal circuitry, is it feasible for solutions to be learned by trial-and-error exploration of this huge hyperspace?

Reasonably complete models of the classical spinal circuits that employ proprioceptive feedback (for the first five spinal circuits above, see Figs. 2 and 3) were constructed for an idealized 2DOF, 4-muscle wrist model (Raphael et al. 2010) and for a 2DOF, 6-muscle planar elbow-shoulder system (Tsianos et al. 2011). In both cases, simple trial-and-error adjustment from initially random states of the spinal cord resulted in kinematically successful and energetically efficient performance of a wide range of typical behaviors (resisting perturbations, rapid reaching to precise postures, compensation for viscous curl-fields, generating precise end-point forces). Success was attributed to the large number of “good-enough” solutions offered by the spinal circuitry, which seems to have little tendency to become entrapped in poor local minima. Solutions to one task provided useful starting points to learn new tasks, and sparse sets of such sequentially learned tasks could be interpolated to achieve intermediate behaviors despite the nonlinearity of the underlying neuromusculoskeletal system Tsianos et al. (in press). Somewhat disconcertingly, this implies that the internal representations of and strategies for a given motor behavior may differ

substantially among individuals. That would be consistent with the differences that emerge when physically “normal” individuals try to learn a new and unusual sport, but it makes it difficult to design and interpret experiments that usually require pooling data from many individuals.

Conclusions

The role of the spinal cord in learned sensorimotor behaviors remains contentious and may be shifting as animals evolve toward a wider repertoire of learned rather than instinctive behaviors. The propriospinal interneurons provide a case in point. In cats, these interneurons and their contribution to reaching movements are relatively easily demonstrated. In nonhuman primates, they are difficult to excite and, therefore, to find at all in anesthetized preparations (Alstermark et al. 2007). One possibility is that the resting bias of the spinal interneurons and perhaps other subcortical circuits may become hyperpolarized to suppress their reflexive responses until the cortex decides what combination of those reflexes will generate a more reasoned response. Another possibility is that the cortical systems that presumably subserve learned behaviors may simply overwhelm the other inputs to the spinal circuitry to take fairly direct control of the musculature, including the responses to perturbations (Kurtzer et al. 2008). Ignoring the phylogenetically old but sophisticated coordination provided by spinal interneurons might make sense if the brain needs to develop an internal model of the plant in order to compute motor programs *de novo*. Conversely, these circuits may be very useful if the brain must learn, store, and recall its repertoire without such online computation. Newly evolved musculoskeletal systems and functions such as dexterous manipulation of objects and vocalized speech may have no choice but to rely on newly evolved direct corticomotoneuronal projections, whether they are computing or recalling motor programs, but even these undergo substantial modulation by spinal circuits (Petersen et al. 2010).

Nevertheless, it is worth remembering that the first problem faced by a newborn brain is system

identification. It does not “know” that the external world and its own body exist, much less what effects its various output axons will have on that body. In the process of self-organizing that knowledge, the brain will discover and learn to cope with whatever musculoskeletal apparatus and local neural circuitry exist. Learning a new task must inevitably involve decisions about which components of the apparatus and the circuitry appear to be useful and which need to be ignored or suppressed. The challenge to the developing organism is to learn those tasks as quickly as possible, not to conform to abstract theories of how those tasks might be learned or performed.

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Spinal Electrical Stimulation

► Epidural Stimulation

Spinal Electromagnetic Stimulation

► Paraspinal Magnetic and Transcutaneous Electrical Stimulation

Spinal Locomotor Network

► Locomotor Pattern Generation in the Rodent Spinal Cord

Spinal Neuromagnetic Stimulation

► Paraspinal Magnetic and Transcutaneous Electrical Stimulation

Spinal Root Stimulation

► Paraspinal Magnetic and Transcutaneous Electrical Stimulation

Spinal Stimulation for Parkinson Treatment

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Synonyms

Dorsal column stimulation; Epidural stimulation;
Spinal cord stimulation

Definition

Spinal stimulation for Parkinson treatment is a neuromodulation procedure proposed as therapy for alleviating the motor symptoms of Parkinson's disease. It requires the epidural implant of bipolar electrodes in the dorsal portion of the spinal cord to deliver electrical pulses at specific frequencies.

Detailed Description

Spinal cord stimulation is a technique used for treating chronic pain conditions which are refractory to pharmacological therapies. In 2009 it was proposed that spinal cord stimulation could be used for treating the motor symptoms of Parkinson's disease (PD). PD is characterized by a lack of dopamine due to the death of the dopaminergic neurons of the substantia nigra. It interferes with the normal functioning of the corticobasal ganglia causing the classical symptoms of hypokinesia and rigidity, that is, slow movements and stiffness of the joints.

Patients and animal models of PD exhibit characteristic low-frequency, high-amplitude synchronous neural activity at the corticobasal ganglia loop. The rationale behind using spinal cord stimulation for PD was that high-frequency stimulation of spinal sensory afferents will convey to the supraspinal structures a signal capable of disrupting the low-frequency pathological rhythms, thus restoring normal functioning of the circuit.

The first experiments showed that dopamine-depleted mice showing strong akinesia would have their locomotion capability restored when receiving spinal cord stimulation. Further, rats with bilateral striatal 6-OHDA lesions, another model of PD, would exhibit the same effect. Electrophysiological recording in the mice showed that spinal cord stimulation caused dramatic changes in the synchrony pattern of the striatum and primary motor cortex, decreasing the low-frequency synchronization (<25 Hz) and increasing the synchronization at higher frequencies (>30 Hz).

The first report of spinal cord stimulation used in two PD patients failed to show any alleviation of motor symptoms. Four additional reports from different clinical groups over the world show that spinal cord stimulation used in PD patients who also suffer chronic pain, primary or secondary to PD, will experiment significant improvement of motor symptoms related to gate, locomotion speed, and posture.

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Spindle Oscillations: Models

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Definition

Sleep spindles appear during the early phases of sleep in all mammals. These 7–14 Hz oscillations are generated by the thalamus, but their triggering and large-scale synchrony depends on the cerebral cortex and thalamocortical interactions. Computational models have been designed to study how these oscillations are generated, what type of intrinsic currents and synaptic receptors is implicated, and how their synchrony is organized in the thalamocortical system.

Detailed Description

Introduction

The mammalian brain generates various types of slow oscillations during slow-wave sleep, such as spindle waves, delta oscillations, and slower oscillations (Steriade 2003). Spindle oscillations, which are mostly visible in the early stages of sleep (stage II in humans), are the best studied sleep oscillation because it is present in all mammals during sleep or anesthesia. Spindles are generated by thalamic circuits under physiological conditions, in contrast to delta and slow oscillations, for which cortical generators also exist. We focus here on sleep spindles, their genesis by thalamic networks, how these oscillations are distributed across the entire thalamocortical system.

Thalamic Pacemakers for Spindle Oscillations

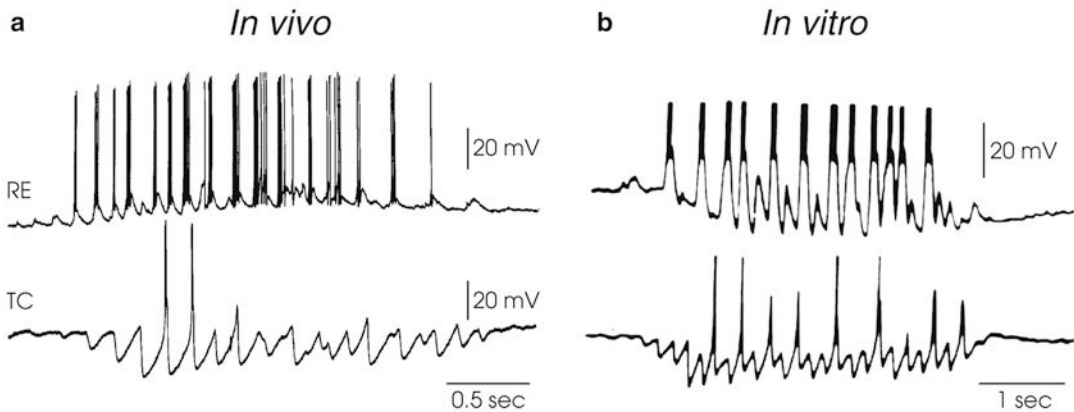
Spindles are visible in the electroencephalogram (EEG), in which they consist of short 1–3 s

periods of 7–14 Hz oscillations, organized within a waxing-and-waning envelope, that recur periodically every 10–20 s. In cats and rodents, spindle waves of similar characteristics appear during slow-wave sleep and are typically more prominent at sleep onset. They are enhanced by some anesthetics, such as barbiturates, which, when administered at an appropriate dose, generate an EEG dominated by spindles.

The first indication that spindles could originate outside the cerebral cortex was from Bishop in 1936, who showed that rhythmical activity was suppressed in the cerebral cortex following destruction of its connections with the thalamus. In 1938, Bremer showed that rhythmical activity is still present in the white matter following destruction of the cortical mantle. Later, Adrian in 1941, and Morison and Bassett in 1945, observed that spindle oscillations persist in the thalamus upon removal of the cortex, providing firm experimental evidence that these oscillations originate in the thalamus. These experiments led to the development of the “thalamic pacemaker” hypothesis (Steriade and Deschênes 1984), according to which rhythmic activity is generated in the thalamus and communicated to the cortex, where it entrains cortical neurons and is responsible for the rhythmical activity observed in the EEG. The more recent discovery of spontaneously occurring spindles in ferret thalamic slices (von Krosigk et al. 1993) confirmed the thalamic pacemaker hypothesis. Furthermore, this *in vitro* model of spindle waves has made it possible to precisely characterize the ionic mechanisms and synaptic receptors involved in spindle oscillations.

Cellular Mechanisms of Spindle Oscillations

The first cellular mechanism to explain the genesis of spindle oscillations was proposed by Andersen and Eccles in 1962. From intracellular recordings from thalamocortical (TC) relay neurons during spindles, they reported that TC cells fired bursts of action potentials interleaved with inhibitory postsynaptic potentials (IPSPs). They



Spindle Oscillations: Models, Fig. 1 Spindle oscillations in thalamic circuits. (a) In vivo intracellular experiments realized in cats under barbiturate anesthesia, showing the activity of thalamocortical (TC) and thalamic reticular (RE) cells during spindle waves (modified from

Steriade and Deschênes 1984). (b) In vitro intracellular experiments realized in ferret visual thalamic slices, showing the activity of the same type of thalamic neurons during spindle waves (modified from von Krosigk et al. 1993)

suggested that TC cells fire in response to IPSPs (post-inhibitory rebound), which was later demonstrated to be a characteristic electrophysiological feature of thalamic cells by Jahnsen and Llinas. Andersen and Eccles suggested that the oscillations arose from the reciprocal interactions between TC cells and inhibitory local-circuit interneurons. This mechanism was later incorporated into a computational model that included a phenomenological description of the inhibitory rebound.

The mechanism proposed by Andersen and Eccles was seminal but was not entirely correct because reciprocal connections between TC cells and thalamic interneurons have never been observed in anatomical studies. It was later found by Scheibel and Scheibel (1966a, b, 1967) that the thalamic reticular (RE) nucleus, a sheet-like structure of inhibitory neurons surrounding the thalamus, could provide the inhibition of TC cells and that “TC-RE” loops could underlie recruitment phenomena and spindle oscillations. They predicted that the output of the RE nucleus should be inhibitory and that the inhibitory feedback from RE cells onto TC cells should be critical for the genesis of thalamic rhythmicity. This hypothesis was supported by the observation that the pattern of firing of RE neurons was tightly correlated with IPSPs in TC neurons.

The involvement of the thalamic RE nucleus in the generation of spindles was firmly established by a series of critical experiments by the group of Steriade in cats in vivo. The typical intracellular features of spindle oscillations in the two thalamic cell types are shown in Fig. 1a. By using intracellular or extracellular experiments, Steriade and collaborators have shown that, first, cortically projecting thalamic nuclei lose their ability to generate spindle oscillations if deprived of input from the RE nucleus (Steriade et al. 1985). Second, the isolated RE nucleus can itself generate rhythmicity in the spindle frequency range (Steriade et al. 1987).

Thus, three different mechanisms were proposed to explain thalamic rhythmicity: the “TC-interneuron” loops of Andersen and Eccles, the “TC-RE” loops of Scheibel and Scheibel, and the “RE pacemaker” hypothesis of Steriade (although Steriade’s work also demonstrated the importance of the cortex – see next section). The introduction of an in vitro model of spindle waves in young ferrets by McCormick’s group (Fig. 1b; von Krosigk et al. 1993) supported the second of these mechanisms. Slices of the visual thalamus that contain the dorsal (lateral geniculate nucleus or LGN) and reticular nuclei (perigeniculate nucleus or PGN), as well as the interconnections between them, generated spindles spontaneously,

confirming earlier experimental evidence for the genesis of spindles in the thalamus.

The great advantage of the *in vitro* preparation is that it allowed a detailed pharmacological investigation of the ionic currents and synaptic receptors underlying the spindle oscillations. The spindle waves disappeared after the connections between TC and RE cells were severed, consistent with the mechanism based on intrathalamic TC-RE loops proposed by Scheibel and Scheibel. This *in vitro* experiment also confirmed the observation that the input from RE neurons is necessary to generate spindles (Steriade et al. 1985). However, the RE nucleus maintained *in vitro* did not generate oscillations without connections from TC cells, in contrast with the observation of spindle rhythmicity in the isolated RE nucleus *in vivo* (Steriade et al. 1987).

Thus, *in vitro* experiments appear to support a mechanism by which oscillations are generated by the TC-RE loop, in contrast with the “RE pacemaker” hypothesis. Computational models are needed to investigate which of these mechanisms are plausible biophysically, as shown in the next section.

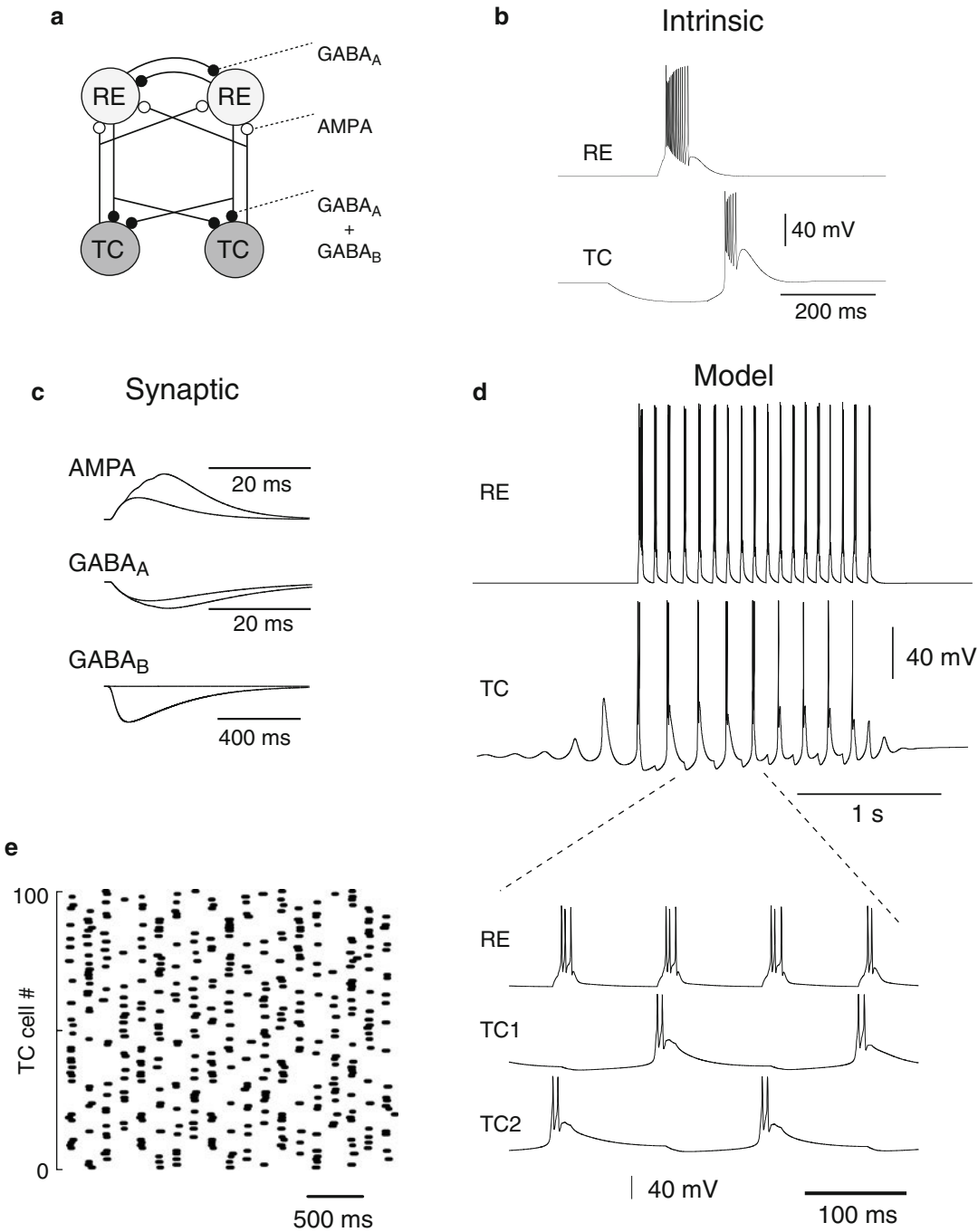
Models of Spindle Oscillations

Computational models investigated different cellular mechanisms of spindle oscillations, to attempt clarifying these contrasting experimental results. First, models investigated whether the RE nucleus is capable of displaying oscillations consistent with experiments. Models found that RE neurons interacting through GABAergic synapses can generate spindle rhythmicity (Wang and Rinzel 1993; Destexhe et al. 1994a; Bazhenov et al. 1999; reviewed in Destexhe and Sejnowski 2001, 2003) and proposed different mechanisms. GABAergic interactions between RE neurons can make them oscillate synchronously through mutual inhibitory-rebound interactions, either with slow GABAergic synapses (Wang and Rinzel 1993) or with fast (GABA_A receptor mediated) GABAergic synapses with extended connectivity (Destexhe et al. 1994a). Synchronized oscillations can also be generated from RE

neurons connected with depolarizing GABAergic synapses (Bazhenov et al. 1999). The presence of gap junctions in the reticular nucleus (Landisman et al. 2002) was also incorporated in models (Fuentelba et al. 2004) and reinforced its propensity to oscillate in the spindle frequency range. Thus, models suggest that the intrinsic properties of thalamic RE neurons, combined with their synaptic or electrical interactions, support the RE pacemaker hypothesis.

Second, models also investigated the TC-RE loop hypothesis for spindle generation (Destexhe et al. 1996; Golomb et al. 1996). This TC-RE loop model is shown in Fig. 2d. Neurons were modeled using Hodgkin-Huxley (1952)-type representations of Na⁺, K⁺, and Ca²⁺ voltage-dependent currents, which were based on voltage-clamp data on thalamic neurons (see details in Destexhe et al. 1996). These models reproduced the most salient intrinsic properties of thalamic neurons, such as the production of bursts of action potentials (Fig. 2b). Synaptic interactions were modeled using conductance-based kinetic models (Kinetic Models of Postsynaptic Currents) which were used to simulate the main receptor types (AMPA, GABA_A, and GABA_B) identified in thalamic circuits (Fig. 2b, right). Under these conditions, the circuit generated 7–14 Hz spindle oscillations with the typical features identified intracellularly in the different thalamic neuron types. The model reproduced the typical mirror image between TC and RE cells during spindles, as well as the phase relations between cells (see Fig. 2d). In particular, TC cells produced bursts once every 2–3 cycles, a feature consistently observed experimentally (compare with Fig. 2c). More irregular behavior, similar to the experiments, was obtained in larger networks (Fig. 2e) or in the presence of the cortex (see below). The oscillations also showed the typical waxing-and-waning envelope of spindles; this property was due in the model to Ca²⁺-mediated slow regulation of the I_h current (Destexhe et al. 1993), a prediction that was later verified experimentally (Lüthi and McCormick 1998).

Thus, models show that taking into account the complex bursting properties of thalamic neurons, combined with their interactions through

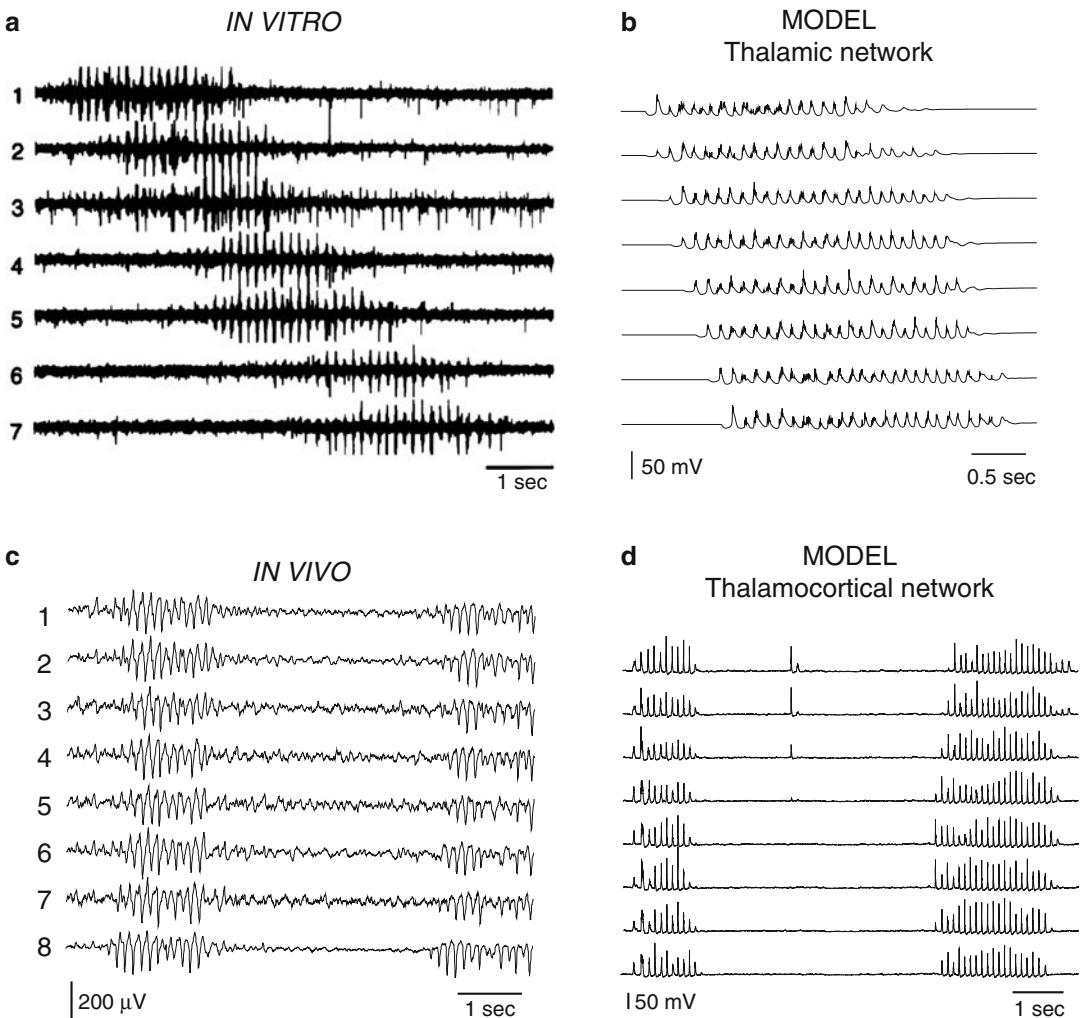


Spindle Oscillations: Models, Fig. 2 Modeling the interactions between intrinsic and synaptic properties to generate spindle oscillations. (a) Circuit of interconnected thalamocortical (TC) and thalamic reticular (RE) neurons with different receptor types. (b) Models of the intrinsic properties of thalamic neurons. (c) Models of the synaptic receptor types mediating their interactions. (d)

Computational model of spindle oscillations in circuits of interconnected TC and RE cells. The expanded trace below shows the phase relations of the two cell types. (e) Phase relations of TC cells during spindle oscillations in a different computational model (a, b, c, d from Destexhe et al. 1996; e From Wang et al. 1995)

well-defined types of synaptic receptors, can account for both RE pacemaker oscillations and spindle oscillations arising from TC-RE loops without assuming pacemaker activity in the RE nucleus. How to resolve such an apparent inconsistency? This question was addressed by a computational model of the RE nucleus which took into account the action of neuromodulators (such as noradrenaline) in depolarizing RE cells. This model produced

oscillations only when a sufficient level of neuromodulator was present (Destexhe et al. 1994b). The difference between *in vivo* and *in vitro* preparations may therefore be explained by the limited connectivity between the RE neurons in the slice and/or by the fact that slices lack the necessary level of neuromodulation to maintain isolated RE oscillations (Destexhe et al. 1994b). The main prediction from this model is that



Spindle Oscillations: Models, Fig. 3 Control of spindle oscillations by the cerebral cortex. (a) Multisite extracellular recordings *in vitro* showing the propagating activity of spindle waves in the visual thalamic slice (modified from Kim et al. 1995). (b) Model of propagating spindle wave activity in thalamic networks with topographic connectivity

(modified from Destexhe et al. 1996). (c) Multisite extracellular recordings in the thalamus of cats *in vivo* showing the large-scale synchrony of spindle waves in the intact thalamocortical system (modified from Contreras et al. 1996). (d) Large-scale synchrony obtained in a thalamocortical model (modified from Destexhe et al. 1998)

applying neuromodulators to slices of the RE nucleus should induce oscillations similar to those observed in vivo. This prediction still awaits to be tested.

Dialogue Between the Thalamus and Cortex: Emergence of Large-Scale Synchrony

The large-scale properties of initiation and distribution of spindle oscillations were investigated more recently by using multiple recordings in vivo and in vitro (Fig. 3a, c). Spindle oscillations in vitro show traveling wave patterns, with the oscillation typically starting on one side of the slice and propagating to the other side, at a constant propagation velocity (Fig. 3a). In contrast to thalamic slices, the intact thalamocortical system in vivo does not display such clear-cut propagation, but spindle oscillations are remarkably synchronized over extended thalamic regions and show very limited traveling wave activity (Fig. 3c), in agreement with early observations. Moreover, a study by Contreras et al. in 1996 showed that large-scale synchrony was lost when the cortex was removed, suggesting that although the oscillation is generated by the thalamus, its synchrony depends on the cortex. However, cutting intracortical connections has no effect on large-scale synchrony, so cortical connections are not responsible for organizing the synchrony of sleep spindles.

Computational models were designed to explore mechanisms to explain the large-scale synchrony of sleep spindles, as shown in detail in another chapter (► [“Corticothalamic Feedback: Large-Scale Synchrony”](#)). Models first simulated the propagating properties found in slices (Fig. 3b). These models assumed a topographic connectivity between TC and RE layers and could generate traveling spindle waves consistent with in vitro data. Second, a thalamocortical model (Destexhe et al. 1998) simulated large networks with bidirectional interactions between cortex and thalamic layers and showed that all experiments could be reproduced under one assumption: that the cortex recruited TC cells primarily through inhibition. This “inhibitory dominant” cortical feedback to

the thalamus is consistently observed experimentally and can explain large-scale synchrony by mutual recruitment of thalamic and cortical networks (Fig. 3d). The same mechanism can also explain the genesis of absence type of epileptic seizures when the excitability of cortical neurons is too high. These points were developed in more detail in another chapter (► [“Slow Oscillations and Epilepsy: Network Models”](#)). The concept of cortical control of thalamic spindle oscillations can be generalized to other oscillation types, and it was proposed by Steriade that the slow oscillation organizes spindle, delta oscillations and more complex patterns such as K-complexes (Steriade 2003).

Cross-References

- [Corticothalamic Feedback: Large-Scale Synchrony](#)
- [Kinetic Models of Postsynaptic Currents](#)
- [Slow Oscillations and Epilepsy: Network Models](#)

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Further Reading

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Spontaneous Activity, Models of

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Synonyms

[Models of ongoing activity](#); [Models of resting-state activity](#)

Definition

Whole-brain computational models of the spontaneous dynamics of coupled brain areas. These models are useful to investigate the origin of ongoing fluctuations observed in brain activity during rest and their correlation structure.

Detailed Description

A growing body of neuroimaging research has revealed that during rest the brain exhibits spontaneous fluctuations in neural activity. These fluctuations emerge spontaneously during quiet wakeful rest and vanish either when triggered by

a task or when falling asleep. This type of spontaneous activity has been mostly detected in the blood-oxygen level-dependent (BOLD) signal using functional magnetic resonance imaging (fMRI) (Biswal et al. 1995). Explorations into the spatial organization of these spontaneous activations have revealed the existence of correlated activity (or *functional connectivity*) between spatially segregated brain areas. These functional connections appear closely related to the underlying map of white matter neuroanatomical connections. However, to understand spontaneous activity from a mechanistic perspective, anatomical information is not sufficient, and it is important to consider the way brain areas interact when they are in the spontaneous state. This is where bottom-up computational models of spontaneous activity come forward, since they allow testing potential theoretical scenarios by comparing the numerical simulation with real resting-state signals in health and disease (Ritter et al. 2013; Deco et al. 2013a; Cabral et al. 2014). In general, models of spontaneous activity consist in a whole-brain network model, where the nodes represent brain areas and the links represent the structural connections between them. Differences between models consist essentially on the equations used to describe the dynamics at the node level, i.e., the behavior of a brain area in the spontaneous state, and the way brain areas interact.

Models of Spontaneous Activity

Anatomical Connectivity

One main component of models of spontaneous activity is the anatomical connectivity matrix, which expresses the coupling weights between brain areas. Typically, these coupling weights are scaled in proportion to the number of white matter fiber tracts connecting each pair of brain areas. The first models of spontaneous activity (Honey et al. 2007; Ghosh et al. 2008; Deco et al. 2009) have used the anatomical connectivity between 38 brain areas from one hemisphere of the macaque brain (Kötter 2004). More recent models (Honey et al. 2009; Cabral et al. 2011; Deco and

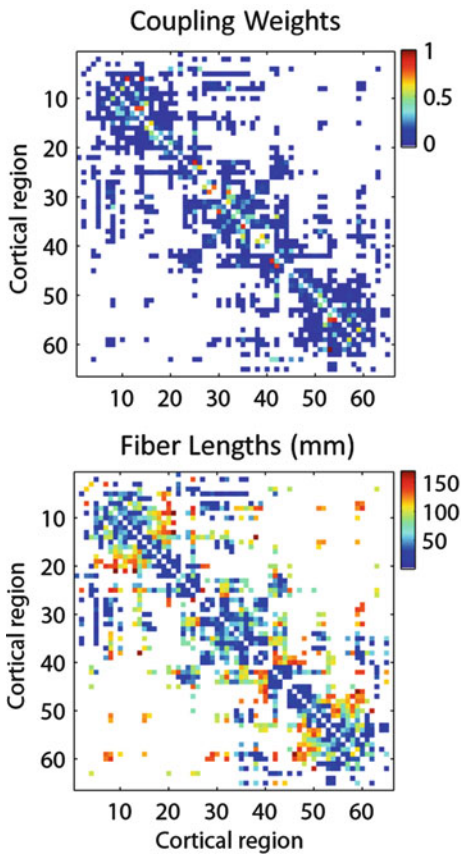
Jirsa 2012; Deco et al. 2013b) have used the human anatomical connectome derived in vivo from diffusion MRI between 66 brain areas covering the whole cortical surface (Hagmann et al. 2008) or 90 brain areas defined according to the AAL template (Cabral et al. 2012). In some models, the structural distance between brain areas is also taken into account, as it induces time-delayed interactions between brain areas (Ghosh et al. 2008; Deco et al. 2009; Cabral et al. 2011, 2012) (Fig. 1).

Local Node Model

Another main component of the models is the type of dynamics assumed at the node level, i.e., the intrinsic behavior of brain areas when they are in the spontaneous state. Assuming that each brain area consists in a system of densely interconnected neurons, the population dynamics can be represented, in a reduced manner, by a small set of differential equations. Existing models of spontaneous activity represent the dynamics of a local brain area in the following ways:

- Conductance-based biophysical neural mass model (Honey et al. 2007, 2009)
- Fitzhugh–Nagumo Model neural mass model (Ghosh et al. 2008).
- Wilson-Cowan Model of excitatory and inhibitory neural pools (Deco et al. 2009).
- Coupled oscillator using an extended version of the Kuramoto model (Cabral et al. 2011).
- Node model in an asynchronous state (Cabral et al. 2012).
- Attractor network of spiking neurons (Deco and Jirsa 2012)
- Dynamic mean field model (Deco et al. 2013b)

Depending on the models, coupled brain areas may display different dynamical regimes, namely, a fixed-point attractor, a limit-cycle attractor, or a chaotic attractor. In the first case, all neurons in a brain area fire irregularly, and the system tends to a stable asynchronous state. In this case, oscillations are damped and manifest as resonances in the network response (Ghosh et al. 2008; Deco and Jirsa 2012; Deco et al. 2013b; Cabral et al.



Spontaneous Activity, Models of, Fig. 1 Anatomical network. Anatomical connectivity between with 66 brain areas derived using DSI averaged over five healthy subjects (Hagmann et al. 2008). (Top-left) The coupling weights are proportional to the number of tracts detected. Weights were normalized so that $0 \leq C_{np} \leq 1$. White = no

connection. (Bottom-left) Distance between regions given as the average length of the fibers connecting a pair of regions. (Right) Schematic representation of the anatomical network, where regions (red spheres) are placed at their center of gravity and the link's thickness is proportional to the number of fiber tracts detected in each connection

2012). On the other hand, when the neurons in a brain area fire synchronously with rhythmic periodicity due to recurrent excitation and inhibition, then neural populations display self-sustained oscillations, and the dynamics is approximated to a limit-cycle attractor (Deco et al. 2009; Cabral et al. 2011). Finally, when the local network exhibits intrinsic instabilities where nonperiodic intermittent oscillations occur due to nonlinear interactions between neurons, then a chaotic dynamics is instantiated (Honey et al. 2007, 2009). Although there is a qualitative difference between models, all scenarios are plausible in the light of the current knowledge in spontaneous neural dynamics.

Systems of Coupled Brain Areas

Coupling local node models according to the whole-brain anatomical network structure, it is possible to simulate the behavior of coupled brain areas at a global scale. In the models, each brain area receives excitatory input from anatomically connected brain areas. In general, the main parameter of the models is the global coupling weight, which scales the anatomical connectivity matrix. When the distance between brain areas is considered, a finite (typically homogeneous) transmission speed is assumed resulting in time-delayed inputs (Ghosh et al. 2008; Deco et al. 2009; Cabral et al. 2011). In addition, some models include an external noisy input (Ghosh

et al. 2008; Deco et al. 2009; Deco and Jirsa 2012; Cabral et al. 2012). Depending on the model, delays and/or noise may – or not – play a role in shaping the dynamics of the brain at rest.

Simulated BOLD Functional Connectivity

To compare the simulated neural activity with data from resting-state fMRI functional connectivity, it is necessary to estimate the BOLD signal changes associated with the simulated signals. Existing models of resting-state activity have used the Balloon-Windkessel hemodynamic model (Friston et al. 2003) to estimate the BOLD signal from simulations. Subsequently, the simulated spontaneous functional connectivity is computed by calculating the correlation matrix between the simulated BOLD signals in all brain areas. For a range of parameters (generally the global coupling weight but also the transmission speed and the noise level when these are considered), the system displays slow BOLD signal fluctuations with a correlation structure that fairly approximates the empirical BOLD functional connectivity. Importantly, for all models, the optimal fit with the empirical data is found for a set of parameters where the system operates at the edge of an instability, i.e., at the critical point of a bifurcation. This intrinsic instability of the system leads to the amplification of the underlying anatomical structure. In other words, at that critical bifurcation point, the global network dynamics reveals correlation patterns that are spatially shaped by the underlying anatomical structure, leading to an optimal fit with the empirical BOLD functional connectivity.

Discussion and Future Directions

Existing models of spontaneous activity point to the direction that the brain during rest reflects an intrinsically unstable regime, where a repertoire of different functional network configurations is temporarily activated. However, the dynamics occurring at time scales faster than the hemodynamic response, as well as the nonstationarity of resting-state functional connectivity, has not been adequately addressed in computational models.

To provide a global picture of the dynamics occurring in the brain at rest, existing and future models need to go beyond reproducing fMRI functional connectivity matrices and explore the non-stationary connectivity dynamics, as well as the faster oscillatory dimension, revealed with other neuroimaging modalities, such as EEG, intracranial recordings, and MEG. Going beyond the BOLD signal, these methods provide pictures of resting-state dynamics from new perspectives, which must be taken into account in future models to deepen our understanding on resting-state activity.

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Spreading Depolarizations

- [Migraines and Cortical Spreading Depression](#)

Squid Axon Model

- [Hodgkin-Huxley Model](#)

STA

- [Spike Triggered Average](#)

Stability and Homeostasis in Small Network Central Pattern Generators

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Synopsis

All animals contain circuits in their central nervous system that produce rhythmic activity. The circuits, often referred to as central pattern generators (CPGs), typically underlie vital activities or behaviors, such as locomotion, respiration, heartbeat, digestion, circadian activity, etc. (Marder

et al. 2005). By the very nature of these behaviors, they require a certain degree of stability of the individual parameters or features that characterize the activity to ensure the survival of the individual. In patterned activity, a key activity feature is the relative timing of activation (phase) of different components of the network. On the other hand, the nervous system is best known for its plasticity and capacity to change in response to many types of inputs. Thus, how stability of activity is ensured is the subject of intense research. In order to attain a stable state, the neurons in these circuits need mechanisms that monitor the state of the system to homeostatically adjust parameters that bring the system to within operational limits. Here, we discuss conditions and likely mechanisms that participate in this process. It is important to note that this field is, as of early 2014, in its early stages of development and much remains to be discovered and understood.

Central pattern generators (CPGs). Networks (or parts of networks) that autonomously produce patterned activity, without requiring timing cues from external sources to the network.

Model Systems

Species with anatomically simple nervous systems that include small CPG-containing networks are among the ones that offer the best opportunities for understanding the basic mechanisms in operation. Such species (and small neuronal networks) include crabs and lobsters (pyloric, gastric, and cardiac networks), leech (heartbeat network), nudibranchs such as *Tritonia* and *Clione* (swimming network), snails such as *Aplysia* and *Lymnaea* (feeding network), etc. (Marder et al. 2005). The simplicity of the networks involved lies primarily in their low number of neurons, of which the majority are identified, large, and often found in low copy number, thus ensuring unequivocal identification of the component neurons involved in the CPG. Modern molecular and optogenetic methods are bringing us closer to the possibility of manipulating large numbers of identified neurons in more complex networks, but identification challenges remain a problem (Carroll et al. 2013). When working with model

systems with large numbers of neurons, great care needs to be exercised to ensure that a subclass within a large neuronal class does not express a gene or protein different enough to determine a distinct function, while expressing the marker that characterizes the broader class. If this latter marker is used to identify the class, one may be wrong in assuming that all cells belong to the same class.

What Is Stable?

In principle, any feature by which network activity may be characterized could be a target for homeostatic mechanisms that stabilize activity. Here, we will focus on network properties primarily but will describe some cases in which the properties of individual cells of small networks are found to be conserved. Additionally, two very different types of stability, likely to depend on distinct types of homeostatic mechanisms, are observed: one is the consistency of activity patterns over many individuals, which we will refer to as *population stability*. Another is the consistency of activity patterns over time within an individual, which we will refer to as *individual stability*.

In pattern generators, it is frequently the case that the phases of activities of the neurons in the network need to be stabilized. This ensures that different segments in the body, for example, bend in the correct sequence to ensure propulsion when swimming (Varkonyi et al. 2008) and that the contraction of agonistic and antagonistic muscle occurs in the appropriate temporal relationship to enable walking instead of hopping or trotting (Kiehn 2011) or to enable the correct sequence of inspiratory and expiratory muscle contractions in the respiratory system (Carroll et al. 2013). In the pyloric network of crustaceans, several neuronal types fire in a specific order and drive the contractions of the about 40 muscles found on the pyloric sac. The phase at which each of the participating neurons starts and ends their bursts of activity is extremely well conserved across individuals (Bucher et al. 2005; Goillard et al. 2009). A similar example of stability has been

observed in the leech heart network, a network of neurons spanning several ganglia along the length of the animal, whose relative order of activity is essential to ensure the proper order of muscle contraction of the heart muscles that spans the length of the animal (Roffman et al. 2012). Thus, it can probably be safely concluded that phase control and stabilization under certain conditions is a general requirement for pattern generating networks.

Phase. A fraction that an event in a pattern takes relative to the duration of one cycle. Thus, the fraction of time during which a neuron is active (e.g., spiking) is its active phase; the onset phase is the point in a cycle when activity begins, etc.

Another feature of small pattern generating networks that has been found to be conserved in some systems is the ability to restore the pattern to a state that is similar to the natural, unperturbed state after it is disrupted by external perturbations. This individual stability property has been observed in a number of different systems and in response to different perturbations, including stroke, spinal cord injury, deafferentation, temperature changes, etc. Although this type of feature has been widely studied at the level of individual synapses or intrinsic properties (and termed homeostatic plasticity in general (Williams et al. 2013)), we will discuss some of the cases that are relevant to small, pattern generating networks in some detail below.

The requirement to stabilize phase of activity is challenged by two different sources of variability in the system. One is the varying nature of the inputs that the nervous system receives and to which it must respond adaptively in a moment-by-moment basis to maintain phase constant. This is, therefore, an issue that applies at the level of individuals and will here be referred to as *individual stability*. Another challenge that has been observed in uniquely identified neurons across animals is the high degrees of variability with which both synaptic and intrinsic ionic currents (which generate the activity of the CPGs) are expressed while maintaining the activity strikingly similar across the population. This issue will here be referred to as *population stability*.

Population Stability

The best known examples of population stability are found in the pyloric network activity of crustaceans, namely, lobsters and crabs, and the heartbeat activity of leeches. When recorded over a large population of unrelated animals, the activity of pyloric network neurons shows large variability in frequency, yet remarkable phase constancy, with each neuron activating and terminating its bursts of activity at a phase that is nearly completely independent of frequency (Bucher et al. 2005; Goaillard et al. 2009). A very similar phenomenon occurs in the network that controls the leech heartbeat (Norris et al. 2006). Phase constancy across individuals is also observed in lampreys and fish, where very precise phase shifts in the contraction of adjacent body segments during swimming are highly conserved across animals and independent of frequency (Lansner et al. 1998). The advantage in studying crustaceans and leeches is that the neurons involved in the generation of the rhythmic pattern are so few that we can be certain to identify each player. Moreover, in each one of these uniquely identified neurons, it has been possible to measure the amplitudes and properties of each of the ionic currents they express. The interplay of synaptic and intrinsic ionic currents is what determines the excitability and overall electric properties of the neurons in a network. Thus, it came as a surprise when a few years ago reports began to appear that showed that these currents are expressed at severalfold different levels between animals whose phase relationships were almost identical (Liu et al. 1998; Schulz et al. 2006; Goaillard et al. 2009; Roffman et al. 2012). Two alternatives can be envisaged to explain such independence of a crucial functional trait (phase) from the amplitudes, and probably also other parameters, of the currents that generate that activity: one is that the variable currents do not play a significant role in determining phase relationships. That is unlikely to be the case since even the synaptic currents that most influence phasing are highly variable (Goaillard et al. 2009; Roffman et al. 2012). The other alternative is that somehow the ionic currents involved compensate for each other in their effects on phase and

other activity features. What compensations are likely to be observed? An intuitively easy relationship to understand is the amplitude of an inward and an outward current. They can in principle be functional antagonists even though their specific kinetic and voltage-dependent properties will determine how complementary they actually are. MacLean et al. showed that this was the case, for example, between the hyperpolarization-activated inward current (I_h) and the transient K^+ current (I_A) in lobster neurons that lead to the constancy of delay to first spike among neurons with different but compensating levels of these currents (MacLean et al. 2003, 2005).

The phenomenon of currents compensating for each other to stabilize an activity feature translates at the population level into the observation of the correlated expression of such ionic currents or conductances between individuals. In other words, correlated currents are currents whose amplitudes track each other, either positively (one grows proportionally to the growth of another) or negatively. This has now been shown in several cases, both in the small networks discussed here (Khorkova and Golowasch 2007; Schulz et al. 2007; Goaillard et al. 2009; Zhao and Golowasch 2012) and in vertebrate neurons from much more complex networks (Amendola et al. 2012; Unal et al. 2012). A growing body of both experimental and theoretical evidence indicates that the correlated expression of different ionic currents, including voltage-gated conductances as well as synaptic conductances, may be required to ensure stability of function (MacLean et al. 2003; Schulz et al. 2006, 2007; Khorkova and Golowasch 2007; Hudson and Prinz 2010; Temporal et al. 2012). In the pyloric network, for example, it has been shown that loss of rhythmic activity is accompanied by the loss of the correlated expression of certain voltage-gated currents, such as I_h and the high-threshold K^+ current, I_{HTK} , in one cell type (Khorkova and Golowasch 2007; Temporal et al. 2012). It has also been observed that a number of activity properties in this network are correlated with more than one conductance (Goaillard et al. 2009; Zhao and Golowasch 2012). This indicates that the maintenance of constant phase relationships in a population of

animals can be achieved in principle if neurons simultaneously control multiple conductances in a coordinated manner.

A similar situation can be observed in the leech heartbeat system. Here, we observe phase relationships between adjacent segments of the animal that are highly preserved across individuals (Norris et al. 2006). Underlying this, we find a wide range of synaptic conductances (Norris et al. 2011; Roffman et al. 2012). Thus, the question of how phases are maintained when synaptic currents are highly variable comes up here again. It had been hypothesized that the relative strengths of the synaptic inputs that the heart motor neurons receive from its presynaptic interneurons would determine the stable output of the network (Norris et al. 2007). However, extensive testing of this hypothesis did not clearly confirm that prediction (Norris et al. 2011), even though recent theoretical work indicates that synaptic conductance correlations are to be expected (Lamb and Calabrese 2013). Instead, it is now suggested that a more complex set of compensatory (or tuning) interactions between intrinsic and synaptic conductances may be responsible for the consistent phase relationships of the motor output (Norris et al. 2011).

Mechanisms

How can ionic currents be linked in a way that correlations appear at the population level? Several possibilities can be envisaged: (1) sets of ion channels are transcriptionally linked by common transcription regulation factors; (2) co-expression of, or co-assembly into, ribosomes (or ribosome granules), of sets of ion channel mRNAs; and (3) shared posttranslational modification or co-localization of distinct ion channels in macromolecular assemblies. A very interesting recent theoretical study showed that ionic conductance correlations will result when a set of correlated ionic currents are all regulated in an activity-dependent manner, with the actual relationship that describes the coupling determined by the relative rates of regulation (O'Leary et al. 2013). Thus, if a target activity trait is regulated in an activity-dependent manner, coupled conductances across a population of cells will naturally arise

from a set of random initial conditions. Furthermore, the relationships that characterize this coupling can be linear (O'Leary et al. 2013), which is fully consistent with a growing number of observations of such relationships, both theoretical and experimental (Burdakov 2005; Schulz et al. 2006, 2007; Khorkova and Golowasch 2007; Ball et al. 2010; Temporal et al. 2012).

Individual Stability

At the individual level, two distinct types of stabilization of phase relationships in CPGs have been described. One is the immediate regulation of phase in response to changing inputs to the CPG and to which it responds quickly to maintain phase constant. Another is the much slower response to drastic perturbation that may be described as recovery of function.

Phase Control

In many systems, phase maintenance depends on mechanisms operating at the level of the synaptic connectivity (circuitry) of the networks. Thus, different synaptic strengths along a gradient of body segments (Williams 1992) or the strength or number of excitatory or inhibitory connections between segments (Skinner and Mulloney 1998) can account for the different types of phase relationships in multisegmented animals (fish, lampreys, etc.). A different mechanism was proposed for the phase maintenance in networks consisting of follower neurons inhibited by oscillating or pacemaker neurons, a case commonly found among CPGs (Manor et al. 2003). Using computational and analytical tools the authors showed that short-term synaptic depression of the inhibitory synapse can create phase maintenance. The idea behind this mechanism is that synaptic depression is dependent on frequency: the longer the synapse is active (such as when rhythm frequency is low), the more it depresses and thus the less effective the synapse becomes. With appropriate parameters, the synaptic delay can be nearly proportional to the change in cycle frequency and thus phase be well maintained (Manor et al. 2003).

A related study shows that the interaction of synaptic depression and the properties of inactivating K^+ currents could further contribute to phase constancy (Greenberg and Manor 2005). These mechanisms act with time constants close to the time constants of synaptic depression and current inactivation, both of which are close to the cycling frequencies of networks. They therefore function to maintain phase constancy at short time scales that are commensurate with the frequency of the network patterns.

Recovery of Function

Several small neuronal networks exhibit robust but much slower compensatory responses to perturbations than those described in the previous section. The responses lead to recovery of function and can bring the entire network back to a state similar to that prior to receiving the perturbation. In the mollusk *Tritonia diomedea*, for example, the escape swimming pattern can be characterized by a series of body flexions induced by sensory stimuli. A fictive motor pattern that underlies this behavior can also be elicited in preparations of the isolated brain in vitro (Katz 2009). When the connections between two of the key components of the swimming CPG are broken, the entire swimming pattern is disrupted and escape responses can no longer be elicited. However, within 1 day after the lesion, the escape responses are restored to levels almost indistinguishable from the control without reconnection of the severed connection (Sakurai and Katz 2009). This recovery of function is driven by a reconfiguration of the dendritic tree whereby one neuropilar region of the cell takes over the function of the dominant one located in the severed region. What molecular mechanism accounts for this is unknown.

In the pyloric network of crustaceans, we observe a similar phenomenon. The pyloric network resides in the stomatogastric ganglion (STG), and its activity is generated in a manner that depends on the uninterrupted release of neuromodulators from projecting neurons whose cell bodies are found in ganglia adjacent to the STG (Selverston and Moulins 1986). When these

axons are severed or their action potential transmission is blocked (a process described as decentralization), pyloric activity rapidly ceases. However, within several hours to a few days, depending on the species, certain aspects of the pyloric rhythm (notably the phase relationships between the members of the network) return to control levels (Thoby-Brisson and Simmers 1998; Luther et al. 2003). What is particularly interesting about this recovery is that the phase relationships in the preparations whose pyloric rhythm has fully recovered are nearly indistinguishable from those observed before decentralization even though the frequency of the rhythm is typically slower. This is reminiscent of the population stability features observed in intact preparations in which phase relationships are tightly maintained but frequency is much more variable (Bucher et al. 2005; Goaillard et al. 2009). Before the recovery has reached its near control levels, however, the phase relationships as well as the frequency are significantly different from the final stable state (Luther et al. 2003). At the same time, ionic conductance amplitudes and their correlation levels change dramatically (Khorkova and Golowasch 2007; Temporal et al. 2012). One possible explanation for this is that whatever mechanisms that keep current amplitudes tied to one another under control conditions (during which neuromodulator levels are relatively high) are released. With this, amplitudes and correlations become free to change within a wide parameter space, perhaps different from the one normally visited by the cells under the normal neuromodulatory state. This may be necessary to find a new set of values for each of the conductances that can sustain stable activity again but now in the continuous absence of neuromodulators. Such robustness of the activity of this network is further revealed in response to temperature changes. Temperature shifts induce large and significant changes in pyloric rhythm frequency, but the network remains capable of maintaining a remarkably stable set of phase relationships even when the temperature changes (and consequently, the frequency) are made quite rapidly (minutes) and over a wide range (Tang et al. 2010). Thus, here again we find that the relative timing of activity between

the component neurons is a crucial parameter that is conserved or stabilized over very different conditions.

What mechanisms may be responsible for these effects? Different mechanisms of homeostatic regulation are found, even though a full picture has not yet emerged. Synaptic plasticity is clearly involved in several of these cases. For instance, the stabilization of phase relationships within the pyloric network when the temperature of the network is changed is accompanied by synaptic strength changes among several of the synaptic connections, as well as intrinsic ionic current modifications (Tang et al. 2010). The recovery of the pyloric rhythm after decentralization also appears to involve synaptic strength changes as well as changes to voltage-gated ionic conductances (Thoby-Brisson and Simmers 2002; Khorkova and Golowasch 2007), perhaps via changes in intracellular calcium regulation mechanisms (Zhang and Golowasch 2011). Interestingly, changes induced by decentralization on the correlation between ionic currents have also been observed, indicating that conductance correlations are somehow under neuromodulatory control (Khorkova and Golowasch 2007).

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State-Dependent Networks

► [Recurrent Network Models, Reservoir Computing](#)

State-Space Models for the Analysis of Neural Spike Train and Behavioral Data

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Definition

An adaptation of the state-space paradigm to the analysis of neuroscience data in which the observation model is either a point process or a time series of binary observations and the state model is typically a linear Gaussian process. The paradigm has been applied to a number of problems including neural spike train decoding, analysis of receptive field dynamics, analyses of learning, neural prosthetic control, and control of brain states under anesthesia.

The state-space paradigm for analyses of point processes and time series of discrete binary observations has been developed for the analysis of neural spike train and behavioral data (Brown et al. 1998; Smith and Brown 2003). The state-space point process (SSPP) paradigm has two standard components. The state equation defines the system dynamics. The observation equation

defines how the system is measured. For the SSPP system the observations can be point processes or time series of discrete binary responses. Point processes are binary (0–1) events defined in continuous time. They are an ideal framework for analyzing series of neuronal action potentials where the binary events are defined as 1 if there is an action potential or spike and 0 otherwise. Data in behavioral studies commonly consist of time series of binary responses such as in a learning experiment where 1 is given for a correct response and 0 is given for an incorrect response. In system neuroscience experiments, the state equation defines the signal, stimulus, or brain state that is being represented by the neural activity or the behavior.

Detailed Description

Derivation of the State-Space Point Process Filter Algorithm

The use of the state-space paradigm to analyze neural spiking activity was introduced by Brown and colleagues, using an inhomogeneous Poisson observation model and a linear Gaussian state model to study the decoding of position from ensemble neural spiking activity in rodents (Brown et al. 1998; see ► [“Neural Coding”](#); ► [“Population Encoding/Decoding”](#)). The objective of the state-space analysis is to estimate the state at time t , given the data, up through time t (Brown et al. 1998; Smith and Brown 2003). The solution to this prediction problem is defined recursively by the associated Bayes’ rule Chapman-Kolmogorov (BCK) system (see ► [“Bayesian Approaches in Computational Neuroscience: Overview”](#)). Bayes’ rule defines the posterior density of the state at time t given all of the observations from the start of the experiment up through time c . The Chapman-Kolmogorov, or one-step prediction equation, defines the probability density of the state at time t given the observations up through time $t - 1$ (Chen et al. 2010). This probability density is computed by integrating the product of the posterior density at time $t - 1$ and the state model that is typically Markov and defines the

probability density of the states at time t given the state at time $t - 1$. Brown and colleagues showed that the state estimation from point process observations could be efficiently conducted by deriving a nonlinear recursive filter (NRF) algorithm to solve the associated BCK system (Brown et al. 1998; see ► [“Digital Filtering”](#)). The derivation used two approximations to derive the algorithm. First, it approximated continuous time as discrete time in small intervals and assumed a single (0 or 1) Poisson observation in each interval. Second, the NRF algorithm is derived by using a Gaussian approximation to integrate the BCK system and a second Gaussian approximation to compute the *maximum-a-posteriori* state estimate and its covariance matrix. The NRF algorithm becomes the Kalman filter algorithm when the observation equation is a linear function of the state and the observation noise is Gaussian and additive.

Extensions of the State-Space Point Process Theory

Brown and colleagues demonstrated that a point process adaptive filter algorithm is a special case of the NRF algorithm (Brown et al. 2001). They next developed an expectation-maximization algorithm to conduct simultaneous state and static model parameter estimation from general point process (non-Poisson) or time series of binary observations (Smith and Brown 2003; see ► [“Generalized Linear Models for Point Process Analyses of Neural Spiking Activity”](#)) and an augmented adaptive filter algorithm to conduct simultaneous state and dynamic model parameter estimation (Eden et al. 2004). The general point process paradigm improved the previously developed decoding algorithms (Brown et al. 1998) and defined explicitly the relationship between decoding the representation of a signal in an ensemble of neurons and measuring dynamically the mutual information between the signal and the ensemble spiking activity (Barbieri et al. 2004; see ► [“Information Theory: Overview”](#)). The SSPP paradigm also provides a principled approach to analyzing binary data series recorded

in learning experiments and explicit criteria to define when learning occurs (Wirth et al. 2003; Smith et al. 2004).

Brown and colleagues extended the SSPP algorithms to derive the exact state estimation algorithms for point processes using sequential Monte Carlo methods (Ergun et al. 2007), conduct state estimation from simultaneously observed point process and binary and continuous observations, (Prerau et al. 2008, 2009; Coleman et al. 2010) and implement deterministic and stochastic control systems (Ching et al. 2013; Shanechi et al. 2013a, b, c). Extensions of the state-space point process framework include the use of Markov chain Monte Carlo computations (Ahmadian et al. 2011; Yuan et al. 2012) and the analysis of interactions among simultaneously recorded neural spike trains using information geometry concepts (Shimazaki et al. 2012; see ► [“Information Geometry as Applied to Neural Spike Data”](#)).

Applications of the State-Space Point Process Paradigm

The first application of the SSPP was as a new paradigm to decode spatial information from ensembles of the hippocampal place cell neurons (Brown et al. 1998; see ► [“Efficient Population Coding”](#); ► [“Estimation of Neuronal Firing Rate”](#)). This analysis showed how ensembles of the hippocampal neurons maintained precise, dynamic representations of a rat’s spatial location during foraging (Brown et al. 1998). The SSPP algorithms outperformed by an order of magnitude ad hoc algorithms in decoding spatial information from ensembles of the hippocampal neurons (Brown et al. 1998). The adaptive filter algorithm special case of the SSPP algorithm was used to study receptive field plasticity in the hippocampal neurons (Brown et al. 2001; Frank et al. 2004). An SSPP analysis showed that rodent hippocampal neurons can form new spatial receptive fields in 5–6 min (Frank et al. 2004) and that in monkeys, hippocampal neuronal activity changes are tightly coupled to the acquisition of newly learned behaviors (Wirth et al. 2003). The SSPP algorithm applied to binary data established a new

paradigm for dynamic analysis of behavior in learning experiments (Wirth et al. 2003; Smith et al. 2004; Prerau et al. 2008; Prerau et al. 2009; see ► [“Behavioural Analysis, Bayesian”](#)).

The SSPP algorithm accurately decoded motor cortex representations of hand positions (Truccolo et al. 2005). SSPP algorithms have been used to track heart rate variability, (Barbieri and Brown 2006) to track brain states under general anesthesia, (Chemali et al. 2013) and to precisely define anesthesia-induced loss and recovery of consciousness (Purdon et al. 2013; Wong et al. 2014). The SSPP algorithms established that during motor learning different groups of neurons can represent different movement components (Shanechi et al. 2012). SSPP algorithms have been used to implement stochastic and deterministic control paradigms: linear-quadratic regulatory algorithms for motor neural prostheses (Shanechi et al. 2013a, b; see ► [“Brain-Machine Interface: Overview”](#)) and proportional-integral, (Ching et al. 2013) linear-quadratic regulator and model predictive control algorithms (Shanechi et al. 2013c) to precisely maintain the brain in a medically induced coma. For motor prosthetic control, Carmena and colleagues recently showed that the SSPP paradigm outperforms by 30% the widely used Kalman filter control paradigm (Shanechi et al. 2013d; see ► [“Brain-Machine Interface: Overview”](#)).

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Behavioural Analysis, Bayesian](#)
- [Brain-Machine Interface: Overview](#)
- [Digital Filtering](#)
- [Efficient Population Coding](#)
- [Estimation of Neuronal Firing Rate](#)
- [Generalized Linear Models for Point Process Analyses of Neural Spiking Activity](#)
- [Information Geometry as Applied to Neural Spike Data](#)
- [Information Theory: Overview](#)
- [Neural Coding](#)
- [Population Encoding/Decoding](#)

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Statistical Analysis of Neuroimaging Data

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Definition

The main goal of “statistical analysis of neuroimaging data” is to use statistical methods to extract useful neuroscientific information, from neuroimaging data such as fMRI, EEG, and MEG, which are derived from measurement of the dynamics of electrical and magnetic activity generated from the neural and vascular activities inside the live brain.

Detailed Description

A typical example is the statistical analysis of fMRI data, where the activation and deactivation of voxels (as measured by the BOLD signal) in response to some specific task of interest may be elucidated in a map called the activation map. Similarly for EEG/MEG data analysis, one of the main interests of statistical analysis is to estimate the activation of areas in response to specific stimuli to the live brain. It provides the basis for further elaborate statistical analysis, such as the analysis of dynamic causalities between the activated voxels in the estimated activation map.

“The statistical methods used in data analysis” very much depend on the type of available data. In neuroscience, the data are often (1) temporally correlated time series data and (2) multi-dimensional data, with dimension as large as 10–100 for EEG/MEG data and as large as 10,000 for fMRI data. Historically, statistical methods for neuroimaging data have been introduced using mostly those methods developed for identically distributed (i.i.d.) data. Direct application of conventional statistical methods to the analysis of high-dimensional temporally correlated neuroscience data often leads to difficulties

precisely because the data is very far from satisfying the i.i.d. assumptions. The “time series modeling approach” has been specifically designed to take temporal correlations and multi-dimensionality into account and so is much more appropriate for application to the analysis of neuroscience data than the conventional i.i.d. approach.

An important and critical point for the statistical analysis of neuroimaging data is not the algorithm we use for computing the activation map, nor is it whether the activation map looks attractive. The most important point is whether the “assumptions” employed for computing and producing the map are statistically valid and appropriate for the observed time series data.

One of the most widely used statistical methods for the analysis of fMRI data is the statistical parametric mapping (SPM) developed by Friston et al. (1995). In the first stage of SPM, the dynamic characteristic of the BOLD signal is identified using a deterministic dynamical system (the hemodynamic response function) embedded in the statistical framework of the general linear model (GLM). Here the model parameters are estimated under the assumption that the GLM errors are i.i.d. and normally distributed. An additional assumption is that the high-dimensional fMRI data is assumed to be spatially independent, meaning that no spatial dynamic interaction is allowed, considered, or tested between the voxels.

In the second stage of SPM, the estimated parameters for each voxel are used to check whether the voxel is activated or not using conventional hypothesis testing methods. The validity of the hypothesis testing approach depends critically on the assumptions behind the models used for evaluating the null and alternative hypotheses. The activated areas judged to be significant by the testing method are often plotted as an activation map on each slice of the scanned MRI figures. The guidelines for producing an activation map are somewhat arbitrary and depend on whether the researcher needs a simple picture of the functioning of the brain or something more complex. However, the use of the deterministic hemodynamic function,

the reliance on required assumptions such as normal i.i.d. errors, and the spatial independence are rather too strong and make SPM rather controversial. Unfortunately the checking of the validity of the assumptions is not provided in the paradigm of the hypothesis testing procedure, and it appears that many analysts may be ignoring this issue.

A less well-known but a rather more orthodox approach to the statistical characterization of the dynamics of the neuroimaging data such as fMRI and EEG/MEG time series data is the direct time series modeling approach (Riera et al. 2004; Galka et al. 2004; Friston et al. 2003). In this approach, the dynamic characteristics of the stimulus-activation relation in the brain function are directly specified by a time series model (or a dynamical system model) with exogenous inputs. A typical example is to use an autoregressive model with an exogenous variable (ARX model), where the activation effect dynamically caused by the exogenous input (i.e., a stimulus) is specified by the exogenous terms. Plotting the activation map is, again, quite arbitrary and depends on the scientists' objectives. Some researchers may plot the exogenous terms (which could sometimes be negative according to whether the vascular flow in the voxel increases or decreases) and some people may prefer to plot the significance of the exogenous terms (i.e., the difference of the log-likelihood of the full model (including exogenous variables) and the sub-model (excluding the exogenous variables)).

There are many other methods developed for the statistical analysis of neuroimaging data (see Poldrack et al. 2011; Ozaki 2012; Li 2014). Some methods employ dynamical system models where the models are assumed, a priori, to be deterministic (e.g., DCM (dynamic causal modeling) in Friston et al. (2003)). Most of the methods rely on the techniques developed in multivariate analysis such as GLM, PLS (partial least squares), SEM (structural equation model), ICA (independent component analysis), PCA (principal component analysis), etc. Here important dynamic information, contained in the data as temporal correlations, is neglected in the i.i.d. assumptions.

The validity of the results of statistical analysis and imaging depends critically on the model

identified from the data, where each model stands on its own assumptions (i.i.d., temporally correlated, deterministic, and stochastic Bayesian or non-Bayesian). In the statistical modeling approach, the most critical issue is how to find the best model using appropriate assumptions for the given data. In contrast to the hypothesis testing case, we can consider more than a hundred candidate models using different assumptions and lag orders. For the identification of the best model among these candidate models, several approaches are available in time series analysis. "The innovation approach" is known to be especially powerful and easy to use in situations where we need to choose the best model among many candidate dynamic models representing the same data. This is because it stands on a very simple principle, i.e., "Choose, among the finite set of candidate models, a model which can predict the future time series best." This principle is essentially equivalent to Akaike's information criterion (AIC) minimization principle which was introduced from the idea of maximizing the expected Boltzmann entropy. By including lagged variables and spatial variables into the model, the prediction error variance is substantially minimized and statistical validity may be achieved, since in the time series case, the temporal independence and the normality of the prediction errors are guaranteed for stationary continuous Markov processes (Doob 1953).

Cross-References

- [Brain Imaging: Overview](#)
- [BrainMap](#)
- [Forward and Inverse Problems of MEG/EEG](#)
- [Imaging Analysis, Bayesian](#)
- [Independent Component Analysis of Images](#)

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Statistical Evaluation of Spatio-temporal Spike Patterns

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Synonyms

Higher-order correlation

Definition

Temporally precise correlations between simultaneously recorded neurons are interpreted as signatures of cell assemblies, that is, groups of neurons that coordinate their spiking activity to process information. Evidence of behavior-related pairwise correlations was found in simultaneous recordings of few neurons. Recent technological advances have enabled the recording of 100 or more neurons in parallel. Increasing the number of simultaneously recorded neurons enhances the chances to detect activities of both more and larger cell assemblies. Also, larger recordings enable to investigate more complex assembly-related activity patterns than synchronous spiking, such as spatio-temporal patterns (STPs) where neurons fire in sequence with specific temporal delays. However, these high-dimensional data raise considerable computational and statistical issues, thus requiring novel statistical tools for the analysis of correlations. SPADE, presented below, is one such a novel method, designed to reliably detect and statistically evaluate STPs for statistical significance in large scale spiking activity data.

Detailed Description

Introduction

Spatio-temporal spike patterns (STPs) are the most general form of temporally precise spike correlation. The definition includes spike synchrony (Grün et al. 2002a, b; see entry on ► “Joint Peri Stimulus Time Histogram (JPSTH)”); Shimazaki et al. 2012), delayed spike correlations and combinations of these, such as sequences of synchronous spike events (Schrader et al. 2008; Torre et al. 2016a). STPs are assumed as the signature of groups of neurons forming a cell assembly involved in information processing. STPs could be also part of larger and more complex forms of propagation of spiking activity, such as synfire chains (Abeles 1991) or synfire braids or polychrony (Bienenstock 1995; Izhikevich 2006, respectively).

The temporal coding hypothesis states that the brain relies on STPs of some sort to process

information at millisecond precision. This contrasts the rate coding hypothesis, which states – loosely speaking – that information is instead encoded in the neuronal firing rates at a slower temporal scale of several tens or even hundreds of milliseconds (Brette 2015; Riehle et al. 1997). Validating the temporal coding hypothesis thus requires to detect STPs in simultaneous neuronal recordings, to demonstrate that they occur beyond the chance level predicted based on the neuronal firing rates alone and to provide evidence that STP occurrence relates to cognitive tasks, such as different behaviors.

A variety of statistical methods have been developed to find statistically significant STPs in simultaneous recordings from few neurons (see, e.g., entry on ► “[Spatial Temporal Spike Pattern Analysis](#)”; Abeles and Gerstein 1988; Prut et al. 1998; Nádasdy et al. 1999). However, these methods do not trivially scale to simultaneous recordings from several tens or hundreds of neurons, where the number of possible patterns that need to be considered grows exponentially (up to billions). Counting the occurrences of each pattern raises a formidable computational issue, and testing for their statistical significance yields a considerable multiple testing problem. SPADE (Spike Pattern Detection and Evaluation) uses a data mining algorithm (frequent itemset mining, or FIM; Borgelt 2012) to count pattern occurrences in an effective way. Then, it uses a dedicated statistical procedure to assess, based on the pattern occurrence count, which patterns are statistically significant.

In Torre et al. (2016b), SPADE was applied to recordings from pre-/motor cortex of two monkeys trained to perform a delayed reach-to-grasp task. Specifically, animals were trained to perform a movement in one of four different options, which differed by the grip type used to grasp an object and the force required to pull the object. The authors focused on synchrony only and found statistically significant synchronous spike patterns with high specificity to the movement type. These patterns mostly involved two or three (and up to five) different neurons. Preliminary results on a broader analysis of nonsynchronous STPs

revealed repeating temporal sequences involving up to eight neurons, which are also highly specific to behavior. SPADE comprises three analysis steps, which are detailed below.

Retrieval of STPs

Identifying statistically significant patterns first requires to count the occurrences of each individual pattern. As the number of patterns grow exponentially with the number of recorded neurons, a linear search becomes infeasible when the number of simultaneously recorded neurons grows past a few units. For instance, $N = 100$ neurons can form up to $2^{100} \approx 10^{30}$ synchronous spike patterns and orders of magnitude more STPs of the general type. SPADE overcomes the hurdle with frequent itemset mining (FIM).

FIM originates from supermarket basket analysis, and searches shopping lists for items that customers frequently buy together. SPADE recasts the problem into that of detecting which neurons frequently spike synchronously (Torre et al. 2013; <https://www.youtube.com/watch?v=MRzwEKAWIYM>). The spike data are structured into a matrix where each column corresponds to a time bin (typically, a few milliseconds long) and each row contains the binary spiking activity (1 = active, 0 = silent) of each observed neuron. A synchronous pattern is defined as any set of active neurons inside the same time bin, and its occurrence count is given by the number of time bins where the pattern occurs. Of all observed patterns, only those occurring more than any of their supersets (closed) and occurring above a minimum number of times (frequent) are actually of interest. The FIM exploits the fact that supersets of infrequent patterns are themselves infrequent to considerably speed up this search.

For detection of spike patterns with temporal delays, that is, STPs, the spike data first need to be reformatted in such a way that STPs fall into the same column of the binary matrix. This is accomplished by sliding a window of w time bins along the original binary matrix in steps of one bin. At each step, the array of n neurons and w time bins covered by the matrix is reshaped into a column

vector of length $w \cdot n$. The column vectors are concatenated horizontally into a new binary matrix (Yegenoglu et al. 2016). FIM then analyzes this matrix to find closed frequent STPs (Quaglio et al. 2017).

STP Statistical Significance

To determine whether a closed frequent pattern is statistically significant, a straightforward approach also used in previous methods would be to compute the significance threshold of the occurrence count based on the neuronal firing rates under the rate coding assumption (e.g., Grün et al. 2002a, b; entry on ► “Unitary Event Analysis”). The pattern is classified as statistically significant if its occurrence count exceeds the significance threshold. A problem with this approach is that, in massively parallel spike train recordings, the large number of possible patterns would require excessively many statistical tests. False positives would be unavoidable, while on the other hand, correcting the significance threshold by the number of tests would yield a large number of false negatives.

SPADE circumvents this hurdle by first grouping patterns into classes based on three pattern features: the size z (number of neurons involved), the pattern occurrence count c , and the number of time bins between the first and the last spike of the pattern d . Instead of testing individual patterns, SPADE tests different pattern signatures $\{z, c, d\}$. A 4-dimensional matrix, called pattern spectrum, is built, containing for each signature the number of patterns with that signature found in the data. The significance of each signature is calculated by means of a Monte Carlo technique that generates surrogates of the original data (Louis et al. 2010; entry on ► “Surrogate Data for Evaluation of Spike Correlation”) under preservation of the firing rates while destroying potential millisecond-precise spike correlation (Stella et al. 2019).

Conditional Testing

Once a pattern signature is found as statistically significant, the patterns with the same signature may be nonchance events. Some of these patterns, however, may actually be the result of a chance

overlap of the actual patterns with background spiking activity. For instance, a cell assembly consisting of $z = 3$ neurons and producing $c = 7$ occurrences of a synchronous ($d = 0$) spike pattern may overlap with a fourth neuron which, by pure chance, happens to fire during 3 of the 7 activations of the assembly. This would produce a spurious synchronous pattern of size $z' = 4$ and an occurrence count $c' = 3$, which by the previous step would be wrongly classified as statistically significant, if the signature $\{4, 3, 0\}$ was also statistically significant. Many more combinations of such pattern overlap with background activity are possible and are very likely in recordings from many neurons. SPADE corrects for this misclassification by further testing the conditional significance of each pattern with a significant signature given any other pattern overlapping with it and also having a significant signature. Patterns resulting from chance overlap of actual patterns and background spiking activity are thereby removed (Torre et al. 2013).

Software

The SPADE analysis method is available as open source Python code (main function: `verbatim`) as part of the electrophysiology analysis toolbox Elephant (RRID:SCR_003833). The code can be found at: <http://python-elephant.org>. The implementation supports multithreading by MPI.

Cross-References

- Joint Peri Stimulus Time Histogram (JPSTH)
- Spatial Temporal Spike Pattern Analysis
- Surrogate Data for Evaluation of Spike Correlation
- Unitary Event Analysis

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Statistical Significance

► Significance Evaluation

STDP

► Spike-Timing Dependent Plasticity, Learning Rules

STEPS: STochastic Engine for Pathway Simulation

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Definition

STEPS is a molecular simulator with a focus on neuroscience applications, and so is designed to preserve and support important neuronal features such as complex morphology and electrical excitability. As such, STEPS simulates stochastic reaction-diffusion kinetics, 3D voltage calculations, ion channels, and membrane currents, all in tetrahedral mesh reconstructions of neuronal geometries. Since version 3.0, STEPS supports parallel solutions with proven scalability.

Detailed Description

Mesoscale Reaction-Diffusion Simulation in Tetrahedral Meshes

STEPS simulates stochastic molecular interactions, spatial concentration gradients, and diffusion. The category of reaction-diffusion simulators to which

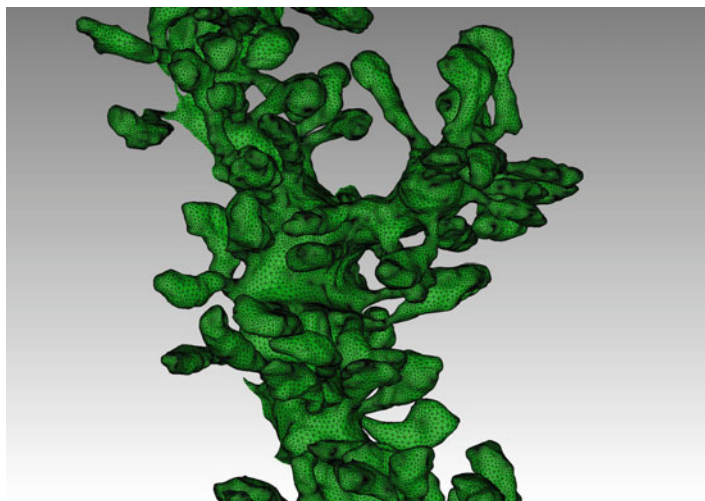
STEPS belongs are often termed “mesoscale” where molecules are not tracked individually but instead space is discretized into small subvolumes in which populations of molecules are tracked. The subvolumes that STEPS supports are tetrahedrons, which allow representation of complex neuronal morphology to high accuracy (Hepburn et al. 2012), as demonstrated in Fig. 1.

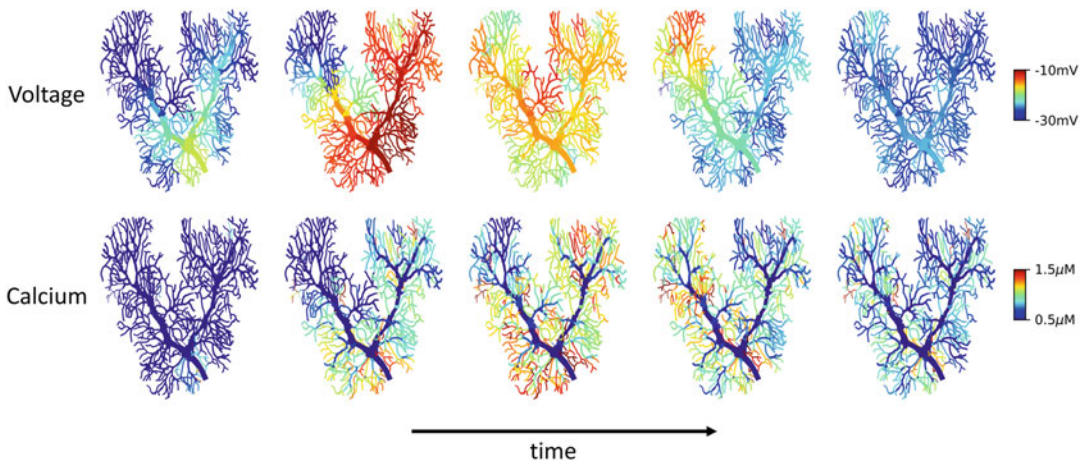
The subvolumes display a characteristic size “window” in which the method is accurate, but errors become apparent with very small subvolumes in the nanometer range (Hepburn et al. 2012). As such, and in comparison to particle-tracking methods, the subvolume method has the advantage of allowing larger, more complex systems to be investigated due to better computational efficiency, although the smaller nanoscale of particle-tracking simulators cannot be reached.

STEPS supports multiple solvers including spatial, nonspatial, deterministic, and stochastic solutions, all of which share model construct within the Python interface. However, the main focus for STEPS development is on spatial stochastic simulation to enable simulations of high realism, particularly where key molecular players are sparsely, inhomogeneously populated, and so deterministic and well-mixed solutions are rendered inaccurate. Serial spatial stochastic simulations are based on Gillespie’s Stochastic Simulation Algorithm (SSA) (Gillespie 1977), extended for diffusion between tetrahedral

STEPS: STochastic Engine for Pathway Simulation,

Fig. 1 Realistic neuronal geometry represented in a tetrahedral mesh supported by STEPS: a section of Purkinje cell spiny dendrite





STEPS: STochastic Engine for Pathway Simulation, Fig. 2 An example parallel STEPS spatial simulation in a fully reconstructed Purkinje cell dendrite, implementing the model of Anwar et al. 2013. The top panel displays

voltage and the bottom panel calcium over the shown ranges at five different time points through a dendritic calcium burst

elements by a finite volume method, an approach that is often termed “Spatial Gillespie” or “Spatial SSA.” The STEPS Spatial SSA method is continuously validated for accuracy with any code developments against a comprehensive set of reaction-diffusion models (Hepburn et al. 2012).

Voltage in 3D Neuronal Morphologies

STEPS implements a 3D voltage solution on tetrahedral meshes (Hepburn et al. 2013), with different options for the voltage calculations, including an original direct method that is suitable for smaller problems, and since version 3.1 a parallel, iterative solution based on the PETSc library (Balay et al. 1997) that is suitable for larger problems. The STEPS validation suite is extended for voltage calculations with the Rallpack benchmarks (Bhalla et al. 1992).

The 3D voltage solution on tetrahedral meshes allows STEPS to support membrane potentials, voltage-gated ion channels, and membrane currents in full 3D neuronal morphology. No 1D cable-like approximation is required, the full neuronal structure can be preserved if available (Chen and De Schutter 2017a). Tight integration with the reaction-diffusion computations allows investigation of the molecular and electrical components of neuronal signaling together, within realistic neuronal geometries. One example application is investigation of local, stochastic calcium

activation of ion channels in dendritic morphologies (Anwar et al. 2013).

Parallel STEPS on High-Performance Computers

Exact SSA methods are known to scale poorly, and so STEPS implements an operator-splitting approximation to the reaction-diffusion system in order to enable parallelism (Chen and De Schutter 2017b). In this approach, the spatial geometry is partitioned with Message Passing Interface (MPI) processes taking ownership of the resulting sets of tetrahedrons, one set per process. Stochastic reactions are then solved within the partitioned SSA in parallel. Diffusion is solved by a multinomial algorithm also in parallel, with cross-process diffusion events involving neighboring data transfer applied at predetermined time intervals. It has been shown that this operator-splitting approach demonstrates good accuracy in realistic biological models (Hepburn et al. 2016).

The MPI implementation of the operator-splitting reaction-diffusion system in STEPS has been shown to scale super-linearly in dendritic morphologies (Chen and De Schutter 2017b), and a known scalable library, PETSc (Balay et al. 1997), is implemented for voltage calculations in parallel STEPS enabling full parallel reaction-diffusion and voltage simulation with good scalability. Such simulations enable STEPS

to reach the whole cell scale with full stochastic reaction-diffusion kinetics of signaling molecules and ion channels, with an accurate, fast voltage solution in 3D neuronal morphologies (Fig. 2), allowing researchers to link biochemistry with electrophysiology to probe neuronal function in a computational setting.

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Stereo Vision, Models of

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Synonyms

Models of 3D vision; Models of stereopsis

Definition

Due to the different location of the eyes in the head, objects at different distances from the observer project to slightly different locations in the two eyes. Stereo vision refers to the perception of depth based on these slight disparities between the images seen by the two eyes (Freeman 2009). This entry reviews models of stereo vision based on the real nervous systems. Stereo vision algorithms have also been developed independently within the machine vision literature, sometimes biologically inspired, but these are not within the scope of this entry.

Detailed Description

Stereo vision has two main steps: (1) extracting disparity from the retinal images and (2) perceiving depth structure from disparity. Although psychophysics experiments have probed both aspects, much more is known about the neuronal mechanisms supporting the extraction of disparity than about how and where in the brain disparity is converted into a perception of depth. This entry therefore concentrates on the first step. It seems that binocular disparity is initially encoded in the primary visual cortex (V1), which therefore acts as the “cyclopean retina” (Julesz 1971), that is, the first neural area which is able to detect features based purely on the differences between the two eyes images. There has been much work in recent years on how to model the response of disparity-selective neurons in V1 and how to decode this population activity in order to arrive at an estimate of the disparity at each point in the visual scene. In this entry, I aim to review this work.

Extracting Disparity from the Retinal Images

In primates, the first processing supporting specifically stereo vision is believed to occur in the primary visual cortex (V1). V1 is the first visual area to contain the neurons which receive inputs from both eyes and to be tuned to binocular disparity (Poggio et al. 1985). The most influential

model of disparity tuning in V1 is the stereo energy model, put forward by Izumi Ohzawa et al. (1990) and based in turn on similar models in the motion literature (Adelson and Bergen 1985).

Stereo Energy Model: Basic Unit

The basic idea behind the stereo energy model is a binocular neuron with a receptive field in each eye (Fig. 1). The input from each eye depends on the inner product of each eye's image with the corresponding receptive field. For example, the input from the left eye is

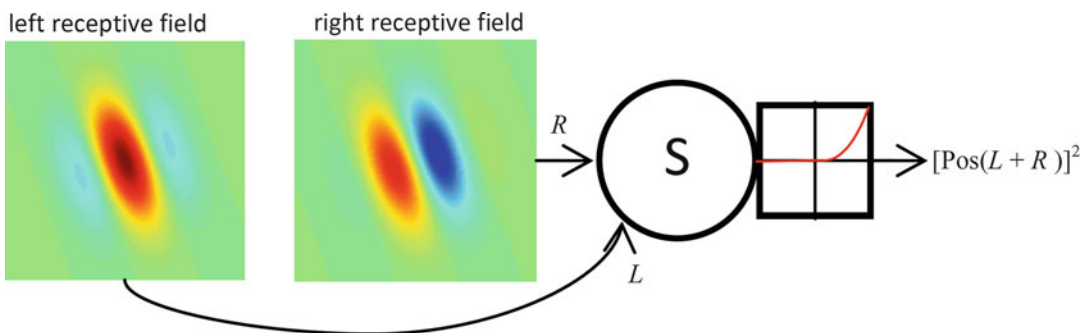
$$L = \int_{\text{retina}} dx dy I_L(x, y) \rho_L(x, y)$$

The function $I_L(x, y)$ represents the retinal image in the left retina, with luminance expressed relative to the mean, e.g., +1 = white, -1 = black, and 0 = gray. The function $\rho_L(x, y)$ represents the classical receptive field in the left retina, with 0 = no response (i.e., areas of the retina that are outside the receptive field), positive values corresponding to ON regions (areas where light stimulation tends to increase the cell's firing rate and dark suppresses it), and negative values to OFF regions (where dark features tend to increase the cell's firing and light suppresses it).

The energy model assumes that inputs from each eye are summed linearly. If the result is negative, the neuron is inhibited and does not fire. If positive, the neuron fires at a rate proportional to the square of the inputs:

$$S = [\text{Pos}(L + R)]^2 \quad (1)$$

where the notation $\text{Pos}(x)$ means half-wave rectification: $\text{Pos}(x) = x$ when $x > 0$, and $\text{Pos}(x) = 0$ otherwise. This model neuron is tuned to disparity both in monocularly visible features, e.g., the bar stimuli used in Ohzawa et al. (1990) and also in "cyclopean" stimuli such as dynamic random-dot patterns (Julesz 1971). Cyclopean stimuli contain features such as depth edges which are not visible monocularly but are revealed only by comparing the two eyes' images. A detailed analysis shows that the cyclopean disparity tuning is due to the output nonlinearity (Read 2005). A unit which simply summed left and right inputs linearly ($L + R$) would be tuned to the disparity of a bar stimulus, but only as a side-effect of its tuning to the position of monocular features. It would respond equally well, on average, to broadband noise images with any disparity. Thus, a nonlinearity is essential to produce cyclopean disparity tuning, i.e., to ensure that the cell responds more on average to broadband noise images with its preferred disparity. The threshold-and-squaring nonlinearity in Eq. 1 is used in many models of V1 neurons because it describes their



Stereo Vision, Models of, Fig. 1 Basic unit of the stereo energy model, after Ohzawa (1998). The graph on the right represents the squaring output nonlinearity. ON and OFF subregions of the receptive fields are shown in red and

blue, respectively. The receptive fields have the same orientation and spatial frequency but different phase. This cell would therefore be tuned to nonzero disparity

responses well. However, from a mathematical point of view, almost any nonlinearity would suffice to produce cyclopean disparity tuning.

The receptive fields are often represented by Gabor functions. Empirically, the spatial frequency and orientation tuning is similar between the eyes (Bridge and Cumming 2001; Read and Cumming 2003) and is usually modeled as being identical.

Position and Phase Disparity

The spatial location and phase (i.e., the location of ON and OFF subregions) of the two receptive fields may vary. These determine the preferred disparity of the unit. Position disparity shifts the disparity curve without altering its shape; phase disparity alters the shape. A phase disparity of 0 produces a curve which is symmetrical about a central peak, known as tuned excitatory. A phase disparity of π inverts this to give a curve with a central trough (tuned inhibitory). A phase disparity of $\pm\pi/2$ produces odd-symmetric curves with equally large peaks and troughs. Several models have been built using pure phase disparity (Sanger 1988; Fleet et al. 1991; Qian 1994; Qian and Mikaelian 2000). However, V1 contains cells with both position and phase disparity (Anzai et al. 1997; Prince et al. 2002). Several models therefore incorporate both position and phase (Chen and Qian 2004; Read and Cumming 2007).

Complex Cells

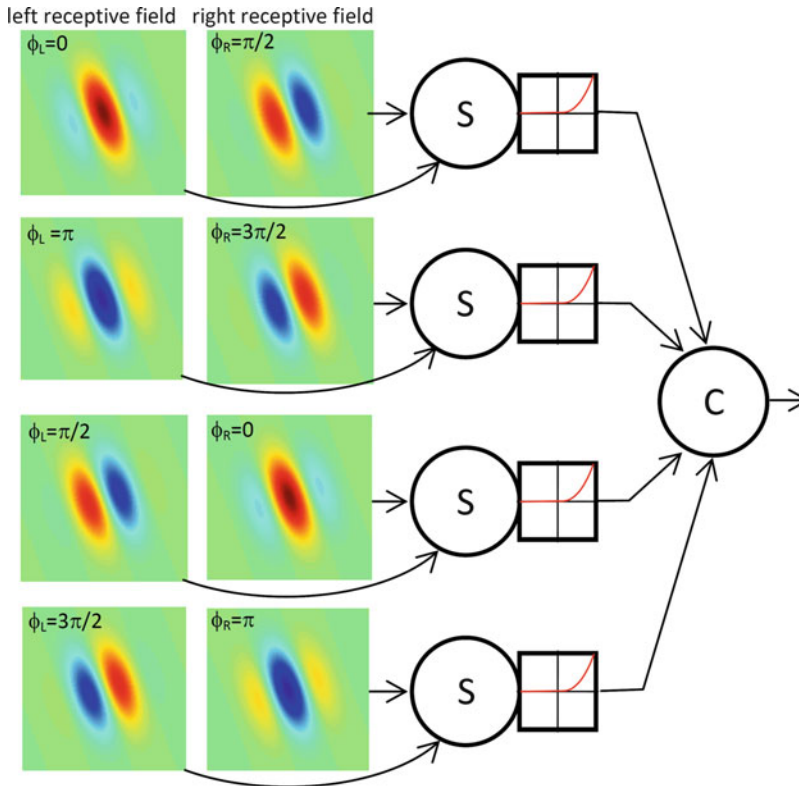
The unit in Eq. 1 is a simple cell, in that it is tuned to the phase of a grating stimulus (Movshon et al. 1978a). To build a complex cell, which is insensitive to grating phase (Hubel and Wiesel 1962; Movshon et al. 1978b), we can sum many such units with different receptive-field phases (Qian and Zhu 1997). A common computational shortcut is to sum just four such units, whose receptive fields differ in phase by multiples of $\pi/2$ (Fig. 2). This produces a complex cell whose response is perfectly independent of grating phase. Note that this difference in phase must not be confused with

the phase disparity discussed above. Phase disparity refers to a difference between the left- and right-eye receptive fields of a given energy-model unit ($\phi_R - \phi_L$ for each unit in Fig. 2). Here, we are talking about a difference in phase between receptive fields of different units, in the same eye (the four different ϕ_L in Fig. 2).

Modifications of the Energy Model

Several modifications have been proposed to the original energy model outlined above. One problem with the original energy model is that it responds equally strongly to disparity in anti-correlated random-dot patterns. These are non-physical stimuli in which one eye's image is the photographic negative of the other (Fig. 3). This manipulation all but destroys depth perception (Cogan et al. 1993; Cumming et al. 1998; Read and Eagle 2000). Since this corresponds to changing the sign of I_R relative to I_L , it simply inverts the disparity tuning of an energy-model unit (Eq. 1). However, the response of real V1 neurons is attenuated as well as inverted (Cumming and Parker 1997). To capture the attenuation, Read et al. (2002) proposed thresholding the inner products L and R before summing them in Eq. 1. A similar approach was also proposed by Tanaka and Ohzawa (2006) to explain second-order stereopsis. Lippert and Wagner (2001) proposed changing the squaring nonlinearity. Adding an expansive nonlinearity to tuned-excitatory cells, or a compressive nonlinearity to tuned-inhibitory cells, can produce the desired effect. Haefner and Cumming (2008) showed that a similar approach captures the response of V1 cells to a wide range of nonphysical stimuli. Samonds et al. (2013) incorporated recurrent connections within V1 to account for the temporal dynamics of disparity tuning, as well as the attenuated response to anti-correlated images.

All these versions of the energy model predict a strong relationship between a cell's preferred orientation with grating stimuli and its tuning to 2D disparity. Binocular disparity is in principle 2D since the two eyes' images can be offset both horizontally and vertically, although

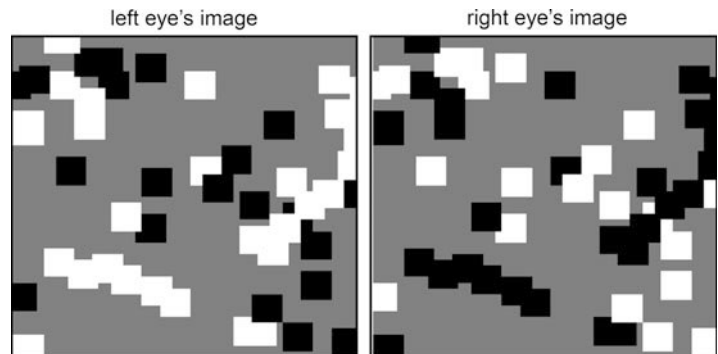


Stereo Vision, Models of, Fig. 2 Stereo energy-model complex cell, after Ohzawa (1998). The complex cell C represents the summed output of 4 of the basic units shown in Fig. 1, with different phases ϕ as labeled. The *top* two units have receptive fields which are the opposites of one another (π out of phase). This has the effect of removing the threshold before the squaring. To see why, let us call the output of the *top* S cell $[\text{Pos}(L_1 + R_1)]^2$. This is $(L_1 + R_1)^2$ when $(L_1 + R_1) > 0$, and 0 otherwise. Since the

second S cell has the same RFs, only inverted, its output will be $[\text{Pos}(-L_1 - R_1)]^2$. This is $(L_1 + R_1)^2$ when $(L_1 + R_1) \leq 0$, and 0 otherwise. Together, the sum of the two S cells is therefore $(L_1 + R_1)^2$. The *bottom* pair of cells is $\pi/2$ out of phase with the *top* pair, an arrangement known as *in quadrature*. This makes the response of the complex cell independent of the phase of the stimulus, essentially due to the trigonometric identity $\cos^2 + \sin^2 = 1$

Stereo Vision, Models of,

Fig. 3 Anticorrelated random-dot stereogram. Note that *black* dots in the left eye are *white* in the right, and vice versa



in normal viewing the horizontal component is much larger (Read et al. 2009). The energy model predicts that cells should be more

sensitive to disparities perpendicular to their preferred orientation than to those parallel to it. This prediction is borne out in the peripheral

visual field in monkey (Durand et al. 2007) and in cat (Sasaki et al. 2010) and represents another success for the energy model. Matthews et al. (2003) exploited this property of the energy model, along with the radial bias of preferred orientations in the visual cortex, in order to develop a model of depth perception from vertical disparity. However, in the central visual field, Cumming (2002) reported that V1 neurons tend to be more sensitive to vertical than to horizontal disparity, irrespective of their orientation. One way to modify the energy model to account for this property is to include multiple subunits scattered more widely horizontally than vertically (Read and Cumming 2004).

The Energy Model and Time

The original energy model included no dependence on time. A more realistic model would include receptive fields whose response depends on time as well as on spatial location. This is important for capturing effects such as our poor temporal resolution for disparity (Norcia and Tyler 1984) or the Pulfrich illusion (Morgan 1976). Qian and Andersen (1997) were the first to modify the energy model to include time. Their model is tuned to both direction and disparity, which is relatively unusual experimentally: many V1 neurons are tuned to disparity but not direction (Read and Cumming 2005). Additionally, in many V1 neurons, interocular delay simply reduces the amplitude of disparity tuning without shifting the preferred disparity (Read and Cumming 2005). It is difficult to reconcile this with the temporally band-pass tuning that V1 neurons typically show to luminance, i.e., they respond better to flickering than to constant stimuli. If one simply adds temporally band-pass receptive fields to the energy model, the model predicts that disparity tuning will invert for certain interocular delays. This is rarely observed (Read and Cumming 2005). Accordingly, work remains to be done on producing a model which captures the disparity response of real V1 neurons in the time domain.

Solving the Correspondence Problem

V1 cells are local, seeing only a small region of each retina. They respond to “false matches,” image features which look similar but are caused by different objects in space, as well as to corresponding views of the same object. To disambiguate these, it is necessary to solve the “correspondence problem,” correctly matching up image features in both eyes’ images (Ohzawa 1998). This process is not completed in V1. Anticorrelated stereograms are one piece of evidence for this. As noted, V1 cells continue to respond to these non-physical stimuli, albeit with attenuation, whereas cortical areas further down the processing pathway, for example, IT, do not (Janssen et al. 2003).

Models of stereo correspondence predate detailed knowledge of disparity encoding in V1 (Marr and Poggio 1979; Pollard et al. 1985). More recently, modelers have sought to understand how the correspondence problem could be solved by appropriately combining populations of V1-like neurons (Qian 1994, 1997).

One approach is to consider a population of cells which differ only in their tuning to disparity and take the stimulus disparity to be the preferred disparity of the maximally responding V1 cell (Qian 1994). However, often this will not be the correct answer, for two main reasons. First, the energy model is not sensitive to the precise arrangement of luminance within the receptive field; this information is lost when the inner product is computed (Eq. 1), and its response depends on image contrast. Therefore, an energy-model unit will respond well to a false match which happens to stimulate the left and right receptive fields strongly, even if the image within each receptive field is quite different. To overcome these problems, it helps first to normalize out the cell’s response to contrast (Sanger 1988; Read and Cumming 2006; Read 2010), e.g.:

$$C = \frac{2LR}{L^2 + R^2} \quad (2)$$

Such divisive normalization has been found in many brain areas and is so widespread that it has been proposed as a canonical computation of the

cortex (Carandini and Heeger 2012). In the present case, the division transforms unnormalized energy, similar to a cross-correlation function (Qian and Zhu 1997), to a normalized correlation, bounded between -1 and $+1$. Now, the preferred disparity of the maximally responding C unit is guaranteed to be the correct stimulus disparity, if the stimulus disparity is exactly constant over the cells' receptive fields (Read and Cumming 2007). However, for more realistic situations, where disparity varies across the image, this approach too can fail.

Greater robustness is obtained by expanding the population under consideration to include cells tuned to a range of orientations and spatial frequencies/spatial scales as well as to a range of disparities. Fleet and colleagues (Fleet 1994; Fleet et al. 1996) proposed a linear pooling of neuronal responses across orientations and scales. Allenmark and Read (2011) showed that by pooling across orientations and spatial frequencies and then normalizing as in Eq. 2, one effectively computes the cross-correlation of the left and right retinal image patches. This linked the physiologically based stereo energy model to a class of more abstract models based on windowed cross-correlation of the retinal images, which had successfully captured several aspects of human vision (Tyler 1974, 1975, 1978; Banks et al. 2004; Nienborg et al. 2004, 2005; Filippini and Banks 2009).

Tsai and Victor (2003) used a template-matching approach pioneered in this area by Lehky and Sejnowski (1990). Their population includes neurons tuned to a range of spatial frequency and phase disparities. They compute the mean response of this population to "template" noise stimuli with uniform disparity. The disparity in any given stimulus is taken to be that of the template which best matches the population response. Their model also allows for the perception of *transparency* (multiple planes at different depths) when multiple templates match similarly well, capturing several aspects of human perception (McKee and Verghese 2002). Other aspects of transparency appear to require excitatory and inhibitory interactions between disparity-tuned neurons (Tsirlin et al. 2012).

Monocular Occlusions

A feature of binocular vision first studied by Leonardo da Vinci is that some image features may be visible to only one eye. These monocular occlusions present a special challenge for establishing correspondence. A few biologically inspired models suggest how these regions may be handled in the brain (Watanabe and Fukushima 1999; Hayashi et al. 2004; Assee and Qian 2007).

Perceiving Depth Structure from Disparity

Once the stereo correspondence problem has been solved, we have a "disparity map" specifying image disparity at every point in the visual field. This must then be converted into a perception of depth. Relative depth (i.e., "object A is in front of object B") can be deduced immediately from the relative disparity between them. Humans are much more sensitive to the relative disparity between objects or surfaces than to the absolute disparity of an isolated object (Westheimer 1979; Parker 2007).

Further evidence that neurons in the primary visual cortex (V1) do not directly support depth perception is provided by the fact that their response is determined by the absolute disparity of the stimulus within their receptive field, not by the disparity relative to other objects in the scene (Cumming and Parker 2000). The extraction of relative disparity appears to begin in the cortical area V2, where neurons that are found are sensitive to relative disparity and are specifically tuned for disparity edges (von der Heydt et al. 2000; Thomas et al. 2002; Bredfeldt and Cumming 2006). These neurons' responses can be modeled by combining the output of different energy-model units (Bredfeldt et al. 2009).

For metric depth (i.e., "object A is 10 cm in front of object B"), disparity must be calibrated by a knowledge of the eye position. In theory, this can be obtained from extra-retinal signals (proprioception, efference copy) or from purely retinal signals if 2D disparity is available. As noted above, disparity in natural viewing is

overwhelmingly horizontal, but vertical disparities also occur, in a pattern which is dependent on the eye position and largely independent of the scene viewed. In theory, therefore, the eye position can be recovered from the 2D disparity map (Longuet-Higgins 1982). There is psychophysical evidence that vertical disparity is indeed detected by the human visual system and used to guide perception (Rogers and Bradshaw 1993, 1995; Garding et al. 1995; Backus et al. 1999). However, little is known about the underlying neuronal mechanisms or the cortical areas involved. Detailed neuronally based models have therefore not been constructed.

Cross-References

► [Large-Scale Neural Networks: Vision](#)

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Stein-Ross Model

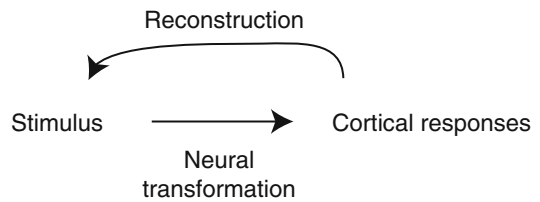
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Stimulus Reconstruction from Cortical Responses

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Definition

Reconstruction is a technique used to recreate a stimulus from its corresponding neural responses. By projecting the cortical representation of stimulus in the neural space back to the physical domain where it is usually better understood, reconstruction provides a straightforward and direct method to study the stimulus features encoded by the population neural data. Reconstruction has also been used to decode the perceived or imagined stimuli from the measurements of brain activity.



Detailed Description

Background

Cortical neurons encode considerable details about stimuli which could be difficult to discern because of the complexity and diversity of cortical receptive fields. The typical approaches used to understand the cortical representation of stimuli include examining the distribution of tuning properties for a population of neurons (De Valois et al. 1982; Ferragamo et al. 1998; Woolley et al. 2005) and pre-stimulus time histogram sorted with respect to selectivity to various stimulus parameters (Sachs et al. 1983; Mesgarani et al. 2008). Although useful, these methods are limited in their scope, especially when not all the relevant parameters of the neural space are understood and when dealing with complex stimuli that vary along numerous, possibly correlated dimensions. Stimulus reconstruction is an alternative for studying what aspects of the stimuli are encoded in the cortical responses and provide a direct comparison with the original signal.

Methods

Estimating the stimulus from responses can be done in various ways, including linear or non-linear transformations applied to the population of neural data (Bialek et al. 1991; Rieke et al. 1995; Warland et al. 1997; Haag and Borst 1998; Stanley et al. 1999; Shpigelman et al. 2005; Mesgarani et al. 2009) or formulating this problem in a statistical inference framework (Pillow et al. 2005; Paninski et al. 2007).

Stimulus Statistics

It has been shown that imposing known stimulus structures and its prior distribution can

significantly improve the accuracy of reconstruction (Mesgarani et al. 2009; Pillow et al. 2011; Ramirez et al. 2011). This is particularly useful if the reconstruction is used to approximate the best possible stimulus from cortical activity. However, if the reconstruction is used to examine stimulus features that are explicitly encoded in the neural data, inclusion of stimulus correlations may result in misleading conclusions. For example, if a correlated feature is not explicitly encoded in the neural data, it can still be reconstructed from its co-occurrence with another aspect of stimulus that is encoded [see Fig. 3 in (Mesgarani et al. 2009) for a simulation explaining this idea].

Applications

Stimulus reconstruction has been used in a variety of contexts, from decoding perceived or imagined information in the brain (Thirion et al. 2006; Naselaris et al. 2011; Pasley et al. 2012) to studying how the dynamic internal state of an organism changes the population encoding of stimulus in the cortex (Ding and Simon 2012; Mesgarani and Chang 2012).

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Stimulus-Specific Adaptation, Models

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Definition

Stimulus-specific adaptation (SSA) refers to a reduction in neural activity due to the repeated presentation of a stimulus, which does not generalize to other stimuli (Ulanovsky et al. 2003). SSA is present in auditory cortex (Ulanovsky et al. 2003), thalamus (Antunes et al. 2010), and inferior colliculus (IC) (Malmierca et al. 2009), but not the cochlear nucleus (Ayala et al. 2013). SSA has attracted interest on account of its similarity to mismatch negativity (MMN) in human auditory evoked potentials (Nelken and Ulanovsky 2007; cf. Farley et al. 2010). Computer models of SSA aim to capture the main features of single and multiunit responses to sequences of stimuli containing rare, or novel, events.

Detailed Description

Measuring SSA

Several methods exist for measuring SSA. In the simplest case, one can measure the effect of one or more *conditioner tones* on the neural response to a *probe tone* with respect to some feature, e.g., frequency (Fig. 1a). Other studies measure the average adaptation to long patterns of tones (Fig. 1b). In this case, each tone in the sequence effectively serves as both a conditioner and a probe.

SSA is most commonly investigated using *oddball sequences*, in which a rare tone (*deviant*) is presented in the context of a common tone (*standard*) (Fig. 1c). Oddball sequences are typically presented twice, with the deviant and standard features exchanged on the second

presentation. A *specificity index* (SI) provides a normalized measure of the degree of SSA:

$$SI = \frac{d_A - s_A + d_B - s_B}{d_A + s_A + d_B + s_B}$$

Here, s_X and d_X measure the activity evoked by tone X in the standard and deviant context, respectively. SSA is indicated when the SI significantly exceeds zero. Oddball sequences typically comprise several hundred tones.

Principal Results from SSA Studies

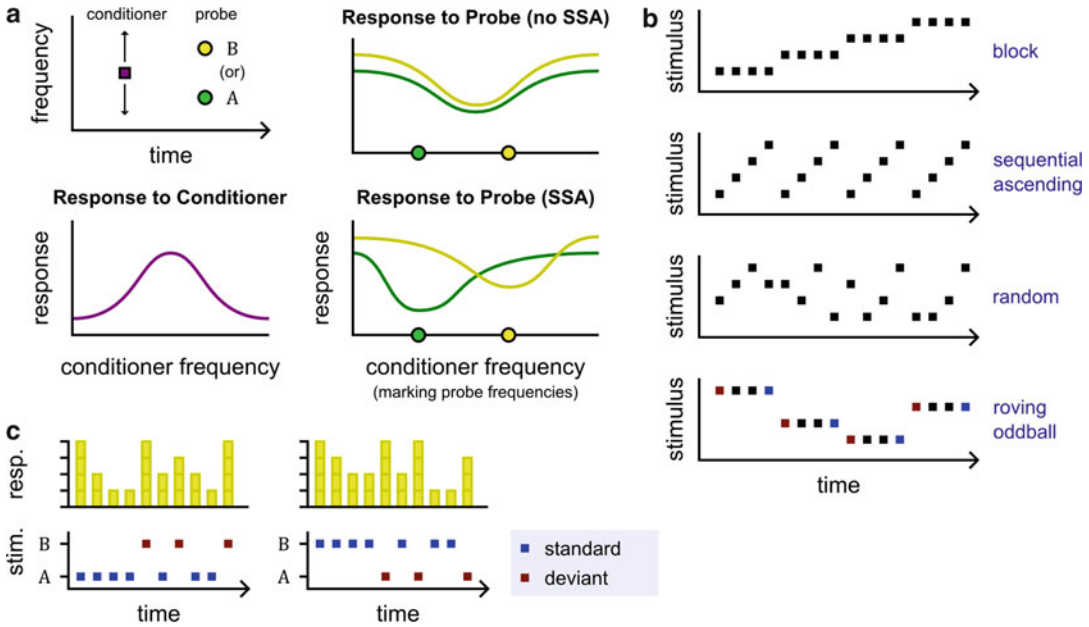
Most SSA studies use oddball sequences containing two frequencies and vary the frequency difference (Δf), the time difference between consecutive tones (Δt), and the probability of the deviant tone (p_{dev}). SI increases monotonically as:

- Δf increases
- Δt decreases
- p_{dev} decreases

How SSA elicited by other deviant features, such as intensity, duration, and amplitude modulation, should be interpreted remains a matter of contention.

Local History Models

Local history models of SSA attempt to account for the response to a tone solely in terms of the tones preceding it (Ulanovsky et al. 2004). For instance, if a tone A presented in the context ...ABAAX, then SSA neurons fire more vigorously when $X = B$ than when $X = A$. An explicit local history model stores recent tones in a finite memory of length L and responds only when this memory indicates that the incoming tone is deviant (Mill et al. 2011a). This type of model is illustrated in Fig. 2a for $L = 3$. Provided that A and B are confusable on the basis of their similarity, the model can account for the Δf and p_{dev} relations described above. However, the



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Fig. 1 Experiments used to explore SSA. (a) Cartoon showing how a conditioner tone (purple) affects the response to a probe tone (yellow and green). The adaptation of the probe may depend only on the response to the conditioner (no SSA, top right) or a combination of the probe and conditioner frequencies (SSA, bottom right) (Brosch and Schreiner 1997; Scholes et al. 2011). (b) Stimuli configurations used in other SSA experiments. The average response to a tone in the block, sequential,

random configurations is smallest for the block stimulus and largest for the random stimulus (Pérez-González et al. 2005). In the roving oddball paradigm, the first and last tones are treated as standards and deviants, respectively (Bäuerle et al. 2011). (c) Schematic responses (above) to oddball stimuli (below). In the first presentation (left), tone B is the oddball. In the second presentation (right), tone A is the oddball. For these example sequences and measurements, SI $\approx$ 0.29

observation that more recent tones exert a stronger suppressive influence on the incoming tone lends greater support to a *decaying memory* model.

Decaying memory models assign to each stimulus X a resource, R_X , possibly corresponding to synaptic neurotransmitter (Taaseh et al. 2011). The activity elicited by X is then proportional to R_X . The resource decays following presentations of stimuli similar to X and undergoes a steady recovery in the meantime. A basic example is a model which, when presented with tone X , first responds with R_X and then updates for R_Y , $Y = \{A, B\}$, according to

$$\begin{aligned} R_Y &\leftarrow \alpha R_Y & \text{if } Y = X \\ R_Y &\leftarrow R_Y + \beta(1 - R_Y) & \text{if } Y \neq X \end{aligned}$$

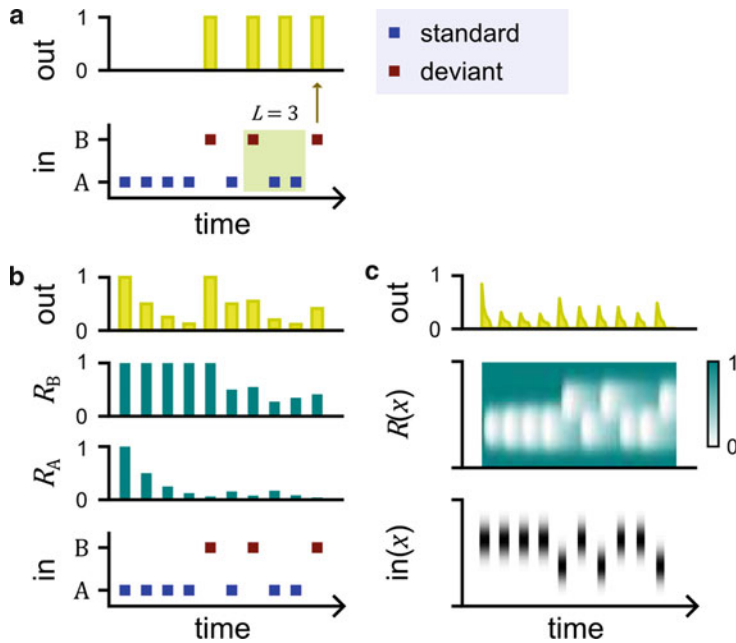
Figure 2b shows the output of this model using $\alpha = 0.5$, $\beta = 0.1$ for a short example oddball

sequence. A model this simple can account for the p_{dev} relation.

In order to also explain the Δf relation, it must be modified so that similar stimuli either consume overlapping resources (Mill et al. 2011b, 2012; Taaseh et al. 2011) or are liable to be confused with each other (Mill et al. 2011a). Figure 2c shows an example output from the model described in Mill et al. (2012), in which resources, $R(x)$, are distributed along a continuous feature axis, x , and are consumed and recovered in continuous time. Inputs are modeled as pulses, separated by Δt in time and Δf in feature space.

Global History Models

Besides the short-term effects captured by a decaying memory model (~ 1 s), neurons exhibit



Stimulus-Specific Adaptation, Models, Fig. 2 Output from simple SSA models. (a) In a two-tone oddball condition, a deviant response is generated to an incoming tone if it represents less than half of the items in a trailing memory of length $L = 3$. The computation of the deviant response to the last tone is highlighted in the figure (see Mill et al. 2011a). (b) Response exemplifying a decaying

memory model (see text). The top row shows the response; the middle rows show the resource state; the bottom row shows the stimulus pattern. (c) Response from the model described by Mill et al. (2012) ($SI \approx 0.04$). Inputs and resources are described in spatially continuous, rather than categorical, terms

additional decay components in their response to both standards and deviants that span longer time scales (~ 10 – 100 s) (Ulanovsky et al. 2004; Zhao et al. 2011; Bäuerle et al. 2011; Pérez-González et al. 2012). Whereas the depression of the thalamocortical synapses provide a plausible mechanism for the rapid time course (e.g., Ulanovsky et al. 2004), the biophysical mechanisms responsible for the slower time courses remain obscure.

Global dependence on the deviant probability, p_{dev} , is captured by a phenomenological regression model (Ulanovsky et al. 2004; Zhao et al. 2011), which fits the response to the n th tone according to the linear combination:

$$y_n = c_0 + c_1 M_n + c_2 p_{\text{dev}}$$

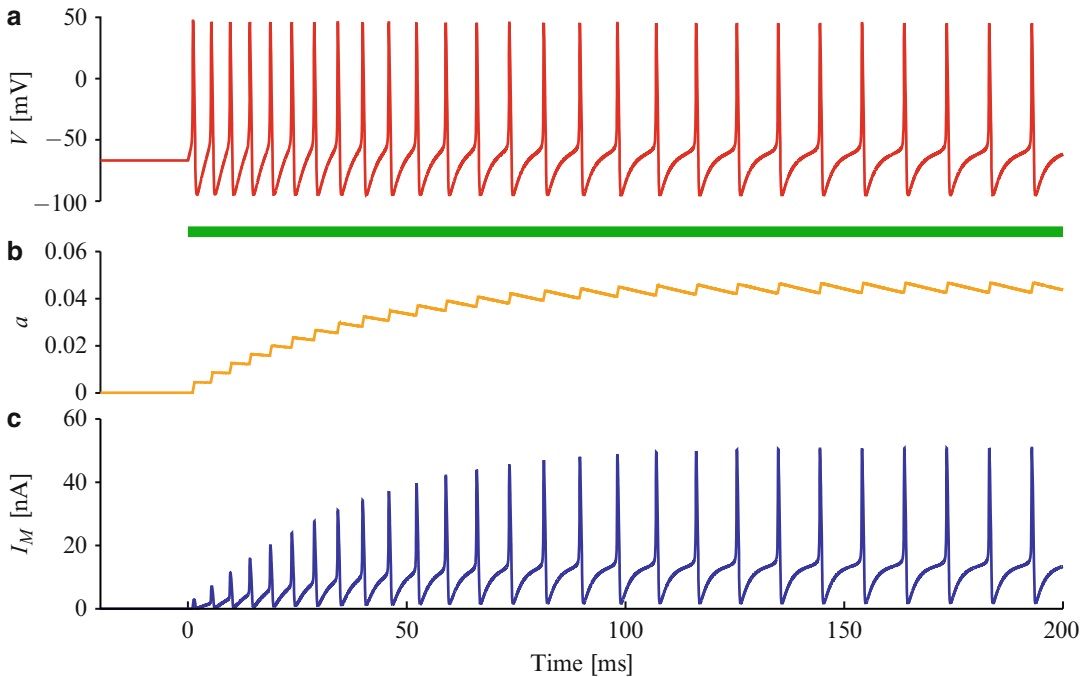
Here the coefficients c_0 , c_1 , and c_2 are free parameters, and M_n is a recent memory term computed using

$$M_n = \left(\frac{1}{Y} - 1 \right) \sum_{i=1}^{\infty} \gamma^i S_{n-i}$$

where γ is a decay parameter and $S_i = 1$ if the $(n - i)$ th tone identical to the n th tone and $S_i = 0$ otherwise.

Information Transmission

Ulanovsky et al. (2004) showed that auditory cortical responses to tones in an oddball sequence are proportional to their *unexpectedness*, defined in terms of the regression model described above. Mill et al. (2011a) reinforced this conclusion by demonstrating that a decaying memory model with rapid adaptation and slow recovery, when presented with a sequence containing multiple stimuli (e.g., $X \in \{X_1, X_2, \dots\}$), responds approximately in proportion to the stimulus entropy, i.e., $E\{-\ln P(X_i)\}$, provided that the stimuli adapt



Stimulus-Specific Adaptation, Models,
Fig. 3 Decaying memory model response versus entropy. Mean response of the decaying memory model ($\alpha = 0.5$, $\beta = 0.1$; see “Local History Models”) to

sequences containing 2 (oddball), 3, or 4 stimuli plotted against the entropy of the sequence. Note that the entropy of an oddball sequence in bits is $-p_{\text{dev}} \log_2 p_{\text{dev}} - (1 - p_{\text{dev}}) \log_2 (1 - p_{\text{dev}})$ (Adapted from Mill et al. (2011a))

distinct channels (Fig. 3). SSA may thus constitute a mechanism to reduce redundancy in the neural signal as it ascends the auditory pathway (cf. Chechik et al. 2006).

Rarity Versus Novelty

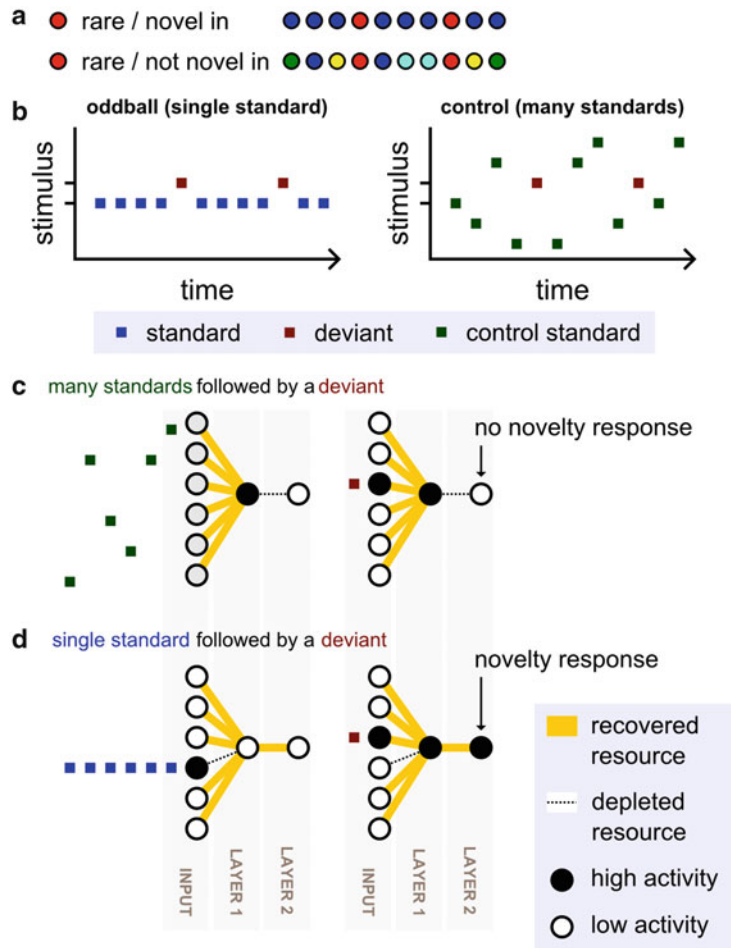
SSA can be interpreted within the oddball paradigm as *novelty detection*: deviant stimuli are conspicuous against the background of a common standard. This prompts a concern that SSA may reflect only rarity and not novelty per se (Fig. 4a). In response, researchers have devised a control condition, in which the deviant tone is presented among many standards, such that it is equally rare but otherwise unremarkable (see Fig. 4b) (Jacobsen and Schröger 2001; Farley et al. 2010; Taaseh et al. 2011).

Single-cell recordings in auditory cortex have revealed both enhanced responses to stimuli presented in the single-standard context (Ulanovsky et al. 2003) and near-equal responses (Farley

et al. 2010; Taaseh et al. 2011). This inconsistency has been attributed to differences in cross-adaptation resulting from the spacing of control standards. Moreover, an equal response in the two conditions fails to demonstrate insensitivity to novelty conclusively. Taaseh et al. (2011) show that a decaying memory model actually predicts appreciably smaller responses to deviants in the single-standard condition than in the many-standards condition. Consequently, an excess in the response to novel stimuli remains to be explained.

Mill et al. (2011b) have proposed a model containing two layers of adaptation in series that enhances responses to genuinely novel stimuli. The model is illustrated in Fig. 4c, d. In this model, adaptation to individual frequencies occurs at the first layer. The outputs from this layer are then subject to further adaptation at the second layer. When many standards are presented, the (representative) unit in the first layer is highly responsive (see “Information Transmission” above) and the unit in the second layer is adapted

Stimulus-Specific Adaptation, Models,
Fig. 4 Control conditions and models of the novelty response. (a) Diagram contrasting rarity versus novelty. The red stimulus appears 20% of the time but is only novel in the *top row*. (b) Illustration of the single-standard condition (*left*) and multiple-standard control condition (*right*). (c) Response of a two-layer model to multiple standards (*left*) followed by a deviant (*right*), which generates little or no novelty response. (d) Response of a two-layer model to a single standard (*left*) followed by a deviant (*right*), which generates a stronger novelty response (Mill et al. 2011b, Adapted from Fig. 2c, d)



(Fig. 4c). Conversely, when a single standard is presented, the unit in the first layer undergoes adaptation, and the unit in the second layer recovers (Fig. 4d). Novelty responses are coded in the second layer.

Modulation of SSA by Inhibition

A convergence of depressing synapses conveying specific-stimulus signals suffices to explain many aspects of SSA (see above). However, recent studies have highlighted the contribution of inhibition in shaping the adaptation. Blocking inhibitory (GABA_A) receptors increases the responsiveness of IC neurons to both standards and deviants, but alters the overall response ratio such that the SI is smaller (Pérez-González et al. 2012). Furthermore, examining the difference between the

poststimulus time histograms for deviant and standard tones reveals a subpopulation of cells that respond more vigorously to the standard than to the deviant after the stimulus onset. This tendency becomes more widespread following the application of the inhibitory blocker gabazine (Pérez-González and Malmierca 2012). Inhibition has to date assumed a marginal role in SSA modeling (e.g., Mill et al. 2011b); it is clear, however, that inhibition strongly modulates SSA, and future detailed models must account for it.

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Stimulus-Specific Information

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Definition

Stimulus-specific information is an information-theoretic measure of how much information the responses of a neuron convey about a particular stimulus. It is closely related to specific information, which is a measure of the information that a given neuronal response provides about which stimuli were presented. The stimulus-specific information is the average of the specific information across all the responses that occur when a particular stimulus is presented.

Detailed Description

Stimulus-specific information (SSI) (Butts 2003; Butts and Goldman 2006) is typically computed for sensory neurons that selectively respond to sensory stimuli, such that their selectivity can be characterized by a tuning curve or receptive field. For example, auditory neurons are typically tuned to sound frequency. SSI is given by

$$SSI(.,f) = \sum_r p(r|f) i_{sp}(r)$$

where f is sound frequency (or, equivalently, any stimulus dimension, such as orientation), r is the neuronal response, and i_{sp} is the specific information (DeWeese and Meister 1999), which is given by

$$i_{sp} = -\sum_f p(,f) \log_2 p(,f) \\ + \sum_f p(f|r) \log_2 p(f|r)$$

Note that $p(f)\log_2 p(f)$ is the entropy $H(f)$, so the specific information can also be written as

$$i_{sp} = H(,f) - H(f|r)$$

Here, $H(f)$ is the entropy of the stimulus ensemble, which can also be thought of as the number of possible stimuli and therefore also as the amount of uncertainty about the stimulus. $H(f|r)$ is this uncertainty given that a particular response r occurred. Thus, $i_{sp}(r)$ measures the reduction in uncertainty about the stimulus that is provided by response r or, in other words, the amount of information provided by the response r . Note that the choice for how to quantify the neuronal response r is not specified. For example, it could be firing rate, spike latency, or any arbitrary temporal code.

$SSI(f)$ is the i_{sp} averaged over all the responses r that occur when stimulus f is presented. It therefore represents how much information a neuron provides, on average, about that stimulus.

An important detail to remember when computing SSI is that information measures are subject to bias. This bias comes from the limited number of trials in experiments, which causes undersampling of the probability distributions in the above equations (for review, see Panzeri et al. 2007). There are several methods that attempt to correct for this bias. Probably, the simplest one is to compute SSI as above, but with all stimulus-response combinations randomly shuffled. In this case, the true SSI is zero, but the calculation will produce some positive value, which is caused by the bias. This value can be averaged and used as an estimate of the bias and subtracted from the raw SSI calculated above:

$$SSI_{\text{corrected}} = SSI - \langle SSI_{\text{shuffled}} \rangle$$

Note that some response types (such as temporal codes) have many more possible values than

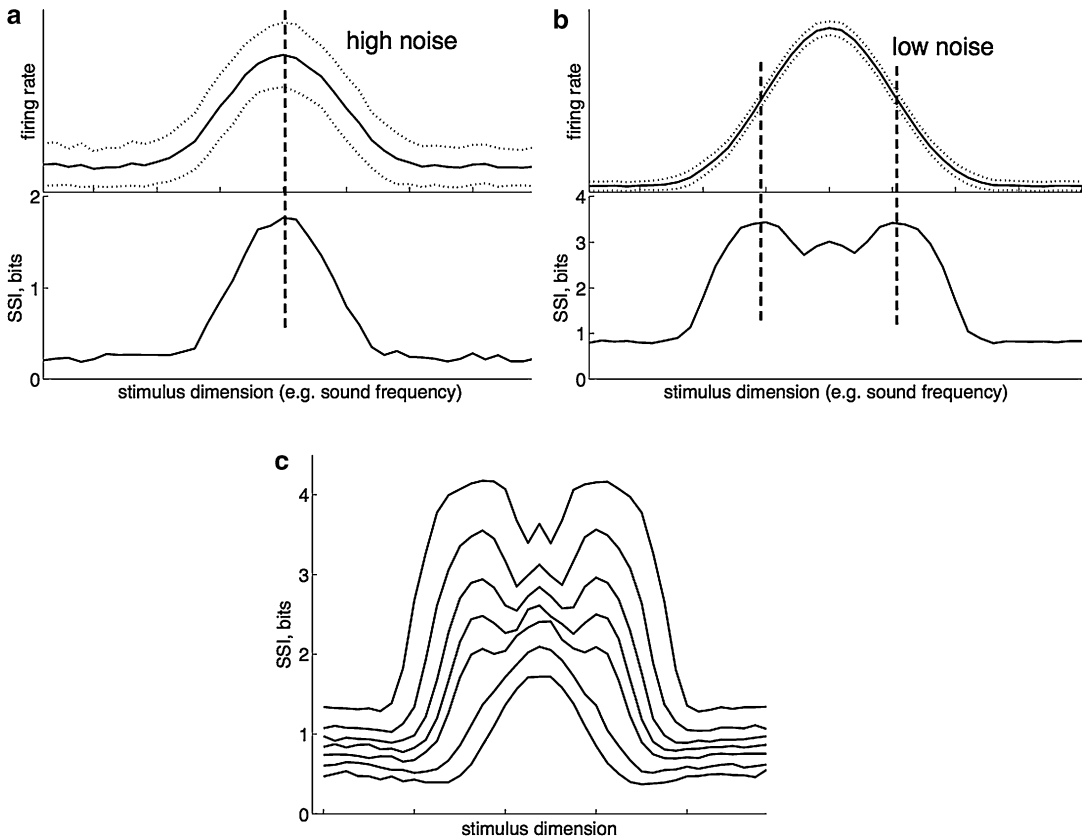
others (such as firing rates). The probability distributions for such codes therefore require correspondingly more data to sample and, for a given data set, would therefore be more susceptible to bias.

SSI can also be computed for a population of neurons, in a similar fashion to that for individual neurons. In this case, the response r is replaced by a vector of responses $\vec{r} = [r_1, r_2, \dots, r_N]$ for the population of N neurons (Butts and Goldman 2006). Again note the expected combinatorial increase in data requirements for sampling the response probability distributions.

Variability and Information

High SSI for a stimulus means that the stimulus is well encoded. This happens when uncertainty about the stimulus is reduced by the response. This hinges on the reliability of the response, and SSI is therefore strongly influenced by variability in neuronal responses. Variability in the response to a given stimulus (many different r s evoked by a single f) will reduce the amount of SSI.

The effect of variability on SSI leads to an intriguing tuning curve phenomenon that has important implications for neural coding (Butts and Goldman 2006). Sensory neurons are often thought of as feature detectors, whose responses signal how close a stimulus is to the preferred stimulus of the neuron. In this view, one would expect maximal SSI for the preferred stimulus, at the peak of the tuning curve. However, the flanks of the tuning curve, which have the steepest slope, also convey information about the stimulus. In the steep flanks, small changes in the stimulus produce large changes in the firing rate. Because the slope of the tuning curve is flat near its peak, responses to neighboring stimuli will be similar, and neurons may therefore be less able to discriminate stimuli near their best stimulus, compared to those in the flanks. In this view, one would expect maximal SSI in the flanks of the tuning curve, not the peak. Thus, these two intuitive views of neuronal tuning make quite different predictions



Stimulus-Specific Information, Fig. 1 The effect of variability on SSI. (a), *Top*, Tuning curve of a model neuron with a high level of additive Gaussian noise (generating high response variability). *Dotted lines* indicate one SD. *Bottom*, SSI across stimuli. Maximal SSI was aligned with peak of the tuning curve (vertical dashed line). (b),

Same tuning curve but with low noise (and low response variability). Maximal SSI has now shifted to the points of steepest slope in the tuning curve (vertical dashed lines). (c), SSI curves across a range of variability levels, showing the transition of maximal SSI from peak to slope of the tuning curve

about the most informative region of the receptive field. The dependence of SSI on response variability reconciles these different predictions, so that both interpretations can be correct depending on neuronal variability (Butts and Goldman 2006). When trial-to-trial variability is high, a model neuron conveys maximal stimulus-specific information at the peak of its tuning curve (Fig. 1a). As trial-to-trial variability is reduced, the maximal information gradually shifts to the steep flanks of the tuning curve (Fig. 1b, c). This unified framework suggests that neural coding strategies depend critically on the level of neuronal variability. A recent study of neurons encoding sound frequency in auditory cortex demonstrated that maximal SSI was always at

the best frequency and never in the tuning curve flanks (Montgomery and Wehr 2010). This suggests that despite the high reliability of auditory cortical neurons, they are too variable to be most informative at the flanks of their tuning curves and instead act as feature detectors for their best frequency.

Cross-References

- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [Information Theory: Overview](#)
- [Neuronal Population Vector](#)

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Stochastic Hopfield Network

► [Boltzmann Machine](#)

Stochastic Neural Field Theory

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Definition

One of the major challenges in neuroscience is to determine how noise that is present at the molecular and cellular levels affects dynamics and information processing at the macroscopic level of synaptically coupled neuronal populations. Often noise is incorporated into deterministic neural network models using extrinsic noise sources. An alternative approach is to assume that noise arises intrinsically as a collective population effect, which has led to a master equation formulation of stochastic neural networks. Stochastic neural fields are obtained by taking a continuum limit of a stochastic neural network with spatially structured synaptic weights.

Detailed Description

The spike trains of individual cortical neurons *in vivo* tend to be very noisy, having interspike interval (ISI) distributions that are close to Poisson (Softky and Koch 1993). The main source of intrinsic fluctuations at the single-cell level is channel noise, which arises from the variability in the opening and closing of a finite number of ion channels (Faisal et al. 2008). On the other hand, extrinsic fluctuations in membrane voltage are predominantly due to synaptic noise. That is, cortical neurons are bombarded by thousands of synaptic inputs, many of which are not correlated with a meaningful input and can thus be treated as background synaptic noise (Brunel 2000). It is not straightforward to determine how noise at the single-cell level translates into noise at the population or network level. Neural field equations can be derived under two basic assumptions: (i) the spike trains of individual neurons are decorrelated (asynchronous) so that the total synaptic input to a neuron is slowly varying and deterministic and (ii) there exists a well-defined continuum limit of the resulting network rate equations. So far there has been no rigorous proof that either of these assumptions hold in large-scale spiking network models of cortex. In particular, there has been no systematic scaling up of spiking networks to derive continuum neural field models that take proper account of noise-induced fluctuations and statistical correlations between neurons at multiple spatial and temporal scales. Consequently, current formulations of stochastic neural field theory tend to be phenomenologically based. One approach is to consider a Langevin version of deterministic neural field equations involving some form of extrinsic spatiotemporal noise (Hutt et al. 2008; Faugeras et al. 2009; Bressloff 2012; Bressloff and Webber 2012a), whereas another is to treat the neural field equations as the thermodynamic limit of an underlying master equation (Buice and Cowan 2007; Bressloff 2009; Buice et al. 2010). In the latter case, a diffusion approximation leads to an effective Langevin equation with multiplicative noise. In order to develop the theory of stochastic neural fields, it is useful to consider discrete network models first (Bressloff 2012).

Langevin Equation Formulation

Consider a set of P homogeneous populations labeled $i = 1, \dots, P$. Suppose that population activity is given by a stochastic variable $A_j(t)$ evolving according to a Langevin equation (stochastic differential equation) of the form

$$\hat{\tau} dA_j(t) = [-A_j(t) + F(U_j(t))]dt + \sigma_j dW_j(t), \quad (1)$$

where F is a population rate function and $U_j(t)$ is a stochastic synaptic current satisfying the integral equation

$$U_j(t) = \sum_{k=1}^P \int_{-\infty}^t \Phi_{jk}(t-t') A_k(t') dt'. \quad (2)$$

Here $\Phi_{jk}(t)$ represents the temporal filtering effects of synaptic and dendritic processing of inputs from any neuron of population k to any neuron of population j . In Eq. 1, $W_j(t)$, $j = 1, \dots, P$, denotes a set of P -independent Wiener processes with

$$\langle dW_j(t) \rangle = 0, \langle dW_j(t) dW_k(t) \rangle = C_{ij} dt. \quad (3)$$

Here C_{ij} incorporates any spatial correlations and σ_j is the strength of noise in the j th population. In general, the resulting stochastic model is non-Markovian. However, if we take $\Phi_{jk}(t) = w_{jk} \Phi(t)$ with $\Phi(t) = \tau^{-1} e^{-t/\tau}$ (exponential synapses), then we can convert the latter equation to the form

$$\tau dU_j(t) = \left[-U_j(t) + \sum_{k=1}^P w_{jk} A_k(t) \right] dt \quad (4)$$

It is important to note that the time constant $\hat{\tau}$ cannot be identified directly with membrane or synaptic time constants. Instead, it determines the relaxation rate of a local population to the mean-field firing rate. In the limit $\hat{\tau} \rightarrow 0$, Eqs. 1 and 4 reduce to a *voltage-based* rate model perturbed by additive noise:

$$\tau dU_j(t) = \left[-U_j(t) + \sum_{k=1}^P w_{jk} F(U_k(t)) \right] dt + d\tilde{W}_j(t) \quad (5)$$

Here $\tilde{W}_j(t) = \sum_{k=1}^P w_{jk} \sigma_k W_k(t)$ so that

$$\begin{aligned} \langle d\tilde{W}_j(t) \rangle &= 0, \langle d\tilde{W}_j(t) d\tilde{W}_k(t) \rangle \\ &= \left[\sum_j C_{kl} w_{jl} w_{kf} \sigma_l \sigma_f \right] dt. \end{aligned} \quad (6)$$

On the other hand, in the limit $\tau \rightarrow 0$, we obtain a stochastic *activity-based* model

$$\begin{aligned} \hat{\tau} dA_j(t) &= \left[-A_j(t) + F\left(\sum_k w_{jk} A_k(t)\right) \right] dt \\ &+ \sigma_j dW_j(t). \end{aligned} \quad (7)$$

Master Equation Formulation

An alternative approach to incorporating noise into the population firing rate has been developed in terms of a jump Markov process (Buice and Cowan 2007; Bressloff 2009, 2010; Buice et al. 2010). Such a description is motivated by the idea that each local population consists of a discrete number of spiking neurons and that finite-size effects are a source of intrinsic rather than extrinsic noise (Soula and Chow 2007; El Boustani and Destexhe 2009). The stochastic output activity of a local population of N neurons is now expressed as $A_j(t) = N_j(t)/(N\Delta t)$ where $N_j(t)$ is the number of neurons in the j th population that fired in the time interval $[t - \Delta t, t]$, and Δt is the width of a sliding window that counts spikes. Suppose that the discrete stochastic variables $N_j(t)$ evolve according to a one-step jump Markov process:

$$\begin{aligned} N_j(t) &\rightarrow N_j(t) \pm 1 \\ &: \text{transition rate } \Omega_{\pm j}(t), \end{aligned} \quad (8)$$

in which $\Omega_j^{\pm}(t)$ are functions of $N_j(t)$ and $U_j(t)$ with $U_j(t)$ evolving according to the integral eq. 2 or its differential version (4). Thus, synaptic coupling

between populations occurs via the transition rates. The transition rates are chosen in order to yield a deterministic rate-based model in the thermodynamic limit $N \rightarrow \infty$. One such choice is

$$\Omega_j^+(t) = \frac{N\Delta t}{\hat{\tau}} F(U_j(t)), \quad \Omega_j^-(t) = N_j(t)\hat{\tau}. \quad (9)$$

A further simplification is obtained in the limit $\tau \rightarrow 0$, since the continuous variables $U_j(t)$ can be eliminated to give a pure birth-death process for the discrete variables $N_j(t)$. Let $P(\mathbf{n}, t) = \text{Prob}[N(t) = \mathbf{n}]$ denote the probability that the network of interacting populations has configuration $\mathbf{n} = (n_1, n_2, \dots, n_P)$ at time t , $t > 0$, given some initial distribution $P(\mathbf{n}, 0)$. The probability distribution then evolves according to the birth-death master eqs. 8–10

$$\begin{aligned} \frac{dP(\mathbf{n}, t)}{dt} = & \sum_{\alpha} \left[(\mathbb{E}_{\alpha} - 1) \left(\Omega_{\alpha}^-(\mathbf{n}) P(\mathbf{n}, t) \right) + (\mathbb{E}_{\alpha}^{-1} - 1) \left(\Omega_{\alpha}^+(\mathbf{n}) P(\mathbf{n}, t) \right) \right], \\ & (10) \end{aligned}$$

where $\Omega_j^+(\mathbf{n}) = (N\Delta/\hat{\tau}) F\left[\sum_k w_{jk} n_k / (N\Delta t)\right]$, $\Omega_j^-(\mathbf{n}) = n_j / \hat{\tau}$ and $\mathbb{E}_j$ are translation operators: $\mathbb{E}_j^{\pm 1} F(\mathbf{n}) = F(\mathbf{n}_{j\pm})$ for any function F with $\mathbf{n}_{j\pm}$ denoting the configuration with n_j replaced by $n_j \pm 1$. Equation 10 is supplemented by the boundary conditions $P(\mathbf{n}, t) = 0$ if $n_j = N + 1$ or $n_j = -1$ for some j . The birth-death master eq. 10 has been the starting point for a number of studies of the effects of intrinsic noise on neural fields, which adapt various methods from the analysis of chemical master equations including system-size expansions and path integral representations (Buice and Cowan 2007; Bressloff 2009; Buice et al. 2010). For large N the master equation can be approximated by a Langevin equation with multiplicative noise and thus reduces to the previous class of stochastic neural field model (Bressloff 2009).

Continuum Limit

A stochastic neural field equation can be obtained from either formulation by taking an appropriate

continuum limit. For simplicity, we will focus on the simplest stochastic rate model given by Eqs. 1 and 4. The continuum limit of Eq. 4 proceeds heuristically as follows. First, set $U_j(t) = U(j\Delta d, t)$, $A_j(t) = A(j\Delta d, t)$, and $w_{jk} = \rho\Delta d w(j\Delta d, k\Delta d)$ where ρ is a synaptic density and Δd is an infinitesimal length scale. Taking the limit $\Delta \rightarrow 0$ and absorbing ρ into w gives

$$\tau dU(x, t) = \left[-U(x, t) + \int_{-\infty}^{\infty} w(x-y) A(y) dy \right] dt. \quad (11)$$

We also assume that the noise strength $\sigma_j = \sigma/\sqrt{\Delta d}$ and define $w_j(t)/\sqrt{\Delta d} = w(j\Delta d, t)$. Taking the limit $\Delta d \rightarrow 0$ in Eq. 1 gives

$$\begin{aligned} \hat{\tau} dA(x, t) = & [-A(x, t) + F(U(x, t))] dt \\ & + \sigma dW(x, t) \end{aligned} \quad (12)$$

With

$$\begin{aligned} \langle dW(x, t) \rangle &= 0, \quad \langle dW(x, t) dW(y, t) \rangle \\ &= C(x-y) dt, \end{aligned} \quad (13)$$

where we have assumed that C_{ij} depends on $|i-j|$. In the limit $\hat{\tau} \rightarrow 0$ we obtain a stochastic version of a voltage-based neural field equation, namely,

$$\begin{aligned} \tau dU(x, t) = & \left[-U(x, t) + \int_{-\infty}^{\infty} w(x-y) F(U(y, t)) dy \right] dt \\ & + \sigma d\tilde{W}(x, t) \end{aligned} \quad (14)$$

with $\langle d\tilde{W}(x, t) \rangle = 0$

$$\begin{aligned} \langle d\tilde{W}(x, t) d\tilde{W}(y, t) \rangle = & \\ dt \int_{-\infty}^{\infty} C(Z-Z') w(x-z) w(y-z') dz dz'. \end{aligned} \quad (15)$$

Similarly, in the limit $\tau \rightarrow 0$ we have a stochastic version of an activity-based neural field equation

$$\begin{aligned} \hat{\tau} dA(x, t) = & \left[-A(x, t) + F\left(\int_{-\infty}^{\infty} w(x-y) A(y, t) dy\right) \right] dt \\ & + dW(x, t). \end{aligned} \quad (16)$$

From a numerical perspective, any computer simulation would involve discretizing space and then solving a time-discretized version of the resulting stochastic differential equation. On the other hand, in order to investigate analytically the effects of noise on spatiotemporal dynamics, it is more useful to work directly with stochastic neural fields. One can then adapt various PDE methods for studying noise in spatially extended systems (Sagues et al. 2007).

Applications

One application of stochastic neural field theory is to binocular rivalry waves (Bressloff and Webber 2012b). The basic model consists of two voltage-based excitatory neural fields of the form (14), which represent right and left eye networks, respectively. The neural fields mutually inhibit each other and also undergo some form of slow adaptation such as synaptic depression. It can be shown that the deterministic model supports a composite traveling front, in which the activity of one network advances while the other retreats – this represents the spatiotemporal switch in eye dominance that has been observed experimentally (Wilson et al. 2001). When multiplicative extrinsic noise is added to the model, one finds that the noise generates two distinct phenomena that occur on different time scales: a diffusive-like displacement of the binocular rivalry wave from its uniformly translating position at long time scales and fluctuations in the wave profile around its instantaneous position at short time scales. Moreover, one can use perturbation methods to calculate the diffusion coefficient characterizing the wandering of the front (Bressloff and Webber 2012b).

Another application of stochastic neural field theory is to modeling spontaneous cortical activity in vitro and in vivo (Beggs and Plenz 2004; Plenz and Thiagarajan 2007). Buice and Cowan (Plenz and Thiagarajan 2007) have used path integral methods and renormalization group theory to establish that a stochastic neural field model based on a continuum version of a birth-death master equation belongs to the universality class of directed percolation and consequently exhibits

power law behavior consistent with measurements of neuronal avalanches in vitro and in vivo (Beggs and Plenz 2004; Plenz and Thiagarajan 2007).

Cross-References

- [Neural Field Model, Continuum](#)
- [Neural Mass Action](#)
- [Neural Population Model](#)
- [Pattern Formation in Neural Population Models](#)
- [Population Density Model.](#)

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Stochastic Resonance: Balance Control and Cochlear Implants

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Synonyms

Noise enhancement of weak subthreshold signals

Definition

Originally discovered in climate data (Nicolis and Nicolis 1981; Nicolis 1982), the phenomenon of stochastic resonance occurs when an intermediate (i.e., neither too large nor too small) amount of noise enhances the transmission of a weak periodic signal (McNamara and Wiesenfeld 1989). The signal is “weak” in the sense that, in the absence of noise, it is below the threshold of detection. Low-amplitude added noise contributes jitter to the weak periodic signal but is not sufficient to push the signal over the detection threshold. Large-amplitude noisy input, in contrast, adds so much jitter that, while the weak signal plus noise does often exceed the threshold, the signal is not separable from the noise (Jung and Hänggi 1991; Dykman et al. 1992). An intermediate-amplitude noisy input allows the weak signal

plus noise to cross the detection threshold sufficiently often that, upon sampling the threshold-crossing events, the original periodicity of the weak signal can be detected. The signal-to-noise ratio exhibits a characteristic peak when plotted as a function of the input noise amplitude. For comprehensive reviews of the phenomenon, see Moss and Wiesenfeld (1995), Wiesenfeld and Moss (1995), and Gammaitoni et al. (1998).

Detailed Description

Because of the periodic firing of neurons (and the periodicity of many other biological rhythms), biological physicists and neuroscientists have searched for evidence of stochastic resonance in various neural domains. Stochastic resonance has indeed been observed in a wide range of neural systems in many species, from the crayfish mechanosensory system (Pei et al. 1996) to the human visual system (Simonotto et al. 1997).

One of the areas where a stochastic resonance-like effect has been investigated with most relevance to the clinical treatment of human disorders has been that of balance control. A pioneering set of studies in this area was initiated by James Collins’s research group in the Center for BioDynamics at Boston University. In a 2002 paper in *Physical Review Letters* (Priplata et al. 2002), they tested a feedback system in which the (roughly periodic) postural sway of humans during quiet standing could be significantly reduced by adding a small amount of mechanical noise to the subjects’ feet. Subjects stood on a platform that contained actuators to provide input noise, with the frequency range and amplitude of the noise controlled by the experimenters. The authors suggested that this approach could lead to the development of vibrating shoe insoles that could enhance balance in the elderly and successfully implemented this idea (Priplata et al. 2003). Noise stimulation applied directly to the tibialis anterior muscle can also improve performance during a challenging balance task in healthy young adults (Severini and Delahunt 2018). Application of mechanical noise to ankle muscle tendons has been shown to improve postural control (Borel

and Ribot-Ciscar 2016). Other studies have shown that stochastic vestibular stimulation can improve locomotor stability and balance in healthy subjects (Goel et al. 2015; Mulavara et al. 2015; Wuehr et al. 2016a, 2018) as well as in patients with bilateral vestibulopathy (Iwasaki et al. 2014, 2018; Wuehr et al. 2016b). Whole-body vibration has also been tested as a means of enhancing balance in the elderly (Rogan et al. 2015) and in subjects with balance disability and a history of falls (Rogan et al. 2014). Yet another recent study implemented a more colloquially literal version of “noise” showing that auditory white noise can reduce age-related fluctuations in balance (Ross et al. 2016).

The underlying dynamics of this process can be related to the familiar task of trying to balance a meter stick on a finger or palm. The task proves far easier when one’s hand is moving underneath the stick. Milton et al. (2009a) combined these two processes in a study of stick balancing by subjects on a vibrating platform and interpreted the vibration-enhanced balance control as a “time-delayed drift and act” effect. In this experiment, the subjects stood on a vibrating platform that produced vertical vibrations in their fingertips. These vibrations reduced the amplitude of fluctuations (in relative horizontal plane position) between the fingertip and the tip of the stick. A nonlinear dynamics-based exploration of the phenomenon can be found in Milton et al. (2009b).

The neural pathways involved in noise-enhanced human balance have not yet been completely elucidated. However, stochastic resonance has already been applied in a variety of clinical situations. A pilot study has been conducted to explore the possibility of using whole-body vibration to enhance chair rising in the elderly (Rogan et al. 2012) and as a possible therapy for Parkinsonian tremor (Kaut et al. 2011). Vibration-enhanced stability studies have been conducted in subjects with ankle instability (Ross and Guskiewicz 2006; Ross 2007; Ross et al. 2013) and with osteoarthritic knees (Collins et al. 2012) and to reduce musculoskeletal stress in metal manufacturing workers (Burger et al. 2012). Stochastic resonance has also been

recently explored in the context of enhancing sensorimotor performance with noise added as a tactile stimulus to the subjects’ fingers (Mendez-Balbuena et al. 2012).

Perhaps one of the most intriguing clinical applications of stochastic resonance is in the area of hearing impairment. After showing that the addition of actual auditory noise to a vowel coded in a cochlear implant enhanced the neural evoked response Morse and Evans (1996, 1999a, b) and Morse and Roper (2000) suggested that stochastic resonance techniques could be applied in the design of cochlear implants. The design of stochastic resonance-based cochlear implants become an active area of research in the early 2000s (Zeng et al. 2000; Chatterjee and Robert 2001; Stocks et al. 2002; Benham and Zeng 2003; Hong and Rubinstein 2003; Rubinstein and Hong 2003; Chatterjee and Oba 2005). It has been suggested that stochastic resonance may play a role in enhancing unimpaired hearing as well, with the Brownian motion of cochlear fluids providing a natural source of noise for the optimization of hair cell response (Ehrenberger et al. 1999). Among the most recent developments in the study of stochastic resonance in normal sound processing, Martignoli et al. (2013) showed that pitch sensation involves stochastic resonance. Regarding hearing pathology, Krauss et al. (2016) have suggested that stochastic resonance may mediate the upregulation of internal noise after hearing loss, leading to tinnitus. The coming decade is sure to bring further developments in the understanding of the role of stochastic resonance in both normal and pathological sensory processing.

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Stochastic Simulation Algorithm

► Stochastic Simulators

Stochastic Simulation Algorithm (SSA)

► Gillespie Algorithm for Biochemical Reaction Simulation

Stochastic Simulation Method

► Stochastic Simulators

Stochastic Simulators

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Synonyms

[Stochastic simulation algorithm](#); [Stochastic simulation method](#)

Definition

A stochastic simulator for reaction-diffusion systems is a computer simulation tool that uses the Monte Carlo method to generate the time evolution of a spatially inhomogeneous chemically reacting system. The main types of stochastic simulators used in neuroscience are particle based and population based. The stochastic simulation algorithm (SSA) is a population-based method that numerically simulates the time evolution of a well-stirred chemically reacting system in thermal equilibrium by defining the state of the system to be the integer numbers of molecular populations. The SSA has been extended to incorporate diffusion, usually called the inhomogeneous SSA (ISSA), by dividing the spatial domain into a collection of well-stirred subvolumes and treating diffusion between neighboring subvolumes as a set of first-order reactions. This entry focuses on stochastic simulators that use the inhomogeneous SSA.

Detailed Description

The small numbers of molecules in various spatial compartments of biological cells give rise to stochastic variations in intracellular microdomains. These stochastic variations affect the behavior of biochemical network components, such as oscillators, switches, and positive and negative feedback loops, and play a significant role in the spatiotemporal activity and behavior of cells, such as cell differentiation, gene regulatory networks, and synaptic plasticity (e.g., reviews by Kotaleski and Blackwell 2010; Bhalla 2014; Harton and Batchelor 2017; Gonze et al. 2018). In addition, the long thin dendrites characteristic of neurons produce spatial gradients and diffusional movement of molecules. Computer simulation enables computational investigation of the stochastic and spatial effects on neuron activity that may be difficult to monitor in detail experimentally (Boulianne et al. 2008), thereby providing a more amenable investigative platform to test hypotheses and gain further insights.

Traditionally, computer simulation of biochemical networks has involved deterministic approaches that represent each molecule population as a continuous-valued concentration. By ignoring spatial heterogeneity, systems of ordinary differential equations can be used to describe the time evolution of concentrations. On the other hand, when the concentrations are spatially heterogeneous, systems of partial differential equations are used. Deterministic models and simulations are valid in the thermodynamic limit of large numbers of molecules and describe the average behavior of the modeled system. However, when molecule populations are small, discrete numbers of molecules rather than mean behavior need to be examined, and stochastic fluctuation in molecule numbers influences the time evolution of the system.

Stochastic simulation methods are categorized as either spatial or nonspatial methods (Takahashi et al. 2005). Nonspatial stochastic simulators (Alves et al. 2006) assume that the system to be modeled is well-stirred, that is, nonreactive collisions between molecules occur much more frequently than reactive collisions such that the

molecules become uniformly randomly distributed in thermal equilibrium (Gillespie 1976, 2006). However, spatial heterogeneity is observed experimentally in neurons for many molecular species, implying that spatial stochastic simulations are required to accurately capture signaling pathway activity and interactions in neurons (Bhalla 2004; Lemerle et al. 2005; Takahashi et al. 2005).

Spatial stochastic simulation methods are further categorized as particle-based or population-based (also known as voxel-based or subvolume-based) methods (Takahashi et al. 2005). Recent, particle-based spatial stochastic simulators use a variety of methods, including molecular dynamics, Brownian dynamics (see entry ► [“Particle-Based Stochastic Simulators”](#)), Green’s function reaction dynamics, and lattice-based approaches, to model the system at a single particle detail (Tolle and Le Novère 2010; Stefan et al. 2014; Andrews 2017; Sbailò and Noé 2017; Ekimoto and Ikeguchi 2018; Sokolowski et al. 2019). With these simulators, the location and reactions of individual molecules are tracked providing the time evolution of the system state at microscopic detail. Two Brownian motion simulators, ► [“MCell”](#) and Smoldyn, have been used most commonly to study signaling pathways in neurons. Rule-based modeling is a recent advanced alternative to specification of the almost countless number of possible reactions in multi-state molecules (Colvin et al. 2010; Ibrahim et al. 2013). Rule-based modeling allows specification of families of reactions (e.g., phosphorylation of multiple sites), and then the simulator implements the particular reactions as needed. Particle-based methods offer high spatial resolution; however population-based stochastic simulation methods are computationally more efficient than particle-based simulation methods (Dobrzyński et al. 2007; Andrews et al. 2010). Population-based spatial stochastic simulators subdivide the simulation volume into a collection of well-stirred subvolumes, and reactions are simulated in each subvolume by using a variant of Gillespie’s stochastic simulation algorithm (see entry ► [“Gillespie Algorithm for Biochemical Reaction Simulation”](#); Gillespie 2006), whereas diffusions

between neighboring subvolumes are simulated as a set of first-order reactions. Population-based simulators keep track of the population number of each molecule species in each subvolume, thereby providing the time evolution of the system state at mesoscopic detail. For both population-based and particle-based simulations, several simulation runs are made from the same initial condition with different random seeds for analysis of the probability distribution, average, and/or variance of the system trajectories.

Here we categorize population-based spatial stochastic simulation methods by the numerical simulation approach. We first briefly explain the extension of Gillespie's stochastic simulation algorithm (SSA) for well-stirred systems to spatial or inhomogeneous systems with well-stirred (homogeneous) subvolumes. We then describe stochastic simulation methods that utilize an exact ISSA approach. Next, we describe stochastic simulation methods that utilize approximate SSA approaches to ameliorate the heavy computational burden placed by the exact approach. We conclude with discussion of limitations and advantages of the current population-based spatial stochastic simulation methods.

Spatial Extension of Gillespie's Stochastic Simulation Algorithm

Gillespie's SSA (see entry ► "Gillespie Algorithm for Biochemical Reaction Simulation") is extended to include diffusion by relaxing the well-stirred requirement. For the inhomogeneous SSA (ISSA), the system volume Ω is partitioned into Q subvolumes $\{V_1, \dots, V_Q\}$, each of which is assumed to be well-stirred. There are N molecular species $\{S_1, \dots, S_N\}$ that are involved in M chemical reaction channels $\{R_1, \dots, R_M\}$ in each subvolume, and each molecular species has a diffusion coefficient D_i ($i = 1, 2, \dots, N$) greater than or equal to zero. The state vector $X_k(t) = (X_{1k}(t), \dots, X_{Nk}(t))$ denotes the number of molecules of S_i ($i = 1, 2, \dots, N$) in subvolume V_k ($k = 1, 2, \dots, Q$) at time t . Then $X(t) = (X_1(t); \dots; X_Q(t))$ denotes the Q by N state matrix of the system at time t . N molecular species in each subvolume V_k are involved in M chemical

reaction channels $\{R_{1k}, \dots, R_{Mk}\}$ and $N \cdot B_k$ diffusion channels $\{R_{ikl}^d\}$ where B_k is the number of V_k 's neighboring subvolumes and l denotes the index of each neighboring subvolume of V_k . Each reaction channel R_{jk} ($j = 1, 2, \dots, M$; $k = 1, 2, \dots, Q$) is characterized by a propensity function a_{jk} and the state change vector v_j : Given the current state of the system $x = X(t)$, $a_{jk}(x)dt$ gives the probability that an R_{jk} reaction will occur in the next time interval $[t, t + dt)$ in subvolume V_k . The state change vector v_j gives the change in the molecule populations produced by one R_{jk} reaction such that $x_k \rightarrow x_k + v_j$. Diffusive transfers of a molecule of species S_i from a subvolume V_k to a neighboring subvolume V_l are treated as unimolecular reactions, $S_{ik} \rightarrow S_{il}$ (Baras and Mansour 1996; Stundzia and Lumsden 1996). Each diffusion channel R_{ikl}^d is characterized by a propensity function $\kappa_{ikl}x_{ik}$ and state change matrix $E_i^l - E_i^k$, where κ_{ikl} is a constant proportional to the diffusion rate constant D_i (e.g., when V_k and V_l are both cuboids with side length u , $\kappa_{ikl} = D_i/u^2$), $E_i^l - E_i^k$ gives the change in the molecular populations produced by one R_{ikl}^d diffusion, and E_i^k denotes the Q by N matrix whose entries are all zero except for the entry (k, i) . Therefore, whereas Gillespie's SSA has M total reaction channels in the system volume Ω , the ISSA has up to $M \cdot Q + \sum_{k=1}^Q (N \cdot B_k)$ reaction channels in the system volume Ω that is subdivided into Q subvolumes. Note that the total number of diffusive transfer reaction channels is less than $\sum_{k=1}^Q (N \cdot B_k)$ when the diffusion coefficient of one or more molecule species S_i ($i = 1, 2, \dots, N$) is zero.

Starting from some initial conditions, the ISSA proceeds by generating the time step τ to the next reaction and determining which reaction occurs in that next time interval and then effecting the reaction by updating the time and the state matrix. Gillespie gave two implementations of his SSA: the direct method and the first-reaction method (Gillespie 1977).

With the first-reaction method, the next time step τ and the next reaction μ are determined by generating up to $M \cdot Q + \sum_{k=1}^Q (N \cdot B_k)$ random numbers r_{jk} from the uniform distribution in the unit interval and calculating

$$\tau_{jk} = \frac{1}{a_{jk}(x)} \ln \frac{1}{r_{jk}} \quad (1)$$

and

$$\tau_{ib_k} = \frac{1}{K_{ikl}x_{ik}} \ln \frac{1}{r_{ib_k}} \quad (2)$$

and then selecting τ to be the smallest and μ to be the reaction R_{jk} or diffusion R_{ikl}^d of the smallest τ . With the direct method, a single time step τ is randomly chosen from an exponential distribution with parameter equal the sum of propensity functions, and then the reaction identity is determined using a second random number. The ISSA generates a trajectory of the corresponding reaction-diffusion master equation (RDME), which describes the time evolution of the spatially varying probability density functions of molecule populations (Baras and Mansour 1996; Isaacson and Peskin 2006).

Exact Spatial (Inhomogeneous) Stochastic Simulation Methods

Several extensions of the exact stochastic simulation algorithm for spatially inhomogeneous conditions (also known as inhomogeneous stochastic simulation algorithm or ISSA) have been used to study signaling pathways in neurons. STEPS (see entry ► “[STEPS: STochastic Engine for Pathway Simulation](#)”; Hepburn et al. 2012) extends the direct method and improves computational efficiency using a composition and rejection method (Slepoy et al. 2008) to optimize propensity value update and to determine the next reaction at each time step. STEPS also uses tetrahedral meshes instead of cuboids, which allows STEPS to simulate more realistic geometries. STEPS has been used to investigate the interaction between a positive feedback loop and glutamate receptor trafficking in cerebellar LTD in a single spine (Antunes and De Schutter 2012). More recently STEPS has been extended with a python interface to facilitate geometry specification, visualization, and analysis of simulation output (Chen and De Schutter 2014). To enhance interaction between neuron membrane potential and signaling pathways, STEPS recently added an algorithm for

calculating changes in electrical potential due to ionic currents and calculation of voltage-dependent gating variables (Hepburn et al. 2013, 2016). URDME (Drawert et al. 2012) uses the next subvolume method (Elf and Ehrenberg 2004) with unstructured tetrahedral meshes. URDME has been further developed to provide a python interface and a cloud computing interface (Drawert et al. 2016b). MOOSE is a general-purpose, compartmental-based neuron simulation tool with a Python interface that facilitates modeling of electrical potential and signaling pathways (Ray and Bhalla 2008). The reaction-diffusion systems can be solved either deterministically or using voxel-based exact stochastic simulation and can interact with the electrical potential, e.g., calcium influx is controlled by the electrical potential and initiates a cascade of reactions. A recent model of signaling pathways connects calcium influx to activation of the mitogen-activated protein kinase (MAPK) to modulation of ionic channels (Bhalla 2017). Simulations showed how the neuron could distinguish the sequences of synaptic inputs.

An important new direction in model and simulator development is including the role of crowding and volume exclusion. In most simulators, molecules are modeled as points that have no volume; thus the number of molecules in the simulated structure is limitless. Reality contrasts sharply with this assumption. Whether using population- or particle-based methods, molecules occupy a small volume of space, which decreases the “empty” space available for diffusion. Recent research has demonstrated that packing a large number of molecules into a small space can reduce diffusion rates. If the molecules crowded together have the ability to react, such crowding can enhance reaction rates, whereas if the molecules do not react, the impeded diffusion can reduce reaction rates. The most recent release of Smoldyn, a particle simulator, allows modeling of crowding caused by excluded volume (Andrews 2017), as does PyURDME (Golkaram et al. 2016), the population simulator. Research on gene expression using the latter showed that crowding reduces noise in gene expression by limiting the diffusion of transcription factors.

Additional simulators or algorithms have been developed to facilitate simulation of crowding (Schöneberg and Noé 2013; Meinecke 2017; Hoffmann et al. 2019), e.g., by taking into account both molecule radius and density to modify the diffusion propensity (Cianci et al. 2017). A recent publication investigated how synaptic domains form despite stochastic turnover and diffusion of molecules (Li et al. 2017). The stochastic algorithm implements the spatial next reaction method (Elf et al. 2003), modified to account for crowding by reducing rate constants of reaction and diffusion as receptor numbers increase. This model predicts that receptors adjacent to synaptic domains are more likely to be removed from the cell membrane than the centrally located receptors, which is consistent with experimental observation.

Another new research direction is being driven by a key outcome of signaling pathway activation, namely, producing changes in cell morphology. For example, during induction of synaptic plasticity, the size of dendritic spines may grow or shrink. During neuronal development, dendrites and axons are extended. The change in compartment size may form a feedback loop through its influence on molecule concentration. Recently, two simulators or algorithms have begun to address changes in morphology. URDME has been extended with the ability to include a moving boundary (Drawert et al. 2016c), and compartment sizes can change during MOOSE simulations, also.

Spatial stochastic simulations, even using voxel-based methods, are computationally intensive, and the simulation of large systems is slow. One solution to improve simulation speed of the ISSA is to use time-dependent propensity functions to account for the change in propensity that would be caused by continuous diffusion (Fu et al. 2014), thereby reducing the typically overwhelming number of diffusion steps. Another method is to parallelize the algorithm, which has been done with STEPS (Hepburn et al. 2016; Chen and De Schutter 2017). Some algorithms, such as Lattice Microbes (Roberts et al. 2013; Hallock et al. 2014), are written directly for parallel simulation and utilize NVIDIA graphics processing units

(GPUs). Even particle simulators are being implemented on GPUs for enhanced computational efficiency (Dematté 2012). Another approach is to provide a simulation service on a high-performance computing platform. Typically these simulation services provide integrated development environments and allow selection of the simulation algorithm from among a variety of deterministic and stochastic solvers (Drawert et al. 2016a; Blinov et al. 2017).

Approximate Spatial Stochastic Simulation Methods

A more common approach to improving computational efficiency of spatial stochastic simulation is to use approximate algorithms. For simulating well-stirred systems, a generally applicable approximate method is the nonnegative Poisson τ -leaping method (Cao et al. 2005; Yates and Burrage 2011). This method advances the state of the system by the largest value of the leap time τ while simultaneously allowing multiple reaction events to occur and satisfying the leap condition (Gillespie 2001; Gillespie and Petzold 2003), which states that no propensity function is likely to change its value by a significant amount during $[t, t + \tau)$. In τ -leaping the state vector is updated as

$$X(t + \tau) \doteq x + \sum_{j=1}^M P_j(a_j(x)\tau) v_j \quad (3)$$

where $P_j(a_j(x)\tau)$ is a statistically independent Poisson random variable. The leap condition specifies τ and bounds the relative change in each propensity function $a_j(x)$ during the leap. An additional control strategy is implemented to prevent any of the population of reactant species from becoming negative due to the unboundedness of the Poisson random numbers (Cao et al. 2005). When τ is both small enough to satisfy the leap condition and large enough such that the expected number of firings of each reaction channel R_j during τ is much greater than one, the τ -leaping strategy is equivalent to the chemical Langevin equation (Gillespie 2007).

The τ -leaping method has been extended to spatial stochastic simulations using a fixed leap

time (Blackwell 2006; Oliveira et al. 2010). At each time step, NeuroRD determines the number of reactions and diffusions from tabulated binomial distributions when the number of reactants in a subvolume is below a threshold, otherwise it uses Poisson or Gaussian distributions. It distributes diffusing molecules from a subvolume among its neighbors with multinomial probabilities. NeuroRD has been used to investigate the role of anchoring proteins in synaptic plasticity (Kim et al. 2011; Oliveira et al. 2012). It has also been used to investigate how different spatiotemporal patterns of synaptic input determine the direction of synaptic plasticity (Kim et al. 2013). Because of the computational efficiency of NeuroRD, it has been used to simulate over a hundred species and over a hundred reactions in a dendrite with multiple spines.

The problem with a fixed leap time is the possibility of producing negative populations or violating the leap condition. Thus, several spatial τ -leap algorithms dynamically select the leap time (Marquez-Lago and Burrage 2007; Rossinelli et al. 2008). However, selecting the next leap time τ requires a larger computational overhead (Cao et al. 2006; Chatterjee and Vlachos 2007) than selecting the next event time with the exact algorithm. The added computational overhead accumulates especially when the leap time τ is repeatedly rejected to prevent potential negative populations and the system must evolve following the exact algorithm, which sometimes makes a τ -leaping simulation slower than an exact simulation (Koh and Blackwell 2011).

Most variants of the nonnegative τ -leap algorithm advance every reaction and diffusion channel by the same τ , which constrains the leap time especially for stiff systems. A common solution, discussed below, is to partition the system into two or more subsystems, e.g., reaction versus diffusion and large versus small populations, and use different methods for different subsystems. However, partitioning is problematic when population size or reaction speed forms a continuum and when the transient events common in neurons require frequent repartitioning. A recent solution to this problem is asynchronous τ -leaping (Jedrzejewski-Szmek and Blackwell 2016), in

which each reaction or diffusion event is simulated either using its own leap time or using an exact simulation event depending on its propensity. This improves computational efficiency without sacrificing accuracy and avoids the need for the user to partition the system.

Despite the problems with partitioning the system, a common approach for enhancing computational efficiency is to create hybrid simulation algorithms, in which the system is partitioned into subsystems, with one system using an exact stochastic simulation and the other system using either approximate stochastic simulation or deterministic simulation. A common hybrid approach partitions the system into reaction and diffusion subsystems, in part because diffusion often limits the leap time, and then various methods are used to accelerate diffusion. The hybrid τ -leaping method (Rossinelli et al. 2008) simulates diffusion deterministically, and the time step for simulating reactions stochastically is chosen with the τ -leaping method. The multinomial simulation algorithm (Lampoudi et al. 2009) simulates diffusion by distributing diffusing molecules from a subvolume among its neighbors with multinomial probabilities until the time to the next reaction event is reached while simulating reactions with the direct method. The adaptive hybrid method (Ferm et al. 2010) simulates reactions with the next subvolume method (Elf and Ehrenberg 2004) while simulating diffusion in three different ways – exact, τ -leaping, and deterministic – depending on the number of diffusing molecules. The spatial direct method with gradient-based diffusion (Koh and Blackwell 2012) uses the direct method but approximates diffusion processes by using diffusion propensities that are based on the net movement of molecules from higher to lower concentration gradients rather than sampling all diffusion events regardless of local concentration gradients. This method also allows the user to control the degree of exactness in simulation with a control parameter. Several algorithms use variants of partial differential equations for the diffusion part. One algorithm uses the deterministic solution (partial differential equation) for diffusion where particle numbers are high, voxel-based stochastic simulation where

the numbers are low, and both methods in an intermediate or overlap region (Harrison and Yates 2016). In the overlap region, the deterministic solution is interpreted as a probability, and the boundary condition ensures that the flux is the same for the PDE and voxel-based simulation. Another algorithm (Kim et al. 2017) simulates the reaction subsystem using an adaptive leap algorithm and simulates the diffusion subsystem using a stochastic Crank-Nicolson solver, which is a type of stochastic partial differential equation. This operator splitting is not without numerical accuracy errors dependent on the time step (Hellander et al. 2014); thus using adaptive time step methods can provide gains in both accuracy and computational efficiency. Note that more recent hybrid algorithms have been developed for efficient particle simulation of diffusion (Donev et al. 2018; Smith and Yates 2018), but their discussion is beyond the scope of this article.

An alternative set of hybrid approaches ignores whether events are reaction versus diffusion and instead partitions based on propensity of the reaction. For example, one algorithm partitions the system into fast and slow subsets and then uses the next subvolume method for slow events and spatial tau leaping for fast events (Strehl and Ilie 2015). The spatial partitioned leaping algorithm (Iyengar et al. 2010) calculates the next leap time τ with the nonnegative Poisson τ -leaping method. It then classifies each reaction and diffusion in the system into one of the four categories – exact-stochastic, Poisson, Langevin, and deterministic – and advances the system based on τ and the category. In all of the above cases, partitioning is done manually, which requires expert knowledge about the system to be partitioned. A solution to this problem (Hellander et al. 2017) not only automates the partitioning but allows for dynamic partitioning. In contrast to most hybrid methods, the two subsystems are simulated using either a particle algorithm or a new voxel-based method called the next particle method.

Even with the speedups obtained from approximate methods, stochastic simulation is still computationally intensive; thus these methods also are being accelerated using parallel

simulation methods. A hybrid method known as the Gillespie multiparticle method has been parallelized for GPUs (Vigelius et al. 2011), with $\sim 10\times$ increase in speed over the non-parallelized version, which itself is faster than the exact methods such as the next subvolume method. A spatial tau-leaping algorithm has been parallelized by implementing each subvolume on a different processor (D'Agostino et al. 2014). This algorithm has the further advantage of implementing a form of crowding, by modifying propensity functions according to particle density.

Advantages and Challenges

The increase in computational power has spurred an increase in development of spatial stochastic simulators and the use of spatial stochastic simulation to make experimental predictions. Population-based spatial stochastic simulators are especially advantageous in allowing quantitative investigation at a mesoscopic detail, corresponding to experiments that measure molecule concentration in dendritic spines (e.g., Hedrick et al. 2016). On the other hand, particle simulations are critical for quantitative investigation at the microscopic detail corresponding to super-resolution microscopy experiments providing dynamic information on single particle location (e.g., MacGillavry and Blanpied 2013). The mesoscopic approximation by subdividing the system volume into subvolumes has the advantage of computational efficiency, but can also be a limitation in terms of accuracy or the ability to use rule-based approaches (see Blinov et al. 2017).

The subdivision of the system volume into subvolumes for mesoscopic simulation can be problematic. The approach of reducing subvolume size until they are small enough to satisfy the assumption of well-stirred is not possible, because if the subvolume size approaches the size of molecules, then reaction propensities are inaccurate (Hellander et al. 2012). At the same time, if the subvolume sizes are too large, they violate the well-stirred requirement and may not accurately capture concentration gradients observed, e.g., within single spines. Thus, when

the subvolume sizes are either too small or too large, simulations are inaccurate (Erban and Chapman 2009; Isaacson 2009; Hellander et al. 2017). For the well-stirred assumption to be physically valid, the width of the subvolume must satisfy $\tau_R \gg \tau_D$, where τ_R and τ_D denote the typical time interval between reaction events and the typical time interval between diffusion events, respectively, and also that the width must be less than the reactant correlation length, which is difficult to predict (Isaacson 2009).

Along with the increase in computational power, which should permit ever more accurate simulations, biological complexity appears to be increasing, requiring increasing details regarding molecule interactions. Thus, simulators that allow rule-based modeling or account for molecule crowding are increasing. For a systematic investigation of cellular processes spanning different spatial and temporal scales at various levels of detail, a remaining challenge is for a simulator to seamlessly and accurately transition among microscopic, mesoscopic, and macroscopic levels of detail, as some recent simulators have introduced (Smith and Yates 2018). Meanwhile, population-based spatial stochastic simulators provide a good balance between sufficient stochastic and spatial details in simulation output and practical simulation speed.

Cross-References

- Gillespie Algorithm for Biochemical Reaction Simulation
- MCell
- Particle-Based Stochastic Simulators
- STEPS: STochastic Engine for Pathway Simulation

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Structure-Aided Drug Design

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Subthalamopallidal Loop and Oscillations

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Definition

The subthalamopallidal loop consists of reciprocally connected glutamatergic neurons of the subthalamic nucleus (STN) and GABAergic neurons of the external globus pallidus (GPe). The STN and GPe are both nuclei within the basal ganglia (BG). Oscillations correspond to regularly recurring spiking activity of a neuronal system.

Detailed Description

Activity Patterns in the Subthalamopallidal Network

During quiet wakefulness, GPe neurons maintain mean firing rates in excess of 40 Hz, while STN neurons average about 20 Hz (Wilson 2010). The neurons fire without rhythm, and there is rarely synchrony between the spontaneous discharges of different neurons in the BG of neurologically normal subjects (Rubin et al. 2012). During voluntary or passive movement, STN and GPe neurons display intricate spatiotemporal changes in activity, which relate in a complex manner to motor activity. During movement, activity is rarely correlated but it is highly structured, so that there is precise somatotopic specificity (Bevan et al. 2002).

In Parkinson's disease, rhythmic bursting activity at 4–10 Hz and 15–30 Hz is observed in the STN, GPe, and other parts of the basal ganglia (Bevan et al. 2002). This activity is often correlated within and between nuclei: Neurons that are close to each other within areas located

throughout the BG and the BG-receiving areas of the thalamus and the cortex tend to fire in synchrony (Rubin et al. 2012).

Microcircuitry of the Subthalamopallidal Network

The subthalamopallidal loop forms an excitatory–inhibitory network: GPe neurons make inhibitory connections onto the STN and STN neurons make excitatory connections onto the GPe. Neurons within the GPe also make inhibitory connections with other GPe neurons and with the output neurons of the basal ganglia. The output nuclei of the basal ganglia consist of the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). Most inputs to the GPe arise from the striatum and are GABAergic. The GPe also receives excitatory inputs from the cerebral cortex and the intralaminar nuclei of the thalamus (Wilson 2010).

STN neurons also make excitatory connections with the output neurons. In addition to inhibitory input from GPe, the STN receives excitatory input from the frontal cortex, from the intralaminar thalamic nuclei, and from the pedunculopontine nucleus (Wilson 2010).

The STN and GPe are made up of repeating neuronal architectures so that functionally related regions of the STN and GPe are reciprocally connected and innervate functionally related regions of the basal ganglia output nuclei. Furthermore, the majority of STN and GPe neurons in rats and monkeys have branched axons that mediate both the reciprocal connections and the innervation of the basal ganglia output nuclei (Bevan et al. 2002).

The principal source of afferent input to the basal ganglia, the cerebral cortex, influences the STN–GPe network, directly via monosynaptic projections or indirectly via GABAergic striatal or glutamatergic thalamic neurons. Neuronal projections from the striatum to the output nuclei through the STN–GPe network are often referred to collectively as the *indirect pathway*. By virtue of their extensive innervation of the GABAergic neurons of the basal ganglia output nuclei, the STN and GPe are in a position to influence powerfully the communication of the basal ganglia with the rest of the brain (Bevan et al. 2002).

Origins of Rhythmic Activity in the STN–GPe Network

There has been considerable debate on the origins of correlated, rhythmic firing in the STN–GPe network. This activity could be an emergent property of the STN–GPe network itself and/or be driven by rhythmic activity outside the STN–GPe network.

Computational Modeling of STN–GPe Network Activity

Computational modeling studies incorporating the known biophysical properties of STN and GPe neurons, using a range of network architectures within the limits of the known anatomy, have been useful in examining the principles that underlie activity patterns in the STN–GPe network. Computer simulations in (Terman et al. 2002), for example, suggest that the STN–GPe network is capable of generating patterned and persistent activity of a variety of types; these include uncorrelated spiking activity, as arises during normal resting conditions, and synchronous bursting activity associated with pathological, Parkinsonian conditions. Rhythmic activity arises in the model through mutually coupled, excitatory–inhibitory interactions between the STN and GPe neurons: Synchronous bursting of GPe neurons generates sufficient hyperpolarization in STN neurons for rebound burst activity, which, in turn, drives bursting activity in GPe neurons and leads to continuation of the rhythm.

Recent studies have examined the role of structures, such as the striatum and cortex, outside the STN–GPe network in generating beta band and other oscillations (Bevan et al. 2002; Rubin et al. 2012). Moreover, the STN–GPe network model has been extended to include other neurons including those within the GPi, the thalamus, and the cortex. These studies have led to new hypotheses concerning mechanisms underlying the therapeutic effects of deep brain stimulation (Guo et al. 2008; Hahn and McIntyre 2010).

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Subthreshold Antiphase: Membrane Potential Antiphase

► [Subthreshold Antiresonance and Antiphase in Single Neurons: 3D Models](#)

Subthreshold Antiresonance and Antiphase in Single Neurons: 3D Models

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Synonyms

Subthreshold antiphase: Membrane potential antiphase; Subthreshold antiresonance: Membrane potential (amplitude) antiresonance; Subthreshold or membrane potential antiphase resonance

Definitions

Subthreshold (or membrane potential) antiresonance refers to the ability of neurons to exhibit a minimum in their voltage amplitude response to oscillatory input currents at a nonzero input (antiresonant) frequency.

Subthreshold (or membrane potential) antiphasonance refers to the ability of neurons to exhibit a zero-phase (or zero-phase-shift) response to oscillatory inputs currents at a non-zero (antiphasonant) frequency separating between delayed and advance responses for frequencies smaller and larger than the antiphasonant frequency, respectively.

Linear subthreshold antiresonance and antiphasonance refers to the occurrence of these phenomena in linear systems.

In this article, we focus on the description of antiresonance and antiphasonance in 3D linearized conductance-based models. Antiresonance and antiphasonance occur in 3D linear systems, but not in 2D ones. 3D linear systems may also exhibit resonance/phasonance without antiresonance/antiphasonance. We refer the reader to the companion article (Rotstein, chapter ► “[Subthreshold Resonance and Phasonance in Single Neurons: 2D Models](#)”) for further details and discussion on resonance and phasonance in 2D systems.

Detailed Description

Introduction

Subthreshold antiresonance has been observed in hippocampal CA1 pyramidal cells (Pike et al. 2000) and other cell types (Fox et al. 2016), and it has been studied theoretically by Richardson et al. (2003) and Rotstein (2017a). To our knowledge, subthreshold antiphasonance has not been experimentally reported in neuronal systems. However, the theoretical studies discussed here and in the references above suggest it should be present in some neurons exhibiting antiresonance.

Conductance-Based Models

In this article, we discuss the subthreshold resonant properties of neurons in the context of biophysical

(conductance-based) models (Skinner 2006; Hodgkin and Huxley 1952) whose subthreshold dynamics are governed by the following equations

$$C \frac{dV}{dt} = -I_L - \sum_{j=1}^3 I_j + I_{app} + I_{in}(t), \quad (1)$$

$$\frac{dx_j}{dt} = \frac{x_{j,\infty}(V) - x_j}{\tau_{j,x}(V)}, \quad j = 1, 2. \quad (2)$$

In the current-balance Eq. 1, V is the membrane potential (mV), t is time (msec), C is the membrane capacitance ($\mu\text{F}/\text{cm}^2$), I_{app} is the applied bias (DC) current ($\mu\text{A}/\text{cm}^2$), $I_L = G_L(V - E_L)$ is the leak current, and $I_j = G_j x_j(V - E_j)$ are generic expressions for ionic currents (with j an index) with maximal conductance G_j (mS/cm^2) and reversal potentials E_j (mV), respectively. The dynamics of the gating variables x_j are governed by the kinetic equations (2) where $x_{j,\infty}(V)$ and $\tau_{j,x}(V)$ are the voltage-dependent activation/inactivation curves and time constants, respectively. The generic ionic currents I_j we consider here are restricted to have a single gating variable x_j and to be linear in x_j . The persistent sodium, h-(hyperpolarization-activated, mixed-cation, inward), and slow-potassium (M-type) currents found to be responsible for the generation of subthreshold resonance in neurons of the hippocampus and the entorhinal cortex have this form (Schreiber et al. 2004; Hu et al. 2002, 2009; Pike et al. 2000; Rotstein et al. 2006; Izhikevich 2006). We focus on three-dimensional models describing the dynamics of V and two gating variables (x_1 and x_2). Additional currents whose gating variables evolve on a fast time, almost instantaneous timescale can be included by using the adiabatic approximation $x_j = x_{j,\infty}(V)$. Here we include one such fast current ($I_3 = G_3 x_{3,\infty}(V) (V - E_3)$). Additional fast currents can be included without significantly changing the formalism used here.

The function $I_{in}(t)$ in Eq. 1 is an oscillatory input current ($\mu\text{A}/\text{cm}^2$) of the form

$$I_{in}(t) = A_{in} \sin(\Omega t) \quad \text{with} \quad \Omega = \frac{2\pi f}{1000}, \quad (3)$$

where f is the input frequency (Hz).

Our discussion of subthreshold resonance can be easily adapted to ionic currents having two gating variables raised to powers not necessarily equal to one such as calcium currents (Hutcheon and Yarom 2000).

Linearized Conductance-Based Models

Linearization of the autonomous part ($I_{in}(t) = 0$) of system (1)–(2) around the fixed-point $(\bar{V}, \bar{x}_1, \bar{x}_2)$ yields (Richardson et al. 2003)

$$C \frac{dv}{dt} = -g_L v - g_1 w_1 - g_2 w_2 + I_{in}(t), \quad (4)$$

$$\tau_1 \frac{dw_1}{dt} = v - w_1, \quad (5)$$

$$\tau_2 \frac{dw_2}{dt} = v - w_2, \quad (6)$$

where

$$v = V - \bar{V}, \quad (7)$$

$$w_1 = \frac{x_1 - \bar{x}_1}{x'_{1,\infty}(\bar{V})}, \quad w_2 = \frac{x_2 - \bar{x}_2}{x'_{2,\infty}(\bar{V})},$$

$$\bar{x}_j = x_{j,\infty}(\bar{V}), \quad \tau_j = \tau_{x,j}(\bar{V}) \quad j = 1, 2, \quad (8)$$

$$g_j = G_j x'_{k,\infty}(\bar{V}) (\bar{V} - E_j), \quad j = 1, 2, 3, \quad (9)$$

and

$$g_L = G_L + G_1 x_{1,\infty}(\bar{V}) + G_2 x_{2,\infty}(\bar{V}) + G_3 x_{3,\infty}(\bar{V}) + g_3. \quad (10)$$

In Eqs. 7 and 9 $x'_{j,\infty} = dx_{j,\infty}/dV$ ($j = 1, 2, 3$). Note that the gating variables w_1 and w_2 in Eq. 7 have units of voltage ($[v] = [w_1] = [w_2] = \text{mV}$).

The signs of the effective ionic conductances g_j determine whether the associated gating variables are either resonant ($g_j > 0$) or amplifying ($g_j < 0$) (Richardson et al. 2003; Hutcheon and Yarom 2000). The effective leak conductance g_L Eq. 10 contains information about the biophysical leak conductance G_L , the ionic conductances, and their associated voltage-dependent

activation/inactivation curves. The fast ionic current I_3 contributes to g_L with an additional term (g_3). All terms in g_L are positive except for the last one that can be either positive or negative. Specifically, g_L can become negative for negative enough values of g_3 .

System (4)–(6) can be rescaled by defining the following dimensionless time and parameters

$$\hat{t} = \frac{t}{\tau_1}, \quad \gamma_L = \frac{g_L \tau_1}{C}, \quad \gamma_1 = \frac{g_1 \tau_1}{C}, \quad (11)$$

$$\gamma_2 = \frac{g_2 \tau_1}{C}, \quad \eta = \frac{\tau_1}{\tau_2}.$$

Substitution of Eq. 11 into Eqs. 4–6 and a further rearrangement of terms yields

$$\frac{dv}{d\hat{t}} = -\gamma_L v - \gamma_1 w_1 - \gamma_2 w_2 + \hat{I}_{in}(t), \quad (12)$$

$$\frac{dw_1}{d\hat{t}} = v - w_1, \quad (13)$$

$$\frac{dw_2}{d\hat{t}} = \eta[v - w_2]. \quad (14)$$

where γ_L , γ_1 and γ_2 are the dimensionless effective conductances and

$$\hat{I}_{in}(t) = \hat{A}_{in} \sin(2\pi f \tau_1 \hat{t}/1000) \text{ with } \hat{A}_{in} = \frac{A_{in} \tau_1}{C}. \quad (15)$$

Voltage Response: Impedance Amplitude and Phase

The voltage response of a neuron receiving an oscillatory input current is typically measured in terms of the so-called impedance function $\mathbf{Z}(f)$. $\mathbf{Z}(f)$ is a complex quantity with amplitude $|\mathbf{Z}(f)|$ and phase $\Phi(f)$. For simplicity, we refer to $|\mathbf{Z}(f)|$ simply as the impedance $Z(f)$.

For a linear system receiving a sinusoidal input current $I_{in}(t)$ of the form (3), the voltage response is given by

$$V_{out}(t, f) = A_{out}(f) \sin(\Omega t - \Phi(f)) \quad (16)$$

where $A_{out}(f)$ is the amplitude and $\Phi(f)$ is the difference between the peaks of $I_{in}(t)$ and $V_{out}(t; f)$. The impedance amplitude is given by

$$Z(f) = \frac{A_{out}(f)}{A_{in}}. \quad (17)$$

We refer the reader to the companion article (Rotstein, chapter ► [“Subthreshold Resonance and Phasance in Single Neurons: 2D Models”](#)) for additional details.

Impedance and Phase Profiles for Linear Systems

Impedance and phase profiles refer to the curves of the impedance and phase, respectively, as a function of the input frequency. For linear systems, the impedance and phase can be computed analytically (Rotstein 2017a) (see also textbooks such as (Boyce and DiPrima 2009) for additional techniques to solve ordinary differential equations).

We use here the following generic forced system

$$\begin{cases} X' = aX + bY + cZ + A_{in} e^{i\Omega t}, \\ Y' = \alpha X + pY, \\ Z' = \beta X + qZ, \end{cases}. \quad (18)$$

for constant $a, b, c, \alpha, \beta, p$ and q .

The characteristic polynomial for the corresponding homogeneous system ($A_{in} = 0$) is given by

$$\begin{aligned} & r^3 - (a + p + q) r^2 \\ & + (ap + aq + pq - c\beta - b\alpha)r + b\alpha q \\ & + c\beta p - apq = 0. \end{aligned} \quad (19)$$

The occurrence and properties of intrinsic subthreshold oscillations in 3D linear and linearized conductance-based models has been investigated by Rotstein (2017b).

Analytic Expressions

The particular solution to system (18) has the form

$$\begin{aligned} X_p(t) &= A_{out} e^{i\Omega t}, \\ Y_p(t) &= B_{out} e^{i\Omega t} \\ \text{and} \\ Z_p(t) &= C_{out} e^{i\Omega t}, \end{aligned} \quad (20)$$

Substituting Eq. 20 into system (18), rearranging terms, and solving the resulting algebraic system one obtains

$$\mathbf{Z}(\Omega) = \frac{A_{out}}{A_{in}} = \frac{P_r(\Omega) + iP_i(\Omega)}{Q_r(\Omega) + iQ_i(\Omega)} \quad (21)$$

where

$$P_r(\Omega) = pq - \Omega^2, \quad (22)$$

$$P_i(\Omega) = -(p + q)\Omega, \quad (23)$$

$$\begin{aligned} Q_r(\Omega) &= (a + p + q)\Omega^2 - apq + b\alpha q \\ &+ c\beta p, \end{aligned} \quad (24)$$

and

$$Q_i(\Omega) = (ap + aq + pq - b\alpha - c\beta - \Omega^2)\Omega. \quad (25)$$

From Eq. 21

$$Z(\Omega) := \frac{A_{out}}{A_{in}} = \sqrt{\frac{P_r^2(\Omega) + P_i^2(\Omega)}{Q_r^2(\Omega) + Q_i^2(\Omega)}} \quad (26)$$

and

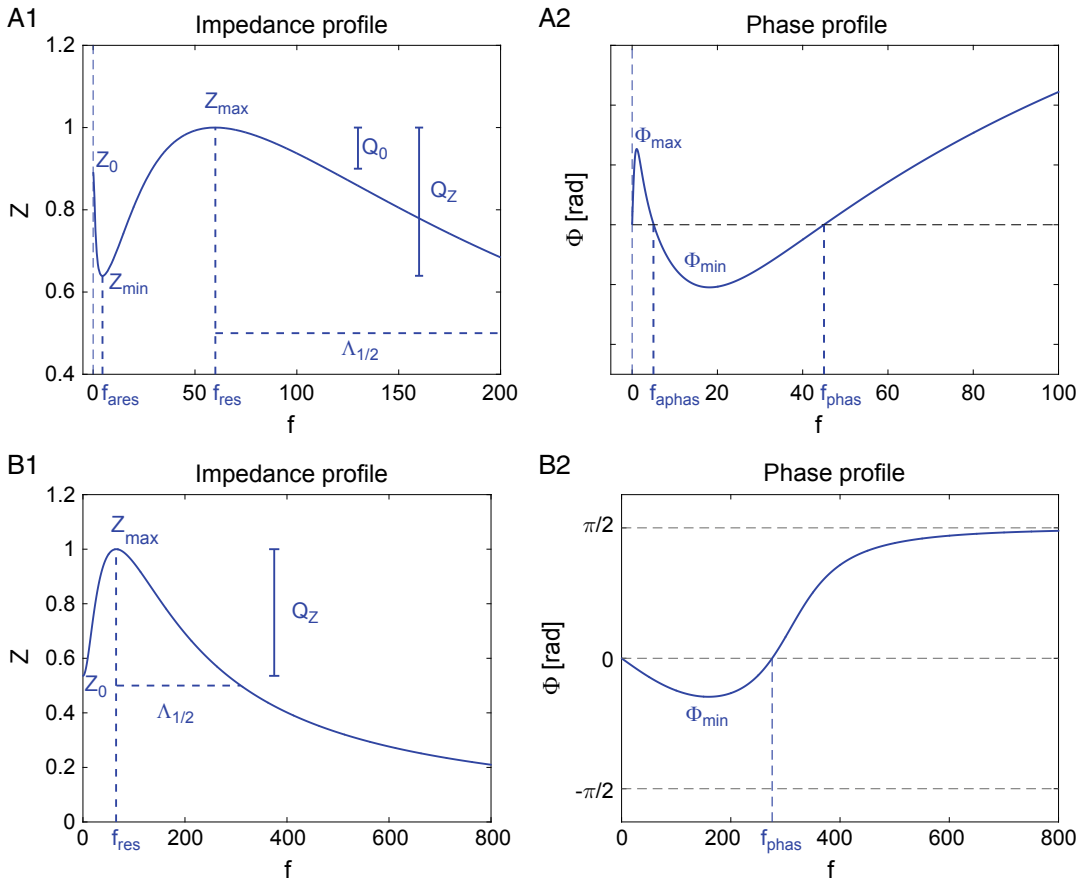
$$\Phi = \tan^{-1} \frac{P_r(\Omega)Q_i(\Omega) - P_i(\Omega)Q_r(\Omega)}{P_r(\Omega)Q_r(\Omega) + P_i(\Omega)Q_i(\Omega)}. \quad (27)$$

For a 2D linear system ($c = q = 0$), the characteristic polynomial for the corresponding homogeneous system ($A_{in} = 0$) and the impedance and phase profiles reduce to those presented in the companion article (Rotstein, chapter ► [“Subthreshold Resonance and Phasance in Single Neurons: 2D Models”](#)) with c and d substituted by α and p .

Antiresonance and Antiphase

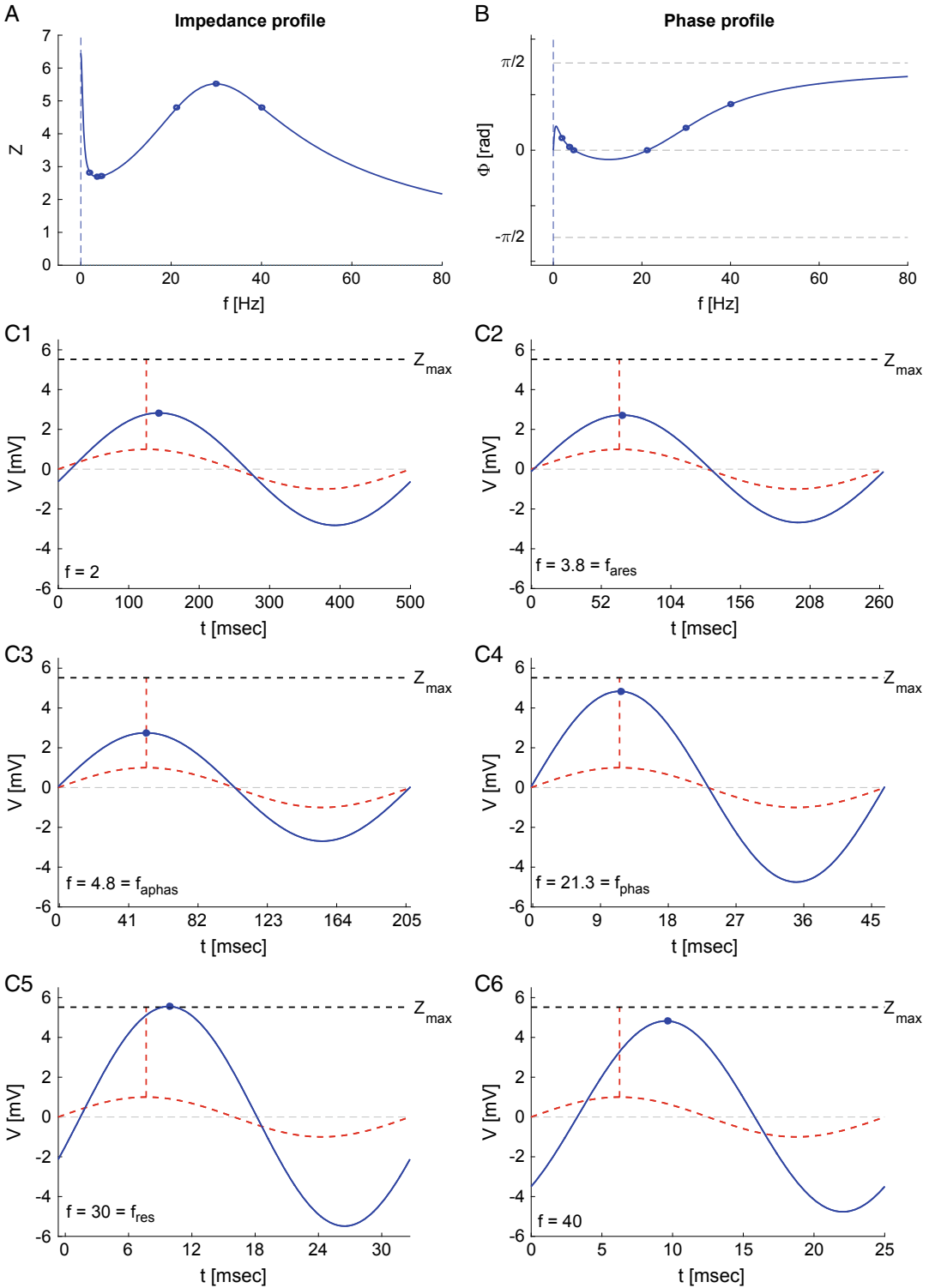
In certain parameter regimes (discussed later in this article), the voltage response for 3D linear systems is more complex than for 2D linear ones (Richardson et al. 2003; Pike et al. 2000; Rotstein 2017a) (see also the companion article (Rotstein, chapter ► “Subthreshold Resonance and Phasance in Single Neurons: 2D Models”). In addition to resonance (impedance profile peak Z_{max} at $f = f_{res}$, Fig. 2-C5) and phasance (zero-phase response with positive

slope at $f = f_{phas}$, Fig. 2-C4), 3D linear models can exhibit antiresonance and antiphase when the impedance profile exhibits a trough Z_{min} at an (antiresonant) input frequency $f = f_{ares}$ (Figs. 1-A1 and 2-C2) and the phase profile has an additional zero-frequency cross at $f = f_{aphas}$ (Figs. 1-A2 and 2-C3) in addition to the one at $f = f_{phas}$. Note that the slope of Φ at f_{aphas} is negative (opposite to the slope of Φ at f_{phas}). For $f = f_{aphas}$ and $f = f_{phas}$, the input current and output voltage peak at the same time (Fig. 2-C3



Subthreshold Antiresonance and Antiphase in Single Neurons: 3D Models, Fig. 1 Schematic diagrams of the impedance (left) and phase (right) profiles for a 3D system (A) and a 2D system (B). The impedance (Z) and phase (Φ) profiles are the curves of Z and Φ as a function of the input frequency f . **A.** The 3D system exhibits antiresonance (A1) and antiphase (A2) in addition to resonance (A1) and phasance (A2). The impedance profile Z is characterized by seven attributes: the resonant frequency f_{res} , the antiresonant frequency f_{ares} ,

the impedance peak Z_{max} , the impedance local minimum Z_{min} , the resonance amplitude $Q_Z = Z_{max} - Z_{min}$, and $Q_0 = Z_{max} = Z_0$ and the half-bandwidth $\Lambda_{1/2}$. The phase profile Φ is characterized by two attributes: the phasant frequency f_{phas} , the antiphase frequency f_{aphas} , the phase minimum Φ_{min} , the phase maximum Φ_{max} . **B.** For a system exhibiting resonance without antiresonance (B1), $Z_{min} = Z_0$ and therefore $Q_Z = Q_0$. For a system exhibiting phasance without antiphase (B2), $\Phi_{max} = 0$



Subthreshold Antiresonance and Antiphase in Single Neurons: 3D Models, Fig. 2 (continued)

and -C4). The voltage response is delayed for $f < f_{phas}$ (Fig. 2-C1) and $f > f_{phas}$ (Fig. 2-C5 and -C6) and advanced for f satisfying $f_{phas} < f < f_{aphas}$ (not shown).

Attributes of the Impedance and Phase Profiles

As for the 2D systems discussed in Rotstein (chapter ▶ “Subthreshold Resonance and Phasonance in Single Neurons: 2D Models”), the tracking of the changes in the impedance and phase profiles as the model parameters change is simplified by using a small number of attributes that capture the salient properties of these curves. For systems exhibiting resonance and antiresonance (Fig. 1-A1), the impedance profile Z is characterized by seven attributes: the resonant frequency f_{res} , the antiresonant frequency f_{ares} , the impedance peak Z_{max} , the impedance local minimum Z_{min} , the resonance amplitude $Q_Z = Z_{max} - Z_{min}$, and $Q_0 = Z_{max} - Z_0$ and the half-bandwidth $\Lambda_{1/2}$. For a system exhibiting resonance without antiresonance (Fig. 1-B1), $Z_{min} = Z_0$ and therefore $Q_Z = Q_0$. For systems exhibiting phasonance and antiphasonance (Fig. 1-A2), the phase profile Φ is characterized by two attributes: the phasant frequency f_{phas} , the antiphasant frequency f_{aphas} , the phase minimum Φ_{min} , the phase maximum ϕ_{max} . For a system exhibiting phasonance without antiphasonance (Fig. 1-B2) $\Phi_{max} = 0$.

Mechanisms of Generation of Antiresonance and Antiphasonance

Antiresonance and antiphasonance emerge as the result of the interplay of a slow resonant gating variable ($g_1 > 0$) and a slower amplifying gating variable ($g_2 < 0$) in systems that exhibit resonance

for $g_2 = 0$. Alternatively, the generation of antiresonance requires $\gamma_2 < 0$ and $\eta < 1$ in the rescaled system (12)–(14). This is illustrated in Fig. 3 for a baseline system ($g_2 = 0$) that exhibits both resonance and phasonance (blue curves in all panels). Each panel shows the effects of decreasing values of $g_2 < 0$ for various representative values of τ_2 that is above (panels A and B), equal to (panel C) and below (panel D) the value of τ_1 .

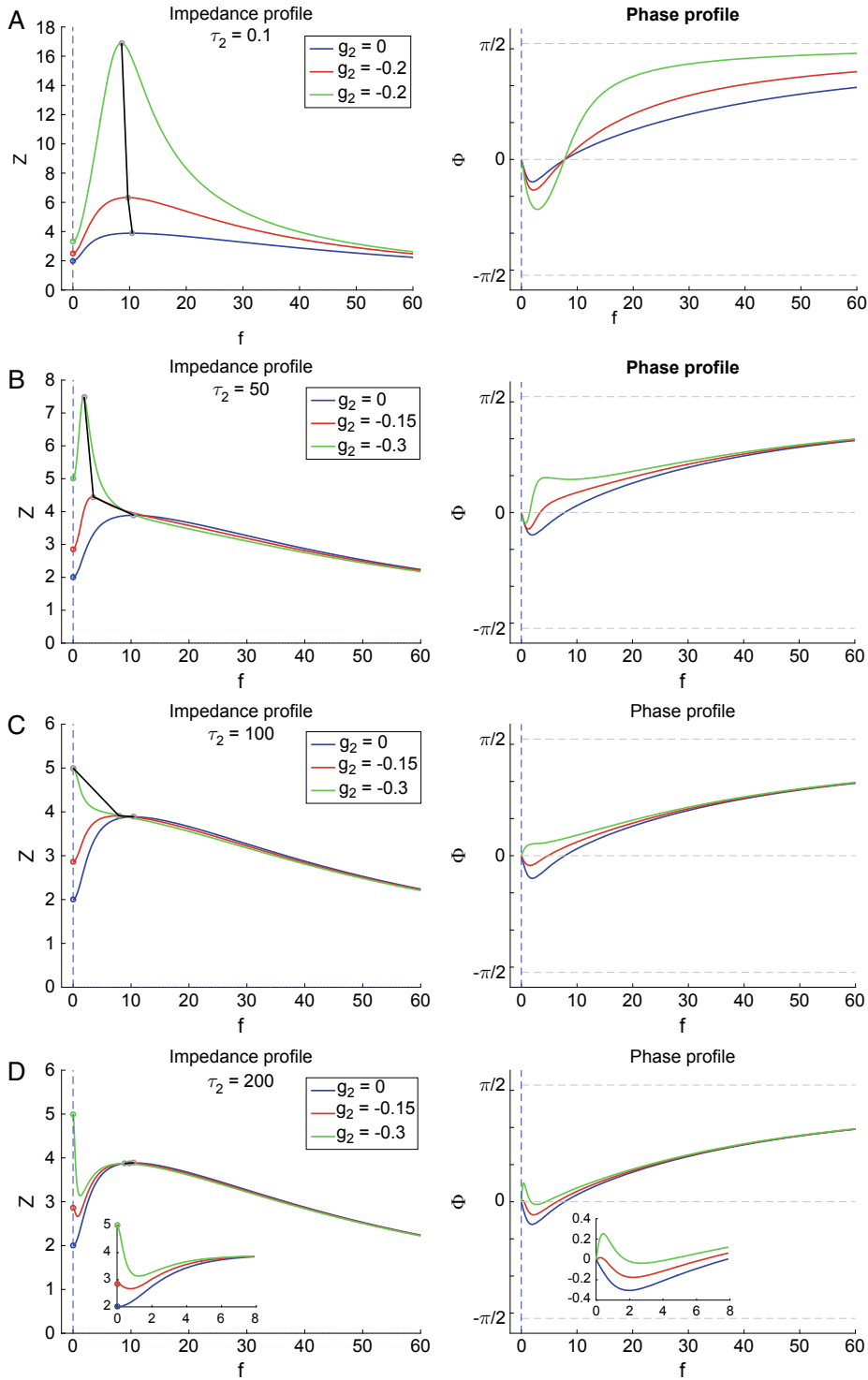
For $\tau_2 = 0.1$ (Fig. 3-A) decreasing values of g_2 cause a strong amplification of the voltage response and a slight decrease in f_{res} and f_{phas} as expected from the effects of amplifying linearized conductances in quasi-2D systems. For larger values of τ_2 , but still $\tau_2 < \tau_1$, the amplification of the voltage response persists, but is less pronounced as τ_2 increases (Fig. 3-B). The changes in f_{res} and f_{phas} are more pronounced as τ_2 increases.

Figure 3-C illustrates the annihilation of resonance and phasonance for $\tau_2 = \tau_1$. In these cases, the 3D system is quasi-2D since after the transients have disappeared $w_2 = w_1$. The opposite signs of the two linearized conductances can cause the system to exhibit resonance or not depending on the net sign of the sum of the two conductances.

Antiresonance and antiphasonance emerge when τ_2 increases above τ_1 (Fig. 3-D). This can be better understood by looking at system (12)–(14) for the limiting case $n \rightarrow 0$. A rescaling of time $f t \rightarrow t$ moves the input frequency f from the sinusoidal input to the denominator of the right hand-side of the three equations. If $f > \eta$ ($n/f \rightarrow 0$), w_2 has no dynamics. The 3D systems behave as the 2D system for $g_2 = 0$ with a resistance given by $Z(0) = (g_L + g_1)^{-1}$. As f decreases with $n < f < f_{res}$, the impedance profile decreases to this value. This 2D reduction is no longer valid when $f < \eta$. Therefore, $Z(0) = (g_L + g_1 + g_2)^{-1}$. As

Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models, Fig. 2 Resonance and phasonance for the linear system (4)–(6) for representative parameter values. **A.** Impedance profile. **B.** Phase profile. **C.** Voltage responses (solid-blue) to sinusoidal input currents I_{in} (dashed-red) for representative input frequencies f (black dots in the impedance and phase profiles). Only one period is shown for each value of f . The input is superimposed to the graph for clarity. The vertical dashed-

red lines indicate the input peak. The horizontal dashed-black lines correspond to Z_{max} (in the impedance profile), which is reached by the voltage response only when $f = f_{res}$. The blue dots indicate the peak of the voltage response. **C1.** Phase delay. **C2.** Antiresonance and phase delay. **C3.** Antiphasonance. **C4.** Phasonance. **C5.** Resonance and phase delay. **C6.** Phase delay. We used the following parameter values: $C = 1$, $g_L = 0.1$, $g_1 = 0.305$, $g_2 = -0.25$, $\tau_1 = 10$, $\tau_2 = 150$ and $A_{in} = 1$



Subthreshold Antiresonance and Antiphase in Single Neurons: 3D Models, Fig. 3 Impedance and phase profiles for system (4)–(6) with $g_2 < 0$ (interaction between a negative and a positive feedback effects) for

representative sets of parameter values. The gray lines in the left panels connect the peaks of the impedance profiles. We used the following parameter values $C = 1$, $g_L = 0.25$, $g_1 = 0.25$, $\tau_1 = 100$, and $A_{in} = 1$

$f \rightarrow 0$, the dynamics is quasi-1D and the impedance increases to this value $Z(0)$ (a decreasing function of g_2). The generation of antiresonance is the only way in which the impedance can satisfy these two opposite behaviors as f changes without losing continuity. Under certain conditions, it occurs in an asymptotic boundary layer in the frequency domain (Rotstein 2017a).

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Subthreshold Antiresonance: Membrane Potential (Amplitude) Antiresonance

► [Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models](#)

Subthreshold or Membrane Potential Antiphase Resonance

► [Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models](#)

Subthreshold Resonance and Phasonance in Single Neurons: 2D Models

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Synonyms

Subthreshold resonance: Membrane potential (amplitude) resonance

Subthreshold phasance: Membrane potential phasance, subthreshold or membrane potential phase resonance

Definitions

Subthreshold (or membrane potential) resonance refers to the ability of neurons to exhibit a peak in their voltage amplitude response to oscillatory input currents at a preferred (resonant) frequency.

Subthreshold (or membrane potential) phasance refers to the ability of neurons to exhibit a zero-phase (or zero-phase-shift) response to oscillatory inputs currents at a nonzero (phasant) frequency separating between advanced and delayed responses for frequencies smaller and larger than the phasant frequency, respectively.

Linear subthreshold resonance and phasance refers to the occurrence of these phenomena in linear systems.

Nonlinear subthreshold resonance and phasance refers to the occurrence of these phenomena in nonlinear systems where at least one of the linearity principles is not satisfied.

In this article we focus on 2D linearized conductance-based models and 2D conductance-based models with parabolic- and cubic-like nonlinearities in the voltage equation for which (i) the input and output frequencies coincide and (ii) the amplitude of the steady state voltage response is uniform across cycles for each input frequency. In the companion article (Rotstein 2017a) we discuss the related phenomena of antiresonance and anti-phasance in 3D linear models, which cannot be exhibited by the 2D models discussed here.

Detailed Description

Introduction

Subthreshold resonance has been observed in various neuron types in the hippocampus and the entorhinal cortex (Hutcheon and Yarom 2000; Pike et al. 2000; Schreiber et al. 2004; Zemankovics et al. 2010; Hu et al. 2002, 2009; Leung and Yu 1998; Erchova et al. 2004; Heyes et al. 2010; Engel et al. 2008; Wang et al. 2006) as

well as in other neural systems (Hutcheon et al. 1996a, 1994; Art et al. 1986; Tohidi and Nadim 2009; Tseng and Nadim 2010; Castro-Alamancos et al. 2007; Wu et al. 2001; Gastrein et al. 2011; Sciamanna and Wilson 2011; Mikiel-Hunter et al. 2016; D'angelo et al. 2001; Ulrich 2002). The functionality of the resonant properties of neurons has not been established yet. However, resonance in single cells (e.g., hippocampal principal cells, medial entorhinal cortex layer II stellate cells, and hippocampal interneurons) has been implicated in the generation of rhythmic activity in the networks in which they are embedded in frequency bands that coincide with the resonant frequency of these neurons (Tikidji-Hamburyan et al. 2015; Tchumatchenko and Clopath 2014; Moca et al. 2014) (but see (Stark et al. 2013)).

Theoretical studies on neuronal resonance have been performed using linear models (either caricature models or linearization of conductance-based models), which are analytically solvable, or nonlinear conductance-based models, by using direct simulations or dynamical systems tools (Richardson et al. 2003; Gutfreund et al. 1995; Schreiber et al. 2004; Haas and White 2002; Alexander et al. 1990; Izhikevich 2001, 2002; Hutcheon et al. 1994, 1996b; Reinker et al. 2004; Rotstein and Nadim 2014; Rotstein 2014, 2015, 2017b).

Conductance-Based Models

We discuss the subthreshold resonant properties of neurons in the context of biophysical (conductance-based) models (Skinner 2006; Hodgkin and Huxley 1952) whose subthreshold dynamics are governed by the following equations

$$C \frac{dV}{dt} = -I_L - I_1 - I_2 + I_{app} + I_{in}(t), \quad (1)$$

$$\frac{dx_1}{dt} = \frac{x_{1,\infty}(V) - x_1}{\tau_{1,x}(V)}, \quad (2)$$

In the current-balance equation (1), V is the membrane potential (mV), t is time (msec), C is the membrane capacitance ($\mu\text{F}/\text{cm}^2$), I_{app} is the applied bias (DC) current ($\mu\text{A}/\text{cm}^2$), $I_L = G_L (V - E_L)$ is the

leak current, and $I_j = G_j x_j (V - E_j)$ are generic expressions for ionic currents ($j = 1, 2$) with maximal conductance G_j (mS/cm²) and reversal potentials E_j (mV), respectively. The dynamics of the gating variables x_j are governed by the kinetic equations (2) where $x_{j,\infty}(V)$ and $\tau_{j,\infty}(V)$ are the voltage-dependent activation/inactivation curves and time constants, respectively.

The generic ionic currents I_j we consider here are restricted to have a single gating variable x_j and to be linear in x_j . Various currents that have been found to be involved in the generation of subthreshold resonance in neurons of the hippocampus and the entorhinal cortex have this form (Schreiber et al. 2004; Hu et al. 2002, 2009; Pike et al. 2000; Rotstein et al. 2006; Izhikevich 2006). Examples include the persistent sodium (I_{Nap}), hyperpolarization-activated, mixed-cation, inward or h- (I_h), slow-potassium, M-type (I_{Ks}), and inward-rectifying potassium (I_{Kir}) currents.

We focus on two-dimensional models describing the dynamics of V and a gating variable (x_1). Additional currents whose gating variables evolve on a very fast, almost instantaneous time scale can be included by using the adiabatic approximation. Here we include one such fast current: $I_2 = G_2 x_{2,\infty}(V) (V - E_2)$ where $x_2 = x_{2,\infty}(V)$. Additional fast currents can be included without significantly changing the formalism used here.

The function $I_{in}(t)$ in Eq. 1 is an oscillatory input current ($\mu\text{A}/\text{cm}^2$) of the form

$$I_{in}(t) = A_{in} \sin(\Omega t) \text{ with } \Omega = \frac{2\pi f}{1000}, \quad (3)$$

where f is the input frequency (Hz).

Our discussion of subthreshold resonance can be easily adapted to ionic currents having two gating variables raised to powers not necessarily equal to one such as calcium currents (Hutcheon and Yarom 2000).

Linearized Conductance-Based Models

Linearization of the autonomous part of system Eqs. 1 and 2 around the fixed-point $(\bar{V}, \bar{x}_1)$ yields (Richardson et al. 2003)

$$C \frac{dv}{dt} = -g_L v - g_1 w_1 + I_{in}(t), \quad (4)$$

$$\tau_1 \frac{dw_1}{dt} = v - w_1, \quad (5)$$

where

$$v = V - \bar{V}, \quad w_1 = \frac{x_1 - \bar{x}_1}{x'_{1,\infty}(\bar{V})}, \quad (6)$$

$$\bar{x}_1 = x_{1,\infty}(\bar{V}), \quad \tau_1 = \tau_{x,1}(\bar{V}) \quad (7)$$

$$g_j = G_j x'_{j,\infty}(\bar{V}) (\bar{V} - E_j), \quad j = 1, 2, \quad (8)$$

and

$$g_L = G_L + G_1 x_{1,\infty}(\bar{V}) + G_2 x_{2,\infty}(\bar{V}) + g_2. \quad (9)$$

In Eqs. 6 and 8 $x'_{j,\infty} = dx_{j,\infty}/dV$ ($j = 1, 2$). Note that the gating variable w_1 in Eq. 6 has units of voltage ($[v] = [w_1] = \text{mV}$).

The effective leak conductance g_L Eq. 9 contains information about the biophysical leak conductance G_L , the ionic conductances, and their associated voltage-dependent activation/inactivation curves. The fast ionic current I_2 contributes to g_L with an additional term (g_2). All terms in g_L are positive except for the last one that can be either positive or negative. Specifically, g_L can become negative for negative enough values of g_2 .

System Eqs. 4 and 5 can be rescaled by defining the following dimensionless time and parameters

$$\hat{t} = \frac{t}{\tau_1}, \quad \gamma_L = \frac{g_L \tau_1}{C}, \quad \gamma_1 = \frac{g_1 \tau_1}{C}. \quad (10)$$

Substitution of Eq. 10 into Eqs. 4 and 5 and a further rearrangement of terms yields

$$\frac{dv}{d\hat{t}} = -\gamma_L v - \gamma_1 w_1 + \hat{I}_{in}(t), \quad (11)$$

$$\frac{dw_1}{d\hat{t}} = v - w_1, \quad (12)$$

where γ_L, γ_1 are the dimensionless effective conductances and

$$\hat{I}_{in}(t) = \hat{A}_{in} \sin(2\pi f \tau_1 \hat{t}/1000) \quad \text{with} \quad = \frac{A_{in} \tau_1}{C}. \quad Z(f) = \frac{A_{out}(f)}{A_{in}}. \quad (15)$$

Conductance-Based Models with Subthreshold Parabolic- and Cubic-like Nonlinearities

In this paper we discuss two models that have the same type of ionic currents, I_h and I_{Nap} , but different parameter values that endow them with different geometric and dynamic properties reflected in the shapes of the voltage V -nullclines in the phase-plane diagram (Rotstein 2017b): parabolic- and cubic-like. $I_{Nap} = G_p p_\infty(V)$ ($V - E_{Na}$) has a fast amplifying gating variable (slave to voltage) and $I_h = G_h r(V - E_h)$ has a slower resonant gating variable. We refer to these models as the parabolic- and cubic-like $I_h + I_{Nap}$ models (Fig. 1-A and -B, respectively). Both models are able to produce subthreshold oscillations (STOs) in the presence of noise (Fig. 1). In the absence of noise, the parabolic-like model produces at most damped STOs, but not limit cycle STOs (Touboul 2008), while the cubic-like model admits limit cycle STOs when the fixed-point is an unstable foci (Rotstein 2017c; White et al. 1995). Other models have the same types of dual nonlinearities and dynamic properties. For example, the $I_{Nap} + I_{Ks}$ model (Rotstein 2017b).

Voltage Response: Impedance Amplitude and Phase

The voltage response of a neuron receiving an oscillatory input current is typically measured in terms of the so-called impedance function $\mathbf{Z}(f)$. $\mathbf{Z}(f)$ is a complex quantity with amplitude $|\mathbf{Z}(f)|$ and phase $\Phi(f)$. For simplicity, we refer to $|\mathbf{Z}(f)|$ simply as the impedance $Z(f)$.

For a linear system receiving a sinusoidal input current $I_{in}(t)$ of the form Eq. 3, the voltage response is given by

$$V_{out}(t, f) = A_{out}(f) \sin(\Omega t - \Phi(f)) \quad (14)$$

where $A_{out}(f)$ is the amplitude and $\Phi(f)$ is the difference between the peaks of $I_{in}(t)$ and $V_{out}(t, f)$. The impedance amplitude is given by

For nonlinear systems, or for linear systems with nonsinusoidal inputs, Eq. 15 does no longer provide an appropriate definition of the impedance function. Assuming the input and output frequencies coincide and the output amplitude is uniform across cycles for a given input (with constant amplitude), the definition of the impedance amplitude can be extended to

$$Z(f) = \frac{V_{max}(f) - V_{min}(f)}{2A_{in}} \quad (16)$$

where $V_{max}(f)$ and $V_{min}(f)$ are the maximum and minimum of the oscillatory voltage response $V_{out}(t, f)$ for each value of the input frequency f . For linear systems receiving sinusoidal inputs, Eqs. 16 and 15 are equivalent. Similarly to the linear case $\Phi(f)$, the phase is computed as the distance between the peaks of the output and the input (within the same input cycle) normalized by the period.

For more general systems and inputs the impedance has been computed as the quotient between the Fourier transforms of the output voltage $V_{out}(t, f)$ and the input current $I_{in}(t)$

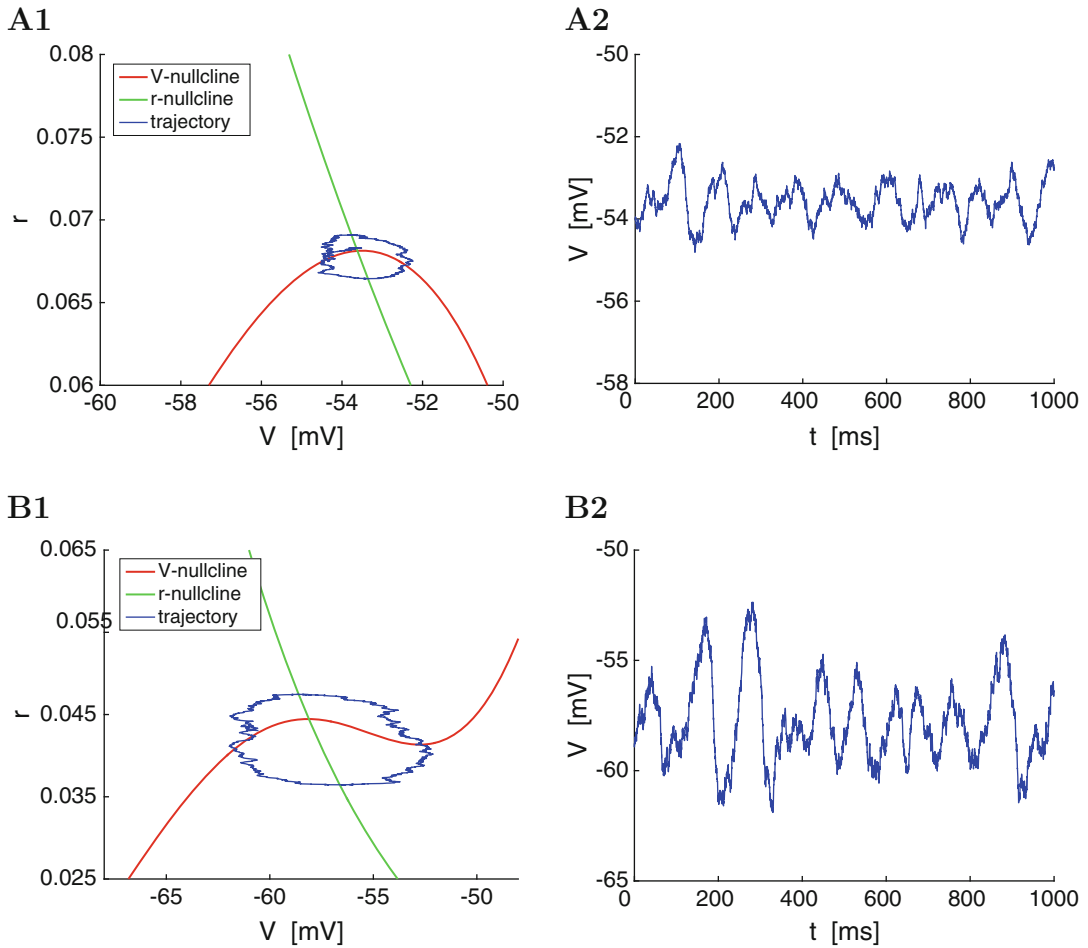
$$\mathbf{Z}(f) = \left| \frac{\mathcal{F}[V_{out}(t, f)](f)}{\mathcal{F}[I_{in}(t)](f)} \right|. \quad (17)$$

For linear systems (15) is equivalent to (17).

Several authors have used the so-called ZAP current (Puil et al. 1986; Hutcheon and Yarom 2000)

$$I_{in}(t) = I_{Zap}(t) = A_{in} \sin(2\pi f(t)t), \quad f(t) = \frac{f_M t}{2T_M}, \quad (18)$$

that sweeps through a given range of frequencies over time with a maximum frequency f_M and a stimulus length T_M (Other types of time-dependent input frequencies have also been used (Tseng and Nadim 2010)). The corresponding impedance function can be computed using 17. Note that Eq. 16 can be thought of as a filtered



Subthreshold Resonance and Phasonance in Single Neurons: 2D Models, Fig. 1 Subthreshold oscillations (STOs) and phase-plane diagrams for the autonomous parabolic-like (A) and cubic-like (B) $I_h + I_{Nap}$ models for representative parameter values. The STOs have been created using white noise. In the absence of noise both models have a stable fixed-point (focus). For visualization purposes, only one STO cycle is shown in the phase-plane diagrams (A1 and B1, left). **A. Parabolic-like $I_h + I_{Nap}$ model.** We used the following parameter values and functions: $C = 1$, $G_L = 0.5$,

$G_p = 0.5$, $G_h = 1.5$, $E_L = -65$, $E_{Na} = 55$, $E_h = -20$, $I_{app} = -2.25$, $\tau_r = 80$, $p_\infty(V) = (1 + e^{-(V+38)/6.5})^{-1}$, and $r_\infty(V) = (1 + e^{(V+79)/10})^{-1}$. The model is adapted from Rotstein et al. (2006) and Rotstein (2017d). **B. Cubic-like $I_h + I_{Nap}$ model.** We used the following parameter values and functions: $C = 1$, $G_L = 0.3$, $G_p = 0.08$, $G_h = 1.5$, $E_L = -75$, $E_{Na} = 42$, $E_h = -26$, $I_{app} = 0.4$, $\tau_r = 80$, $p_\infty(V) = (1 + e^{-(V+54.8)/4.4})^{-1}$, and $r_\infty(V) = (1 + e^{(V+74.2)/7.2})^{-1}$. The model is adapted from Remme et al. (2012) and Rotstein (2017d).

version of the impedance function computed using the ZAP functions. ZAP currents are useful for some experimental purposes, but make strong assumptions about the underlying ionic process, particularly their time scales, and should be used with caution.

Impedance and Phase Profiles for 2D Linear Systems

Impedance and phase profiles refer to the curves of the impedance and phase, respectively, as a function of the input frequency. For linear systems, the impedance and phase can be computed

analytically (Rotstein 2014) (see also textbooks such as Boyce and DiPrima 2009 for additional techniques to solve ordinary differential equations).

We use the following generic forced system

$$\frac{dx}{dt} = ax + by + A_{in} \sin(\Omega t), \quad (19)$$

$$\frac{dy}{dt} = cx + dy, \quad (20)$$

for constant a, b, c , and d .

The roots of the characteristic polynomial for the corresponding homogeneous system ($A_{in} = 0$)

$$r^2 - (a + d)r + ad - bc = 0, \quad (21)$$

are given by

$$r_{1,2} = \frac{(a + d) \pm \sqrt{(a - d)^2 + 4bc}}{2}. \quad (22)$$

Impedance and Phase Profiles: Analytic Expressions

The unforced system displays oscillations for values of the parameters satisfying $4bc + (a - d)^2 < 0$ with the natural frequency given by

$$\Omega_{nat} = \frac{\sqrt{-4bc - (a - d)^2}}{2}. \quad (23)$$

The impedance and phase profiles are given by (Rotstein 2014)

$$Z(\Omega) = \sqrt{\frac{d^2 + \Omega^2}{[ad - bc - \Omega^2]^2 + (a + d)^2 \Omega^2}} \quad (24)$$

and

$$\Phi(\Omega) = \tan^{-1} \frac{(ad - bc - \Omega^2)\Omega - (a + d)\Omega d}{(ad - bc - \Omega^2)d + (a + d)\Omega^2}, \quad (25)$$

respectively, and the resonant frequency is given by

$$\Omega_{res} = \sqrt{-d^2 + \sqrt{b^2 c^2 - 2abcd - 2d^2 bc}}, \quad (26)$$

provided the quantities inside the radicals are both positive.

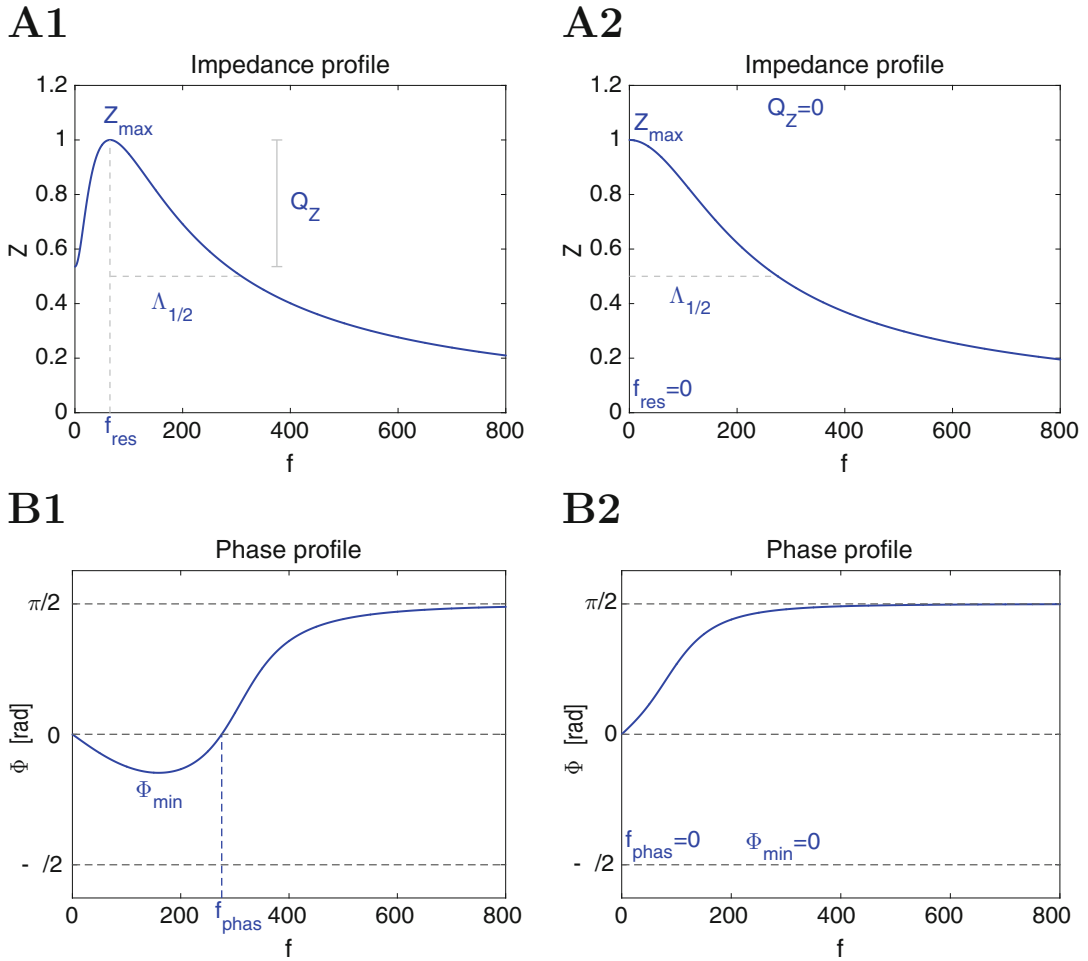
Impedance and Phase Profiles: Resonance and Phasance

For 2D linear systems the impedance profile is either a decreasing function of f (Fig. 2-A2) representing a low-pass filter response, or it exhibits a peak at a nonzero (resonant) input frequency f_{res} (Fig. 2-A1) representing a band-pass filter. The phase profile is either an increasing function of f converging asymptotically to $\Phi = \pi/2$ (Fig. 2-B2) representing a delayed response for all values of f , or it exhibits a zero-phase response at a nonzero (phasant) input frequency f_{phas} (Fig. 2-B1). For input frequencies $f = f_{phas}$ the input current and output voltage peak at the same time (Fig. 3-C2). For input frequencies $f < f_{phas}$, the voltage response is advanced (Fig. 3-C1), while for input frequencies $f > f_{phas}$ the voltage response is delayed (Fig. 3-C3 and -C4).

Phase advance and delay have also been observed in the so-called phase response curves (PRCs) (Winfree 2001; Kuramoto 1984; Canavier 2014) where one computes the transient response of a steady state oscillation to a small, brief, non-oscillatory perturbation.

Impedance and Phase Profiles: Attributes

In order to track the changes in the impedance and phase profiles as the model parameters change it is useful to identify a small number of attributes of these curves that capture their salient properties. For 2D linear systems the impedance profile can be characterized by four attributes (Fig. 2-A1): the resonant frequency f_{res} , the maximum impedance Z_{max} , the resonance amplitude $Q_Z = Z_{max} - Z(0)$, and the half-bandwidth $\Lambda_{1/2}$. Some authors define the resonance amplitude as $Q = Z_{max}/Z(0)$. For a low-pass filter response



Subthreshold Resonance and Phasonance in Single Neurons: 2D Models, Fig. 2 Schematic diagrams of the impedance (A) and phase (B) profiles. The impedance (Z) and phase (Φ) profiles are the curves of Z and Φ as a function of the input frequency f . The impedance Z is characterized by four attributes: the resonant frequency f_{res} , the impedance peak $Z_{\max}$, the resonance amplitude $Q_Z = Z_{\max} - Z(0)$, and the half-bandwidth $\Delta_{1/2}$. **A2**: The

phase Φ is characterized by two attributes: the zero-crossing frequency f_{phas} and the phase minimum $\Phi_{\min}$. **A1**. Resonance (band-pass filter). **A2**. Absence of resonance (low-pass filter). **B1**. Phasonance. The voltage response is advanced for $f < f_{\text{phas}}$ and delayed for $f > f_{\text{phas}}$. **B2**. Absence of phasonance. The voltage response is delayed for all values of f .

$Q_Z = 0$ ($Q = 1$). Resonance requires $Q_Z > 0$ ($Q > 1$). The phase profile can be characterized by two attributes (Fig. 2-B1): the phasont frequency f_{phas} and the minimum phase $\Phi_{\min}$. A phasont response requires $\Phi_{\min} < 0$.

Subthreshold Resonance, Phasonance, and Intrinsic Oscillations

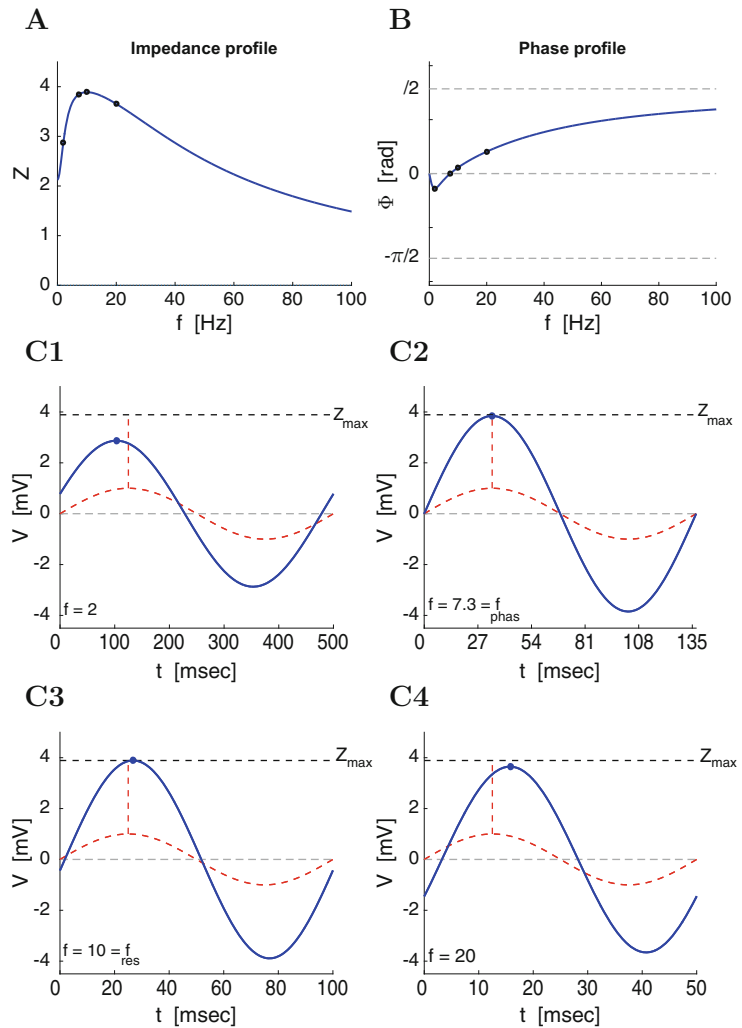
Subthreshold resonance, phasonance, and intrinsic (damped) oscillations are different phenomena

generated by different, though related, mechanisms (Richardson et al. 2003; Rotstein and Nadim 2014; Rotstein 2014). This is illustrated in Fig. 4 for the rescaled linear system Eqs. 11 and 12. The values of the natural, resonant, and phasont frequencies for the linear system Eqs. 4 and 5 are given, respectively, by

$$\Omega_{\text{nat}} = \frac{1}{2\tau_1 C} \sqrt{4g_1\tau_1 C + (C - g_L\tau_1)^2}, \quad (27)$$

Subthreshold Resonance and Phasance in Single Neurons: 2D Models,

Fig. 3 Resonance and phasance for the linear system Eqs. 4 and 5 for representative parameter values. **A.** Impedance profile. **B.** Phase profile. **C.** Voltage responses (solid blue) to sinusoidal input currents I_{in} (dashed red) for representative input frequencies f (black dots in the impedance and phase profiles). Only one period is shown for each value of f . The input is superimposed to the graph for clarity. The vertical dashed red lines indicate the input peak. The horizontal dashed black lines correspond to Z_{max} (in the impedance profile), which is reached by the voltage response only when $f = f_{res}$. The blue dots indicate the peak of the voltage response. **C1.** Phase advance. **C2.** Phasance. **C3.** Resonance and phase delay. **C4.** Phase delay. We used the following parameter values: $C = 1$, $g_L = 0.25$, $g_1 = 0.22$, $\tau_1 = 100$, and $A_{in} = 1$



$$\Omega_{res} = \frac{1}{\tau_1} \times \sqrt{\sqrt{\frac{g_1^2 \tau_1^2 + 2g_L g_1 \tau_1^2 + 2g_1 \tau_1 C}{C^2}} - 1}, \quad (28)$$

and

$$\Omega_{phas} = \frac{1}{\tau_1} \sqrt{\frac{g_1 \tau_1 - C}{C}}. \quad (29)$$

Note that substituting $C = \tau_1 = 1$, $g_L = \gamma_L$, and $g_1 = \gamma_1$ in Eqs. 27 and 29 gives the natural, resonant and phasant frequencies for the rescaled linear system Eqs. 11 and 12.

The differences between these phenomena are also exemplified by the simpler so-called $\lambda - \omega$ system (Kopell and Howard 1973)

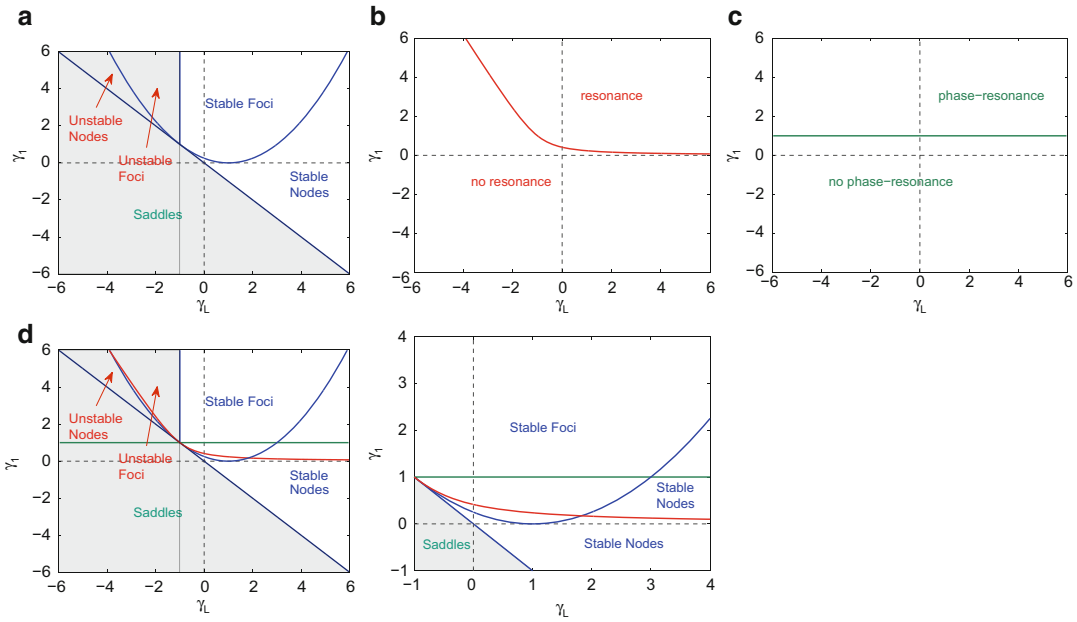
$$\frac{dx}{dt} = -\lambda x - \omega y, \quad (30)$$

$$\frac{dy}{dt} = \omega x - \lambda y, \quad (31)$$

with $\lambda > 0$ and $\omega > 0$, whose complex eigenvalues are given by

$$r_{1,2} = -\lambda \pm i\omega. \quad (32)$$

The natural, resonant, and phase-resonant frequencies, which are given by



Subthreshold Resonance and Phasonance in Single Neurons: 2D Models, Fig. 4 Stability and resonance diagrams for the reduced 2D linear system Eqs. 11 and 12 in the γ_L - γ_1 parameter space. **A.** Stability diagram. The blue curves separate between regions with different stability properties. **B.** Resonance diagram. The red curves separate between regions where the system does (above) and does not (below) exhibit resonance. **C.** Phase-resonance

diagram. The green line separates between regions where the system does (above) and does not (below) exhibit phase-resonance. **D.** Superimposed stability (blue curves), resonance (red curves), and phase-resonance (green line) diagrams showing that intrinsic oscillations and resonance may occur in the absence of the other and resonance may occur in the absence of phase-resonance. The right panel is a magnification of the left one

$$\Omega_{nat} = \omega \quad \Omega_{res} = \sqrt{-\lambda^2 + \omega \sqrt{4\lambda^2 + g\omega^2}} \quad \text{and} \quad \Omega_{phas} = \sqrt{\omega^2 - \lambda^2}, \quad (33)$$

only coincide for $\lambda = 0$ when the system is a harmonic oscillator.

Note that system Eqs. 30 and 31 can be transformed into a rescaled system of the form Eqs. 11 and 12 by defining

$$v = \omega x, \quad w = \lambda y, \quad \hat{t} = \lambda t \quad \gamma_L = 1 \quad \gamma_1 = \frac{\omega^2}{\lambda^2}. \quad (34)$$

Resonant and Amplifying Currents and Gating Variables

Subthreshold resonance results from a combination of low- and high-pass filter mechanisms that have

been described in terms of ionic currents (Hutcheon and Yarom 2000) and the interplay of the neuronal effective time scales and the time scales of the oscillatory inputs (Rotstein 2014, 2015).

Passive currents (in particular capacitive currents) act as low-pass filters (see Fig. 2-A2). The so-called resonant currents provide the slow negative feedback effects necessary to create a preferred frequency band. Amplifying currents, on the other hand, have been argued to generate a positive feedback effect that enhances voltage changes, and hence make existing resonances more pronounced (Hutcheon and Yarom 2000) but they are not able to create resonance by themselves in the absence of a resonant current. Amplifying currents also affect the resonant frequency and other attributes of the voltage response such as f_{res} and f_{phas} (Rotstein and Nadim 2014).

The signs of the effective ionic conductances g_j Eq. 8 determine whether the associated gating

variables are either resonant ($g_j > 0$) or amplifying ($g_j < 0$) (Richardson et al. 2003; Hutcheon and Yarom 2000). Restorative and regenerative currents having a single gating variable can be referred to as resonant and amplifying, respectively. The former include I_h (inward inactivating) and I_{Ks} (outward activating), while the latter include I_{Nap} (inward activating) and I_{Kir} (outward inactivating) (Haas and White 2002; Schreiber et al. 2004; Hutcheon et al. 1996a; Gutfreund et al. 1995; Richardson et al. 2003). Some ionic currents may have both resonant and amplifying gating variables (e.g., I_A , I_{CaT}) (Hutcheon and Yarom 2000).

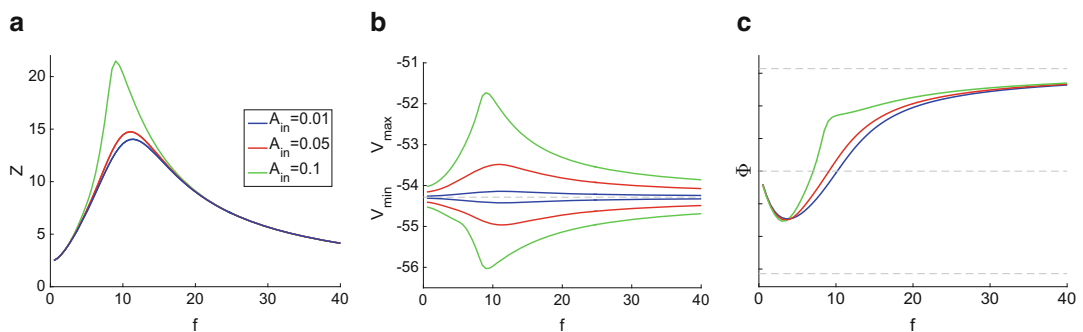
Mechanisms of Generation of Subthreshold Resonance and Phasonance

The investigation of the biophysical mechanisms of generation of resonance and phasonance consists of tracking the changes in the impedance and phase profiles as certain model parameters of interest change while keeping the remaining parameters fixed. This task is greatly simplified if one uses the attributes of the impedance and phase profiles instead of the full graphs.

This mechanistic investigation can be performed at different modeling levels by looking at (i) the dimensionless effective parameters in the rescaled system Eqs. 11 and 12, (ii) the effective parameters in the linearized system Eqs. 4 and 5,

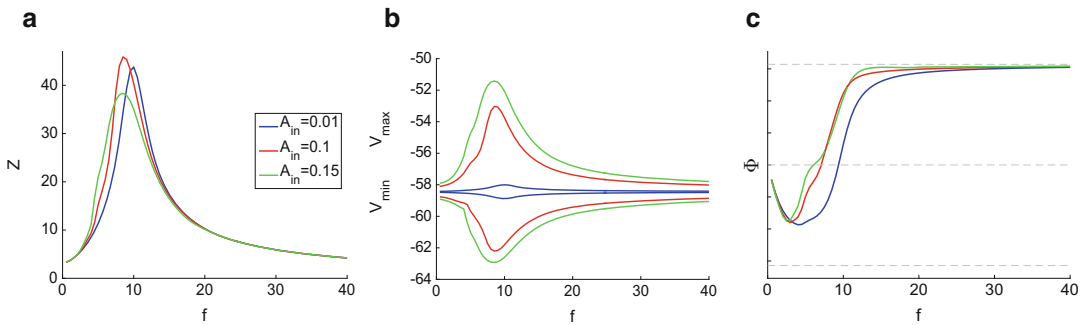
or (iii) the biophysical parameters in the original conductance-based model.

For the rescaled system Eqs. 11 and 12 heat graphs of the impedance and phase profiles attributes can be plotted in the γ_L - γ_1 parameter space presented in Fig. 4 (Rotstein and Nadim 2014). These graphs can be used to investigate the effects of changes in parameters at the different levels of description mentioned above including (i) the effects of changes in the dimensionless effective conductances γ_L and γ_1 , by moving in either horizontal (γ_L) and vertical (γ_1) directions, respectively; (ii) the effects of changes in the effective conductances g_L and g_1 , by moving in either horizontal (g_L) and vertical directions (g_1) using the rescaling Eq. 10 to account for the values of τ_1 and C ; (iii) the effects of changes in the time constant τ_1 , by moving along oblique lines (parametrized by τ_1) with slope g_1/g_L in the attribute graphs; and (iv) the effects of changes in the biophysical parameters of the original conductance-based model to the linear level of approximation, by using the formulas (8) and (9) for the effective ionic (g_1 and g_2) and leak (g_L) conductances in terms of the biophysical conductances (G_L , G_1 , and G_2), the resting potential, and other biophysical parameters. Changes in the biophysical conductances generate non-linear curves in the γ_L - γ_1 parameter space



Subthreshold Resonance and Phasonance in Single Neurons: 2D Models, Fig. 5 Impedance (left columns), voltage envelope (middle columns), and phase (right columns) profiles for the sinusoidally forced

$I_h + I_{Nap}$ model with parabolic-like nonlinearities in the subthreshold voltage regime. We used the same parameter values and functions as in Fig. 1-A



Subthreshold Resonance and Phasonance in Single Neurons: 2D Models, Fig. 6 Impedance (left columns), voltage envelope (middle columns), and phase (right columns) profiles for the sinusoidally forced

$I_h + I_{Nap}$ model with cubic-like nonlinearities in the subthreshold voltage regime. We used the same parameter values and functions as in Fig. 1-B

(Rotstein and Nadim 2014). These nonlinear curves reflect the different effects caused by different types of resonant and amplifying currents (Rotstein and Nadim 2014).

Nonlinear Resonance and Phasonance in Models with Subthreshold Parabolic- and Cubic-like Nonlinearities

The linear steady state responses to sinusoidal inputs satisfy three properties: (i) the input and output frequencies coincide, (ii) the output is proportional to the input for each input frequency, and (iii) the maximum and minimum voltage responses for each input frequency are symmetric with respect to the equilibrium point from which they are perturbed. The $I_h + I_{Nap}$ models in the parameter regimes considered here satisfy (i), but not necessarily (ii) and (iii). In Figs. 5 and 6 we illustrate the gain modes exhibited by these models.

Supra-Linear Amplification of the Voltage Response in Nonlinear Models with Parabolic-like Nonlinearities

This phenomenon is characterized by an increase in the impedance profile with increasing values of A_{in} (Fig. 5-A). The underlying dynamic mechanism has been described in Rotstein (2015, 2017c) and involves a canard-related nonlinear amplification of the voltage response due to the combination of the parabolic shape of the V -nullcline and the time scale separation between the participating variables. The

envelope of the voltage response (Fig. 5-B) is not symmetric: the upper envelope (V_{max}) exhibits a stronger change than the lower envelope (V_{min}). Both f_{res} (Fig. 5-A) and f_{phas} (Fig. 5-C) decrease with increasing values of A_{in} .

Sublinear Amplification of the Voltage Response in Nonlinear Models with Cubic-like Nonlinearities

This phenomenon is characterized by a decrease in the impedance profile with increasing values of A_{in} (red to green curves in Fig. 6-A). The underlying dynamic mechanism has been described in Rotstein (2017c). As for the previous case, the envelope of the voltage response (Fig. 5-B) is not symmetric: the upper envelope (V_{max}) exhibits a stronger change than the lower envelope (V_{min}). Both f_{res} (Fig. 5-A) and f_{phas} (Fig. 5-C) decrease with increasing values of A_{in} but the change in f_{res} during the response sublinear amplification is very small in this example.

Cross-References

- [Subthreshold Antiresonance and Anti-phasonance in Single Neurons: 3D Models](#)

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Summary of Information-Theoretic Quantities

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Definition

Information theory is a practical and theoretic framework developed for the study of

communication over noisy channels. Its probabilistic basis and capacity to relate statistical structure to function make it ideally suited for studying information flow in the nervous system. As a framework, it has a number of useful properties: it provides a general measure sensitive to any relationship, not only linear effects; its quantities have meaningful units which, in many cases, allow a direct comparison between different experiments; and it can be used to study how much information can be gained by observing neural responses in single experimental trials rather than in averages over multiple trials. A variety of information theoretic quantities are in common use in neuroscience – including the Shannon entropy, Kullback–Leibler divergence, and mutual information. In this entry, we introduce and define these quantities. Further details on how these quantities can be estimated in practice are provided in the entry ► [“Estimating Information-Theoretic Quantities,”](#) and examples of application of these techniques in neuroscience can be found in the entry ► [“Applications of Information Theory to Analysis of Neural Data.”](#)

Detailed Description

Information Theoretic Quantities

Entropy as a Measure of Uncertainty

Information theory derives from Shannon’s theory of communication (Shannon 1948; Shannon and Weaver 1949). *Information*, as we use the word technically, is associated with the *resolution of uncertainty*. The underpinning theoretic concept in information theory is thus the measurement of uncertainty, for which Shannon derived a quantity called *entropy*, by analogy to statistical mechanics. Shannon proved that the only quantity suitable for measuring the uncertainty of a discrete random variable X is

$$H(X) = -K \sum_x P(x) \log_2 P(x) \quad (1)$$

where X can take a number of values x according to the probability distribution $P(x)$. The constant

K we take to be one. When the logarithm is taken to base 2, the resulting units of the entropy $H(x)$ are called *bits* (when the natural logarithm is used, the term is *nats*).

Entropy can be thought of as a nonparametric way to measure the variability of a distribution. Spread-out distributions (with high variability) will have high entropy since all potential outcomes have similar probabilities and so the outcome of any particular draw is very uncertain. On the other hand, concentrated distributions (with low variability) will have lower entropy, since some outcomes will have high probability, allowing a reasonable guess to be made about the outcome of any particular draw. In this respect, entropy can be thought of as a generalized form of variance; unlike variance, which is a second-order statistic and only meaningful for unimodal distributions, entropy can give meaningful values for any form of distribution. For a normal distribution, the differential entropy (the continuous analogue of the discrete entropy discussed here) is proportional to the logarithm of the variance, but for other types of distribution the two measures are not so closely related.

As an example, consider the roll of an unbiased six-sided die performed under a cup. With no external knowledge about the roll, an observer would believe any of the numbers are equally likely – a uniform distribution over the six possible faces. From Eq. 1, the entropy of this distribution is $\log_2 6$. Now a third party peeks under the cup and tells our observer that the die is showing an even number. This knowledge reduces the uncertainty about the result of the roll, but by how much? After being told that the die is showing an even number, the number of possibilities is reduced from six to three, but each of the even numbers remains equally likely. The entropy of this distribution is $\log_2 3$. So the reduction in the observers uncertainty, measured as the difference in entropy, is $\log_2 6 - \log_2 3 = \log_2 2$, or 1 bit. We can quantify the knowledge imparted by the statement “the result is even” as 1 bit of information. This corresponds to a reduction in uncertainty of a factor of 2 (from six to three possible outcomes). For this example, in both the before and after situations, all the possibilities were equally likely

(uniform distributions), but the methodology can be applied to any possible distribution. Note that the uniform distribution is the maximum entropy distribution over a finite set. Any other distribution would have lower entropy since it is not possible to be less uncertain about a possible outcome than when all possibilities are equally likely – there is no structure to allow any sort of informed guess. For further applications of the concept of *maximum entropy*, see the entry on ► “Estimating Information-Theoretic Quantities.”

The fact that $H(X)$ should be maximized by a uniform distribution is one of three axioms Shannon started from in order to derive the form of Eq. 1. The others are that impossible events do not contribute to the uncertainty and that the uncertainty from a combination of independent events should be the sum of the uncertainty of the constituent events. These three conditions necessarily lead to Eq. 1, although it can be reached via many other routes as well (Chakrabarti and Chakrabarty 2005).

Mutual Information

The example of a die roll motivates how a difference between entropies can quantify the information conveyed about a set of possible outcomes. In the case of two discrete random variables – here we consider S , representing a set of stimuli which are presented during an experiment, and R , a set of recorded responses – this is formalized in a quantity called the *mutual information*. This is a quantity measuring the dependence between the two random variables and which can be defined in terms of entropies in the following three equivalent forms:

$$\begin{aligned} I(R; S) &= H(S) - H(S, R) \\ &= H(R) - H(R, S) \\ &= H(R) + H(S) - H(R, S) \end{aligned} \quad (2)$$

where $H(R)$ and $H(S)$ are the individual entropies of each random variable as discussed above, $H(R, S)$ is the *joint entropy* of the two variables, and $H(R|S)$ and $H(S|R)$ are *conditional entropies*. The conditional entropy is defined as

$$H(X|Y) = \sum_y P(y) H(X|Y = y) \quad (3)$$

where $H(X|Y = y)$ is defined as in Eq. 1 but with $P(x)$ replaced by the conditional probability $P(x|y)$. The conditional entropy $H(X|Y)$ represents the average entropy of X when the value of Y is known.

The three forms of Eq. 2 above each illustrates a particular interpretation of the mutual information. From the first form, we can see that it quantifies the average reduction in uncertainty about which stimulus was presented based on observation of a response R answering the question “if we observe R , by how much does that reduce our uncertainty about the value of S ?” Equivalently, the second form shows us that it similarly answers the question “if we observe S , by how much does that reduce our uncertainty about the value of R ?” As the third form shows explicitly, mutual information is symmetric in its arguments. The third form also shows that information is the difference in entropy between a model in which the two variables are independent (given by $P(r)P(s)$ with entropy equal to $H(R) + H(S)$) and the true observed joint distribution, $P(r, s)$ (with entropy $H(R, S)$). This shows that for two independent variables, the mutual information between them is equal to zero and illustrates that information measures how far responses and stimuli are from independence.

A well known measure of difference between probability distributions is the Kullback–Leibler (KL) divergence (Kullback and Leibler 1951):

$$D_{KL}(P \parallel Q) = \sum_x P(x) \log_2 \frac{P(x)}{Q(x)} \quad (4)$$

Note that this is not a true “distance” metric since it is not symmetric – the KL divergence between p and q is different to that between q and p . As can be seen from the third expression of Eq. 2, the mutual information is just the KL divergence between the joint distribution and the independent model formed as the product of the marginal distributions:

$$\begin{aligned} I(R; S) &= D_{KL}(P(r, s) \parallel P(r)P(s)) \\ &= \sum_{rs} P(r, s) \log_2 \frac{P(r, s)}{P(r)P(s)}. \end{aligned} \quad (5)$$

In the above, S and R represent discrete random variables where one is viewed as a stimulus and the other is a recorded neural response – but these could of course be any two discrete random variables (e.g., a variable representing a wild-type vs. a genetic manipulation, behavioral responses, or other intrinsic signals). We will see shortly that information and entropy can be easily generalized to continuous signals.

A natural question is “does mutual information correspond to a measure of discriminability?” If by discriminability one means the measure d -prime (Green and Swets 1966), the answer is in general “no.” However, in the specific case where we are measuring the transmission of information about one of two equiprobable stimuli (or equivalently, presence/absence of a stimulus), mutual information has such an interpretation. This can be seen by reaching for another “distance-like measure” – this time, one that is symmetric, the Jensen–Shannon (JS) divergence, a symmetrized version of the KL divergence (Lin 1991; Fuglede and Topsoe 2004):

$$D_{JS}(P\|Q) = \frac{1}{2}D_{KL}\left(P\left\|\frac{P+Q}{2}\right.\right) + \frac{1}{2}D_{KL}\left(Q\left\|\frac{P+Q}{2}\right.\right) \quad (6)$$

It can be fairly easily seen that in the case where we have only two stimuli, s_1 and s_2 , the mutual information $I(R;S)$ can be written as

$$I(R;S) = D_{JS}(P(r|s_1)\|P(r|s_2)). \quad (7)$$

Thus the mutual information can be considered to measure how far apart (how discriminable) the distributions of responses are, given the two stimuli. Note that while mutual information generalizes to multiple stimuli, it is not entirely clear that the concept of discriminability does, in a useful way.

In summary, the mutual information is a measure of how strongly two variables are related, similar in spirit to correlation but with some

specific advantages. Firstly, it is a completely general measure; it places no assumptions or models on the variables under consideration and is sensitive to any possible relationships, including nonlinear effects and effects in high-order statistics of the distributions. Second, it has meaningful units allowing direct comparison across different experiments and even with behavioral performance. Finally, it permits several nice interpretations related to its calculation as a single trial property and involving its relationship to decoding performance.

Other Information Theoretic Quantities

Similar procedures to those used to estimate entropy and mutual information can be used to estimate a number of other information theoretic quantities. We mention several such quantities here for completeness.

Multi-information

Note that the mutual information between a pair of random variables naturally generalizes to the concept of the multivariate mutual information, or *multi-information*, the mutual information between n variables,

$$\begin{aligned} I(X_1; \dots; X_n) &= \sum_{x_1, \dots, x_n} P(x_1, \dots, x_n) \log_2 \frac{P(x_1, \dots, x_n)}{\prod_i P(x_i)} \\ &= I(X_1; \dots; X_{n-1}) - I(X_1; \dots; X_{n-1}|X_n) \end{aligned} \quad (8)$$

Note that multi-information, unlike standard mutual information, can take negative values. Multi-information has found use in neuroscience in the study of patterns of activity in neural ensembles (Schneidman et al. 2006). Note that this is not the only way to generalize mutual information beyond two variables, and a related quantity, the interaction information, can also be defined (McGill 1954; Bell 2003; Jakulin and Bratko 2003).

Conditional Mutual Information

The conditional mutual information is the expected value of the mutual information

between two variables given a third (Cover and Thomas 1991),

$$I(X; Y|Z) = H(X|Z) - H(X|Y, Z). \quad (9)$$

This quantifies the relationship between variables X and Y while controlling for the influence of Z . In neuroscience, this can be useful, for example, to investigate the coding of correlated stimulus features (Ince et al. 2012). Consider two correlated stimulus features S_1 and S_2 . If it is found that $I(R; S_1) > 0$, this could be because the response is modulated by feature S_1 , but it might be that the response is modulated by feature S_2 and the relationship between response and S_1 follows from the correlation between the features. Considering $I(R; S_1|S_2)$ can resolve this situation and reveal if the feature S_1 is truly represented.

Entropy and Information Rates

Most biological systems function not as discrete realizations from a static process (like the roll of a die), but rather operate continuously as time-varying dynamic processes. This brings to mind the notion of the *rate* at which a source generates information – e.g., if we were tossing a coin once per second and the outcomes of the coin tosses were independent, then we would be generating information at a rate of 1 bit/s. In general, the *entropy rate* of a stochastic process is defined as

$$h(X) = \lim_{n \rightarrow \infty} \frac{1}{n} H(X_1, X_2, \dots, X_n). \quad (10)$$

By extension, the *mutual information rate* is

$$i(R; S) = \lim_{n \rightarrow \infty} \frac{1}{n} I(r_1, r_2, \dots, r_n; S) \quad (11)$$

with units of bits/s. Asymptotic entropy and information rates can therefore be estimated indirectly by calculating information for sufficiently long sequences of time bins. If the calculation is repeated for smaller and smaller time bins, it is

possible to extrapolate the resulting discrete information value to the instantaneous limit, making the rate calculation independent of both sequence length and bin width (Strong et al. 1998). It is also possible to calculate them directly using a Bayesian probabilistic model (Kennel et al. 2005; Shlens et al. 2007).

Information Theoretic Quantities for Continuous Variables

The quantities above are all defined on random variables taking discrete values. However, entropy and other information quantities can also be defined on continuous spaces. In the case of entropy, replacing summation by integration yields the *differential entropy*:

$$h_{\text{diff}}(X) = \int_x p(x) \log_2 p(x). \quad (12)$$

Other information theoretic quantities can be defined analogously, in general, by replacing sums over the discrete spaces with integrals over the continuous spaces. Note that differential entropy does not entirely generalize the properties of the discrete Shannon entropy, and thus, this quantity has not been widely used in neuroscience and is therefore beyond the scope of this entry. In contrast, the Kullback–Leibler divergence and mutual information both generalize in a straightforward manner to continuous spaces. For instance, the mutual information between two random variables with joint density $p(x, y)$ is

$$I(X; Y) = \int p(x, y) \log_2 \frac{p(x, y)}{p(x)p(y)} dx dy. \quad (13)$$

Cross-References

- [Applications of Information Theory to Analysis of Neural Data](#)
- [Estimating Information-Theoretic Quantities](#)

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Surrogate Data for Evaluation of Spike Correlation

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Definition

In the correlation analysis of experimentally recorded parallel spike trains, one has to thoroughly consider the statistical features of the data in order to prevent false-positive results. Surrogate data, i.e., modified versions of the original spike trains, are used to assess the significance of spike correlation. The objective of surrogate data generation is to leave all statistical features of the original experimental data intact except those one wants to test for: these are to be destroyed.

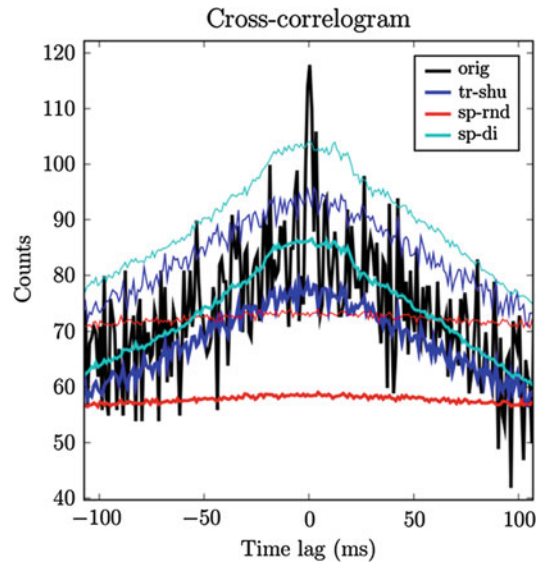
Detailed Description

Generating artificial data from experimental data as a means for implementing a null hypothesis is becoming widely used. The reason is twofold: increasing computer power now allows for this type of approach, and it has become clear that the complexity of experimental data does not in general permit an analytical formulation of the null hypothesis. This is particularly true for the correlation analysis of parallel spike trains. Neglecting statistical features of experimental data such as nonstationarity of the firing of individual neurons in time or across trials, the spike train structure deviating from Poisson, or a co-occurrence of such features in parallel spike trains can lead to the occurrence of false-positive results. Problems can be avoided by including those features in the null hypothesis of the significance test. To this end surrogate data are used to generate the predictor by modifying the

original data in such a way that the feature of interest, here as an example the temporal coordination of spikes, is destroyed, but other features of the data are preserved. These data are then analyzed like the original experimental data, and the outcomes are compared (see ► “Significance Evaluation”; Harrison et al. 2013). Such data are used for bootstrap approaches in the significance estimation of the occurrence of features, e.g., spatiotemporal spike patterns (see ► “Statistical Evaluation of Spatio-temporal Spike Patterns”). In the case of precise joint spike events (see ► “Unitary Event Analysis”), the interest is to keep the statistical features of the spike trains of the individual neurons as similar to the original as possible but to destroy the exact relative timing of spikes from different neurons (for a comprehensive list of references, see Grün (2009) and Louis et al. (2010a, b)).

Modeling spike trains as stochastic processes is an elegant way to generate surrogate data. Often used are inhomogeneous Poisson processes that reproduce the dynamics of the firing rate according to the estimated firing rate profiles. More complicated processes which in addition reproduce the interspike interval (ISI) or higher-order interval statistics or even change their internal structure as a function of time can be modeled (see ► “Population Encoding/Decoding,” ► “State-Space Models for the Analysis of Neural Spike Train and Behavioral Data,” and ► “Generalized Linear Models for Point Process Analyses of Neural Spiking Activity”). Although often not all parameters can be estimated from the experimental data, a formal characterization of neuronal spiking dynamics (the stochastic model) is helpful since it constitutes a precise description of the assumptions. Consequently, it enables more specific statements about the experimental data.

Other methods for generating surrogate data operate directly on the original data and modify them according to specific rules. Spike time randomization, i.e., random shuffling of the spikes of a neuron within a given time interval, assumes stationary rate within the window (Fig. 1, red). The procedure is closely related to the generation of a stationary Poisson process, but here the spike counts are additionally matched. The ISI structure



Surrogate Data for Evaluation of Spike Correlation, Fig. 1 Comparison of original and surrogate cross-correlograms (CCHs) (see ► “Correlation Analysis of Parallel Spike Trains”). The CCH of an original data set (black), composed of two neurons simulated with background firing activity as nonstationary co-modulating gamma processes, inhomogeneous across trials (40 trials), with additionally injected coincident spike events (rate: 3 Hz, coincidence width: ± 1 ms). Surrogate CCHs are generated by trial shuffling (*tr-shu*, blue), by spike time randomization (*sp-rnd*, red), or by spike dithering (*sp-di*, cyan) and are shown as the mean over 1,000 surrogates (thin lines) and the mean plus twice the standard deviation over the surrogates (thick lines). Only the surrogate CCH based on dithering reproduces well the overall shape of the original CCH reflecting chance coincidences due to the firing rates but destroys the narrow central peak due to correlated activity. The other two surrogates underestimate the chance coincidences and thus may lead to false-positive results in independent data of the same rates but without correlated spike events. (Modified from Louis et al. 2010b)

of the original data, however, is destroyed. Other methods particularly focus on the conservation of the ISI distribution by shuffling the ISIs of a neuron within a trial, thereby simultaneously preserving the spike count of each trial. Furthermore, a potential covariation of spike counts across neurons is automatically preserved. In attempts to additionally account for nonstationarity in time, ISI shuffling may be performed in shorter time windows across trials, which, however, assumes cross-trial stationarity.

Trial shuffling is a way of destroying the relationship between simultaneously recorded spike trains. Trial data of one neuron are randomly assigned to trials of other neurons, thereby destroying potential spike correlation but leaving the internal structure of the spike trains and thus the spike counts intact. Potential covariation of spike counts across the neurons is thereby destroyed. Thus, nonstationarity across trials cannot be tolerated, since a recombination of these features, e.g., rate, may additionally change the chance occurrence of joint spike events (Fig. 1, dark blue). For the shift predictor, spike trains are not randomly assigned, but trial IDs of the two neurons are shifted systematically against each other. The shift predictor is mainly of historical interest as an approximation to the full shuffle. However, e.g., in the presence of slow changes of statistical features across trials, the shift predictor may still be favorable.

Surrogate methods based on exchanging or randomizing spikes across neurons within the same trial may serve well for the evaluation of spatiotemporal spike pattern (see ► [“Spatial Temporal Spike Pattern Analysis”](#)). These surrogates preserve the population histogram of each trial but preserve neither the PSTHs nor the ISI distributions and assume co-stationary data.

Spike dithering, often also called jittering or teetering, i.e., independent randomization of the individual spike times within a small predefined time interval, destroys the exact spike timing and therefore also exacts relative spike timing across the neurons (see ► [“Statistical Evaluation of Spatio-Temporal Spike Patterns”](#)). This effectively leads to some smoothing of the firing rates and also to a slight modification of the ISI distribution (Fig. 1, cyan). The latter can be minimized by weighting the dither according to the joint interspike interval distribution.

However, if firing rates change strongly on a short time scale, the smoothing effect of dithering becomes stronger, which in turn tends to lead to false-positive results. Therefore, it was suggested to first transform the data by time rescaling according to the firing rate into operational time, such that firing rates become stationary. Dithering is then applied in this representation. After transformation back into the original representation,

joint spike events are detected. Even for strong rate changes, this surrogate method does not introduce false positives (Louis et al. 2010a).

Instead of modifying the individual spike times, it was suggested to shift the complete spike trains, or parts of it, against the others by random amounts (Amarasingham et al. 2012; Pipa et al. 2008; Wu et al. 2011). Thereby the structure of the spike trains or large parts of them are conserved; only the PSTHs are smoothed depending on the maximal shift. To have an effective destruction of joint spike events, the maximal shift needs to be chosen by a factor larger than the temporal precision of the joint spike events. This variant of dithering seems to be most appropriate to account for the features of the single-neuron statistics and can also be done in operational time (Louis et al. 2010a).

The creation of surrogate data is an attractive way to generate control data and is conceptually simple. However, for a proper choice of the surrogate, one has to be clear about the implicit assumptions and affected spike train features. This implies that the choice of surrogate may depend on the correlation analysis method used and that a particular surrogate method needs to be tested in the context of the intended analysis.

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Generalized Linear Models for Point Process Analyses of Neural Spiking Activity](#)
- [Population Encoding/Decoding](#)
- [Significance Evaluation](#)
- [Spatial Temporal Spike Pattern Analysis](#)
- [State-Space Models for the Analysis of Neural Spike Train and Behavioral Data](#)
- [Statistical Evaluation of Spatio-Temporal Spike Patterns](#)
- [Unitary Event Analysis](#)

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Sweeping the Parameter Space of Neuron Models

- [Neuronal Parameter Space Exploration](#)

Swimming and Walking Modes of the Salamander

- [Control of Aquatic and Terrestrial Gaits in Salamander](#)

Synapse-Astrocyte Bidirectional Signaling

- [Neuron-Glial Interactions](#)

Synaptic Connectivity in Neural Population Models

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Synonyms

[Synaptic footprint in neural population models](#)

Definition

Synaptic connectivity refers to the ensemble of direct chemical and electrical connections between neurons. In chemical synapses afferent presynaptic neuroelectric activity is mediated via neurotransmitters to the postsynaptic terminal, at which the postsynaptic activity can be either increased or decreased as a function of the excitatory/inhibitory character of the synapse. In electrical synapses the presynaptic and postsynaptic cell membranes are connected by special channels called gap junctions that are capable of directly passing electrical current between neurons. In neural population models the various aspects of synaptic connectivity are absorbed, typically through mean field techniques, by connectivity functions, parameters, and/or nonlinear response functions.

Detailed Description

A synapse is a connecting structure that permits a (presynaptic) neuron to pass an electrical or chemical signal to another (postsynaptic) neuron. There are hence two fundamentally different types of synapses: chemical and electrical synapses.

In a chemical synapse, electrical activity in the presynaptic neuron is converted (via the activation of voltage-gated calcium channels) into the release of a neurotransmitter that binds to receptors located in the postsynaptic cell. The binding

process of the neurotransmitter initiates an electrical response on the postsynaptic neuron that may either depolarize (excitation) or hyperpolarize (inhibition) the postsynaptic neuron. The process of presynaptic neurotransmitter release, migration through the synaptic cleft, and binding on the postsynaptic side requires time, and its time course is characteristic of different neurotransmitter types giving a range of fast synapses (GABA_A, AMPA) to slower synapses (GABA_B, NMDA). Models of synaptic dynamics are typically nonlinear and expressed through ordinary differential equations involving transmitter concentration and release time, conductance strength, or reuptake time (Destexhe et al. 1994). Synaptic couplings between neurons are effectively of nonlinear and multiplicative nature. The time of synaptic transmission delay. Kinetic models of synaptic transmission are often used in the modeling of network dynamics (Destexhe 1998), as they provide a good compromise of accurate level of biological detail and computational efficiency. A simpler model of synaptic transmission is the so-called alpha function, which captures the time course of the postsynaptic response to a delta-spike (Gerstner and Kistler 2002).

In an electrical synapse, communication is electrically conductive through the cell's membrane and considered nearly instantaneous; thus, its transmission delay is negligible. Mathematically symmetric linear difference couplings between pre- and postsynaptic neurons are based on Kirchhoff's current law and alter the respective neuronal membrane voltages. Electrical couplings between neurons are effectively of linear nature.

On the neural population level, synaptic coupling is the predominant connectivity considered. Neural population models that were derived from single neuron models (such as Brunel and Wang (2003), Wong and Wang (2006), Stefanescu and Jirsa (2008, 2011)) preserve the nonlinear nature and time scales of the synaptic couplings. Neural population models that were not derived from a microscopic level, but were rather being posed ad hoc, typically absorb the coupling's (spatial, temporal, (non)linear) effects in the nonlinear population response function and then rely on additive

linear couplings between neural populations (such as Wilson and Cowan (1972, 1973), Nunez (1974), Jirsa and Haken (1996), Robinson et al. (1997)). Excitatory coupling then enters as an input that increases the rate of the neural population's activity and inhibitory coupling decreases its activity. This procedure has been justified in Jirsa and Haken (1996) by the conversion properties of synaptic activities (wave) and firing rates (pulse) on the population level. Walter Freeman (1975) demonstrated that these population measures show robust dependencies; in particular wave-to-pulse conversion is highly nonlinear showing saturation, whereas the pulse-to-wave conversion is limited to the linear regime.

Other means of introducing features of synaptic connectivity into neural population models are through manipulations of the axonal propagator. A plus and minus sign may be assigned to the distribution of connection weights (see, for instance, Amari (1977)) to create coupling functions such as the Mexican hat function with central excitation and lateral inhibition. The latter has been shown to be essential for the realization of self-sustained spatial patterns thought to be involved in working memory. Local circuits of mutually coupled populations via excitatory and inhibitory connections are well known to give rise to the emergence of rhythmic firing patterns. To characterize the time scales of synaptic processes in neural fields, linear convolutions have been introduced postsynaptically to modulate the effects of axonal propagation (see (Hutt and Atay 2005) for treatments of gamma-distributed synaptic footprints). Plasticity changes of synaptic connectivity rely on the timing of pre- and postsynaptic neuronal discharges and are established in cellular models of neurons (Abbott and Nelson 2000), but less well understood on the population level.

Cross-References

- [Amari Model](#)
- [AMPA Glutamate Receptor \(AMPA Receptor\), Conductance Models](#)
- [Axon, Modeling](#)

- [Connectome, General](#)
- [Dynamic Causal Modelling with Neural Population Models](#)
- [Gamma-Aminobutyric Acid Type-A \(GABA-A\) Receptors, Kinetic Models](#)
- [Gap Junctions, Neural Population Models and](#)
- [Mesoscopic Anatomy and Neural Population Models](#)
- [Modeling Synapses](#)
- [Multiscale Brain Connectivity](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Model](#)
- [N-Methyl-D-Aspartate \(NMDA\) Receptors, Conductance Models](#)
- [Propagator, Axonal](#)
- [Synaptic Dynamics: Overview](#)
- [Wilson-Cowan Model](#)

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Synaptic Footprint in Neural Population Models

- [Synaptic Connectivity in Neural Population Models](#)

SYNOD

- [NEST: The Neural Simulation Tool](#)

Synthetic Neuronal Circuits/Networks

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Definition

Processing of information in neuronal networks involves communication between cells with complex dendritic and axonal arbors, belonging to multiple populations each having characteristic firing properties. This complex 3D structure, where synaptic connectivity between groups of cells can also be restricted to specific anatomical

layers, is believed to be an important determinant of network behavior.

While many initiatives aim to reconstruct the full connectome of specific brain regions by mapping each neuron and synaptic connection in a block of tissue, other approaches take existing information on the known cell types and their overall connectivity rules and attempt to generate synthetic neuronal circuits from these. This can be useful for checking the completeness of knowledge of the circuit and to provide input to large-scale simulations of network behavior.

Detailed Description

Reconstructed and Synthetic Neurons

Recent developments in the field of connectomics are paving the way toward having access to the complete wiring diagram of specific networks in the brain. These will comprise full 3D reconstructions of all cells in the network along with all of the synaptic locations. Significant progress has been made on the complete neuronal wiring diagrams for simple species (White et al. 1986), but even a fully reconstructed cortical microcircuit from a mammalian brain is many years away. However, some regions such as the retina (Helmstaedter et al. 2013) have already been studied in greater detail than previously possible with these methods.

For many regions however, while no complete wiring diagrams exist, plenty of statistical data is available on the overall anatomical layout of the neuronal circuitry, the types of cells present, their densities in specific layers, overall morphological features of the cell classes, connection probabilities between cell populations, as well as electrophysiological properties of the cells and synapses. This has led to various attempts to create synthetic versions of such circuits from these data, both as a means of cataloging what's known about the structure and connectivity of specific brain regions and for creating *in silico* models of the networks. These models can be used to gain a greater

understanding of the networks through visualization or simulation of their electrical activity.

Simplified Synthetic Networks

Many point neuron network models (e.g., using leaky integrate and fire neuron models or two state variable extensions of this (Izhikevich 2003; Brette and Gerstner 2005)) have been created which seek to examine general operating principles of generic neural networks (Brunel 2000). Increasingly however, abstract network models are being created which incorporate data from specific brain regions on the specific cell types present, their relative densities/soma locations, and connectivity. A recent example is Potjans and Diesmann (2012), which describes a full-scale anatomically constrained model of the local cortical microcircuit using integrate and fire neurons. This can reproduce various experimentally observed features of the circuit including layer-specific cell activity patterns and propagation of transient thalamic inputs.

Conductance-based cell models aim to explain the firing patterns of cells in terms of the ion channels known to be present on the cell membrane. A number of anatomically inspired network models have been created taking this approach, often built up from detailed studies of single-cell properties. Solinas et al. (2010) describe a 3D model of the granule cell layer of the cerebellum incorporating conductance-based models of granule and Golgi cells. This network has been used to study not only temporal signal processing but also the spatial spread of activity following focused synaptic input.

Another example of an anatomically and electrophysiologically constrained network model of a distinct brain region is that of the dentate gyrus in Santhakumar et al. (2005). This contains reduced (9–17 compartments) multicompartmental models of granule, basket, HIPP, and mossy cells from this region and investigates how changes in cell number and connectivity following head trauma can lead to network

hyperexcitability. This model is being used as the basis for a much larger-scale model which will incorporate cell numbers in line with the actual rat dentate gyrus (Schneider et al. 2012).

The single-column thalamocortical network model of Traub et al. (2005) is one of the most detailed network models produced to date, featuring 14 cell types from the thalamus and multiple layers of the cortex, tuned to cell-type-specific firing behavior and incorporating known patterns of layer-specific synaptic connectivity. While this model too has reduced numbers of compartments in each of the cells (~80), it still requires the use of parallel computing resources to run. However, it represents a useful middle ground between more abstract cortical models and the highly detailed simulations used, for example, in the Blue Brain Project (see below), incorporating as it does sufficient detail to ask detailed questions about the contribution of specific cells, ion channels, and synaptic properties to network function, on computing resources which would be available to most researchers.

Synthetic Networks with Morphologically Detailed Cells

While abstract cells with reduced numbers of compartments are useful for generating, analyzing, and simulating large-scale networks, there is a growing need to use more morphologically realistic neurons to examine the full range of computations possible in single cells (Silver 2010) and networks. Using morphologies of reconstructed cells is an option due to the availability of databases of these (e.g., NeuroMorpho.org; Parekh and Ascoli 2013). For network analyses, however, there are usually not sufficient numbers of reconstructions of cells of given types to create a realistic network without using multiple, morphologically identical cells in a network. Generating a set of synthetic cells with similar morphological properties to reconstructed cells is a possible route toward more realistic large-scale models (Evans and Polavaram 2013).

TREES toolbox (Cuntz et al. 2010; ► [TREES Toolbox: Code for Neuronal Branching](#); <http://www.treestoolbox.org>) is an application which has various features which can help address this. While it can be used for semiautomated reconstruction of cells from image stacks, it also allows generation of new morphologies based on extracted features of cells or groups of cells (e.g., 3D densities of branch points). This can potentially be used for generating multiple different cells of a particular class for use in network models. NETMORPH (Koene et al. 2009; <http://netmorph.org>) is an application which can also be used to generate synthetic neurons. It is based on the growth of neurons, with rules for how neurites should elongate, branch, and turn in 3D. Neural networks can be created based on the proximity of axonal and dendritic sections. NeuGen (Eberhard et al. 2006; <http://atlas.gcsc.uni-frankfurt.de/%7Eneugen>) is a similar tool with a focus on generating 3D networks of specific cortical regions (e.g., cortex, hippocampus) using rules extracted from morphological features of the cells present in those regions. Cx3D: Cortex Simulation in 3D (Zubler et al. 2013; <http://www.ini.uzh.ch/%7Eamw/seco/cx3d>) is a tool for simulating the growth of neural tissue, not only the growth of axons and dendrites in confined 3D spaces but also movement of cells. Chemical gradients can be added which influence the movement of specific entities. A recent version of this tool allows execution across multiple processors speeding up the generation of large-scale networks. More details on the different strategies and algorithms used for generation of synthetic neuronal morphologies can be found in this article.

A comparison of a number of the tools mentioned above is presented in Ćimović et al. (2011). Each of these tools has a slightly different focus and may be more or less appropriate for use depending on the research question to be addressed. None is a simulator of electrophysiological network activity; instead, they concentrate on exporting to other formats making it easier to simulate such behavior. Export to NeuroML

(Gleeson et al. 2010) is supported by TREES toolbox and CX3D (and is also an option at NeuroMorpho.org) allowing generated networks to be imported into simulators like NEURON and visualized/analyzed by other applications, e.g., neuroConstruct (Gleeson et al. 2007).

Large-Scale Simulations of Synthetic Networks

A number of initiatives have started to look at the generation of simulations of morphologically detailed neural networks at the scale of macroscopic brain regions. The Neural Tissue Simulator (Kozloski and Wagner 2011) aims to make it possible to simulate a whole block of neural tissue by efficiently segmenting the region into sections, each of which is simulated on a separate processor in a parallel environment. There is initiative to reconstruct and simulate the rodent barrel cortex (Egger et al. 2012), which is developing new methods to register cell morphologies obtained from different animals against a common anatomical reference frame. The Blue Brain Project (<http://bluebrain.epfl.ch>) has been gathering data and developing methods for creating a simulation of a complete cortical column for a number of years. This work will continue as part of the 10-year EU-funded Human Brain Project (<https://www.humanbrainproject.eu>).

More details on software applications for creating detailed models of neuronal systems can be found in the entry ► “Software Tools for Modeling in Computational Neuroscience: Overview.”

Conclusions

While initiatives to reconstruct the complete wiring diagrams of various species or brain regions are gaining pace, there is much that can be learned by consolidating the vast amounts of data on different brain regions into models, both describing the structure and connectivity of the networks and potentially allowing detailed simulations of the activity of the cells. This task is larger than one lab can manage on its own, and a key part of this

process will be the availability of appropriate software tools and databases required to construct such models. Thankfully, more and more resources are becoming available for sharing data on neurons and their properties (e.g., ► [NeuroMorpho.org](#), ► [NeuroElectro Project](#), SenseLab: Integration of Multidisciplinary Neuroscience Data; Bezaire and Soltesz 2013) and for sharing models (► [ModelDB](#), ► [Open Source Brain](#)) and the software required to simulate them (► [Software Tools for Modeling in Computational Neuroscience: Overview](#)).

Cross-References

- [CX3D: Cortex Simulation in 3D](#)
- [ModelDB](#)
- [neuroConstruct](#)
- [NeuroElectro Project](#)
- [NeuroML](#)
- [NeuroMorpho.org](#)
- [NEURON Simulation Environment](#)
- [Open Source Brain](#)
- [SenseLab: Integration of Multidisciplinary Neuroscience Data](#)
- [Software Tools for Modeling in Computational Neuroscience: Overview](#)
- [Synthetic Neuronal Morphology](#)
- [TREES Toolbox: Code for Neuronal Branching](#)

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Synthetic Neuronal Morphology

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Synonyms

Algorithms for generating neuronal morphologies; Morphogenetic algorithm; Virtual neuron generation

Definition

A synthetic neuronal morphology is a digital representation of a neuron's morphology that is not acquired experimentally but rather generated by an algorithm. The input to such an algorithm is often a prototype, experimentally reconstructed morphology (or a set thereof). A synthesis algorithm then incorporates this prototype data in some way to generate a new digital reconstruction from scratch. Thus, synthetic neurons are *de novo*, algorithmically created digital reconstructions not originating directly from experimental data.

History of Synthesizing Neuronal Morphologies

Since the pioneering work of Golgi to visualize neurons *in vitro* and the subsequent beautiful drawings by Ramon y Cajal, neuroscientists have been fascinated by neuronal morphologies. The attempt of Hillman (Hillman 1979) to quantify neuronal morphologies kick-started the field investigating synthetic morphologies. Hillman described a set of so-called fundamental parameters that were sufficient to describe neuronal morphologies. Hence, the idea for later sampling algorithms to synthesize morphologies was born: if there exist a set of fundamental parameters that adequately capture morphologies, you can, in principle, sample from the statistical distribution of these parameters to create a new morphology that shares statistical properties with the original.

However, it took another decade before the first algorithms were presented to synthesize morphologies. One set of algorithms was based on the ideas of Hillman to sample from statistical distributions of parameters describing morphologies (Burke et al. 1992; Nowakowski et al. 1992). The other algorithms were based on L-systems (Pellionisz 1989; Hamilton 1993; McCormick and Mulchandani 1994). An L-system or Lindenmayer system is a mathematical formalism to generate recursively branched structures that had been successfully applied earlier to synthesize digital representations of botanical trees (Lindenmayer 1968). Quantification of morphologies per se also generated many insights, which resulted in rigorous descriptions of morphologies (for instance, Uylings et al. 1986; Van Pelt et al. 1992; Tamori 1993). These combined efforts lead to a synergy between L-systems and solid quantification of fundamental parameters that accumulated in L-Neuron (Ascoli and Krichmar 2000), a sampling algorithm implicitly implementing a stochastic L-system to create a topology while relying on sampling from fundamental parameters to create a geometry. L-Neuron has become the most visible tool for the synthesis of neuronal morphologies.

Around the same time, due to advances in computational resources and recording techniques, the interest in dendritic morphologies

and their role in computation grew (Traub et al. 1991; De Schutter and Bower 1994). Because of the labor-intensive nature of experimentally reconstructing morphologies, many algorithms to synthesize neurons were proposed (see next section). This recent *raison d'être* contrasts with the historical reason to algorithmically generate morphologies, namely, as a testing bed to investigate hypotheses about morphological traits and their variance.

Detailed Description

Today, there are many different types of algorithms to synthesize neuronal morphologies. Most of them are specifically designed to study or mimic a particular characteristic of neurite morphology. Consequently, any classification of the algorithms is inherently artificial and post hoc. But a classification creates order and increases understanding. Therefore, the algorithms are here classified into two categories: context-independent and context-dependent ones. Clearly, neurons do not grow in a vacuum but rather take their shape from interactions with the neuronal matrix, i.e., their context (Jan and Jan 2010). But treating neurons as if they were in a vacuum makes their study more straightforward; and hence, this abstraction is widely adopted.

Context-Independent Algorithms

Sampling Algorithm

Most current algorithms are instances of the so-called sampling algorithms briefly introduced before and treat morphologies as if they were floating in a vacuum. Sampling algorithms start with a statistical description of fundamental parameters, i.e., a set of parameters that is considered sufficient to fully describe a neuronal morphology (Hillman 1979). Then, they iteratively synthesize a morphology by sampling features of the morphology under construction from the statistical model (Burke et al. 1992; Tamori 1993). The majority of morphology synthesis algorithms are of the “sampling type” and one of the best

known implementations is L-Neuron (Ascoli and Krichmar 2000). Differences between sampling algorithms are manifested in different characteristics of the algorithms. Firstly, the statistical descriptors can be parametric (Ascoli and Krichmar 2000; Eberhard et al. 2006) or nonparametric (Lindsay et al. 2007; Torben-Nielsen et al. 2008). In parametric models, the researcher has to define the type of distribution that best fits the prototype data (e.g., a Gaussian distribution parametrized by its mean and standard deviation). This can be an advantage when there is little data available, and human judgment is needed to see the true distribution in the data. Nonparametric statistical models on the other hand do not make any assumptions on the type of distribution underlying the data. As such, the researcher using these models does not impose a bias on the distribution, and thus, in principle, the data is described more accurately (Torben-Nielsen et al. 2008). Also, the selection and description detail of the fundamental parameters can be different: fundamental parameters can be considered independent from each other (e.g., a univariate description) or dependencies can be introduced by using multivariate descriptions (Burke et al. 1992; Ascoli and Krichmar 2000; Torben-Nielsen et al. 2008). For instance, the segment length can be considered to be independent of other features (=univariate) or dependent on the topological order (=bivariate) or on the topological order and the Euclidean distance to the soma (=trivariate). Generally, these dependencies are tuned to achieve the best match between prototype and de novo data.

Growth Algorithm

One of the very first algorithms to synthesize parts of the dendritic structure is developed by van Pelt and colleagues (van Pelt et al. 1986; Uylings et al. 1986; van Ooyen 2001). Initially, they aimed at quantifying dendritic branching patterns. To this end, they developed an algorithm to synthesize dendritic topologies that captured experimentally observed variation. The algorithm is based on the simultaneous extension of growth cones and uses probabilities conditioned on the local branching order to decide the fate of a cone: elongate, bifurcate, or terminate. They demonstrated that

plausible branching patterns of distinct morphological classes could be generated solely based on differential dependencies on branch order and the number of growing cones at any moment. Only recently, they extended their models to include a geometrical component that spatially embeds a dendrite topology into 3D, i.e., complete synthetic morphologies. The NETMORPH simulator can now be used to grow large networks of morphological model neurons (Koene et al. 2009).

Context-Dependent Algorithms

Interactions Through Competition over Resources

A straightforward way to introduce interactions between synthetic neurons is by growing them simultaneously and having them compete of “resources.” A first attempt to capture competition over resources and its influence on morphology was reported in Nowakowski et al. (1992). However, they extracted the hypothesized influence of competition and inserted it as a rule into generated single morphologies. The approaches listed below synthesize multiple truly interacting morphologies.

An approach based on diffusion-limited aggregation was developed by Luczak (2006) and aimed at investigating the role of competition over resources on dendritic morphology. In his approach a developing morphology starts out as a seed located in a bounded space. Inside the bounding space, “neurotrophic particles” randomly move around and adhere to the seed (a 1-particle aggregate) and hence expand the developing morphological structure (to an $n + 1$ aggregate). The final morphology is obtained when all particles are aggregated into the synthesized morphology. By starting with several seeds in a bounded space, the growing morphologies compete over the resources (e.g., neurotrophic particles) and interactions between developing morphologies emerge. He showed that only by varying the bounding space and the initial distribution of neurotrophic particles, dendrites of distinct morphological classes could be synthesized. The resultant claim is therefore that morphologies can be interpreted as being shaped exclusively by

environmental interactions through competition and without the need of detailed statistical descriptors.

A different approach is developed by Cuntz et al. (2010) who first analyzed the tree structure of dendrite morphologies as well as functional implications of the dendritic diameter on voltage propagation in neurons. Based on these findings they proposed an algorithm in which “points of interest” are drawn from a distribution describing the density of the dendritic field before connecting these points by a modified minimal spanning tree (MST) algorithm. The modification consists of the introduction of a balancing factor so that not only the total wiring length (as in a pure MST algorithm) is taken into account but also the path length to the soma. Diameters are assigned during a post-processing step. The main advantage is that the algorithms have a direct biological interpretation in terms of one of the functions of dendrites, namely, its role in collecting inputs. Suppose that the sampled points of interest represent synapse (i.e., axonal boutons). Then, Cuntz’s approach is based on synthesizing a morphology that samples these inputs under the biological parsimony constraint (Cuntz 2012). By growing multiple morphologies at the same time in the same volume, competition occurs and shapes the morphologies.

Growth in the Midst of Attractors and Repellents

Other approaches are developed specifically with the goal of capturing environmental interactions that underlie biological growth of neurons (Scott and Luo 2001; Jan and Jan 2010).

One of the first to generate dendrite morphologies based on environmental interaction were Samsonovich and Ascoli (2003). In their work they studied factors that influenced the direction of growth of neurons. They found that the strongest factor influencing the direction was the location of the soma: pyramidal cells seem to grow away from their somata. Subsequently, they constructed a synthesis algorithm based on a hidden Markov model that computed the direction of growth of dendritic branches and found that the virtual dendrites had a

similar spatial embedding as their biological counterparts (Samsonovich and Ascoli 2005).

A slightly more detailed proposal involved a context-dependent L-system to model axon guidance under environmental cues (Feng et al. 2005). Rather than to sample the parameters for the L-system (as in L-Neuron), the values for the parameters are computed depending on the context, i.e., the modeled neuronal substrate containing attracters and repellents exerting influence on the speed of growth and direction. In the substrate, attracters and repellents were placed by the researcher and the developing axon queried their locations.

A recently developed approach by Memelli et al. (2013) explicitly uses environmental interactions to grow dendritic morphologies. In their approach, the topology is generated according to a straightforward bifurcation process (i.e., Galton-Watson process; Uemura et al. 1995). The geometry, however, is wholly based on environmental cues. Cues are then used to bias the growth direction. As a proof of principle they demonstrated how self-referential cues, that is, cues generated by the neuron itself (i.e., inertial stiffness, somatic repulsion, and self-avoidance), can readily synthesize dendrites of different neuronal classes. So far the environmental interaction is thus limited to interactions within the neuron being generated. However, a cue coming from another neuron is conceptually identical to a cue coming from the neuron itself: it is a bias on the direction of growth. Hence, this approach does not require statistical descriptors and morphologies emerge from environmental interactions.

The most elaborate approach in this category of synthesis algorithms, CX3d, is developed by Zubler and Douglas (2009). They developed a framework in which neurons can grow in accordance to growth rules that allow interaction with the environment. Each growth cone contains the growth rules for this neuron encoded in a gene-like format (Zubler et al. 2011). The growth rules may use environmental cues such as chemical gradients or other contextual information. In addition, a growing neurite can leave cues as it grows

and switch on or off growth rules depending on its environment. With this setup, many of the complexities of cortical circuits can be modeled (at least at a phenomenological level).

The list of treated synthesis algorithms is not an exhaustive list of proposed synthesis algorithms. Rather the aforementioned approaches illustrate a tendency in the development of such algorithms directing away from purely statistical, context-independent approaches towards context-dependent approaches that use biophysical mechanisms (albeit phenomenological) to generate morphologies.

Outlook

Neuronal morphologies are receiving increasing attention because of improved experimental techniques to visualize and manipulate neurons at the level of dendrites and axons and because the influence of dendritic morphology on neuronal processing in normal (Silver 2010; London and Häusser 2005; Koch and Segev 2000) and pathological cases (Emoto 2011; Moolman et al. 2004; Irwin et al. 2000) is becoming more apparent. Consequentially, a great deal of effort is invested in identifying genetic and transcription factors that underlie the formation of neuronal morphologies. These studies already resulted in better knowledge of transcription factors involved in neuronal self-avoidance, tiling, and space filling (e.g., Scott and Luo 2001; Jan and Jan 2010). Such knowledge will harness a big leap forward in the synthesis of neuronal morphologies and their variation, because, finally, neurons do grow in interaction with other neurons and agents in the neuronal matrix.

Cross-References

- ▶ [Algorithmic Reconstruction of Motoneuron Morphology](#)
- ▶ [Reconstruction, Electron Microscopy](#)
- ▶ [Reconstruction, Techniques and Validation](#)

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Systems Biology

► [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Systems Biology Markup Language (SBML)

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Synonyms

[SBML](#)

Definition

SBML (the Systems Biology Markup Language, <http://sbml.org>) is a representation format designed to enable software systems to communicate and store computational models of biological processes. It is not intended as a universal language for quantitative models; rather, SBML's purpose is to serve as a *lingua franca* for exchanging the essential aspects of a computational model between widely different software systems and databases.

Detailed Description

A vast number of modeling and simulation software tools are available today for research in biological domains such as computational neuroscience. This wealth of resources is a boon to researchers, but it also presents interoperability problems. Different software tools for systems biology are implemented in different programming languages, run on different operating systems, express models using different

mathematical frameworks, provide different analysis methods, present different user interfaces, and support different data formats. Despite working with different tools, researchers want to disseminate their work widely, as well as reuse and extend the models of other researchers. They do not want to hardcode their models as software programs nor assume everyone uses the same computing environment; they need common exchange formats for representing their models in such a way that a variety of software systems can read and write them.

SBML (the Systems Biology Markup Language) is such an exchange format for communicating and storing computational models of biological processes (Hucka et al. 2003). It is not a universal language for representing all possible models; rather, it enables communication of the essential aspects of a model, together with annotations that permit any aspect of the model to be elaborated and linked to external data resources. An important principle in SBML is that models are decomposed into explicitly labeled constituent elements (e.g., substances involved in processes, compartments where they are located, etc.); models are *not* cast directly into a specific form such as differential equations. This abstract approach makes it possible for a software tool to translate the SBML form of a model into whatever internal form the tool actually uses – whether that be differential equations, stochastic systems, or some other framework. Although SBML has its roots in general simulations of biochemical reaction networks, it can be used more generally to express other types of models where biological entities are involved in, and modified by, processes that occur over time. It is used today in research on a number of topics, including cell signaling pathways, metabolic pathways, biochemical reactions, gene regulation, and many others.

The latest generation of SBML, which is called SBML Level 3, is modular in the sense of having a defined core set of features and optional *packages* that add features on top of the core. This modular approach means that models can declare which feature-sets they use, and likewise, software tools can declare which packages they support. It also means that the development of SBML Level 3 can proceed in a modular fashion. SBML Level

3 package development is today an ongoing activity, with packages being created to extend SBML in many areas that its core functionality does not directly support. Examples include models whose species have structure and/or state variables, models with spatially nonhomogeneous compartments and spatially dependent processes, and models in which species and processes refer to qualitative entities and processes rather than quantitative ones.

Cross-References

- [Bimolecular Reactions, Modeling of](#)
- [CellML](#)
- [Dynamical Systems: Overview](#)
- [Enzyme Kinetics, Modeling of](#)
- [Gillespie Algorithm for Biochemical Reaction Simulation](#)
- [Model Reproducibility: Overview](#)
- [Numerical Integration Methods](#)
- [Signaling Pathways, Modeling of](#)
- [Software Tools for Modeling in Computational Neuroscience: Overview](#)

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Systems with Two or More Phase-Spaces

- [Multistability: Stopping Events with Single Pulses](#)

Tactile Motion

► [Somatosensory Cortex: Neural Coding of Motion](#)

Tactile Motion Integration

► [Somatosensory Cortex: Neural Coding of Motion](#)

Tactile Sensing in Insects

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Definition

The sense of touch, or tactile sense, belongs to the modality of *mechanoreception* and, more specifically, *somatosensation*. It is an exteroceptive sense that encodes information about physical contact events between a body part and an external object, thus informing the animal about object location, shape, and texture. In insects, the major organs for tactile sensing are the antennae (or feelers), although most body parts carry

mechanoreceptive sensilla, too. Antennae are segmented, actively moveable appendages of the head. Despite the actuation, the antennae are held still in some tactile sensing behaviors (passive sensing), whereas in others they are moved actively (active sensing).

Detailed Description

Passive and Active Tactile Sensing Behaviors

Insect antennae can have very different shapes, with the shape reflecting their use in behavior. Antennae serve other sensory modalities than touch, too (e.g., smell and taste). Generally, insects with elongate, unbranched antennal segments use them for tactile sensing during locomotion. For course control, e.g., in flying bees or running cockroaches, antennae are held relatively still at a constant angle, essentially serving as passive sensors for measuring wind speed or lateral clearance (e.g., distance to a wall, Camhi and Johnson 1999). During walking, antennae are often moved rhythmically, thus actively sampling the near-range environment. In such tactile exploration behavior, antennae serve as active sensors. Active exploration movements consume energy but allow sampling of a 3D volume, thus improving information gain. If, as in stick insects, the joint axis orientation vectors of the antennal joints are known, this searching movement can be

analyzed at the level of individual joint movements (e.g., Krause et al. 2013). Upon antennal contact with an obstacle, the typical searching pattern of antennal movement changes into a sampling pattern with different properties, e.g., higher cycle frequency and lower amplitude (Krause and Dür 2012). By means of active tactile sensing, insects can localize obstacles or potential foothold locations in space and respond by appropriate leg movements (Schütz and Dür 2011), whole-body orientation (Okada and Toh 2006), or make decisions about obstacle negotiation (Harley et al. 2009). Active tactile sensing with antennae also occurs in non-locomotion behaviors, for example, in aggressive behavior of crickets. For a review of antennal mechanoreception in various behaviors, see Staudacher et al. (2005).

Sensors Involved in Tactile Localization and Movement Control

Contact location along the antenna is sensed by thousands of sensilla, many of which contain mechanoreceptors (see Staudacher et al. 2005, for review of antennal mechanoreceptors). For spatial localization of a contact site, additional information is required about the antennal posture. Indeed, several proprioceptors encode postural information about antennal orientation or bending direction. These comprise a strand receptor in the head capsule (Bräunig 1985), hair fields at the two antennal joints (e.g., Okada and Toh 2000; Krause et al. 2013), and strain-encoding campaniform sensilla (e.g., Heinzel and Gewecke 1979). Encoding properties of these proprioceptors are best studied for hair fields, which encode both positional and velocity components (Okada and Toh 2001).

Kinematics of Antennal Movement

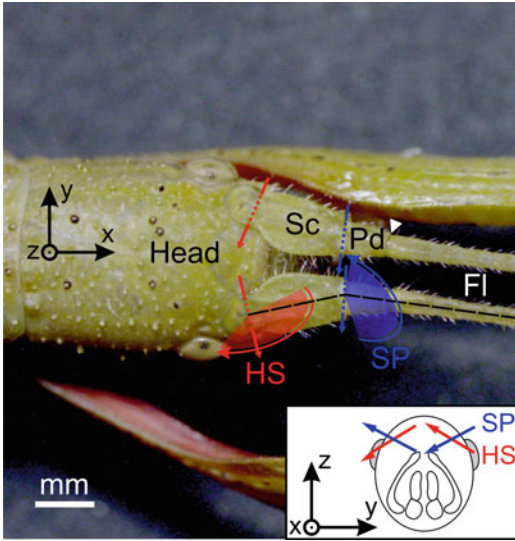
Most insect species (the *Ectognatha*, a group comprising all winged and secondarily wingless insects) have only two true antennal joints. One of them connects the head capsule to the scape (first antennal segment; synonym: Scapus), the other connects the scape to the pedicel (second antennal segment; synonym: Pedicellus). The distal flagellum cannot be moved actively relative to the pedicel, since only the head capsule and the scape contain muscles. In many insect species, like crickets, locusts, and stick insects, both antennal joints have only a single degree of freedom of motion (DoF), i.e., they function as hinge joints (Fig. 1). In this case, there is a unique set of joint angles for any antennal pointing direction. Accordingly, the inverse problem is solvable, too: the joint angles can be calculated from the 3D pointing direction, provided the joint axis vectors are known (see Krause and Dür 2004, for inverse kinematics of antennae with two hinge joints).

Given the resting position of the antennal tip, $\mathbf{p}_{\text{rest}}$, relative to the SP joint, the resting position of the SP joint, $\mathbf{p}_{\text{SP}}$, relative to the HS joint, and the orientation vectors of both joints, $\mathbf{r}_{\text{HS}}$ and $\mathbf{r}_{\text{SP}}$, the position of the antennal tip given the joint angles α and β (direct kinematics) is

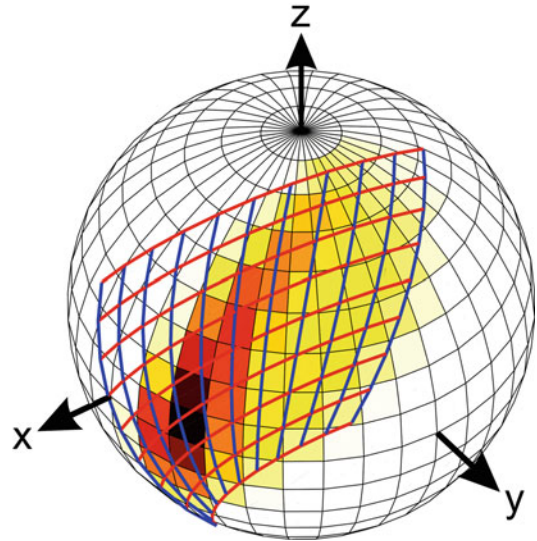
$$\mathbf{p}(\alpha, \beta) = \mathbf{R}(\alpha, \mathbf{r}_{\text{HS}})\mathbf{T}(\mathbf{p}_{\text{SP}})\mathbf{R}(\beta, \mathbf{r}_{\text{SP}})\mathbf{T}(\mathbf{p}_{\text{rest}})(0, 0, 0, 1)^T,$$

where $\mathbf{R}(\varphi, \mathbf{r})$ is a homogeneous rotation matrix describing the rotation around joint axis $\mathbf{r} = (r_x, r_y, r_z)$ by angle φ , and $\mathbf{T}(\mathbf{v})$ is a homogeneous translation matrix describing a shift by vector $\mathbf{v} = (v_x, v_y, v_z)$ within the reference coordinate system.

$$\mathbf{R}(\varphi, \mathbf{r}) = \begin{pmatrix} \cos \varphi + r_x^2(1 - \cos \varphi) & r_x r_y(1 - \cos \varphi) - r_z \sin \varphi & r_x r_z(1 - \cos \varphi) + r_y \sin \varphi & 0 \\ r_x r_y(1 - \cos \varphi) + r_z \sin \varphi & \cos \varphi + r_y^2(1 - \cos \varphi) & r_y r_z(1 - \cos \varphi) + r_x \sin \varphi & 0 \\ r_x r_z(1 - \cos \varphi) - r_y \sin \varphi & r_y r_z(1 - \cos \varphi) - r_x \sin \varphi & \cos \varphi + r_z^2(1 - \cos \varphi) & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$



Tactile Sensing in Insects, Fig. 1 *Left: Top view of a stick insect head. The left antennal segments are labeled with Sc for scape, Pd for pedicel, and Fl for flagellum. The arrowhead indicates the junction between Pd and Fl. Red and blue arrows indicate the orientation of the joint axes of the head-scape joint (HS) and scape-pedicel joint (SP), respectively. Shaded sectors and round arrows indicate the slanted planes of motion of the scape (red) and pedicel*



(blue). See insert for a schematic frontal view. Right: Antennal working range during active searching behavior of a walking stick insect. Red and blue grid lines show 10° steps in joint angles of the left HS and SP joints, respectively. The underlying heat map shows the likelihood of the antenna to pass through a given sector of the spherical grid, with darker colors indicating higher likelihood. The head-fixed reference coordinate system is indicated by (x, y, z)

$$T(\mathbf{v}) = \begin{pmatrix} 1 & 0 & 0 & v_x \\ 0 & 1 & 0 & v_y \\ 0 & 0 & 1 & v_z \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Note that each joint axis orientation vector, $\mathbf{r}$, may be significantly slanted with respect to the head-fixed reference coordinate system (e.g., in Fig. 1). The direction of $\mathbf{r}$ determines how the rotation direction of $\mathbf{R}(\varphi, \mathbf{r})$ corresponds to the sign of the angle φ . This is because rotation angles obey the right-hand rule: if the thumb of the right

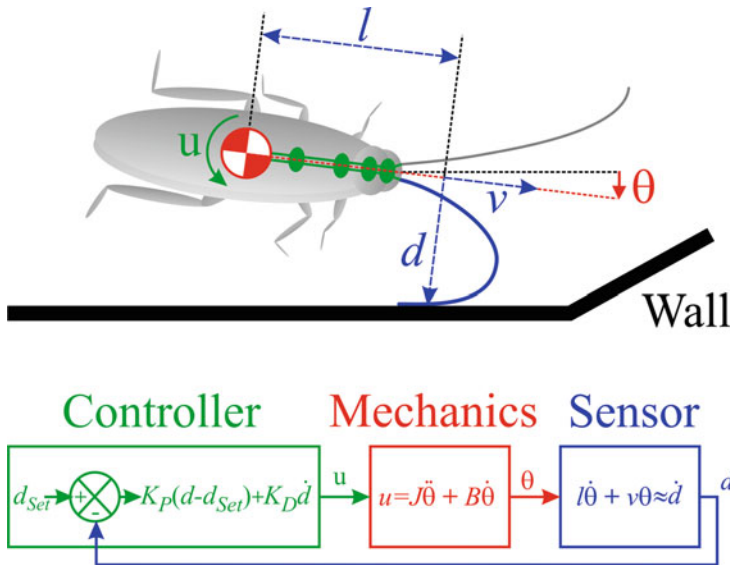
hand is aligned with $\mathbf{r}$, then the flexed fingers of the same hand indicate the direction of positive φ .

As the SP joint always has a single DoF only, the right three matrices of the direct kinematics equation are the same for all insect species. Additional DoF of the HS joint can be added by multiplying an additional $\mathbf{R}(\varphi, \mathbf{r})$ for each DoF. For example, for a ball-and-socket HS joint with 3 DoF (e.g., of a honey bee), the direct kinematics equation reads

$$p(\psi, \theta, \phi, \beta) = \mathbf{R}(\psi, \mathbf{x})\mathbf{R}(\theta, \mathbf{y})\mathbf{R}(\phi, \mathbf{z})\mathbf{T}(\mathbf{p}_{\text{SP}})\mathbf{R}(\beta, \mathbf{r}_{\text{SP}})\mathbf{T}(\mathbf{p}_{\text{rest}})(0, 0, 0, 1)^T,$$

where $\mathbf{x}$, $\mathbf{y}$, and $\mathbf{z}$ are the unit vectors of the reference coordinate system and ψ , θ , and ϕ are

the *roll*, *pitch*, and *yaw* rotation angles about these axes.



Tactile Sensing in Insects, Fig. 2 *Top:* Schematic of the wall-following paradigm for tactual course control in running cockroaches. The bent antenna (blue) maintains contact to the wall and transmits information about the lateral distance, d , which depends on the contact distance, l , and velocity, v . Based on the estimated value of d , the nervous

system (green) has to adjust the net polar moment u at the point of rotation (red). *Bottom:* Block diagram of the control model proposed by Cowan et al. 2006, where the neural PD controller (green) adjusts u , thus affecting the body mechanics (red) and, in turn, the lateral contact distance experienced by the tactile sensor (blue)

Tactually Mediated Course Control During Running

A nice example for tactually mediated course control in locomotion is the wall-following paradigm in cockroaches, in which a running cockroach maintains a constant distance to a wall by use of information from antennal mechanoreceptors (Camhi and Johnson 1999). Figure 2 sketches an experiment by Cowan et al. (2006), in which a cockroach is following a straight wall until a corner, where the antenna senses a change in body-to-wall distance and causes the body to turn away from the wall. Assuming the simple case where the velocity heading of the animal's point of rotation coincides with the body orientation angle, the change of the lateral distance to the wall, d , depends on the contact distance, l , the velocity, v , and the body orientation angle θ according to $\dot{d} \approx l\dot{\theta} + v\theta$ (see Fig. 2, top). The control of the body orientation can be modeled by a Proportional-Derivative controller (PD controller) that adjusts the net polar moment, u , according to both the sensed distance to the wall, d , and the sensed rate of approach, $\dot{d}$, with $u = K_P(d - d_{Set}) + K_D\dot{d}$,

where K_P and K_D are the gains of the proportional and the derivative term of the difference between d and its set value, d_{Set} (Fig. 2, bottom). This moment is then filtered by the rotational dynamics of the body according to $u = J\ddot{\theta} + B\dot{\theta}$, where J is the polar moment of inertia, and B is a damping coefficient. The free parameters of this model may be estimated from stride-to-stride changes in kinematic measures from motion capture, using non-linear regression analysis (for details, see Cowan et al. 2006).

Cross-References

- [Cercal System](#)
- [Proprioception](#)
- [Leech Local Bend: Neural Coding of Touch Location](#)

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Target Selection vs. Response Selection

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Definition

Target selection refers to the process of selecting a single object from a field of multiple objects as the goal of a movement. It can also be used to refer to the deployment of covert attention to a selected object, even when an overt movement is not

ultimately made. For overt actions, target selection specifies the movement goal (or end point), but not necessarily the effector that will be used or the trajectory that will be taken to reach the goal. In contrast, response selection is the process of choosing the appropriate action to take in response to a given stimulus. It is the intermediate process occurring between discrimination of a stimulus and planning of an action and usually involves a learned stimulus-to-response (S-R) mapping. For example, when driving a car toward an intersection, the usual response to a red traffic light (stimulus) is to press the brake pedal in order to stop the car (response).

Detailed Description

Target Selection

Natural environments are often complex and crowded with many different objects. Thus, the production of accurate goal-directed actions requires the selection of a single movement target and suppression of competing potential targets. A similar selection process is thought to underlie our ability to covertly shift attention to a target object of interest while ignoring distracting objects. Target selection is often modeled as a competition among potential targets occurring on a hypothetical “priority map” (e.g., Koch and Ullman 1985; Wolfe 1994; Itti and Koch 2001; Zelinsky 2008). The level of activation in the priority map associated with each potential target is dependent upon both top-down factors (such as the behavioral relevance of the target) and bottom-up factors (such as perceptual salience). In models where bottom-up factors are used exclusively, the priority map is often called a “saliency map.” Target selection occurs when the object with the highest level of activation in the map is selected and distracting objects are suppressed.

Much of the empirical research on target selection has focused on eye movements or arm-reaching movements. Based on physiological evidence, there does not appear to be a single priority map in the brain that is used for target selection. Rather, neural activity with the properties expected of a priority map can be found in several different regions of the brain, including areas in

the frontal and parietal cortices (e.g., the frontal eye field (Schall and Thompson 1999) and the lateral intraparietal area (Bisley and Goldberg 2010) for eye movements and the dorsal premotor area (Cisek and Kalaska 2010) and parietal reach region (Scherberger and Andersen 2007) for reaching movements). Subcortical areas involved in target selection include the basal ganglia (Shires et al. 2010), superior colliculus (McPeck and Keller 2004; Song et al. 2011; Krauzlis et al. 2013), and pulvinar (Wilke et al. 2010). It is largely unknown how target selection-related activity is coordinated across these different areas.

Response Selection

While target selection implies the spatial selection of a target, response selection describes a more abstract process: specifically, the linkage between a percept and a motor response. This link is usually described in terms of a stimulus-to-response (S-R) mapping, which indicates the appropriate response to make given a particular stimulus. The difficulty of response selection is dependent upon both the number of S-R pairs in the mapping (Hick 1952) and the compatibility of the mapping itself (Fitts and Seeger 1953; Kornblum et al. 1990). For example, in a task in which subjects are presented with four vertical lines in a row and told to press one of four buttons to indicate which line is the shortest, response selection is easier when the relative location of the correct response button corresponds to the location of the line (compatible S-R mapping) than if the arrangement of response buttons is shuffled relative to the positions of the lines to which they correspond (incompatible S-R mapping).

In many situations (especially those involving incompatible S-R mappings), it is difficult or impossible for subjects to perform response selection using more than one S-R mapping at a time, even when the two mappings involve different sensory modalities and different response effectors. This has led to the suggestion that response selection is a significant processing bottleneck for

humans (Pashler 1994). Neural activity related to response selection can be found across a network of brain areas, including the prefrontal, premotor, cingulate, and parietal cortices (Bunge et al. 2002; Schumacher and Jiang 2003; Rushworth et al. 2004; Hoshi and Tanji 2007).

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Temperature Coefficient

- [Q10: The Effect of Temperature on Ion Channel Kinetics](#)

Temporal Coding

- [Somatosensory Neurons: Spike-Timing](#)

Temporal Difference (TD) Learning

- [Reinforcement Learning in Cortical Networks](#)

Temporal Recurrent Neural Networks

- [Recurrent Network Models, Reservoir Computing](#)

Tempotron Learning

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Definition

Tempotron learning is an online gradient-based supervised learning rule for spiking neuron models that implement a binary classification of multi-neuronal spike patterns. A neuronal classifier whose synaptic efficacies are controlled by the tempotron learning rule is referred to as tempotron. The tempotron implements a binary decision rule: A spike pattern is classified as *target* pattern if the tempotron fires at least one output spike in response to the pattern. If the neuron remains silent, the pattern is classified as *null* pattern. The tempotron is trained on a training set consisting of labeled target and null patterns. When the tempotron misclassifies an input pattern during training, i.e., when its output does not match the desired response specified by the label, the tempotron learning rule adjusts each of the neuron's synaptic efficacies according to its contribution to the maximal postsynaptic membrane potential: increasing it when the desired response is to fire at least one spike and decreasing it if the correct response is to remain silent.

Detailed Description

Architecture and Task

The tempotron (Gütig and Sompolsky 2006) refers to a deterministic spiking neuron model with N synaptic afferents whose synaptic efficacies ω_i with $i = 1, \dots, N$ are governed by the tempotron learning rule. In the below treatment, the scalar efficacy ω_i refers to amplitude of the

postsynaptic potential (PSP) that is elicited by a single spike of the i th afferent, but more complex synapse models are possible. The task of the tempotron is to implement a binary classification of set of input spike patterns, each of which is labeled either as target or as null pattern. A correct classification requires the neuron to fire at least one spike in response to input patterns from the target class and to remain silent in response to input patterns from the null class.

Learning Rule

The tempotron learning rule solves the temporal credit assignment problem underlying the task of changing a neuron's response from not firing to firing. Since the tempotron classification task does not specify or constrain at what time an output spike in response to a target pattern should occur, the learning rule must choose an appropriate time and credit the neuron's synaptic efficacies accordingly. Tempotron learning uses the maximum postsynaptic potential $V_{\max}$ as objective function such that synaptic efficacies are modified along the gradient

$$\Delta\omega_i \propto \frac{\partial V_{\max}}{\partial \omega_i} = \frac{\partial V(t)}{\partial \omega_i} \Big|_{t=t_{\max}} \quad (1)$$

after each error trial. Each synaptic efficacy is changed according to its contribution to the postsynaptic membrane potential at the time $t_{\max}$ of the maximal postsynaptic depolarization. When the tempotron fails to fire in response to a target pattern, synaptic updates can be obtained by straightforward application of the above rule. However, when erroneous spikes are elicited by null patterns, a direct application of the above rule would require the evaluation of the subthreshold postsynaptic membrane potential without reset. Because it is unclear whether and if so how a neuron could gain access to this quantity, $V(t)$ in the original tempotron model (Gütig and Sompolinsky 2006) was replaced by a "shunted" voltage trace, which ignores all input spikes that arrive after the first action potential is fired.

Implementations

Tempotron learning has been implemented with current- (Gütig et al. 2013; Gütig and

Sompolinsky 2006) and conductance-based (Gütig and Sompolinsky 2009) leaky integrate-and-fire (LIF) neuron models. In the current-based LIF, the subthreshold membrane potential can be written as linear sum of PSPs, i.e.,

$$V(t) = \sum_{i=1}^N \omega_i \sum_{t_i^j < t} K(t - t_i^j) + V_{\text{rest}}, \quad (2)$$

where t_i^j denote the spike times of the i th afferent. The kernel

$$K(t - t_i^j) = V_0 \left(\exp \left[-\left(t - t_i^j \right) / \tau_m \right] - \exp \left[-\left(t - t_i^j \right) / \tau_s \right] \right)$$

is the normalized PSP contributed by each incoming spike with τ_m denoting the membrane integration time constant and τ_s denoting time constant of the exponentially decaying synaptic currents. The factor V_0 normalizes PSP kernels to 1 such that unitary PSP amplitudes are given by ω_i . The filter $K(t - t_i)$ is causal and vanishes for $t_i > t$. When $V(t)$ crosses the firing threshold at 1, the neuron fires a spike, and the voltage undergoes a smooth reset to V_{rest} by shunting all incoming spikes that arrive after the output spike (Gütig and Sompolinsky 2006).

Evaluation of the gradient (Eq. 1) for the voltage kinetics of the current-based LIF (Eq. 2) results in the synaptic update rule:

$$\Delta\omega_i = \pm \lambda \sum_{t_i^j < t_{\max}} K(t_{\max} - t_i^j)$$

where the plus sign refers to increases in synaptic efficacies when the tempotron failed to fire in response to a target pattern and the minus sign to a reduction of the weights when an erroneous spike was fired in response to a null pattern. The learning rate λ controls the overall scale of the synaptic updates.

Note that in the conductance-based LIF, the tempotron update rule is substantially more complex. This is due to the global coupling of input spikes through their contribution to the total postsynaptic conductance, which modulates the

effective integration time constant of the postsynaptic compartment (Gütig and Sompolinsky 2009).

Applications

Tempotron learning has been applied to a number of diverse neural classification tasks. Together, these applications have demonstrated the high capacity of simple neural architectures to read out a broad range of spike-timing-based neural representations including spike latency and temporal correlation codes (Gütig and Sompolinsky 2006). In an application to electrophysiologically recorded spike trains, the tempotron has been successfully used to decode visual stimulus information encoded by the relative spike latencies of retinal ganglion cell population activity (Gütig et al. 2013). In an application to auditory processing, a conductance-based implementation of the tempotron has been shown to be capable of subserving time-warp-invariant information processing (Gütig and Sompolinsky 2009). The storage capacity of the tempotron and the structure of its solution space have been studied analytically in Rubin et al. (2010).

Context

A growing number of electrophysiological studies in the 1990s and 2000s have described instances of neural information processing in central nervous pathways, where sensory information is encoded by the precise relative timing of action potentials within multi-neuronal spiking activity (VanRullen et al. 2005). During the same period, synaptic physiologists have uncovered novel rules of synaptic plasticity in which the precise timing of presynaptic and postsynaptic action potentials influences changes in synaptic efficacies (Feldman 2012). The tempotron has been developed to answer the question whether and if so how neurons can learn to decode spike-timing-based neural representations. In a parallel line of research, computational neuroscientists have also asked to what degree neuronal architectures are capable of encoding information in precise sequences of output spikes (Gütig 2014; Pfister et al. 2006; Ponulak and Kasinski 2010; Xu et al. 2013).

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The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks

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Definition

The Virtual Brain (TVB) (TVB main site <https://www.thevirtualbrain.org/>) ecosystem offers a simulation environment for Large-Scale Brain Networks: by manipulating network parameters, in particular the brain's structural connectivity,

The Virtual Brain simulates a whole brain behavior as it is commonly observed in clinical scanners (e.g., EEG, MEG, fMRI).

Though The Virtual Brain incorporates the complex world of neuro-chemistry only to a small degree, it gains a lot by not becoming as complex as the brain itself. Instead, The Virtual Brain embraces and extends concepts from computational, cognitive, and clinical neuroscience in order to drastically reduce the model’s complexity while still keeping it sufficiently realistic and delivering the same output as clinical brain-scanners.

Recent efforts are now linking TVB’s large scale modeling approach with other scales in brain simulation.

Detailed Description

Application

We started developing TVB with one main objective in mind: to be useful for a large variety of computational neuroscience research and clinical efforts by enhancing accessibility, performance, and understanding of primary and auxiliary modeling tools. This translated into the software being open-source (TVB source code repositories: <https://github.com/the-virtual-brain>) (under GPLv3), available on all major operating systems, and having both a web graphical user interface (for fast access to features and an easy learning curve) but also a command line interface for fine tuning by experts (Table 1).

Packages

TVB’s code base is modular, resulting in multiple packages to release and distribute. The principal packages are as follows:

- tvb-library (<https://pypi.org/project/tvb-library/>) is our most critical package, holding the simulator code. It can be used by itself through command line access in a Python environment.
- tvb-framework (<https://pypi.org/project/tvb-framework/>) depends on tvb-library, and adds

The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Table 1 Technical stack for TVB ecosystem: supports all major operating systems, it is Python based (only version 3 supported as of 2020), with many 3rd party dependencies, a rich project management set of tools (Jira) and extensive documentation (Sphinx, Confluence, Wiki)

TVB technical features	
License	GPL v3
Citation	Sanz Leon & others (2013) The Virtual Brain: a simulator of primate brain network dynamics <i>Frontiers in Neuroinformatics</i> 7:10. https://doi.org/10.3389/fninf.2013.00010
Supported OS	Windows, Mac, Linux
Access	Console (Command Line API) and Web GUI
Main Prog. Language	Python (version 3)
Main 3rd party dependencies	Numpy, Scipy, Numba, CherryPy, WebGL, HDF5
Project Mng	Atlassian Jira ^a
Code Repository	Github (public repo) ^b
Continuous Integration	Jenkins, Travis
Documentation	Sphinx ^c , Confluence ^d

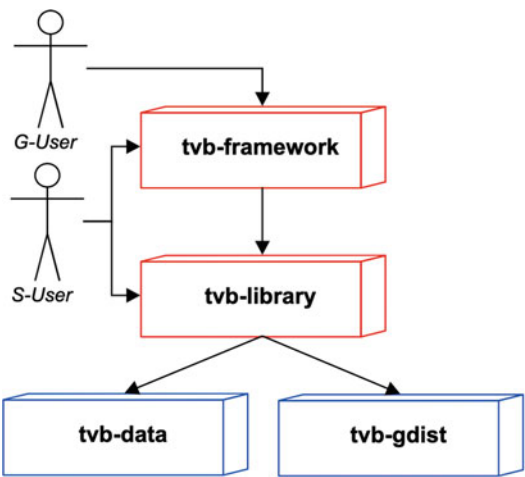
^aJira TVB <https://req.thevirtualbrain.org/>
^bTVB source code repositories: <https://github.com/the-virtual-brain>
^cTechnical docs: <http://docs.thevirtualbrain.org/>
^dConfluence <https://conf.thevirtualbrain.org/>

- storage functionality (HDF5 and PostgreSQL DB) as well as a web graphical interface.
- TVB-gdist (<https://pypi.org/project/tvb-gdist/>) is a small C++ module used for computing geodesic distances on a surface (like the cortical waved surface) for the Local Connectivity calculus in TVB. tvb-gdist is an optional dependency for tvb-library (as long as surface simulations are not necessary to be launched).
 - tvb-data (Zenodo <https://zenodo.org/record/3688773#.XwCPUJMzaL8>) is a collection of demo data compatible with TVB software. It can be used for quickly testing our functionality. Personal datasets are usually preferred when working with TVB (Fig. 1).

TVB’s main packages are stable, in terms of software maturity, having had regular publicly releases since 2012. Since then, we have constantly added new features and fix bugs in these packages, but the API mostly remains unchanged,

unless signaled by the version number change (e.g., from version 1.5.* to 2.0).

Under the TVB umbrella, we developed an ecosystem of packages that communicate through APIs and serve various use-cases (e.g., The Virtual Epileptic Patient, data preprocessing); thus, the main packages are not the only ones we maintain and distribute. Part of this ecosystem can be observed in Fig. 2.

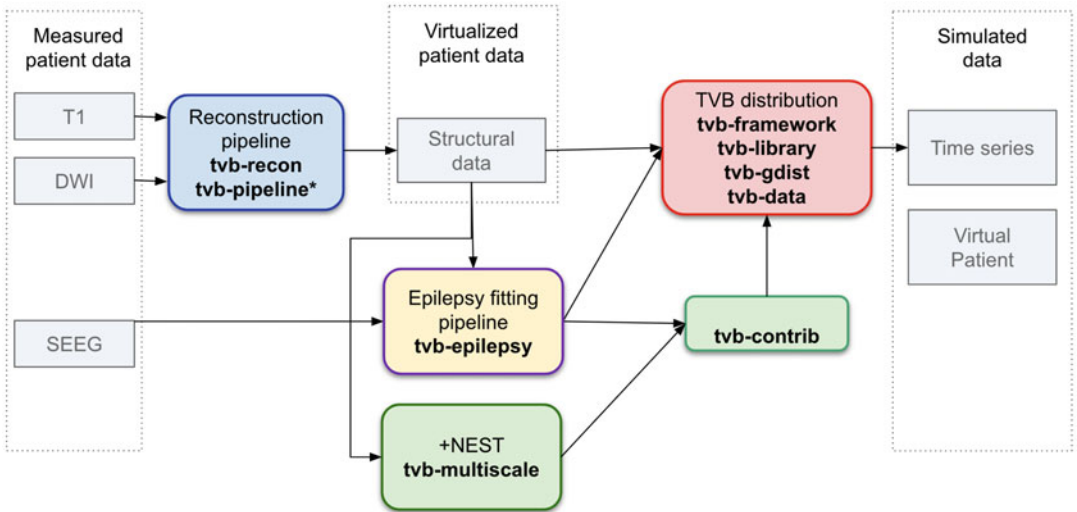


The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 1 TVB main packages and their direct relations. Packages with a RED border are the main ones. Packages in BLUE are optional. S-User access TVB through scripting or command line access. G-User access TVB through a graphical user interface (web based)

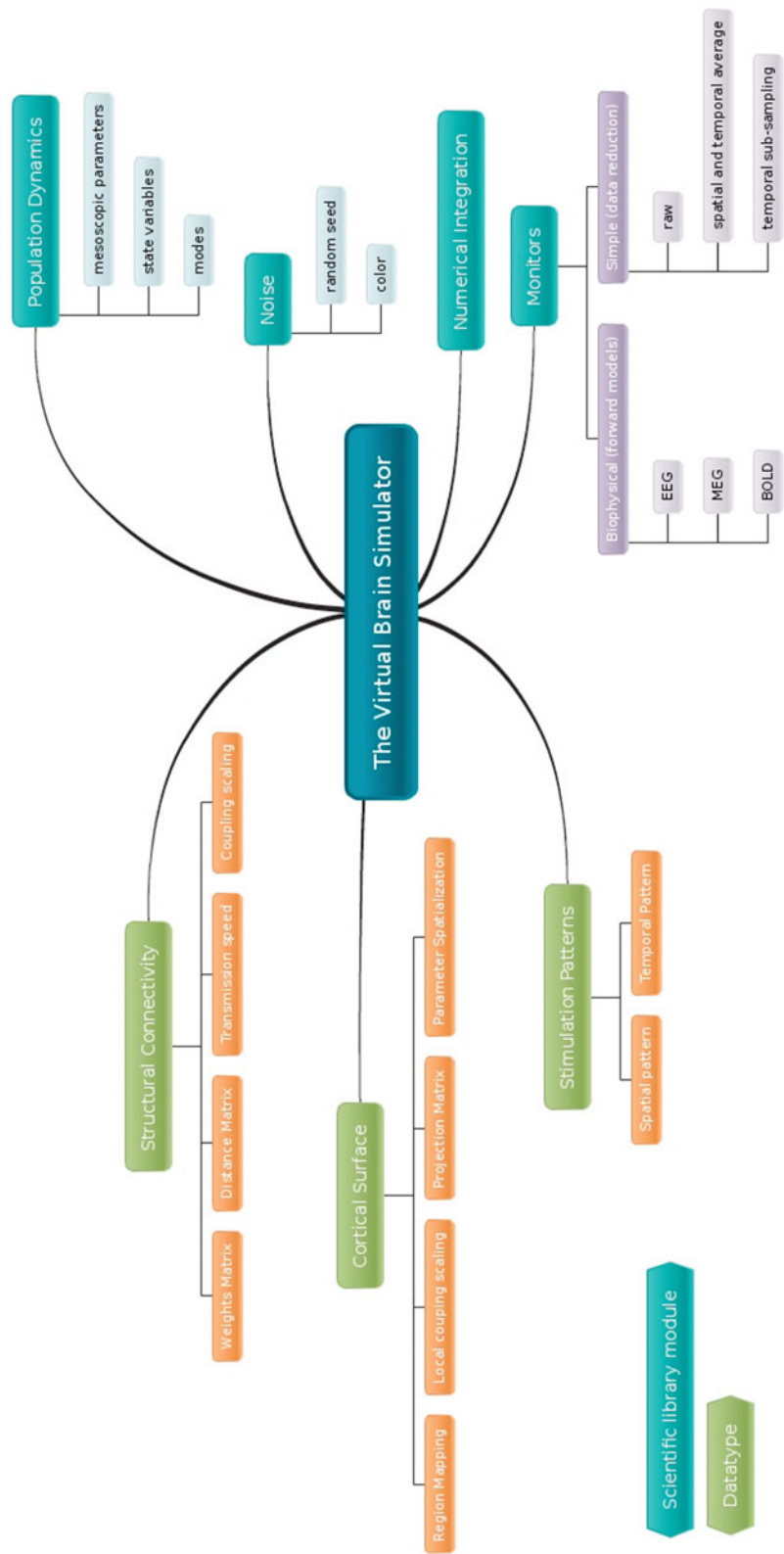
Architecture of tvb-Library

tvb-library package holds the code for our main feature: the simulator, which will be represented by a Simulator class, capable of receiving all input parameters configurable by the users, loop over time steps, and return at each step the numeric results (as TimeSeries steps) (Fig. 3).

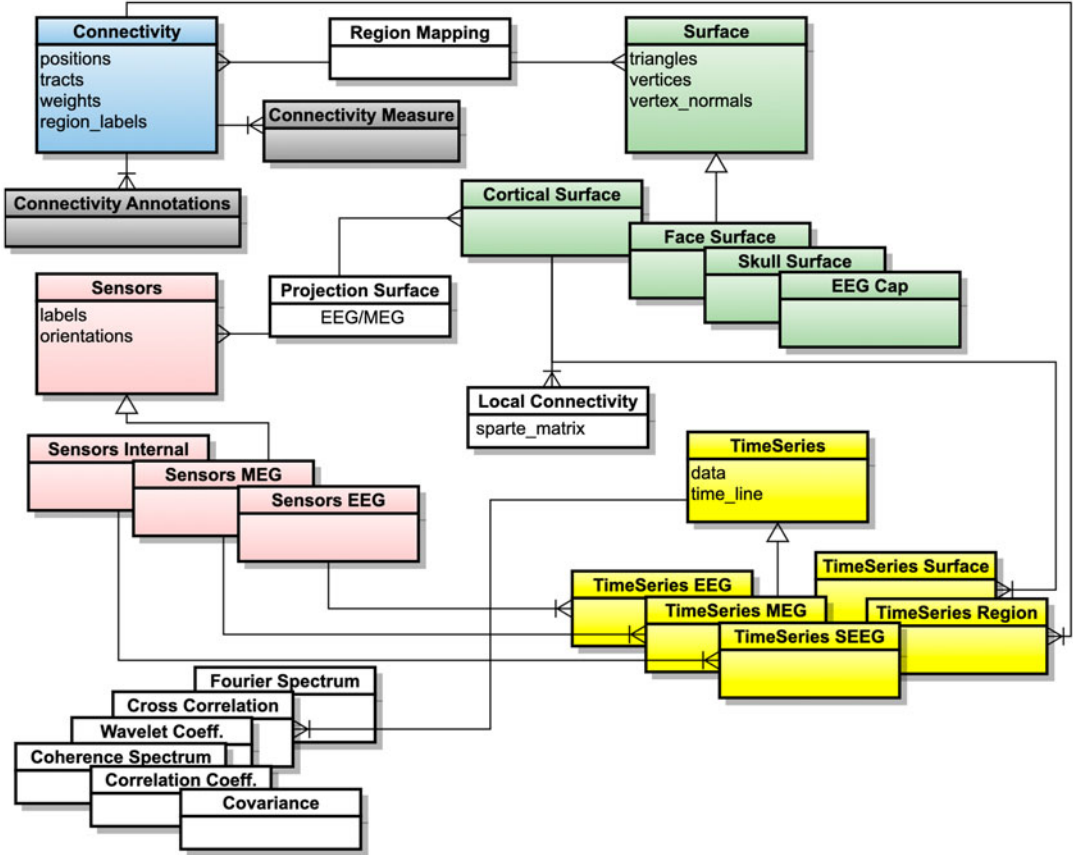
The Simulator class will work with generic Large Scale Connectivity (often referred to as the Connectome), Neuronal Mass Models, generic Integrators, Coupling Methods (between simulated regions), and generic Monitors (for integrating the results). This is implemented in Python through inheritance, and then at runtime, we polymorphically use the right differential equation, integration method, etc., based on the current configuration given by the user. This makes our simulator flexible and easy to extend



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 2 Part of TVB ecosystem with our main packages from Fig. 1 (collapsed under the red shape) plus adjacent other packages



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 3 TVB simulator main components. (Sanz Leon & others (2013) *The Virtual Brain: a simulator of primate brain network dynamics* *Frontiers in Neuroinformatics* 7:10. <https://doi.org/10.3389/fninf.2013.00010>)



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 4 TVB data model – classes diagram

(e.g., by adding new Model classes) without losing too much in performance or simplicity.

Next to the simulator, still part of *tvb-library*, we also keep our base data model. It consists again of a series of Python classes, with various relations between them (inheritance, aggregation, association). They all inherit from `HasTraits` base class, and they annotate each of their fields with at least a type, plus short documentation and optionally an accepted range interval (useful especially if we are to run parameter space explorations) (Fig. 4).

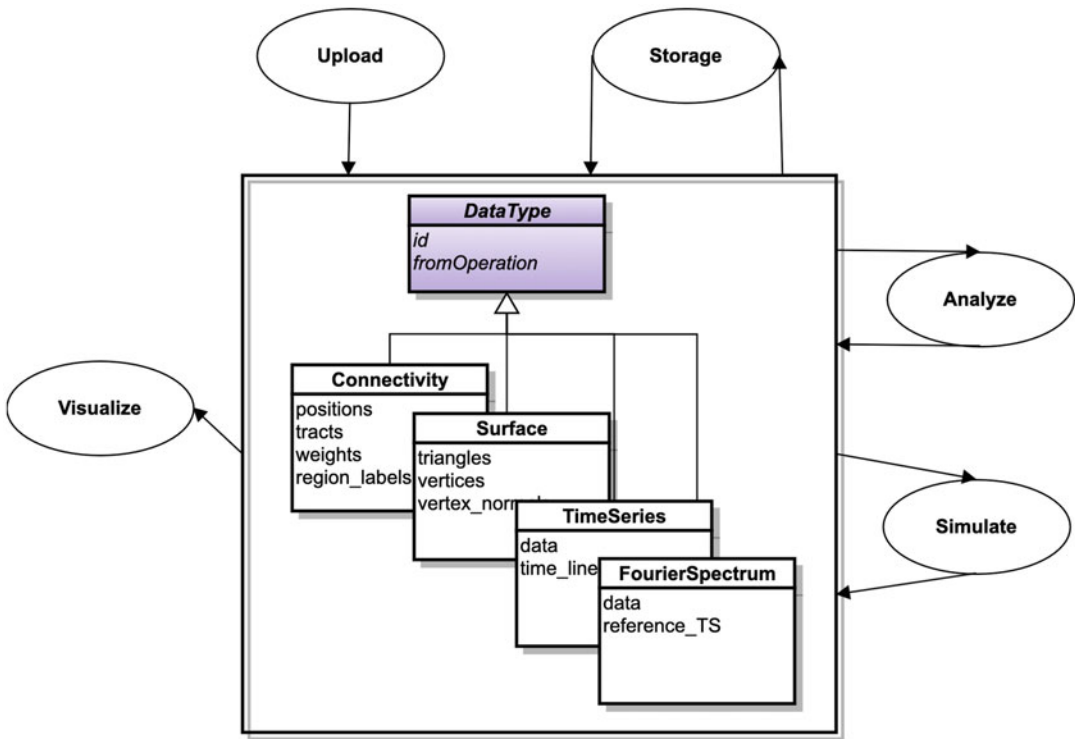
Architecture of *tvb-Framework*

tvb-framework contains several extra features for the TVB ecosystem: a data storage, a small flow

orchestrator for running multiple operation types, a web GUI, a REST API.

tvb-framework depends on *tvb-library*, both for the simulation operation, but also for its data types, which will be central into our orchestrations as we want to have it data-oriented: `DataTypes` are the most important resource in TVB, stored in (possibly very large) HDF5 files, and indexed in a relational DB (Fig. 5).

tvb-framework introduces an important grouping entity named **Project**, which is left flexible at the user’s need of what it represents (one single subject, one group case-study, one patient recording, etc.) but it is the central piece used when sharing data: everything under a project can be shared with colleagues using the same TVB installation (Fig. 6).



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 5 Data oriented architecture. Each TVB operation can get DataTypes as input and can produce other DataTypes

TVB Web GUI can be installed either on a local machine (then used by a single user) or on a shared server or cloud environment, and then someone will assume the role of administrator, and others can manage their own Projects in this installation, without being able to see the other's work, unless explicitly shared by the Project creator (Fig. 7).

tvb-framework uses a relational database with indexed metadata for quick access. For example, when we want to check if a compatible Surface and RegionMapping exists in the current Project for using it with the current Structural Connectivity for launching a surface based simulation, the PostgreSQL DB responds very fast with an answer. Also, we use the shared relational DB together with a shared file storage, as synchronization point, when Operations are launched in a distributed manner from TVB (cloud or cluster installations).

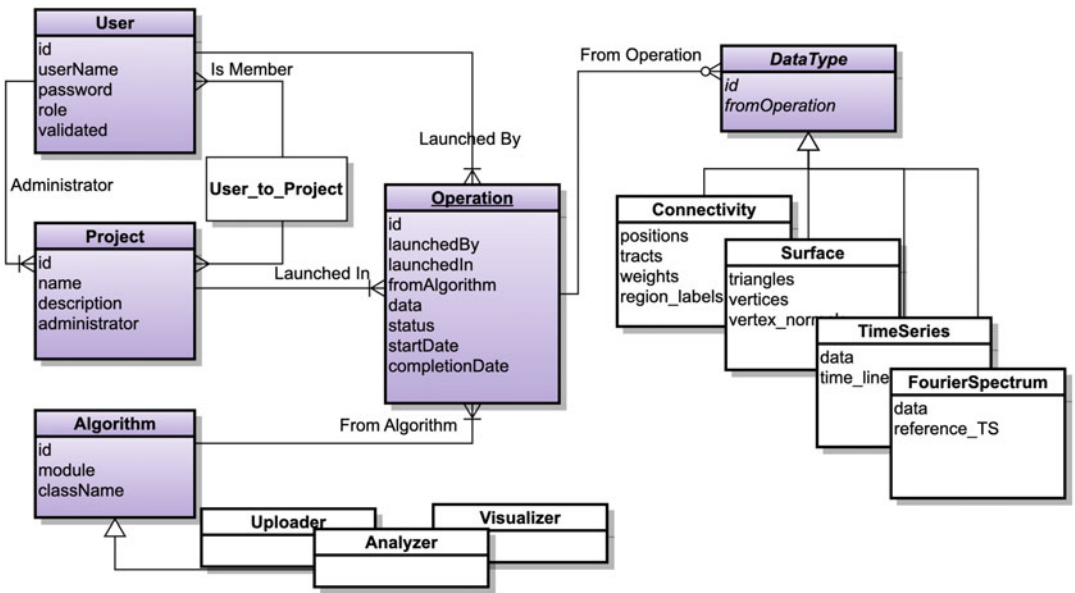
Example Code

Coding with TVB requires Python knowledge. One would start by preparing a Simulator instance and changing the defaults as necessary. Full example code: https://github.com/the-virtual-brain/tvb-root/blob/master/framework_tvb/tvb/interfaces/command/demos/operations/run_simulation.py:

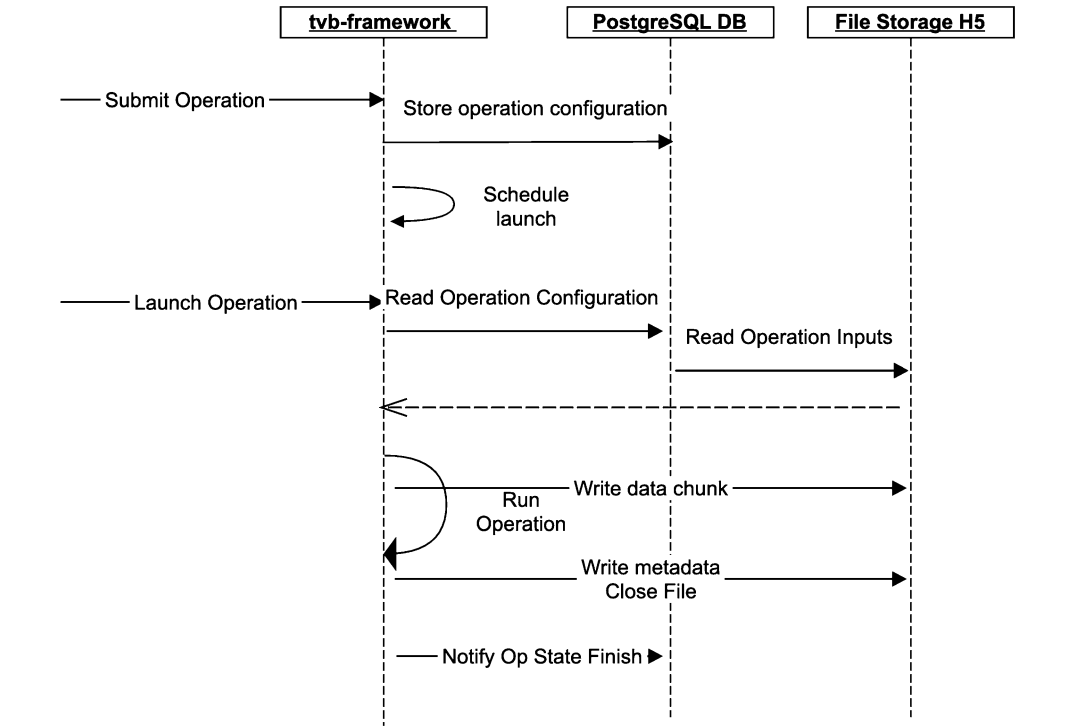
```
simulator = Simulator()
simulator.connectivity = my_c
simulator.coupling = Scaling()
simulator.simulation_length = 100
```

Then, instantiate a SimulatorService and launch the configured simulation as a framework operation:

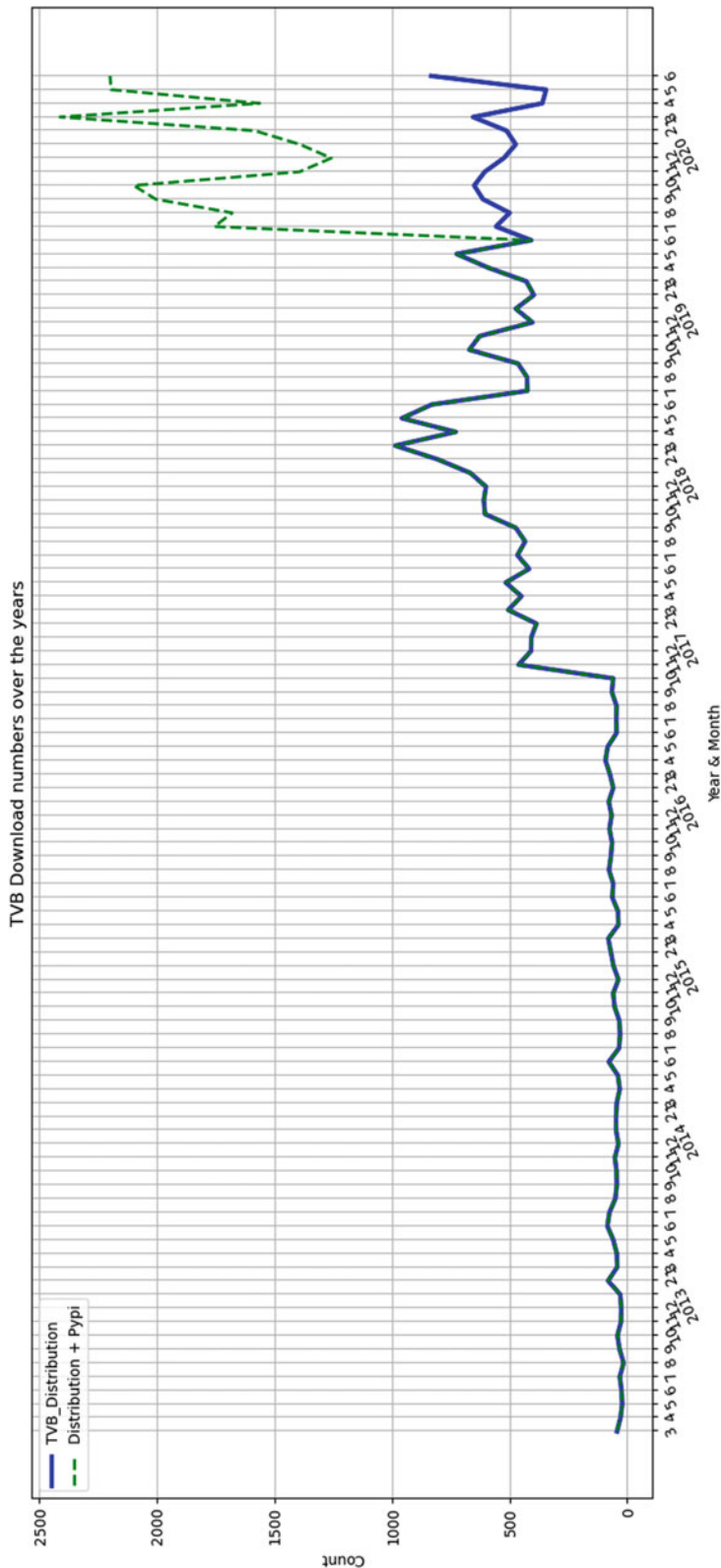
```
service = SimulatorService()
operation = service.
async_launch_and_prepare_simulation
    (BurstConfiguration(proj.id),
    proj.administrator, proj,
    algo, simulator)
```



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 6 TVB flow models inside tvb-framework



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 7 Sequence diagram for running an operation with TVB-framework



The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks, Fig. 8 TVB downloads number evolution since 2012 (when the first release happened) until the end of June 2020. The blue line counts downloads of TVB_Distribution (ready to use package). The green dotted line adds the Pypi downloads for tvb-library also (not counted before June 2019)

Now, it only remains to wait for the operation to finish and to collect the result:

```
while not operation.has_finished:
    sleep(5)
operation = get_operation_by_id(
    operation.id)
if operation.status == FINISHED:
    ts = dao.get_generic_entity(
        TimeSeriesRegionIndex,
        operation.id,
        "fk_from_operation")[0]
```

History

In October 2010, Viktor Jirsa, Randy McIntosh, Jochen Mersmann, and Lia Domide convened in Marseille, France, and drafted the first architecture of TVB in the foundational TVB white paper (TVB White Paper in its raw form: https://github.com/the-virtual-brain/tvb-root/tree/master/tvb_documentation/manuals/DeveloperReference). With the addition of Petra Ritter as applications coordinator, the TVB team advanced rapidly resulting in the first public release version 1.0 in November 2012. Since then the code base has evolved steadily with major contributions made by Stuart Knock, Marmaduke Woodman, Paula Sanz-Leon, Paula Popa, Mihai Andrei, and many others. In 2020 TVB has over 30,000 recorded downloads. TVB is today a product with a lifespan spreading over multiple projects (often equivalent to funded grants), notably the European IT flagship Human Brain Project (Human Brain Project: <https://www.humanbrainproject.eu/en/>) (Fig. 8).

Since 2014 TVB participates with proposed projects and mentors in the Google Summer of Code program (<https://summerofcode.withgoogle.com/>), under the INCF umbrella, thus giving students around the world the chance to contribute and learn interesting things about neuroscience in a real project. The original TVB reference is Sanz-Leon et al (2013). Integration of neuroinformatics tools for TVB are provided in Ritter et al (2013) and Woodman et al (2014). TVB theory is elaborated in Sanz-Leon et al (2015). All other references provide applications of TVB in diverse domains including basic and clinical neuroscience.

Cross-References

- [NEURON Simulation Environment](#)
- [NEST: The Neural Simulation Tool](#)
- [LFPy: Multimodal Modeling of Extracellular Neuronal Recordings in Python](#)

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Thermodynamic Models of Ion Channels

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Definition

Thermodynamic models provide a kinetic description of ion channels starting from first principles. Instead of using empirical functions for the voltage dependence of the parameters of the ion channel, they are deduced from a physically plausible framework. This framework formalizes the effect

of the interaction between the electric field and the ion channel. This interaction can be linear or non-linear, leading to different classes of models for voltage-dependent ion channels.

Detailed Description

Introduction

The first quantitative description of the voltage dependence of ionic currents and their role in generating action potentials was provided by Hodgkin and Huxley (1952). This description, however, was semiempirical. They postulated that the ionic conductance was dependent on the assembly of “gating particles,” acting independently and in a voltage-dependent manner. This formalism gave rise to the well-known Hodgkin-Huxley set of equations, which could account quantitatively for the genesis of action potentials in squid giant axon. However, the voltage dependence of the rate constants in the model was fit to voltage-clamp measurements using empirical functions of voltage.

Instead of using empirical functions, it is also possible to deduce the functional form of the voltage dependence of the rate constants from thermodynamics and in particular from the effect of the electric field on the free energy of the transition between conformational states of the channel. These *thermodynamic models* (Eyring et al. 1949; Tsien and Noble 1969; Hill and Chen 1972; Stevens 1978; Hille 2001) provide a firm physical basis to constrain and parameterize the voltage dependence of rate constants, which are then used to fit voltage-clamp data.

In this chapter, we review these thermodynamic models of ion channels by contrasting two types of models. We first review the *linear thermodynamic models*, which assume that the effect of the electric field is linear on the free energy, which results in simple exponential dependences of transition rates. Second, we review *nonlinear thermodynamic models* (Destexhe and Huguenard 2000), where the effect of the electric field on the free energy can be nonlinear, capturing more realistic effects that can be fundamental for ion channel function.

Thermodynamic Models

Thermodynamic models explore the possibility of deducing the exact functional form of the voltage dependence of the model from thermodynamics. This type of model assumes that the gating of ion channels operates through successive conformational changes of the ion channel protein. Consider an elementary transition between an initial (I) and a final (F) state, with a rate constant $r(V)$ that is voltage dependent:



According to the theory of reaction rates (Eyring 1935; Johnson et al. 1974), the rate of the transition depends exponentially on the free energy barrier between the two states:

$$r(V) = r_0 e^{-\Delta G(V)/RT}, \quad (2)$$

where r_0 is a constant and $\Delta G(V)$ is the free energy barrier, which can be written as

$$\Delta G(V) = G^*(V) - G_0(V) \quad (3)$$

where $G^*(V)$ is the free energy of an intermediate state (activated complex) and $G_0(V)$ is the free energy of the initial state. The relative values of the free energy of the initial and final states (G_0 and G_1) determine the equilibrium distribution between these states, while the kinetics of the transition depend on the size of the free energy barrier $\Delta G(V)$.

Linear Thermodynamic Models It is usually assumed that a linear voltage dependence of the free energy is sufficient to describe the gating of ion channels (Tsien and Noble 1969; Stevens 1978; Borg-Graham 1991; Andersen and Koeppe 1992; Hille 2001). According to these “linear thermodynamic models,” the free energy of a given state i can be written as

$$G_i(V) = A_i + B_i V \quad (4)$$

where the constant A_i corresponds to the free energy that is independent of the electrical field and the linear term $B_i V$ to the effect of the electrical

field on isolated charges and rigid dipoles (Hill and Chen 1972; Stevens 1978; Andersen and Koeppe 1992). For example, linear terms in V will result if the conformations differ in their net number of charges or if the conformational change is accompanied with the translation of a freely moving charge inside the structure of the channel.

Applying Eqs. 2, 3, and 4, the rate constant can be written as

$$r(V) = r_0 e^{-(a+bV)/RT}, \quad (5)$$

where $a = A^* - A_0$ and $b = B^* - B_0$ represent differences between the constant and linear components of the free energy of the initial and activated states (according to Eq. 4).

Consider the particular case of a reversible open-closed transition



where C and O are, respectively, the closed and open states and α and β are the forward and backward rate constants. Applying Eq. 5 to forward and backward reactions leads to the following expression for the voltage dependence of rate constants:

$$\begin{aligned} \alpha(V) &= \alpha_0 e^{-(a_1+b_1V)/RT} \\ \beta(V) &= \beta_0 e^{-(a_2+b_2V)/RT} \end{aligned} \quad (7)$$

where a_1 , a_2 , b_1 , and b_2 are constants specific for this transition. In the following, this form with simple exponential voltage dependence of rate constants will be called *linear thermodynamic model*.

A further simplification is to consider that the conformational change consists of the movement of a freely moving gating particle with charge q (Hodgkin and Huxley 1952; see also Borg-Graham 1991). The forward and backward rate constants can be written as

$$\begin{aligned} \alpha(V) &= A e^{-\gamma q F(V-V_H)/RT} \\ \beta(V) &= A e^{(1-\gamma) q F(V-V_H)/RT}, \end{aligned} \quad (8)$$

where γ is the relative position of the energy barrier in the membrane (between 0 and 1), V_H is the half-activation voltage, and A is a fixed constant. This form was introduced by Borg-Graham (1991) to parameterize Hodgkin-Huxley models. Its parameters are very convenient for fitting experimental data: V_H and q affect the steady-state activation/inactivation curves, whereas A and γ only affect the time constant with no effect on steady-state relations.

Nonlinear Thermodynamic Models Although linear thermodynamic models have proved to be accurate for many purposes (reviewed in Hille 2001), their major drawback is that the time constants can reach arbitrarily small values, which may lead to aberrant behavior. In reality, the complex molecular structure of ion channels imposes bounds on their transition rates. Because exponential functions of voltage cannot account for rate-limited transitions, this problem is usually solved by introducing an artificial minimal rate (Borg-Graham 1991), forcing the rate constants to saturate (Willms et al. 1999) or using additional voltage-independent rate-limiting transitions. These procedures are, however, largely empirical, which contradicts with the initial aim of physical plausibility of thermodynamic models.

Nonlinear thermodynamic models (Destexhe and Huguenard 2000) were proposed as a physically plausible framework to solve this problem. These models are based on a functional form for the voltage dependence of rate constants that takes into account more realistic effect of the electrical

field on the ion channel protein. This functional form naturally accounts for rate-limiting effects, and its applicability was illustrated by modeling the complex voltage dependence of T-type calcium currents (Destexhe and Huguenard 2000, 2010).

In general, the effect of the electrical field on a protein will depend on the number and position of its charged amino acids, which will result in both linear and nonlinear components in the free energy. Without assumptions about the underlying molecular structure, the free energy of a given state i can be written as a Taylor series expansion of the form

$$G_i(V) = A_i + B_i V + C_i V^2 + \dots \quad (9)$$

where A_i corresponds to the free energy that is independent of the electrical field, the linear term $B_i V$ to the interaction between electrical field with isolated charges and rigid dipoles, as described above. The higher-order terms describe effects such as electronic polarization and pressure induced by V (Hill and Chen 1972; Stevens 1978; Andersen and Koeppe 1992), as well as mechanical constraints (see below).

In general, each conformational state of the ion channel protein will be associated with a given distribution of charges and will therefore be characterized by a given set of coefficients in Eq. 9. This is also true for the activated state, which is a particular case of conformation. Applying Eqs. 2 and 9, the rate constant can be written more generally as

$$\begin{aligned} r(V) &= r_0 e - [(A^* + B^* V + C^* V^2 + \dots) - (A_0 + B_0 V + C_0 V^2 + \dots)] / RT \\ &= r_0 e - (a + bV + cV^2 + \dots) / RT, \end{aligned} \quad (10)$$

where $a = A^* - A_0$, $b = B^* - B_0$, $c = C^* - C_0$, ... represent differences between the linear and nonlinear components of the free energy of the initial and activated states (according to Eq. 9).

Applying these considerations to the reversible open-closed transition (Eq. 6) leads to the following general expression for the voltage dependence of rate constants:

$$\begin{aligned}\alpha(V) &= \alpha_0 e - (a_1 + b_1 V + c_1 V^2 + \dots)/RT \\ \beta(V) &= \beta_0 e - (a_2 + b_2 V + c_2 V^2 + \dots)/RT\end{aligned}\quad (11)$$

where $a_1, a_2, b_1, b_2, c_1, c_2, \dots$ are constants specific of this transition.

It is important to note that, in general, these parameters are not necessary interrelated because the three different conformations implicated here (initial, activated, final) may have very different distributions of charges, resulting in different coefficients in Eq. 9 and thus also resulting in different values for $a_1 \dots c_2$. In the following, this general functional form for the voltage dependence of rate constants will be called *nonlinear thermodynamic model*.

In the “low-field limit” (during relatively small transmembrane voltages), the contribution of the higher-order terms may be negligible, and one can approximate the free energy in various ways. The simplest approximation would only consider first-order terms in V , which gives the linear thermodynamic model (Eq. 7). Other approximations would consist in quadratic or higher-order expansions of the free energy. These approximations include nonlinear effects of the voltage on the free energy and may lead to saturating rate constants, as we will show below.

For example, the quadratic expansion of Eq. 11 can be written as

$$\begin{aligned}\alpha(V) &= Ae - [b_1(V - V_H) + c_1(V - V_H)^2]/RT \\ \beta(V) &= Ae [b_2(V - V_H) + c_2(V - V_H)^2]/RT,\end{aligned}\quad (12)$$

where $A, b_1 \dots c_2$ are constants as defined above.

In addition to the effect of voltage on isolated charges or rigid dipoles, described in Eq. 7, these forms account for more sophisticated effects such as electronic polarization or the deformation of the protein by the electrical field (Hill and Chen 1972; Stevens 1978). This contribution, however, was estimated to be small (see Sigworth 1993). Higher-order terms would also take into account the presence of mechanical constraints on the gating process (Destexhe and Huguenard 2000).

If gating results from the movement of a freely moving charge, the free energy will depend linearly on voltage. However, if gating depends on the movement of a gating charge subject to a mechanical constraint (which was modeled as a spring of constant k ; Destexhe and Huguenard 2000), the force due to this constraint will contribute for a nonlinear term in the free energy ($-k V^2$ in the case of a spring). This model is probably more realistic than using a freely moving charge, because charged residues in general are strongly constrained by the structure of the protein and are therefore not moving freely. Adding more complex constraints will likely result in adding further nonlinear contributions to the free energy.

Applications

Applications to Hodgkin-Huxley Models

As discussed above, an important caveat of linear thermodynamic models is that the time constants may be arbitrarily close to zero. This is due to the fact that rate constants described by simple exponentials of voltage (Eq. 7) can reach arbitrarily large values. Different solutions to this problem have been proposed (Borg-Graham 1991; Willms et al. 1999) and consisted in artificial alterations of the Hodgkin-Huxley formalism by either setting minimal values for the rate constants or forcing the rate constants to saturate at extreme voltages, but these alterations were largely empirical, which was inconsistent with the initial aim of thermodynamic models.

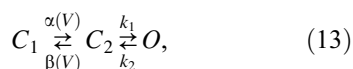
A physically plausible basis for more realistic voltage-dependent rates was proposed under the form of nonlinear thermodynamic models (Destexhe and Huguenard 2000). The basis of these models is that in reality, the rate of conformational changes of proteins is necessarily bounded by mechanical constraints, and consequently, the transition time constants have a minimum value. Nonlinear thermodynamic models have explored the hypothesis that this minimum value is due to nonlinear effects of the voltage on the ion channel. Such models have examined functional forms for the voltage dependence of rate constants which include effects such as

deformation of the protein by the electric field (Hill and Chen 1972; Stevens 1978; Andersen and Koeppel 1992) or mechanical constraints on the gating process (Destexhe and Huguenard 2000). These considerations lead to a more general form of the voltage dependence of the free energy. The resulting model can capture the saturation of the rate constants at some voltages and naturally leads to time constants saturating to a minimal value. (In addition to be more realistic, models with a minimal time constant are also more stable numerically.) This type of model were shown to capture experimental data showing such a minimal time constant, as illustrated for the T-type calcium current (Destexhe and Huguenard 2000).

It must however be kept in mind that models in which the free energy is represented by a quadratic or third-order polynomial of V are approximations. In its non-approximated form (Eq. 9), the free energy can be expressed as an infinite-order polynomial of V (Stevens 1978). Approximating this form by a second or third-order polynomial relies on the hypothesis that the voltage is not too large (the “low-field limit”). Consequently, these forms are only adequate for describing the behavior of the channel in a specific range of membrane potential.

Applications to Markov Models

The nonlinear thermodynamic formalism is not specifically related to the Hodgkin-Huxley model but is also applicable to any type of voltage-dependent model, including Markov representations. For example, when macroscopic voltage-clamp data reveal that the time constants saturate to a minimum value for activation, it is usually assumed (e.g., Chen and Hess 1990) that this behavior requires two successive transitions:



where C_1 and C_2 are two distinct closed states of the gate and the rate constants α and β are simple exponentials of voltage (Eq. 7). Because the second transition is not dependent of voltage, it will act as a rate-limiting factor when α and β reach

high values. In this case, the system will be governed essentially by k_1 and k_2 , which impose a limit on the rate of activation/inactivation.

Although this scheme may be more realistic, it is still unrealistic that the simple exponential representation for α and β permits the first transition to occur arbitrarily fast at some voltages. This problem can be solved by using nonlinear thermodynamic models for α and β , leading to a simpler scheme with only one transition:



Here, the rate constants $\tilde{\alpha}$ and $\tilde{\beta}$ are rate constants described by nonlinear thermodynamic models (Eq. 11). Thus, in this case, the minimum value of the time constant is not interpreted as due to the existence of a rate-limiting transition, but due to mechanical constraints in the effect of the electrical field on the protein. Nonlinear thermodynamic models therefore open the possibility of describing the gating of ion channels using more compact models with few states, which may be of great value to obtain physically plausible models.

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Theta Neuron Model

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Definition

Theta-neuron is a one-dimensional neural model that describes the state of the neuron with a phase variable:

$$\theta' = (1 - \cos \theta) + (1 + \cos \theta) \times (\beta + \text{Inputs}(t)) \quad (1)$$

where θ is between 0 and 2π , β is a constant parameter, and $\text{Inputs}(t)$ summarize the time-dependent inputs to the model.

Theta-neuron is equivalent to the quadratic integrate-and-fire (QIF) neuron or the quadratic normal form for the SNIC bifurcation, making the theta-neuron a canonical neural model: in a sense all models exhibiting the SNIC bifurcation can be reduced (in a sufficiently local neighborhood of the bifurcation) to the theta-neuron.

Detailed Description

The theta-neuron, also known as the Ermentrout-Kopell canonical model, was first derived in Ermentrout and Kopell (1986) to study bursting activity in coupled networks. While the initial intent of this model was to model neuronal oscillators, subsequent works used the theta-neuron as a general neuronal model for both the oscillatory regime (above the bifurcation) and the excitable regime (below the bifurcation).

The theta-neuron is equivalent to the quadratic integrate-and-fire neuron, as it is derived by a change of variables from the quadratic normal form for the SNIC bifurcation.

Let us start with a dynamical equation that describes the dynamics of a system near a SNIC bifurcation. It can be shown that any system of arbitrary dimension admitting a SNIC can be described by a canonical equation on $R(1)$:

$$x'(t) = x^2(t) + \beta \quad (2)$$

Here β determines if we have two steady states or if the solutions blow up in real time periodically. When $\beta < 0$, the two states are stable and unstable points (given by $x = -\sqrt{\beta}$; $x = \sqrt{\beta}$ respectively). Note that in the full system the latter corresponds to a saddle point with a one-dimensional unstable manifold that is invariant. If $x(t)$ is perturbed beyond that upper steady state, the solution blows up in finite time. Note that this equation is a bit cumbersome as there are infinities involved. So we can wrap the solutions on a phase:

$$x(t) = \tan(\theta/2) \quad (3)$$

and then recall that

$$\begin{aligned} x'(t) &= \frac{d(\tan(\theta/2))}{dt} = \frac{1}{\cos^2(\theta/2)} \frac{1}{2} \theta' \\ &= x^2 + \beta \end{aligned} \quad (4)$$

or

$$\frac{1}{\cos^2(\theta/2)} \frac{1}{2} \theta' = \tan^2(\theta/2) + \beta \quad (5)$$

Now we use the half-angle formulas and we get:

$$\theta' = (1 - \cos \theta) + (1 + \cos \theta)(\beta) \quad (6)$$

Here, the solution is reset at $\theta = 0 = 2\pi$. The flow is slow around the fixed points and speeds up as θ nears π . This is exactly what happens in full models. We can define the spike to be in the neighborhood of $\theta = \pi$. Note that it is quite convenient since the discontinuity is not at the spike (as opposed to the integrate-and-fire family of neural models). The spike can be easily visualized by plotting $y(t) = (1 + \cos \theta)$ (Figs. 1 and 2).

When β is below zero, we have an excitable model (steady states: stable $\theta_{\text{unst}} = 2 \tan^{-1}(-\sqrt{\beta})$ and unstable $\theta_{\text{unst}} = 2 \tan^{-1}(\sqrt{\beta})$). When β is above zero, we

have a periodic solution (traversing from 0 to 2π). The period of these oscillations is proportional to $\sqrt{\beta}$. Note also that the excitability parameter β is now included multiplicatively, where the term $(1 - \cos \theta)$ corresponds to the infinitesimal phase-response curve of the model (see below).

This tells us how we can incorporate time-dependent inputs into the model:

$$\begin{aligned} \theta' &= (1 - \cos \theta) + (1 + \cos \theta) \\ &\times (\beta + \text{Inputs}(t)) \end{aligned} \quad (7)$$

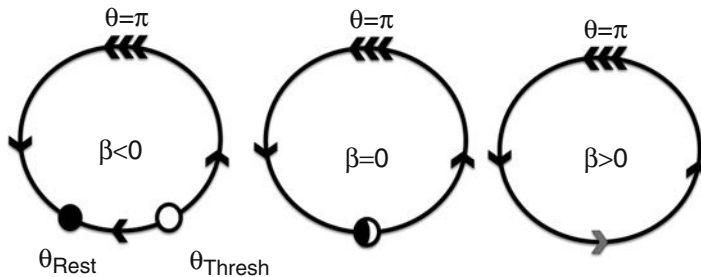
We can easily write an equation for synaptic variables as inputs (as was done in Gutkin et al. 2001).

$$\begin{aligned} \theta' &= (1 - \cos \theta) + (1 + \cos \theta) \\ &\times \left(\beta + \sum g_{ij} s_{ij} \right) \end{aligned} \quad (8)$$

where g_{ij} is the synaptic weight (positive for excitatory, negative for inhibitory) and

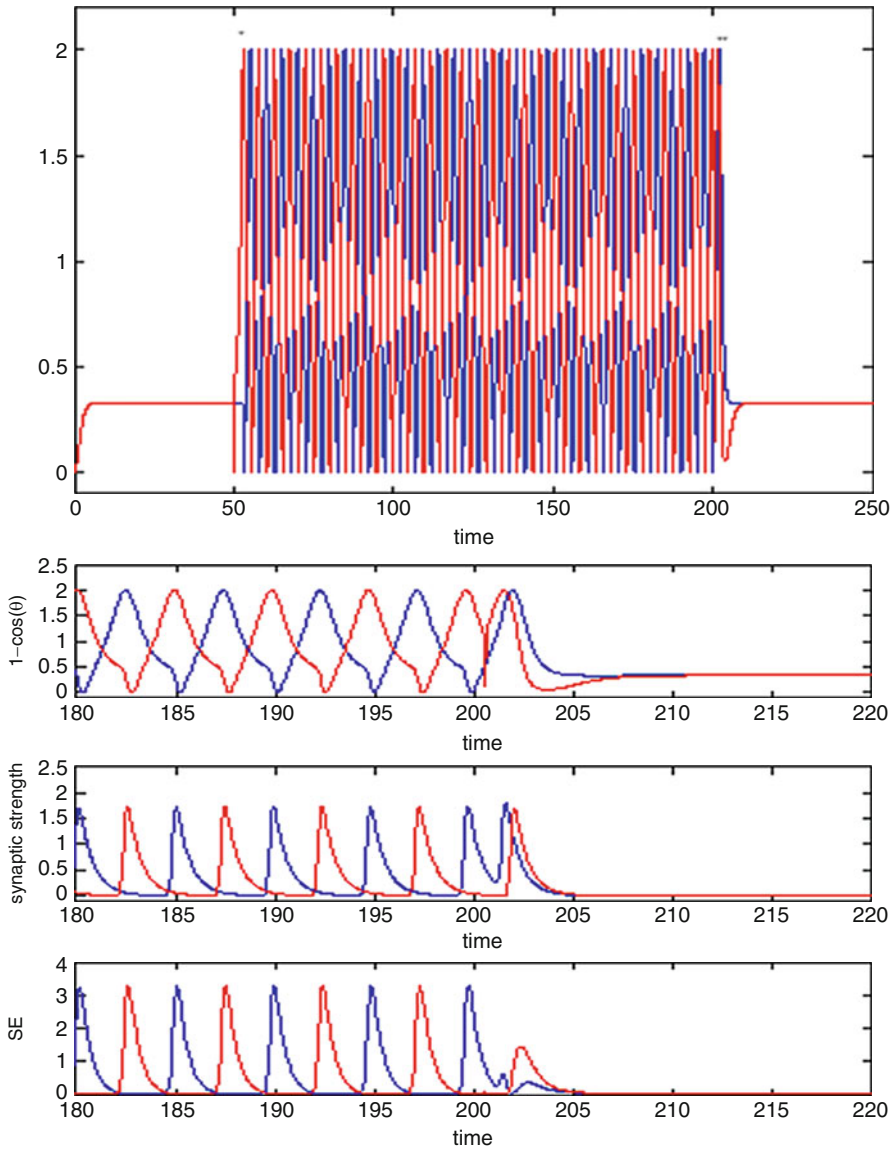
$$s'_{ij}(t) = -\frac{s_{ij}}{\tau_s} + (1 - s_{ij})e^{-\rho(1 - \cos(\theta_r - \theta_{\text{thresh}}))} \quad (9)$$

Where ρ is roughly speaking the rise time of the synapse (in Gutkin et al. 2001, ρ is taken as 20 for AMPA-like synapses), θ_{thresh} is the threshold above which the synapse activates: it should



Theta Neuron Model, Fig. 1 Diagram of theta-neuron. Here we show the structure of the theta-neuron dynamics. *Left* diagram is for the theta-neuron on the excitable regime, where $\beta < 0$. Below the θ_{thresh} the phase θ converges to θ_{rest} . When perturbed above the threshold, the phase makes a procession past $\theta = \pi$ (note that π is at the top of the phase diagram). The flow is slow near the threshold and the rest and is fast near π , where the spike takes place. The reset of the phase θ is at $\theta = 0 = 2\pi$, which

not at all near the spike. Note that as β moves near zero, the two fixed points θ_{thresh} and θ_{rest} move closer to each other. *Center* diagram is right at the bifurcation where $\beta = 0$ and the two fixed points have coalesced to form a saddle-node complex: this is the saddle-node bifurcation. When β moves above zero, the fixed point disappears leaving a limit cycle. *Right* diagram: on this limit cycle the flow is slow near the former saddle-node (or its ghost) and still fast near π . This indeed looks like repetitive spiking



Theta Neuron Model, Fig. 2 Coupled theta-neurons. Example of two theta-neurons coupled with strong recurrent excitatory synapses of AMPA type. *Upper panel* shows the sustained activity in the pair; here we plot $y(t) = 1 + \cos\theta$ for the two neurons: blue and red. *Middle panel* shows an expanded end of the sustained episode, showing that it terminates because the two neurons are synchronized – the basic mechanism is the refractory period

inherent in the theta-neuron dynamics. *Third panel* shows the synaptic variables $s(t)$ that are triggered by the spiking. The *lower panel* shows the impact that each synapse has on the postsynaptic phase θ which we can call the synaptic efficacy $(1 + \cos\theta) * s(t) * g_s$; this is the synapse multiplied by the PRC. Note that for the synchronized spikes, the efficacy drops. (Modified from Gutkin et al. 2001)

be close to the spike or θ_{thresh} approx. π (in Gutkin et al. 2001 taken $\theta_{\text{thresh}} = 3$); τ_s is the synaptic decay time scale. A slightly different formula is given in Borghers and Kopell (2003).

One can also write down synaptic equations taking into account the synaptic reversal potentials (i.e., modeling the synapses as conductances). Following the derivation from Borghers

and Kopell (2003), let us say that in the QIF equation we have a synapse $g_s s(t)$ ($V - E_{\sin}$). Then we do the change of variables as above to get the theta-neuron (Fig. 2):

$$\theta' = (1 - \cos \theta) + (1 + \cos \theta) \times (\beta + K g_s s(t)) - g_s s(t) \sin \theta \quad (10)$$

where K is a constant dependent on the synaptic reversal potential E_{syn} . For example, in Borghers and Kopell (2008), $K = 12$ for the excitatory synapses and $K = -3/2$ for the inhibitory synapses.

Including the synapses allows for the theta-neuron to be used in circuits (e.g., Gutkin et al. 2001) and networks (e.g., see Borghers and Kopell 2003). Similar equations can be written down for gap junction coupling and for NMDA synapses.

Stochastic Theta-Neuron

We can also incorporate noise in the theta-neuron. Starting from the stochastic differential equation for the quadratic normal form:

$$dx = (x^2 + \beta)dt + \sigma dW_t \quad (11)$$

Here things are a little bit tricky as stochastic calculus implies an additional drift term (deterministic term) after the change of variables from $x(t)$ to $\theta(t)$:

$$d\theta = \left[(1 - \cos \theta) + (1 + \cos \theta) \left(\beta + I(t) + \frac{\sigma^2}{2} \sin \theta \right) \right] dt + \sigma(1 + \cos \theta) dW_t \quad (12)$$

This is the equation derived in Lindner et al. (2003) and reader can follow the arguments on converting Stratonovich to Ito interpretation in that paper.

Note that early use of the stochastic theta-neuron (Gutkin and Ermentrout 1998) tacitly presumed that the variance of the noise is small enough to ignore the σ^2 term giving

$$d\theta = [(1 - \cos \theta) + (1 + \cos \theta)(\beta + I(t))]dt + \sigma(1 + \cos \theta)dW_t \quad (13)$$

Adaptive Theta-Neuron

We can incorporate a slower adaptation current (or slower regenerative currents):

$$\theta' = (1 - \cos \theta) + (1 + \cos \theta)(\beta - \mu z) \quad (14)$$

$$\tau_z z' = D(\theta)(1 - z) - z \quad (15)$$

$$D(\theta) = \kappa \exp - C(1 - \cos(\theta - \theta_z)) \quad (16)$$

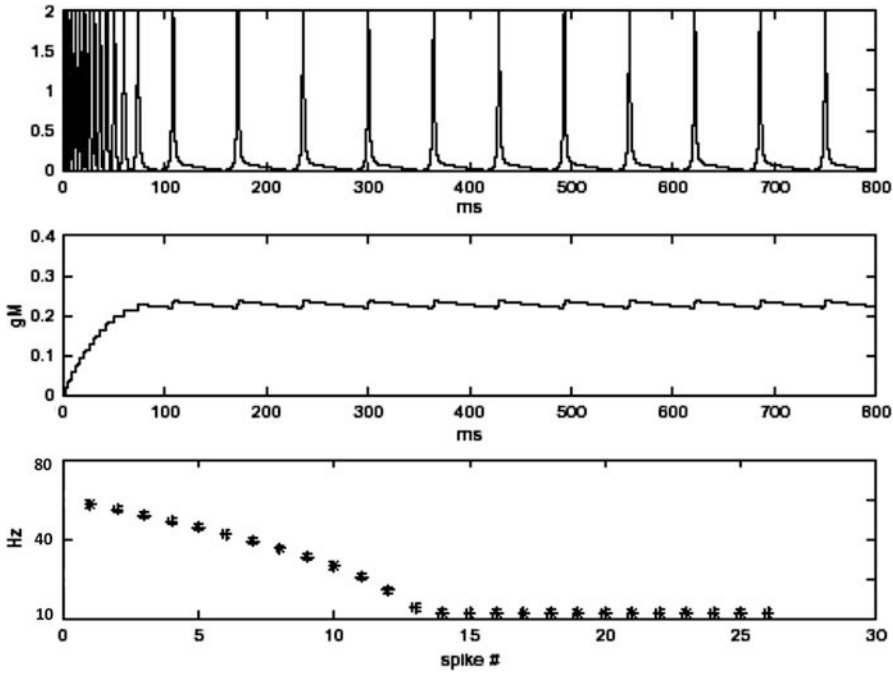
Here μ is the strength of the adaptation current, and the parameter θ_z controls if the adaptation current is voltage dependent (e.g., M current; with θ_z relatively low) or spike dependent (e.g., the AHP current; with θ_z close to π). This makes the adaptive theta-neuron analogous to the Izhikevich neuron (Izhikevich 2004). Parameters are as follows: τ_z is the adaptation time constant, on the order of 100 ms; κ and C are scaling parameters in the activation term D (in Gutkin et al. 2005 $\kappa = 8$, $C = 2$) (Fig. 3).

Some Properties, Dynamics, and Facts

The theta-neuron is a canonical model for class I excitability: its equivalent to the quadratic normal form for the saddle-node on an invariant cycle bifurcation (SNIC). Its FI curve is continuous, with zero onset frequency for the oscillatory response and period scaling as:

$$T_{\text{period}} = \frac{\pi}{\sqrt{\beta}} \quad (17)$$

Interestingly in the excitable regime, perturbing the phase above the upper unstable fixed point $\theta_{\text{unst}} = 2 \tan^{-1}(\sqrt{\beta})$, which acts as the spike-generating threshold, results in a spike; however, the delay to this spike in time can be arbitrarily long as the perturbation gets nearer to



Theta Neuron Model, Fig. 3 Adaptive theta-neuron. Dynamics of the adaptive theta-neuron. The *upper panel* shows the spiking with a characteristic adaptation of the firing rate. The *middle panel* shows the activation of the $z(t)$

parameterized to act as $I-M$ (muscarine-sensitive voltage-dependent K current). *Lower panel* shows the instantaneous firing frequency. (Modified from Gutkin et al. 2005)

the θ_{unst} . This points out an important property of the theta-neuron: spikes are really all-or-none events with a hard spiking threshold. However, the timing of the spikes evoked is “soft” as it depends exquisitely on the size of the peri-threshold stimulus. We can even calculate explicitly how the time to the spike depends on the size of the peri-threshold perturbation ϵ (meaning that we perturb $\theta \in$ above the threshold or $\theta(t=0) = \theta_{\text{unst}} + \epsilon$) as well as the excitability parameter β :

$$T_{\text{spike}} = \frac{-\tanh^{-1}\left(1 + \frac{\epsilon}{\sqrt{\beta}}\right)}{\sqrt{\beta}} \quad (18)$$

Note that this function blows up as ϵ goes to zero and also it gets “flatter” as β tends to zero. The last point implies that as the model tends to the bifurcation point, or closer to the onset of oscillations, the range of possible spike delays for the same range of variable ϵ s gets larger.

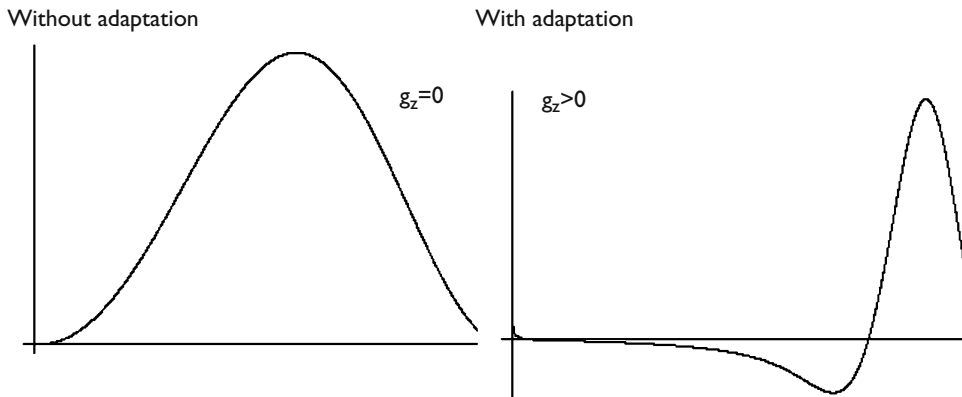
The theta-neuron is a one-dimensional model, which makes it easy to compute explicitly its phase-response curve (PRC). The infinitesimal PRC is the adjoint of solution and is given by:

$$PRC(t) = 1 - \cos\left(\frac{2\pi t}{T}\right) \quad (19)$$

where T is the period of the oscillation and t ranges from 0 (time of spike 0) to T (time of spike 1). In terms of phase ranging from $-\pi$ to π :

$$PRC(\theta) = 1 + \cos \theta \quad (20)$$

Note that this is exactly the term that pre-multiplies the inputs to the theta-neuron. The PRC of the theta-neuron is positive, which is indicative of SNIC. Interestingly, for the adaptive theta-neuron, when the adaptation threshold is low and the strength is sufficiently high, the PRC can have a significant negative region, implying type II excitability. In fact, in this case, one can find a subcritical



Theta Neuron Model, Fig. 4 PRC theta-neuron. *Left panel:* infinitesimal PRC (iPRC) for the basic theta-neuron computed using the adjoint method. Note that it is positive and symmetric. *Right panel:* iPRC for the theta-neuron

with $I-M$ -like adaptation of sufficient strength. Note that the negative region in the iPRC (delay of spike) and a strong skew to the *right*. Both iPRCs we computed for the same firing frequency

Andronov-Hopf bifurcation leading to the onset of oscillations. So, the theta-neuron with adaptation unites both the type I (SNIC) excitability and type II excitability. For the adapting theta-neuron one cannot really compute the PRC explicitly, but it is easily determined numerically, either through direct simulations or using XPPAUT (Fig. 4).

Who Has Used the Theta-Neuron (Some Examples)

The first use of the model was by Ermentrout and Kopell (1986) to explore the mathematics of parabolic bursting. Subsequently, the theta-neuron was used not only for neural oscillators but also, as a general, for hyper-reduced models of neuronal spike generation. Ermentrout (1996) looked at the theta-neuron as a canonical model for type I excitability and derived the infinitesimal PRC: this has important implications for synaptic mechanisms of synchronization as the strictly positive PRC of the theta-neuron implies inhibition to be synchronizing and excitation leading to non-synchronous states. Gutkin and Ermentrout (1998) used the theta-neuron to show how the type I spike-generating dynamics can lead to highly variable spike timing. They wrote down the stochastic theta-neuron and looked at the

spiking responses to noisy current injections in the excitable regime and as the model is driven past the bifurcation to the oscillatory regime. They found spike times to be highly variable in the excitable regime; the key here was the sensitivity of spike delays to the peri-stimulus noise amplitude. In fact they showed that the variability of the spike times can be much higher than predicted by the linear integrate-and-fire neurons, and high CVs do not require detailed balance of inputs. Lindner et al. (2003) took a closer look at the stochastic derivation and made appropriate corrections for the strong noise case (see above Eqs. 12 and 13). In this case there is an additional noise-induced drift term, implying that noise itself can push the model past the bifurcation into the oscillatory regime and regularize the spike times. Gutkin et al. (2005) used the adaptive theta-neuron to fit experimentally determined PRCs from cortical pyramidal neurons, to explore how the PRC depends on the mean firing rate as well as the strength of the adaptive currents. Stiefel et al. (2009) showed that the adaptive theta-neuron can account for the effects of cholinergic modulation on spike-generating dynamics in cortical neurons.

The theta-neuron has also been used to study the properties of coupled networks. The advantage of this model is that at the spike, it has continuous dynamics (as opposed to the integrate-

and-fire family of models where there is a jump at the spike), making more amenable to analysis. Gutkin et al. (2001) used small circuits of synaptically coupled theta-neurons to understand how the relative timing of the spikes and recurrent excitatory synapses influences the stability of sustained neural activity (correlate of working memory maintenance). Notably they showed that synchrony is not compatible with sustained activity and later that correlated noise can quench sustained activity (Gutkin et al. 2008a, b). Borgers and Kopell (2003) used networks of theta-neurons to study synchronization properties of neuronal oscillators in the gamma band. They developed a “river” technique to analyze how inhibitory synaptic pulses in networks of interneurons and pyramidal neurons might synchronize and create the PING gamma oscillations. Subsequently they used networks of theta-neurons to show how gamma oscillations can lead to competition between incoming stimuli (Borgers et al. 2008; Borgers and Kopell 2008) and gamma synchrony under heterogeneity and noise (Borgers and Kopell 2005). Osan and Ermentrout considered a one-dimensional network of theta-neurons and analyzed how traveling waves can form (Osan et al. 2002). More recently Monteforte and Wolf (2010) studied chaos in networks of sparsely connected theta-neurons in the balanced state, showing that chaos is present in purely inhibitory network and becomes more intense with excitatory neurons added.

Code Sources

Neuron code <http://hodgkin.sourceforge.net/doc/neuron/ThetaNeuron.html>

XPPAUT Script

This is the theta-neuron with m-current adaptation.

```
x' = (1 - cos(x)) + (1 + cos(x)) * (beta-gahp*z + blip)
z' = (kz(x)*(1 - z) - z)/tauz
```

```
kz(x) = az * exp(-bz * (1 - cos(x - xtz)))
```

```
x(0) = 3.20151
```

```
z(0) = 0.1831576
```

```
par beta = -0.001
```

```
par gahp = 4, tauz = 400, az = 8, xtz = 3, bz = 2
```

```
auxfr = 1 - cos(x)
```

```
auxim = -gahp * z
```

```
done
```

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Theta-Gamma Cross-Frequency Analyses (Hippocampus)

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Synonyms

Amplitude-amplitude coupling; n:m phase-locking; Phase-amplitude coupling; Phase-frequency coupling; Phase-phase coupling

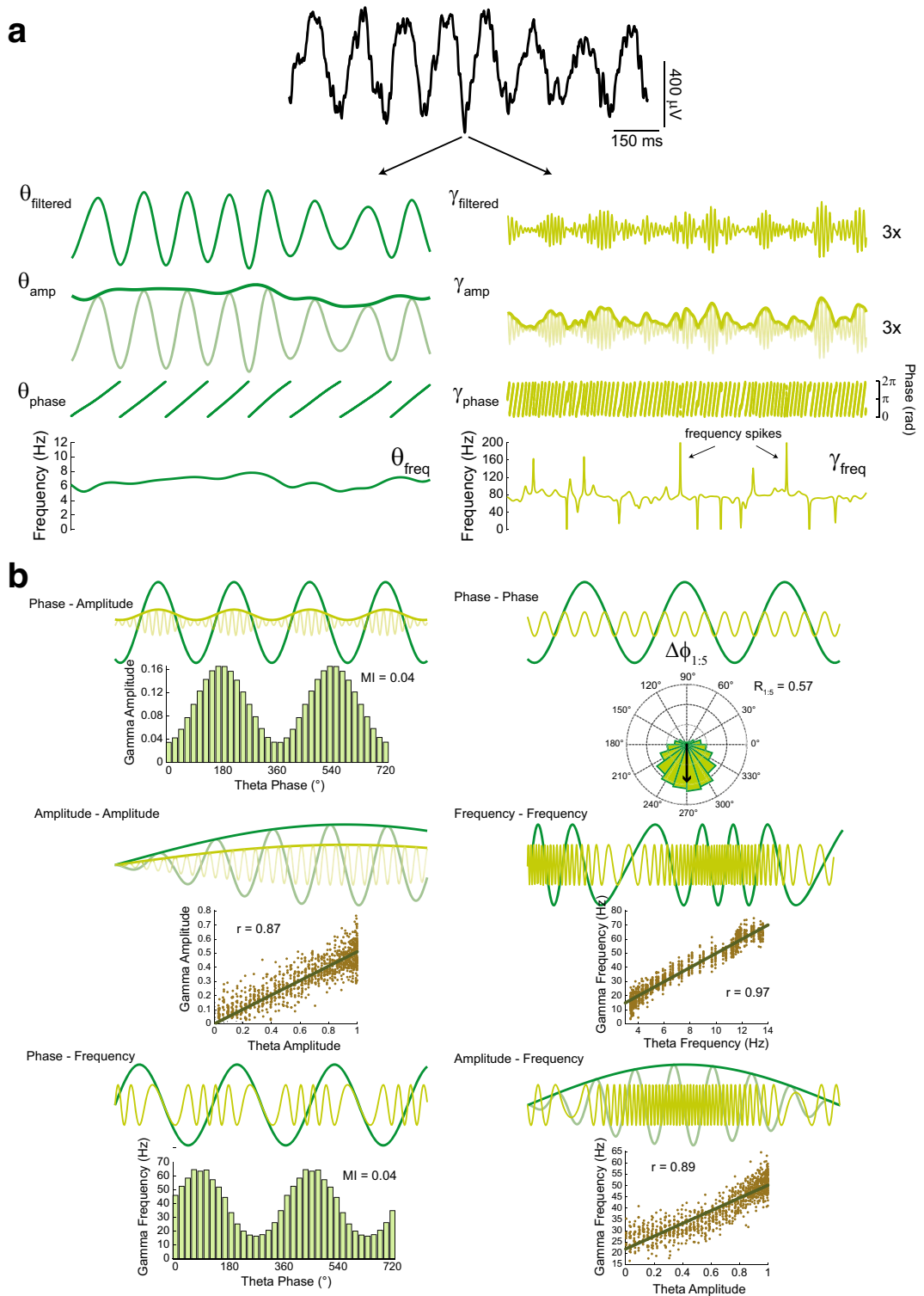
Definition

Brain oscillations of different frequencies can coexist and influence each other. A cross-frequency interaction occurs when a feature from one oscillation (i.e., instantaneous amplitude, phase, or frequency) depends on a feature from another oscillation at a distinct frequency. These phenomena have been collectively called cross-frequency coupling (CFC). There are multiple types of CFC, such as phase-amplitude coupling, amplitude-amplitude coupling, and n:m phase-locking. Several metrics have been devised to quantify CFC.

Detailed Description

The study of the electrical activity produced by the brain dates back to Richard Caton in 1875, who employed a galvanometer to record from the cortex of rabbits (Geddes 1987). Neuronal spikes and extracellular field potentials have been since recorded from several brain regions of different species, and spectral analyses have shown that they are often rhythmical. Scientists usually classify brain oscillations according to their frequency, waveform shape, local of origin, and associated behavior. Among them, the hippocampal formation of rats and mice produces a prominent rhythm in the 4–12 Hz range when animals explore their surroundings or during REM sleep, the so-called theta oscillations (Buzsáki 2002). In addition, faster oscillations appear associated with theta waves, such as gamma rhythms (30–100 Hz) and high-frequency oscillations (HFOs; 120–160 Hz) (Scheffer-Teixeira and Tort 2017). A new field of higher-level analysis emerged with the discovery that oscillations of distinct frequencies might not only coexist but also interact with each other (Canolty and Knight 2010; Hyafil et al. 2015). Oscillatory interaction can occur through any of the main features of a rhythm: amplitude, phase, or frequency (Fig. 1). These phenomena are collectively known as cross-frequency coupling (CFC). To date, the most studied CFC types are phase-amplitude coupling, amplitude-amplitude coupling, and n:m phase-locking, while other CFC types remain to be further explored (Hyafil et al. 2015).

Measures of synchronization between brain waves were first motivated by the study of coupled oscillators (Ermentrout and Kopell 1991; Tass et al. 1998; Strogatz 2000; Rosenblum et al. 2001). However, despite local regularities and short-term predictability, neural oscillations do not behave as stationary sinusoids and are not easily described by a set of equations. Rather, local field potentials (LFPs) are subject to several sources of variability, most unknown or uncontrolled, and exhibit noisy states and chaotic components. While not formally demonstrated, the coupling between brain signals is believed to



Theta-Gamma Cross-Frequency Analyses (Hippocampus), Fig. 1 (continued)

fall into the category of “weakly coupled oscillators” (Hoppensteadt and Izhikevich 1998). Several approaches were proposed to infer the existence and quantify the degree of coupling based on a general statistical sense: two oscillations are assumed to be coupled if knowledge of the state of one oscillation predicts the state of another oscillation. Notice that this statistical definition ignores the underlying mechanisms. In particular, it does not inform about directionality and causality, that is, whether an oscillation modulates, is modulated, or both, whether coupling is externally or internally driven, direct or indirect.

The following sections summarize common CFC metrics. For simplicity, we often refer to theta and gamma as canonical examples of slow and fast oscillations of interest, but the metrics are general enough to be applied to any cross-frequency pair.

Filtering and Feature Extraction

Phase, frequency and amplitude can be extracted from brain signals (LFP, EEG, MEG) using standard signal processing techniques. The first step is to filter the raw data into the desired frequency range, which can be achieved by many different types of filters. Of note, to detect phase-amplitude coupling, the bandwidth of the filtered fast oscillation component (i.e., gamma) must include its peak frequency (f_γ) and the side-band frequencies at $f_\gamma \pm f_\theta$, where f_θ is the frequency of the slow oscillation (i.e., theta) (Berman et al. 2012; Aru et al. 2015).

After filtering, the phase and amplitude time series can be obtained from its analytic representation, defined as $Z(t) = X(t) + iH(X(t))$, where the real part, $X(t)$, is the filtered signal and the imaginary part, $H(X(t))$, its Hilbert transform, which is a version of $X(t)$ shifted by -90° . The instantaneous amplitude at each time t is defined as

the absolute value of $Z(t)$, given by $|Z(t)| = \sqrt{X(t)^2 + H(X(t))^2}$, while the instantaneous phase at time t is defined as $\varphi(t) = \tan^{-1}(H(X(t))/X(t))$. Notice that $Z(t)$ can be expressed in polar form as $Z(t) = |Z(t)|e^{i\varphi(t)}$. Alternatively, the amplitude and phase time series can be obtained as the absolute value and angle of a complex wavelet transform (with the due caution of the filtered bandwidth). The instantaneous phase can also be estimated by linear interpolation: peaks and valleys of the filtered signal are first identified and set to predefined phases (e.g., 0° for peak and 180° for valley). Subsequently, the samples between each peak-to-valley and valley-to-peak interval are attributed to linearly spaced phase values (Belluscio et al. 2012).

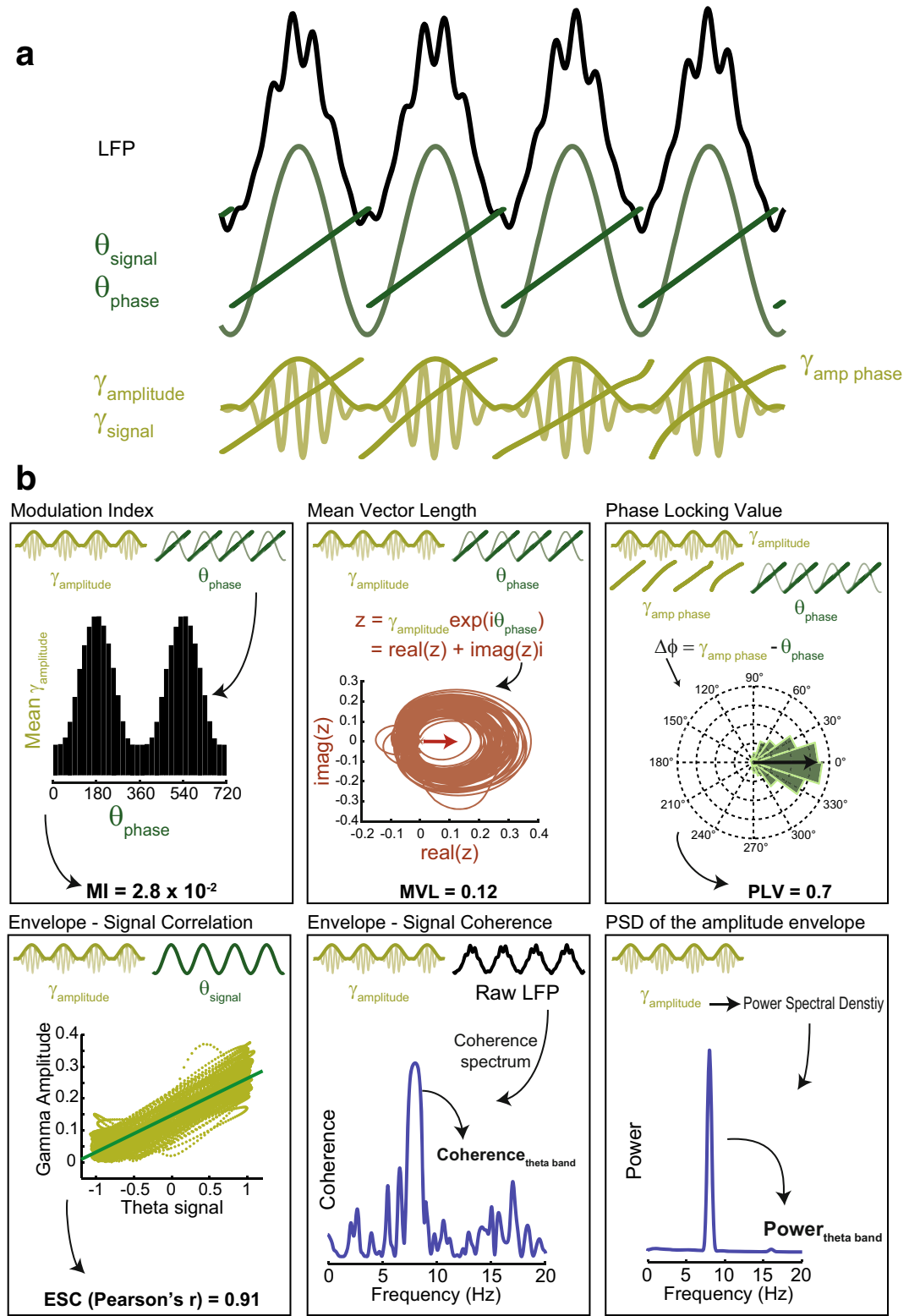
Finally, the instantaneous frequency is estimated from the first derivative of the unwrapped phase time series: $f(t) = \frac{1}{2\pi} \frac{d\varphi(t)}{dt}$.

CFC Metrics

Several of the metrics below assume that the signal has already been band-pass filtered into the theta and gamma ranges of interest and the relevant features extracted (i.e., phase and amplitude time series). Ideally, the frequency boundaries of the band-pass filter should be selected based on visual inspection of the power spectrum, so as to encompass the power “bumps” at the corresponding frequencies. However, while theta is usually associated with a discernable power peak, the frequency boundaries of gamma activity are often difficult to determine due to the much lower signal-to-noise ratio, especially for the faster gamma subbands. In these cases, the choice of the filtered band may be based on the inspection of comodulation maps (see below) or on previous studies.

Theta-Gamma Cross-Frequency Analyses (Hippocampus), Fig. 1 Multiple CFC types. (a) Feature extraction from a rat LFP epoch containing theta and gamma oscillations during REM sleep. Theta and gamma signals are obtained through band-pass filtering and their phase

and amplitude series extracted using the Hilbert transform. The instantaneous frequency time series is derived from the phase time series. (b) Each subpanel depicts one possible CFC type by means of simulated data



Theta-Gamma Cross-Frequency Analyses (Hippocampus), Fig. 2 (continued)

Phase-Amplitude Coupling (PAC)

PAC has been identified in different types of brain signals and received much attention in recent literature. We summarize some of the PAC metrics in this section (Fig. 2), but we note that the list is nonexhaustive and novel metrics are continuously being devised.

Measures Based on the Maximal and Minimal Values of the Amplitude Distribution

Several PAC metrics require first computing the mean gamma amplitude as a function of the phase of the theta cycle. This is obtained by partitioning theta phases into nonoverlapping bins and calculating the average gamma amplitude (A_j) associated with each phase bin j . Phase bins are usually 10° to 30° wide.

A straightforward metric for PAC strength is obtained by taking the ratio between the maximum (A_{max}) and minimum (A_{min}) average gamma amplitude within the theta cycle (Lakatos et al. 2005):

$$PAC_{strength} = \frac{A_{max}}{A_{min}}$$

Notice that this ratio is not bounded. Other variants include ratios that vary between 0 and 1, such as:

$$PAC_{strength} = \frac{A_{max} - A_{min}}{A_{max}}$$

and

$$PAC_{strength} = \frac{A_{max} - A_{min}}{A_{max} + A_{min}}$$

Modulation Index (MI)

Tort et al. (2008) defined the PAC MI as an adaptation of a phase synchrony metric based on information theory introduced by Tass et al. (1998). The MI first requires normalizing the average

amplitude per phase bin (A_j) to generate a discrete probability-like distribution (P):

$$p_j = \frac{A_j}{\sum_{j=1}^{N_b} A_j}$$

whose Shannon's entropy ($H(P)$) is:

$$H(P) = - \sum_{j=1}^{N_b} p_j \log(p_j)$$

where j indexes the phase bins and N_b is the total number of bins. The PAC MI is obtained as an "inverted" normalization of $H(P)$:

$$PAC_{strength} = MI = \frac{H_{max} - H(P)}{H_{max}}$$

where $H_{max} = H(U) = \log(N_b)$ is the maximum possible entropy, achieved for a uniform distribution $U(p_j = 1/N_b \text{ for all } j)$. Thus, $MI = 0$ when the phase-amplitude distribution is uniform, and $MI = 1$ in the (hypothetical) case in which gamma only appears in one phase bin of theta ($p_k = 1$ for a single bin k , and $p_j = 0$ for all $j \neq k$).

The MI is related to the Kullback-Leibler divergence (D_{KL}) by the equation $D_{KL}(P, U) = \log(N_b) - H(P)$. In other words, the MI can be viewed as the normalized Kullback-Leibler divergence between the uniform distribution and the observed phase-amplitude distribution:

$$MI = \frac{D_{KL}(P, U)}{H_{max}}$$

In practical terms, a Dirac-like distribution is improbable for real LFP signals and the MI values are skewed towards zero. In LFP recordings, significant theta-gamma MI values usually lie between 10^{-3} and 10^{-2} ; values around 10^{-4} are considered weak and may be borderline for statistical significance, especially for short epochs. The

Theta-Gamma Cross-Frequency Analyses (Hippocampus), Fig. 2 Diversity of PAC metrics. (a) Simulated signal containing theta and gamma oscillations in which

theta phase modulates gamma amplitude. The phase of the gamma amplitude time series is extracted after demeaning. (b) Panels depict different measures for PAC (see text)

MI can also be computed using the distribution of gamma bursts, that is, the counts of events per theta phase where gamma amplitude is higher than a threshold.

Mean Vector Length (MVL)

Canolty et al. (2006) introduced a PAC metric based on the complex time series $A_\gamma(t)e^{i\varphi_\theta(t)}$, where $A_\gamma(t)$ is the instantaneous gamma amplitude at time t and $\varphi_\theta(t)$ the instantaneous theta phase. The existence of PAC can be visually inferred by plotting these vectors in the complex plane: if theta and gamma are phase-amplitude coupled, the higher gamma amplitude in a subset of theta phases leads to an asymmetric distribution of vector lengths (amplitude values) around the origin. PAC strength can be estimated by measuring this asymmetry by means of the length of the mean vector:

$$PAC_{strength} = \left\| \frac{1}{N} \sum_{j=1}^N A_\gamma(t_j) e^{i\varphi_\theta(t_j)} \right\|$$

where N is the number of time points. The absence of PAC is characterized by a roughly uniform circular distribution of individual vectors, which will cancel each other out and lead to a low MVL. On the other hand, an asymmetry (polarization) in the complex plane leads to a resultant mean vector of larger length. The larger the polarization, the larger the MVL.

In the original formulation, the MVL was normalized and expressed as z-score in relation to a surrogate distribution of 200 MVL values (obtained from $A_\gamma(t)$ and $\varphi_\theta(t)$ not matched in time) (Canolty et al. 2006). Thus, the normalized metric reflected the statistical significance of PAC more than its strength.

Phase-locking Value (PLV)

In addition to being used to assess phase synchrony (Lachaux et al. 1999), the PLV can be readily adapted to measure PAC strength (Vanhatalo et al. 2004; Cohen 2008; Penny et al. 2008). As the MVL, the PLV also relies on computing the length of a mean vector, but in this case the time series is composed of unitary vectors. To

compute the PLV, the instantaneous gamma amplitude must be first demeaned (or detrended), so that it assumes positive and negative values. For the case of a theta-modulated gamma, the demeaned amplitude time-series oscillates around zero at theta frequency. The PLV is the length of the mean over unit vectors whose angle is the difference between the phase of theta (φ_θ) and the phase of gamma amplitude (φ_{A_γ}):

$$PAC_{strength} = \left\| \frac{1}{N} \sum_{j=1}^N e^{i\Delta\varphi(t_j)} \right\|$$

where $\Delta\varphi(t_j) = \varphi_{A_\gamma}(t_j) - \varphi_\theta(t_j)$. The more the gamma amplitude is phase-locked to theta, the more constant their phase difference is. The PLV is 1 if $\Delta\varphi(t_j)$ is exactly constant for all t , and 0 if the circular distribution of phase differences is uniform.

Envelope-Signal Correlation (ESC)

The ESC metric is the correlation between the theta-filtered signal (x_θ) and the amplitude envelope of gamma (A_γ) (Bruns and Eckhorn 2004):

$$\begin{aligned} PAC_{strength} &= \text{corr}(x_\theta, A_\gamma) \\ &= \frac{1}{N} \sum_{j=1}^N \frac{(x_\theta(t_j) - \bar{x}_\theta)(A_\gamma(t_j) - \bar{A}_\gamma)}{\sigma_{x_\theta} \sigma_{A_\gamma}} \end{aligned}$$

Penny et al. (2008) introduced a variation that normalizes for the amplitude of theta, which is achieved by correlating gamma amplitude with the cosine of the instantaneous theta phase ($\cos(\varphi_\theta)$):

$$PAC_{strength} = \text{corr}(\cos(\varphi_\theta), A_\gamma)$$

The correlation metrics vary between -1 and 1 ; when gamma amplitude is maximal near the trough of theta, the correlation is negative, while positive correlations occur when gamma amplitude is maximal near the theta peak. The correlation may be zero even in the presence of phase-amplitude coupling if gamma has maximal amplitude when theta crosses zero (i.e., at 90° from the cycle peak or

trough), the so-called “null phases” (Cohen 2008; Penny et al. 2008; Tort et al. 2010).

General Linear Model (GLM)

To circumvent the fact that the correlation metrics are not well suited to detect coupling if gamma is maximal at the null phases (i.e., zero crossings at $\cos(\pi/2)$ and $\cos(3\pi/2)$), Penny et al. (2008) proposed a generalization using GLM. In this framework, gamma amplitude is modeled as:

$$A_\gamma = \beta_0 + \beta_1 \cos(\varphi_\theta) + \beta_2 \sin(\varphi_\theta) + \varepsilon$$

where β_j ($j = 0, 1, 2$) are the regression coefficients and ε is the error (noise) term. Since the sine and cosine of the same phase is never simultaneously zero, the GLM metric has no “null phases.” Finding the regression coefficients can be achieved by standard linear regression techniques. The GLM-based PAC metric is then defined as:

$$PAC_{strength} = \frac{SS(A_\gamma) + SS(\varepsilon)}{SS(A_\gamma)}$$

where $SS(A_\gamma)$ is the explained sum of squares of the model and $SS(\varepsilon)$ the sum of squared errors (residuals).

Envelope-Signal Coherence

PAC can also be estimated from the coherence spectra between the instantaneous gamma amplitude time series and the unfiltered LFP signal (Colgin et al. 2009). The standard (i.e., Fourier-based) phase coherence between two signals X and Y is defined as:

$$C_{XY}(f) = \frac{\left\| \langle F_X(f) \cdot \overline{F_Y(f)} \rangle \right\|}{\left\| \langle F_X(f) \rangle \right\| \left\| \langle F_Y(f) \rangle \right\|}$$

where $F_X(f)$ and $F_Y(f)$ are the Fourier transforms at frequency f of X and Y, respectively. Oftentimes the “magnitude-squared” coherence (C_{XY}^2) is used. Both C_{XY} and C_{XY}^2 vary between 0 and 1. A theta-gamma coupling metric can then be obtained as the average coherence in the theta frequency range.

Power Spectral Density (PSD) of the Amplitude Envelope

If phase-modulated by theta, gamma amplitude tends to oscillate at theta frequency. Therefore, decomposing A_γ into its frequency components by means of Fourier spectral analysis may be used to infer PAC (Cohen 2008; Tort et al. 2010). Similarly to the coherence metric above, in this framework PAC is estimated by integrating (or averaging) the PSD of A_γ over the theta range. Such a method may provide meaningless estimates if the A_γ PSD has no peak at theta frequency.

Mutual Information

Theta-gamma PAC can be assessed using Shannon’s mutual information, which computes how much the joint probability of phase and amplitude values deviates from the product of their marginal distributions. By definition, mutual information is zero for independent variables (joint probability equal to the product of the marginal probabilities). To estimate the joint and marginal probability distributions, the range of phase (i.e., 0 to 2π) and amplitude values must be first binned; each bin count is subsequently normalized by the total counts ($N_{\text{total}} = \text{sampling rate} \times \text{epoch length}$), yielding:

$$p(\varphi_i) = \frac{N_{\varphi_i}}{N_{\text{total}}}, \quad p(a_j) = \frac{N_{a_j}}{N_{\text{total}}}, \quad \text{and}$$

$$p(\varphi_i, a_j) = \frac{N_{\varphi_i \cap a_j}}{N_{\text{total}}},$$

where N_{φ_i} is the number of counts in phase bin i , N_{a_j} the number of counts in amplitude bin j , and $N_{\varphi_i \cap a_j}$ the number of joint counts. Mutual information is then estimated as:

$$PAC_{strength} = I(\Phi; A) = \sum_{i=1}^{M_b} \sum_{j=1}^{N_b} p(\varphi_i, a_j) \log \left(\frac{p(\varphi_i, a_j)}{p(\varphi_i)p(a_j)} \right)$$

where M_b and N_b are the number of phase and amplitude bins, respectively. This estimator is

considered naïve since it does not correct for the positive bias associated with the use of finite samples to estimate the probability distributions; more sophisticated estimators that correct for such bias can be used (Panzeri et al. 2007).

Comodulation Maps

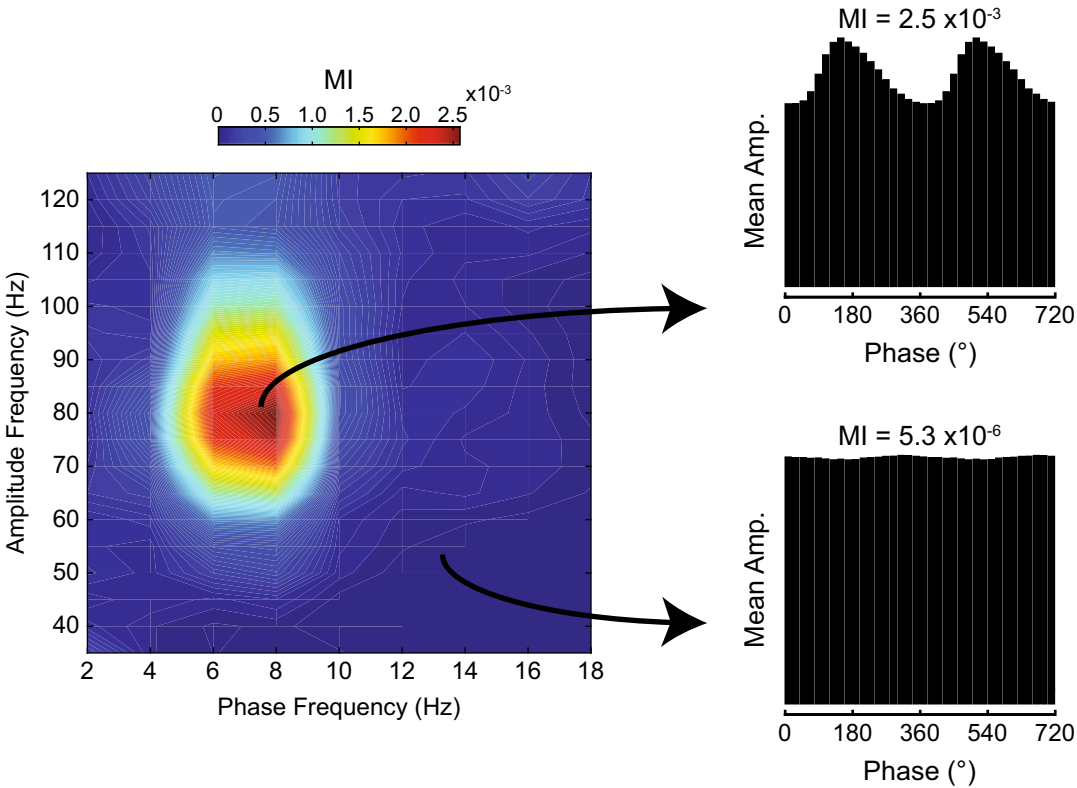
Comodulation maps, or “comodulograms,” are 2D heatmaps that simultaneously express PAC strength values for multiple frequency pairs, and can be constructed for any of the metrics above (Fig. 3). Usually, the x-axis represents the phase-providing frequency and the y-axis the amplitude-modulated frequency, while the color represents PAC strength. In some cases, the color represents the statistical significance of PAC.

Phase-Phase Coupling (PPC)

Cross-frequency PPC is defined as a consistent phase relation between multiple gamma cycles within theta cycles. This type of CFC is also called $n:m$ phase-locking. For example, 1:5 phase-locking is characterized by five gamma cycles consistently nested within theta cycles, in which each gamma cycle (i.e., the first, the second, etc.) starts/finishes at a similar theta phase across cycles. In PPC, theta and gamma would adjust their instantaneous frequencies in order to keep the same ratio of cycles; therefore, PPC can also be considered as frequency locking.

Mean Radial Distance ($R_{n:m}$)

The mean radial distance ($R_{n:m}$) – also called mean resultant length – is a common metric of



Theta-Gamma Cross-Frequency Analyses (Hippocampus), Fig. 3 Comodulation maps. PAC strength for several pairs of phase- and amplitude-providing frequency ranges can be simultaneously depicted by means of a bidimensional pseudocolor map, in which the color scale

denotes the value of the PAC metric (in this example, the MI). The coordinates usually represent the center frequency of the filtered signals. Comodulation maps can also be constructed for other CFC types

PPC strength. This metric is similar to the PLV, but with phasors defined as unitary vectors whose angle is the phase difference between accelerated theta and gamma phases (Tass et al. 1998):

$$PPC_{strength} = R_{n:m} = \left\| \frac{1}{N} \sum_{j=1}^N e^{i\Delta\varphi_{nm}(t_j)} \right\|$$

where $\Delta\varphi_{nm}(t_j) = n\varphi_\gamma(t_j) - m\varphi_\theta(t_j)$, and $n\varphi_\gamma$ ($m\varphi_\theta$) represents the phase of gamma (theta) accelerated n (m) times. In the case of theta-gamma PPC, $R_{n:m}$ “curves” are usually obtained by varying m with $n = 1$ (Belluscio et al. 2012; Scheffer-Teixeira and Tort 2016). PPC strength can also be expressed for multiple n and m values by means of 2D heatmaps (Palva et al. 2005).

Shannon Entropy-Based Index

Tass et al. (1998) proposed two metrics of $n:m$ phase-locking. One of the metrics is defined as an inverted normalization of the Shannon entropy of the probability distribution of $\Delta\varphi_{nm}$ (Ψ_{nm}):

$$PPC_{strength} = \frac{H_{max} - H(\Psi_{nm})}{H_{max}}$$

where H_{max} is the entropy of the circular uniform distribution. The probability distribution Ψ_{nm} is estimated by binning the circle into non-overlapping phase bins, counting the number of $\Delta\varphi_{nm}$ values within each bin, and normalizing the bin counts by the total counts. Notice that this metric is essentially the same as the PAC MI (actually, the latter was adapted from the former), but applied to the circular distribution of phase difference values instead of amplitude values.

Conditional Probability-Based Index

The second measure introduced by Tass et al. (1998) relies on assessing instantaneous gamma phases conditioned to fixed theta phase bins. In this framework, the theta phases are first binned into N_θ nonoverlapping bins; then, the following vector is computed for each phase bin θ_l :

$$R_{\theta_l} = \frac{\sum_{j=1}^{N_l} e^{i\varphi_\gamma(t_j)}}{N_l}$$

where $\varphi_\gamma(t_j)$ is the instantaneous gamma phase at t_j , and N_l is the total number of timestamps t_j belonging to θ_l (i.e., t_j is such that $\varphi_\theta(t_j) \in \theta_l$). Therefore, each theta phase bin is associated with a mean vector over phasors whose angles are the instantaneous gamma phases falling in it. If gamma has the exact same phase within a fixed theta phase bin, the magnitude of R_{θ_l} is 1. On the other hand, if $\varphi_\gamma(t_j)$ values are random (i.e., gamma is not phase-locked), the unit vectors will cancel each other out, and $|R_{\theta_l}|$ will be small. The PPC metric is defined as the average vector length over all theta phase bins:

$$PPC_{strength} = \frac{\sum_{l=1}^{N_\theta} |R_{\theta_l}|}{N_\theta}$$

Pairwise Phase-Consistency

Phase-locking metrics based on the addition of phase difference vectors are positively biased for small samples. To circumvent this issue, Vinck et al. (2010) proposed the pairwise phase consistency, which is defined as the average dot product over all vector pairs, or, equivalently, the average cosine between all vector pairs. Scheffer-Teixeira and Tort (2016) recently used Vinck’s metric to measure $n:m$ phase-locking by applying it to the difference between accelerated gamma and theta phases ($\Delta\varphi_{nm}$):

$$PPC_{strength} = \frac{2}{N(N-1)} \sum_{j=1}^{N-1} \sum_{k=(j+1)}^N \cos(\Delta\varphi_{nm}(t_j) - \Delta\varphi_{nm}(t_k))$$

where N is the total number of time samples. If the accelerated phase differences $\Delta\varphi_{nm}$ are constant, meaning perfect $n:m$ phase-locking, $\cos(\Delta\varphi_{nm}(t_j) - \Delta\varphi_{nm}(t_k)) = \cos(0) = 1$ and consequently $PPC = 1$. If $\Delta\varphi_{nm}$ values are random and uniformly distributed over the circle, the expected value of PPC is 0.

Mutual Information

Theta-gamma PPC can also be measured using Shannon's mutual information in a similar way as described above for PAC assessment. Namely, the joint and marginal probability distributions are first estimated from phase bin counts ($N_{\text{total}} = \text{sampling rate} \times \text{epoch length}$):

$$p(\varphi_{\theta_i}) = \frac{N_{\theta_i}}{N_{\text{total}}}, \quad p(\varphi_{\gamma_j}) = \frac{N_{\gamma_j}}{N_{\text{total}}}, \quad \text{and} \\ p(\varphi_{\theta_i}, \varphi_{\gamma_j}) = \frac{N_{\varphi_{\theta_i} \cap \varphi_{\gamma_j}}}{N_{\text{total}}},$$

and mutual information is subsequently calculated as:

$$PPC_{\text{strength}} = I(\Phi_{\theta}; \Phi_{\gamma})$$

$$= \sum_{i=1}^M \sum_{j=1}^N p(\varphi_{\theta_i}, \varphi_{\gamma_j}) \log \left(\frac{p(\varphi_{\theta_i}, \varphi_{\gamma_j})}{p(\varphi_{\theta_i})p(\varphi_{\gamma_j})} \right)$$

Amplitude–Amplitude Coupling (AAC)

Correlation Between Amplitude or Power Values

Theta-gamma AAC can be estimated as the correlation between the amplitude envelopes of theta (A_{θ}) and gamma (A_{γ}) (Bruns et al. 2000; Bruns and Eckhorn 2004):

$$AAC_{\text{strength}} = \text{corr}(A_{\theta}, A_{\gamma}) \\ = \frac{1}{N} \sum_{j=1}^N \frac{(A_{\theta}(t_j) - \overline{A_{\theta}})(A_{\gamma}(t_j) - \overline{A_{\gamma}})}{\sigma_{A_{\theta}} \sigma_{A_{\gamma}}}$$

Alternatively, the correlation can be performed using integrated power over the desired frequency ranges. To that end, the analyzed epoch must be first partitioned into contiguous, nonoverlapping windows and Fourier-transformed within windows to compute the power spectra (Masimore et al. 2004). With either framework, an amplitude–amplitude comodulogram can be plotted by representing the correlation coefficients of multiple frequency pairs by means of a 2D heatmap (Masimore et al. 2004).

Phase-Locking of Amplitude Envelopes

The phase-locking value (PLV) can also be adapted to measure AAC (Jirsa and Müller 2013). Instead of using the filtered signal, the phase time series are extracted from the detrended amplitude envelopes of theta (A_{θ}) and gamma (A_{γ}). AAC is then estimated as:

$$AAC_{\text{strength}} = \left\| \frac{1}{N} \sum_{j=1}^N e^{i(\varphi_{A_{\theta}}(t_j) - \varphi_{A_{\gamma}}(t_j))} \right\|$$

Mutual Information

As all CFC types, theta-gamma AAC can also be assessed by mutual information. To that end, the range of amplitude values of each oscillation must be binned into nonoverlapping bins. Estimations of the joint and marginal probability of amplitude values are then obtained by normalizing bin counts and used to compute the mutual information.

Phase–Frequency Coupling (PFC), Amplitude–Frequency Coupling (AFC), and Frequency–Frequency Coupling (FFC)

PFC, AFC, and FFC have been considerably less explored than the other CFC types (Hyafil et al. 2015). Nevertheless, several of the metrics described above can be adapted to measure these interactions. For instance, Hyafil (2015) proposed that standard PAC measures could assess PFC by using the instantaneous frequency time series instead of the amplitude envelope. More generally, the values achieved by each oscillatory feature (e.g., amplitude or frequency) can always be binned and transformed into probability distributions to allow for computing the mutual information.

Sources of Biases and Spurious Coupling

There are several possible sources of bias and spurious results in CFC research (Kramer et al. 2008; Aru et al. 2015; Hyafil 2015; Scheffer-Teixeira and Tort 2016); among them:

1. *Asymmetric waveform*: recent studies have explored the influence of waveform shape on CFC measures (Gerber et al. 2016; Lozano-

- Soldevilla et al. 2016; Scheffer-Teixeira and Tort 2016; Cole et al. 2017). For instance, hippocampal theta oscillations are asymmetric, in that the rising phase is faster than the falling one, and such asymmetry increases with locomotion speed (Belluscio et al. 2012). Waveform asymmetry may induce spurious PAC and PPC, since the filtered signals will reflect a set of harmonic waves that naturally couple to the fundamental oscillation and to each other (Aru et al. 2015; Scheffer-Teixeira and Tort 2016). Another side-effect of asymmetric waveforms is nonuniform phase distributions, which may produce biased CFC estimates (van Driel et al. 2015).
2. *Sharp edges*: Kramer et al. (2008) recognized that sharp signal deflections are a potential confound factor in CFC analyses. The sharp edges in EEG and LFP signals may have either biological origin (e.g., event-related potentials or spike-and-wave mu rhythms) or be due to stimulation artifacts. At any event, the abrupt deflections give rise to spurious fast oscillatory activity in filtered signals, which in turn may mislead CFC estimates.
 3. *Nonmeaningful features and filtering-induced sinusoidality*: standard filtering methods tend to produce sinusoid-like signals even in the absence of genuine brain oscillations in the filtered frequency range. As a consequence of the sinusoidality imposed by the filter, the phase and frequency time series may temporally appear as coupled and lead to PPC overestimation, especially in short time epochs (Scheffer-Teixeira and Tort 2016; Hyafil 2017).
 4. *Wrong bandwidth choice*: In PAC analysis, the filtered bandwidth should contain both the amplitude-modulated frequency and the side bands (modulated frequency $\pm$ modulating frequency). Therefore, narrowly filtered frequency bands may not detect genuine PAC (Berman et al. 2012; Aru et al. 2015). Curiously, however, Hyafil (2015) pointed out that PFC can be mistaken as PAC in narrowly filtered signals, since cyclic variations of the instantaneous gamma frequency outside the filtered range will be associated with cyclic amplitude variations. For a similar reason, Hyafil (2015) further pointed out that variations in instantaneous frequency may be mistaken as AAC.
 5. *Phase slips and frequency spikes*: Instantaneous frequency is estimated as the first derivative of the phase time series. Fast signal perturbations may cause “jumps” in the phase time series, the so-called “phase slips” (Hurtado et al. 2004). Such events produce large deviations of the instantaneous frequency (“frequency spikes”), much above or below the filtered frequency range (it may even assume negative values), even though the frequency of the rhythm may not change on a larger time-scale (see Fig. 1A for an actual example). Of note, phase slips and frequency spikes are also common in aperiodic or noisy signals. Abundant phase slips may thus bias the assessment of frequency coupling. One method to overcome this issue is to detect the associated frequency spikes and smooth them out (Hurtado et al. 2004).
- Ideally, the investigated oscillations (i.e., theta and gamma) should exist in the analyzed signal, as inferred by peaks in the power frequency spectrum. As a rule of thumb, CFC estimates are most “trustable” when one can observe such interaction by visual inspection of raw (unfiltered) signals. Theta- and gamma-filtered signals can be plotted along with the unfiltered signal to facilitate such inspection.
- Statistical Assessment**
- Statistical analyses may be used to infer if CFC exists (i.e., beyond chance levels) or to compare CFC strength among different groups (e.g., different manipulations, cognitive states, frequency pairs, or brain regions). While the latter can be performed with standard statistical tests, the former usually requires the construction of surrogate distributions of coupling strength. As a general rule, a good surrogate method should preserve data continuity and spectral properties, as well as it should use the same epoch length as the original data (Scheffer-Teixeira and Tort 2016). A typical surrogate procedure is to analyze theta and

gamma time series not matched in time. The existence of theta-gamma coupling is then assessed by comparing the actual CFC metric with the chance distribution of surrogate values.

On the Choice of the CFC Metric

As summarized above, several CFC metrics were proposed to quantify the presence or absence of interacting brain oscillations. However, the repertoire of metrics may lead to confusion when choosing one of them, which motivated some comparative studies (e.g., Penny et al. 2008; Tort et al. 2010; Onslow et al. 2011). As a starting point, one can assume that a good metric should present (1) unbiased estimators, (2) tolerance to noise, and (3) strength representation (i.e., different coupling levels are separately represented by the metric). Regarding these characteristics, we make the following observations:

(1) Vinck et al. (2010) showed that the metrics based on vector addition, such as MVL, PLV, and coherence, are positively biased for shorter epochs. (Although Vinck et al. have originally referred to phase synchrony metrics devised for oscillations of the same frequency, these metrics were eventually adapted to measure PAC and inherited the same caveats.) This is because – in the absence of coupling – a large enough number of vectors should be sampled to produce a null resultant vector. But we note that the positive bias for short epochs is not unique to these metrics. In general, to confidently assess PAC, one needs to analyze enough cycles to infer whether consistent variations of the gamma amplitude exist within theta cycles. In practice, the instantaneous gamma amplitude is never constant within the time window of a theta cycle (~125 ms), and hence, a phase-amplitude distribution computed using a single theta cycle will never be uniform. Therefore, the presence of nonuniform phase-amplitude distributions should be interpreted with caution for short time epochs and, most importantly, must be compared with chance distributions (c.f., last section above). While we cannot advocate a minimal epoch length for CFC analysis due to

the great variability of brain signals, metrics, and research settings, we recommend always to perform internal checks using real and simulated data, such as to assess metric convergence as a function of the analyzed epoch length and chance distributions (Tort et al. 2010; Scheffer-Teixeira and Tort 2016).

(2) The addition of noise to phase-amplitude coupled signals may differentially affect some PAC metrics. Tort et al. (2010) found that PLV, ESC, GLM, and coherence are negatively affected by noise, which leads them to underestimate PAC strength. On the other hand, the ratio-based metrics, MI and MVL, are more tolerant to noise, while the amplitude PSD overestimates PAC strength with higher noise levels. This occurs because the added noise increases power in all frequency bands.

(3) Some measures may better track “coupling consistency” across cycles, defined as the proportion of theta cycles in which gamma appears modulated by theta, but are less sensitive to “coupling strength,” defined as the magnitude of the amplitude modulation within theta cycles (Tort et al. 2010). For instance, PLV and coherence both are based on the phase transformation of the gamma amplitude. Because of that, the amplitude modulations will be treated as cycles with phases varying from 0° to 360°, irrespective of the magnitude (e.g., an amplitude variation of $\pm 10\%$ or $\pm 50\%$ from the mean may lead to similar phase time series). Correlation-based indexes, such as GLM and ESC, also do not represent the coupling strength well, but for a different reason: the presence of higher modulations shifts the regression slope or the Y-intercept, but does not necessarily change the correlation/regression coefficient (Tort et al. 2010). Finally, by design, some PAC metrics such as the MVL and the amplitude PSD take into account the absolute amplitude of gamma and will thus also depend on gamma power irrespective of the “relative” coupling strength, as defined by the percentage of change from the mean amplitude (Tort et al. 2010).

Of note, some may also be interested that the metric is capable of detecting multimodal coupling (e.g., when gamma amplitude has two maxima within a theta cycle). By their definitions, the MI and the mutual information would be better suited in these cases (Tort et al. 2010).

Despite these particularities, it should be noted that hippocampal theta-gamma PAC is usually a phenomenon robust enough to be detected by any of the metrics. Ultimately, one should choose a metric whose advantages and limitations are well understood, and also bear in mind that the very definition of CFC will depend on this choice. In this sense, since it is presently unclear whether the assessment of “coupling consistency” or “coupling strength” (c.f. definitions above) would be cognitively more relevant, we cannot point to a single PAC metric as the best one.

Lastly, we note that PPC has received less attention regarding comparative studies among metrics. Shannon entropy, conditional probability, and mutual information-based indexes are not as widely used as the mean radial distance. The mean radial distance, however, is based on vector addition and is thus a positively biased estimator (small epochs result in higher values). Recently, Scheffer-Teixeira and Tort (2016) showed computationally that Vinck’s pairwise phase consistency could be adapted and used as an unbiased index for PPC.

Novel CFC Metrics

The study of cross-frequency interactions is an active field of research, which involves scientists working at different levels, brain regions, species, and brain signals (e.g., EEG, ECOG, LFP, MEG). CFC has also been described outside the brain, such as in the gut (Huizinga et al. 2014), and also in non-biological fields such as atmospheric dynamics (Paluš 2014). As an active field, new CFC metrics are continuously being elaborated; there are certainly far more CFC metrics than the ones summarized in this chapter. Important advances include metrics designed to infer coupling directionality (Paluš 2014; Jiang et al. 2015; Li et al. 2016), to improve time-resolution (Voytek et al. 2013; Dvorak and Fenton 2014; Samiee and Baillet 2017), to provide confidence

intervals and higher statistical rigor (Kramer and Eden 2013; van Wijk et al. 2015), to avoid standard filters by using autoregressive models (Tour et al. 2017) or empirical mode decomposition (Pittman-Polletta et al. 2014), and to cope with multiple channel data and spatial filtering (Cohen 2017).

Cross-References

- [Hippocampus, Theta, Gamma, and Cross-Frequency Coupling](#)

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Time Constant, Tau, in Neuronal Signaling

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Definition

The membrane time constant τ with $\tau = R_m C_m$ is a measure of the rate of voltage decay (or charging) in a cell (Rall 1977). Quantitatively τ is the time it takes for the voltage to decay to 1/e or 37% of its initial value in an isopotential or uniformly polarized cell.

Detailed Description

As given in the definition above, the membrane time constant τ with $\tau = R_m C_m$ is a measure of the rate of voltage decay (or charging) in a cell. Quantitatively τ is the time it takes for the voltage to decay to 1/e or 37% of its initial value in an isopotential or uniformly polarized cell. This can be seen from the solution of the differential equation for a uniformly polarized cell,

$$C_m dV/dt + V/R_m = 0$$

which can be solved as

$$\begin{aligned} V(t) &= V_0 \exp(-t/\tau) \text{ or } V(t) \\ &= V_\infty - (V_\infty - V_0) \exp(-t/\tau) \end{aligned}$$

when initial voltage is V_0 and voltage decays to zero in the first equation or to a resting voltage V_∞ in the latter equation. The latter equation can also be used to describe voltage charging in response to current injection by letting V_0 be the resting potential and V_∞ be the steady-state voltage which is $V_0 + IR_N$ where I is the injected current and R_N is input resistance.

The importance of τ is that it determines how synaptic inputs are integrated in time (temporal summation). If τ is small, individual inputs decay quickly and will not sum, but if τ is large, inputs will decay slowly and are much more likely to sum.

Because $\tau = R_m C_m$, its value will depend on the density of open ion channels in the membrane as well as on membrane capacity. However, τ does not depend on membrane area; it has units of time, typically milliseconds.

Voltage decay depends strictly on τ only for a uniformly polarized cell and becomes more complicated when voltage is not spatially uniform. While voltage falls to 37% of its initial value in time τ in a uniformly polarized cell, voltage falls to 16% of its final value in time τ in an infinite cable; in a finite cable, the decay rate lies in between, although the final decay rate does reflect τ . Interestingly, when voltage is not spatially uniform, the total charge will still decay according to τ .

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Time-Delayed Neural Networks: Stability and Oscillations

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Definition

A time-delayed neural network is a model for a biological or artificial neural network which is formulated in terms of a delay differential equation, i.e., an equation relating the derivative of the state of the system to the state of the system at some past times. Time delays can have profound effect on the network behavior; in particular, they can induce nonlinear transient or steady-state oscillations.

Detailed Description

Biological Background

In biological neural networks, if the axon is thick and myelinated, then the transportation of signals is fast. However, a considerable portion of the axons (estimated range: 20–40 percent) are very fine myelinated fibers or unmyelinated ones. These axons play quite an important role since they give rise to long delays, up to 100–200 ms (Herz et al. 1989; Miller 1994; Swadlow and Waxman 2012). In addition, there may be (post) synaptic delays, so that long-term potentiation even occurs if the signal from the source neuron has arrived some time before the target neuron becomes active. In general, axonal signal propagation corresponds to discrete time delays, while diffusion processes across the synapses and along the dendrites are modeled by distributed delays. Time delays are also omnipresent in artificial

Time Histogram

► Estimation of Neuronal Firing Rate

neural networks and, in particular, in the electronic hardware implementation, due to the finite propagation velocity of neural signals and due to the finite switching speed of amplifiers (neurons).

Time-delayed network models and prototypes. Consider a network of n neurons modeled by the equations:

$$\begin{aligned}\dot{x}_i(t) &= f_i(x_i(t)) + \sum_{j=1}^n f_{ij}(x_i(t), x_j(t)), i \\ &= 1, \dots, n,\end{aligned}$$

in which x_i represents all the variables describing the physical state of the cell body of the i -th neuron in the network. For example, in the standard Hodgkin-Huxley model, it would represent the membrane voltage and gating variables. The function f_i represents the intrinsic dynamics of the i -th neuron, and the function f_{ij} , often called the coupling function, represents the input to the i th neuron from the j th neuron. Neurons can be connected via chemical synapses or gap junctions, giving rise to different forms of the coupling functions. There are also different ways to incorporate the time delays in a neural network model, to reflect the different sources of delay in the neural system. For example, time delays due to propagation of action potentials can be incorporated into the model by including spatial dependence of the variables or multiple compartments representing different parts of the neuron (Ermentrout and Terman 2010). However, if we are primarily interested in the effect of the action potential when it reaches the end of the axon, then a simpler approach is to include a time delay in the coupling term. In this case, the general coupling term becomes $f_{ij}(x_i(t), x_j(t - \tau_{ij}))$, where $\tau_{ij} > 0$ represents the time taken for the action potential to propagate along the axon connecting neuron j (the presynaptic neuron) to neuron i (the postsynaptic neuron). The above assumes that the axon of neuron j connects on or close to the cell body of neuron i . Some cells may have synapses or gap junctions on dendrites far from the cell body. In this case, there can also be a delay associated with propagation of the action potential along the dendrite. This will introduce an additional time

delay, viz., $f_{ij}(x_i(t - \tau_{ij}^d), x_j(t - \tau_{ij}^d - \tau_{ij}^a))$, where τ_{ij}^a and τ_{ij}^d represent the time delays due to the propagation of the action potential along the axon and dendrite, respectively. Another delay can occur in the transmission of the electrical signal across the synapse. That is, once the action potential from neuron j reaches the synapse, there is some time before an action potential is initiated in neuron i . A common way to model this is to augment the model equations above by equations modelling the chemical kinetics of the synapse. Alternatively, this can be incorporated by increasing the delay τ_{ij} .

A prototype biological model is the following setup in Campbell and Kobelevskiy (2012) for a network of two neurons:

$$\begin{aligned}\dot{v}_1(t) &= -g_{Ca}m_\infty(v_1(t)) - g_Kw_1(t)(v_1(t) - v_K) \\ &\quad - g_L(v_1(t) - v_L) + I + g_{syn}s(v_2(t - \tau)) \\ &\quad \times (v_1(t) - E_{syn}) \\ \dot{w}_1(t) &= \phi\lambda(v_1(t)) \times (w_1 - w_\infty(v_1(t))) \\ \dot{v}_2(t) &= -g_{Ca}m_\infty(v_2(t)) - g_Kw_2(t)(v_2(t) - v_K) \\ &\quad - g_L(v_2(t) - v_L) + I + g_{syn}s(v_1(t - \tau)) \\ &\quad \times (v_2(t) - E_{syn}) \\ \dot{w}_2(t) &= \phi\lambda(v_2(t)) \times (w_2 - w_\infty(v_2(t)))\end{aligned}\tag{1}$$

Here each neuron is modeled by the Morris-Lecar model, and the neurons are joined with delayed synaptic coupling, with delay τ , coupling strength, g_{syn} . The functions $m_\infty(v)$, $w_\infty(v)$, and $s(v)$ are sigmoidal (specifically, hyperbolic tangents), while $\lambda(v)$ is the reciprocal of a normal distribution (specifically, a hyperbolic cosine). When uncoupled, the individual neurons can be in one of two states depending on the size of the input current I . If I is sufficiently small, the neuron is quiescent, i.e., v_j and w_j are constant in time. If I is large enough (greater than rheobase), the neuron is spiking, i.e., v_j and w_j vary periodically in time.

Another example, referred as a delayed additive or Grossberg-Hopfield network, is given by the model:

$$Cu'_i(t) = -\frac{1}{R}u_i(t) + \sum_{j=1}^n \times \frac{1}{R_{ij}}f_j(u_j(t-\tau_j)). \quad (2)$$

This describes an artificial neural network consisting of electronic neurons with voltages u_i and input impedance described by a combination of a resistor R and a capacitor C interconnected through a matrix of resistors (R_{ij}). Scaling time by the relaxation time, RC , of the individual neurons, shows that an important parameter in determining the dynamics and the computational performance of the network is the relative delay size $r_j = \tau_j/(RC)$. In particular, designing a network so that the individual neurons operate more quickly will increase this relative size of the delay. This model is also used in a biological context to study networks of spiking neurons, i.e., neurons that are intrinsically oscillating. In this context, it is either called a *firing rate* model, in which case u_i is interpreted as the firing rate (frequency of spiking) of the i th neuron (Dayan and Abbott 2001), or a *neural activity* model, in which case u_i is interpreted as the synaptic conductance of the i th neuron averaged over one period of spiking (Ermentrout 1994). Ermentrout (1994) shows how, under certain assumptions and with no time delays, the model (2) can be derived from a model similar to (1).

We have focused here on models for networks in the brain. Time delays are also important in neural networks in the peripheral nervous systems, for example, in the balance control system (Cabrera and Patzwelt 2013).

Mathematical Background and Tools for Analysis

Given a model such as (1) or (2), one would like to determine how the behavior of the network evolves in time, for a particular initial state of the network. In mathematical terms, this means solving an initial value problem for the system of differential equations that defines the model. For an ordinary differential equation model, the initial state is a point, and the solution describes how this point evolves in time in the (finite-dimensional)

state space. Hence it defines a finite-dimensional dynamical system. For a delay differential equation system, the initial state is a function which specifies the values of the variables from the delay time up to the present. For example, for Eq. (2) an initial condition is

$$u_i(t) = \phi_i(t), \quad -\tau \leq t \leq 0$$

where the ϕ_i are known functions. The solution of the initial value problem describes how this initial state evolves in time in an (infinite-dimensional) space of functions. Hence this defines an infinite-dimensional dynamical system. Despite the fundamental differences between finite-dimensional and infinite-dimensional systems, many of the tools used to study the dynamical behavior of ordinary differential equations may be extended to delay differential equations, as summarized in the fairly accessible books of Kolmanovskii and Nosov (1986), Smith (2011), and Stépán (1989). For complete accounts of the theory of delay differential equations, we refer the reader to the books of Hale and Verduyn Lunel (1993) and Diekmann et al. (1995).

Since the initial value problem described above cannot in general be solved in a closed form, a common starting point is to describe the constant (equilibrium) solutions of the system. One then considers the **stability** of these equilibrium solutions. This will give at least a partial picture of the long-term behavior of the network.

For models such as (1) and (2), the equilibrium solutions are the same as the system with no delay (i.e., the ODE system found by setting $\tau = 0$ or $\tau_i = 0$ for all i). They are found by solving the set of algebraic equations determined by the right-hand sides of the differential equations. The equilibrium solutions may, however, change their stability due to the presence of the delay. This delay-induced instability is a common phenomenon, and periodic solutions may bifurcate from these equilibrium solutions when model parameters, especially the time delay, are varied near certain critical values. Detecting these critical values is more technically involved. It requires describing the roots of the characteristic equation, which is a complex transcendental equation. An example is

the Hopf bifurcation (Kazarinoff et al. 1978), where a family of periodic solutions emerges due to the change of stability of the equilibrium solution. In this case, the critical parameter value corresponds to the characteristic equation having a pair of purely imaginary roots. The Hopf bifurcation theorem for delay differential equations (Hale and Verduyn Lunel 1993; Kuang 1993; Smith 2011) determines whether a Hopf bifurcation occurs at such a critical value. Various approaches have been developed for determining the bifurcation direction (subcritical or supercritical) and stability of the resulting periodic orbits (Das and Chatterjee 2002; Erneux 2009; Faria and Magalhães 1995). For an in-depth account of the bifurcation analysis of delay differential equations, see the recent monograph by Guo and Wu (2013). These approaches have been implemented both numerically (Gilsinn 2008; Aboud et al. 1988) and using symbolic algebra systems (Campbell et al. 2006; Campbell 2008; Qesmi et al. 2006).

There are two basic numerical tools which can aid in the study of delayed neural networks: numerical simulation and numerical bifurcation analysis. In numerical simulation, one attempts to determine an approximate solution of a differential equation corresponding to a given initial state. A key issue in numerical integration of delay differential equations is keeping track of the past history of the solution. Both fixed stepsize (Ermentrout 2002) and variable stepsize (Shampine and Thompson 2001) methods have been implemented. In numerical bifurcation analysis, one attempts to determine how the existence and stability of equilibrium points and periodic orbits vary with one or more parameters. To accomplish this, one must bring together tools for finding and approximating equilibrium and periodic solutions of delay differential equations with tools for analyzing characteristic equations (Breda et al. 2004; Engelborghs et al. 2002; Olgac and Sipahi 2002; Szalai et al. 2006).

Creation, Death, and Global Continuation of Oscillations

As discussed above, time delays can be associated with oscillations created by a Hopf bifurcation.

This is sometimes referred to as a *delay-induced oscillation*. One of the simplest examples of this is the following model for recurrent inhibition due to Plant (1981):

$$\begin{aligned}\dot{v}(t) &= v(t) - \frac{1}{3}v^3(t) - w(t) + c(v(t - \tau) - v_0) \\ \dot{w}(t) &= \rho(v(t) + a - bw(t)).\end{aligned}$$

This is a Fitzhugh-Nagumo model neuron with a delayed term which represents recurrent feedback.

In a neural network, the structure of the network can be important for determining if delay-induced oscillations can occur. As noted in (Bélair et al. 1996), for a neural model of the form (2), an important necessary condition for the occurrence of this phenomenon is the presence of frustration, that is, a directed pathway from a neuron to itself such that the product of the connection weights along the path is negative. By contrast, in some network structures, delay does not alter the asymptotic behavior of the system. A globally asymptotically stable contractive network is one example. Cooperative irreducible networks is another. An irreducible network is one in which there is a directed path connecting any pair of neurons. It is referred to as cooperative when, possibly after a change of variables, all interactions are excitatory. Such systems, with or without delay, generate an eventually strongly monotone semiflow, so that the asymptotic behavior of the network with delay is essentially the same as that of the corresponding network without delay (Smith 1995).

Not only can time delays *create* oscillations, but in systems where the uncoupled neurons are oscillating, delays in the coupling can *destroy* the oscillations. This phenomenon, usually called **oscillator death** or **amplitude death**, was first noted by Ramana Reddy et al. (1998), in their analysis of a simple oscillator model with gap junctional coupling.

Much of the existing work on the creation and death of oscillations has focused on the bifurcation near a critical delay or other parameter value. How these oscillations are globally continued when the parameter is far away from the critical

value is a very challenging but an important component of the global dynamics of such a network. Technical tools including the global Hopf bifurcation theory, the discrete Lyapunov functional, and some geometric arguments have been inspired by and applied to this global dynamics issue (Guo and Wu 2013).

Multistability

Incorporating a time lag τ into even a simple neural circuit with feedback yields a scalar delay differential equation $u'(t) = -\beta u(t) + wf(u(t - \tau))$ that defines a semiflow on the infinite-dimensional phase space $C = C([- \tau, 0]; \mathbb{R})$ of continuous functions on the initial interval $[- \tau, 0]$. It has been shown that a network of neurons with delayed signal transmission is capable of storing and retrieving spatiotemporal patterns (Herz 1996; Herz et al. 1989), but the capacity of such a network in the aforementioned studies still relies heavily on the size of the networks and the variable delays associated with different synaptic connections. In particular, if $f' > 0$ (a strictly increasing signal function) and $f(0) = 0$ (normalization), then trajectories of such a network generically converge to a set of two stable equilibria (if $w > 0$, positive feedback, see Krisztin et al. (1999)) or a slowly oscillating periodic solution (if $w < 0$, negative feedback, see Mackey and Glass (1977); Marcus and Westervelt (1989); Walther (1995); Mallet-Paret and Nussbaum (1989)). The simplicity of dynamics limits the application of such a network as an associative memory device – the memory capacity is too low. Additional neural signal processing features must be further incorporated into the model in order for a small network with delay to possess a large number of stable attractors. Such features as firing and the existence of an absolute refractory period are reflected in the well-known Hodgkin-Huxley model (Hodgkin and Huxley 1952), and Foss et al. (1996) showed that neural recurrent inhibitory delayed loops based on the Hodgkin-Huxley model (Hodgkin and Huxley 1952) can indeed exhibit the coexistence (multistability) of three stable equilibria. Ma and Wu (2007, 2010) and Zhou et al. (2012) showed

that the phenomenological spiking model with two neurons, incorporating a firing process and an absolute refractory period, can generate a large number of asymptotically stable periodic solutions with predictable patterns of oscillations.

Time Delay and Network Symmetry

In a network of identical neurons of the form (2) and in the absence of synaptic delays, the asymptotic behaviors of the network can be characterized by the convergence to the set of synchronized equilibria, i.e., equilibria $u_i = u^*$, $\forall i$. Delay-induced instability, however, can give rise to stable phase-locked oscillations and other asynchronous behaviors. The type of behavior is determined by the network topology (Krawcewicz and Wu 1999; Wang and Campbell 2017). In networks of identical, inherently oscillatory neurons, such as given by Eq. (1), multiple different phase-locked states can exist. These states are often called clustered solutions as the neurons are grouped into clusters. Neurons within a cluster are synchronized (phase-locked with zero-phase lag), while neurons between clusters are phase-locked with nonzero-phase lag. The presence of time delay can stabilize otherwise unstable phase-locked solutions (Campbell and Koelevskiy 2012; Dahms et al. 2012; Orosz 2014).

Other Effects of Time Delay

Other issues related to the dynamic behaviors of networks with delay have also been widely considered. Below we describe a few important phenomena observed in networks with delay.

- *Delay-induced chaotic oscillations:* It should be emphasized that delay-induced oscillation need not be periodic and even a two-neuron network can provide a tractable prototype for the study of delay-induced chaos in neural networks (Gilli 1993).
- *Delay-induced change of the domain of attraction:* Even for a cooperative irreducible system whose quasiconvergence is guaranteed, delay may affect the shape and structure of the basins of attraction of equilibria which has significant

impact on its application to content-addressable memory (Pakdaman et al. 1998).

- *Delay-induced transient oscillations*: All the phenomena described above are related to the influence of delay on the long-term behaviors of the system. It should be noted that the delay also affects the transient behavior of networks. As discussed in Pakdaman (2013), for some neural networks, delay may lead to long-lasting transient oscillations whose duration increases exponentially with the delay.

Summary and Implications

In summary, in the study of the effect of signal delays on the network dynamics, an important issue is how signal delays change the stability of equilibria, causing nonlinear oscillations and inducing periodic solutions. While the existence of periodic solutions creates some problems in neural network applications such as content-addressable memory, periodic sequences of neural impulses are the fundamental means of communication in the brain (Buzsa'ki, Buzsáki 2006) and have been investigated in the context of epileptic seizures (Yang and Robinson 2017). Understanding how oscillations are created, destroyed, and modulated is of vital importance in understanding brain function and disfunction. The questions how neural networks can sustain highly periodic activity for a long period of time and what makes them fail under certain conditions are thus of vital interest (Mu"ller and Reinhart 1990).

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Time-Dependent Modeling

- **Metabotropic Receptors (G Protein Coupled Receptors)**

Time-Frequency Analysis of Analog Neural Signals

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Definition

Time-frequency analysis is a signal processing method that involves extracting frequency-specific information from temporally localized windows of a signal. Time-frequency analysis is most useful for interpreting signals that are non-stationary, meaning that the spectral characteristics change over time.

Detailed Description

Why Spectral Analysis?

Population-level neural activity, as reflected by the local field potential and electroencephalogram, often exhibits rhythmic temporal patterns with characteristic frequencies, for example, at 10 Hz (“alpha”) or 40 Hz (“gamma”). These rhythmic patterns are called neural oscillations and have been linked to myriad perceptual, cognitive, and motor phenomena (Buzsáki 2006). Careful inspection of rhythmic neural time series suggests that these rhythms are not purely sinusoidal (Cole and Voytek 2017; Jones 2016) yet are sinusoidal enough to justify analysis methods that use sine waves as basis functions, such as the Fourier transform (Cohen 2014).

Spectral Analysis for Stationary Signals

The basic spectral analysis method is the Fourier transform. The Fourier transform involves computing the dot product (a measure of similarity that is also used to compute the correlation coefficient) between the signal and a series of sine waves at a range of frequencies. The more the signal “looks like” the sine wave, the larger the dot product between them. The squared dot

product is termed power and, when plotted over a range of sine wave frequencies, produces the power spectrum that is used to identify rhythmic activity.

Neural time series data (like many other biological and nonbiological signals) often exhibit a decrease in power with increasing frequency, a phenomenon known as “1/f” and implicated in scale-free dynamics reminiscent of fractal-like behavior often observed in nature (Hardstone et al. 2012). Positive deviations from the 1/f – “bumps” in the spectrum – are the spectral manifestations of characteristic frequencies and are taken as evidence of neural oscillations.

Time-Frequency Analysis for Nonstationary Signals

The primary disadvantage of the Fourier transform is that the power spectra it reveals are easily interpretable only for stationary signals, meaning that the features of the signal remain constant over time. Time-varying fluctuations in amplitude, variance, and frequency are not readily visible in power spectra. On the other hand, it is precisely these fluctuations that neuroscientists are interested in studying (e.g., changes in neural activity during stimulus processing or motor planning).

Fortunately, rhythmic nonstationary signals can be understood using a class of analysis methods termed time-frequency analyses. The idea is to assess rhythmic activity over short windows of time, typically hundreds of ms to a few seconds. The “windows” are tapering functions that start and end at or close to 0 and peak at 1. Different time-frequency methods utilize windowing in different ways, but in general, either the data or the template sine waves are windowed. The resulting two-dimensional time-frequency plots indicate changes in the signal over both frequency and time. Two common time-frequency analysis methods are the short-time Fourier transform and wavelet convolution.

Data and Experiment Requirements

Application of spectral analysis methods requires signals that are sampled at regular intervals. This is typically the case in electrophysiology and imaging. A strict requirement is that the

frequencies of interest must be less than one-half of the data sampling rate, as described by the Nyquist theorem. This is generally not a limitation for electrophysiology, as sampling rates can be orders of magnitude higher than the highest frequency of interest. However, the Nyquist theorem does have implications for modern imaging methods (e.g., calcium or glutamate imaging, or magnetic resonance-based imaging), in which sampling rates may be in the range of 0.5–120 Hz, while frequencies of interest may be in the same or higher range. For example, a 60 Hz framerate camera used in a two-photon experiment could not measure activity higher than 30 Hz, which is the lower range of gamma-band oscillations.

Temporal filtering methods often produce “edge effects” at sharp transitions in the signal or at edges of a cut signal. Edge effects should be avoided by removing data that contain sharp edges (such features are typically the result of an artifact such as mechanical or electrical interference), and one should be careful that edges are sufficiently far away from the time windows of interest such that the edge effects will subside in the time window of interest. Thus, a second data requirement is to have clean signals that are sufficiently long to separate filter edge effects from true neural effects.

Perhaps the most important requirement is to have a theoretical motivation or set of hypotheses that spectral methods can provide evidence for or against. Spectral decomposition increases the dimensionality of the data and can increase the statistical and interpretational complexity of the research. Without a clear goal of applying spectral methods, the results may be difficult to interpret.

How to Implement Spectral and Time-Frequency Analysis Methods

There are many open-source toolboxes and proprietary software packages for implementing spectral and related data analyses. Three of the commonly used toolboxes in the MATLAB software program include EEGLAB, Fieldtrip, and Chronux.

Because the mathematics and their numerical implementations in computer programs are not extremely difficult, many research groups prefer

to write in-house code for some or all of the data analyses. There are many educational resources in books and online for learning about these techniques, some of which can be found at sincxpress.com.

Interpreting Time-Frequency Results

Neural oscillations often exhibit fluctuations in amplitude and frequency over time, which is why time-frequency methods are commonly applied to test hypotheses about neural oscillations. Transient oscillations manifest as changes in color or grayscale intensity in the time-frequency plane (an informative color bar should be included to facilitate interpretation).

On the other hand, one must be mindful that transient non-oscillatory events may also have a representation in the time-frequency plane, particularly if those transients have a curved waveform that will be captured by a sine wave or wavelet. Thus, the observation of a feature in the time-frequency plane on its own does not provide unambiguous evidence for the presence of a transient oscillation. For this reason, terms like “narrow-band” or “band-limited” have softer connotations than the term “neural oscillation.”

A commonly used rubric for an interpretation of a neural oscillation is that the feature must be restricted to a canonical frequency band, such as delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and so on; and it must exist for several cycles at that frequency. Features in the time-frequency plane that span multiple frequency bands or are present for one cycle are generally not considered evidence of neural oscillations.

Equally or perhaps more important for an interpretation of time-frequency results reflecting neural oscillations is a strong theoretical justification or expectation.

Cross-References

- ▶ [Basal Ganglia: Beta Oscillations](#)
- ▶ [Computational Models of Modulation of Oscillatory Dynamics](#)
- ▶ [Corticothalamic Feedback: Large-Scale Synchrony](#)

- [Hippocampal Oscillations, Mechanisms \(PING, ING, Sparse\)](#)
- [Local Field Potential, Synchrony of](#)
- [Multistability of Coupled Neuronal Oscillators](#)
- [Subthalamopallidal Loop and Oscillations](#)

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Timulus Locking

- [Phase-Locking Methods](#)

Tinnitus, Models

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Definition

Tinnitus, the perception of a sound in the absence of an acoustic stimulus, often develops after hearing loss. Human neuroimaging studies as well as animal models have shown that the phantom auditory sensation is related to altered patterns of spontaneous neuronal activity in the central auditory system. Computational models have been used to explore which plasticity mechanisms could lead to the development of

neurophysiological correlates of tinnitus. The models show that if a homeostatic plasticity mechanism attempts to stabilize neuronal activity at a certain target level despite the loss of input after hearing loss, the resulting shift in the excitation/inhibition balance can lead to an amplification of spontaneous activity in the central auditory system, thus creating the basis for a tinnitus sensation.

Detailed Description

The phantom auditory sensation of tinnitus is a frequent phenomenon; it is estimated that up to 10% of the population experience chronic tinnitus. The occurrence of tinnitus can be linked to hearing loss in most cases, and even tinnitus patients with normal hearing thresholds show signs of cochlear damage in psychophysical tests and auditory brainstem response measurements (Schaette and McAlpine 2011). Moreover, the pitch of the tinnitus sound is usually matched to frequencies where hearing is impaired.

Tinnitus cannot be abolished by sectioning the auditory nerve, suggesting that the generator of the phantom sound is located in the brain itself. Human neuroimaging studies and animal models have shown that tinnitus is correlated with aberrant patterns of spontaneous neuronal activity in the central auditory system. In animals, cochlear damage can lead to increased spontaneous firing rates of neurons in the cochlear nucleus, the inferior colliculus, and the auditory cortex (see Roberts et al. 2010, for a review). However, the plasticity processes and functional mechanisms that are involved in the generation of such neurophysiological correlates of tinnitus have not been pinpointed yet. To address this open question, computational modeling has been used to study how hearing loss affects activity patterns in the auditory system, which plasticity mechanisms might be activated, and how spontaneous activity is altered in the process. The models therefore provide an interpretational framework for the diverse sets of data from human and animal studies on tinnitus and allow the identification of candidate mechanisms for tinnitus development

by comparing their predictions to experimental data. So far, three main mechanisms have been explored in computational modeling studies of tinnitus: lateral inhibition (Gerken 1996; Bruce et al. 2003), homeostatic plasticity (Schaette and Kempter 2006, 2009; Chrostowski et al. 2011; Schaette and McAlpine 2011), and gain adaptation (Parra and Pearlmutter 2007; Norena 2011). All three mechanisms are ubiquitous in sensory pathways and have been observed in a variety of processing stages of the auditory system.

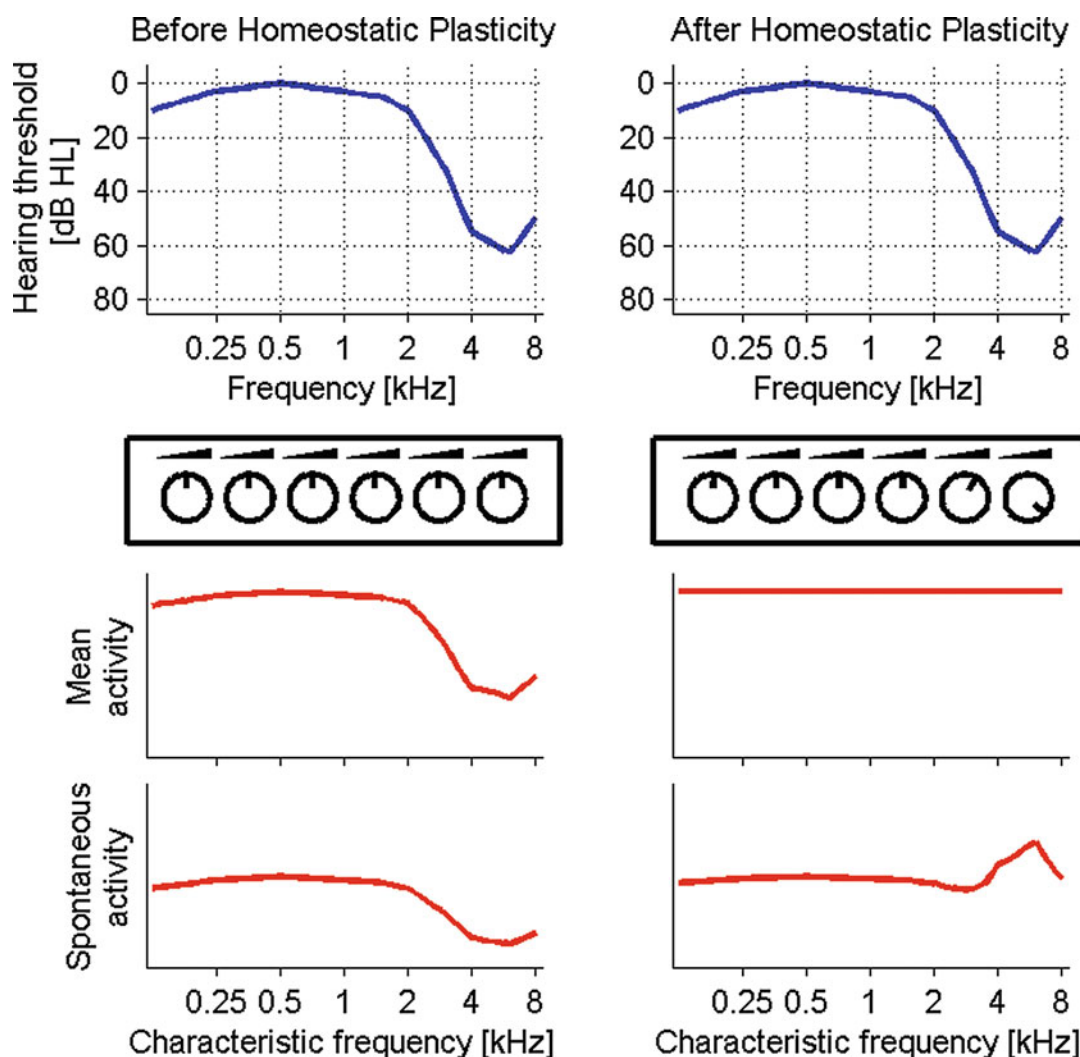
Lateral inhibition, e.g., inhibition between neurons in the auditory pathway with characteristic frequencies that are close, but not identical, can enhance the activity difference between neurons with high and low levels of activity in a neuronal network. Noise-induced hearing loss can create such an activity difference, as it reduces the spontaneous activity of auditory nerve fibers predominantly in the high-frequency range. When the resulting spontaneous activity pattern with a drop in activity toward the hearing loss region is processed by a neuronal network with lateral inhibition, the neurons just below and at the edge receive less lateral inhibition than their counterparts at lower frequencies, and the neurons just above the edge receive more lateral inhibition. As a consequence, the edge in the activity profile is amplified, leading to a peak in the profile of spontaneous activity. When this activity peak is erroneously interpreted as sound-evoked activity by higher stages of the auditory system, a tinnitus sensation could result (Gerken 1996). However, the resulting tinnitus pitch predictions are systematically too low, as lateral inhibition models generally predict tinnitus pitch to be at the audiogram edge instead of in the region of hearing loss (Schaette and Kempter 2009).

Homeostatic plasticity is a plasticity mechanism that stabilizes the mean activity of neurons on time scales of hours to days (Turrigiano 1999). Several models have explored how this mechanism could contribute to the development of a neural correlate of tinnitus after hearing loss, either in the brainstem (Schaette and Kempter 2006, 2009; Schaette and McAlpine 2011) or in the auditory cortex (Chrostowski et al. 2011):

Hearing loss reduces AN activity with a concomitant reduction in excitatory drive to the central auditory system (Fig. 1, left panels). In order to stabilize mean neuronal activity, homeostatic plasticity then increases excitation and decreases inhibition. The resulting shift in the excitation/inhibition balance increases the overall gain of the neuronal circuits downstream of the AN, which can restore average neuronal activity to normal levels. However, as neurons become more excitable that way, even uncorrelated spontaneous inputs can be amplified, causing an increase of spontaneous firing rates (Fig. 1, right panels). The model thus suggests that tinnitus could be an unwanted side effect of a stabilization of neuronal activity levels in the central auditory system after hearing loss. When the model is applied to audiograms of tinnitus patients with noise-induced hearing loss, the greatest increases in spontaneous firing rates are seen in the region of hearing loss, and tinnitus pitch predictions based on these spontaneous are consistent with observed pitch (Schaette and Kempter 2009).

Gain adaptation is a central feature of sensory processing, as it enables sensory systems to cope with input signals with a wide dynamic range. When gain adaptation is implemented in an abstract model through a running average of input activity that serves as a normalization factor, neural activity in frequency channels that receive little input, e.g., because of hearing loss, is amplified, which then also causes an amplification of spontaneous activity (Parra and Pearlmutter 2007). Gain adaptation models of tinnitus generation have been further explored by Norena (2011), who studied their relation to neural coding efficiency and stabilization of a certain level of mean activity. For long time scales of hours to days, gain adaptation can be regarded as functionally equivalent to homeostatic plasticity, and gain adaptation models also predict tinnitus to be in the region of hearing loss.

Computational modeling has contributed a functional perspective to the study of tinnitus, suggesting that very basic mechanisms like homeostatic plasticity could play a key role in



Tinnitus, Models, Fig. 1 Schematic illustration of homeostatic plasticity models, based on results from Schaette and Kempter 2009. The “knobs” represent the effective response gain of neurons in the central auditory system, determined by the strength of excitatory and inhibitory synapses. Before homeostatic plasticity (*left*), noise-induced hearing loss (e.g., audiogram in the *top panel*) has reduced mean and spontaneous activity of central auditory

neurons with high characteristic frequencies (*bottom panels*). After homeostatic plasticity (*right*), the response gain has been increased in the high-frequency range to restore mean neuronal activity back to the target level. However, due to the increased gain, spontaneously active inputs are amplified, causing an increase in spontaneous firing rates in the region of hearing loss

the development of neural correlates of tinnitus after hearing loss. Computational models of tinnitus have helped to advance theories of tinnitus development and to inspire new experimental investigations.

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Further Reading

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Tissue Conductivity

- [Resistivity/Conductivity of Extracellular Medium](#)

Tissue Impedance

- [Resistivity/Conductivity of Extracellular Medium](#)

Tissue Loading and Pathology

- [Biomechanical Model of Low Back Pain](#)

Tissue Resistivity

- [Resistivity/Conductivity of Extracellular Medium](#)

7TM Receptors

- [Metabotropic Receptors \(G Protein Coupled Receptors\)](#)

Topographic Independent Component Analysis

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Definition

Independent component analysis of images provides a probabilistic theory on the receptive fields of simple cells in the primary visual cortex (V1). Topographic ICA extends this to a model of the spatial arrangement (columnar structure) of simple cells, as well as their pooling into complex cells. The components (simple cell outputs) are assumed to have statistical dependencies whose strength depends on the distance of the cells on the cortical surface. Furthermore, complex cell outputs are constructed by pooling the energies of simple cells which are close to each other. When the model is estimated from natural images, the spatial organization and the complex cell properties learned are qualitatively similar to what has been observed in mammalian V1.

Detailed Description

Limitations of ICA on Images

Independent component analysis of images, as well as topographic ICA, is based on a linear

superposition model of natural image patches. Denoting the grayscale value of a pixel with 2D coordinates x and y by $I(x, y)$, the linear superposition model assumes

$$I(x, y) = \sum_{i=1}^k A_i(x, y) s_i$$

where the A_i are features or basis vectors and the components s_i are the coefficients of the features in the particular image patch being analyzed. Here, k is the number of components, usually taken to be equal to the number of pixels. The vector I is considered a random vector in the sense of taking different values from patch to patch. The components s_i model outputs of simple cells in V1, and the features A_i , or the inverse coefficients that give the s_i as a function of I , model simple cell receptive fields.

In ICA, the coefficients in s_i are assumed to be statistically independent of each other. However, this assumption is just a rough approximation of the real structure of natural images and is clearly violated when ICA is estimated from real image data. In fact, the ICA model does not have enough degrees of freedom to force the estimated components to be strictly independent.

A prominent form of dependencies that remains after ICA is correlation of energies, i.e., of the squares of the components:

$$\text{cov}(s_i^2, s_j^2) > 0$$

where cov means the covariance. An intuitive meaning of such a nonlinear correlation is “simultaneous activation,” i.e., the components tend to have nonzero values at the same time, but the values need not be linearly correlated (see Fig. 1).

Topographic Extension of ICA

In topographic ICA, we use the dependencies of the linear components s_i to further model the statistical structure of natural images. We start by arranging the simple cells spatially on a two-dimensional surface which models the cortical surface. In mathematical terms, such arrangement means that each component s_i modeling a simple



Topographic Independent Component Analysis, Fig. 1 Two signals which are uncorrelated but have energy correlations or “simultaneous activation.” For illustration purposes only, the signals are plotted as time series

cell is associated with a point on a grid on the 2D plane, as illustrated in Fig. 2. Components which are close to each other are allowed to have strong statistical dependencies, in particular energy correlations. To formalize the notion of two cells being close to each other, we define a *neighborhood function* $\pi(i, j)$ so that $\pi(i, j) = 1$ for components which are close to each other on the grid and zero otherwise.

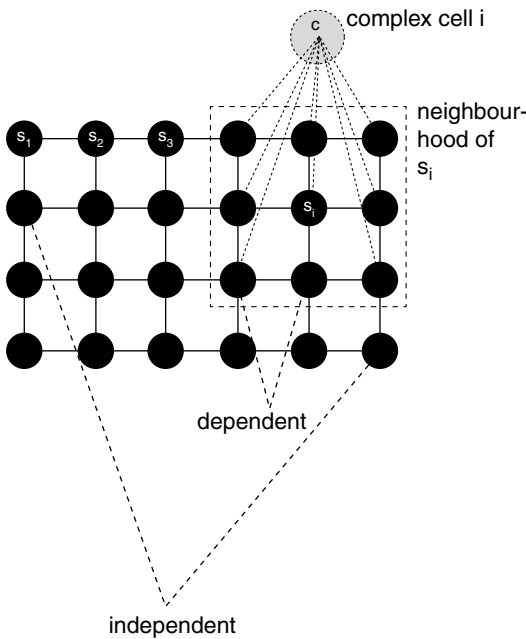
The neighborhood function is further used to define the complex cell pooling so that complex cells pool energies of simple cells inside each set of neighboring simple cells, giving the complex cell outputs as

$$c_i = \sum_{j=1}^k \pi(i, j) s_j^2 \quad (1)$$

This is essentially a classic energy model of complex cells.

To construct a probabilistic model with the desired dependencies, the probability density function of the images is assumed to depend on complex cell outputs only. This leads to the correlation of energies inside neighborhoods.

The estimation of topographic ICA is performed by maximizing the sparsities of the complex cell outputs c_i . This can be compared with ICA estimation, which is performed by maximizing the sparsities of simple cell outputs s_i . In

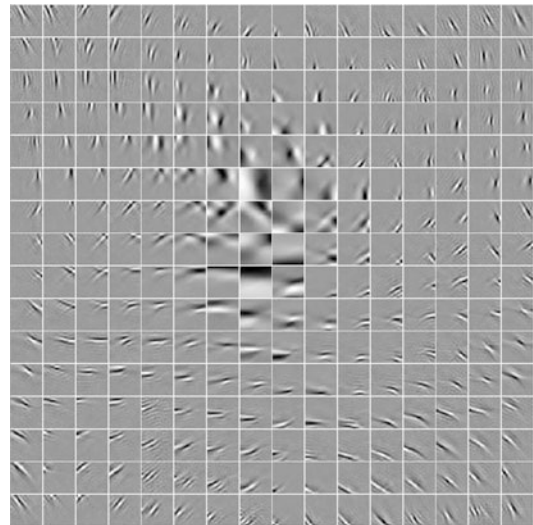


Topographic Independent Component Analysis, Fig. 2 Illustration of topographic arrangement of components. The components (*black circles*), each modeling a simple cell, are arranged on a two-dimensional grid. Components which are next to each other are statistically dependent, while components far away are (practically) independent. The grid defines a neighborhood for each component, and pooling into complex cells (*gray circles*, only one shown here) happens inside each neighborhood. (Adapted from Hyvärinen et al. 2009)

fact, the model reduces to basic ICA if the neighborhood function is defined to consist of single components, i.e., when $\pi(i, j) = 1$ if and only if $i = j$ and zero otherwise.

Results on Natural Images

Topographic ICA is applied on natural images in essentially the same way as ICA. Typical results are shown in Fig. 3. The features A_i are very similar to those obtained by ICA. While in ICA the ordering of the cells is completely arbitrary, here we see a clear topographic arrangement of the cells. What is particularly striking is that the preferred orientation of the simple cells changes smoothly as a function of the cortical location (i.e., when moving from one simple cell to the neighboring ones). The same applies for other parameters such as the location of the nonzero



Topographic Independent Component Analysis, Fig. 3 The whole set of vectors A_i obtained by topographic independent component analysis, from Hyvärinen et al. (2009). The size of the patches was 32×32 pixels, the number of patches was 50,000, and the PCA dimension was 256. Each *small square* here corresponds to one component s_i or one feature A_i ; only the A_i can be easily visualized, by representing them like image patches in the original image space. The spatial arrangement of the features in this plot is the topographic one originally defined by the model

part of the receptive field, as well as spatial frequency. These continuities are qualitatively very similar to what has been observed in the mammalian primary visual cortex. However, the model is quite abstract, so direct comparisons to neurophysiological quantities must be approached with caution, like in the case of ICA.

One parameter which does not change continuously with respect to topographic location is the spatial phase of the receptive field, which tells, for example, if the receptive field is odd symmetric (like an edge) or even symmetric (like a bar). Precisely because of this lack of continuity, the complex cells learn to pool over simple cells which are otherwise similar but have different phase preferences, and thus, the complex cells learn to be invariant to the phase of the input. Such phase invariance is the hallmark property of complex cells.

Cross-References

- [Independent Component Analysis of Images](#)
- [Spatiotemporal Energy Models](#)

References

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Topographic Map Formation

- [Retinotopic Development, Models of](#)

Topographic Maps

- [Cortical Maps, Activity-Dependent Development](#)

Topographica

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Synonyms

[FeatureMapper](#); [ImaGen](#); [Param](#); [ParamTk](#);
[Topographica neural map simulator](#)

Definition

Topographica is a simulator for large-scale neural models, with special support for neurons organized into topographic maps and for modelling activity-dependent development. A typical Topographica model will cover a complete pathway from the sensory periphery to regions in the cortex, modelling at least several square

millimeters of cortical tissue. To make working at this scale practical, Topographica groups neurons into Sheets, which each typically correspond to a large subpopulation of cells organized in two dimensions across the surface of a neural area. Using this abstraction, Topographica can implement a very large variety of possible models with relatively little coding and thus provides a platform for understanding properties that emerge only when large numbers of neurons are interconnected. The Topographica project also provides reusable, general-purpose components for other scientific computing, which can each be used independently from the main simulator.

Detailed Description

A large fraction of the central nervous system of mammals is organized into systematic topographic maps, with nearby neurons sharing some similar properties (reviewed in the Maps entry). Topographic maps can be implemented using many different simulators, such as NEURON or NEST, but other simulators provide little dedicated support for specifying, analyzing, and visualizing topographic maps. Implementing networks that map between different regions can be complex and error prone, because of the coordinate transformations required and the border conditions that occur for maps and connection patterns of different sizes. Providing good support for modelling maps is important, because the maps provide a level of abstraction that makes it feasible to work with very large numbers of neurons and connections on limited computer hardware and with limited amounts of experimental data available for validation. Topographica is designed to make these large-scale simulations practical, to allow progress in understanding systems-level behavior of neural circuits.

General-Purpose Building Blocks

Topographica has a modular, open design in Python, and many of the major components developed in the project are maintained as completely

independent, general-purpose subprojects that can easily be used with other simulators and other scientific software:

- **FeatureMapper:** Measures and plots feature maps (e.g., ocular dominance maps) tuning curves, and receptive fields, for any model of any sensory modality. Works well with Topographica but can be used with any simulator that can accept an input pattern and return a neural response (e.g., an average activity level).
- **ImaGen:** Generates never-ending streams of resolution-independent, hierarchically composable 0D, 1D, and 2D input patterns (e.g., two-dimensional visual images) for any simulator or other software program. Can be used to simulate the sensory experience of an animal, to generate visual stimuli for experiments, and to specify connection patterns or for any other purpose where parameterizable pattern families are needed.
- **Param/ParamTk:** Extends any Python program with user-controllable, range-checked, automatically documented parameters. Because it has no dependencies outside the Python standard library, the Param module can be used freely for any scientific program, to simplify it, to make it easier to use, and to make it more robust against user errors.
- **Lancet:** Runs large numbers of simulations or any other complex or time-consuming programs (in Python or any other language) and collects the output for analysis or display. Lancet is useful for testing sensitivity to parameters or evaluating model options and when combined with IPython Notebook is part of a comprehensive toolchain for doing reproducible research, starting from model specification and culminating in figures to be used in publications.

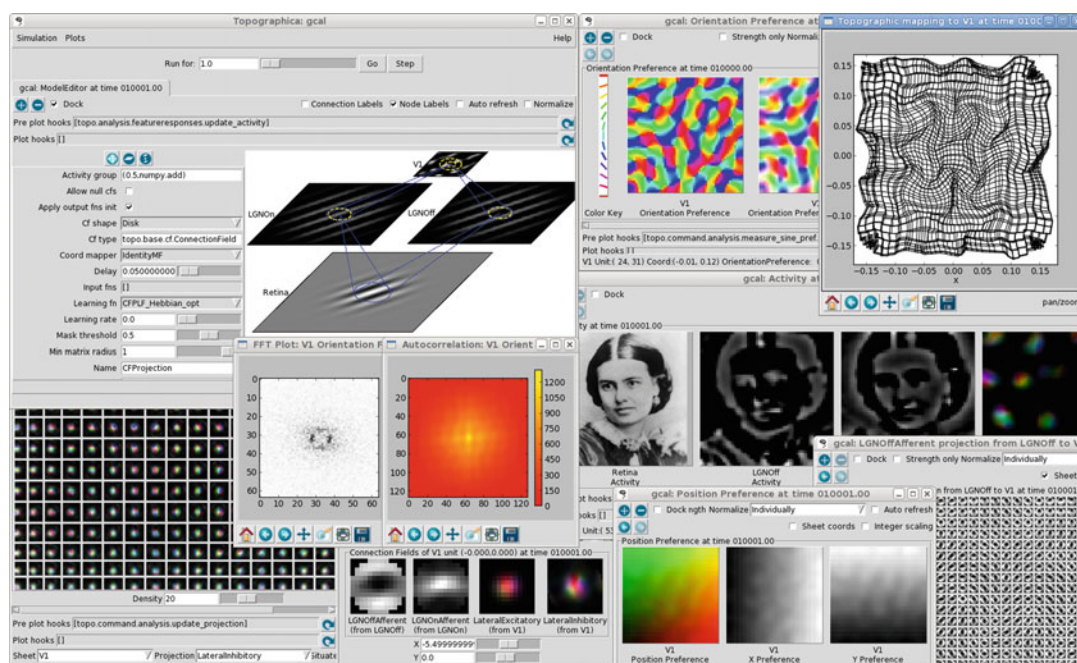
Simulations in Topographica

Starting with the separately distributed building blocks above, Topographica adds a general-purpose event-driven simulator (capable of

simulating any causal physical system), automatic plotting via the Matplotlib and PIL libraries, a general-purpose graphical user interface (GUI) allowing any simulated system to be visualized and analyzed without requiring GUI-specific code, and specific support for simulating neurons and topographic maps. Topographica includes libraries of commonly used neural modelling primitives (such as response functions, plasticity rules, and connection types). Each of these components is written in pure Python, which can easily be extended and modified by the user, but the most CPU intensive of these components are also available in high-performance C++-optimized multi-threaded (parallel-processing) versions.

Topographica's support for neural simulations is organized around the idea of a Sheet, a two-dimensional population of similar neurons differing by their location and by their individual connection patterns, but not by their overall properties (such as types of connections, extents of connections, synaptic modification rules, etc.). A Topographica model is typically a set of Sheets and Projections between them, where a Projection consists of a large number of neural connections. Figure 1 shows an illustrative but highly simplified Topographica visual-system model, visualized in the GUI interface.

To run a model, input patterns (from ImaGen) are presented to the input Sheets, such as the retina for this visual system model. Each Sheet will then respond after a specified delay, when the input is received through an incoming Projection. Any network of arbitrary complexity can be modelled in this way, with each Sheet having appropriate detail for the modelling task at hand, and any number of Sheets and Projections used to represent a neural region. Unlike other simulators, all parameters and measurements in Topographica are independent of the actual number of neurons simulated in a Sheet in any particular run, making it simple for the user to select dynamically between coarse but fast, or detailed but slow, approximations to the underlying neural system (Bednar et al. 2004). Even more detailed simulations can be performed by using a Topographica Sheet to wrap around calculations performed in an external simulator (Bednar 2009).



Topographica, Fig. 1 Sample Topographica model. This Topographica screenshot shows a simple visual system model made up of four Sheets (Retina, LGNOff, LGNON, and V1), illustrated in the Model Editor (main Topographica window, *top left*). These Sheets are connected by eight projections (in blue, two from Retina to the lateral geniculate nucleus (LGN), two from LGN to primary visual cortex (V1)), and four lateral projections (in yellow, between cells in the LGN and V1). More complicated models can have dozens or hundreds of such Sheets, representing different subpopulations in different laminae. The other windows show analyses from the FeatureMapper package (Orientation Preference and Topographic mapping windows, *top right*; and Position Preference, *bottom middle right*), along with other types of plots

(LGNOFFAfferent projection, *bottom right*; V1 LateralInhibitory projection, *left*; Connection Fields to a V1 Neuron, *bottom middle left*; Fourier transform of Orientation Preference map (*middle left*); Autocorrelation of Orientation Preference (*middle right*); and Activity for each Sheet, *middle right and top left*). The Activity plots also show two ImaGen input patterns (out of the more than 40 types currently available), and the main Topographica window (*top left*) shows how the ParamTk package is used to generate a GUI interface to edit simulation parameters without any neuroscience-specific code. The layout and look of these windows differs between different versions and different platforms, but this general functionality should be available in any version

Obtaining Topographica and Related Packages

Topographica and all of its subpackages are open source community projects with a BSD license, supporting any platform with Python (including Linux, Mac OS X, and Windows). The code is tested nightly on multiple platforms under a continuous integration framework. All versions of files are tracked via the Git distributed version control system, which makes it simple for users to make local modifications while staying up-to-date with changes to the main repository.

Installable packages and all source code are freely available at topographica.org and [ioam.github.io](https://github.com/iaam).

Cross-References

- [Adaptation in Sensory Cortices, Models of](#)
- [Center-Surround Processing, Network Models of](#)
- [Cortex: Overview](#)
- [Cortical Columns, Models of](#)
- [Cortical Maps, Activity-Dependent Development](#)
- [Cortical Maps, Intrinsic Processes](#)

- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [GENESIS, the General NEural Simulation System](#)
- [Hebbian Learning](#)
- [Hierarchical Models of the Visual System](#)
- [Lateral Geniculate Nucleus \(LGN\) Models](#)
- [Learning Rules: Overview](#)
- [MOOSE, the Multiscale Object-Oriented Simulation Environment](#)
- [NEST: the Neural Simulation Tool](#)
- [Neural Population Models and Cortical Field Theory: Overview](#)
- [neuroConstruct](#)
- [NEURON Simulation Environment](#)
- [Pattern Formation in Neural Population Models](#)
- [PyNN: a Python API for Neural Network Modelling](#)
- [Software Tools for Modeling in Computational Neuroscience: Overview](#)
- [Somatosensory Cortex: Organization](#)
- [Spike-Frequency Adaptation](#)
- [Stereo Vision, Models of](#)
- [Stimulus Reconstruction from Cortical Responses](#)
- [Visual Aftereffects, Models of](#)
- [Visual Illusions, Models of](#)

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Transcriptional Control Dysfunction, Modeling

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Definition

Neurons communicate within networks using electrical signals. These signals are processed by single neurons, translating the electrical code into biochemical signals that subsequently reach the cell nucleus, where transcriptional responses are regulated by highly diverse intracellular space- and time-dependent ionic fluxes. Calcium plays an important role in communicating electrical activity in networks – and on the plasma membrane of neurons – to the cell nucleus (Hardingham et al. 1997; Chawla et al. 1998; Dolmetsch et al. 1998; Milner et al. 1998; Bading 2000; West et al. 2002). Through diffusion and reaction with second messengers (Allbritton et al. 1992, Starovasnik et al. 1992; De Koninck and Schulman 1998; Mermelstein et al. 2001, Schmidt et al. 2003) and intricate calcium exchange mechanisms, e.g., mitochondrial (Kirichok et al. 2004; Popov et al. 2005; Chouhan et al. 2010; Dash et al. 2009; Pradhan et al. 2010) and endoplasmic calcium store exchange (De Young and Keizer 1992; Martone et al. 1993; Keizer and Levine 1996; Spacek and Harris 1997; Higgins et al. 2006; Ryglewski et al. 2007; Chakroborty et al. 2009; Gin et al. 2009), calcium signals can propagate from remote synaptic sites to the nucleus, triggering survival-relevant transcriptional responses (Hardingham et al. 1997; Chawla et al. 1998; Dolmetsch et al. 1998). This enables the cell to regulate its morphology and intracellular architecture based on the neuronal electrical activity within the neural network (Muller et al. 2002; Van Aelst and Cline 2004; Hayashi and Majewska 2005; Tada and Sheng 2006; Wittmann et al. 2009).

Topographica Neural Map Simulator

- [Topographica](#)

Detailed Description

Transcriptional responses in neurons are triggered by cellular signals. In order to understand the intricate interplay between many regulatory pathways of ionic signals, interdisciplinary approaches are becoming even more important. Combining experimental methods ranging from electrophysiology to modern imaging techniques, detailed spatial and time-resolved data can be compiled, defining a foundation for rigorous theoretical investigation of the underlying biophysical cellular processes. As an example, we will focus on cellular calcium signaling, as calcium is one of the most prominent ions involved in a wide variety of cellular tasks.

In order to understand the role of the detailed cellular architecture and cellular and organelle morphologies in relaying information to the cell nucleus, detailed three-dimensional models that include spatiotemporal experimental data as well as the three-dimensional architecture of neurons can be employed (Wittmann et al. 2009; Xylouris et al. 2010; Queisser et al. 2011; Queisser and Wittum 2011). Pathological states in which various parameters are affected, e.g., synapse loss in Alzheimer’s disease (Penzes et al. 2011), changes in receptor and channel densities (Stutzmann et al. 2006; Cheung et al. 2008; Goussakov et al. 2010), or morphological alterations can then systematically be simulated and evaluated. With respect to calcium signaling, models need to include the most relevant calcium-controlling cellular components (see Table 1 for a list of some important key regulators).

Modeling three-dimensional and time-dependent neuronal processes requires advanced mathematical and numerical methods. Typically biophysical processes in space and time can be formulated by systems of partial differential equations using continuum mechanics theory (Wittmann et al. 2009; Xylouris et al. 2010; Queisser et al. 2011). Since the model equations describing neuronal signaling on highly complex morphologies cannot be solved with analytical mathematical tools, numerical approaches are needed to solve the underlying partial differential

equations. Combining these methods with morphology reconstruction tools and automated network generators, based on raw microscopy imaging data and anatomical reconstructions of cells (Queisser et al. 2008; Wolf et al. 2013), allows to develop and solve highly detailed models. Thus, models can include the detailed geometry of cells and organelles, which is relevant for investigating cellular structure/function interplay. Systematic simulations of cellular signals, e.g., under varying parameter sets, allow to identify key components in healthy and pathological neuronal states.

Since transcriptional responses at the nucleus are regulated by the signal that invades the nucleus, it becomes necessary to model the signal that “enters” the nucleus through its nuclear pore complexes (Bading 2000; Wittmann et al. 2009; Queisser et al. 2011). Using models that include the components listed in Table 1, one can investigate the effect of spatial cellular reorganization, ranging from changes in the morphology of the cell, changes in synapse numbers, and distributions all the way to variable receptor densities and positions. First simulations show that the cell can finely regulate calcium signals that are involved in transcriptional responses by employing *neuronal plasticity*. Thus, spatial reorganization of the neuronal structure of dendrites, endoplasmic reticulum, or the position of mitochondria show to be critical in relaying signals to the nucleus.

Transcriptional Control Dysfunction, Modeling, Table 1 Relevant cellular components for synapse to nucleus communication

Cellular components	Relevant parameters
Plasma membrane	PMCA _s , NCX, VDCC
Synapses	NMDA, AMPA receptors, enzymatic production of IP ₃
Cytosol	Diffusion/reaction of calcium, IP ₃ , calbindin, calmodulin
Endoplasmic reticulum	IP ₃ receptors, ryanodine receptors, SERCA pumps
Mitochondria	Uni- and antiporters for calcium
Cell nucleus	Nuclear pore complexes, nuclear calcium diffusion

T

Identifying the key players in these transcriptions, relevant pathways have the potential of evaluating ways on how cells can compensate neuropathological degeneration.

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Transcutaneous Posterior Root Stimulation

- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Transcutaneous Spinal Cord Stimulation

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)
- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Transcutaneous Spinal Stimulation

- [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Transfer Function, Electroconvulsive

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Definition

An electroconvulsive transfer function derives from the linearization of an electroconvulsive model about one of its equilibrium points. Such transfer functions determine the characteristics of the frequency content of simulated electroconvulsive activities in response to input noise(s) to the model.

Detailed Description

For a nonlinear system that started in a stable equilibrium state, small amplitude noise will result in the system fluctuating about this equilibrium state. Characteristics of the fluctuations can be well approximated by linearizing the system about its equilibrium state. The spectra of the fluctuations of the linearized system can be expressed in closed-form mathematical formulas. Analytically expressing the spectra of system fluctuations lets us formulate the effects of a given parameter of the system on system fluctuations. In the following, theoretical and practical aspects of linearization of nonlinear electroconvulsive models

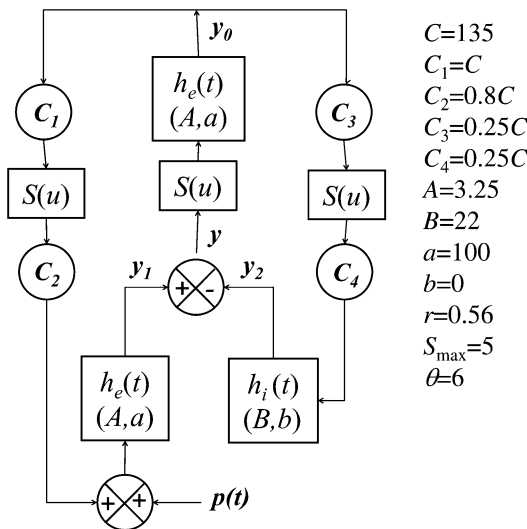
are presented using a simple model described in (Jansen and Rit 1995). This model provided the basis of enhanced models developed in the field of epilepsy (see entry ► “Epilepsy, Neural Population Models of”). Readers may find linearization aspects for a family of more complex electrocortical models in Molaee-Ardekani et al. (2007), Steyn-Ross (2002; Wilcocks 2001), and Bojak and Liley (2005) publications.

Transfer Function of a Template Model

The Template Model

The model we chose as a template is that proposed by Jansen and Rit (1995) for the study of visual evoked potentials. This is a simple neuronal population model (see Fig. 1) as it only includes three subpopulations of cells: pyramidal neurons, excitatory neurons, and inhibitory interneurons. The connections between these subpopulations establish the following linked equations:

$$\left(\frac{d^2}{dt^2} + 2a\frac{d}{dt} + a^2\right)y_0(t) = AaS(y_1(t) - y_2(t)) \quad (1)$$



Transfer Function, Electrocortical, Fig. 1 Schematic diagram of the Jansen and Rit model (1995)

$$\left(\frac{d^2}{dt^2} + 2a\frac{d}{dt} + a^2\right)y_1(t) = Aa(p(t) + C_2S(C_1y_1(t))) \quad (2)$$

$$\left(\frac{d^2}{dt^2} + 2b\frac{d}{dt} + b^2\right)y_2(t) = BbC_4S(C_3y_0(t)) \quad (3)$$

where C_X is the strength of connection between subpopulations. A , B are EPSP and IPSP (excitatory/inhibitory postsynaptic potential) average amplitudes, and a , b are EPSP and IPSP rate constants. $p(t)$ is the (sub)cortical input noise. Finally, S is the sigmoid wave-to-pulse function which is expressed as $S(u) = S_{\max}/(1 + e^{(\theta - u)})$. The output signal of the model $y(t)$ is expressed as $y(t) = y_1(t) - y_2(t)$.

Equilibrium State of the Model

To calculate the equilibrium solution of the model, all d/dt and the variance of the input noise p should be set to zero in Eqs. (1)–(3). This yields the following equations:

$$y_0 = AS(y_1 - y_2)/a \quad (4)$$

$$y_1 = A(p + C_2S(C_1y_0))/a \quad (5)$$

$$y_2 = BC_4S(C_3y_0)/b \quad (6)$$

Substituting Eq. (4) in Eqs. (5) and (6) and then expressing $y = y_1 - y_2$ yields the following nonlinear equation that should be solved numerically for y :

$$y = \frac{A}{a}p + \frac{A}{a}C_2S\left(\frac{A}{a}C_1S(y)\right) - \frac{B}{b}C_4S\left(\frac{A}{a}C_3S(y)\right) \quad (7)$$

The equilibrium state of the model can also be found by an iterative method. y_0 can be treated as an independent variable. Then, y_1 and y_2 are estimated as functions of y_0 and they can be used to estimate y_0 . The solution is reached when $|y_0 - \hat{y}_0|$ is minimized.

Another general way to calculate the equilibrium state of a system is to generate time series of

the system variables from initial starting points. The system should not be perturbed by input noise fluctuations so that system variables can settle down in their equilibrium states. There exists a MATLAB[®] toolbox so-called *matcont* for analyzing dynamical systems (Dhooge et al. 2003).

Hereafter, equilibrium values of the model variables are indicated by filled dots (e.g., y_1^*). Figure 2 illustrates the equilibrium solution of the variable y as a function of the mean input firing rate value p .

Linear Stability of the System

For linear stability analysis, we have to linearize the system differential equations and rewrite the system of equations so it contains only first-order derivatives and then calculate the eigenvalues of the corresponding Jacobian matrix evaluated at the equilibrium state. If a system is defined by N first-order differential equations as $\frac{dx}{dt} = f_m(x_1, \dots, x_N)$, then the Jacobian is the matrix $J_{mn} = \left. \frac{\partial f_m}{\partial x_n} \right|_{\text{equilibrium}}$. The stability of an

equilibrium state is determined by the signs of the real parts of the eigenvalues of the Jacobian matrix. A detailed description about the calculation of the Jacobian matrix for two different electrocardiac models can be found in (Molaei-Ardekani 2007; Wilcocks 2001).

If the Jacobian matrix has an eigenvalue with positive real part, then that equilibrium state is unstable. If all the eigenvalues of the Jacobian matrix have negative real part, then that equilibrium state is stable. In the template model $N = 6$ and $x = \{y_0, y_1, y_2, y_0, y_1, y_2\}$ where the dot symbol represents the derivative operator, stable and unstable equilibrium state solutions of the model for the variable y are represented by blue and red lines in Fig. 2, respectively. Two different types of singularities (i.e., Limit Point and Hopf bifurcations, beyond the scope of the present topic) are also presented in Fig. 2.

Transfer Function of the Linearized System

In the following, the system Eqs. (1)–(3) are linearized. For the sake of simplicity, we do not exactly compute the elements of the Jacobian matrix. Instead, we will directly linearize the second-order system equations. Each of the variables of the model is written as its equilibrium value (indicated by filled circle) plus a time-dependent perturbation from its equilibrium value (indicated by a hat mark); e.g., $\varphi(t) = \varphi^* + \hat{\varphi}(t)$.

For the Eq. (1), we will have

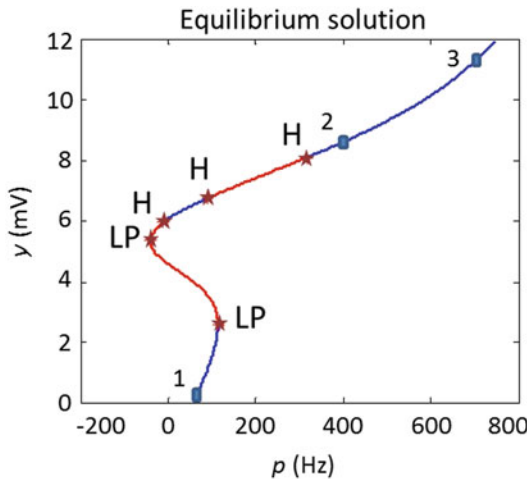
$$\begin{aligned} \left(\frac{d^2}{dt^2} + 2a \frac{d}{dt} + a^2 \right) (y_0^* + \hat{y}_0(t)) \\ = Aa(S^* + \hat{S}(t)) \end{aligned} \quad (8)$$

where

$$S^* = S(u)|_{u=y_1^*-y_2^*}$$

$$\hat{S}(t) = \hat{y}_1(t) \frac{dS(u)}{du} \Big|_{u=y_1^*-y_2^*} - \hat{y}_2(t) \frac{dS(u)}{du} \Big|_{u=y_1^*-y_2^*}$$

Since in the equilibrium state the first and second derivative of the constant value y_0^* is zero and $a^2 y_0^* = Aa S^*$, Eq. (8) can be written as



Transfer Function, Electrocardiac, Fig. 2 Equilibrium state solutions of the template model (Jansen and Rit 1995) for the output variable of the model as a function of input mean firing rate. Stable and unstable solutions are presented by blue and red lines, respectively. H and LP symbols indicate Andronov-Hopf and Limit Point bifurcations. Results were obtained using *matcont* MATLAB toolbox (Dhooge et al. 2003). Numbered indicated points are the points about which the model is linearized. They correspond to values of p equal to 60, 400, and 700

$$\begin{aligned} & \left(\frac{d^2}{dt^2} + 2a \frac{d}{dt} + a^2 \right) \hat{y}_0(t) \\ &= Aa(\alpha_1 \hat{y}_1(t) - \alpha_1 \hat{y}_2(t)) \end{aligned} \quad (9)$$

α_1 is a constant value and represents the derivative value of sigmoid function at the equilibrium point:

$$\begin{aligned} \alpha_1 &= \left. \frac{dS(u)}{du} \right|_{u=y_1^*-y_2^*} \\ &= \left. \frac{S_{\max} r \exp(r(\theta - u))}{(\exp(r(\theta - u)) + 1)^2} \right|_{u=y_1^*-y_2^*} \end{aligned} \quad (10)$$

Similarly, Eqs. (2) and (3) are linearized as follows:

$$\begin{aligned} & \left(\frac{d^2}{dt^2} + 2a \frac{d}{dt} + a^2 \right) \hat{y}_1(t) \\ &= Aa(\hat{p}(t) + C_2 C_1 \alpha_2 \hat{y}_0(t)) \end{aligned} \quad (11)$$

$$\begin{aligned} & \left(\frac{d^2}{dt^2} + 2b \frac{d}{dt} + b^2 \right) \hat{y}_2(t) \\ &= BbC_4 C_3 \alpha_3 \hat{y}_0(t) \end{aligned} \quad (12)$$

where $\alpha_2 = \left. \frac{dS(u)}{du} \right|_{u=C_1 y_0^*}$, $\alpha_3 = \left. \frac{dS(u)}{du} \right|_{u=C_3 y_0^*}$

Taking the Fourier transform from Eqs. (8), (11), and (12) yields

$$\begin{aligned} & (-\omega^2 + 2ai\omega + a^2) \tilde{y}_0(\omega) \\ &= Aa(\alpha_1 \tilde{y}_1(\omega) - \alpha_1 \tilde{y}_2(\omega)) \end{aligned} \quad (13)$$

$$\begin{aligned} & (-\omega^2 + 2ai\omega + a^2) \tilde{y}_1(\omega) \\ &= Aa(\tilde{p}(\omega) + C_2 C_1 \alpha_2 \tilde{y}_0(\omega)) \end{aligned} \quad (14)$$

$$\begin{aligned} & (-\omega^2 + 2bi\omega + b^2) \tilde{y}_2(\omega) \\ &= BbC_4 C_3 \alpha_3 \tilde{y}_0(\omega) \end{aligned} \quad (15)$$

where the tilde symbol is used to express the variable in Fourier domain. Substituting $y_0(\omega)$ from Eq. (13) into Eqs. (14) and (15) and then expressing $\tilde{y}(\omega) = \tilde{y}_1(\omega) - \tilde{y}_2(\omega)$ yields the following transfer function $T(\omega)$:

$$\begin{aligned} \tilde{y}(\omega) &= T(\omega) \tilde{p}(\omega) \Rightarrow T(\omega) \\ &= \frac{\tilde{y}_1(\omega) - \tilde{y}_2(\omega)}{\tilde{p}(\omega)} = \frac{AaL_b(\omega)L_a(\omega)}{D(\omega)} \end{aligned} \quad (16)$$

where

$$L_a(\omega) = (i\omega + a)^2, L_b(\omega) = (i\omega + b)^2,$$

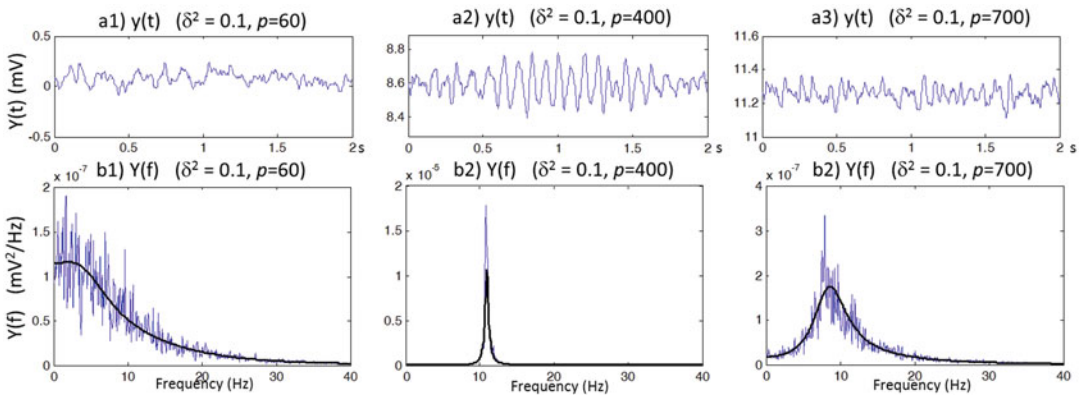
$$\begin{aligned} D(\omega) &= L_a(\omega)L_a(\omega)L_g(\omega) \\ &\quad - A^2 a^2 C_1 C_2 \alpha_1 \alpha_2 L_b(\omega) \\ &\quad + AaBbC_3 C_4 \alpha_1 \alpha_3 L_a(\omega) \end{aligned}$$

Roots of the denominator $D(\omega)$ may determine the stability mode of the model. Indeed, another method to evaluate the stability of a system is to obtain the linear transfer function between the input and output signal in the Fourier domain. Locations of the poles in this transfer function may determine if the system is stable or not. In addition, this transfer function characterizes system fluctuations in response to a given input signal.

Comparison of Numerical and Analytical Solutions

The model was numerically simulated to obtain a time series of 100 s. The power spectrum of the simulated time series was compared with the analytical power spectrum. The input-driving noise was a white Gaussian noise $p(t) = \mathcal{N}\left(p, \frac{\delta^2}{\Delta t}\right)$. The standard deviation of the input noise was set to be a function of Δt in order to conserve the energy of the noise signal when using different time step sizes (for model simulations, see (Wilcocks 2001) for more details). Simulations were performed using Euler method where $\Delta t = 0.1$ ms. Numerical power spectrum was obtained by taking Fourier transform (“fft” function in MATLAB) from 10-s signal epochs (i.e., 10×10 s). The power spectrum was multiplied by $\frac{\Delta t}{Nfft \times 1,000}$ to get a dimension of mV/Hz . The analytical power spectrum was obtained by $Y(f) = \delta^2 |T(2\pi f)|^2 / 1000$.

Figure 3 illustrates simulated time series (2 s) and power spectrum of the model (numerical and



Transfer Function, Electrocortical, Fig. 3 (a) Output time series of the Jansen and Rit model when the variance of the input noise is set to 0.1 and the mean value takes here

different values of 60, 400, and 700. (b) Numerical and analytical (*solid black line*) power spectrums corresponding the conditions given in (a)

analytical) for three different mean input firing rates $p = \{60, 400, 700\}$. Analytical and numerical solutions match well especially where the equilibrium state is far from the unstable region (Hopf bifurcation points). Note that the increase of the variance of the input noise can lead to small differences between analytical and numerical solutions (results not shown).

Cross-References

- [Anesthesia, Neural Population Models of](#)
- [Bifurcations, Neural Population Models and](#)
- [Jansen-Rit Model](#)
- [Neural Population Model](#)
- [Phase Transitions, Neural Population Models and](#)

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Transient Potassium Currents

- [Delayed Rectifier and A-Type Potassium Channels](#)

Transspinal Electrical Stimulation

- [Finite Element Models of Transcutaneous Spinal Cord Stimulation](#)

Transspinal stimulation

► [Paraspinal Magnetic and Transcutaneous Electrical Stimulation](#)

Treatment of Lower Urinary Tract Dysfunction

► [Methodologies for the Restoration of Bladder and Bowel Functions](#)

TREES Toolbox: Code for Neuronal Branching

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Definition

The TREES toolbox is a software package in MATLAB (MathWorks) that provides tools for reconstructing neuronal branching structures from microscopy image stacks and for generating synthetic axonal and dendritic trees. Furthermore, it enables the analysis, visualization, and editing of these trees for which it provides a large set of dedicated MATLAB functions. The TREES toolbox is freely available as open source at www.treestoolbox.org.

Detailed Description

Accurate predictions of neural computation and network connectivity are well known to require detailed morphological representations. In 2010, we launched a freely distributed open-source software package, the TREES toolbox (Cuntz et al.

2010, 2011), written in MATLAB (MathWorks, Natick, MA). This software package introduces a simple general description of neuronal morphology as a graph connecting targets (e.g., synapses) that are distributed in space. The underlying principle is based on the idea that a dendrite connects these targets in a manner to minimize costs for total cable length and conduction times in the tree (Fig. 1a; Cuntz et al. 2007, 2010). The targets thus become nodes in a graph with dendritic segments being the connecting edges (Fig. 1b). The TREES toolbox provides methods for redistributing nodes on the tree and labelling them to provide a unique representation of the tree (Fig. 1c; Cuntz et al. 2010). Diameter values associated with each node may be mapped to a given tree structure to promote “synaptic democracy” (Häusser 2001; Fig. 1d; Cuntz et al. 2007). The resulting synthetic dendrites are indistinguishable from their real counterparts for synthetically generated cortical pyramidal cells, Purkinje cells, fly interneurons, retina starburst amacrine cells (Cuntz et al. 2010), and periglomerular neurons of the olfactory bulb (Cuntz et al. 2012).

Reconstructing Dendrites and Axons

The process of extracting tree structures from 3D microscopy image stacks is often the first step in studying a neural circuit morphologically. This process remains laborious and no fail-safe automated tracing method exists. The reconstruction procedure typically consists of a sequence of image enhancement, automated or manual tracing, and post-editing. The TREES toolbox is equipped with a user interface that enables all these steps (Fig. 2) and can considerably enhance the speed and accuracy of reconstructions.

Generation of Synthetic Circuits

Generating synthetic branching structures, such as axonal and dendritic trees, also involves a sequence of steps: (1) analyzing branching statistics of real trees, (2) defining a geometric or statistical description of target distributions,

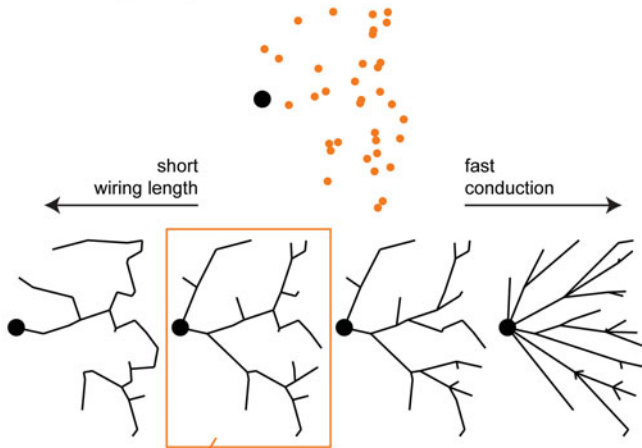
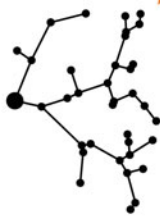
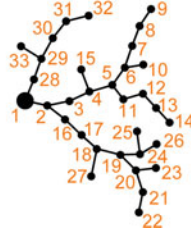
a Minimum spanning trees**b Synthetic tree****c Unique representation****d Refined synthetic tree****TREES Toolbox: Code for Neuronal Branching,**

Fig. 1 Representation of a dendritic tree in the TREES toolbox. **(a)** Targets (*orange dots*) are connected to a dendritic root (*black dot*) to form a tree by minimizing cable length and conduction times within the tree. Four trees are shown connecting the same targets using a different balance between the two costs. **(b)** The result is a graph connecting the targets with edges corresponding to dendritic segments. **(c)** A unique representation of the tree with

equal spacing between nodes (here: large spacing for illustrative purposes) and node labels that conserve the sub-tree structure. **(d)** Diameter values are mapped onto the tree to optimize synaptic democracy (i.e., to equalize the current transfer to the root) and spatial jitter is added to better reproduce biological trees that meander in order to grow through the dense nervous tissue

(3) detailing of the growth process, and then (4) post-editing such as pruning, diameter mapping, and more. The resulting synthetic dendrites are then subjected to a comparison with the real dendrites and the procedure is calibrated to obtain a good match (Fig. 3).

Brief Overview of the TREES Toolbox Functions

Since most of the applications can be divided into recurring modules used in a sequential manner, the TREES toolbox provides many small modular functions to handle neuronal trees. These

individual functions can then easily be recombined to form sophisticated yet comprehensible code. Functions relating to topological features (e.g., branch order or number of termination points) are, for example, separated from those relating to metric features (e.g., segment lengths or diameters). These simple features can then be combined using meta-functions (e.g., that sum up any feature along the path of a tree). A wide variety of traditional measures are available in such a way within one line of code. Editing functions exist at the level of single or groups of nodes but also at the level of entire trees or groups of trees within a network. Concatenating, morphing, resampling, or smoothing is implemented using dedicated MATLAB

The TREES toolbox user interface



TREES Toolbox: Code for Neuronal Branching, Fig. 2 The TREES toolbox user interface. A screenshot of the graphical user interface, which enables the tracing of trees while navigating 3D fluorescent image stacks of a neuron (Here from the medial superior olive, Courtesy of

Philipp Rautenberg et al. (2009)). In the user interface, a user can also easily explore the functions provided with the TREES toolbox. The control panels are indicated with orange shading

functions. Branching as well as electrotonic features can easily be mapped as colors onto cylinder-based neuronal tree models, as morphometric transforms, in density plots or different contours and tree surrounding hulls directly in MATLAB. The resulting OpenGL graphic handles can then be modified at the command line or in the user interface. Neural circuits can further be exported to Blender (<http://www.blender.org/>) or to the Persistence of Vision Raytracer, POV-Ray (<http://www.povray.org/>), for further graphical refinement (Fig. 4). Also, while many electrotonic features are available directly in the TREES toolbox, neural circuits prepared in that environment can be exported to NEURON (Hines and Carnevale 1997) directly for sophisticated compartmental modelling studies.

documentation and demonstration movies are provided on the same website and a developer's website is available at <https://code.google.com/p/treestoolbox>.

Cross-References and Compatibility

Neuronal morphologies in the TREES toolbox can easily be exported to tools for compartmental modelling such as ► “NEURON Simulation Environment” (Hines and Carnevale 1997), ► “GENESIS, the General Neural Simulation System” (Bower and Beeman 1998) and ► “neuroConstruct” (Gleeson et al. 2007). Export functions to ► “NeuroML” (Gleeson et al. 2010) are also available.

Availability and Links

The TREES toolbox is freely available as open source at www.treestoolbox.org. An extensive

Cross-References

► GENESIS, the General Neural Simulation System

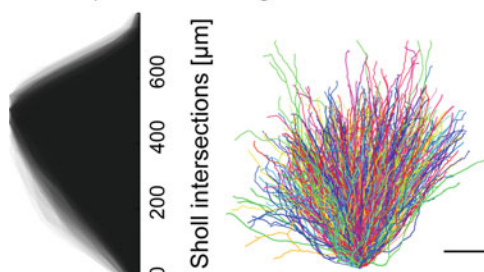
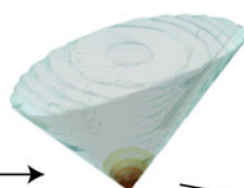
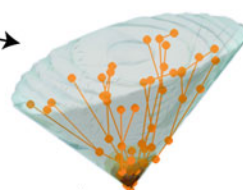
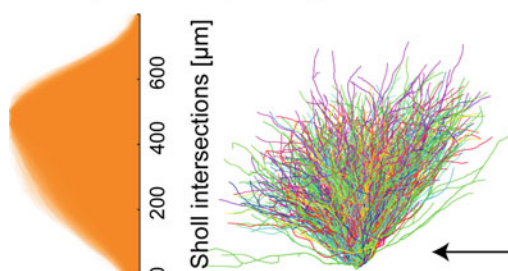
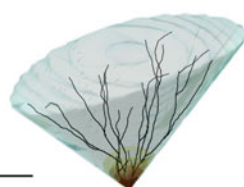
a Real dentate gyrus granule cell**b** Population of real granule cells**c** Dendrite density field**d** Synthetic tree**f** Population of synthetic granule cells**e** Refined synthetic tree**TREES Toolbox: Code for Neuronal Branching,**

Fig. 3 Generating synthetic hippocampal granule cells with the TREES toolbox. Typical steps in generating a synthetic dendritic tree. **(a)** A reconstruction of a real dentate gyrus granule cell. **(b)** A large set of real granule cells and a representative branching statistic, the Sholl intersections diagram: for each tree, one counts the number of intersections between the dendrite and a sphere centered around the dendritic root. The number of intersections is shown as a function of the radius of the sphere. **(c)** Dendrite

density field to distribute targets. In this case the density field is defined geometrically. **(d)** Distributed targets according to the density field (*orange dots*) are connected to a tree while optimizing a dendrite's wiring constraints as in Fig. 1a. **(e)** Refining the synthetic tree (*black*) as in Fig. 1c. **(f)** Comparison of synthetic trees with real trees using the same branching statistics (Original data are from granule cells by Rihn and Claiborne (1990); see details in Cuntz et al. (2010))

- [neuroConstruct](#)
- [NeuroML](#)
- [NEURON Simulation Environment](#)

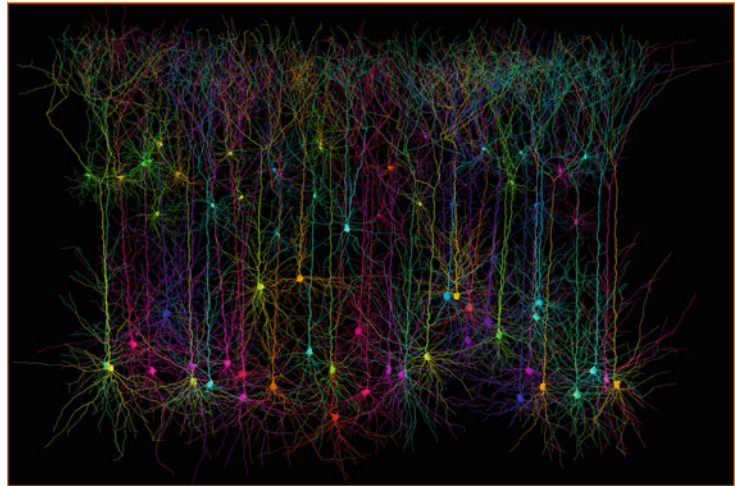
Acknowledgments I thank all users of the TREES toolbox and am grateful for all the feedback I received. I also wish to thank Friedrich Förstner,

Alexander Borst, and Michael Häusser for their active role in the development of the software package and for their comments on this manuscript. The development of the TREES toolbox was supported financially by the Max Planck Society, the Wellcome Trust, the Gatsby Charitable Foundation, the Alexander von Humboldt Foundation, and the European Research Council.

TREES Toolbox: Code for Neuronal Branching,

Fig. 4 Visualization of a neuronal circuit prepared in the TREES toolbox.

Wellcome Image Awards 2011: synthetic cortical pyramidal cells generated by the TREES toolbox and rendered by the POV-Ray (see <http://www.wellcomeimageawards.org/About/Previous-awards/2011/WTDV033740.htm>)



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Trial-and-Error Learning

► Reinforcement Learning in Cortical Networks

Tripartite Synapse (Neuron–Astrocyte Interactions), Conductance Models

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Definition

The old paradigm considering brain function solely relying on communication between the pre- and the postsynaptic neuronal compartments has been altered in recent years by the addition of glial cells and in particular astrocytes, as integral actors of this communication process. The close association of astrocytes with presynaptic terminals and postsynaptic spines generates a complex interconnected hub referred to as the *tripartite*

synapses in which astrocytes ensheath the synapses, thereby providing an additional level of complexity to classical synaptic communication (Volterra et al. 2002). Such interaction involves a complex and multifaceted bidirectional communication between astrocytes and pre- and postsynaptic components. A number of computational models have been developed throughout the years to help shed some light on the mechanisms that take place in tripartite synapses and regulate synaptic potency, synaptic plasticity, and consequently learning and memory.

Detailed Description

An action potential reaching the presynaptic terminal of a tripartite glutamatergic synapse triggers a long series of biochemical events. Globally, voltage-dependent calcium channels open, leading to an increase in calcium concentration in the presynaptic terminal; this in turn leads to neurotransmitter release in the synaptic cleft, which is sensed by astrocytes via activation of metabotropic glutamate receptors and glutamate transporters expressed on their surface. This results in an astrocytic increase in calcium concentration, which then triggers the release of gliotransmitters, which have been shown to modulate pre- and postsynaptic functions. All these major steps will be described in greater detail in the following sections, with a focus on astrocytic bidirectional communication in glutamatergic tripartite synapses (Fig. 1).

Neuron to Astrocyte Communication

It is now well established that astrocytes express a number of receptors for neurotransmitters and can therefore sense synaptic activity. Among metabotropic glutamate receptors, mGluR3 and mGluR5 are the most abundant. Activation of mGluR3 inhibits the synthesis of cyclic AMP (cAMP), while mGluR5 activation stimulates PLC, increases IP3 production, and leads to Ca^{2+} release from the endoplasmic reticulum (ER). This astrocytic cascade of events has been

described in a detailed yet compact manner in the G-ChI model (De Pittà et al. 2009), originally derived from the Li–Rinzel model (Li and Rinzel 1994), and faithfully replicates calcium oscillations with endogenous IP3 metabolism.

It is important to note that astrocytic increase in calcium concentration may not only be activated by the very same synapse that is regulated by the astrocyte but also by a different stimulus, thereby providing a heterosynaptic modulation (through distant synapses or astrocytic gap junctions). This heterosynaptic type of communication is generally the one that is modeled, as it permits a more direct measurement of astrocytic activation and gliotransmitter release without interference or need from a direct presynaptic stimulation. Astrocytic sensing mechanisms also involve glutamate transporters, especially EAAT1 and EAAT2 (also called GLAST and GLT-1, respectively), which notably impact the amount of neurotransmitter molecules sensed by synaptic receptors (and to a larger extent extrasynaptic receptors).

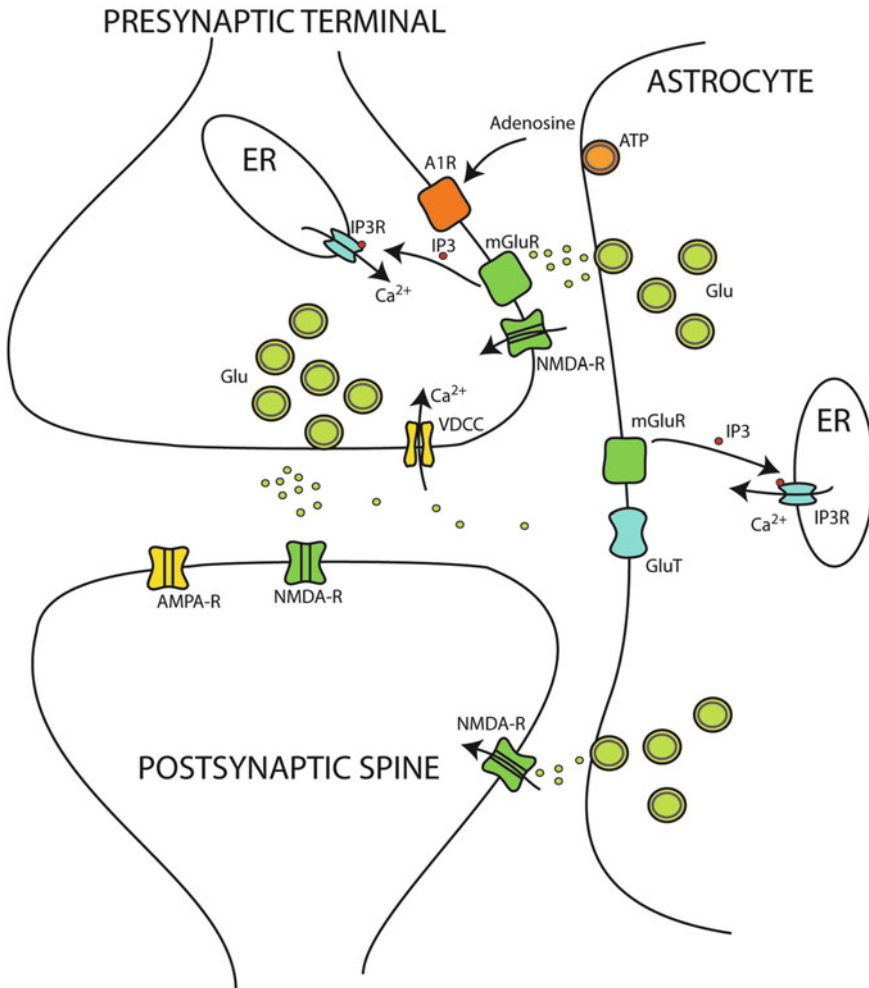
Astrocyte to Neuron Communication

Limitation of Synaptic Glutamate Availability

Astrocytic glutamate transporters have been shown to influence synaptic functions by reducing glutamate concentration sensed by postsynaptic receptors following neurotransmitter release and spillover (Volterra and Meldolesi 2005). An illustration of the impact of this mechanism was studied in the computational model proposed by Allam (Allam et al. 2012), which provided evidence indicating that GLT-1 is critical at preventing glutamate buildup during neurotransmission, thereby preventing excitotoxicity.

Gliotransmission

Astrocytic modulation of neuronal function is also mediated by astrocytic release of neurotransmitters or *gliotransmitters*. The major gliotransmitters released from astrocytes are glutamate, ATP, and D-serine; the main targets for glutamate are kainate receptors, metabotropic receptors, and NMDA receptors; P2X, P2Y, and A1 receptors for ATP; and NMDA-R for D-serine. For more details on the underlying



Tripartite Synapse (Neuron–Astrocyte Interactions), Conductance Models, Fig. 1 Illustration of the different interactions that take place at a tripartite glutamatergic synapse

mechanisms, the reader is advised to refer to Parpura and P. G. Haydon (2009).

Release of Glial Neurotransmitter

Even though the exact mechanisms by which astrocytes release gliotransmitters are not fully determined, the release of glutamate is believed to follow the same principles as those occurring in presynaptic terminals (i.e., through a calcium-dependent vesicular process), and different computational models have been proposed to describe the release mechanism (Tsodyks and Markram 1997; Bertram et al. 1996).

Activation of NMDA-R

Glutamate released from astrocytes activates presynaptic metabotropic glutamate receptors and NMDA receptors and, in particular, presynaptic NR2B-containing NMDA receptors at the perforant path–granule cell synapses, which increase presynaptic vesicular release (Jourdain et al. 2007). Such evidence is supported by ultrastructural studies showing close proximity between astrocytes and presynaptic NMDA receptors (the extracellular space being comparable in size to the synaptic cleft). Similarly, astrocytic glutamate release has been shown to

activate extrasynaptic NR2B-containing NMDA receptors on the dendrites of CA1 pyramidal cells, triggering slow inward currents. Additionally, the effect of astrocytic glutamate release on NMDA receptors current may be potentiated by co-release of D-serine, an NMDA receptor co-agonist.

Gliotransmitter-Induced Presynaptic mGluR Activation

The mechanisms underlying presynaptic release modulation via activation of presynaptic metabotropic receptors are still controversial. Despite this, astrocytic release of glutamate has been shown to activate presynaptic metabotropic receptors group I (type 1 and 5) (Perea and Araque 2007). Activation of group I mGluRs induces the formation of IP3 which diffuses to the endoplasmic reticulum where it induces, via binding to a specific receptor, the opening of calcium channels. This in turn increases cytosolic calcium concentration, thereby increasing presynaptic residual calcium concentration. To account for these mechanisms, Tewari (Tewari and Majumdar 2012) proposed a modified Li–Rinzel model that simulates the production of IP3 in a glutamate-dependent process.

Activation of Adenosine A1 Receptors

Activation of astrocytes leads to the release of ATP, which, upon its degradation to adenosine, results in activation of presynaptic A1 receptors. A1-Rs activation in turn inhibits presynaptic release through modulation of intracellular calcium concentration via decrease in cyclic AMP concentration, activation of potassium channels, and inactivation of voltage-dependent calcium channels.

Astrocytic Modulation of Presynaptic Calcium-Dependent NT Release

Presynaptic calcium-dependent release mechanisms conceptually consist of two mechanisms: (i) a calcium concentration increase due to voltage-dependent calcium channels, which open following presynaptic depolarization, and (ii) slower calcium processes, which result from either slow entry from other calcium-permeable

pores or through release from intracellular stores. Presynaptic calcium modulation from astrocytic release has been modeled by modulating the basal release probability in the Tsodyks–Markram release model (Tsodyks and Markram 1997), as proposed by De Pittà (De Pittà et al. 2011) or Tewari (Tewari and Majumdar 2012). Another approach, used by Nadkarni (Nadkarni and Jung 2007), has used a linear relation between the increase of Ca^{2+} concentration in the presynaptic terminal and the increase of Ca^{2+} in the astrocyte, which in turn affects presynaptic vesicular dynamics and subsequently neurotransmitter release.

Conclusion

The involvement of astrocytes in synaptic communication and modulation within the tripartite synapse is a relatively new investigation field. Computational models in particular still rely on a relatively small amount of experimental evidence to describe the different complex processes underlying modulation mechanisms, and much more remain to be discovered. Yet as experimental procedures encounter limitations in uncovering the subtleties of the mechanisms involved, modeling and simulation are needed to help experimentalists to ask the critical questions and to shed some light onto these complex and convoluted interactions.

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T-Type Calcium Channel

► Low-Voltage-Activated Calcium Channels

Tufted Cells

► Large-Scale Models of the Olfactory Bulb

Turing-Hopf Bifurcation

► Pattern Formation in Neural Population Models

Two-Dimensional Optical Imaging Spectroscopy

► Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

Two-Level Model of Mammalian Locomotor CPG

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Abbreviations

AB	Anterior biceps
EDL	Extensor digitorum longus
GS	Combined LGS and MG
LG	Lateral gastrocnemius
LGS	LG combined with soleus
MG	Medial gastrocnemius
PerL	Peroneus longus
Plant	Plantaris
Psoas	Iliopsoas
Quad	Quadriceps
Sart	Sartorius
Sm	Semimembranosus
SmAB	Semimembranosus combined with anterior biceps
TA	Tibialis anterior

Definition

Locomotor central pattern generator (CPG) in vertebrates is a neural network located in the spinal cord and capable of generating rhythmic neural activities enabling animal's movements in the environment. The locomotor CPG produces the coordinated rhythmic activities of motoneurons driving contractions of the corresponding muscles resulting in the coordinated limb movements underlying locomotion. The two-level architecture of the mammalian locomotor CPG has been proposed from analysis of spontaneous deletions (errors in rhythmic motoneuron activity) and effects of afferent stimulations during fictive locomotor activity evoked in the decerebrate, immobilized cat preparation by continuous brainstem stimulation. The model suggests that the locomotor CPG contains a separate half-center rhythm generator (RG) and a pattern formation

network (PF) controlled by the RG and defining the coordinated rhythmic pattern of motoneuron activity. The two-level model of the locomotor CPG reproduced and suggested an explanation for a number of features of rhythmic locomotor activity observed in cat locomotion, such as the maintenance of the phase of motoneuron activations after spontaneous deletions and afferent stimulations, that would be difficult to explain in the framework of the classical single-level CPG architecture.

Detailed Description

Motivation for the Proposed Two-Level Organization of the Locomotor CPG

Walking in mammals is characterized by alternating rhythmic activity of flexor and extensor muscles controlling movement of each limb and coordinated movements of different limbs. The corresponding coordinated activity of motoneurons, so-called fictive locomotion, can be evoked in vivo in the decerebrate immobilized preparations or in vitro in the isolated spinal cord of neonatal rodents by brainstem electrical stimulation or administration of some pharmacological agents (Edgerton et al. 1976; Shik and Orlovsky 1976; Grillner and Zangger 1979; Kercut and Bagust 1995; Schmidt and Jordan 2000; Whelan et al. 2000; Burke et al. 2001; Noga et al. 2003). The ability of the spinal cord to generate such rhythmic locomotor-like activity without patterned supraspinal or afferent inputs is considered as a strong proof for the existence of neural circuits representing the spinal locomotor central pattern generator (CPG) (Graham Brown 1911; Grillner 1981; Rossignol 1996; Orlovsky et al. 1999). Graham Brown (1914) proposed the first schematic of the CPG, based on interacting flexor and extensor half-centers. This idea was later elaborated by Lundberg and colleagues (Jankowska et al. 1967a, b; Lundberg 1981). According to this schematic, the locomotor oscillations result from reciprocal inhibition between the flexor and extensor half-centers, mediated by the corresponding inhibitory interneurons. The mutual inhibitory interconnections between the

half-centers ensure that only one half-center can be active at a time. Its activity reduces gradually which results in activation of the antagonistic half-center and switching of the locomotor phase. It was suggested that the flexor and extensor half-centers project to and activate flexor and extensor motoneurons, respectively. Thus, the alternating basic pattern of motoneuron activity is defined by the alternating activity in the half-centers. In addition, under normal conditions, this pattern is modulated by a variety of sensory and descending signals (Lundberg 1981). With such a classical half-center CPG architecture, single CPG network controls both the locomotor rhythm and the pattern of motoneuron activity during locomotion.

Two types of experimental studies of fictive locomotion in the decerebrate, immobilized cat have motivated the concept of two-level architecture for the locomotor CPG. The first series of studies focused on investigation of the effects of afferent stimulations on the activity of motoneurons and step-cycle timing (Guertin et al. 1995; Perreault et al. 1995; McCrea 2001; Stecina et al. 2005). These studies revealed that in many cases, afferent stimulation can delay or cause a premature phase switching within the ongoing step cycle without changing the timing of the following step cycles, i.e., without changing the phase of post-stimulation rhythm.

The other important studies focused on the investigation of so-called deletions – spontaneous errors in the rhythmic activity of motoneurons occurring during fictive locomotion (Lafreniere-Roula and McCrea 2005). Deletions are characterized by brief periods of inactivity (missing bursts) occurring simultaneously in multiple synergist motoneuron populations. During deletions, the activity of antagonist motoneuron populations becomes tonic or maintains rhythmic pattern (Lafreniere-Roula and McCrea 2005). The widespread effect of deletions on the activity of multiple motoneuron pools throughout the limb represents strong evidence that they are produced by failures in the operation of some common spinal circuitry, such as the CPG, and are not a result of local perturbations affecting the excitability of particular motoneurons. An analysis of motoneuron activities after deletions revealed that

some deletions, called “resetting deletions,” were accompanied by a shift in the phase of the rhythm reemerging after deletion relative to the pre-deletion rhythm (Lafreniere-Roula and McCrea 2005). However, most of the deletions observed during fictive locomotion were “non-resetting”: they were characterized by maintenance of the phase of locomotor oscillations after deletions. In fact non-resetting deletions occur during fictive locomotion more frequently than the resetting (78% vs. 22%, see Lafreniere-Roula and McCrea 2005). These observations suggest that the internal structure of the CPG can “remember” the locomotor rhythm when motoneuron activity falls silent. Such rhythm and phase maintenance cannot be explained in the framework of the classical single-level CPG organization, in which a single network is responsible for both rhythm generation and motoneuron activation.

To explain the existence of non-resetting deletions and phase maintenance after afferent stimulations observed during fictive locomotion, Rybak et al. (2006a, b) proposed that the locomotor CPG has a two-level organization and contains a separate half-center rhythm generator (RG) responsible for generation of locomotor rhythm and a pattern formation network (PF) that is controlled by the RG and shapes and coordinates the firing patterns of motoneurons. The two-level CPG organization allows a separate control of the locomotor rhythm (at the RG level) and the pattern of motoneuron activity (at the PF level). Consequently, afferent or descending signals or spontaneously occurring perturbations may affect CPG operation at the RG level, altering the locomotor rhythm (producing a phase shift or rhythm resetting), or act at the PF level, altering the pattern of motoneuron activation without general resetting the rhythm, i.e., without changing the locomotor phase after applied or spontaneously occurring perturbation.

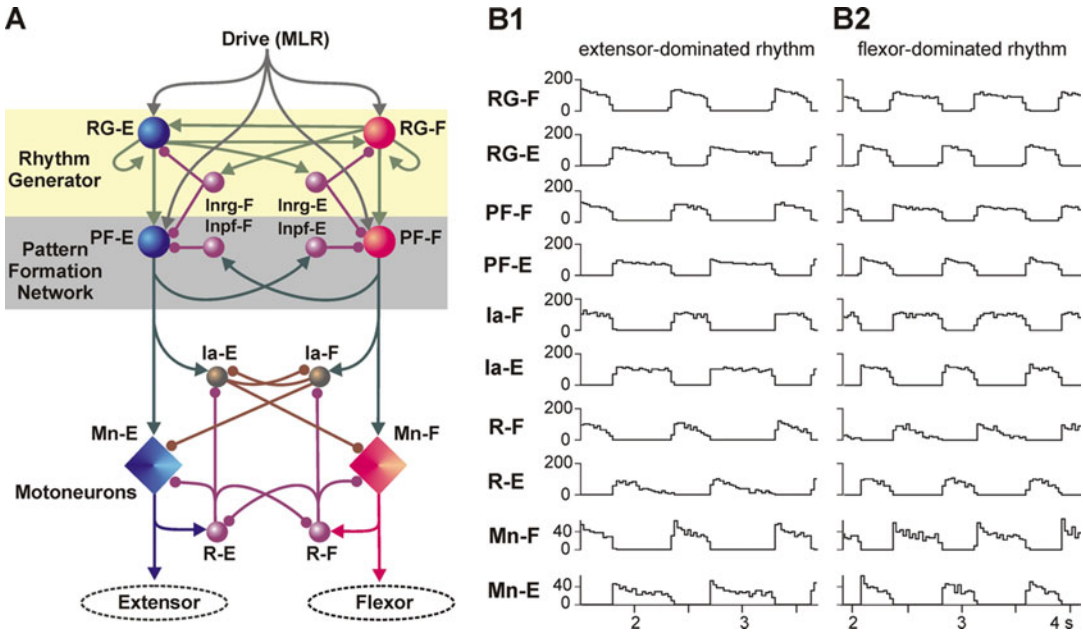
Model Description

Model Structure

Figure 1A shows the architecture of the two-level locomotor CPG model. The top level in the model

represents a half-center RG that controls an intermediate PF network, representing the second level of the CPG and coordinating the activities of flexor and extensor motoneuron populations. The RG consists of two populations of excitatory neurons, RG-E and RG-F, with mutual excitatory synaptic connections within and between these populations. The RG-E and RG-F populations receive external tonic excitatory drive (from the “MLR,” representing the brainstem mesencephalic locomotor region) and are mutually inhibited via the Inrg-E and Inrg-F interneuron populations. The neurons in the RG-E and RG-F populations contain the persistent (slow inactivating) sodium current, I_{NaP} , and possess I_{NaP} -dependent pacemaker properties, which, in combination with reciprocal inhibition between the RG-E and RG-F populations, provide their alternating rhythmic activity. The activities of RG-E and RG-F half-centers define the locomotor rhythm and durations of the extensor and flexor phases, respectively. Alternating firing of the RG-E and RG-F populations provides periodic, alternating excitation (in the homonymous phase) and inhibition (in the opposite phase, via Inrg-E and Inrg-F populations, see Fig. 1) of the excitatory PF-E and PF-F populations.

The PF network, containing the excitatory PF-E and PF-F and inhibitory Inpf-E and Inpf-F populations, represents the second level of the two-level CPG. Each of the PF-E and PF-F populations receives the excitatory tonic MLR drive, alternating excitation and inhibition from the corresponding inhibitory RG populations, and reciprocally inhibits the antagonist PF population via the inhibitory interneuron population (Inpf-E and Inpf-F). Alternating activity of the PF-E and PF-F populations projects to the homonymous motoneuron populations (Mn-E and Mn-F) and to the inhibitory Ia interneuron populations (Ia-E and Ia-F), representing a third level of reciprocal inhibition in the system and rhythmically inhibiting antagonistic motoneuron populations during the inactive phase of the step cycle. The model also includes populations of Renshaw cells (R-E and R-F) that receive collateral excitatory inputs from the homonymous motoneuron populations and provide feedback inhibition to



Two-Level Model of Mammalian Locomotor CPG, Fig. 1 Two-level model of the locomotor CPG. (A) Schematic of the model. Populations of spinal interneurons are represented by *spheres*. Populations of motoneurons are represented by *diamonds*. Excitatory and inhibitory synaptic connections between neural populations are shown by *arrows* and *small circles*, respectively. *RG* rhythm generator circuits are outlined by *yellow rectangle*. The *PF* pattern formation network is outlined by *grey rectangle*. Symbols *E* extension and *F* flexion in names of populations indicate the locomotor phase in which each population is active during fictive locomotion. See details

in the text. (B1, B2) Examples of locomotor patterns generated by the model. Activity of each population in this and following simulation figures is represented by a *histogram* of average firing frequency (number of spikes per second per neuron, bin = 30 ms). In B1, the RG-E population receives a larger MLR drive than the RG-F population, and the extensor phase is longer than the flexor phase (an extensor-dominated rhythm). In B2, the RG-F population receives a larger drive, and the model generates a flexor-dominated rhythm. (Adapted from Rybak et al. (2006a) with permission)

motoneurons. Depending on the input from the RG and the interactions within the PF network, each PF population is active during a particular phase of the step cycle and produces a phase-specific synchronized activation of the corresponding group of synergist motoneuron pools.

Modeling Single Motoneurons and Interneurons

The detailed mathematical description of the modeled motoneurons and interneurons can be found in the original paper by Rybak et al. (2006a). Briefly, all neurons were modeled in the Hodgkin-Huxley style. Motoneurons had two compartments, soma and dendrite, and were described based on the previous model by Booth

et al. (1997) with additional incorporation of the persistent sodium current (I_{NaP}) in the dendrite compartment. Specifically, the following ionic currents were included into the soma compartment (Booth et al. 1997; Rybak et al. 2006a): fast sodium, I_{Na} ; potassium rectifier, I_K ; calcium-N, I_{CaN} ; calcium-dependent potassium, I_{KCa} ; and leakage, I_L currents. The motoneuron dendrite compartment included the following currents: I_{NaP} , I_{CaN} , I_{CaL} (calcium-L current), I_K , and I_L . All interneurons were simulated using single-compartment models. The neurons of the RG-E, RG-F, PF-E, and PF-F populations contained I_{Na} , I_{NaP} , I_K , and I_L . For simplicity, all other interneurons contained only a minimal set of ionic currents: I_{Na} , I_K , and I_L (for details, see Rybak et al. 2006a).

Modeling Neural Populations

Each functional neuron type was represented by a population of 20 neurons. Connections between the populations were established so that if a population A was assigned to receive an excitatory or inhibitory input from a population B or external drive D, then each neuron of population A received the corresponding excitatory or inhibitory synaptic input from each neuron of population B or from drive D, respectively. The heterogeneity of connections was provided by a random distribution of connection weights between individual neurons. The heterogeneity of neurons within each population was set by a random distribution of leak reversal potentials and initial conditions for values of membrane potential, calcium concentrations (in motoneurons), and channel conductances between neurons (for details, see Rybak et al. 2006a).

Model Performance

Generation of Alternating Flexor-Extensor Activity in the Model

Figure 1B1, B2 shows examples of locomotor rhythm and flexor and extensor motoneuron activity generated by the model. In this figure, the activity of each population is represented by a histogram of average neuron activity (number of spikes in the population per second per neuron). The basic locomotor rhythm is generated by the RG network. The alternating rhythmic bursts of the RG populations (top two traces in Fig. 1B1, B2) define the durations of extensor and flexor phases and hence the locomotor (step-cycle) period. An increase in the MLR excitatory drive to one of the two RG populations reduces the opposite phase duration (see for explanation Rybak et al. 2006a). In Fig. 1B1, the MLR drive to the RG-E population is higher than that to the RG-F population resulting in a longer duration of extensor phase. In Fig. 1B2, a higher drive to the RG-F population results in a flexor phase-dominated rhythm. Only a reduced model was considered, in which the PF network consisted of only two (extensor and flexor) populations reciprocally inhibiting each other. As seen in the

figure, the activity of each PF population closely followed the activity of the corresponding RG population, and the activities of Ia inhibitory interneurons, motoneurons, and Renshaw cells followed the activity of the homonymous (extensor or flexor) PF populations (see the corresponding traces in Fig. 1B1, B2).

Comparison of the Experimental and Modeling Results

The results of simulations were compared with the previous experimental data of Lafreniere-Roula and McCrea (2005), whose investigation focused on deletions, and the data of Guertin et al. (1995) and Stecina et al. (2005) who studied the effects of afferent stimulations. All these data represented simultaneous recordings of electroneurogram activity (ENG) (and intracellular recordings) from motoneurons controlling the major hind limb muscles during MLR-evoked fictive locomotion in the decerebrate, immobilized cat.

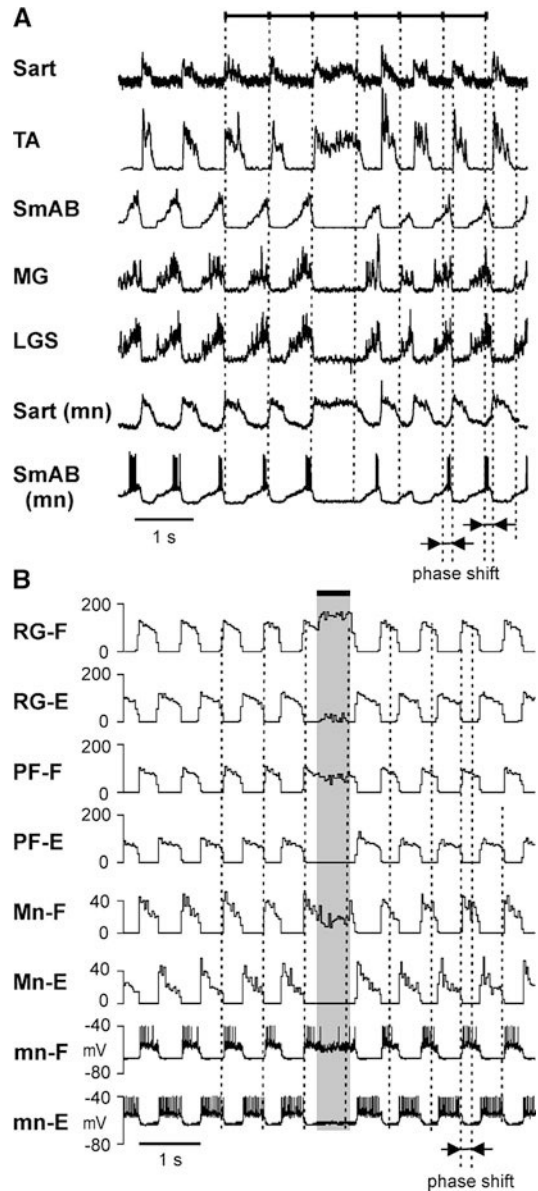
Modeling Deletions

Deletions represent brief failures in the alternating rhythmic activity of flexor or extensor motoneurons spontaneously occurring during fictive locomotion. During deletions the activity of multiple agonist motoneuron populations is missing for some time period, while the activity of their antagonists becomes tonic or continues to be rhythmic (Lafreniere-Roula and McCrea 2005). Deletions are classified to be “resetting”, if the phase of post-deletion rhythmic activity changes with respect to the pre-deletion rhythm, or “non-resetting”, if there is no phase shift in the reappearing post-deletion activity. The type of the deletion in the model depends on where in the network the perturbation occurs (is applied during simulation). The onset and offset of such perturbation can occur at arbitrary times (phase) with respect to the locomotor rhythm. Therefore, if these perturbations represent temporary changes at the RG level of the CPG (e.g., in the excitability of one of the RG population), the post-deletion rhythm should be generally phase shifted with respect to the pre-deletion rhythm. In contrast, temporal changes in the excitability of one of the PF populations do not affect the RG and hence should

cause only deletions occurring without phase shift of the post-deletion rhythm. Thus, it can be suggested that resetting deletions are caused by some spontaneous perturbations in excitability of neurons at the RG level of the spinal locomotor CPG, while perturbations at the PF level result in non-resetting deletions.

An example of an experimentally observed resetting deletion is shown in Fig. 2A (Lafreniere-Roula and McCrea 2005). In these records, rhythmic activity of extensors (hip, SmAB, and ankle, MG and LGS) was suppressed, and the activity of flexors (hip (Sart) and ankle (TA)) was prolonged. This behavior was closely reproduced in the model (see Fig. 2B) by applying a brief increase in the excitatory drive to the RG-F population. This increase in the excitatory drive prolonged activity of the RG-F half-center (top trace in Fig. 2B) and substantially inhibited the opposite (RG-E) half-center (second trace in Fig. 2B). The sustained activity of the RG-F population projected to the PF-F population (third trace in Fig. 2B). As a result, the activity of the PF-E (fourth trace) population was completely suppressed which resulted in a deletion of extensor motoneuron activity with a sustained activity of flexor motoneurons (see two bottom traces in Fig. 2B). The vertical dashed lines in the figure indicate the beginning of the expected flexor bursts if the deletion did not occur. In both the experimental and modeled examples, there is an obvious phase shift of the post-deletion rhythm. A similar deletion of extensor motoneuron activity can be produced by temporary reducing (or eliminating) the MLR drive to the extensor side of the RG.

Figure 3A1 shows an example of a non-resetting deletion of flexor activity obtained during fictive locomotion (Lafreniere-Roula and McCrea 2005). The failure of flexor motoneuron activation (hip, Sart, and ankle, EDL) is accompanied by the continuous activity of extensors (hip, SmAB, knee, Quad, and ankle, Plant). The vertical dashed lines indicate the beginning of the expected flexor bursts if the deletion did not occur. This behavior was simulated with the model by applying a temporary increase in the total excitatory drive to the PF-E population (Fig. 3B1). The



Two-Level Model of Mammalian Locomotor CPG,

Fig. 2 An example of resetting deletion and its simulation. (A) A short episode containing deletion of extensor activity that occurred during MLR-evoked fictive locomotion. Four *upper traces* show ENG recordings from hip (Sart) and ankle (TA) flexors and hip (SmAB) and ankle (MG, LGS) extensors. Two *bottom traces* are intracellular recordings from single Sart and SmAB motoneurons. In this and the following figures, the vertical *dotted lines* are plotted at the intervals representing the average period calculated for the five step-cycle periods preceding the deletions. These *lines* indicate where the onsets of anticipated flexor bursts that would have occurred if there had been no deletion. *Arrows* at the *bottom* indicate the phase

locomotor period (defined by neural activity at the RG level) was unaffected (see two top traces in Fig. 3B1) during and after deletion though there was a failure to excite flexor motoneurons (see second trace from below). This resulted from activities of the PF-E and PF-F populations (see third and fourth traces). As mentioned above, the PF-E population in this simulation received an additional excitation that overcame its inhibition by the Inrg-F and Inpf-F populations (see Fig. 1A) during the flexor phase, which resulted in a sustained activity of the PF-E population. Note that a continuing rhythmic inhibition of the PF-E population by the Inrg-F population resulted in a rhythmic modulation of the sustained activity of extensor motoneurons and a temporal interruption of the PF-E activity and emergence of a brief burst of flexor activity in the PF-F and Mn-F populations. A rhythmic modulation of the sustained activity of extensor motoneurons (Mn-E) during flexor deletion in Fig. 3B1 and the emergence of a flexor burst at the fourth (from the left) vertical dashed line are strikingly

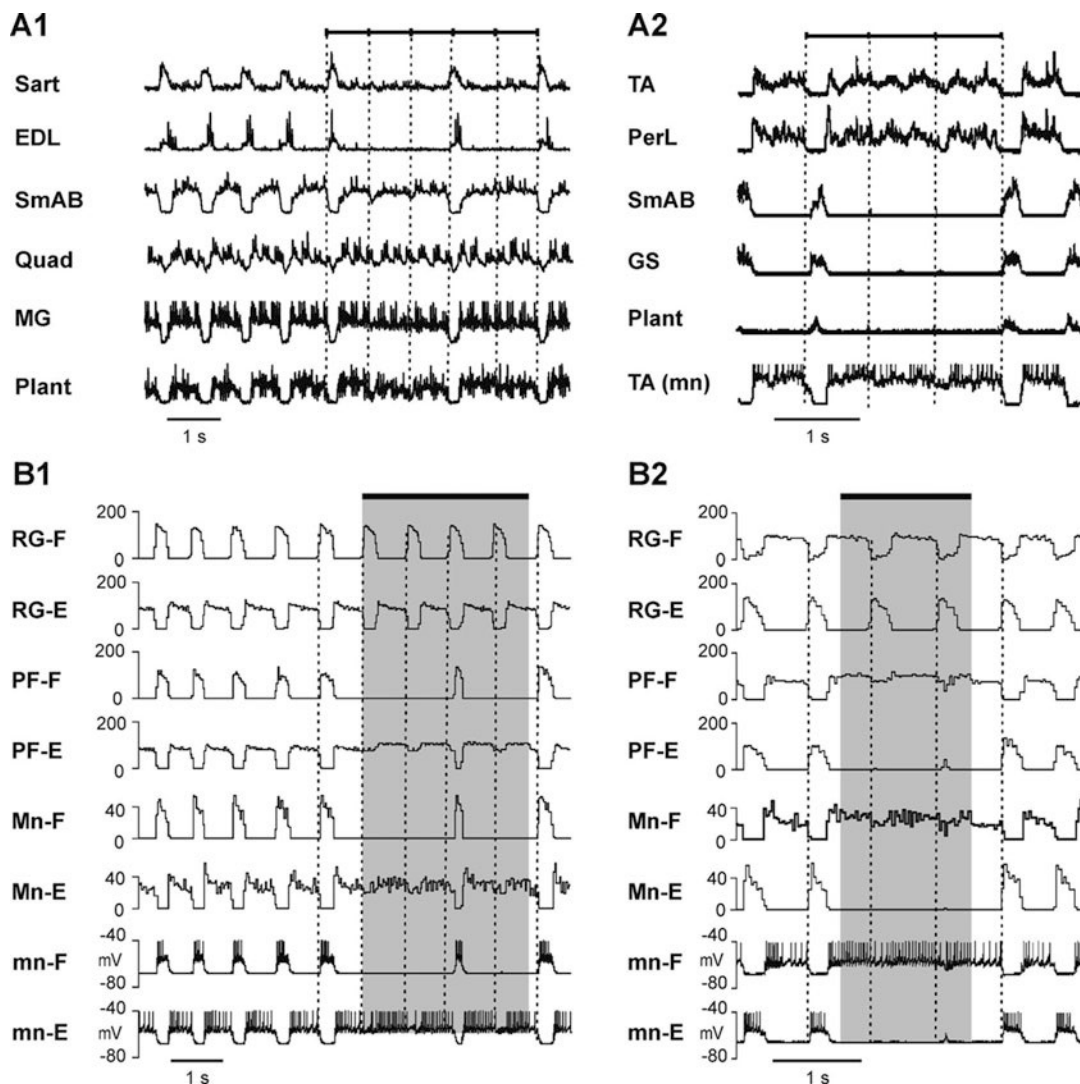
similar to that observed in the extensor ENGs during fictive locomotion (Fig. 3A1).

Figure 3A2 shows an example of a non-resetting deletion of extensor activity during fictive locomotion (Rybak et al. 2006a). In this example, an unknown spontaneous perturbation caused the deletion of activity of extensor motoneurons operating at hip (SmAB) and ankle (GS and Plant) accompanied by a sustained activity of flexor motoneurons (ankle, TA and PerL). The failure of flexor motoneurons to hyperpolarize during this period is illustrated in the intracellular record from a TA motoneuron (Fig. 3A2, bottom trace). The reappearance of extensor ENG activity occurred at the time expected if the deletion did not occur. Note the hyperpolarization of the TA motoneuron when extensor motoneuron activity reappears following the deletion. This behavior was simulated with the model by applying a temporary increase in total excitatory drive to the PF-F population (see Fig. 3B2) and showed a striking similarity to the deletion occurring during fictive locomotion including the weak modulation of flexor activity at the moments of expected extensor activity.

Sometimes, during non-resetting deletions of agonist motoneurons, antagonist motoneurons continue to be rhythmic (Lafreniere-Roula and McCrea 2005). Such example is shown in Fig. 4A where the failure of excitation of extensor motoneurons (hip, SmAB, and ankle, MG and LGS) is accompanied by continuous rhythmic activity of flexor motoneurons (hip, Sart, and ankle, TA and PerL). After deletion, the extensor activity reappears without phase shift, i.e., similar to that during other non-resetting deletions. This behavior could be simulated with the model by a temporary suppression of excitatory drive to the PF-E population (see Fig. 4B). Note that this suppression was decreased with time. Under these conditions, the model reproduced the deletion of activity of extensor motoneurons accompanying by continued bursting activity of the flexor motoneuron population and appearance of extensor bursts of a reduced amplitude after the deletion, which strikingly resembles the experimental data shown in Fig. 4A. Similar to the experimental recordings in Fig. 4A, the locomotor

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Two-Level Model of Mammalian Locomotor CPG, Fig. 2 (continued) shift of the post-deletion rhythm in respect to the pre-deletion activity. **(B)** Simulation reproducing the deletion shown in A. In this simulation, the MLR drives were adjusted to approximately fit phase durations in experimental recordings shown in A. The deletion of extensor activity was produced by an additional excitatory drive to the RG-F population (illustrated by the horizontal black bar at the top of traces). The deletion episode is highlighted by grey rectangle. Two upper traces show the activities of the RG-F and RG-E populations. The increased total drive to the RG-F population caused a prolongation of the RG-F activity and a delay in the transition to the extensor phase. This produced a corresponding prolongation of the activity of the PF-F (third trace) and Mn-F (fifth trace) populations and a delay in the onset of activity of the PF-E (fourth trace) and Mn-E (third trace from below) populations during the simulated deletion episode. Two bottom traces show changes in the membrane potential of single flexor and extensor motoneurons (*mn-F* and *mn-E*, respectively; action potentials are truncated at -40 mV). As in the case of experimental recordings shown in A, the “perturbation” applied to the RG-F population produced a resetting extensor deletion accompanied by a shift in the phase of the post-deletion rhythm (see arrows at the bottom). (Modified from Rybak et al. (2006a) with permission)



Two-Level Model of Mammalian Locomotor CPG, Fig. 3

Examples of non-resetting deletions with sustained activity of antagonists. (**A1**, **A2**) Two episodes of non-resetting deletions occurred during MLR-evoked fictive locomotion. The *traces* are rectified-integrated recordings from hind limb flexors and extensors. The *vertical dotted lines* indicate where the onsets of flexor (**A1**) or extensor (**A2**) bursts would have occurred if there had been no deletion. It can be seen that the phase of the locomotor rhythm is maintained after deletion in both episodes. In **A1**, the ENG recordings from hip (*Sart*) and ankle (*EDL*) flexors and hip (*SmAB*), knee (*Quad*), and ankle (*MG*, *Plant*) extensors are shown. During two successive flexor deletions, all extensors demonstrate a sustained activity, while all flexors are silent. In **A2**, the ENG recordings are shown from ankle flexors (*TA*, *PerL*) and hip (*SmAB*) and ankle (*GS*, *Plant*) extensors. The *bottom trace* shows an intracellular recording from *TA* motoneuron. The activity

of all extensors is suppressed during the extensor deletion with a sustained activity of flexors. It can be seen that the phase of the locomotor rhythm is maintained after deletions shown in **A1** and **A2**. (**B1**, **B2**) The results of simulations reproducing experimental recordings shown in **A1** and **A2**. In these simulations, the MLR drives were adjusted to fit phase durations in the corresponding experimental data. Two *upper traces* show activities of the RG populations, the *third and fourth traces* demonstrate the activities of the PF-F and PF-E populations. Two *bottom traces* show changes in the membrane potential of single flexor and extensor motoneurons (*mn-F* and *mn-E*, respectively, action potentials truncated at -40 mV). The deletion episodes are highlighted by *grey rectangles*. In the simulation shown in **B1**, a deletion of flexor activity was produced by an additional excitatory drive to the PF-E population (see *horizontal black bar* at the top of traces). Similar to the experimental recordings in **A1**, the phase of the locomotor

period (defined by the RG activity) remained unaffected when flexor motoneuron activity fell out.

Modeling Afferent Stimulations

Although the spinal CPG can operate in the absence of sensory feedback (e.g., during fictive locomotion), afferent activity plays a critical role in adjusting the locomotor pattern to the motor task, environment, and biomechanical characteristics of the limbs and body (Pearson 2004; Rossignol et al. 2006). In this connection, Rybak et al. (2006b) considered the effects of activation of the extensor and flexor afferents using the two-level CPG model. An important point for the modeling effect of afferent stimulation is the demonstration that afferent stimulation can affect (delay or advance) the ongoing phase transition with or without affecting the phase of post-stimulation locomotor rhythm (timing the following cycles) (see details in Rybak et al. 2006b). Briefly, it was suggested that both extensor and flexor afferents access the locomotor spinal CPG at several levels (see Figs. 5 and 8).

Effects of Extensor Afferent Stimulation

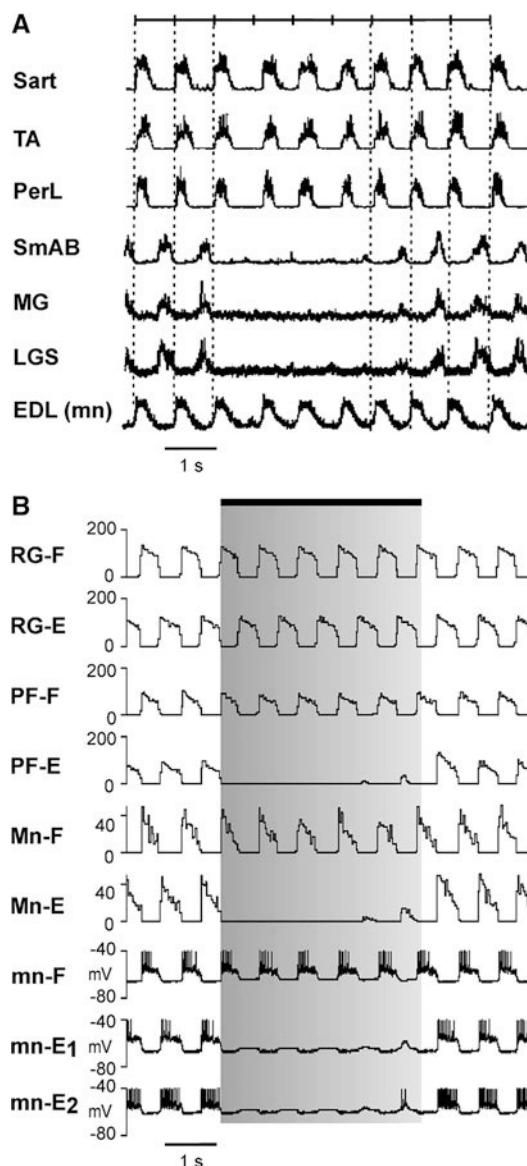
Figure 5 shows the schematic of the model used to simulate the effects of extensor afferent (both Ia muscle spindle and Ib tendon organ) stimulation using the two-level locomotor CPG. It was hypothesized that there are separate pathways for extensor afferents to the RG and the PF levels of the CPG via the hypothetical Irg-E and Ipf-E populations, respectively. The synaptic weights of inputs to the PF-E population in the model

(controlling extensor activity at the PF level) are stronger than that to the RG-E population (the extensor half-center of the RG). Accordingly, the model suggests that if sensory stimulation changes the excitability of the RG-E population, it may alter the cycle period. The model also includes monosynaptic excitation of homonymous motoneurons and disynaptic inhibition of antagonists by group Ia afferents. To reflect the presynaptic inhibition of extensor and flexor afferents during locomotor state (Gosgnach et al. 2000; McCrea 2001), the weight of Ia monosynaptic excitation of motoneuron populations in the model has been made low. The model also includes the locomotor-dependent disynaptic excitation of motoneurons (see Angel et al. 2005) that is mediated by the excitatory population Iab-E. During extension (i.e., when the PF-E and Inpf-E populations are active), the Inpf-E population inhibits an additional In-E population, thus removing the In-E inhibition of Iab-E interneurons. This disinhibition permits a phase-dependent disynaptic excitation of extensors by group I extensor afferents (Schomburg and Behrends 1978; McCrea et al. 1995; Angel et al. 1996, 2005). In addition, excitation of Iab-E interneurons from the PF-E population creates rhythmic extensor-phase activity in Iab-E interneurons in the absence of sensory stimulation that was found experimentally (Angel et al. 2005). Thus the Iab-E population also provides a portion of excitation to the extensor motoneurons during locomotion. Nonetheless, the Iab-E population is not considered to be an integral part of the locomotor CPG. This is because this interneuron



Two-Level Model of Mammalian Locomotor CPG, Fig. 3 (continued) rhythm is maintained after deletions. Note that during deletion, the simulated flexor motoneuron (*mn-F*) is hyperpolarized. The extensor motoneuron (*mn-E*) shows phasic modulation in its spiking without hyperpolarization similar to that observed in ENG of extensors (*SmAB*, *Quad*, and *Plant*) in **A1**. In **B2**, the performed simulation reproduces the extensor deletion shown in **A2**. In this simulation, a deletion of extensor activity was produced by an additional temporal excitatory drive to the PF-F population (see *horizontal black bar* at the *top of traces*) providing a prolonged activity of this

population (*third trace*). Similar to the experimental recordings in **A2**, the phase of the locomotor rhythm was maintained after deletion. As in the simulation shown in **B1**, rhythmic activity of the RG-E (*second trace*) and Inrg-E (not shown) populations persisted and provided phasic modulation of Mn-F activity (*fourth trace* from the *bottom*). Note that during deletion, the extensor motoneuron was hyperpolarized, whereas the flexor motoneurons showed phasic modulation without obvious hyperpolarization similar to that in an intracellular recording from TA motoneuron (two *bottom traces* in **A2**) (Modified from Rybak et al. (2006a) with permission)



Two-Level Model of Mammalian Locomotor CPG, Fig. 4 Example of non-resetting deletion with rhythmic activity of antagonist motoneurons. (A) Example of a deletion of extensor activity accompanied by continuing rhythmic activity of flexor motoneurons. The ENG recordings made from hind limb flexors (hip, *Sart*, and ankle, *TA*, *PerL*) and extensors (hip, *SmAB*, and ankle, *MG* and *LGS*) are shown. The bottom trace shows intracellular recording from a flexor (*EDL*) motoneuron that did not generate action potentials during fictive locomotion but shows rhythmic modulation of the membrane potential. Interestingly, the first extensor burst reappearing after deletion has lower amplitude. The vertical dotted lines indicate where the termination of extensor bursts would have occurred if there had been no deletion. They show that the phase of the

locomotor rhythm is maintained after deletion. (B) Simulation results similar to the experimental data shown in panel A. The MLR drives are adjusted to fit the locomotor phases in the experiment. In this simulation, a deletion of flexor activity (highlighted by grey rectangle) was produced by a temporal, gradually decreasing reduction of excitatory drive to the PF-E population (fourth trace), which is illustrated by gradual change in grey-level intensity of the rectangle. Three bottom traces show changes of membrane potentials of single flexor (*mn-F*) and two extensor motoneurons (*mn-E₁* and *mn-E₂*, respectively; action potentials truncated at -40 mV). Similar to the experimental data shown in A, the first burst after the deletion has lower amplitude. Note that during this burst, *mn-E₁* motoneuron is depolarized but did not generate

population does not participate in rhythm generation, and in some locomotor preparations, excitability of Iab-E interneurons is low and disynaptic excitation of motoneurons by group I extensor afferents cannot be evoked (e.g., in low spinal cats, McCrea et al. 1995). A detailed discussion of how group I disynaptic excitation emerges during locomotion and replaces the inhibitory effects evoked at rest is presented elsewhere (Rybak et al. 2006b).

A large body of experimental evidence shows that proprioceptive feedback from extensor afferents results in a strong excitation of extensor motoneurons that contributes to a substantial portion of stance-phase extensor activity in cats during treadmill locomotion (Donelan and Pearson 2004; Rossignol et al. 2006) and in man (Sinkjaer et al. 2000). In reduced preparations, activity in extensor afferents can also control the transition from extension to flexion, regulate the duration of the extensor phase, and entrain the step-cycle period (Guertin et al. 1995; Pearson 2004; Rossignol et al. 2006).

Figure 6A shows the effects of a brief stimulation applied to group I ankle extensor (LGS) afferents during the flexor phase in fictive locomotion preparation. In this example (Guertin et al. 1995), flexor motoneuron activity (ankle, TA) is truncated soon after stimulus onset (black rectangle), and a burst of extensor activity occurs (hip, AB, and knee, Quad). Figure 6B shows a result of modeling the effects of extensor afferent stimulation during flexion which reproduces experimental results shown in Fig. 6A. In this example, a brief stimulation of extensor afferents (see black rectangle at the top of traces) is delivered to the RG-E and PF-E populations (via the Irg-E and Ipf-E populations, respectively, see Fig. 5) during flexion, i.e., when the flexor motoneuron population (Mn-F) is active. During the flexor phase both the RG-E and PF-E populations are inhibited by activity in the flexor half-center (via the Inrg-F

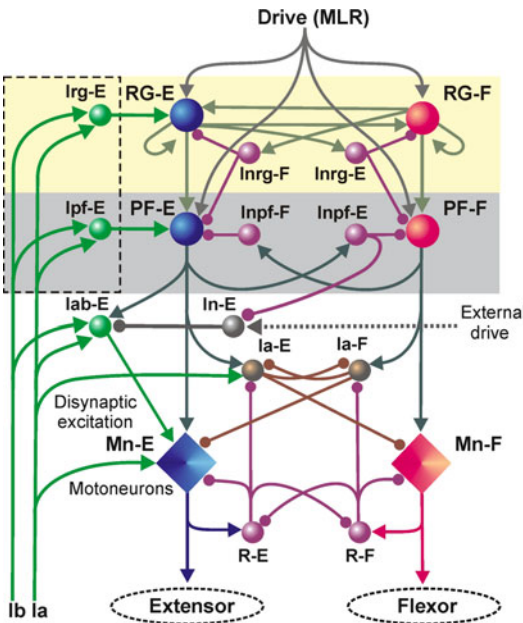
and Inpf-F populations, see Fig. 5). The relatively weak synaptic input from extensor afferents to the Irg-E population cannot overcome the flexion phase-related inhibition of the RG-E population (by the Inrg-F population) and excite it. Thus, the RG activity (first and second traces in Fig. 6B) is unaffected by the afferent stimulation. However, the stronger synaptic weights of the afferent input to the Ipf-E population can evoke a brief excitation of PF-E interneurons, which in turn, (via the Inpf-E population, see Fig. 5) inhibit the PF-F activity (third and fourth traces in Fig. 6B). As a result there is a resetting of the PF activity to extension (without affecting the RG activity) that evokes a brief burst of extensor motoneuron activity (Mn-E) and a corresponding inhibition (cessation of activity) of flexor motoneurons (Mn-F) (see two bottom traces in Fig. 6B). In both the experiment (Fig. 6A) and the model (Fig. 6B), the duration of the evoked extensor activity and the following flexor phase are shortened such that phase shift of the locomotor rhythm does not occur. This is illustrated in Fig. 6A, B by the dashed lines indicating intervals equal to the step-cycle period preceding stimulation and by the arrows at the bottom of the figure. According to the model, the fictive locomotor data in Fig. 6A can be explained by the suggestion that extensor afferent stimulation during flexion produces a temporary resetting to extension at the level of the PF network without affecting the RG level of the CPG and hence, without any change in the timing of the following step cycles.

During real locomotion, extensor group I afferent feedback occurs mainly during the extension phase when Ib afferents are active because of extensor muscle contractions (Prochazka and Gorassini 1998). Figure 7A1, A2 shows the experimental data in which Plant nerve stimulation enhanced and prolonged extensor motoneuron activity (hip, AB, knee, Quad, and ankle, MG). It can be seen that there is a



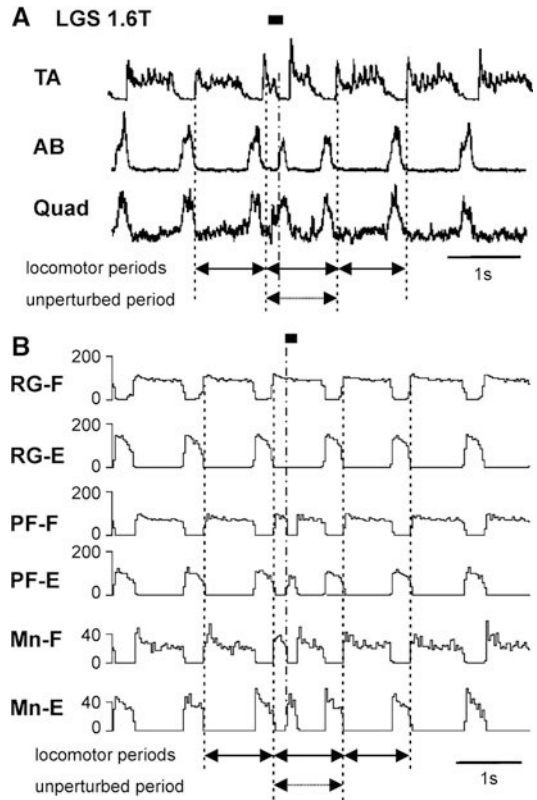
Two-Level Model of Mammalian Locomotor CPG, Fig. 4 (continued) action potentials, while mn-E₂ generates a reduced burst of activity. As in the experimental

recordings shown in A, the phase of the locomotor rhythm did not change after deletion. (Modified from Rybak et al. (2006a) with permission)



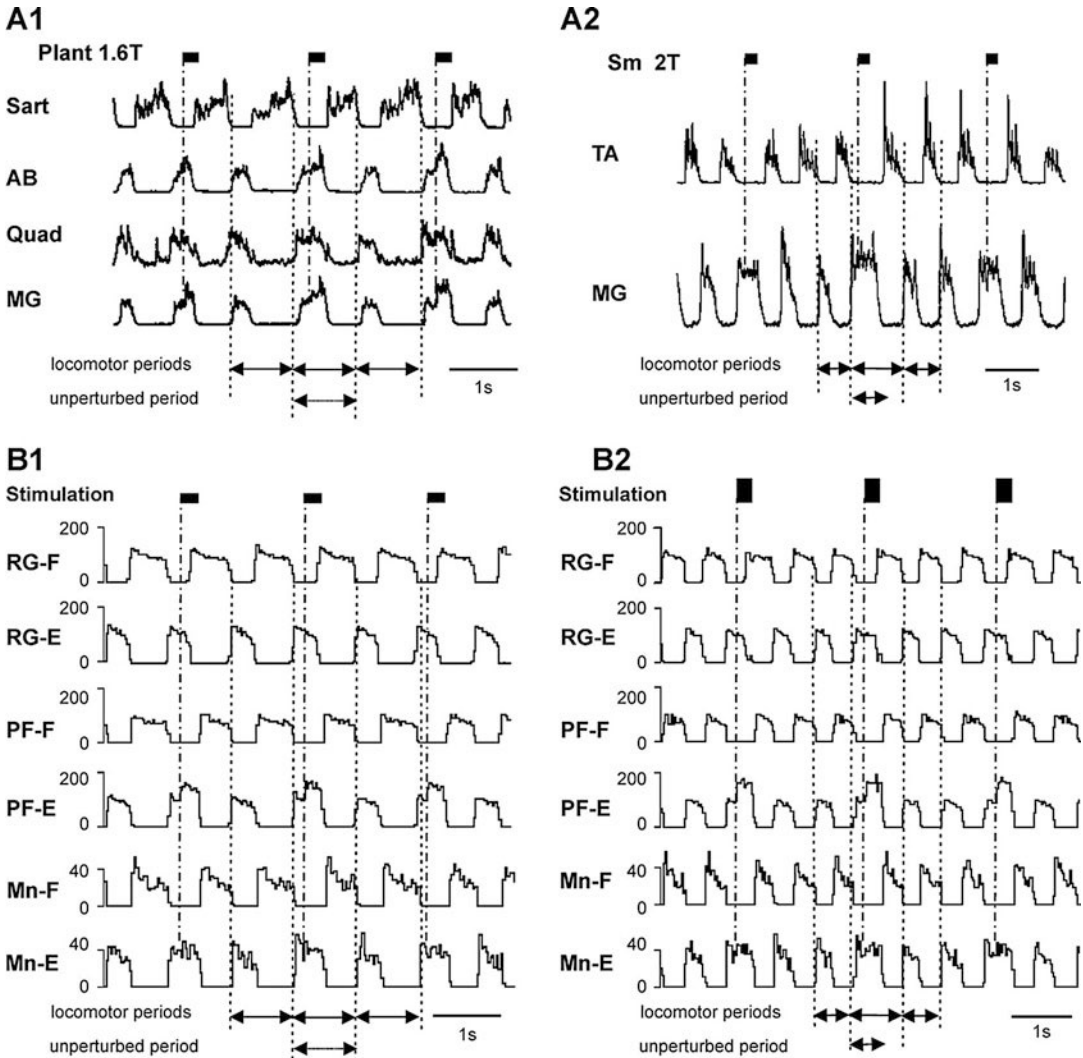
Two-Level Model of Mammalian Locomotor CPG, Fig. 5 Schematic of the spinal cord circuitry with the two-level model locomotor CPG used for simulating the effects of stimulation of extensor group I afferents. The two-level locomotor CPG model (see Fig. 1A) is extended by incorporating additional neural populations Irg-E and Ipf-E (green) that receive group I (Ia and Ib) afferents (shown by green lines) and provide excitatory inputs to the RG-E or PF-E populations, respectively. The Iab-E population mediates disynaptic excitation of extensor motoneurons during the extensor phase of locomotion. See text for details. (Modified from Rybak et al. (2006b) with permission)

shortening of the subsequent flexor phase such that the step-cycle period remained unchanged (see arrows at the bottom of Fig. 7A1). Figure 7B1 shows the results of simulation consistent with the experimental data shown in Fig. 7A1. The stimulation in Fig. 7B1 (shown by black rectangles at the top of the traces) had the same amplitude as in Fig. 6B and produced little effect on the activity of the RG populations and hence did not change the ongoing locomotor rhythm generated by the RG (see first and second traces in Fig. 7B1). The applied stimulation did, however, enhance and prolong the PF-E population activity, thus delaying the switching to the flexion phase at the PF-F level (see third and fourth traces in Fig. 7B1) and enhanced and



Two-Level Model of Mammalian Locomotor CPG, Fig. 6 Effects of extensor afferent stimulation during flexion. (A) Example of stimulation of extensor group I afferents in LGS (1.6 times threshold, T; 20 shocks, 100 Hz, black rectangle) during flexion terminated the ongoing flexor phase (see the activity of TA (ankle flexor)) and produced a premature onset of extension as seen in ENG of the hip (AB) and knee (Quad) extensors. (B) Results of simulation of the experimental data shown in panel A. Small black rectangle at the top of traces shows time and duration of sensory stimulation applied to group I (Ia and Ib) afferents. The MLR drives to the RG-E and RG-F populations are adjusted to fit phase durations in the experiment shown in A. Note that in panel B, similar to A, stimulation resulted in a short extensor burst and a shortened next flexion so that the timing of the following step cycles did not change: i.e., the locomotor rhythm was not reset. The arrows at the bottom show that the locomotor periods before, during, and after application of stimulation are the same. (Adapted from Rybak et al. (2006b) with permission)

prolonged extensor motoneuron firing (see the bottom trace in Fig. 7A1). Because the RG level in the locomotor CPG model was not affected, the subsequent flexion phase was shortened and the step-cycle duration remained unchanged.



Two-Level Model of Mammalian Locomotor CPG, Fig. 7 Effects of group I extensor afferent stimulation during extension. (**A1**, **A2**) Examples of stimulation of extensor group I afferents during MLR-evoked fictive locomotion. In **A1**, stimulation of Plant group I afferents during extension (1.6 T, 20 shocks, 100 Hz) increased the amplitude and duration of extensor motoneuron activity (hip, *AB*, knee, *Quad*, and ankle, *MG*) and shortened the duration of the following flexor phase as seen in *Sart* (hip/knee flexor). In **A2**, an example of electrical stimulation of hip extensor (*Sm*) muscle afferents during extension (2 T, 20 shocks, 100 Hz, from Rybak et al. (2006b), used with permission) is shown. Note that the intensity of stimulation was increased (2 T vs. 1.6 T in **A1**). Similar to the experimental results shown in panel **A1**, stimulation increased the amplitude and duration of ankle extensor motoneuron activity (*MG*). However, in contrast to **A1**,

each flexion phase following the prolonged extension phase was not shortened. Therefore, each stimulus shifted the locomotor rhythm in time, which resulted in an increase in the locomotor period (see arrows at the bottom). (**B1**, **B2**) Examples of modeling the effects of stimulation of the group I extensor afferents during extension shown in **A1** and **A2**, respectively. The drives to the RG-F and RG-E populations are adjusted to fit the corresponding experimental recordings. The applied stimuli are shown as black rectangles at the top of traces. The increased height of the rectangles in panel **B2** compared to **B1** symbolically illustrates the increased stimulation intensity. Note that in **B1**, the low-intensity stimulation did not cause any perturbation in the RG activity (see two upper traces), and, similar to **A1**, the locomotor periods did not change because duration of each flexion phase following the prolonged extension phase was shortened (see equal length arrows

A different experimental example is shown in Fig. 7A2. In this example, stimulation applied to extensor afferents (hip, Sm) evoked enhancement of extensor motoneuron activity similar to the experiment shown in Fig. 7A1; however, the ongoing step-cycle period increased. Each stimulus in Fig. 7A2 enhanced and prolonged extensor (ankle, MG) burst. The following flexor phase had an unchanged duration, and hence, the locomotor rhythm was shifted in time (see arrows at the bottom of the panel). These experimental results are reproduced in simulation shown in Fig. 7B2. In this simulation, the amplitude of stimulation was increased as compared to the simulation shown in Fig. 7B1 (illustrated by the increased height of black rectangles at the top of the traces), while maintaining the same relative weightings to the PF-E and RG-E populations. In contrast to Fig. 7B1, stronger stimulation prolonged the RG-E activity which in turn delayed the transition to flexion at the RG level (see first and second traces in Fig. 7B2). This stimulation also prolonged and enhanced the PF-E activity (see fourth trace in Fig. 7B2). The net effect was an increase and prolongation of extensor motoneuron firing, but there was, however, no compensatory change in the duration of the subsequent flexor phase (see two bottom trace in Fig. 7B2). Consequently, each stimulus prolonged the duration of the ongoing locomotor cycle and hence produced a phase shift of the poststimulation locomotor rhythm (see arrows at the bottom of Fig. 7B2).

Based on the results of these simulations, it can be concluded that stimulation of extensor afferents during extension may prolong the current extension phase with or without changing the duration of ongoing locomotor cycle and the phase of poststimulation rhythm. The exact effect in the two-level locomotor CPG model depends on how strongly the applied stimulation influences the RG level of the CPG.

Effects of Flexor Afferent Stimulation

The flexor side of the reflex circuitry operating during fictive locomotion has an organization with several similarities to that affecting the extensor side of the CPG. Flexor afferent stimulation can also evoke disynaptic excitation in flexor motoneurons that are modulated with cycle phase (Degtyarenko et al. 1998; Quevedo et al. 2000). However, compared to the disynaptic excitation of extensors by extensor afferents, the disynaptic excitation of flexors has a more complex phase dependency and a more limited distribution to hind limb flexor motoneurons (Quevedo et al. 2000). Therefore, a disynaptic excitation of flexors has not been included in the reduced model containing only two motoneuron pools.

There is experimental evidence that activation of group II afferents in flexor nerves during fictive locomotion can either terminate the ongoing flexor phase and switch the step cycle to extension (e.g., following TA nerve stimulation) or prolong ongoing flexor activity (e.g., EDL nerve stimulation) (Perreault et al. 1995; Stecina et al. 2005). Occasionally, these actions reverse spontaneously (Stecina et al. 2005). In the same preparations, flexor group I afferent activation can enhance and prolong flexor motoneuron activity in a manner analogous to the extensor-promoting actions of extensor group I afferents (Perreault et al. 1995; Stecina et al. 2005). These observations support the suggestion that the group I flexor afferents are excitatory to the flexor part of the CPG (i.e., to the RG-F and PF-F populations in the model). The hypothesis was suggested that while flexor group I afferents excite the flexor part of the CPG (both the RG-F and PF-F populations), flexor group II afferents are excitatory to the extensor part of the CPG (see Stecina et al. 2005). Accordingly, the effects of simultaneous activation of group II and group I flexor afferents work against each other. The resulting effect is, therefore, dependent upon

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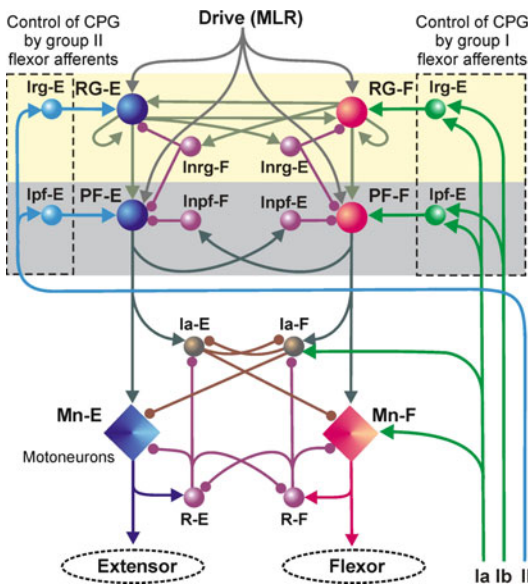


Two-Level Model of Mammalian Locomotor CPG, Fig. 7 (continued) at the *bottom*). In contrast, in the simulation shown in B2, similar to the experimental example shown in A2, the flexor phases following the stimulus-

evoked prolonged extensor phases did not shorten, and the corresponding step-cycle periods increased. (Adapted from Rybak et al. (2006b) with permission)

the interplay between the two influences on the CPG.

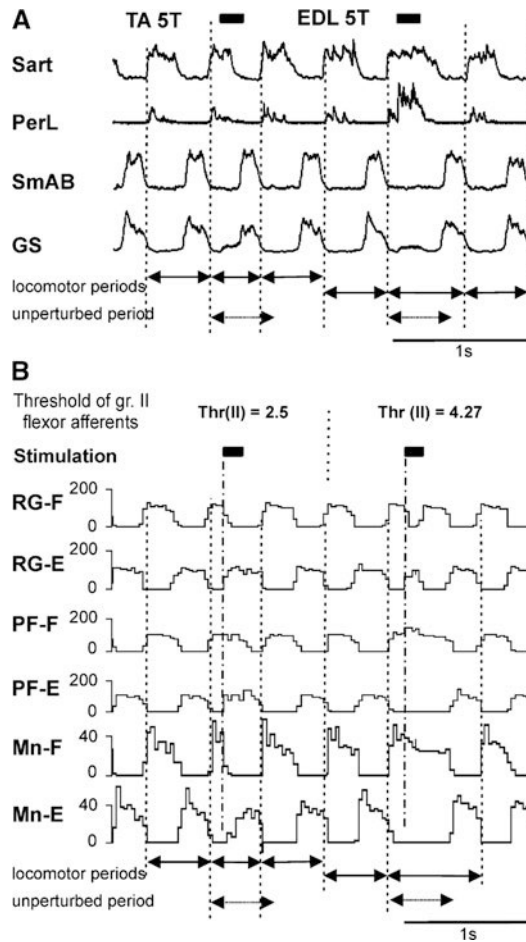
The schematic of the model used for flexor afferent stimulation is shown in Fig. 8. Similar to the organization postulated for extensor afferents, the hypothetical Irg-F and Ipf-F populations were incorporated to mediate the effect of flexor group I afferents on the RG and PF levels, respectively (Fig. 8). The excitatory effect of flexor group I afferents on PF-F interneurons (via the Ipf-F population) was relatively strong compared to their effect on the RG-F population (via Irg-F). To reflect the hypothesis that flexor group II afferents have an excitatory influence to the extensor part of the CPG, connections from flexor group II muscle spindle afferents to the Irg-E and Ipf-E populations were incorporated in the model. Because of the strong weighting of group II afferent input to the RG-E population (via Irg-E), activation of these afferents may strongly affect



Two-Level Model of Mammalian Locomotor CPG, Fig. 8 Schematic of the model used for simulation of flexor afferent stimulation. Flexor group I afferents (*Ia* and *Ib*) (green lines) access the RG-F and PF-F populations of the CPG through interneuron populations (*Irg-F* and *Ipf-F*, respectively, both are shown green). Flexor group II afferents (blue lines) project to the extensor side of the CPG via the *Irg-E* and *Ipf-E* populations, respectively (shown blue). (Reproduced from Rybak et al. (2006b) with permission)

the rhythm generator (e.g., produce a resetting the RG to extension).

Figure 9A shows an example of the effects of flexor afferent stimulation during flexion. Stimulation of TA afferents at an intensity recruiting group II fibers (5 T, where T is the threshold for activation of group I afferents in the peripheral nerve) terminated ongoing flexor phase activity (hip/knee flexor, Sart) and reset extensor activity (hip, SmAB, and ankle, MG), while stimulation of EDL nerve prolonged flexion (hip/knee, Sart, PerL). The first stimulus in this experiment reduced the ongoing cycle period shifting the rhythm to the left, while the second stimulus of a higher intensity caused a prolongation of the duration of both the ongoing flexion and the total cycle period (and the corresponding shifting of the rhythm to the right). Figure 9B shows an example of simulation of the effects of flexor afferent stimulation during flexion. To match the experimental procedure, all stimuli were applied to both flexor group I (*Ia* and *Ib*) and group II afferents. The first stimulus (left, see black rectangles at the top of traces in Fig. 9B) strongly recruits both group I and II afferents. This stimulus terminated the ongoing flexion phase and reset the cycle to extension (see the RG-F and RG-E activities, first and second traces, in Fig. 9B). In order to mimic a less effective recruitment of group II afferents, the threshold for activation of group II flexor afferents was increased prior to the application of the second stimulus. Such stimulation prolonged the ongoing flexor phase because the relatively stronger group I activation evoked excitation of the PF-F population and prevented phase resetting at the PF level (see third and fourth traces in Fig. 9B) and hence at the level of motoneurons (see two bottom traces in Fig. 9B). Therefore, the net result of strong activation of flexor group I and relatively weak activation of group II afferents was a prolongation of the ongoing flexion phase. It is important to notice that both stimuli reset the RG rhythm in the model (see first and second traces in Fig. 9B). Note that increasing the threshold of group II afferents in the model reduced their input to the *Irg-E* and *Ipf-E* populations and produced an effect similar to the experimental data shown in Fig. 9A. It can be suggested that the



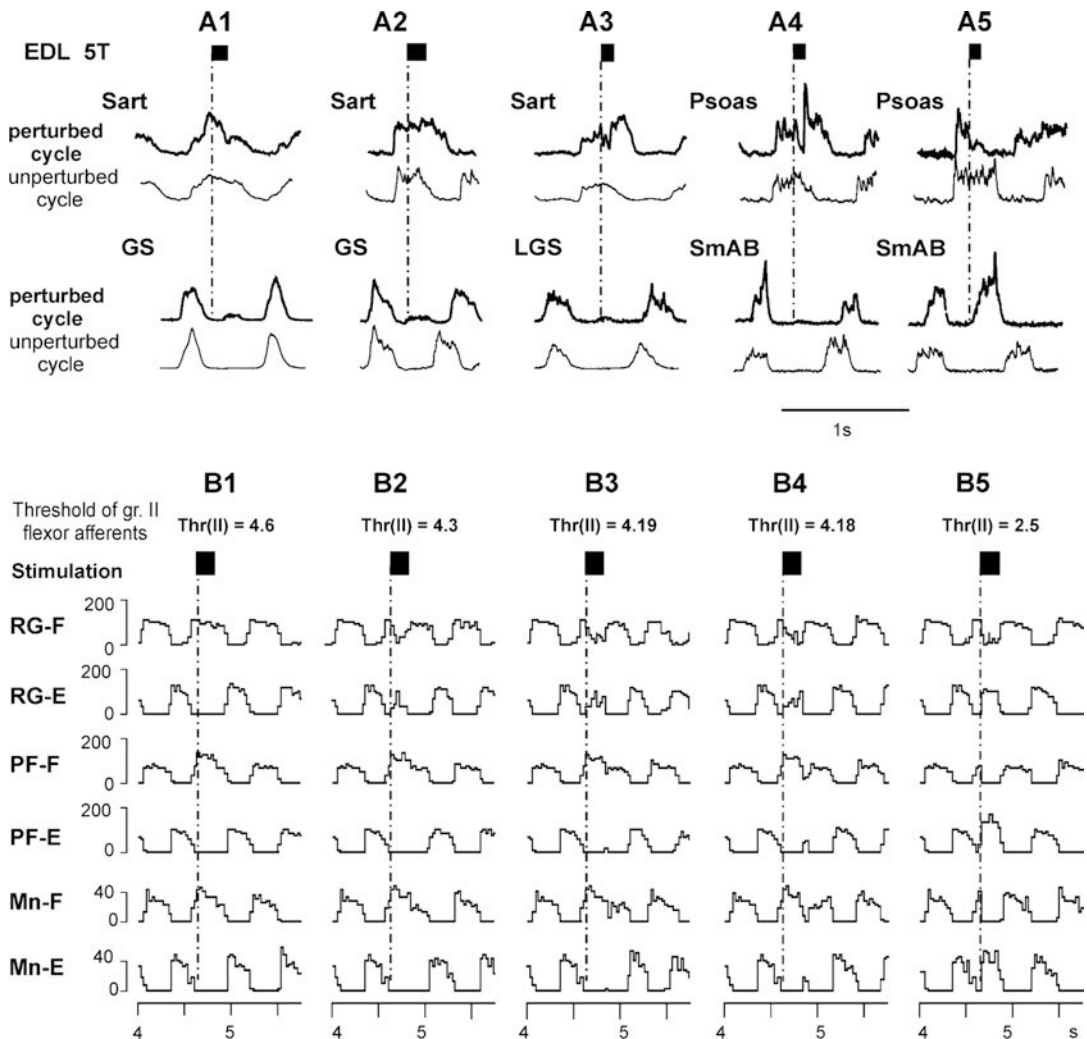
Two-Level Model of Mammalian Locomotor CPG, Fig. 9 Modeling the effects of stimulation of flexor afferents during flexion. **(A)** Example of stimulation of TA afferents (5 T) during flexor phase in fictive locomotion experiments. Stimulation of TA afferents terminated the flexion phase (hip/knee, *Sart* and *PerL*) and advanced the onset of extensor (hip, *SmAB*, and ankle, *GS*) activity. Stimulation of another flexor nerve (*EDL*) in the same run of fictive locomotion prolonged the ongoing flexion phase (see activities of *Sart* and *PerL*). **(B)** Results of simulation reproducing the effects of stimulation of the group II flexor afferents during flexion shown in **A**. Tonic drives to the RG-F and RG-E populations were adjusted to fit the experimental data. The applied stimuli are shown as black rectangles at the top of traces. The first stimulus

terminated ongoing flexion and initiated a premature onset of extension. Before application of the second stimulus (see vertical dotted line between two stimuli), the threshold of group II flexor afferent activation was increased from $\text{Thr(II)} = 2.5$ to $\text{Thr(II)} = 4.27$ (see labels at the top). As a result, the second stimulus produced the prolongation of the ongoing flexion phase (PF-F and Mn-F activities, *third* and *fifth* traces). Note that both stimulus presentations reset the RG activity (RG-F and RG-E, see *top two traces*). In both the simulation and experiment, the locomotor rhythm was affected by stimulation of the flexor nerve with the first stimulation shortening and the second prolonging the ongoing locomotor period (see *arrows below traces*). (Adapted from Rybak et al. (2006a) with permission)

reflex actions of group II afferents between different flexor nerves could vary according to either the numbers of group I and II afferents in each nerve or their central excitatory effectiveness.

Figure 10A1–A5 shows experimentally recorded effects of EDL nerve stimulation taken

from different fictive locomotion experiments (McCrea 2001; Stecina et al. 2005). During these experiments, the same intensity of stimulation (activating both group I and II afferents) resulted in a variety of effects on the step cycle. This variety of effects may result from the differences



Two-Level Model of Mammalian Locomotor CPG,

Fig. 10 Modeling the variable effects on locomotor output evoked by flexor muscle afferent stimulation during flexion. (**A1–A5**) Experimentally recorded effects of 5 T stimulation of EDL afferents during the flexion phase of MLR-evoked fictive locomotion. Averaged ENG records during cycles in which stimulation was applied (*perturbed cycle*) are shown by *thick lines*. The records during control (*unperturbed*) cycles are shown below the corresponding perturbed cycles. These observations were selected from different experiments and formed the basis of the simulations shown in **B1–B5**. Note the variety of effects observed following 5 T EDL stimulation. In **A1**, EDL stimulation resulted in a slight increase in flexor (*Sart*) activity and with no effect on the timing of flexor or extensor motoneuron bursts. In **A2**, there was a prolongation of the ongoing flexion phase and a delay in the activation of extensors. In **A3** and **A4**, flexor afferent stimulation also prolonged the flexion phase (see *Sart* in **A3** and *Psoas* in **A4**), but there

was also a brief reduction in flexor motoneuron activity in the middle of the flexor phase and a corresponding small but visible activation of extensors (see hint of extensor activity in *LGS* in **A3**). Both these effects presumably indicate a fast resetting of flexor activity. Another stimulus trial from the same run of fictive locomotion as shown in panel **A4**, shows a rare example of a spontaneous reversal of EDL actions (see **A5**). In this example, stimulation of EDL afferents initiated a premature onset of extension, terminating the flexion phase. (**B1–B5**) Simulation results illustrating variable effects of stimulation of flexor afferents (*black rectangles*) during the flexion phase. The threshold of group II flexor afferent activation, Thr(II) , was sequentially decreased from *left to right* (see values of Thr(II) at the *top* of each panel). *Black rectangles* at the *top* of traces indicate timing and duration of the applied stimuli. Note that the applied stimuli reset the rhythm generator in all simulations except for **B1** (see *first* and *second* traces showing the RG-F and RG-E population

in the excitability of the CPG networks or from the differences in the effectiveness of synaptic transmission from group I and II afferents to the CPG network (Perreault et al. 1999). In the first example (Fig. 10A1), EDL stimulation produced only a slight increase in hip flexor (Sart) activity, and there was no effect on step-cycle period (compare the cycle period in the perturbed cycle to that in the unperturbed cycle). In the second experiment (Fig. 10A2), EDL stimulation prolonged the ongoing flexor motoneuron bursts (hip, Sart) and delayed the onset of extensor bursts (ankle, GS). In Fig. 10A3, A4, flexor afferent stimulation also prolonged the flexion phase (hip, Sart and Psoas), but there was also a brief reduction in flexor motoneuron activity in the middle of the flexor phase and a corresponding small but visible activation of extensors (in Fig. 10A3). Both of these effects presumably indicate a fast resetting of flexor activity. Figure 10A5 shows an example of the unusual effect of EDL nerve stimulation terminating flexion and initiating a premature onset of extension (Stecina et al. 2005). This example was from the same run of fictive locomotion as shown in Fig. 10A4 and represents an example of a spontaneous reversal of EDL actions. This “reversed” extension-promoting action of EDL stimulation is similar to the common effect seen with TA nerve stimulation (Perreault et al. 1995; Stecina et al. 2005).

Figure 10B1–B5 shows the effects of a progressive increase in the influence of flexor group II afferents on the RG-E and PF-E populations in the model. This progressive increase was produced by reducing the threshold for group II flexor afferent activation (see threshold value at the top of each panel). At the lowest level of group II activation (highest threshold, Fig. 10B1), the

stimulation had little effect on the RG populations and produced a mild enhancement and prolongation of flexor motoneuron activity due to the activation of the PF-F population by flexor group I afferents (see third and fourth traces in Fig. 10B1). These effects can be compared to the experimental data shown in Fig. 10A1. In Fig. 10B2–B5, the threshold for group II flexor afferent activation was sequentially reduced until it was the same as the first stimulus in Fig. 9B. In Fig. 10B2, B3, the group II activation resets the RG (see first and second traces), but this resetting was not expressed at the PF level (see third and fourth traces). As a result the flexor motoneuron activity was prolonged similar to the experimental data shown in Fig. 10A2, A3, even though activity in the flexor half-center of the CPG (RG-F) was shortened. In Fig. 10B4, the increased group II input (further threshold reduction) produced further excitation of the extensor side of the CPG (RG-E, see second trace). This partially overcame the group I actions on the flexor side, and a phase resetting occurred at both the RG and PF levels, as happened in experiment shown in Fig. 10A4. There was, however, only a small brief burst of extensor motoneuron activity and a short break in flexor activity. Further reduction of the threshold for group II flexor afferent produced much stronger group II effects on the CPG (see Fig. 10B5): the flexion phase was terminated, and there was a clear resetting to a new extensor phase, which reproduces the experimental results shown in Fig. 10A5. As seen in Fig. 10B5, this resetting to extension could be reproduced in the model by further recruitment of flexor group II fibers. In all but one (Fig. 10B1) of the simulations shown in Fig. 10B1–B5, the prolongation of flexion or resetting to extension was accompanied by a resetting of the rhythm at the RG level of the CPG.

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Two-Level Model of Mammalian Locomotor CPG, Fig. 10 (continued) activities). In **B2** and **B3**, the concomitant activation of PF-F by flexor group I afferents (see Fig. 8) prevented resetting at the PF level (*third and fourth traces in B2 and B3*) and the level of motoneurons (*bottom two traces*). The result, therefore, was a prolongation of the flexion phase. In **B4**, the applied stimulus produced only a

short break in the middle of flexor activity and a small, short extensor burst (Mn-E, *bottom trace*). In **B5**, with the lowest Thr(II), sensory activation was strong enough to produce an irreversible resetting to extension (see text for details). (Adapted from Rybak et al. (2006a) with permission)

Conclusion

In summary, the modeling studies have demonstrated that the two-level CPG organization with separate RG and PF networks can provide a plausible explanation for a number of features of real CPG network operation, such as spontaneous resetting and non-resetting deletions and the effect of afferent stimulations observed during fictive locomotion. The proposed two-level model of the locomotor CPG may create a flexible basis for development of a more elaborated and realistic model of neural control of locomotion.

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Ultralow Vision Assessment

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Unitary Event Analysis

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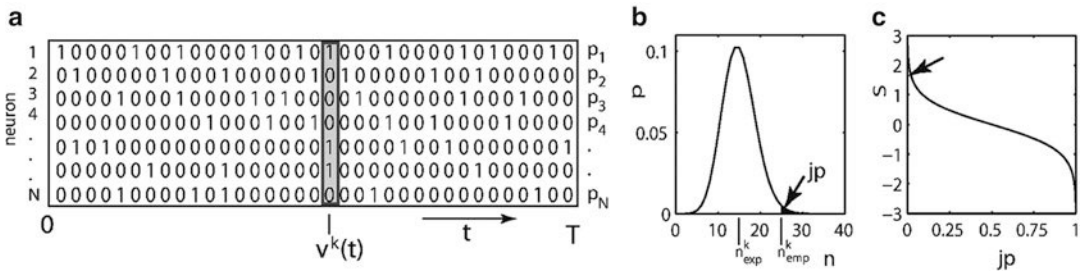
Definition

The unitary event (UE) analysis is a statistical method that detects conspicuous patterns of

synchronous spiking activity among simultaneously recorded spike trains. Significant patterns are identified by comparison of their occurrence counts to the null hypothesis of statistical independence based on the activity of the neurons.

Detailed Description

It has been proposed that cortical neurons organize dynamically into functional groups (“cell assemblies”) by the temporal structure of their joint spiking activity. The unitary event analysis method is designed to detect such patterns of coincident spiking activity occurring more often than expected by chance among simultaneously recorded single neurons. To this end, the spiking activity of all simultaneously recorded neurons is represented, after appropriate time discretization (e.g., $h = 1$ ms), as parallel sequences of zeros and ones, “1” indicating the existence of at least one spike (clipping) and “0” the absence of spikes (Fig. 1a). From this representation, the number of occurrences for each of the individual 0–1 patterns across the neurons is counted. There are at most 2^N different coincidence patterns in data of N simultaneously observed neurons. Due to the finite recording time and the dominance of zeros, however, the actual number of different coincidence patterns found is typically much lower. A unique index k is assigned to each existing pattern based on some arbitrary sorting. Next, for each pattern k , the number of occurrences



Unitary Event Analysis, Fig. 1 Binary data representation of N parallel spike trains within a data stretch of T bins of width h . **(b)** Distribution of coincidences given the expected number n_{exp} . Significance (p-value, black area)

of the number of empirically found coincidences n_{emp} . **(c)** Transformation of the p-value into the surprise measure S . The arrow indicates the surprise value corresponding to the identified p-value (jp) in **b**. (Modified from Grün (2009))

termed the empirical count is determined. To derive the *significance* of a pattern k , the p-value of its number of occurrences is calculated by comparison to the probability distribution derived under the null hypothesis of statistical independence of the processes. The distribution either can, under certain conditions, be assumed and adjusted by parameters estimated from the data (parametric approach) or can be derived with Monte Carlo methods by the generation of surrogate data on the basis of the original data (nonparametric approach).

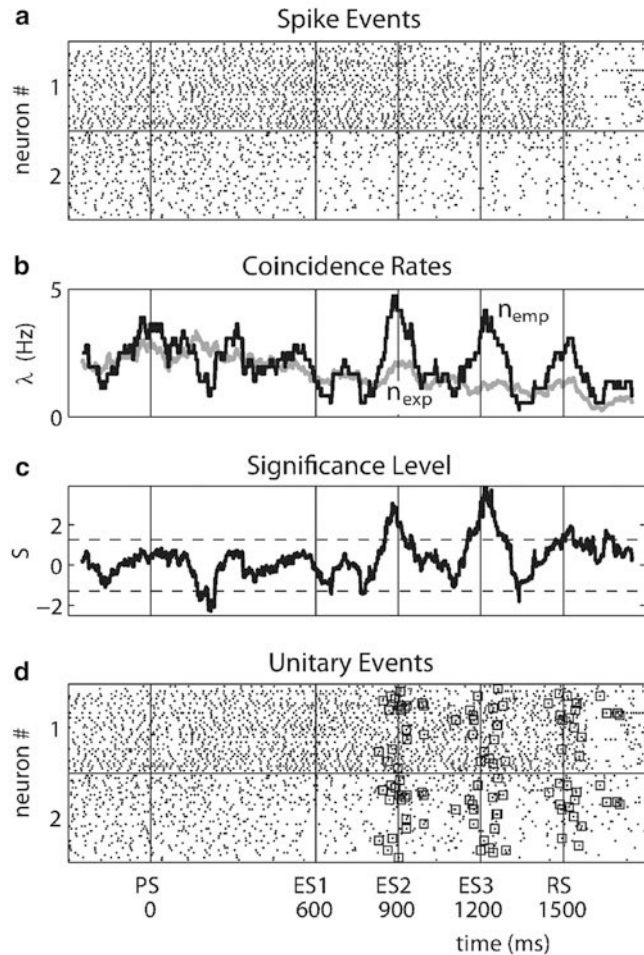
The parametric approach has the following assumptions: (a) the firing rates are stationary within the time span of the observation T , and (b) the processes have Poisson properties. Then the expected number of occurrences of a pattern k can *analytically* be calculated based on the firing rates of the neurons. For each neuron i , the probability of firing within a bin p_i is derived by dividing the number of bins occupied by a spike c_i by the total number of bins in T , i.e., T/h , with h the bin width. The joint probability for pattern k , P_{exp}^k , to occur by chance is then calculated as the product of the firing probabilities p_i for the neurons contributing a spike in pattern k and probabilities $1 - p_i$ for neurons contributing a 0 to the pattern. The expected number of occurrences of pattern k is derived as $n_{\text{exp}}^k = P_{\text{exp}}^k \cdot T/h$. This quantity defines the mean of the Poisson distribution that is used to estimate the significance of the pattern by calculation of its p-value, i.e., the area under the distribution from n_{emp}^k to infinity. If the p-value is smaller or equal to a predefined

significance level α , the pattern is considered to occur significantly more often than by chance. If the p-value is larger or equal to $1 - \alpha$, the pattern is occurring significantly less often than expected. The p-value may be expressed as the surprise measure (Fig. 1c), a logarithmic transformation of the p-value (Grün et al. 2002a) for better visualization (Fig. 2c).

Often experimental data exhibit violations of the above assumptions, i.e., firing rates may change even on a short timescales or spike trains deviate from Poisson statistics. In the latter case, the coincidence distribution is not well described anymore by a Poisson distribution (e.g., Pipa et al. 2013), since the process type influences the distribution. If firing rate changes are not properly considered, the estimated mean of the distribution may not be correct. If such cases are ignored, this may lead to false-positive outcomes and wrong interpretation of the data (Grün 2009; Grün et al. 2010). Thus, an alternative approach for the estimation of the significance is based on a numerical (Monte Carlo) method, in which the original data are manipulated to destroy potential spike synchrony but conserve all other features of the spike trains. One example is spike dithering, i.e., the random displacement of each individual spike within a small time window (e.g., Pipa et al. 2003; for details and alternative approaches, see Louis et al. 2010a, b). The resulting surrogate data are then analyzed like the original data for the number of occurrences of patterns of interest. Pattern counts from many repetitions of this procedure realizing the null hypothesis of independence form the distribution, which

Unitary Event Analysis, Fig. 2 Temporal

modulation of synchronous activity. UE analysis of two simultaneously recorded single neurons from motor cortex of awake behaving monkey. The monkey was involved in a delayed pointing task, where the duration of the preparation period (after PS) to the requested movement (RS) was selected randomly from four possible durations (600, 900, 1200, 1500 ms) from trial to trial. Here trials (36) with the longest duration (1500 ms) were pooled. (a) Raster displays of spike discharges of two neurons. (b) Comparison of measured (black) and expected (gray) coincidence rates. Allowed coincidence width ± 2 ms. (c) Surprise as a function of trial time. (d) Dot display with unitary events (squares) detected based on a significance level of $\alpha = 0.05$, in sliding windows of $T = 100$ ms. (Modified from Riehle et al. (1997))



is then used for the significance estimation of the empirical pattern count.

When aiming at the analysis of the correlation structure of the neuronal spiking activity in relation to behavior, which is dynamic by nature, the analysis has to be performed in a time-dependent manner. Also the firing rates typically change in time which needs to be accounted for. Therefore, the UE analysis is applied within a time window of length T (i.e., 100 ms duration) that is slid along the data (for proper choice of the analysis window, see Grün et al. 2002b). This enables the study of the dynamics of the correlation structure. It was found in a number of studies that spike synchronization modulates in time in relation to the behavioral context (e.g., Riehle et al. 1997; Grün et al. 1999; Riehle et al. 2000; Maldonado et al. 2008; Kilavik et al. 2009; Ito et al. 2011).

The experiments are typically repeated over several trials to improve the statistics of the analysis. For this purpose, the trial data are aligned to an (behavioral) event of interest. The analysis window is then slit along the aligned data, and at each window position, the data of the same time segment are jointly considered. The empirical pattern counts are derived by summing the occurrence counts of the same pattern in the different trials to provide the empirical count ($\hat{n}_{\text{emp}}^k = \sum_j n_{\text{emp}}^{kj}$). In the parametric approach, the expected number is calculated trial by trial and then summed to the total number ($\hat{n}_{\text{exp}}^k = \sum_j n_{\text{exp}}^{kj}$) providing the mean of the distribution as introduced above. Taking the sum instead of an estimate based on average firing rates across trials has the advantage to account

for cross-trial non-stationarities in the firing rates (Grün et al. 2003). For the nonparametric approach, the count across trials is compared to the count distribution derived from surrogates by the sum of counts of the surrogates across the trials. For population measures, i.e., for statistics of the data across several sessions, one may proceed by adding more trial data, however now resulting from the different sessions (see for details Kilavik et al. 2009).

In 2017 the unitary event analysis was newly implemented in Python and is available in the open source Electrophysiology Analysis Toolbox (Elephant, RRID:SCR_003833) at <http://python-elephant.org>. One of the unit tests of the Python UE implementation is the reimplement of the UE analysis performed in Riehle et al. (1997) published as Rostami et al. (2017) in ReScience. Therein Rostami et al. showed that the UEs are identically and correctly detected on a spike-by-spike basis. The data and code is fully available from <https://github.com/ReScience-Archives/Rostami-Ito-Denker-Gruen-2017/tree/master/article>.

This method is not designed to detect higher-order correlations, since the null hypothesis is statistical independence. Shimazaki et al. (2012) extended the approach within the information geometry framework. This identifies in a time-dependent manner higher-order spike correlation patterns. The analyses of massively parallel spike data (e.g., in the range of 100 neurons) require statistical methods that either ignore the individual spike patterns (e.g., Staude et al. 2010a, b) or pool across patterns to avoid severe multiple testing problems (Picado-Muiño et al. 2013; Torre et al. 2013, 2016a, b; Stella et al. 2019).

Cross-References

- [Correlation Analysis of Parallel Spike Trains](#)
- [Estimation of Neuronal Firing Rate](#)
- [Gravity Analysis of Parallel Spike Trains](#)
- [Information Geometry as Applied to Neural Spike Data](#)
- [Joint Peri Stimulus Time Histogram \(JPSTH\)](#)
- [Significance Evaluation](#)

- [Spike Train](#)
- [Surrogate Data for Evaluation of Spike Correlation](#)
- [Statistical Evaluation of Spatio-Temporal Spike Patterns](#)

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Up and Down States

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V

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Vestibular Adaptation and Compensation

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Definition

There are two forms of adult neuroplasticity associated with the vestibular system: *vestibular adaptation* and *vestibular compensation*. Vestibular adaptation describes the routine changes in sensitivity (gain) of reflexive eye movements (vestibulo-ocular reflex, VOR) responsible for stabilizing images on the retina during head movements. Vestibular compensation, however, is a form of plasticity only precipitated by catastrophic events such as loss of vestibular input on one side.

Detailed Description

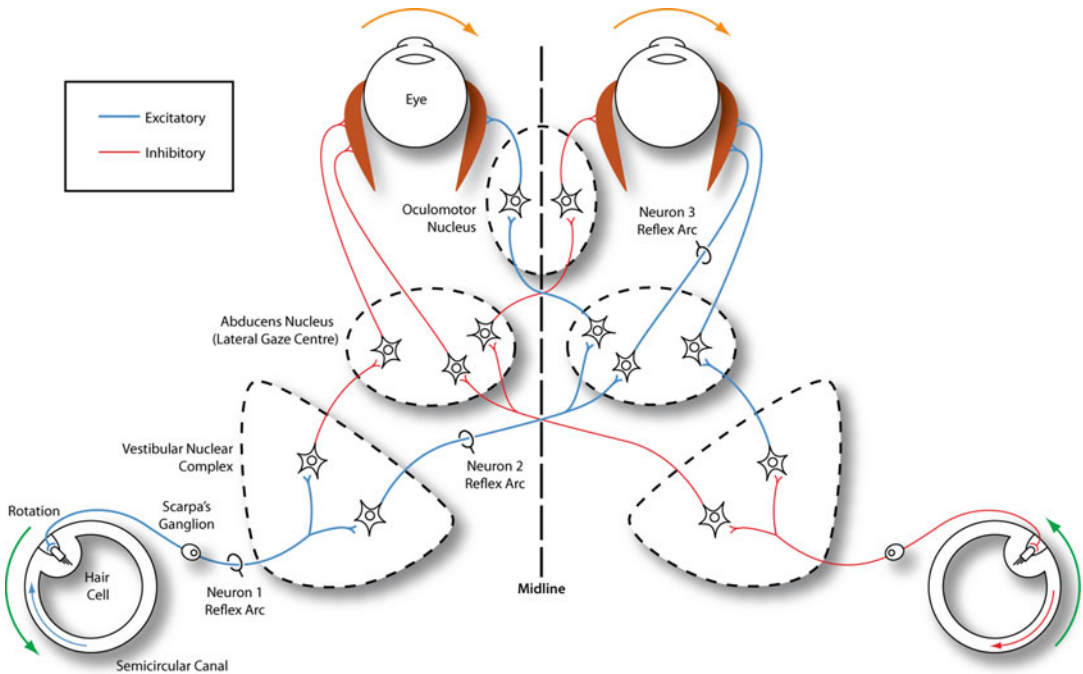
The balance or vestibular system is often overlooked as a major sensory system (Goldberg et al. [2012](#)).

Even less appreciated is the vestibular system's inherent plasticity and capacity for self-repair. Two phenomena known as *vestibular adaptation* and *vestibular compensation* are exquisite examples of innate plasticity. The extent and limits of these restorative mechanisms can be observed and measured by using the important vestibulo-ocular reflex (VOR) as an example.

Vestibulo-Ocular Reflex (VOR)

In all animals, including humans, the VOR is a vestibular-mediated reflex that helps maintain a stable image on the retina, a critical prerequisite for visual acuity. In response to head movement in

one direction, the VOR generates compensatory eye movements that are usually equal in magnitude but opposite in direction. The VOR is very rapid and has one of the shortest activation latency (9–15 ms) of any reflex that involves motor output (Aw et al. 1996; Minor et al. 1999). This speed is due in large part to its deceptively simple circuitry, often described as a three-neuron arc that consists of the following: (1) vestibular primary afferent neurons that transmit balance signals from the inner ear to vestibular nuclei, (2) vestibular nucleus (VN) neurons that receive additional multisensory information and send “balance” signals to various motor nuclei that control eye movements, and (3) motor neurons that innervate extraocular eye muscles (Fig. 1).



Vestibular Adaptation and Compensation, Fig. 1 A circuit diagram emphasizing the three-neuron arc involved in the horizontal vestibulo-ocular reflex (VOR). The VOR is responsible for generating compensatory eye movements during changes in head orientation. In this example, rotation of the head to the left (green arrows) results in eye movements to the right (orange arrows). Turning the head to the right causes inner ear fluid, in the right horizontal semicircular canal, to flow in the excitatory direction (blue arrow), thereby increasing signals from associated hair cells and primary afferents. Simultaneously, in the

right horizontal semicircular canal, fluid flows in the inhibitory direction (red arrow) resulting in *decreased* signals from associated hair cells and primary afferents. Peripheral signals from both sides are transmitted to their respective vestibular nuclear complexes and preferentially target the medial vestibular nuclei (MVN). From the MVN, signals are conveyed along either excitatory (blue) or inhibitory (red) pathways via cranial motor nuclei (abducens and oculomotor) to extraocular muscles, resulting in compensatory eye movements

Vestibular Adaptation

While the concept of a three-neuron arc may help explain the speed of the VOR, it does not adequately describe the VOR's remarkable ability to adapt. When viewing a far object, the eyes move as described above – equal but opposite to head movements. Under these conditions, therefore, we can quantify VOR sensitivity or *gain* as being equal to unity (dividing eye velocity by head velocity). However, there are common situations where VOR gain must be modified to maintain visual stability (Angelaki 2004; Migliaccio and Schubert 2013). For example, if an object is viewed nearer to the subject, eye movements increase and have to be corrected not only for their larger excursions but also for *vergence*, where both eyes deviate inwards towards the nose. It is therefore a basic requirement that the VOR and eye movements reflexively adapt to the viewing context, including viewing distance and vergence angle (Migliaccio et al. 2003). In short, to minimize retinal image slip, when the vestibular-evoked eye movements are not perfectly compensatory, the VOR must undergo a process of *vestibular adaptation* (Melvill Jones and Gonshor 1982; Baker et al. 1987; Clendaniel et al. 2002). An extreme example of the VOR's remarkable adaptive capacity is known as *cross-axis adaptation*. Here a visual scene is moved at right angles to head motion. Within 30–120 min of training, the VOR can reduce vertical eye movements in response to horizontal head rotations in the dark, with no visual or proprioceptive cues (Schultheis and Robinson 1981; Khater et al. 1990). Although cross-axis adaptation would rarely occur in nature, it is a manifestation of vestibular adaptation, an astonishing and poorly understood or appreciated example of adult neuronal plasticity. How vestibular adaptation is achieved at the cellular level is not known, but a detailed analysis of the neuronal circuitry involved and the changes it undergoes are a necessary first step.

Vestibular Compensation

Another striking example of adult neuronal plasticity associated with the vestibular system is a phenomenon known as *vestibular compensation*

(Smith and Curthoys 1989; Curthoys 2000). Immediately after disruption or loss of peripheral nerve activity on one side, due to disease or damage (e.g., neuritis, labyrinthitis, or unilateral labyrinthectomy), there is a stereotyped series of behavioral deficits including imbalance, spontaneous nystagmus (slow eye drift towards the injured side with fast corrections in the opposite direction), head tilt, postural deficits, and reduced VOR (Curthoys and Halmagyi 1999; Lasker et al. 2000). Over the following several days to 1 week, there is a near resolution of *static symptoms* (i.e., symptoms in the absence of head movement). This process of recovery is the result of changes in central rather than peripheral vestibular system, since compensation occurs independent of peripheral nerve activity. There are, however, limits to vestibular compensation, despite the recovery from static symptoms (Curthoys and Halmagyi 1995). Deficits observed during head movements, *dynamic symptoms*, such as reduced VOR, are never fully restored.

Vestibular Nucleus (VN) Activity

The cellular basis of the stereotyped compensatory responses and subsequent vestibular compensation is also not fully understood. From classical in vivo recordings (Precht and Shimazu 1965; Shimazu and Precht 1965), we know, at rest, VN neurons on both sides maintain similar spontaneous background discharge rates. In response to a rotation of the head to the left, there is an increase in primary afferent and VN neuronal activity on the *left* side with a concomitant decrease in primary afferent and VN neuronal discharge on the right side. Both left and right VN signals contribute to VOR-induced compensatory eye movements and in this case move the eyes to the *right*.

Cellular Mechanisms Underlying Plasticity and Self-Repair

Acute loss of peripheral input on the left side induces decreased VN activity on the left and increased VN activity on the right (Curthoys and Halmagyi 1995; Ris and Godaux 1998). This

condition simulates an apparent head movement to the *right*. In response, the VOR produces compensatory nystagmus with slow eye movements to the *left*, towards the affected side. During the subsequent period of vestibular compensation, however, the asymmetry between VN neuronal activity on the left and right sides begins to abate as background discharge of left VN neurons is reestablished. This realignment of activity is on a similar time scale to the resolution of static vestibular deficits, including nystagmus. Further studies suggest, however, this rebalance of background activity in VN neurons may be one of many factors responsible for the resolution of static symptoms (Curthoys 2000). As with *adaptation*, the cellular mechanisms underlying *compensation* in the central vestibular system still remain a major goal for vestibular neuroscience.

Cross-References

- [Central Vestibular Signal Processing](#)
- [Vestibular System: Overview](#)

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Vestibular Function After Cochlear Implantation

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Synonyms

[Balance following cochlear implantation](#); [Equilibrium following cochlear implantation](#)

Definition

Cochlear implantation is a surgical procedure where an electrode array is implanted into the cochlea (hearing part of the inner ear). The electrode electrically stimulates the cochlear nerve resulting in auditory percepts that assist with speech reception. Vestibular function estimates the response of the semicircular canals to angular velocity and the utricle and saccule to linear acceleration. The sense of equilibrium results from the integration of visual, proprioceptive and vestibular sensory information within the brainstem and central nervous system. In other words, vestibular function is a vital, but not the sole, factor contributing to the sense of balance.

Detailed Description

Vestibular function is vulnerable during cochlear implantation because the latter breaches the integrity of the labyrinth, putting both residual hearing and vestibular function at risk.

The response of the lateral semicircular to bithermal stimulation (the “caloric” response) is reduced following cochlear implantation. The unilateral weakness score (as calculated from Jongkees’ formula) is typically increased by an average of 20–30% towards the implanted ear (Ito 1998; Enticott et al. 2006, 2011). While it has been suggested that the surgery to the temporal bone done in preparation to implantation may change the caloric response, by altering thermal conduction through the temporal bone, this has been shown to make a relatively small contribution to the caloric response, compared with that made by cochlear implantation (Kondoh et al. 2009). Approximately 10% of patients lose the majority of their caloric function in the implanted ear, suggesting significant injury to the vestibular system in that ear.

The vestibular ocular reflex (VOR) gain estimated from quantitative head impulse testing (by video assessment, or scleral search coils) does not change after cochlear implantation in the majority of patients (Jutila et al. 2013; Melvin et al. 2009). However, the VOR gain is lost in approximately 10% of patients.

More than half of patients experience a reduction in their cervical vestibular evoked myogenic potentials following cochlear implantation, and the potentials are lost in approximately 10% of patients (Melvin et al. 2009; Licameli et al. 2009). These potentials are thought to arise from the saccule.

In summary, in studies conducted in the 1990s and early 2000s a significant reduction in vestibular function within the implanted ear was found in approximately 10% of patients. The incidence of dizziness after CI surgery is much greater, ranging from between 30% and 50% patients (Enticott et al. 2006; Fina et al. 2003; Ito 1998). The majority of patients experience a transient dizziness in the first few weeks after surgery that resolves completely (Enticott et al. 2011; Ito 1998), but the onset of the dizziness can be delayed for months after implantation. Delayed dizziness can be either head-position dependent and respond to treatment for benign paroxysmal positional vertigo, or fluctuate and resemble that experienced in Meniere’s disease (endolymphatic hydrops) (Ito 1998). Risk factors for delayed post-operative dizziness include poorer pre-operative vestibular dysfunction and older age at the time of implantation and duration of hearing loss (Fina et al. 2003). The incidence of post-operative dizziness can be reduced by the local application of glucocorticosteroids to the round window during cochlear implant surgery, prior to electrode insertion (Enticott et al. 2011).

Injury to the cochlear duct following cochlear implantation might explain the loss of vestibular function seen in some patients after cochlear implantation (Handzel et al. 2006). Histology from human cochlear implant patients has revealed that electrode insertion can lead to injury of the cochlear duct, and subsequent fibrosis and obliteration of the endolymphatic space. The cochlear duct is vulnerable because it is located just above the basilar membrane, and in close proximity to the electrode path within scala tympani. The cochlear duct may be injured through incorrect placement of the cochleostomy, or by the electrode passing inadvertently through the basilar membrane. Scarring within the endolymphatic space has been associated with collapse of the saccule in human temporal bones (Handzel et al.

2006; Tien and Linthicum 2002), likely due to a reduction in the endolymphatic flow from the cochlea to the vestibular labyrinth. This provides one potential explanation for the significant loss of vestibular function seen in some patients after cochlear implantation.

The reason(s) why so many patients become dizzy for a short period of time after cochlear implantation are not well understood. Potential mechanisms include the development of serous labyrinthitis in response to inner ear surgery, and injury to the lateral cochlear wall during electrode insertion, resulting in a loss of regulation of ionic homeostasis within the inner ear. The latter might lead to endolymphatic hydrops and consequently dizziness in patients with a patent cochlear duct (Handzel et al. 2006). The presence of hydrops in human temporal bones (Handzel et al. 2006) may also explain the delayed Meniere's-like vertigo seen in some cochlear implant patients.

A rare cause of dizziness following cochlear implantation is direct electrical stimulation of the vestibular nerve (Coordes et al. 2012). This has presented as dizziness when some or all of a cochlear implant's electrodes have been electrically stimulated. Cervical vestibular evoked myogenic potentials have on occasion been elicited through electrical stimulation of the implant electrodes (Coordes et al. 2012). It has been postulated that low-level electrical stimulation of the vestibular nerve may in fact *improve* the balance of cochlear implant recipients; several studies have shown that the sense of balance is improved when the cochlear implant is functioning (Cushing et al. 2008). It remains unclear as to whether this is due to a direct effect upon the vestibular system, or improved situational awareness through being able to hear.

Clinically, the majority of patients do not experience any lasting disturbance of their sense of balance following cochlear implantation, even when there was been a significant reduction in the vestibular function within the implanted ear. This can be attributed to central compensation following peripheral vestibular injury, and that the sense of equilibrium results from an integration of vestibular, visual and proprioceptive

inputs. The risk of on-going disequilibrium increases slightly following bilateral cochlear implantation, presumably because of the associated risk of bilateral injury to the vestibular system. For this reason, vestibular function testing is recommended prior to cochlear implantation, and in particular second-side surgery in vulnerable individuals, such as older persons where a loss of balance may compromise independence of living or those involved in jobs that require exquisite balance.

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Vestibular Otoliths, Response to Vibration and Sound

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Definition

Vestibular receptors are hair cells, which are very similar in structure and operation to cochlear hair cells. Recently it has been shown that afferent nerves from otolithic receptor hair cells in the striola of the otolithic sense organs – the utricular and saccular maculae – respond to vibration and sound. That has quickly been translated to clinical application by measuring myogenic potentials elicited by sound and vibration. The saccular macula and the utricular macula have differential projections to various muscle groups, and that has been used to index the differential function of saccular and utricular maculae. The cervical vestibular evoked myogenic potential (cVEMP) indicates mainly the saccular function and the ocular vestibular evoked myogenic potential (oVEMP) indicates mainly the utricular function.

Detailed Description

Introduction

The otolithic receptors of the vestibular system of the inner ear (the utricular and saccular maculae) sense linear acceleration and generate a host of compensatory responses and perceptions. However, assessment of the functional state of the otolithic receptors has been a major challenge. The standard approach has been to deliver linear accelerations and measure the responses to that stimulus. Various methods of delivering linear accelerations have been used – e.g., tilt chairs, sleds, and centrifuges. These systems are excellent devices for research but not for everyday clinical practice where it is necessary to obtain accurate data safely, simply, and quickly.

One solution to this problem was the discovery of small myogenic potentials recorded by

electromyographic (EMG) electrodes on the surface of the skin over the activated muscles (Colebatch and Halmagyi 1992). These EMG potentials triggered by sound and vibration are now called vestibular evoked myogenic potentials (VEMPs). This approach is built on two important premises:

1. Control experiments that show that VEMPs are vestibular and are not of cochlear origin – deaf patients with vestibular function have VEMPs, whereas patients without vestibular function but with good hearing do not have VEMPs (Colebatch and Halmagyi 1992; Colebatch et al. 1994).
2. Neurophysiological evidence that vestibular receptors are activated by sound and vibration which is discussed below

The two most commonly measured VEMPs are the ocular VEMP (oVEMP) measuring the myogenic potentials of the inferior oblique (IO) eye muscle (Rosengren et al. 2005; Weber et al. 2012) and the cervical VEMP (cVEMP) measuring the potentials in the tensed sternocleidomastoid (SCM) neck muscle (Colebatch and Halmagyi 1992). These two VEMPs are evoked by sound and vibration, but they have very different characteristics. The first negative component of the oVEMP (n10) is a small ($\sim 5\text{--}10\ \mu\text{V}$) negative myogenic potential at a latency of about 10 ms recorded from beneath the eyes as the subject looks up. It is a crossed negative (excitatory) potential from the IO originating primarily from utricular afferents coursing in the superior division of the vestibular nerve. In contrast the first positive component of the cVEMP (p13–n23), recorded over the SCM tensed by the subject lifting or turning their head, is an uncrossed positive (inhibitory) potential originating primarily from saccular afferents coursing in the inferior vestibular nerve (Curthoys 2010, 2012; Rosengren and Kingma 2013; Shin et al. 2012; Manzari et al. 2012).

The Stimulus

In these studies the stimulus is an air-conducted sound (ACS) or a bone-conducted vibration

(BCV), and a brief tap or burst of 500 Hz BCV has been shown to be very effective. BCV applied to the head causes waves to travel through and around the skull and cause linear accelerations at the mastoids (Iwasaki et al. 2008b). A vibration or light tap to the midline of the forehead at the hairline (a location called Fz) with a tendon hammer causes linear accelerations at the mastoids, with both mastoids moving outward, obviously not by much, but the linear acceleration is present and otoliths sense linear accelerations. That has been shown by using miniature lightweight surface-mount triaxial linear accelerometers on the mastoid to measure the linear accelerations at the mastoid in response to a tap of the forehead. Fz is a valuable location because a tap at that location causes simultaneous equal linear acceleration stimulation of both mastoids. The magnitude of the linear acceleration is greatly attenuated from the forehead to the mastoid, so a light tap by a tendon hammer measures 20 g at the forehead, but at the mastoid this is a 0.2 g linear acceleration – an attenuation by a factor of 100.

The evidence that the VEMPs are vestibular comes from tests on patients with a surgically verified loss of unilateral vestibular function which show a greatly reduced or absent oVEMP beneath the eye contralateral to the affected ear (the oVEMP is crossed) and a greatly reduced or absent cVEMP response of the neck muscles on the same side as the affected ear (the cVEMP is uncrossed).

Projections

Afferent neurons from the vestibular receptors project to the brainstem vestibular nuclei and thence to the neurons controlling many different motor functions to generate oculomotor and postural responses.

Neural Evidence

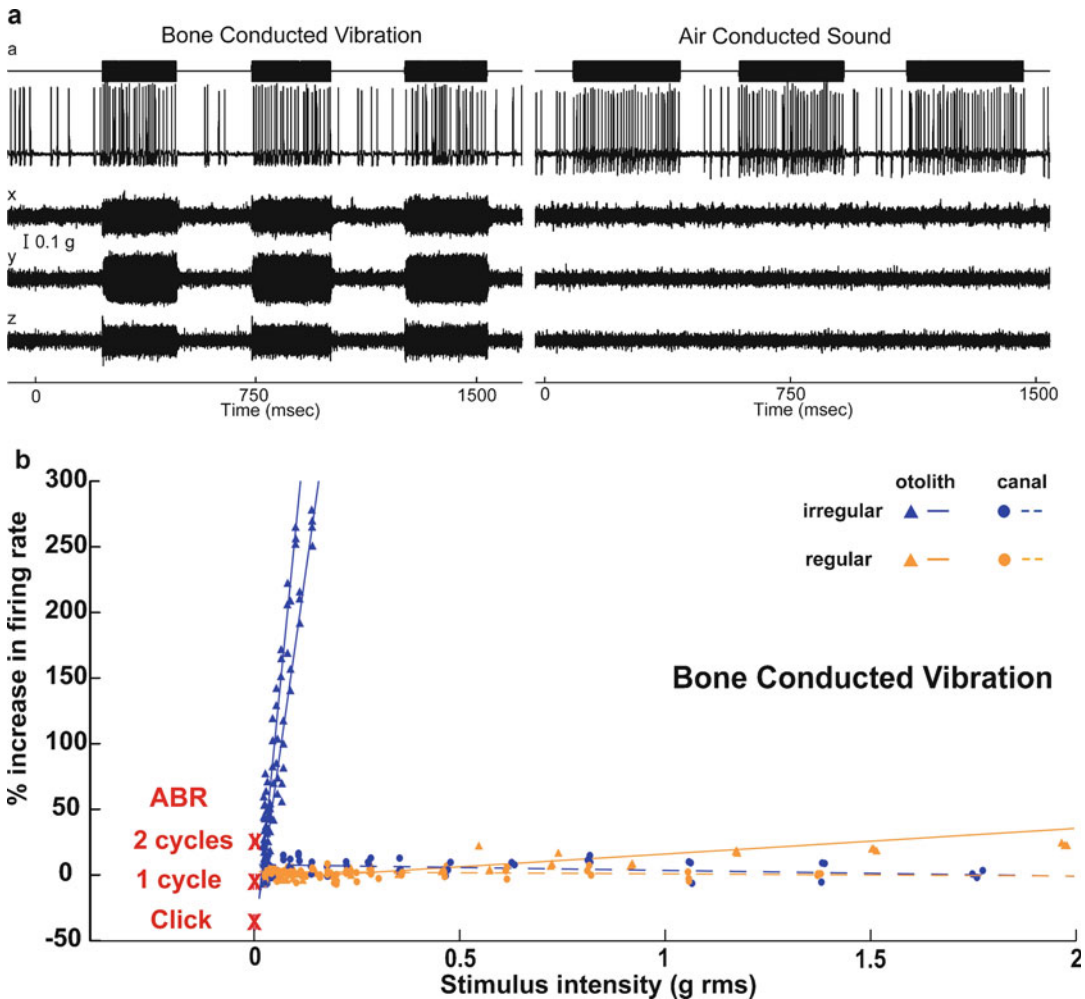
What is needed is a strong evidence that sound and vibration activate vestibular receptors and afferents. The major questions here are whether both the otolith and semicircular canal neurons are equally affected and whether both the utricular and saccular afferents are activated by both ACS and BCV.

Extracellular single neuron recording of primary vestibular afferents shows that it is almost exclusively otolith afferents with irregular resting discharge which respond to 500 Hz ACS and BCV (Curthoys et al. 2006) (Fig. 1). Semicircular canal neurons and regular otolith neurons are only rarely activated by this frequency and then only at very high intensities. The sites of origin of these neurons have been shown by using electroporation (juxtacellular injection) of neurobiotin on these otolith irregular neurons and then removing the whole utricular and saccular maculae and using immunohistochemistry to stain and then trace the labeled neurons (Curthoys et al. 2012). Since the maculae were removed, it was possible to see from which macula the labeled neurons originated and precisely where on the macula they originate from. The axons of activated neurons originate from the receptors in or close to the striolar area of both the utricular and the saccular maculae (Curthoys et al. 2012). There is now no doubt that both utricular and saccular afferents show sensitive response to *both* ACS and BCV stimuli – conclusively falsifying what was the widely held view that ACS only activates the saccular afferents (Curthoys and Vulovic 2011).

The origin of these otolith irregular afferents from the region of the striola is in agreement with evidence from Goldberg (2000) – calyx afferents innervating type I receptors are localized preferentially to the striola of the utricular and saccular maculae, and these otolith irregular afferents are especially sensitive to changes in linear acceleration (jerk) and that jerk sensitivity may be the reason why these afferents are so sensitive to bone-conducted vibration. 500 Hz BCV consists of 500 rapid changes in linear acceleration per second. It is the type I receptors at the striola which are especially vulnerable to the effects of ototoxic antibiotics.

Recent evidence is that low-frequency vibration (100 Hz) does activate semicircular canal afferents, but 500 Hz is selective just for otolith neurons.

In 2010 Curthoys put forward the hypothesis that by measuring the different *responses* to otolith stimuli, it is possible to assess the utricular as opposed to the saccular function because these

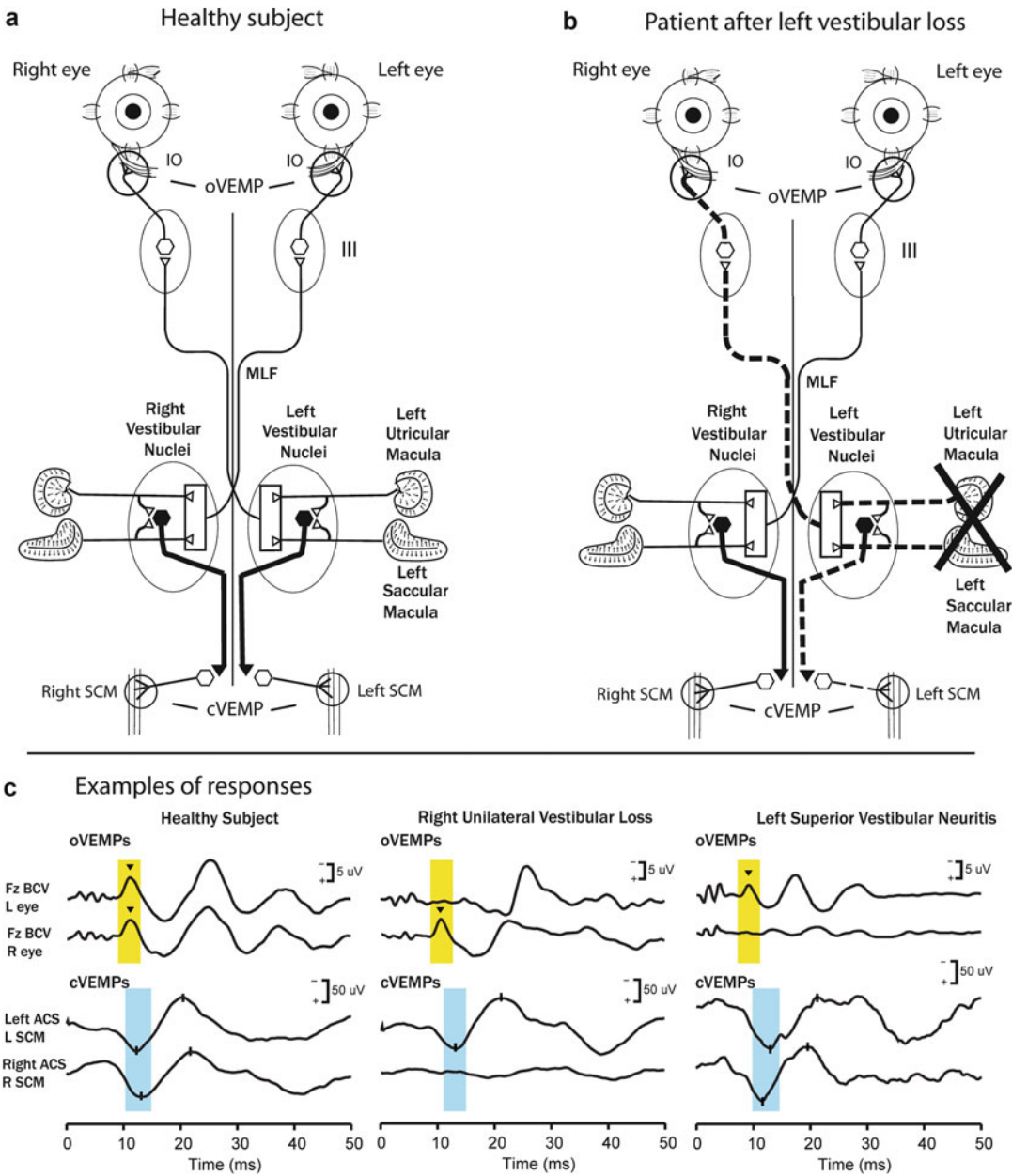


Vestibular Otoliths, Response to Vibration and Sound, Fig. 1 (a) Time series of an irregular otolith neuron during stimulation by 500 Hz BCV and ACS. The top trace (a) shows the command voltage indicating when the stimulus is presented. The second trace shows the extracellular recording. The three bottom traces (x, y, z) show the triaxial accelerometer recording of the stimulus. The left panel is an example of BCV stimulation, and the right panel is an example of ACS stimulation of the same neuron. Note the scale of stimulus intensity in g units at the left margin between traces x and y. (b) Examples of

sensitivity plots of the neurons to BCV. Each point shows the increase in firing rate as the percentage of baseline firing rate during a single stimulus presentation. The stimulus intensity is calculated in g units and is the root mean square of three axes, as recorded by the accelerometers, for BCV, and for ACS, intensity is given in dB SPL. Each line shows the linear best fit of the responses for one neuron. The red X marks show the mean ABR thresholds with 95% confidence intervals for clicks, one- and two-cycle tone stimuli (Reproduced with permission from Curthoys and Vulovic (2011))

different otolithic sensory regions have predominantly different projections (Curthoys 2010), specifically that:

- Utricular function is probed by recording VEMPs from electrodes beneath the eyes (the oVEMP n10) to 500 Hz ACS or BCV as the patient looks upward because the utricular afferents have a strong projection to the eye muscles.
- Saccular function is probed by recording VEMPs from electrodes on tensed SCM muscles in the neck (the cVEMP p13–n23) to 500 Hz ACS or BCV, because the saccular afferents have a strong projection to the neck muscles.



Vestibular Otoliths, Response to Vibration and Sound, Fig. 2 (a, b) A simplified schematic version of some of the known neural vestibuloocular and vestibulo-colic projections that appear to underlie the asymmetric oVEMP and cVEMP responses after unilateral vestibular loss. It is based on known anatomical projections and physiological results that high-frequency electrical stimulation of the utricular nerve results in the activation of the contralateral inferior oblique (IO) and the ipsilateral superior oblique. Electrodes over the inferior oblique (circles) record the oVEMP. Afferents from the saccular and

utricle maculae project to the vestibular nuclei, but the exact termination of these afferents is not presently known, so this figure represents the present uncertainty about the exact neural connections of these afferents within the vestibular nuclei as an open box. The otolithic projections to other eye muscles are not shown. The projections of the saccular macula in the inferior vestibular nerve, synapsing on an inhibitory neuron in the vestibular nucleus (black hexagon), projecting to spinal motoneurons controlling the SCM, are established by Uchino et al. (2005). Electrodes over contracted SCM muscles record the cVEMP.

The crucial point is that the neural studies show that the same stimuli (ACS and BCV) activate both the utricular and saccular afferents, so it is not possible to deduce the utricular or saccular function according to the stimulus (ACS or BCV) presented; *receptors in both maculae respond to both stimuli*. By assessing the responses due to the differential neural projections, it is possible to come up with specific tests of the utricular and saccular function. The published evidence supports this hypothesis.

Practical Application

To apply these neural data to the measurement of patient responses in the clinic, we use a vibrator – a Bruel and Kjaer 4810 minishaker – to deliver 7 ms bursts typically of 500 Hz BCV at Fz. Usually 50 presentations of these stimuli at a rate of 3/s at moderate intensities (about the strength of a body massager) are used which is not stressful or uncomfortable. High-intensity 120 dB SPL 500 Hz air-conducted sound also evokes oVEMPs and cVEMPs. For the oVEMP the subject must be looking up in order to maximize the oVEMP n10. The small excitatory potential, the n10 component of the oVEMP, occurs at a latency of around 10 ms, and in response to stimulation at Fz, the n10 beneath both eyes in healthy subjects is about equal. In contrast, in patients after complete unilateral vestibular nerve loss, the oVEMP n10 is greatly reduced or absent beneath the eye opposite to the affected ear – the oVEMP is a crossed utriculo-ocular response. In these patients there is a large asymmetry of the oVEMP n10 response (Iwasaki et al. 2008a; Manzari et al. 2010a).

These same unilateral patients show a reduced or absent cVEMP p13 on the side of the affected ear – the cVEMP is an uncrossed sacculo-colic response. Since the oVEMP n10 is predominantly of utricular origin, then patients with loss of *just* the superior division of the vestibular nerve show reduced or absent oVEMP n10 beneath the contralateral eye because all the utricular afferents course in the superior vestibular nerve and eventually project to the contralateral IO. In these patients the cVEMPs are unaffected (Manzari et al. 2010b; Iwasaki et al. 2009). Conversely patients with loss of *just* the inferior division of the vestibular nerve show reduced or absent cVEMP p13–n23 on the ipsilesional side, because the saccular afferents course in the inferior division of the vestibular nerve and project to ipsilateral SCM, but the oVEMP n10 is unaffected (Manzari et al. 2012; Fig. 2).

Clinical Significance of These Results

This basic scientific work has very clear benefits for clinical testing of human otolithic function, since it allows most clinics to assess the functional status of the otoliths very simply by using an averager and audiometer (which most audiological clinics have) just by changing the location of the recording electrodes. The clinician can use air-conducted sound via the audiometer headphones to measure mainly the utricular and saccular function (Curthoys 2012).

Summary

Anatomically identified otolithic afferents are activated by BCV (and many also by ACS) at low

Vestibular Otoliths, Response to Vibration and Sound, Fig. 2 (continued) Unilateral vestibular loss results in reduced or absent contralateral oVEMP n10 and a reduced or absent ipsilateral cVEMP p13–n23. (c) Examples of averaged EMG responses: oVEMP and cVEMP responses for a healthy subject (*column 1*), a patient with right unilateral vestibular loss (*column 2*), and a patient with left superior vestibular neuritis (*column 3*). The yellow and blue vertical bands mark the time of healthy oVEMP n10 and cVEMP p13 responses, respectively. The healthy subject displays n10 responses of similar magnitude and likewise p13–n23 responses of similar amplitude. The patient with right unilateral vestibular loss has normal n10 responses beneath the right (ipsilesional) eye and in

the left (contralesional) SCM and absent responses beneath the left (contralesional) eye and in the right (ipsilesional) SCM. Because oVEMPs are a crossed response (Iwasaki et al. 2007) and cVEMPs are an uncrossed response, these results are consistent with complete loss of otolithic function on the right side. The patient with left superior vestibular neuritis, on the other hand, shows absent oVEMPs beneath the right (contralesional) eye, a normal oVEMP response beneath the left (ipsilesional) eye, and normal cVEMPs on both sides. This is consistent with oVEMPs being a predominantly utricular response and cVEMPs being a predominantly saccular response (Reproduced with permission from Curthoys et al. (2011))

threshold and high sensitivity. Anatomical evidence shows that these sensitive afferents originate from both the utricular and saccular maculae.

In conclusion, otolith irregular afferents are activated at low threshold and high sensitivity by 500 Hz BCV and ACS. These afferents come from both the utricular and saccular maculae. The same BCV elicits vestibular, not auditory, eye movements in animals and humans. It has been shown conclusively that single afferents from the utricular macula do respond to both ACS and BCV, and that result justifies the use of ACS to test oVEMPs in the clinic as an indicator of mainly the utricular function (Curthoys 2012). This result also firmly establishes that what is important in clinical testing of otolith function is not the method of stimulation (ACS vs BCV) but rather the response that is measured.

Cross-References

- ▶ [Auditory-Nerve Response, Afferent Signals](#)
- ▶ [Auditory Sensing Systems: Overview](#)
- ▶ [Peripheral Nerve Interface Applications, EMG/ENG](#)
- ▶ [Peripheral Vestibular Signal Processing](#)
- ▶ [Vestibular System: Overview](#)
- ▶ [Vestibular, Canal Testing: the Head Impulse Test](#)

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Vestibular Prosthesis, Interface

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Definition

A vestibular prosthesis is an implantable neural stimulator system designed to restore sensation of head movement for individuals who have lost the mechanotransduction function of hair cells in both inner ear labyrinths. Similar to cochlear implants (which sense sound using a microphone, decompose that sound into independent components, and then electrically stimulate the cochlear nerve), a vestibular prosthesis senses head motion using inertial sensors and conveys head angular velocity information to the corresponding branches of the vestibular nerve.

Detailed Description

Normal Vestibular Function

In normal individuals, sensation of head rotation, orientation, and translation originates in the semi-circular canals (SCCs) and otoconial end organs in each labyrinth. The two labyrinths modulate activity on afferent fibers within each of the five vestibular nerve branches so as to provide the

central nervous system with information regarding the head's 3-dimensional (3D) rotational velocity, translational acceleration, and tilt with respect to gravity. Vestibular sensory input drives compensatory reflexes that stabilize gaze and posture, maximizing clarity of vision during head movement, minimizing the risk of falling, and helping to maintain normal perception of body position and trajectory (Carey and Della Santina 2005).

Input of Prosthesis: Interface Between Head Movement and Prosthesis Input

Inputs to a vestibular prosthesis are provided by micromachined sensors, which can be either single-axis (Gong and Merfeld 2000, 2002) or three-axis gyroscopes and linear accelerometers (Della Santina et al. 2007; Chiang et al. 2011). Gyroscope signals are filtered digitally and/or via analog circuitry to attenuate noise and frequency components outside the range of normal SCC performance. Additional filtering may be performed in an attempt to better fit the dynamics and latency of electrically evoked responses to natural VOR responses. Linear accelerometer signals can be used to report the orientation of a stationary device with respect to the skull (which must be measured to later map sensor signals to output channels of the prosthesis) (Chiang et al. 2011).

Prosthesis Processing: Interface Between Input Signal and Output Signals Through Microcontroller/Processor

The filtered signals from each of the three mutually orthogonal gyroscope sensors are sampled by a microcontroller and assembled into a vector representing 3D head angular velocity in a multi-channel vestibular prosthesis (Della Santina et al. 2007; Chiang et al. 2011). The microcontroller then maps head rotation signals to changes in the pulse frequency and amplitude of current pulse trains delivered to the vestibular nerve's branches via an array of electrodes in the implanted labyrinth (Gong and Merfeld 2000, 2002; Della Santina et al. 2007; Chiang et al. 2011).

To prevent electrode corrosion and evolution of gas or other toxic substances at each electrode's

metal-saline interface due to faradaic (oxidation-reduction) reactions (Robblee and Rose 1990; Merrill et al. 2005), vestibular prosthetic stimulation pulses are typically biphasic and charge-balanced between phases (Bonham and Litvak 2008). Some implementations also allow pulses to be asymmetric, typically using a “cathodic pseudomonophasic” approach in which a relatively brief and high-amplitude cathodic phase is charge-balanced by a relatively long and low-current anodic phase (Hayden et al. 2011; Macherey et al. 2011).

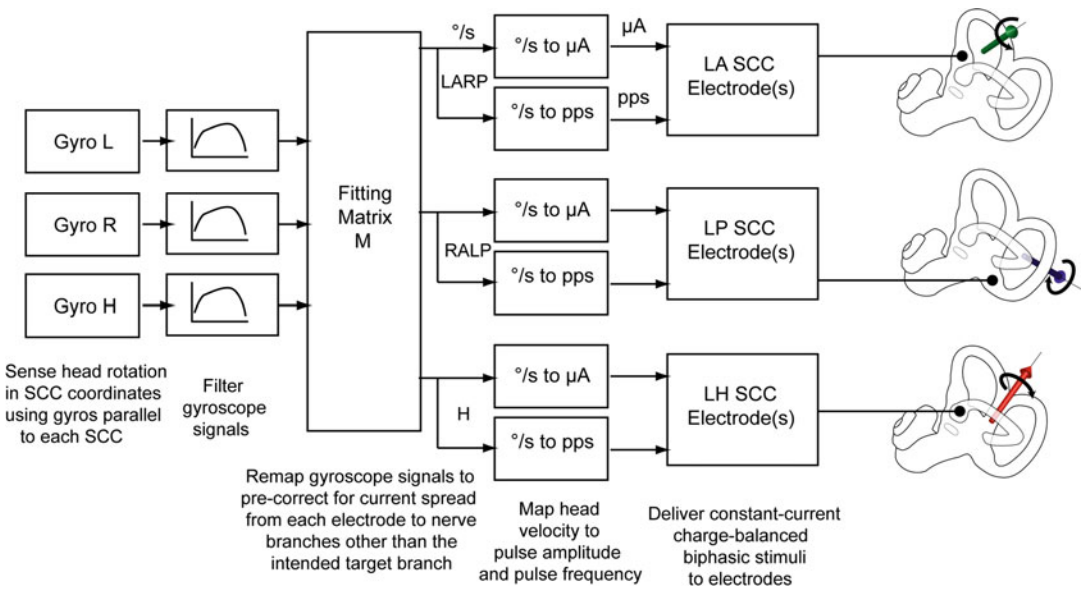
A multichannel vestibular prosthesis may contain multiple, independent current sources that allow the microcontroller to distribute stimulus current across multiple electrodes simultaneously in tripolar and quadropolar arrangements intended to steer current toward target axons and away from nontarget tissue (Fridman and Della Santina 2012). Improved spatial resolution in cochlear

implants has been achieved using similar current steering approaches (Bonham and Litvak 2008).

Prosthesis Output: Interface Between Electrode Stimulation and Afferent Vestibular Nerve

The efficacy of vestibular prosthesis stimulation largely depends on accuracy of targeting each SCC nerve branch, which requires precise surgical placement of electrodes in the vestibular labyrinth to maximize electrode-nerve coupling with a target ampullary nerve branch while minimizing misalignment of the head motion percept (and resulting reflexive eye and postural movements) due to spurious stimulation of nontarget branches.

Selectivity of stimulation depends on the stimulation paradigm employed. Monopolar stimulation via a single active electrode in each ampulla (with current returned via a distant electrode



Vestibular Prosthesis, Interface, Fig. 1 Common signal processing elements used in vestibular prosthesis design (Fridman and Della Santina 2012). Gyroscopes sense head rotation about each axis corresponding to the SCC orientations. These angular velocity signals are filtered to more closely emulate the transfer function of the SCC hydrodynamics. Linear coordinate transformation uses matrix M to pre-correct for misalignment between the axis and velocity of the actual head rotation and those of the head movement sensation evoked by electrode

stimulation. The corrected velocity signals are then mapped to amplitude and pulse rate specifications for each electrode implanted in the left anterior and right posterior (*LARP*), right posterior and left anterior (*RALP*), and horizontal (*H*) SCCs. These pulse rate and pulse-amplitude specifications are combined with constant stimulus parameters (stimulation and reference electrode selection and pulse width of current pulses) by the pulse-generation algorithm and circuitry to deliver biphasic charge-balanced stimuli to the electrodes

outside the labyrinth) achieves strong coupling with the target nerve branch but also significant current spread to nontarget branches. Bipolar electrode pairs positioned transverse to the axis of the ampulla and perpendicular to the distal trajectory of the target nerve elicit more focal stimulation and greater selectivity, but they must be positioned precisely to achieve these benefits (Hayden et al. 2011). Electrode array designs that incorporate a trio of electrodes within each of three silicone leads are designed to self-orient and locate electrodes near target tissue when surgically inserted into the ampullae (Chiang et al. 2011). By positioning multiple electrode contacts near the sensory neuroepithelium of each SCC, these electrode designs increase the probability that at least one electrode will be adjacent to the target tissue, allow the use of bipolar and tripolar stimulation paradigms (Chiang et al. 2011), and facilitate estimation of how stimulation coupling and misalignment depend on electrode location (Fig. 1).

Cross-References

- [Brain-Machine Interface: Overview](#)
- [Vestibular System: Overview](#)

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Vestibular System: Introduction

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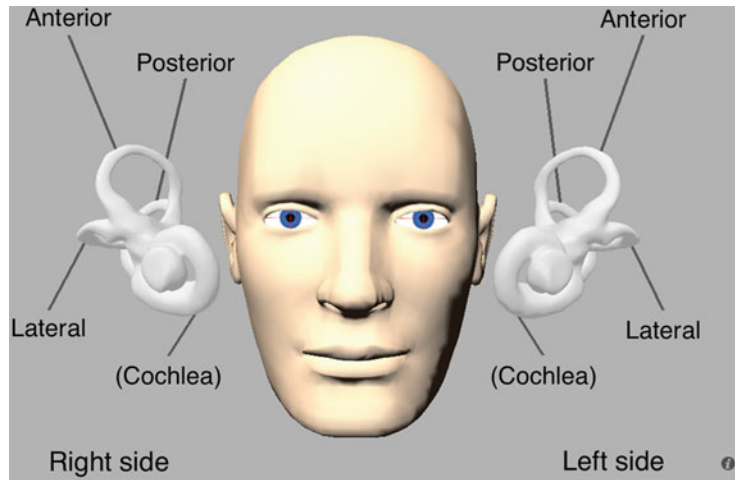
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Definition

The peripheral vestibular system comprises ten three-dimensional inertial motion sensors, five in each inner ear. They are mirrored pairs; the four otoliths (utricle and saccule) sense the linear acceleration and position of the head in space, and the six semicircular canals (Fig. 1) sense angular acceleration of the head. It is an ancient system even present in some invertebrates (Carey and Della Santina 2010; Baloh and Kerber 2011; Goldberg et al. 2012).

Vestibular System: Introduction,

Fig. 1 Labyrinth. Showing the orientation of the semicircular canals in the human



Detailed Description

When hair cell processes on the maculae of the otoliths in each inner ear are deflected by the inertia of the otoconia, or those on the cristae of the canals by inertia of the endolymphatic fluid in the canal duct, action potentials are generated in the vestibular nerves, proportional to head position and motion (Figs. 2 and 3).

The vestibular nerves connect with neurons in the vestibular nuclei which then connect to other brainstem nuclei, the cerebellum, the cortex, and the spinal cord (Fig. 4).

What benefit is vestibular information? The best answer to this question is the human who has lost all vestibular function but is otherwise intact. In such cases it is only the loss of vestibular information to the brainstem and the spinal cord that seems to cause problems: jiggling vision while moving (oscillopsia) due to loss of vestibulo-ocular reflexes (Fig. 5), and postural imbalance especially on uneven surfaces and in the dark due to loss of vestibulospinal reflexes.

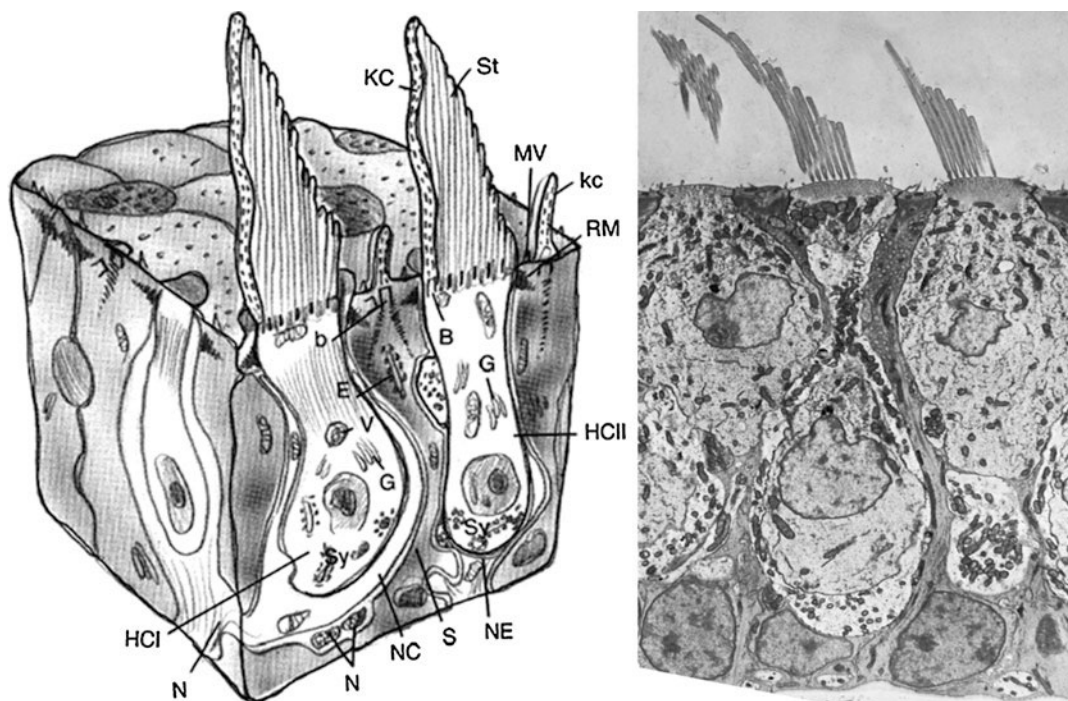
Since any angular motion of the head is immediately counteracted by an (almost) irresistible, exactly equal, and opposite reflex motion of the eyes, measuring these vestibulo-ocular reflexes is an accurate and robust way to measure canal function. The eyes are in a sense the speedometers of the ears – they will rotate at exactly the same speed about exactly the same axis as does the head. Without (angular) vestibulo-ocular reflexes motion

of the head is no longer opposed by motion of the eyes so that the line of sight is no longer fixed. Retinal images now move with head motion and the result is oscillopsia. The otoliths, especially the utricle, also produce vestibulo-ocular reflexes and these can be measured by recording short latency electromyography (EMG) activity in extraocular muscles in response to sound or vibration (Rosengren and Kingma 2013; see also Fig. 6).

Testable human vestibulospinal reflexes mainly originate from the saccule and loss of these causes imbalance especially when vision and proprioception are both impaired. These can also be tested by measuring short latency EMG activation in response to sound and vibration, especially in certain neck muscles.

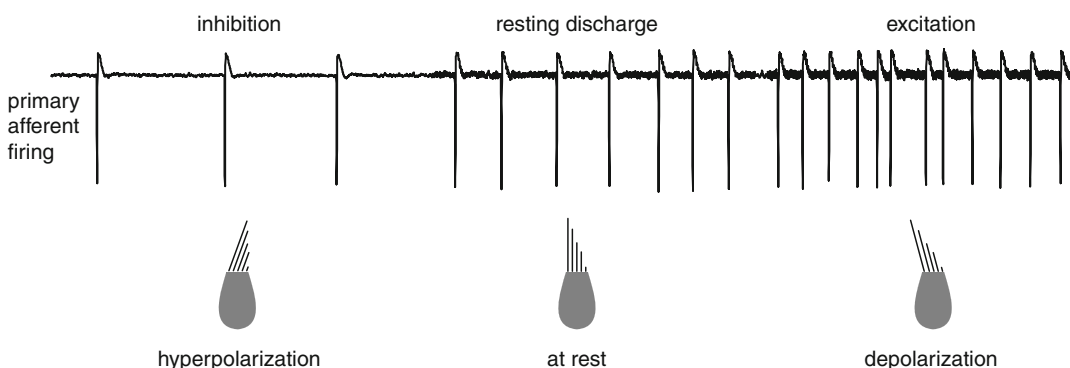
Vestibular information to the cerebellum is widespread and complex, but from a functional basis only its interaction with the angular vestibulo-ocular reflex is testable. There can be an additive interaction when a subject views an earth fixed target (the visual vestibulo-ocular reflex) or a subtractive interaction when the subject views an head-fixed target (visual suppression of the vestibulo-ocular reflex) (Fig. 7).

Vestibular information to the cerebral cortex can be tested but reliably only in rigorous, arduous psychophysical experiments in normal subjects. It is, however, important to the patient with a common clinical problem: acute unilateral loss of vestibular function (“doctor, I feel so dizzy”). And so is vestibular information to brainstem



Vestibular System: Introduction, Fig. 2 (a) Vestibular sensory epithelium and its innervation. *HCI* type I hair cell, *HCII* type II hair cell, *St* stereocilia, *KC* kinocilia [*kc*, modified kinocilia and roots (*b*) of supporting cells, (*S*)]; *N* nerve fiber, *NC* nerve calyx, *NE* nerve endings, *Sy* synaptic structures, *G* Golgi membranes, *RM* multi-vesicular reticular membrane, *E* endoplasmic reticulum,

MV microvilli, *V* vesicle, *B* basal body (Modified from Spoendlin HH. The ultrastructure of the vestibular sense organ. In: Wolfson RJ, ed. The vestibular system and its diseases. Philadelphia: University of Pennsylvania Press, 1966:39, with permission). (b) Electronmicrograph of vestibular hair cell (Courtesy of Dr Anna Lysakowski)

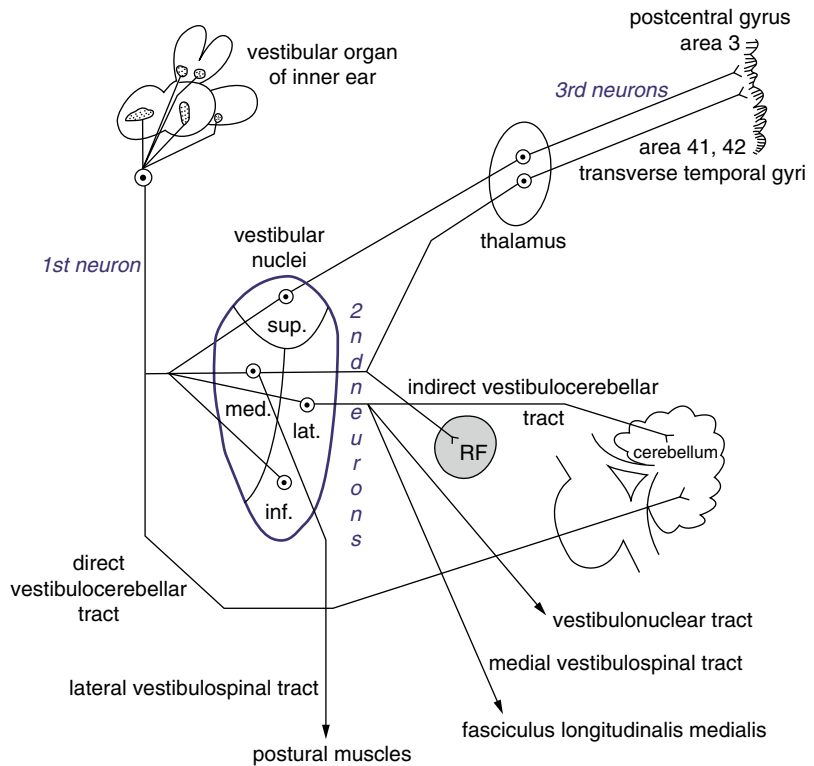


Vestibular System: Introduction, Fig. 3 The bidirectional responses of a single vestibular hair cell. There is a level of resting activity. Displacement of the hair cell processes (stereocilia) in one direction (that is towards the largest hair cell process – the kinocilium) increases the firing rate of the vestibular neuron synapsing with the

hair cell, whereas displacement in the opposite direction reduces the firing rate. Whereas it is nearly impossible to saturate the firing rate in the excitatory direction it is easy to do in the inhibitory direction. This inherent asymmetry is the physiological basis of the Head Impulse Test (see below)

Vestibular System: Introduction,

Fig. 4 Schematic representation of the vestibular pathways from primary afferent neurons in Scarpa's ganglion to the ipsilateral vestibular nuclei and from there to the cerebellum, spinal cord, reticular formation (RF) and cerebral cortex. The contralateral projections are not shown. Note there is a direct project of primary afferents to the cerebellum (Figure by David Kachlik; with permission from http://anatomie.lf3.cuni.cz/anglickaverze/cns_drahavestibulami_eng.htm)

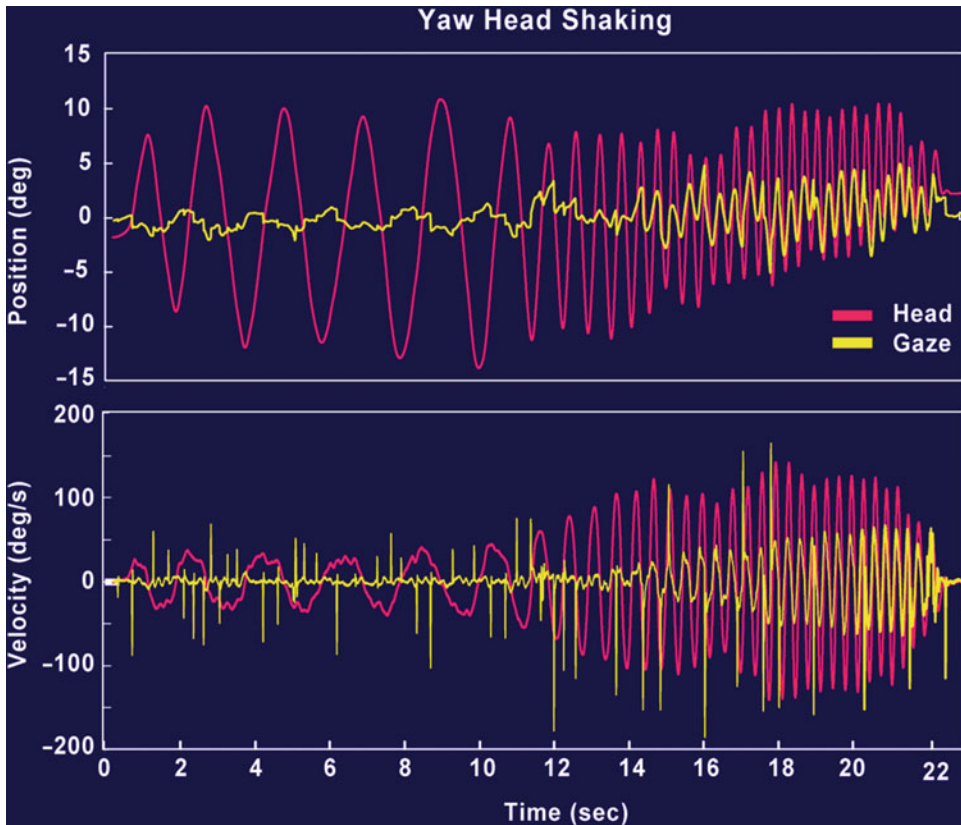


autonomic nuclei, especially area postrema (“doctor, I feel so sick”).

What then happens if the vestibular system on one side (one labyrinth) is destroyed by disease or design? The functional deficit produced by a unilateral lesion of the vestibular system is determined by whether the lesion developed suddenly or slowly and, if suddenly, how long ago. Acute destruction or deafferentation of one entire intact labyrinth, in animal or human, by disease or by design, invariably produces an acute, temporary, stereotyped clinical syndrome of profound motor and sensory abnormalities. There is, due to otolithic deafferentation, a complete or, more often, partial ocular tilt reaction that is always ipsiversive (toward the side of the lesion) (Fig. 8). The complete ocular tilt reaction consists of ipsilesional head tilt, ipsilesional conjugate binocular eye torsion, and an ipsilesional hypotropia due to skew deviation (vertical dysconjugacy of the visual axes causing double vision). Owing to semicircular canal deafferentation, there is also a spontaneous horizontal-torsional nystagmus (a continuous

rhythmic saw-tooth wave-form jerking of the eyes, with the slow phases toward the side of the lesion), as well as vomiting. Humans, and perhaps animals, experience vertigo and nausea. These symptoms and signs make up the syndrome of acute unilateral vestibular deafferentation (uVD). Although normally both humans and animals recover, more or less completely, from the acute uVD syndrome by the process of vestibular compensation, the vestibulo-ocular reflex is permanently damaged. From studies of the acute uVD syndrome and of the processes of vestibular compensation in experimental animals, one could infer that peripheral vestibular disorders produce vertigo when there is asymmetric neural activity between corresponding parts of the left and right vestibular nuclei, and that recovery from the acute uVD syndrome is due to rebalancing of the neural activity in the vestibular nuclei on the two sides. One could also infer that a person not experiencing vertigo should, at that time, have symmetrical vestibular nucleus activity.

Once vestibular compensation is complete, so that there is a chronic stable uVD, the patient will



Vestibular System: Introduction, Fig. 5 Measurement of horizontal eye movement in response to sinusoidal horizontal head rotation in a patient with total bilateral vestibular loss from gentamicin toxicity staring at an earth-fixed target. During head shaking up to about 1.5 Hz and 50 deg/s angular head velocity, gaze velocity (i. e., eye-in-space) velocity is close to zero, as it would be in a normal subject, so that the patient would perceive no target movement. (There are some tiny saccadic eye

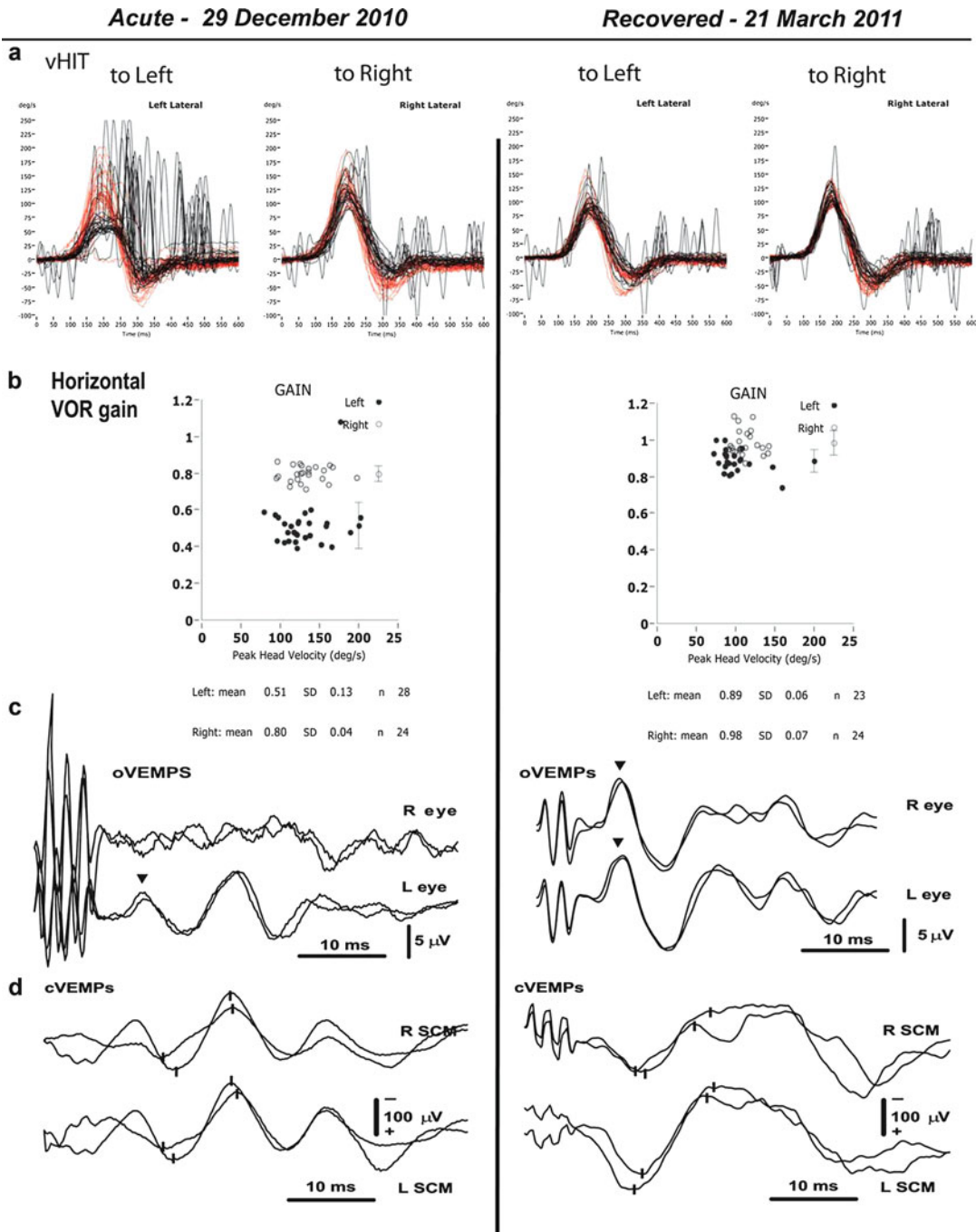
movements – spikes on the velocity recording; these are irrelevant). As the frequency of head shaking increases, gaze velocity increases so that at 5 Hz and 100 deg/s peak angular head velocity, gaze velocity is about 50 deg/s. The basic explanation is simple: at low frequencies and angular head velocities the visual reflexes (pursuit and optokinetic) will generate accurate compensatory eye movements; at high frequencies and velocities only the vestibulo-ocular reflex is able to do so

no longer experience vertigo, and most patients will experience no symptoms at all. In other words, most patients cannot tell if they have unilateral vestibular loss. A minority of patients, about 20 %, with a chronic stable uVD will experience postural imbalance and oscillopsia, symptoms experienced by all patients with bilateral vestibular deafferentation and described in more detail below.

In contrast, chronic progressive uVD, as would occur with a slowly growing tumor such as a vestibular schwannoma, does not produce the acute uVD syndrome of vertigo, nausea, vomiting, nystagmus, and ocular tilt reaction.

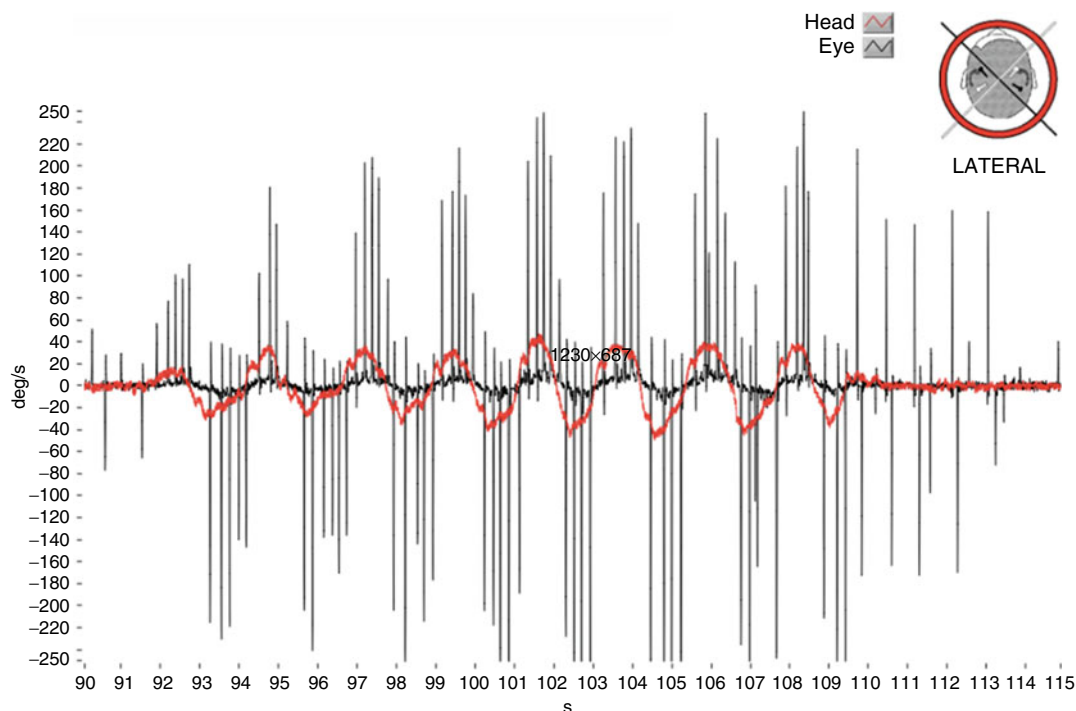
This is presumably because there is never a prolonged period of asymmetrical neural activity in the vestibular nuclei. In fact, if a patient presents with signs of uVD and categorically denies ever having experienced an attack of acute spontaneous vertigo, one can be almost sure that the uVD has not been acute, and one should therefore look for a potential progressive cause of uVD.

What happens if now the other labyrinth is destroyed? After compensation for uVD has occurred, acute deafferentation of the other labyrinth produces a second acute uVD syndrome. If, however, the second uVD is carried out soon after the first, before compensation has occurred, a



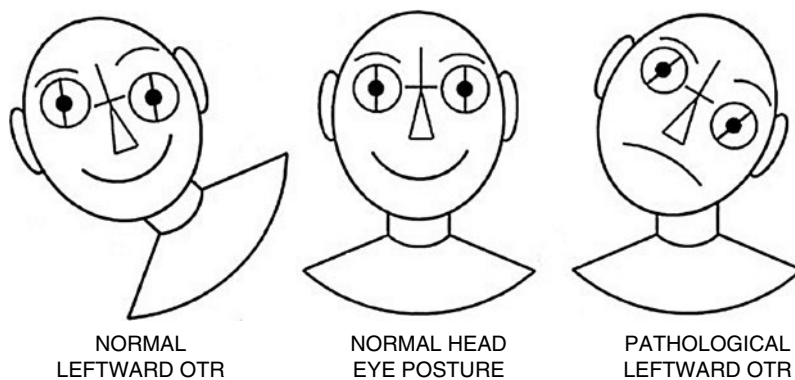
Vestibular System: Introduction, Fig. 6 Absent ocular vestibular evoked myogenic potentials (*oVEMPs*) during the acute phase of left superior vestibular neuritis. The n10 potential of the *oVEMP* (c) is missing from the right eye recording (originates in the left utricle) whereas the left

cervical VEMP (d; originates in the the left saccule) is present. Video Head Impulse Test (a, b) shows the expected impairment of left lateral semicircular canal function (see also Fig. 11) (From Manzari et al. 2011, with permission)



Vestibular System: Introduction, Fig. 7 Absent visually enhanced horizontal vestibulo-ocular reflex in a patient with combined loss of semicircular canal function and of cerebellar function impairing both the vestibulo-

ocular reflex and smooth pursuit. Horizontal head velocity is in *red*, inverted horizontal eye velocity is in *black*. Note the salvos of catch-up saccades (grey trace)



Vestibular System: Introduction, Fig. 8 Head-eye posture in a normal, gravitationally vertical subject (*center*), in a normal subject tilted to the right (*left*), and in a patient with a leftward ocular tilt reaction (*right*). The *left panel* shows the normal compensatory leftward ocular tilt reaction in response to rightward roll-tilt stimulation. The *right panel* shows a pathologic tonic leftward ocular tilt reaction which could be due to a lesion of the left

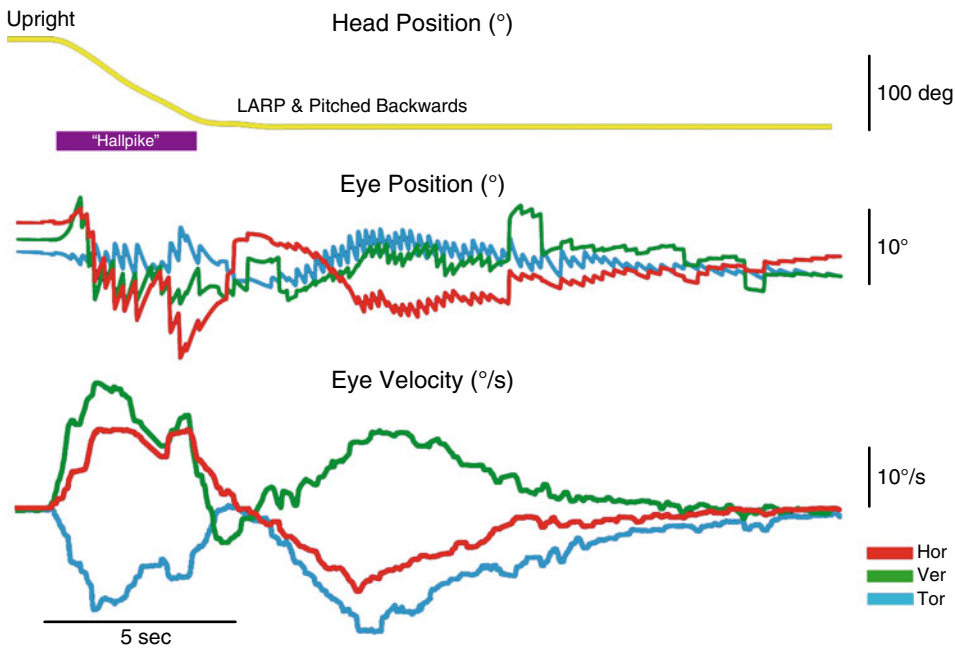
labyrinth, left vestibular nerve, left vestibular nucleus, or right meso-diencephalon. The normal subject's response to rightward roll-tilt stimulation is leftward head tilt, leftward eye torsion (i.e., counter-rolling), and a left skew deviation (left hypotropia). Note that alone and even together the head tilt and eye torsion are normally incompletely compensatory (From Halmagyi et al. 1990)

second uVD syndrome will not develop. Indeed, if the second uVD is carried out while the symptoms of the first are at their peak, the uVD symptoms will terminate – the so-called Bechterew effect – If the two labyrinths are deafferented simultaneously, either suddenly or slowly, the patient will not experience vertigo, since there is no left-right asymmetry in vestibular nucleus activity. The long-term effects of bilateral vestibular deafferentation are the same irrespective of whether uVD occurred simultaneously or sequentially (Curthoys and Halmagyi 2014). The patient will be off balance and have oscillopsia (but will never again be motion sick).

What then happens if one labyrinth is stimulated? Each semicircular canal (SCC) has its signature nystagmus, so that it is possible to deduce from an analysis of the nystagmus rotation axis the exact SCC which gives rise to it, for example, in patients with benign positional vertigo, paroxysmal nystagmus due to stimulation of ampullary

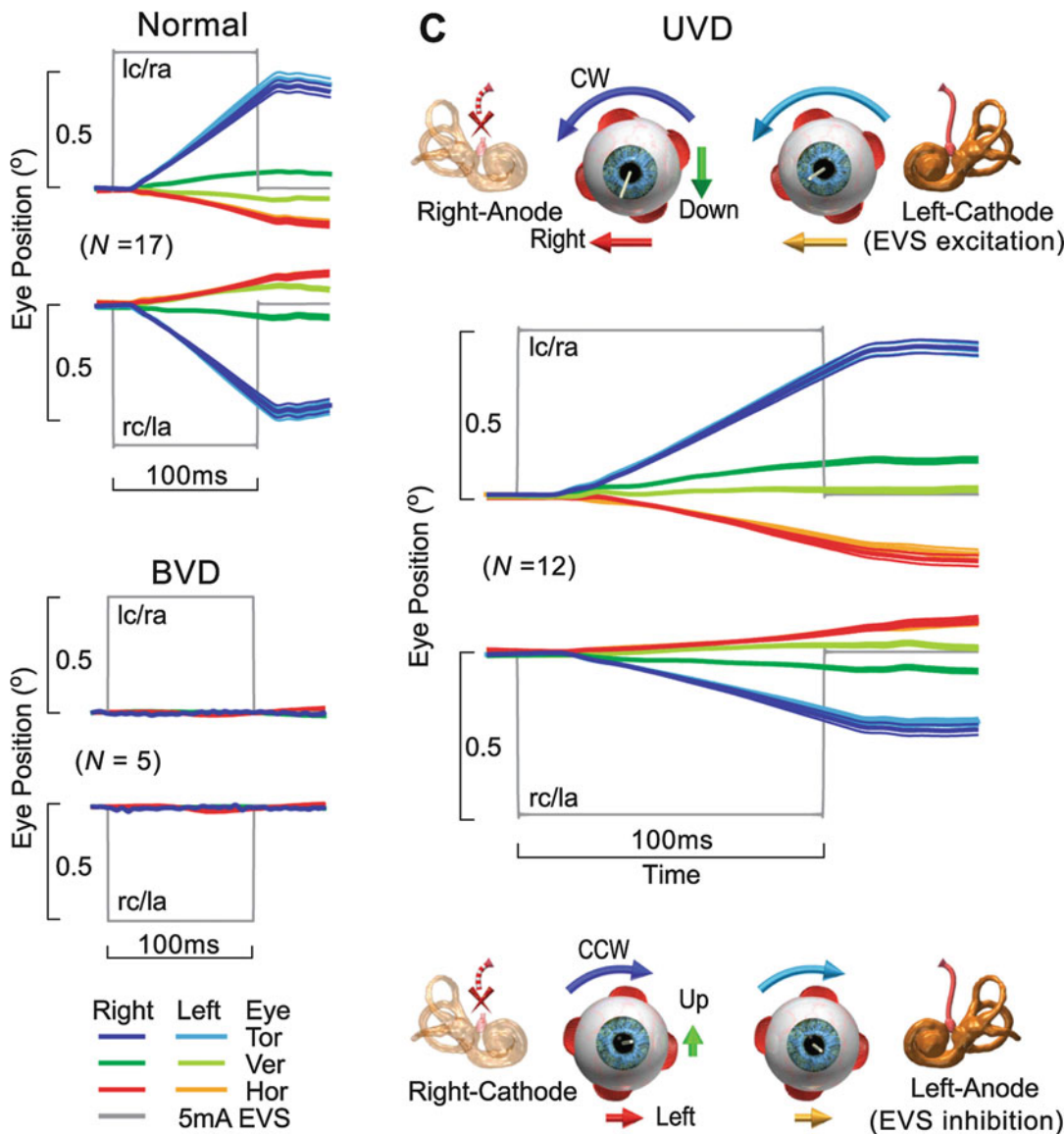
hair cells by otoconia in one SCC (Fig. 9). If the nystagmus is predominantly horizontal, then the otoconia are in the lateral SCC. If the nystagmus is upbeat and torsional, then the otoconia are in the posterior SCC. The rotation axis of the nystagmus is orthogonal to the plane of the affected SCC in these patients. In patients with sound- and pressure-induced vestibular symptoms due to superior (anterior) semicircular canal dehiscence, the induced nystagmus has downbeat and torsional quick phases, so that the rotation axis of the nystagmus is orthogonal to the plane of the superior (anterior) SCC.

The standard caloric test is also based on labyrinthine stimulation. Warm (44 °C) or cool (30 °C) water infused into the patient's external auditory canal creates a thermal gradient across the labyrinth and generates a convective movement of lateral canal endolymph, which then deflects the cupula and either increases or decreases the firing rate of SCC primary afferent



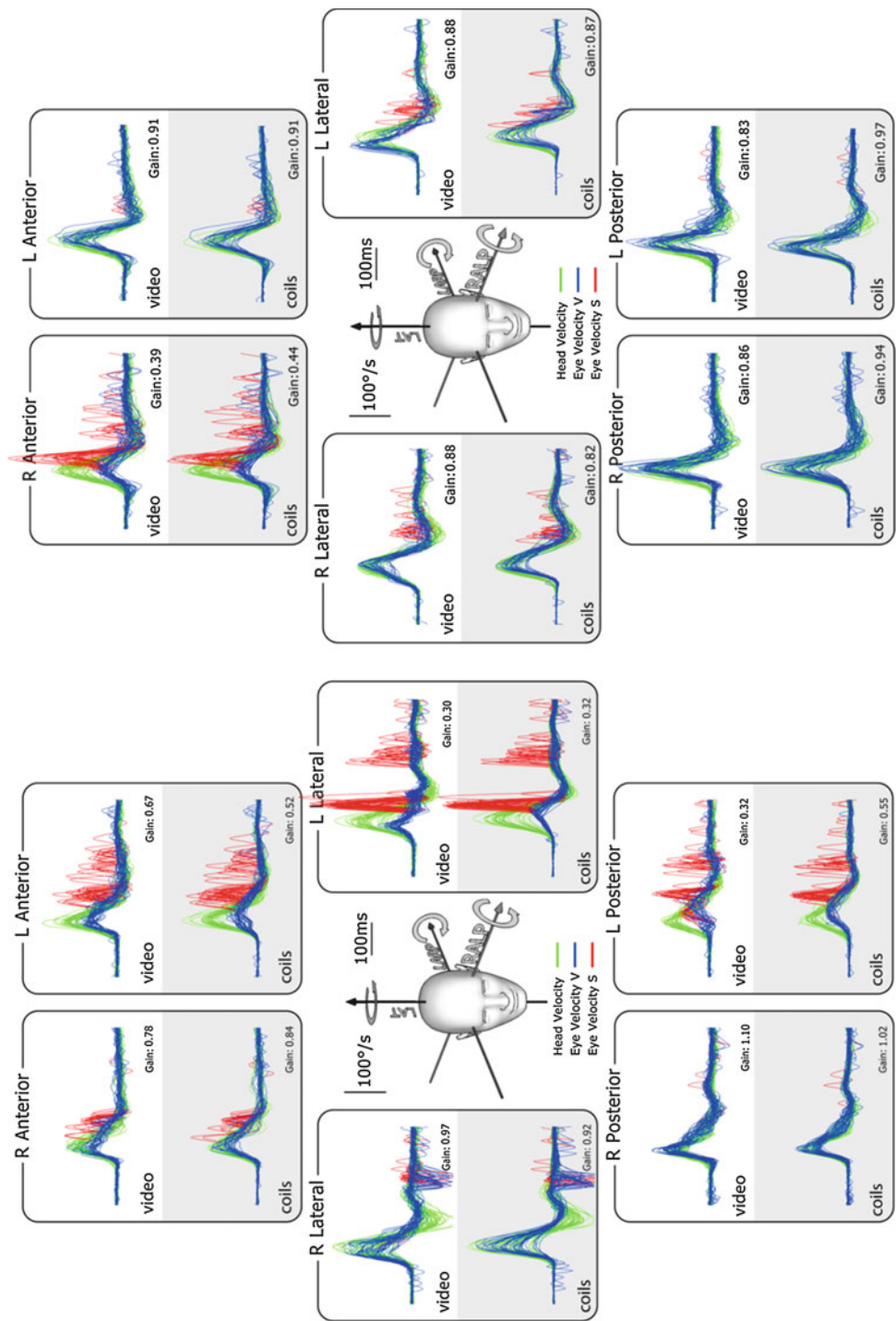
Vestibular System: Introduction, Fig. 9 The nystagmus of benign positional vertigo (BPV). Horizontal, vertical and torsional position and velocity of the left eye during the provocative Hallpike test in a patient with canalithiasis of the right posterior semicircular canal producing benign paroxysmal positioning vertigo and as shown here nystagmus. As the patient is pitched backwards with the right ear

down there is a normal vestibulo-ocular reflex. Almost as soon as the patient reaches this position there is a paroxysm of nystagmus lasting about 10 s with quick phases beating clockwise (from the patient's point of view) upward and to the left – slow phases in the opposite direction (For more details see Aw et al. (2005))



Vestibular System: Introduction, Fig. 10 Electrically evoked VORs to human bipolar electrical vestibular stimulation (EVS) in healthy subjects, bilateral and unilateral vestibular deafferented patients. (A) Normal eVOR from healthy subjects (N = 17) (group means $\pm$ 6 SEM) comprised conjugate torsional and horizontal eye rotations, binocularly equal in amplitude, rotated away from cathode towards anode, and vertical divergence with the intorting eye upwards (cathode side) and extorting eye downwards (anode side). (B) EVOR was absent from patients with bilateral vestibular deafferentation (BVD) (N = 5) with torsional, vertical and horizontal eVOR positions. (C)

Bidirectional eVOR from grouped as right UVD patients with left functioning ear (N = 12). The excitatory eVOR to left-cathode/right-anode (lc/ra) cathodal EVS comprised conjugate torsional and horizontal eye rotations away from cathode and a vertical divergence with the eye on the anodal side moving downwards. The inhibitory eVOR to right-cathode/left-anode (rc/la) anodal EVS was in the opposite direction and at about half the amplitude of the excitatory eVOR with the eye on the anodal side moving upwards. (The schemes illustrate EVS polarities and eye rotation directions) (From Aw et al. 2013)



Vestibular System: Introduction, Fig. 11 (continued)

neurons. The caloric test is mainly a test of lateral SCC function, because the lateral SCC is the closest to the thermal stimulus and, with the patient supine and the head elevated 30° from horizontal, it is earth vertical resulting in a large convective effect.

It is also possible to stimulate the otolithic organs on one side. In the cat, electrical stimulation of the utricular nerve results in a contraversive ocular tilt reaction comprising conjugate contraversive eye torsion, contraversive head tilt, and skew deviation with contralateral hypotropia. In humans, galvanic mastoid stimulation produces a similar response (Fig. 10). Loud clicks will activate the saccule and the utricle and produce an inhibitory potential, the vestibular-evoked myogenic potential (VEMP), in the tonically contracting ipsilateral sternomastoid neck muscles and contralateral inferior oblique extraocular muscles as well as in jaw muscles.

What then is the best way to test semicircular canal function in humans? These days the answer would have to be impulsive testing in which an examiner holds and turns the subject's head rapidly in one direction. The rotation need not be large. It should be a 20–30 deg peak amplitude, 150–300 deg/s peak velocity, and 2000–5000 deg/s/s peak acceleration, unpredictable, head rotation approximately in the plane of a SCC pair. The physiological principles behind impulsive testing are understood. Due to the bidirectional, morphological, and physiological polarization of the hair cell bundles on the cristae, the SCCs operate as push-pull pairs. During any head rotation, displacement of the stereocilia toward the kinocilium depolarizes the hair cell and generates excitation, while displacement of stereocilia away from the kinocilium hyperpolarizes the hair cell and generates inhibition. In response to a head rotation such

as a head impulse, one SCC of the push-pull pair is excited while the other is inhibited, generating the total angular vestibulo-ocular reflex (VOR) from direct excitation and indirect disinhibition. In the lateral (horizontal) SCC, ampullopetal endolymph flow causes excitation while ampullofugal flow causes inhibition whereas in the vertical SCCs ampullofugal flow causes excitation and ampullopetal flow causes inhibition. It is this directional polarization which produces the on-off directional asymmetry of the VOR generated by a single SCC summarized in what is called Ewald's 2nd Law and is a means of identifying impairment of individual SCC function.

The smooth eye movement response to a head impulse is too fast to allow any contribution to the compensatory eye movement from smooth pursuit or cervico-ocular reflexes: it is generated exclusively by the VOR. During the head impulse in normal subjects with close to unity VOR gain (eye velocity/head velocity magnitudes), both eyes rotate instantly and smoothly in the compensatory direction and thus keep fixing on target whereas a patient with reduced VOR gain cannot keep looking at the fixation target and has to make a usually observable catch-up saccade in order to refixate the target. Scaled head impulses can be produced manually with a visual head velocity feedback signal for the examiner. Individual lateral SCCs can be tested with head impulses about the yaw axis to excite the ipsilateral and inhibit the contralateral lateral canal. Individual vertical SCCs can be tested along their approximate right-anterior and left-posterior (RALP) and left-anterior and right-posterior (LARP) planes (Fig. 11).

The search coil technique has been the gold-standard method to measure head and eye position in impulsive VOR testing. Head and eye positions

Vestibular System: Introduction,
Fig. 11 Simultaneous video and scleral search coil Head Impulse Test in a patient with loss of function of all three semicircular canals on the left following intratympanic gentamicin treatment (figure on *left*) and in a patient with right superior semicircular canal dehiscence and selective loss of right anterior (i.e., superior) canal function (figure on *right*). Normally smooth eye velocity (here

inverted and shown in *green*) matches head velocity (*blue*). If there is a deficit in the vestibulo-ocular reflex from any semicircular canal then smooth vestibulo-ocular reflex eye velocity will be less than head velocity and will be compensated by catch-up saccades (shown in *red*). The readily available video method gives essentially the same result as the traditional research based search coil method. For more details see MacDougall et al. (2013)

can be recorded in two dimensions with single-search coils or in three dimensions with dual-search coils. Recent work shows that simple-to-use video methods, which for clinical diagnostic purposes produce results equivalent to the search-coil method, have been rapidly incorporated into clinical practice (MacDougall et al. 2013; Curthoys et al. 2014).

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Vestibular, Canal Testing: The Head Impulse Test

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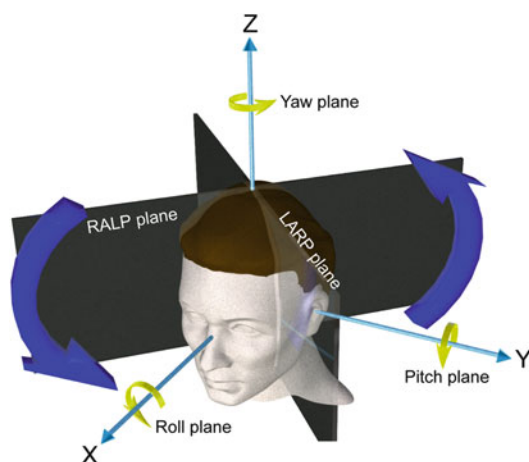
Definition

The head impulse test (HIT) measures individual horizontal (lateral), superior, and posterior semicircular canal function in the high-frequency range (Aw et al. 2001; Halmagyi and Curthoys 1988). The HIT is an unpredictable, passive, low-amplitude (10–20°), high-acceleration (2000–4000°/s²) head rotation approximately along the semicircular canal planes executed manually either by an operator or by an electro-mechanical device. It is performed with subjects seated upright fixating on a straight-ahead target.

How the Head Impulse Test Works

The angular vestibulo-ocular reflex (VOR)'s function is to stabilize vision during head rotations and is mediated by the horizontal, superior, and posterior canals in the labyrinth which transduce rotational head accelerations. During the HIT, one semicircular canal of the push-pull pair in the plane of the head rotation is excited, while the other is inhibited, generating the total angular VOR from direct excitation and indirect disinhibition. Mechano-electrical transduction converts the deflection of the unidirectionally polarized hair cell stereocilia (the canal sensors) during head rotation into electrical receptor potentials to generate neural impulses and vestibular responses.

Yaw (horizontal) plane impulses (rotations about the Z-axis) excite the ipsilateral and inhibit the contralateral horizontal canal (Fig. 1). The vertical canal pairs can also be individually



Vestibular, Canal Testing: The Head Impulse Test, Fig. 1 Head-fixed coordinate system obeying the right-hand rule used to express angular eye position and velocity vectors. Yaw plane impulses are head rotations about the Z-axis used to test the horizontal (lateral) canals. Head impulses, respectively, in LARP (*left-anterior right-posterior*) and RALP (*right-anterior left-posterior*) canal planes test the vertical canal pairs. Other impulses include pitch plane impulses, i.e., head rotations about the Y-axis and roll plane impulses, i.e., head rotations about the X-axis

excited along their approximate right-anterior and left-posterior (RALP) and left-anterior and right-posterior (LARP) planes to activate the respective superior and posterior canal pairs. Pitch plane impulses (rotations about the Y-axis) excite both superior and inhibit both posterior canals during pitch-down and vice versa during pitch-up. Roll plane impulses (rotations about the X-axis) excite the ipsilateral superior and posterior canals and inhibit the contralateral superior and posterior canals. Clinically, the HIT provides fast, reliable, bedside screening of semicircular canal dysfunction by observation of the overt refixation saccade to HIT towards the paretic canal with an angular VOR deficit.

Recording the Head Impulse Test

Search Coil System: The search coil technique is the preferred method of measuring the HIT. Head and eye positions can be recorded in 2D

(horizontal and vertical) with single-search coils or in 3D (horizontal, vertical, and torsional) with dual-search coils using two- or three-field magnetic field systems (CNC Engineering, or Rempel, USA). The subject is seated with the head in the center of the magnetic fields wearing pre-calibrated monocular or binocular search coils on the eyes to measure angular eye positions, while another search coil is attached to a dental impression bite bar (recommended to prevent head coil slippage) to measure angular head positions (Aw et al. 2001; Carey et al. 2002; Cremer et al. 1998).

Video-Oculography System

Video-oculography has been used recently to measure yaw head impulses. It comprises goggles mounted with one to two video cameras worn by the subject (GN Otometrics and EyeSeeCam). Angular (orientation in yaw, pitch, and roll coordinates) and linear (position in X, Y, and Z coordinates) head movements in six degrees-of-freedom are recorded by an inertial measurement unit. Limitations in its use include video-camera detector slip which can be mistaken as a normal VOR response. Measurement of vertical canal function with video is only an approximation when using 2D (pupil-tracking) techniques.

Data Analysis

Head, gaze, and eye positions are analyzed in 3D as rotation vectors, quaternions, or Euler angles. Head and gaze positions are the head and eye orientations in space-fixed coordinates, and eye position is the eye orientation in head-fixed coordinates. Head, gaze, and eye velocities are calculated from their respective positions in 3D. To analyze the angular VOR related to the superior and posterior canal pairs, the coordinate reference frame is rotated by 45° about the yaw (Z)-axis to allow re-expression of these vectors as rotations about the approximate preferred axis of individual vertical canals (Fig. 1). The angular VOR in response to a head impulse is analyzed in the first 80–100 ms period after impulse onset because saccades and blinks are usually absent in this period.

Individual Semicircular Canal Function

Angular VOR Gain

Individual semicircular canal function measured with the HIT is quantified as angular VOR gain at close to peak head velocity using: (a) velocity gain, i.e., eye velocity divided by head velocity; (b) acceleration gain determined as the ratio between the slopes of eye and head velocities for a fixed period; and (c) impulsive canal paresis, which measures the gaze instability in 3D when the head is rotated towards a paretic canal, defined as the ratio of gaze velocity to head velocity in semicircular canal coordinates.

VOR Direction

The direction of the input-output kinematics of the angular VOR can be quantified as a misalignment angle in 3D, the instantaneous angle by which the eye rotation axis deviates from perfect alignment with the head rotation axis.

VOR Latency

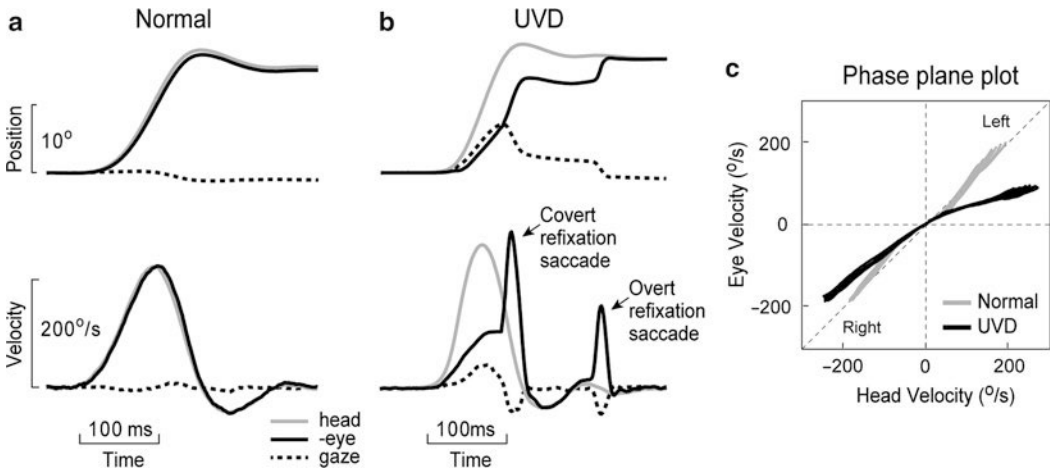
The VOR latency to head impulses has been estimated to be ~6–10 ms and is defined as the minimum time interval between least square fits to the head and eye velocity traces, respectively, while head velocity is in the range between 20°/s and 70°/s.

Refixation Saccade

When the head is rotated rapidly about the plane of a semicircular canal, the angular VOR generates compensatory eye movements approximately equal in amplitude but in the opposite direction in order to stabilize gaze in space. During rapid rotation towards the side of a peripheral vestibular lesion, any angular VOR deficit results in loss of normal compensatory eye movements, and the patient makes a “catch-up” or refixation saccade in order to relocate the target as instructed. Observation of these refixation saccades forms the basis of a clinical judgment of individual semicircular canal function at the bedside. These refixation saccades have been classified as covert or overt saccades. Covert saccades occur during head rotation and are imperceptible to a clinical observer. Overt saccades appear after head rotation and are detectable by the clinician (Fig. 2b).

Head Impulse Response in Normals and After Total Unilateral Loss

Figure 2 shows typical examples of the angular VOR in response to yaw head impulses from a normal subject and a subject with total unilateral loss after unilateral vestibular deafferentation



Vestibular, Canal Testing: The Head Impulse Test, Fig. 2 Typical examples of eye rotation responses to yaw head impulses from (a) a healthy normal subject and (b) a patient after left unilateral vestibular deafferentation (UVD). Eye signals are inverted for comparison with head signals. In the normal subject, the compensatory horizontal

eye velocity to a yaw-left impulse is equal and opposite to head velocity and results in stable gaze. The loss of left horizontal canal function after UVD results in lower compensatory horizontal eye velocity than head velocity, and thus, an eye position error occurs. Both covert and overt refixation saccades (arrows) were used to stabilize the gaze

(UVD). In the normal subject, eye velocity is approximately equal and opposite to head velocity, and normal VOR gain in response to yaw impulses is ~ 0.9 – 1.0 in humans (Figs. 2a and 3a). After UVD, the angular VOR in response to yaw head impulses directed towards the left deafferented semicircular canal is deficient, and the VOR gain was low at ~ 0.1 – 0.3 and eye position errors occur (Fig. 2b). The HIT response can be spatially compared between normal and UVD by plotting eye velocity as a function of head velocity. In the left UVD subject, there was a significant deficit during yaw-left (ipsilesional) head impulses (Fig. 2c) (Weber et al. 2008).

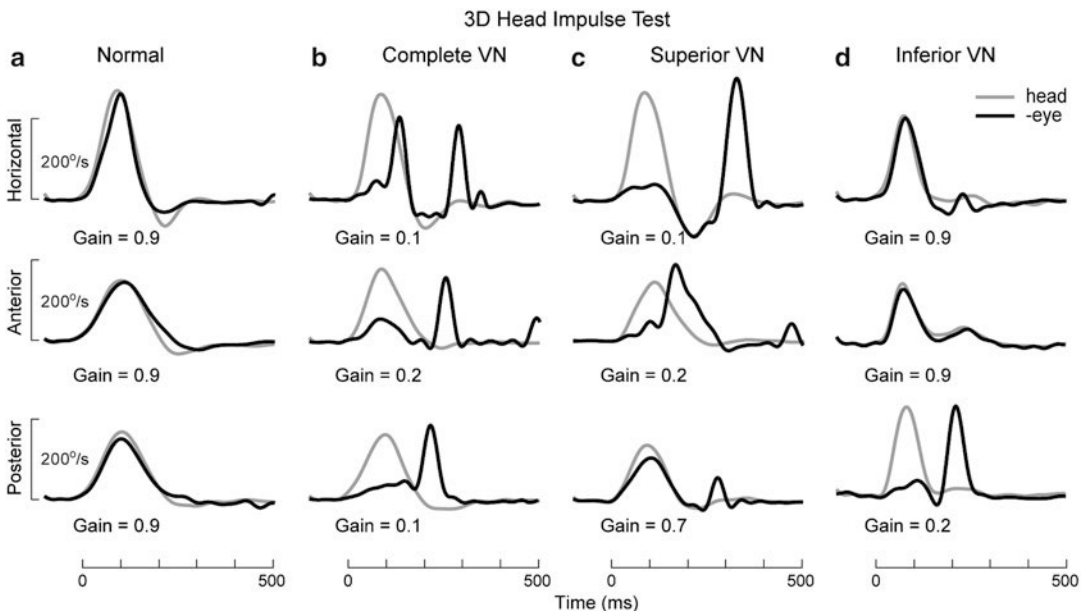
Loss of Semicircular Canal Function in Vestibular Neuritis

Vestibular neuritis is an acute unilateral peripheral vestibulopathy presenting with a clinical syndrome of vertigo, nystagmus, postural imbalance, nausea, and vomiting without brain stem dysfunction. HIT of individual semicircular canal function enabled the assessment of the extent of

involvement of the vestibular nerve or the labyrinth by vestibular neuritis (Fig. 3). The superior vestibular nerve innervates the lateral and anterior canals, utricle, and a part of the saccule, whereas the inferior vestibular nerve innervates the posterior canal and most of the saccule. Due to this semicircular canal innervation pattern, complete functional loss from all three canals on one side suggests a complete vestibular neuritis involving both the superior and inferior vestibular nerves (Fig. 3b). Horizontal and superior canal deficits suggest superior vestibular neuritis (Fig. 3c), while posterior canal deficit alone suggests inferior vestibular neuritis (Fig. 3d) (Aw et al. 2001).

Other Assessments of Semicircular Canal Function

The HIT is useful for measuring individual semicircular canal function after medical intervention. Benign paroxysmal positional vertigo is due to lithiasis whereby misplaced otoconia inappropriately stimulate hair cells in response to changes in head position. It is most common in the posterior



Vestibular, Canal Testing: The Head Impulse Test, Fig. 3 Comparison of the head impulse tests from (a) normal subject with three vestibular neuritis (VN) patients; (b) left complete VN with horizontal, superior, and

posterior canals deficits; (c) left superior VN with horizontal and superior canal deficits; and (d) left inferior VN with only posterior canal deficit

canal but also occurs in horizontal and anterior canals. Surgical canal occlusion has been used to treat intractable disease that is not relieved by particle repositioning maneuvers. Superior canal dehiscence is a bony defect in the superior canal roof, leading to hypersensitivity of the vestibular and cochlear receptors to sound and raised middle ear or intracranial pressure. Surgical superior canal plugging or canal reroofing has been used to treat the condition. The HIT is important for assessing the semicircular canal's functional status after surgery. The occluded semicircular canal will show a positive HIT, but superior canal reroofing will preserve the superior canal function.

HIT can also be used to assess any unintended injury to the canals in surgical interference of the labyrinth such as in cochlear implantation, which has been shown to carry a low risk of destruction of semicircular canal function. HIT provides a quantitative index of individual semicircular canal functional ablation following intratympanic gentamicin (Carey et al. 2002) for partial ablation of canal function or selective vestibular neurectomy with preservation of hearing for Meniere's disease. Parenteral gentamicin is a cheap and effective antibiotic for life-threatening gram-negative infections with the rare but potentially devastating risk of vestibulotoxicity.

The HIT can clinically monitor the development of vestibular hypofunction by visually detecting the refixation saccade or quantitatively tests for any development of bilateral vestibular hypofunction.

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Vestibular, Eye Movement Testing

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Detailed Description

Why Measure Eye Movements to Test the Vestibular System of the Inner Ear?

Clear vision requires a stable image on the retina. However during normal everyday activities there are considerable head movements and so to provide a stable retinal image during head movements there has to be a mechanism to stabilize the eye. Receptors in the vestibular (balance) system of the inner ear detect head movement because head movements cause fluid flow in the semicircular canals of the inner ear resulting in receptors being activated. Neurons from those receptors drive the eyes via short fast pathways and act to correct for the head movement. In healthy people the eye movement is equal and opposite to the head movement so the image on the retina of the eye is stable and visual perception is clear. This process is called the vestibulo-ocular reflex (VOR). So while jogging it is possible to read signs because the vestibular receptors correct for head movements and provide stable gaze, or in other words, stable eye position in space.

Patients with vestibular disorders complain of *visual* problems as their head moves. So they report that during head movements their vision is blurred or bouncing (bouncing vision is called

“oscillopsia”) and to many of these patients it seems as if there is something wrong with their eyes. It is not their eyes but the vestibular system of their inner ear which has the problem. Their inadequate vestibular function means their eye movement correction for head movement is incomplete so their gaze is not stable - the image of the world is smeared across the retina during head movements and such retinal smear causes the subjective experience of blurred or bouncing vision and is unpleasant.

The direct short very fast neural transmission from the vestibular receptors to the eye muscles has led to the use of the eye movement response to head movements to provide a measure of the functional status of the vestibular sense organs of the inner ear. One such test of vestibular function is the eye movement response to small unpredictable passive head movements – this is called the head impulse test. Initially this was just a clinical test relying on the clinician to move the patient’s head and (subjectively) observe the eye movement response. More recently objective measures of the eye movement have become available as is explained below.

The clinical head impulse test (HIT) consists of the clinician facing the patient and holding the patient’s head at arm’s length and then turning the patient’s head with a small abrupt unpredictable horizontal head turn of about 10–20° to the left or right in less than 0.5 s while the patient is asked to keep staring at the tip of the clinician’s nose. Such a head turn is called a *head impulse*. Although it is small and very brief this kind of abrupt passive unpredictable head rotation has a peak angular velocity of around 200°/s and a peak angular acceleration of about 2500–3000°/s/s. These numbers sound enormous but they are simply the values of head velocity and acceleration encountered in everyday activities – for example turning your head to the left or right to check traffic while driving. In healthy subjects this brief passive head turn results in a short latency (about 10 ms) smooth compensatory vestibular eye movement response which compensates for the head movement so that the person’s gaze remains fixed on the target irrespective of whether the head turn is to the left or right. The eye

movement is equal and opposite to the head movement –so in healthy subjects it is said that VOR gain is close to 1.0. (VOR gain is a measure of the performance of the whole system from receptors to response and is defined as the ratio of eye velocity to head velocity.) (Halmagyi and Curthoys 1988; Halmagyi et al. 1990).

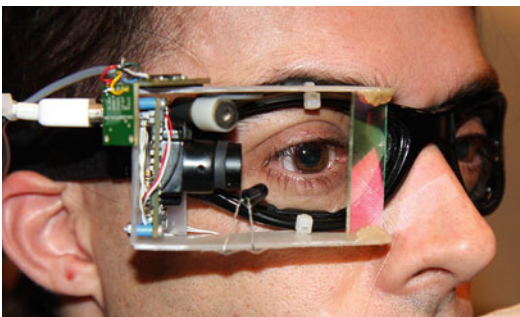
For a patient with unilateral loss of vestibular function (UVL) the result on the HIT is very different. If the patient’s head is passively but abruptly turned to their healthy side the VOR gain is about the normal value or only modestly reduced. But if the patient’s head is passively turned towards their affected side there is a marked reduction in VOR gain. The eye velocity does not match the head velocity and so the visual image is smeared across the retina. As a result at the end of the head turn the patient will not be looking at the target but somewhere over to the same side as the head has turned because the eye has been dragged with the head off the target. So to obey the instructions to keep looking at the target the patient must make a rapid corrective eye movement – a saccade - back to the target and that corrective saccade at the end of the head turn is what the clinician sees. It is the “tell-tale” sign of inadequate vestibular function. In many patients repeating the head turns a few times shows the affected side clearly.

Why is HIT such a specific test of semicircular canal function? Because the response is *too early* for other eye movement control mechanisms to be able to generate the appropriate eye velocity to correct for the head rotation. This has been shown by measuring the responses of patients with known vestibular loss due to surgery. In such patients all the other sources of eye movement control – such as volition, visual and neck input - are all functional but the vestibular input is not. The results show that the earliest part of the eye movement response to brief unpredictable passive head angular acceleration is inadequate. There is simply not enough time for other oculomotor control systems (such as vision or volition) to operate. The early response is purely vestibular. So this very simple head turn stimulus is a very effective way of probing vestibular function specifically free of visual neck or cognitive control

(Halmagyi and Curthoys 1988; Halmagyi et al. 2003).

However it has been shown that some patients with vestibular loss can generate the corrective saccade *during* the head turn itself so there is no tell-tale “overt” saccade at the end of the head turn and so the clinician wrongly concludes the person has a healthy vestibular system. Such a corrective saccade occurring during the head turn is called a *covert saccade* in contrast to the *overt saccade* at the end of the head turn. It is called “covert” because the clinician cannot detect it by the naked eye.

The way around this significant problem is to obtain *objective measures* of the eye movement during the head movement. This is not a trivial exercise but it is what the video head impulse test (vHIT) does. By using a lightweight very fast video camera in goggles securely attached to the head it is possible to measure accurately the eye movement during the head movement (MacDougall et al. 2009; Fig. 1). Sensors embedded in the goggles measure the head movement. The video head impulse test is able to quantify the VOR quickly accurately and *objectively* and show objectively the presence of covert or overt corrective saccades (Weber et al. 2008). In particular covert catch-up saccades are readily detected by this technology. The vHIT test has been validated against the research gold standard for eye movement measurement - the magnetic scleral search coil technique – by comparing simultaneous measures of the same eye in healthy subjects and patients by both search coil and video methods and the results are almost identical (MacDougall et al. 2009).



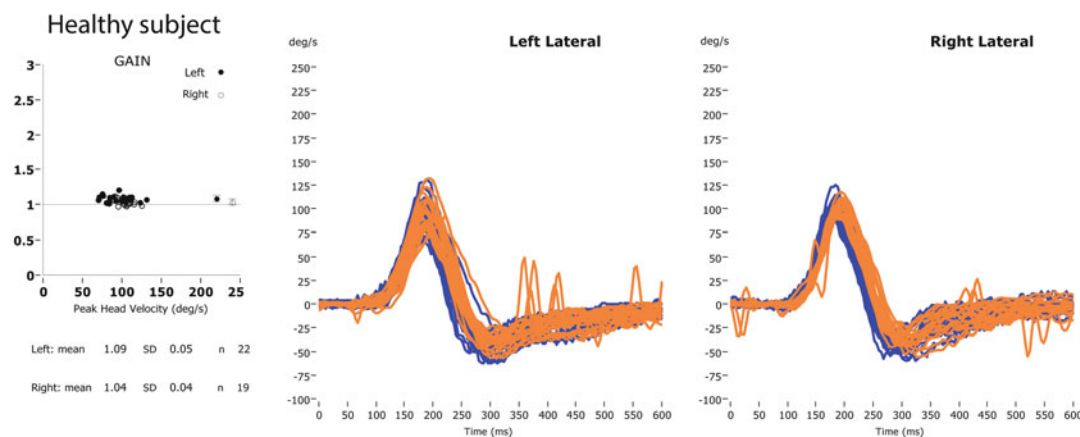
Vestibular, Eye Movement Testing, Fig. 1 A close up view of the head mounted camera system for the vHIT

Notice that this simple example has shown you that there are basically two types of eye movements involved in vestibulo-ocular response – relatively slow compensatory eye movements and very rapid ballistic movements (saccades).

How Does vHIT Work?

The image of the eye is usually reflected from an infra-red reflecting mirror (a “hot” mirror) into a side-mounted or top-mounted lightweight camera attached by a tight strap to the subject’s head. In this way the subject can see visual stimuli through the hot mirror whilst the image of the eye is reflected from the mirror and recorded by the camera. Improvements in camera and computer technology have transformed this area so that now very small lightweight high speed, high resolution cameras are readily available. And fast computers running fast software have transformed the once demanding task of measurement of eye movement into a simple process. Development of a lightweight head-mounted camera and software system which measures the eye movement and the head movement at high speed and with great accuracy quantifies the vestibulo-ocular response (VOR) (MacDougall et al. 2009). Below are records from vHIT testing of a healthy subject. There are three graphs. The larger two show the superimposed time series records of the head velocity stimulus and the eye velocity response for every head turn. The graph on the left shows the result for leftwards head turns testing the left horizontal canal and the graph on the right shows the results for rightwards head turns testing the right horizontal canal.

In all cases the records have been aligned to the onset of the head movement. Head velocity (blue traces) and eye velocity (orange traces) are superimposed so that even small but systematic deviations in eye velocity response can be seen. The eye velocity records have been inverted to show how closely the eye velocity matches and thus compensates for head velocity. The summary figure at the left shows the VOR gains for rightwards (open circles) and leftwards head turns (filled circles) for every single head turn in both directions. As is



Vestibular, Eye Movement Testing, Fig. 2 Records from vHIT testing of a healthy subject. There are three graphs. The larger two show the superimposed time series records of the head velocity stimulus and the eye velocity response for every head turn. The graph on the *left* shows the result for leftwards head turns testing the *left horizontal* canal and the graph on the *right* shows the results for rightwards head turns testing the *right horizontal* canal. In all cases the records have been aligned to the onset of the head movement. Head velocity (*blue traces*) and eye velocity (*orange traces*) are superimposed so that even

small but systematic deviations in eye velocity response can be seen. The eye velocity records have been inverted to show how closely the eye velocity matches and thus compensates for head velocity. The summary figure at the left shows the VOR gains for rightwards (*open circles*) and leftwards head turns (*filled circles*) for every single head turn in both directions. As is clear from the raw data and the VOR gains (around 1.0) this person has normal VOR for both directions of head rotation so we can infer that horizontal semicircular canal function is normal on both sides

clear from the raw data and the VOR gains (around 1.0) this person has normal VOR for both directions of head rotation so we can infer that horizontal semicircular canal function is normal on both sides (Fig. 2).

There are some (very small) overt saccades (the “stalagmites”) after the head turns. Healthy people have overt and occasional covert saccades during head impulse testing but they are usually very small and infrequent. The important thing is not the occurrence of a few small saccades but whether the saccades occur in combination with the reduced eye velocity during the head impulse. Here the VOR gain is obviously excellent so the tiny saccades have no clinical significance. With patients the saccades are large as the next example shows (Fig. 3).

Safety

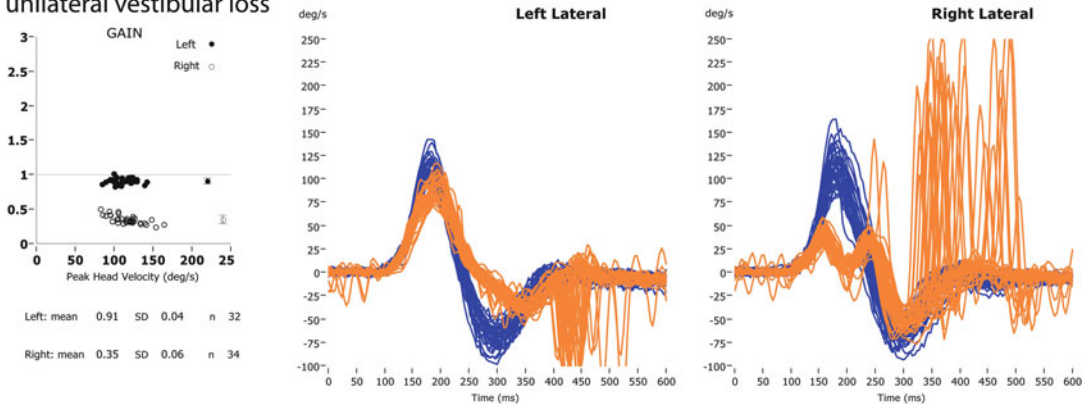
Video systems for recording eye movements have the advantage that they are non-invasive – no

electrodes are attached to the person. The video goggles are simply worn much as any normal goggles are worn. The level of infra-red illumination is very low and far below the internationally agreed infra-red hazard criteria (Delori et al. 2007). The goggles can be worn for long periods without discomfort or danger to eye health. The actual movement of the head is very small, smaller than carried out by physiotherapists or chiropractors.

Slippage

If the camera moves relative to the eye – if it slips on the head – then the system erroneously records that slippage as an eye movement since the image of the eye moves across the camera plate. Since the whole eye movement during a head impulse is very small the camera only needs to slip by a very small amount to cause a big measurement error. Trying to get acceptable eye movement data from large relatively heavy camera/goggles just does not work.

Patient with right unilateral vestibular loss



Vestibular, Eye Movement Testing, Fig. 3 Comparable vHIT results from a patient who had a unilateral vestibular loss on the right side as shown very clearly by the reduced slow-phase compensatory eye velocity – so the VOR gain for rightwards head turns is about 0.3 (rather than 1.0) complemented by the overt and

covert saccades for rightwards head turns. The saccades which occur while the head is still moving as opposed to after the end of the head movement, are called covert saccades. They would be extremely difficult to detect by the naked eye. The low VOR gain is confirmed by the presence of the saccades

The Video Camera

The camera *must* be high speed. The vHIT cameras acquire images much faster than standard video cameras – at around 250 frames/s – whereas standard video camera frame rate is about 30–60 frames/s. Obviously to measure a moving eye speed is important. And saccades (overt and covert) are the very fastest eye movements there are and they only last a very short time so a very fast camera is needed to catch them. We know that 60 frames/s is too slow to give accurate measures of saccades and VOR and that 250 frames/s does give accurate measures. We know this from direct comparison of fast and slow cameras on the same patient - low speed cameras miss or greatly reduce the saccades. So in one patient at low camera speed the eye movement of the patient with known unilateral vestibular loss looked normal but with the high speed camera the unilateral loss was clear both because of the reduced VOR gain and also the confirmatory covert saccades which the high speed camera detected but the low speed camera missed. Direct comparison of a video camera with a 250 Hz frame rate to scleral search coils at 1000 Hz sampling rate showed there was no systematic difference in measured

eye velocity so we deem that video data acquired at 250 Hz is acceptable.

The camera must be high resolution. The image of the eye is small and the total movement of the eye during a head impulse is small – just a few degrees – so a camera with inadequate resolution will not be able to detect these small eye movements accurately. Similarly the image of the eye should be sharp since a blurred image will sacrifice accuracy.

Acquisition and Geometry

Underlying all the data analysis is a robust well defined geometrical coordinate frame since the mathematics of eye rotations are not trivial (Haslwanter 1995). Usually the eye movement is derived from finding the pupil centre and tracking that centre relative to the head-fixed camera. So it is imperative that the image of the eye be of sufficient quality to allow an accurate determination of the pupil centre. Even with the coordinate frame a geometric correction is needed because the eye movement is measured from the image of a three dimensional sphere projected onto a two dimensional plane (Moore et al. 1996).

Acquisition to computers is presently by high speed fire-wire or USB 3 systems. After the centre of the pupil is found and tracked the data analysis requires filtering and differentiating to yield eye velocity. Parameters in filter order, filter cut-offs and differentiator characteristics all influence the actual measured eye velocity.

Calibration

In order to measure eye velocity the system needs information about the size of the signal caused by an eye rotation through a known angle. The usual calibration is two spots on the wall located a known distance apart and the patient has to look at each in turn and the computer logs that data and uses it to calculate eye velocity. If there is an error here then all the eye velocity measures will be in error and so the VOR gain calculations will be in error.

Practical: The Video Head Impulse Test

The operator stands behind the patient with their hands on the patient's head but away from the goggle strap. The operator aims to turn the head to the left or right *unpredictably* through a small angle – about 10–20° is ideal. It is not necessary (or advisable) to make large head turns. The important part of the test is what the eye does at the very early part of the head turn so the key is to make the start of the head turn abrupt – a small abrupt head turn is ideal. The ideal head impulse is “turn and stop”. There should be as little overshoot (or rebound) as possible.

Each head turn is a separate test of vestibular function of the semicircular canal on the side to which the head is turned. Each extra head turn just repeats the test and this is valuable for providing increased clinician confidence about the functional state of the canals.

Active head impulses where the patient turns their head voluntarily do not reveal the VOR deficit (Black et al. 2005) probably because the patients who actively generate the head turn can also actively generate covert saccades.

Testing the Vertical Semicircular Canals

If one attempts to turn the head in the plane of the vertical canals (which are about 45° to the median plane of the head) with head facing forward and gaze centrally located then it is necessary to measure ocular torsion (at high sampling rates) because the eye movement response to these diagonal head movements has a vertical and a torsional component. (Torsion is rotation around the line of sight.) High speed accurate measures of torsion are computationally expensive and so time expensive. Moving the patient's head in these planes whilst the patient faces straight ahead is awkward for the operator and uncomfortable for the patient.

Both of these problems can be overcome if prior to the first impulse the patient's head is turned on their shoulders so that their nose faces 30° to the left or right of their body median plane. Then pitching the head forward and back *in the body median plane* is relatively straightforward and tests the vertical canal response by measuring the vertical eye velocity component (MacDougall et al. 2013a, b). The head pitch is in the median plane of the body but it is aligned with the vertical canals in the (turned) head. So head pitches like this activate the vertical canals and elicit corrective eye movements which are mainly vertical (no torsion). So simple fast computer algorithms can be used to measure the eye movement response and calculate VOR gain of the vertical semicircular canals (Curthoys 2012).

VOR Gain

VOR gain is a performance indicator taken at one point in time or over a narrow time window. VOR gain is defined as the ratio of eye velocity to head velocity and it arose from an engineering analysis of the response to sinusoidal rotation stimuli. The value of VOR gain can vary from 0 (with no compensatory eye movement) up to values of 1.0 and greater. Perfect compensatory eye movements have a gain of 1.0 where eye velocity is equal and opposite to head velocity. But the question becomes – *which* value of head velocity

should be used for this calculation? In the past the VOR gain has been calculated using eye velocity at peak head velocity. It has become very clear that trying to quantify this entire complex vestibular-elicited response by a single number is a very inadequate representation of performance. For example, some patients to an abrupt head turn show an initial high-gain vestibular-driven response early which rapidly decays as the head turn continues – so VOR gain may be well above 1.0 at the start and well below 1.0 at the end of the response. For the present, VOR gain will continue to be used since it is so widely understood but VOR gain has severe inadequacies and improved metrics of performance will be a focus of future research.

Why is the gain not exactly 1.0? Textbooks give the impression that the VOR should be exactly 1.0. In fact this is very rarely true. Perfectly healthy people who have no symptoms of visual blur or oscillopsia can have gains much smaller than 1.0 (0.85 or less) or gains much higher (1.2 or more). These people do not complain of blur or oscillopsia during head movements. Why? There are probably a host of reasons. One is that wearing spectacles modifies the VOR gain even when the spectacles are removed.

Repeatability

VOR gain is not necessarily constant in patients from day to day – it has been shown in early Ménière's Disease patients that there are fluctuations in VOR gain from occasion to occasion especially around the time of the attack (Manzari et al. 2011). These fluctuations are almost certainly occurring because of the changes within the membranous labyrinth.

Historical Note

Up to 1987 the tradition for vestibular testing was to deliver slow sinusoidal rotations (0.2–1.0 Hz) and measure the eye movement response. That tradition was overturned when it was shown that a patient with no semicircular canal function

following bilateral surgical vestibular nerve removal could still generate compensatory eye movements to such predictable low frequency sinusoidal stimuli (Halmagyi and Curthoys 1988; Halmagyi et al. 1990). However this patient with bilateral vestibular loss could not generate compensatory eye movement response during the first 100 ms of an unpredictable high acceleration head turn. As a result the modern approach to testing vestibular function has been to deliver natural values of angular acceleration using the safe means of the operator's hands – but to *measure* the stimulus exactly and to relate the response to that stimulus. This has proved to be a very effective way of quantifying the VOR and identifying deficits.

Central Problems

It is important to be aware that using eye movement in response to head movements to indicate peripheral vestibular dysfunction rests on the assumption that the neural pathways from the inner ear to the eye muscles are functioning correctly. Clearly if there are deficits in pathways from the vestibular nuclei to the oculomotor nuclei the eye movement response will be affected. For example, demyelination of axons in patients with multiple sclerosis reduces the transmission speed of central neurons so there are clear delays in the eye movement response even though the peripheral vestibular function is normal.

Transmission of the neural signals is under the control of two major control systems: the cerebellum and the reticular formation. Cerebellar inhibition can modulate the neural transmission from the inner ear to the eye muscles even silencing it entirely so that as the head moves there is no compensatory eye movement response (Robinson 1976). Or reduced cerebellar inhibition can enhance that transmission so that the eye movement response more than compensates for the head movements (the VOR gain is then greater than 1.0). Cerebellar inhibition suppresses the VOR so it is possible to read a newspaper on a bus as it goes around a corner – the eyes are not reflexively driven off the page by the angular

stimulation but thanks to the cerebellum remain on the page even though the semicircular canals are being activated by the turn. Another source of control comes from the nuclei in the brainstem - the reticular formation where alertness can cause profound changes in the eye movement characteristics – reducing slow phase eye velocity and slowing saccades in drowsiness or drunkenness.

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Vestibular, Rehabilitation

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Definition

The vestibuloocular reflex (VOR) has been created with an amazing plasticity that counters the inevitable forces of disease and aging that barrage the reflex. In fact, this plasticity prevents us from suffering significant functional impairments – namely, gaze and gait instability. One example of the critical and extreme plasticity within the VOR includes complete reversal of the VOR when fit with lenses that demand it. The three primary functions of the peripheral vestibular system are (1) stabilizing visual images on the fovea of the retina during head movement to allow clear vision; (2) maintaining postural stability, especially during movement of the head; and (3) providing information used for spatial orientation. The purpose of this article is to outline how vestibular rehabilitation must incorporate head rotation in order to improve gaze and gait instability due to a deficient VOR.

Detailed Description

Semicircular Canals

Within the petrous portion of each temporal bone (base of the skull between the sphenoid and occipital bones) lies the membranous vestibular labyrinth. Each labyrinth contains five neural structures that detect head acceleration: three semicircular canals and two otolith organs. For this article, emphasis will be the semicircular canal anatomy and physiology. The three semicircular canals (SCCs) (horizontal, posterior [inferior], and anterior [superior]) respond to angular acceleration and are orthogonal with respect to one another. Alignment of the SCCs in the temporal bone is such that each canal has a contralateral coplanar mate. The horizontal canals form a coplanar pair while the posterior and contralateral anterior SCCs form coplanar pairs. The anterior aspect of the horizontal SCC is inclined 30° upward from a plane connecting the external auditory canal to the lateral canthus. The posterior and anterior SCCs are inclined about 92° and 90°, respectively, from the plane of the horizontal SCC (Della Santina et al. 2005).

Because of this alignment in the head, the SCC can detect rotational head velocity in any combination of directions (yaw, pitch, roll). The SCCs are filled with endolymph (fluid) that has a density slightly greater than water (Smith et al. 1954). Endolymph moves freely within each canal in response to the direction of the angular head rotation. The SCCs enlarge at one end to form the ampulla. Within the ampulla lies the cupula, a gelatinous barrier that contains the sensory hair cells. The kinocilia (mechanosensing cilia involved in the sense of movement) and stereocilia (mechanosensing organelles) of the hair cells are seated in the crista ampullaris (sensory organ of angular rotation). Deflection of the stereocilia caused by motion of the endolymph results in an opening (or closing) of the transduction channels of hair cells, which results in changes in the membrane potential of the hair cells. Deflection of the stereocilia toward the kinocilia in each hair cell leads to depolarization and deflection of the stereocilia away from the

kinocilia leads to hyperpolarization. As a result of this sensory hair cell anatomy, the SCCs have a dual sensory and motor function.

Abnormal SCC Function and Abnormal Gait

Postural and gait instability can result from semicircular canal hypofunction. This instability is typically related to a hypermetric postural response that occurs when posture is challenged. Measures of acceleration reveal an age-related inability to attenuate head acceleration during postural perturbations and gait. In contrast, healthy younger controls can reduce joint acceleration for the head (and upper trunk) even as their walking speed increases (Kavanagh et al. 2004; Latt et al. 2008). In vestibular hypofunction, a greater than normal amount of head (and gaze) oscillation occurs when subjects make active head rotations – suggesting head motion instability (Lehnen et al. 2009). Additionally, patients with vestibular loss have more irregular head and whole-body velocity trajectories (Lafond et al. 2004). These pathomechanical changes may be a direct result of the loss of vestibular afferents (due to age and disease) onto Purkinje cells or direct damage to the central vestibular pathways thereby releasing the normal inhibition of central vestibular neurons mediating the vestibulospinal tract resulting in postural instability and an increased fall risk.

Few studies have examined SCC hypofunction and parameters of balance. In postural studies, static center of pressure (COP) refers to an excursion trace that identifies the location of the resultant ground reaction forces from the feet (Lafond et al. 2004). When the COP sway excursion or velocity is greater, balance is worse. COP velocity is greater in patients with SCC hypofunction compared with control subjects (Krebs et al. 1993; Crane and Demer 1998; Sevilla-Garcia et al. 2009). In SCC hypofunction, gaze and COP velocities are correlated – as gaze velocity increases, so does center of pressure velocity (Crane and Demer 1998). In addition, patients

with abnormal semicircular canal function have greater gaze velocity during tilt than control subjects (Crane and Demer 1998). Recent studies measuring gaze stability during balance perturbations show an inverse correlation between gaze fixation and latency to step (Diehl and Pidcoe 2010).

Based on canal-mediated (and otolith-mediated) compensatory eye rotations that stabilize gaze (vision) during both passive whole-body rotation and ambulation, Crane suggested a model that illustrated that cues such as proprioception, motor efference copy, and prediction were not important to the generation of compensatory eye movements during ambulation (Crane and Demer 1999). It remains impractical, therefore, that optimal VOR function rely on proprioception, prediction, or even visual feedback during ambulation since latencies from these systems would at best be 80 ms – well above that of the VOR (Carl and Gellman 1987; Bronstein and Gresty 1988; Lisberger 1990; Crane and Demer 1997). Evidence therefore suggests that gaze stability and VOR gain (eye velocity/head velocity, ideally the gain is equal to unity during typical viewing) correlate with balance, which indirectly implies that SCC excitation through VOR gain adaptation exercises may improve the vestibulospinal response of patients. This has not been directly verified.

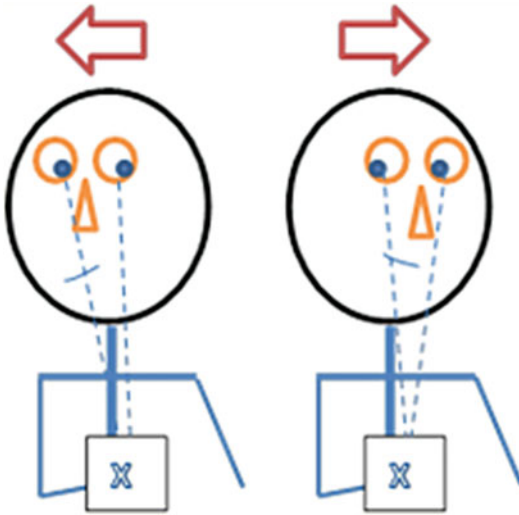
Abnormal SCC Function and Abnormal Dynamic Visual Acuity

Dynamic visual acuity (DVA) refers to the ability to see clearly during head rotation. DVA therefore is a functional measure of SCC function and other mechanisms of gaze stability the brain may recruit. Patients with abnormal SCC function (unilateral and bilateral) have been found to have improved DVA only when performing VOR adaptation exercises compared with placebo exercises (Herdman et al. 2003, 2007). The strategy the brain uses to improve DVA appears to be increasing the gain of the VOR and recruiting a unique type of saccade that occurs in the same direction of the deficient VOR (Schubert et al. 2008).

Role of Vision and Head Motion in Recovery from SCC Deficit

Two sensory stimuli are required for significant adaptation of the VOR: vision and head motion. Traditionally, adaptation paradigms designed to enhance the gain of the VOR have been done with short-term (less than 1 h) or long-term (greater than 1 day) time exposure. A number of VOR adaptation studies have demonstrated a robust capability for changing the normal VOR by coupling head motion with target motion. When the viewed targets move in such a manner that the image slips on the retina, the VOR is recalibrated. The direction of the recalibrated VOR (increased or decreased gain) depends on the direction of the target motion in relation with the head motion. During head rotation, visual following of targets that move at a velocity different from the head rotation will create an adaptation (change) in the gain of the VOR. This is commonly achieved by 1 of two means: (1) targets are viewed wearing lenses that magnify the visual world (increases target velocity) or minimize the visual world (decreases target velocity); (2) targets are viewed that move in a direction opposite the head rotation (increases target velocity) or move in the same direction of head rotation (decreases target velocity). The difference between the target velocity and the eye velocity is termed retinal slip and can be quantified. Retinal slip is therefore a velocity error signal, thought to be the most effective means for changing VOR behavior, e.g., VOR gain (Ito 1982; Eggers et al. 2003).

Clinical experience suggests that some patients with vestibular hypofunction adopt a strategy of avoiding rapid head rotations toward their lesioned side, thereby reducing retinal slip but perhaps also missing an opportunity to generate a retinal slip stimulus that would otherwise drive VOR compensation (Herdman 1998; Cromwell et al. 2004; Kvåle et al. 2008). Reducing this gaze error through vestibular rehabilitation appears to improve gaze stability (Schubert et al. 2008, 2010).

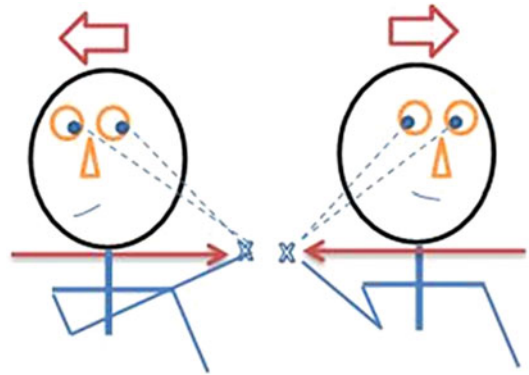


Vestibular, Rehabilitation, Fig. 1 Times one VOR adaptation exercise. The patient is instructed to keep the target (letter X) still and in focus while moving the head *left to right* (and separately *up* and *down*). The speed of the head rotation depends on the clarity of the target. If the target blurs or appears to move, the patient should be instructed to slow down. *Arrows* denote head rotation

VOR Adaptation Exercises

The purpose of adaptation exercises is to improve the VOR and other systems that are used to assist gaze stability. VOR adaptation exercises are designed to expose patients to retinal slip. Because the brain can tolerate small amounts of retinal slip without perceiving image instability, the patient should be instructed to keep the target in focus. Otherwise, head motion that is too rapid will result in excessive retinal slip. The two primary VOR adaptation exercises are $\times 1$ (times 1) and $\times 2$ (times 2). In the $\times 1$ exercise, the patient is asked to move the head horizontally (and separately, vertically) as quickly as possible while maintaining focus on a stable target (Fig. 1).

The patient must learn to slow the head movement if the target becomes blurred. A good target to use is a business card, asking the patient to focus on a word or a letter within a word. The exercise can be modified in many ways: (1) changing the target distance (i.e., near and far), (2) providing a busy visual background while the patient attempts to keep visual focus on the target during



Vestibular, Rehabilitation, Fig. 2 Times two VOR adaptation exercise. The patient is instructed to keep the target (letter X) in focus while moving the head and target in opposite directions. The speed of the head rotation depends on the clarity of the target. If the target blurs or appears to move, the patient should be instructed to slow down. *Thick arrows* denote head rotation. *Thin arrows* denote target motion

head motion, and (3) doing the exercise while walking. The $\times 2$ paradigm requires the patient to move the head and target in opposite directions (Fig. 2).

Conclusion

Vestibular adaptation exercises are an excellent starting point for rehabilitation of patients with semicircular canal deficits (i.e., vestibular hypofunction). Research supports the beneficial effects of vestibular adaptation exercises on gait, posture, and visual acuity.

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Virtual Neuron Generation

► Synthetic Neuronal Morphology

Virtual Stick Balancing

► Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights

Vision Prosthesis

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Synonyms

Artificial retina; Artificial vision; Bionic eye; Intraocular retinal prosthesis; Retinal chip; Retinal prosthesis

Definition

An electronic system, usually comprised of external and implanted components, that can sense light, convert light to an electronic signal, and apply that signal to the retina, as a treatment for blindness secondary to photoreceptor loss.

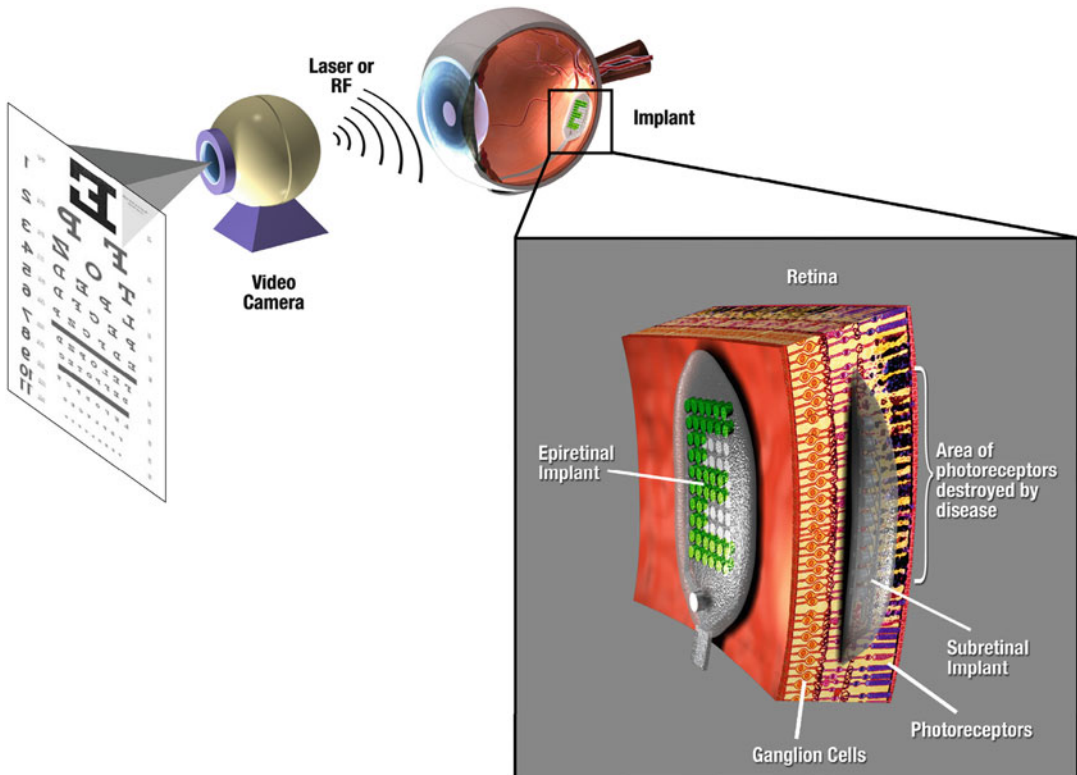
Detailed Description

In a healthy retina, light is detected by photoreceptors (rods and cones) via photosensitive molecules in the outer segments of the photoreceptors. These molecules, once transformed by light, trigger a cascade of neurochemical events that lead to other neural cells in the retina (ganglion cells), sending signals to the downstream visual centers of the brain. Retinal degenerative diseases, like retinitis pigmentosa and age-related macular degeneration, affect primarily photoreceptors, leaving the retina unable to sense light, but remaining neurons in the retina (bipolar cells and ganglion cells) can be electrically activated, based on established techniques for nerve stimulation.

A typical retinal prosthesis has multiple components each with a specific function (Fig. 1). These include an imager to convert light to electrical signal, electronics to process and condition the image and generate electrical stimulus pulses,

and an array of microelectrodes to stimulate the retina. Other important components found in one form or another on most implants include hermetic packaging and wireless data/power transmission. However, retinal prostheses are often categorized based on the location of the electrode array, which forms the functional interface with the retina. The locations where an electrode array can be implanted to stimulate the retina include epiretinal (on the top surface of the retina), subretinal (under the retina), and suprachoroidal (between the sclera and choroid).

Several prototype systems of chronic implantable devices have been tested in clinical trials. These fall into two types of implants. The first type of device was designed to show feasibility in humans, but not intended to be a commercially viable medical device. Thus, the main concern for these devices was patient safety, and they generally were not refined to the same degree as a commercial product. For example, a number of



Vision Prosthesis, Fig. 1 Retinal prosthesis concept – an external camera captures an image. Wireless transmission of image data to an implant specifies the stimulation pattern that is applied to the retina via a microelectrode array

these early chronic implants could only be activated when the patient visited the clinic. The second type of devices are intended as commercial devices, so they are engineered not only for robustness and safety but also for expected longevity of over a decade and with human factors considerations. One device, the Argus II retinal prosthesis (Second Sight Medical Products, Inc.), has received approval in both Europe and the United States to be sold as a treatment for retinitis pigmentosa. A summary of current and past clinical trials of retinal implants can be found at www.clinicaltrials.gov; search “retinal prosthesis.”

Epiretinal implants involved in feasibility studies include the Argus I from Second Sight and devices from Intelligent Medical Implants, GmbH (IMI), and the Epi-Ret Consortium (Epi-Ret). All three of these systems used wireless power and data delivery (to avoid transcutaneous wires).

The Argus I device was implanted in six subjects between 2002 and 2004 (de Balthasar et al. 2008). Argus I was a modified cochlear implant. As such, the electronics were implanted behind the ear and a cable run along the temple, into the orbit, and, finally, into the eye, terminating in a 4×4 grid of platinum electrodes, either 520 or 260 mm diameter. With training, subjects were able to distinguish objects from a small set and detect motion of a moving bar. Subjects have been implanted for as long as 8 years with the device still functional.

The IMI device was implanted in a total of seven subjects (Hornig et al. 2007). This device utilized a microfabricated array with a total of 49 electrodes. The implant was entirely in the orbit, with the electronics module on the outside of the eye and the electrode array in the eye (via a cable across the eye wall). This system could only be activated in the clinic as no camera system was available. Using this device, subjects could see spots of light and some simple patterns. Since the electronics were not hermetically packaged, but only sealed with polymer coatings, the implants were removed after several months or, in one case, 1.5 years.

The Epi-Ret device was implanted in six patients (Klauke et al. 2011 Jan). The stimulating array had 25 electrodes and also was miniaturized to the point where the entire device could be

implanted in the eye. A unique feature of the stimulating array was protruding electrodes, which improved contact with the retina and resulted in low perceptual thresholds. Like the IMI device, the Epi-Ret system was designed only for semi-chronic implantation (4 weeks) and did not have a camera system so the implant could only be activated in the clinic.

Commercial Design

Approval to sell a medical device as a treatment for a specific disease is only granted after approval by government agencies. The Argus II epiretinal prosthesis has received approval in Europe and the United States. The Argus II is similar to the IMI device, in that the electronics are on the outside of the eye and the electrode array is on the retina, connected by a cable across the eyewall to the electronics (Humayun et al. 2012). The Argus II, however, has a camera system that provides input to the implant, and the electronics are protected with a hermetic package, so that implant longevity is decades. Thus, patients with implants can leave the clinic with the system. Sixty electrodes are arranged in a 6×10 format.

Thirty subjects were enrolled between 2007 and 2009. All subjects were able to perceive light during electrical stimulation. Other tasks on which subjects performed well include object localization and motion detection. Letter reading was tested in 22/30 subjects (da Cruz et al. 2013). Six of these subjects were able to identify any letter of the alphabet at a 63.5% success rate (vs. 9.5% with the system off). In all 22 subjects, a small set of eight letters was identified 72.5% correctly vs. 16.8% with the system off. Subjects were free to take as much time as needed to make a judgment. Adverse events that occurred during the trial included low eye pressure and infection, but such events decreased in later implants.

Conclusion

Epiretinal prostheses have proven that they have the capability to improve the lives of people blind

from retinal degenerative disease. Multiple systems have been tested in humans, with one device receiving approval for sale.

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Visual Aftereffects, Models of

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Synonyms

[Adaptation](#); [Illusions](#)

Definition

Visual aftereffects are systematic changes in perception of a visual stimulus after adaptation to a previous stimulus. For instance, the tilt aftereffect affects the perception of tilted lines – after staring

at an oriented line, slightly rotated lines appear to be much more different in orientation. Similar effects occur for a very wide variety of stimuli and have prompted a range of computational explanations primarily focusing on changes in responsiveness of feature-selective neurons in the visual cortex. Aftereffects are one type of visual illusion, which are discussed further in the entry.

Detailed Description

Visual aftereffects have been described for an extremely wide range of visual stimuli in a variety of contexts. A well-studied example is the motion aftereffect, which was originally reported (somewhat ambiguously) by Aristotle and has been independently rediscovered many times since. One of the most influential descriptions of this effect, also known as the waterfall illusion, is from Robert Addams in 1834 (Fig. 1).

After extended exposure to a pattern moving in one direction (such as a waterfall), viewing a roughly similar but static pattern (such as an adjacent rocky cliff) produces a sensation of motion in the opposite direction. Here the moving stimulus is called the adaptation pattern (to which the visual system becomes adapted), and the static pattern is called the test stimulus. No effect is seen without a suitable test stimulus.

In the tilt aftereffect (Gibson and Radner 1937), adaptation to lines of one orientation changes the perception of subsequent test lines differing in orientation. Specifically, test lines slightly rotated from the adaptation pattern appear shifted in orientation in a direction away from that of the adaptation pattern (though not opposite, as in the motion aftereffect), while test lines very different in orientation are perceived as being slightly more similar to the adaptation pattern's orientation (Fig. 2).

Similar direct and indirect effects have been found for the motion direction aftereffect, which is a variant of the motion aftereffect that uses moving test stimuli of various orientations (Schrater and Simoncelli 1998). Other aftereffects involve further levels of complexity. For instance,



Visual Aftereffects, Models of, Fig. 1 Motion aftereffect. While visiting this waterfall (the Falls of Foyers, near Loch Ness, Scotland), Robert Addams watched the falling water for some time. He then looked over to the adjacent rock face and noticed that the rocks appeared to be moving upward. He was later able to replicate this effect mechanically using a visual pattern drawn on a moving belt, which helped make the phenomenon suitable for scientific study (Photo © 2000, James A. Bednar)

in the McCollough effect (McCollough 1965), viewers perceive orientation-specific changes in color of a black and white test stimulus, after exposure to multiple-oriented colored lines (Fig. 3).

Many other aftereffects have been reported, such as various types of face aftereffects (e.g., changes in perceived gender of androgynous stimuli after exposure to a male or female face; Leopold et al. 2001; Zhao et al. 2011) and even blur aftereffects (changes in perceived blur after exposure to a certain level of sharpness or blurriness). See Thompson and Burr (2009) and Webster (2012) for reviews of additional types of aftereffects.

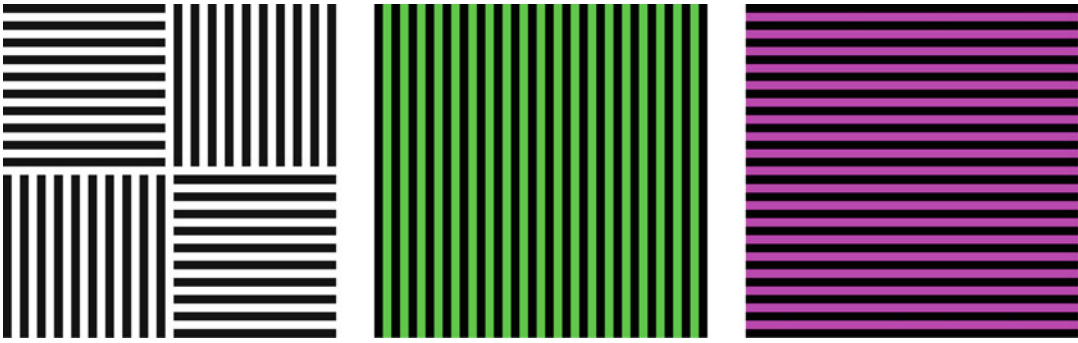
Aftereffect Mechanisms

Over the centuries, a wide variety of explanations have been offered for the various effects. For instance, Addams' explanation for the movement aftereffect was in terms of entrained eye movements, though this was later disproved by showing that the effect is specific to an area of the retina. After neurons selective for visual features were discovered in the primary visual cortex in the 1960s, explanations began to focus on adaptation (changes in the responsiveness) of these neurons over time. A common assumption was that "if you can adapt it, it's there" (Mollon 1974), suggesting that behind each aftereffect



Visual Aftereffects, Models of, Fig. 2 Tilt aftereffect. If you look briefly at the set of lines in the middle and then look over to a blank area such as the margin, you are likely to see an afterimage, a simple type of aftereffect with a sensation of the same pattern but the colors swapped. To experience the tilt aftereffect instead, try staring at various locations inside the small circle, moving your eyes around

regularly to minimize the afterimages. After 30–60 s, look at the circle in the *left* (vertical) pattern. The vertical pattern should now look tilted slightly clockwise (the direct TAE). The horizontal pattern on the right may look slightly tilted anticlockwise, though this indirect effect is smaller and more variable and so not always noticeable



Visual Aftereffects, Models of, Fig. 3 McCollough effect. Before adaptation, the test pattern on the left should appear *black* and *white*. To reproduce the McCollough effect, stare alternately at the two colored patterns for 3 min, moving your gaze regularly to avoid developing

strong afterimages, and then look back at the *black* and *white* test pattern. *Vertical bars* should now be slightly tinged with *magenta*, and *horizontal bars* should be slightly tinged with *green*. The effect should reverse if you tilt your head 90° and disappear if you tilt 45°

lies a corresponding set of feature-selective cells undergoing adaptation.

For instance, negative color afterimages from looking at any bright pattern could be explained as adaptation of light-sensitive cells in the retina, perhaps interpreted mechanistically as depletion of some limited resource within a single cell, such as what occurs in cone pigment photobleaching. Most explanations of afterimages do focus on the retina, because afterimages are specific to retinal location and to each eye, which matches the properties of retinal (and thalamic) cells.

Explaining effects more complex than afterimages requires either more complex models incorporating additional areas of the visual system, more complex mechanisms for reading out the illusory percept from the neural activity, or both. For instance, many explanations for the motion aftereffect have been based on responses in two sets of motion-selective neurons, with opposite preferred directions of motion. If the perceived motion is the balance or average value of these two population activities, a movement aftereffect will be seen when one of the populations adapts more than the other (Fig. 4).

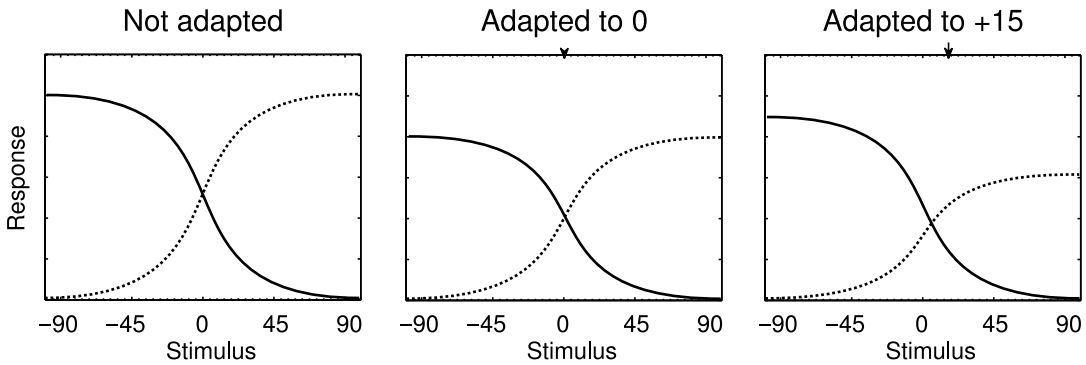
The opponent-code idea has been used to explain aftereffects for color and for various types of face perception, using an opponent axis of, e.g., red versus green, male versus female, or face versus anti-face (Webster 2012).

An alternative explanation is in terms of multichannel coding. Here, neurons are no longer

specifically separated out into opposing pools but instead represent a wide variety of different preferences, each characterized as narrow band-pass (e.g., bell-shaped) tuning. Each such neuron would adapt independently, and the net effect could be computed as some sort of population average or overall probabilistic estimate (Series et al. 2009). For instance, the motion aftereffect can be explained as changes in the average or net perceived direction of motion, across a wide-ranging population (Fig. 5).

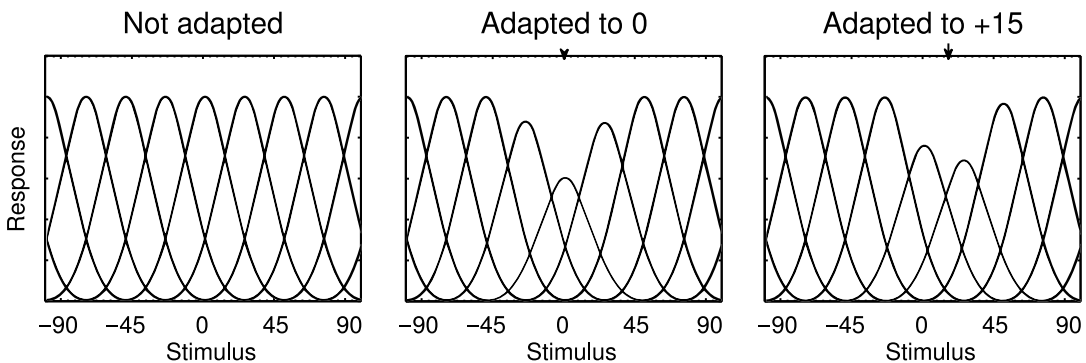
Similar multichannel explanations could apply to other phenomena like the tilt aftereffect, based on orientation-selective cells in V1 (Bednar and Miikkulainen 2000).

Deciding between opponent and multichannel explanations can be complex. For instance, even though retinal ganglion cells are chromatically opponent, the underlying photoreceptors are still band pass in terms of wavelength, rather than responding more strongly to longer and longer wavelengths (e.g., infrared). Thus, color can also be considered a multichannel encoding, albeit with only a small number of channels. Similarly, motion direction is arguably a multichannel encoding despite any opponency that may be involved, because neurons with a very wide variety of motion direction preferences have been found (Weliky et al. 1996). Multichannel models have been able to explain the motion aftereffect and color aftereffects without any explicit implementation of opponent coding as a physical



Visual Aftereffects, Models of, Fig. 4 Opponent-code adaptation. Some aftereffects, such as movement and some kinds of color effects, can be described in terms of opponent processes between two pools of neurons. Here the population response (the total response to a stimulus of a given speed) is plotted for all the upward-preferring neurons (*dotted line*); these respond best to stimuli with a positive velocity (stimulus >0). Similarly, the *solid line* shows the population response of the downward-preferring neurons to each velocity; they respond best to negative velocities. For a given test stimulus, the perceived velocity would be calculated as some sort of average or net activation between these two pools. Before adaptation (*left*), both populations respond equally to a static (stimulus 0) test

pattern, and so the pattern would correctly be perceived as static. Similarly, after adaptation to a static pattern, responsiveness has decreased overall, but a static test pattern continues to be perceived correctly as static, since both populations have adapted similarly. However, after adapting to downward motion of speed 15 (in arbitrary units), the net population activity in response to a static pattern will tend toward upward motion (*right*). Here the central “norm value” is special in terms of defining the two opposing populations; aftereffect strengths will increase as adaptation patterns become more dissimilar to this norm and thereby more specifically activate one or the other of the two populations



Visual Aftereffects, Models of, Fig. 5 Multichannel-code adaptation. A multichannel model for the movement aftereffect might be based on neurons that are each selective for a specific direction of motion, such that many different direction selectivities are represented (here visualized as a set of direction tuning curves plotted along the x axis, with x being the motion direction angle in retinal space). The strength of each neuron’s response would be modulated by the stimulus velocity, such that each neuron responds only slightly to a static pattern. The perceived direction and speed of motion would be perceived as a population average of the responses of all the neurons, such that a moving stimulus will activate a small subset of these neurons strongly (thus having an average corresponding to a specific motion direction). A static

pattern would activate all of these weakly and equally, resulting in no net perceived motion direction. After adapting to, e.g., vertical motion (stimulus 0, *center panel*), the neurons whose tuning curves overlap with the stimulus have become less responsive (in proportion to their amount of overlap), and so the population average shifts to the direction opposite to the adapted direction. Similar processes happen for all adaptation directions (e.g., $+15^\circ$ in the *right panel*). The result will thus act like an opponent code in some ways, since the effect is opposite the adaptation pattern and again there will be no net effect of adaptation to a static pattern. One difference is that this model does not require any specifically designated pairs of opponent pools and can thus use a single readout for all motion directions

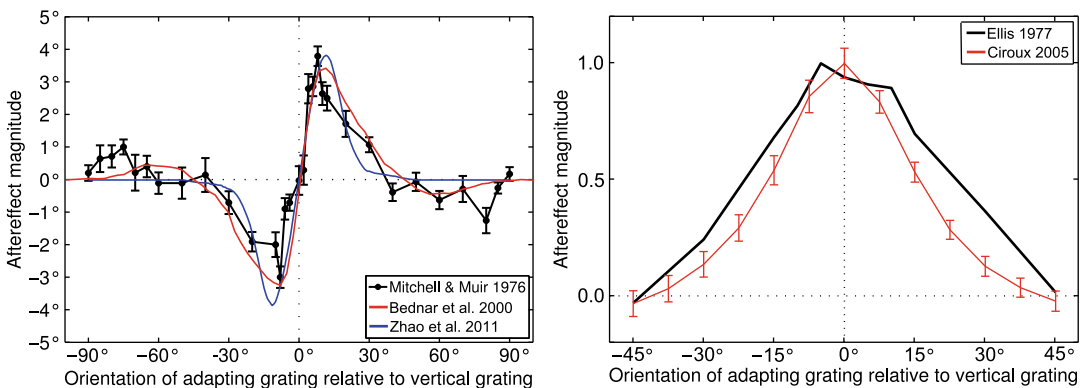
process (Ball 2005; Ciroux 2005; Mather 1980). Instead, the apparent opponency of those dimensions may come from how the aftereffect is read out – using a population average, opposite directions of motions and opposite values along a hue dimension cancel out, which makes those dimensions be in opposition for perception and for aftereffects even though the actual mechanics of the neural model are multichannel.

Fatigue Versus Synaptic Inhibition

So far, adaptation has been described generically as a reduction in responsiveness, but we have not specified what makes the responsiveness decrease. Early neural explanations were in terms of “fatigue,” such as temporary depletion of some crucial resource inside a single cell. However, cortical cells do not appear to fatigue from repeated activation; they continue to respond vigorously to repeated electrical (non-synaptic) input

(Vidyasagar 1990). Instead, the observed reduced responsiveness appears to be synaptic in origin, primarily via inhibition from other neurons (Tollhurst and Thompson 1975; Webster 2012).

Moreover, an explanation in terms of synaptic changes seems more suitable for the McCollough Effect, in part because it does not require there to be large sets of neurons that are highly selective for both color and orientation (and every other similar feature conjunction for which a contingent aftereffect has been found). More importantly, the McCollough effect can last for days or even months, which would be difficult to reconcile with the time scale of recovery from any fatigue process, but is compatible with long-term storage of synaptic weights. Figure 6 shows results from multichannel TAE models of both types, either modeling reduced responsiveness directly (Series et al. 2009; Zhao et al. 2011) or via changes in lateral inhibition (Bednar and Miikkulainen 2000), and from the synaptic inhibition model applied to the McCollough effect (Ciroux 2005).



Visual Aftereffects, Models of, Fig. 6 Tilt aftereffect and McCollough effect in humans and models. (Left) Tilt aftereffect. Changes in perceived orientation are systematically related to the angle between the adapting and test stimuli, with a peak aftereffect (difference in perceived orientation) of several degrees for a 10–15° difference between the adapting and test orientations and an area of opposite (“indirect”) effect for the largest (45–90°) differences. Representative human data from one subject from Mitchell and Muir (1976) is shown with a black line; other subjects have similar shapes but with small differences in the peak orientations and location of the indirect effects. A multichannel model where responsiveness is reduced directly (Zhao et al. 2011; blue line) is a good match to the human direct effect, though it does not have any mechanism for generating indirect effects. A model based on

small increases to a large number of lateral inhibitory synapses (Bednar and Miikkulainen 2000; red line) also matches the direct effect but shows indirect effects as well due to homeostatic mechanisms limiting the total amount of synaptic efficacy (Bednar and Miikkulainen 2000). The synaptic model can also account for the McCollough effect (right) where the amount of perceived color difference (y axis) varies as a function of orientation (Ciroux 2005; human data from Ellis 1977). In this case, lateral interactions between color-selective neurons and orientation-selective neurons change as the test patterns are presented, gradually encoding the correlation between the color and orientation that reduces responsiveness to that pattern, causing a subsequent imbalance (and thus aftereffect) for the opposite-color test pattern

In this case, both approaches can fit the simple, direct tilt aftereffect and motion aftereffects. But the synaptic inhibition model can also explain contingent effects like the McCollough effect (via modification of lateral inhibitory interactions between orientation and color-selective neurons), as well as indirect tilt aftereffects (via whole-cell homeostatic plasticity mechanisms that lead to disinhibition of dissimilar neurons; Bednar and Miikkulainen 2000). Thus, the synaptic inhibition approach appears to be more widely applicable and also fits data not compatible with fatigue-type models (Webster 2012).

High-Level and Hierarchical Aftereffects

The aftereffects discussed so far have primarily been for relatively simple stimuli, for which specific feature-selective cells have been established clearly in animal and human visual systems. Aftereffects for many other types of patterns have also been demonstrated, but it is much more difficult to model these mechanistically given how little is known about the neural representation of such stimuli. For instance, a very wide variety of aftereffects have been reported for images of human faces, including aftereffects of identity, gender, emotion, and shape distortion, and there is as yet little agreement about appropriate models for these phenomena. For one thing, it is quite unclear even which level(s) of the visual system might be involved – assuming that neurons are adapting at lower levels, by the time the putatively face-selective neurons in higher areas are reached, the lower levels may well have adapted significantly. It has already been established that the presumably high-level task of detecting emotion can be dramatically affected by low-level adaptation to curved or tilted lines (Dickinson and Badcock 2013; Xu et al. 2006, 2008), indicating that many of the aftereffects thought to be “high-level” may instead be the combination of several low-level aftereffects. In the absence of hard data about the neural organization, there remains a lively debate between norm-based opponent coding and multichannel coding for explaining face aftereffects. A few

papers support multichannel encoding for putatively high-level features like gender (Storrs and Arnold 2012; Zhao et al. 2011), but a large community argues strongly for norm-based opponent coding for faces and face aftereffects (Leopold et al. 2001; Pond et al. 2013).

Functional Role of Aftereffects

In many cases, aftereffects are studied because of what they reveal about the organization and function of sensory systems, but one can also ask what function they themselves serve in visual processing. An influential theory due to Horace Barlow (1990) is that they reflect continuously ongoing neural processing to remove temporal correlations in the incoming sense data, leaving a temporally sparse representation that allows us to focus on novel items and changes. Many of the models mentioned above are based implicitly on this principle, and several of them show how aftereffects can arise from decorrelating processes identical to those that may drive the original emergence of feature selectivity during longer-term development (Ball 2005; Bednar and Miikkulainen 2000; Ciroux 2005). Note that each of these explanations relies crucially on having an “unaware” decoder (Series et al. 2009), one that is temporarily fooled by the changes in responsiveness, which may be important for drawing our attention to subtle stimulus changes. If the sensory bias due to adaptation persisted over time, presumably downstream neurons would themselves adapt, eventually erasing the effect. These processes can also be interpreted as a form of dynamic gain control (Mather et al. 2008), with the nervous system continuously adjusting its responsiveness to make the best use of its limited dynamic range. In any case, the ubiquity of aftereffects indicates that they are likely to be involved in functionally relevant aspects of sensory processing.

Cross-References

- [Adaptation in Sensory Cortices, Models of](#)
- [Hebbian Learning](#)

- [Learning Rules: Overview](#)
- [Spike-Frequency Adaptation](#)
- [Visual Illusions, Models of](#)

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Visual Cortical Implants

- [Visual Prosthesis, Cortical Devices](#)

Visual Function

- [Prosthetic Vision, Assessment](#)

Visual Hallucinations and Migraine Auras

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Definition

Elementary visual hallucinations are geometric patterns that move with the eyes and are seen by almost all humans. They can be triggered in many ways. This article describes mathematical models

developed over the last 40 years of how such images are generated in the visual cortex, as a consequence of its circuitry and dynamics. The models use the Turing mechanism for pattern formation to generate cortical patterns of neural activity which are seen as hallucinations in the visual field. It provides an alternative to the standard way of studying vision using external stimuli, in using geometric patterns generated by internal changes in the stability of cortical activity. It provides a theory of how the four classes of patterns which are seen as hallucinations are formed in the visual cortex as a consequence of the way it is wired. It appears to be capable of also replicating the patterns seen in migraine auras.

Detailed Description

Elementary Visual Hallucinations

Elementary visual hallucinations are usually geometric patterns seen in the visual field that move with the eyes. They are seen under a variety of conditions, including sensory deprivation, flickering light, following the administration of anesthetics such as ketamine, and of course the use of psychedelic drugs such as peyote, marijuana, psilocybin, and LSD. They are also seen by some observers when falling asleep, or when waking up, or during meditation. There are also reports of hallucinations associated with schizophrenia, and under certain epileptic conditions. Interestingly many prehistoric cave paintings and rock carvings, dating back at least 30,000 years, appear to

contain examples of hallucinatory motifs, as do images found on pottery, dating back some 3000 years. Hominids have had a long history with hallucinations.

Klüver Form Constants

One of the first relatively modern studies was carried out by Purkinje early in the nineteenth century, who studied flicker phosphenes [see Purkinje (1918) and ► “Flicker-Induced Phosphenes” by Ermentrout & Billock in this volume]. However, the first modern study was carried out in the late 1920s by Heinrich Klüver. His observations were based on a personal study of the effects of peyote on perception and were summarized in Klüver (1966). Klüver organized the imagery he saw into four classes: (a) lattices, honeycombs, and chessboards, (b) cobwebs, (c) tunnels and funnels, and (c) spirals. He called these classes *form constants*. Figures 1 and 2 show examples of each form constant.

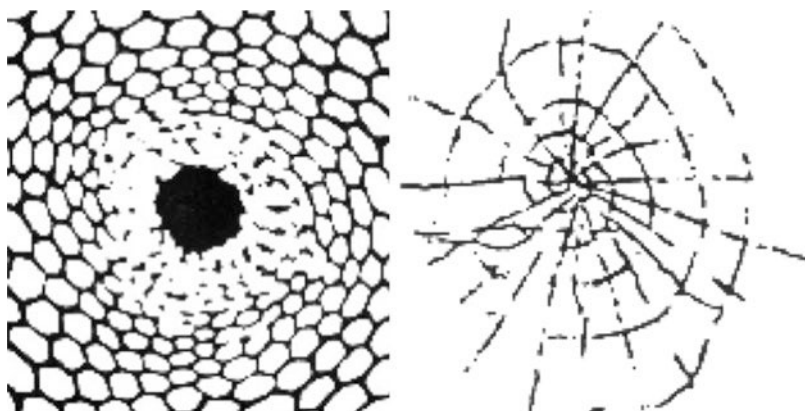
Note that based on such figures, elementary visual hallucinations can be further classified as comprising (I) *contoured* images, i.e., the form constants (a) and (b), and (II) *non-contoured* images such as stripes of blobs, i.e., the form constants (c) and (d).

Complex Hallucinations

There are, of course, much more complex hallucinations, many of which are also described in

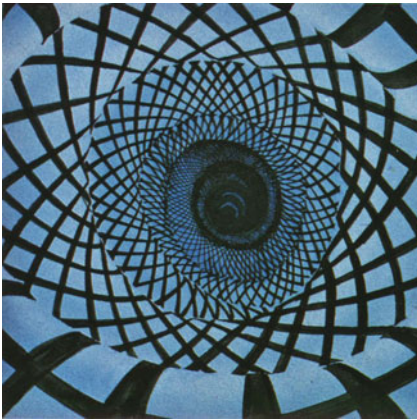
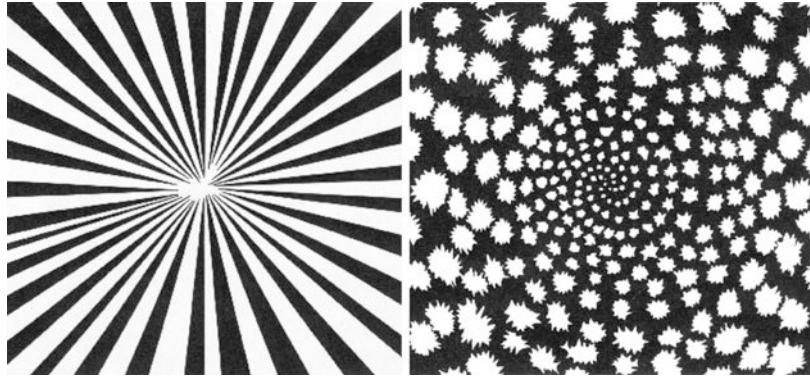
Visual Hallucinations and Migraine Auras,

Fig. 1 Left panel: Class (a) Honeycomb hallucination generated by Marijuana (Redrawn from Clottes and Lewis-Williams 1998). Right panel: Class (b) Cobweb petroglyph (Redrawn from Patterson 1992)



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Fig. 2 Left panel: Classes (c) and (d) funnel and spiral hallucinations generated by LSD (Redrawn from Oster 1970)



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Fig. 3 Lattice tunnel hallucination (Reproduced from Siegel (1977), with permission from the artist Alan D. Iselin)

Klüver (1966). Figure 3, for example, shows an artist's impression of a hallucination which is *colored* and contains both lattice and tunnel elements.

In addition it seems that the first images to form during the experience are the elementary geometric forms, but later more complex forms appear. Figure 4 shows an impression of the progression of hallucinatory imagery from simple to complex.

Modeling the Neocortex

In order to develop an explanatory theory of how and where such imagery is generated in the brain, it is necessary to find a mathematical way to reduce the immense complexity of neural circuitry to something that is much simpler. This was the

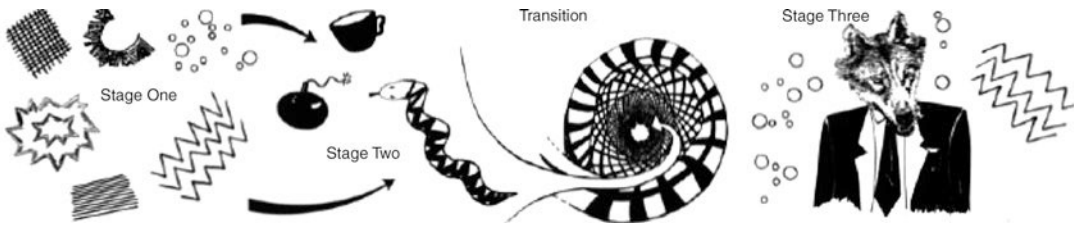
starting point of the initial theory developed by Wilson and Cowan (1972, 1973), and used later by Ermentrout and Cowan (1979) to model hallucinations. In this theory the neocortex, specifically the visual cortex (V1), is modeled as a two-dimensional spatially homogeneous slab, with translation and rotation symmetry. It therefore has the symmetry of rigid body motions in the plane $\mathbb{R}^2$, i.e., the symmetry of the Euclidean group in the plane, $\mathbb{E}(2)$. It follows that the normal modes of vibration of V1 are *plane waves* of the form $\exp(i\mathbf{k} \cdot \mathbf{x})$, where $\mathbf{k}$ is the wave number or spatial frequency of the waves. This implies that if the form constants are generated in V1, then the type II non-contoured form constants are likely to be superpositions of such normal modes.

Pattern Formation in Neural Networks

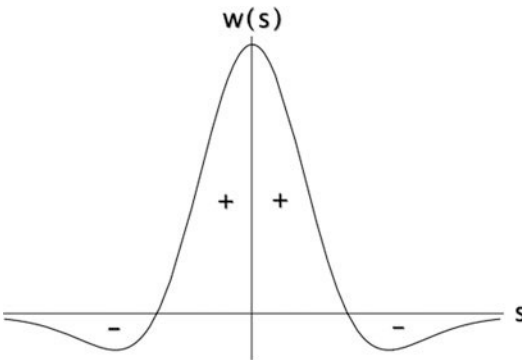
This immediately poses the problem: how do stripes form in neural networks? This problem was solved by Ermentrout and Cowan by exploiting an analogy between neural networks with excitatory and inhibitory connections and Turing's theory of the formation of periodic patterns of stripes and spots in diffusion-coupled chemical reactions (Turing 1952). We can summarize the neural model in terms of the equation:

$$\frac{\partial}{\partial t} u(\mathbf{x}, t) = -\alpha u + \mu \int w_{\text{lat}}(|\mathbf{x} - \mathbf{x}'|) f[u(\mathbf{x}')] d\mathbf{x}' \quad (1)$$

where $u(\mathbf{x}, t)$ is neural activity, α is the decay constant, μ is the coupling strength parameter, w_{lat} is the effective Mexican Hat weighting



Visual Hallucinations and Migraine Auras, Fig. 4 Stages in the development of complex hallucinations (Redrawn from Clottes and Lewis-Williams 1998)

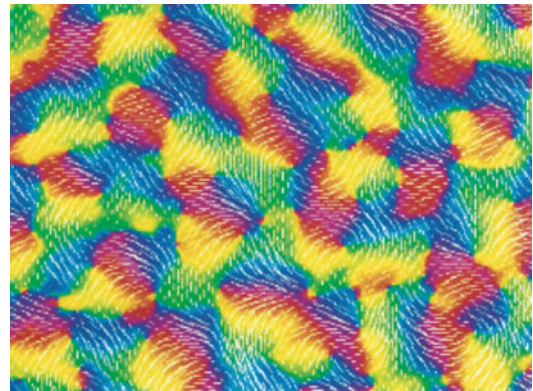


Visual Hallucinations and Migraine Auras, Fig. 5 The effective "Mexican Hat" weighting function

function shown in Fig. 5, and $f[u]$ is a nonlinear current function. [Note that because w_{lat} depends on the *magnitude* of the distance between $\mathbf{x}$ and $\mathbf{x}'$, it is invariant to rotations and is thus isotropic.]

Depending on the nature of the nonlinear function $f[u]$, Eq. 1 will generate periodic stripe or spot patterns. Thus, if f is dominated by the quadratic term in its Taylor series expansion, it will generate spots. Conversely if f is predominantly cubic, it will generate stripes. (See the article by Ermentrout & Billock in this volume for more details.) Note that periodic spot patterns are really superpositions of plane waves, i.e., stripe patterns (Fig. 6).

However, there is one other essential aspect to the theory. This concerns the fact that there exists a *topographic map* from the retina and visual field onto V1, the cortical retina. Away from the fovea this map from visual field coordinates (r, θ) to V1 coordinates (x, y) takes the form $x = \log r, y = \theta$, which is a form of the complex logarithm (Schwartz 1977; Cowan 1977). The remarkable fact is that under such a map, type II form



Visual Hallucinations and Migraine Auras, Fig. 6 Distribution of orientation preferences in Macaque V1 obtained via optical imaging. Different orientation preference patches are pseudo-colored (Redrawn from Blasdel 1992)

constants transform into superpositions of plane waves. This is the content of the Ermentrout-Cowan theory.

A Theory of Type I and II Form Constants

The extension of the Ermentrout-Cowan theory to account for the generation of type I form constants took 22 years. In large part this was due to the lack of experimental data on the distribution of iso-orientation preference patches in V1. It was not until Blasdel (1992) published the first optical imaging study of orientation tuning in V1 (see 6) that a solution began to emerge (Wiener 1994; Cowan 1997). Further studies combining cell staining techniques with optical imaging by Bosking et al. (1997) and Eysel (1999) led to a detailed theory (Bressloff et al. 2001).

This theory is based on the discoveries of Hubel and Wiesel (1959, 1962, 1974) that V1 is organized to detect visual features of retinal images, especially the orientation of contrast edges. Hence the organization into locally iso-orientation preference patches. This suggested to me circa 1993 that orientation preference should be treated as an internal V1 coordinate. This ultimately led to the Bressloff et al. model in which the V1 coordinate system becomes (x, y, ϕ) and the space $\mathbb{R}^2 \times \mathbb{S}$ where $\mathbb{S}$ is the circle. But the normal modes of vibration of the circle are sinusoidal, and in the case of orientation preference, they take the form $\cos 2\phi$, since orientation preference is a π -periodic variable. It immediately follows that the normal modes of vibration of V1 should be plane waves whose amplitude is modulated by $\cos 2\phi$, e.g., $\cos 2\phi \cos(\mathbf{k} \cdot \mathbf{x})$.

A Modified Retino-Cortical Map

However, there is now a new problem with the retino-cortical map. Inspection of the Bosking et al. paper indicated that there is an additional symmetry in V1 connectivity. Bosking et al. found that in the tree shrew, the horizontal connections between V1 Hubel-Wiesel hypercolumns connect corresponding iso-orientation patches of similar preference, and remarkably, the direction of such connections is *parallel* to this preference. Thus, if the orientation preference changes from ϕ to ϕ' , the direction must shift by $\phi - \phi'$. It turns out that this symmetry is used in computer vision (Zweck and Williams 2000, 2004) and is called a *shift-twist* symmetry. Remarkably it is used to preserve Euclidean symmetry in the plane when transforming to a discrete lattice, as is V1. This tells us that any model of V1 requires the rotation operator to have the shift-twist symmetry property. Thus, the retino-cortical map must express this symmetry. This is part of the Bressloff et al. model. Figure 7 shows the details of V1 circuitry.

Extending the Ermentrout-Cowan Model

Equation 1 is easily extended to incorporate such a connectivity pattern. The modified equation takes the form:

$$\frac{\partial}{\partial t} u(\mathbf{x}, \phi, t) = -\alpha u + (\mathbf{x}, \phi, t) + \mu \int_0^\pi \int_{\mathbb{R}^2} w(\mathbf{x}, \phi | \mathbf{x}', \phi') f[u(\mathbf{x}', \phi', \dots, t)] \frac{d\mathbf{x}' d\phi'}{\pi} \quad (2)$$

where $w(\mathbf{x}, \phi | \mathbf{x}', \phi')$ is the weight of connections between neurons at $\mathbf{x}$ tuned to the orientation ϕ , and neurons at $\mathbf{x}'$ tuned to ϕ' . We take the weighting function to decompose as

$$w(\mathbf{x}, \phi | \mathbf{x}', \phi') = w_{\text{loc}}(\phi - \phi') \delta(\mathbf{x} - \mathbf{x}') + \beta w_{\text{lat}}(\mathbf{x} - \mathbf{x}', \phi') \delta(\phi - \phi') \quad (3)$$

where $w_{\text{loc}}(-\phi) = w_{\text{loc}}(\phi)$, and β is the strength of the lateral coupling. The effects of the Dirac delta functions $\delta(\mathbf{x} - \mathbf{x}')$ and $\delta(\phi - \phi')$ acting inside the integrals are to *localize* the action of w_{loc} to $\mathbf{x}$ and w_{lat} to ϕ . The weighting function then contains a local part that is *isotropic* in ϕ (and inhibitory), and a lateral part that is *anisotropic* (and excitatory). In addition because lateral connections lie only along the direction of the orientation preference, we can see that

$$w_{\text{lat}}(\mathbf{x}, \phi) = w(R_{-\phi} \mathbf{x}) \quad (4)$$

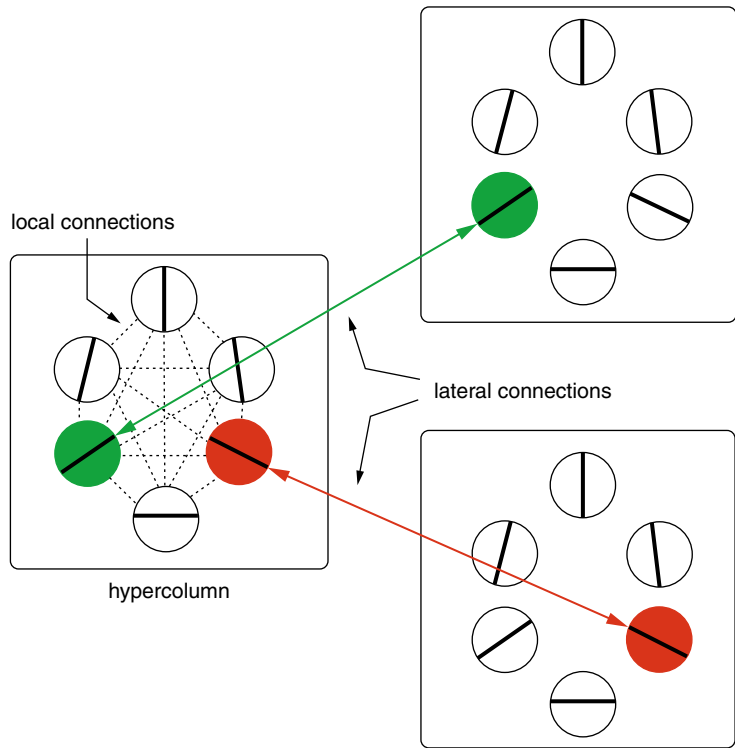
where R_θ is the matrix operation that rotates the vector $\mathbf{x}$ by the angle θ . The effect of this rotation is that we can rewrite $w_{\text{lat}}(\mathbf{x} - \mathbf{x}', \phi)$ as $w_{\text{lat}}(R_{-\phi}(\mathbf{x} - \mathbf{x}'))$. The net effect of all this is that we can preserve Euclidean symmetry by redefining the rotation operation to express the above property of the weighting function, by defining the rotation operator to be not only $R_{-\phi} \mathbf{x}$; but also a label change of the orientation variable from ϕ to $\phi - \phi'$.

From the Euclidean Plane to the Euclidean Lattice

Figure 6 indicates that we need to model V1 as a lattice rather than a plane. This implies that V1 is almost *crystalline*. It follows that only the finite subgroups of $\mathbb{E}(2)$ are relevant in calculating the normal modes of vibration of V1. These subgroups are the *dihedral* groups $\mathbb{D}_n$, with $n = 2, 3, 4$, and 6 , and rotation angles that are multiples

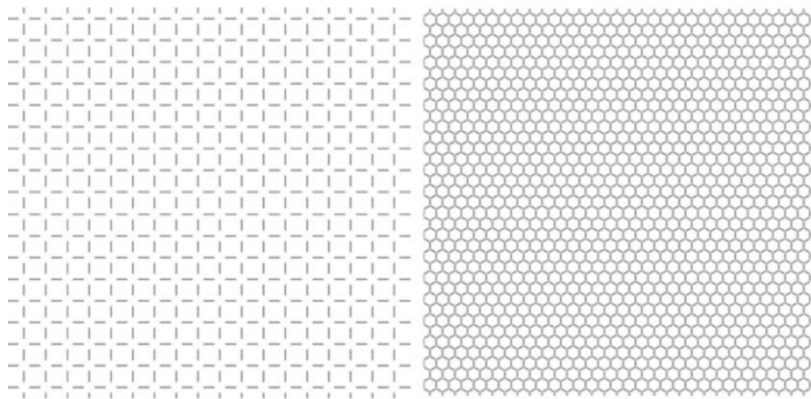
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Fig. 7 Illustration of the isotropic local connections within a hypercolumn and the anisotropic lateral connections between hypercolumns. Connections between iso-orientation patches within any hypercolumn are inhibitory. Connections between iso-orientation patches in different hypercolumns are excitatory (Redrawn from Bressloff et al. 2001)



Visual Hallucinations and Migraine Auras,

Fig. 8 (Left panel) Contoured even axial planform on the square lattice. (Right panel) Contoured even axial planform on the hexagonal lattice



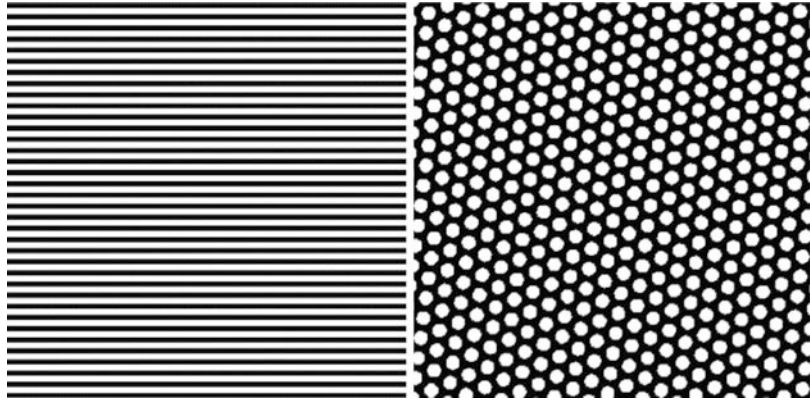
of π/n , corresponding to rectangular, rhombic, triangular, square, and hexagonal symmetry. Thus, the normal vibration modes of the lattice model of V1 are periodic lattice patterns with such symmetries. In what follows we refer to these patterns as *doubly periodic planforms*.

As a consequence, stable solutions of Eq. 2 comprise both even and odd contoured planforms of the forms, respectively, $u_E(x) = \cos 2\phi \cos(\mathbf{k} \cdot \mathbf{x})$ and $u_O(x) = \sin 2\phi \cos(\mathbf{k} \cdot \mathbf{x})$. Only the

even solution $u_E(\mathbf{x})$ generates contour completing even planforms, and it can be selected for by introducing a little spread in the lateral connectivity. In addition the non-contoured form $u(\mathbf{x}) = \cos(\mathbf{k} \cdot \mathbf{x})$ is also a stable solution. Thus, type I planforms are obtained from the even contour completing solutions, and type II planforms are obtained as in the original Ermentrout-Cowan theory. Figures 8 and 9 show the appearance of these solutions in V1 spatial coordinates, and

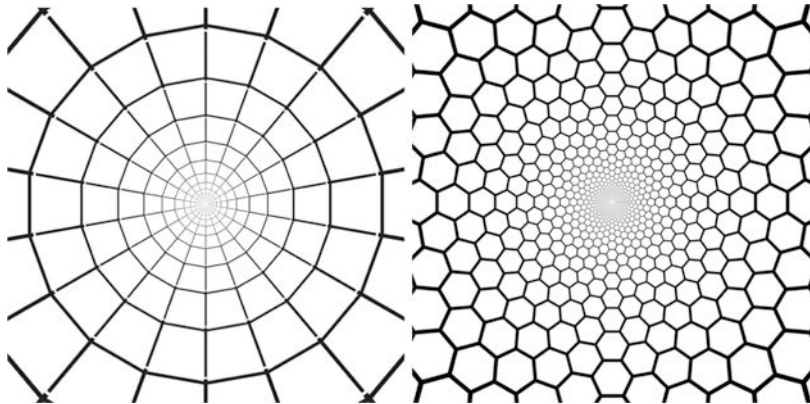
Visual Hallucinations and Migraine Auras,

Fig. 9 (Left panel) Non-contoured even axial planform on the square lattice. (Right panel) Non-contoured even axial planform on the hexagonal lattice



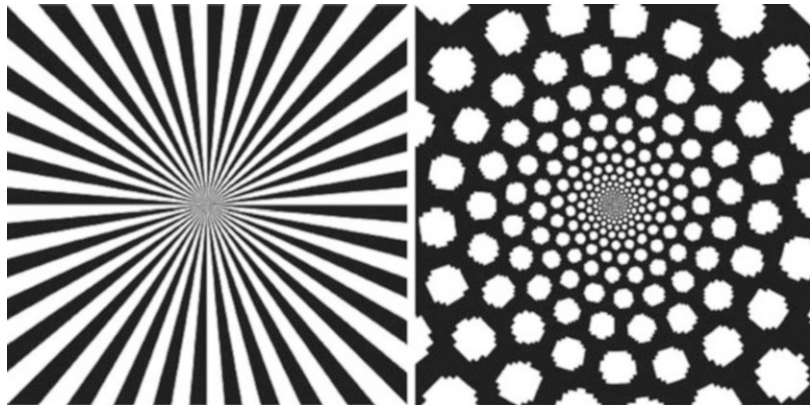
Visual Hallucinations and Migraine Auras,

Fig. 10 (Left panel) Contoured even axial planform on the square lattice. (Right panel) Contoured even axial planform on the hexagonal lattice



Visual Hallucinations and Migraine Auras,

Fig. 11 (Left panel) Non-contoured even axial planform on the square lattice. (Right panel) Non-contoured even axial planform on the hexagonal lattice



Figs. 10 and 11 show their appearance in the visual field.

It will be seen that these visual field planforms correspond precisely to type I and type II form

constants. Thus, the Bressloff et al. extended Ermentrout-Cowan model solves the problem of modeling the V1 origin of the Klüver form constants.

Further Extensions of the Model

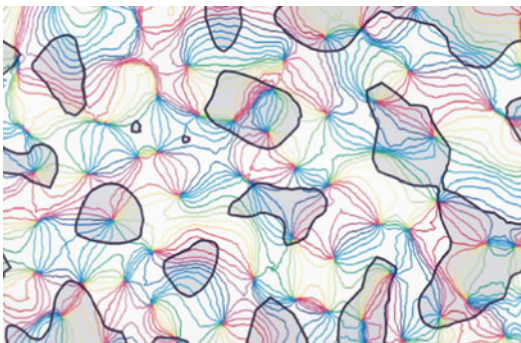
Spatial Frequency Tuning

There are many other problems involving hallucinations. For example, optical image studies by Hübener et al. (1997) revealed that V1 is also organized into iso-spatial frequency preference patches, as shown in Fig. 12. This suggested to Bressloff and Cowan (2002) an extension of the model introduced in Bressloff et al. (2001) in which a second internal coordinate $\theta \propto \log p$, where p is the spatial frequency preference; and θ is a second angular component of the sphere S^2 . Thus, the space of V1 is now $\mathbb{R}^2 \times S^2$, and the two internal coordinates ϕ and θ are the angular coordinates of the sphere, with ϕ denoting the longitude; and θ the latitude. The poles of the sphere correspond to points where $p = p_{\min}$ and $p = p_{\max}$. It follows that the normal modes of the sphere S^2 now modulate the normal modes of the plane $\mathbb{R}^2$. But the normal modes of the sphere are *spherical harmonics*, the lowest order terms of which are products of terms such as $\cos 2\phi$ and $\cos 2\theta$. Thus, the requisite normal modes of $S^2 \times \mathbb{R}^2$ are of the form $\cos 2\phi \cos \theta \cos(\mathbf{k} \cdot \mathbf{x})$. The resulting Bressloff-Cowan spherical model can account successfully for the generation of both type

I and type II form constants, within a single unified framework, and therefore has some advantages over the earlier models. It has the further advantage that it may be possible to extend such a formulation to include hallucinatory images with color, depth, and motion.

Intrinsic Fluctuations

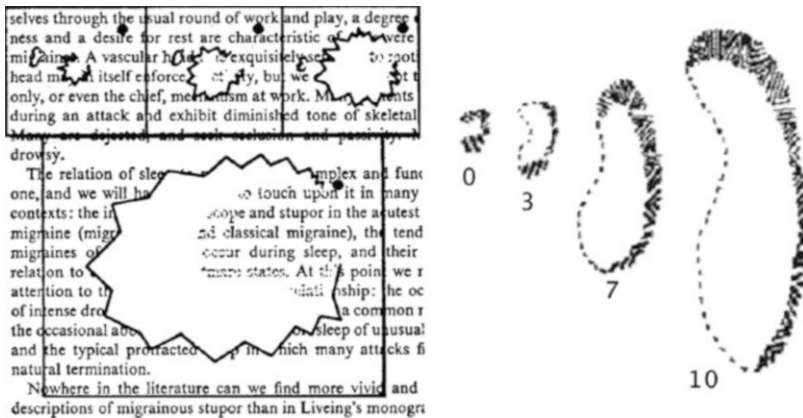
The work described earlier is all carried out within the framework established in the Wilson-Cowan equations. But these are *mean field* equations: they do not take account of the effects of correlations between differing neural sites, nor of the effects of intrinsic fluctuations of neural activity. It took just over 40 years to develop the required extensions. The resulting Stochastic Wilson-Cowan equations (Buice and Cowan 2007, 2009; Buice et al. 2010) can be used to analyze the effects of correlations and intrinsic fluctuations on the threshold for triggering hallucinations (Butler et al. 2012). The results indicate that in a general randomly connected network, fluctuation-induced hallucinations are ubiquitous. However, in a network connected with the V1 architecture described earlier, hallucinations only appear under mean field conditions, i.e., they only appear when parameters such as connection strengths change. This is consistent with data on the occurrence of hallucinations. Thus, it can be inferred that the long-range horizontal connections between V1 hypercolumns *stabilize* it against the effects of intrinsic noise. A similar result was found by Kaschube et al. (2010) in connection with the development of V1 iso-orientation preference patches.



Visual Hallucinations and Migraine Auras, Fig. 12 Relationship between spatial frequency and orientation maps. Gray regions denote low spatial frequency. Note that iso-orientation contours tend to cross the border of spatial frequency domains at right angles and that the *pinwheel centers* or singularities of orientation preference are often located at the centers of either low or high spatial frequency domains (*not highlighted*) (Redrawn from Hübener et al. 1997)

Migraine Auras

The final topic to be reviewed in this article concerns the *fortification* patterns, sometimes called *scintillating scotomas*, seen in migraine auras. Figure 13 shows two well-known examples of such scotomas. From these and similar sequences, it is possible to estimate the propagation velocity in V1 coordinates at about 1.5–3 mm/min, using the retino-cortical map. The scotomas look like



Visual Hallucinations and Migraine Auras, Fig. 13 *Left panel:* the development of a scintillating scotoma experienced while reading a book. The sequence starts with the upper-left panel and proceeds clockwise.

The entire episode lasts for about 20–30 min (Redrawn from Gowers 1904). *Right panel:* another scintillating scotoma observed during a migraine attack. Observed at times $t = 0, 3, 7$ and $t = 10$ min (Redrawn from Lashley 1941)

expanding circular waves in V1 coordinates (Grüsser 1995).

There have been a number of attempts to model the spread of such patterns, essentially by propagating a traveling wave of spreading depression over a model of V1, based largely on an early paper by Tuckwell and Miura (1978). Several papers along these lines have subsequently been published, e.g., Reggia and Montgomery (1996) and Dahlem and Müller (2004). The paper by Reggia and Montgomery (1996) tries to take into account V1 circuitry but lacks any representation of orientation preference and therefore fails to generate the appropriate local patterns seen by observers. It remains to develop a model including orientation preference in V1 circuitry that is capable of generating the patterns shown in Fig. 13.

Concluding Remarks

The topic of visual hallucinations covers many aspects which we have not touched on in this short article, which has been written in a somewhat parochial fashion. The reader is referred to a recent extensive review of the topic by Billock and Tsou (2012) for a less technical, but more extensive review.

Cross-References

► [Flicker-Induced Phosphenes](#)

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Visual Illusions

► Visual Illusions, Models of

Visual Illusions, Models of

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Synonyms

[Computational models of visual illusions; Perceptual errors; Visual illusions](#)

Definition

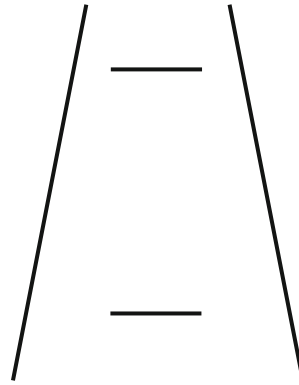
A visual illusion is a discrepancy between perception and reality that stands out as an anomaly. This entry describes general approaches as well as specific models that have influenced our current understanding of the mechanisms leading to visual illusions. A “model” here means a set of computations aimed at making quantitative

predictions about the appearance of a visual stimulus. In some cases the computations are couched in terms of neural machinery, and in others the language of perceptual psychology. All the models discussed are generic in the sense that they aim to explain more than one illusion; however, none can be said to be truly universal. Importantly, the models are not necessarily mutually exclusive: many of them echo back to the “perceptual hypothesis” approach that is first described. Each model is accompanied by an example or two of the illusions it aims to explain. The entry does not however provide a comparative appraisal of the various models – this is beyond its scope – but references to critiques of many of the models are included. An important class of illusion that is not discussed is visual aftereffects, the perceptual distortions observed following adaptation (typically the result of prolonged viewing) to a related stimulus. The mechanisms of adaptation deserve an entry of their own, and the interested reader should consult the entry on aftereffects by James Bednar.

Detailed Description

What Are Visual Illusions?

Although there is no universally accepted definition of a visual illusion, most have defined it as a discrepancy between perception and reality (e.g., Gillam 1998; Gregory 2004; Wade 2005). This definition is arguably too broad, however, since it encompasses perceptual phenomena that in spite of being discrepant with reality do not make it into the pantheon of illusions that adorn the books, websites, and blogs that deal with the subject. A rainbow, for example, is perceived as a series of distinct bands of color (red, orange, yellow, green, etc.), yet physics informs us that its component wavelengths vary continuously not categorically across its width, a clear-cut instance of perception contradicting reality. Yet rainbows are not considered to be visual illusions. Dejan Todorovic (personal communication) suggests that we ascribe illusions to phenomena that are “exceptions to the rule,” the rule being that the dimension of interest is normally perceived



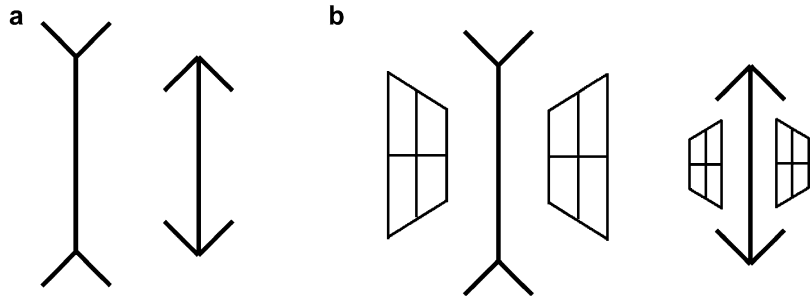
Visual Illusions, Models of, Fig. 1 The Ponzo illusion. The two horizontal lines are the same length

accurately. Thus, for example, the Ponzo and Müller-Lyer illusions in Figs. 1 and 2 are illusions because our perception of length, or rather relative length, is generally accurate, so the misperceptions stand out as anomalies. Color vision, on the other hand, due to its physiological limitations, is unable to tell us about a stimuli’s precise wavelength composition, so the rainbow does not strike us as an anomaly. In Todorovic’s words, for something to qualify as an illusion, it does not suffice that you are wrong; you must also be able to be right.

Perceptual Hypothesis Approach

One of the most influential theories of visual illusions is that we construct perceptual hypotheses about what we see based on our knowledge of the visual world acquired during evolution and/or development. Because the information provided by our senses is often limited or ambiguous, perceptual hypotheses impose structure to our visual experience, making up for the deficiencies of sense data. In general this results in more accurate perception, but under some circumstances, it leads to mistakes. The origins of the perceptual hypothesis approach lies in Helmholtz’s notion of “unconscious inference” (Helmholtz 1866/1962) and to some extent in the “organizational principles” of Gestalt psychologists (reviewed by Todorovic 2008). Its most notable proponent

Visual Illusions, Models of, Fig. 2 (a) the Müller-Lyer illusion. The vertical lines are the same length. (b) Gregory's explanation – see text for details



was the psychologist Richard Gregory (1966/1967, 2004), while the “empirical” theory of Purves and Lotto (2003) and the Bayesian approach to illusions (e.g., Weiss et al. 2002), both discussed below, are arguably its recent expressions.

The Ponzo illusion in Fig. 1 is a textbook example of the approach. The horizontal lines in the figure appear different in length even though they are physically the same. According to the perceptual hypothesis approach, we make the reasonable assumption that the upper line is further from view because the lines on either side appear to recede into the distance. However, because the retinal-image length of the horizontal lines is the same, we infer that the upper line must be physically longer, and that is how it is perceived.

Gregory's explanation for the Müller-Lyer illusion in Fig. 2 follows a similar logic (though see a different explanation in the section on “Channel Models”). Gregory suggests that the vertical line with the inward-pointing fins is interpreted as the outside corner of a building, whereas the line with outward-pointing fins is interpreted as the inside corner of a room. According to Gregory we assume we are closer to the outside corner than the inside one, so the line with inward-pointing fins, which casts the same-size image on our retina as the line with outward-pointing fins, by inference must be shorter, and that is how it is perceived.

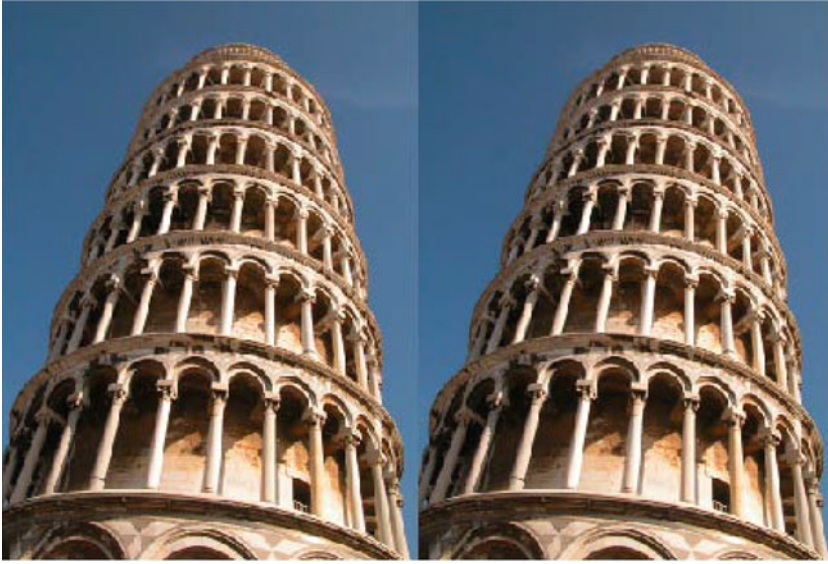
Another illusion that lends itself readily to the perceptual hypothesis approach is the leaning tower illusion shown in Fig. 3 (Kingdom et al. 2007). The two photographs are identical, yet the tower on the right appears to lean more. The reason for the illusion is straightforward. If the

two towers rose physically at the same angle, their corresponding outlines would converge in the photograph due to perspective but be perceived as parallel because of the brain's inbuilt knowledge of perspective. However, in the pair of photographs in Fig. 3, the corresponding outlines do not converge but are parallel, so the visual system infers that the two towers must be diverging as they recede, and this is how they are perceived.

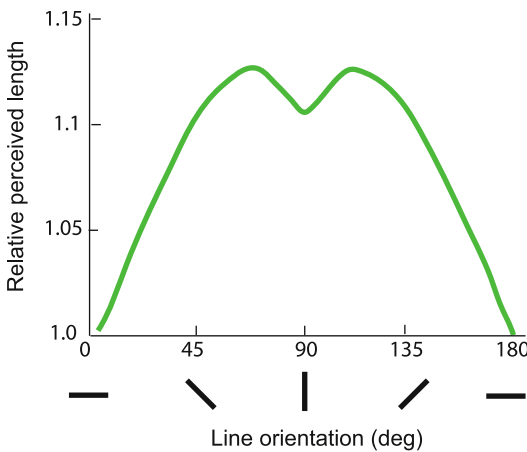
Empirical Model

An influential variant of the perceptual hypothesis approach is the “empirical” model best associated with Dale Purves and Beau Lotto (summarized in Purves and Lotto 2003) but which has many antecedents (e.g., Craven 1993). The model emphasizes the effect on perception of inbuilt knowledge of the statistical relationships in natural scenes acquired through accumulated experience, i.e., “empirically.” The empirical model has been applied to an impressive number of illusions (Purves and Lotto 2003). The general idea can be gleaned by considering how the model applies to the relationship between the orientation and perceived length of lines, as shown in Fig. 4. The figure shows that although perceived length is longer for vertical than horizontal lines – this is the well-known horizontal-vertical illusion shown in Fig. 5 – lines that are angled 20–30° off vertical are perceived to be the longest.

Craven (1993) measured the density of features along various orientations of lines in the 2D projection of images of natural scenes and found that feature density followed closely the pattern of perceived length shown in Fig. 4. Assuming feature density correlates with physical line length, Fig. 4 therefore embodies the relationships

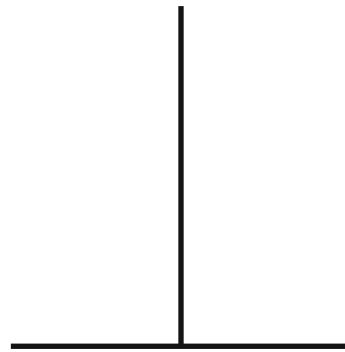


Visual Illusions, Models of, Fig. 3 The leaning tower illusion. The two photographs of the Leaning Tower of Pisa are identical



Visual Illusions, Models of, Fig. 4 Perceived length of lines as a function of orientation (Based on Fig. 7.8 in Purves and Lotto (2003))

between the lengths of lines in the 3D image that project to the same length in the 2D image. More recently, Howe and Purves (2002) confirmed this physical relationship using a range finder that measured the actual length of lines in natural scenes as a function of their orientation and 2D projection lengths. Both groups of investigators conclude that variations in perceived length as a function of orientation reflect the variations in the



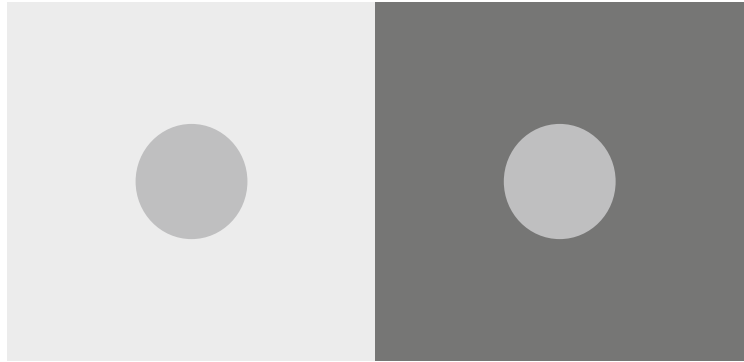
Visual Illusions, Models of, Fig. 5 The horizontal-vertical illusion. The two lines are the same length

physical lengths of 3D contours that give rise to equal-length contours in the 2D projection. In other words we perceive vertical lines as longer than horizontal lines because we have learned that lines that project vertically are on average longer than lines that project horizontally.

The physical variations in line length in the 2D projection are likely due in part to foreshortening, since the ground plane, upon which many objects lie, is tilted around the horizontal axis. However, foreshortening does not explain why perceived length is longest for lines 20–30° off vertical

Visual Illusions, Models of,

Fig. 6 Simultaneous brightness/lightness contrast. The two *gray* patches have the same luminance



(Craven 1993). The validity of the empirical approach however is not contingent on its ability to explain the physical basis of the image statistics that it assumes drives perception, only on showing a correlation between image statistics and perception.

The empirical approach has also been applied to a variety of brightness illusions (Purves and Lotto 2003). In the case of the simultaneous contrast illusion shown in Fig. 6, Purves and Lotto argue that patches on dark backgrounds are more likely to be lying in shadow compared to patches on bright backgrounds, and hence, two equal-in-luminance patches, one on a dark and one on a bright background, will likely have different reflectances, and that is how they are perceived (Purves and Lotto 2003 – for details see Williams et al. 1998). This explanation of simultaneous brightness contrast echoes back to Helmholtz’s explanation of simultaneous color contrast (Helmholtz 1866/1962; Kingdom 1997). Other brightness illusions such as the Craik-Cornsweet-O’Brien illusion (Fig. 10) and Mach bands (Fig. 12) are also explained in terms of image relations: in these cases it is suggested that the illusory percepts match physical illumination patterns that often arise because of the way non-diffuse illumination is reflected from the surfaces of three-dimensional objects. The relationship between the empirical and alternative models of brightness illusions is discussed further in Kingdom (2011).

Bayesian Models

Bayesian models of visual illusions also emphasize the importance of prior knowledge on

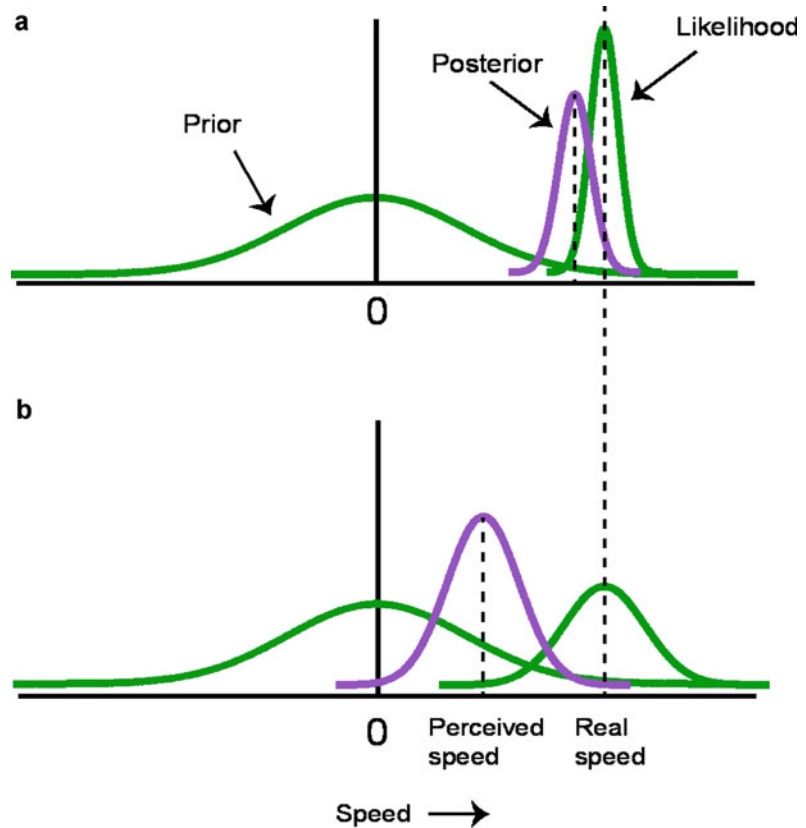
perception but incorporate it into a formal probabilistic framework. In a Bayesian model perception is based on the product of a “likelihood function” derived from sense data and a “prior probability” founded on previously acquired long-term knowledge. This product is referred to as the “posterior probability”; thus

$$\text{Posterior probability} = \text{likelihood function} \\ \times \text{prior probability}$$

To understand how this equation might underpin certain visual illusions, consider why objects appear to move more slowly at low contrast, as one observes when a car moves in fog (Stone and Thompson 1992). According to the Bayesian model applied to perceived speed (Weiss et al. 2002; Hürlimann et al. 2002), our perception of speed is influenced by an inbuilt assumption – the “prior” – that the speed of objects follows a Gaussian function centered on zero (i.e., stationary) with slow speeds being more likely than fast speeds, as shown in Fig. 7. Our primary source of information about an object’s speed however comes from sensory information, but because of internal noise, this information is uncertain. The speed derived from a sensory measurement can thus be modeled as a probability distribution centered on the actual speed of the object, with a spread determined by the amount of uncertainty. This is the likelihood function in Fig. 7. To arrive at a perceptual estimate of speed, the prior and likelihood functions are multiplied to form the “posterior” distribution, and perceived speed is given by the peak of the

Visual Illusions, Models of,

Fig. 7 Bayesian model of the “slow-speed-in-fog” illusion. (a) Model for a high-contrast moving stimulus. (b) Model for a low contrast moving stimulus. See text for details (Figure adapted from Fig. 1 in Hürmann et al. (2002))

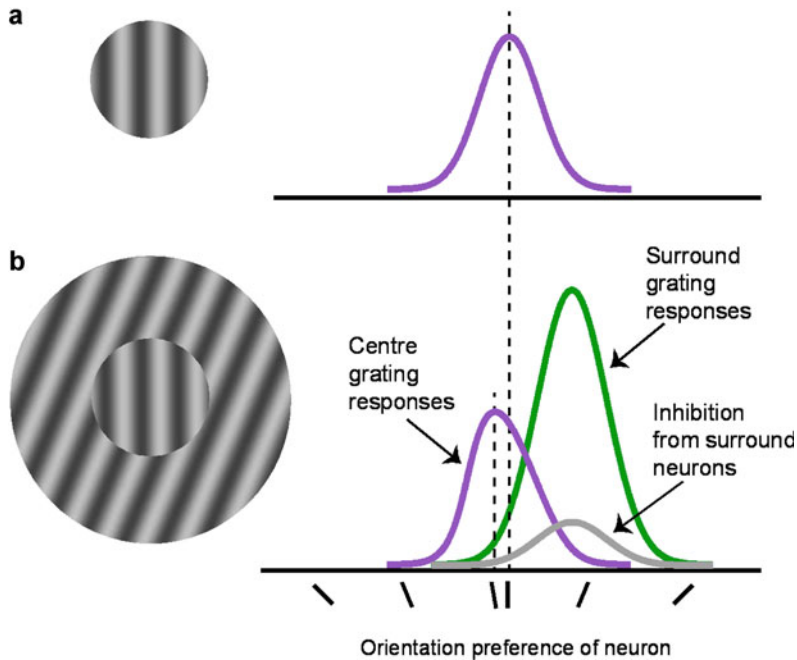


posterior. This peak will tend to be lower than the physical speed because of the influence of the prior but importantly by an amount that depends on the spread, or uncertainty of the likelihood function. At high contrasts the likelihood function is sharp due to a high signal-to-noise ratio and hence will be little affected by the prior, but at low contrasts, the relatively lower signal-to-noise ratio results in a wider spread, and thus the peak of the posterior will shift to the left, resulting in a lower perceived speed. Other motion illusions have been wholly or in part explained by the influence of the prior assumption that motion is slow or zero (Weiss et al. 2002). A critique of the Bayesian approach as applied to the speed illusion and to cognitive neuroscience in general can be found in Bowers and Davis (2012).

Channel Models

A number of visual illusions have been explained in terms of the activities of visual neurons with

narrowband spatial-frequency and orientation tuning, such as the simple cells found in primate area V1, often termed “channels.” Critical to this class of model is that the channel outputs are subject to nonlinear interactions such as orientation inhibition (Blakemore et al. 1970; Motoyoshi and Kingdom 2003; Schwartz et al. 2009) and contrast normalization (Carandini and Heeger 2012). Consider the standard model of the tilt illusion, an illusion first reported by Gibson (1937). Figure 8 shows that a vertical grating embedded in a rightward-tilted surround grating appears slightly tilted to the left. The explanation of this illusion is that it is caused by inhibitory interactions between orientation-selective neurons responding to the different parts of the stimulus (Blakemore et al. 1970; Carpenter and Blakemore 1973; Georgeson 1973; Schwartz et al. 2009). In Fig. 8, the green and purple Gaussian-shaped plots represent the responses of orientation-selective neurons as a function of their



Visual Illusions, Models of, Fig. 8 Tilt illusion and orientation-inhibition model. When the vertical grating in (a) is embedded in a tilted surround (b), it appears tilted slightly in the opposite direction. The model on the right shows the responses of orientation-selective neurons as a function of their orientation preference to the center

(purple curve) and surround (green curve) gratings. Inhibition from the surround neurons is modeled as a the gray Gaussian distribution that when subtracted from the center, grating response causes it to become slightly skewed to the left, resulting in the shift in perceived orientation of the grating

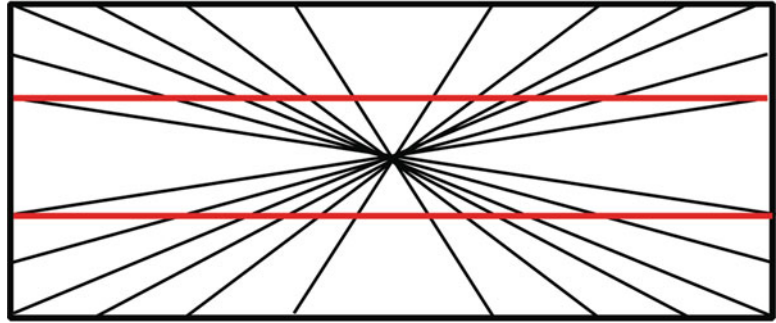
preferred orientation. For the vertical grating in Fig. 8a, the response distribution is centered on the orientation of the stimulus. According to the model, perceived orientation is determined by the centroid or some other measure of central tendency of the distribution, resulting in veridical, i.e., “accurate,” perception of the grating’s orientation. However, when the grating is embedded in the rightward-tilted surround (Fig. 8b), the neurons responding to the surround (green plot) inhibit those responding to the center grating (subtract gray plot from unskewed purple plot), causing the latter’s response distribution to become slightly skewed to the left, together with its centroid.

The tilt illusion is sometimes referred to as “acute-angle expansion,” a term that characterizes other geometrical distortion illusions such as the Poggendorff, Zöllner, and Hering illusions (Westheimer 2008), the last of which is shown in

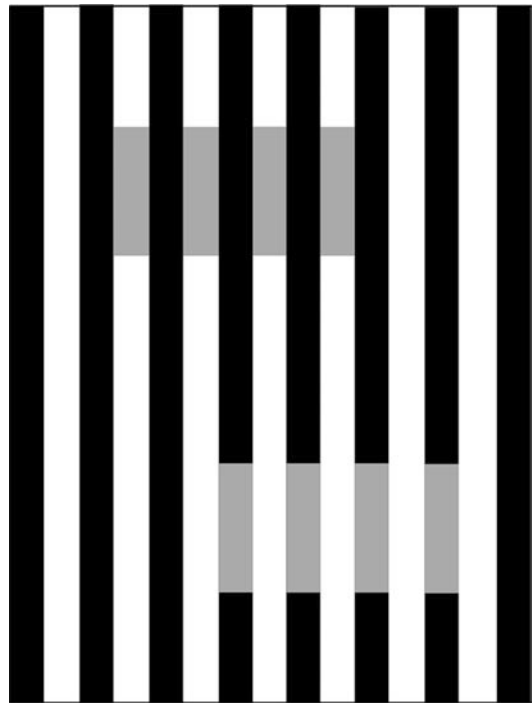
Fig. 9. Orientation inhibition is thus a possible explanation for these illusions as well.

In the above channel model, the perceived orientation of a pattern is given by the centroid (or some other measure of central tendency) of the distribution of neural responses across orientation preference. Centroids figure also in the explanation of geometrical illusions, but in this instance, it is the centroid of the distribution of pattern elements in space. Morgan et al. (1990) (see also Bulatov et al. 2011) have suggested that the computation of spatial centroids by vision serves to facilitate the fast and reliable estimation of an object’s location independently of its size and shape complexity and propose that the automatic extraction of centroids is the cause of the Müller-Lyer illusion (Fig. 2a). The idea is that the positions of the ends of the horizontal lines are perceptually shifted toward the centroids of the adjacent fins.

Visual Illusions, Models of, Fig. 9 The Hering illusion. The *red lines* are straight yet appear curved

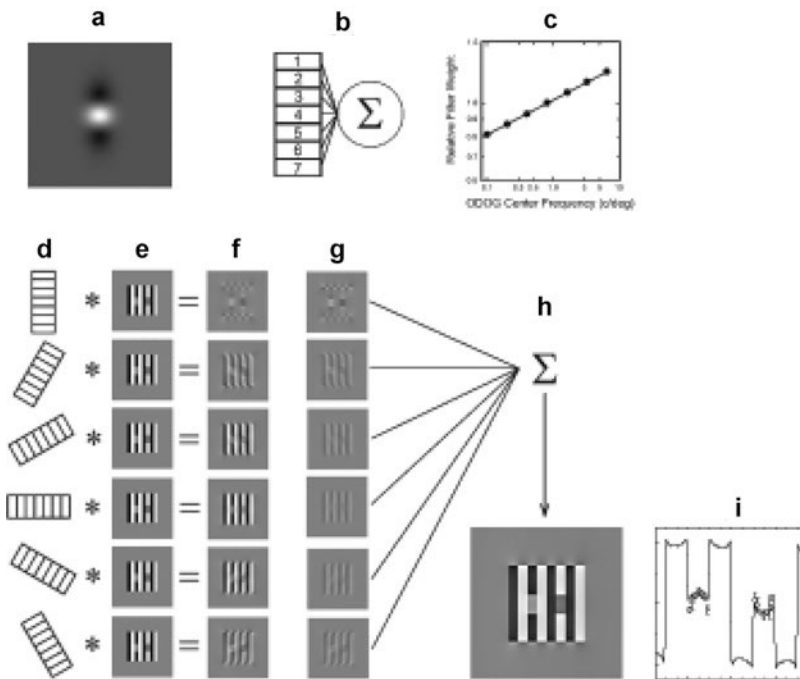


A type of channel nonlinearity that has become the focus for explaining many brightness illusions is contrast normalization. Contrast normalization is the mechanism that tends to equalize the magnitudes of channel responses in a local region of space (Carandini and Heeger 2012). The best-known model of brightness illusions that incorporates contrast normalization is the ODOG (oriented difference-of-Gaussian) model of Blakeslee, McCourt, and colleagues (Blakeslee and McCourt 1999; Blakeslee et al. 2005). Closely related contrast normalization models have been proposed by Dakin and Bex (2003) and by Robinson et al. (2007). Convolving an image with an array of narrowband, linear filters tuned to different spatial frequencies and orientations, and then summing their outputs does not itself predict brightness illusions, because if the filters form a “complete” set, the output will be a more or less veridical copy of the original. In the Blakeslee and McCourt approach, two processes conspire to produce brightness errors. First, very low spatial frequencies are attenuated, and this accounts for a variety of contrast errors such as the well-known illusion of simultaneous contrast shown in Fig. 6 (see also Shapiro et al. 2008). The second is contrast normalization, which has the effect of boosting channels that produce relatively weak responses. Figure 10 shows the illusion known after its discoverer as White’s Effect (White 1979), and Fig. 11 the ODOG model of the illusion. In White’s Effect the gray bars lying on the dark phase of the grating appear lighter than those lying on the white phase, in spite of the fact that the bars on the black phase are surrounded more with white than black and the



Visual Illusions, Models of, Fig. 10 White’s Effect. The short *gray* bars are all of the same luminance, yet the bars on the *white* phase of the grating appear darker than those on the *dark* phase

bars on the white phase more with black than white. Thus, the direction of the illusion is the opposite to that of the simultaneous contrast display in Fig. 6 and is thus in its conventional form an example of “assimilation” (Kingdom 2014a). In the ODOG model, contrast normalization equates the root-mean-square (RMS) output across six orientation channels, each of which is a weighted linear sum of seven spatial-frequency



Visual Illusions, Models of, Fig. 11 ODOG model applied to White's Effect. (a) Filter profile, (b) filters of different spatial scales are summed at a given orientation, (c) filter gains as a function of center spatial frequency, (d) orientations of combined filters, (e) stimulus, (f) result of convolving each stimulus with d, (g) contrast normalization equates RMSs of filter outputs, (h) outputs are

summed across filter orientation, (i) the continuous line is the predicted brightness of a horizontal cross section of the stimulus, while circles are the results of point-wise brightness matching (Figure supplied by B. Blakeslee and M. McCourt, based on Fig. 1 in Blakeslee and McCourt (1999))

channels. The most responsive channels to White's stimulus are the relatively high spatial frequency, vertically oriented channels tuned to the inducer grating. Contrast normalization has the effect of enhancing the relative contribution of the horizontally oriented low-spatial-frequency channels that pool the luminances of the flanking bars with those of the test patches, causing the illusion.

In Dakin and Bex's (2003) model, contrast normalization equates channel responses across spatial frequency, not orientation, and they show that this provides a good explanation for the well-known Craik-Cornsweet-O'Brien illusion (see examples in Todorovic 1987), a version of which is shown in Fig. 12. The figure is created by attenuating the low spatial frequencies, a process termed high-pass filtering, of a two-tone image of Einstein. The result is that the luminances of the uniform regions on either side of the face are

identical yet appear very different in brightness. In Dakin and Bex's model, it is these physically attenuated low spatial frequencies that are enhanced perceptually by contrast normalization, causing the illusory brightness differences. Finally, contrast normalization has been suggested as the cause of the illusory bars known as Mach bands shown in Fig. 14 (Kingdom 2013).

For some illusions, the absence of channels at the high-spatial-frequency end of the spectrum is believed to be the cause. A close relative of the chromatic version of White's Effect is the ring pattern stimulus created by Monnier and Shevell (2003, 2004) shown in Fig. 13. A yellow-orange test ring (Fig. 13a) is embedded in either the lime (Fig. 13d) or purple (Fig. 13e) phases of a circular lime-purple grating, resulting in dramatic differences in hue. The hue of the test ring shifts toward that of the adjacent ring's chromaticity. Yet color

Visual Illusions, Models of, Fig. 12

A version of the Craik-Cornsweet-O'Brien illusion. The luminances on the “dark” on the *left side* and “bright” on the *right side* of the face are the same, as can be seen from the horizontal *rectangle* in the *top middle* that passes across the edge dividing the two sides



assimilation is insufficient to explain the magnitude of the illusion; if one surrounds each test ring with a uniform field of the same chromaticity as the corresponding adjacent ring in the ring pattern (Fig. 13b, c), the illusion is significantly reduced. Monnier and Shevell suggest that the assimilation from the adjacent rings is augmented by contrast effects from the nonadjacent rings. The purple and lime colors stimulate primarily the short-wavelength-sensitive “S” cones of the human color vision pathway, the purple eliciting positive and the lime negative S-cone responses. Monnier and Shevell propose that cortical neurons whose receptive fields have spatially antagonistic S-cone inputs (Conway 2001) cause the shifts in color, as illustrated in Fig. 13f, g. In Fig. 13f the response of the neuron is increased by + S-cone stimulation from the purple adjacent to the test ring and further by -S-cone stimulation from the nonadjacent lime ring, causing the test ring to shift dramatically toward purple. In Fig. 13g the combination produces instead a strong negative response, causing an opposite shift toward lime. If very fine-scale S-cone-sensitive neurons were present, they would tend to counteract the shifts produced

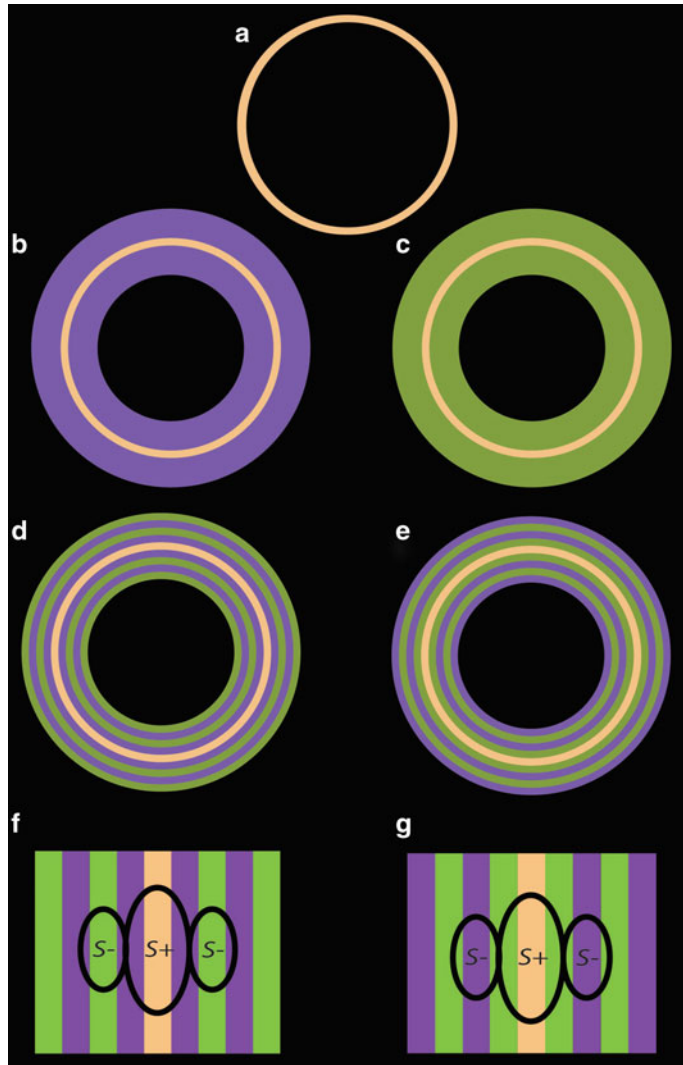
by the neurons whose receptive fields are shown in the figure with the result that there would be no illusion.

Edge-Bar Feature Models

A class of channel model that deserves a section of its own proposes that channel responses are interrogated by rules designed to produce a representation of the input image in terms of “edges” and “bars” (Watt and Morgan 1985; Morrone and Burr 1988; Kingdom and Moulden 1992; Wallis and Georgeson 2012). A good example of how these models apply to visual illusions is their application to one of the best-known brightness illusions, Mach Bands, which are the illusory bands seen at the foot and knee of a luminance trapezoid (Fig. 14a). Although edge-bar feature models differ in the details of the computations involved, the schematic in Fig. 14b–d captures the general idea. In the figure the trapezoid is processed by two channels, one with an “odd-symmetric” response profile (shown in purple) and the other with an “even-symmetric” response profile (shown in green). The “even” channel gives a strong response at the foot and knee of the trapezoid,

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Fig. 13 Monnier and Shevell's (2004) ring patterns and proposed explanation for the illusory differences in hue. The ring shown in **a**, when embedded in the circular lime-purple gratings, **d** and **e** appears to be markedly different in hue depending on the phase of the grating it replaces (lime phase replaced on left, purple phase replaced on right). The effect is not simply due to assimilation from the neighboring bars, as shown in **b** and **c**, which show a reduced effect. **f** and **g** show the explanation based on a center-surround receptive field with antagonistic S-cone inputs – see text for details (The figure is based on Fig. 1 in Monnier and Shevell (2004), reproduced with permission of the authors)

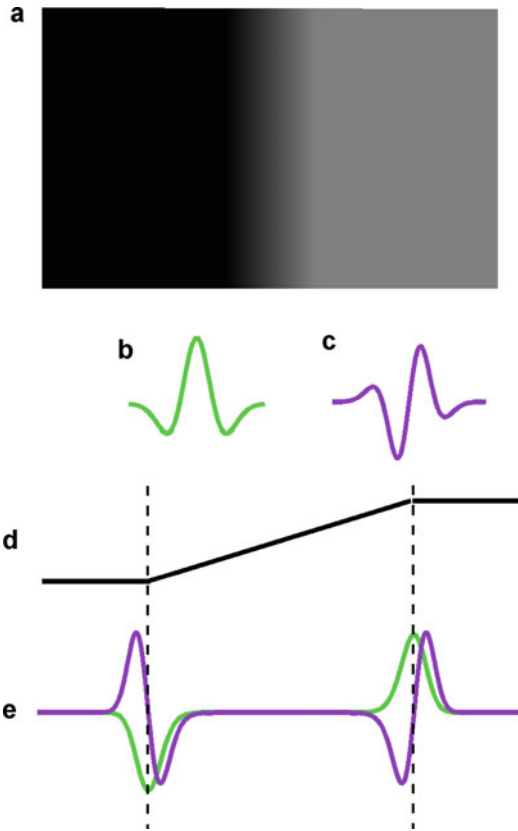


whereas the “odd” channel’s response is zero at these points (the “odd” channel would produce a strong response at the location of a step edge, whereas the response of the even channel would be zero). The relatively greater “even” compared to “odd” response is interpreted as a “bar,” and that is what is perceived. A critical evaluation of edge-bar feature models as applied to brightness illusions can be found in Kingdom (2011).

Gestalt Models

The word Gestalt is German for “shape” or “form,” and in the context of vision is a byword for an organizational principle that groups parts of

stimuli into perceptual wholes, such that the whole is perceived to be greater than the sum of its parts (reviewed by Todorovic 2008). Gestalt grouping principles are believed to underpin a variety of visual phenomena, including illusions. One example is the model of lightness illusions proposed by Gilchrist and colleagues (Gilchrist et al. 1999; Gilchrist 2006) and in a significantly modified form by Bressan (2006), known generically as the “Gestalt anchoring model.” Lightness is the perceived reflectance or “shade of gray” of an object. The term anchoring refers to the process that converts relative lightness values into absolute ones, by associating a particular lightness



Visual Illusions, Models of, Fig. 14 Feature model of Mach bands. (a) a luminance trapezoid, whose profile is shown in (d), produces Mach bands – the illusory dark and bright bars on either side of the vertical midline. (b and c) show, respectively, the receptive-field profiles of an even-symmetric and an odd-symmetric filter. (e) shows the result of convolving the luminance profile in d with the two filters. Note that at the foot and knee of the trapezoid, there is a peak in even-symmetric (*green*) response but zero in the odd-symmetric (*purple*) response. Feature models interpret this relationship as indicating the presence of bars at this point. Note that due to the limitations of electronic reproduction, the pattern in a will not be rendered as accurately as in the laboratory display

(e.g., mid-gray, white) to a particular luminance (mean, maximum). In the Gestalt anchoring model, lightness perception results from the combined operation of multiple anchors within nested image frameworks, with the frameworks determined by Gestalt grouping principles such as “belongingness,” “common depth,” “common fate,” etc.

The principle of Gilchrist and colleagues’ model can be grasped by considering how it applies to the simultaneous contrast display in Fig. 6. The idea is that the stimulus is first divided into two local and one global framework. The global framework comprises the stimulus as a whole, whereas the local frameworks consist of the two surrounds and their respective test patches. Within each framework the anchor is the highest luminance, which is assigned white, and all other regions within the same framework are assigned grays according to their luminance ratio with respect to the anchor. Within the global framework, the white background of the stimulus as a whole is the highest luminance and therefore assigned white, and the two test patches are assigned identical lower lightnesses, since their luminance ratios with respect to the background are the same. However, for the two local frameworks, the patch lightness assignments are different. For the patch on the dark surround, the patch is the highest luminance and therefore assigned white. For the test patch on the light surround, the surround is the highest luminance and therefore assigned white, so the patch is assigned a value relative to it, i.e., mid-gray. The net patch lightnesses are the averages of the lightness values computed from the global framework (both patches equal and mid-gray) and the lightness values computed from the local frameworks (patch on dark surround white, patch on light surround mid-gray). The result is a higher lightness value for the patch on the dark compared to the light surround. Thus, although the global framework has an important influence on the lightnesses of the patches, it is the influence of the two local frameworks that causes the difference in patch lightness and hence the illusion. A critical evaluation of Gestalt anchoring models can be found in Kingdom (2011).

Layer Decomposition Approach

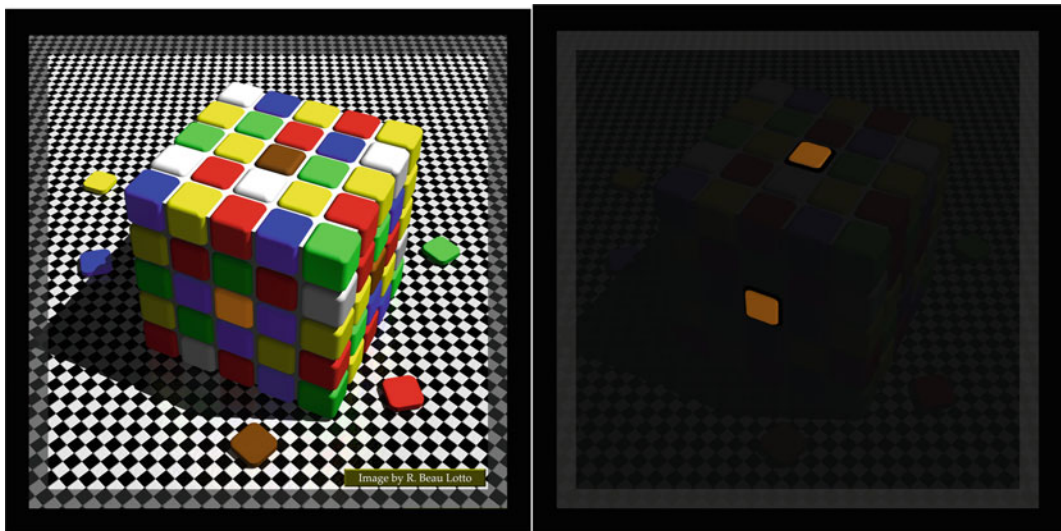
This approach, sometimes referred to as “intrinsic-image models,” posits that many visual illusions, but primarily those of brightness and lightness, are a consequence of the perceptual

decomposition of an image into “layers.” The main layers of interest in this regard are the reflectance (the physical correlate of perceived color and shade of gray), nonuniform illumination (e.g., shadows and shading), and transparency (a material that you can see through) layers. The layer decomposition approach has focused mainly on compelling demonstrations of the influence of nonuniform illumination and transparency on surface lightness, brightness, and color. Some proponents of the layer decomposition approach however go further and suggest that even in displays containing no obvious regions of nonuniform illumination or transparency, layer decomposition occurs with profound consequences for perception (Anderson 1997, 2001; Ekroll et al. 2004). This latter viewpoint has been termed by Kingdom (2011) the “strong” form of layer decomposition approach, to differentiate it from the “weak” form described above that deals only when visible regions of illumination/transparency are present.

The layer decomposition approach has its origin in the studies by Gilchrist and colleagues (Gilchrist et al. 1983; see also Gilchrist 1988), who observed that the magnitude of simultaneous lightness contrast was enhanced when two gray patches, normally seen as surrounded by materials

of different reflectance, were instead seen as lying in different illuminations. The luminance contrasts between the patches and their immediate surrounds were the same under both configurations, so Gilchrist argued that the enhancement of simultaneous contrast could not be due to the effects of local contrast but instead due to the presence of nonuniform illumination.

Computer-graphics technology has led to a plethora of demonstrations of a similar ilk, showing how depictions of transparency (e.g., Adelson 1993; Logvinenko et al. 2005), shading/shadows (Knill and Kersten 1991; Logvinenko 1999; Adelson 1993, 2000; Purves and Lotto 2003), and figure-ground relationships (Anderson and Winawer 2005) have a profound influence on brightness, lightness, and color. A good example is Beau Lotto’s figure of a cube made of colored squares with one side lying in shade (note however that Lotto does not hold to the layer decomposition approach – see Purves and Lotto 2003), shown in Fig. 15. The figure demonstrates that a depiction of nonuniform illumination causes two regions that are identical in color on the page (as revealed on the right of Fig. 15) to appear dramatically different in color. The difference in perceived color is in a direction toward that of the colors the blocks would need to be painted in



Visual Illusions, Models of, Fig. 15 The *middle* blocks on the *top* and *near* faces of the cube are identical in color on the page, as revealed on the *right* when the rest of the image is occluded (Figure courtesy of Beau Lotto)

order to produce the same image were the cube a real object and the shading real illumination (which raises the thorny philosophical question as to whether we should think of such figures as illusions at all!). The central claim of the layer decomposition approach is that the magnitude of the illusory differences in brightness and color in Fig. 15 is much greater than would be expected on the basis of simultaneous contrast (Fig. 6) and that therefore it is the process of layer decomposition, which aims to uncover the “true” lightnesses and colors of the squares, that causes the illusion (Adelson 1993; Anderson and Winawer 2005). However, other researchers have argued that brightness and color contrast play a much bigger role in these illusions than might be supposed and may even be the sole cause of the illusion (Todorovic 2006; Blakeslee and McCourt 2012; Kingdom 2011).

An example of the “strong” form of the layer decomposition approach is Anderson’s (1997,

2001) account of White’s Effect (Fig. 10). According to Anderson, the junctions formed by the ends of the letter bars with the two grating phases, known as “T” junctions, facilitate a process of perceptual scission, such that the gray stripes are treated as if part of a thin transparent veil overlaying the grating bars. According to this account, the gray stripes that are in phase with the dark phase of the grating are perceptually “split” into dark and light layers, with the dark layer simply part of the grating that runs continuously “underneath” and the light layer forming a thin veil “above.” On the other hand, the gray stripes on the white phase are split into a light background layer and a dark veil. Since the veil is the foreground layer, it dominates our perception and hence causes the illusion.

The role of layer decomposition is also revealed in a different type of color (chromatic) visual illusion that is shown in Fig. 16. Our visual system tends to attribute perceived color changes to the reflectance layer, and in the photograph of the tower block, this leads to the misperception that the orange color is paint, whereas in fact it is a sunset illumination on a gray surface. Other examples of such misperceptions are described in Kingdom (2008, 2014b).

Conclusion

A variety of models seek to explain visual illusions. Some models compete to explain the same illusion, as, for example, with White’s Effect (contrast normalization vs. layer decomposition) and the Müller-Lyer illusion (perceptual hypothesis vs. centroid feature vs. empirical). It is unlikely however that any one model/approach will ever explain all visual illusions. For example, it is hard to see how the leaning tower illusion will ever invite the same type of explanation as Mach bands, since the former involves relatively high-level physiological processes concerned with the computation of perspective, whereas the latter involves relatively low-level physiological processes concerned with the extraction of simple image features. What is certain is that visual



Visual Illusions, Models of, Fig. 16 In this photograph of a tower block, the orange color looks like paint, whereas it is in fact a sunset illumination on a gray surface (Reproduced with permission from B. Micklethwait)

illusions will continue to serve as critical tests for all computational models of visual processing.

Cross-References

- [Bayesian Approaches in Computational Neuroscience: Overview](#)
- [Behavioural Analysis, Bayesian](#)
- [Center-Surround Processing, Computational Role of](#)
- [Center-Surround Processing, Network Models of](#)
- [Color Vision, Computational Methods for](#)
- [Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling](#)
- [Hierarchical Models of the Visual System](#)
- [Perception, Bayesian Models of](#)
- [Receptive Field Modeling](#)
- [Visual Aftereffects, Models of](#)

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Further Reading

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Visual Motion Detection in *Drosophila*

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Synonyms

[Elementary motion detection](#); [Motion vision](#)

Definition

Visual motion detection describes the process by which directional information about local image motion is extracted from the spatiotemporal excitation pattern of the photoreceptor array.

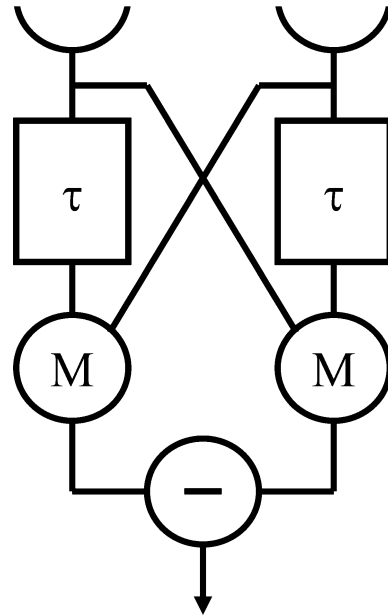
Detailed Description

Visual motion information is of utmost importance for all animals including man: motion information can signal the direction in which a prey, a predator, or a conspecific is moving. Furthermore, motion information can also signal the movement of the observer in space: during movement, the images of the environment will constantly shift across the observer's eyes, causing an optic flow that is specific for the various kinds of maneuvers executed. However, at the level of the photoreceptors, the direction in which the image is shifting locally is not explicitly represented. Rather, directional motion information needs to be extracted from the photoreceptor array by comparing the signals of neighboring photoreceptors over time. The exact nature of this process as implemented in the visual system of *Drosophila* is currently being studied in great detail, and much progress has recently been made in determining the neural circuits giving rise to directional motion information in this species.

The Reichardt Model of Elementary Motion Detection

Analyzing the turning tendency of the beetle *Chlorophanus viridis* walking on a spherical Y-maze, Hassenstein and Reichardt (1956) proposed a specific model of elementary motion detection that could account for their observations in a quantitative way. This algorithmic model for elementary motion detection consists of two subunits, which are mirror symmetrical to each other (Fig. 1; Reichardt 1961, 1987; Borst and Egelhaaf 1989). Each subunit reads the luminance values measured in two adjacent facets and multiplies them after one has been delayed by a temporal low-pass filter. The output values of both subunits are finally subtracted.

In contrast to a simple speedometer, for which the output increases linearly with image speed, the model predicts a speed optimum at which the response is maximal. This optimum speed is set by the time constant of the low-pass filter. Beyond the optimum speed, the response decreases again.



Visual Motion Detection in *Drosophila*, Fig. 1 The Reichardt model of elementary motion detection. The model consists of two mirror-symmetrical subunits sharing the same two input lines. Within each subunit, the signal from one input is processed by a temporal low-pass filter with time constant τ and subsequently multiplied (M) with the instantaneous signal derived from the neighboring input. The signals from both subunits are subtracted ($-$), giving rise to a directionally selective output

Furthermore, the optimum speed of periodic gratings is a linear function of the pattern wavelength. Thus, optimum speed divided by pattern wavelength remains constant. The dimension of this ratio is a temporal frequency. Thus, the Reichardt detector responds maximally to a certain number of spatial periods passing by a single photoreceptor, not to a certain image speed. In more general terms, the model predicts a highly counterintuitive dependence of the motion detection process on pattern properties, such as its spatial wavelength as well as its contrast. Following these seminal studies of Hassenstein and Reichardt, a number of experiments were performed showing the Reichardt detector to also underlie motion vision in house flies (Fermi and Reichardt 1963; Eckert 1973) and fruit flies (Goetz 1964, 1965). The optimum temporal frequency of both species was determined at ~ 1 Hz, which allows to infer the time constant of the filters involved. To assess

the sampling base of the elementary motion detector, sine-wave gratings of different wavelengths were used: for pattern wavelengths smaller than twice the sampling base, an inversion of the response, called “spatial aliasing,” is expected. Determining the wavelength at which the response becomes negative revealed a sampling base of 4.6° for *Drosophila* (Goetz 1964, 1965; Buchner 1976). This result matches exactly the inter-ommatidial angle of this fly species. Thus, nearest-neighbor interactions within the retina form the input to the Reichardt detector in the fruit fly.

General Architecture of the Fly Optic Lobe

The fly’s nervous system consists of two ganglia: the head and the thoracic ganglion (for an overview, see Strausfeld 1976). The largest parts of the head ganglion, the optic lobes, are devoted to the processing of information coming from the eyes. The optic lobes (Fig. 2) consist of four different neuropiles called the lamina, the medulla, the lobula, and the lobula plate. All these neuropiles exhibit the same columnar structure as the retina. The principle underlying this building plan is retinotopy, i.e., neighboring image points are

processed by neighboring facets in the eye and by neurons within neighboring columns in each of the neuropiles of the optic lobes.

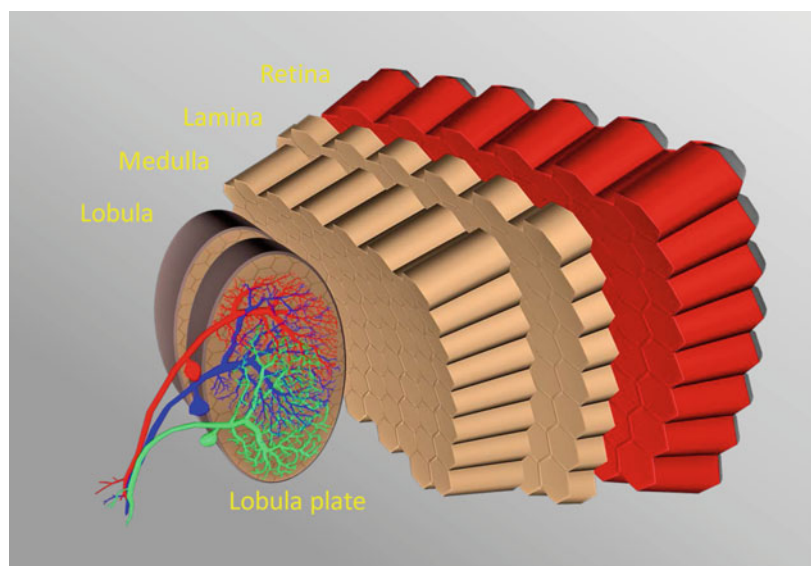
The fly’s eye is composed of facets or ommatidia which are equipped with a set of eight photoreceptors, with six outer photoreceptors, R1–R6, surrounding the two central ones, R7 and R8. When activated by light, all fly photoreceptors become depolarized (for review, see Hardie and Raghu 2001). This depolarization is a fast process; thus, fly photoreceptors can follow sinusoidal luminance modulations up to 200–300 Hz depending on the fly species. The different photoreceptors in one ommatidium have different optical axes, but certain groups of photoreceptors within neighboring ommatidia have parallel optical axes. By connecting these groups of photoreceptors to the same postsynaptic target (Braitenberg 1967), the sensitivity of the system is increased without sacrificing acuity (Kirschfeld 1967). This principle is called “neural superposition.” Whereas the axons of photoreceptors R1–R6 stop in the lamina where they connect to large monopolar cells and amacrine cells, the axons of photoreceptors R7 and R8 run through the lamina and terminate in the specific layers of the medulla.

The lamina contains, in addition to wide-field amacrine cells, eight different cell types per column, which connect it to the medulla: five lamina

Visual Motion Detection in *Drosophila*,

Fig. 2 Schematic of the optic lobe of *Drosophila*.

The retina (red) built from repetitive facets is followed by four layers of neuropile, called lamina, medulla, lobula, and lobula plate. All these neuropile layers consist of retinotopically arranged columns. Within the lobula, the group of three HS cells is shown as reconstructed from stained tissue



monopolar cells, L1–L5, two centrifugal cells called C2 and C3, and the T1 cell (Meinertzhagen and O’Neil 1991). Photoreceptor synaptic transmission involves the release of histamine by R1–R6 (Hardie 1989). Histamine-gated chloride channels are expressed on the postsynaptic target cells of R1–R6 and mediate signal-inverting synaptic communication: a strong, transient hyperpolarization upon illumination onset of the eye, which is followed by a sustained component that disappears with increasing light intensity. When the light is switched off, a rebound depolarization is observed. The response of large monopolar cells L1 and L2 readily adapts to the mean luminance over several orders of magnitude while leaving its contrast sensitivity almost unchanged (Jaervilehto and Zettler 1971; Laughlin et al. 1987; Straka and Ammermüller 1991; Zheng et al. 2009).

Starting with the work of Cajal and Sanchez (1915), the columnar cell types of the medulla, lobula, and lobula plate have been identified and described on the basis of Golgi impregnations in the housefly (Strausfeld 1976) as well as in *Drosophila* (Fischbach and Dittrich 1989). Each medulla column houses more than 60 different cells. They can be roughly grouped into medulla intrinsic (“Mi”) and trans-medulla (“Tm”) neurons. The terminals of all neurons coming from the lamina ramify in specific layers of the medulla (Takemura et al. 2008, 2011). This layout suggests a splitting of photoreceptor signals into several parallel pathways that might subserve different functions such as the detection of form, polarization patterns, color, and motion processing. However, because of the small diameter of columnar neurons’ processes, until now, only a few electrophysiological recordings from identified neurons have been described (DeVoe 1980; Gilbert et al. 1991; Douglass and Strausfeld 1995, 1996). Therefore, the visual response properties of most columnar neurons in the medulla are unknown.

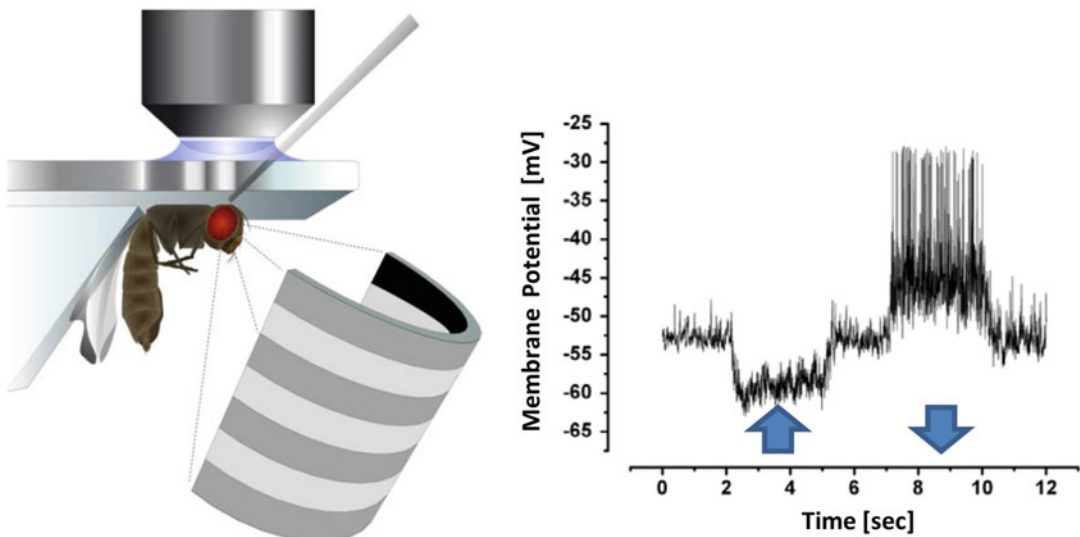
In the lobula plate, large neurons run perpendicular to the columns covering many hundreds or thousands of them with their dendrites. These are the lobula plate tangential cells, investigated in great detail in blowflies first by Hausen and Hengstenberg (Hausen 1984; Hengstenberg et al.

1982). A total of 60 different cells are found in the blowfly *Calliphora vicina*, all of which are motion sensitive. Some of these cells have also been described for *Drosophila melanogaster* (Fischbach and Dittrich 1989; Scott et al. 2002; Raghu et al. 2007; Joesch et al. 2008; Schnell et al. 2010). In both species, tangential cells can be grouped, according to their preferred axis of motion, into horizontal or vertical cells. Best studied are the groups of three HS (*horizontal system*) cells and, depending on the species, 6–10 VS (*vertical system*) cells. Interestingly, the same cells in different individuals turn out to be highly stereotyped with respect to the area covered by their dendrites within the lobula plate, but not with respect to the branching pattern (Cuntz et al. 2008). Using ablation experiments (Heisenberg et al. 1978; Geiger and Nässel 1981; Hausen and Wehrhahn 1983) as well as optogenetic activation (Haikala et al. 2013), lobula plate tangential cells are concluded to control the fly’s optomotor response.

Reichardt-Type Motion Computation in the Optic Lobe

The most significant response characteristic of the lobula plate tangential cells is their directional selectivity (Fig. 3): if a grating moves in one direction (the cell’s preferred direction), the cell depolarizes or fires a train of action potentials. When the grating moves in the opposite direction (the cell’s null direction), the cell hyperpolarizes or ceases to fire. In contrast, the photoreceptor signal is nondirectional, i.e., a single photoreceptor displays the same response regardless of whether the grating moves in one or the opposite direction. Thus, somehow a non-directional response at the photoreceptor level is transformed into a directional signal at the lobula plate tangential cell level. The Reichardt detector describes this transformation in amazing detail.

As mentioned above, one of the hallmarks of the Reichardt detector is its temporal frequency optimum: the larger the pattern wavelength, the higher the optimum speed. As already verified in



Visual Motion Detection in *Drosophila*, Fig. 3 Experimental setup (*left*) and recording of directionally selective responses of a VS-tangential cell (*right*). With the fly mounted underneath the objective of a fluorescence microscope, the neuron is whole-cell

patched at the soma while the fly views a grating moving up and down. During upward motion (“null direction”), the cell hyperpolarizes; during downward motion (“preferred direction”), it depolarizes and fires bursts of action potentials

the optomotor response, this property is also found in the visual responses of lobula plate tangential cells of fruit flies (Joesch et al. 2008). In contrast to the optomotor response, which is inherently slow, recordings in blowfly tangential cells also allowed for a comparison between the transients of cellular responses and the ones of the Reichardt detector. When the velocity of a grating is stepped from zero to a constant value, the Reichardt detector exhibits a transient ringing at the temporal frequency of the pattern motion before settling at the steady state (Borst and Bahde 1986). Such a transient ringing could indeed be observed in lobula plate tangential cells of the blowfly (Egelhaaf and Borst 1989). Furthermore, the amplitude of the ringing showed a characteristic time constant by which it decays to the steady state, which depended on the contrast of the moving pattern as well as on the pattern contrast before the onset of motion (Reisenman et al. 2003; Joesch et al. 2008). These findings led to an elaborated Reichardt detector with high-pass filters inserted in the crossarms, the time constant of which rapidly adapts (Borst et al. 2003). Given these modifications, the Reichardt model can

account for both the steady state and all transient response features of the lobula plate tangential cells in a detailed way. This statement applies not only to stimulus situations using velocity steps but also to Gaussian white-noise velocity profiles. When using such stimuli with different standard deviations, the response exhibited a velocity gain control, i.e., the response–velocity function was found to be steeper as the velocity fluctuations become smaller (Brenner et al. 2000). The Reichardt detector replicates this velocity gain control even when all its filter time constants are fixed (Borst et al. 2005). Finally, even though tangential cells spatially integrate the output signals of local motion detectors and, thus, should represent their summated output, the signals of individual motion detectors can be observed experimentally, when spatial integration is prevented either by presentation of grating motion through a slit or by local calcium measurements in fine dendritic branches. Both these techniques revealed local signals that have all the characteristics of local motion detectors of the Reichardt type (Egelhaaf et al. 1989; Single and Borst 1998; Haag et al. 2004).

Neural Implementation of the Reichardt Detector

Given the evidence that has been accumulated for Reichardt-like motion computation in the optic lobes of different fly species, the question naturally arises about its neural implementation: which neurons form the Reichardt detector? This problem has remained essentially unsolved for over half a century, with no or only little progress for many decades. Only recently, the advent of sophisticated neurogenetics methods in *Drosophila* allowed to elucidate the circuits for elementary motion detection. These techniques are all based on a two-component expression system where a so-called driver line defining the neurons where a certain effector gene is expressed is crossed with another line, the so-called reporter line, defining what gene is expressed (Brand and Perrimon 1993). Today, thousands of different driver lines are available, many of which reveal a high degree of specificity for expression in individual cell types of the optic lobe (Pfeiffer et al. 2008). Furthermore, many reporter lines have been developed allowing for blocking the synaptic output from neurons, activating neurons optogenetically as well as recording from neurons via genetically encoded calcium indicators (for review, see Borst 2009, Venken et al. 2011). Applying these techniques to the problem of local motion detection revealed (a) that luminance information from fly photoreceptors R1–R6 is split into two parallel motion circuits, specialized to detect the motion of luminance increments (ON channel) and decrements (OFF channel) separately, (b) that lamina neurons L1 and L2 are the prime input neurons to these circuits (L1- > ON channel, L2- > OFF channel), and (c) that T4 and T5 cells carry their output signals (ON- > T4, OFF- > T5) (Joesch et al. 2010, 2013; Eichner et al. 2011; Maisak et al. 2013).

Input Elements

As mentioned above, a single facet of the fly eye comprises two sets of photoreceptors: the

peripheral photoreceptors R1–R6 and the central R7 and R8. Early work on different mutants where either the central or the peripheral ones were defective indicated that motion vision relies primarily on R1–R6, and not on R7 and R8 (Heisenberg and Buchner 1977). The two most prominent target neurons of the peripheral photoreceptors R1–R6 are the large monopolar cells L1 and L2 of the lamina. This suggested that they conveyed the input signal to downstream motion detection circuits. First, evidence along these lines was provided by experiments where either behavioral responses (Rister et al. 2007) or electrophysiological recordings from lobula plate tangential cells were used as a read-out (Joesch et al. 2010): blocking both L1 and L2 led to a complete abolishment of the responses to gratings moving along any direction. The individual contribution of L1 and L2 was discovered in flies where either L1 or L2 was blocked, and, instead of gratings, edges of different contrast polarity were moved to probe the responses of lobula plate tangential cells (Joesch et al. 2010): while control flies responded to moving brightness increments (ON edges) and decrements (OFF edges) with about the same amplitude, flies with lamina neurons L1 blocked completely lost their response to moving ON edges, while their response to moving OFF edges was largely intact. The opposite was found for flies with lamina neuron L2 blocked: here, the response to moving ON edges was roughly as large as the one of control flies, whereas the response to moving OFF edges was severely reduced. These results were later confirmed in a study on behavioral responses of walking fruit flies (Clark et al. 2011). Together, these experiments suggest that the photoreceptor input from R1–R6 is split into parallel channels depending on the contrast polarity of the incoming signal: while lamina neurons L1 specifically transmit information about brightness increments to downstream motion circuits, lamina neurons L2 only allow information about brightness decrements to be passed onto further motion processing. Technically, such signal processing is referred to as “half-wave rectification.”

General Layout

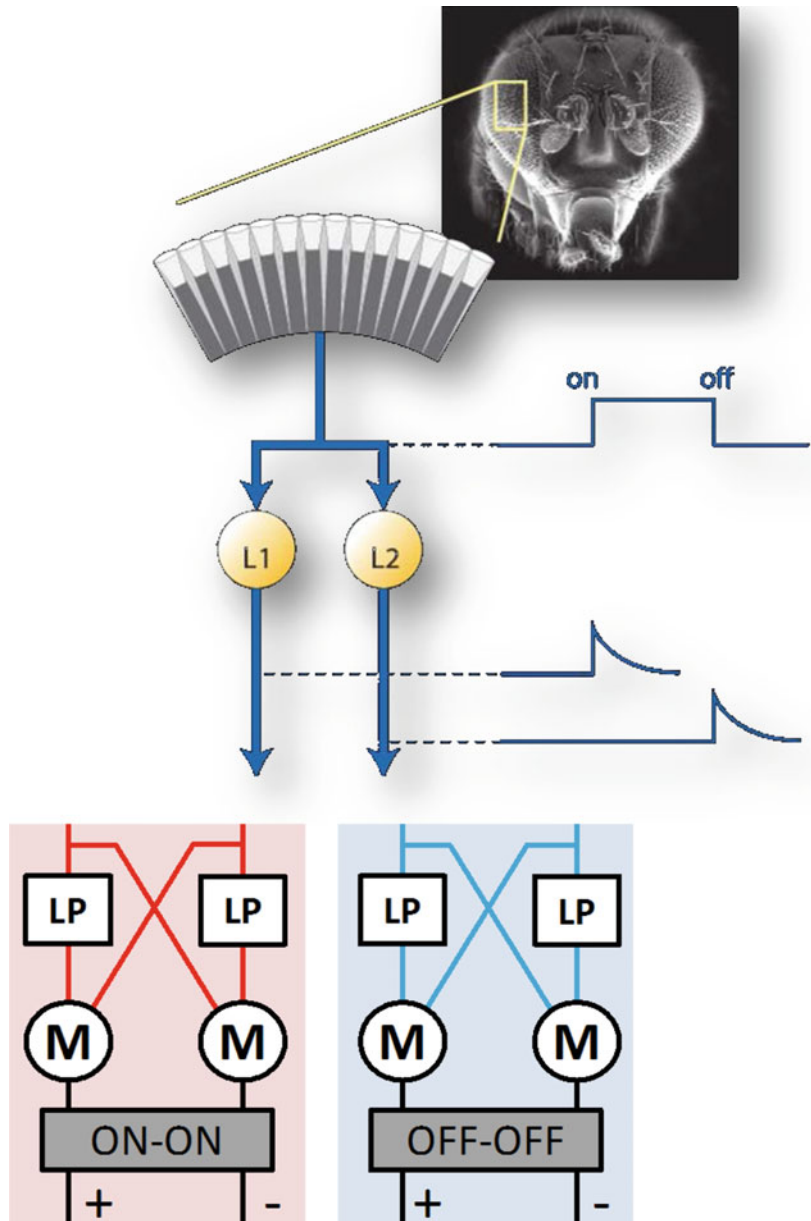
The findings about the specific contribution of L1 and L2 to motion processing of brightness increments and decrements immediately suggest that in *Drosophila*, motion is detected in several separate circuits. Theoretically, there could be four such channels comprising all possible combinations between ON and OFF signals. However, apparent motion experiments in blowflies suggested that only two such channels exist, one for the interaction of ON signals and one for the interaction of OFF signals between neighboring image points (Riehle and Franceschini 1984). In these experiments, pairs of single photoreceptors were stimulated by light-ON and light-OFF flashes while recording from a motion-sensitive lobula plate neuron H1. Recordings from lobula plate tangential cells in *Drosophila* arrived at the same conclusion: only sequences of light pulses of the same contrast polarity (ON–ON and OFF–OFF) elicited significant responses, while light pulses of differing contrast polarity (ON–OFF and OFF–ON) failed to evoke any responses in lobula plate tangential cells (Eichner et al. 2011). Interestingly, using brightness steps instead of brightness pulses led to different results: while, again, ON–ON and OFF–OFF sequences along the preferred direction of the cell led to positive responses, ON–OFF and OFF–ON sequences elicited negative responses. While this so-called reverse phi phenomenon (Anstis and Rogers 1975) was usually taken as evidence for an interaction between ON and OFF stimuli, as in the original Reichardt detector, careful simulations of such circuits as well as experiments with flies with lamina neurons either L1 or L2 blocked revealed that such an inversion of the response is not necessarily indicative of an interaction between ON and OFF channels. Rather, it can be explained by the residual sustained response component of the lamina neurons taking into account the contribution of motion detectors at the edge of the stimulated areas in the visual field of the fly (Eichner et al. 2011; Joesch et al. 2013).

In summary, thus, the Reichardt detector is implemented in the visual system of the fly in two parallel circuits, one dealing with brightness

increments (ON channel) and the other one with brightness decrements (OFF channel) (Fig. 4). What could be the advantage of such a doubling of wiring expenditure? Without splitting and half-wave rectification, i.e., with just a single motion detector dealing with brightness going positive as well as negative, a multiplicative interaction – according to the sign rule of multiplication – would imply the output being positive when both input signals go positive as well as when both go negative. Such a processing rule seems hard to be implemented biophysically and indeed is unheard of in cellular neuroscience. If, however, the input signals are split according to their polarity with the negative ones being sign-inverted, subsequent circuits only deal with positive input signals reducing the problem of multiplication to a supralinear input–output characteristic as can easily be implemented by a voltage-gated ion channel. Interestingly, neurobiology is not the only area where such problems arise: analog electronics faced the same problem of multiplying positive as well as negative signals, and the solution in these days was what is called a “4-quadrant multiplier.” There, the input signals, prior to multiplication, were half-wave rectified, split into parallel ON and OFF channels carrying positive signals only, and subsequently multiplied in four separate multipliers. Their output signals were then added with the appropriate sign, with outputs from ON–ON and OFF–OFF multipliers having positive and the ones from ON–OFF and OFF–ON units having negative sign (Hassenstein and Reichardt 1956). This looks similar to what we find in the fly, except that the fly seems to discard two of the four units, reducing a true multiplication to a “2-quadrant multiplier.” In the context of motion detection, however, this does not have any functional consequences: since motion of rigid objects gives rise to spatial correlations between time-delayed signals at subsequent image pixels, an ON event at one location will always correlate with an ON event at a later point in time at a neighboring location, and the same holds true for OFF events. In other words, no correlations between ON and OFF events at neighboring locations will be indicative for physically moving objects. Consequently, a

Visual Motion Detection in *Drosophila*,

Fig. 4 Input organization and general layout of the Reichardt detector as implemented in the *Drosophila* nervous system. At the level of the lamina, the photoreceptor input is split and half-wave rectified into an ON (*L1*) and an OFF (*L2*) signal. Both signals feed into separate motion detection circuits



comparison of a 4- and a 2-quadrant detector reveals no significant differences in response to visual motion (Eichner et al. 2011).

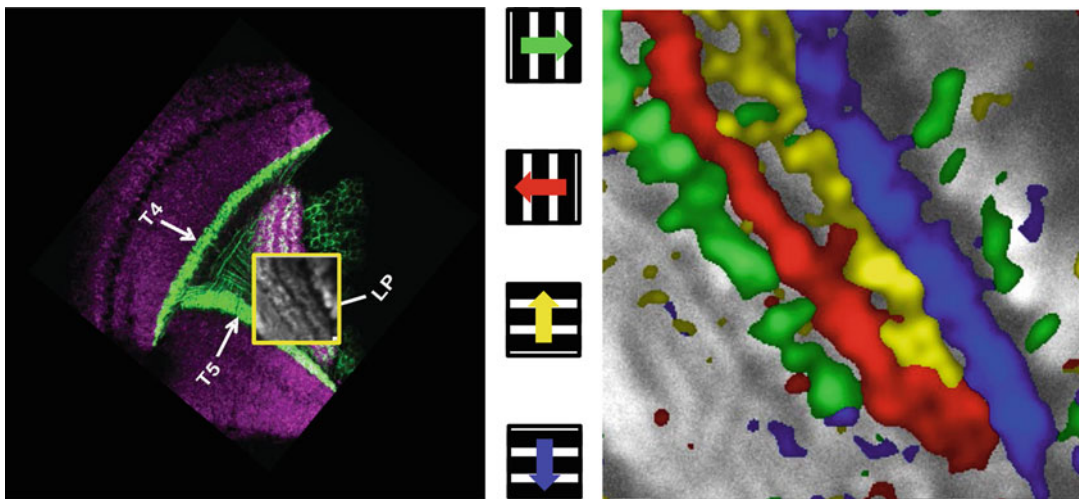
Output Elements

Having identified lamina neurons *L1* and *L2* as the decisive input elements to two parallel motion

detector circuits allowed anatomy to guide the next steps. Indeed, two parallel processing streams had previously been postulated in the fly visual system, based on careful investigation of co-stratification of Golgi-stained columnar cells (Bausenwein et al. 1992), as well as cell-unspecific activity labeling using the deoxy-glucose method (Bausenwein and Fischbach 1992). These studies indicated that an *L1* pathway

should indirectly lead to columnar T4 cells and an L2-pathway to columnar T5 cells, with both T4 and T5 cells projecting to the lobula plate. Given that 4 different subtypes of T4 and T5 cells exist terminating in four different layers of the lobula plate (Fischbach and Dittrich 1989) and deoxy-glucose labeling indicated activity in one of the four layers according to the direction of the stimulus (Buchner et al. 1984), T4 and T5 cells were prime candidates for local elementary motion detectors and for representing the output signals of the ON and the OFF motion pathways, respectively. Their small size, however, prohibited electrophysiological recordings, and their visual response properties remained for long unknown. A recent study (Maisak et al. 2013) circumvented this problem by using driver lines specific for T4 and T5 cells and combining them with a high-sensitivity genetically encoded calcium indicator GCaMP5 (Akerbom et al. 2012). Using 2-photon

calcium imaging and stimulating the flies with grating motion in four cardinal directions (front to back, back to front, upward, downward), Maisak and colleagues recorded directionally selective activity from T4 and T5 cells in each one of the four lobula plate layers depending on the direction in which the grating was moving (Fig. 5). To assess the particular contribution of T4 and T5 cells to the signals observed in the above experiments, driver lines specific for T4 or T5 cells were used, respectively. Applying the same stimulus protocol and data evaluation as before, identical results were obtained for both the T4- and the T5-specific driver lines. Further experiments revealed similar response properties for T4 and T5 cells with respect to their orientation and velocity tuning (Maisak et al. 2013). If, however, instead of gratings, moving edges with either positive or negative contrast polarity were used as visual stimuli, T4 cells were found to



Visual Motion Detection in *Drosophila*, Fig. 5 T4 and T5 cells represent the elementary motion detector outputs. *Left:* confocal image of a driver line giving rise to expression in both T4 and T5 cells, shown as a horizontal cross section (Modified from Schnell et al. 2012). Neurons are marked in *green* (Kir2.1-EGFP labeled), revealing clear labeling (in *green*) in the medulla (T4 cell dendrites), in the lobula (T5 cell dendrites), and in four distinct layers of the lobula plate, representing the terminal arborizations of the four subpopulations of both T4 and T5 cells. The neuropile is stained in *red* by an antibody against the postsynaptic protein Dlg. The image within the *yellow square* is from a 2-photon microscope and contains the

area shown enlarged to the *right*. *Right:* 2-photon calcium imaging in the lobula plate reveals directionally selective signals. Following stimulation of the fly with grating motion along four cardinal directions (*front to back*, *back to front*, *upward*, and *downward*), activity is confined to mostly one of the four layers, depending on the direction in which the grating is moving. The outcome of all four stimulus conditions is combined into a single image by assigning a particular color to each pixel depending on the stimulus direction during which it responded most strongly. Depending on their preferred direction, T4 and T5 cells project into different layers of the lobula plate (Modified from Maisak et al. 2013)

strongly and selectively respond to moving ON edges, with little or no responses to moving OFF edges, while T5 cells selectively responded to moving OFF edges and mostly failed to respond to moving ON edges.

To investigate whether the specific response properties of T4 and T5 cells are visible in post-synaptic lobula plate cells and visually driven behavior, T4 and T5 cells were genetically blocked and flies subsequently tested. Blocking both T4 and T5 cells led to a complete loss of the motion response in lobula plate tangential cells (Schnell et al. 2012) and of the optomotor response of tethered walking flies (Bahl et al. 2013). Blocking T4 cells specifically led to selective loss of the responses to moving ON edges, in the electrical signal of tangential cells as well as in optomotor behavior. Conversely, blocking T5 cells led to a loss of the responses to moving OFF edges, again both in the electrical signal of tangential cells and in optomotor behavior (Maisak et al. 2013). In summary, the selective defects of T4 block flies for ON edges and of T5 block flies for OFF edges not only corroborate the above findings about the selective preference of T4 and T5 cells for different contrast polarities but also demonstrate that the signals of T4 and T5 cells are indeed the major, if not exclusive, inputs to downstream circuits and motion-driven behaviors.

Conclusion and Outlook

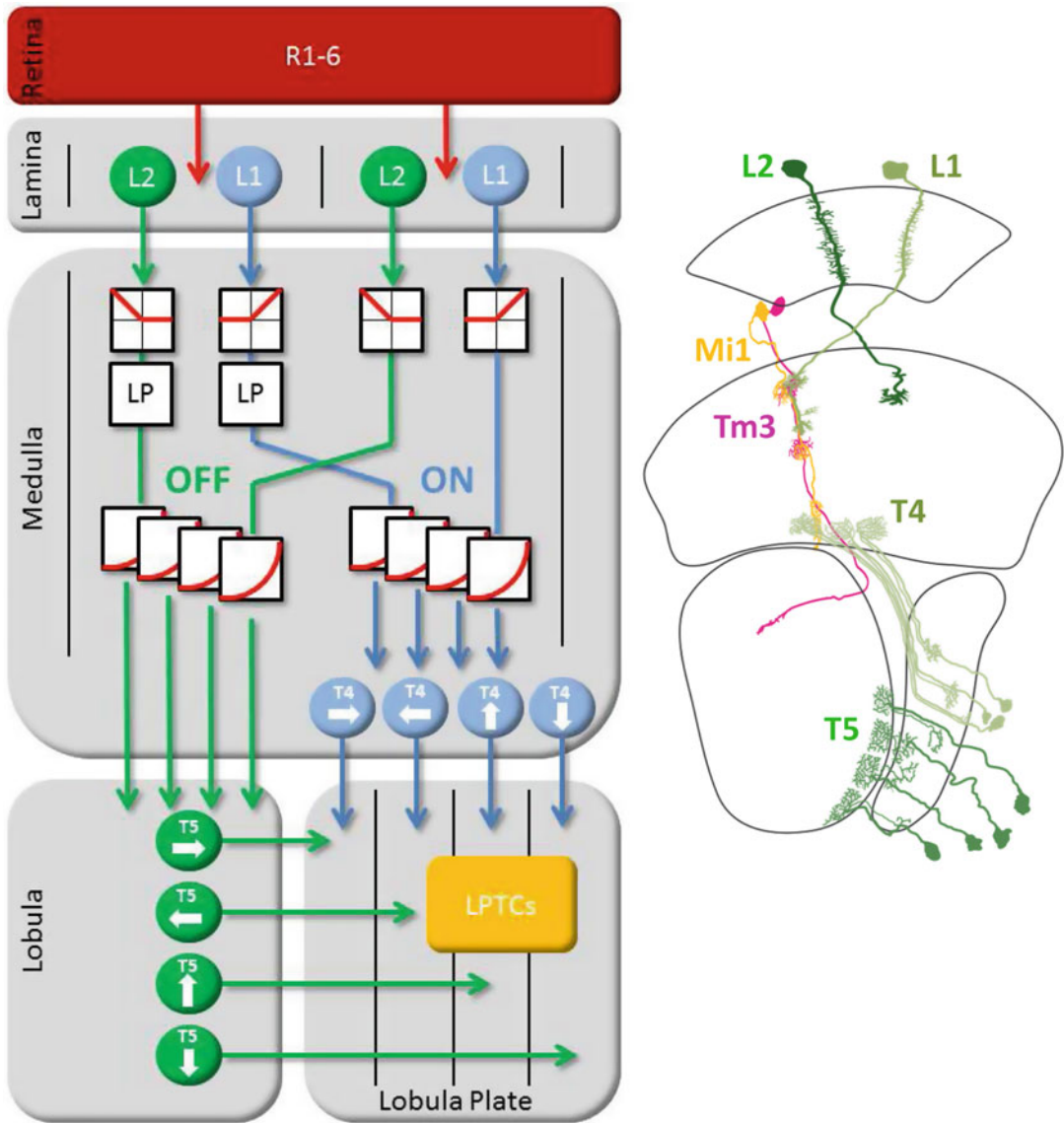
Local motion detection in *Drosophila* has long been shown to follow the predictions of the Reichardt detector. However, only the last few years have witnessed a major breakthrough in our understanding of its neural implementation. Making use of technology targeting genetically individual cell types and expressing proteins that either block synaptic transmission or signal neural activity led to the following picture (Fig. 6): starting with L1 and L2, the visual input is split into separate ON and OFF pathways, and motion along all four cardinal directions is computed separately within each pathway. The output of these eight different motion detectors is then

sorted such that ON (T4) and OFF (T5) motion detectors with the same directional tuning converge in the same layer of the lobula plate, jointly providing the input to downstream circuits and motion-driven behaviors.

As an immediate hypothesis derived from these findings, the dendrites of T4 and T5 cells could be the place where the signals from neighboring facets converge, giving rise to T4 and T5 cells direction selectivity. In the case of T4 cells, these cells have recently been described anatomically: using large-scale serial sectioning transmission electron microscopy and computer-aided reconstruction, Takemura and colleagues found two neurons, Mi1 and Tm3, to connect the output terminals of L1 neurons to the dendrites of T4 cells (Takemura et al. 2013). They furthermore observed an asymmetry of T4 cells' dendrites in their wiring to Tm3 and Mi1 going along with the lobula plate layer they project to, i.e., their direction selectivity. All this points in the direction that, indeed, processing as described by each subunit of the Reichardt detector is implemented in the fly's optic lobe. Future studies will have to determine which of the cells carries the delayed and which one carries the instantaneous signal, as well as characterize the nature of their interaction within the dendrites of T4 cells. In a similar way, the input signals to T5 cells, after their anatomical identification, will have to be investigated.

Another open question concerns the cellular nature of the subtraction stage in the Reichardt detector. Here, evidence exists in both blowflies and fruit flies that this subtraction is realized by a synaptic push–pull organization with local motion detectors of opposite preferred direction providing excitatory and inhibitory input onto the dendrites of lobula plate tangential cells (Borst and Egelhaaf 1990; Borst et al. 1995; Joesch et al. 2008). However, it is not known at present whether and how individual T4 and T5 cells could provide, at the same time, excitation to one and inhibition to the adjacent lobula plate layer.

Finally, the picture as shown in Fig. 6 will certainly be extended and elaborated by future studies, revealing more and more details of the motion detection circuitry. Indeed, recent studies



Visual Motion Detection in *Drosophila*, Fig. 6 Circuit diagram of the fly elementary motion detector (*left*) and some of the neurons involved (*right*). *Left*: visual input from photoreceptors R1–R6 is split into parallel pathways, L1 and L2, at the level of the lamina. Two neighboring columns are shown. The outputs from both L1 and L2 are half-wave rectified, such that downstream elements carry information about ON (L1 pathway) and OFF (L2 pathway) signals separately. After temporal low-pass filtering (LP), the signals from one column interact in a supralinear way with the instantaneous signals derived

from the other column. This interaction takes place, separately in both pathways, along all four cardinal directions. Directionally selective signals are carried via T4 and T5 cells to the four layers of the lobula plate where T4 and T5 cells with the same preferred direction converge again on the dendrites of the tangential cells (LPTCs) (From Maisak et al. 2013). *Right*: Golgi stains of L1 and L2 neurons, as well as of T4 and T5 cells. The signal from L1 terminals is conveyed to the T4 cell dendrites via two neurons, Mi1 and Tm3 (Takemura et al. 2013) (Modified after Fischbach and Dittrich 1989)

suggested an additional contribution of lamina neuron L3 to the OFF motion pathway (Silies et al. 2013), described the center-surround organization of the receptive fields of L2 neurons (Freifeld et al. 2013), and indicated more detailed response defects in motion-driven behavior following highly selective blockade of each of 12 lamina cell types (Tuthill et al. 2013). Thus, thanks to all the sophisticated tools available in *Drosophila*, the problem of the neural implementation of the Reichardt detector, after resisting for decades, will soon be understood in great detail.

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Further Reading

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objects, landing on environmental structures, overcoming narrow gaps in cluttered environments, locating a previously learned target based on environmental information, or tracking fast-moving targets. With regard to solving such tasks, insects often outperform man-made autonomous flying systems, especially if computational costs and energy efficiency are taken as benchmarks. To accomplish their extraordinary performance, several insect groups have been shown to actively shape the dynamics of the image flow on their eyes (“optic flow”) by the characteristic way they move when solving behavioral tasks. The neural processing of spatial information is greatly facilitated by such active vision strategies, for instance, by segregating the rotational from the translational optic flow component by way of a saccadic flight and gaze strategy. Flying insects acquire at least part of their strength as autonomous systems through active interactions with their environment, which lead to adaptive behavior in surroundings of a wide range of complexity. Model simulations and robotic implementations show that the smart biological mechanisms of motion computation and visually guided flight control might be helpful to find technical solutions for problems related to micro air vehicle navigation.

Visual Neuroprosthesis

► Visual Prosthesis, Cortical Devices

Visual Processing in Free Flight

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Definition

With their miniature brains, many insects are able to control highly aerobatic flight maneuvers and to solve spatial vision tasks, such as avoiding collisions with stationary obstacles and moving

Detailed Description

Flying animals, but also autonomous man-made flying systems, have to solve a number of fundamental tasks. Most basically, they need to control their attitude in three-dimensional space and to stabilize their intended flight course against disturbances. Moreover, they have to accomplish a number of tasks that rely on information about the spatial layout of their surroundings, for instance, when avoiding collisions with obstacles, negotiating narrow gaps in cluttered surroundings, or finding their way back to a previously learned location, such as a profitable food source or the often inconspicuous entrance of their home. In other situations, an animal may encounter other moving animals and either needs to avoid them in the case of a predator or may pursue one of

them, for instance, when it is searching for a prey or a mate. Visual information and its processing by the nervous system are crucial for solving such tasks in free flight. Self-motion through three-dimensional environments but also movements of other animals induce image displacements on the eyes and, thus, brightness changes on the two-dimensional array of photoreceptors, i.e., the input site of the visual system. All visual information required for solving any of the abovementioned fundamental tasks needs to be processed from these changes in the two-dimensional intensity distributions recorded at the photoreceptor level.

There are many ways how this may be accomplished. One particularly well-analyzed and functionally highly relevant possibility is based on the concept of optic flow that results from the image displacements on the eyes induced by self-motion and/or object motion. The optic flow depends on the dynamic characteristics of self-motion and of object motion, as well as on the three-dimensional structure of the environment. Therefore, the optic flow contains rich information on the way the animal moves around but also on the three-dimensional layout of the environment. Since the optic flow vectors defined by the retinal image displacements are not immediately available to the brain of the animal, representations of optic flow fields and of behaviorally relevant information that is contained in them need to be computed by the nervous system from the time-varying retinal brightness changes as sensed by the lattice of photoreceptors. This processing is done in a sequence of steps before the extracted information can be used by the animal to solve visual tasks. Optic flow as a source of information is particularly relevant for fast-flying animals, including many insects, but also some bird species: (1) Given that during flight animals do not have direct contact to the ground, they rely much more on visual information and, in particular, optic flow information for controlling their attitude in space than when walking. (2) Since flight takes place in three dimensions, the resulting optic flow may be much more complex than during locomotion on the ground: Movements are characterized by six degrees of freedom, three rotational

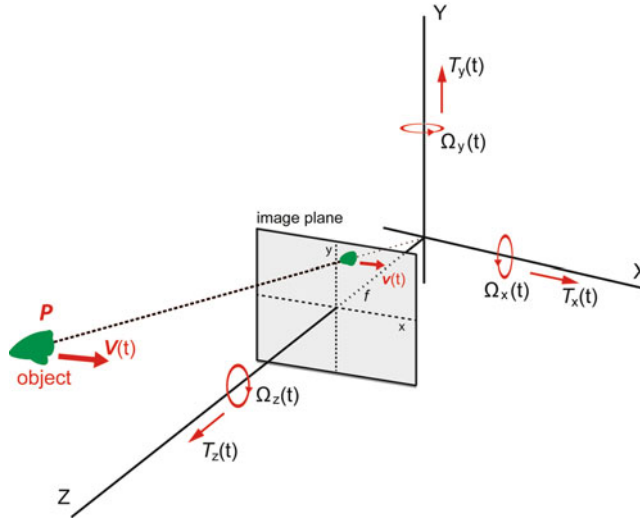
and three translational components reflected in the corresponding optic flow components. (3) Especially during the often highly aerobatic flight maneuvers of many insects, the optic flow fields may have complex dynamical properties that are related to both the characteristic dynamics of flight behavior but also the animal's spatial relation to the objects and surfaces in its surroundings. (4) In contrast to most current technical flying systems, which frequently employ systems such as infrared sensors and the global positioning system for obtaining positional, distance, and range information, animals apparently do not have access to such systems and have to rely on optic flow information for solving spatial tasks during flight.

Geometry of the Retinal Motion Patterns Induced by Self-Motion and Object Motion

The optic flow generated by self-motion in a stationary environment has characteristic geometrical properties which depend on the movement vector as well as on the three-dimensional layout of the environment. A point on a surface in the environment is given by the position vector $\mathbf{P} = (X, Y, Z)^T$ relative to the eye-centered coordinate system (T represents the transpose of the vector). When the eye moves in the environment, $\mathbf{P}$ moves in time t along the corresponding three-dimensional path $\mathbf{P}(t) = (X(t), Y(t), Z(t))^T$ in the eye-centered coordinate system (Fig. 1). Its velocity is given by the time derivative of this path

$$\begin{aligned} \mathbf{V}(t) &= d\mathbf{P}(t)/dt \\ &= (dX(t)/dt, dY(t)/dt, dZ(t)/dt)^T \quad (1) \end{aligned}$$

If we assume that the eye moves in a stationary and rigid environment, all points of an object share the same three rotational and translational motion vectors in the eye-centered coordinate system. Then the time-dependent velocity vector $\mathbf{V}(t)$ can be expressed in terms of the



Visual Processing in Free Flight, Fig. 1 Relationship between self-motion and the motion of the retinal image of an object in the environment. The optic flow generated by self-motion in a stationary environment has characteristic geometrical properties which depend on the movement vector as well as on the three-dimensional layout of the environment. A point on an object in the environment is given by the position vector $\mathbf{P}$ in the eye-centered

coordinate system. When the eye moves in the environment according to a translation vector $\mathbf{T}(t) = (T_x(t), T_y(t), T_z(t))^T$ and a rotation vector $\mathbf{\Omega}(t) = (\Omega_x(t), \Omega_y(t), \Omega_z(t))^T$, $\mathbf{P}$ moves with velocity $\mathbf{V}(t)$ in the eye-centered coordinate system. This results in a time-dependent displacement of the image of the object on the retina, i.e., the image plane of the eye at a velocity $\mathbf{v}(t)$. f represents the distance between the eye's nodal point and the image plane

instantaneous translation $\mathbf{T}(t) = (T_x(t), T_y(t), T_z(t))^T$ and rotation $\mathbf{\Omega}(t) = (\Omega_x(t), \Omega_y(t), \Omega_z(t))^T$ vector, respectively (Longuet-Higgins and Prazdny 1980; Heeger and Jepson 1992)

$$\mathbf{V}(t) = d\mathbf{P}(t)/dt = (dX/dt, dY/dt, dZ/dt)^T = (\mathbf{\Omega} \times \mathbf{X} + \mathbf{T}) \quad (2)$$

Any motion of the eye in the environment results in a time-dependent displacement of the brightness values on the retina, i.e., the image plane of the eye. The retinal image sequence can be described as a function $\mathbf{L}(x, y, t)$, with the brightness value $\mathbf{L}$ at image position (x, y) and time t . The velocities of the image points are then given in the most general form by

$$\mathbf{v} = (dx(t)/dt, dy(t)/dt)^T \quad (3)$$

The optic flow vectors are geometrically related to the movement vector of the eye and the location of the surface points in the environment as well as their spatial relationship. The

surface points in the environment $\mathbf{P}(X, Y, Z)^T$ project to the image point $\mathbf{L}(x, y)^T$ according to

$$x = fY/Z \text{ and } y = fX/Z \quad (4)$$

f represents the distance between the eye's nodal point and the image plane. Substituting Eqs. 2 and 4 into Eq. 3 leads to the following expression for the image velocity after some conversion

$$\mathbf{v} = (dx(t)/dt, dy(t)/dt)^T = 1/Z(x, y)\mathbf{M1}(x, y)\mathbf{T} + \mathbf{M2}(x, y)\mathbf{\Omega} \quad (5)$$

Z is the distance of each image point on the eye to its corresponding surface point in the environment. $\mathbf{M1}$ and $\mathbf{M2}$ are matrix expressions that only depend on the image position and the distance of the image plane f from the nodal point of the eye (for details see Heeger and Jepson 1992). The field of velocity vectors $\mathbf{v}$ at all points in the image plane of the eye represents the optic flow field.

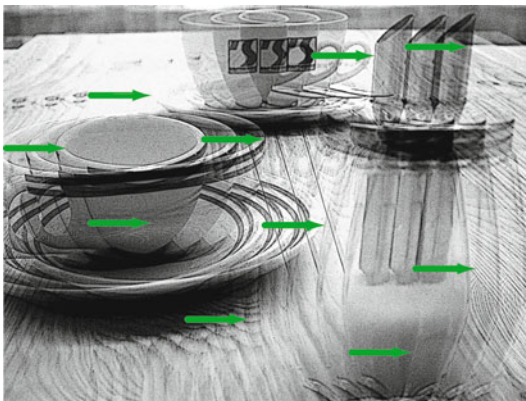
The most important conclusion from a functional point of view that can be drawn from Eq. 5

is that the velocity vectors consist of two terms: The first term is referred to as the translational component of the flow field; it depends on translation velocity T of the eye in three dimensions and on the depth structure of the environment, i.e., the distance to environmental objects. The second term reflects the rotational component; it only depends on rotation velocity of the eye Ω in the environment, but not on the distance to objects (Fig. 2). Since the distance term $1/Z$ and translation velocity are multiplied, both a larger distance and a slower translation velocity result in a slower image velocity. This implies that the spatial information in the translational optic flow component is ambiguous. Accordingly, spatial information can be extracted from the optic flow field only in relative terms unless the translation velocity is known (Longuet-Higgins and Prazdny 1980).

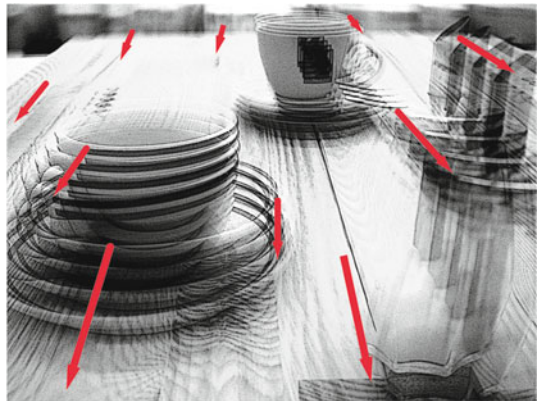
Additional complexities may arise in natural environments where, for instance, brightness often varies over time, i.e., when clouds occlude the sun. In the latter case, not every change in brightness at the level of photoreceptors is generated by motion. Moreover, not every motion yields a change in brightness values: If the eye passes an un-textured surface, the optic flow within the object area cannot be recovered without

additional information. Even at object edges, where the brightness of the background differs from that of the object, the direction of object motion can only be recovered if more information is available, for example, at object corners. As a consequence of this aperture problem and the other aspects sketched above, it is not possible to derive the geometrically correct optic flow vectors from the displacements of individual image points without additional information about the physical structure of the environment and the way the observer moves (Heeger and Jepson 1992; Borst and Egelhaaf 1993).

The degrees of freedom of stimulus space and, thus, the abovementioned ambiguities are constrained by physics. Environmental structures tend to change only on a rough spatial scale; as a consequence, the probability is large that neighboring image points are similar (“spatial smoothness constraint”). Moreover, animals cannot change their direction of motion instantaneously but are limited by the physics of force production through muscles as well as by friction and inertia, depending much on the shape and mass of the body (“temporal smoothness constraint”). However, input dynamics might also be shaped – beyond constraints imposed by physics –



Rotation



Translation

Visual Processing in Free Flight, Fig. 2 Schematic illustration of the consequences of rotational (left diagram) or translational self-motion (right diagram) for the resulting optic flow. Superimposed images were either generated by rotating a camera around its vertical axis or by translating it forward. Rotational self-motion leads to image movements (green arrows) of the same velocity

(indicated by arrow length) irrespective of the distance of environmental objects from the observer. In contrast, the optic flow elicited by translational self-motion (red arrows) depends on the distance between objects from the observer. Hence, translational optic flow contains information about the spatial layout of the environment

by active flight and gaze strategies. All these features may help to reduce the ambiguities when it comes to optic flow estimation and to facilitate processing of information about the animal's self-motion and the three-dimensional layout of the environment.

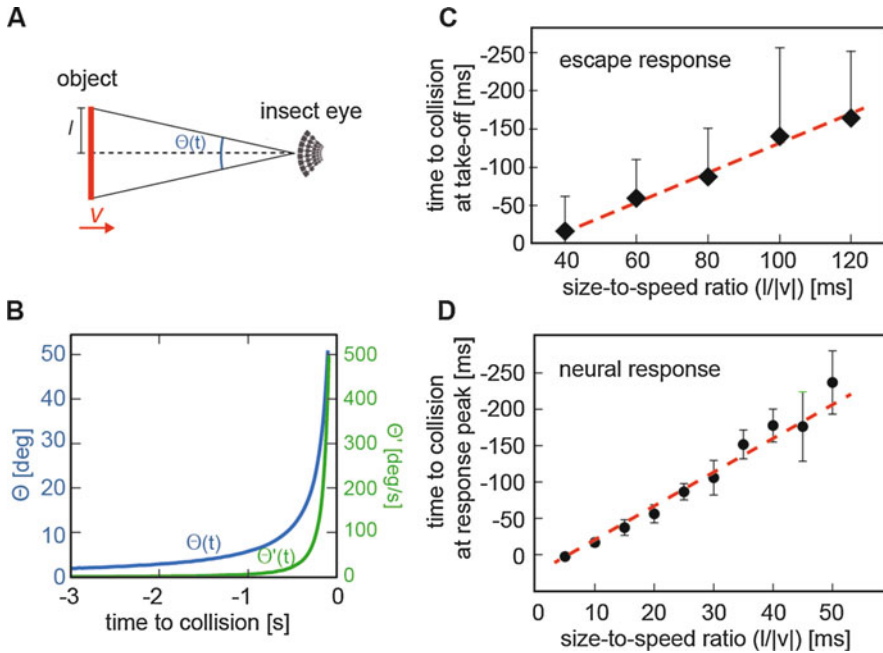
If the environment is not entirely stationary but contains moving objects, the motion patterns generated on the eyes are constrained not only by the animal's self-motion but also by the velocity and trajectory of the moving objects. Assume for convenience that the eye is stationary and a single object of half-size l approaches the eye on a straight collision course at a constant velocity v . Further assume $x > 0$ being the object's position relative to the eye (i.e., $x = 0$ corresponds to the eye's position) and $t < 0$ representing the time before an impending collision (i.e., $t = 0$ corresponds to the time of expected collision). Consequently, the object's velocity, v , is < 0 when the object is approaching. The object's position during a collision course is then given by $x(t) = vt$, and, by trigonometry, its retinal angular size θ can be determined by $\theta(t) = 2 \tan^{-1}[l/(vt)]$. Hence, the temporal dynamics of the retinal image is fully determined by its size-to-speed ratio, $l/|v|$. For a given $l/|v|$, the retinal size of an object on a constant collision course initially increases only slowly, i.e., the retinal expansion velocity is small, but then its size appears to explode increasingly with decreasing distance to the eye, with the velocity vectors always pointing away from the center of the approaching object (Fig. 3a, b). Exactly the same time course of θ is obtained for all pairs of l and v as long as the ratio $l/|v|$ is kept constant (Fotowat and Gabbiani 2011).

Constraints Imposed on the Visual Input During Free Flight

The dynamical properties of retinal image displacements that are generated during free flight are largely shaped by the animal's flight style and how its gaze direction is controlled. Flight and gaze strategies have been analyzed in detail for some insect species, especially flies and flying hymenopterans, such as bees, but also for some

bird species. They are characterized by sequences of rapid saccade-like turns of body and head interspersed with translational flight phases during which the gaze direction is kept largely constant (Fig. 4) (Land 1999; Zeil et al. 2008; Egelhaaf et al. 2012; Kress et al. 2015; Ros and Biewener 2017). Saccadic gaze shifts have a rather uniform time course; in insects they are shorter than 50 ms. Angular velocities of up to several thousand degrees can occur during saccades. Since roll movements of the body, which are performed for steering purposes during saccades and also during sideways translations, are compensated by counter-directed head movements, the animal's gaze direction is virtually kept constant during intersaccades, with details depending on the particular species under consideration. Hence, turns that are inevitable to reach a behavioral goal are minimized in duration and separated from translational flight phases.

This peculiar time structure facilitates the processing of spatial information because only the optic flow component induced by translations contains information about the relative distance of environmental surfaces and objects from the animal: Surfaces and objects nearby pass quickly, while those far-off appear virtually stationary (Fig. 2). A saccadic flight and gaze strategy thus constrains the spatiotemporal properties of the optic flow on the eyes in such a way that visual information processing in spatial tasks as diverse as collision avoidance, flight speed control in cluttered environments is facilitated (Egelhaaf et al. 2012). Moreover, in many behavioral situations, e.g., when negotiating narrow gaps in cluttered environments or learning the spatial layout of the surroundings of a goal, such as an inconspicuous nest hole in the case of foraging bumblebees, the insects may use additional active vision strategies and perform characteristic flight maneuvers with pronounced lateral translational components that appear to be specifically tuned to gather spatial information by systematically scrutinizing the outside world. In other behavioral situations, the motion patterns being perceived are not only generated as a consequence of self-motion of the animal. If another object, such as a predator, a prey, or a potential mate, moves in the



Visual Processing in Free Flight, Fig. 3 Escape from an impending collision with a moving object. (a) Variables characterizing looming stimuli generated by an approaching object viewed by an insect eye. A solid object (red disk) with half-size, l , approaches the eye at a constant speed, v . $t = 0$ is the time of expected collision and $t < 0$ before collision. Consequently, the object's velocity, v , is < 0 when the object is approaching and $|v|$, the absolute value of v . $\theta(t)$ is the angular size of the object as seen by the eye. The time course of θ is fully determined by the size-to-speed ratio, $l/|v|$. (b) Kinematics of looming stimuli. Both the angular size, $\theta(t)$, (blue curve), and speed, $\dot{\theta}(t)$,

(green curve) of an approaching object grow nonlinearly with time. (c) If a locust is approached by a moving object, it initiates an escape response. The time to collision at takeoff is linearly related to the size-to-speed ratio of the looming stimulus. (d) The response to a looming stimulus of an identified wide-field neuron in the locust third visual neuropile increases with increasing retinal size of the object and reaches a peak before the impending collision. The relation between the peak time and the size-to-speed ratio of the looming stimulus is close to linear. (Adapted from Fotowat and Gabbiani 2011)

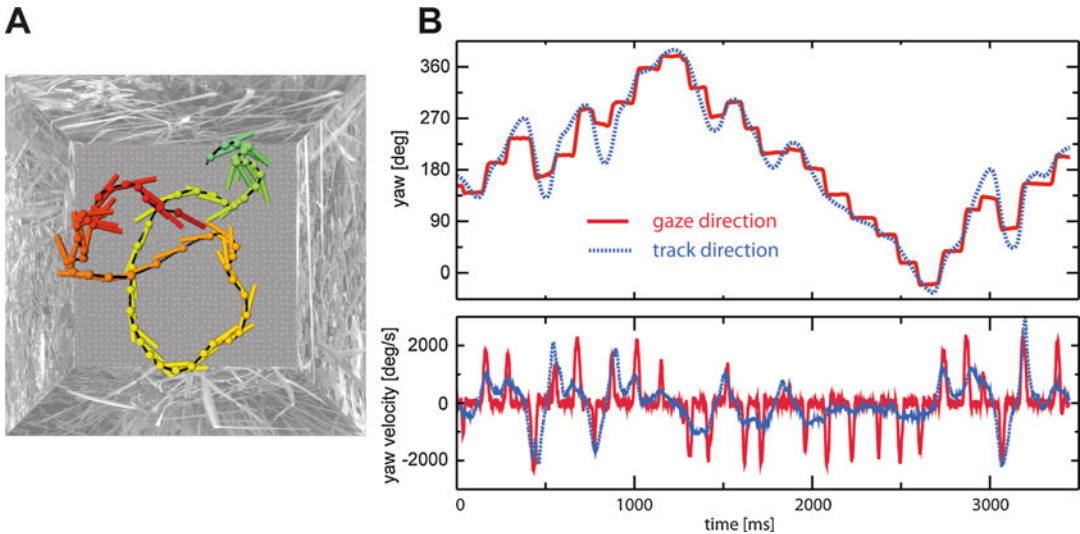
animal's visual field, the visual input is shaped by both the animal's self-motion and the direction and velocity of the moving object relative to the animal.

Processing of Visual Motion Information

The velocity vectors characterizing the retinal optic flow patterns during both self-motion and object motion are not directly available to the visual system. Rather the two-dimensional array of photoreceptors has access to only the two-dimensional pattern of time-dependent brightness changes. The first stage of visual motion processing is generally thought to be the computation

of local motion information from the brightness changes at neighboring locations in the retinal lattice (Fig. 5a). The second stage of visual motion processing is the interpretation of this neural representation of optic flow in terms of the direction and velocity of the animal's self-motion and of object motion, on the one hand, but also in terms of the properties and distances of stationary surfaces in the three-dimensional world, on the other hand. Although much is known about how these visual processing steps may be accomplished by flying animals, there are still many open questions.

Biological motion detection mechanisms get their input from a retinotopic array of discrete sampling points given in insects by the



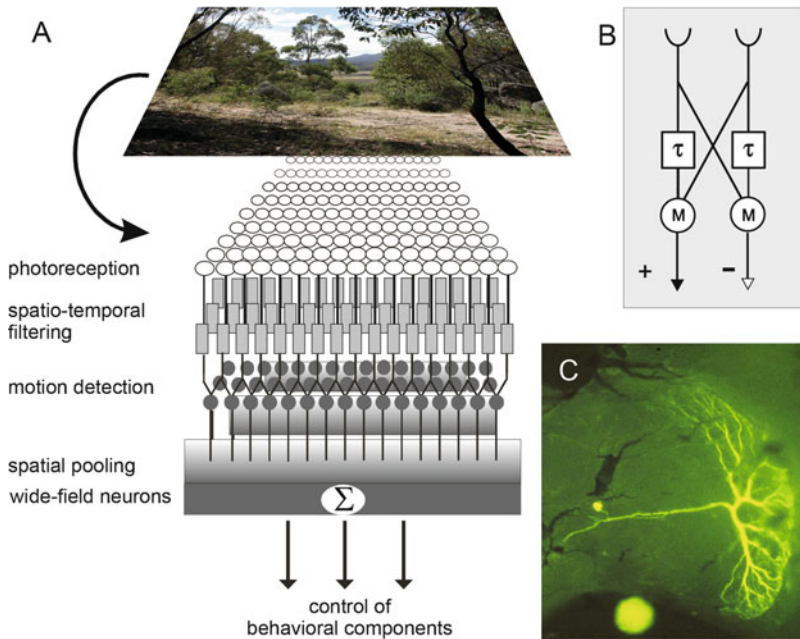
Visual Processing in Free Flight, Fig. 4 Saccadic flight and gaze strategy of free-flying blowflies. (a) Sample flight trajectory of a blowfly flying in a flight arena with textured walls. Downward view of a flight trajectory (dotted line), with head position and orientation shown every 50 ms (time color coded: start, red; finish, green). (b) Orientation of the fly's longitudinal body axis (solid red line) and flight direction (dotted blue line) in the external coordinate

system. (c) Angular velocity of the body orientation of the fly (solid red line) and of the flight trajectory (dotted blue line). The fly changed its gaze and heading direction through a series of short and fast body turns. Flight direction and body axis orientation frequently deviate. The body axis already points in the new flight direction while the fly continues moving on its previous course. (Adapted from van Hateren et al. 2005)

ommatidial lattice. The number of ommatidia (facets) ranges from only some tens to up to 10,000 (Land 1997). Thus, compared with technical imaging systems, the number of sampling points and the spatial resolution of insect eyes is very low. Nonetheless, this low spatial resolution appears not to be detrimental given the fact that many insects are well able to perform highly aerobic flight maneuvers and to solve sophisticated spatial tasks that are based on optic flow information (see below).

The most prominent computational mechanism proposed as the basis of local visual motion processing in flying insects, but also birds and even humans, is the correlation-type motion detector (Reichardt 1961; Borst and Egelhaaf 1989, 1993; Egelhaaf and Borst 1993). This mechanism was originally proposed on the basis of behavioral experiments with beetles but has been characterized in detail by electrophysiological analyses in the visual system of flies. In its simplest form, a local motion detector is composed of two mirror-symmetrical subunits

(Fig. 5b). In each subunit, the signals of adjacent light-sensitive cells receiving spatially and temporally filtered brightness signals from neighboring points in visual space are multiplied after one of them has been delayed. The final detector response is obtained by subtracting the outputs of two such subunits with opposite preferred directions, thereby considerably enhancing the direction selectivity of the motion detection circuit. Each motion detector responds with a positive signal to motion in a given direction, i.e., either horizontally or vertically, and with a negative signal to motion in the respective opposite direction. Various elaborations of this basic motion detection scheme have been proposed to account for the responses of insect motion-sensitive neurons under a wide range of stimulus conditions, including even natural optic flow as experienced under free-flight conditions (Egelhaaf et al. 2012; Borst 2018). During the last years, much progress has been made by combining the sophisticated repertoire of genetic and molecular approaches in *Drosophila* with



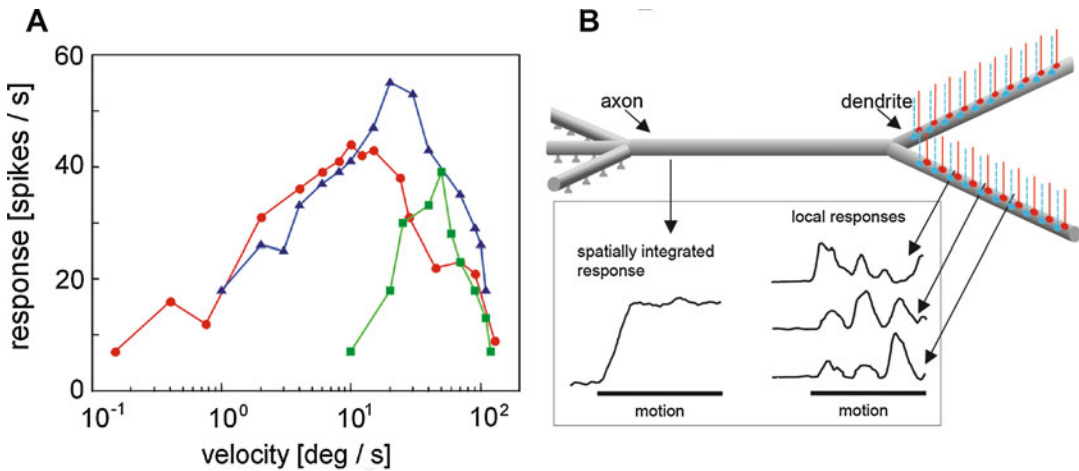
Visual Processing in Free Flight, Fig. 5 Major processing steps of visual motion computation in insects. (a) Schematic of the visual motion pathway. Images of the moving environment are projected on the array of photoreceptors. The input is spatially and temporally filtered before signals originating from neighboring points in the visual space interact with each other. These interactions lead to local motion measurements. The outputs of many retinotopically organized local movement detectors are spatially pooled by wide-field neurons. Their output signals are involved in the control of various motion-driven behavioral components. (b) Organization of a local movement detector in its simplest form. The movement detector

receives spatially and temporally filtered signals from neighboring points in space. The detector consists of two mirror-symmetrical subunits. In each subunit, one of the inputs is temporally delayed (τ), before it interacts nonlinearly with the undelayed signal of the other detector input. A multiplication-like interaction (M) is the lowest-order nonlinearity that is sufficient to account for many aspects of motion detection. The subunit outputs contribute to the response of the wide-field neurons with opposite polarity, i.e., the two signals are subtracted. (c) Example of a wide-field neuron in the third visual neuropile of the blowfly. The cell was filled with a fluorescent dye, before it was visualized under a fluorescence microscope

electrophysiological and imaging techniques to identify the different components of the neural circuits underlying the correlation motion detection scheme. From a computational point of view, an especially relevant result is the separation of the input circuits of the movement detector into an ON and OFF pathway processing separately brightness increments and decrements (Mauss et al. 2017; Yang and Clandinin 2018; Strother et al. 2017).

The local motion measurements provided by correlation-type movement detectors do not provide a veridical representation of the optic flow vectors. Even if at each retinal location the corresponding pair of local movement detectors most sensitive to horizontal and vertical motion,

respectively, is combined to a local motion vector, its direction and amplitude may considerably deviate from the geometrically correct velocity vector. Several aspects of biological motion detectors are of particular functional relevance (Egelhaaf and Borst 1993; Egelhaaf et al. 2014): (1) *Velocity dependence* – Local motion detectors do not operate like odometers, even if the time or spatial average of their responses is taken into account. Their mean response increases with increasing velocity, reaches a maximum, and then decreases again and, thus, does not reflect pattern velocity unambiguously. The response characteristics of biological motion detection systems are even more complex, since their velocity maximum depends on the textural properties of



Visual Processing in Free Flight, Fig. 6 (a) Time-averaged velocity responses of a wide-field neuron in the blowfly third visual neuropile to grating patterns of different spatial wavelengths (red curve: 6.6°; blue curve: 21.5°; green curve: 36.3°) moving horizontally in the neuron's preferred direction. Velocity-response curves strongly depend on the pattern properties; their optima are shifted to higher velocities with increasing spatial wavelength of the pattern. (Data from Eckert 1980) (b) Consequences of dendritic integration on the representation of visual motion: Schematic of a directionally selective wide-field neuron with two branches of its dendrite, the axon and the axon terminal. The wide-field neuron receives

retinotopically organized input from many local motion detectors (vertical lines terminating with "synapses" red dots (excitatory synapses) and blue dots (inhibitory synapses) on the dendrite). As a consequence of this input, the cell is excited by motion in its preferred direction and inhibited by motion in the null direction. Even when the velocity of motion is constant, the activity of the local movement detectors is modulated depending on the texture of the surround within its receptive fields. Traces on the right indicate the time-dependent signals of three local input elements of the wide-field neuron. By dendritic pooling of many local elements, this pattern dependence in the time course of the responses is reduced (left trace)

the moving stimulus pattern (Fig. 6a). The pattern dependence of velocity tuning is reduced if the stimulus pattern consists of a broad range of spatial frequencies, as is characteristic of natural scenes. Despite these ambiguities, free-flying flies and bees appear to regulate their translation velocity to keep the retinal velocities in that part of the operating range of the motion detection system in which its response increases monotonically with retinal velocity (see below). (2) *Time course of local motion responses* – The responses of the local movement detectors do not represent the local pattern velocity unambiguously because they prominently depend on the local pattern properties that are perceived by their input elements. Since these response modulations of neighboring movement detectors are phase shifted with respect to each other, spatial pooling of many of these, especially along the direction of motion, mainly reduces – depending on the spatial extent of pooling – those pattern-dependent

response modulations that originate from the high spatial frequencies of the stimulus pattern (Fig. 6b). (3) *Motion adaptation* – Motion-sensitive neurons adapt to the prevailing stimulus conditions, at the expense of veridical speed coding, thereby increasing their sensitivity to velocity changes, such as those that can be induced during translation by nearby objects. This feature has been interpreted as an adaptation to facilitate spatial vision (Liang et al. 2008; Li et al. 2017; Kurtz 2012).

Not in all instances is optic flow processing in flying insects based on directionally selective movement detectors described by the correlation model. In a specialized circuit tuning wide-field neurons in locusts and, probably, also in the fruit fly *Drosophila*, to looming stimuli as evoked by an approaching object, the retinotopic excitatory inputs of these neurons have been concluded not to rely on the direction of motion. Rather their responses depend on the brightness changes

evoked by retinal image displacements and the increase of these changes when the object comes closer to the eye. With increasing retinal speed, as the object comes closer, the latency of the inputs decreases, favoring synchronization of inputs sequentially activated throughout the looming sequence making the neuron maximally sensitive to an impending collision (Fotowat and Gabbiani 2011; Dewell and Gabbiani 2018). Whereas this computationally parsimonious principle serves a special circuit for detecting an object on a collision course, correlation-type movement detectors are thought to be employed by flying insects in solving a broad variety of motion-dependent orientation tasks, such as course control, object-induced orientation, collision avoidance with stationary surfaces in the environment, or even landmark-based local navigation, which require robust motion information and need to combine local movement detectors in versatile, task-dependent arrangements.

Optic flow elicited by self-motion is specified by global rather than merely local features depending on flight direction and on whether the animal basically translates or rotates but also on the three-dimensional layout of the environment (see above). This implies that mechanisms extracting optic flow information from the retinal input need to combine local motion measurements from large areas of the visual field. Accordingly, local motion information has been shown to be spatially pooled on the extended dendrites of wide-field neurons in the insect visual system or, more specifically, the third visual neuropile, the lobula complex (Figs. 5c and 6b). The way how this may be accomplished is likely to depend on the task that is solved by the respective system. In flies, where the mechanisms of task-dependent spatial pooling of local motion information have been analyzed in detail, a population of some tens of individually identifiable neurons and their synaptic interactions has been characterized in the third visual neuropile. Due to their spatial input organization and specific synaptic interactions, these neurons respond preferentially to retinal motion patterns that may be relevant in different behavioral contexts (Hausen 1984; Krapp 2000; Borst et al. 2010;

Borst 2014; Egelhaaf et al. 2012; Egelhaaf 2006; Egelhaaf and Kern 2002).

Local motion information from different parts of the visual field needs to also be combined in an appropriate way if, for instance, an approaching object is to be detected. To a large extent, this situation is characterized by looming stimulation, i.e., by moving motion vectors pointing away from the edges of the object, while its retinal size increases as a consequence of the approach (see above). Again in locusts and, most recently, flies where flight behavior induced by approaching objects has been analyzed, wide-field neurons have been characterized in detail in the third visual neuropile and at later processing stages that appear to process this kind of retinal image expansion and to be tuned to such looming stimuli (Fotowat and Gabbiani 2011; Dewell and Gabbiani 2018).

Optic Flow as Information Source for Flight Control

Flying animals have to solve a variety of behavioral tasks that all rely on different aspects of visual motion information. These can be grouped into three different functional classes depending on what the motion information is used for: (1) to determine the attitude and self-motion of the animal in three-dimensional space, (2) to obtain spatial information on the environment from the translational optic flow component, and (3) to gain information about other moving objects. Some particularly well-analyzed behaviors will be addressed in the following – whenever possible, with respect to the neural mechanisms involved.

Estimation of Self-Motion in the Context of Attitude Control and Course Stabilization

Wide-field neurons that are thought to sense self-motion of the animal and to play a role in determining self-motion for course control have been characterized in a number of insect species. The underlying neural mechanisms have been investigated in flies in great detail. The preferred directions of the local motion detectors that synapse onto a given wide-field neuron appear to coincide to some extent with the directions of the velocity

vectors characterizing the optic flow induced during particular types of self-motion. The specificity of wide-field neurons for certain types of optic flow is much enhanced by synaptic interactions with other wide-field neurons in the ipsilateral and/or contralateral half of the visual system. As a consequence, individual wide-field neurons strongly respond to certain types of self-motion, such as rotations around the vertical axis of the visual system or different axes in the horizontal plane (Hausen 1984; Krapp 2000; Taylor and Krapp 2008; Borst 2014).

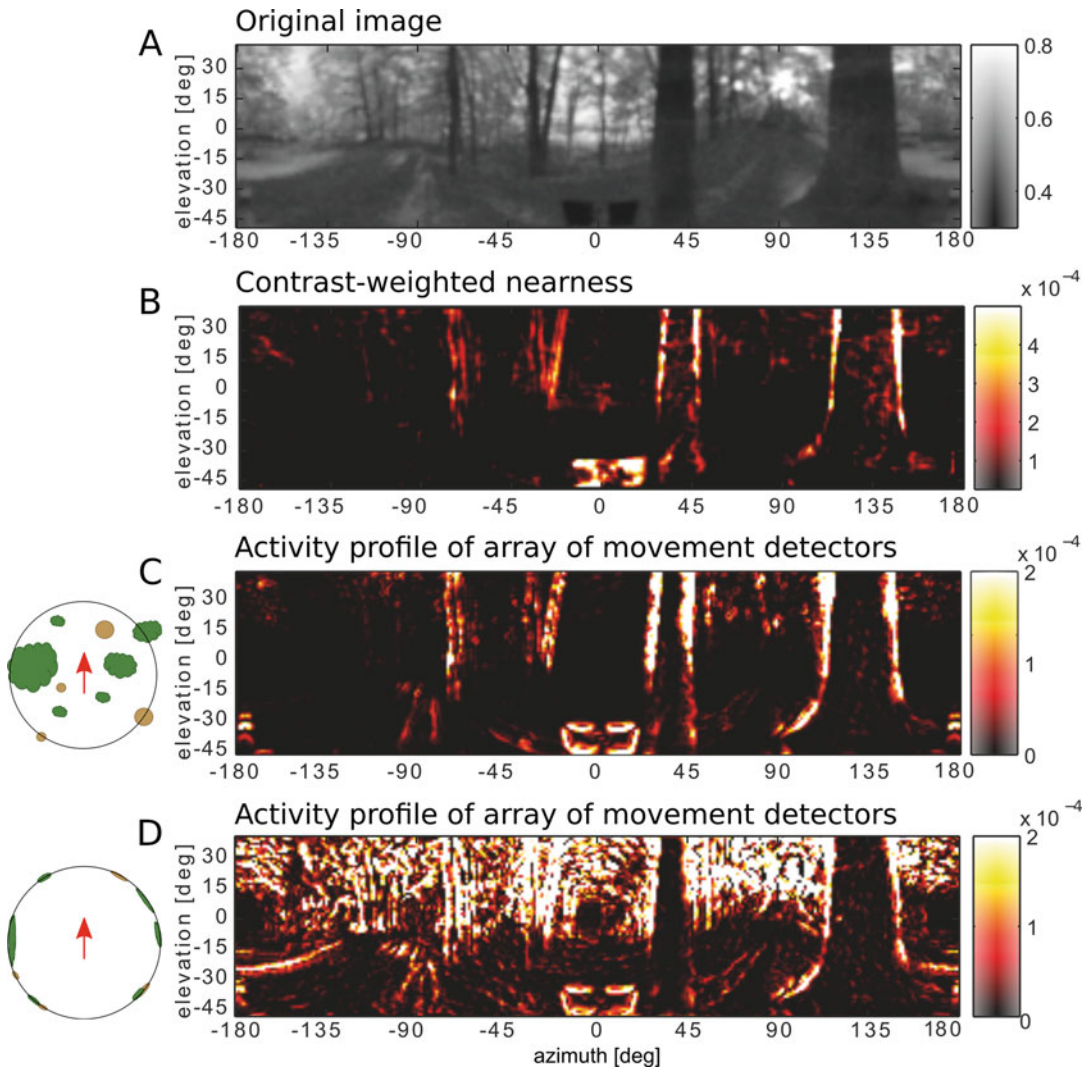
These wide-field neurons are commonly thought to mediate compensatory optomotor turning movements of the head and/or of the entire body. These behavioral responses have commonly been analyzed in flight simulators in tethered flight rather than in free flight. The fly generates turning movements of the head and the body to follow the moving pattern. These are usually interpreted to reflexively stabilize gaze direction and/or the flight course by minimizing the retinal velocities, for instance, resulting from external and/or internal disturbances (Taylor and Krapp 2008; Hengstenberg 1993; Hardcastle and Krapp 2016). As a general feature, compensatory optomotor turning responses are relatively slow: During maintained motion stimulation, they build up over several hundreds of milliseconds. Hence, optomotor feedback is likely to play a role on a slow timescale, for instance, to compensate for steady asymmetries at the level of the sensory input (e.g., internal gain differences) or the motor output (e.g., worn-out wings). Hence, the motion-sensitive wide-field neurons in the third visual neuropile may play a role in compensating unintended slow deviations of the animal from its flight course, after their output signals are considerably temporally low-pass filtered. So far, it is not clear where in the nervous system and by what mechanisms this filtering is accomplished. Since in free cruising flight gaze stabilization during intersaccadic intervals with their duration of only some ten milliseconds appears to be very fast, it is unlikely to be controlled by optomotor feedback (Egelhaaf et al. 2012). In addition to the body, the head of many analyzed insects, such as flies and bees, performs compensatory optomotor

movements on a fast timescale. In free flight, compensatory head movements are most prominent during roll rotations of the body, as are generated during banked saccadic turns and during sideways translations. Although head muscles receive synaptic input from motion-sensitive wide-field neurons, the functional role of visual motion for mediating compensatory head movements under free-flight conditions is still not entirely clear given the extremely rapid timescale at which gaze direction is stabilized during saccadic flight maneuvers, the response latencies, and the relatively slow time course of visually mediated head responses (Rosner et al. 2009).

Optic Flow as a Source of Spatial Information About the Environment

To facilitate the evaluation of spatial information from the optic flow, a range of flying animals such as many insects but also some bird species are thought to largely separate the translational and rotational optic flow components not by computational means but by behavioral strategies (see above). During cruising flight, the time that flies and bees keep their gaze direction largely constant amounts to more than 80% of the overall flight time. Rotations are comparatively short and very rapid (Fig. 4). This saccadic flight and gaze strategy has been interpreted as a way to facilitate gathering environmental cues and, in particular, spatial information from the retinal image flow during intersaccadic transitory self-motion (see above). In addition, insects can further adapt their flight and gaze strategies in an apparently targeted way to the environmental situation depending on the particular behavioral task the animal needs to solve.

Three distance-dependent features of the optic flow are of special functional significance. (1) Since the retinal velocity of an object scales with distance, an object nearby will lead to larger intersaccadic movement detector responses than a more distant one. A cluttered spatial scenery is segmented in this way, without much computational effort, into nearby and distant objects (Schwegmann et al. 2014; Egelhaaf et al. 2014). The representation of nearby objects is further enhanced by motion adaptation at the level of local motion detectors (Li et al. 2017) (Fig. 7).



Visual Processing in Free Flight, Fig. 7 Encoding of spatial information by two-dimensional arrays of local movement detectors during translatory locomotion in a natural environment. All images represent one instant of time during a longer translation sequence. (a) Original input image (after a nonlinear Naka-Rushton-like transformation of brightness values). (b) Contrast-weighted nearness map: The nearness (i.e., the inverse distance of the observer to any point in the 3D environment) is multiplied by the local contrast at the corresponding image location, resulting in the largest contrast-weighted nearness values at the edges of nearby objects (color code in arbitrary units). (c) Activity profile of the array of movement detectors while the observer moves through a natural environment

staggered in depth (see inset). The activity profile is given by the local motion energy, i.e., the absolute values of horizontally and vertically aligned local movement detectors; model simulations based on an elaborated version of the correlation-type movement detector (color code arbitrary units). The activity profile reflects the contrast-weighted nearness structure of the three-dimensional environment. (d) Activity profile of the array of movement detectors at one instant of translatory motion after the depth structure of the forest environment has been equalized by projecting it on the surface of a sphere (see inset). Model simulation as in c. The activity profile now reflects all contours in the environment irrespective of their distance. (Data from Schwegmann et al. 2014)

(2) The retinal velocity range and, thus, the spatial range that can be encoded by the motion vision system are limited by, among other factors, neuronal noise resulting from the biophysical mechanisms of neural computation (Laughlin 1994; Warzecha et al. 2013). Under spatially constrained conditions where flies fly at translational velocities of only slightly more than 0.5 m/s, the spatial range within which significant distance-dependent intersaccadic responses are evoked in motion-sensitive neurons amounts to approximately 2 m. Since a given retinal velocity is determined in a reciprocal way by the distance of objects and velocity of self-motion, respectively, the spatial range that is represented by such neurons increases with increasing translational velocity. Hence, the behaviorally relevant spatial range scales with intersaccadic flight velocity. From an ecological point of view, this scaling of the behaviorally relevant depth range is economical: A fast-moving animal should, for instance, initiate a turn leading to an avoidance maneuver at an earlier point of time and at a greater distance from an obstacle than when moving slowly (Egelhaaf et al. 2012). (3) The optic flow is largest orthogonal to the direction of translation. Therefore, the corresponding part of the visual system is most sensitive to distance changes. Hence, an animal should move sideways, if spatial information needs to be gathered in the frontal visual field. Indeed, prominent sideways flight components can be observed in many behavioral situations when the animal appears to scrutinize the spatial layout of its environment (see below).

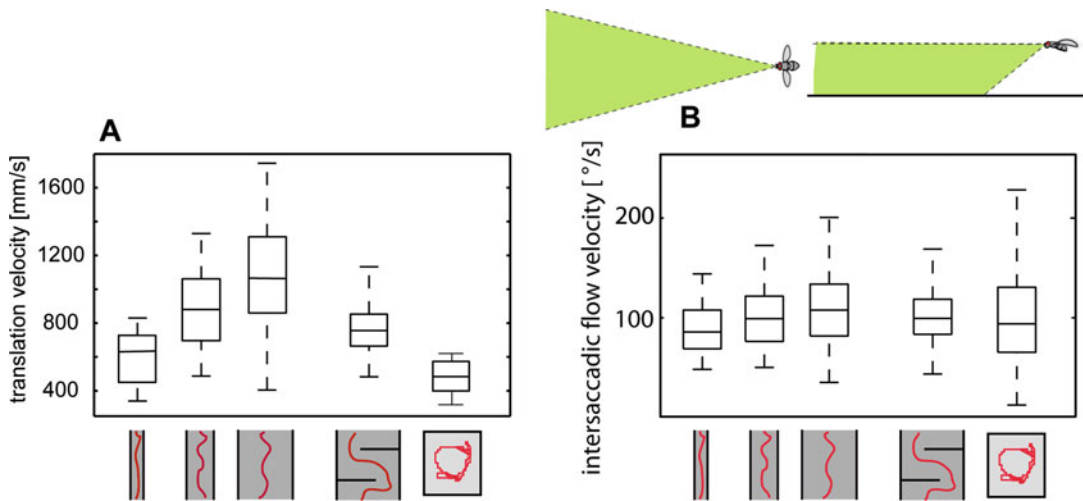
Spatial information derived from optic flow and represented in the visual motion pathway is used by free-flying insects in a variety of behavioral contexts. Five of these will be sketched here:

- **Control of Translatory Flight in Spatially Constrained Environments** All flying insects investigated appear to regulate their overall translation velocity depending on spatial layout of the environment and, in particular, on the width of the corridor available for flight. Insects decelerate if the width of a flight tunnel used for experimental analysis becomes

narrower or if the flight path is obstructed by objects. Flight speed is thought to be controlled by optic flow generated during translational flight. Flies, bees, and moths were concluded to keep the optic flow on their eyes at a “preset” total level by adjusting their flight speed. Accordingly, they decelerate when the translational optic flow increases, for instance, while passing a narrow segment of a flight corridor (Srinivasan 2011; Srinivasan and Zhang 2004; Lecoeur et al. 2019; Linander et al. 2016; Egelhaaf et al. 2012; Kern et al. 2012). Not all parts of the visual field equally contribute to the input of the flight velocity controller: The most prominent role can be attributed to the intersaccadic optic flow generated in eye regions looking in front of the insect (Fig. 8). In these regions of the visual field, the intersaccadic retinal velocities are kept in a range of the motion vision system where the responses of the motion vision system still increase monotonically with increasing velocity and decrease with decreasing velocity (Egelhaaf et al. 2012).

- **Avoiding Collisions with Environmental Surfaces by Controlling Saccadic Turns**

In many situations, objects or other structures in the environment may interfere as obstacles with the animal’s trajectory that need to be avoided. Thus, collision avoidance represents a basic but highly relevant spatial task. Optic flow information is the most relevant cue involved in mediating collision avoidance with environmental structures in fast-flying insects. This has been shown in detail both for tethered and free-flying flies. The evasive responses in free flight are based on the characteristic saccadic turns of insects, whereas those observed in tethered flight are much slower and, thus, only reflect to some extent what is going on under free-flight conditions. There is consensus between studies that the largely translational optic flow during intersaccadic intervals is relevant in controlling the direction and amplitude of saccades that lead to collision avoidance. However, it is still inconclusive which optic flow parameters may be most relevant. Nevertheless, all



Visual Processing in Free Flight, Fig. 8 (a) Control of translational velocity in free-flying blowflies. Boxplot of the translational velocity in flight tunnels of different widths, in a flight arena with two obstacles and in a cubic flight arena (sketched below data). Translation velocity strongly depends on the geometry of the flight arena. (b) Boxplot of the retinal image velocities within intersaccadic intervals experienced in the fronto-ventral

visual field (see sketches above data diagram) in the different flight arenas. In this area of the visual field, the intersaccadic retinal velocities are kept roughly constant by regulating the translation velocity according to clearance with respect to environmental structures. The upper and lower margins of the boxes in a and b indicate the 75th and 25th percentiles, and the whiskers the data range. (Data from Kern et al. 2012)

proposed mechanisms of evasive saccadic responses rely on some sort of asymmetry in the optic flow pattern in front of the two eyes. The asymmetry may be due to the location of the expansion focus of the flow pattern in front of one eye or to a difference between the overall optic flows in the visual fields of the two eyes (Bertrand et al. 2015; Lecoœur et al. 2019; Serres and Ruffier 2017). Not all parts of the visual field appear to be involved in saccade control in the context of collision avoidance. In blowflies, for instance, the optic flow in the lateral visual field does not play a role in determining the direction of evasive saccades. This feature is likely to be related to the flight style of blowflies (Egelhaaf et al. 2012). During intersaccades they predominantly fly forward with some sideways components immediately after saccades that shift the pole of expansion of the flow field slightly toward frontolateral locations (Kern et al. 2012). In contrast, *Drosophila*, hoverflies, but also bees are able to hover to some extent and to fly sideways. Here, also lateral and even rear parts of the eye

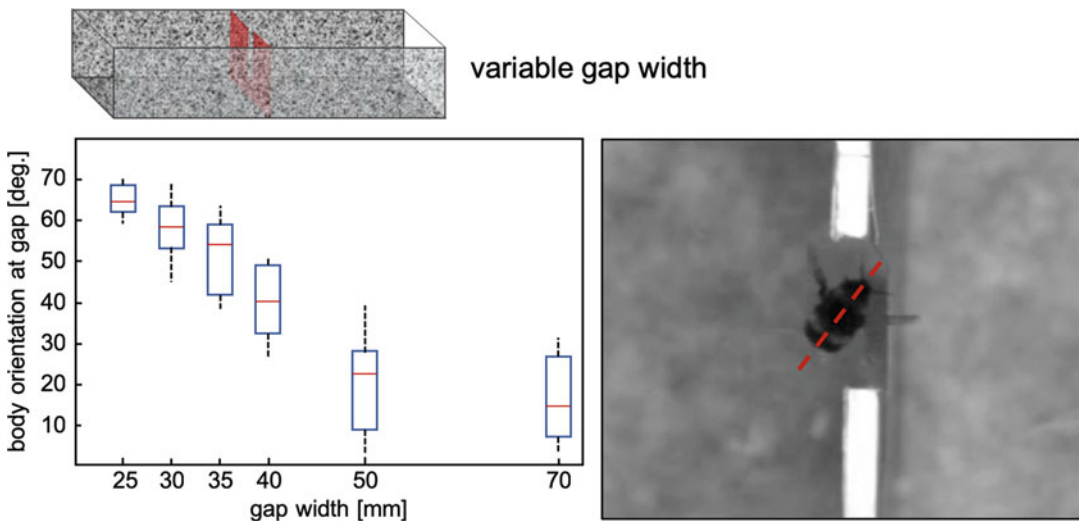
may be involved in eliciting evasive saccades in the context of collision avoidance (Muijres et al. 2014; Braun et al. 2012; Geurten et al. 2012).

- **Active Visual Strategies to Facilitate Spatial Vision when Negotiating Narrow Gaps** In cluttered natural environments, insects are not only confronted with having to avoid obstacles. They often have to fly through small gaps without damaging their wings. This requires estimating whether a gap is wide enough to get through unharmed. The identification of gaps and the assessment of their passability are therefore elementary aspects of aerial navigation. The optic flow generated on the eyes during self-motion is the most plausible source of the spatial information necessary to accomplish this task. It has been shown for bumblebees that they follow a dedicated active vision strategy to generate the optic flow that provides the relevant information necessary to estimate the width of a gap and to control an adequate flight maneuver that ensures injury-free passage through it. When

approaching a gap, bumblebees decelerate at some distance to the gap, if the gap appears to have a critical width. The bees then gradually trade off their longitudinal velocity to lateral velocity and approach the gap with increasing lateral displacements. When the gap becomes more difficult to pass, the bees spent an increasing amount of time moving laterally in front of the gap. During these repeated lateral maneuvers, which generate pronounced translatory optic flow in the frontal visual field, the bees are probably assessing gap geometry and passability by using motion parallax (Ravi et al. 2019). By this active flight strategy, the bees are able to assess whether the gap is sufficiently wide to be able to fly through head first in normal flight orientation or whether they have to pass in an oblique or sideways orientation (Fig. 9). The bees thus seem to “know” their own body size along their different axes, since they behave in this peculiar way even if they had no prior experience with the respective environment. Hence, bumblebees adapt their flight and gaze

strategies to the situational context in such a way that they are able to cope with a multitude of unexpected spatial challenges in cluttered environments in order to fulfil their overarching foraging tasks.

- Active Visual Strategies During Local Navigation Based on Landmark Information** Whereas all flying insects should be able to avoid collisions with obstacles and to overcome narrow gaps, local navigation is a special ability of hymenopteran insects, such as bees, some wasps, and ants, which care for their brood and, thus, have to return to their nest after foraging (Zeil 2012; Zeil et al. 2009; Collett and Collett 2002; Collett et al. 2013). Nevertheless, basic elements of local navigation could also be found in *Drosophila* where the underlying neural circuits can be unraveled to some extent thanks to the broad repertoire of genetic approaches (Kim and Dickinson 2017; Green et al. 2017; Dewar et al. 2017; Turner-Evans and Jayaraman 2016). Visual landmarks represent crucial spatial cues and are employed to localize a goal, especially if it is barely



Visual Processing in Free Flight, Fig. 9 Bumblebees are able to relate the width of a gap to their body-size when they want to pass it. The experimental analysis was done in a flight tunnel with an obstructing wall containing a gap of variable width. Bumblebees decelerated at some distance to the wall and approached the gap with increasing lateral displacements depending on the width of the gap. During

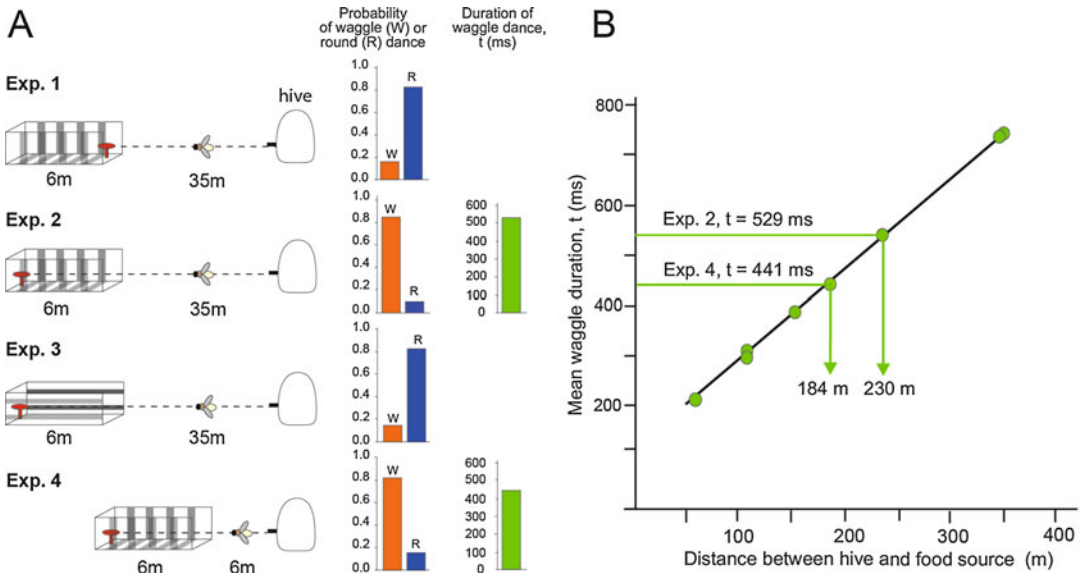
the lateral maneuvers, the bees are likely assessing whether the gap was sufficiently wide to be able to fly through headfirst in normal flight orientation or whether it had to pass in an oblique orientation. Because the wingspan is larger than the body length, the bumblebees flew almost sideways through narrow gaps. (Data from Ravi and Egelhaaf)

visible. Information about the landmark constellation around the goal is memorized by bees during elaborate learning flights: The animals perform characteristic flight sequences while facing the area around the goal. During these learning flights, the animal somehow gathers relevant information about the landmark constellation that is subsequently used to relocate the goal when returning to it after an excursion. Although a variety of visual cues, such as contrast, texture, and color, are relevant in defining landmarks and are employed to find the goal, it is getting increasingly clear that also the spatial layout of the landmark constellation plays an important role and that landmarks that are defined by motion cues alone can be used by bees to locate the goal (Egelhaaf et al. 2012; Dittmar et al. 2011). Although the mechanisms by which the landmark constellation is learned and the memorized information is eventually used to locate the goal are not fully understood so far, it is clear that optic flow information actively generated during the bees' typical learning and searching flights is essential for the acquisition of a spatial memory of the goal environment (Zeil 2012; Zeil et al. 2009). Moreover, in the vicinity of landmarks, the animals adjust their flight movements depending on the specific textural landmark properties (see above). Since landmarks close to the goal are, for geometrical reasons, most suitable to pinpoint the goal location because the retinal locations of close landmarks are displaced more than distant ones during translational movements, the relevance of environmental objects to serve as landmarks for local navigation in the vicinity of the goal is weighed without any additional computational effort – just as a consequence of the geometrical properties of the optic flow induced during intersaccadic translational movements (see above). Processing of behaviorally relevant visual information is, thus, facilitated by the characteristic active gaze strategy employed during free flight (Egelhaaf et al. 2012).

The neuronal mechanisms underlying visual landmark navigation are not yet

known, although a variety of models for navigation on different spatial ranges have been proposed on the basis of behavioral experiments, anatomical evidence, functional imaging, and electrophysiological recordings (Philippides et al. 2016; Hoinville and Wehner 2018; Stone et al. 2017; Webb and Wystrach 2016; Schulte et al. 2019; Baddeley et al. 2012; Honkanen et al. 2019). At the level of motion-sensitive wide-field neurons, the spatial landmark constellation that guides bees to their goal could be shown to lead to a characteristic time-dependent response profile during the intersaccadic intervals of navigation flights providing unique information about the vicinity of the goal (Mertes et al. 2014; Egelhaaf et al. 2014).

- **Estimation of Travelled Distance** Optic flow information is also used at least by bees for spatial tasks in the context of navigation over long distances away from their nest location, such as for the estimation of distances travelled during flights. Bees acquire distance (and direction) information on foraging excursions in an unknown environment to be able to return to their nest and to communicate the location of rewarding food sources to their fellow foragers. They gauge distance in terms of the optic flow experienced during the flight to a food source and use this information (in addition to direction information) during their return flights. Since the optic flow generated during translational movements depends on the three-dimensional layout of the environment, distance information gathered in this way is ambiguous. These ambiguities do not lead to problems as long as the recruited bees tend to fly on the same route as the forager and the environment does not change much between the flight of the forager and that of recruited bees (Fig. 10). Since distinctive changes in the spatial layout of the environment occur only rarely in natural settings over a couple of days, such a relatively simple mechanism of distance estimation is likely to be sufficient for the specific needs of navigating bees under normal behavioral conditions (Srinivasan 2011; Wolf 2011).



Visual Processing in Free Flight, Fig. 10 Honeybees measure distances in terms of optic flow generated during flight and communicate this information to their hive mates by the waggle dance. Behavioral analysis revealed how honeybees estimate the distance travelled between their hive and a food source. (a) Layout for the experiments using tunnels and probabilities of waggle dance (W; orange bars) and round dance (R; blue bars). A tunnel with a length of 6 m and a width of 11 cm was positioned either at a distance to the hive of 35 m (not drawn to scale) or at a distance of only 6 m. The walls of the tunnel were either covered with a texture that contained vertically oriented (Exp. 1, Exp. 2, Exp. 4) or horizontally aligned stripes (Exp. 3). The bees were trained to collect sugar water from a food source (indicated by red object). When the food source was placed at the entrance of the tunnel (Exp. 1), the bees performed mainly round dances after returning to their hive, signaling a short distance to the food source. When the food source was placed at the end of the tunnel containing vertically oriented texture (Exp. 2), the returning bees performed mainly waggle dances, signaling

much larger distances to the hive, although the actual travel distance was not much larger. A food source at the same distance, however, located in a tunnel with horizontally oriented stripes (Exp. 3), again led mainly to round dances. The main difference between Exp. 2 and Exp. 3 is that in the former, much optic flow is evoked on the eyes of the honeybee while flying along the tunnel, whereas in the latter case, there is only little optic flow, because the contours are oriented along the flight direction. When the tunnel covered with vertical contours and the food source close to its end is placed near to the hive (Exp. 4), mainly waggle dances are performed, which are shorter than those performed in Exp. 2 (compare green bars). These experiments suggest that travelled distance is measured in terms of optic flow. (b) Calibration of the odometer of the bee. Mean duration of waggle dances elicited by outdoor feeders at various distances to the hive. Also shown are the mean durations of waggle dances measured in Exp. 2 and Exp. 4 and their equivalent outdoor flight distances, as read from the regression line. (Adapted from Srinivasan et al. 2000)

Visual Motion as a Source for Information About Other Moving Objects

In some free-flight situations, retinal image motion does not originate primarily from the self-motion of the animal relative to a largely stationary environment but from other moving objects.

- **Escape from Impending Collisions with Moving Objects** Objects that may elicit an escape from an impending collision are not necessarily stationary in the environment.

Rather they may also move toward the animal. Examples are predators but also conspecifics in a swarm. The size of the retinal image of an object increases in a characteristic way when it directly approaches the animal. Under the simplifying assumption that the object moves on a straight collision course at a constant velocity, the temporal dynamics of its retinal image can be fully characterized by its size-to-speed ratio (see above; Fig. 3). For a given object size, a faster approach velocity implies a faster expansion rate and a smaller size-

to-speed ratio. In the locust, but also in *Drosophila*, escape behavior has been concluded not to occur at a fixed time before collision but rather at a fixed delay after the stimulus reaches a threshold angular size on the retina. This could be different in other systems and for other behavioral contexts, where the time it would take for the object to collide with the animal is critical, unless appropriate action is taken (Fotowat and Gabbiani 2011; Dewell and Gabbiani 2018).

There is good evidence, mainly from detailed studies on flight behavior and visual processing in locusts and most recently *Drosophila*, that there is a dedicated pathway in the visual system which is tuned to the characteristics of looming stimuli during an impending collision. The computations performed by the underlying sensory and motor processes could be analyzed in great detail both experimentally and by computational modeling. An identified wide-field neuron plays a key role in the neural circuit. The characteristic time course of its response encodes an impending collision with an approaching object. This information is conveyed via further identified neurons to motor centers that eventually generate escape behavior. The neural mechanisms of the angular threshold computation relevant for collision avoidance rely on three distinct processes: (1) motion-sensitive excitation evoked by the brightness changes resulting from displacements of the approaching object's retinal image activating retinotopically a dendritic subfield of the wide-field neuron, (2) an inhibitory network acting onto the motion-sensitive pathway presynaptically to the wide-field neuron, and (3) feedforward inhibition impinging on two additional dendritic subfields of the wide-field neuron. Eventually, the wide-field neuron's output performs a kind of multiplication by a nonlinear transformation of the overall postsynaptic potential into spike activity. This multiplication of an input that depends on the size of the approaching object with another input that depends on angular velocity of the edges of the object has been concluded to be

decisive in computing object approach (Fotowat and Gabbiani 2011; Dewell and Gabbiani 2018).

- **Pursuit of a Moving Target** Many insects follow moving objects, such as potential prey or mates. Dragonflies pursue other insects in highly aerobatic flight maneuvers to catch and eventually eat them. They appear to compute an interception course which somehow requires prediction of the moving target's future locations. In their third visual neuropile, neurons that are sensitive to small objects in restricted parts of the visual field have been characterized electrophysiologically and modeled. The outputs of such small target-selective local neurons are pooled by a population of individually identified descending neurons which have been concluded to represent a vector that reflects the direction of target motion with high accuracy (Gonzalez-Bellido et al. 2016; Olberg 2011; Nordström 2012).

In the context of mating behavior, male blow- and houseflies chase females in aerobic visually controlled flight maneuvers. The forward velocity of the chasing fly is controlled by the angular size of the target, whereas the turning velocity depends on the angle from which the target is seen as well as on its speed. The pursuing fly generates catch-up saccades when the target changes its direction too rapidly for the pursuer to follow smoothly. Pursuit of moving objects is, so far, the only flight behavior described in detail where, at least in flies, no clear flight phases characterized by almost pure translational movements are observed. During their rapid pursuit maneuvers, male flies, thus, abandon the possibility to gather information about the environment apart from information about their moving target. This may be functional given the fact that when closely following the course of its moving target, the pursuing fly will hardly collide with stationary obstacles in its surroundings. Accordingly, the gain of the optomotor course stabilizing system (see above) appears to be much reduced while the male fly is chasing (Egelhaaf et al. 2012; Trischler et al. 2010).

Constraints Imposed on Visual Information Processing by a Timescale of Natural Behavior

During free flight the retinal motion patterns continually change. As a consequence of the typical saccadic flight and gaze strategy of insects (see above), optic flow dynamics during natural locomotion deviate considerably from motion stimuli (e.g., constant velocity motion, white-noise velocity fluctuations) that are often employed when characterizing neural computations. In the context of spatial vision, the translatory flight segments and especially the intersaccadic intervals are the most likely times during which the flying insect can gather information about the spatial layout of the outside world. Although intersaccadic intervals have the largest share of the entire flight time, they may be as short as 30 ms. Hence, information processing during free flight needs to take place on very short timescales. Rapid information processing is not only an issue in the context of intersaccadic spatial vision but often highly relevant when the flying insect encounters moving objects and has to respond to them in an appropriate way (i.e., either escape or pursue; see above).

Why is rapid information processing during flight and the short timescales during which information about the environment needs to be computed an issue at all? One reason is that neurons are relatively unreliable computing devices. In insects the problem of reliability is particularly daunting, as there is not much redundancy at the output level of the visual system which would allow for the pooling of information across equivalent neurons (de Ruyter van Steveninck and Bialek 1995; Warzecha et al. 2013; Warzecha and Egelhaaf 2001).

When the same stimulus is repeatedly presented to a neuron, the responses may vary much between trials. Neuronal activity continually fluctuates even during constant velocity motion. On the basis of individual response traces, it is not easily possible to discern stimulus-driven activity changes from those that are due to sources not associated with the stimulus (“noise”). The origin of various potential noise sources in the visual motion pathway and the consequences of the

unreliable nature of neural signals can be attributed in part to the input of the visual system, i.e., photon noise, but arise mainly from a host of biophysical and cellular processes in the nervous system. Examples of such noise sources are the mechanisms involved in synaptic transmission and action potential generation. The impact of these noise sources on the precision with which motion information can be encoded is still not entirely clear. However, one aspect that appears to be especially relevant in the context of computing spatial information during intersaccadic intervals could be resolved to some extent: Given that neuronal responses are noisy, it will take some time to reliably infer behaviorally relevant environmental information from neuronal activity. Statistical analyses of noisy intersaccadic responses of individual and populations of fly wide-field neurons in the third visual neuropile reveal that sufficiently reliable information about translatory self-motion and, thus, about spatial parameters of the environment can already be decoded on a timescale of little more than 5 ms and, thus, on a timescale relevant for processing behaviorally relevant information (Egelhaaf et al. 2005).

Conclusions

Vision is only one information source for behavioral control in free flight. Other sensory modalities, especially a wide variety of mechanosensors, are also important, for instance, for stabilizing the attitude of the animal (Hengstenberg 1993; Frye 2010; Sane 2016; Dickinson and Muijres 2016). However, behavior is a phenomenon that takes place in space and is intricately entangled with it. Thus, its control requires information about its environment, which to a large extent can only be provided by the visual system. It is safe to conclude that flying insects, such as flies, bees, locusts, and dragonflies, rely primarily on their visual system to perform their highly aerobatic flight maneuvers and to solve complex spatial tasks, such as avoiding collisions with obstacles, negotiating gaps, landing on objects, or even finding hardly visible goals on the basis of spatial

landmark information, but also to detect and pursue other moving insects that may serve, for instance, as a prey or a mate. Insects accomplish all this with the help of tiny brains with less than a million neurons and a spatial resolution of their eyes much smaller than technical camera systems. Hence, if resource efficiency with respect to computational effort and energy consumption is conceived as a benchmark, insects outperform man-made autonomous flying systems in the abovementioned tasks. Moreover, insects successfully solve these tasks at flight velocities that imply rapid time-varying image flow on their eyes. The processing of the fast retinal image flow presents the neuronal machinery with great challenges in view of the limited reliability of neurons as computing devices. Obviously, as a consequence of millions of years of evolution, insect nervous systems have become well adapted to successfully cope with these computational challenges and to solve those computational tasks that are relevant for the success of the species efficiently and parsimoniously.

One way to achieve such exceptional performance is for insects to actively shape the image flow on their eyes by their characteristic flight behavior, for instance, by segregating through a saccadic flight and gaze strategy their translational and rotational movements and, thus, the corresponding optic flow components on their eyes. In this way neural processing of spatial information about surfaces and objects in the environment is greatly facilitated. More generally, and also taking into account other behavioral contexts, such as the encounter with other moving animals, it is suggested that by tuning the neural networks for visual information processing to the characteristic spatiotemporal properties of the retinal motion patterns as generated during free flight allows the nervous system to solve apparently complex vision tasks efficiently and parsimoniously.

Most conclusions on how visual information is processed in free flight are based on electrophysiological experiments performed on completely restrained animals because recording from most of the analyzed cells has not been possible during flight. In some recent analyses,

conventional experimenter-defined visual stimulation was abandoned. Instead, analyses at the neuronal level were carried out by simulating the complex spatiotemporal visual stimulus conditions during free flight and presenting the tethered animal motion sequences that free-flying animals had previously experienced in various behavioral contexts. From this type of experiment, it has been possible to draw conclusions about the significance of intersaccadic neuronal responses for providing the animal with spatial information (Egelhaaf et al. 2012; Kern et al. 2012). Although recent studies suggest that the overall behavioral state of the animal influences motion-sensitive wide-field neurons at the output level of the visual system by increasing their response level and slightly shifting their velocity tuning (Maimon 2011), the overall specificity of these neurons to different optic flow patterns and, thus, the major conclusions on visual processing in free flight appear not to be affected (Egelhaaf et al. 2012; Rien et al. 2013). However, the output signals of these neurons may be affected in a highly specific way by motor-related inputs, which quantitatively silence the predicted visual responses to rotations around the relevant axis while preserving sensitivity to “unexpected” visual input (Kim et al. 2017). This kind of efference copy signal, thus, can be expected to reduce the responses of motion-sensitive wide-field neurons to the rotational optic flow during saccadic turns while leaving the cell fully responsive to the optic flow perceived during intersaccadic intervals. This kind of behavioral modulation of visual signals would thus further facilitate optic flow-based spatial vision. While all the above conclusions about the impact of the behavioral state on visual information processing were based on tethered flying or walking animals, recent successful attempts to monitor neural activity at least in large free-flying insects (i.e., locusts, dragonflies) show great promise to challenge these conclusions in more natural conditions (Harrison et al. 2011; Yue et al. 2018).

In any case, it is reasonable to conclude from the experimental work on visually guided free-flight behavior of insects and the underlying neural mechanisms that insects with their tiny brains

derive part of their power as autonomous systems from dynamic animal-environment interactions that lead to adaptive behavior in environments of a wide range of complexity. Model simulations and robotic implementations reveal that the smart biological mechanisms of motion computation and flight control might be helpful when designing micro air vehicles that may carry an onboard processor of only relatively small size and weight (Floreano et al. 2009).

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Visual Prosthesis

► Visual Prosthesis, Optic Nerve Approaches

Visual Prosthesis, Cortical Devices

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Synonyms

Intracortical microelectrodes for visual rehabilitation; Visual cortical implants; Visual neuroprosthesis

Definition

Cortical prostheses are a subgroup of visual neuroprostheses capable of eliciting visual percepts in profoundly blind people through direct stimulation of the visual part of the brain. This approach is the only treatment available for blindness caused by glaucoma, optic atrophy, or by diseases of the central visual pathways such as brain injuries or stroke.

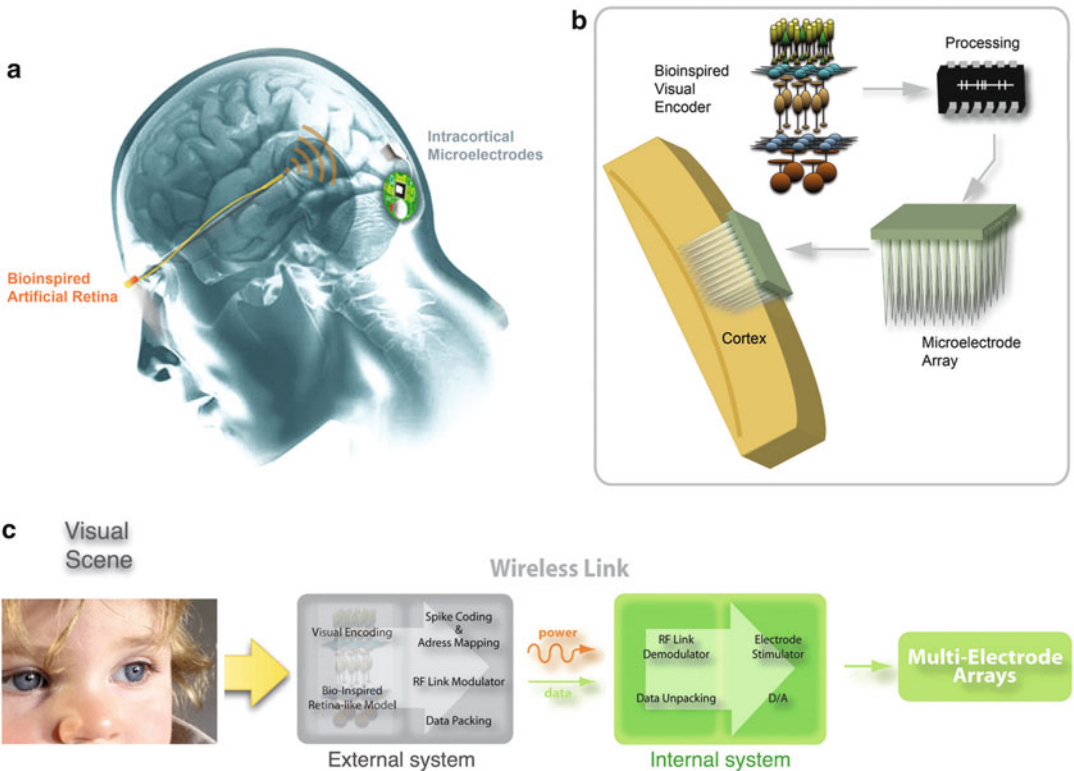
Detailed Description

As blindness results from an interruption in the normal flow of signals along the visual pathways, a visual prosthesis has to excite the neurons of the pathway at some point after the damage site (Normann et al. 1996). The only requirement is that the device should contact with still functioning neural elements. Since retinal diseases frequently reduce visual acuity and result in non-curable blindness, several groups worldwide are working on the development of different

prostheses designed to interact with the remaining healthy retina, optic nerve, and lateral geniculate nucleus (LGN) (Fernandez and Hofmann 2011; Dagnelie 2012; Fernandes et al. 2012; Guenther et al. 2012; Shepherd et al. 2013). However, the output neurons of the eye, the ganglion cells, often degenerate in many retinal blindnesses (Marc et al. 2008), and therefore, a retinal, an optic nerve, or even an LGN prosthesis would not be always helpful. This extensive degeneration usually spares the neurons in the higher visual regions of the brain, highlighting the enormous potential of a cortical prosthesis designed to stimulate cortical neurons (Troyk et al. 2003; Fernandez et al. 2005; Normann et al. 2009; Tehovnik and Slocum 2013). Thus, if these higher visual centers could be stimulated with visual information in a format somewhat similar to the way they were stimulated before the onset of blindness, a blind individual could be able to use this stimulation to extract

information about the physical world around him/her.

Figure 1 illustrates the basic components of this approach. One or two cameras provide image acquisition, which is then processed by a bioinspired retina-like encoder in order to transform the visual world into electrical signals (Morillas et al. 2007). This first stage performs a multichannel spatiotemporal filtering to extract and enhance the most relevant features of the scene and also re-encodes this information into a neuromorphic stream of electrode addresses. The second stage serializes the information and transmits it through a radio-frequency (RF) link to the implanted device. This RF block provides a wireless transfer of power and data to the internal system. The implanted electronics package must decode the signals, identifying the target electrodes and stimulus waveform applied to the corresponding electrodes located near the target



Visual Prosthesis, Cortical Devices, Fig. 1 Basic components of a cortical visual neuroprosthesis

neurons (Romero et al. 2007; Rush and Troyk 2012).

While the full restoration of vision seems to be impossible, it is expected that a cortical device can create truly meaningful visual percepts that can be translated into functional gains such as the recognition, localization, and grasping of objects or skillful navigation in familiar or unfamiliar environments resulting in a substantial improvement in the standard of living of visually impaired persons.

The Case for a Cortical Visual Neuroprosthesis

The concept of a cortical visual prosthesis began with studies of the functional architecture of the cerebral cortex and has a long history in biomedical engineering. A German neurosurgeon, Foerster, was the first to expose the human occipital pole under local anesthesia and to electrically stimulate it (Foerster 1929). He noted that electrical stimulation induced the perception of points of light, called phosphenes and usually described as “stars in the sky,” “clouds,” and “pinwheels” that were dependent on where the stimulation probe was placed. These findings together with the earlier studies of Wilder Penfield and coworkers during the course of neurosurgical interventions for the treatment of epilepsy (Penfield and Rasmussen 1950) settled the physiological basis for present efforts to develop a visual prosthesis for the blind.

Subsequent experiments by the group of Giles Brindley in England, William Dohelle at the University of Utah, and others showed that stimulation of multiple electrodes simultaneously allowed blind volunteers to recognize simple patterns, including letters and Braille characters (Brindley and Lewin 1968; Dohelle et al. 1976; Dohelle 2000). Unfortunately, these early efforts did not culminate in the restoration of a useful visual sense. Problems with this early work were associated mainly with the large-surface electrodes that were used to evoke phosphenes. Thus, relatively high electrical currents were required to evoke phosphenes, and when multiple

electrodes were stimulated, these large currents could interact in a nonlinear fashion, evoking phosphenes with unpredictable spatial properties. Furthermore, they also found that a visual prosthesis based on relatively large-surface electrodes implanted subdurally would have limited usefulness because of occasional elicitation of pain due to meningeal or scalp stimulation and the risk of inducing epileptic seizures.

A promising approach, which can activate populations of neurons with greater spatial specificity and lower levels of stimulation than is possible with larger electrodes on the surface of the brain, is the use of intracortical microelectrodes (Schmidt et al. 1996).

Selection of Suitable Subjects for a Cortical Visual Prosthesis

The selection of a specific person for a cortical visual implant is not straightforward, and currently there are no strict standardized criteria for accepting or rejecting a candidate nor for the best rehabilitation procedure for every type of blindness (Merabet et al. 2007).

In general it is considered crucial that the subject should have at best bare light perception and have no significant benefit from a conventional visual aid. Furthermore, previous visual experience is needed. In this context, it has been presumed that if blindness occurs after the age of 10 years, visual pathways should develop normally and thus remain Excitable.

Advantages of the Approach

Penetrating arrays of microelectrodes have been successfully used in long-term animal studies, and the skull provides a stable and rugged housing for the implant. Furthermore, this approach provides a potential solution to pathologies affecting the entire retina, optic nerve, thalamus, or brain. Thus, it is the only treatment available for blindness caused by glaucoma or optic atrophy as well as for diseases of the central visual pathways such as brain injuries or stroke.

Limitations

The main problem of a cortical implant is the lack of preliminary processing by the brain, particularly in the retina where much of the information reduction takes place. Some other impediments are related with the development and implementation of strategies designed to interface with a visually deprived brain that can be specifically tailored for the own needs of each patient.

On the other hand, cortical prosthesis must be implanted into the nervous system and remain fully functional for periods that will eventually extend to many decades. Therefore, these devices must be highly biocompatible and be able to resist the attack of biological fluids, proteases, macrophages, or any substances of metabolism (Marin and Fernandez 2010). Likewise, it is necessary to take into account the possible damage of neural tissues by permanent charge injection. These considerations place unique constraints on the architecture, materials, and surgical techniques used in the implementation of a cortical prosthesis (Normann et al. 1999).

Challenges and Future Perspectives

A key issue that has often been utterly underrated in the field of visual prosthesis is the role of neural plasticity. Thus, a helpful visual prosthesis should take into consideration not only standardized methods and employ current clinical and technological expertise but also consider newly emerging developmental and neurophysiological evidence. For example, there is considerable evidence that adaptive and compensatory changes occur within the brain following the loss of sight (Fernandez and Merabet 2011; Merabet 2011). The modulation and understanding of these neuroplastic processes are crucial for the success of any visual neuroprosthesis and can provide useful strategies for improved rehabilitation and teaching methods for the blind.

Other future challenges are related with the development of advanced bidirectional interfaces with the human nervous system.

Cross-References

- [Computational Models of Neural Retina](#)
- [Neural Coding](#)
- [Retinal Disease and Remodeling](#)
- [Retinal/Visual Interfaces \(Models, Theory, Techniques\): Overview](#)

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Visual Prosthesis, Epiretinal Devices

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Synonyms

Artificial retina; Artificial vision; Bionic eye; Intraocular retinal prosthesis; Retinal chip; Retinal prosthesis

Definition

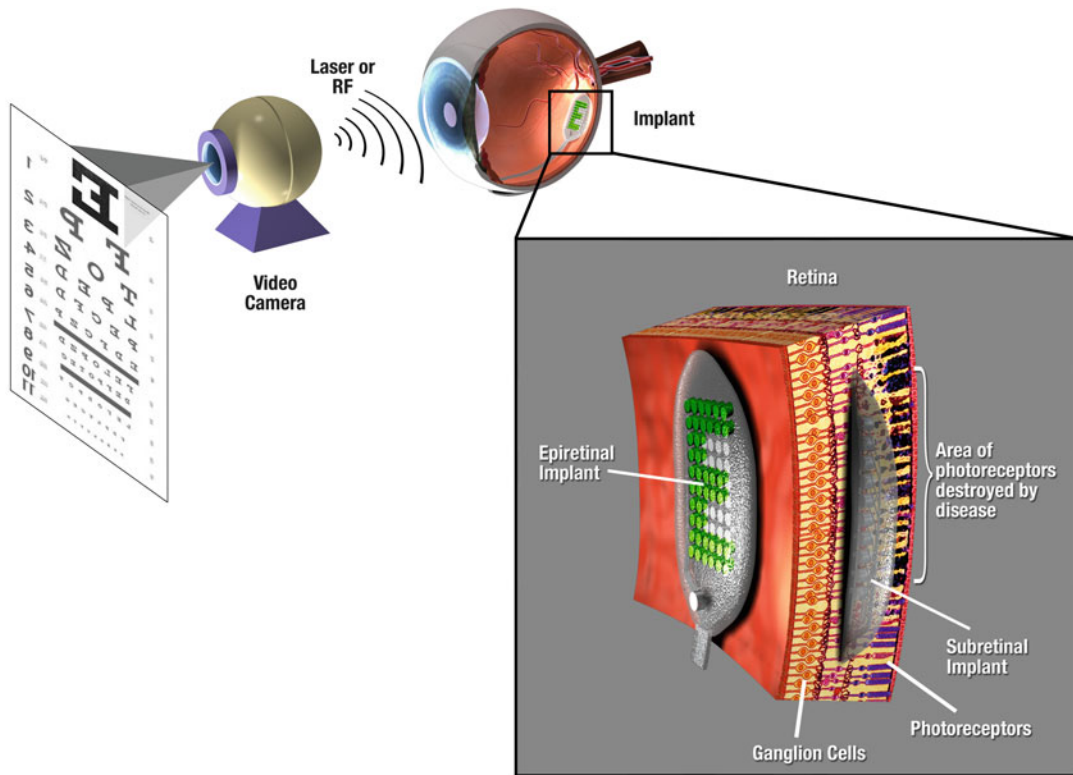
An electronic system, usually comprised of external and implanted components, that can sense light, convert light to an electronic signal, and apply that signal to the retina, as a treatment for blindness secondary to photoreceptor loss.

Detailed Description

In a healthy retina, light is detected by photoreceptors (rods and cones) via photosensitive molecules in the outer segments of the photoreceptors. These molecules, once transformed by light, trigger a cascade of neurochemical events that lead to other neural cells in the retina (ganglion cells) sending signals to the downstream visual centers of the brain. Retinal degenerative diseases, like retinitis pigmentosa and age-related macular degeneration, affect primarily photoreceptors, leaving the retina unable to sense light, but remaining neurons in the retina (bipolar cells and ganglion cells) can be electrically activated, based on established techniques for nerve stimulation.

A typical retinal prosthesis has multiple components each with a specific function (Fig. 1). These include an imager to convert light to electrical signal, electronics to process and condition the image and generate electrical stimulus pulses, and an array of microelectrodes to stimulate the retina. Other important components found in one form or another on most implants include hermetic packaging and wireless data/power transmission. However, retinal prostheses are often categorized based on the location of the electrode array, which forms the functional interface with the retina. The locations where an electrode array can be implanted to stimulate the retina include epiretinal (on the top surface of the retina), subretinal (under the retina), and suprachoroidal (between the sclera and choroid).

Several prototype systems of chronic implantable devices have been tested in clinical trials. These fall into two types of implants. The first type of device was designed to show feasibility in humans, but not intended to be a commercially viable medical device. Thus, the main concern for these devices was patient safety and they generally were not refined to the same degree as a commercial product. For example, a number of these early chronic implants could only be activated when the patient visited the clinic. The second type of devices is intended as commercial devices, so they are engineered not only for robustness and safety but also to have expected longevity of over a decade and with human factor



Visual Prosthesis, Epiretinal Devices, Fig. 1 Retinal prosthesis concept: an external camera captures and image. Wireless transmission of image data to an implant specifies

the stimulation pattern that is applied to the retina via a microelectrode array

considerations. One device, the Argus II retinal prosthesis (Second Sight Medical Products, Inc.), has received approval in both Europe and the United States to be sold as a treatment for retinitis pigmentosa. A summary of current and past clinical trials of retinal implants can be found at www.clinicaltrials.gov; search “retinal prosthesis.”

Epiretinal implants involved in feasibility studies include the Argus I from Second Sight and devices from Intelligent Medical Implants, GmbH (IMI) and the Epi-Ret Consortium (Epi-Ret). All three of these systems used wireless power and data delivery (to avoid transcutaneous wires).

The Argus I device was implanted in six subjects between 2002 and 2004 (de Balthasar et al. 2008). Argus I was a modified cochlear implant. As such, the electronics were implanted behind the ear, and a cable run along the temple, into the orbit, and, finally, into the eye, terminating in a

4×4 grid of platinum electrodes, either 520 mm or 260 mm diameter. With training, subjects were able to distinguish objects from a small set and detect motion of a moving bar. Subjects have been implanted for as long as 8 years with the device still functional.

The IMI device was implanted in a total of seven subjects (Hornig et al. 2007). This device utilized a microfabricated array with a total of 49 electrodes. The implant was entirely in the orbit, with the electronics module on the outside of the eye and the electrode array in the eye (via a cable across the eye wall). This system could only be activated in the clinic as no camera system was available. Using this device, subjects could see spots of light and some simple patterns. Since the electronics were not hermetically packaged, but only sealed with polymer coatings, the implants were removed after several months or, in one case, 1.5 years.

The Epi-Ret device was implanted in six patients (Klauke et al. 2011). The stimulating array had 25 electrodes and also was miniaturized to the point where the entire device could be implanted in the eye. A unique feature of the stimulating array was protruding electrodes, which improved contact with the retina and resulted in low perceptual thresholds. Like the IMI device, the Epi-Ret system was designed only for semichronic implantation (4 weeks) and did not have a camera system so the implant could only be activated in the clinic.

Commercial Design

Approval to sell a medical device as a treatment for a specific disease is only granted after approval by government agencies. The Argus II epiretinal prosthesis has received approval in Europe and the United States. The Argus II is similar to the IMI device in that the electronics are on the outside of the eye and the electrode array is on the retina, connected by a cable across the eyewall to the electronics (Humayun et al. 2012). The Argus II, however, has a camera system that provides input to the implant and the electronics are protected with a hermetic package so that implant longevity is decades. Thus, patients with implants can leave the clinic with the system. Sixty electrodes are arranged in a 6×10 format.

Thirty subjects were enrolled between 2007 and 2009. All subjects were able to perceive light during electrical stimulation. Other tasks on which subjects performed well include object localization and motion detection. Letter reading was tested in 22/30 subjects (da Cruz et al. 2013). Six of these subjects were able to identify any letter of the alphabet at a 63.5% success rate (vs. 9.5% with the system off). In all 22 subjects, a small set of eight letters was identified 72.5% correctly vs. 16.8% with the system off. Subjects were free to take as much time as needed to make a judgment. Adverse events that occurred during the trial included low eye pressure and infection, but such events decreased in later implants.

Conclusion

Epiretinal prostheses have proven that they have the capability to improve the lives of people blind from retinal degenerative disease. Multiple systems have been tested in humans, with one device receiving approval for sale.

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Visual Prosthesis, Optic Nerve Approaches

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Synonyms

Neural interface; Prosthetic device; Visual prosthesis

Definition

An optic nerve-based visual prosthesis is one type of viable visual prosthetic device, potentially allowing those with profound vision loss to have a usable level of vision. Visual impairment usually arises from degenerative diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). An implantable microelectronic device can be used to electrically stimulate the optic nerve with surface or penetrating electrodes for vision recovery. The axon bundles could be stimulated and a larger visual field produced than through other approaches such as visual cortex prostheses and retinal prostheses.

Detailed Description

Since the human brain is extremely intricate and fragile, surgically implanting electrode arrays poses a high risk to the visual cortex. Although visual cortex prostheses were put forward firstly, it has always imposed great psychological pressure on the patient. A visual prosthesis based on a retinal placement is currently the most widely adopted approach for vision restoration (Zrenner 2002; Humayun et al. 2003; Rizzo and Wyatt 1997). The channels of micro-current stimulators as well as the density of microelectrode arrays are, however, limited by current technology. It is not possible to provide high spatial resolution by covering a large area of the retina with present implantable device technologies and microelectrode array fabrication techniques.

Visual information is transmitted via the optic nerve which is composed of the axonal process from millions of retinal ganglion cells. Thus, this makes a visual prosthesis based on optic nerve electrical stimulation a reasonable approach for vision restoration. Compared with a retinal prosthesis, it is possible to provide more meaningful visual cues by applying the same amount of electrodes to the optic nerve. A contact spiral cuff electrode has been designed for optic nerve stimulation (Veraart et al. 1998). However, the spatial resolution of the recovered vision was limited due to the fact that surface-stimulating electrodes were

used. In order to improve the spatial resolution, penetrating microelectrode arrays have been invasively inserted into the optic nerve (Ren et al. 2007; Chai et al. 2008; Sui et al. 2009). With advanced processing techniques, the size of the microelectrode arrays may be minimized greatly, resulting in reduced optic nerve damage and high spatial resolution. Compared with many retinal prostheses, an optic nerve visual prosthesis has a significant advantage in that the surgical approaches are considerably simple and there is no need to breach the scleral wall. The Chinese Project for Sight (C-Sight) is an interdisciplinary group project with the aim of developing this type of visual prosthesis.

Hardware Structure of the C-Sight Prosthesis System

The visual prosthesis from C-Sight consisted of external and implantable parts. The external part included image capturing, processing, and wireless communications. The visual scene was captured by a CMOS camera which was mounted at the center of a set of glasses. The processed visual information was encoded into trains of digital signals with a specific spatiotemporal stimulation pattern by a neural electrical stimulator and forwarded by radio transmission. An implanted neurostimulator received the radio signals and after decoding was used to activate various channels of an implanted multichannel penetrating microelectrode array configured as a 3-by-6 grid of penetrating electrodes.

In vivo Electrophysiological Study on Electro-Neural Tissue Interface

In vivo experiments conducted in rabbits and cats by the C-sight group showed that visuotopic stimulation could be achieved by an optic nerve implant. Low-threshold, localized, and discriminable stimulation could be achieved by using appropriate stimulating modes, waveforms, electrode size, interelectrode distance, and electrode distribution. Electrically evoked potentials (EEPs)

could be elicited by optic nerve stimulation. Current stimuli with cathodic-first pulses in a monopolar mode could elicit up to $1 \sim 2^\circ$ localized cortical responses. Two electrodes with inter-distance of $150 \mu\text{m}$ along the optic nerve axis could elicit discriminable cortical responses with a spatial resolution of $2\text{--}3^\circ$ (Sun et al. 2011).

Psychophysical Study Using Simulated Phosphenes

Due to the limited number of electrodes eliciting limited discrete phosphenes, one of the most important problems is how to provide the most useful visual information to prosthesis wearers. Therefore, it is significant to study the minimal information requirement and optimization of artificial vision based on simulated prosthetic vision. The simulated prosthetic vision processor consists of image acquisition and processing, a phosphene processor, and a simulated prosthetic vision renderer.

A precise description of phosphene characteristics (mapping, size, and so on) plays an important role in determining image processing for visual prostheses. Psychophysical experiment results demonstrated that combined training using tactile information and visual prosthetic stimulation may be potentially useful when training blind subjects to estimate phosphene characteristics. Simulated object recognition experiments showed that resolution, distortion, and dropout had a significant impact on the performance of the visual tasks.

Optic Nerve Exposure Surgery for Visual Prosthesis Implantation

The exposed space of the optic nerve is limited during surgery. After many animal experiments, the conclusion was drawn that the exposure of the optic nerve through stripping of the surrounding tissue around the eyeball is not desirable. To this end, our group proposed a novel, more feasible surgery solution based on tissue stripping in combination with craniofacial surgery. In brief, a high-

resolution, preoperative CT image of the eye is made in order to evaluate the incision size of the zygomatic bone on the temporal side of the eye socket. During the surgery, the zygomatic bone is cut and the orbital soft tissue is moved to maximize the available surgery space. The microelectrode array is permanently implanted in the optic nerve, with the array's wiring fixed to the orbital muscle. The removed section of zygomatic bone will be returned to its original position after the array is successfully implanted.

Cross-References

- [Prosthetic Vision, Perceptual Effects](#)
- [Retinal Disease and Remodeling](#)
- [Retinal Neurophysiology](#)
- [Retinal/Visual Interfaces \(Models, Theory, Techniques\): Overview](#)

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Visual Prosthesis, Optoelectronic Devices

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Definition

Retinal degenerative diseases lead to blindness due to loss of the “image capturing” photoreceptors, while the “image processing” inner retinal neurons and the “output” ganglion cells are relatively well preserved. Electronic retinal prostheses seek to reintroduce visual information and thereby restore sight by patterned electrical stimulation of the surviving neurons.

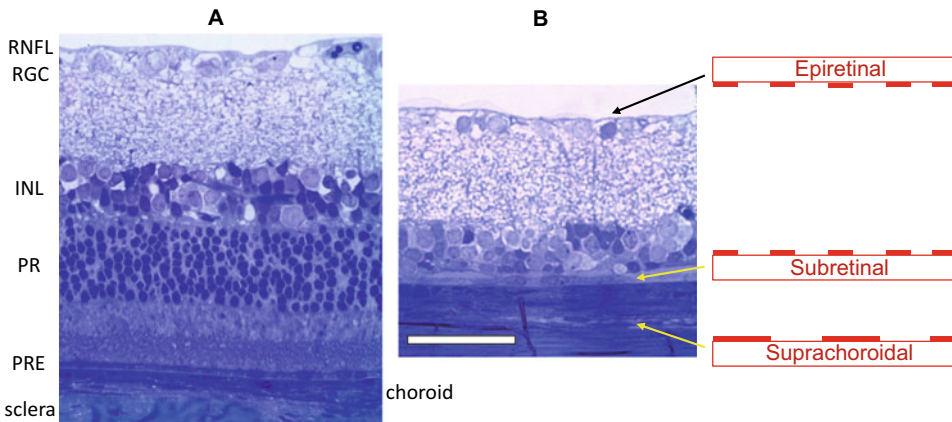
Detailed Description

Photoreceptors convert light into neural signals, which are processed by the inner retinal neurons, leading to generation of action potentials in the retinal ganglion cells (RGCs). These signals travel through the optic nerve to the brain and serve as the basis for visual perception. In retinal degenerative diseases, such as Retinitis Pigmentosa or Age-Related Macular Degeneration, photoreceptors gradually disappear, leading to loss of sight, even though the inner retinal cells remain largely intact. Electrical stimulation of the remaining retinal neurons can reintroduce visual information, creating patterned percepts of light, called phosphenes.

Retinal implants are usually classified into epiretinal, subretinal, and suprachoroidal, according to their anatomical placement in the eye. In the *epiretinal* approach (Ahuja et al. 2013), stimulating array is placed on top of the

retinal surface and typically targets the ganglion cells (RGC), as shown in Fig. 1b. Epiretinal arrays can be implanted with relative ease and can also be removed in case of postsurgical complications or device failure. The ultimate goal of direct stimulation of RGCs is to emulate the natural retinal code (Jepson et al. 2013). Rapid (1–3 ms) response of RGCs to electrical stimulus with a single action potential enables precise control of the elicited spikes sequence (Grosberg et al. 2017). Since different types of ganglion cells respond to different aspects of the image (increase or decrease in light, direction of motion, etc.), they require different encoding of the visual information. Identification of cell types in diseased retina and selective activation of them is very challenging. Another problem with epiretinal electrodes is that they stimulate not only the nearby cells, but also the axons from distant cells passing underneath the electrodes (Grosberg et al. 2017). Consequently, patients report distorted arcuate visual percepts instead of round localized spots (Nanduri et al. 2012).

In the *subretinal* approach, electrodes are located underneath the inner nuclear layer, replacing the degenerated photoreceptors (Fig. 1b, Stingl et al. 2013; Lorach et al. 2015). Graded responses induced in the inner retinal neurons by electrical stimulation are transmitted via the retinal network to the ganglion cells, which convert them into bursts of action potentials. This way, part of the retinal signal processing is preserved and encoding of the visual information by subretinal implant is simplified, compared to the binary encoding of the output spikes in RGCs using epiretinal implants. Preserved features include flicker fusion at high frequencies (Lorach et al. 2015), antagonistic center-surround organization (Ho et al. 2017), and nonlinear summation of subunits in receptive fields (Lorach et al. 2015), as well as ON and OFF responses (Ho et al. 2018). Subretinal placement also provides very close and stable proximity of electrodes to the target neurons, while epiretinal implants often float above the retina and shift over time. However, implantation in the subretinal space can be more difficult than on epiretinal side, and removal of the implant is also more challenging.



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Fig. 1 Placement of the retinal stimulation arrays. (a) Histological cross-section of a healthy rat retina. Signal generated in photoreceptors (PR) is processed in neurons of the inner nuclear layer (INL) and then in the retinal ganglion cells (RGC), which generate action potentials

(spikes) that propagate via the retinal nerve fiber layer (RNFL) to the brain. (b) Epiretinal implants are placed on top of the nerve fiber layer, while subretinal implants replace photoreceptors in a degenerate rat retina, facing the inner nuclear layer. Suprachoroidal implants are placed between the choroid and the sclera. Scale bar: 50 μm

In *suprachoroidal* approach, the implant is placed between the choroid and the sclera, the hard shell that encapsulates the eye (Fig. 1b). Larger distance between stimulating electrodes and retinal neurons greatly restricts attainable spatial resolution in this approach. Therefore, such implants are designed to help with low-resolution peripheral vision, primarily for ambulation (Ayton et al. 2014).

Another major distinction is the way information and power are delivered to the implant:

(A) In ARGUS II (Second Sight Inc. Sylmar, CA), information from a head-mounted camera, as well as power, are transmitted to the implant via an RF antenna (Ahuja et al. 2013). The signals are decoded and processed inside the extraocular implant, before being delivered to the 6×10 stimulating electrode array via a trans-scleral cable. A flexible foil with an array of 200 μm electrodes spaced by 575 μm is attached to the epiretinal surface with a trans-retinal tack. The Argus II has now been implanted in more than 200 patients, with a best grating visual acuity of 20/1260 (Ho et al. 2015). The device tends to improve patients' spatial mobility, despite its low resolution. Disconnect between the visual information

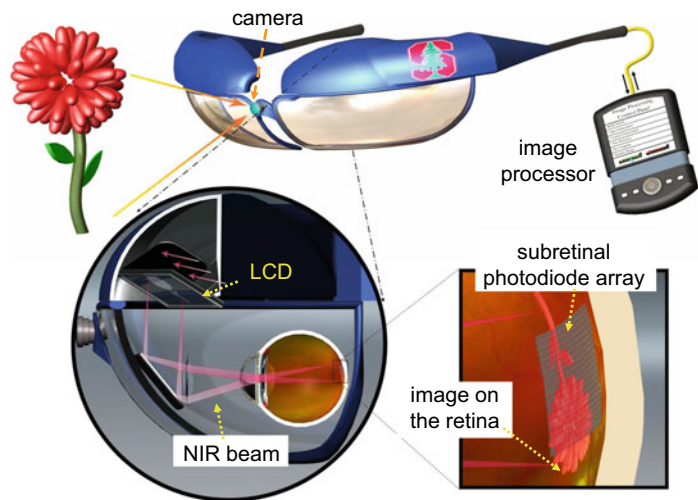
transmitted to the implant and the eye movements creates a perceptual mismatch since the brain expects the images to shift on the retina during eye movements. In principle, this issue can be rectified using eye tracking to electronically shift the image transmitted to the implant. Suprachoroidal RF-powered devices developed and implanted by Bionic Vision Australia (three patients (Ayton et al. 2014)) and by Osaka University (two patients (Fujikado et al. 2011)) have even larger electrode spacing (2 mm), so that the equivalent visual acuity is in the range of 20/4000 to 20/20,000.

(B) In the Alpha AMS prosthesis (Retina Implant AG, Reutlingen, Germany) (Stingl et al. 2013), a subretinal camera consisting of 1600 pixels of 70 μm in size converts natural images on the retina into electrical currents that stimulate neurons in the inner nuclear layer. Power is delivered to the implant via a trans-scleral cable connected to an RF power receiver positioned behind the ear, like in cochlear implants. Optical transmission of the images retains the natural coupling between the visual information and the eye movements. Typically, visual acuity with this device is no better than 20/1200 (Zrenner et al. 2011), but a few

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Fig. 2 Simplified diagram of the photovoltaic retinal prosthesis (PRIMA).

Images captured by a camera are displayed in the video goggles and projected onto the retina using pulsed near-infrared (880 nm) light. Pixels in the subretinal photodiode array convert this pulsed light into electric current flowing through the tissue and stimulating the nearby neurons



patients demonstrated acuity up to 20/550 (Stingl et al. 2015).

- (C) In the PRIMA system (Pixium Vision, Paris, France) (Lorach et al. 2015), images captured by the head-mounted camera are projected onto the retina from augmented-reality goggles using pulsed near-infrared (~ 880 nm) light (Fig. 2). Wireless photovoltaic subretinal prosthesis directly converts light into pulsed electric current in each pixel, stimulating the nearby neurons. Preclinical studies with $70\text{ }\mu\text{m}$ pixels demonstrated grating visual acuity matching the pixel pitch. Clinical study with patients blinded by geographic atrophy started in 2018. It demonstrated safety of subretinal implantation of the 2 mm wide $30\text{ }\mu\text{m}$ thin chips, and bright visual percepts in retinotopically correct locations within the former scotoma. Measurements of the visual acuity are in progress. In the future versions of the implant, the pixel pitch is expected to decrease below $50\text{ }\mu\text{m}$, to provide visual acuity above the threshold of legal blindness (20/200).

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Visual Prosthesis, Optogenetic Approaches

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Synonyms

Bionic eye; Bionic vision

Definition

A visual prosthesis is a device which can artificially restore vision to blind patients. The optogenetic approach involves reverse engineering remaining pathways in the visual system to be photosensitive with light-activated pumps and channels. Illuminating these with optoelectronics encoding visual scenes can then return a sense of vision.

Detailed Description

The human visual system consists of the eye, the optic nerve, and the visual processing centers in the thalamus and visual cortex of the brain. The eye is responsible for optics, image stabilization, transduction and acquisition, with the latter two occurring in the retina. Retinal ganglion cells (RGCs) send information from the eye to the thalamus, which is responsible for sorting left and right eye information. The final projection is to the visual cortex which reconstructs the information to allow the individual to recognize their environment.

Any damage to this sophisticated but delicate system through trauma or disease will impair subsequent vision. Globally, there are 285 million sufferers of visual impairment, of which almost 40 million are blind (WHO 2012). The Royal

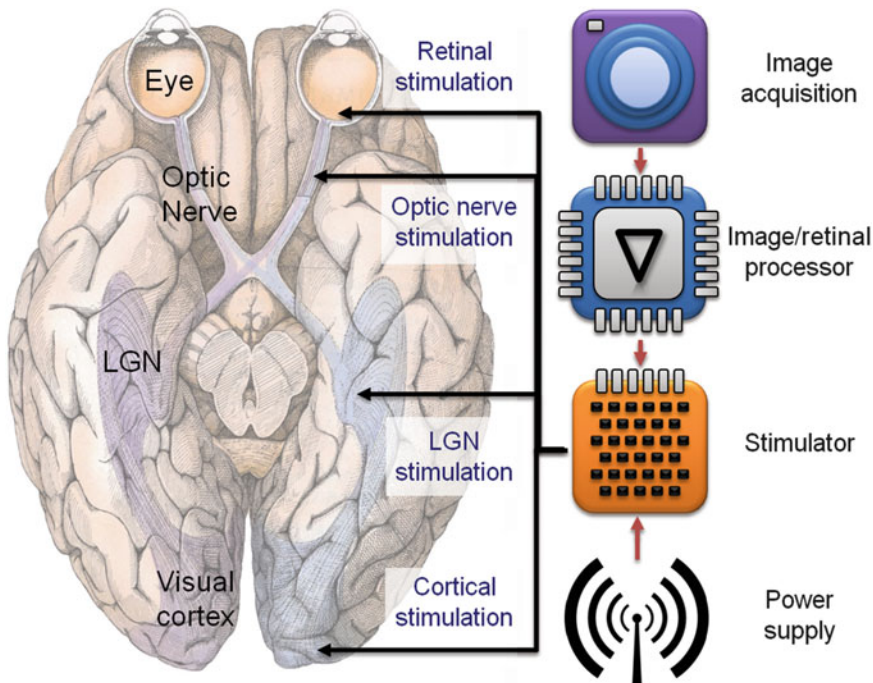
National Institute for Blind People, UK, estimates Two-thirds of registered blind and partially sighted people of working age are not in paid employment (RNIB 2012).

Despite increasing availability of retinal pharmaceuticals, there is presently no treatment for those with retinitis pigmentosa (RP), which causes degeneration of the light-sensing rod and cone cells. For those that have become completely blinded by this condition, a retinal prosthesis holds strong promise for visual restoration. For those with a damaged optic nerve (i.e., *glaucoma* or trauma), a more invasive thalamic or visual cortical prosthesis is required. At the time of writing, electronic retinal implants capable of returning rudimentary vision are commercially available, and there are a number of groups investigating optogenetic approaches to both retinal and visual cortical prosthesis. The scheme of such systems can be seen in Figs. 1 and 2.

History

The “stars” that are seen when the head is struck is due to mechanical stimulation of the visual cortex as it hits the back of the skull. Such “phosphenes” are reported in the literature as far back as the fifth century BC (Grüsser and Hagner 1990) and may have been pondered upon by those who had lost vision. Early attempts at vision restoration started in 1929 when Förster showed that electrical stimulation of the visual cortex could elicit phosphenes (Förster 1929). This was followed up in 1968 by Brindley (Brindley and Lewin 1968) and Dobelle (Dobelle et al. 1974) in the 1960s and 1970s. Many practical difficulties then effectively stopped further progress. Then in 1992 Stone and coworkers (Stone et al. 1992) discovered that patients with RP still had functioning RGCs in their retinæ. Subsequently, the dominant focus of the visual prosthesis community shifted to retinal prosthesis. After two decades of effort, the first retinal prosthesis became commercially available in 2012 with 60 stimulating electrodes.

In 2003 a group investigating the basic properties of algae demonstrated optical



Visual Prosthesis, Optogenetic Approaches, Fig. 1 The main concept of visual prosthesis. The prosthesis conceptually consists of image acquisition (camera), image processing (mobile phone processor), a stimulator (electrode array or optoelectronic array), and some form of

power transmission such as RF. Target areas for stimulation are then either the retina, the optic nerve, the lateral geniculate nucleus (visual part of the thalamus), or the visual cortex

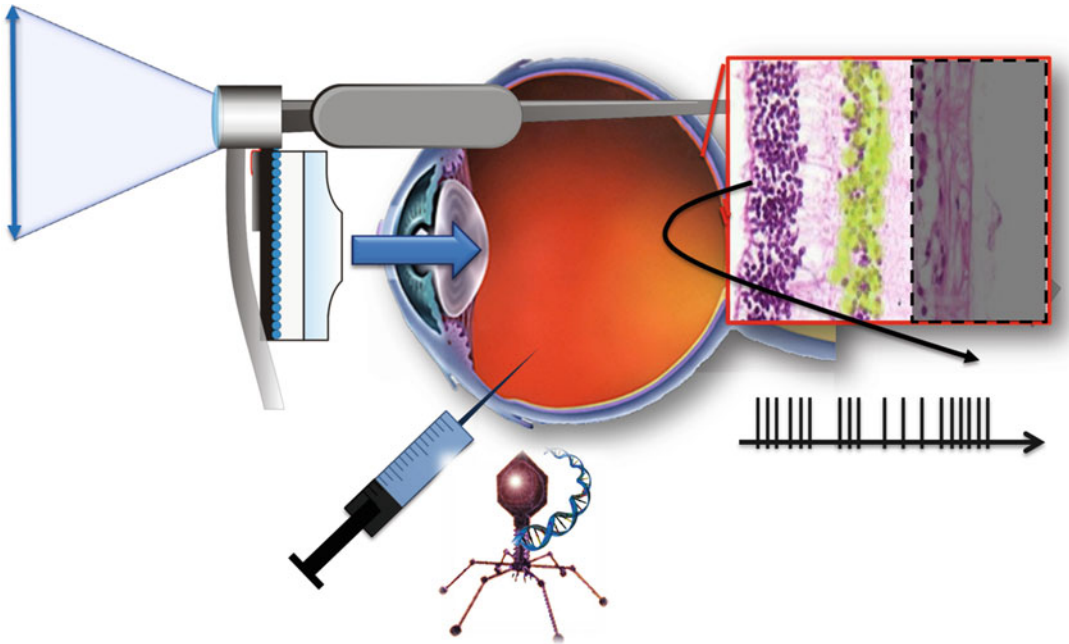
depolarization of cells by genetically incorporating a photosensitive ion channel called channelrhodopsin (Nagel et al. 2003). Later in 2007 (Zhang et al. 2007) it was shown that light-activated chlorine pumps could be used to hyperpolarize cells. The two approaches – allowing full control of neural activity of neuron cells by genetically expressing light-activated channels and pumps in their membranes – became known as “optogenetics.” The key advantage of this technique over previous electronic approaches is that it allows for specific targeting of neural sub-circuits – allowing much more control over the transmission of neural code. Additional advantages include the ability to both stimulate and inhibit and durability as there are no stimulating electrodes which can degrade with time.

Expression of channelrhodopsin was first shown in RGCs in 2005 (Bi et al. 2006). Then in 2008 it was shown that selective expression could be achieved in the ON bipolar pathways (Lagali

et al. 2008). The visual system splits information between ON and OFF pathways; thus, the ability to selectively stimulate one over the other is important in restoring high-quality vision. Later in 2010 it was shown that it was possible to reactivate nonfunctional photoreceptors with halorhodopsin (Busskamp et al. 2010). At the time of writing, some initial expression has been achieved in the visual cortex (Lee et al. 2012), but work in this area is still at a preliminary stage.

Optogenetic Retinal Prosthesis

In comparison to electronic prostheses optogenetic forms of retinal prosthesis simply require an injection of a virus to encode channelrhodopsin or halorhodopsin into a target retinal layer: ganglion cells, bipolar cells, or degenerate cone cells. Then rather than implanting, a headset akin to present augmented reality systems could



Visual Prosthesis, Optogenetic Approaches, Fig. 2 Optogenetic retinal prosthesis. In the case of optogenetic retinal prosthesis, a virus is injected into the eye to make one of the remaining cell layers

photosensitive. High-brightness miniature screens using, for example, microLED arrays then project the appropriate stimulating light pattern into the eye

be worn with a display that illuminates the retina through the existing optical system. A key issue is that both channelrhodopsin and halorhodopsin, including their advanced derivatives, require a very high intensity of illumination. Thus, a display system orders of magnitude brighter than normal mobile phone-type displays is required. A number of methods have been proposed including laser scanning, holography, micromirrors, and microLEDs. Perhaps the most promising for efficiency and thus battery life is the latter (Degenaar et al. 2009). In all cases, scalability to hundreds of thousands of stimulation points is possible, significantly more than electronic approaches. In addition to stimulation optoelectronics, an imaging system and image processing system is required. The general processing scheme of the retina is well understood and has been implemented in various forms of hardware over the years. However, with the advent of highly powerful mobile phone technologies, such processing can now be readily integrated with off-the-shelf technology.

For those requiring more invasive brain-level visual prosthesis, the same front-end imaging and imaging processing system can be used, integrated with a pair of glasses. However, rather than having an augmented reality projection unit, information will have to be wirelessly transmitted to a receiver unit which can relay it to the target thalamus or visual cortex. Once there, a special optoelectronic unit will have to transmit light into the target cortical layers using an optrode light delivery system. This would probably look similar to an optical bed of nails. The key challenges as with any brain implant will be to ensure that the system is efficient enough to be able to stimulate the target tissue without causing thermal damage.

Perspectives

Optogenetic forms of retinal prosthesis could present a significant cost-benefit improvement over electronic prostheses, i.e., a large increase in effective vision for a significantly reduced cost

(no implant required). Developing brain-level visual prostheses will be at least as challenging as previous electronic approaches. Furthermore, despite the many advantages of optogenetics, it still requires the introduction of transgenes into human patients. The key question as various groups move toward human trials is whether there are any long-term adverse effects associated with chronic expression of optogenetic proteins. This will be critical to the future of the field.

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Visual Prosthesis, Subretinal Devices

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Synonyms

Artificial retina; Artificial silicon retina (ASR); Electronic retinal implants; Microphotodiode arrays (MPDA); Retina chip; Retinal prosthesis

Definition

Subretinal implants that have been used in clinical trials so far do not use a camera outside the eye for image capturing but a light-sensitive array that is implanted beneath the retina within the layer of lost photoreceptors, utilizing the retinal processing power of the remaining neurons in the inner retina.

Detailed Description

In the human eye, images are captured by natural photoreceptors that are adaptive and highly

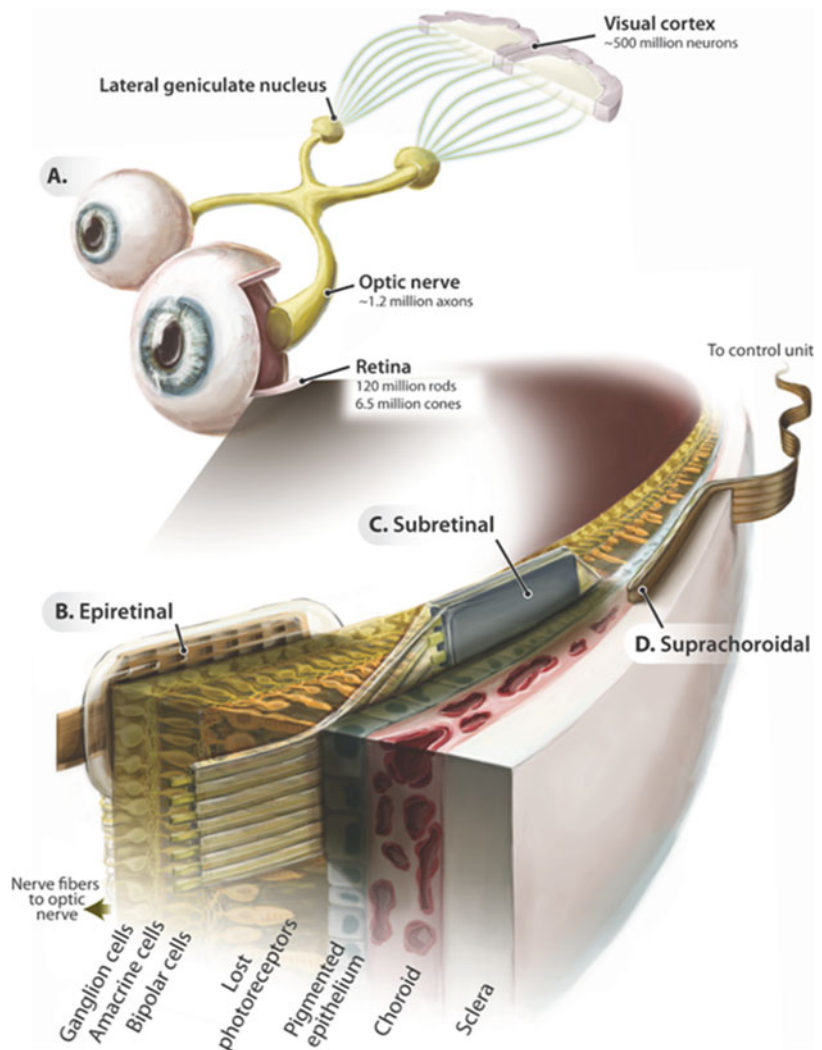
sensitive photo-transducers directly connected to a most efficient neuro-processor, the inner retina. Altogether, the inner retina is only $\sim 200\ \mu\text{m}$ thick, optically transparent, and it contains many millions of bipolar, amacrine, and retinal ganglion cells (RGCs). These nerve cells compress visual information in a way that it can be forwarded to the brain via the relatively small number of ganglion cell axons forming the optic nerve. With degenerative loss within the photoreceptor layer, blindness is inevitable although neuronal processing and signal propagation is still functioning in the inner retina.

There exists no cure for blindness caused by hereditary retinal degeneration of the

photoreceptors (e.g., retinitis pigmentosa (RP)), but restoration of vision by various electronic retinal implants has made rapid progress in recent years with remarkable results concerning visual localization of objects, mobility, even reading, and face recognition in some cases. There are, in principle, three different approaches (Fig. 1, from Zrenner 2013): (a) *Epiretinal* implants are positioned on top of the neuroretina, placing electrodes, controlled by a camera outside the body, at the functional *output* of the retina, i.e., near the RGC fibers; (b) *subretinal* implants that (usually) contain light-sensitive photodiodes, each connected to an electrode, are placed beneath the retina, contacting the functional *input* of the retina

Visual Prosthesis, Subretinal Devices,

Fig. 1 The human ascending visual pathway (A) and sites in the retina where epiretinal (B), subretinal (C), and suprachoroidal (D) implants are inserted. (From Zrenner 2013)



on the photoreceptor side; and (c) the *suprachoroidal* approach that inserts electrode arrays from the back of the eye, positioning them on top of the choroid.

Subretinal light-sensitive implants possess several advantages over other types of retinal implants (Zrenner 2002). They provide functional replacement at the retinal input level, substituting for damaged photoreceptors in a retinotopically correct way. Image formation is provided by incident light which reduces the number of external and implanted electronic components. Also, little signal processing is needed because subretinal devices utilize the processing power of the inner retina still present in RP patients after many years of blindness (Santos et al. 1997). Moreover, eye movements can be used to localize objects, and microsaccadic movements of the eye refresh the image which would quickly disappear without such involuntary micro-movements.

The Various Subretinal Implant Developments

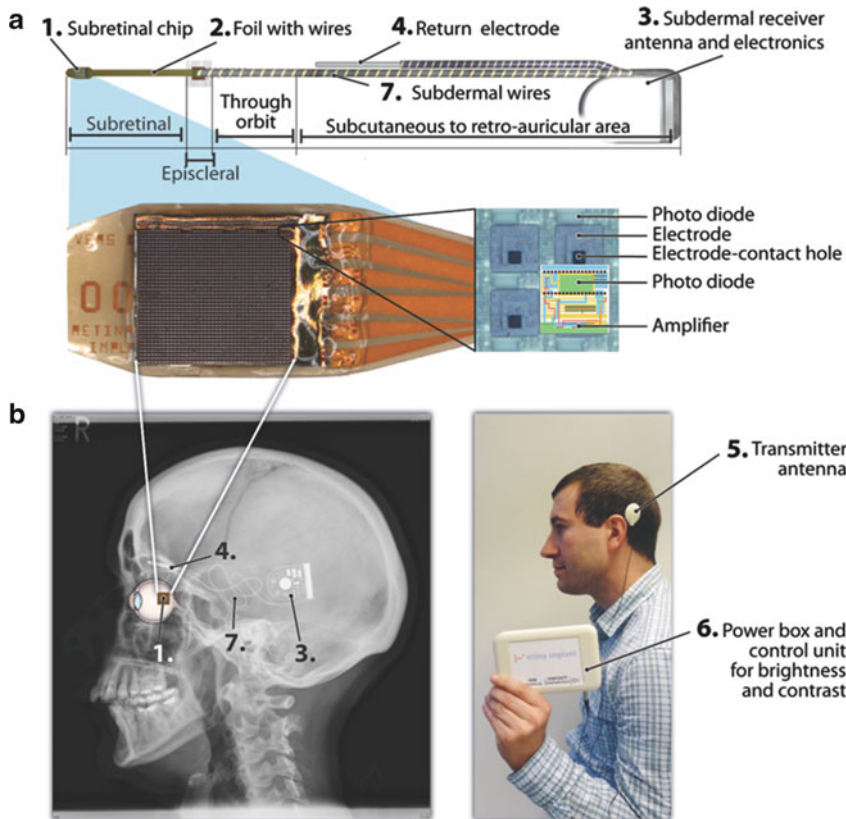
The first application of a subretinal implant is by Tassicker (1956), who positioned a selenium photodiode beneath the retina of a blind patient who subsequently reported the sensation of light.

An “artificial silicon retina” (ASR) has been developed since the early 1990s by Chow et al. (cf. Chow’s summary of his studies, 2010) consisting of a 2-mm-diameter microchip that contains approximately 5000 microelectrode-tipped microphotodiodes. The ASR is a passive device without external power, driven solely by the light contained in the image falling onto the retina. The ASR was also applied in clinical trials sponsored by Optobionics (Chicago, IL, USA); it was implanted subretinally in ten RP patients. It was well tolerated and patients were followed up for several years. Improvement and/or slowing of vision loss occurred in six patients, however, not at the site of implantation in retinal periphery but at central retinal areas where some natural photoreceptors had still been functioning. It was hypothesized that the continuous electrical stimulation had induced retinal neurotrophic rescue of

visual acuity, contrast, and color perception in the central retina of these patients. In preclinical studies this group and other groups could indeed show the release of growth factors upon repetitive electrical stimulation, an effect which was confirmed in clinical studies in RP patients (Schatz et al. 2012).

However, the ASR approach – using simple “passive” photodiode arrays powered with natural light – failed, as the small amount of light falling onto a photodiode of a single pixel is not strong enough to restore visual perception point by point in people blind from photoreceptor degeneration. Therefore, one solution, described next, was to use “active” electronic amplification of the photons falling on each pixel of the image receiver.

The *subretinal implant* Alpha-IMS from Retina Implant AG (Reutlingen, Germany) is such an active electronic implant that contains 1500 photodiodes, driving amplifiers and electrodes, spaced 70 μm on a 3×3 mm chip providing the highest pixel density available for patients so far (Fig. 2a). Power and control signals are generated in a small unit that the patient carries and are supplied to the chip by inductivity via a subdermal retroauricular coil from which a subdermal cable leads to the eyeball (Fig. 2b). This type of retinal implant has passed proof of concept in a wire bound pilot study in all patients (Zrenner et al. 2011). A wireless version has been implanted up to now in 40 patients (study ongoing) by a surgical procedure that advances the implant through a window in the sclera transchoroidally into a subretinal channel to the foveal region. In the first, monocentric part of a main study with the Alpha-IMS implant in Tübingen, Germany, Stingl et al. (2013) report restored light perception (8/9 patients), light localization (7/9), motion detection (5/9, angular speed up to 35 deg/s), grating acuity measurement (6/9, up to 3.3 cycles per degree), and visual acuity measurement with Landolt C-rings (2/9) up to Snellen visual acuity of 20/546 (corresponding to a decimal value of 0.037). Identification, localization, and discrimination of objects improved significantly ($p = 0.05$ for each subtest) in repeated tests over a 9-month period. Patients reported numerous beneficial visual experiences in daily life with regained



Visual Prosthesis, Subretinal Devices, Fig. 2 The subretinal implant. (a) The subretinal implant Alpha-IMS device (Retina Implant AG, Reutlingen, Germany) consists of a subretinal chip (#1) containing 1500 light-sensitive photodiodes, amplifiers, and electrodes placed in the region of the retina where photoreceptors have been lost. The brightness of the image projected by the optical lens through the retina onto the chip is analyzed point by point and, after amplification, is forwarded to the bipolar cells of the inner retina. From there, the neuronal network of retinal ganglion cells processes the “electrical image” normally and forwards it to the visual cortex. (b)

The electronic circuits in the chip are powered and controlled by a subdermal receiver behind the ear (#3) that receives power and signals wirelessly through the skin via a transmitter antenna coil (#5) kept in place behind the ear with a subdermal magnet. As seen in the X-ray image, an implanted cable (#7) leads from the subdermal receiver box to the intraorbital space, where it connects to a subretinal foil (#2) with printed gold wires. The battery box (#6) contains electronics that allow the patient to adjust brightness and contrast to the ambient light of the environment. (From Zrenner 2013)

recognition of unknown objects, recognition of facial or clothes characteristics, recognition of moving objects in nature and traffic, improved self-sustaining actions (recognition of doors, door handles), recognition of small objects (glasses, telephone, stapler, washing basin, even dice and numbers of dots on dice), and improved mobility. Control tests were performed each time with the implant’s power source switched off. These data show that subretinal implants can restore visual functions that are useful for daily

life. The Alpha-IMS device has been approved for use in Europe (CE mark) and is under review as an investigational device for US trials. A multi-center trial in Tübingen, Oxford, Hong Kong, London, Dresden, Budapest, and Singapore is underway (see www.clinicaltrials.gov, NCT01024803).

The Boston Retinal Implant (summarized by Rizzo 2011) is not yet in clinical use. It utilizes a hybrid approach where the electrode array is positioned subretinally, but the image-capturing unit is

a camera outside the body, mounted on a spectacles-frame structure that collects visual images. The Boston Retinal Implant Project has focused its efforts on developing scalable technologies to create a hermetic device that can deliver individually controlled pulses of electrical stimulation to each of hundreds of electrodes, but proof of concept in patients has not yet been performed.

The Stanford Retinal Implant comprises a group led by Palanker (Mathieson et al. 2012) and has worked to overcome the difficulties that the passive ASR approach of Chow et al. (2010) has faced. Their subretinal implant which has been tested so far in laboratory situations uses a photovoltaic subretinal array with three serially connected silicon photodiodes in each pixel (70 μm or 140 μm) that receive power and data directly through pulsed infrared illumination; their output current directly stimulates neighboring neurons. With a laboratory-based near-infrared laser (NIR) image projection system, they were able to drive such photodiode arrays *in vitro* in rat retinæ with outer retina degeneration. The application of their approach in humans may still be a number of years away, as biocompatibility with retinal tissue, biostability of the material, and safe surgical procedures have yet to be firmly established. Moreover, the proposed goggles that provide the necessary high brightness images to the subretinal photovoltaic array need to be developed in such a way that they stimulate the subretinal array in a spatially correct manner through the pupil, despite continuing eye movements; it will be a challenge to direct the high-energy radiation of the goggles safely to predetermined retinal locations of a moving blind human eye but it may be possible.

Limitations

Stett et al. (2000) have shown in experiments with multi-electrode arrays in rodent retinæ that the space constant, reflecting the spread of excitation picked up at retinal output neurons, is approximately 50–70 μm . As 280- μm distance between two points on the human retina reflects 1° of visual angle, a maximum resolution of

approximately 12 min of visual angle can be expected, while 1 min can easily be resolved in normal vision. Moreover, images provided by planar electrodes may be able only to provide vision of scenes in various shades of gray, as such electrodes stimulate the red-, blue-, and green-sensitive neurons under each electrode equally; therefore, the chromatic information in visual scenes cannot directly be transmitted in true color.

Summary

Implants positioned in the subretinal space near the fovea can restore useful vision in daily life up to reading of letters and recognition of facial expression for a large group of the approximately 1.5–2 million patients blind from RP worldwide. Only one subretinal implant, the Alpha-IMS (Retina Implant AG, Reutlingen, Germany) is commercially available so far in specialized centers. Development of visual recognition abilities via learning effects and the role of eye movements need to be studied further over the next years.

Cross-References

- [Prosthetic Vision, Assessment](#)
- [Retinal Disease and Remodeling](#)
- [Retinal Neurophysiology](#)
- [Retinal Prosthesis](#)
- [Retinal/Visual Interfaces \(Models, Theory, Techniques\): Overview](#)

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Visual Prosthesis, Suprachoroidal and Trans-retinal Devices

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Detailed Description

While the number of people with visual impairment is a staggering 285 million (Pascolini and Mariotti 2012), thankfully very few people are profoundly blind, and indeed most people maintain some degree of useful vision. This is particularly true in cases of prevalent degenerative

disorders of the retina such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) where the typical outcome is legal blindness – defined throughout the developed world typically as being central vision less than 20/200 (6/60 in SI units) or peripheral visual fields constricted to less than 10° or 20° – as opposed to profound blindness. This is further evidenced in that AMD patients make up the majority of blind people in developed nations. Despite the introduction of ranibizumab therapy (Rosenfeld et al. 2006), AMD is still likely to remain the most common cause of legal blindness in developed countries as it addresses the neovascular component of the disease, but there is still no treatment for the atrophic component.

A clinical visual prosthesis is thus most plausibly targeted towards blind people with some remaining visual function such that the prosthesis can work in concert with the visual capacity the implant recipient maintains. In order to interface such a stimulating electrode array with the neural retina while at the same time providing an unobstructed optical pathway, it is desirable to place the array behind the retina as opposed to the interface between the vitreous body and the ganglion cell layer. This approach leaves the subretinal space, a site explored in greatest detail by Stingl et al. (2013), or suprachoroidal and trans-retinal devices – the topic of this entry.

The first suprachoroidal visual prosthesis was initially intended for the subretinal space but was inaccessible during surgery. In 1953, an Australian inventor and radio engineer, Graham Tassicker, patented a retinal stimulator design based upon the Becquerel effect (1839), utilizing the photosensitive material selenium (Tassicker 1956a). This device is the first known visual prosthesis (retinal or otherwise). The first human subject was an “elderly woman,” and the device was implanted at the location between the choroid and sclera owing to the inseparability of the retina from the choroid resulting from the patient’s “advanced condition” of a large central scotoma. Following an apparently event-free recovery, the patient reported seeing “uniform white light” in the region of the implant where a “great dark patch” existed before the operation. The patient

also reported increased confidence in mobility (Tassicker 1956b).

More recently, Korean (Zhou et al. 2008), Australian (Matteucci et al. 2013), and Japanese (Fujikado et al. 2012) researchers have explored the suprachoroidal space as a means of delivering controlled, focal stimuli to the visual system. In the first device to be reported in humans, Japanese researchers have tested two, chronically implanted, 9-electrode devices placed within the sclera. Phosphores were reported to be most effectively elicited using a 20 Hz stimulation frequency.

Further from the neural retina, episcleral devices have also been found to be able to elicit focal responses in the feline (Chowdhury et al. 2008), lending further evidence that trans-retinal devices are feasible for long-term visual prosthesis.

The advantages associated with the placement of suprachoroidal and more distal devices are many. First, the surgical approach is significantly simplified, as there is no need for vitrectomy or any immediate contact with the neural retina. Second, the separation of electrodes from excitable tissue may serve to sequester potentially damaging by-products of electrical stimulation. Third, the placement of stimulating electrode arrays requires no fixation such as retinal tacks and adhesives that can cause trauma or increase the difficulty of removal. Fourth, as mentioned above, the devices do not interfere with remaining vision and may indeed be able to serve as a complimentary therapy to improve mobility to the visually impaired.

The distance from retinal neurons, and the need to balance the charge carrying capacity of stimulating electrodes with the ability to elicit psychophysical perceptions, requires that the management of electric fields (Matteucci et al. 2013) be achieved before suprachoroidal or trans-retinal devices can produce clinically relevant outcomes for the blind.

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Visual Rivalry

► Multistability in Perception Dynamics

Visual Sensations of Visual Prostheses

► Prosthetic Vision, Perceptual Effects

Voltage Clamp Technique

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Definition

Voltage clamp is an electrophysiological technique to record electrical currents in biological membranes. It is based on the principle that the current flowing through a cell membrane can be estimated by “clamping” the membrane potential to a constant value using the injection of a mirror current – a current of the same amplitude but reversed polarity.

In practice, the method is used primarily to characterize voltage-dependent conductances in the membrane of neurons by clamping the cells to different stepping potentials. The clamp is achieved with a circuit that quickly detects deviations from the stepping potential and generates currents to correct this deviation. Knowing this current gives the current in the membrane.

Detailed Description

History

The first implementations of voltage clamp go back to Cole (1949) and Hodgkin et al. (1952) and were instrumental in elucidating the mechanism of action potential generation.

In these early implementations, voltage clamp was applied to the giant squid axon using wire electrodes. The clamping amplifier was essentially an operational amplifier that would issue a current proportional to the mismatch of measured membrane potential and command voltage.

Purpose-built amplifiers were designed to eliminate longitudinal (axial) currents so that the action potential occurred only at one locus, a “patch,” and allowed membrane currents in the

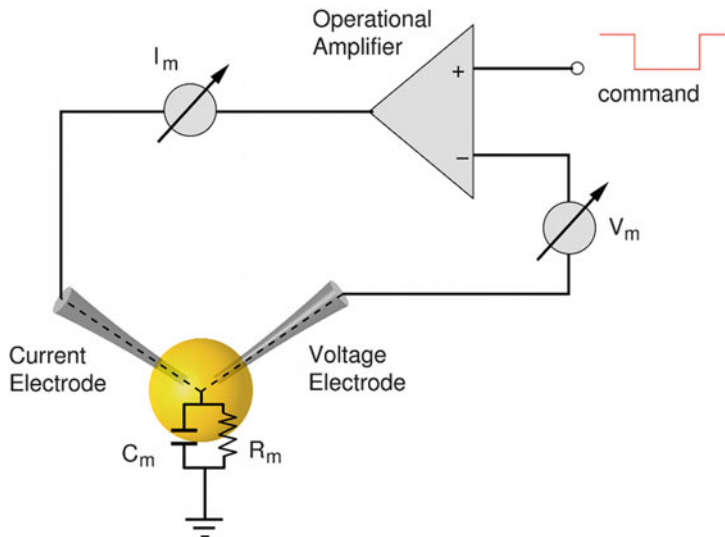
patch to be measured as a function of time at any given voltage.

Implementation Details

Modern amplifiers are equipped with a dedicated voltage-clamp mode. It is straightforward to demonstrate (Halliwell et al. 1994) that the voltage clamp is most precise for large amplification factors. However, there is a practical limitation for the amplification factor in that too large amplification can lead to uncontrolled oscillations, essentially caused by overly amplified noise. These oscillations are known as “ringing” and usually result in the destruction of the cell being recorded.

In contrast to the original method, modern methods for voltage clamp (Fig. 1) use glass electrodes instead of wires which allows recording from cells smaller than the giant squid axon. The glass pipettes have very fine tips ($<1\ \mu\text{m}$) which can create difficulties in accurate measurement. First, they are less good conductors than the wires used by Cole and sometimes cannot pass current rapidly enough to compensate for strong cellular currents. This is particularly relevant for fast currents where both the ohmic resistance of the electrode and its capacitive resistance become problematic. A related problem is that current injections cannot control the membrane potential on the entire cell surface for cells where the isopotential condition is not met, at least on fast timescales. This so-called “space clamp” problem was solved in Cole’s device by using a long wire that clamped the squid axon uniformly along its entire length but is acute with glass electrodes.

When using high-impedance glass electrodes, the injected current will create a drop of the electrical potential along the electrode. These electrode artifacts can be considerable, and to allow precise voltage clamp, two separate electrodes are often used for recording and current injection (two-electrode voltage clamp). However, the two-electrode voltage clamp is difficult to use, in particular in smaller mammalian cells, because penetrating neurons with two electrodes is problematic and can cause damage to the cell resulting in leakage of cellular contents and large leakage



Voltage Clamp Technique, Fig. 1 Diagram of a typical voltage-clamp configuration. A cell is impaled by two independent electrodes, one of which is used to monitor the membrane potential and the other to inject currents such that this potential is “clamped” to follow an externally supplied voltage command. The command signal is typically a voltage step from a holding potential to a stepping

potential as shown. The injected current is generated by an operational amplifier or equivalent circuit that compares the observed membrane potential against the command voltage and emits a proportional current. The current is monitored continuously and is the primary source of data in voltage clamp

currents across the membrane. Furthermore, in many preparations, cells are hard to see making it virtually impossible to impale them with a second electrode. To overcome these problems, a number of single-electrode voltage-clamp techniques have been developed.

Single-Electrode Voltage Clamp

Single-electrode voltage clamp allows recording from small cells that would be impossible to impale with two electrodes. There are a number of methods for achieving single-electrode voltage clamp.

Patch Clamp

The ► [“Patch Clamp Technique”](#) allows the study of individual ion channels. It uses an electrode with a larger tip ($>1\ \mu\text{m}$) that has a smooth circular opening. This electrode is pressed against a cell membrane, and suction is applied to the electrode to pull the cell’s membrane until a tight seal with the electrode – preferably more than a gigaohm –

is created. Following the formation of the seal, the membrane is broken by negative pressure, and a continuum is created between the intracellular solution and the electrode inside. Due to the larger diameter of the electrode, the impedance of the electrode is considerably lower, allowing fast, high-current injections with smaller electrode artifacts. Voltage clamp in this configuration has been successfully employed with minimal electrode capacitance and resistance compensation, though other problems such as cytoplasm washout arise.

Discontinuous Single-Electrode Voltage Clamp

In discontinuous single-electrode voltage clamp (SEVC-d), current injection and membrane potential measurement are not performed continuously and simultaneously as in continuous voltage clamp. Instead, the system undergoes a rapid cycle of alternating between passing current and measuring voltage. The amplifier measures voltage in the first few milliseconds of the duty cycle, generates the error signal, and then passes current for the remainder of the cycle to reduce that error.

The method relies on the cell capacitance being significantly larger than the electrode capacitance, typically by at least one order of magnitude, so that electrode artifacts caused by current injection decay until the next membrane potential measurement is obtained, but the membrane potential does not change a lot over the cycle duration. The frequency of the duty cycle must be optimized to match the timescale of the electrode to minimize the remaining artifact when measuring the membrane potential and maximizing the constancy of the membrane potential. The lower the electrode capacitance is, the shorter the cycle can be and the better the voltage control will be.

While discontinuous voltage clamp allows voltage clamp with higher-impedance electrodes, it has limited time resolution and takes more skill than continuous voltage clamp. One of the practical problems often encountered is that the problem of oscillations due to high amplifier gain is much more critical due to the rapid switch between injection and measurement that adds considerable noise.

Current Isolation

The current measured in voltage clamp is a sum of all currents in the cell membrane. To identify individual ionic currents, additional methods for current isolation are necessary, based on some known properties of the currents under investigation. In order to record a single ionic current, one can block other known currents pharmacologically if specific chemical blockers are available.

On rare occasions where the expected voltage sensitivity range of a current of interest is known and is not overlapping with the range of other currents, one can simply limit the test currents to that range. In most other cases, the property of many currents to inactivate at certain membrane

potentials can be used by clever manipulations of the holding voltage and by using so-called pre-steps to selectively inactivate currents. Pre-stepping the holding potential to a level that inactivates currents other than the current under investigation practically blocks them. Finally, currents can be manipulated by altering external ion composition, creating an environment that would not be conducive for certain currents.

Data Analysis and Modern Developments

Traditionally, voltage-clamp data is analyzed by measuring the steady-state activation of a current toward the end of the voltage step, and the slope of the current rises in the early part of the response to inform Hodgkin-Huxley-type phenomenological models of the ionic currents in the cell membrane. An example of a minimal set of a Na and K current to describe a hippocampal cell is shown in Table 1. With the advent of faster computers, the traditional analysis methods have been replaced by more precise parameter estimation methods on the full trace of the current response (Willms et al. 1999; Willms 2002). Some recent extensions have continued this trend by introducing novel clamping potential waveforms (Gurkiewicz and Korngreen 2007; Drix and Nowotny 2011) as the full trace method does not require constant voltage steps.

A different modern development has been active electrode compensation (Brette et al. 2008; Samu et al. 2012) where instead of using discontinuous current injections in single-electrode voltage clamp, a computer is used to estimate the voltage artifacts on a single electrode in real time and digitally subtracts them from the

Voltage Clamp Technique, Table 1 A typical Hodgkin-Huxley model of a hippocampal cell (Traub and Miles 1991)

$C \frac{dV}{dt} - I_{Na} - I_{Kd} - g_{leak}(V - V_{leak}) + I_{ext}$	V membrane potential, C capacitance, g_{leak} , V_{leak} leak current, I_{ext} externally applied current
$I_{Na} = g_{Na} m h^3 (V - V_{Na})$, $I_{Kd} = g_{Kd} n^4 (V - V_{Nd})$	g_{Na} , g_{Kd} maximal conductances
$\frac{dx}{dt} = a_x(1 - x) - \beta_x x$	$x = m, n$ activation variables, $x = h$ inactivation variable
$\alpha_x = \sigma_{\alpha x}(V)$, $\beta_x = \sigma_{\beta x}(V)$	$\sigma_{\cdot x}$ denote sigmoid function with three parameters for each $x = m, h, n$

measured membrane potential. This new method allows continuous single-electrode voltage clamp with relatively high-impedance electrodes.

Cross-References

- [Dynamic Clamp Technique](#)
- [Patch Clamp Technique](#)

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Voltage Sensitive Dye (VSD) Imaging, Neural Population Models of

- [Neuroimaging, Neural Population Models for](#)

Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

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Abbreviations

di-4-ANEPPS Pyridinium
4-(2-(6-(dibutylamino)-2-naphthalenyl)ethenyl)-1-(3-sulfopropyl)-hydroxide

Synonyms

[Fluorescence imaging](#); [Intrinsic optical imaging](#); [Optical imaging spectroscopy](#); [Two-dimensional optical imaging spectroscopy](#)

Definition

Voltage-sensitive dye imaging is an experimental technique to measure neuronal network activity from *in vivo* brains or live brain slices. In this technique, exogenous chemical agents are employed to continuously and rapidly transduce changes in cell membrane potential into changes in fluorescence emission.

Intrinsic optical imaging uses light at various wavelengths to probe activity-induced changes in the intrinsic optical properties of the brain tissues. The most common changes measured by intrinsic optical imaging are hemoglobin oxygenation and concentration because hemoglobin is a major chromophore in brain tissues within the visible wavelength region.

Detailed Description

Voltage-sensitive dye imaging (VSDI) and intrinsic optical imaging (IOI) are both spatiotemporal neuroimaging methods. However, measurements from VSDI are direct reflections of changes in neural electrical activity, whereas measurements from IOI are related to changes in hemoglobin concentration and hemoglobin oxygenation.

Voltage-Sensitive Dyes

Voltage-sensitive dyes (VSDs) are chemical agents which, when embedded to a cell membrane, change their fluorescence properties in response to changes in the cell membrane potential. The earliest VSDs (such as merocyanines) were photosensitizing agents obtained from commercial suppliers such as Kodak™ and BASF™ and were originally designed to be used in photochemical processes in the photographic industry. While modern VSDs such as di-4-ANEPPS (a styryl dye from Invitrogen) and RH1691 (an oxonol dye synthesized by Rina Hildesheim at Optical Imaging Ltd.) are now synthesized specifically for use in research applications, it took the screening of hundreds of commercially available photosensitizing agents and their analogues before the chemical groups necessary for a successful fluorescence dye were identified. Within the chemical structure of a VSD, a hydrophobic group is required to anchor the VSD directly to the lipid-rich cell membrane. This allows VSD to be aligned perpendicularly to the membrane surface and hence reliably transduce the weak transmembrane potential.

The concept of using molecular transducers to optically indicate electrical activity was first proposed in the 1950s, but it took more than 10 years to successfully realize it in cell cultures (Tasaki et al. 1968) and invertebrate ganglia (Salzberg et al. 1973). These early studies were crucial in recognizing the importance of signal-to-noise ratios of VSDs and identifying undesirable properties of VSDs that should be removed or at least reduced in order to use VSDI to reliably record the neuronal network activity from either the *in vivo*

brains or the *in vitro* brain slices. The first of such properties is direct pharmacological side effects of VSDs that can change ionic conductances and therefore disrupt basic properties of electrical cellular activity. The second undesirable property is that the interaction of the dye molecule with light can provide further damage to the tissue by the formation of highly toxic free radicals, a property of a VSD known as phototoxicity. Finally, the overall fluorescence signal received from the stained tissue may decrease over time because of the irreversible photobleaching of VSDs.

Voltage-Sensitive Dye Imaging

The intensity of the VSDI signal is linearly correlated with the changes in the magnitude of the membrane potential and the area of membrane elements stained. The initial VSDI studies – which used relatively simple cell cultures in conjunction with intracellular electrophysiological recordings – demonstrated the similarity between the signals at the electrode tip produced by VSDI and the intracellular electrode (Cohen et al. 1974). Thus, VSDI has the potential to generate real-time data that is comparable to signals obtained from two-dimensional arrays of electrophysiological recording electrodes.

Although some modern VSDs still exhibit some unwanted side effects (e.g., Grandy et al. 2012), the overall improvement in VSDI over the past decades has allowed this technique to be used successfully in a range of applications involving *in vivo* brains and *in vitro* brain slices which in turn provides a greater understanding of the network properties of many cortical processing systems. For example, VSDI was used to visualize the interactions between incoming sensory information and ongoing activity on the surface of the brains of awake, behaving rodents (Ferezou et al. 2006). VSDI was also used to study *in vivo* and *in vitro* brain tissues to reveal how the horizontal connections among neighboring cortical regions and the vertical connections between different cortical layers uniquely influence cortical function (Reynaud et al. 2012; Sato et al. 2008; Tucker and Katz 2003; Wester and Contreras 2012). The same

technique was used to visualize the communication between the visual cortical and the subcortical structures, such as the thalamus (MacLean et al. 2006). Finally, the combination of VSDI and the computational models of cortical functions has begun to shed light on the fundamental means by which the cortex encodes the rich complexity of incoming sensory information (Zhou et al. 2013).

Limitations of VSDI

Despite the excellent spatial resolution (in tenths of micrometers maximum) and temporal resolution (in the millisecond range), the depth of the investigation of VSDI is greatly limited by the high scattering properties of biological tissue. Therefore, VSDI can only be used to study superficial structures, such as cerebral cortex, and brain slices.

Intrinsic Optical Imaging

IOI is used mainly for two purposes: to map focal activation in the cerebral cortex, such as pinwheel and ocular dominance structures in the visual cortex, and to investigate mechanisms of neurovascular coupling by measuring the changes in cerebral hemodynamics induced by neural activities. In general, the contrast in IOI is originated from the changes in hemoglobin concentration and oxygenation within the tissue volume imaged. The technique can be performed with either a single-wavelength or a multiple-wavelength illumination light depending on the research question being asked.

Single-Wavelength IOI

It is generally used for, for example, pinwheel structures, ocular dominance, or retinotopic mapping in the cortex (Frostig et al. 1990; Grinvald et al. 1991). The choice of the illumination light wavelength determines the aspect of the intrinsic response monitored. If the wavelength is an

isosbestic point in the oxyhemoglobin and deoxyhemoglobin absorption spectra, the changes in the diffusely reflected light will mostly reveal the changes in regional hemoglobin concentration or blood volume. This type of measurement by IOI tends to be more robust. Other wavelengths can also be used to investigate the changes in hemoglobin saturation. To generate a spatial map of activation from the images of IOI, sophisticated image processing is often required to remove so-called “global” components of the response, common to each stimulation type, to reveal the “mapping” components.

Multiwavelength IOI

It is often referred to as optical imaging spectroscopy (OIS) or 2-dimensional optical imaging spectroscopy (2D-OIS). In an OIS system, the cortex is illuminated by a broadband light source and the reflected light from the area of investigation is dispersed by a diffraction grating and recorded (Malonek and Grinvald 1996). In a 2D-OIS system, the cortex is illuminated by a specific number of wavelengths of light selected through a filter wheel, LED, or galvanometer-based system (Berwick et al. 2008; Devor et al. 2008). By measuring the reflected light at multiple wavelengths and then comparing their intensity with the absorption spectra of oxy- and deoxyhemoglobin, the changes in the concentration of these two chromophores in the brain tissue can be estimated. This technique has led to many advances in the understanding of neurovascular coupling, a mechanism by which the brain controls its blood supply.

Limitations of IOI

IOI is an invasive brain imaging technique because light used to illuminate the cortex is generally within the visible wavelength range (450–630 nm) and does not penetrate through the skull due to scattering. Therefore, the majority of the research involving IOI is carried out on the rodent preparation with the skull either removed

or thinned to translucency. Further surgery to remove the dura is needed for experiments on primate and feline animal models.

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Voltage-Gated Na⁺ Channels

► Sodium Channels

Volume Conductor Model

► Finite Element Models of Transcutaneous Spinal Cord Stimulation

Voluntary Behavior

► Spinal Cord, Integrated (Non CPG) Models of

Wavelet Analysis

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Definition

Wavelet analysis is a powerful signal processing method that represents a signal in terms of wavelets. A wavelet or small wave is a wavelike function, upon scaled and translated, that can be used to decompose a signal into its basic constituent components at different scales. Each scale component can be converted into a frequency range. The resulting wavelet transform measures the time-frequency variations of frequency components in a nonstationary signal. Wavelet analysis is thus a natural choice for the analysis of neural data in which the nonstationarity is abundant.

Detailed Description

Techniques for wavelet analysis generally consist of continuous and discrete wavelet transforms that are below described and related to each other. Wavelet analysis is then contrasted with Fourier analysis, followed by its applications in neural data analysis.

Continuous and Discrete Wavelet Transforms

Continuous wavelet transform (CWT) is used to decompose a continuous time signal into scaled and translated wavelets, which is defined as (Daubechies 1992; Mallat 1998)

$$w(a, b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(t) \psi^* \left(\frac{t-b}{a} \right) dt$$

where a is the scale parameter, b is the translation parameter, and $\psi(t)$ is the wavelet basis function or mother wavelet, with $*$ representing the complex conjugate. For example, the commonly used Morlet wavelet, $\psi(t) = \exp(i\omega_0 t) \exp(-t^2/2)$, which is just a complex sine wave modulated by a Gaussian envelope. ω_0 is the wavenumber, specifying the number of the cycles of each wave that the wavelet measures. Although time and frequency do not appear explicitly in the transform, the scale and translation parameters, respectively, provide the frequency range and the time location of an event. Whereas dilated versions of $\psi(t)$ match low-frequency components, contracted versions match high-frequency oscillations. Hence, the CWT exhibits the property of “zooming” in on the sharp temporal variations in a signal. The scalogram of a signal, wavelet analogy of the spectrogram,

is generated by varying parameters in the scale dilation and translation, giving rise to multiresolution analysis.

The CWT still uses discretely sampled data; however, the translating operator smoothly varies along the data sample, and the scaling operator allows much finer encoding resolution as it is defined on a frequency range. This improved resolution of the CWT comes at the expense of increase in time, memory, and computational complexity required to calculate the continuous wavelet coefficients. The discrete wavelet transform (DWT), on the other hand, is not merely a discretized CWT. Instead, the scale and translation parameters are discretized, and for fast numerical implementation, the scale normally varies along a dyadic sequence (the scaling and translation operators are based on powers of 2).

Comparisons with Fourier Analysis

Wavelet analysis is similar to Fourier analysis in that it splits a signal down into its basic constituent components. Whereas the Fourier transform represents the signal as a series of sine waves of different frequencies, the wavelet transform represents signals as linear combinations of wavelets. In comparison to Fourier analysis, it becomes clear that (1) the basis functions in the WT are not limited to the sinusoidal waves, but rather are chosen by the user; and (2) wavelets are localized in both time and frequency, but the Fourier transform is only localized in frequency. In terms of time-frequency localization, the WT is more similar to the short-time Fourier transform (STFT). The main difference is that the STFT uses a single analysis window width, whereas the WT principally uses short windows at high frequencies and longer windows at low frequencies. Nonetheless, both the STFT and wavelet analysis are limited by the fundamental uncertainty principle, in which both time and frequency cannot simultaneously be resolved with the same precision.

Applications in the Analysis of Neural Data

The WT has emerged as a powerful tool for analyzing signals of a nonstationary nature. Applications of wavelet transform to the analysis of neural data mainly include efficient signal representation, signal estimation, and signal compression. Most of its applications have been in time-frequency spectral representation of neurophysiologic data such as EEG (e.g., Tallon-Baudry et al. 1996; Blanco et al. 1998), where the WT is employed for the detection and extraction of significant events of varying frequencies, such as localized rhythmical changes or transient events. Since wavelet transform was used for evoked potential analysis of EEG in the 1990s (Bartnik et al. 1992; Bertrand et al. 1994; Quian Quiroga and Schürmann 1999), single-trial evoked potential estimation using wavelets has attracted growing attention (Quian Quiroga and Garcia 2003; Wang et al. 2007, 2009). In the analysis of spike train data, the WT has been used for signal denoising, feature extraction and decoding, and spike sorting and detection (Hulata et al. 2000; Letelier and Weber 2000; Laubach 2004; Quian Quiroga et al. 2004; Nenadic and Burdick 2005).

The advantage of wavelet analysis lies in its resolution flexibility attributable to a set of wavelets which make the WT suitable for the description of nonperiodic and nonstationary processes, even in the presence of discontinuities and sharp peaks. In practice, the analysis results depend on the choice of basis wavelet function, which is arbitrary and may not be well adapted to represent the signals. The problem is therefore how to select an appropriate basis, among a large set of different wavelets, for analyzing a particular class of signals. An alternative is to use data-driven empirical mode decomposition method, which seems to be promising in the analysis of cortical field potential data (Liang et al. 2005a, b).

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Weak Coupling Theory

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Detailed Description

The theory of weak coupling (Kuramoto 1984; Kopell and Ermentrout 2002; Brown et al. 2004; Izhikevich 2007; Schwemmer and Lewis 2012) has been extremely helpful in developing our understanding of synchronization in neuronal networks. The theory allows one to reduce the dynamics of a weakly coupled network of neuronal oscillators to a system of equations involving only the phase of each oscillator. The resulting “phase models” are given in terms of the neurons’ infinitesimal phase response curves (iPRCs) and the input to the neuron via coupling. This article provides an explanation of how the phase models are derived and gives an example of how the theory can be used to determine phase-locking in a pair of neurons connected by reciprocal inhibition.

Model Neuronal Networks and Phase Models

A network of M weakly coupled heterogeneous neurons can be represented by

$$\frac{dX_j}{dt} = F(X_j) + \varepsilon \tilde{F}_j(X_j) + \sum_{k=1}^M \varepsilon \sigma_{kj} I(X_j, X_k),$$

$$j = 1, \dots, M$$
(1)

where X_j is an N -dimensional vector, containing the state variables of the neuron j (e.g., membrane potential(s), gating variables for ionic membrane conductances, ion concentrations, and perhaps

variables describing the output of chemical synapses). $F(X_j) + \varepsilon \tilde{F}_j(X_j)$ is a vector function describing the state-dependent rates of change of the state variables of the isolated neurons in time; $\varepsilon \tilde{F}_j(X_j)$ accounts for heterogeneity between cells. The term $\varepsilon \sigma_{kj} I(X_j, X_k)$ describes the influence of neuron k on neuron j , where σ_{kj} is the relative coupling strength. ε is a small parameter that scales the magnitude of the heterogeneity and the coupling, ensuring that both are “weak.” All neurons in the network are assumed to be intrinsic oscillators. Specifically, in the unperturbed case ($\varepsilon = 0$), all neurons exhibit stable T -periodic firing. This corresponds to an asymptotically stable T -periodic limit cycle solution for the system $\frac{dX_j}{dt} = F(X_j)$. We will denote this limit cycle solution as the N -dimensional T -periodic vector function $X_{LC}(t + \phi)$, where ϕ is an arbitrary phase shift.

Because the neurons are weakly coupled, the neurons’ intrinsic dynamics are dominant, and the system remains close to the limit cycle. However, small phase shifts due to the coupling can accumulate systematically and eventually, lead to phase-locked states, i.e., fixed relationships between the phases of the neurons. The theory of weakly coupled oscillators reduces the dynamics of the neuronal network to a “phase model” that captures these effects of coupling on the phases of the neurons.

In the phase model for the network, the state of each neuronal oscillator is completely described by its phase θ_j , and the evolution of θ_j is given by

$$\frac{d\theta_j}{dt} = 1 + \varepsilon \omega_j + \varepsilon \sum_{k=1}^M \sigma_{jk} H(\theta_j - \theta_k), \quad (2)$$

$j = 1, \dots, M.$

The function H , which is called the *interaction function*, is determined by

$$\varepsilon H(\theta_j - \theta_k) = \frac{1}{T} \int_0^T Z(\tilde{t}) \cdot (\varepsilon I(X_{LC}(\tilde{t}), X_{LC}(\tilde{t} + (\theta_j - \theta_k)))) d\tilde{t}. \quad (3)$$

The frequency of the unperturbed neuronal oscillators is taken into account by the 1 on the

right-hand side of Eq. 2. The term $\varepsilon \omega_j$ accounts for the small deviations away from this frequency due to heterogeneity and is given by

$$\varepsilon \omega_j = \frac{1}{T} \int_0^T Z(\tilde{t}) \cdot (\varepsilon \tilde{F}_j(X_{LC}(\tilde{t}))) d\tilde{t}. \quad (4)$$

The function $Z(t)$ in the interaction function (Eq. 3) and the heterogeneity term (Eq. 4) is the *infinitesimal phase response curve* (iPRC), which characterizes the phase shift of the neuronal oscillator to a small abrupt (delta-function-like) perturbation.

Note that the theory of weakly coupled oscillators reduces the dimension of the system from the original NM to M , and the system can be further reduced to $M - 1$ when the phase difference between the neurons is considered. For example, a pair of neurons described by the four-variable Hodgkin-Huxley model (Hodgkin and Huxley 1952) augmented by a one-variable chemical synapse can be reduced from a ten-dimensional system to a one-dimensional system. The reduction method can also be readily applied to more complex models, including multicompartment model neurons and network oscillators (e.g., Zahid and Skinner 2009; Zhang and Lewis 2013), which can render a significantly larger dimension reduction. In fact, the method has been applied to real neurons as well (e.g., Mancilla et al. 2007).

The reduction to the phase model makes several approximations that require the coupling between neurons and heterogeneity of the neurons to be sufficiently weak. “Sufficiently weak” implies that the effects of the coupling and heterogeneity account for only a small fraction of the instantaneous frequency of each neuronal oscillator ($d\theta_j/dt$) at each point in the cycle. That is, for the phase model to quantitatively capture the dynamics of the original network (Eq. 2), the influence of heterogeneity and coupling $|\varepsilon \tilde{F}_j(X_j) + \sum_{k=1}^M \varepsilon \sigma_{kj} I(X_j, X_k)|$ should be an order of magnitude smaller than the effects of the intrinsic dynamics of the neurons $|F(X_j(t))|$. However, it is important to point out that phase models often capture the qualitative behavior of systems for moderate levels of heterogeneity and coupling strengths (Lewis and Rinzel 2003; Netoff et al. 2005).

In the following section, we further describe the components of phase models and provide a derivation of phase models. We then show how the theory can be used to analyze phase-locking dynamics in a pair of reciprocally connected Morris-Lecar neurons. Note that more extensive descriptions of the theory of weakly coupled oscillators can be found in Schwemmer and Lewis (2012), as well as many other reviews.

Derivation of Phase Models

There are several methods of deriving phase models, and each method has its own benefit. A geometric approach, which was originally introduced by Kuramoto (1984), gives a beautiful geometric interpretation of the iPRC and deepens the understanding of the mechanisms underlying the phase response properties of neurons. A systematic singular perturbation approach, which was developed independently by Malkin (1956), Neu (1979), and Ermentrout (1981), provides an efficient method for computing iPRCs for model neurons. The reduction method presented here is in the spirit of Winfree's early work with phase models (Winfree 1980) and regards the iPRC as an impulse response function for oscillatory systems. While it is least rigorous, it is probably the most intuitive approach, and it clearly highlights the key idea of the theory of weakly coupled oscillators, which is that neurons behave linearly in response to small perturbations and therefore obey the principle of superposition. Furthermore, this method most closely relates the iPRC to PRCs that can be experimentally measured. Schwemmer and Lewis (2012) describe all three methods and show how they relate to one another.

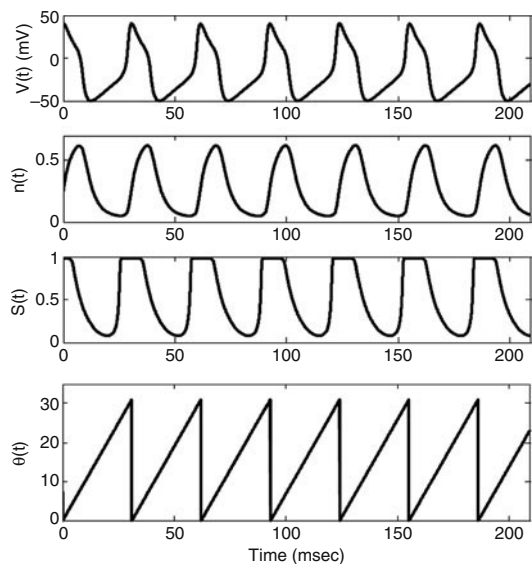
The Phase of Oscillators

The phase of a neuronal oscillator is a measure of the time that has elapsed as the neuron moves through its periodic cycle, starting from an arbitrary reference point in the cycle. We define the phase of an unperturbed periodically firing neuron j at time t to be

$$\theta_j(t) = (t + \phi_j) \bmod T, \quad (5)$$

with $\theta_j = 0$ set to be at the peak of the neurons' spike (Fig. 1). (Phase is often normalized by the period T or by $T/2\pi$, so that $0 \leq \theta_j < 1$ or $0 \leq \theta_j < 2\pi$, respectively. Here, we do not normalize phase and take $0 \leq \theta_j < T$.) The constant ϕ_j , which is referred to as the *relative phase* of the j th neuron, is determined by the position of the neuron on the limit cycle at time $t = 0$. Thus, for the unperturbed neuron, $\frac{d\theta_j}{dt} = 1$ (as indicated in the phase model equation (2) with $\varepsilon = 0$). Note that each phase corresponds to a unique position on the neuron's T -periodic limit cycle, and any solution of the unperturbed neuron that is on the limit cycle can be expressed as

$$X_j(t) = X_{LC}(\theta_j(t)) = X_{LC}(t + \phi_j). \quad (6)$$



Weak Coupling Theory, Fig. 1 Phase in an oscillating Morris-Lecar model augmented by an output synapse (see section “Derivation of Phase Models”). From top to bottom Membrane potential V , gating variable n , synaptic variable S and phase $\theta(t)$ during T -periodic firing. The phase, $\theta(t)$, increases linearly from 0 to T . Zero phase is assumed to occur at the peak of the voltage spike

When a neuron is subjected to perturbations, the exact correspondence of time to phase (Eq. 5) is no longer valid. However, when the perturbations are weak, the neuron remains close to the asymptotically stable limit cycle, and the only significant effects of the perturbations are to adjust the relative phase of the neuron by slightly accelerating or decelerating the progression around the limit cycle. Therefore, the state of neuron j can be well approximated by $X_j(t) \simeq X_{LC}(t + \phi_j(t))$, where the relative phase ϕ_j is now a function of time t . The goal now is to understand how the relative phase of the neuron $\phi_j(t)$ is affected by perturbations due to heterogeneity, coupling to other neurons, and any other input to the oscillating neuron.

The Infinitesimal Phase Response Curve

Before considering how perturbations in general affect the relative phase of an oscillating neuron, first consider the response of a neuron to a small abrupt perturbation. Specifically, suppose that a small brief square current pulse of amplitude εI_0 and duration Δt is delivered to a neuron when it is at phase θ^* . This small, brief current pulse causes the membrane potential to abruptly increase by $\Delta V \simeq \varepsilon I_0 \Delta t / C$, i.e., the change in voltage will approximately equal the total charge delivered to the cell by the stimulus, $\varepsilon I_0 \Delta t$, divided by the capacitance of the neuron, C . The perturbation can cause the cell to fire sooner (phase advance) or later (phase delay) than it would have fired without the perturbation. The magnitude and sign of this *phase shift* depends on the amplitude and duration of the stimulus, as well as the phase in the oscillation at which the stimulus was delivered. This relationship is quantified by the phase response curve (PRC), which gives the phase shift $\Delta\phi$ as a function of the phase θ^* for a fixed $\varepsilon I_0 \Delta t$ (Fig. 2).

For sufficiently small and brief stimuli, the neuron will respond in a linear fashion, and the PRC will be proportional to the magnitude of the current stimulus:

$$\begin{aligned} \Delta\phi(\theta^*) &\simeq Z_V(\theta^*) \\ \Delta V &= Z_V(\theta^*) \left(\frac{1}{C} \varepsilon I_0 \Delta t \right), 0 \leq \theta^* < T, \end{aligned} \quad (7)$$

where $Z_V(\theta^*)$ describes the proportional phase shift as a function of the phase of the stimulus. The function $Z_V(\theta)$, which is known as the infinitesimal phase response curve (iPRC) or the phase-dependent sensitivity function for voltage perturbations, quantifies the normalized phase shift due to an infinitesimally small δ -function-like voltage perturbation delivered at any given phase on the limit cycle. Note that Eq. 7 implies that

$$Z_V(\theta^*) = \frac{\partial \theta}{\partial V}(\theta^*)$$

In principle, any state variable of a neuronal oscillator can be perturbed (e.g., the different voltage variables in a multi-compartmental model, any gating variables or ionic concentrations, as well as firing rate variables in Wilson-Cowan-type models), and therefore, an iPRC for any variable can be measured. Indeed, the iPRC for a neuronal oscillator can be generalized to be a vector function $Z(t)$ in which each component describes the iPRC corresponding to a particular state variable. For example, a Morris-Lecar model augmented by an output synapse (see section on “Derivation of Phase Models” and Fig. 1) has state variables $X = [V, n, S]^T$ and the iPRC is the vector $Z(t) = [Z_V(t), Z_n(t), Z_S(t)]^T$, as shown in Fig. 2.

Phase Models for Weakly Forced Neurons

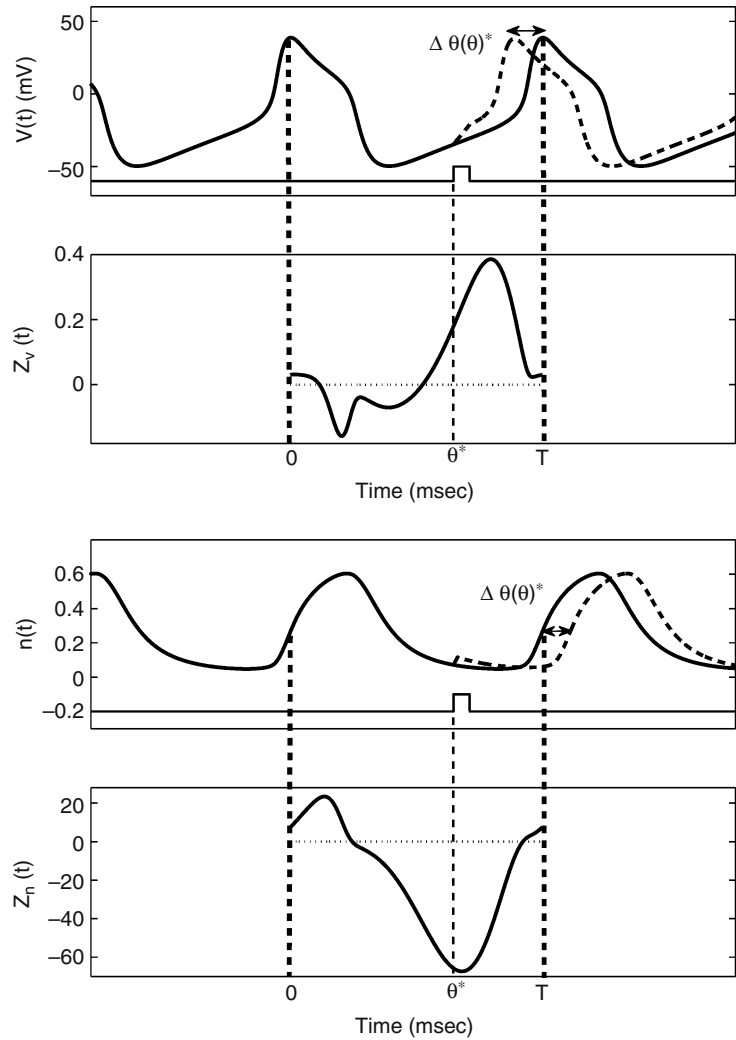
Now, consider the response of neuron j to weak input $\varepsilon P_j(t)$ in general:

$$\frac{dX_j}{dt} = F(X_j) + \varepsilon P_j(t). \quad (8)$$

Note that $\varepsilon P_j(t)$ is an N -dimensional vector function containing perturbation in any or all state variables. As mentioned earlier, because

Weak Coupling Theory,

Fig. 2 iPRCs for an oscillating Morris-Lecar neuron augmented by an output synapse (see section “Derivation of Phase Models” and Fig. 1). The voltage $V(t)$ and gating variable $n(t)$ components of limit cycle oscillations are plotted along with their corresponding iPRCs. The iPRCs are measured by (i) delivering a small brief perturbation to the variable at phase θ^* and measuring the subsequent change in period $\Delta\theta$ and then (ii) plotting the change of phase normalized by the magnitude of the stimulus as a function of θ^* . The iPRC for a synaptic output variable S (not shown) is zero for input at all phases. Because it is strictly an output variable, perturbations to it will not affect the oscillations of the neuron directly



the input is weak, the neurons' intrinsic dynamics dominate the dynamics of the system, and $X_j(t) \simeq X_{LC}(\theta_j(t)) = X_{LC}(t + \phi_j(t))$. This assumes that the input affects the speed at which cells move around the neuron's limit cycle but it does not affect the amplitude of the oscillations. Thus, the effects of the weak input are entirely captured in the dynamics of the relative phases of the cells $\phi_j(t)$. The assumption of weak input also ensures that the perturbations to the neuron are sufficiently small so that the neuron responds linearly to the input. This implies that (i) the small phase shifts of the neuron due to the presence of the input for a brief time Δt can be

approximated using the iPRC (Eq. 7) and (ii) these small phase shifts in response to the input sum linearly (i.e., the principle of superposition holds). That is, (i) the iPRC can be used to determine the phase shift due to the input from t_i to $t_i + \Delta t$

$$\begin{aligned} \Delta\phi_j(t_i) &= \phi_j(t_i + \Delta t) - \phi_j(t_i) \\ &= Z(\theta_j(t_i)) \cdot (\varepsilon P_j(t_i)) \Delta t. \\ &= Z(t + \phi_j(t_i)) \cdot (\varepsilon P_j(t_i)) \Delta t, \end{aligned}$$

and (ii) the accumulated phase shifts due to the input $\varepsilon P_j(t)$ from 0 to $t = m\Delta t$ are

$$\phi_j(t) - \phi_j(0) = \sum_{i=1}^m Z(t + \phi_j(t_i)) \cdot (\varepsilon P_j(t_i)) \Delta t.$$

Taking the limit as $\Delta t \rightarrow 0$, we obtain an integral equation for the evolution of the relative phase of neuron j :

$$\phi_j(t) - \phi_j(0) = \int_{t=0}^t Z(\tilde{t} + \phi_j(\tilde{t})) \cdot (\varepsilon P_j(\tilde{t})) d\tilde{t}. \quad (9)$$

Note that this integral equation has a form similar to a convolution of the iPRC and the input, which indicates that the iPRC is analogous to an impulse response function or Green's function for an oscillating system.

The standard form of a phase model, which governs the evolution of the relative phase of a neuron subjected to weak input, can be obtained by putting the integral equation (9) in its differential equation form:

$$\frac{d\phi_j}{dt} = Z(t + \phi_j) \cdot (\varepsilon P_j(t)). \quad (10)$$

Note: The Link Between the iPRC and General PRCs

The iPRC measures the normalized phase shift in response to small abrupt stimuli. If the neuron is being stimulated with a general small amplitude time-dependent input $\varepsilon I_0(t)$ rather than an abrupt pulse, we can take advantage of the property of superposition and see that the PRC for general

small amplitude stimuli can be estimated from the iPRC by

$$PRC(\phi) = \int_0^\infty Z(t) \cdot (\varepsilon I_0(t - \phi)) dt. \quad (11)$$

Note that as the amplitude of the perturbation increases, the assumption of linearity (superposition) breaks down and the PRC is not necessarily well approximated by a scaled version of the iPRC.

Phase Model for Networks of Coupled Neurons

The input $\varepsilon P_j(t)$ to neuron j described in the previous subsection could be due to an externally applied stimulus, but it could also be due to weak coupling to other neurons in the network or weak heterogeneity. It could also arise from a combination of these perturbations, which is the case for the network of M weakly coupled neurons with weak heterogeneities in the intrinsic properties, described in Eq. 1, i.e.,

$$\begin{aligned} \varepsilon P_j(t) &= \varepsilon \tilde{F}_j(X_j(t)) + \sum_{k=1}^M \varepsilon \sigma_{kj} I(X_j(t), X_k(t)) \\ &= \varepsilon \tilde{F}_j(X_{LC}(t + \phi_j(t))) \\ &\quad + \sum_{k=1}^M \varepsilon \sigma_{kj} I(X_{LC}(t + \phi_j(t)), X_{LC}(t + \phi_k(t))). \end{aligned}$$

Thus, the phase model for this network is

$$\frac{d\phi_j}{dt} = Z(t + \phi_j(t)) \cdot \left(\varepsilon \tilde{F}_j(X_j) + \sum_{k=1}^M \varepsilon \sigma_{kj} I(X_{LC}(t + \phi_j(t)), X_{LC}(t + \phi_k(t))) \right). \quad (12)$$

Note that the limit cycle solution $X_{LC}(t)$ and the iPRC $Z_\nu(t)$ are T -periodic functions and the scaling of the right-hand side of Eq. 12 by the small parameter ε indicates that changes in the relative

phases ϕ_j occur on a much slower timescale than the period of oscillation T . Therefore, we can integrate the right-hand side over the full period T holding the values of ϕ_j constant to find the

average rate of change of the ϕ_j over a cycle. This eliminates the explicit time dependence on the right-hand side of phase equation (12) to obtain

autonomous system of differential equations that approximate the slow-time evolution of the relative phases ϕ_j :

$$\begin{aligned} \frac{d\phi_j}{dt} = & \frac{1}{T} \int_0^T Z(\tilde{t} + \phi_j) \cdot \left(\varepsilon \tilde{F}_j(X_{LC}(\tilde{t} + \phi_j)) + \right. \\ & \left. \sum_{k=1}^M \varepsilon \sigma_k = \varepsilon \frac{1}{T} \int_0^T Z(\tilde{t}) \cdot \tilde{F}_j(X_{LC}(\tilde{t})) d\tilde{t} + \right. \\ & \left. \varepsilon \sum_{k=1}^M \sigma_{kj} \frac{1}{T} \int_0^T Z(\tilde{t}) \cdot \left(I(X_{LC}(\tilde{t}), X_{LC}(\tilde{t} + (\phi_j - \phi_k))) \right) d\tilde{t} \right) = \varepsilon \omega_j + \varepsilon \sum_{k=1}^M \sigma_{kj} H(-(\phi_j - \phi_k)). \end{aligned} \quad (13)$$

Note that the relative phases ϕ_j are assumed to be constant with respect to the integral over T in $\tilde{t}$, but they vary in t . (This averaging process is made rigorous by averaging theory (Guckenheimer and Holmes 1983; Ermentrout and Kopell 1991).) The phase model presented in Eq. 2, which is written in terms of the actual phase of the neuronal oscillator, is obtain from the phase model Eq. 13, which is in terms of relative phase, by using the definition $\theta_j(t) = t + \phi_j(t)$. Both equations show that (i) the effects of weak heterogeneity in the intrinsic properties of the neurons in the network are captured by a constant shift in the intrinsic frequency of each neuron $\varepsilon \omega_j$ and (ii) the effects of the coupling between any pair of neurons are captured by the interaction function H , which is a

function of the phase difference between the two cells.

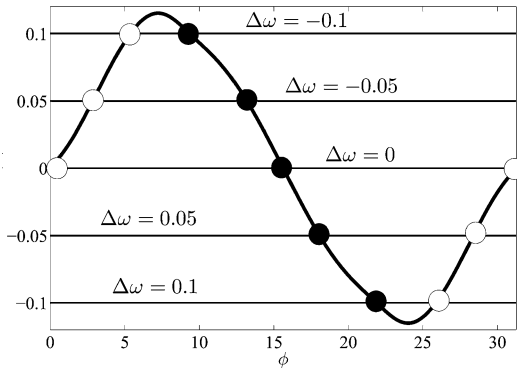
Example: Phase Model for a Pair of Morris-Lecar Neurons Coupled by Reciprocal Inhibition

As a concrete application of the theory of weakly coupled oscillators, consider a pair of the Morris-Lecar neurons with heterogeneity in their leakage conductances and coupled by inhibitory synapses (as described in Fig. 1). That is, (i) the intrinsic dynamics of the neurons are given by the Morris-Lecar (ML) model (Morris and Lecar 1981) with $X_j = [V_j, n_j, S_j]^T$ and

$$F(X_j) = \begin{bmatrix} \frac{1}{C} (-g_{Na} m_\infty(V_j)(V_j - E_{Na}) - g_K n_j(V_j - E_K) - g_L(V_j - E_L) + I) \\ \frac{n_\infty(V_j) - n_j}{\tau_n(V_j)} \\ \frac{S_\infty(V_j) - S_j}{\tau_S(V_j)} \end{bmatrix},$$

where the standard ML system has been augmented with the variable S_j that describes the dynamics of the synaptic output of the neuron; (ii) the heterogeneity between cells is

$$\varepsilon \tilde{F}(X_j) = \begin{bmatrix} \frac{1}{C} (\tilde{g}_{Lj}(V_j - E_L)) \\ 0 \\ 0 \end{bmatrix},$$



Weak Coupling Theory, Fig. 3 G -function for two Morris-Lecar neurons coupled by reciprocal inhibition. The G -function $G(\phi)$ is plotted as a thick line. $G(\phi^*) = -\Delta\omega$ indicate phase-locked states at ϕ^* . Phase-locked state for various levels of heterogeneity ($\Delta\omega$). Phase-locked states at which $G'(\phi^*) < 0$ are stable (filled circles), and phase-locked states at which $G'(\phi^*) > 0$ are unstable (open circles)

where $\tilde{g}_{Lj}$ is the difference between the leakage conductance of neuron j and the mean leakage conductance of the population g_L ; and (iii) the coupling is modeled by conductance-based synapses (e.g., Proctor and Holmes 2010) with a homogeneous coupling strength ($\sigma_{jk} = 1$),

$$\varepsilon I(X_j, X_k) = \begin{bmatrix} \frac{1}{C} \left(g_{syn} S_k (V_j - E_{syn}) \right) \\ 0 \\ 0 \end{bmatrix}.$$

Following the derivation in the previous section, one can obtain the phase model that governs the slow evolution of the relative phases of the two coupled neurons:

$$\begin{aligned} \frac{d\phi_1}{dt} &= \varepsilon\omega_1 + \varepsilon H(\phi_2 - \phi_1) \\ \frac{d\phi_2}{dt} &= \varepsilon\omega_2 + \varepsilon H(-(\phi_2 - \phi_1)), \end{aligned} \quad (14)$$

where

$$\varepsilon H(-\phi) = \frac{1}{T} \int_0^T Z_V(\tilde{t}) \left(\varepsilon g_{syn} S_{LC}(\tilde{t} + \phi) (V_{LC}(\tilde{t}) - E_{syn}) \right) d\tilde{t}$$

and

$$\varepsilon\omega_j = \frac{1}{T} \int_0^T Z_V(\tilde{t}) \left(\varepsilon \tilde{g}_{Lj} (V_{LC}(\tilde{t}) - E_L) \right) d\tilde{t}.$$

Subtracting the phase equation for neuron 1 from that of neuron 2, the dynamics are reduced to a single equation that governs the evolution of the phase difference between the cells, $\phi = \phi_2 - \phi_1$

$$\begin{aligned} \frac{d\phi}{dt} &= \varepsilon(\omega_2 - \omega_1) + \varepsilon(H(-\phi) - H(\phi)) \\ &= \varepsilon(\Delta\omega + G(\phi)), \end{aligned} \quad (15)$$

where $\varepsilon\Delta\omega = \varepsilon(\omega_2 - \omega_1)$ is the difference between the intrinsic frequencies of the neurons due to their heterogeneity in leakage conductance.

Note that the function $G(\phi)$ or “ G -function” can be used to easily determine the phase-locking behavior of the coupled neurons. The fixed points of Eq. 15, which correspond to the phase-locked states of the pair of neurons, are given by $G(\phi^*) = -\Delta\omega$. If $G'(\phi^*) < 0$, then the phase-locked state with phase difference ϕ^* is stable; if $G'(\phi^*) > 0$, then the phase-locked state is unstable.

Figure 3 shows an example G -function for parameters corresponding to the limit cycle solution $X_{LC}(t) = [V_{LC}(t), n_{LC}(t), S_{LC}(t)]^T$ and the iPRCs $Z(t) = [Z_V(t), Z_n(t), Z_S(t)]^T$ shown in Fig. 1. For identical neurons ($\Delta\omega = 0$), this system has two steady states: synchrony ($\phi^* = 0, T$), which is unstable, and antiphase ($\phi^* = T/2$), which is stable. The addition of the heterogeneity shifts the phase-locked states of the coupled neurons. For example, if neuron 1 is made to be slightly faster than neuron 2 ($\Delta\omega < 0$), the stable antiphase state will be shifted to a phase difference that is less than $T/2$ and the unstable synchronous state will be shifted to a positive phase difference. This is seen in Fig. 3 when $\Delta\omega = -0.05$ and -0.1 . Furthermore, if $\Delta\omega$ is decreased further (below $\Delta\omega \simeq -0.13$), a saddle node bifurcation occurs in which the fixed points associated with stable and unstable phase-locked states collide and annihilate each other. This corresponds to the loss of 1:1 phase-locking.

Appendix: Computing the iPRC Using the Adjoint Method

As mentioned previously, the major practical asset of the singular perturbation approach to deriving phase models (Malkin 1956; Neu 1979; Ermentrout 1981) is that it provides a method to efficiently compute the iPRC for model neurons. Specifically, the iPRC is a T -period solution to

$$\frac{dZ}{dt} = -DF(X_{LC}(t))^T Z \quad (16)$$

subject to the normalization constraint

$$Z(0) \cdot X'_{LC}(0) = 1. \quad (17)$$

This equation is the adjoint equation for the unperturbed model neuron (Eq. 1) with $\varepsilon = 0$, i.e., $\frac{dX}{dt} = F(X)$ linearized around the limit cycle solution $X_{LC}(t)$.

In practice, the solution to Eq. 16 is found by integrating the equation backwards in time (Williams and Bowtell 1997). The adjoint system has the opposite stability of the original system Eq. 1, which has an asymptotically stable T -periodic limit cycle solution. Thus, we integrate backwards in time from an arbitrary initial condition so as to dampen out the transients and arrive at the (unstable) periodic solution of Eq. 16. To obtain the iPRC, we normalize the periodic solution using Eq. 17. This algorithm is automated in the software package XPPAUT (Ermentrout 2002), which is available for free on Bard Ermentrout's webpage www.math.pitt.edu/~bard/bardware/.

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Wilson-Cowan Equations

► Large-Scale Neural Networks: Vision

Wilson-Cowan Model

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Definition

The Wilson-Cowan model describes the evolution of excitatory and inhibitory activity in a synaptically coupled neuronal network. As opposed to being a detailed biophysical model, the system is a coarse-grained description of the overall activity of a large-scale neuronal network, employing just two differential equations. Key parameters in the model are the strength of connectivity between each subtype of population (excitatory and inhibitory) and the strength of input to each subpopulation. Varying these generates a diversity of dynamical behaviors that are representative of observed activity in the brain, like multistability, oscillations, traveling waves, and spatial patterns.

Detailed Description

Many regions of the brain process large-scale spatiotemporally structured inputs (Wang 2010). Understanding the resulting neural activity requires macroscopic models that can track the average firing rate across many areas of a neuronal network (Ermentrout 1998). This was the approach in the seminal work of Wilson and Cowan (1972, 1973), who derived effective equations for the macroscopic behavior of a large network of neurons. The approach is analogous to using statistical thermodynamics to relate the Brownian motion of particles to a mean ensemble motion of a whole fluid or gas (Reichl and Prigogine 1980). Thus, Wilson and Cowan

(1972, 1973) derive an effective system for the mean field of an underlying statistical process.

Space-Clamped Model

Starting with a large population of densely coupled neurons, Wilson and Cowan (1972) derived effective equations for the proportion of cells in a population that are active per unit time. Crucially, the effective behavior of the population relies on interactions between excitatory and inhibitory cells, where $a_e(t)$ and $a_i(t)$ are the proportion of excitatory and inhibitory cells firing per unit time at instant t . Thus, $a_{e,i}(t) = 0$ corresponds to a low-activity resting state. Excitatory (inhibitory) neurons make their neighbors more (less) likely to become active, and activation is a nonlinear function $F_e(F_i)$ of the presently active proportion of cells. These assumptions yield the system

$$\begin{aligned} \tau_e \frac{da_e}{dt} = & -a_e(t) \\ & + [1 - r_e a_e(t)] F_e(w_{ee} a_e(t) - w_{ei} a_i(t) + I_e(t)), \end{aligned} \quad (1a)$$

$$\begin{aligned} \tau_i \frac{da_i}{dt} = & -a_i(t) \\ & + [1 - r_i a_i(t)] F_i(w_{ie} a_e(t) - w_{ii} a_i(t) + I_i(t)). \end{aligned} \quad (1b)$$

Thus, the activity variables $a_{e,i}(t)$ obey first-order kinetics with timescales $\tau_{e,i}$, tracking the response of each subpopulation. The nonlinearities are typically chosen to be sigmoidal

$$F_j(x) = \frac{1}{1 + e^{-\gamma_j(x - \theta_j)}}, j = e, i, \quad (2)$$

where the gain γ_j and threshold θ_j can depend on the population type $j = e, i$. The argument x is a weighted sum of the proportion of active excitatory and inhibitory cells, where $w_{jk} \geq 0$ describes the strength of connection from cell type k to j . The system Eq. (1) also captures the refractory dynamics of both populations, defined by the prefactors $[1 - r_j a_j(t)]$, tracking the period of time

during which cells are incapable of stimulation following an activation. This term has often been neglected in subsequent considerations of the model, and Pinto et al. (1996) showed that it effectively rescales the parameters of the nonlinearities $F_{e,i}$. The inputs $I_j(t)$ represent the sum of currents arriving to population j from external sources (e.g., other brain areas or an implanted electrode). The derivation of Eq. (1) also presumes important characteristics of time-dependent rates $a_{e,i}$ for large-scale computation that are captured by temporally coarse-grained traces (Wilson and Cowan 1972).

By performing a phase plane analysis on Eq. (1), to find the stability of fixed points $(a_e(t), a_i(t)) = (\tilde{a}_e, \tilde{a}_i)$ Wilson and Cowan (1972) observed two typical modes of behavior. First, when the strength of synapses between excitatory cells is sufficiently strong, multiple stable fixed points can exist: a high excitation and a low excitation state. Alternatively, when the strength of connections between inhibitory subpopulation is sufficiently weak, the system Eq. (1) supports limit cycle solutions. In these limit cycles, a small proportion of active excitatory cells kindle other cells' activation, eventually recruiting inhibitory cells that turn all cells off, starting the cycle over. Thus, Wilson and Cowan (1972) presented a simple mechanism for oscillations in firing rate activity, an ubiquitous neural phenomenon (Wang 2010). Notably, mutually inhibitory models were adapted from Eq. (1) by considering an arbitrary number N of neural populations coupled together solely by inhibition. Each population is then conceived of as representing a separate stimulus or percept, making such models ideal for studying the neural mechanisms of decision making (Usher and McClelland 2001; Bogacz et al. 2006) and perceptual rivalry (Laing and Chow 2002; Wilson 2003).

Spatially Structured Model

The model Eq. (1) ignores potential spatial structure in the network of synaptic connections or the external inputs to the network. Upon considering a spatially organized network of neurons, Wilson

and Cowan (1973) described the connectivity between different regions of the network using functions that depend on the position of the origin y and target x of a synaptic connection. In doing so, this yields a set of partial integral equations

$$\tau_e \frac{\partial a_e(x, t)}{\partial t} = -a_e(x, t) + [1 - r_e a_e(x, t)] F_e(w_{ee} * a_e - w_{ie} * a_i + I_e(x, t)) \quad (3a)$$

$$\tau_i \frac{\partial a_i(x, t)}{\partial t} = -a_i(x, t) + [1 - r_i a_i(x, t)] F_i(w_{ei} * a_e - w_{ii} * a_i + I_i(x, t)) \quad (3b)$$

where $w_{jk} * a_k$ is a convolution operator

$$w_{jk} * a_k = \int_{\Omega} w_{jk}(x - y) a_k(y, t) dy \quad (4)$$

representing the effective drive to population j at location x received from population k . Writing the network of synaptic interactions as a spatial convolution gives a more general definition of the geometry of the network than discrete neural network models that use matrices to describe connectivity (McCulloch and Pitts 1943; Hopfield 1984). Typical weight functions are the Gaussians

$$w_{jk}(x - y) = k_{jk} e^{-(x-y)^2 / \sigma_k^2} \quad (5)$$

which represent a distance-dependent decay in cortical connectivity. The spatial domain Ω can be of arbitrary dimension and size, but it is usually taken to be one or two dimensional as we describe below. The nonlinearities $F_{e,i}$ are often sigmoids Eq. (2), and refractoriness is modeled by the term $[1 - r_j a_j]$ as before. We note that in Eq. (3), it is possible to track the spatiotemporal evolution of inputs, not just the temporal evolution. A key assumption in deriving Eq. (3) is that the intricacies in firing rate variation that occur on very fine spatiotemporal scales can be coarse-grained (Wilson and Cowan 1973). This results in a system of partial integrodifferential equations that are amenable to mathematical analysis (Bressloff 2012).

Applications and Extensions

Originally, Wilson and Cowan (1973) developed the spatial model Eq. (3) to analyze neural hysteresis phenomena related to binocular vision. Since then, the system Eq. (3) has been used as a canonical model of visual cortical activity, since higher mammals' visual systems possess spatially organized feature maps (Hubel and Wiesel 1977). For instance, a mathematical theory of geometric visual hallucination patterns was developed by using symmetric bifurcation theory to analyze the emergence of Turing patterns when Eq. (3) evolved in $\Omega = \mathbb{R}^2$ (Ermentrout and Cowan 1979; Bressloff et al. 2001). Aside from spontaneous visual experience, the model Eq. (3) was also modified with an additional equation for Hebbian plasticity in the weights w_{jk} to understand the spontaneous organization of the cortical feature maps that underlie the processing of spatiotemporally structured inputs (Kohonen 1982). All the periodically ordered maps for certain features like ocular dominance and orientation selectivity can be incorporated into Eq. (3) by employing the appropriate spatial domain Ω (Ben-Yishai et al. 1995; Bressloff and Cowan 2003).

Since its inception, the system Eq. (3) has also been used to model a variety of other sensory, memory, and motor processes. Early on, work in a related model to Eq. (3) showed the combination of short-range excitation and long-range inhibition ($\sigma_e < \sigma_i$ in Eq. (5)) could stabilize persistent activity into the shape of a bump (Amari 1977). Thus, even in the absence of inputs $I_i(x, t)$, the system Eq. (3) can support a nontrivial profile of spatiotemporal activity due to the activity sustained by recurrent excitation w_{ee} . This mechanism has now been used extensively as a model of visuospatial working memory (Camperi and Wang 1998), since the spatial position of a transient stimulus is known to be stored in cortex as persistent activity that can last for up to several seconds (Durstewitz et al. 2000). Related to this, lateral inhibitory networks have also been employed as idealized models of spatial navigation (Samsonovich and McNaughton 1997) and movement preparation (Erlhagen and Schoner

2002), whose neural correlates are also known to be spatially localized, tuned, persistent activity.

The Wilson-Cowan model Eq. (3) has been extended in many ways to account for the rich diversity of currents, synaptic processes, and fluctuations present in the brain. Spike rate adaptation was considered by Hansel and Sompolinsky (1998), who showed that this resulted in traveling waves of neural activity. Similar phenomena arise upon considering the effects of short-term plasticity (Kilpatrick and Bressloff 2010), which dynamically modulates the strength of the synaptic weight functions w_{jk} . Finally, there has been a lot of interest recently in capturing the effects of fluctuations on spatially extended rate models like Eq. (3). Early efforts have simply considered additive spatiotemporal noise processes (Hutt et al. 2008), but a great deal of progress has been made in deriving effective Langevin equations from stochastic neural networks using path integral methods (Buice and Cowan 2007) or a system size expansion (Bressloff 2012).

Cross-References

- [Amari Model](#)
- [Bifurcations, Neural Population Models and](#)
- [Embodied Cognition, Dynamic Field Theory of](#)
- [Neural Field Model, Continuum](#)
- [Neural Population Model](#)
- [Pattern Formation in Neural Population Models](#)
- [Stochastic Neural Field Theory](#)

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Wireless Microstimulation

► Wireless Microstimulators

Wireless Microstimulators

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Synonyms

Wireless microstimulation; Wireless stimulators

Definition

Electrical currents for neural stimulation have conventionally been delivered via metal wires to

the electrode that is in contact with the tissue. The wire connections attached to these rigid electrodes, floating in a very soft medium like neural tissue, not only damage the surrounding cells from tethering forces but also limit the longevity of the implant due to wire breakage in chronic implants. Wireless transfer of stimulus energy as well as the pulse parameters to a floating electrode or an array of electrodes has gained interest in recent years as a method to eliminate the associated problems with tethering wires. Considering the properties of the neural tissue, different types of energy transfer mechanisms have been proposed for energizing the implant wirelessly: electromagnetic radio-frequency (RF), optical, and acoustic waves. The implanted electrode(s) may or may not have active electronics for storing the pulse parameters. Active devices also require an energy storage mechanism for powering the circuit. On the other hand, passive devices that can instantaneously convert the incident energy into the electric stimulus do not need to store energy or require programming, often maximizing the stimulus energy and implantation depth.

The enthusiasm for replacing wired stimulators with wireless versions is primarily motivated from the complications that arise from tethering forces associated with the micromotions of the electrode assembly, the risk of infection from percutaneous connections, and the failures from wire breakage. Additionally, with passive versions of the wireless devices, the electrode shank needed for housing

the electrode contacts and the connecting wires is no longer needed, thus displacing less tissue. This entry discusses the critical parameters associated with microstimulators that use wireless links. The wireless microstimulation concept is illustrated in Fig. 1.

Detailed Description

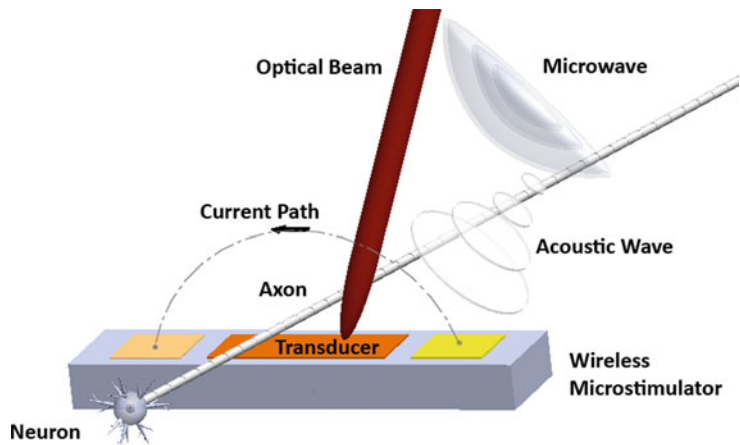
Active and Passive Microstimulators

The stimulation pulse parameters (amplitude, duration, frequency) need to be adjustable in most neuroprosthetic applications to achieve the best results. Thus, when discussing wireless microstimulators, it is useful to classify the devices as either active or passive, depending on whether the device is actively controlling the stimulation signals or if the device passively converts transmitter energy directly into electrical stimulation. In the passive case, the pulse parameters must be controlled by the external unit in the form of energy packages. Passive wireless devices can have the benefit of maximizing the device area for energy conversion. Active devices often contain complex electronics that control the pulse parameters and stimulus rates and must dedicate area to this function. On the other hand, active wireless devices can operate autonomously with minimal intervention and only at times when the pulse parameters need to be modified or the battery needs to be recharged.

Wireless

Microstimulators,

Fig. 1 Illustration of a wireless microstimulator. Energy can be transmitted to the stimulator using RF, optical, or acoustic waves. Current generated by the microstimulator travels from the anode to the cathode of the device, inducing action potentials in nearby neurons



Energy Transfer

Battery Storage

The stimulus energy may be provided from a battery incorporated into the implant. The latest version of the BION™ is a good example of an implantable wireless stimulator with a battery (Loeb et al. 2001; Schulman 2008; Kane et al. 2011). Battery systems are attractive because they do not depend on a wireless link for uninterrupted operation, and they are not bound by energy transfer limitations inherent to wireless energy transfer through tissue. Drawbacks include their large volume, required for the battery, and battery capacity. Batteries need to be replaced or recharged (through a wireless link), limiting their use in chronic implants. The BION™ stimulator reportedly requires charging every few days.

RF Electromagnetics

The most common wireless paradigm for microstimulation is via RF links due to the low absorption of these electromagnetic waves in the tissue. The size of the loop antenna, critically the receiver, can be the limiting factor in the case of RF-powered devices (Rabaey et al. 2011). Other important parameters are whether to use near-field inductive coupling (for increased power coupling efficiency, relevant at lower frequencies) or far-field coupling (larger distances at higher frequencies, but with lower coupling efficiencies) and the RF center and bandwidth (Poon et al. 2010). Heetderks in the 1980s analyzed this system and defined the characteristics of magnetically coupled power transfer systems (Heetderks 1988). Magnetic induction devices work best when the external exciter coil and the internal power receiving coil are in their near fields. This means that very small loop antennas associated with injectable-sized neurostimulators must be located relatively close to the body surface. Otherwise, the nearly cubic rate of decay of the magnetic intensity in the loop far field requires substantial power generation and battery drain on the body surface exciter to overcome such losses.

It is worth noting that radio waves will be shortened when traveling through the tissue,

allowing smaller antennas as compared to those used in air. This can become important at microwave frequencies above 300 MHz, reducing the antenna size of the microstimulator.

Direct conversion of microwave energy to generate neurostimulation electrical pulses in potentially injectable devices has been reported (Towe et al. 2012). These devices are basically small dipoles of about 1 cm length and 800 μm or less diameter that are capacitively coupled by way of electric field coupling to a body surface antenna (Towe et al. 2012). These devices differ from more traditional methods of powering neuroimplants by low-frequency magnetic induction coil systems that depend primarily on the magnetic field component of the EM wave to induce power into open-loop induction coils implanted in tissue.

Advantages

Powering implants at microwave frequencies through electric field coupling has been treated at length by Poon et al. who showed that efficient power transfer to moderately deep implanted devices can be accomplished at GHz frequencies (Poon et al. 2010). Emission of significant RF power from a body surface transmitter and radiating antenna is limited by most countries to specific frequency bands. In the USA, unlicensed operation is permitted at 915 MHz and 2.45 GHz defined as the industrial, scientific, and medical (ISM) bands. These frequencies can be used for efficient energy transfer, as reported by Poon.

Disadvantages

Microwave penetration into the human body varies substantially depending on the tissue type and frequency. Tissue heating is the main concern at elevated microwave pulse powers needed to provide sufficient energy for an injectable size implant at a depth of 5–7 cm. Such an application might be, for example, for pain relief in the spinal canal. The specific absorption rate (SAR) is the primary indicator of microwave dosimetry in biological objects. The regulatory limit in the USA, for example, is 1.6 W/kg for 1 g of tissue (Poon et al. 2010). Since neurostimulation currents are pulsed and have low duty cycles (typically on the

order of 1%), the peak pulse power of microwave radiation can be relatively large, for example, in 5–20 W and higher while maintaining an SAR-limited average power of less than a watt applied to the skin surface by an antenna over the implant. By using relatively high peak pulse powers in the tens of watts range, the microwave exciter antenna can be spaced away from the body by fractions of a meter (Towe et al. 2012) if the stimulation current demands of the implant are low, e.g., less than a milliamperere with 250 μ s pulse widths at 10 Hz.

Current State of the Art

In reported works, implanted microwave dipoles are generally untuned to the microwave frequency in order to achieve small size, and so they depend entirely on capacitive electric field coupling through the tissue. Reported versions have the dipole coupled to a low-threshold Schottky diode that rectifies the high-frequency microwave and turns it into a high-frequency pulsating DC current that is functionally applied directly to the excitable nerves and tissues.

Optical

Microstimulators using light in the near-infrared (NIR) spectrum (wavelengths on the order of 700–900 nm) can be used for wireless power transfer. NIR light has relatively low absorption and low scattering in the neural tissue, as compared to visible light, and it can be converted into electric currents with high efficiencies using semiconductors. Advantages of the optical method include the ability to focus light before the beam enters the tissue, which maximizes energy transfer, and that optical radiation frequency bands are not regulated by governments, unlike RF waves. Floating light-activated microelectrical stimulators (FLAMES) have been shown to produce functional forelimb forces via stimulation of the rat spinal cord gray matter (Abdo et al. 2011b). An optical stimulator with a fiber-optic pigtail has also been demonstrated to generate muscle activation by stimulation of a frog sciatic nerve (Song et al. 2007). Fiber-optic connections prevent classifying this approach as a wireless method; nonetheless, a pigtail fiber connection has a potential to increase the number of optical channels easily

without adding a new fiber for each additional stimulation channel. Active stimulators with optical links are still under development and have yet to be demonstrated *in vivo* (Freedman et al. 2011).

Advantages

Optical power transfer for passive neurostimulation is a relatively less complex method of energy transfer due to the lack of carrier-wave generating systems needed for radio and acoustic techniques. Laser diode infrared emitters and photodetectors are readily available. When powering neurostimulators placed within a few millimeters, they can be more efficient in energy conversion compared to other methods. The elimination of a rigid substrate and the electrode shank is a shared benefit by all wireless methods with a single stimulation channel. The FLAMES are reportedly in the submillimeter range and therefore suitable for CNS applications with minimal tissue replacement. Optical methods also allow addressing of multiple single-channel stimulators via wavelength selectivity.

Disadvantages

Light scattering in the tissue makes it difficult to activate a large number of disjoint stimulators. Passive stimulators of reported designs intrinsically generate monophasic pulses and so must either use classic capacitive coupling to perform electrode charge balancing or engage the use of an integrated circuit for more precise control which then entails additional complexity and requirements for its own powering. All reported passive wireless stimulators, including RF, optical, acoustic, and microwave excited, have an intrinsic orientation dependency in their coupling to the body surface exciters. For example, photodetectors must be oriented planar relative to the optical driving source. This requires that the physician would have to be aware of this with device implantation.

Current State of the Art

A small number of optically powered microstimulators are currently being researched. Wavelength-selective optical devices have

reported efficiencies around 11% (Abdo et al. 2011b) and 43% (Song et al. 2007) for non-wavelength-selective devices.

Stimulation Depth

Although NIR light penetration into the neural tissue is greater compared to visible light, the light attenuation is still relatively strong. In the rat brain, the intensity was reduced to 1.85% of the subdural intensity at 1000 μm and to 0.15% at 2000 μm (Abdo et al. 2013). However, the prototype devices were able to stimulate the spinal cord gray matter and produce forces above 0.8 N (Abdo et al. 2011b) at an implantation depth of 2.35 mm. Scattering of light photons is the dominant effect that limits the penetration depth in the neural tissue, although the g factor (diversion of photon from straight path after scattering) strongly favors the forward direction ($g = \sim 0.9$). The scattering coefficient, which indicates the number of scattering events on average per unit length of the photon path, is larger than 100 per cm in the rat brain (Abdo et al. 2013). Thus, the primary limitation on stimulus power is the temperature increase near the surface where the photons enter the tissue. Direct measurements of temperature with a micro-thermocouple sensor suggest that the power level used in the rat spinal cord (Abdo et al. 2011a) study would only cause a small fraction of a degree elevation in temperature.

Acoustic

Ultrasonic techniques can efficiently transfer energy to a microstimulator through mechanical vibrations at high frequencies. The work by Towe et al. showed that millimeter-order-sized chips of PZT were capable of intercepting sufficient ultrasound power to accomplish direct conversion of the energy to do neurostimulation through 7 cm or more of tissue while maintaining a form factor that was consistent with direct tissue injection of the neurostimulator (Towe et al. 2009). These systems depend on a body surface ultrasound exciter to generate the needed pulse characteristics modulated in the ultrasound carrier wave to evoke the desired neurostimulation waveform from the piezoelectric converter system in tissue.

Advantages

The advantage of acoustic powering of implants is that relatively high-energy densities can be carried by ultrasound waves compared to electromagnetic and optical techniques, and this improves power transfer and allows significant functional depths. This is because they are waves in matter rather than coupled through the electric or magnetic permeability of free space. High frequencies of ultrasound in the MHz region are associated with high accelerations but minuscule displacement of the tissue, with the end result being significant momentum carried by the waves compared to a similar amount of power in generating, for example, an RF magnetic field. Another advantage is that unlike electromagnetic field frequencies below 400 MHz used for power and communication with conventional neurostimulators, ultrasound energy in the medical frequency region can be focused into tight beams by small acoustic lenses and hence has high-energy transfer efficiency in targeting a neuroimplant at a known location. This focality of ultrasound can thus result in reduced battery power consumption in some cases compared to lower-frequency magnetic induction techniques, particularly where the neural implant lies deep in the tissue to small devices where magnetic coupling techniques require relatively large coils.

Disadvantages

Ultrasound energy is strongly absorbed by the bone at MHz frequencies, and so ultrasound losses along the path length through the bone are severe amounting to 3–5 dB/cm (Wells 1977). The losses result from both absorption and scattering of the sound and can cause a disproportionate amount of the beam energy to be deposited in the bone leading to concerns about temperature rise. Ultrasound dosimetry is a limitation if trying to reach targets through the skull in the deep brain or possibly underneath the vertebrae to reach the spinal cord. Employing highly focal transducers to further reduce battery drain or reach deep implants is accompanied by the need to keep the skin surface or shallowly implanted transducer aimed with precision at the implant, a task which may not be practical in all patient applications

where the patient wears the ultrasound exciter on his body. A potential method to overcome this problem was reported to be based on electronic feedback by way of monitoring remote skin potentials produced by an implanted neurostimulator and the use of an ultrasound scanning beam (Gulick and Towe 2012).

Current State of the Art

Conversion efficiency of ultrasound energy by piezoelectric elements integrated as part of a neurostimulator system can be on the order of 10% or more (Ozeri and Shmilovitz 2010). Ultrasound attenuation due to viscoelastic path losses in the tissue amounts to 1–3 dB/cm at 1 MHz, depending strongly on the tissue along the beam path and the ultrasound frequency. Ultrasound path losses increase nonlinearly as the frequency increases (Wells 1977), and so optimal frequencies for power transfer are not the same as diagnostic ultrasound imaging but rather lower and typically in the range of 500 kHz to 1 MHz depending on the path length to the powered implant.

Stimulation Depth

The primary biological effects of concern using ultrasound as an energy transfer medium to an implant are those of tissue heating. FDA limits medical diagnostic ultrasound average intensities to 720 mW/cm² and peak pulse intensities to 190 W/cm² (Center for Devices and Radiological Health 2008). The safe peak pulse intensity specification means that very large 40–50 dB path losses of ultrasound can be tolerated since typically less than a milliwatt is required for neurostimulation.

Concerns and Limitations of Wireless Microstimulators

Tissue Heating

Essentially all reported energy transfer methods are limited in their ability to power deeply implanted device by their energy dissipation along the tissue path length. This dissipated energy can cause tissue heating. Tissue, especially

water-rich tissues, such as the brain, muscles, or skin, can absorb and convert significant amounts of RF, optical, acoustic, or microwave energy into heat. It is imperative that the temperature at any focal point in the tissue is kept at minimal. A temperature elevation limit of 0.5 °C may be taken as a conservative value until more definitive data becomes available, based on the finding that 1 °C produces observable changes (Kiyatkin 2004).

Material Safety

Like all biomedical implants, they must be hermetically sealed and not release any harmful chemicals into the tissue. Encapsulation and sealing sufficient to last a person's lifetime can add significantly to the overall size of these devices. Whether active or passive, implantable stimulators are typically made with semiconductors that may contain materials, such as copper oxides or arsenic oxides, and can be toxic. Solutions include encapsulation of the microstimulator with dielectrics, such as ceramics, glass, and/or organic polymers, such as parylene-C or polyimide.

Channel Selection

Effective microstimulation for some applications such as brain-machine interfaces or spinal cord stimulators requires addressability of multiple different stimulation sites or channels. Optical energy transfer methods can permit some spatial directivity and by an ability to encode, over a range, in infrared wavelengths. Digital encoding for optical device selection is technically possible (Freedman et al. 2011). However, simplicity and some efficiency are lost with the requirement to divert received power to digital logic. Such digital approaches that incorporate microwave or ultrasound powering methods have not been reported so far. Multichannel ultrasound is enabled in principle by the ability to scan a focal beam over a tissue region and serially power multiple devices.

Bipolar Versus Monopolar

Wireless stimulators contain both cathodic and anodic contacts on the device, and thus, the inter-contact distance is limited by the device

size. Multichannel, active stimulators may have a few millimeters between the cathode and anode, and they may be considered to behave as monopolar stimulators especially if the reference electrode is significantly larger than the stimulating contacts. However, with single-channel passive devices, the primary objective is to make the device as small as possible, perhaps a few hundred microns, to minimize the tissue replacement. Thus, the cathodic–anodic contact distance is similarly very short, and the device should be considered as a bipolar stimulator.

Device Size

An ideal microstimulator would displace zero volume in the tissue. Realistically, a stimulator will use the minimum volume needed. In bipolar stimulation, the stimulation strength decreases steeply with distance from the electrodes (Sahin and Píkov 2011). However, simulations suggest that the structures in a volume that is in the same order as the size of the device should be feasible to stimulate while keeping the current in the microampere range (Abdo and Sahin 2011).

Device Geometry and Contact Placement

Large aspect ratios of device geometry should be preferred to maximize the anode–cathode separation and thus the stimulation effect for a given stimulus current. In a 3D device fabrication process, the contacts can be placed at each end of a longitudinal structure. This may be difficult to achieve using standard micro-fabrication processes that are typically applied on wafer-like structures. If the contacts have to be placed on the top surface of a rectangular prism with dimensions in proportions of 2:2:5, the stimulus strength reduces by 8.5% compared to the case where the contacts are placed on each end (2:2 surfaces, (Abdo and Sahin 2011)). A high aspect ratio is also advantageous for insertion of the stimulator into the targeted neural tissue. Electronic device fabrication utilizes only a very shallow region of the semiconductor on the surface, allowing the total device thickness to be reduced down to 50 μm or less. Mechanical strength of the semiconductor substrate becomes the practical limiting factor that determines the maximum aspect ratio

of the structure that renders the device too fragile under bending. In the case of acoustic devices, similar issues apply to piezoelectric ceramic materials like the PZT, in addition to the fact that the piezoelectric device geometry also determines its resonance frequency at which the energy harvesting efficiency is at a maximum. With all three energy transfer paradigms considered here, the device orientation inside the tissue with respect to the external energy source is critical in order to maximize the energy transfer.

Contact Material

The interface between the stimulator and tissue is a critical parameter because the available energy in a wireless microstimulator is always limited. Thus, materials with high charge-injection capacity are desired for the contacts of a wireless microstimulator. Examples include porous platinum or platinum–iridium alloys, sputtered or electroplated iridium oxide, titanium nitride, and conductive polymers like PEDOT (Cogan 2008). The area and the roughness of the electrode contacts also have a significant effect on the charge-injection capacity and typically have a nonlinear relationship between geometric area and the charge-injection capacity. For example, a sputtered iridium oxide microelectrode with a 200 nm surface coating has a charge-injection capacity of 5.3 mC cm^{-2} when the area is approximately $2000 \mu\text{m}^2$ but decreases to 1.7 mC cm^{-2} with a relationship that decays exponentially with increasing surface area.

Voltage Compliance

Simulations suggest that the output voltage of a microstimulator is an important parameter to optimize the energy transfer from the implant to the surrounding neural tissue (Abdo and Sahin 2011). There is a trade-off between the contact size and the required device output voltage. The electrode–electrolyte interface voltages at the contacts are in series to the voltage that develops across the tissue. The device output voltage (compliance) has to be large enough to accommodate the electrode impedance, which is inversely proportional with the contact size for a given material (i.e., charge-injection capacity), and the device current.

Therefore, one can choose large contacts, allowing the device surface area to increase, in return for a smaller output compliance requirement. Thus, larger contact sizes permit a smaller output voltage and so allow a larger stimulus current assuming the total stimulus energy is constant. Conversely, if the device electrode surface area has to be kept below a certain level, this dictates an upper bound for the stimulus current as well. In conclusion, the design of a microstimulator is an optimization problem that intertwines geometrical and electrical parameters of the device.

Representative Examples

RF (Inductive Coupling)

The BION™ neural stimulator (Loeb et al. 2001; Schulman 2008; Kane et al. 2011) is an example of an active floating microstimulator that uses magnetic inductive RF coupling (2 MHz) to transfer energy and also incorporates pulse synthesis and decoding of channel data for neural stimulation. It has an internal capacitor which integrates energy supplied continuously over time that is then metered out according to digital instructions. Externally, the exciter is characterized by a battery pack and relatively large exciter applicator compared to optical or ultrasound methods. The exciter is worn as a coil placed over the implant and connected to a remote battery pack. The diameter of the implant device is 2 mm and the length ranges from 10 to 16.7 mm. Current generations of the device have 256 individual channels that can be independently addressed and a custom ASIC as a pulse former. Stimulation parameters allow currents to be generated in the hundreds of microamperes, up to

40 mA, with voltage compliance values between 8.5 and 17 V. Using iridium and tantalum or platinum–iridium electrodes, the BION™ can deliver up to 50 pulses per second. A distinguishing feature of the BION™ stimulator is its hermetic sealing of either glass or ceramics. Accelerated moisture testing of recent devices shows excellent device reliability for use in multiyear implants.

Optical (NIR Coupling)

The FLAMES (Abdo et al. 2011b) neural stimulator is a passive floating microstimulator that uses diffused near-infrared light to transfer energy for neural stimulation. The device size is approximately $500\ \mu\text{m} \times 200\ \mu\text{m}$ and about $100\ \mu\text{m}$ thick and is shown in Fig. 2. The devices can be addressed by using different wavelengths of infrared light. Stimulation parameters allow currents to be generated on the orders of tens to hundreds of microamperes with voltage compliance values below 2 V. Contacts have been made out of gold coated with PEDOT for good charge-injection capacity under zero bias conditions. Other contact materials and long-term encapsulation with parylene-C are currently being investigated.

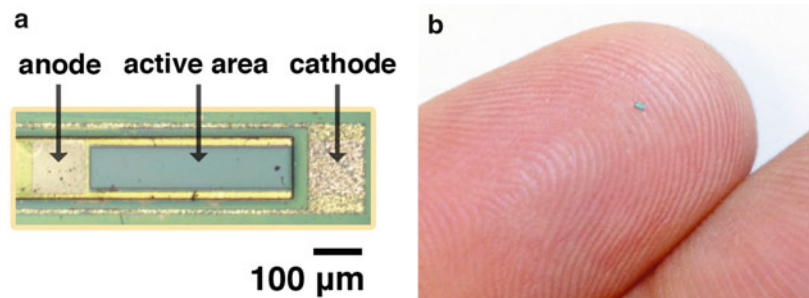
Acoustical (Ultrasonic Coupling)

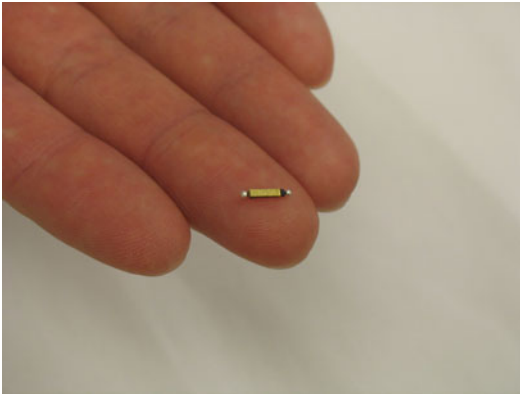
Ultrasound-powered microstimulators have been demonstrated (Towe et al. 2009). In this system, a 1 MHz ultrasonic emitter with a diameter of 26 mm at a distance of 12 cm was used. A piezoelectric receiver, made of PZT-5A, with a 1.13 mm diameter and 1 mm thickness, was used. In a Sprague-Dawley rat, currents on the order of a milliamperere were generated with average powers between $10\ \text{mW}/\text{cm}^2$ and $147\ \text{mW}/\text{cm}^2$. Figure 3 shows a photograph of this type of device.

Wireless

Microstimulators,

Fig. 2 (a) Micrograph of an optically powered microstimulator with the anode, cathode, and active area of the device shown. (b) Photo of the optical-powered microstimulator device





Wireless Microstimulators, Fig. 3 Photograph of an ultrasound-powered microstimulator made from the piezoelectric plastic polyvinylidene fluoride (PVDF)



Wireless Microstimulators, Fig. 4 Photograph of a 915 MHz microwave-powered passive neurostimulator (center) along with a 16-gauge syringe needle and a multi-electrode catheter used for spinal neurostimulation (Medtronic)

Microwave Coupling

Coupling through primarily the EM wave electric field component at microwave frequencies using a thin dipole antenna doubling as an electrode system was demonstrated in the stimulation of a rat sciatic nerve (Towe et al. 2012). An example of this type of device is shown in Fig. 4. This device has a size on the order of 800 μm in diameter and 1.5 cm length, and it was constructed using a low-bias Schottky diode connected to an internal 100 μm diameter platinum wire dipole antenna. This device operates untuned in the ISM band at 915 MHz (US) or 2.45 GHz (international). It

develops milliampere-order currents at 7 cm tissue depths when pulsed at 10 W peak.

Cross-References

- [Brain-Machine Interface and Neuroimaging](#)
- [Brain-Machine Interface: Overview](#)

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Wireless Stimulators

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Wiring Principles, Optimization

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Definition

Wiring principles determine the topological and spatial layout of connections and nodes of neural

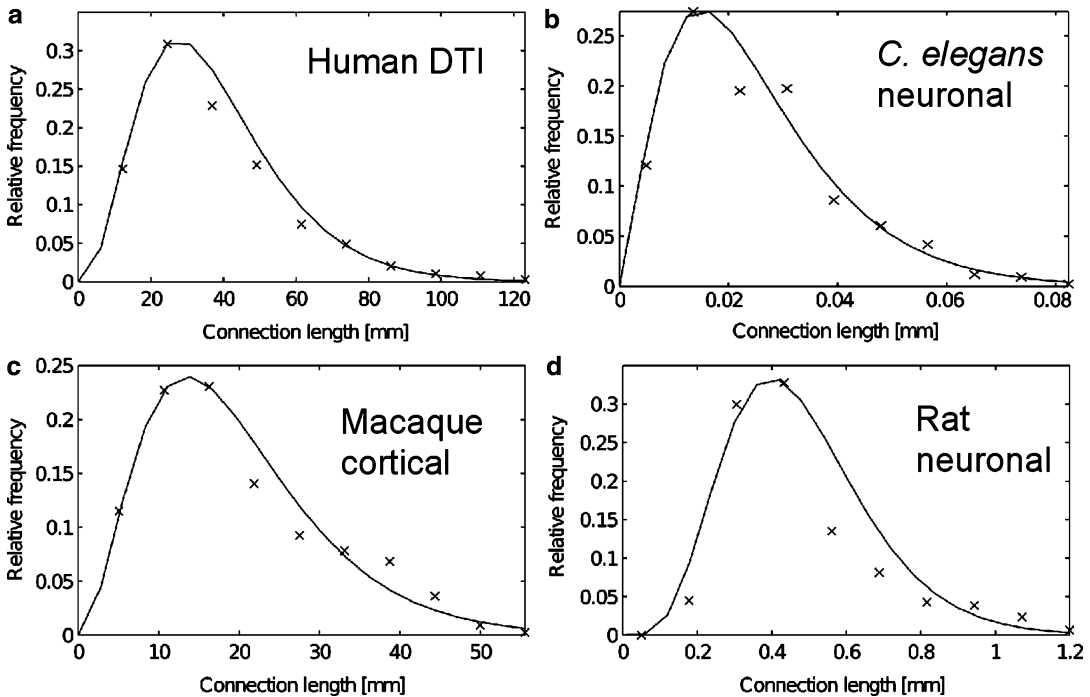
networks. The organization of brain connectivity is subject to several, synergistic or conflicting, constraints, such as low metabolic cost, restrictions of white matter volume by the skull size, and high efficiency of signal processing as reflected in a small number of processing steps.

Detailed Description

Brain connectivity can be analyzed from the perspective of topological or spatial properties of the network. Traditionally, wiring principles have been discussed in the context of spatial properties of brain networks, that is, defined by the location of network nodes and the length of connections among them.

Wiring can be considered at the local scale, reflected by axons and dendrites between individual neurons, or at the global scale, by fiber tracts among brain regions. A lower bound for the wire length is the Euclidean distance between two connected network nodes, measured as straight line between the nodes' mass centers. As some fibers are curved, the three-dimensional trajectory can give a more accurate representation of fiber lengths in a system. However, traditional anatomical tract-tracing techniques make it difficult to determine axonal trajectories directly. Alternative approaches focus on fiber volume rather than connection length, taking into account both fiber length and fiber density (thickness).

While most connections in brain networks are formed at short distance, there exist a substantial number of long-distance connections in diverse examples of neural systems (Fig. 1). The wiring length distribution, in which the frequency of connection lengths decays with distance, can be best approximated by a Gamma distribution (see Kaiser et al. (2009) for details). On the one hand, long-distance connections are costly, in that their establishment and functional maintenance (e.g., action potential propagation) requires energy. On the other hand, long-distance connections can form topological shortcuts (Watts and Strogatz 1998) that may lead to faster and more efficient signal transmission and may result in accelerated reaction times (Kaiser and Hilgetag 2006).



Wiring Principles, Optimization, Fig. 1 Connection length distribution. (a) Fiber tract length distribution among human cortical regions, based on diffusion tensor imaging (DTI). (b) *Caenorhabditis elegans* length of axonal connections within the head of the animal, based on electron microscopy (distance between the mass centers of

somata). (c) Rhesus monkey fiber tract length distribution among cortical areas, based on tract-tracing studies. (d) Rat axonal connection length distribution between neurons in layers 2 and 3 of the primary visual cortex. (Adapted from Kaiser et al. 2009; Kaiser 2011)

Spatial Wiring Constraints

Neural networks should be spatially compact to minimize transmission delays, volume, and metabolic demands associated with neurite development and maintenance as well as signal transmission. It is important to keep in mind that different optimal wiring arrangements might exist for different scales of neural organization, from global systems (e.g., corticocortical connections) to local neuronal connectivity (Murre and Sturdy 1995).

Mechanisms through which a compact design may be achieved are (1) spatial growth models (e.g., Kaiser and Hilgetag 2004b; Kaiser et al. 2009) and (2) self-organization through axonal tension minimization (Van Essen 1997; Hilgetag and Barbas 2006).

The presence of connections involves structural metabolic costs (especially for myelinated

axons) as well as costs for transmitting action potentials (Laughlin et al. 1998; Laughlin and Sejnowski 2003). It is intuitive to assume that, in order to increase organismal fitness, these costs should be kept as low as possible (Cherniak 1992; Chklovskii et al. 2002; Wen and Chklovskii 2008) leading to the idea of wiring optimization.

Wiring optimization (Cherniak 1994; Chklovskii 2004) is often observed at the cellular level, including neural morphology (Cherniak 1992; Cherniak et al. 1999; Chklovskii et al. 2002; Wen and Chklovskii 2008) or connections between cortical maps (Chklovskii and Koulakov 2004). Optimization was also found for white matter volume (Wen and Chklovskii 2005). While these studies were often focused on mammalian brains, the economy of neural circuits was also studied in *Drosophila* (Rivera-Alba et al. 2011) and *Caenorhabditis elegans* (Varshney et al. 2011).

What is the actual evidence for minimal wiring in neural systems? Distributions for brain networks at different scales show mostly neighborhood connections but typically also have a substantial tail of long-distance projections. Thus, the networks are not strictly minimally wired. This observation resulted in a refined assumption of minimal wiring, component placement optimization (CPO): the optimal placement of components under the assumption of fixed connectivity (Fig. 2). In a network obeying CPO, any rearrangement of node positions, while keeping their connectivity fixed, would result in a higher total wiring length of the network. While initial evidence appeared to be in favor of CPO (Cherniak 1992, 1994; Chklovskii et al. 2002), analyses of more extensive and detailed datasets (e.g., Chen et al. 2006; Kaiser and Hilgetag 2006) contradicted the generality of CPO, showing that both *C. elegans* and macaque cortical networks do not obey CPO. Therefore, neural networks do not appear to be solely optimized for minimal wiring, and additional constraints on network organization should be considered.

Efficient Signal Processing

Structural connectivity alone, without actual information on network dynamics, can only be a proxy for information on signal processing. In analogy to highway systems, structural connectivity can indicate the existence and number of lanes of a highway, but not the actual

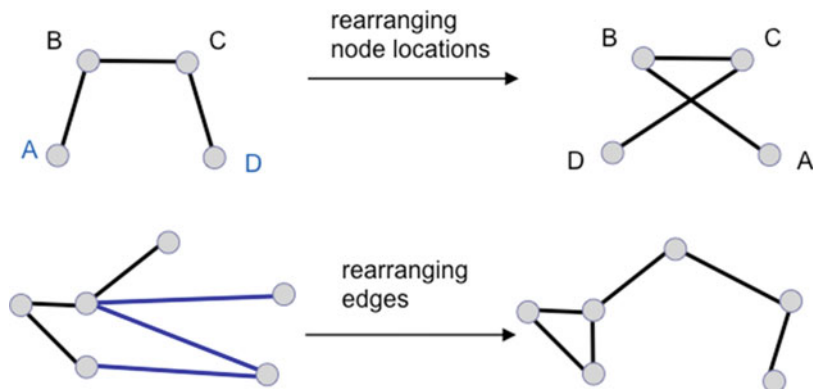
traffic. Nonetheless, the underlying network for information propagation, which is given by anatomical connectivity, may inform on the likelihood of functional connectivity (Stephan et al. 2009) and provide a lower bound on the potential processing speeds in neural systems-based transmission delays influenced by the metric length of a fiber (Swadlow 1991) and its myelination (Koch 2004).

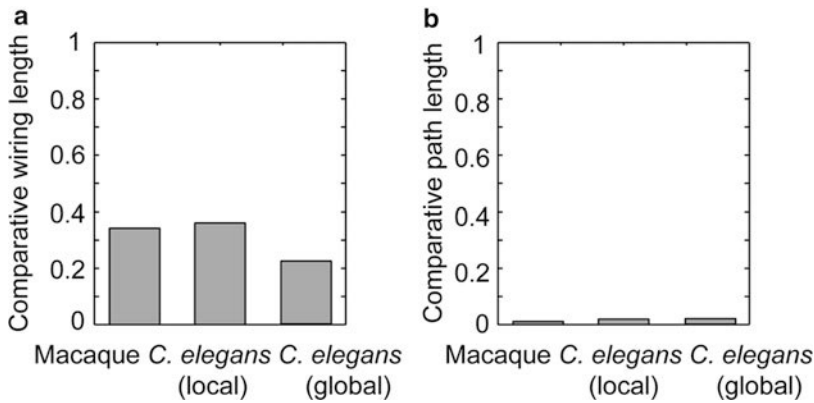
Particularly, processing speed may be related to the number of links that, on average, has to be crossed from one node to another. This measure is called average shortest path (ASP) or characteristic path length (L) (Watts and Strogatz 1998). A now widely adopted related measure is global efficiency, the inverse of ASP (Latora and Marchiori 2001). Alternatively, one might only be interested in information transfer at the local level. The clustering coefficient (Watts and Strogatz 1998) shows what proportion of potentially existing links between the neighbors of a node (nodes that are directly connected to a node) actually exist. A more recent measure at this level is local efficiency, defined as the average value over all nodes of the inverse of the path lengths between neighbors of each node (Latora and Marchiori 2001). Generally, a low number of links in a path potentially reduce delays and increase the speed and reliability of processing.

Studies on macaque and *C. elegans* structural connectivity (Kaiser and Hilgetag 2006) indicate that the reduction of path lengths appears at least as important as the minimization of total wiring length (Fig. 3). These studies showed that there

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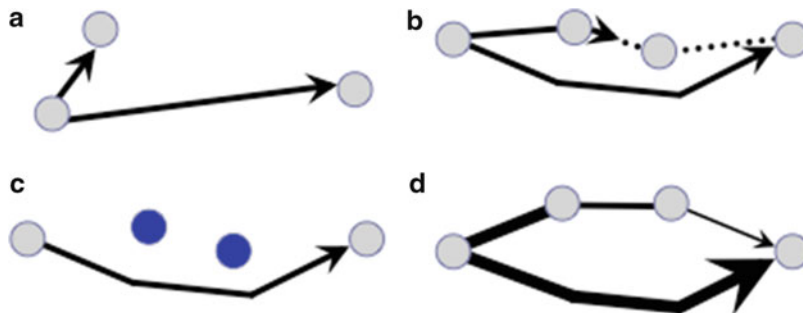
Fig. 2 Approaches to alternative wiring (*top*). Swap node locations (here: nodes *A* and *D*) while connections of each node remain the same (*bottom*). Swap connections (here: blue lines) where the location but not the connectivity pattern remains the same





Wiring Principles, Optimization, Fig. 3 Wiring arrangement of neural networks compared to minimum and maximum case benchmark networks. (a) Actual total wiring length relative to the minimum wiring length solution (value “0,” yielded by simulated annealing of component positions) and to networks optimized for maximum total wiring length (value “1,” also yielded by simulated annealing). The wiring of the different neural networks lies close to the middle between minimum and maximum case

component arrangements. (b) The average shortest path length (characteristic path length) in neural networks relative to networks optimized for minimum path length (value “0,” yielded by simulated annealing of wiring organization) and maximum path length (value “1”). The topological path lengths of the biological neural networks are close to the lower bound of networks optimized for minimum paths. (Adapted from Kaiser and Hilgetag 2006)



Wiring Principles, Optimization, Fig. 4 Benefits of long-distance connections. (a) Facilitated synchronization of near and distant regions, (b) reduced internode

transmission delays, (c) reduced (cross-modal) interference, and (d) increased reliability of transmission. (Adapted from Kaiser and Hilgetag 2006)

are more long-distance connections than would be expected by component placement optimization. Long-distance connections, while carrying metabolic costs for establishment and signal propagation, have the benefit of reducing the average number of connections between nodes; in other words, long-distance connections are often shortcuts that reduce the ASP of neural connectivity.

Minimizing path lengths, that is, reducing the number of intermediate transmission steps in neural integration pathways, has several functional advantages (Fig. 4). First, the number of intermediate nodes, which may introduce interfering

signals and noise, is limited. Second, by reducing transmission delays from multiple internode connections, the speed of signal processing and, ultimately, behavioral decisions may be increased. Third, long-distance connections enable neighboring as well as distant regions to receive activation nearly simultaneously (Kaiser and Hilgetag 2004a; Masuda and Aihara 2004) and thus facilitate synchronous information processing in the system (cf. König et al. 1995; von der Malsburg 1995). Fourth, the structural and functional robustness of neural systems increases when processing pathways (chains of nodes) are shorter.

Each extra node introduces an additional probability that the signal is not transmitted that may be substantial. For example, failure rates for transmitter release in individual synapses are between 50% and 90% (Laughlin and Sejnowski 2003). Even when the signal survives, longer chains of transmission may lead to an increased loss of information. A similar conclusion, on computational grounds, was first drawn by John von Neumann (von Neumann 1958) by comparing the organization of computers and brains. Von Neumann argued that due to the low precision of individual processing steps in the brain, the number of steps leading to the result of a calculation (“logical depth”) should be reduced, and highly parallel computing would be necessary.

Complexity and Robustness

Complexity may be expressed as balance between measures of segregation and integration. One way to support this balance is through modularization, as demonstrated by graph evolution (Sporns et al. 2000). Modularity is a ubiquitous feature of brain connectivity (e.g., Hilgetag and Kaiser 2004; Meunier et al. 2009). Mechanistically, it may arise from an unequal spatial distribution of neural nodes (e.g., Chen et al. 2013) or from developmental time windows (Kaiser and Hilgetag 2007; Nisbach and Kaiser 2007). Network modularity also serves to support structural and functional robustness. Particularly, it increases the resilience to random node and link lesions. Hierarchical modularity also stabilizes self-sustained network activity (Kaiser and Hilgetag 2010). Thus, ubiquitous modularity of neural connectivity may be a reflection of constraints of complexity and structural and functional robustness.

Combination of Multiple Wiring Constraints

Combinations of different constraints on neural network organization are not yet very well explored, due to the large number of potential combinations (Kaiser and Hilgetag 2006). An exploration of the balance of minimal wiring and

minimal path length in a combined objective function (Chen et al. 2013) demonstrated that this trade-off is well served by networks with mostly neighborhood links (to save wiring) and global or local hubs (to reduce path lengths). However, as most biological networks do not have hubs that are as pronounced as predicted by this model, it can be speculated that network organization is affected by additional factors, such as robustness and protection against lesion of global hubs. Notably, the analysis of multiple constraints has recently been applied to functional connectivity, showing that many features of these networks can be captured by combining spatial distance and topological constraints (Vertes et al. 2012).

Summary

While a number of constraints, such as minimization of wiring length and processing steps, appear to play a role in shaping neural networks, no single constraint can completely explain the observed neural connectivity, and brain network organization likely arises from the combined, potentially antagonistic influence of multiple constraints.

Cross-References

- [Connectivity Analysis in Normal and Pathological Brains](#)
- [Human Connectome Project](#)
- [Multiscale Brain Connectivity](#)

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Working Memory, Models of

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Definition

Working memory is the ability to temporarily hold and manipulate information to produce goal-

directed behavior. Drawing biological plausibility from *in vivo* electrophysiological studies, models of working memory attempt to identify cellular, synaptic, and network mechanisms of working memory functions. Current theoretical frameworks largely focus on persistent activity which is thought to be the main neuronal correlate of active maintenance of information.

Detailed Description

All theoretical constructs of working memory (WM) rest on a key notion, which is that of “active maintenance” of information (Miyake and Shah 1999). The adjective “active” refers to the fact that the information being held is able to affect, or even interfere with, the processing of further incoming information. What are the neurophysiological correlates of “active maintenance”?

Electrophysiological investigation of WM is routinely conducted within the delayed-response paradigm. A sensory cue provided at the beginning of the trial must be used, following a delay period, to produce an appropriate (i.e., cue-dependent) motor response, possibly in combination with some additional information provided at the end of the delay. As cue information is mandatory for performance and hence must be maintained across the delay, delay-response paradigms engage WM. Extracellular recordings of neuronal activity in animals performing delayed-response tasks reveal that a large proportion of cells in several cortical regions, e.g., frontal and parietal, modulate their activity during the delay period (Amit and Mongillo 2003). In its basic form, this modulation consists of enhanced/suppressed single-cell spiking rate during the delay as compared to the pre-stimulus period. This rate modulation, also called persistent activity because it is maintained after stimulus removal, is the identifying criterion for “WM cells.” It is widely held that the prime function of persistent activity is active memory maintenance (Goldman-Rakic 1995; Fuster 2008).

The most popular theoretical account for the phenomenology of persistent activity is based on the notion of attractor network (Amit 1989). In

this account, the network underlying memory maintenance possesses multiple “preferred” states of activity (attractors), typically as a result of some learning process. These activity states, which consist of patterns of neuronal activity self-generated by the collective network dynamics, are stable in the absence of external inputs and differ by the spatial distribution of activity across the network (i.e., which cells are firing at which rate). External inputs to the network (e.g., as a result of stimulus presentation) can cause the network to switch state according to the following mechanism. A sufficiently strong external input will impose a specific pattern of neuronal activation within the network. When the input is removed, this activity state will evolve into the “closest” attractor state, that is, the one which is the most similar to the activity state imposed by the external input. Once reached, this state will persist until new stimulation. The state eventually selected by the network dynamics depends, thus, upon the specific input received. The existence of multiple attractor states, their stimulus selectivity and their stability, allow the network to keep track of previous inputs. Attractor models have been extremely successful in reproducing several features of observed patterns of neuronal activity in WM experiments (Amit and Mongillo 2003; Brunel 2003). Numerical simulations of biophysically realistic models of cortical circuits have shown that attractor dynamics is a robust property of the resulting collective dynamics (Wang 2001; Compte 2006). Despite these successes, experimental evidence for attractor dynamics being implemented in cortical circuits is far from being conclusive.

An alternative class of models posits that sustained changes in the firing rates are the result of single-cell mechanisms rather than an emergent property of the collective network dynamics. In this scenario, the single neuron possesses two stable states of activity: a quiescent state and a high firing rate state. External inputs can switch the neuron between states. Modeling studies of single-cell dynamics, which include a sufficiently detailed description of the kinetics of the various ionic channels present in real neurons, have shown that cellular bistability is possible. The

mechanisms proposed include high-voltage-activated calcium channels in combination with calcium-activated cationic currents, post-spike after depolarization induced by neuromodulation, and the nonlinear current-voltage curve of NMDA receptors (Marder et al. 1996; Durstewitz et al. 2000; Major and Tank 2004). Single-cell bistability has also been demonstrated in *in vitro* studies (Durstewitz et al. 2000; Major and Tank 2004). Models based on single-cell bistability come short in explaining the strong temporal irregularity of persistent activity. In numerical simulations as well as in *in vitro* studies, spiking in the high firing state is far more regular than the one observed *in vivo* (Major and Tank 2004; Compte 2006). On the other hand, they can easily explain memory maintenance of previously unexperienced stimuli which is, instead, problematic to account for in the attractor framework where new attractors are assumed to be formed through “slow” synaptic modifications.

The models described so far assume that memory is maintained by enhanced spiking activity. An alternative model proposes that memory is maintained through the fast, stimulus-dependent modifications of synaptic efficacies induced by short-term facilitation (Mongillo et al. 2008). Active maintenance through (temporary) changes in the efficacy of recurrent synaptic transmission offers several advantages. As the time scales associated to short-term facilitation (order of a second) are significantly longer than those associated to the membrane potential dynamics (order of tens of milliseconds), memory maintenance requires little spiking activity with correspondingly low metabolic costs. Electrophysiological studies have indeed shown that persistent activity can occur at quite low rates. Importantly, the temporary perturbation of the ongoing neuronal activity has little effect on the information being held, as that is stored in the levels of synaptic facilitation. This results in a memory network that is robust to noise and is able to maintain multiple items

concurrently. The above features are not straightforwardly reproduced within the attractor and the single-cell bistability frameworks.

Modeling studies have been instrumental in identifying physiological mechanisms that could underlie WM functions and more specifically active memory maintenance. These mechanisms are not exclusive. It is very likely that they all play a role in WM functions to allow the flexible maintenance and manipulation of information that is required for complex adaptive behavior.

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